Nanovector-based therapies in advanced pancreatic cancer

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ABSTRACT Systemic therapy for advanced pancreatic cancer has been largely disappointing owing to the unfavorable pharmacokinetic profile and poor penetration of current chemotherapeutic agents ,as well as the fragile patient population with compromised tolerance to toxic chemotherapies. Nanovectors can provide passive drug delivery through abnormal tumor neo-vasculature microanatomy or active targeting via binding to receptors or macromolecules associated with the tumor. In such a manner, nanovector-based therapy may not only modulate the pharmacokinetics and therapeutic index of chemotherapeutic agents but also provide new treatment options in patients with advanced pancreatic cancer. In this article, we present the rationale and currently available clinical results of nanovector-based therapies to highlight the potential use of this class of agent in patients with advanced pancreatic cancer.

KEYWORDS nanovector; pancreatic cancer; liposome; PEP02; nab-paclitaxel; EndoTAG-1; nanoplatin; platinum; CPT-11

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Introduction

Pancreatic cancer is one of the most detrimental malignancies and the fourth most common cause of cancer-related death in the United Stated. There were 43,140 newly diagnosed cases and 36,800 deaths in 2010 (1). Early detection is uncommon with no more than 15–20% of the patients being amenable for curative intent surgery at the time of diagnosis. Gemcitabine either alone or in combination with erlotinib are the only approved treatments for patients with advanced pancreatic cancer, of whom the overall survival time is generally around 6 months (2-5). Recently, Conroy et al showed that a gemcitabine-free triplet chemotherapy, FOLFIRINOX regimen consisting of oxaliplatin, irinotecan and infusional 5-FU/leucovorin, could achieve significantly better tumor response rate, progression-free survival and overall survival than gemcitabine monotherapy in patients with metastatic pancreatic cancer in a randomization phase III trial (6,7). However, the application of either doublet of triplet combination chemotherapy in patients with advanced pancreatic cancer is often hindered by their toxicity and the performance status of the patients.

New treatment strategies are mandatory to improve the therapeutic outcomes of patients with advanced pancreatic cancer. Recently, two major potential new approaches are emerging that may have the chance to change our practice in treating advanced pancreatic cancer. The first one is molecular targeted agent targeting on dysregulated signaling pathway and the second is the use of nanovector drug delivery system to provide 'passive" or "active" targeting drug delivery thus to modulate the pharmacokinetics and therapeutic index of chemotherapeutic agents in pancreatic cancer (8).

This review will focus on the selective nanovector treatments in pancreatic cancer, especially those with available clinical data, including albumin-bound nanoparticles, liposome-encapsulation nanoparticle, cationic liposomal nanoparticle, polymeric micellar agents, and a non-replicating, retroviral vector delivered gene therapy construct.

Albumin-bound Nanoparticle Paclitaxel (Nab-

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paclitaxel)

Albumin is a particular vehicle for drug delivery in oncology because it is a natural carrier of hydrophobic molecules with reversible, noncovalent binding characteristics and able to enhance the delivery of drug into the extravascular space through a process of receptor-mediated endothelial transcytosis. Such process is initiated by the binding of albumin to an endothelium surface, 60-kDa glycoprotein (gp60) receptor (albondin), which will then bind with an intracellular protein (caveolin-1) to result in the invagination of the endothelium membrane to form transcytotic vesicles, the caveolae (9). The caveolae will subsequently move across the cytoplasm and release the albumin and its conjugated compound into the extracellular space (the peritumoral microenvironment) where the albumin will bind to SPARC (secreted protein acid and rich in cysteine), an extracellular matrix albumin-binding glycoprotein that is structurally and functionally closely related to gp60, and overexpressed in a variety of cancers, including breast cancer, gastric cancer and pancreatic cancer.

Nab-paclitaxel (Abraxane®) is a cremophor (CrEL)-free, albumin-bound, nanoparticle formulation of paclitaxel. Its CrEL-free formulation permits nab-paclitaxel to be administered within a shorter infusion period of time (30 minutes) and without the requirement of routine pre-medications for preventing the hypersensitivity reactions in association with the administration of cremophor solvent-based paclitaxel (10). In preclinical study, the transport of radiolabeled paclitaxel across the endothelial cell monolayer *in vitro*, and intratumor paclitaxel accumulation after equal doses of paclitaxel *in vivo* were both significantly enhanced by 4.2-folds ($P < 0.0001$) and 33% ($P < 0.0001$), respectively, for *nab*-paclitaxel as compared with CrEL-paclitaxel with an increase 4.2 folds. In addition, endothelial transcytosis was completely inhibited by inhibitor of gp60/caveolar transport, methyl ß-cyclodextrin (11). These observations supported that gp60-mediated transcytosis and SPARC-aided sequestration may be an important biological pathway to target tumor cells by novel albumin-bound therapeutics.

In a phase I trial, the maximum tolerated dose (MTD) of intravenous injection nab-paclitaxel monotherapy, every 3 weeks in 19 patients with standard therapy-failure solid tumors was 300 mg/m^2. No acute hypersensitivity reactions were observed. The most frequent toxicities were myelo-suppression, sensory neuropathy, nausea/vomiting, arthralgia and alopecia (12). The drug has subsequently approved for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. The commonly used dose/schedule was 260 mg/m^2, 30-min intravenous injection, every 3 weeks.

Because SPARC is frequently overexpressed and associated with poor clinical outcomes in pancreatic cancer, Von Hoff et al conducted a phase I/II study to evaluate the MTD of weekly nab-paclitaxel (100 – 150 mg/m^2/week) in combination with gemcitabine (1000 mg/m^2/week), and the therapeutic efficacies of the regimen. Both agents were given on day 1, 8, and 15 every 28 days (13). A total of 67 patients were treated. Despite MTD of nab-paclitaxel was determined as 125 mg/m^2/week, dose reduction was required in 30% (6/20), 18% (8/44) and 33% (1/3) of patients receiving 100 mg/m^2, 125 mg/m^2 and 150 mg/m^2, respectively. The most common grade 3-4 toxicity at the MTD dose were fatigue 23%, neutropenia 59% (grade 4 in 23%), thrombocytopenia 20% (grade 4 in 9%) and sensory neuropathy in 9%. Of the 58 patients whose CT image were revaluated with RECIST criteria by independent reviewer, the best tumor response was partial response in 40% and stable disease in 37%, with an overall disease control rate of 78%. The median progression-free and overall survival of the intent-to-treat (N=67) patients were 6.9 months and 10.3 months, respectively; while the survival parameters for the 44 patients receiving MTD dose were 7.9 months and not yet reached, respectively. Of 54 patients with available CA19.9 level, 42 (77.8%) patients had a more than 50% reduction of CA19.9 level after the treatment (14). The therapeutic efficacy of nab-paclitaxel in combination with vandetanib, a potent inhibitor of VEGF2, RET and EGFR, has also been evaluated in a phase I trial with expansion cohort of patients with pancreatic cancer (15). The MTD of vandetanib in combination with two different schedule of nab-paclitaxel, either 100 mg/m^2 weekly or 260 mg/m^2 every 3 weeks, was 300 mg daily. Of the 29 enrolled gemcitabine-refractory pancreatic cancer patients, the best tumor was partial response in 6 (20.7%) and stable disease in 10 (34.5%), and the median progression-free survival and overall survival were 5.3 (95% CI: 3.7 to 7.3) months and 8.2 (95% CI: 6.2 to 11.5) months, respectively. No statistical significant correlation between SNP (rs1059829 and rs3210714) of SPARC and clinical outcomes was observed.

Liposome-based Drugs

A liposome is often a spherical vesicle with a bilayer membrane whose size typically ranges from ~40 nanometers to several microns. Because the micro- or nanoparticles can form spontaneously and are generally easier to prepare compared to viral-mediated systems, this nontoxic phospholipid-based drug carrier has become a favorable drug delivery system for various purposes since the 1970s.

However, so-called conventional liposomes are easily bound with insoluble circulating plasma protein, i.e. opsonins and lipoproteins, and the complex will be subsequently eliminated from the circulation by reticuloendothelial cells system. Stealth liposome technology, with incorporationof high molecular weight polymers (i.e., polyethylene-glycol (PEG)) to the liposome surface, can effectively protect the liposome from circulating protein binding and subsequently phagocytosis by RER system, and thus improving its plasma clearance, prolonging the circulation time, and enhancing drug delivery efficacy.

Besides its characteristic slow-release pharmacokinetic property, liposome encapsulated drugs can potentially provide improved tumor localization via the "enhanced permeability and retention" (EPR) effect. Such agents can therefore, (i) lower drug elimination to increase systemic circulation time, (ii) lower maximum plasma concentration (C_{max}) to reduce drug side effects, (iii) enhance tumor tissue uptake and exposure to the anti-cancer drug; these principles can in turn yield an improved therapeutic index for cancer therapy.

Several liposomal formulated cancer drugs have been evaluated in various cancers, but only a limited number have been applied to pancreatic cancer.

Liposomal Doxorubicin

The first liposomal anti-cancer drug approved by the Food and Drug Administration (FDA) was pegylated liposomal doxorubicin (Caelyx®/Doxil®) in 1995 for Karposi's sarcoma (16-18). It has been subsequently approved for the treatment of multiple myeloma and recurrent epithelial ovarian cancer as well. It also has been evaluated for the treatment of pancreatic cancer in animal xenograft model and in clinical trials. In a preclinical study, Vagge et al showed that pegylated liposomal doxorubicin was significantly more effective in inhibiting the growth of human pancreatic cancer xenograft in nude mice as compared to free form doxorubicin (19). Using confocal laser scanning microscopy and microfluorimetry to quantitate the uptake of intravenously injected doxorubicin in tumor tissue, the authors found that the content of doxorubicin in tumor site of animal receiving liposomal formulated drug was 6 folds or higher compared to free doxorubicin. Based on the results, Halford et al conducted a phase II trial to evaluate the therapeutic efficacy of Caelyx® in 22 chemo-naïve patients with unresectable pancreatic carcinoma. The dose was escalated from 30 mg/m^2 (in the first two patients) to 50 mg/m^2 intravenous injection every 3 weeks (20). Of the 20 patients received the treatment, the most common grade 3 toxicity were stomatitis (20%) and nausea (10%), the best tumor response was stable diseases in 6 (30%), and the median overall survival was 3.2 months with one year survival rate of 10%. These finding excluded the use of Caelyx® monotherapy in the treatment of advanced pancreatic cancer.

The combination of Caelyx® with infusional 5-FU/leucovorin and mitomycin-C has been evaluated in a phase I trial in patients with upper gastrointestinal cancer. In that study, escalating dose of Caelyx® (15 – 35 mg/m^2) day 1 and 29 in combination with weekly 24-hour infusion of 5-FU and leucovorin (2,000 and 500 mg/m^2, respectively) for 6 weeks, and mitomycin-C 7 mg/m^2 day 8 and 36, every 8 weeks as one cycle. The most common grade 3-4 toxicities were nausea/vomiting (29%), diarrhea (18%) and leucopenia (12%). Of the 14 accruals with pre-treated pancreatic cancer, the best tumor response was partial response in one and minor response in 2, and the overall survival after the study treatment was 6.5 months (21).

Liposomal Platinum

Platinum is one of the most active and wildly used anti-cancer agents in the world, including in combination with gemcitabine to treat non-small cell lung cancer and pancreatic cancer. Although each single trial had failed to demonstrate the superiority of gemcitabine/platinum combination over gemcitabine single agent in the prolongation of the survival in patients with advanced pancreatic cancer, however, the survival benefit of gemcitabine/platinum doublets was demonstrated in a pooled, meta-analysis survival with a hazard ratio of 0.81, p = 0.031 (22).

It is also well known that the use of cisplatin is frequently limited by its nephrotoxicity, peripheral sensory neuropathy, ototoxicity and the aggravation of hematological toxicity while in combination with other cytotoxic agents. Therefore, several liposomal formulations of cisplatin have been developed aiming to reduce its toxicity profile and hopefully to enhance it activity. Based on previous experience of gemcitabine/cisplatin combination and the result of meta-analysis, several liposomal formulated cisplatin have been evaluated in patients with pancreatic cancer.

Lipoplatin is one of the pegylated liposome cisplatin, whose nanoparticulate liposomes are reverse-miscelles, composed of dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy- polyethylene glycol-distearoyl phosphatidylethanolamine (mPEG2000-DSPE). Lipoplatin exhibits the fundamental pharmacologic characteristics of pegylated liposomal agents, for example, protecting from the engulfment of reticuloendotheralial system

to prolong circulating time, and extravasating from the fenestrate between endothelial cells of tumor vasculature to preferentially localize in per-tumor interstitial tissue and uptake by tumor cells. The anionic, fusogenic nature of the DPPG lipids enables lipoplatin to cross cell membranes more easily than native cisplatin. In addition, with intraperitoneal injection of a "sheath" liposomes wrapped reporter β-galactosidase gene, which had same structure like lipoplatin, into human tumor bearing nude mice, Boulikas et al were able to demonstrate the preferential expression of the reporter gene in the tumor and the tumor neo-vasculature. The findings indicate the potential antiangiogenic activity of the lipoplatin (23).

In phase I trial of lipoplatin monotherapy, the drug was diluted in 5% glucose water and administered as 8 hour intravenous infusion every 14 days. The dose was escalated from 25 mg/m^2 to 125 mg/m^2. Even at the targeted dose of 125 mg/m^2, only grade 1-2 gastrointestinal and hematological toxicities were observed, but neither nephrotoxicity nor neuropathy. Higher doses, 200, 250 and 300 mg/m^2, were also tested in one each patient, respectively. The half-life of lipoplatin was estimated ranging from 60 – 117 hours. Of the 27 accruals (19 with pretreated, advanced pancreatic cancer) in this phase I trial, the objective tumor response rate and disease control rate were 11.1% and 63.0%, respectively. Based on the exciting results, the drug has been further tested in combination with gemcitabine in non-small cell lung cancer and pancreatic cancer patient cohorts (24).

In a phase I/II study, Stathopoulos GP et al evaluated the maximum tolerated dose of lipoplatin in combination with gemcitabine in patients with previously treated advanced pancreatic cancer (25). Lipoplatin was given as an 8-hour infusion followed by 60 minutes infusion of 1,000 mg/m^2 of gemcitabine at day 1 and 15 every 28 days. The dose of lipoplatin was stepwise escalated from 25 mg/m^2 to 125 mg/m^2. Of the 24 enrolled patients, two of four patients at 125 mg/m^2 experienced grade 3-4 neutropenia. Therefore, the MTD of lipoplatin in this combination was determined to be 100 mg/m^2. In this dose escalating study, there were two (8.3%) partial responders and 14 (58.3%) disease stabilizers, and the median overall survival was 4 month. Further randomized phase II/III trial against gemcitabine monotherapy is under evaluation.

Liposome-entrapped *cis*-bisneodecanoato-*trans*-R,*R*-1,2-diaminocyclohexane (DACH) platinum(II) (L-NDDP, Aroplatin™) is a lipophilic cisplatin analog that has been formulated in relatively large-size multi-lamellar liposomes measuring from 1 to 3 μm in diameter. L-NDDP has been demonstrated to be non–cross-resistant with cisplatin in cisplatin-resistant Lovo DDP 3.0 (human colon cancer cells) and L1210/PPD (human leukemia cells) both *in vitro* and *in vivo* models. In a phase I study, L-NDDP was given intravenously once every 4 weeks, ranging from 7.5 mg/m^2 to 390 mg/m^2 (26). The infusion rate was set at 4 mg NDDP per minute for all cases. In this particular study, intra-patient dose escalation was allowed. Grade 1-2 nausea/vomiting, diarrhea and fever were frequently observed in patients receiving 100 mg/m^2 or higher dose of L-NDDP. Six out of the 10 patients who had 390 mg/m^2 experienced grade 4 hematological toxicities manifesting as thrombocytopenia, granulocytopenia or both. The MTD of intravenous L-NDDP every 4 weeks was determined as 300 mg/m^2. In 2004, Aronex Pharmaceuticals had registered a phase I/II study of L-NDDP and gemcitabine combination in patients with advanced pancreatic cancer resistant to standard therapy in a public clinical trial registration website, the clinicaltrials.gov, with an indentifier of NCT00081549. Unfortunately, the latest trial information was updated in June 2005, and no further publication on this trial can be found.

Liposomal Irinotecan (Nanoliposomal CPT-11, PEP02, MM-398)

Irinotecan hydrochloride (CPT-11) is a water-soluble semi-synthetic derivative of camptothecin targeting topoisomerase I, and has been an approved agent for the treatment of metastatic colorectal cancer worldwide, and also for gastric cancer (Japan and Korea), non-small cell lung cancer, small cell lung cancer, cervical cancer, and non-Hodgkin's lymphoma in Japan. In pancreatic cancer, earlier trial showed that combination of gemcitabine and CPT-11 did not provide any survival benefit over gemcitabine monotherapy in patients with advanced pancreatic cancer, and thus CPT-11 has not been considered to be a clinically useful drug in this disease. However, in the recent PRODIGE 4/ACCORD 11 trial, Conroy et al demonstrated that a gemcitabine-free, CPT-11-containing regimen, FOLFIRINOX (CPT-11, oxaliplatin plus intermittent infusion of 5-FU/leucovorin), provided significantly better objective tumor response rate, progression-free survival and overall survival versus gemcitabine monotherapy in patients with metastatic pancreatic cancer. Notable and not unexpectedly, this triplet regimen is associated with significant hematologic toxicity including higher rates of grade-3/4 febrile neutropenia. The results of the PRODIGE/ACCORD 11 trial have revived interest in CPT-11-based therapy in advanced pancreatic cancer (6,7).

Although the original CPT-11 drug is now of interest in pancreatic cancer management, potentially superior versions incorporating drug delivery technologies offer a

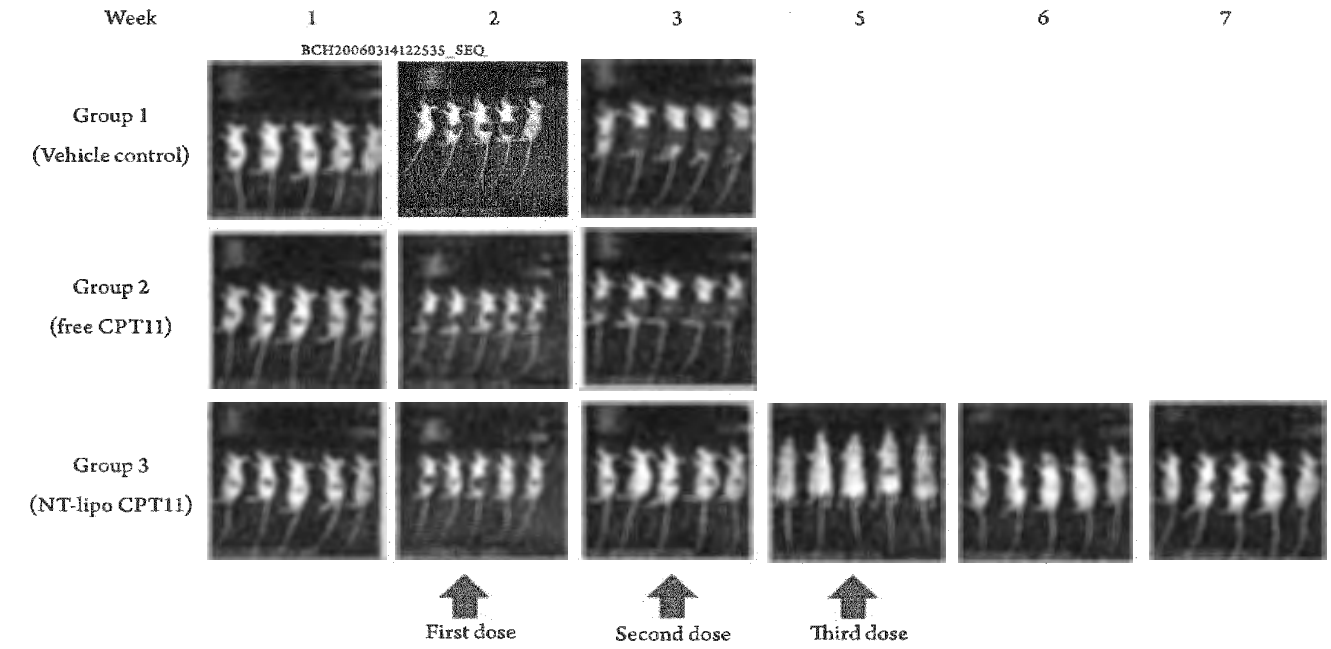
next generation approach. CPT-11 exhibits well-known pharmacologic liabilities and significant associated toxicities, which in turn make it an obvious candidate for drug delivery strategies The camptothecins exist in a pH-dependent equilibrium between an inactive carboxylate form (predominant at neutral-to-basic pH) and an active lactone form (predominant under acidic conditions); hence, intravenous injection of free CPT-11 results in rapid inactivation as well as clearance. Furthermore, CPT-11 is largely a prodrug which is converted into the much more potent metabolite SN-38. Hepatic activation and hepatobiliary excretion of SN-38 result in substantial risk of GI injury, especially in individuals having impaired SN-38 glucuronidation. These metabolic conversions contribute to notable heterogeneities in both efficacy and toxicity, and ultimately to a rather narrow therapeutic index. The concept of nanoparticle delivery of CPT-11 is thus very attractive based on potential advantages including: overcoming solubility limitations of the camptothecins; protecting drug in the active lactone configuration; chaperoning drug away from sites of toxicity such as the GI tract; prolonging circulation time and increasing tumor accumulation via the enhanced permeability and retention (EPR) effect; and providing sustained release and prolonged tumor exposure.

To realize the potential advantages of nanoparticle delivery, a novel liposome-based construct termed "nanoliposomal CPT-11 (nLs-CPT-11)" was developed, which encapsulates CPT-11 with unprecedented efficiency and stability (27). PK studies showed long circulation times for the carrier and undetectable drug release in plasma. Furthermore, nanoliposomal CPT-11 provides protection of drug in its active lactone form within the liposome aqueous interior, preventing its hydrolysis as well as premature conversion to the potent and toxigenic metabolite, SN-38. This contrasts markedly with free CPT-11, which is rapidly cleared from circulation, is subject to immediate hydrolysis of the lactone ring, and is also converted to SN-38 contributing to its dose-limiting GI toxicity.

In a series of preclinical studies, nanoliposomal CPT-11 demonstrated significantly superior efficacy when compared to free CPT-11 at the same or higher dose, including frequent cures in some models. The superiority of nanoliposomal CPT-11 over free CPT-11 has been observed in different tumor models including colorectal, gastric, breast, cervical, glioma, pancreatic and lung cancer models. In addition to superior efficacy, nanoliposomal CPT-11 has shown a more favorable pharmacologic profile and reduced toxicity in multiple preclinical models.

In order to evaluate this novel agent as a potential therapy for pancreatic cancer, a bioluminescence-based orthotopic xenograft model of pancreas cancer was developed (28). COLO357, a human pancreatic cell line, was passaged multiple times in vivo to generate the subline L3.6pl. This cell line was then modified by lentiviral transduction (L3.6pl-T) to express firefly luciferase. L3.6pl-T cells were implanted during open surgery directly into the pancreas of a nude mouse to form an orthotopic tumor xenograft. Therapeutic studies in this model compared nanoliposomal CPT-11 versus free drug at the equivalent dose, along with vehicle control (Figure 1). All treatments were administered intravenously by tail vein beginning at 7 days post-tumor implantation and continued weekly for a total of 3 planned treatments. At 20 mg/kg, free CPT-11 showed some tumor growth inhibition, but all mice required euthanization after 2 doses due to massive tumor progression. In contrast, nanoliposomal CPT-11 at the equivalent 20 mg/kg dose showed potent antitumor activity, including complete tumor inhibition during the entire post-treatment period. Systemic toxicity was not observed with any treatment. These studies indicated that nanoparticle- mediated delivery via nanoliposomal CPT-11 greatly enhances antitumor efficacy in the COLO357/L3.6pl-T orthotopic pancreatic xenograft model.

In the first-in-human phase I trial, patients with standard therapy-failure solid tumor were enrolled to determine the maximum tolerated dose, safety profile and pharmacokinetics of nanoliposomal CPT-11 (formerly PEP02, PharmaEngine, Inc., Taiwan, and now under the designation of MM-398, Merrimack Pharmaceuticals, Inc, USA). The drug was delivered intravenously for 90 minutes, once every 3 weeks, with starting dose of 60 mg/m^2. The maximum tolerated dose was 120 mg/m^2. Two patients achieved partial response including cervical cancer in one and pancreatic cancer in one (29). The observation was further extended in a phase I trial for nanoliposomal CPT-11in combination with weekly 24-hour infusion of high-dose 5-FU/LV (HDFL). In the two phase I trials, 7 pancreatic cancer patients who failed gemcitabine/HDFL +/- platinum had received PEP02 with or without HDFL. The best response was partial response in one, stable disease in 4 and progressive disease in 2, which indicated a potential activity of PEP02 in treating gemcitabine-refractory advanced pancreatic cancer. Based on these clinical observations and preclinical results, clinical testing of nanoliposomal CPT-11 was pursued in patients with gemcitabine-based chemotherapy failure advanced pancreatic cancer in an international phase II trial with the target of the primary end-point of 3-month overall survival rate ($OS_{3\text{-month}}$) = 65%. The results have been presented at the 2011 ASCO meeting (30). Of the 40 treated patients, more than three fourths had failed to first-line gemcitabine-based doublet or triplet chemotherapy. Mean cycle of treatment



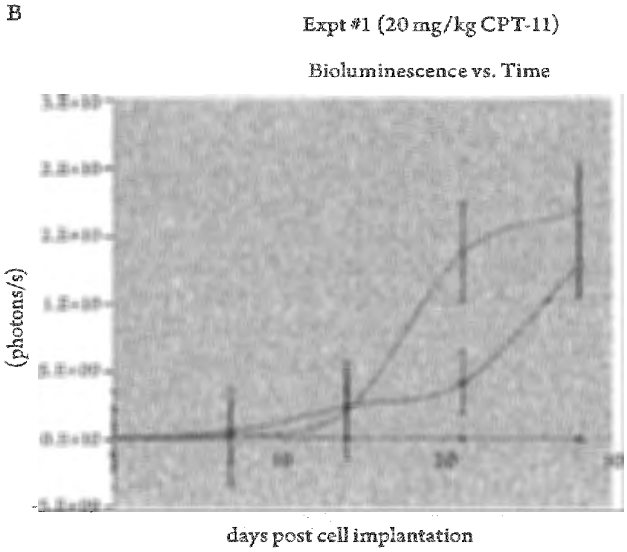


Figure 1 Nude mice were orthotopically implanted with COLO357/L3.6pI-T xenografts into the pancreas. Following ip administration of luciferin, animals were immediately imaged using a Xenogen IVIS 100 bioluminescence system, and subsequently imaged at weekly intervals. The signal was quantified by defining regions of interest (ROIs) and measuring photons/sec/str. Quantitative BLI values at post implantation day 7 were used to assign mice to treatment groups of five mice per group. Treatments included nanoliposomal CPT- 11 at 20 mg/kg, free CPT-11 at 20 mg/kg or vehicle control. All treatments were administered i.v. by tail vein injection beginning at 7 days post- tumor implantation and continued weekly for a total of 3 planned treatments. (A) Bioluminescence images of nude mice on weeks 1-7. (B) BLI values over time. Free CPT-11 treatment (diamonds) produced partial inhibition of tumor growth at initial time points, followed by rapid growth approaching that of the vehicle control group (+). Nanoliposomal CPT-11 treatment (circles) produced complete inhibition of tumor growth at all time points.

was 5.4 (range, 1 – 26) cycles. The most common G3/4 toxicities were: neutropenia (30%), leucopenia (22.5%), anemia (15%), diarrhea (7.5%), and fatigue (7.5%). Dose modification due to adverse events was required in 10 (25%) patients. The best tumor response rate was partial response in 7.5% and stable disease in 40% (overall disease control rate of 47.5%). The overall survival was 5.2 months with a 3-month and 6-month survival rate of 75% and 42.5%, respectively. The results highlight the feasibility and activity of nanoliposomal CPT-11 in previously heavily treated patients with gemcitabine-refractory advanced pancreatic cancer, which deserves further exploration.

Cationic Liposome Encapsulated Paclitaxel (EndoTAG™-1)

Tumor angiogenesis, the formation of neovasculature from pre-existed peri-tumor vessels, is a crucial process in supporting the development and growth of tumor mass, and the dissemination of tumor metastases. Tumor angiogenesis is mainly triggered by growth factors that are secreted by tumor cells per se and/or by miscellaneous types of cell within the microenvironment, for example, tumor associated macrophages or fibroblasts. Tumor vessels are often dilated and torturous, and characterized by large inter-endothelial cell gap (up to 100 – 600 nm *versus* < 6 nm in normal vessels), aberrant pericytes and basement membrane coverage, overexpression of specific surface receptor or antigen, and the presence of negative charged macro-molecules for example, anionic phospholipids and glycoprotein. Based on these characters, several strategies have been used to develop neo-vascular targeting liposomal drugs, which include conjugating with specific antibody again surface antigen or receptor and modified, non-functional receptor binding ligand, or incorporating positive (cationic) charged molecules in the surface of liposome. Of them, cationic liposome is a unique and interesting approach (31). In a preclinical study, Kalra and Campbell showed 5-FU and doxorubicin-loaded cationic liposome could preferentially bind with human endothelial (HMEC-1 and HUVEC) rather than pancreatic cancer cells. (HPAF-II and Capan-1)(32). Subsequently, Eichhorn et al showed that both cationic lipid complexed paclitaxel (EndoTAG™-1) and camptothecin (EndoTAG™-2) could preferentially bind at endothelial cells of neo-vasculature in solid tumor preclinical model (33-35). The selectively targeting of both agents on tumor microvasculature was confirmed by quantitative fluorescence microscopy. Further study suggested the anti-vascular effect of cationic liposome encapsulated paclitaxel (EndoTAG™-1) is schedule-dependent with metronomic schedule better than the maximum tolerated dose schedule. In addition, the combination of EndoTAG™-1 and gemcitabine could significantly inhibit the incidence of metastatsis in L3.6pl orthotopic pancreatic cancer mice model.

Based on these data, EndoTAG™-1, a cationic liposome (prepared from 1,2 dioleoyl-3-trimethyl- ammonium-propane (DOTAP) and 1,2 dioleoyl-sn-glycero-3-phosphocholine (DOPC)) encapsulated paclitaxel, has been used in combination with gemcitabine to treat chemo-naïve pancreatic cancer patients. The latest follow-up data of the four-arm randomized, phase II trial comparing weekly gemcitabine 1,000 mg/m^2 alone *versus* gemcitabine plus twice weekly EndoTAG™-1 at three different doses, 11, 22 and 44 mg/m^2) was presented in the 2009 ASCO Annual Meeting (36). Of the 200 chemo-naïve advanced pancreatic cancer patients who participated the study, 80% had metastatic diseases and 20% had locally advanced diseases. Disease-control rates in the gemcitabine monotherapy arm and the three gemcitabine plus EndoTAG-1 arms was 43% and ranging from 53% to 69%, respectively. The median progression-free survival time in corresponding group of patients were 2.7 months versus 4.1 to 4.6 months, respectively. The median overall survival time of patients receiving gemcitabine plus either high-dose (44 mg/m^2) or intermediate-dose of EndoTAG-1 were 9.4 months and 8.7 months, respectively, as compared with the 7.2 months in the gemcitabine monotherapy arm. The adjusted hazard ratio for overall survival for either arm was 0.72 (95% CI, 0.46 to 1.13) and 0.67 (95% CI, 0.43 to 1.07), respectively. The data is exciting but large-scale study to validate the data is mandatory.

Polymeric Micelles

Polymeric micelles-based anticancer drug, consisting of the incorporation of chemotherapeutic agent into polymeric micelles in size of 20–100 nm, was originally developed by Professor Kataoka(37). The polymeric micelle has two major components, a polyethylene glycol (PEG) constituted hydrophilic outer shell and a cytotoxic chemotherapeutic agent incorporated hydrophobic inner core. The main action mechanism of the polymeric micelles is similar to lipomosal agents and through the passive targeting based on the enhanced permeability of tumor neo-vasculature and the impeding clearance of macromolecules from lymphatic-deficient tumor interstitial tissue. Several cytotoxic chemotherapy-incorporating polymeric micellar nanoparticles have been in clinical trials, including paclitaxel-incorporating PEG-polyaspartate (NK105), cisplatin-incorporating PEG-polyglutamate/cisplatin complex (NC-6004) and SN-38-incorporating PEG-

ployglutamate/SN-38 (NK012). Of them, NC-6004 is currently evaluated in a phase Ib/II trial for patients with advanced pancreatic cancer, and will be discussed (38-41).

Cisplatin-incorporating Polymeric Micelles, NC-6004

In animal study, NC-6004 showed characteristic delayed total body clearance and higher area-under curve as compared with free cisplatin with a ratio of 1/19 and 65 folds, respectively (42). In addition, both histopathological and biochemical studies suggested NC-6004 significantly reduced cisplatin-associated nephrotoxicity. In phase I trial for patients with refractory advanced solid tumor, escalating dose of NC-6004 was administered intravenously every 3 weeks. Despite the implantation of pre-medication and post-therapy hydration, nephrotoxicity and allergic reaction were observed in patients receiving 120 mg/m^2 and further dose escalation was withheld. The MTD and the recommended dose were determined as 120 mg/m^2 and 90 mg/m^2, respectively. Pharmacokinetic study showed the maximum plasma concentration and area under curve of ultra-filterable platinum after 120 mg/m^2 of NC-6004 were 1/34 and 8.5 folds of those with free cisplatin (43). Seven out of 17 accruals achieved stable diseases, including two of two pancreatic cancer patients who had NC-6004 at dose level of 90 mg/m^2. Perhaps owing to earlier meta-analysis showed he combination of gemcitabine and platinum could significantly improved the overall survival of advanced pancreatic cancer patients as compared to gemcitabine monotherapy, NC-6004 is currently proceeded into a phase Ib/II trial to evaluate the maximum tolerated dose of NC-6004 in combination with gemcitabine and the therapeutic efficacy of the combination in patients with chemo-naïve advanced pancreatic cancer, clinicaltrials.gov identifier NCT00910741.

Rexin-G

Rexin-G is a highly engineered, nonreplicating retroviral vector displaying a von Willebrand factor–derived collagen-binding motif at its amphotropic envelope, and expressing a dominant negative cyclin G1 gene (44-46). This Willebrand factor-derived collagen-binding motif on the retrovector' s surface enables the nanoparticle drug to seek and be selectively delivered to primary and secondary tumor sites where angiogenesis and collagen matrix exposure characteristically occur. The encoded dominant negative cyclin G1 gene will thus to disrupt tumor cell cyclin G1 activity to lead to the destruction and/or growth inhibition of tumor.

There were two dose escalating phase I trials evaluating different dose/schedule of Rexin-G in patients with gemcitabine-failed advanced pancreatic cancer. The first trial evaluating 3 dose levels of Rexin-G administered intravenously, level I, 7.5 x 10^9 colony forming units (CFU) per day, days 1-7 and 15-21 every 28 days; level II, 1.1 x 10^{10} CFU per day, days 1-7 and 15-21 every 28 days; and level III, 3 x 10^{10} CFU per day, 5 days per week x 4 weeks/cycle with 6 weeks rest between two cycles. A total of 12 patients were enrolled, only one patient with dose-limiting toxicity manifesting as grade 3 transaminitis was observed at dose level II. However, the best tumor response was stable disease in one (8.3%) and the median time to tumor progression and overall survival of intent-to-treat population were 32 days and 3.5 months, respectively (47). In the second trial, the dose of Rexin-G was increased to 1 x 10^{11} CFU per day, twice or thrice per week for 4 weeks as one cycle (dose levels 0 and I), and 2 x 10^{11} CFU per day, thrice per week for 4 weeks as one cycle (dose levels II). A total of 13 patients were enrolled, 6 in dose level 0-I and 7 in dose level II. There was no DLT observed. On intent-to –treat analysis, the tumor control rate was 50% (3/6) and 85.7% (6/7 with one partial responder) of patients at dose level 0-I and II, respectively. The median overall survival in corresponding group of patients was 2.6 months and 9.3 months, respectively (48). Based on the results, the US FDA has granted Rexin-G fast-track designation as second-line treatment for pancreatic cancer in June 2009. Currently, a phase II/III pivotal two-arm randomized study aiming to validate the survival benefit of Rexin-G monotherapy *versus* physician's choice in gemcitabine-refractory pancreatic cancer is under discussion.

Conclusion

Systemic therapy for advanced pancreatic cancer has been largely disappointed owing to the unfavorable pharmacokinetic profile and poor penetration of current chemotherapeutic agents and the fragile patient population hard to tolerate toxic combination chemotherapy. Nanovector can provide passive or active targeting drug delivery to reduce the system exposure and enhance local drug retention in tumor tissue. In this review, we provide pre-clinical and clinical evidence to support the potential use of nanovector-based therapy in patients with advanced pancreatic cancer. Unfortunately, most of trials reported here are relatively small and without control group. Prospective, large-scale randomization trials are warranted to confirm their efficacy in this difficult tumor. In addition, the combination of the relatively low toxic nanoparticle drug with conventional cytotoxic agent and/or

Table 1 Nanovectors in pancreatic cancer treatment

Name	Compound	Nanocarrier	Size	Status
Abraxane™	Paclitaxel	Nanoparticle-albumin	130 nm	Phase I/II
Caelyx™	Doxorubicin	Liposome	100 nm	Phase I/II
Lipoplatin™	Cisplatin	Liposome	110nm	Phase I/II
Aroplatin™	Platunum	Liposome	1-3 μm	Phase I/II
MM-398	Irinotecan	Liposome	110±30 nm	Phase II
Endotag-1™	Paclitaxel	Liposome	180-200 nm	Phase II
Nanoplatin™	Cisplatin	Polymer Micelle	30 nm	Phase I/II
Rexin-G™	Cyclin G1 gene	Viral vector	110 nm	Phase I/II

recently emergent molecular targeted agent should also be investigated to improve the clinical outcomes of patients with advanced pancreatic cancer.

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Clinical Studies

A randomised phase II study of modified FOLFIRI.3 *vs* modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer

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BACKGROUND: Only a few clinical trials have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine-based chemotherapy. Therefore, there is no current consensus on the treatment of these patients. We conducted a randomised phase II study of the modified FOLFIRI.3 (mFOLFIRI.3; a regimen combining 5-fluorouracil (5-FU), folinic acid, and irinotecan) and modified FOLFOX (mFOLFOX; a regimen combining folinic acid, 5-FU, and oxaliplatin) regimens as second-line treatments in patients with gemcitabine-refractory pancreatic cancer.

METHODS: The primary end point was the 6-month overall survival rate. The mFOLFIRI.3 regimen consisted of irinotecan (70 mg m^{-2}; days 1 and 3), leucovorin (400 mg m^{-2}; day 1), and 5-FU (2000 mg m^{-2}; days 1 and 2) every 2 weeks. The mFOLFOX regimen was composed of oxaliplatin (85 mg m^{-2}; day 1), leucovorin (400 mg m^{-2}; day 1), and 5-FU (2000 mg m^{-2}; days 1 and 2) every 2 weeks.

RESULTS: Sixty-one patients were randomised to mFOLFIRI.3 ($n=31$) or mFOLFOX ($n=30$) regimen. The six-month survival rates were 27% (95% confidence interval (CI) = 13–46%) and 30% (95% CI = 15–49%), respectively. The median overall survival periods were 16.6 and 14.9 weeks, respectively. Disease control was achieved in 23% (95% CI = 10–42%) and 17% patients (95% CI = 6–35%), respectively. The number of patients with at least one grade 3/4 toxicity was identical (11 patients, 38%) in both groups: neutropenia (7 patients under mFOLFIRI.3 regimen *vs* 6 patients under mFOLFOX regimen), asthaenia (1 *vs* 4), vomiting (3 in both), diarrhoea (2 *vs* 0), and mucositis (1 *vs* 2).

CONCLUSION: Both mFOLFIRI.3 and mFOLFOX regimens were tolerated with manageable toxicity, offering modest activities as second-line treatments for patients with advanced pancreatic cancer, previously treated with gemcitabine.

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Pancreatic cancer accounts for 3% of all cancers, but is the fifth leading cause of cancer death in Western countries (Yeo *et al*, 2005). At the time of diagnosis, approximately half of the patients have metastases, and the median survival time barely exceeds 6 months, whereas approximately one-third of patients diagnosed with locally advanced disease have median survival times ranging between 6 and 9 months. Thus, a small proportion of patients are eligible for surgery, the only curative treatment option, at diagnosis (Bilimoria *et al*, 2007). Even with surgery, prognosis remains poor; the 5-year overall survival was only 23.4% for patients undergoing pancreatectomy (Sener *et al*, 1999).

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Although 5-fluorouracil (5-FU)-based chemotherapy has been reported to be superior to best supportive care alone (Palmer *et al*, 1994; Glimelius *et al*, 1996), and a pivotal phase III trial showed that gemcitabine offers a survival advantage over a weekly bolus infusion of 5-FU, accompanied by an improved clinical benefit (Burris *et al*, 1997), the overall therapeutic results are still disappointing; the response rate was 5.4% with a clinical benefit response rate of 23.8% and a 1-year survival rate of 18% in patients treated with gemcitabine.

Therefore, a number of clinical studies have been undertaken to enhance the effectiveness of front-line chemotherapy. Despite promising results in early-phase clinical studies, the majority of newer approaches have failed to show clinically meaningful therapeutic advantages over the standard infusion of gemcitabine alone. Although regimens consisting of gemcitabine in combination with erlotinib or capecitabine have shown statistically significant increases in survival duration, the small amount of survival benefit and accompanying toxicities result in difficulties related to their translation into clinically meaningful improvements (Cunningham *et al*, 2005; Moore *et al*, 2007).

Considering the poor response rate (20% or less) of gemcitabine-based doublet treatment in the first-line setting, the short progression-free survival (PFS) (<4 months), and the increased use of gemcitabine as adjuvant treatment (Oettle *et al*, 2007), an additional problem in the therapeutic management of this common malignant disease, is the need for effective treatment alternatives in patients failing to respond to gemcitabine-based chemotherapy. To date, few studies have assessed second-line chemotherapy, primarily because of poor prognosis (Nakachi *et al*, 2007) and because of the limited life expectancy of those with advanced pancreatic cancer after failure of first-line chemotherapy (Kozuch *et al*, 2001; Tsavaris *et al*, 2005; Kulke *et al*, 2007; Xiong *et al*, 2008; Novarino *et al*, 2009). There is, therefore, a growing unmet need for a second-line chemotherapy regimen to treat patients with gemcitabine-refractory pancreatic cancer (Boeck and Heinemann, 2008; Kang and Saif, 2008).

The clinical benefit and safety of the FOLFIRI and FOLFOX regimens have been well established in a study of gastrointestinal cancer patients (Tournigand *et al*, 2004). In several phase II trials, irinotecan-based and oxaliplatin-based regimens have shown modest activity against advanced pancreatic cancer. A French group has reported that the FOLFIRI.3 regimen, composed of a split irinotecan infusion on days 1 and 3, with 5-FU for 2 days, showed promising activity in chemotherapy-naive and pre-treated patients with advanced pancreatic cancer. The confirmed response rate was 37.5%, with a median PFS of 5.6 months (Taieb *et al*, 2007). The study also suggested that there was no cross-resistance between gemcitabine and FOLFIRI.3 regimen. Furthermore, an oxaliplatin and 5-FU combination, at various doses and schedules, has been evaluated as second-line chemotherapy in pancreatic cancer patients after gemcitabine failure (Tsavaris *et al*, 2005; Gebbia *et al*, 2007; Novarino *et al*, 2009). Recently, a German group has reported that the 5FU/folinic acid (FA) plus oxaliplatin (OFF) regimen could prolong survival and improve the quality of life of advanced pancreatic cancer patients after gemcitabine failure compared with best supportive care alone with or without 5FU/FA (FF) (Oettle *et al*, 2005; Pelzer *et al*, 2008).

On the basis of these results, we conducted a randomised phase II study of the modified FOLFIRI.3 (mFOLFIRI.3) and modified FOLFOX (mFOLFOX) regimens as second-line treatments in patients with gemcitabine-refractory pancreatic cancer. The aim of this study was to select a better regimen, which should be investigated in future studies.

MATERIALS AND METHODS

Patients

Patients at least 18 years of age with histologically confirmed, locally advanced, or metastatic pancreatic adenocarcinoma, who were previously treated with gemcitabine-based first-line chemotherapy were eligible for this study if they met the following inclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria; no previous second-line chemotherapy; adequate bone marrow function, defined as a condition with leukocyte count >4000 per μl, absolute neutrophil count >1500 per μl, haemoglobin >9.0 g per 100 ml, platelets >100 000 per μl; adequate renal and hepatic function, defined as a condition with serum creatinine <1.5 mg per 100 ml, bilirubin <1.5 mg per 100 ml (<2.5 mg per 100 ml in patients with obstructive jaundice and adequately decompressed bile duct obstruction), and serum transaminase <three-fold the upper normal limit (<five-fold the upper normal limit for patients with liver metastasis); adequate nutritional status, defined as a condition with albumin >3.0 g per 100 ml; and the giving of written informed consent. Patients were excluded if they had histology indicating a condition other than adenocarcinoma, brain metastasis, significant gastrointestinal bleeding or obstruction, any serious co-morbidity, axial skeletal radiotherapy within 6 months before study commencement, or peripheral neuropathy of grade 2 or worse. This study was initially approved by the Institutional Review Board of the Asan Medical Center. The study was conducted according to the tenets of the Declaration of Helsinki and guidelines on good clinical practice. The clinical trial registration number was NCT00786006.

Study design and randomisation

This was an open-label, single-centre, randomised phase II trial using the two treatment arms of mFOLFIRI.3 and mFOLFOX. Random assignment was performed at a 1:1 ratio and patients were stratified by age (≤65 years *vs* >65 years), ECOG PS (0–1 *vs* 2), and an earlier best overall response to gemcitabine (non-disease progression *vs* disease progression).

Treatment dose and schedule

The mFOlFIRI.3 regimen consisted of irinotecan 70 mg m^{-2} (over 1 h) on day 1, leucovorin 400 mg m^{-2} (over 2 h) on day 1, 5-FU 2000 mg m^{-2} (over 46 h) from day 1, and irinotecan 70 mg m^{-2} (over 1 h) at the end of the 5-FU infusion every 2 weeks. The mFOLFOX regimen was composed of oxaliplatin 85 mg m^{-2} (over 2 h) on day 1, leucovorin 400 mg m^{-2} (over 2 h) on day 1, and 5-FU 2,000 mg m^{-2} (over 46 h) every 2 weeks. When haematologic or non-haematologic toxicities of grade ≥2 occurred, chemotherapy was delayed until recovery to grade ≤1. The doses of subsequent schedules were reduced by 25% in patients with grade ≥3 haematologic and non-haematologic toxicities, and if toxicity was considered to be attributable, by the attending physician, to only one drug; the doses of other drugs were not modified. Treatment was continued until the occurrence of disease progression, unacceptable toxicity, or patient's refusal to continue. If disease progression was observed and patient performance was good, crossover to the alternate treatment arm was permitted.

Pre- and on-treatment evaluation

Within 2 weeks before study enrolment, patients gave a complete medical history; underwent a full physical examination including ECOG PS; were sampled for a complete blood count, serum chemistry with electrolyte levels, a coagulation battery, and carbohydrate antigen 19–9 (CA 19–9) level; underwent urinalysis; underwent a chest X-ray; were assessed by electrocardiography; and were evaluated by computed tomography of the abdomen and pelvis (chest or any other region, if metastasis was suspected or previously detected). Before the administration of each cycle of chemotherapy, each patient was examined and reviewed for complete and differential blood counts and serum chemistry. More frequent review and monitoring were performed if clinically indicated. Tumour response was assessed every three cycles according to the RECIST criteria (Therasse *et al*, 2000). For each of these assessments, similar imaging techniques as used at baseline were used. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used to assess toxicity.

Statistical analysis

The primary end point was the 6-month survival rate. The randomised two-arm phase II design was used to select the more promising regimen of the two in terms of this criterion (Simon *et al*, 1985). Using this design, the regimen with the better survival rate is selected, irrespective of the difference between protocols. To permit at least a 90% probability of selecting a truly better regimen when the absolute difference in the 6-month survival rate was 15%

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Page 12 of 447

or greater, 29 evaluable patients were needed in each arm. Survival time was calculated from the date of randomisation to the date of death from any cause. The secondary end points were overall response rate, PFS, overall survival (OS), and toxicity. Overall response rate was analysed on an intention-to-treat basis. PFS was defined as the time from randomisation to disease progression or death from any cause. PFS was censored at the date of the last visit for those patients who were alive without documented disease progression. OS and PFS were estimated by the Kaplan–Meier method. Patients were considered assessable if they had received at least two cycles of chemotherapy (over 4 weeks) and had at least one follow-up imaging study. However, patients were also considered assessable if they received less than two cycles because of rapid tumour progression. Survival curves were compared by the log-rank test. In multivariate analysis, Cox's proportional hazards model was used to identify independent prognostic factors for PFS and OS. All tests were two-sided and a P-value <0.05 was considered to be statistically significant. SPSS version 14.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Patient characteristics

From January 2007 to December 2008, 61 pancreatic cancer patients were enrolled at the Asan Medical Center, Seoul, Korea; 31 were randomly assigned to the mFOLFIRI.3 arm and 30 to the mFOLFOX arm. One patient in the mFOLFIRI.3 arm withdrew consent after the first cycle of chemotherapy and was lost to follow-up. Baseline characteristics were well balanced between the two treatment arms (Table 1). The median patient age was 55 years (range 35–73 years) and all but one patient was of ECOG PS 0 or 1. Twenty-one patients (34%) had undergone previous surgery and two (3%) had received palliative radiotherapy. Of the 16 patients who were prescribed adjuvant chemotherapy, gemcitabine was administered to three patients. Gemcitabine plus capecitabine was given to most patients (75%). After disease progression to a stage at which a salvage regimen was required, a crossover to the alternate protocol was undertaken by 12 patients (39%) in the mFOLFIRI.3 arm and by 7 (23%) in the mFOLFOX arm. The median time to crossover to the alternate treatment was 8.3 weeks (range 3.3–18.1 weeks) in the mFOLFIRI.3 arm, and 15 weeks (range 7.0–32.6 weeks) in the mFOLFOX arm.

Primary end points

A total of 98 cycles of the mFOLFIRI.3 and 93 cycles of the mFOLFOX regimens were delivered with a median of 3 cycles (range 1–12 and 1–10 cycles, respectively) in both arms. With a median follow-up period of 24.4 weeks (range 0.8–40.8 weeks), 50 of 61 patients (82%) died. The 6-month survival rate was 27% in the mFOLFIRI.3 arm (95% confidence interval (CI) = 13–46%) patients and 30% for those in the mFOLFOX arm (95% CI = 15–49%). Except for two patients who died because of treatment-related complications, all deaths were attributable to disease progression *per se*.

Secondary end points

The overall response rate values are listed in Table 2. Response evaluation was possible in 28 patients in the mFOLFIRI.3 arm and in 26 patients in the mFOLFOX arm. In the mFOLFIRI.3 arm, two patients could not be evaluated because of early death, and were lost to follow-up before the first response evaluation. In the mFOLFOX arm, response evaluation could not be achieved in four patients because of early death (two patients), loss to follow-up (one patient), and patient's refusal to continue with the trial (one patient). The overall response rate in the intention-to-treat population was 7% in the mFOLFOX arm (95% CI = 1–22%). Overall response could not be ascertained in the mFOLFIRI.3 arm. The disease control rate (PR and stable disease) was 23% in the mFOLFIRI.3 arm (95% CI = 11–40%) and 17% in the mFOLFOX arm (95% CI = 7–34%).

Table 1 Patient characteristics

Characteristic	mFOLFIRI.3 ($n=31$) No. of patients (%)	mFOLFOX ($n=30$) No. of patients (%)
Age, median (range)	55 (37–73)	55 (35–69)
<60 years	19 (61)	18 (60)
⩾60 years	12 (39)	12 (40)
Gender		
Male	24 (77)	20 (67)
Female	7 (23)	10 (33)
ECOG PS		
0	5 (16)	5 (17)
1	26 (84)	24 (80)
2	0 (0)	1 (3)
Metastatic site		
Liver	19 (61)	21 (70)
Peritoneum	19 (61)	11 (37)
Lung	6 (19)	5 (17)
Lymph nodes	15 (48)	14 (47)
Others	9 (29)	5 (17)
Prior treatment		
Surgery	10 (32)	11 (37)
Palliative radiotherapy	1 (3)	1 (3)
Adjuvant chemotherapy	7 (23)	9 (30)
Neoadjuvant chemoradiotherapy	0 (0)	1 (3)
Prior gemcitabine-based regimen		
Gemcitabine	4 (13)	2 (7)
Gemcitabine/capecitabine	20 (64)	26 (86)
Gemcitabine/erlotinib	4 (13)	2 (7)
Gemcitabine/cisplatin	3 (10)	0 (0)
Previous response to gemcitabine-based regimen		
CR	0 (0)	1 (3)
PR	10 (32)	9 (30)
SD	11 (35)	13 (43)
PD	10 (32)	7 (23)
Survival at analysis		
Alive	6 (20)	5 (17)
Dead	25 (81)	25 (83)
Crossover to alternative regimen	12 (39)	7 (23)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2 Overall response rate

Overall Response	mFOLFIRI.3 No. of patients (%, 95% CI)	mFOLFOX No. of patients (%, 95% CI)
PR	0 (0, 0–10)	2 (7, 1–22)
SD	7 (23, 11–40)	3 (10, 3–26)
PD	21 (68, 49–83)	21 (70, 52–84)
Not evaluable	3 (10, 3–26)	4 (13, 5–30)
Disease control	7 (23, 11–40)	5 (17, 7–34)

Abbreviations: PR = partial response; SD = stable disease; PD = progressive disease.

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CSPC Exhibit 1120
Page 13 of 447

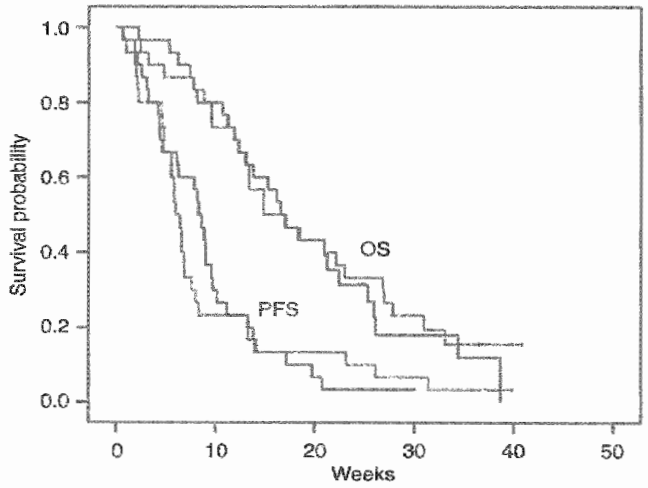

Figure 1 Survival curves for progression-free survival (PFS) and overall survival (OS). Modified FOLFIRI.3 (a regimen combining 5-fluorouracil, folinic acid, and irinotecan) is depicted as solid lines and modified FOLFOX (a regimen combining folinic acid, 5-FU, and oxaliplatin) as dotted lines.

The median PFS was 8.3 weeks for patients treated with mFOLFIRI.3 (95% CI = 6.9–9.6 weeks) and 6.0 weeks for those given mFOLFOX (95% CI = 5.1–6.9 weeks) (Figure 1). The median OS was 16.6 weeks for patients treated with mFOLFIRI.3 (95% CI = 12.5–20.6 weeks) and 14.9 weeks for those given mFOLFOX (95% CI = 8.0–21.8 weeks) (Figure 1). Turning to survival outcomes from the commencement of first-line chemotherapy, the median PFS was 34.9 weeks (95% CI = 30.8–38.9 weeks) and 37.0 weeks (95% CI = 32.0–42.0 weeks) for mFOLFIRI.3 and mFOLFOX, respectively. The median OS was identical at 47.1 weeks (95% CI = 39.0–55.2 weeks and 36.0–58.3 weeks, respectively).

Toxicity

The numbers of patients experiencing adverse events are presented in Table 3. In each treatment arm, 29 patients were available for toxicity assessment, and only two patients in the mFOLFOX arm were free from adverse events. The prevalence of severe toxicities was the same between the two regimens (38%); however, grade 3/4 asthaenia (3% *vs* 14%) developed more frequently in patients receiving mFOLFOX, whereas grade 3/4 diarrhoea (7% *vs* 0%) was more common in patients prescribed mFOLFIRI.3. Treatment-related mortality occurred in one patient in each group. One patient in the mFOLFIRI.3 arm died of septic shock complicated by febrile neutropaenia after 2 weeks of the first cycle. In one patient in the mFOLFOX arm, early death after the first cycle of chemotherapy was caused by severe pneumonia.

Prognostic factors

In a univariate analysis of survival outcomes according to the clinical variables of all 60 patients (gender, age, ECOG PS, hypoalbuminaemia, anaemia, resectability at initial diagnosis, liver metastasis, and PFS under gemcitabine), hypoalbuminaemia ($\leqslant 3.5\,mg\,100\,ml^{-1}$) and ECOG PS $\geqslant 1$ were significant prognostic factors for poor PFS and OS. In multivariate analysis, however, only hypoalbuminaemia predicted poor PFS ($P = 0.02$, hazard ratio = 1.97, 95% CI = 1.14–3.39), but not OS.

DISCUSSION

Pancreatic cancer is well known to be refractive to chemotherapy and to show rapid progression. Until recently, patients with pancreatic cancer after gemcitabine-based chemotherapy failure have had little opportunity to receive second-line chemotherapy because of rapid performance deterioration (Nakachi *et al*, 2007; Kang and Saif, 2008). Therefore, few studies have focused on patients with advanced pancreatic cancer in a second-line setting. Moreover, as gemcitabine is known to be effective when used as adjuvant therapy, many patients who underwent curative resection received gemcitabine in this setting. This means that oncologists urgently require data on other chemotherapeutic options for gemcitabine-pretreated patients.

Gemcitabine plus oxaliplatin (GEMOX), oxaliplatin plus capecitabine (XELOX), capecitabine plus erlotinib, docetaxel plus gefitinib, and FOLFOX have been tested in gemcitabine-refractory pancreatic cancer patients and showed disease control rates of 19–53% and a median OS range of 2.9–6.7 months (Tsavaris *et al*, 2005; Demols *et al*, 2006; Kulke *et al*, 2007; Xiong *et al*, 2008; Brell *et al*, 2009; Novarino *et al*, 2009). Recently, another oxaliplatin-based regimen, 5-FU/FA plus oxaliplatin (OFF), was shown to offer significantly improved survival compared with 5-FU/FA (FF) in a phase III trial (CONKO 003) (Pelzer *et al*, 2008). In this randomised trial, including 160 gemcitabine-pretreated patients with advanced pancreatic cancer, patients receiving OFF achieved a median PFS of 13 weeks ($P = 0.012$) and a median OS of 26 weeks ($P = 0.014$), compared with 9 and 13 weeks, respectively, for FF-treated patients. However, there is no current consensus on optimal second-line therapy for gemcitabine-refractory advanced pancreatic cancer (Boeck and Heinemann, 2008; Kang and Saif, 2008). Both FOLFIRI.3 and FOLFOX have shown modest activity as first-line and second-line chemotherapy regimens (Tsavaris *et al*, 2005; Gebbia *et al*, 2007; Taieb *et al*, 2007; Novarino *et al*, 2009). We were also of the view that neither regimen showed significant cross-resistance to gemcitabine-based protocols (Gebbia *et al*, 2007; Taieb *et al*, 2007).

The results of this trial show that both combination regimens showed favourable efficacy and toxicity profiles in gemcitabine-pretreated patients with advanced pancreatic cancer. The 6-month survival rates were 27 and 30% and disease control rates were 23% and 17%, in patients treated with mFOLFIRI.3 and mFOLFOX, respectively. Of the 12 patients whose disease was controlled by these regimens, disease stabilisation was previously achieved in nine patients in gemcitabine-based regimens. The median PFS and median OS were 8.3 weeks and 16.6 weeks in the mFOLFIRI.3 arm, and 6.0 weeks and 14.9 weeks in the mFOLFOX arm, respectively. These were in line with the survival data of several previous studies (Tsavaris *et al*, 2005; Gebbia *et al*, 2007; Novarino *et al*, 2009).

Toxicities related to both regimens were quite expectable and generally manageable. Patients with toxicities of grade 3 or worse constituted 38% of each treatment arm. Common toxicities of both regimens included anaemia, neutropenia, asthaenia, nausea, vomiting, and mucositis. In accordance with the known toxicities of both regimens, diarrhoea developed more frequently in mFOLFIRI.3 arm patients and neuropathy was more common in those in the mFOLFOX arm. Although half the patients treated with mFOLFOX experienced peripheral neuropathy, this was mostly of grade 1. This may be related to a lower cumulative dose of oxaliplatin because of the early dropout caused by rapid disease progression. However, treatment-related mortality occurred in patients prescribed either regimen, and hence physicians need to guard against infectious complications in patients treated with these protocols.

Turning to prognostic factors affecting PFS and OS, hypoalbuminaemia, implying poor nutritional status, was a poor prognostic factor for PFS in this study. In contrast to a previous study (Herrmann *et al*, 2008), we could not find an association between the time to progression under first-line chemotherapy ($\leqslant 6$ months) and PFS under second-line therapy, or residual survival. However, it is hard to draw conclusions with regard to this, because this study had small sample sizes, which might result in insufficient statistical power detecting significant prognostic factors.

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CSPC Exhibit 1120
Page 14 of 447

Table 3 Treatment-related toxicities

Toxicity	mFOLFIRI.3 no. of patients (%)			mFOLFOX no. of patients (%)		
	G 1-2	G 3-4	All G	G 1-2	G 3-4	All G
Anaemia	14 (48)	1 (3)	15 (52)	15 (50)	1 (3)	16 (55)
Neutropenia	6 (20)	7 (24)	13 (45)	8 (27)	6 (20)	14 (48)
Thrombocytopenia	3 (10)	1 (3)	4 (14)	9 (31)	1 (3)	10 (34)
Febrile neutropenia		1 (3)	1 (3)		0 (0)	0 (0)
Alopecia	3 (10)	0 (0)	3 (10)	0 (0)	0 (0)	0 (0)
Asthaenia	17 (58)	1 (3)	18 (62)	22 (76)	4 (14)	26 (90)
Diarrhoea	10 (34)	2 (7)	12 (41)	5 (17)	0 (0)	5 (17)
Anorexia	5 (17)	1 (3)	6 (21)	6 (21)	2 (7)	8 (28)
Nausea	12 (41)	1 (3)	13 (45)	13 (45)	1 (3)	14 (48)
Vomiting	6 (20)	3 (10)	9 (31)	11 (38)	3 (10)	14 (48)
Mucositis	8 (27)	1 (3)	9 (31)	8 (28)	2 (7)	10 (34)
Neurotoxicity	1 (3)	0 (0)	1 (3)	13 (44)	0 (0)	13 (45)
Maximum/patients*	18 (62)	11 (38)		16 (57)	11 (38)	

Abbreviation: G = grade. *Maximum/patients, maximal toxicity in an individual patient. The numbers of patients experiencing adverse events are listed.

Clinical Studies

Although this trial used adequate primary and secondary outcomes to represent the characteristics of the two regimens, the lack of assessment of clinical benefit or quality of life is a limitation of our study.

In conclusion, our trial not only showed that both mFOLFIRI.3 and mFOLFOX regimens could be safely used but also showed modest anti-cancer activities in gemcitabine-pretreated patients. Although further clinical trials are necessary for comparison with other regimens, these protocols may be reasonable therapeutic options in a second-line setting for patients with advanced pancreatic cancer, who were previously treated with gemcitabine-based chemotherapy.

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CSPC Exhibit 1120
Page 15 of 447

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CSPC Exhibit 1120
Page 16 of 447

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Therapeutics, Targets, and Chemical Biology

Cancer Research

Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion

Ashish V. Kalra, Jaeyeon Kim, Stephan G. Klinz, Nancy Paz, Jason Cain, Daryl C. Drummond, Ulrik B. Nielsen, and Jonathan B. Fitzgerald

Abstract

A major challenge in the clinical use of cytotoxic chemotherapeutics is maximizing efficacy in tumors while sparing normal tissue. Irinotecan is used for colorectal cancer treatment but the extent of its use is limited by toxic side effects. Liposomal delivery systems offer tools to modify pharmacokinetic and safety profiles of cytotoxic drugs. In this study, we defined parameters that maximize the antitumor activity of a nanoliposomal formulation of irinotecan (nal-IRI). In a mouse xenograft model of human colon carcinoma, nal-IRI dosing could achieve higher intratumoral levels of the prodrug irinotecan and its active metabolite SN-38 compared with free irinotecan. For example, nal-IRI administered at doses 5-fold lower than free irinotecan achieved similar intratumoral exposure of SN-38 but with superior antitumor activity. Tumor response and pharmacokinetic modeling identified the duration for which concentrations of SN-38 persisted above a critical intratumoral threshold of 120 nmol/L as determinant for antitumor activity. We identified tumor permeability and carboxylesterase activity needed for prodrug activation as critical factors in achieving longer duration of SN-38 in tumors. Simulations varying tumor permeability and carboxylesterase activity predicted a concave increase in tumor SN-38 duration, which was confirmed experimentally in 13 tumor xenograft models. Tumors in which higher SN-38 duration was achieved displayed more robust growth inhibition compared with tumors with lower SN-38 duration, confirming the importance of this factor in drug response. Overall, our work shows how liposomal encapsulation of irinotecan can safely improve its antitumor activity in preclinical models by enhancing accumulation of its active metabolite within the tumor microenvironment. *Cancer Res; 74(23); 7003–13. ©2014 AACR.*

Introduction

Liposomal carriers have become clinically accepted in cancer therapy as delivery systems that can enhance the utility of existing anticancer drugs (1). The potential benefits of these macromolecular carriers include overcoming solubility issues for certain drug classes, protecting the drug from unwanted metabolism and extending the residence time in plasma and tissue. In particular, liposomes tend to preferentially accumulate in tumors as a result of an enhanced permeability and retention (EPR) effect. The EPR effect is attributed to the abnormal tumor vasculature permitting extravasation of macromolecules, as well as impaired lymphatic drainage that promote the retention of these molecules within the tumor microenvironment, thereby providing sustained release at the tumor site mimicking a metronomic dosing (2). Increased tumor deposition via the EPR effect may also prevent drug resistance by overcoming the activity of multidrug resistant proteins (3, 4) and may offer possible means of improving safety aspects by reducing systemic exposure relative to tumor exposure (5). There are potential pharmacologic advantages of the EPR effect, particularly for antineoplastic agents that have to engage their target over a longer time period or have little binding activity; for example drugs of the camptothecin class with topoisomerase 1 enzyme (TOP1) as the primary target.

Irinotecan (CPT-11), a clinically approved camptothecin, is a prodrug that is activated by carboxylesterase (CES) enzymes, present primarily in liver and colon tissue to the active form, SN-38. (In the article, CPT-11 is used when referring to the prodrug levels in plasma or tumor samples following either free irinotecan or nal-IRI administration. SN-38 is used when referring to the active metabolite of CPT-11.) The active SN-38 can be subsequently inactivated through glucuronidation by members of the UDP glucuronosyltransferase family (6). The principal mechanism of action leading to cell death is through DNA damage after replication-fork collisions with transient drug-TOP1 cleavage complexes, thus emphasizing the time of drug exposure as important driver for cytotoxicity of camptothecins (7, 8). Recently, we described the development of a novel nanoliposomal formulation of irinotecan, nanoliposomal formulation of irinotecan (nal-IRI; also known as MM-398 or PEP02; ref. 9). nal-IRI features very high drug loading efficiency, a high drug payload, and marked *in vivo* drug retention that

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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CSPC Exhibit 1120
Page 17 of 447

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also stabilizes the active lactone configuration of irinotecan. The pharmacokinetic (PK) properties of the encapsulated irinotecan were dramatically altered in the plasma of female rats, with a 344× increase in the area under the curve (AUC), an 8.5× decrease in the volume of distribution, and a 39.6× increase in the half-life of the total drug. Pharmacokinetic analysis in a clinical study confirmed these performance characteristics of nal-IRI in patients (10).

Plasma drug concentrations cannot readily be translated into therapeutic effect; a sufficient amount of active therapeutic agent must be transported to the tumor site of action (i.e., be available for uptake by cancer cells) to observe favorable drug activity (11). The transport of macromolecules across the tumor vasculature is a complex process depending on vessel perfusion, surface area, and permeability, as well as tumor and drug characteristics. Several studies have used mathematical models to understand liposomal drug delivery within solid tumors (12, 13). Of particular interest is work done by Hendriks and colleagues (14), where the authors constructed a computational model to describe the parameters that affect the tumor delivery of pegylated liposomal doxorubicin, the first liposomal anticancer agent to receive clinical approval. The study concluded that liposome PK and tumor permeability to liposomes (tumor deposition) were the most important parameters controlling liposomal drug delivery to tumors.

In the case of nal-IRI, the complex metabolism (15) and mechanism of action (8, 16) of free irinotecan, in addition to the above-mentioned parameters, may play a role in the overall liposomal irinotecan delivery within tumors. In this study, we describe a systems pharmacology approach to identify critical parameters that differentiate nal-IRI from free irinotecan with regard to *in vivo* activity. A mechanistic tumor PK model was developed and trained to describe CPT-11 and SN-38 levels observed in plasma and tumor, following administration of either nal-IRI or free irinotecan in tumor xenografts. A model sensitivity analysis was performed to identify the critical parameters driving *in vivo* activity, which were then experimentally confirmed by measuring these factors in multiple cell line and patient-derived xenograft models. The findings in this study highlight critical parameters that could serve as potential biomarkers to identify cancer indications and patient populations with an increased likelihood of nal-IRI responsiveness.

Materials and Methods

Materials and nal-IRI preparation

nal-IRI was prepared as previously described (9) using a lipid composition of DSPC, cholesterol, and PEG-DSPE (3:2:0.015, mol:mol:mol), an initial drug-to-lipid ratio of 500 g drug/mol phospholipid, and extrusion through 0.1 μm polycarbonate filters. The resulting preparations displayed a particle size of 111 nm (with polydispersity index of 0.04), and a drug load of 473 mg irinotecan-HCl/mmol phospholipid. All lipids were obtained from Avanti Polar Lipids Inc. Irinotecan hydrochloride was purchased from the pharmacy. Acetic acid, methanol, and acetonitrile were from EMD Chemicals Inc. Water and trifluoroacetic acid (TFA) were from J.T. Baker. Fetal bovine serum was from Tissue Culture Biologicals and phosphate-buffered saline (PBS) was purchased from Life Technologies.

Cell culture

Cell lines [HT-29 (colon), SK-ES-1 (Ewing's sarcoma), A549 (lung), LoVo (colon), MDA-MB-231 (breast)] were obtained from the ATCC, whereas A2780 cells (ovarian) was obtained from Sigma-Aldrich. Cells from the ATCC and Sigma were received in 2010. All cells were authenticated before receipt and were propagated for less than 6 months after resuscitation. Cultures are regularly tested for *Mycoplasma*. All cell lines were cultured in humidified CO_2 atmosphere at 37°C using media recommended by the manufacturer.

Pharmacokinetic and tissue biodistribution study

Five-week-old female NOD/SCID mice were purchased from Charles River Laboratory. The care and treatment of experimental animals were in accordance with the Institutional Animal Care and Use Committee guidelines. Subcutaneous tumors were established by injecting 10 million HT-29 cells into the right flank of mice. When the average tumor volume reached approximately 200 mm^3, mice were randomized into groups (n = 4/time point) that received a single intravenous (i.v.) dose of nal-IRI at 5, 10, 20, or 40 mg/kg. Following 1, 4, 8, 24, 48, 72, and 168 hours after a single dose, mice were sacrificed and perfused with PBS before harvest of tumor and other normal tissues.

Antitumor activity studies

Five-week-old female NOD/SCID mice were purchased from Charles River Laboratory. Subcutaneous tumors were established by injecting 10 million HT-29 and SK-ES-1 cells or 5 million A549 cells into the right flank of mice. Tumor growth was measured twice per week by calipers and calculated with formula: width^2 × length × 0.52. When the average tumor volume reached approximately 200 mm^3, mice were randomized into treatment groups (n = 5–8/group) that received weekly i.v. dose of PBS (control), free irinotecan (50 mg/kg), or nal-IRI at various doses ranging from 1.25 to 20 mg/kg.

Tumor growth inhibition (TGI) was calculated with formula:

$$\mathrm{TGI}(\%) = \left[1 - \frac{(V_{\mathrm{treated}}(d_{\mathrm{final}}) - V_{\mathrm{treated}}(d_0))}{(V_{\mathrm{control}}(d_{\mathrm{final}}) - V_{\mathrm{control}}(d_0))}\right] \quad \text{(A)}$$

where $V_{treated}$ and $V_{control}$ represent the volumes of tumor at a given time point following treatment with drug or PBS, and d_0 and d_{final} represent first day and final day of treatment, respectively.

Characterizing tumors from cell-line and patient-derived xenografts

The cell line–derived xenografts (HT-29, SK-ES-1, A549, MDA-MB-231, LoVo, AsPC-1, and A2780) were established as described above. The patient-derived tumor models [CTG-0062 (colorectal), CTG-0079 (colorectal), CTG-0252 (ovarian), CTG-0288 (pancreatic), CTG-0158 (lung), and CTG-0283 (pancreatic)] were established by Champions Oncology using their Champions TumorGraft (CTG) technology. When the

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CSPC Exhibit 1120
Page 18 of 447

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average tumor volume reached approximately 300 mm^3, mice were randomized into treatment groups ($n = 4$/group) that received single i.v. dose of either PBS or nal-IRI at 10 mg/kg. Before tumor collection, intracardial perfusion was performed to remove the blood components from the tumor compartment. Briefly, a butterfly needle (23G) connected to a 10-mL syringe filled with PBS is inserted into the left ventricle. Inferior vena cava is cut and animal is perfused with 10-mL PBS (within 1–2 minutes). The control tumors were harvested 24 hours after PBS administration and used for the irinotecan activation assay, whereas the treated tumors were harvested either 24 or 72 hours following nal-IRI treatment and used for high-performance liquid chromatography (HPLC) analysis.

HPLC quantification of CPT-11 and SN-38

Tumor and normal tissues were analyzed for CPT-11 and SN-38 concentrations using a modification of the method previously described (9). Briefly, tissues were weighed and homogenized for 2 minutes in 20% w/v water using a TissueLyser (Qiagen). The homogenates were extracted by mixing 0.1 mL homogenate with 0.9 mL 1% acetic acid/methanol followed by 10 seconds vortexing and placing at −80°C for 1 hour. The samples were centrifuged at 10,000 rpm for 10 minutes at room temperature and supernatants collected for HPLC analysis (Dionex). The samples and standards (CPT-11 and SN-38) were analyzed using a C18 reverse phase column (Synergi Polar-RP 80A 250 × 4.60 mm 4 μm column). The drug metabolites were eluted running a gradient from 30% acetonitrile; 70% 0.1% TFA/H_2O to 68% acetonitrile; 32% 0.1% TFA/H_2O during a 13 minutes span at a flow rate of 1.0 mL/min. The initial elute composition was restored after 14 minutes and continued for 6 minutes before the next injection. The CPT-11 peak was detected at approximately 7.7 minutes and the SN-38 peak eluted at approximately 8.4 minutes, using an in-line fluorescence detector excited at 372 nm and emitting at 556 nm.

Irinotecan activation assay

Tumor tissue lysates were prepared by homogenizing the tissue in 6% w/v 0.1 M Tris HCL/1% Triton X-100 solution (pH7.5) using a TissueLyser for 2 to 4 minutes. Protein concentration of lysates was measured using the BCA reagent (Thermo Scientific). Lysates (250 μg of protein) were mixed with an equal volume of 10 μmol/L irinotecan and incubated at 37°C. Following 24 hours of incubation the reaction was terminated by adding an equal volume of 1% acetic acid/methanol and samples centrifuged at 10,000 rpm for 15 minutes. The supernatant was processed for HPLC quantification of CPT-11 and SN-38 as described above.

Statistical analysis

The statistical significance of differences between groups was analyzed with the one-way ANOVA test. Results were considered statistically significant at $P < 0.05$. The analysis was performed using GraphPad Prism 6.01.

Model development and simulation

Pharmacokinetic profiles of metabolites in plasma and tumor from free irinotecan and nal-IRI were described by using multi-compartmental models (Fig. 1B). The model equations are explained and summarized in the Supplementary

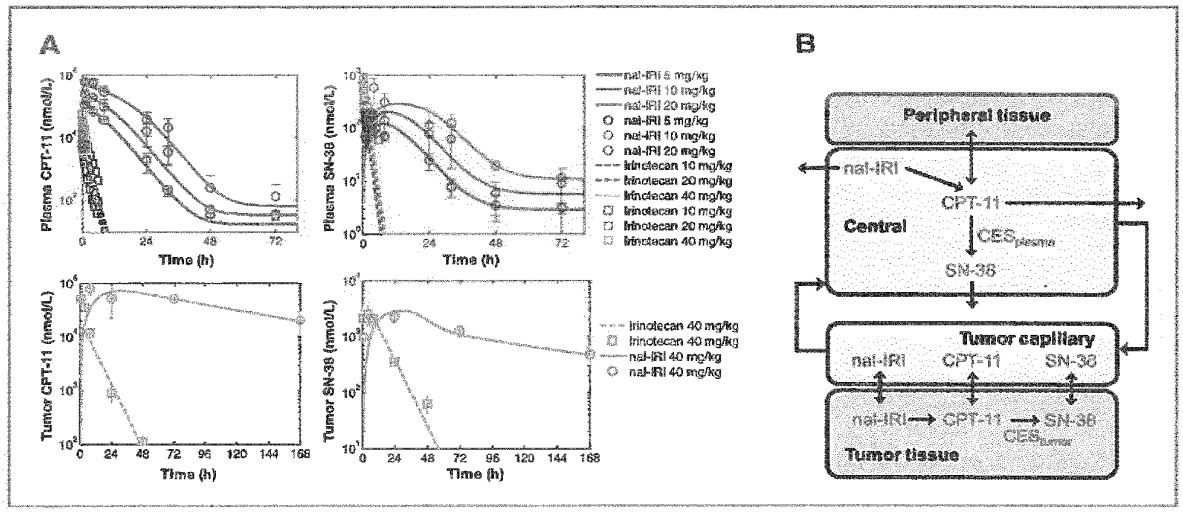

Figure 1. Pharmacokinetic profile of nal-IRI and free irinotecan. A, plasma and tumor PK of nal-IRI were compared with free irinotecan in HT-29 xenograft bearing mice. NOD/SCID mice bearing HT-29 tumors were treated with single i.v. dose of free irinotecan or nal-IRI. Plasma and tumors were collected at various intervals; CPT-11 and SN-38 were measured by HPLC analysis ($n = 4$ animals/time point). Plasma PK data for free irinotecan were taken from Kaneda and colleagues (35). Solid lines represent the model simulations for nal-IRI, whereas dashed lines represent the model simulations for free irinotecan. B, diagram of the mechanistic tumor pharmacokinetic model developed to describe the various steps in metabolism, pharmacokinetics and tumor deposition of nal-IRI.

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CSPC Exhibit 1120
Page 19 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

Table 1. Summary of model parameters for plasma PK and tumor deposition models

Name	Value	Units	Description	Reference
Plasma PK model parameters				
For free irinotecan				
Cl_{CPT-11}	1.222e−4	L/min	Plasma clearance rate of CPT-11	Estimated
Cl_{SN-38}	2.138e−5	L/min	Plasma clearance rate of SN-38	Estimated
$k_{12,CPT-11}$	8.444e−5	1/min	Rate of CPT-11 transport from plasma to peripheral compartment	Estimated
$k_{21,CPT-11}$	4.213e−2	1/min	Rate of CPT-11 transport from peripheral to plasma compartment	Estimated
$k_{12,SN-38}$	2.656e−5	1/min	Rate of CPT-11 transport from plasma to peripheral compartment	Estimated
$k_{21,SN-38}$	3.44e−4	1/min	Rate of CPT-11 transport from peripheral to plasma compartment	Estimated
$V_{max,CES,p}$	2.263e−1	nmol/min	Maximum rate coefficient for CES enzyme in plasma compartment	Estimated
$K_{m,CES,p}$	2.67e5	nmol/L	Michaelis-Menten constant for CES enzyme in plasma compartment	Estimated
V_p	9.46e−5	L	Volume of plasma compartment	Estimated
V_{ph}	0.02	L	Volume of peripheral compartment	Fixed (14)
For nal-IRI				
$Cl_{nal-IRI}$	1.87e−7	L/min	Plasma clearance rate of nal-IRI	Estimated
Cl_{CPT-11}	1.634e−5	L/min	Plasma clearance rate of CPT-11	Estimated
Cl_{SN-38}	2.957e−6	L/min	Plasma clearance rate of SN-38	Estimated
$k_{12,CPT-11}$	1.619e−4	1/min	Rate of CPT-11 transport from plasma to peripheral compartment	Estimated
$k_{21,CPT-11}$	5.349e−7	1/min	Rate of CPT-11 transport from peripheral to plasma compartment	Estimated
$V_{max,Release,p}$	8.443e−6	nmol/min	Maximum rate coefficient for CPT-11 release from nal-IRI in plasma compartment	Estimated
$K_{m,Release,p}$	2.04	nmol/L	Michaelis-Menten constant for CPT-11 release from nal-IRI in plasma compartment	Estimated
$V_{max,CES,p}$	5.943e−2	nmol/min	Maximum rate coefficient for CES enzyme in plasma compartment	Estimated
$K_{m,CES,p}$	1.198e−5	nmol/L	Michaelis-Menten constant for CES enzyme in plasma compartment	Estimated
V_p	1.12e−3	L	Volume of plasma compartment	Estimated
V_{ph}	0.02	L	Volume of peripheral compartment	Fixed (14)
Tumor deposition model parameters				
Q_{tumor}	2.119e−6	L/min	Blood flow rate to tumor	(14)
$PS_{nal-IRI}$	7.858e−5	L/min/kg	Tissue permeability coefficient of nal-IRI	Estimated
PS_{CPT-11}	1.851e−3	L/min/kg	Tissue permeability coefficient of CPT-11	Estimated
PS_{SN-38}	2.687e−2	L/min/kg	Tissue permeability coefficient of SN-38	Estimated
$\sigma_{nal-IRI}$	3.181e−3		Tissue-capillary partition coefficient of nal-IRI	Estimated
σ_{CPT-11}	5.24e−1		Tissue-capillary partition coefficient of CPT-11	Estimated
σ_{SN-38}	2.109e−1		Tissue-capillary partition coefficient of SN-38	Estimated
$k_{Release,t}$	1.681e−4	1/min	Rate coefficient for CPT-11 release from nal-IRI in tumor tissue compartment	Estimated
$V_{max,CES,t}$	2.17e−2	nmol/min	Maximum rate coefficient for CES enzyme in tumor tissue compartment	Estimated
$K_{m,CES,t}$	2.3e−6	nmol/L	Michaelis-Menten constant for CES enzyme in tumor tissue compartment	Estimated
V_{cap}	7e−7	L	Volume of tumor capillary compartment	(14)
V_t	1e−5	L	Volume of tumor tissue compartment	Fixed

Data. The models were built and implemented using Simbiology toolbox in MATLAB 8.2 (The MathWorks).

Results

nal-IRI displays a prolonged exposure in both plasma and tumor compared with free irinotecan

The pharmacokinetic profiles of the prodrug CPT-11 and its active metabolite SN-38 were measured in plasma and tumors following administration of either free irinotecan or nal-IRI (Fig. 1A). At similar doses of both free irinotecan and nal-IRI, the CPT-11 and SN-38 plasma levels cleared rapidly from circulation within 8 hours after free irinotecan injection, whereas the levels of CPT-11 and SN-38 following nal-IRI administration were persistent and remained in circulation for over 50 hours. An approximately 10-fold higher plasma CPT-11 peak level was observed with nal-IRI as compared with free irinotecan. However, the plasma peak level of SN-38 achieved with nal-IRI was 10-fold lower compared with free irinotecan, probably due to the ability of the lipid bilayer to protect the conversion of prodrug CPT-11 to SN-38 by the systemic CES enzyme present in mouse models (17). Administration of free irinotecan resulted in the clearance of greater than 90% of CPT-11 from tumors within 24 hours; however, following nal-IRI administration, CPT-11 levels persisted above

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CSPC Exhibit 1120
Page 20 of 447

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10,000 nmol/L levels for 168 hours. Similar peak levels of SN-38 were achieved with both free irinotecan and nal-IRI in HT-29 tumors, though a prolonged SN-38 exposure for up to 168 hours (measured as the AUC from 0 to 168 hours) was achieved with nal-IRI as compared with less than 48 hours tumor exposure with free irinotecan. In summary, CPT-11 and SN-38 were still present in tumors at 168 hours following nal-IRI administration, though both CPT-11 and SN-38 had cleared from plasma.

Tumor SN-38 duration drives *in vivo* activity

We developed a mechanistic PK model to identify the determinants that may differentiate the plasma and tumor PK profiles between free irinotecan and nal-IRI (Fig. 1B). The experimental PK data were used to estimate the optimal model parameters (Table 1) fitting the model simulations within the standard deviations of *in vivo* PK profiles of both CPT-11 and SN-38 (Fig. 1A). As the *in vitro* cytotoxic effects of irinotecan on tumor cells is dependent on the concentration and the time of exposure of cells to active metabolite SN-38 (7, 8), we sought to understand if the overall plasma and tumor SN-38 exposure predicts the *in vivo* activity of both nal-IRI and free irinotecan. The trained model determined that a 5-fold higher dose of free irinotecan (50 mg/kg) was required to achieve similar SN-38 exposure in both plasma and tumor as compared with nal-IRI (10 mg/kg; Fig. 2A). The TGI of HT-29 xenograft model at these equal exposure doses, was significantly greater with nal-IRI (~110%) treatment as compared with free irinotecan (~40%), despite the 5-fold lower total dose administered (*, $P < 0.05$,

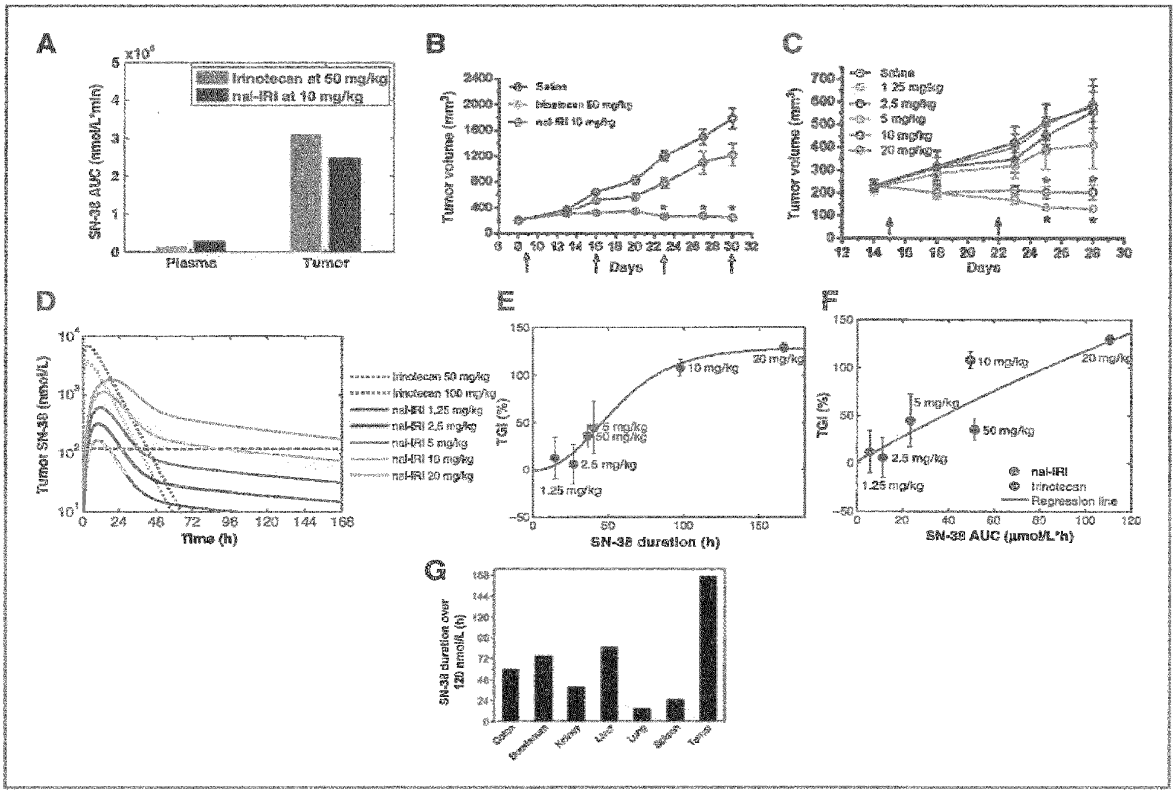

Figure 2. Relation of nal-IRI *in vivo* activity to tumor SN-38 duration. A, model predictions for similar SN-38 AUC in plasma and tumor following free irinotecan (50 mg/kg) and nal-IRI (10 mg/kg) administration. B, tumor response observed in HT-29 xenograft following weekly administration (arrows) of 50 mg/kg free irinotecan and 10 mg/kg nal-IRI ($n = 6$/group). The tumor volumes for nal-IRI (10 mg/kg) were significantly lower (*, $P < 0.05$) compared with saline and irinotecan groups (one-way ANOVA test). C, tumor response in HT-29 xenografts following weekly administration (arrows) of various nal-IRI doses ($n = 5$/group). The tumor volumes for nal-IRI (10 mg/kg) and nal-IRI (20 mg/kg) groups were significantly lower (*, $P < 0.05$) compared with saline tumors on day 25 and day 28 (one-way ANOVA test). D, model simulations were used to compare tumor SN-38 concentration following the administration of varying doses of free irinotecan or nal-IRI. Black dashed line represents threshold concentration of 120 nmol/L to determine tumor SN-38 duration. E and F, TGI(%) achieved by nal-IRI and free irinotecan treatment in HT-29 xenografts were compared with the tumor SN-38 duration above 120 nmol/L (E) and SN-38 AUC (F) at varying doses of nal-IRI or free irinotecan. Solid lines represent nonlinear regression lines based on five parameter logistic curve fitting. G, the SN-38 duration over a threshold of 120 nmol/L was computed from the pharmacokinetic profiles of SN-38 in tumor and normal tissues following 20 mg/kg of nal-IRI.

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CSPC Exhibit 1120
Page 21 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

one-way ANOVA test; Fig. 2B). In addition, other studies have shown no additional HT-29 TGI at the maximum tolerated dose of free irinotecan (100 mg/kg; ref. 18). To identify a dose level of nal-IRI that gave comparable *in vivo* activity to 50 mg/kg free irinotecan, we performed a dose escalation study in the HT-29 xenograft model (Fig. 2C). nal-IRI at 5 mg/kg showed partial inhibition of tumor growth (~40% TGI) that was comparable with 50 mg/kg free irinotecan, whereas 10 mg/kg and 20 mg/kg nal-IRI showed significant (*, $P < 0.05$, one-way ANOVA test) TGI compared with saline (~110%–130% TGI). Furthermore, we have previously tested control liposomes (that have comparable composition with nal-IRI except for the absence of irinotecan, the active pharmaceutical ingredient) and did not observe any TGI (data not shown).

The intratumor SN-38 concentrations achieved from 50 to 100 mg/kg doses of free irinotecan and 1.25, 2.5, 5, 10, and 20 mg/kg doses of nal-IRI were then simulated using the trained mechanistic PK model (Fig. 2D). Although a nal-IRI dose of 5 mg/kg achieved similar TGI as 50 mg/kg free irinotecan, the tumor SN-38 AUC and peak levels were approximately 2-fold and 6-fold lower respectively for nal-IRI as compared with free irinotecan. Furthermore, we noted at these doses both drugs were able to maintain the tumor SN-38 concentration above 120 nmol/L for the same duration of approximately 40 hours. To determine if the tumor SN-38 concentration impacts *in vivo* activity, we used the tumor SN-38 concentration of 120 nmol/L as a threshold. We also determined the duration for which the various doses of nal-IRI or free irinotecan could maintain the tumor SN-38 concentration above 120 nmol/L, hereon referred to as "tumor SN-38 duration." A sigmoidal relationship between TGI (%) and tumor SN-38 duration (Fig. 2E) was observed for both nal-IRI and free irinotecan ($R^2 = 0.62$). However, when comparing TGI (%) with tumor SN-38 AUC (Fig. 2F) the relationship was less significant ($R^2 = 0.45$), due to the lower TGI (%) achieved by 50 mg/kg free irinotecan compared with 10 mg/kg nal-IRI. We also observed longer SN-38 duration in tumors (>100 hours) compared with normal tissues (<72 hours; Fig. 2G and Supplementary Fig. S1).

Identification of liposome tumor permeability and local tumor activation as critical determinants for tumor SN-38 duration

A local sensitivity analysis on the model parameters was performed to identify processes impacting the tumor SN-38 duration (Supplementary Data). In response to the administration of free irinotecan (50 mg/kg), the tumor SN-38 duration was relatively insensitive to most model parameters (Fig. 3A), suggesting the inability of free irinotecan to modulate it. In contrast, several model parameters were found to significantly impact tumor SN-38 duration following the administration of nal-IRI (10 mg/kg; Fig. 3B). The sensitive parameters for nal-IRI can be classified into three different categories: (i) PK, rate of breakdown of liposomes in blood (Release rate in blood, $V_{max,Release,p}$), (ii) activation of prodrug CPT-11 to SN-38 by CES enzyme (CES activity in tumor; $V_{max,CES,t}$ and blood; $V_{max,CES,p}$), and (iii) liposome uptake within tumors, that is, nal-IRI tumor deposition (nal-IRI tumor permeability, $PS_{nal\text{-}IRI}$). Among these parameters, the release rate in plasma negatively affected tumor SN-38 duration due to a decrease in the overall systemic exposure of nal-IRI. CES enzyme activity, particularly from tumor CES (local tumor activation of irinotecan) and nal-IRI permeability (tumor deposition), positively affected the tumor SN-38 duration. To assess the identifiability of parameter estimates, log likelihood profiling was performed for the sensitive parameters, $V_{max,CES,t}$ and $PS_{nal\text{-}IRI}$ (19). The confidence intervals suggested that both parameters were precisely estimated (Supplementary Fig. S2).

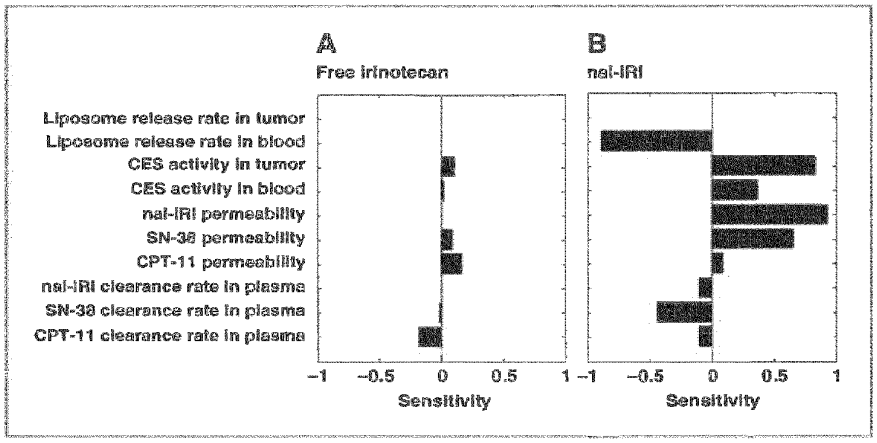

Figure 3. Model parameters impacting tumor SN-38 duration. Sensitivity analyses for free irinotecan (A) and nal-IRI (B) were performed on key model parameters that are responsible for plasma clearance, tissue deposition and metabolic reactions. Parameters whose values were not estimated in this study, including compartment volumes and tumor blood flow, were excluded from the analysis. The doses of free irinotecan (50 mg/kg) and nal-IRI (10 mg/kg) that achieved similar SN-38 plasma and tumor exposure were used for sensitivity analysis. The model parameters were modulated by 10% and their effect on tumor SN-38 duration was determined as a sensitivity index (Supplementary Equation S6).

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CSPC Exhibit 1120
Page 22 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

Biologic variability and simulated perturbation of nal-IRI tumor deposition and local activation

To determine the biologic relevance of these sensitive parameters toward driving tumor SN-38 duration (namely nal-IRI tumor deposition and local tumor activation of irinotecan), the parameters were measured in a panel of 13 xenograft models. We used the total CPT-11 concentrations in tumors as a surrogate for nal-IRI tumor deposition as model simulations based on nal-IRI pharmacokinetics showed that majority of CPT-11 in plasma and tumor was encapsulated and protected within the liposomes and less than 10% was available as free CPT-11 (Supplementary Fig. S3). The intratumor concentrations of CPT-11 varied substantially across the tumor panel (Fig. 4A). The tumor models from cell-lines displayed overall higher levels of prodrug CPT-11 deposition (from 5,000–15,000 ng/g) as compared with patient-derived tumor models (1,000–2,000 ng/g). In addition, a high degree of variability was observed between individual tumors within the same xenograft model (66% average coefficient of variation). Model simulations were used to test the effect of altering nal-IRI tumor deposition on tumor SN-38 duration (Fig. 4B). By decreasing the nal-IRI permeability parameter to zero, which simulates an impermeable tumor microenvironment, the tumor SN-38 duration of approximately 100 hours achieved

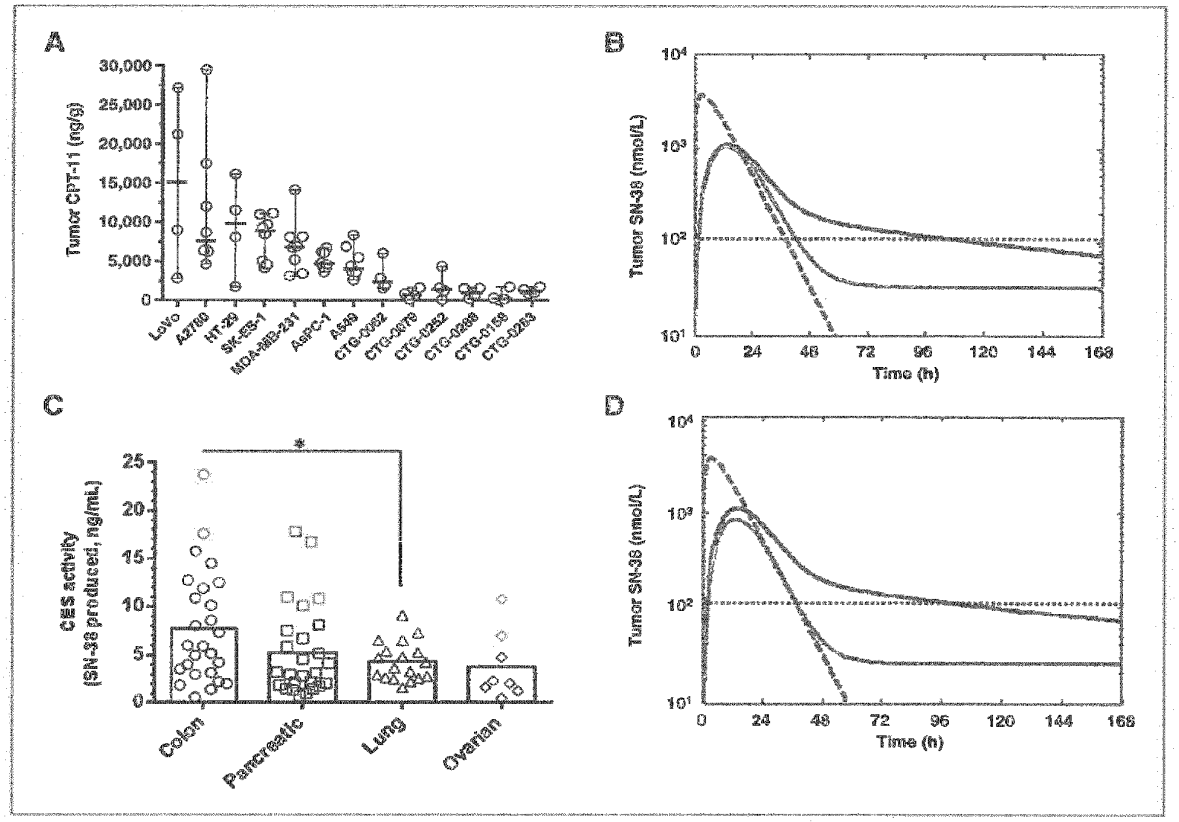

Figure 4. *In vivo* variability in nal-IRI tumor deposition and local activation. A, Intratumor CPT-11 concentrations were measured across cell-line–derived (HT-29, SK-ES-1, A549, MDA-MB-231, LoVo, AsPC-1, and A2780) and patient-derived (CTG-0082, CTG-0079, CTG-0252, CTG-0288, CTG-0158, and CTG-0283) tumor models. Tumor-bearing mice were administered a single i.v. dose of 10 mg/kg nal-IRI and tumors excised 24 hours later. CPT-11 concentrations were determined in the tumor lysates using HPLC analysis as described in Materials and Methods ($n = 4$–8 tumors/model). B, the effect of nal-IRI permeability on tumor SN-38 concentrations was simulated by reducing the nal-IRI permeability parameter $PS_{nal\text{-}IRI}$ to zero. The simulated tumor SN-38 concentrations were compared at the equal exposure doses of 10 mg/kg nal-IRI and 50 mg/kg free irinotecan. Black solid line, nal-IRI (10 mg/kg) with base $PS_{nal\text{-}IRI}$. Gray solid line, nal-IRI (10 mg/kg) with zero $PS_{nal\text{-}IRI}$. Black dashed line, free irinotecan (50 mg/kg). Dotted line, threshold concentration of 120 nmol/L. CES activity (C) for 80 patient-derived xenograft tumors across different indications was determined using *ex vivo* irinotecan activation assay. Tumor lysates (250 μg of protein) from untreated mice was incubated with free irinotecan (5 μmol/L) for 24 hours at 37°C and the amount of SN-38 produced was measured with HPLC analysis (*, $P < 0.05$; *t* test). D, the effect of knocking out tumor CES activity on tumor SN-38 duration was simulated by reducing the tumor CES parameter $V_{max,CES,t}$ to zero. The simulated tumor SN-38 concentrations were compared at the equal exposure doses of 10 mg/kg nal-IRI and 50 mg/kg free irinotecan. Black solid line, nal-IRI 10 mg/kg with base $V_{max,CES,t}$. Gray solid lines, nal-IRI 10 mg/kg with zero $V_{max,CES,t}$. Black dashed line, free irinotecan 50 mg/kg with base $V_{max,CES,t}$. Dotted line, threshold concentration of 120 nmol/L.

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CSPC Exhibit 1120
Page 23 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

with 10 mg/kg nal-IRI was substantially reduced to approximately 50 hours and approached the levels observed with 50 mg/kg free irinotecan. Taken together, these results suggest that the tumor deposition of nal-IRI is highly tumor specific and will dramatically impact tumor SN-38 duration.

To determine the degree to which local tumor activation of irinotecan varied in human tumors, we measured CES activity using an *ex vivo* assay in a panel of 80 patient-derived tumors. The tumor lysates varied in their ability to activate prodrug irinotecan and produce SN-38 (1–25 ng/mL SN-38 produced), suggesting a high degree of variability in local tumor activation of irinotecan across indications. A significant difference in local tumor activation of irinotecan was observed between colon and lung tumors ($P < 0.05$). However, there was no significant difference between other indications, which may be due to high variability observed within each indication (Fig. 4C). The impact of varying the tumor CES activity on tumor SN-38 duration was evaluated by simulating a knockout of tumor CES enzyme (Fig. 4D). In the absence of local tumor activation, tumor SN-38 duration with nal-IRI (10 mg/kg) decreased from approximately 100 to 40 hours, similar to that achieved by free irinotecan (50 mg/kg).

nal-IRI tumor deposition and local activation collectively predict tumor SN-38 duration

The relative contribution of nal-IRI tumor deposition and local tumor activation on tumor SN-38 duration was evaluated using model simulations. On the basis of the findings from the sensitivity analysis (Fig. 3B), nal-IRI permeability ($PS_{nal\text{-}IRI}$) and tumor CES activity ($V_{max,CES,t}$) values were used to create a map relating these parameters to tumor SN-38 duration following nal-IRI administration (Fig. 5A). Model simulations predicted a concave relationship, where the tumor SN-38 duration is dependent upon both the tumor permeability and the tumor CES activity. The tumor SN-38 duration could be increased by either increasing the $PS_{nal\text{-}IRI}$ or $V_{max,CES,t}$ (white arrows) and the maximum tumor SN-38 duration of 168 hours was only reached with CES activity at 0.025 nmol/min and tumor permeability at 1.5E−4 L/min/kg.

To experimentally test the model predictions, we used the same panel of 13 xenograft models to measure the tumor concentrations of CPT-11 (as a surrogate for tumor deposition, Supplementary Fig. S4A); tumor SN-38 concentrations (as a surrogate for tumor SN-38 duration; Supplementary Fig. S4B) and CES activity (for local tumor activation of irinotecan). The experimental data supported the model simulations, confirming that the SN-38 concentration within tumors was dependent on both the tumor CPT-11 concentration and tumor CES activity (Fig 5B). All tumor models with high CPT-11 concentration >2,000 ng/mL or high CES activity > 5 ng/mL displayed high tumor SN-38 concentrations ("red") ranging from 25 to 125 ng/mL (Supplementary Table S2). In certain tumor models, one of the parameters contributed predominantly toward higher SN-38 concentrations (black arrows). A2780 and SK-ES-1 tumors displayed high tumor SN-38 concentrations of 97 ng/mL and 127 ng/mL respectively (Supplementary Table S2), which was mainly due to high CPT-11 concentrations (>2,000 ng/mL), whereas in other tumor models (CTG-0062 and AsPC-1) the CES activity (>5 ng/mL) was the dominant factor contributing toward high tumor SN-38 concentrations. Further tumor models with the lowest tumor SN-38 concentrations ranging from 5 to 12 ng/mL ("blue"), including several patient-derived tumor models (boxed area) also displayed lower tumor CPT-11 concentrations (<2,000 ng/mL) and CES enzyme activity (<5 ng/mL).

Tumor SN-38 duration correlates with nal-IRI *in vivo* activity

In vivo tumor response studies were performed in three tumor models in which different tumor SN-38 durations had been observed (as indicated by tumor SN-38 concentration at 72 hours) to determine the impact of tumor SN-38 duration on *in vivo* activity of nal-IRI. The tumor volumes observed for both HT-29 (Fig. 6A) and SK-ES-1 (Fig. 6B) models were significantly

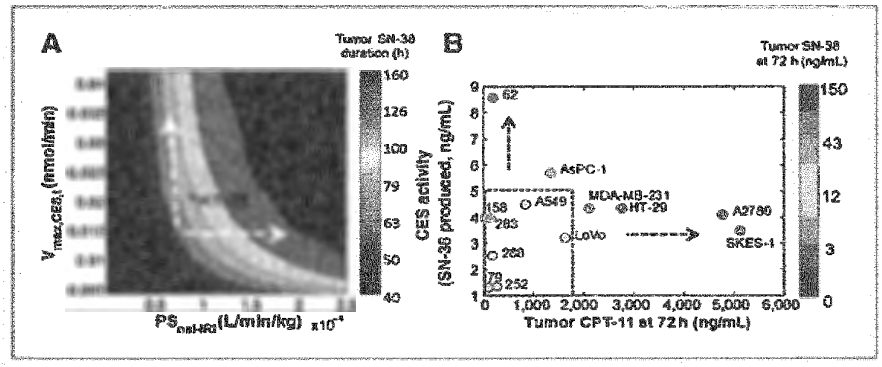

Figure 5. nal-IRI tumor deposition and local activation impacts tumor SN-38 duration. A, the effect of changing tumor CES activity and nal-IRI permeability parameters (arrows) on tumor SN-38 duration (color-coded in hours) in tumors was simulated. The optimal parameter values for HT-29 were marked with the symbol "*". B, experimental data in tumor xenograft models showing the impact of tumor CPT-11 and CES activity on tumor SN-38 concentrations. Tumor CES activity (as surrogate for local tumor activation of irinotecan) and tumor CPT-11 concentration at 72 hours (as surrogate for tumor deposition) for different xenograft models were plotted and color-coded on the basis of their SN-38 concentrations in the tumor 72 hours after nal-IRI (each data point represents median of $n = 4$–8 tumors). Dotted arrows, dependence of tumor SN-38 concentrations on tumor CPT-11 concentration and CES activity.

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CSPC Exhibit 1120
Page 24 of 447

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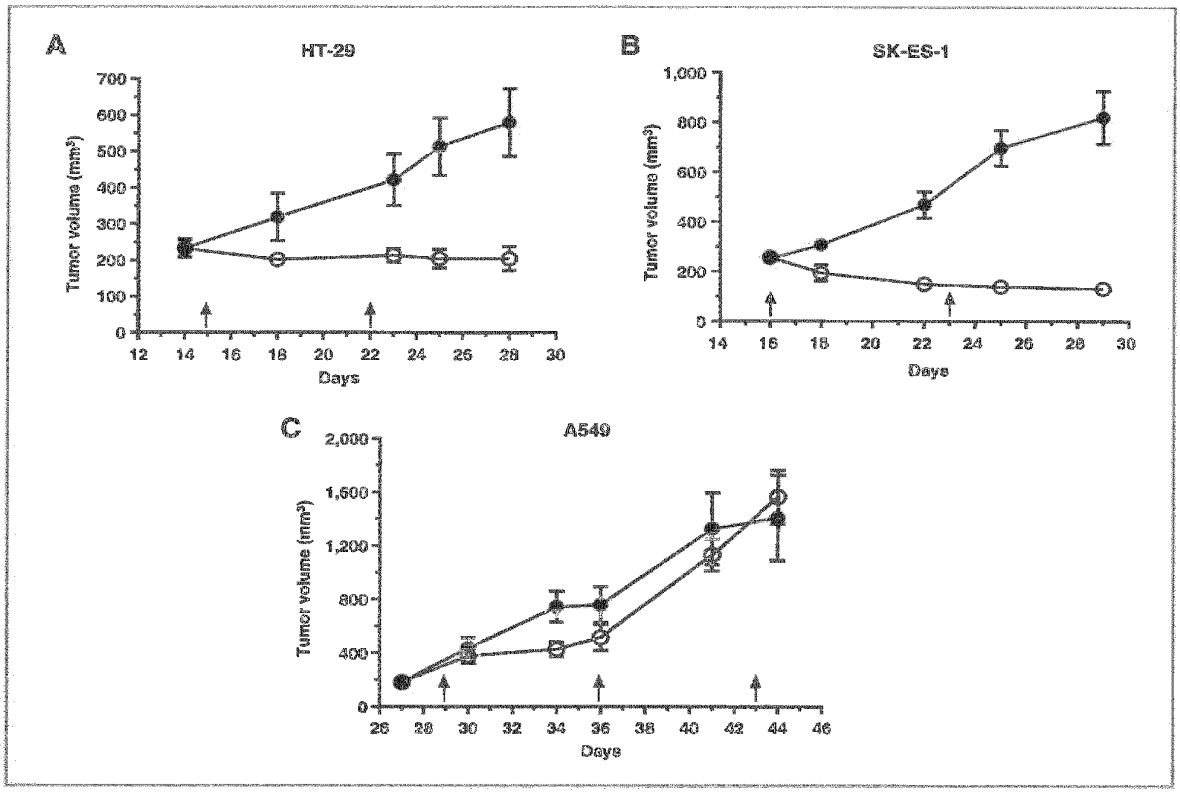

Figure 6. *In vivo* tumor response for nal-IRI. NOD/SCID mice were inoculated with HT-29; colon (A), SK-ES-1; Ewing's (B) and A549; lung (C) cell lines. Tumor-bearing mice were randomized when the tumor volume was approximately 200 mm^3. Each group received weekly i.v. dose (arrows) of either saline (●) or 10 mg/kg dose of nal-IRI (○). Tumor volumes were measured twice per week (n = 5–10 animals/group).

lower ($P < 0.05$) following 10 mg/kg nal-IRI as compared with untreated tumors. In both these models, tumor regression was observed immediately after the first dose and was sustained through the course of the study. A549 tumors achieved lower SN-38 tumor levels (Fig. 4A) and did not respond to nal-IRI treatment (Fig. 6C). Interestingly, both A549 and HT-29 cells displayed similar *in vitro* sensitivity to SN-38 with IC_{50} values of 53 and 44 nmol/L, respectively (20). In summary, nal-IRI induced stronger responses (~100%TGI) in tumor models that had higher tumor SN-38 duration (>~100 hours).

Discussion

The nal-IRI formulation dramatically alters the pharmacologic properties of irinotecan as well as its active metabolite, SN-38 (9). In this study, we identified a pharmacologic parameter—namely, tumor SN-38 duration—as a driver of irinotecan-based *in vivo* activity and propose biomarkers that can impact tumor SN-38 duration achieved by nal-IRI. Our study indicates that nal-IRI can completely inhibit tumor growth compared with free irinotecan, despite administering doses that achieve similar SN-38 exposure (measured as the AUC). Instead, the duration of prolonged exposure of SN-38 within tumors achieved by nal-IRI was shown to be a major pharmacologic determinant for *in vivo* activity in mice.

Several studies have shown improved *in vitro* cytotoxic activity of SN-38 when cells are exposed to drug for longer duration (21). The *in vitro* cell doubling time for HT-29 cells is approximately 20 hours (21), whereas *in vivo* the tumor volume doubles (Fig. 2B) at a slower rate (~8–9 days). In addition, at a given time only 35 to 50% of cells are in the S-phase of cell cycle wherein the maximum cytotoxicity of free irinotecan has been observed (21). Thus, to exert maximum cytotoxic effects across different cell-cycle phases, the cells have to be exposed to free irinotecan across multiple cell cycles. Our *in vivo* study confirms these findings as the free irinotecan is rapidly cleared from plasma and tumor tissue (tumor SN-38 duration of approximately 40 hours), thereby not allowing sufficient time for tumor cells to be exposed to SN-38 (for only 2 cell-cycle doubling time) as compared with more than 5 cell-cycle doubling times with nal-IRI (tumor SN-38 duration for >100 hours). Thus the extended exposure of tumor cells to SN-38, which is achieved by nal-IRI, can contribute toward the enhanced cytotoxicity as compared with free irinotecan.

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CSPC Exhibit 1120
Page 25 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

We observed higher tumor concentrations of CPT-11 and SN-38 at 168 hours following administration of nal-IRI. In contrast, the peak plasma concentrations of SN-38 was lower with nal-IRI as compared with free irinotecan, suggesting that most of the CPT-11 from nal-IRI remains inside the liposomes and is protected from systemic conversion as described with free irinotecan (17). In addition, prolonged SN-38 duration from nal-IRI administration was observed only in tumors and much less in normal tissues, suggesting that toxicity might not be exacerbated by nal-IRI treatment. The preferentially accumulation of nal-IRI in tumors as compared with normal tissues can be attributed to the EPR effect, where the leaky vasculature in tumor facilitates the extravasation of liposomal nanoparticles and the defective lymphatic drainage helps increase the retention within tumor (1, 2). Thus, with the EPR effect, nal-IRI creates a large depot of CPT-11 only in tumors thereby prolonging tumor SN-38 duration. In contrast, free irinotecan can easily be transported in and out of the tissues with a short plasma half-life, resulting in minimal SN-38 duration in tumors.

The enhanced *in vivo* activity of nal-IRI as compared with free irinotecan was attributed to the ability of nal-IRI to extend the tumor SN-38 duration. Sensitivity analysis identified two key determinants that impact the ability of nal-IRI to extend tumor SN-38 duration—(i) nal-IRI tumor deposition, as measured by the extent of prodrug CPT-11 deposition within tumors and (ii) nal-IRI local activation, from prodrug CPT-11 to SN-38 facilitated by the local tumor CES enzyme. The experimental data, in this study supported the importance of each of these determinants. We observed high degree of variability in the overall nal-IRI tumor deposition across the 13 xenograft models that were tested. Several studies have highlighted a role for tumor permeability, tumor perfusion, and stromal matrix in limiting the delivery of therapeutic agents into tumors (22). In our model simulations, when the nal-IRI tumor permeability was decreased to zero, the benefit of higher tumor SN-38 duration with nal-IRI was negatively impacted and reduced to levels simulated for free irinotecan. We also observed that the tumors with lower nal-IRI deposition had considerable lower SN-38 tumor levels. These data are consistent with other findings suggesting that a dense tumor stroma can impede drug permeability and limit drug delivery within tumors (23, 24).

Use of tumor CES activity as a cellular parameter for predicting free irinotecan response had limited success both in preclinical (25, 26) and clinical studies.(27). Through the sensitivity analysis performed in this study, we identified CES activity as a critical parameter for nal-IRI activity. Tumor models that displayed high ability to activate CPT-11, achieved high tumor SN-38 concentrations despite limited deposition of CPT-11, thus suggesting the importance of local tumor CES enzyme expression in facilitating longer SN-38 exposure following nal-IRI administration. In fact, others have shown that *in vitro* and *in vivo* activity of free irinotecan can be enhanced by overexpressing of CES enzyme in tumor cells (28, 29). In addition to tumor cells expressing CES enzyme (30), other components of the extracellular matrix such as tumor-associated macrophages (TAMs) express CES1 enzyme and play a role in CPT-11 activation (31). In fact, we performed *in vitro* studies that confirmed the ability of TAMs to hydrolyze CPT-11 to SN-38 (Supplementary Fig. S5). Thus our data suggests the extended tumor PK achieved by nal-IRI provides high local depot of prodrug CPT-11 for prolonged time, thus allowing for activation by tumor CES enzymes. Collectively our data provides rational for investigating tumor CES enzyme activity as a potential marker for nal-IRI activity.

Pharmacogenetic and pharmacodynamic markers such as TOP1 have shown limited correlations with free irinotecan response (6, 32–34). In addition to the intrinsic sensitivity of tumor cells to SN-38, our data indicate that the duration for which tumor cells are exposed to SN-38 (tumor SN-38 duration) also plays a critical role in driving treatment response to irinotecan. Tumor models with extended SN-38 duration (HT-29, SK-ES-1) showed robust *in vivo* response to nal-IRI, whereas A549 with shorter tumor SN-38 duration did not respond to therapy. The fact that *in vitro* sensitivity of both HT-29 and A549 to SN-38 is very similar (20) corroborates the finding that the duration of SN-38 is driving the tumor response.

In conclusion, our data demonstrate that nal-IRI enhances the pharmacokinetic profile of tumor SN-38, prolonging tumor exposure to SN-38 compared with free irinotecan, and therefore has the potential for therapeutic effect in human cancers. Liposome permeability and CES activity were the critical factors that emerged from model simulation of tumor SN-38 duration, which were experimentally shown to vary across and within tumor indications. Thus, translational research exploring the utility of tumor liposome permeability and local activation of irinotecan as biomarkers for nal-IRI clinical activity is warranted.

Disclosure of Potential Conflicts of Interest

D.C. Drummond and J.B. Fitzgerald have ownership interest (including patents) in Merrimack Pharmaceuticals, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.V. Kalra, J. Kim, S.G. Klinz, D.C. Drummond, U.B. Nielsen, J.B. Fitzgerald
Development of methodology: A.V. Kalra, J. Kim, S.G. Klinz
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.V. Kalra, N. Paz, J. Cain
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.V. Kalra, J. Kim, D.C. Drummond, J.B. Fitzgerald
Writing, review, and/or revision of the manuscript: A.V. Kalra, J. Kim, S.G. Klinz, D.C. Drummond, U.B. Nielsen, J.B. Fitzgerald
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Kim, N. Paz
Study supervision: A.V. Kalra, J.B. Fitzgerald

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CSPC Exhibit 1120
Page 26 of 447

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CSPC Exhibit 1120
Page 27 of 447

Published OnlineFirst October 1, 2014; DOI: 10.1158/0008-5472.CAN-14-0572

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Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion

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PROPRIETOR'S RESPONSE TO O1'S SUBMISSION OF 1ST FEBRUARY 2022

EUROPEAN PATENT 3 337 478 B1

In the name of IPSEN BIOPHARM LTD.
Opposed by SANDOZ AG (O1) and GENERICS [UK] LIMITED (O2)
DERIVING FROM 16758337.6 | O008382EP

1 INTRODUCTION

1.1 The proprietor responded to the oppositions on 7th December 2021. In this response, it was explained why the Main Request (MR) was entitled to the earliest priority date, and why the MR involves an inventive step. On 1st February 2022, O1 filed a further written submission. In this submission, new facts and arguments on both priority and inventive step were provided, and certain points from O1's opposition statement were repeated. O1 also made allegations about non-compliance with the requirements of Rule 80 EPC for the auxiliary requests. New evidence in the shape of D25, D26, and D27 was also filed with O1's written submission, i.e. after expiry of the 9-month opposition period provided for in Article 99 EPC. The Opponent has not adequately justified why the opposition has been filed in such a piecemeal manner.

1.2 Should the Opposition Division (OD) be minded to take any of O1's new facts, arguments, and evidence into consideration in relation to priority entitlement, inventive step and Rule 80 EPC, it will be explained below that none of these advance O1's case. The proprietor would be grateful if the Opposition Division would consider this submission when preparing its preliminary opinion. With regard to the points in O1's latest submission which simply repeat points made in O1's opposition statement, these points were already addressed in the response to the oppositions, and so the proprietor's arguments on these points will not be repeated in full here purely for the sake of brevity.

1.3 For the avoidance of doubt, all of the requests, facts, arguments, and evidence set out by the proprietor in the response to the oppositions are maintained.

2 THE MR IS ENTITLED TO THE EARLIEST PRIORITY DATE

2.1 The proprietor explained in the response to the oppositions why the MR is entitled to the earliest priority date, and this explanation will not be repeated in full here purely for the sake of brevity. However, the proprietor offers the following comments in response to the new facts, arguments, and evidence provided by O1.

"MM-398 liposomal irinotecan"

2.2 Granted claim 1 contained a reference to "*liposomal irinotecan*". In the MR filed with the response to the oppositions, granted claim 1 was amended to state that "*the liposomal irinotecan is irinotecan sucrose octasulfate liposome injection*". This amendment is directly and unambiguously derivable from P1. For example, paragraph [0006] of P1, reproduced below with emphasis added, states that:

> "*Provided are methods for treating pancreatic cancer in a patient (i.e., a human patient) not previously treated with a chemotherapeutic agent in the metastatic setting, the method comprising administering to the patient liposomal irinotecan (e.g.,* ***irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398****) in combination with oxaliplatin, leucovorin and 5-fluorouracil (5-FU), according to a particular clinical dosage regimen.*" [emphasis added]

Paragraph [0018] of P1, first sentence states that:

> "*In another embodiment, the liposomal irinotecan is formulated as irinotecan sucrose octasulfate salt liposome injection (MM-398).*"

Paragraph [0047] and paragraph [0048] (first sentence) provide further support:

> "***A. Irinotecan sucrose sulfate liposome injection (Nal-IRI, MM-398)***
>
> *As provided herein, irinotecan is administered in a stable liposomal formulation as irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"), the formulation referred to herein as "MM-398" (also known as PEP02, see US 8,147,867).*"

2.3 As the OD will appreciate, the above passages of P1 demonstrate that the amendment made in claim 1 of the MR finds direct and unambiguous basis in P1.

2.4 However, O1 maintains that the amendment made to claim 1 does not have basis in P1, seemingly because claim 1 of P1 refers to "*MM-398 liposomal irinotecan*" without referring explicitly to "*irinotecan sucrose octasulfate liposome injection*". However, when assessing priority, one must focus not just on the disclosure of the claims of P1, but on the disclosure of P1 as a whole[1]. When one considers the disclosure of P1 as a whole (e.g. paragraphs [0006], [0018], [0047], and [0048] discussed above), it can be seen that "*irinotecan sucrose octasulfate liposome injection*" is directly and unambiguously disclosed in P1, and that it is disclosed as an equivalent term to "*MM-398 liposomal irinotecan*" contrary to O1's assertion[2]. It is not correct to focus solely on the disclosure of the claims of P1 to the detriment of what is directly and unambiguously disclosed elsewhere in P1, as O1 has done.

2.5 O1 also alleges that D4 and D17 contain some information about "*MM-398*"[3]. However, neither document mentions "*MM-398*" even once, and so O1's reliance on these documents is misplaced. Moreover, neither D4 nor D17 are representative of the common general knowledge, because they are respectively the prescribing information of a single drug and an isolated research article[4]. As they are not representative of the common general knowledge, D4 and D17 are not relevant to how the skilled person would interpret P1. O1 also provides some general statements about liposomes, alleging that their characteristics influence "*their ability of delivering the active* ingredient".[5] No supporting evidence is provided for these statements, and the relevance of them is unexplained. Thus, they cannot advance O1's case.

[1] Guidelines H-IV, 2.2. This extract is concerned with Article 123(2) EPC. However, as the OD will appreciate, this passage is also relevant to priority entitlement, which is also assessed using the "gold standard".
[2] O1 submission of 1st February 2022, paragraph 2.1.4.
[3] O1 submission of 1st February 2022, paragraph 2.1.3.
[4] Guidelines, G-VII, 3.1.
[5] O1 submission of 1st February 2022, paragraph 2.1.3.

"The claimed doses"

2.6 O1's submission re-iterates that there is allegedly no basis in P1 for the 60 mg/m^2 doses of liposomal irinotecan and oxaliplatin which appear in the MR. O1's arguments suggest that these features of the MR are the result of selections from two lists, and that there is no pointer towards this combination. This is not a correct interpretation of P1.

2.7 O1 suggests that claims 5 and 8 of P1 cannot provide basis for the 60 mg/m^2 doses of liposomal irinotecan and oxaliplatin because selections from two lists are allegedly needed. However, as the OD will be aware, selections from two lists only result in new subject matter when, *inter alia*, the two lists are lists of some length[6,7]. To the extent that claims 5 and 8 of P1 can be viewed as "*lists*" (which is not conceded), these "*lists*" have two and three options, respectively. Lists containing two or three options are clearly not lists of some length and therefore, to the extent that any selections need to be made (which, again, is not conceded), these selections cannot result in new subject matter being generated. Thus, O1's arguments about selections from lists are not prejudicial to the priority claim.

2.8 In any case, even if selections are necessary to arrive at the doses which appear in the MR (which is not conceded), this is not prejudicial to the priority claim at least because P1 contains a pointer towards the 60 mg/m^2 doses of both liposomal irinotecan and oxaliplatin being preferred. This pointer can be found in Table 7 in paragraph [00288] of P1 which, in the row labelled "*-1*", a dosage regimen requiring the administration of 60 mg/m^2 doses of both liposomal irinotecan and oxaliplatin is disclosed (along with identical 5-FU and leucovorin doses as claimed). Therefore, the doses in the MR are directly and unambiguously derivable from P1.

2.9 P1 also provides at least a pointer towards the use of 60 mg/m^2 doses of liposomal irinotecan and oxaliplatin in patients with metastatic adenocarcinoma of the pancreas. For example, in the claims of P1, claim 29, which explicitly discloses metastatic adenocarcinoma of the pancreas, depends on claims 5 and 8 which disclose 60 mg/m^2 doses of both liposomal irinotecan and oxaliplatin. Moreover, Table 7 of P1 discussed above appears in a section of P1 which describes a clinical trial in which patients have been diagnosed with metastatic adenocarcinoma of the pancreas[8].

2.10 O1's arguments on the doses which appear in the MR essentially suggest that, because P1 discloses other possible dosages of oxaliplatin and liposomal irinotecan, and that the claimed doses are allegedly "*less preferred*", the priority claim is not valid. This is not correct. These arguments were largely already dealt with in the response to the oppositions[9]. However, it should be emphasised here that the only relevant consideration when assessing priority is whether the subject matter of the MR is directly and unambiguously derivable, explicitly or implicitly, from P1. It has been explained above and in the response to the oppositions that the doses which appear in the MR meet this requirement. It is of no relevance in this case

[6] Guidelines G-VI, 8. This passage of the Guidelines refers to lists "*of a certain length*", although the underlying case law (e.g. T2/81) refers to lists "*of some length*". This wording is also used in the Case Law of the Boards of Appeal, 9th Edition, I.C.6 and II.E.1.6.2.
[7] In addition, even if selections from two lists of some length are made, this does not necessarily result in new subject matter being created because, for example, there may be a pointer to the combination of selected features.
[8] See, for example, P1, paragraph [0136].
[9] Response to oppositions, e.g., paragraphs 4.26 – 4.28.

when considering priority entitlement whether further subject matter, which is outside the scope of the MR, (e.g. dosages other than those claimed) might also be directly and unambiguously derivable, explicitly or implicitly, from P1. The applicant/proprietor is not obliged to claim each and every embodiment which is disclosed in their application[10], and the proprietor should not be penalised for pursing narrow claims. So, even if O1 is correct to argue that doses of 80 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin are "*preferred*" and that the claimed doses are allegedly "*less preferred*" (which is not conceded), this does not change the fact that the 60 mg/m^2 doses of both liposomal irinotecan and oxaliplatin are directly and unambiguously derivable from P1, meaning that the priority claim is valid.

"The administration frequency"

2.11 O1 reiterates that the feature "*a total of once every two weeks*", which appears in the MR, is not supported by paragraph [0075] of P1. O1 relies on D26 in support of its arguments, stating that the disclosure of D26 would influence the skilled person's interpretation of the disclosure of P1[11]. This is not correct.

2.12 Whilst the skilled person will consider the disclosure of P1 in light of their common general knowledge, D26 is not representative of the common general knowledge because it is a single, isolated publication, which is not a broad review or survey of the topic, but a report of a single clinical study[12], and therefore would not have led the skilled person to interpret paragraph [0075] in any particular way[13]. Therefore, D26 (should it be admitted) is not relevant when considering how the skilled person would interpret P1.

2.13 First, O1 has forced an arbitrary interpretation of "*a total of once every two weeks*" as used in claim 1, alleging that this wording cannot allow for "*multiple administrations*". O1 refers to D26 to support this argument, but O1 reads D26 and this feature of claim 1 in such a way that it distorts the real technical teaching. There is nothing from the wording "*a total of once every two weeks*", nor any of the wording in P1, that indicates that this means that the total dosage amounts (provided in claim 1) cannot, for example, be administered in multiple administrations that sum to the total dose. Claim 1 of the MR states that the method comprises "administering an antineoplastic therapy to the patient a total of once every two weeks". The antineoplastic therapy, i.e. the total doses, that need to be administered a total of once every two weeks, and this wording allows for the dose to be split into multiple administrations. Claim 1 does not state that this administration must be all in one single day, as O1 appears to imply. O1's arbitrary interpretation of claim 1 does not represent how the skilled person would interpret the claim, and therefore this argument must fail[14].

[10] See, e.g., G2/10, Reasons 4.5.5.
[11] O1 submission of 1st February 2022, paragraph 1.7.
[12] Guidelines, G-VII, 3.1.
[13] In addition, had O1 wished to file evidence on how the skilled person would have interpreted the term "*once every two weeks*", this evidence should have been filed during the opposition period because the term "*once every two weeks*" appeared in five of the fourteen granted claims, including claim 1.
[14] This is also confirmed repercussively in claim 2 of the MR (claim 3 as granted) where the 5-FU is administered as an infusion over 46 hours (see also [0012] of P1). This is equivalent, of course, to dosing part of the 5-FU on day 1 of the cycle and part of day 2 of the cycle, i.e. multiple administrations.

Claim 22 of P1

2.14 O1 disputes that claim 22 of P1 can provide basis for claim 1 of the MR, although detailed arguments have not been provided. Therefore, the proprietor refers the OD to paragraphs 4.20 – 4.25 of its response to the oppositions. In addition, the proprietor wishes to emphasise that, contrary to O1's suggestion, no cherry-picking of features is necessary to arrive at the features of claim 1 of the MR from P1. As was explained in the response to the oppositions and above, the features of claim 1 of the MR are all disclosed in P1, and this remains the case if one starts from claim 22 of P1, and no cherry-picking is necessary. Moreover, P1 provides at least a pointer towards the combination of features which appears in claim 1 of the MR (see Example 1, particularly Table 7 thereof). Therefore, the MR finds basis in P1, and O1 is wrong to argue otherwise.

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3 INVENTIVE STEP

3.1 As was the case for priority entitlement, the proprietor already explained in its response to the oppositions why the MR involves an inventive step. This explanation will not be repeated in full here for the sake of brevity. However, the proprietor offers the following comments in response to the new facts, arguments, and evidence on inventive step provided by O1. In this section, the proprietor will order its arguments in the same way as O1 in its most recent submission. That is, inventive step at the filing date will be discussed first before moving on to inventive step at the earliest priority date, although it is of course the proprietor's position that the claims are entitled to the earliest priority date.

Inventive step at the filing date

3.2 It has been explained above and in the response to the oppositions that the MR is entitled to the earliest priority date. However, even if the priority claim is found to be invalid (which is not conceded), it remains the case that the MR is inventive.

3.3 O1 states that either D1 or D6 should be taken as the closest prior art. The proprietor disagrees for the reasons given in the response to the oppositions[15]. In addition, the proprietor notes that O1's argument that, when considering closest prior art, "*the only relevant question is whether the document used is a feasible starting point for assessing inventive step*"[16] is at odds with recent case law on this point[17]. Moreover, whilst the Boards of Appeal have previously taken clinical trial protocols which do not contain any data or disclosure of treatment as the closest prior art, in these cases (e.g. T239/16) no other suitable document existed. This is in contrast to the present case where other, more suitable documents (e.g. D10) exist which do disclose actual treatment of the claimed therapeutic indication.

[15] See, for example, response to oppositions, paragraph 5.88.
[16] O1 submission of 1st February 2022, paragraph 3.2.7.
[17] T2759/17, Reasons 5.3 – 5.6. In this decision, the Board rejected a suggestion that "*each and every disclosure… can be selected as the starting point for assessing inventive step*".

3.4 In addition, O1 attempts to support its position by arguing that D4, D5, D7, and D25 should be considered together in combination with D1 when deciding what the most promising springboard is[18].

3.5 In respect of D25, O1 relies on this document as it allegedly provides information about "*irinotecan sucrose octasulfate salt liposome injection*". O1 seemingly justifies not filing these documents within the 9-month opposition period by pointing out that the requirement in claim 1 of the MR that the liposomal irinotecan "*is irinotecan sucrose octasulfate salt liposome injection*" was not included in any of the granted dependent claims[19]. On this basis, O1 appears to suggest that evidence about "*irinotecan sucrose octasulfate salt liposome injection*" could not have been filed earlier. This is not correct. In particular, whilst the precise wording "*irinotecan sucrose octasulfate salt liposome injection*" was not present in any of the granted claims, two granted claims referred to "*irinotecan sucrose octasulfate*" in "*liposome[s]*" (claims 2 and 13). Moreover, the disclosure of the earliest priority document (P1 – US 62/208,209), the application as filed and the patent makes it clear that dosage regimens which use "*irinotecan sucrose octasulfate*" / "*irinotecan sucrose octasulfate salt liposome injection*" represent preferred embodiments of the invention[20]. Thus, O1 is wrong to suggest that evidence relating to "*irinotecan sucrose octasulfate salt liposome injection*" could not have been filed earlier (i.e. within the 9-month period given in Article 99 EPC).

3.6 Additionally O1's approach of deciding what the most promising springboard is represents an incorrect application of the problem-solution approach. In particular, it is not permissible to consider the cumulative disclosure of four prior art documents, and then use this cumulative disclosure to influence the decision as to what is taken as the closest prior art. This argument therefore cannot advance O1's case.

3.7 O1 also justifies its choice of D1 as closest prior art by arguing that "*it makes use of the recently approved (see D4) liposomal formulation of irinotecan*". This argument fails because there is nothing in either of D1 or D4 which would allow the skilled person to conclude that the "*liposomal irinotecan*" referred to in D1 is that same as the medicinal product "*Onivyde™*" referred to in D4. In particular, D1 does not once mention "*Onivyde™*", and D4 does not once mention, for example, "*nal-IRI*" or "*MM-398*".

3.8 O1 also alleges that the proprietor selected Arm 2 of D1 as the closest prior art in the response to the oppositions[21]. This is wrong. By contrast, the inventive step arguments starting from Arm 1 of D1 were provided in the response to oppositions[22].

3.9 However, purely for the sake of argument, <u>the remainder of this section will focus on inventive step if one assumes Arm 1 of D1 is taken as the closest prior art</u>. Arm 1 of D1 is directed to "*nal-IRI + 5-FU/LV + oxaliplatin*" which, it is stated, will be administered to "*patients with advanced pancreatic adenocarcinoma who have not received prior chemotherapy*". D1 discussed administration using the future tense, indicating that no patients had been dosed in

[18] O1 submission of 1st February 2022, paragraph 3.2.3.
[19] O1 submission of 1st February 2022, paragraph 1.3.
[20] See, for example, P1, paragraphs [0006], [0018], [0021], and [0048]; application as filed, pages 15, 16, 26, 62, and claim 14; patent specification, paragraphs [0027], [0028], [0031], [0154], [0155], and claims 2 and 13. "Irinotecan sucrosofate" is synonymous with "irinotecan sucrose octasulfate".
[21] O1 submission of 1st February 2022, paragraph 3.2.2 and 3.2.6.
[22] See, for example, response to oppositions, paragraph 5.91, which listed the features which distinguish claim 1 of the MR from Arm 1 of D1.

the clinical trial at the time of publication. D1 states that the "*nal-IRI*" can also be referred to as "*MM-398*", and also states that these are a type of "*nanoliposomal irinotecan*".

3.10 Claim 1 of the MR differs from Arm 1 of D1 at least because:

i. Claim 1 requires the tolerable, safe, and effective treatment of metastatic adenocarcinoma of the pancreas;

ii. Claim 1 requires that the liposomal irinotecan is *"irinotecan sucrose octasulfate salt liposome injection"*;

iii. Claim 1 requires a specific dosing frequency of the antineoplastic therapy – "*once every two weeks*";

iv. Claim 1 uses a **60 mg/m² dose** of *"irinotecan sucrose octasulfate salt liposome injection*";

v. Claim 1 uses a **60 mg/m² dose** of oxaliplatin;

vi. Claim 1 uses a **2,400 mg/m² dose** of 5-fluorouracil; and

vii. Claim 1 uses either a **200 mg/m² dose** of the (l)-form of leucovorin or **400 mg/m² dose** of the (l+d) racemic form of leucovorin.

3.11 In its submission of 1st February 2022, O1 seems to acknowledge the existence of distinguishing features i, iii, and iv above. O1 has seemingly not acknowledged that feature ii represents a distinguishing feature, although it should be noted that O1 has provided no arguments or explanation as to where it believes feature ii is disclosed in D1. For the avoidance of doubt, it is not permissible for O1 to rely on documents such as D4 to somehow compensate for the lack of teaching in D1, as O1 is seemingly doing in its latest submission[23]. The contents of D4 would not have formed part of the common general knowledge, and in any case the skilled person would not have assumed that the liposomal irinotecan mentioned in D4 is the same as that mentioned in D1 (see paragraph 3.7 above).

3.12 The technical effect of the above differences is that a tolerable, safe, and effective treatment for metastatic adenocarcinoma of the pancreas in patients who have not previously received chemotherapy for this condition is provided. The objective technical problem is therefore the provision of a tolerable, safe, and effective treatment for metastatic adenocarcinoma of the pancreas in patients who have not previously received chemotherapy for this condition.

3.13 It has already been explained that the claimed solution would not have been obvious[24], and so the proprietor's comments below will focus on the arguments in O1's latest submission. However, before analysing O1's arguments in detail, it is important to note several important flaws which permeate throughout O1's analysis.

3.14 Firstly, at no point in O1's obviousness arguments has it been explained where the use of "*irinotecan sucrose octasulfate salt liposome injection*" is disclosed or suggested in the prior art. Rather, O1 appears to simply cite documents which refer generally to "*liposomal irinotecan*" and then assume without justification that this must be a reference to "*irinotecan*

[23] O1 submission of 1st February 2022, paragraph 3.2.3.
[24] Response to oppositions, paragraphs 5.94 – 5.108.

sucrose octasulfate salt liposome injection". This is not the correct approach, and for this reason alone O1's arguments must fail because O1 has failed to explain how the skilled person would have arrived at one of the mandatory features of claim 1.

3.15 Secondly, the crux of O1's argument appears to be that the dosages and administration frequency recited in claim 1 of the MR simply represent "*routine adaptations of the known dosages*"[25]. However, from a brief review of O1's arguments it can be seen that O1's approach is nothing more than an attempt to compensate for the fact that the dosage regimen recited in claim 1 is not disclosed or suggested anywhere in the prior art. For example, O1 has failed to point to any prior art disclosure of a 60 mg/m^2 dose of oxaliplatin or a 60 mg/m^2 dose of "*irinotecan sucrose octasulfate salt liposome injection*" administered once every two weeks. Therefore, even without looking at O1's arguments in detail, one can conclude that the skilled person would not have been led to the claimed subject matter with a reasonable expectation of success.

3.16 Thirdly, O1's position appears to be that the skilled person starting from D1 would have cherry-picked certain pieces of information from both D3 and D5 to arrive at the claimed subject matter. That is, O1's arguments rely on a three-way combination of prior art documents, which is not permissible. Even if D3 and D5 are deemed to be representative of the common general knowledge (which is not conceded), that does not mean that O1 is permitted to arbitrarily select passages from each document and combine them together using hindsight in an effort to deny inventive step. This is a further reason why O1's arguments fail.

3.17 However, even if one does consider O1's arguments in detail notwithstanding the above, they fail to advance O1's case. In its arguments, O1 acknowledges that D1 fails to disclose any sort of dosage regimen, but argues that the skilled person would have consulted documents such as D3 to find a suitable dosage regimen. O1 points to the disclosure of the "*FOLFIRINOX*" regimen in D3, the safety and efficacy of which had been confirmed in a Phase III trial[26]. According to D3, this regimen involved the administration of the following drugs and dosages every 14 days:

(Non-liposomal) irinotecan	180 mg/m^2
Oxaliplatin	85 mg/m^2
Leucovorin	400 mg/m^2
5-FU	400 mg/m^2 bolus, then 2400 mg/m^2 infusion

3.18 If, for the sake of argument, the skilled person had consulted D3 in an effort to, for example, obtain information on how the drugs mentioned in D1 should be dosed, the most straightforward thing to do would be to use doses which had shown efficacy and safety in the treatment of first line pancreatic cancer. For example, the skilled person would have been led to use an 85 mg/m^2 dose of oxaliplatin because D3 states that this dose was used successfully in FOLFIRINOX. It cannot be correct to argue, as O1 has, that the skilled person, faced with doses which are said to be safe and effective, would instead have chosen a

[25] O1 submission of 1st February 2022, paragraphs 3.2.5 and 3.4.2.
[26] D3, paragraph spanning pages 853 and 854.

different dose such as 60 mg/m² oxaliplatin which is not disclosed in D3 and which had not been shown to be safe and efficacious.

3.19 O1's arguments then refer to the section on page 855 of D3 which discusses how any toxicity of FOLFIRINOX should be managed. Table 1 of D3 (reproduced below), summarises D3's teaching on this point. It can be seen that, in the "*Strategy*" column, "*Decrease doses of one or more of the drugs*" is mentioned as one of several options for managing toxicity in certain circumstances. However, the table makes clear that a "*Concern*" associated with this approach is "*Decreased efficacy of therapy*". So, D3 teaches the skilled person that dose reduction of one or more of the drugs used in FOLFIRINOX was one of several options which could be pursued if toxicity was a concern, but that this potential reduction in toxicity may be accompanied by a reduction in therapeutic efficacy. This would, of course, be unacceptable for the skilled person seeking to solve the objective technical problem.

Table 1. Management of FOLFIRINOX toxicity.

Toxicity	Strategy	Concern
Low blood counts, fatigue, diarrhea, mucositis	Decrease doses of one or more of the drugs; lomotil/pegfilgrastim	Decreased efficacy of therapy; bone pain
Low platelet counts despite appropriate dose reduction	Splenectomy—surgical or via interventional radiology	Pain; abscess formation; treatment delay
Acute allergic reaction to oxaliplatin infusion	Desensitization protocol and possible discontinuation	Ineffective to resolve problem; resources
Hypercholinergic reaction with cramping and sweating	Slow infusion rate and premedicate with atropine	Prolonged treatment time; resources
Oral dysesthesia with sense of swollen tongue	Slow infusion rate and warm drink	Prolonged treatment time; anxiety; resources
Weakness, paralysis, and even coma	Maintenance of normal potassium and calcium prior to and during infusion	Patient anxiety; staff anxiety; imperfect results

3.20 D3 then on page 855 goes on to discuss how FOLFIRINOX can be modified to give "*mFOLFIRINOX*". In mFOLFIRINOX, the bolus of 5-FU is removed, and pegfilgrastim (a colony-stimulating factor) is added[27], meaning that the following drugs in the following amounts are administered every 14 days:

Non-liposomal irinotecan	180 mg/m²
Oxaliplatin	85 mg/m²
Leucovorin	400 mg/m²
5-FU	2400 mg/m² infusion (no bolus)
Pegfilgrastim	6 mg

3.21 D3 reports that the mFOLFIRINOX was in common use at D3 publication date. As the authors of D3 put it, mFOLFIRINOX "*seems to be the way* [the FOLFIRINOX regimen] *is often used today*". Again, had the skilled person consulted D3 to find a suitable dosage regimen for the drugs mentioned in D1, they would have been led to use doses which had been shown to be safe and effective in the relevant patient population. For example, 85 mg/m² of oxaliplatin. The skilled person would have had no reason to use other doses, particularly doses which are not disclosed and which have not been shown to be safe and effective. The skilled person certainly would not have reduced the doses (e.g. to go from 85 mg/m² of oxaliplatin to

[27] Table 2 on page 855 of D3 confirms that in all instances where the 5-FU bolus was removed, 6 mg pegfilgrastim was added.

60 mg/m^2) which had been shown to be safe and effective because of the warning in Table 1 that reduced doses could result in "*decreased efficacy*".

3.22 O1 continues its arguments by discussing Table 2 of D3 (reproduced below). This table is concerned with modifications that had been made to the FOLFIRINOX and mFOLFIRNOX regimens discussed in D3. As the OD will note, a large number of further options for modification are provided, including options which reduce the dosage of irinotecan to 165 mg/m^2 or 135 mg/m^2, options which reduce the oxaliplatin dose to 50 mg/m^2, and options which reduce the 5-FU dose to 2000 mg/m^2.

Table 2. FOLFIRINOX dose modifications and results.

Author	Modification	Results/comments
Mahaseth et al. [18]	Drop 5FU bolus Add pegfilgrastim 6 mg	Grade 4 neutropenia 3% Grade 3/4 diarrhea 13%, fatigue 13% OS 9.0 months, PFS 8.5 months
Blazer et al. [24]	Drop 5FU bolus Decrease irinotecan to 165 mg/m^2 Add pegfilgrastim 6 mg	Grade 3/4 neutropenia or thrombocytopenia 0% 46% further dose reductions for other toxicities
Gunturu et al. [25]	Median dose intensity 5FU bolus 57% Median dose intensity oxaliplatin 88% Median dose intensity irinotecan 64%	Grade 3/4 neutropenia 6.4% Grade 3/4 fatigue 9.6% CR plus PR 31.6%
Metges et al. [27]	Median dose intensity 5FU bolus 82% Median dose intensity oxaliplatin 78% Median dose intensity irinotecan 81%	Grade 3/4 hematologic and neurotoxicity 32% Response rate 39% PFS 6.5 months OS 10.9 months
Alessandretti et al. [26]	Drop 5FU bolus Decrease 5FU infusion to 2000 mg/m^2 Decrease oxaliplatin to 50 mg/m^2 Decrease irinotecan to 135 mg/m^2 Add pegfilgrastim 6 mg	Grade 3/4 neutropenia 21% or thrombocytopenia 5% Grade 3/4 fatigue 15.7% CR plus PR 31.7% OS and PFS not reached at 4 months
James et al. [22]	Decrease 5FU bolus 25% Decrease irinotecan 25% Add pegfilgrastim 6 mg	Grade 3/4 neutropenia 17% or thrombocytopenia 11.3% Grade 3/4 fatigue 11.3% CR plus PR 29%

3.23 As discussed above, the skilled person consulting D3 would have been presented with the FOLFIRNOX and mFOLFIRINOX regimens, both of which are said to be safe and effective. Therefore the skilled person would have used the doses of, for example, oxaliplatin, which had been shown in these regimens to be safe and effective – they would have had no motivation to further consult Table 2 of D3. Even if the skilled person had consulted Table 2 of D3, the skilled person would have been faced with a large number of possible modifications, none of which are said to be preferred over the others. Several of the medications given in Table 2 involve reducing the doses of various drugs. However, the skilled person would have been aware of the warning given in Table 1 that reduced doses could result in "*decreased efficacy*". With this in mind, the skilled person would only have used a reduced dose of, for example, oxaliplatin, had there been a strong motivation or suggestion for doing so. Neither D3 nor D1 provides any such motivation, and therefore the skilled person would not have pursued a dose reduction strategy, and certainly not one that would have arrived at the claimed dosages.

3.24 O1 argues that the skilled person would have been led to use reduced doses because "*it belongs to the common general knowledge to reduce the dosages of anticancer drugs when given in combination*"[28]. O1 cites D3, D9, and T2506/12 in support of this. However, this argument is misplaced and is based on a misinterpretation of D3, D9, and T2506/12. In particular, the "*lower*" and "*reduced*" doses for combination therapies mentioned in the cited

[28] O1 submission of 1st February 2022, paragraph 3.4.9.

passages of D9 and T2506/12 are mentioned in the context of dose reductions which take place on going from a monotherapy (i.e. a therapy using a single drug) to a combination therapy (which uses multiple drugs)[29]. For example, if a drug is usually administered at a certain dose when used as a monotherapy, D9 and T2506/12 state that it might sometimes be appropriate to use a lower dose of the same drug when it is administered in a combination therapy. This is totally irrelevant to the present situation because both D1 and D3 relate to four-drug combination therapies – no additional drugs are being added to the combination, and therefore O1 is wrong to argue that the skilled person would have been led to use reduced doses. Moreover, the passage of D3 cited by O1 would only be relevant had the skilled person had particular concerns about very specific side effects. However, D3's general teaching is that both FOLFIRINOX and mFOLFIRINOX are effective and generally safe, and so this passage of D3 would not have led the skilled person to use any reduced dose, and certainly not a reduced dose which is not disclosed or suggested anywhere in D3. This is particularly true in view of the teaching of Table 1 of D2, which would have warned the skilled person that dose reduction might cause "*decreased efficacy*".

3.25 At this point, it should be reiterated that D3 does not disclose "*irinotecan sucrose octasulfate salt liposome injection*", meaning of course that no doses of this drug are disclosed or suggested either. O1 tries to compensate for this by referring to a third document (D5)[30], and then cherry-picking the 80 mg/m^2 (hydrochloride trihydrate salt form, used in the NAPOLI-1 trial) dose which is mentioned therein. The fact that O1 needs to cite a third document in its obviousness arguments demonstrates O1's use of hindsight. In any case, the skilled person would not have consulted this passage of D5 because it is concerned with a second-line therapy[31] rather than a first-line therapy as claimed, and because it refers to a different drug combination to that which is discussed in D3. Further, this passage of D5, and D3, refer to clinical trials which were carried out in different patient populations so, as O1 acknowledges, "*it is not possible to directly compare the results of two different clinical studies* [i.e. those of D3 and D5]*, because of the differences in the patient population*"[32].

3.26 However, even if the skilled person had taken the 80 mg/m^2 dose of liposomal irinotecan from D5 and considered this together with the teaching of Table 2 of D3 which is concerned with regimens which use non-liposomal irinotecan (as O1 suggests), the skilled person would not have been led to the claimed subject matter without hindsight knowledge of the invention. As stated above, neither D3 nor D5 discloses or suggests the administration of a 60 mg/m^2 dose of oxaliplatin together with a 60 mg/m^2 dose of "*irinotecan sucrose octasulfate salt liposome injection*" to treat metastatic adenocarcinoma of the pancreas in the first line. Therefore, the skilled person would not have been led to the claimed subject matter with a reasonable expectation of success.

3.27 O1 seemingly acknowledges the lack of relevant teaching in D3 and D5, and attempts to argue that the claims are obvious notwithstanding this. Specifically, O1 suggests that, by

[29] This point was discussed in detail in the proprietor's response to the oppositions in, for example, paragraphs 5.50 and 5.98.
[30] O1 submission of 1st February 2022, paragraph 3.4.6.
[31] The passage of D5 cited by O1 refers to the "*NAPOLI-1 trial*" in which MM-398, 5-FU, and leucovorin were administered to patients "*refractory to gemcitabine-based therapy*" (D5, page 462 RH column, first complete sentence), i.e. as a second-line therapy.
[32] O1 submission of 1st February 2022, paragraph 3.6.5.

carrying out some manipulation of the percentage values mentioned in Table 2 of D3, one can arrive at the dosage values given in claim 1[33]. It is not possible to provide a full rebuttal to these arguments as O1 has not explained, for example, exactly which calculations need to be performed and exactly which percentage values need to be used in the calculations[34]. O1 indicates that the alleged common general knowledge dose reductions "*necessarily applies to liposomal irinotecan as well*", but (i) does not explain whether this applies to the specific "*irinotecan sucrose octasulfate salt liposome injection*" in the claims, and (ii) provides no evidence to substantiate the assertion about liposomal irinotecan. O1 has also failed to explain exactly how these calculations and values actually lead to the dosages which appear in claim 1. At best, all O1's arguments demonstrate is that one could, using hindsight knowledge of the invention, manipulate dosages disclosed in the prior art in some undisclosed manner to arrive at the dosages claimed. The arguments are therefore not relevant at least because they fail to establish why the skilled person would have been led to the claimed subject matter with a reasonable expectation of success.

3.28 Therefore, O1's latest arguments on inventive step at the filing date fail to advance its case. Therefore, the MR meets the requirements of Article 56 EPC even if the priority claim is invalid.

Inventive step at the earliest priority date

3.29 As explained above, the MR finds basis in P1, and so it is entitled to the earliest priority date. O1 argues that D3 should be taken as the closest prior art. For the reasons given in the response to the oppositions[35], the proprietor disagrees and submits that D10 should be taken as the closest prior art. These arguments will not be repeated here for the sake of brevity, but the proprietor notes that the skilled person would not consider the mFOLFIRINOX regimen as a "concrete starting point"[36] or "the most promising springboard towards the invention"[37], because the mFOLFIRINOX regimen described on page 855 of D3 is only one of "*many modifications*" made to FOLFIRINOX (so is not concretely disclosed), and that this regimen could have a "*loss of efficacy*" (and therefore would not be a promising springboard).

3.30 However, we note that in its submission, O1 has provided a further argument why D3 should be taken as the closest prior art. In particular, O1 argues that because D3 allegedly states that FOLFIRINOX is "*very frequently modified*", D3 should be taken as the prior art because it allegedly provides "*a pointer to another modification, the replacement of conventional irinotecan with liposomal irinotecan*"[38]. However, D3 could not have provided any such pointer because its disclosure is restricted to dosage regimens which use non-liposomal irinotecan, and nowhere in D3 is any kind of liposomal irinotecan disclosed or suggested. In addition, it is not relevant in this case when selecting the closest prior art what the document in question provides a "*pointer*" to (i.e. beyond what is actually disclosed in D3). To the extent that a

[33] O1 submission of 1st February 2022, paragraphs 3.4.11 – 3.4.12.
[34] Additionally, O1 has not reconciled the fact that the three studies relied upon for the dose reductions used in its calculations (Gunturu et al, Metghes et al, and Alessandretti et al) all used 5-FU doses that are different to the claims, rendering this comparison irrelevant to the claimed subject matter.
[35] Response to oppositions, paragraphs 5.6 – 5.10.
[36] See T1194/00, Reasons 3.1. Indeed, O1 appears to acknowledge that this is not a concrete starting point, which it states that D3 discloses the regimen in "more general terms" (O1 submission of 1st February 2022, paragraph 3.5.1).
[37] Case Law of the Boards of Appeal, 9th Edition, 3.4.2.
[38] O1 submission of 1st February 2022, paragraph 3.5.4.

"*pointer*" is relevant at all, it is only relevant in the final stage of the problem-solution approach when one considers whether or not the claimed solution is obvious. This is a further reason why O1's arguments on closest prior art fail.

3.31 Nevertheless, and purely for the sake of argument, the remainder of this section will provide a problem-solution analysis starting from the disclosure of the mFOLFIRINOX regimen disclosed in D3.

3.32 Claim 1 of the MR differs from the mFOLFIRINOX regimen in D3 because:

a. Claim 1 requires the use of "*liposomal irinotecan*", specifically, the use of "*irinotecan sucrose octasulfate salt liposome injection*";

b. Claim 1 requires that this irinotecan sucrose octasulfate salt liposome injection is administered at a dose of 60 mg/m^2; and

c. Claim 1 requires the administration of a 60 mg/m^2 dose of oxaliplatin.

3.33 O1 does not seem to acknowledge that feature b above represents a distinguishing feature over D3. However, O1 has failed to cite any passages of D3 where this feature is disclosed. Therefore, feature b must also be acknowledged as a distinguishing feature.

3.34 As was explained in the response to the oppositions with reference to D18 and D19, the technical effects of these differences are that a more efficacious treatment for metastatic adenocarcinoma of the pancreas in patients that have not previously received chemotherapy for this condition is provided which is acceptably safe and tolerable. Of course, D18 and D19 provide a comparison versus FOLFIRINOX (which uses an identical antineoplastic therapy to mFOLFIRINOX in D3, but also including a 400 mg/m^2 bolus of 5-FU). However, as is clear from page 855 of D3, the removal of the bolus of 5-FU in mFOLFIRINOX is for improvements over FOLFIRINOX in safety only. Additionally, it is reported in D3 that removal of the 5-FU bolus could in fact lead to "loss of efficacy" (c.f. FOLFIRINOX)[39]. Therefore, the improvement in treatment efficacy demonstrated between the claimed regimen and D10 would also be demonstrated between the claimed regimen and the mFOLFIRINOX regimen in D3. Indeed, if the removal of the 5-FU bolus results in a loss of efficacy, the claimed regimen could be comparatively even more efficacious over mFOLFIRINOX than over FOLFIRINOX. Therefore, the objective technical problem can be formulated as the provision of a more efficacious treatment for metastatic adenocarcinoma of the pancreas in patients that have not previously received chemotherapy for this condition which is acceptably safe and tolerable[40].

3.35 In its submission, O1 argues that the objective technical problem must be formulated less ambitiously. The proprietor disagrees and will address O1's arguments on this point later in this submission. However, purely for the sake of argument, and without conceding to any of the points made by O1, we will assume in the following section that the objective technical problem is formulated less ambitiously as the provision of a safe and effective treatment for metastatic adenocarcinoma of the pancreas in patients who have not previously received chemotherapy for this condition.

[39] D3, page 855, left-hand column, second paragraph.
[40] Response to oppositions, paragraphs 5.13 – 5.27.

3.36 The skilled person starting from D3 and faced with this less ambitious objective technical problem would still not have been led to the claimed subject matter with a reasonable expectation of success. O1 is wrong to argue otherwise, as will be explained below.

3.37 O1's arguments on obviousness begin by relying on the disclosure of D18[41]. However, D18 is not prior art and is therefore irrelevant to the assessment of obviousness. O1's reliance on D18 here is indicative of the hindsight-riddled analysis that permeates O1's most-recent submission.

3.38 O1 then moves on to D2, which refers only to "*MM-398*", and does not disclose or suggest the use of "*irinotecan sucrose octasulfate salt liposome injection*". O1 attempts to compensate for this deficiency in D2 by citing D17 and D25[42]. However, D17 discloses several different liposomal formulations, and does not mention "*MM-398*" at all, and so it would not have assisted the skilled person had they, for example, consulted D17 in an effort to establish what the "*MM-398*" referred to in D2 is. D25 (should it be admitted) does mention "*MM-398*". However, D25 equates "*MM-398*" with "*Nanoliposomal CPT-11*", and D25 also defines "*CPT-11*" as irinotecan hydrochloride[43]. So, had the skilled person looked to D25 to determine what "*MM-398*" is, they would, if anything, have concluded that "*MM-398*" is a liposomal form of irinotecan hydrochloride. Nowhere in D25 is the use of "*irinotecan sucrose octasulfate salt liposome injection*" disclosed or suggested. Therefore, O1's argument fails.

3.39 On this point, it should also be noted that O1 is attempting to rely on no fewer than four prior art documents in its inventive step attack – D3 (which O1 believes is the closest prior art), D2, D17, and D25. Even after making this four-way combination of documents, O1 has failed to establish that the skilled person would have been led to a solution which requires the use of "*irinotecan sucrose octasulfate salt liposome injection*", and has failed to point to any teaching which would have led the skilled person to a 60 mg/m^2 dose of this drug and a 60 mg/m^2 dose of oxaliplatin. Again, these arguments demonstrate that O1's analysis is based on nothing more than hindsight knowledge of the claimed invention.

3.40 O1 also cites the preclinical data which is discussed in D25 and D27[44], and argues that these disclosures would have led the skilled person to conclude that a dosage regimen using the "*MM-398*" (referred to in D25) or the "*Nal-IRI*" (referred to in D27) would have resulted in improved safety and efficacy[45]. These arguments relying on D25 and D27 (should they be admitted) fail however at least because the preclinical studies cited by O1 are preclinical studies of "*MM-398*" / "*Nal-IRI*" as a monotherapy (not in combination with oxaliplatin, 5-FU, and leucovorin), and there is no justification for stating that the conclusions drawn in these monotherapy experiments would also apply for a four-drug combination therapy. Moreover, the alleged improvements reported in these clinical studies are improvements relative to non-liposomal irinotecan monotherapy and not, for example, FOLFIRINOX or mFOLFIRINOX, which O1 believes must be taken as the closest prior art. Thus, these studies would not have instilled the skilled person with a reasonable expectation that a therapy using "*MM-398*" / "*Nal-IRI*" would have shown improved safety and efficacy.

[41] O1 submission of 1st February 2022, paragraph 3.7.2.
[42] O1 submission of 1st February 2022, paragraph 3.7.3.
[43] D25, page 188, RH column, Heading and first sentence following heading.
[44] The proprietor's comments in 3.5 above, in respect of D25, apply *mutatis mutandis* to D27.
[45] O1 submission of 1st February 2022, paragraphs 3.7.4 and 3.7.5.

3.41 However, even if these preclinical results had led the skilled person to use of "*MM-398*" / "*Nal-IRI*" with a reasonable expectation of providing improved safety and efficacy (which is not conceded), the skilled person would have been at a loss as to how to administer or dose "*MM-398*" / "*Nal-IRI*", how frequently to administer it, and whether any additional drugs should be co-administered with it. As discussed above at paragraphs 3.17 – 3.27, the skilled person would not have been led to use a dose of, for example, 60 mg/m^2 of oxaliplatin, or a 60 mg/m^2 dose of "*irinotecan sucrose octasulfate salt liposome injection*" with a reasonable expectation of success. It should again be emphasised that O1 has failed to cite anything in the prior art which would have led the skilled person to either of these doses, and certainly not both of them in combination.

3.42 Therefore, if the priority claim is valid (which it is), the skilled person would not have been led to the claimed subject matter with a reasonable expectation of success even if the objective technical problem is formulated less ambitiously as set out in 3.35. The MR therefore meets the requirements of Article 56 EPC.

3.43 Of course, the proprietor's position, as set out in 3.34, is that the objective technical problem should be formulated as the provision of a more efficacious treatment. Therefore, on this basis, the skilled person certainly would not have been led to the claimed subject matter with a reasonable expectation of providing this improved treatment, because there was no pointer in the prior art to the features of the claims, and nothing to suggest that the claim features would provide a more efficacious treatment.

It is permissible to formulate the objective technical problem as the provision of an improvement

3.44 It was explained in detail with reference to D18 and D19 in the response to the oppositions that the claimed subject matter is improved relative to FOLFIRINOX (D10), and these arguments will not be repeated here purely for the sake of brevity[46]. However, O1 argues that it is not permissible to formulate the objective technical problem as an improvement. O1 is wrong here, and it will be explained below that it has been made credible that the claimed subject matter is improved over FOLFIRINOX.

3.45 O1 suggests that no conclusions about efficacy can be drawn from D18 because its primary objectives were "*safety and tolerability*"[47]. However, O1 omitted to mention that efficacy was a secondary objective of the study. In addition, the efficacy data resulting from D18 were sufficient to make a comparison with the FOLFIRINOX regimen described in D10, which was outlined in the discussion section of D18, thus confirming that the present efficacy comparison is entirely valid.

3.46 O1 then goes on to cite passages of D18 which allegedly demonstrate that no comparisons can be made between FOLFIRINOX and the claimed subject matter[48]. However, O1's arguments ignore several important points, most notably the subgroup analysis given in D19 which demonstrates that, even when patients without metastatic disease are removed from the analysis, the NALFIRINOX regimen still shows a median progression-free survival (PFS)

[46] Of course, and as mentioned above in 3.34, the claimed subject matter is improved relative to mFOLFIRINOX (D3) should this be considered the closest prior art, which the proprietor disputes.
[47] O1 submission of 1st February 2022, paragraph 3.6.4.
[48] O1 submission of 1st February 2022, paragraph 3.6.5.

of 9.2 months (95% CI: 7.69-11.96) and an overall survival (OS) of 12.7 months (95% CI: 8.74-19.12). That is, if the analysis is restricted to patients with metastatic disease, it remains the case that there was a numerical improvement in PFS and OS when patients were treated according to claim 1 compared to when patients were treated with the prior art FOLFIRINOX regimen. Furthermore, the passage of D18 (page 21, left-hand column, last paragraph) cited by O1 indicates that it is the safety of NALIRIFOX that cannot be reliably compared with that of established therapies without head-to-head studies. O1 will appreciate that it is the efficacy that has been compared, and upon which the improved objective technical problem is based.

3.47 In addition, in the passages of D18 relied on by O1, the authors of D1 are discussing comparisons between data sets in the strict, clinical sense. These criteria are far more stringent than those imposed by the problem-solution approach, which only requires that an alleged advantage or improvement be **credible** on the basis of the evidence on file. In this case, the numerical improvements seen in PFS and OS, and the fact that these improvements are still seen in the subgroup analysis, demonstrate that the claimed subject matter is associated with a credible improvement.

3.48 Turning to the two specific points raised by O1, D18 notes slight differences in the proportions of patients with liver metastases (43.8% for NALIRIFOX (D18) and 87.6% for FOLFIRINOX (D10)), and a minor difference in median ages (58 for NALIRIFOX (D18) and 61 for FOLFIRINOX (D10)). Regarding the difference in patients with liver metastases, when removing the 3 non-metastatic patients from the D18 cohort (who, by definition, cannot have liver metastases), 48.3%[49] of the D18 population had liver metastases, diminishing the difference to the 87.6% with liver metastases in D10. For both differences, they are merely factors of the trial design which cannot, on grounds of ethics, select only certain patients for treatment in order to make comparisons with earlier trials. Furthermore, there is no attributed significance to either of these differences in D18, in any case, beyond being noted as "important differences", and therefore absent any indication of why these differences are important, they do not call into question the improved technical effect.

3.49 Finally, O1 attempts to discredit the contents of declaration D19, on the basis that it is written by the vice president and global asset lead of the patentee. The data presented in D19 represents a subset of the D18 data, and includes commentary to explain this subset. The fact that O1 has not been able to state any reasons why D19 should not be treated as simple factual evidence that confirms the improvement shown in D18, and has certainly provided no evidence to the contrary, demonstrates that O1 ultimately concedes that D19 allays any concerns about the differences between the metastatic population in D18 and D10.

3.50 Therefore, contrary to the arguments of O1, it is permissible to formulate the objective technical problem as an improvement.

Inventive step - conclusion

3.51 It has been demonstrated above that, regardless of whether the objective technical problem is formulated ambitiously or unambitiously, or whether or not the priority claim is valid, that the

[49] This is the same as the population in D19: 14 of the 32 total pooled population in D18 had liver metastases (i.e. 43.8%), so removing the 3 non-metastatic patients from this analysis results in 14 of the 29 subgroup population in D19 with liver metastases (i.e. 48.3%).

skilled person would not have been led to the claimed subject matter. Therefore, the requirements of Article 56 EPC are met.

4 AUXILIARY REQUESTS - RULE 80 EPC

4.1 O1 alleges that the three auxiliary requests (AR1-3) filed with the response to oppositions cannot comply with the requirements of Rule 80 EPC, because the patentee provided "no arguments in this respect"[50]. This is not correct: at least section 6 of the response to oppositions provides adequate reasoning as to why these amendments comply with Rule 80 EPC. Nevertheless, for the OD's convenience, further comments are included below.

4.2 In 6.4 of the response to oppositions, the proprietor outlined why AR1 confirms P1 priority entitlement and thus improves the proprietor's position on inventive step. This, combined with the comments in 4.21 and 4.22 of the response to oppositions in respect of P1 priority entitlement when starting from claim 22 of P1, provides a full explanation of compliance with Rule 80 EPC.

4.3 In AR2, all of the dependent claims as granted are deleted. No attack was raised by O1 in either its opposition of its submission of 1st February 2022 against P1 priority entitlement of the dependent claims (N.B. this attack was also not raised by O2). However, analogous arguments to those presented against claim 1 could have been made against the P1 priority entitlement for the dependent claims and on that basis, a lack of inventive step could have been pleaded against any of the dependent claims, separately to claim 1. Thus, in order to strengthen P1 priority entitlement, and to avoid lack of inventive step attacks on this basis, the dependent claims as granted have been deleted in AR2. Therefore, this amendment strengthens the proprietor's position on Article 56 EPC, and thus is occasioned by a ground of opposition. The requirements of Rule 80 EPC are met.

4.4 AR3 is a combination of AR1 and AR2 and therefore Rule 80 EPC is complied with for the reasons mentioned above.

[50] O1 submission of 1st February 2022, paragraph 4.3.

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ARTICLE

Population pharmacokinetics of liposomal irinotecan in patients with cancer and exposure–safety analyses in patients with metastatic pancreatic cancer

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Abstract

Liposomal irinotecan is a liposomal formulation of irinotecan, which prolongs circulation of irinotecan and its active metabolite SN-38. A population pharmacokinetic (PK) model was developed based on data from seven studies ($N = 440$). Adequacy of the model was assessed using multiple methods, including visual predictive check. Associations between PK exposure and the incidence of diarrhea (grade ≥3) and neutropenia adverse events (AEs) (grade ≥3) at first event in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) were investigated using logistic regression based on data from two studies (the phase III NAPOLI-1 [$N = 260$] and phase I/II NCT02551991 [$N = 56$] trials). The PKs of total irinotecan was described by a two-compartment model with first-order elimination, with SN-38 formed directly by a first-order constant from the central compartment of irinotecan or after using a transit compartment. Clearance was 17.9 L/week (0.107 L/h) and 19,800 L/week (118 L/h) for total irinotecan and SN-38, respectively. The UGT1A1*28 7/7 homozygous genotype had no significant impact on SN-38 clearance. Model evaluation was satisfactory for both irinotecan and SN-38. The incidence of diarrhea (grade ≥3) at first event was significantly higher with increasing average concentrations of total irinotecan and SN-38; there was no significant association between an increased risk of neutropenia AEs (grade ≥3) at first event and average SN-38 concentrations. In summary, the PKs of total irinotecan and SN-38 after administration of liposomal irinotecan were well-described by the model. The UGT1A1*28 status had no significant impact on the PKs of liposomal irinotecan.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Liposomal encapsulation prolongs the circulation of irinotecan and its active metabolite SN-38, and previous population pharmacokinetic (PK) analyses have

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CSPC Exhibit 1120
Page 46 of 447

identified the main covariates affecting the PK profile. Irinotecan and SN-38 were characterized by two independent population PK models with the assumption of encapsulated and unencapsulated SN-38 based on in vitro data for the metabolite.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to improve characterization of liposomal irinotecan PKs by developing a joint parent-metabolite model in 440 patients and identify covariates (including, for the first time, oxaliplatin co-administration) that affect total irinotecan (encapsulated and unencapsulated) and SN-38 exposure. The associations between estimated PK exposure metrics and key safety endpoints (grade ≥3 diarrhea and neutropenia adverse events [AEs]) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) were also investigated.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study confirms that UGT1A1*28 status had no significant impact on the PKs of liposomal irinotecan. In patients with mPDAC (first line or second line), there were significant associations between total irinotecan and SN-38 exposure and diarrhea (grade ≥3), but not between SN-38 exposure and neutropenia AEs (grade ≥3). Oxaliplatin co-administration seems to have an impact on both total irinotecan and SN-38 exposures.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

There is insufficient evidence to suggest a need for dose adjustments of liposomal irinotecan based on UGT1A1*28 genotype, similar to low doses of non-liposomal irinotecan.

INTRODUCTION

Worldwide, pancreatic cancer is the seventh most common cause of cancer-related death and remains an exception to the general trend for improvements in cancer-related mortality.[1,2] Current recommendations for the first-line (1L) treatment of metastatic pancreatic cancer include gemcitabine-based therapy and, more recently, the FOLFIRINOX regimen (5-fluorouracil [5-FU]/folinic acid [leucovorin (LV)]/irinotecan/oxaliplatin).[3,4]

Liposomal irinotecan (ONIVYDE; historical names include nal-IRI, MM-398, and PEP02), in combination with 5-FU/LV, is a recommended treatment option for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy, based on the results of the phase III NAPOLI-1 trial.[4,5] The active drug, irinotecan, and its metabolite, SN-38, which is 100- to 1000-fold more active than irinotecan, bind reversibly to the topoisomerase 1 DNA complex and prevent religation of the single-strand breaks, causing double-strand DNA damage and preventing replication, thereby arresting uncontrolled cell growth.[6–8] SN-38 is cleared via glucuronidation in the liver, primarily by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and then by biliary excretion.[6,7] Studies in patients treated with non-liposomal irinotecan suggest that UGT1A1*28 7/7 homozygosity (prevalence, 13% and 5% in the White and Asian populations, respectively[9]) is associated with increased SN-38 concentrations, which are linked to higher incidence of hematological toxicity than other genotypes, and that these associations are dose-dependent.[10–13]

With liposomal irinotecan, a lipid bilayer vesicle encapsulates irinotecan, protecting it from hydrolysis and rapid metabolic conversion, leading to prolonged systemic circulation.[14] In a re-analysis of data from a phase II trial in patients with gastric cancer, the geometric mean irinotecan maximum plasma concentration (C_{max}), area under the plasma concentration–time curve (AUC), and half-life were 13.4, 46.2, and two times higher, respectively, with liposomal irinotecan 100 mg/m^2 free base (120 mg/m^2 irinotecan hydrochloride trihydrate) every 3 weeks compared with non-liposomal irinotecan 260 mg/m^2 free base (300 mg/m^2 irinotecan hydrochloride trihydrate) every 3 weeks.[15] The liposomal formulation also facilitates targeted delivery of the drug to solid tumors. In mouse pancreatic tumor models, liposomal irinotecan improved delivery of the active drug to tumors, compared with non-liposomal irinotecan, and was taken up by tumor-resident macrophages and tumor/stromal cells and locally converted to SN-38.[16,17] Furthermore, DNA damage was mostly observed in tumor cells, including those outside of the liposomal deposition area, with only minimal DNA damage and apoptosis in non-tumor cells.[16,17]

In the phase III trial, NAPOLI-1 (NCT01494506), liposomal irinotecan + 5-FU/LV significantly increased both

CSPC Exhibit 1120
Page 47 of 447

median overall survival and progression-free survival compared with 5-FU/LV alone in patients with mPDAC that had progressed after previous gemcitabine-based therapy.[18,19] The most common treatment-emergent adverse events (AEs) of grade 3 or greater liposomal irinotecan + 5-FU/LV in the final analysis of NAPOLI-1 were neutropenia (32%, which also included decreased neutrophil count, neutropenic sepsis, and febrile neutropenia), fatigue (14%), diarrhea (13%), and vomiting (12%).[19] One-year follow-up data from a phase I/II dose-exploration and dose-expansion trial (NCT02551991) of 1L liposomal irinotecan + 5-FU/LV + oxaliplatin in patients with mPDAC who had not previously received treatment in the advanced/metastatic setting showed that treatment-emergent AEs of grade 3 or greater were reported in 22 of 32 patients (68.8%), with neutropenia being the most common (31.3%).[20]

A population pharmacokinetic (PK) model was previously developed in order to describe the PKs of liposomal irinotecan and SN-38 independently and to assess associations between derived PK parameters and safety outcomes.[15] In the present study, this model was re-assessed by jointly analyzing concentrations of total irinotecan (encapsulated and unencapsulated) and SN-38 with the inclusion of data from the phase I/II 1L mPDAC dose-exploration and dose-expansion trial. The associations between post hoc estimated PK exposure metrics and key safety endpoints (grade ≥3 diarrhea and grade ≥3 neutropenia AEs at first event) in the NAPOLI-1 and phase I/II 1L mPDAC trials were also investigated.

METHODS

Study data

The population PK analysis was based on data from seven clinical trials, including the phase III NAPOLI-1 trial (NCT01494506), the phase I/II 1L mPDAC study (NCT02551991), and five phase I/II studies in patients with solid tumors (PEP0201, NCT02884128, NCT00813072, NCT00940758, and NCT01770353; Table 1). The design, patient population, and results for each of these studies have been described previously.[6,19–25] The exposure–safety analyses were based on a subset of data focused on patients with mPDAC from the NAPOLI-1 trial and the phase I/II 1L mPDAC study.

The timing and frequency of PK sampling varied among the seven studies, with samples collected at between four and 13 time points, and up to 8 or 15 days postdose or at end of treatment (Table 1). Plasma samples were analyzed to determine concentrations of total (encapsulated and unencapsulated) irinotecan and SN-38 using validated, specific, and sensitive liquid chromatography–mass spectrometry methods, with lower limits of quantification (LLOQs) varying between analytes and within and across studies (0.002–1 μg/mL for irinotecan and 0.441–1 ng/mL for SN-38).

Data management procedures were performed using SAS (version 9.4; SAS-Institute) and R (versions 3.5.2 and 3.5.3; R Development Core team, Foundation for Statistical Computing). The population PK analysis data set included full study data from all seven studies and contained both parent (irinotecan) and metabolite (SN-38) plasma concentration data in mass and molar units, patient characteristics, and additional relevant covariates. Patient characteristics and covariates are shown in Table S1. Actual concentrations of total irinotecan, as the free base (molecular weight of 586.678 g/mol), were used.

Population PK model development

Prior to model development, the PK data were explored by visually inspecting the following profiles/plots created using R (version 3.5.3): dose-normalized concentration–time profiles of total irinotecan and SN-38, overall and stratified by study; percentage of data below the LLOQ for each analyte, overall and by study; incidence of categorical covariates (i.e., gender, race, liver metastasis at baseline, UGT1A1*28 genotyping, manufacturing site, and tumor location at baseline) via bar charts, overall and by study; distribution of continuous covariates (i.e., weight, body surface area, age, creatinine clearance, and alanine aminotransferase [ALT], aspartate transaminase [AST], albumin, and bilirubin levels) via histograms, overall and by study; and potential correlations among covariates. Exploratory graphical evaluations of the data were performed to detect outlier observations or individuals, to guide the selection of an initial structural model, and to identify important features to be considered in the development of the base model.

PK data were analyzed using nonlinear mixed effects modeling (NONMEM) software (version 7.4.1; ICON Development Solutions), running under PsN (Perl-speaks-NONMEM) 4.8.1 on a grid of CentOS Linux servers, and the Intel Fortran compiler, version 12.0.4 (Intel Corporation). Graphical analysis was performed using R.

PK parameters for total irinotecan and SN-38 following liposomal irinotecan administration were estimated jointly using NONMEM. The first-order conditional estimation method with the INTERACTION option was used for all model runs.

Base model

Two- and three-compartment linear disposition models were investigated for total irinotecan, which was assumed

TABLE 1 The seven liposomal irinotecan clinical trials included in the population PK analysis

Study	Phase	Population	N	Liposomal irinotecan dose, mg/m^2 [a]	Concomitant drugs	PK sample collections
PEP0201[6]	1	Various tumor types	11	50, 100, or 156 Q3W	None (monotherapy)	Cycle 1: 0 (predose), 0.5, 1.0, 1.5, 2.5, 3.5, 4.5, 7.5, 10.5, 13.5, 25.5, 49.5, 73.5, and 169.5 h after drug infusion. Cycle 2: 0 (predose)
PEP0203 (NCT02884128)[21]	1	Various tumor types	16	50, 70, 85, or 100 Q3W	5-FU/LV	Cycle 1: 0 (predose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5, and 169.5 h after drug infusion. Cycle 2: 0 (predose)
PEP0206 (NCT00813072)[22]	2	Various tumor types	37	100 Q3W	None (monotherapy)	Cycle 1: 0 (predose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5, and 169.5 h after drug infusion. Cycle 2: 0 (predose)
PIST-CRC-01 (NCT00940758)[23]	1	Metastatic colorectal cancer	18	70, 80, 85 Q2W	None (monotherapy)	Cycle 1: 0 (predose), 0.5, 1.0, 1.5, 2.5, 4.5, 10.5, 25.5, 49.5, 73.5, and 169.5 h after drug infusion.
CITS (NCT01770353)[24]	1	Various tumor types	42	35, 50, 70 Q2W	None (monotherapy)	Cycle 1 (pilot): 0 (predose), 1.5, 3.0, 72.0, 168.0 and 336.0 h Cycle 2 (expansion): 0 (predose), 1.5, 3.0, 48.0, 168.0 and 336.0 h
NAPOLI-1 (NCT01494506)[18,19]	3	mPDAC	260	70 Q2W or 100 Q3W	None (monotherapy) or 5-FU/LV	Cycle 1: 0 (predose), 1.5, 2.5, 48.0 (arm 3 only) and 168.0 h
NCT02551991[20,25]	1/2	mPDAC	56	50, 55, or 70 Q2W	5-FU/LV + oxaliplatin	Cycle 1: 0 (predose), 1.5, 6.0, 48.0, 169.5, 336.0 h and end of treatment

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks.

[a]Expressed as free base.

CSPC Exhibit 1120
Page 49 of 447

to be converted into SN-38. One- and two-compartment linear disposition models were investigated for SN-38, with part of irinotecan total elimination clearance forming SN-38. The central volume of distribution of SN-38 had to be assumed equal to the central volume of distribution of irinotecan to prevent identifiability issues. Interindividual variability (IIV) was modeled assuming a log-normal distribution for patient-level random effects (equation is provided in the Supplementary Material).

Residual unexplained variability (RUV) was tested as additive, proportional, or combined (additive + proportional) on the dependent variable (equation for the combined RUV is provided in the Supplementary Material).

Correlations among the IIV of various parameters were also investigated by including additional off-diagonal elements to the OMEGA (Ω) matrix to test correlation between random effects.

For hierarchical (or nested) models, the significance of adding or removing a parameter was assessed using the likelihood ratio test (LRT). For non-nested models, the Akaike information criterion (AIC) and/or the Bayesian information criterion (BIC) were used to compare models following the principle that the lower the AIC and/or BIC, the better the model.

Covariate model building

Covariate analysis was conducted to explain the variability in total irinotecan and SN-38 concentrations. Covariates examined included: the continuous covariates age, body size (body weight, height, body mass index, or body surface area), dose, liver function tests (e.g., ALT, AST, bilirubin, and albumin), and creatinine clearance; and the categorical covariates gender, race, concomitant therapy (i.e., 5-FU/LV and oxaliplatin), and UGT1A1*28 polymorphism. A stepwise covariate model-building approach was applied to the final base joint PK model using an iterative addition and deletion model selection strategy, based on the LRT (p forward = 0.05 and p backward = 0.005).

Continuous covariates were included in the population PK model as power functions, whereas categorical covariates were implemented as factors (equation is provided in the Supplementary Material).

Final model

Following completion of the covariate model building, further model refinements were evaluated. These included evaluation of the residual error structure, assessment of off-diagonal elements of the Ω block to check the need for all included correlations, and a last attempt to account for data below the LLOQ for both analytes. Initially, below limit of quantification (BLOQ) samples were excluded from the analysis (M1 method). However, there are some instances in which their exclusion can bias PK parameter estimates (e.g., if the proportion of BLOQ samples is high). Therefore, initial models were also evaluated to include BLOQ samples and the likelihood methodology (i.e., "M3"[26,27]) was used. With the M3 method, the likelihood is maximized for all the data considering different LLOQ values across studies and the BLOQ data are treated as censored. The impact of including the BLOQ samples on the overall goodness-of-fit (visual predictive check [VPC]) and parameter estimates was assessed.

Model evaluation

In accordance with industry guidelines,[28,29] the performance of the final population PK model was evaluated using several methods, including goodness-of-fit plots, prediction-corrected VPCs (pcVPCs), and uncertainty assessment of PK parameter estimates.[28–30]

The goodness-of-fit plots comprised: observed concentrations versus population-predicted concentrations and individual-predicted concentrations, with line of identity and trend line; conditional weighted residuals versus population-predicted concentrations, with zero line and trend line; and conditional weighted residuals versus time after dose, with zero line and trend line. Based on the population PK parameter estimates of the final population PK model, time profiles of concentrations of the analytes were simulated in 1000 replicates. Within each bin, 95% prediction intervals of the 2.5th, 50th, and 97.5th percentiles of simulated concentrations were computed across the 1000 replicates and compared with the 2.5th, 50th, and 97.5th percentiles of observed concentrations.

Finally, the robustness of the final population PK model was evaluated by a nonparametric bootstrap procedure. This model evaluation consisted of repeatedly fitting the model to 1000 data sets replicated by randomly sampling individual patient data (including concentration–time data, dosing history, and covariates) with replacement from the original analysis data set. Parameter estimates obtained from the original dataset were compared with the median and 95% confidence intervals derived from a bootstrap based on 1000 replicated data sets.

Drug exposure derivation

The final population PK model was used to derive individual PK parameters. Maximum concentration at steady state ($C_{max,ss}$), C_{max} at first AE, AUC at steady-state during

the dosing interval ($AUC_{ss,tau}$) and AUC_{tau} at first AE were derived from noncompartmental analysis applied to concentration simulated at steady state or at first AE using the final population PK model, by considering individual PK primary parameters and by applying simulation time steps (0, 0.5, 1, 1.5, 2.5, 5.5, 12, 24, 48, 72, 96 to 144, 192, 240, 288, 336, 384, 432, 480, and 504 h). The dosing interval (tau) could be once every 2 or 3 weeks, depending on the study. Average concentration (C_{avg}) was calculated as the ratio between $AUC_{ss,tau}$ or AUC_{tau} at first AE and the relative dosing interval (tau). These parameters were then used for the exposure–safety analyses.

Exposure–safety analyses

Logistic regression analyses were conducted to assess the relationship between exposure and the two safety end points, diarrhea (grade ≥3) and neutropenia AEs (grade ≥3), for all patients receiving liposomal irinotecan-based regimens, in the NAPOLI-1 trial and the phase I/II 1L mPDAC trial. Neutropenia AEs were defined as neutropenia, decreased neutrophil count, and febrile neutropenia (umbrella approach). Only the earliest event (if any) for each patient and each endpoint was reported in the logistic regression analysis data set. Both data sets were then enriched with all the covariates included in the population PK data set.

The relationships between C_{avg} at steady state ($C_{avg,ss}$) or C_{avg} at first AE for total irinotecan and SN-38 and the probability of diarrhea (grade ≥3) and neutropenia AEs (grade ≥3) at first event were assessed with the logistic regression models and the glm function in R, as performed in a previous analysis.[17] The alternative exposure parameters ($C_{max,ss}$ or C_{max} at first AE) were also considered. Logistic regression models were each time applied to exposure metrics or log-transformed exposure metrics in order to improve handling of a wide number of exposure metrics.

RESULTS

Observed data

For the PK analysis, data were available for a total of 440 patients from seven studies (Table 1). These patients received liposomal irinotecan at dose regimens ranging from 35 mg/m^2 free base (40 mg/m^2 irinotecan hydrochloride trihydrate) every 2 weeks to 156 mg/m^2 free base (180 mg/m^2 irinotecan hydrochloride trihydrate) every 3 weeks. Overall, 51% (226/440) of patients were men and 35% (154/440) of patients were Asian. The incidence of the UGT1A1*28 homozygous 7/7 genotype was 6.1% across all studies.

Overall, there were 5735 observations: 2879 for total irinotecan and 2856 for SN-38, of which 23% and 25% of values, respectively, were below the LLOQ; 16 observations (9 for total irinotecan and 7 for SN-38) corresponded to unexpected quantifiable predose levels and were excluded. The remaining 1887 and 1827 observations for total irinotecan and SN-38, respectively, were included in the population PK model. Exploratory plots of total irinotecan and SN-38 plasma concentration–time profiles normalized by actual doses are presented by study in Figure S1.

Population PK model and derived parameters

Initially, irinotecan alone (molar unit) was modeled to identify the best base structural model between two and three compartments: a two-compartment structural model was more stable and was statistically more significant than a three-compartment model. A joint model of irinotecan and SN-38 (both in molar units) was explored assuming two compartments for irinotecan and exploring whether one or two compartments were needed for SN-38. One compartment was selected for SN-38. Several approaches were implemented to try to capture the multiple peaks in SN-38. The Adiwijaya model,[15] which added an impurity term to account for the quick peak in the SN-38 profile, was investigated without success, affecting the structural model of irinotecan. An enterohepatic recycling model and a model fixing the fraction of irinotecan converted to SN-38 (0.15)[31] were tested but both had poor fitting and parameter estimates. The final population PK model for total irinotecan after administration of liposomal irinotecan comprised two compartments for irinotecan and one compartment for SN-38, with linear transformation of parent to metabolite through two metabolic pathways: one direct with a first-order constant from the central compartment of irinotecan (9%) and one delayed via a transit compartment (35%; Figure 1). Considering M3 methods with the base model (without covariates), no impact on goodness-of-fit plots and parameter estimates were observed except a large increase in relative standard errors and model instability compared with the M1 method (i.e., a lower rate of successful minimizations and covariance steps). Additional VPCs for the model using the M3 method were performed by considering the proportion of BLOQ samples. Because LLOQ values differed between studies, VPCs were split by LLOQ values. For irinotecan, considering the highest LLOQ value (1 μg/mL), the proportion of predicted BLOQ samples was higher than the observed number of BLOQ samples (Figure S2). A table comparing the base model with M1 and M3 methods

CSPC Exhibit 1120
Page 51 of 447

is provided in the Supplementary Material (Table S2). Owing to the large residual standard error (RSE; >1000%) obtained with the run using the M3 method, no statistical differences were found for all fixed parameters (except for total irinotecan clearance [CLP]). The high RSE values of the distribution parameters for irinotecan obtained with the M3 method suggested that irinotecan should be defined by one compartment. However, this is not aligned with the two compartments found when irinotecan data were first analyzed, or with data reported in the literature.[31] Thus, owing to the lack of accuracy of estimates in NONMEM (even after trying several reruns by changing initial estimates using the "retries" function in Psn), it was decided to continue covariate model building (stepwise covariate modeling process) without retaining BLOQ samples by applying the M1 method.

Total irinotecan clearance was estimated at 17.9 L/week and was 20% higher in Asian patients than in individuals of other ethnicities (Table 2). Central and peripheral volumes of distribution were 4.09 L and 0.421 L, respectively, and distribution of the total irinotecan volume increased with increasing body surface area. Clearance of SN-38 was estimated to be 19,800 L/week; high bilirubin levels were associated with low SN-38 clearance. Clearances of both total irinotecan and SN-38 were 20% lower in women than in men. Co-administration of oxaliplatin was associated with an increase in clearance of total irinotecan of ~34% and a decrease of equivalent magnitude in clearance of SN-38. Drug manufacturing site (previous site vs. current site) was associated with a 37.6% increase in the fraction of liposomal irinotecan elimination feeding the transit compartment, a 12.8% decrease in irinotecan central volume of distribution, and a 51.5% increase in irinotecan total elimination clearance. Liposomal irinotecan manufactured at the previous site was used in phase I studies conducted before 2012; liposomal irinotecan manufactured at the current site was used in all pivotal studies (e.g., NAPOLI-1 and phase I/II 1L mPDAC study).

There was no significant association between UGT1A1*28 polymorphism (homozygous 7/7 vs. others) and SN-38 clearance based on the LRT. Box plots of SN-38 clearance by UGT1A1*28 polymorphism (homozygous 7/7 and others) are shown in Figure 2. The final NONMEM code is available in Supplementary Materials.

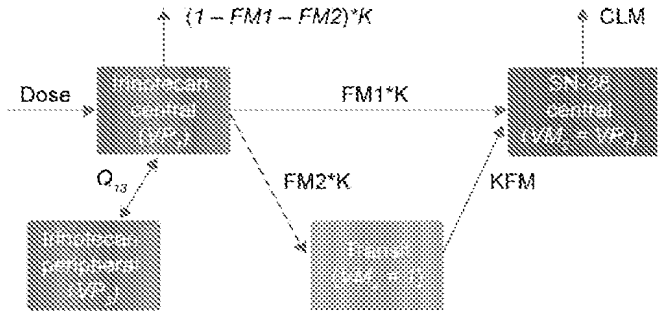

FIGURE 1 Structural population PK model for irinotecan and SN-38 after administration of liposomal irinotecan. CLM, SN-38 clearance; K, irinotecan total clearance/irinotecan central volume; FM1, fraction of irinotecan metabolized via first-order process; FM1*K, fraction of total clearance to SN-38 (first-order); FM2, fraction of irinotecan metabolized via transit; FM2*K, fraction of total clearance to SN-38 (transit); $(1 - FM1 - FM2)*K$, fraction of total clearance not transformed to SN-38; KFM, rate of transformation after delay; PK, pharmacokinetic; Q_{13}, intercompartmental clearance; VP_1, irinotecan central volume; VP_3, irinotecan peripheral volume; VM_2, SN-38 central volume (fixed to VP_1); VM_4, transit compartment

Model evaluation

Goodness-of-fit plots for the final model were in line with expectations and confirmed the appropriateness of the selected model for both total irinotecan and SN-38 (Figure S3). Relative standard errors for all model parameters were below 50%, indicating good precision.

The pcVPCs were satisfactory for both total irinotecan and SN-38, and were considered to describe the variability well overall (Figure 3 and Figure S4) and by study (Figure S5). However, it appeared that the model did not properly describe the high concentrations of SN-38, mainly in the fifth percentile. Of the 1000 bootstrap runs, 721 minimized successfully; all parameter estimates from the model were consistent with the relative median values and fell within 95% confidence intervals of the bootstrap parameter estimates, indicating robustness and stability of the model (Table S3). Thus, the model was considered acceptable for its intended purpose, which was to predict exposures in patients with mPDAC for the exposure–safety analyses. Caution is required regarding the risk of underprediction of SN-38 C_{max}.

Exposure–safety analyses

The data set for exposure–safety analyses included 316 patients (260 from NAPOLI-1 and 56 from the phase I/II 1L mPDAC study) and 316 observations. For each safety parameter examined, no difference was found between $C_{max,ss}$ and C_{max} at first AE; the same was observed for C_{avg} as detailed in the Supplementary Material (Figures S6 and S7). Thus, only derived exposure metrics at steady state are presented in this analysis. Additional logistic regression plots are also provided in the Supplementary Material comparing exposure metrics and log-transformed exposure metrics (Figures S8–S15). The same conclusions were obtained from both approaches.

CSPC Exhibit 1120
Page 52 of 447

TABLE 2 Estimated population PK parameters from the final model

Parameter	Estimate	RSE, %	IIV (% CV)	RSE, % of variance
Irinotecan total clearance, L/week	17.9	5.14	0.545 (85.2)	11
Asian race[a]	1.204	44.6		
Manufacturing site[a]	1.515	27.9		
Gender[a]	0.799	23.5		
Oxaliplatin administration[a]	1.339	28.1		
Irinotecan central volume, L	4.09	2.23	0.066 (26.1)	27.5
Body surface area[b]	$(BSA/1.71)^{0.573}$	17.9		
Manufacturing site[a]	0.872	29.4		
Gender[a]	0.886	22.9		
Fraction of delayed irinotecan total rate of elimination	0.629	23.4	0.188 (45.4)	26.4
Manufacturing site[a]	1.376	41		
Fraction of direct irinotecan total rate of elimination	0.152	22.4	0.928 (124)	10.9
Irinotecan inter-compartmental clearance, L/week	1.35	28.6		
Irinotecan peripheral volume, L	0.421	22.6		
SN-38 total clearance, L/week	19,800	12.8	0.126 (36.6)	13.6
Bilirubin[b]	$(BIL/0.41)^{-0.266}$	17.5		
Creatinine clearance[b]	$(CrCL/85.04)^{0.25}$	28.7		
Gender[a]	0.802	20.3		
Oxaliplatin administration[a]	0.656	14.1		
Rate of transformation after delay, 1/week	2	5.1	0.135 (38)	29.1
Covariance (correlation) between irinotecan total clearance and fraction of direct transformation	−0.558 (−0.785)	12		
Covariance (correlation) between irinotecan total clearance and central volume	0.117 (0.617)	17.8		
Covariance (correlation) between irinotecan central volume and fraction of direct transformation	−0.103 (−0.416)	24.4		
Residual error				
Proportional error on irinotecan	0.243 (CV, 24.3%)	6.25		
Proportional error on SN-38	0.291 (CV, 29.1%)	5.23		
Correlation between irinotecan and SN-38 errors	0.323	26.4		

Abbreviations: BIL, bilirubin; BSA, body surface area; CrCL, creatinine clearance; CV, coefficient of variation; IIV, interindividual variability; PK, pharmacokinetic; RSE, relative standard error.

[a]Categorical covariates

[b]Continuous covariates: irinotecan total clearance, $i = 17.9 \times 1.304^{\text{Asian}} \times 1.515^{\text{Manufacturing site}} \times 0.799^{\text{Gender}} \times 1.339^{\text{Oxaliplatin coadministration}}$

irinotecan central volume, $i = 4.09 \times \left(\frac{\text{BSA}, i}{1.71}^{0.573}\right) \times 0.872^{\text{Manufacturing site}} \times 0.886^{\text{Gender}}$

fraction of delayed irinotecan total rate of elimination, $i = 0.629 \times 1.376^{\text{Manufacturing site}}$

fraction of direct irinotecan total rate of elimination, $i = 0.152$

irinotecan inter-compartmental clearance, $i = 1.35$

irinotecan peripheral volume, $i = 0.421$

SN−38 total clearance, $i = 19,800 \times \left(\frac{\text{BIL}, i^{-0.266}}{0.41}\right) \times \left(\frac{\text{CrCL}, i^{0.25}}{85.04}\right) \times 0.802^{\text{Gender}} \times 0.656^{\text{Oxaliplatin coadministration}}$

Diarrhea

Overall, 17.7% of patients experienced diarrhea AEs (grade ≥3) at first event (16.9% and 21.4% in the NAPOLI-1 and phase I/II 1L mPDAC studies, respectively).

There were statistically significant exposure–safety relationships between the log-transformed C_{avg} for both total irinotecan and SN-38 and the probability of diarrhea AEs (grade ≥3) at first event (odds ratio [OR] 8.70, $p = 0.001$ for total irinotecan; OR 7.30, $p = 0.013$ for

CSPC Exhibit 1120
Page 53 of 447

SN-38), with increasing exposure associated with increasing probability of an event (Figure 4). In equivalent exposure–safety analyses using C_{max}, there was a significant association between total irinotecan C_{max} and the probability of diarrhea AEs (grade ≥3) at first event. However, the association between SN-38 C_{max} and the probability of diarrhea AEs (grade ≥3) did not reach statistical significance.

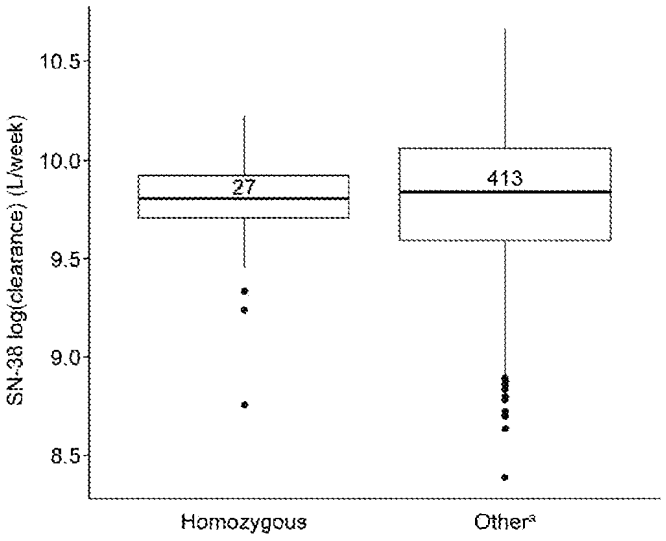

FIGURE 2 Impact of UGT1A1*28 homozygous 7/7 genotype on SN-38 clearance. Each box plot shows the median, interquartile range, and sample size. Outliers are represented by black circles. [a]Heterozygous 6/7, homozygous wild-type 6/6, and negative/unknown/missing genotypes

Neutropenia AEs (neutropenia, decreased neutrophil count, and febrile neutropenia)

At least one neutropenia AE (grade ≥3) at first event was reported for 24.7% of patients overall and for 20.8% and 42.9% of patients from the NAPOLI-1 and phase I/II 1L mPDAC studies, respectively.

The probability of neutropenia AE (grade ≥3) at first event decreased with increasing exposure to total irinotecan, and the exposure–safety relationship was statistically significant (total irinotecan log10 C_{avg} as a predictor: OR 0.33, $p = 0.012$; Figure 5a). In the equivalent analysis for SN-38, there was no statistically significant exposure–safety relationship for neutropenia AE (grade ≥3) at first event (SN-38 log10 C_{avg} as a predictor: OR 3.14, $p = 0.115$; Figure 5b). The same analyses conducted with C_{max} provided similar results.

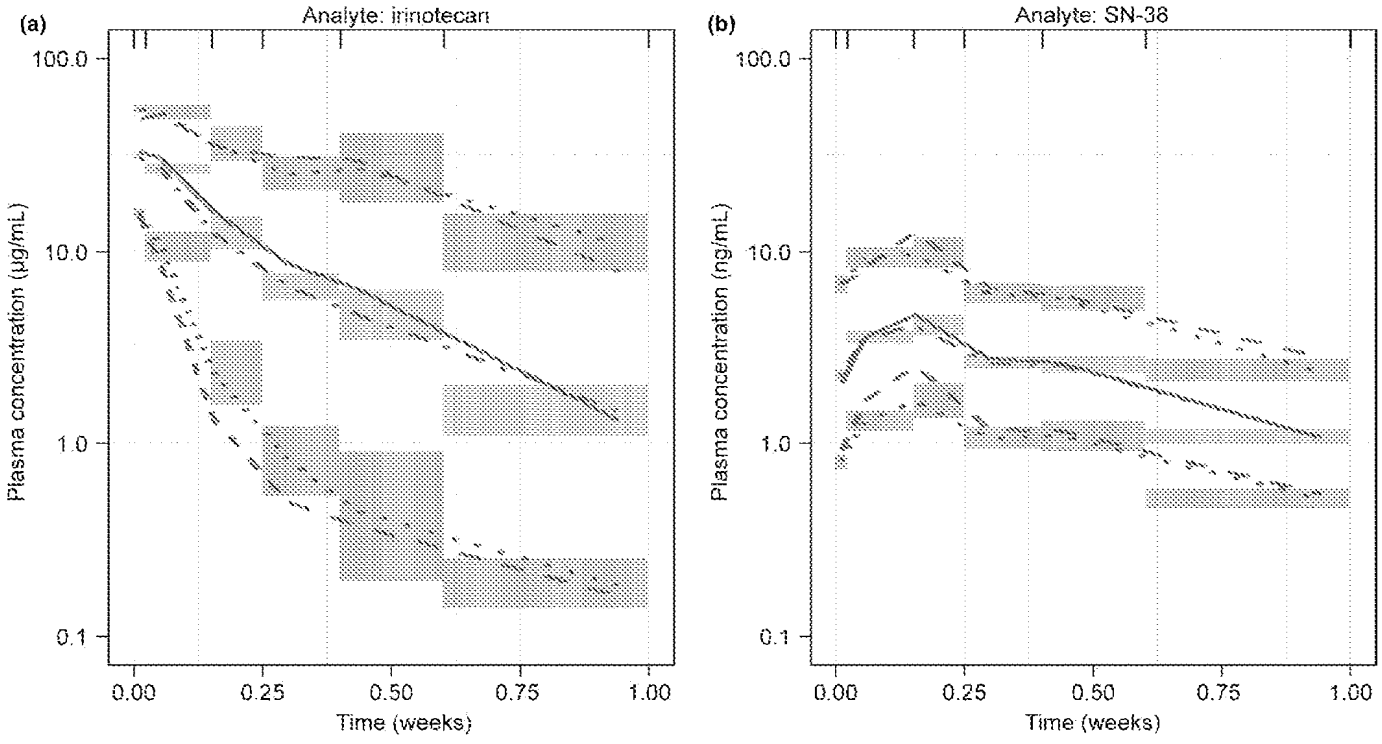

FIGURE 3 The pcVPCs for total irinotecan (a) and SN-38 (b) concentrations over time. Data are presented on a semi-log scale. The observed median (green bold line) and 2.5th and 97.5th percentiles (green dashed lines) are compared with the 95th confidence intervals (shaded area) for the median (gray area) and the 2.5th and 97.5th percentiles of the simulated ($n = 1000$) data (blue area). Simulated median (red semi-dashed line) and 2.5th and 97.5th simulated percentiles (red dotted line) are overlaid. pcVPC, prediction-corrected visual predictive check

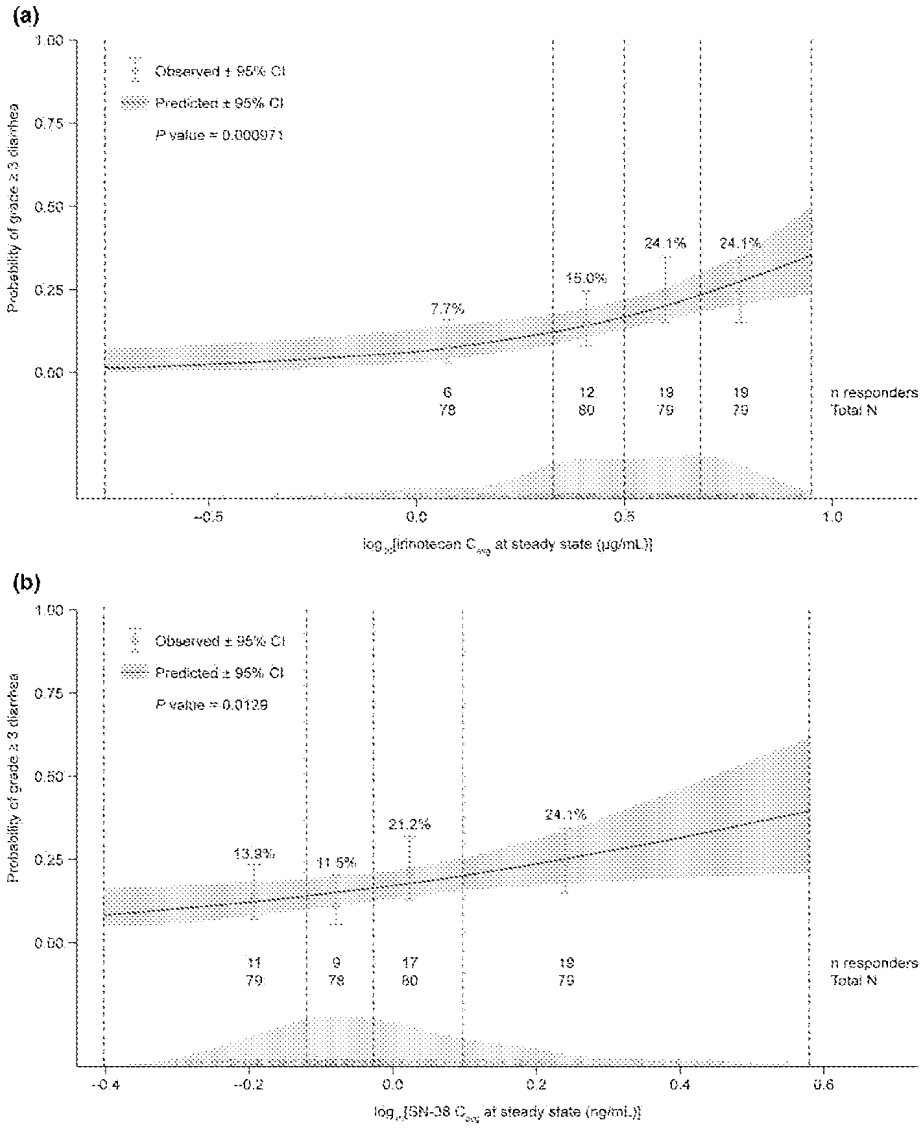

FIGURE 4 Probability of developing diarrhea (grade ≥3) as a function of log-transformed $C_{avg,ss}$ for total irinotecan (a) and SN-38 (b) after administration of liposomal irinotecan. $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

DISCUSSION

The present analyses were performed to jointly characterize the PKs of total irinotecan and SN-38 after administration of liposomal irinotecan, and to understand the relationship between total irinotecan and SN-38 exposure and the incidence of key safety outcomes in patients with mPDAC.

The final population PK model appeared to be sufficiently robust to characterize the joint relationship between total irinotecan and SN-38, and therefore their relative exposures, in patients with mPDAC in the NAPOLI-1 and phase I/II 1L mPDAC trials. The overall model estimate for the total clearance of SN-38 was relatively high, at 118 L/h. This is probably a result of the lack of data supporting the estimate of the real volume of distribution for SN-38 and the prolonged elimination of irinotecan as a consequence of liposomal encapsulation. Thus, the true elimination of SN-38 is most likely masked by the prolonged release and metabolism of liposomal irinotecan, leading to formation rate-limited kinetics for SN-38.

The model developed in a previous analysis performed by Adiwijaya,[15] which included 353 of the 440 patients included in the present model, was not selected as a starting model for the following reasons. Firstly, in the Adiwijaya model, irinotecan and SN-38 were developed independently (i.e., this was not a joint model) and only irinotecan clearance was included as a covariate in the SN-38 model. Non-joint models are not optimal for parent-metabolite model development (e.g., for testing drug-drug interactions, or for pediatric extrapolation). Second, the assumption of total versus unencapsulated SN-38 concentrations (with a fraction of encapsulated SN-38 measured in vitro of 0.015%) seems to be less meaningful than the assumption that 95% of irinotecan remains liposome-encapsulated during circulation when liposomal irinotecan is measured directly. Thus, the fraction of unencapsulated liposome could directly be metabolized in SN-38, which corresponds to the first order part of the final model developed here. This joint model also allows improved characterization of SN-38 clearance when SN-38 is obtained directly from the

CSPC Exhibit 1120
Page 55 of 447

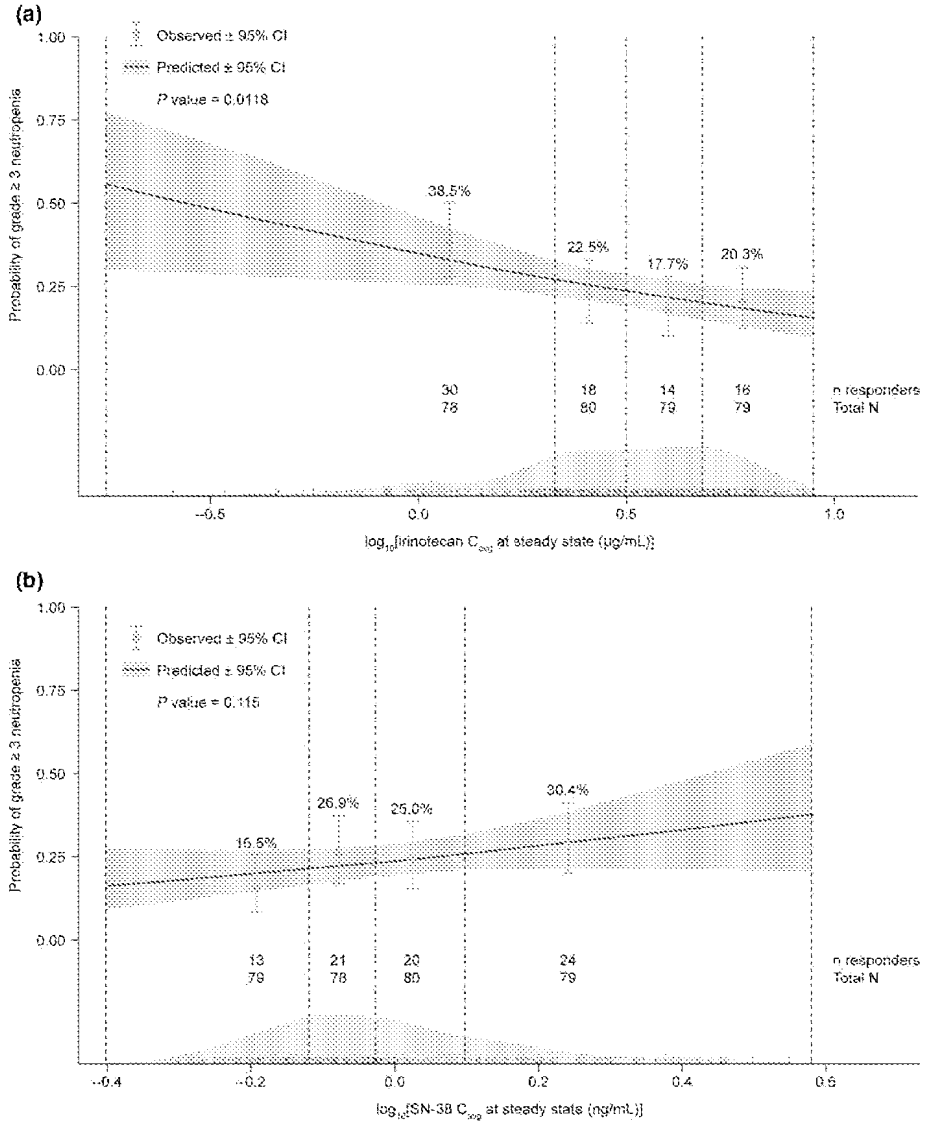

FIGURE 5 Probability of developing neutropenia AEs (grade ≥3) as a function of log-transformed $C_{avg,ss}$ for total irinotecan (a) and SN-38 (b) after administration of liposomal irinotecan. AE, adverse event; $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

fraction of unencapsulated liposome. Otherwise, SN-38 elimination coming from encapsulated irinotecan is driven by the rate of SN-38 formation.

Multiple covariates were incorporated into the model to test their role in the interpatient variability of PK exposures. The PK metrics affected by the largest number of covariates were total clearance of irinotecan and total clearance of SN-38. The 20% higher clearance of total irinotecan in Asian patients versus patients of other ethnicities is consistent with a previous report of lower levels of total irinotecan in Asian patients compared with White patients following administration of liposomal irinotecan.[15] The covariates gender and co-administration of oxaliplatin affected clearance of both irinotecan and SN-38, although oxaliplatin administration was associated with an increase in clearance of total irinotecan and a decrease in clearance of SN-38. The lower clearances of irinotecan and SN-38 in women versus men after administration of liposomal irinotecan are consistent with previous reports of higher exposure of SN-38 in women after administration of non-liposomal irinotecan.[32,33] Given that liposomal formulation is complex, some manufacturing adjustments were performed between the previous manufacturing site (mainly dedicated to phase I studies) and the current site (used for all pivotal studies).

UGT1A1 is the key enzyme responsible for the inactivation of SN-38 via glucuronidation in the liver to form SN-38G, which is primarily eliminated by biliary excretion.[6] The presence of the UGT1A1*28 allele has been reported to reduce expression of the UGT1A1 enzyme by 70%, leading to increased exposure to SN-38 and an increase in risk of irinotecan-related toxicity, most notably neutropenia and/or diarrhea (both grade ≥3).[6,34,35] In the present analysis, there was no significant association between UGT1A1*28 polymorphism and SN-38 clearance, consistent with the finding in a previous analysis of liposomal irinotecan and SN-38 PK that UGT1A1*28 genotype was not a significant covariate to SN-38 clearance.[15] A possible explanation for this is that the liposomal encapsulation slows the release of irinotecan and therefore reduces the load of SN-38,

such that the release of irinotecan is the rate-limiting step, and metabolism by UGT enzymes does not become saturated, even in patients with reduced UGT activities (e.g., UGT1A1*28 7/7 homozygous).[15] It follows that patients with reduced UGT activities may not have higher SN-38 exposure. It should be noted that the limited number of patients with the UGT1A1*28 7/7 homozygous genotype and the lower starting dose of liposomal irinotecan (reduced by 20 mg/m^2) in patients with this genotype in the NAPOLI-1 trial preclude firm conclusions from being drawn regarding the impact of this variable. Nevertheless, this analysis, which demonstrated that UGT1A1*28 status had no significant impact on the PKs of total irinotecan and SN-38 after administration of liposomal irinotecan-containing regimens, suggests that there is insufficient evidence of a need for dose adjustment based on UGT1A1*28 genotype. These results are also consistent with the decision tree for UGT1A1 genotyping depending initially on the dose of non-liposomal irinotecan (UGT1A1 genotyping not recommended for doses <180 mg/m^2 of irinotecan).[36]

The sparse sampling design of the NAPOLI-1 study (cycle 1: 1.5, 2.5, 48, and 168 h), could affect the ability to estimate C_{max}, mainly for the metabolite SN-38. Lack of information from NAPOLI-1 could result in an underestimation of C_{max} compared with values obtained from studies with richer PK sampling designs.

Logistic regression analyses have demonstrated that both total irinotecan and SN-38 C_{avg} were significant predictors of diarrhea (grade ≥3), with the increase in probability of diarrhea AEs at first event explained as a function of increasing exposures. Irinotecan appeared to be a slightly stronger predictor than SN-38 based on the lower p value (0.001 vs. 0.013) and higher OR (8.70 vs. 7.30). Analyses using C_{max} were consistent with these results for total irinotecan, but no significant association was seen between SN-38 C_{max} and the probability of diarrhea AEs (grade ≥3). The results with C_{max} must be interpreted with caution, however, owing to the difficulty of reliably capturing the maximum exposures in the model.

There was no significant relationship between SN-38 C_{avg} and the probability of neutropenia AEs (grade ≥3). This absence of a relationship between SN-38 exposure and severe neutropenia could be explained by the difference in SN-38 PK profile between non-liposomal and liposomal irinotecan—the concentration profile is flatter for liposomal than for non-liposomal irinotecan. A link between SN-38 exposure and severe neutropenia has previously been demonstrated after administration of non-liposomal irinotecan[37]; however, given that SN-38 PK profiles (including exposure) were deemed to be similar regardless of UGT1A1*28 status, no impact of SN-38 exposure on severe neutropenia is expected from UGT1A1*28 genotype status. The reduction in the probability of grade 3 neutropenia with increasing exposure to total irinotecan was unexpected and further investigation will be performed in ongoing phase III studies (e.g., the effects of granulocyte colony stimulating factor supplementation on neutropenia will be evaluated).

Further investigations will be performed by updating the population PK model and exposure–safety assessment with new data from the ongoing phase III NAPOLI-3 trial (NCT04083235). This study will compare the efficacy and safety of 1L gemcitabine/nab-paclitaxel with NALIRIFOX in patients with mPDAC, using the doses established in the 1L PDAC phase I/II study. It is planned that 750 patients (375 in each arm) will be enrolled, which will allow improved understanding of the relationship between total irinotecan and/or SN-38 exposure and diarrhea and neutropenia AEs. In addition, a lower LLOQ for the analysis of both total irinotecan and SN-38 implemented during the NAPOLI-3 trial will allow for improved characterization of the terminal phase and lead to a more accurate determination of total clearance for both compounds.

In conclusion, the final population PK model appeared to be robust in characterizing the exposures of total irinotecan and SN-38 after administration of liposomal irinotecan. The results suggest that UGT1A1*28 status has no significant impact on the PK of liposomal irinotecan. In the exploratory exposure–safety analyses in patients with mPDAC, the risk of diarrhea (grade ≥3) was associated with both total irinotecan and SN-38 C_{avg}, but there was no significant association between an increased risk of neutropenia (grade ≥3) and SN-38 C_{avg}. In clinical practice, appropriate use of anti-diarrheal medication is an important factor when managing patients receiving irinotecan.[38]

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CONFLICT OF INTEREST

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CSPC Exhibit 1120
Page 57 of 447

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AUTHOR CONTRIBUTIONS

K.B., T.B.-S., P.M.B., F.D., A.D., T.M., F.M., K.M., A.P.-D., Z.A.W., and B.Z. wrote the manuscript. K.B., F.M., A.P.-D., and B.Z. designed the research. K.B., T.B.-S., P.M.B., F.D., A.D., T.M., F.M., K.M., A.P.-D., Z.A.W., and B.Z. performed the research. K.B., T.B.-S., P.M.B., F.D., A.D., T.M., F.M., K.M., A.P.-D., Z.A.W., and B.Z. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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BMC Cancer

STUDY PROTOCOL Open Access

Study protocol of an open-label, single arm phase II trial investigating the efficacy, safety and quality of life of neoadjuvant chemotherapy with liposomal irinotecan combined with Oxaliplatin and 5-fluorouracil/Folinic acid followed by curative surgical resection in patients with hepatic Oligometastatic adenocarcinoma of the pancreas (HOLIPANC)

Florian Gebauer[1*†], Alexander Ioannis Damanakis[1†], Felix Popp[1], Alexander Quaas[2], Fabian Kütting[3], Katrin Lutz[4], Swantje Held[4], Burkhard Deuß[4], Tobias Göser[3], Dirk Waldschmidt[3†] and Christiane Bruns[1†]

Abstract

Background: According to current guidelines, treatment of patients with hepatic oligometastasis in pancreatic cancer is not reflected and systemic chemotherapy is recommended in those patients. Retrospective data suggest beneficial outcomes in patients with hepatic oligometastasis, though prospective data from clinical trials addressing this particular patient group is not available.

Methods: In this single arm, phase-2 trial, survival data from patients receiving neoadjuvant chemotherapy followed by R0/R1 resection will be compared to historic data from patients with oligometastatic adenocarcinoma of the pancreas.

The clinical trial will focus on a well-defined patient collective with metastatic load limited to the liver as target organ with a maximum of five metastases. The combination of liposomal irinotecan (nal-IRI), oxaliplatin (OX) and 5-fluouracil (5-FU)/folinic acid (FA) (nal-IRI + OX+ 5-FU/FA, NAPOX) was chosen as neoadjuvant chemotherapy; the choice was based on an ongoing clinical study in which NAPOX appeared manageable, with promising anti-tumor activity in first-

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line treatment of patients with metastatic pancreatic adenocarcinoma.
In total 150 patients will be enrolled for this trial with an aim of 55 patients receiving a complete macroscopic synchronous tumor and metastatic resection.

Discussion: This is the first clinical study to prospectively evaluate the value of multimodality therapy concepts in oligometastatic pancreatic cancer.

Trial registration numbers: EudraCT 2019-002734-37; NCT04617457.

Keywords: Chemotherapy, Clinical trials, Liver metastasis, Pancreatic cancer, Pancreatic surgery

Background

In 2018, approximately 460,000 persons worldwide were diagnosed with pancreatic cancer and 430,000 patients died from this disease; the 5-year prevalence was 3.7% [1, 2]. Pancreatic cancer is among the deadliest malignancies and expected to become the second most common cause of cancer death by 2030 [3]. Once distant metastases have been detected, tumor or metastases resection is not recommended according to the current diagnostic and treatment guidelines, regardless of the location or number of metastases [4, 5]. Therefore, patients with hepatic oligometastatic adenocarcinoma of the pancreas currently receive palliative treatment.

In different tumor entities including colon and kidney cancer, synchronous tumor and hepatic metastases resection indicated survival benefits [6, 7]. Clinical studies are ongoing e.g. for gastric cancer (RENAISSANCE, NCT02578368) [8]. However, prospective clinical data on multimodal treatment in pancreatic cancer including complete tumor resection are not available so far.

Two recent retrospective studies showed that patients with hepatic oligometastatic pancreatic cancer benefited from complete tumor resection including resection of liver metastases: In an analysis of six European pancreas centers, 69 patients with pancreatic cancer were identified who had undergone synchronous tumor and hepatic metastases resection and who had a median OS of 14.5 months compared to 7.5 months in a control group without resection [9]. In another study, data of patients with oligometastatic pancreatic cancer undergoing tumor and metastases resection revealed a median OS of 12.3 months for patients with hepatic metastases [10]. Further reports including case reports revealed similar trends [11–16]. However, because of the limitations of retrospective study designs and of case reports as well as missing adequate control groups, the evidence level of these studies and reports is insufficient to allow for modifying diagnostic and treatment guidelines towards synchronous tumor and metastases resection in patients with oligometastatic pancreatic cancer.

The assumption that oligometastatic pancreatic cancer is biologically more similar to non-metastatic than to highly aggressive pancreatic cancer with multifocal tumor spread justifies the testing of a new therapeutic approach with curative intend for patients with a limited number of metastases [17, 18]. Additionally, retrospective data showed a survival benefit for patients that matched criteria of hepatic oligometastasis and only underwent standard palliative chemotherapy compared to patients with polymetastatic disease [19].

Since the establishment of novel, effective chemotherapy regimens, for the first time multimodal therapy in the post-gemcitabine monotherapy era is feasible to achieve long-term tumor control even in the metastatic stage [20–22]. novel chemotherapy regimes based on liposomal-irinotecan combined with 5-fluouracil and oxaliplatin showed promising anti tumor activity in metastasized pancreatic cancer in phase I/II trials [23]. Therefore, two approaches will be combined in this clinical trial: The goal is to test the efficacy and safety of neoadjuvant chemotherapy followed by complete synchronous resection of the primary tumor and hepatic metastases in curative intent in patients with adenocarcinoma of the pancreas and oligometastatic hepatic disease. The hypothesis of the clinical trial is that neoadjuvant chemotherapy sufficiently controls systemic disease and tumor progression, thus allowing the complete resection of the tumor and all hepatic metastases in case of stable disease or tumor response, so that these patients profit from it in terms of overall survival.

The study is planed as investigator initiated trial (IIT) and the sponsor of the study is the University of Cologne.

Objectives and endpoints

Objectives

The primary objective of the HOLIPANC trial is to assess the efficacy of neoadjuvant multimodal chemotherapy followed by complete tumor and metastases resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas. Secondary objectives are to determine the efficacy and safety of the treatment concept and health-related quality of life (HR-QoL).

Endpoints

The primary endpoint is overall survival after R0/R1 resection (OS-res) (only patients with R0/R1 resection).

Secondary efficacy endpoints are OS of the entire patients cohort, R0/R1 resection rate and progression-free survival (PFS). Secondary safety endpoints are type, frequency and severity of adverse events with severity according to NCI CTCAE version 5.0 (neoadjuvant chemotherapy) and perioperative morbidity and mortality (Table 1).

Methods/study design

This is an interventional, open-label, non-randomised, multicentre, single-arm phase II clinical trial organized and sponsored by the University of Cologne. The study will be conducted at 10 centers in Germany.

Eligible patients with hepatic oligometastatic adenocarcinoma of the pancreas will receive neoadjuvant combination chemotherapy (liposomal irinotecan (nal-IRI), oxaliplatin (OX), 5-fluouracil (5-FU), folinic acid (FA) (NAPOX)) in cycles of 14 days (Fig. 1).

Table 1 Objectives and endpoints of the HOLIPANC trial

1. **Objectives**

1.1. **Primary Objectives**

- To assess the efficacy of neoadjuvant multimodal chemotherapy followed by R0/R1 resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas

1.2. **Secondary Objectives**

- To determine efficacy and safety of the treatment concept
- To determine health-related quality of life (HR-QoL)

1.3. **Other Exploratory Objectives**

- To analyze HR-QoL-adjusted overall survival

2. **Endpoints**

2.1. **Primary Endpoint**

- Overall survival after R0/R1 resection (OS-res) (only patients with R0/R1 resection)

2.2. **Secondary Endpoints**

Efficacy

- R0/R1 resection rate after neoadjuvant chemotherapy
- Overall survival
- Progression-free survival (PFS) after R0/R1 resection according to RECIST v1.1

Safety

- Type, frequency and severity of adverse events with severity according to NCI CTCAE version 5.0 (neoadjuvant chemotherapy)
- Perioperative morbidity and mortality

Health-Related Quality of Life

- HR-QoL according to EORTC QLQ-C30 and EORTC QLQ-PAN26 questionnaires

2.3. **Other, Exploratory Endpoints**

- HR-QoL-adjusted OS

Trial population

Patients with hepatic oligometastatic ductal adenocarcinoma of the pancreas fulfilling the inclusion criteria will be eligible to participate in this clinical trial.

Inclusion criteria

1. Histologically confirmed diagnosis of treatment-naïve oligometastatic hepatic metastatic adenocarcinoma of the pancreas
   Definition of oligometastatic hepatic metastasis: 1 to 5 metastases in CT/MRI and/or contrast-enhanced ultrasound scan, which are potentially resectable or treatable by ablative procedures (Note 1: Patients also fulfill this inclusion criterion if a hepatic metastasis was partly or entirely removed as part of the diagnosis and is thus not detectable by CT/MRI and/or contrast-enhanced ultrasound scan at screening. Note 2: If more than 5 metastases are unexpectedly detected during surgery, it is not a violation of this inclusion criterion if the excess metastases had not been detectable by CT/MRI and/or contrast-enhanced ultrasound scan at screening.)
2. Measurable disease according to RECIST v1.1
3. ECOG performance status 0–1
4. Adequate renal, hepatic and bone marrow function, defined as

- Calculated creatinine clearance ≥60 mL/min according to CKD-EPI formula
- Total bilirubin ≤2 mg/dL; patients with biliary stent may be included if bilirubin level decreased to ≤2 mg/dL after stent insertion
- ALT and AST ≤5 × upper limit of normal (ULN)
- Absolute neutrophil count (ANC) ≥1.5 × 109/L
- Thrombocytes ≥100 × 10^9/L
- Haemoglobin ≥9 g/dL
- aPTT ≤1.5 × ULN and Quick value ≥70%

1. Patients ≥18 years at the time of signing the informed consent
2. Females of childbearing potential (FCBPs) must agree to use highly effective contraceptive measures (Pearl index < 1) or practice true abstinence from any heterosexual intercourse for the duration of treatment and for at least 1 month after the last IMP administration (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient). A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through

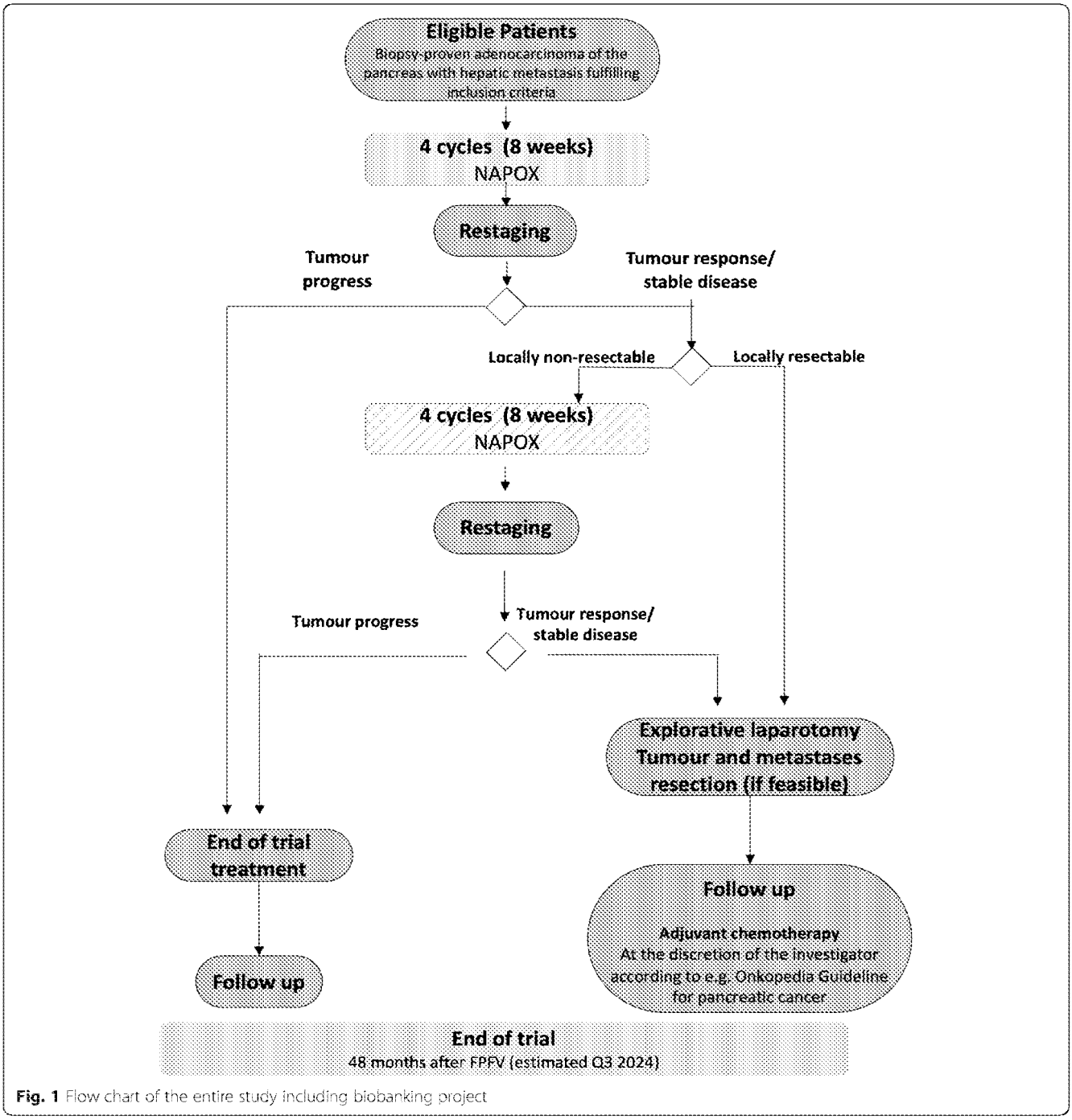

Fig. 1 Flow chart of the entire study including biobanking project

menopause for at least 2 years or has been surgically sterilized.

3. Males must agree to use condoms or practice true abstinence from any heterosexual intercourse for the duration of IMP treatment and at least 6 months after the last IMP administration (true abstinence is acceptable if this is in line with the patient's preferred and usual lifestyle). Male patients must furthermore refrain from donating sperm during the clinical trial until at least 6 months after the last IMP administration.
4. Patient's written informed consent prior to any trial-specific procedure
5. Patient's legal capacity to consent to participation in the clinical trial

Exclusion criteria

1. Acinar cell carcinoma and/or neuroendocrine carcinoma of the pancreas
2. Symptomatic clinically significant ascites
3. Evidence of any distant metastases other than oligometastatic hepatic metastases as defined in inclusion criterion 1.
4. Any tumor-specific pretreatment of the adenocarcinoma of the pancreas (including but not limited to surgery, radiation therapy, chemotherapy or ablative procedures)
5. Any malignancies other than adenocarcinoma of the pancreas in the 5 years before the start of the clinical trial except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, breast cancer, prostate cancer or superficial bladder tumors (Ta, Tis and T1)
6. Hypersensitivity to any of the IMPs or any of the excipients
7. Any major surgery within 4 weeks before the first IMP administration
8. Pregnant or breast-feeding female
9. Known chronic inflammatory bowel disease, bowel obstruction, chronic diarrhea, Grade ≥ 2 according to NCI CTCAE version 5.0
10. Peripheral polyneuropathy, Grade ≥ 2 according to NCI CTCAE version 5.0
11. Known interstitial lung disease or pulmonary fibrosis
12. Radiographic evidence of severe portal hypertension
13. Liver cirrhosis ≥ Child Pugh B
14. Cholestasis or cholangitis despite adequate biliary stenting; treatment with anti-infectious agents is permitted; patient must be disease-free and without anti-infectious treatment for 7 days before the first IMP administration
15. Active infection requiring systemic therapy
16. Known HIV seropositivity
17. Active or chronic Hepatitis B or Hepatitis C infection
18. Known glucoronidation deficiency (Gilbert's syndrome) (specific screening not required)
19. Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (specific screening according to the recommendations of the SmPC in effect for 5-FU; patients with a known complete DPD deficiency must be excluded; patients with a known partial DPD deficiency may be included at the discretion of the investigator)
20. Clinically significant cardiovascular or vascular disease or disorder ≤6 months before enrolment into the clinical trial (e.g., myocardial infarction, unstable angina pectoris, chronic heart failure NYHA ≥ Grade 2, uncontrolled arrhythmia, cerebral infarction)
21. Pulmonary embolism, deep venous thrombosis or arterial thromboembolism ≤6 months before the first IMP administration
22. Any other severe concomitant disease or disorder, which could influence patient's ability to participate in the clinical trial and his/her safety during the trial or interfere with interpretation of results; e.g., severe hepatic, renal, pulmonary, cardiovascular, metabolic or psychiatric disorders
23. Requirement for live vaccination within 4 weeks before the first IMP administration and during neoadjuvant chemotherapy
24. Use of strong CYP3A4 inhibitors (Strong CYP3A4 inhibitors have to be discontinued at least one week prior to start of trial treatment.) Use of strong UGT1A1 inhibitors or strong CYP3A4 inducers unless there are no therapeutic alternatives
25. Treatment with nucleoside analogues such as brivudine within 4 weeks before the first IMP administration or requirement for concomitant antiviral treatment with brivudine or analogues
26. Participation in a clinical trial or experimental drug treatment within 4 weeks before the first IMP administration or within a period of 5 half lives of the substances administered in a clinical trial or during an experimental drug treatment before the first IMP administration, depending on which period is longest, or simultaneous participation in another clinical trial while taking part in this clinical trial until 28 days after last administration of any IMP
27. Continuing abuse of alcohol, drugs or medical drugs
28. Patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
29. Patients possibly dependent from the investigator including the spouse, children and close relatives of any investigator

Gender and age selection

Adults of all genders are eligible for this clinical trial.

Tumor imaging

CT or MRI of abdomen with intravenous contrast agents according to specific protocols for imaging of the pancreas and local institutional practice; CT/MRI may be used for imaging of the abdomen, but investigators have to adhere to the same imaging method. Additive imaging such as MRI liver imaging with gadoxetate disodium (e.g., Primovist™) as contrast agent or, alternatively, a contrast-enhanced ultrasound scan will be required in

case of unclear findings or suspicion of further hepatic metastases. Chest imaging by CT for detection of lung metastases. Additional imaging may be required in symptomatic patients if clinically indicated.

Treatment regimen

This is an interventional, open-label, non-randomised, multicentre, single-arm phase II clinical trial. Eligible patients with hepatic oligometastatic adenocarcinoma of the pancreas will receive neoadjuvant NAPOX chemotherapy in cycles of 14 days.

In patients with progressive disease during or after the first 4 cycles, neoadjuvant chemotherapy will be permanently discontinued (Table 2). Patients with tumor response or stable disease after the first 4 cycles according to RECIST v1.1 but a non-resectable primary tumor according to the evaluation of an interdisciplinary tumor board will receive 4 more cycles of neoadjuvant chemotherapy. Patients with tumor response or stable disease and a resectable primary tumor after the first 4 cycles will undergo explorative laparotomy and synchronous resection of the tumor and hepatic metastases, if feasible; these patients may receive 4 more cycles of neoadjuvant chemotherapy 2 4 weeks after the explorative laparotomy if the surgeon rated the primary tumor as non-resectable during the explorative laparotomy.

All patients who received a total of 8 cycles and who then have tumor response or stable disease according to RECIST v1.1 will undergo exploratory laparotomy surgery and synchronous resection of the tumor and hepatic metastases, if feasible according to the surgeon, 2 6 weeks after the last IMP treatment.

Dose modifications and prerequisites for the start of a new cycle

Doses will be reduced for haematological and non-haematological toxicities. In case of concurrent toxicities, all dose modifications should be based on the worst preceding toxicity. Nal-IRI, OX and 5-FU doses may be reduced by two dose levels. Patients who require further dose reduction should discontinue treatment. The FA dose does not require adjustment, but FA has to be discontinued if 5-FU is permanently discontinued. Special attention should be paid to toxicities associated with 5-FU due to a deficiency in DPD activity. To this end, therapeutic drug monitoring may be considered. In general, the recommendations of the SmPC in effect for 5-FU have to be followed.

The following criteria for dosing delays and holidays due to adverse events apply:

- A cycle may be delayed, e.g., due to adverse events, by a maximum of 7 days.
- If adverse events would require a cycle delay of more than 7 days, this cycle is cancelled and the next cycle started according to schedule (e.g., Cycle 1 starts on Day 1; Cycle 2 is cancelled; Cycle 3 starts on Day 29).
- If adverse events require cycle delays of more than 28 days, treatment should be permanently discontinued. (e.g., Cycle 1 starts on Day 1; Cycle 2 and Cycle 3 are cancelled; Cycle 4 has to start on Day 43 or treatment will be discontinued).

Adjuvant treatment

Adjuvant treatment will not be part of the trial treatment and may be given at the investigator's discretion in accordance with the guidelines for pancreatic cancer [24].

Surgical procedures

Exploratory laparotomy and resection should be performed within 2 to 6 weeks after the last IMP administration according to local institutional practice. All procedures necessary to prepare for surgery, during surgery and after surgery that are standard of care will also follow local institutional practice. Based on the intraoperative findings during exploratory laparotomy, the surgeon will evaluate and decide whether resection of the primary tumor in curative intent can be performed. Intraoperative rapid section analyses are obligatory for the pancreatic transection margin and optional for the resection margin of the common bile duct to ensure safe and margin-free resection. If the primary tumor is macroscopically non-resectable, intraoperative tumor biopsies are obligatory to confirm diagnosis of viable tumor cell at the origin of assumed non-resectability (e.g., superior mesenteric artery, common hepatic artery, celiac artery). For the removal of hepatic lesions, resection is recommended. However, radiofrequency ablation or microwave

Table 2 Investigational medicinal products (IMP) used in the HOLPANC trial during neoadjuvant treatment

IMP	Dosing schedule [Day of 14-day cycle]	Dose [mg/m^2]	Route of administration
Liposomal irinotecan (nal-IRI) anhydrous free base*	1	50	i.v. over about 90 min
Oxaliplatin (OX)	1	60	i.v. over 2 to 6 h
Folinic acid (FA)	1	400	i.v. over about 30 min
5-fluorouracil (5-FU)	1–2	2400	i.v. over about 46 h

* Equivalent to 60 mg/m^2 irinotecan hydrochloride trihydrate

ablation of hepatic lesions are permitted on a case-by-case basis.

Resected tissue and tumor samples will be sent to and analyzed by the local pathology department.

Statistical considerations

This is an interventional, open-label, non-randomized, multi-center, single-arm phase II clinical trial. The primary objective is to assess the efficacy of neoadjuvant NAPOX chemotherapy followed by R0/R1 resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas. To this end, overall survival after R0/R1 resection (OS-res) for patients with R0/R1 resection after neoadjuvant chemotherapy will be used as the primary endpoint.

Details of the statistical analysis will be described in a statistical analysis plan (SAP), which will be written before the data cut-off date for analysis. The statistical analysis will be carried out by ClinAssess GmbH, Leverkusen, the CRO contracted with this task by the sponsor.

Statistical hypotheses and sample size determination

OS after R0/R1 resection (OS-res) will be used as the primary endpoint to assess the efficacy of NAPOX in patients with oligometastatic adenocarcinoma of the pancreas.

Hence, the hypotheses to be tested are:

H_0: median OS-res ≤10 months
H_1: median OS-res ≥14 months

The hypothesis will be tested with a one-sided log-rank test.

Since median OS-res of ≥14 months is expected, 53 patients and 42 OS-res events are required to test the null hypothesis with a power of 80% at a one-sided significance level of 0.1 (one-sample testing using log-rank test) if an accrual period of 14 months (period from FPI to resection approx. 4 months) and a minimum follow-up of 24 months after resection is assumed. The longer the follow-up duration, the higher is the power to detect a specific alternative effect size. Assuming a R0/R1 resection rate of 35%, 150 patients will be included in this clinical trial.

Statistical analysis

All study practices and statistical methods are based on the ICH document 'Statistical Principles for Clinical Trials'.

In general, standard descriptive methods will be used for all relevant data. Distribution parameters (mean, standard deviation, minimum, median and maximum) will be given for continuous data and counts and percentages for categorical data. For selected parameters, 95% confidence intervals will be presented. If required, appropriate tests (Fisher's exact test or chi-square test for proportions, Wilcoxon rank-sum test for continuous parameters, log-rank test for time to event parameters, Cox proportional hazard model for hazard ratio) will be used for comparisons between groups. Multivariate analyses may be performed using appropriate regression models (e.g., Cox proportional hazard model, logistic regression). For tests and confidence intervals, a two-sided significance level $\alpha = 5\%$ will be used except for the primary endpoint and unless otherwise specified. Missing data will not be replaced. Incomplete data will be imputed adequately if necessary.

Time-to-event data will be analyzed according to the Kaplan-Meier method (product-limit analysis). Patients who are not known to have had an event by the time of the analyses will be censored based on the last recorded date the patient was known to be event-free. HR-QoL data will be scored according to the algorithms described in the relevant scoring manuals. It is planned to evaluate the HR-QoL-adjusted OS, preferably using the Q-TWIST (quality-adjusted time without symptoms of disease progression of toxicity) method. Safety data will be continuously monitored, documented and reported as described in this protocol. The safety analysis includes type, incidence and severity of adverse events (severity according to CTCAE version 5.0), exposure to IMPs and laboratory parameters. If statistical methods described herein prove unsuitable during analysis, methods that are more appropriate will be used and any changes documented in the clinical study report (CSR).

Assessment of severity/intensity

For the grading of the severity/intensity of an adverse event (AE), the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 5.0 must be used. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require an intervention to prevent one of the outcomes listed in the definition above. These events should also usually be considered serious (SAE). All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The investigator must report the outcome of AEs and SAEs. All SAEs that have not resolved by the end of treatment visit or discontinuation of IMP treatment, whichever is later, must be followed until the outcome is recovered, recovered with squeal, unchanged/not recovered until death (death due to another cause) or death (due to the SAE).

Investigators must report all SAEs immediately within 24 h of knowledge of the event.

Regulatory, ethical, legal and trial oversight considerations

The protocol was developed and approved by the sponsor. The clinical trial will be conducted in accordance with the ethical principles of the Declaration of Helsinki and ICH Good Clinical Practice guidelines and the applicable European and domestic law concerning the conduct of clinical studies. The local ethics committee of the University of Cologne (20–1544-AMG) and the local ethic committees of the participating centers throughout Germany approved the study and the protocol with the protocol number Uni-Koeln-4067 V6.0. The sponsor, the competent authorities and the ethics committee may stop the clinical trial or participation of a clinical trial site in the clinical trial for medical, safety, regulatory, administrative or other reasons consistent with ICH-GCP, the respective European Union's and national legislation. The study is registered at the 'European Union Drug Regulating Authorities Clinical Trials' (EudraCT 2019–002734-37) and clinicalstrials.gov (NCT04617457).

Informed consent

Informed consent is the free and voluntary agreement of a patient to participate in a clinical trial after having been informed of all aspects of the clinical trial relevant to the patient's decision to participate. Patient's written informed consent prior to any trial-specific procedure for study inclusion. The investigators must obtain freely given informed consent from every patient prior any procedures related to the clinical trial including the documentation of results of clinical routine procedures for trial purposes as set forth in the GCP ICH guidelines, the respective European Union's and national legislation.

Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of patients are protected, the reported trial data are accurate, complete and verifiable from source documents and that the conduct of the trial complies with the currently approved protocol/amendment(s), with GCP and with the applicable regulatory requirement(s). Periodic monitoring of the trial will be performed on-site in the trial centers, i.e., in terms of visits by Clinical Research Associates (CRAs), using a risk-based monitoring approach.

Following written Standard Operating Procedures (SOP), monitors will verify that the clinical trial is conducted and data generated, collected, recorded and reported according to GCP and the applicable regulatory requirements. The activities the CRA should carry out when relevant and necessary to the trial and the trial site will be described in detail in the monitoring plan. Among others, the activities will include the following:

- Availability of the patient's informed consent
- Verification that the investigator is enrolling only eligible patients
- Verification that written informed consent was obtained before each patient's participation in the trial
- Verifying that the investigator and site staff are adhering to the protocol and GCP
- Ensuring the completeness of the trial documents in the trial centre
- Source document verification by cross-checking the electronic CRFs against the investigator's records
- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained
- Determination whether all AEs/SAEs are appropriately reported within the time periods required by GCP, the protocol, the sponsor and the applicable regulatory requirement(s)

Audits

The sponsor may conduct or commission audits in the course of the trial, which are independent of and separate from routine monitoring or quality control functions, to evaluate trial conduct and compliance with the protocol, SOPs, GCP and the applicable regulatory requirements. The appointed auditors should be independent of the clinical trial and qualified by training and experience to conduct audits properly. The audit will be conducted according to an audit plan that is guided by the importance of the trial to submissions to regulatory authorities, the number of patients in the trial, the type and complexity of the trial, the level of risks to the trial patients and any identified problem(s).

Trial oversight

Safety data will be assessed by a Data and Safety Monitoring Committee (DSMC) composed of individuals with relevant expertise, including surgery and oncology. Members of the DSMC should be independent from trial conduct and free of conflict of interest. The DSMC will operate under the rules of an approved DSMC charter.

Confidentiality and data protection

The sponsor affirms the patient's right to protection against invasion of privacy. All pertinent provisions of European and national data protection legislation in order to guarantee confidentiality and protection of privacy will be fully observed.

All records identifying the patients will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly

available. The investigator must assure that the patient's anonymity will be maintained and that the identities are protected from unauthorized parties. The investigator should maintain documents not for submission to the sponsor, e.g. patients' written consent forms, in strict confidence. On the eCRFs and other documents patients should not be identified by their names or birth dates. All clinical and scientific data are collected under a patient-identification code.

All data transfer with the trial centres will be made without any exception via the patient-code. All participating trial centres are obliged to keep a strictly confidential patient identification list at a safe locked place.

Persons who are authorized by the sponsor or regulatory authorities (e.g. CRAs, auditors or representatives of regulatory authorities) may be permitted to patient-related data medical records relevant to the clinical trial for review or inspections respectively in accordance with local laws and the patient's statement in the informed consent.

Trial results and publication

The clinical trial will be registered in a public register in accordance with the recommendations of the International Committee of Medical Journal Editors' (ICMJE).

A clinical trial report will be prepared within 1 yr after the end of the clinical trial. Within 1 yr after the end of the trial, the competent authority and the ethics committee will be supplied with the summary of the clinical trial report according to the regulatory requirements including the publication of results. The sponsor is furthermore required to post the results in the EudraCT database within 1 yr after the end of the trial.

Translational research program

Residues of tumour and metastases tissue from biopsies and resection, as well as stool and blood samples collected before the start and during the clinical trial, will be used for translational research if the patient gives his/her consent to participating in the translational research programme. Eligible patients may participate in the clinical trial without consenting to translational research procedures.

Patients with hepatic oligometastatic adenocarcinoma of the pancreas usually do not undergo surgery; thus, biomaterials of these patients are not available. The main goals of this translational research programme therefore are to build a biobank with samples from this patient group and to perform comprehensive analyses signatures.

Discussion

Once distant metastases have been detected tumor resection is not recommended neither according to German, nor to NCCN guidelines [4, 25]. In the palliative setting chemotherapy regimes such as FOLFIRINOX or gemcitabine/nab-Paclitaxel have been recently established, showing a significantly increased OS with a median of 11 and 8.5 months, respectively, compared to 7 or 6.7 months with gemcitabine mono therapy [20, 21]. Though, recommendations towards surgery in the metastasized stage are not given, based on individual decisions physicians have performed surgical resections in patients with hepatic metastases in the past. So far, prospective data facing this specific patient subgroup has not been published in any of the searched databases or registered as clinical trial (MEDLINE, the Cochrane library, clinicaltrials.gov, Deutsches Register Klinischer Studien (DRKS)). However, two recent studies showed for the first time data with a reasonable sample size of patients who underwent synchronous liver and primary tumor resection that patients with hepatic oligometastatic disease could potentially benefit from a complete tumor resection including resection of the liver metastases [9, 10]. These studies showed for the first time, apart from single case reports [11, 12, 15, 16, 26–28], a promising survival of 12.3 and 14 months OS, respectively. Due to several limitations in the retrospective study design and missing adequate control groups, the evidence level is by far too low to modify treatment guidelines towards synchronous liver resection in patients with oligometastatic PDAC.

The treatment of metastatic tumor diseases is a challenge not only in pancreatic cancer. More than 70% of gastrointestinal (GI) cancers are diagnosed with metastases either at the time of diagnosis (synchronous) or later (metachronous) [2, 29]. Interestingly, metastasis remains limited to a single lesion or few foci for longer periods of time in some patients, where local treatment suffices to obtain long term tumor control. However, current treatment of metastatic cancer is still based on the paradigm that metastatic spread beyond regional lymph nodes is considered uniformly as systemic disease. This concept results in non-selective, non-individualized systemic treatment without discriminating the substantial variety of clinical outcomes and potentially excluding patients accessible to curatively intended innovative local or multimodality treatments. Oligometastatic disease is poorly understood and its recognition is based upon imaging of metastatic lesions of limited number in distant organs. High-level evidence based on prospective randomized trials is lacking and clinical definitions of oligometastasis are still at a premature stage with very limited consensus across the scientific community [30]. So far, the single existing preliminary attempt of a definition of oligometastatic GI cancers is related only to colorectal cancer and has been formulated in the ESMO consensus guidelines [31]. Here, oligometastatic CRC is characterized by a limitation of the disease to few sites and lesions and multimodality treatment strategies including local therapies are recommended to improve disease control

and clinical outcome in these patients. Distinct clinical courses of oligo- and polymetastasis occur in tumors of different origins and an inclusion of more than one entity is needed to identify common underlying mechanisms. In pancreatic cancer, the concept of oligometastasis has not been established in the clinical routine, moreover, today it is fully unknown if there is are real oligometastastic disease in pancreatic cancer compared to the stages we know from colorectal cancer. Based on a non-surgical patient collective, our group had proposed for the first time a definition for the oligometastatic disease in pancreatic cancer [19], however prospective data about clinical and molecular details of this particular patients group is still missing.

The HOLIPANC study aims therefore to evaluate the effectiveness of multimodal therapy in patients with the clinical picture of oligometastasis in pancreatic cancer. The combination of a highly effective polychemotherapy followed by a complete tumor resection will foster the intention of a possible curative treatment of these patients, a group of patients which has been considered as exclusively palliative until now. The primary objective of this single arm phase II study is to demonstrate the efficacy of this therapeutic concept in terms of overall survival. Depending on the results, further clinical study concepts will be developed to offer new individualized therapy options to selected patient groups in the future.

Abbreviations

ADR: Adverse Drug Reaction; AE: Adverse event; CT: Computer tomography; CTCAE: Common Terminology Criteria for Adverse Events; CR: Complete response; DCR: Disease-control rate; DPD: Dihydropyrimidine dehydrogenase; DSMC: Data and Safety Monitoring Committee; eCRF: Electronic case report form; ECOG: Eastern Cooperative Oncology Group; FA: Folinic acid; FCBP: Females of childbearing potential; FPFV: First patient first visit; 5-FU: 5-fluorouracil; GCP: Good clinical practice; GCP-V: GCP ordinance; German: *Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen*; HR-QoL: Health-related quality of life; IB: Investigator's brochure; ICH: International Conference on Harmonization; IEC: independent ethics committee; ILD: interstitial lung disease; IMP: Investigational medicinal product; ITT: Intention-to-treat; i.v.: Intravenous; MRI: Magnetic resonance imaging; MSI: Microsatellite instability; NCI CTCAE: National Cancer Institute Common Toxicity Criteria for Adverse Events; nal-IRI: Liposomal irinotecan; NAPOLI-1: Treatment regimen with liposomal irinotecan and 5-fluorouracil/folinic acid; NAPOX: Treatment regimen with liposomal irinotecan, oxaliplatin and 5-fluorouracil/folinic acid; NCI: National Cancer Institute; ORR: Objective response rate; OS: Overall survival; OX: Oxaliplatin; PFS: Progression-free survival; PR: Partial response; RECIST: Response evaluation criteria in solid tumours; RR: Response rate; SAE: Serious adverse event; SAR: Serious adverse reaction; SAS: Statistic software, SDV: Source data verification; SmPC: Summary of product characteristics; SUSAR: Suspected unexpected serious adverse reaction; TEAE: Treatment-emergent adverse event; TMF: Trial master file; TNM: Classification of malignant tumours

Supplementary Information

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Additional file 1. Table 1: Clinical trial schedule.

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none.

Authors' contributions

All authors have read and approved the manuscript. FG study design, PI of the HOLIPabANC trial, manuscript preparation; AD study design, Co-PI; FP study design, design of surgical procedures; AQ translational research program, study design, specimen handling, KL medical writing, project management; SH trial statistician, BD project management, study design; TG gastrointestinal oncology, study design, manuscript preparation; DW gastrointestinal oncology, study design, manuscript preparation, Co-PI; CB study design, Co-PI of the HOLIPANC trial, manuscript preparation.

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Availability of data and materials

The full study protocol and all regulatory documents can be provided by the sponsor upon request.

Declarations

Ethics approval and consent to participate

The local ethics committee of the University of Cologne (20–1544-AMG) and the local ethic committees of the participating centers throughout Germany approved the study. Patient's written informed consent prior to any trial-specific procedure must be given before study inclusion.

Consent for publication

not applicable.

Competing interests

There are no competing interests.

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The Association of Real-World CA 19-9 Level Monitoring Patterns and Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma

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Background: Pancreatic cancer is expected to be the third deadliest cancer in the US in 2021. Evaluation of treatment response in patients with mPDAC necessitates scheduled clinical and radiographic assessments along with monitoring serum CA 19-9 levels. Currently available single-institution data examining the importance of CA 19-9 monitoring cannot be generalized to real-world settings. We investigated the impact of serum CA 19-9 monitoring and its association with clinical outcomes in patients with mPDAC in a population-based setting.

Methods: Data were extracted from the Flatiron Health electronic health record (EHR)-derived de-identified database for patients diagnosed with mPDAC between January 1, 2015, and June 30, 2020. Serum CA 19-9 levels at baseline – defined as the values obtained ≤ 60 days prior to treatment initiation - and during treatment were extracted. CA 19-9 levels > 40 IU/mL were considered elevated. Survival outcomes were compared based on testing frequency, baseline CA 19-9 levels, and change in CA 19-9.

Results: 6,116 patients with mPDAC who received treatment were included in the analysis. The median age at diagnosis was 68 years (IQR: 61-75). Patients with normal baseline CA 19-9 experienced longer median survival than patients with elevated levels [1L: 8.8 months (95% CI: 7.9 - 10) *vs.* 7.2 months (6.8 – 7.5), $p < 0.001$; 2L: 7.2 months (6.1 – 9.2) *vs.* 5.2 months (4.9 – 5.6), $p < 0.001$; 3L: 6.1 months (5.4 – 9.1) *vs.* 3.9 months (3.4 – 4.3), $p < 0.001$]. Patients with decreasing/stable CA 19-9 during treatment experienced longer survival than patients who experienced an increase in CA 19-9 levels [1L: 10.9 months (10.5 – 11.3) *vs.* 5.4 months (5.1 – 5.9), $p < 0.0001$; 2L: 8.2 months (7.7 – 8.5) *vs.* 4.3 months (4.1 – 4.7), $p < 0.001$; 3L: 7.5 months (6.6 – 9.2) *vs.* 3.7 months (3.4 – 4.3), $p < 0.001$].

Conclusions: In one of the largest, contemporary, real-world studies of patients with mPDAC, elevated CA 19-9 level at treatment initiation demonstrated a prognostic impact.

CSPC Exhibit 1120
Page 71 of 447

Routine serial monitoring of CA 19-9 levels during treatment may be warranted, in addition to clinical and radiographic assessment, and may translate into better patient outcomes. Further validation studies are needed to understand the generalizability of these results.

Keywords: CA 19-9, metastatic pancreatic cancer, overall survival, prognostic factor, chemotherapy

INTRODUCTION

Pancreatic cancer is a lethal malignancy and has the highest mortality rate among all cancers (1). Although pancreatic cancer accounts for an estimated 3.6% of all cancers in the US, it is currently the 3rd leading cause of cancer-related death in the US after lung and colon cancers (1). Pancreatic ductal adenocarcinoma (PDAC) is the most frequent type of pancreatic cancer, representing approximately 85% of cases (2). Over 48,220 deaths by PDAC are reported annually in the US, and the incidence rate of PDAC is rising year-over-year. Despite the rapid advancement of treatment options for PDAC patients in recent years, the survival rates remain abysmal (3). The 5-year relative survival rate for all patients diagnosed with PDAC is 10% while the survival rate for patients with metastatic disease is below 3% (1).

Surgery remains the only potentially curative treatment for patients with PDAC (4) Due to the propensity of PDAC cells to metastasize early, up to 80% of patients receive a diagnosis at an advanced stage, by which time the tumor is unresectable (4). Only 10-20% of patients would have resectable tumors after careful neoadjuvant treatment, and chemotherapy is the only option for metastatic patients (5, 6).

Due to the aggressive nature of the disease, regular monitoring of patients on PDAC treatment is performed using clinical assessments supplemented with radiographic imaging in order to determine response to treatment and rule out disease progression (7). Currently, serum carbohydrate antigen 19-9 (CA 19-9) is the only biomarker approved by the Food and Drug Administration (FDA) for the management of pancreatic cancer (8). Serum CA 19-9, a sialylated Lewis blood group antigen, is an antigen associated with pancreatic cancer (9). The sensitivity and specificity of CA 19-9 tests are 80% and 80-90% respectively (10). CA 19-9 has been validated as an effective prognostic biomarker that can be used to aid in treatment decisions for patients with metastatic PDAC (mPDAC) (11–16). The objective of this study was, for the first time in a large, contemporary database, to assess the real-world use and outcomes associated with serum CA 19-9 monitoring in a population-based setting of mPDAC patients.

METHODS

Data Source

his retrospective descriptive analysis utilized the nationwide Flatiron Health® longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data. This database includes data from over 280 cancer clinics representing approximately 800 sites of care and more than 2.4 million active US cancer patients. The majority of patients in the database originate from the community oncology setting. The database meets the requirements of the Health Insurance Portability and Accountability Act of 1996 for fully de-identified data sets and subject to obligations to prevent re-identification to protect patient confidentiality. As the study was observational in nature and utilizes de-identified patient data, it is exempt from institutional review board review.

Study Population

For the primary study analysis, four mutually exclusive cohorts were constructed based on the CA 19-9 testing patterns. Patients were required to have an mPDAC diagnosis between January 1, 2015, and June 30, 2020 to be screened for eligibility. The date of the first-line (1L) treatment initiation during this timeframe denotes the study index date. Eligible patients were required to have at least 1 recorded activity within 90 days, on or after, their mPDAC diagnosis date. Patients were also required to be at least 18 years old at diagnosis, treated with 1L systemic therapy for PDAC, and have at least one recorded follow-up activity after the start of 1L treatment. If the patients were treated in second- (2L) and third-line (3L), they were required to have follow-up activity recorded in the database after initiating those respective lines of therapy. Exclusion criteria included the following: 1. absence of activity (visit/administration) on or after the respective index date; and 2. initiation of 1L therapy after the date of death.

Study Measures

The primary study measure was CA 19-9 testing pattern during systemic treatment stratified by the timing of testing and the number of tests that occurred during treatment. Overall survival (OS) was characterized by CA 19-9 testing patterns. CA 19-9 test timing, the duration of treatment stratified by CA 19-9 testing, the proportion of patients who proceeded to the next line of therapy, and OS from treatment initiation were evaluated. OS was assessed from the start of each line of therapy and patients with a death event were assigned the 15th day of the month of death as the event date. Patients without a death recorded in the database were censored at their last recorded clinical activity. OS was stratified based on the following: 1. CA 19-9 testing patterns (no tests observed, baseline tests, one test during treatment, multiple tests during treatment); 2. baseline CA 19-9 levels (Normal, Elevated, Missing); and 3. CA 19-9 change from baseline relative to the lowest value recorded during treatment (Decreasing/Same, Increasing, Missing).

Demographic characteristics, including age, gender, US geographic region (Northeast, South, Midwest, West, Other), race/ethnicity (Black, White, Hispanic, Asian, Other/Unknown), index year and practice type were assessed at the index date. Baseline clinical characteristics including stage at initial PDAC diagnosis, site of the primary tumor, Eastern Cooperative Oncology

CSPC Exhibit 1120
Page 72 of 447

Group (ECOG) Performance Status (closest score within 30 days prior or 7 days after the start of systemic treatment), presence of any previous surgery, surgery type, and the baseline serum CA 19-9 levels within 60 days prior the start of therapy were assessed. CA 19-9 levels greater than 40 U/mL were considered elevated.

Statistical Analysis

Descriptive analyses were performed for all study variables. Summary statistics such as mean and standard deviation were calculated for all continuous variables, and frequency counts and percentages were calculated for categorical variables. Kaplan-Meier methods were used to calculate median overall survival, and a p-value < 0.05 was considered statistically significant. Statistical significance for overall survival was evaluated using the log-rank test. All analyses were conducted using R (version 4.0.0).

RESULTS

Study Cohort

8,776 patients were identified with mPDAC diagnosis between January 1, 2015, and June 30, 2020. Most (n=8,134) of these patients had recorded activity within 90 days, on or after, the metastatic diagnosis date and were > 18 years of age at mPDAC diagnosis. About three-quarters (n=6,142) of these patients were treated with 1L systemic therapy. 6,118 patients met all the study selection criteria (**Supplementary Figure 1**). The final study analysis included four mutually exclusive cohorts defined by CA 19-9 testing patterns: no testing cohort (n=781), baseline test only cohort (n=1,082), one test during 1L treatment cohort (n=896), and multiple tests during 1L treatment cohort (n=3,359).

Demographic and Clinical Characteristics

Demographic and clinical characteristics for each treated cohort are presented in **Table 1**. Of the 6,118 mPDAC patients included, 39.3% (n=2,402) of patients were treated in 2L, and 12.9% (n=790) in 3L. The median age at metastatic diagnosis of patients across all cohorts was 68 years (IQR: 61-75), and 55% of the mPDAC patients were male. Overall, the majority of patients (67.1%) were White, while 8.5% were Black, 1.8% were Asian and only 0.2% were Hispanic. While all patients in the study were diagnosed with mPDAC, the majority (67.1%) of patients were initially diagnosed with stage IV disease while the

TABLE 1 | Patient demographics.

Characteristic	First Line Treated Patients, N = 6,118	Second Line Treated Patients, N = 2,402	Third Line Treated Patients, N = 790
Sex			
Female	2,782 (45%)	1,106 (46%)	372 (47%)
Male	3,336 (55%)	1,296 (54%)	418 (53%)
Age			
Mean [SD]	68 [10]	66 [10]	66 [9]
Median [IQR]	68 [61 - 75]	67 [60 - 73]	67 [60 - 73]
Race			
Asian	108 (1.8%)	54 (2.2%)	17 (2.2%)
Black or African American	519 (8.5%)	191 (8.0%)	53 (6.7%)
Hispanic or Latino	14 (0.2%)	6 (0.2%)	2 (0.3%)
White	4,106 (67%)	1,673 (70%)	582 (74%)
Other Race	788 (13%)	284 (12%)	82 (10%)
Missing/Unknown	583 (9.5%)	194 (8.1%)	54 (6.8%)
Geographic Region			
Midwest	698 (11%)	308 (13%)	100 (13%)
Northeast	913 (15%)	339 (14%)	104 (13%)
South	2,653 (43%)	990 (41%)	319 (40%)
West	847 (14%)	335 (14%)	110 (14%)
Unknown	1007 (16%)	430 (18%)	157 (20%)
Stage IV at Initial Diagnosis	4,120 (67%)	1,590 (66%)	540 (68%)
Tumor Location			
Body	1,188 (19%)	504 (21%)	169 (21%)
Head	3,045 (50%)	1,184 (49%)	385 (49%)
Overlapping Sites	588 (9.6%)	225 (9.4%)	72 (9.1%)
Pancreas, Nos	188 (3.1%)	61 (2.5%)	20 (2.5%)
Tail	1,109 (18%)	428 (18%)	144 (18%)
ECOG PS			
0	1,368 (22%)	473 (20%)	146 (18%)
1	2,045 (33%)	893 (37%)	315 (40%)
2+	795 (13%)	368 (15%)	119 (15%)
Missing	1,910 (31%)	668 (28%)	210 (27%)
Progressed to next line	2,324 (38%)	792 (33%)	217 (27%)
Duration of therapy, weeks			
Mean [SD]	17 [21]	14 [19]	17 [18]
Median [IQR]	10 [3 - 22]	8 [3 - 18]	12 [6 - 23]

ECOG, Eastern Cooperative Oncology Group; SD, Standard Deviation; IQR, Interquartile range.

CSPC Exhibit 1120
Page 73 of 447

remainder progressed to metastatic disease from earlier stage PDAC. Among patients who had their CA 19-9 assessed in the baseline period, most (84.7%) had elevated baseline CA 19-9.

Testing and Treatment Patterns

The median time between CA 19-9 tests was 3.5 weeks (IQR 2.1 - 5.6). 63% of patients with elevated baseline CA 19-9 received multiple tests while 54% of patients with normal baseline CA 19-9 level received multiple tests (**Table 2**). The testing interval among patients with elevated baseline CA 19-9 was lower than patients with normal CA 19-9 level (elevated: 4.1 weeks *vs.* normal: 6.6 weeks, $p < 0.001$). The median duration of 1L therapy among patients with the normal baseline CA 19-9 levels was 11 weeks (IQR: 4-24) while the median duration was 10 weeks (IQR: 3-23) among patients with the elevated baseline CA 19-9 levels and 8 weeks (IQR: 2-20) for those who were not assessed for CA 19-9 levels ($p < 0.001$). However, patients with elevated CA 19-9 levels at the start of treatment had worse median OS (mOS) compared to those with normal CA 19-9 levels at baseline (**Figure 1** and **Table 3**). The mOS for the patients who received 1L, 2L, and 3L treatments with elevated baseline CA 19-9 level was lower than the mOS of the patients with the normal baseline CA 19-9 (**Table 3**).

Patients who had baseline CA 19-9 assessments were more likely to have multiple CA 19-9 evaluations throughout the course of treatment, and these patients were also more likely to have elevated CA 19-9 levels. The majority (62.9%) of patients who were assessed for CA 19-9 prior to or during 1L treatment received multiple evaluations.

Further, mPDAC patients with multiple CA 19-9 tests were more likely to have better performance status and longer mOS (**Figures 2–4**). Patients who received multiple CA 19-9 assessments during their treatment course had the lowest proportion of patients with ECOG PS scores of 2+. Patients with multiple tests during their treatment had longer mOS than those with only 1 test or a test that only occurred prior to treatment (**Table 3**).

1L mPDAC treatment appeared to be associated with stable or decreasing CA 19-9 levels. Among the patients who were evaluable for CA 19-9 change during the 1L treatment (n=3,486), 73.6% had decreasing/the same CA 19-9 levels with a median change in CA 19-9 level of 70% (563 U/mL) while only 26.4% had an increase in CA 19-9 levels with a median change in CA 19-9 level of 56% (359 U/mL). Patients with stable and decreased CA 19-9 during 1L treatment relative to baseline had better mOS than patients whose CA 19-9 increased during treatment (**Table 3** and **Supplementary Figure 2**). Increasing CA 19-9 level from the baseline was associated with shorter median OS, and these trends remained when stratified by lines of therapy (**Table 3** and **Supplementary Figures 3, 4**). When stratified by tertile of CA 19-9 decrease, patients treated in 1L with the largest decrease experienced the longest mOS (**Supplementary Figure 5**).

TABLE 2 | CA 19-9 testing patterns and results.

Characteristic	First Line Treated Patients, N = 6,118	Second Line Treated Patients, N = 2,402	Third Line Treated Patients, N = 790
CA 19-9 Testing Frequency			
No Testing	781 (13%)	273 (11%)	97 (12%)
Baseline Only	1,082 (18%)	388 (16%)	163 (21%)
One Test During 1L	896 (15%)	418 (17%)	148 (19%)
Multiple 1L Tests	3,359 (55%)	1,323 (56%)	382 (48%)
Baseline CA 19-9 result			
Normal	701 (11%)	293 (12%)	94 (12%)
Elevated	3,867 (63%)	1,683 (70%)	569 (72%)
Missing	1,550 (25%)	426 (18%)	127 (16%)
CA 19-9 Baseline Value (U/mL)			
Mean [SD]	19,054 [80,993]	10,546 [43,473]	13,468 [39,493]
Median [IQR]	929 [106 - 6,271]	886 [132 - 4,309]	1,346 [148 - 7,386]
Unknown	1,550	426	127
CA 19-9 Trend during treatment			
Decreasing/Same	2,566 (42%)	924 (38%)	252 (32%)
Increasing	920 (15%)	664 (28%)	248 (31%)
Missing/No Tests	2,632 (43%)	814 (34%)	290 (37%)
CA 19-9 Change, Baseline to Nadir (U/mL)			
Mean [SD]	-6,831 [77,786]	-1,649 [32,215]	2,802 [36,261]
Median [IQR]	-111 [-1,892 - 2]	-12 [-656 - 236]	0 [-376 - 866]
Unknown	2,632	814	290
CA 19-9 Change, Baseline to Nadir (%)			
Mean [SD]	53 [2,710]	183 [5,413]	128 [914]
Median [IQR]	-47 [-85 - 5]	-13 [-61 - 47]	0 [-44 - 62]
Unknown	2,632	814	290
Time between CA 19-9 Tests, weeks			
Mean [SD]	4.9 [6.0]	4.1 [4.2]	8 [11]
Median [IQR]	3.5 [2.1 - 5.6]	3.1 [2.0 - 5.0]	4 [2 - 9]
Unknown	1,863	661	260

SD, Standard Deviation, IQR, Interquartile range.

CSPC Exhibit 1120
Page 74 of 447

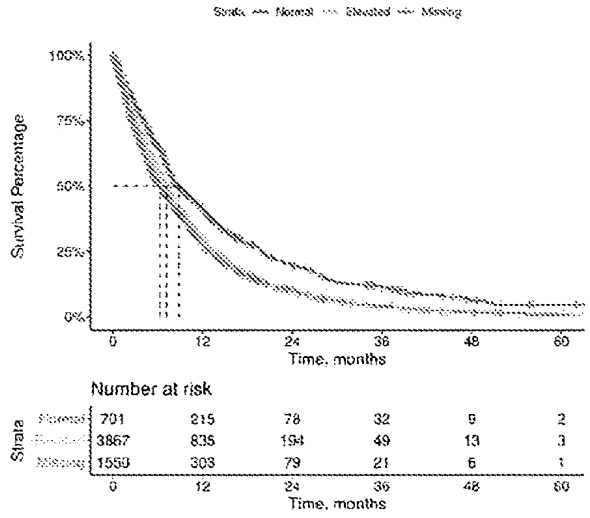

FIGURE 1 | Overall survival by Baseline Carbohydrate Antigen 19-9.

DISCUSSION

The results from this large retrospective observational study suggest serum CA 19-9 may serve as a prognostic tool to aid in decision-making for patients with mPDAC. An elevated CA 19-9 level at the start of treatment was associated with worse survival regardless of the line of therapy. Increasing CA 19-9 levels during the treatment relative to baseline was associated with shorter survival as well. This analysis suggests that in patients with mPDAC, both elevated and increasing CA 19-9 levels predict worse survival outcomes.

The clinical findings of this population-based study in the real-world setting are consistent with published data from prospective clinical trials (5, 17–20). The MPACT trial (NCT00844649) and the ACCORD11/PRODIGE4 trial (NCT00112658) were phase 3 randomized controlled trials (RCTs) which also investigated the role of CA 19-9 as a biomarker for mPDAC patients treated with chemotherapy in 1L settings (17, 18). The MPACT trial reported that any decline in CA 19-9 at 8-weeks from the baseline served as an early marker for chemotherapy efficacy. Additionally, the study noted CA 19-9 was more useful than radiologic assessments in identifying patients with a survival benefit. Likewise, ACCORD11/PRODIGE4 trial reported that a greater than 20% reduction in CA 19-9 at week-8 from the baseline was a predictor of significantly improved OS. The current analysis suggests that, in patients with mPDAC, stable and decreasing CA 19-9 levels (median reduction was 70%) was associated with improved median OS. A retrospective review of 8 clinical trials between April 1997 and May 2016 by Reni et al. reported that a more robust CA 19-9 response during chemotherapy (nadir), was associated with better outcome (19). mPDAC patients with CA 19-9 reduction by <50%, 50–89%, or >89% had a median survival of 7.4, 9.8, and 14.7 months, respectively ($p \leq 0.001$). mPDAC patients in our study experienced a median reduction in CA 19-9 of 70% during 1L treatment and their mOS from the start of 1L was 10.9 months (IQR: 10.5-11.3). Compared to the range of OS by Reni and et al., the OS in our analysis appears to be consistent. Reni et al. also reported that the basal CA 19-9 level and the time to CA 19-9 nadir were independent predictors of OS whereas CA 19-9 reduction was not. In our study, time to CA 19-9 reduction was not measured. However, both non-elevated basal CA 19-9 levels and CA 19-9 reduction during the treatment were associated with the survival benefit. An analysis of 181 prospectively enrolled patients at a single center by Pelzer et al. reported that increased CA 19-9 was associated with a lower survival rate indicating treatment failure (20). Our analysis also reports that increasing CA 19-9 level from the baseline was associated with shorter median OS regardless of the line of therapy.

Although our study did not correlate CA 19-9 response to radiographic response, it has been reported CA 19-9 can serve as

TABLE 3 | Overall survival by CA 19-9 baseline value, testing frequency, and trends.

Baseline CA 19-9 level*	1L Median Overall Survival, months (95% CI)	2L Median Overall Survival, months (95% CI)	3L Median Overall Survival, months (95% CI)
Overall	7.2 (6.9, 7.5)	5.4 (5.2, 5.8)	4.3 (3.9, 4.7)
Normal	8.8 (7.9, 10)	7.2 (6.1, 9.2)	6.1 (5.4, 9.1)
Elevated	7.2 (6.8, 7.5)	5.2 (4.9, 5.6)	3.9 (3.4, 4.3)
Missing	6.3 (5.7, 6.8)	5.5 (4.8, 6.5)	4.3 (3.5, 5.5)
CA 19-9 Testing Status*			
No Testing	3.8 (3.4, 4.4)	3.7 (3.3, 4.8)	3.4 (2.8, 4.5)
Baseline Only	1.9 (1.7, 2.0)	1.9 (1.6, 2.2)	1.9 (1.5, 1.9)
One Test During Treatment	4.2 (3.9, 4.5)	3.3 (3.0, 3.7)	2.8 (2.4, 3.6)
Multiple Tests During Treatment	10.6 (10.2, 10.9)	7.8 (7.3, 8.2)	6.5 (5.7, 7.4)
Change in CA 19-9 from baseline*			
Decreasing/Stable	10.9 (10.5, 11.3)	8.2 (7.7, 8.5)	7.5 (6.6, 9.2)
Increasing	5.4 (5.1, 5.9)	4.3 (4.1, 4.7)	3.7 (3.4, 4.3)
Missing/No Tests	3.9 (3.6, 4.2)	3.3 (3.0, 3.8)	2.5 (2.0, 3.2)

*p-value < 0.001 for each line of therapy based on the log-rank test.

CSPC Exhibit 1120
Page 75 of 447

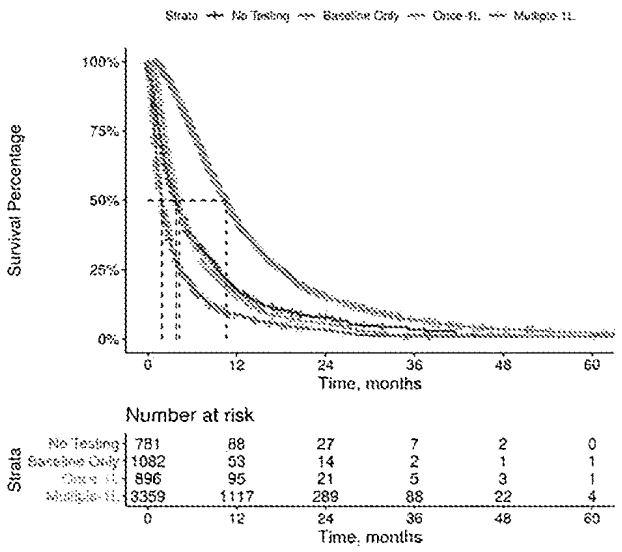

FIGURE 2 | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in first line.

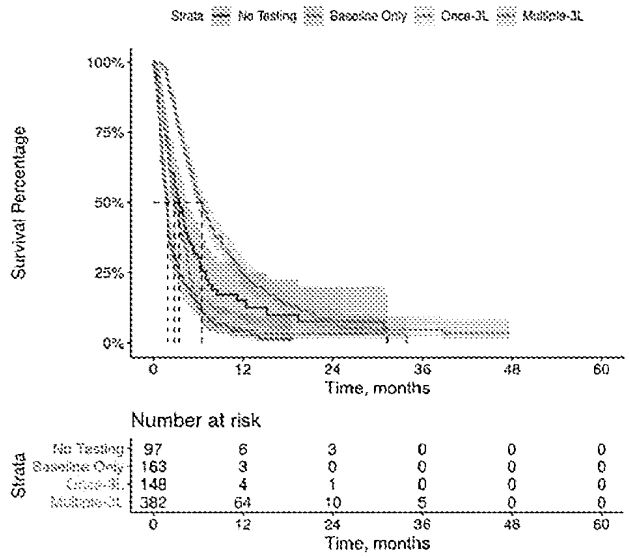

FIGURE 4 | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in third line.

the prognostic marker in predicting tumor growth rate (5). A CA 19-9 reduction of 20% or more from the baseline has been associated with improved survival as well as significant tumor shrinkage of -0.4% per day (21).

In the past decade, a plethora of biomarkers have been evaluated to assess their predictive and prognostic utility in mPDAC management; however, CA 19-9 remains the most clinically useful and investigated biomarker for PDAC (21). Clinical assessment of treatment response in patients with mPDAC may be confounded early in their treatment course due to the difficulty in separating disease related symptoms from treatment related toxicity. A robust biomarker like CA 19-9 can help differentiate the responders from non-responders before radiographic response assessment, thus maximizing treatment benefit for the responders and minimizing toxicity for the non-responders. Since the vast majority of patients with mPDAC experience a modest survival benefit with treatment, early identification of non-responders is pivotal, so that they do not lose the window for subsequent lines of therapy. Further, a down trending CA 19-9 may be an early indication for dose attenuation in a responder experiencing treatment related toxicity. Therefore, CA 19-9 monitoring should be employed early and serially in mPDAC patients with an elevated CA 19-9 level at diagnosis. Further, the prognostic value associated with CA 19-9 trends during treatment can inform providers, patients, and their families to make meaningful treatment choices while dealing with a devastating disease.

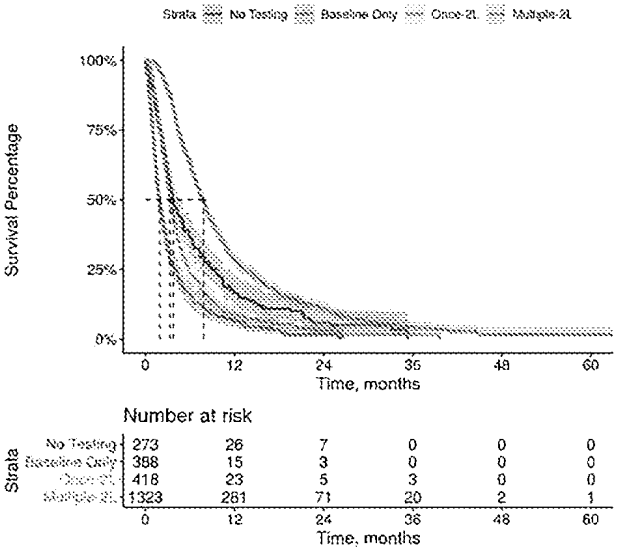

FIGURE 3 | Overall Survival by Carbohydrate Antigen 19-9 Testing Status among patients treated in second line.

Limitations

Our study provides important validation regarding the utility of CA 19-9 as a biomarker for the mPDAC population in real-world settings with one of the largest and most up-to-date data sources. However, some limitations inherent to retrospective observational studies are important to consider when interpreting our findings. The data collected are retrospective and collected for routine clinical care and not for research purposes. The clinical data were derived from an EHR. The recording of patient age is capped at 85 years in the database to protect patient confidentiality. The true age of some elderly patients with mPDAC and associated clinical outcomes could not be determined. In addition, these data are collected from primarily the community setting and may not be generalizable to other settings of care. Treated patients were subject to non-random allocation. The reason to forgo treatment by the patient

CSPC Exhibit 1120
Page 76 of 447

or physician is not available in these data. Similarly, the reasons why labs were not performed for patients are unavailable. Lastly, this study did not evaluate how specific treatment regimens impacted CA 19-9 levels and further research is necessary to characterize individual treatment regimens.

CONCLUSION

This study highlights the clinical utility of CA 19-9 levels and trends as a prognostic marker in patients with mPDAC. Further this study suggests the importance of serially monitoring CA 19-9 levels in patients with mPDAC to inform treatment decisions and optimize clinical outcome. Our analysis represents one of the largest contemporary real-world studies for mPDAC patients to date. In mPDAC patients with elevated CA 19-9 levels, routine serial monitoring during treatment is warranted.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health. Requests to access these datasets should be directed to DataAccess@flatiron.com.

AUTHOR CONTRIBUTIONS

BG: conceptualization, methodology, visualization, and review and editing. MK: conceptualization, formal analysis, investigation, methodology, project administration, resources, visualization, and writing—review and editing. AS: conceptualization, formal analysis, investigation, methodology, project administration, resources, visualization, and writing—review and editing. NL: analysis, resources, visualization, and review and editing. PC: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, and visualization. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.754687/full#supplementary-material

Supplementary Figure 1 | Study Cohort Attrition

Supplementary Figure 2 | Overall Survival by Carbohydrate Antigen 19-9 Trend among patients treated in first line

Supplementary Figure 3 | Overall Survival by Carbohydrate Antigen 19-9 Trend among patients treated in second line

Supplementary Figure 4 | Overall Survival by Carbohydrate Antigen 19-9 Trend among patients treated in third line

Supplementary Figure 5 | Overall Survival by Carbohydrate Antigen 19-9 decrease among patients treated in first line

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CSPC Exhibit 1120
Page 77 of 447

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CSPC Exhibit 1120
Page 78 of 447

Check for updates

Original Article

RESILIENT part 1: A phase 2 dose-exploration and dose-expansion study of second-line liposomal irinotecan in adults with small cell lung cancer

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BACKGROUND: RESILIENT (NCT03088813) is a phase 2/3 study assessing the safety, tolerability, and efficacy of liposomal irinotecan monotherapy in patients with small cell lung cancer and disease progression on/after first-line platinum-based therapy. Here, we present results from RESILIENT part 1. **METHODS:** This open-label, single-arm, safety run-in evaluation with dose-exploration and dose-expansion phases included patients ≥18 years old with Eastern Cooperative Oncology Group performance status of 0/1; those with asymptomatic central nervous system metastases were eligible. The primary objectives were to evaluate safety and tolerability and recommend a dose for further development. Efficacy end points were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **RESULTS:** During dose exploration, 5 patients received intravenous liposomal irinotecan at 85 mg/m^2 (deemed not tolerable; dose-limiting toxicity) and 12 patients received 70 mg/m^2 (deemed tolerable). During dose expansion, 13 additional patients received intravenous liposomal irinotecan at 70 mg/m^2. Of these 25 patients (median age [range], 59.0 [48.0-73.0] years, 92.0% with metastatic disease), 10 experienced grade ≥3 treatment-related treatment-emergent adverse events (TEAEs), most commonly diarrhea (20.0%) and neutropenia (16.0%), and 3 had serious treatment-related TEAEs, of whom 2 died. ORR was 44.0% (95% confidence interval [CI]: 24.40-65.07; 1 complete response, 10 partial responses) and median (95% CI) PFS and OS were 3.98 (1.45-4.24) months and 8.08 (5.16-9.82) months, respectively. **CONCLUSION:** Overall, no new safety signals were identified with liposomal irinotecan, and antitumor activity was promising. RESILIENT part 2, a randomized, controlled, phase 3 study of liposomal irinotecan versus topotecan, is ongoing.
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LAY SUMMARY:

- Small cell lung cancer (SCLC) is an aggressive disease with few treatment options after platinum-based therapy.
- Administering 1 option, irinotecan, as a "liposomal" formulation, may extend drug exposure and improve outcomes.
- The RESILIENT part 1 trial assessed the safety and efficacy of liposomal irinotecan in 25 adults with SCLC after disease progression despite platinum-based therapy.
- No new safety concerns were reported.
- The most common moderate-to-severe side effects were diarrhea (20% of patients) and neutropenia (16%).
- Tumors responded to treatment in 44% of patients.
- Average survival was 8.08 months, and time to disease progression was 3.98 months.
- Liposomal irinotecan trials are ongoing.

KEYWORDS: chemotherapy, liposomal irinotecan, platinum-resistant disease, small cell lung cancer, subsequent therapy.

INTRODUCTION

Small cell lung cancer (SCLC) is a rapidly progressive lung cancer accounting for approximately 15% of all lung cancers.[1] Most patients (60%-70%) have extensive-stage (ES) or metastatic disease at diagnosis, with a median overall survival (OS) of 8 to 12 months.[2,3] Although SCLC is usually sensitive to first-line treatment with etoposide, cisplatin, or carboplatin

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This trial was registered at ClinicalTrials.gov (NCT03088813; https://www.ClinicalTrials.gov/) and EudraCT (2017-004261-26; https://www.clinicaltrialsregister.eu/).

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alone or combined with atezolizumab or durvalumab, almost all patients with ES SCLC relapse, most commonly during the first year after initial treatment.[4-6]

Few treatment options exist in the second-line setting for patients with relapsed SCLC. Topotecan, the only treatment with full approval by the Food and Drug Administration in the United States and the European Medicines Agency in Europe for the second-line treatment of SCLC,[7,8] is associated with modest and transient antitumor activity, and its use is limited by hematological toxicities.[9,10] Other regimens for patients with relapsed SCLC have failed to improve outcomes compared with topotecan in the second-line setting[11-15] or have shown low or modest clinical activity.[16,17]

Based on an overall response rate of 35.2% in the phase 2 study,[18] lurbinectedin, an alkylating agent, was granted accelerated approval in 2020 by the US Food and Drug Administration for the treatment of adult patients with metastatic SCLC whose disease progressed on or after platinum-based chemotherapy.[19] However, the ATLANTIS phase 3 study, which compared lurbinectedin in combination with doxorubicin with the physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) in adults with SCLC whose disease had progressed following 1 prior platinum-containing line, did not meet the primary end point of improving OS.[20,21] Compared with topotecan or CAV in the ATLANTIS study, objective response rate (ORR) was 31.6% with lurbinectedin/doxorubicin versus 29.7% (P = .6616), median progression-free survival (PFS) was 4.0 months with lurbinectedin/doxorubicin versus 4.0 months (hazard ratio [HR], 0.831; P = .0437), and median OS was 8.6 months with lurbinectedin/doxorubicin versus 7.6 months (HR, 0.967; P = .7032).[20,21] Therefore, there is an unmet need for new treatments for patients with relapsed SCLC.

Although nonliposomal irinotecan is a well-established component of the ES SCLC treatment landscape in the first- and second-line settings,[22] increased gastrointestinal toxicity relative to etoposide/platinum-based regimens and topotecan has limited the use of this compound outside of Japan.[23-26] However, preclinical and clinical data suggest that liposomal irinotecan (ONIVYDE, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM-398, and PEP02) may provide additional benefits compared with nonliposomal irinotecan. Liposomal irinotecan shows prolonged circulation compared with nonliposomal irinotecan,[27] and preclinical data suggest that prolonged exposure to irinotecan may be more important than high concentrations for cytotoxic activity and may be better tolerated.[28] Liposomal irinotecan plus 5-fluorouracil/leucovorin is recommended in US and European guidelines for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy, on the basis of the NAPOLI-1 study.[22,29-31]

RESILIENT (ClinicalTrials.gov identifier NCT03088813) is a 2-part phase 2/3 study designed to assess the safety, tolerability, and efficacy of liposomal irinotecan monotherapy as a second-line treatment for patients with SCLC. Here, we report the results of the final analysis of part 1, which includes dose-exploration and dose-expansion phases, and is the phase 2 part of the study.

MATERIALS AND METHODS

Patients

Eligible patients were 18 years of age or older with histopathologically or cytologically confirmed SCLC according to the International Association for the Study of Lung Cancer classification; evaluable disease defined by the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1); Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1; and radiologically confirmed disease progression on or after first-line platinum-based chemotherapy. Patients with asymptomatic, radiologically stable central nervous system (CNS) metastases were eligible. Full details of inclusion and exclusion criteria are provided in the Supporting Information.

Study Design and Treatment

RESILIENT part 1 was an open-label, single-arm, safety run-in evaluation with dose-exploration and dose-expansion phases. Patients received intravenous liposomal irinotecan at 85 or 70 mg/m^2 (free base; approximately equivalent to 100 or 80 mg/m^2, respectively, for the hydrochloric trihydrate salt) over 90 minutes every 2 weeks in a 6-week cycle. Treatment was continued until disease progression or unacceptable toxicity related to study treatment; pauses in treatment were permitted as detailed in the Supporting Information. A follow-up visit was conducted 30 days after treatment discontinuation; patients then entered long-term follow-up, during which survival data were collected every month until the patient died or withdrew consent or the study ended.

Dose exploration and dose expansion were performed according to a "6 + 6 + 12" design as described in the Supporting Information. Patients were initially

CSPC Exhibit 1120
Page 80 of 447

allocated to receive liposomal irinotecan 85 mg/m^2 with a contingency plan for enrollment into a 70 mg/m^2 cohort according to dose-limiting toxicity (DLT) rules (described in detail in the Supporting Information). DLTs were evaluated for the first 12 patients treated during the first 28 days of treatment, or up to 14 days after the second dose if there was a treatment delay for reasons other than DLT. A safety review committee comprising the investigators and the medical monitor(s) of the sponsor was responsible for supervising review of DLTs and other safety data and the decision to implement enrollment into the 70 mg/m^2 cohort.

Use of granulocyte-colony stimulating factor (G-CSF) was not mandatory, but could be used to manage neutropenia at the discretion of the investigator.

Study Oversight

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. The protocol was approved by the local institutional review board and independent ethics committees of the participating centers. Patients provided written informed consent at screening. Protocol amendments made after the study started are described in the protocol.

Assessments and End Points

The primary objectives of RESILIENT part 1 were to describe the safety profile and tolerability of liposomal irinotecan monotherapy and to determine the recommended dose for the second (phase 3) part of the study. The secondary objective was to assess preliminary efficacy. Post hoc descriptive analyses of efficacy outcomes in patients with platinum-sensitive and platinum-resistant disease and in those with brain and/or CNS metastases at baseline were also conducted. The effect of liposomal irinotecan on cardiac safety was described as an exploratory objective.

Adverse events (AEs) and treatment-emergent AEs (TEAEs) were recorded, and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Vital signs, serum chemistry, and full blood counts were also assessed.

Tumor assessments were performed by computed tomography or magnetic resonance imaging at screening (baseline), every 6 weeks until progressive disease using RECIST (version 1.1) guidelines, and at the 30-day follow-up visit. Preliminary efficacy end points were ORR, PFS, and OS. The date of data cutoff for safety and preliminary efficacy analyses was August 20, 2020.

Among patients receiving the recommended dose of liposomal irinotecan, post hoc subgroups were defined by patients' platinum sensitivity. Platinum-sensitive and platinum-resistant groups were defined as patients without progression and with progression, respectively, while receiving, or in the 90 days after completion of, first-line platinum-based therapy. Analyses of ORR and disease control rate at 12 weeks (DCR_{12wks}) in these subgroups were conducted when all patients had received at least 12 weeks of follow-up (date of data cutoff: May 8, 2019).

Electrocardiogram measurements were taken during the first treatment cycle on day 1 (pre dose, at the end of infusion, and 2 hours after the end of the infusion), on day 2 (at approximately 24 hours after infusion), on day 8, and on day 15 (pre dose). QTc interval was evaluated using the Fridericia method (QTcF), and the relationship between changes in QTcF and plasma concentration of irinotecan and its active metabolite, SN-38, was investigated using a linear mixed-effects modeling approach.

Statistical Analyses

A sample size of 24 patients (at the selected dose level of liposomal irinotecan) was considered sufficient to provide a preliminary assessment of efficacy end points; therefore, evaluation of data from up to 36 patients was planned in the dose-exploration and dose-expansion phases. Safety and efficacy profiles were summarized descriptively in the safety and efficacy populations, which each comprised all patients who received at least 1 dose of liposomal irinotecan. Statistical analyses were performed using SAS software, version 9.3 or higher (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Dose Exploration and Expansion

Between April 25, 2018, and February 26, 2019, 30 patients were enrolled from sites in Spain, the United States, and Australia. Four of the 5 patients allocated to receive intravenous liposomal irinotecan at 85 mg/m^2 experienced DLTs (grade 3 diarrhea [n = 3] and grade 3 abnormal liver function test [n = 1]). Following review of DLTs, liposomal irinotecan at 85 mg/m^2 was not considered tolerable and enrollment into the 70 mg/m^2 cohort was initiated. Two of the first 6 patients enrolled in the 70 mg/m^2 cohort experienced DLTs (grade 5 abdominal

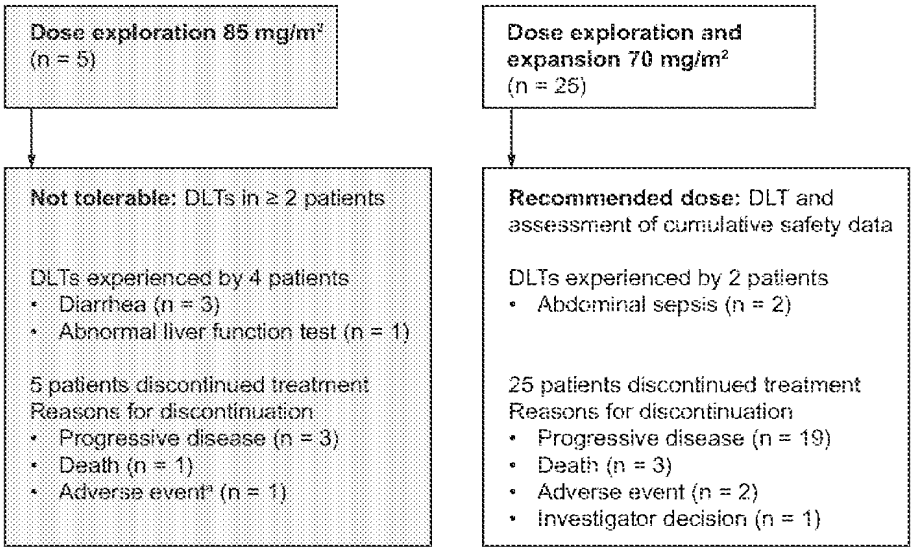

Figure 1. The flow of patients through the study. [a]Study drug-related adverse event before disease progression. DLT indicates dose-limiting toxicity.

sepsis [n = 2]) (Fig. 1). Both patients with abdominal sepsis presented with neutropenia; 1 patient presented with confirmed influenza A infection, whereas in the other patient the cause was unknown. A further 6 patients were enrolled into the 70 mg/m^2 cohort during dose exploration; no DLTs were observed in these patients. Following review of safety in this cohort, liposomal irinotecan at 70 mg/m^2 was selected as the recommended dose for expansion, and a further 13 patients were enrolled.

Baseline Characteristics

In total, 25 of the 30 patients enrolled in the study received liposomal irinotecan at the recommended dose of 70 mg/m^2 (Table 1). Patients receiving liposomal irinotecan at 70 mg/m^2 were of the median age of 59.0 years (range, 48.0-73.0 years), 64.0% were women, 88.0% had an ECOG PS score of 1, and 92.0% had metastatic disease. Three patients had brain and/or CNS metastases, of whom 1 had received prior radiotherapy for CNS lesions.

Treatment

Patients received intravenous liposomal irinotecan at 70 mg/m^2 for a mean (standard deviation) duration of 17.7 (14.9) weeks (Table 2). The median (range) number of treatment cycles was 2 (1-11). Dose reduction occurred in 7 patients, all of which were due to AEs. Eleven patients had doses delayed, interrupted, or withdrawn. All 25 patients discontinued treatment; reasons for discontinuation were disease progression (19 patients), death (3 patients), AEs (2 patients), and the investigator's decision (1 patient) (Fig. 1). Among those who had received liposomal irinotecan at 70 mg/m^2, 18 patients went on to receive subsequent therapy, most commonly paclitaxel (7 of 18 patients, 39%).

Safety and Tolerability

All patients enrolled in the study experienced at least 1 TEAE, and 29 patients (96.7%) experienced at least 1 TEAE considered related to study treatment (Table 2 and Supporting Table 1). Of those receiving liposomal irinotecan at 70 mg/m^2, 10 patients (40.0%) experienced grade 3 or higher treatment-related TEAEs, most commonly diarrhea (5 patients, 20.0%) and neutropenia (4 patients, 16.0%); 1 patient (4.0%) experienced febrile neutropenia (Table 2 and Supporting Table 2).

Thirteen patients receiving liposomal irinotecan at 70 mg/m^2 experienced serious TEAEs, of whom 3 experienced TEAEs that were considered related to study treatment (Table 2 and Supporting Tables 2 and 3). Two patients died of treatment-related TEAEs (abdominal sepsis) and 4 died of TEAEs considered unrelated to treatment. TEAEs led to discontinuation in 2 patients and dose reductions in 7 patients (Table 2).

There was no prophylactic use of G-CSF during the study, and 3 of the 25 patients who received liposomal irinotecan at 70 mg/m^2 received G-CSF after initiation of study treatment. Laboratory and other safety assessment results were in line with the expected safety profile of liposomal irinotecan.

CSPC Exhibit 1120

Page 82 of 447

TABLE 1. Demographic and Disease Characteristics at the Baseline

Characteristic	Liposomal Irinotecan 85 mg/m^2 (n = 5)	Liposomal Irinotecan 70 mg/m^2 (n = 25)	All Patients (N = 30)
Age, y			
Mean (SD)	63.4 (5.03)	59.8 (7.22)	60.4 (6.96)
Median (range)	62.0 (59.0-72.0)	59.0 (48.0-73.0)	61.5 (48.0-73.0)
Women, No. (%)	2 (40.0)	16 (64.0)	18 (60.0)
White, No. (%)	5 (100.0)	25 (100.0)	30 (100.0)
ECOG PS score, No. (%)			
0	1 (20.0)	3 (12.0)	4 (13.3)
1	4 (80.0)	22 (88.0)	26 (86.7)
Smoking status, No. (%)			
Current	0	7 (28.0)	7 (23.3)
Former	5 (100.0)	18 (72.0)	23 (76.7)
Never	0	0	0
Disease status, No. (%)			
Locally advanced	0	2 (8.0)	2 (6.7)
Metastatic	5 (100.0)	23 (92.0)	28 (93.3)
Key metastatic site(s), No. (%)			
Brain and/or CNS	0	3 (12.0)	3 (10.0)
Hepatic	1 (20.0)	3 (12.0)	4 (13.3)
Bone and locomotor	3 (60.0)	4 (16.0)	7 (23.3)
Time since diagnosis, wk			
Mean (SD)	40.3 (19.2)	44.8 (30.8)	43.9 (28.8)
Median (range)	35.0 (20.1-68.3)	37.7 (9.9-142.7)	35.1 (9.9-142.7)
Time since recent progression, wk			
Mean (SD)	4.3 (3.3)	3.5 (2.8)	3.7 (2.9)
Median (range)	3.4 (0.4-9.3)	3.2 (0.1-12.1)	3.3 (0.1-12.1)
Prior radiotherapy, No. (%)			
Yes	4 (80.0)	17 (68.0)	21 (70.0)
Previous therapies, No. (%)			
Platinum-etoposide	5 (100.0)	25 (100.0)	30 (100.0)
Immunotherapy	0	1 (4.0)	1 (3.3)
Other	0	0	0
Best response to previous therapies, No. (%)			
Complete response	0	1 (4.0)	1 (3.3)
Partial response	2 (40.0)	16 (64.0)	18 (60.0)
Stable disease	1 (20.0)	2 (8.0)	3 (10.0)
Progressive disease	2 (40.0)	3 (12.0)	5 (16.7)
Unknown	0	3 (12.0)	3 (10.0)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

TABLE 2. Duration of Treatment, Cumulative Doses, and Overview of TEAEs

	Liposomal Irinotecan 85 mg/m^2 (n = 5)	Liposomal Irinotecan 70 mg/m^2 (n = 25)	All Patients (N = 30)
Duration of treatment, mean (SD), wk	12.3 (9.2)	17.7 (14.9)	16.8 (14.2)
Total dose received, median (range), mg	687.0 (160.0-1109.4)	714.0 (146.0-2295.8)	696.0 (146.0-2295.8)
TEAEs, No. (%)			
Any TEAE	5 (100.0)	25 (100.0)	30 (100.0)
Any treatment-related TEAE	5 (100.0)	24 (96.0)	29 (96.7)
Grade ≥3	5 (100.0)	10 (40.0)	15 (50.0)
Any TEAE leading to discontinuation	1 (20.0)	2 (8.0)	3 (10.0)
Any TEAE leading to dose reduction	4 (80.0)	7 (28.0)	11 (36.7)
Any serious TEAE	4 (80.0)	13 (52.0)	17 (56.7)
Leading to death	1 (20.0)	6 (24.0)	7 (23.3)
Related to treatment	2 (40.0)	3 (12.0)	5 (16.7)
Treatment-related TEAE of grade ≥3 occurring in ≥5% of patients			
Diarrhea	3 (60.0)	5 (20.0)	8 (26.7)
Neutropenia	1 (20.0)	4 (16.0)	5 (16.7)
Abdominal sepsis	0	2 (8.0)	2 (6.7)
Anemia	0	2 (8.0)	2 (6.7)
Asthenia	0	2 (8.0)	2 (6.7)
Thrombocytopenia	0	2 (8.0)	2 (6.7)
Fatigue	1 (20.0)	1 (4.0)	2 (6.7)
Hypokalemia	1 (20.0)	1 (4.0)	2 (6.7)
Hypomagnesemia	1 (20.0)	1 (4.0)	2 (6.7)

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse event.

TABLE 3. Summary of Antitumor Activity and Outcomes

	Liposomal Irinotecan 85 mg/m^2 (n = 5)	Liposomal Irinotecan 70 mg/m^2 (n = 25)	All Patients (N = 30)
Best overall response, No. (%)			
CR	0	1 (4.0)	1 (3.3)
PR	2 (40.0)	10 (40.0)	12 (40.0)
Stable disease	1 (20.0)	7 (28.0)	8 (26.7)
Progressive disease	1 (20.0)	5 (20.0)	6 (20.0)
NE	1 (20.0)	2 (8.0)	3 (10.0)
Objective response rate, % (95% CI)			
CR + PR	40.0 (5.27 to 85.34)	44.0 (24.40 to 65.07)	43.3 (25.46 to 62.57)
Duration of response			
Median (95% CI), mo	8.80 (4.11 to NE)	2.99 (2.37 to 7.03)	3.78 (2.43 to 7.03)

Abbreviations: CI, confidence interval; CR, complete response; NE, not evaluable; PR, partial response.

Preliminary Efficacy

In 25 patients receiving liposomal irinotecan at 70 mg/m^2, complete response was observed in 1 patient, partial response was observed in 10 patients, and stable disease was observed in 7 patients. The ORR was 44.0% (95% confidence interval [CI], 24.40-65.07) and the median duration of objective response (DOR) was 2.99 months (95% CI, 2.37-7.03) (Table 3). The median (95% CI) PFS and OS were 3.98 (1.45-4.24) months (Fig. 2A) and

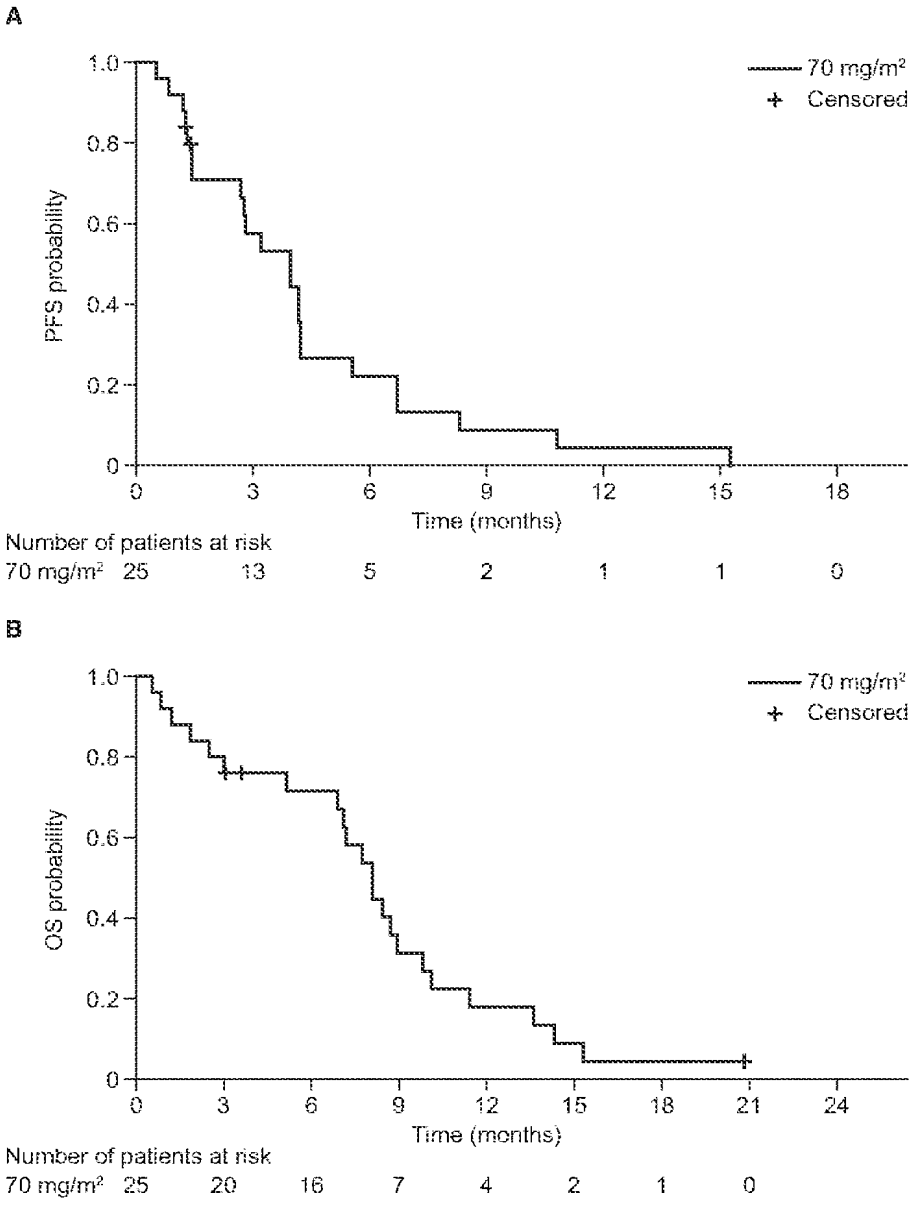

Figure 2. (A) PFS and (B) OS in patients receiving liposomal irinotecan 70 mg/m^2. OS indicates overall survival; PFS, progression-free survival.

8.08 (5.16-9.82) months (Fig. 2B), respectively, with 22 deaths reported. Among 3 patients with censored data, 1 was still receiving treatment.

Post Hoc and Exploratory Analyses

Among patients receiving liposomal irinotecan at the recommended dose of 70 mg/m^2, baseline characteristics were balanced between the platinum-sensitivity subgroups (Supporting Table 5). Median duration of exposure was numerically higher in the platinum-sensitive subgroup than in the platinum-resistant subgroup, and a higher proportion of patients in the platinum-sensitive subgroup remained on treatment at data cutoff. In 15 patients with platinum-sensitive disease, partial response was observed in 8 patients, and stable disease was observed in 3 patients. In 10 patients with platinum-resistant disease, partial response was observed in 3 patients, and stable disease was observed in 4 patients. No patients in either subgroup had a complete response. ORR and DCR_{12wks} were 53.3% and 60%, respectively, in the platinum-sensitive subgroup and 30% for both measures in the platinum-resistant subgroup. Tumor

CSPC Exhibit 1120
Page 84 of 447

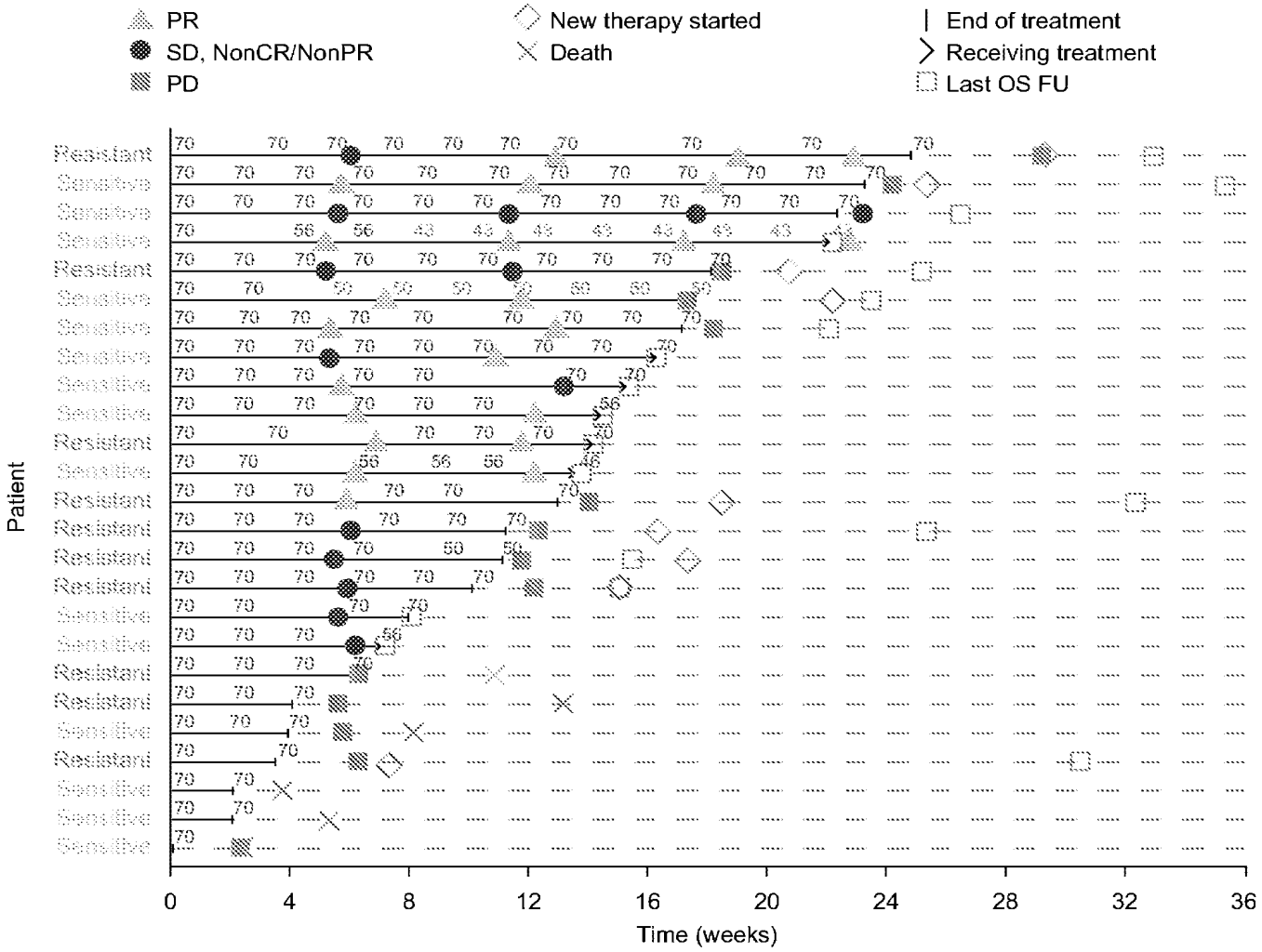

Figure 3. Duration of response by platinum-sensitivity subgroups. Date of data cutoff: May 8, 2019. CR indicates complete response, OS FU, overall survival follow-up; PD, progressive disease; PR, partial response; SD, stable disease.

response over time is shown in Figure. 3. These data (based on a data cutoff of May 8, 2019) were not part of the formal analysis of the study and should be considered as hypothesis-generating only. The efficacy of 70 mg/m^2 liposomal irinotecan in patients with platinum-sensitive and platinum-resistant disease will be explored as part of the ongoing RESILIENT part 2 study.

Among the 3 patients with brain and/or CNS metastases at baseline, stable disease was observed in 2 patients, and disease progression was observed in 1 patient, as per RECIST (version 1.1). In 1 of the patients with stable disease, PFS was 5.52 months and OS was 7.82 months.

Mean changes from baseline QTcF in patients receiving liposomal irinotecan at 70 mg/m^2 (baseline, n = 20; on treatment, n = 12) ranged from 6.9 milliseconds (ms) on day 1 to −6.2 ms on day 8. Analyses of the relationship between QTcF and plasma concentrations of irinotecan and SN-38 demonstrated that, at the dose studied, there was no clinically concerning effect of liposomal irinotecan on QTcF (ie, an increase of >20 ms).

DISCUSSION

Extensive-stage SCLC remains a difficult-to-treat disease with limited treatment options for patients. The data presented here, from part 1 of the phase 2/3 RESILIENT study, indicate that liposomal irinotecan monotherapy was well-tolerated and has promising antitumor activity when used as a second-line treatment for patients with SCLC whose disease has progressed following platinum-based first-line therapy.

The safety profile of liposomal irinotecan (as monotherapy and in combination with 5-fluorouracil/leucovorin) is well-established; the most common TEAEs are severe diarrhea and myelosuppression or severe neutropenia.[32] Without head-to-head studies, the safety profile of liposomal irinotecan monotherapy cannot be reliably compared with that of established SCLC therapies; however, based on the known safety profile of liposomal irinotecan, no unexpected safety outcomes were observed in RESILIENT part 1. The most common grade 3 or higher TEAEs in patients receiving the recommended dose of liposomal irinotecan (70 mg/m^2) were diarrhea (20%) and neutropenia (16%). TEAEs led to discontinuation in 2 patients and dose reductions in 7 patients. These findings are in line with those from studies of liposomal irinotecan-containing regimens in patients with mPDAC, although meaningful comparisons are limited by the fact that these trials examined combination therapies and used different doses of liposomal irinotecan.[31,33,34]

Although the safety profile of liposomal irinotecan in the current study was in line with previous data, and the 70 mg/m^2 dose is expected to be manageable, the level of toxicity was not insignificant. In particular, 3 patients receiving the recommended dose of liposomal irinotecan experienced serious treatment-related TEAEs, 2 of whom died as a result. As the study of liposomal irinotecan in patients with SCLC moves into phase 3, it will be important to gain further understanding of how best to manage TEAEs in these patients and how to minimize any negative impact on their quality of life.

Topotecan and lurbinectedin are currently the only approved therapies for the second-line treatment of patients with SCLC, but CAV and platinum rechallenge are also recommended treatment options.[22,35] Hematological toxicities are common among patients receiving topotecan and lurbinectedin; over 50% and 46% of patients receiving topotecan and lurbinectedin, respectively, experienced grade 3 to 4 neutropenia.[15,18,36] With the caveats of cross-trial comparison, the proportion of patients with neutropenia in RESILIENT part 1 was lower than that observed in trials of topotecan and lurbinectedin. Data from RESILIENT part 1 indicate that head-to-head comparisons between liposomal irinotecan monotherapy and other recommended treatment options are warranted.

The efficacy of liposomal irinotecan monotherapy in the second-line SCLC setting also warrants further investigation. The ORR in patients receiving the recommended dose of 70 mg/m^2 was 44.0%, and the median DOR was 2.99 months. The median OS was 8.08 months, which is notable, given that the population included patients with resistant disease and a small number with brain and/or CNS metastases. Preliminary analyses of ORR and DCR_{12wks} in post hoc subgroups conducted after at least 12 weeks of follow-up demonstrated that liposomal irinotecan 70 mg/m^2 has antitumor activity in patients with platinum-sensitive disease and in those with platinum-resistant disease.

To date, ORRs reported with topotecan (0%-37% and 0%-12% in patients with platinum-sensitive and platinum-resistant disease, respectively) and CAV (18.3%) have been modest.[36,37] Indeed, among patients with platinum-sensitive relapsed SCLC (defined as those who experienced relapse ≥90 days after completion of first-line etoposide doublet treatment), rechallenge with carboplatin/etoposide was superior to topotecan monotherapy as a second-line treatment.[38] In this previous study by Baize et al,[38] with a more favorable patient group than that of RESILIENT part 1, topotecan produced an ORR of 25%, a median PFS of 2.7 months, a median OS of 7.4 months, and 22% of the patients had grade 3 to 4 neutropenia. The standard 5-day intravenous administration schedule for topotecan can be burdensome for some patients. The ongoing RESILIENT part 2 study will compare 70 mg/m^2 liposomal irinotecan with that of topotecan administered intravenously, however, oral topotecan is also available, and has been shown to have similar efficacy to the intravenous formulation.[39]

Although lurbinectedin recently demonstrated an ORR of 35.2% (45.0% and 22.2% in patients with platinum-sensitive and platinum-resistant disease, respectively) in a single-arm phase 2 study that excluded patients with brain and/or CNS metastases at baseline,[18] the impact of lurbinectedin on disease progression is unclear because the phase 3 trial failed to meet its primary end point.[20] However, lurbinectedin in combination with irinotecan has demonstrated antitumor activity in a phase 1b-2 trial, with an ORR of 61.5% in 13 patients with SCLC.[40]

Nonliposomal irinotecan is an established treatment option for patients with SCLC whose disease is sensitive to platinum-based first-line therapy.[22,41] Studies in patients treated with nonliposomal irinotecan suggest that UGT1A1*28 7/7 homozygosity is associated with increased SN-38 concentrations and a higher incidence of hematological toxicity than other genotypes and that these associations are dose-dependent.[42] Preliminary data describing the pharmacokinetics of liposomal irinotecan in patients enrolled in RESILIENT part 1 have been

CSPC Exhibit 1120

Page 86 of 447

reported elsewhere and indicate that UGT1A1*28 status does not have a significant impact on the clearance of SN-38 in patients with SCLC.[43] Given the small number of patients included in the current study, and the fact that few patients had the UGT1A1*28 7/7 homozygous genotype, a detailed pharmacokinetic characterization was not possible; additional data will be generated as part of the ongoing phase 3 RESILIENT part 2 study, and this will allow a full pharmacokinetic analysis to be undertaken in the future.

The main strength of this study is the enrollment of a representative population, including patients with platinum-resistant disease and a small number of patients with brain and/or CNS metastases. Limitations inherent in the design of this study include: the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the nonrandomized design; and the absence of a control group. In addition, only 1 patient in this study had received immunotherapy plus chemotherapy as their first-line treatment, which may limit the interpretation of these data given the increasing use of immunotherapy in the first-line setting.

In conclusion, the promising results from this single-arm phase 2 study in patients with SCLC whose disease had progressed with platinum-based first-line therapy indicate that further evaluation of the efficacy and safety of liposomal irinotecan monotherapy at the recommended dose of 70 mg/m^2 is warranted. RESILIENT part 2, a phase 3, randomized, controlled trial is ongoing and will compare the efficacy and safety profile of liposomal irinotecan with that of topotecan in patients with SCLC in the second-line setting.

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CONFLICT OF INTEREST DISCLOSURES

Luis Paz-Ares is cofounder of Altum Sequencing and an external board member for Genomica; has received travel and accommodation grants from AstraZeneca, Bristol-Myers Squibb, Lilly, MSD, Pfizer, and Roche and honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, Ipsen, Lilly, Merck Serono, Mirati, MSD, Novartis, Pfizer, PharmaMar, Roche/Genentech, and Sysmex; and has other relationships (immediate family member) with Amgen, Ipsen, Merck, Novartis, Pfizer, Roche, Sanofi, and Servier. David R. Spigel is a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Genentech/Roche, Novartis, and Pfizer; has received institutional research/grant funding from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, Eli Lilly, Genentech/Roche, Merck, Novartis, Peregrine Pharmaceuticals, Pfizer, OncoGenex, OncoMed, Verastem Oncology, and the University of Texas Southwestern Medical Center—Simmons Cancer Center; and has a relationship with Bristol-Myers Squibb. Yuanbin Chen has received honoraria from Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Guardant Health, Heron Therapeutics, Merck, Novartis, Pfizer, and Takeda; is a consultant for Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Genentech, Heron Therapeutics, Novartis, Pfizer, and Takeda; serves on speakers' bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Guardant Health, Merck, Novartis, and Takeda; has received institutional research/grant funding from AstraZeneca, Bristol-Myers Squibb, Guardant Health, Helsinn, Ipsen, and Roche; gives expert testimony for AstraZeneca and Takeda; and participates in clinical trials for AstraZeneca, Bristol-Myers Squibb, Ipsen, and Roche. Maria Jove is a consultant for Boehringer Ingelheim and has received travel and accommodation support from Bristol-Myers Squibb, MSD, and Roche. Oscar Juan-Vidal is a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, and Merck; has received institutional research/grant funding from AstraZeneca and Bristol-Myers Squibb; and has received travel and accommodation support from Boehringer Ingelheim, Merck, and Roche. Reyes Bernabe Caro is a consultant for AstraZeneca, Bristol-Myers Squibb, and Roche and has received travel and accommodation support from Bristol-Myers Squibb and Roche. Alejandro Navarro is a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Roche; gives expert testimony for Oryzon Genomics; and has received travel and accommodation support from Boehringer Ingelheim and Pfizer. Afshin Dowlati is a consultant for AbbVie/Stemcentrx and ARIAD Pharmaceuticals and has received institutional research/grant funding from Amgen, Bristol-Myers Squibb, Eli Lilly/ImClone Systems, EMD Serono, MedImmune, and OncoMed. Santiago Ponce is a consultant for Roche, serves on a speakers' bureau for Bristol-Myers Squibb, and has received travel and accommodation support from RSD Pharma. Paul A. Bunn is a consultant for AstraZeneca, Ascentage, C-Stone, Celgene, Genentech, Imidex, Ipsen, Merck, and Viecure. Bin Zhang is an employee of Ipsen. Yan Moore is an employee of Ipsen. Xiaopan Yao is an employee of Ipsen. Jaba Kokhreidze was an employee of Ipsen at the time of the study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Luis Paz-Ares: Acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **David R. Spigel:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Yuanbin Chen:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Maria Jove:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Oscar Juan-Vidal:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Patricia Rich:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Theresa Hayes:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Vanesa Gutiérrez Calderón:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Reyes Bernabe Caro:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Alejandro Navarro:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects

of the work. **Afshin Dowlati:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Bin Zhang:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Yan Moore:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Xiaopan Yao:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Jaba Kokhreidze:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Santiago Ponce:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work. **Paul A. Bunn:** Conception and design, acquisition, analysis, or interpretation of data for the work, drafting of the work or its critical revision for important intellectual content, final approval of the manuscript, and accountability for all aspects of the work.

DATA AVAILABILITY

Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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CSPC Exhibit 1120

Page 88 of 447

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CLINICAL TRIAL

Phase I study of liposomal irinotecan in patients with metastatic breast cancer: findings from the expansion phase

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Abstract

Purpose Metastatic breast cancer (mBC) remains incurable and is associated with low survival rates. This study assessed the efficacy and safety of liposomal irinotecan in heavily pretreated patients with mBC, with or without active brain metastases (BM).

Methods Following the dose escalation phase and determination of recommended phase 2 dose, the expansion phase of this phase I, open-label, non-randomized study, assigned adult women to cohorts based on mBC subtype: cohort 1, hormone receptor +/human epidermal growth factor receptor 2−; cohort 2, triple-negative breast cancer; or cohort 3, any mBC subtype with active BM. Patients received liposomal irinotecan 50 or 70 mg/m^2 free base every 2 weeks. Here, we report secondary outcomes including best overall response (BOR), objective response rate (ORR), and treatment-emergent adverse events (TEAEs).

Results For non-central nervous system (non-CNS) disease across all cohorts (intent-to-treat population, $N=29$), the ORR was 34.5% (95% confidence interval: 17.94–54.33), with a BOR of partial response in 10 patients (34.5%), stable disease in five (17.2%), progressive disease in 10 (34.5%); four patients were unevaluable (13.8%). The ORR for the CNS cohort was 30.0% (95% confidence interval: 6.67–65.25) using modified Response Evaluation Criteria in Solid Tumors. Common grade 3 or higher TEAEs were diarrhea (27.6%), nausea (17.2%), fatigue (13.8%), asthenia (10.3%), and hypokalemia (10.3%). Serious treatment-related TEAEs were reported in six patients (20.7%). No treatment-related TEAEs resulted in death.

Conclusions Liposomal irinotecan monotherapy demonstrated antitumor activity in heavily pretreated patients with mBC, with or without BM. The observed safety profile was consistent with that in previous studies.

Clinical trial registration: Trial registration ID NCT01770353.

Keywords Liposomal irinotecan · Metastatic breast cancer · Objective response rate · Phase I clinical trial · Brain metastases · Heavily pretreated patients

Introduction

An estimated 276,480 women in the USA are predicted to be diagnosed with invasive breast cancer in 2020 [1]. Despite recently improved outcomes, the 5-year survival rate for women with metastatic breast cancer (mBC) in the USA remains low at 27% [1]. The estimated incidence of brain metastases (BM) in patients with mBC is 24%; the estimated survival time of patients with BM is 15 months from diagnosis. BM are associated with morbidity and negatively impact functional status and quality of life [2]. Because women with mBC are living longer, cases of BM are expected to increase.

Systemic treatments for mBC are selected based on multiple factors, including age, comorbidities, hormone receptor and human epidermal growth factor receptor 2 (HER2) status, previous cancer treatments, and tumor burden [3]. In patients with mBC and BM, systemic treatments have limited central nervous system (CNS) efficacy, and disease progression after localized treatment(s) (i.e., whole brain radiation therapy, stereotactic radiosurgery, and/or surgical resection) presents a significant clinical challenge [2].

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Currently, tucatinib, in combination with trastuzumab and capecitabine, is the only systemic therapy approved by the Food and Drug Administration (FDA) for the treatment of adult patients with advanced unresectable or metastatic HER2+ breast cancer, including patients with BM, who have received one or more prior anti-HER2-based regimens in the metastatic setting [4].

The anticancer prodrug irinotecan has a mechanism of action that is distinct from other medications used for mBC treatment; therefore, the risk of cross-resistance from previous cancer therapies is considered low. The active metabolite of irinotecan, SN-38, reversibly binds to the topoisomerase I–DNA complex and prevents religation of single-strand breaks, leading to double-strand DNA damage and cell death [5]. Irinotecan can cross the blood–brain barrier and has shown promising results for BM treatment in two phase II studies; one in primary CNS tumors [6] and another in triple-negative breast cancer (TNBC) when administered with iniparib [7].

Liposomal irinotecan (ONIVYDE®; Ipsen Biopharmaceuticals, Inc.; historical names include nal-IRI, MM-398, or PEP02) is an intravenously delivered formulation [5]; individual liposomes have a diameter of approximately 110 nm [8], which is close to the nanoscale (1–100 nm) [9]. Liposomal encapsulation increases the nominal plasma half-life of irinotecan [10]. Deposition in tumor lesions occurs through leaky vasculature within the lesion via the enhanced permeability and retention (EPR) [11] effect before conversion of the payload to SN-38 [12]. Liposomal irinotecan is approved, in combination with 5-fluorouracil and leucovorin, for the treatment of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy [5]. Preclinical data suggest that liposomal irinotecan may have utility as a treatment for mBC with BM [13].

To investigate this potential activity in heavily pretreated patients with mBC, including active BM, we report efficacy and safety outcomes from the expansion phase of a phase I cross-indication translational study (ClinicalTrials.gov identifier: NCT01770353).

Methods

Study design

This multicenter, non-comparative, open-label, non-randomized, phase I study was conducted in the USA between November 19, 2012 (first patient, first visit) and October 2, 2018 (last patient, last visit). The study comprised a pilot phase followed by an expansion phase (Fig. 1). The pilot phase was previously reported by Ramanathan et al. [14]. The expansion phase was conducted in patients with mBC (first liposomal irinotecan dose in first patient, May 18, 2015), and the primary outcome was to investigate ferumoxytol quantitation in tumor lesions (to be reported elsewhere).

Here, we report secondary outcomes from the expansion phase: the efficacy and safety of liposomal irinotecan in adult patients with mBC, including active BM.

Expansion phase population

Adult women aged ≥ 18 years were recruited into three cohorts (target 10 patients per cohort) based on historical archival receptor subtyping: cohort 1, estrogen receptor (ER)+ and/or progesterone receptor (PgR)+/HER2−; cohort 2, ER− and PgR−/HER2− (TNBC); or cohort 3, any mBC subtype with active BM (mBCBM). In cohort 3, patients were required to have radiographic evidence of new or progressive BM after radiation therapy with ≥ 1 lesion

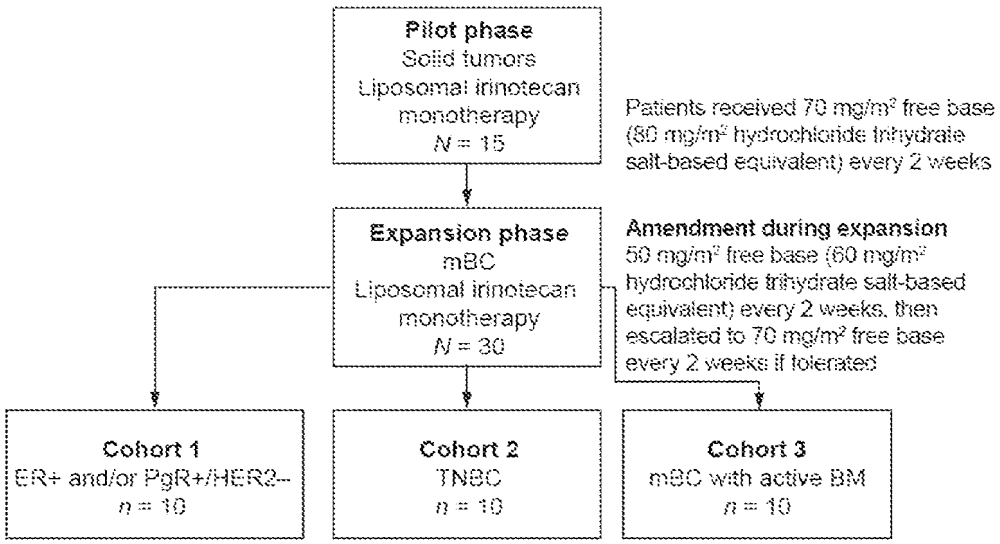

Fig. 1 Study design. *BM* brain metastases, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *mBC* metastatic breast cancer, *PgR* progesterone receptor, *TNBC* triple-negative breast cancer

CSPC Exhibit 1120
Page 91 of 447

measuring ≥ 1 cm in the longest dimension on gadolinium-enhanced MRI, and to be considered neurologically stable. In all cohorts, key inclusion criteria included locally advanced or metastatic disease with ≥ 2 radiologically measurable lesions; an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow reserves, and adequate hepatic and renal function; and 1–5 prior lines of chemotherapy in the metastatic setting. Patients with active CNS metastases were excluded from cohorts 1 and 2. See Supplementary Table S1 for full inclusion and exclusion criteria, including those specifically relating to patients with BM.

Expansion phase treatment

On day 1, patients received a single dose of intravenous ferumoxytol 5 mg/kg infused over 15 min, used here as a magnetic resonance imaging (MRI) lesion-imaging agent (reported elsewhere) [14, 15]. Within 7 days after ferumoxytol infusion, patients received their first dose of intravenous liposomal irinotecan 70 mg/m^2 free base, infused over 90 min. Extracranial biopsies from a single lesion were acquired either prior to dosing with liposomal irinotecan or approximately 72 h after the first dose. Subsequent doses of liposomal irinotecan were administered every 2 weeks (± 2 days). Protocol Amendment 4 (November 3, 2016) reduced the starting dose to 50 mg/m^2 free base, with allowance for escalation to 70 mg/m^2 free base, depending on patient tolerance.

In all cohorts, treatment continued until disease progression was observed (as assessed using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria), unacceptable tolerability had occurred, or consent was withdrawn. In cohorts 1 and 2, treatment could continue in patients with radiographic disease progression without symptomatic deterioration if they had derived clinical benefit, based on a consensus between the investigator, medical monitor, and sponsor. In cohort 3, CNS and non-CNS disease were assessed separately, and treatment was discontinued in patients with radiographic evidence of CNS disease progression. Treatment continuation was permitted, at the investigator's discretion, in patients with non-CNS disease progression in the absence of CNS disease progression. Cohort 3 patients with symptomatic CNS disease progression but without radiographic confirmation were permitted to continue treatment.

During the study, all concurrent medical conditions and complications of the underlying malignancy could be treated at the discretion of the investigator, according to acceptable local standards of medical care. Patients could receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as deemed necessary. Further details of concomitant therapy are provided in supplementary materials. Information on post-trial treatments was not collected.

Efficacy assessments

Efficacy assessments were included in the expansion phase as secondary study endpoints; primary endpoints did not include efficacy and will be reported elsewhere. Tumor assessments, both non-CNS (all cohorts) and CNS (cohort 3 only) by computed tomography (CT) or magnetic resonance imaging, were performed at baseline and at 8-week intervals. RECIST v1.1 and modified RECIST (Supplementary Table S2) were utilized to assess non-CNS systemic disease and CNS disease, respectively. To be considered evaluable, patients were required to have received liposomal irinotecan and to have completed at least one CT scan at the 8-week post-treatment time point. For post-baseline assessments, overall tumor response was classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE). A non-CR/non-PD was also available for non-target lesions. Based on tumor response assessments, additional efficacy outcomes included best overall response (BOR), objective response rate (ORR), clinical benefit rate (CBR; defined as CR or PR, and SD lasting at least 24 weeks), duration of objective response (DOR), and progression-free survival (PFS); definitions are provided in supplementary materials.

Safety assessments

All treatment-emergent adverse events (TEAEs) were recorded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.02. Final safety assessments were completed 30 days (± 7 days) after the patient received their last dose of liposomal irinotecan.

Metastatic tumor receptor status—exploratory, post hoc analyses

See Supplementary Materials for details of retrospective analyses of metastatic tumor receptor status for on-study biopsy materials.

Statistical analysis

All patients who received at least one dose of liposomal irinotecan were included in the liposomal irinotecan safety population. The liposomal irinotecan efficacy population comprised all patients who received liposomal irinotecan and had evaluable efficacy data. No formal hypothesis testing was performed; therefore, this study was not powered to

CSPC Exhibit H20
Page 92 of 447

detect statistical differences in any parameter. Descriptive results are reported.

Results

Patients

A patient disposition flowchart is provided in Supplementary Fig. S1. In total, 30 patients (10 per cohort) were enrolled in the expansion phase (Table 1). All enrolled patients were women with a median age of 53 (range 29–70) years. In each cohort, most patients were white, and most were heavily pretreated with a median of three (range 0–6) prior cytotoxic anticancer regimens in the metastatic setting.

The safety population comprised 29 patients who had received at least one dose of liposomal irinotecan. All these patients had evaluable efficacy data and comprised the liposomal irinotecan efficacy population. One patient enrolled in cohort 2 (TNBC) died owing to PD before receiving liposomal irinotecan and was not included in the liposomal irinotecan safety or efficacy analyses.

In total, 13 patients initiated liposomal irinotecan at 70 mg/m^2 free base, and 15 patients initiated at 50 mg/m^2 free base. One patient initiated liposomal irinotecan at 35 mg/m^2 free base based on the investigator's clinical decision and their UGT1A1*28 allele homozygous polymorphism. Median exposure to liposomal irinotecan among all patients was 12.3 (range 0.1–105.3) weeks. All patients had discontinued the study by week 114 (Fig. 2). Reasons for discontinuation of liposomal irinotecan were PD radiographically confirmed as per RECIST v1.1 (18 patients, 62.1% [percentages rounded]), other (seven patients, 24.1%), investigator decision (three patients, 10.3%), and TEAEs (one patient, 3.4%). 'Other' was an option on the electronic case report form and included clinical deterioration or clinical PD in six patients, and toxicity-related diarrhea and clinical PD in one patient.

Efficacy

Response to treatment

The BOR for non-CNS disease across all cohorts was PR in ten patients (34.5%), SD in five patients (17.2%), and PD in ten patients (34.5%); four patients (13.8%) were NE (Table 2). No patients had a CR. The BOR was: cohort 1 (ER+ and/or PgR+/HER2−), PR in 40.0%, and PD in 50.0%, with one patient NE; cohort 2 (TNBC), PR in 33.3%, SD in 33.3%, and PD in 22.2%, with one patient NE; cohort 3 (mBCBM) for non-CNS disease, PR in 30.0%, SD in 20.0%, and PD in 30.0%, with two patients NE. For non-CNS disease across all cohorts, both the ORR and the CBR were 34.5% (Table 2). For CNS disease in cohort 3, the BOR was PR in 30.0%, SD in 30.0%, and PD in 20.0%, with two patients NE, and the ORR and CBR were 30.0% and 50.0%, respectively (Table 2).

Table 1 Demographics and baseline characteristics (ferumoxytol safety population, $N=30$)

	Cohort 1 ($n=10$)	Cohort 2 ($n=10$)	Cohort 3[a] ($n=10$)	Total population ($N=30$)
Sex, female, *n* (%)	10 (100)	10 (100)	10 (100)	30 (100)
Age, years, median (range)	56.0 (49–68)	52.5 (37–70)	45.5 (29–63)	53.0 (29–70)
Race, *n* (%)				
White	8 (80.0)	8 (80.0)	7 (70.0)	23 (76.7)
Black or African American	0	1 (10.0)	1 (10.0)	2 (6.7)
American Indian or Native Alaskan	0	0	0	0
Asian	1 (10.0)	0	1 (10.0)	2 (6.7)
Native Hawaiian or other Pacific islander	1 (10.0)	0	0	1 (3.3)
Other	0	1 (10.0)	1 (10.0)	2 (6.7)
Time since metastatic diagnosis, months, median (range)	63.7 (16–87)	20.7 (0–34)	32.4 (8–55)	24.0 (0–87)
Number of prior cytotoxic anticancer regimens, median (range)	3.0 (1–6)	3.0 (0–5)	3.0 (1–6)	3.0 (0–6)

Percentages are subject to rounding

BM brain metastases, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *mBC* metastatic breast cancer, *PgR* progesterone receptor, *TNBC* triple-negative breast cancer

[a]Four patients had TNBC; three patients were ER+ and/or PgR+/HER2+, two patients were ER+ and/or PgR+/HER2−, and one patient was ER− and/or PgR−/HER2+. Of the four patients with HER2+ mBC based on pre-study biopsies, three had received HER2 blockade prior to study entry. The patient who had not received prior HER2 blockade had TNBC before their diagnosis of BM. Brain tissue biopsy from this patient showed ER+ HER2+ tissue. At diagnosis of BM, after surgery, radiotherapy and letrozole, the patient had stable BM and was subsequently enrolled in the expansion phase of the present clinical trial

CSPC Exhibit 1120
Page 93 of 447

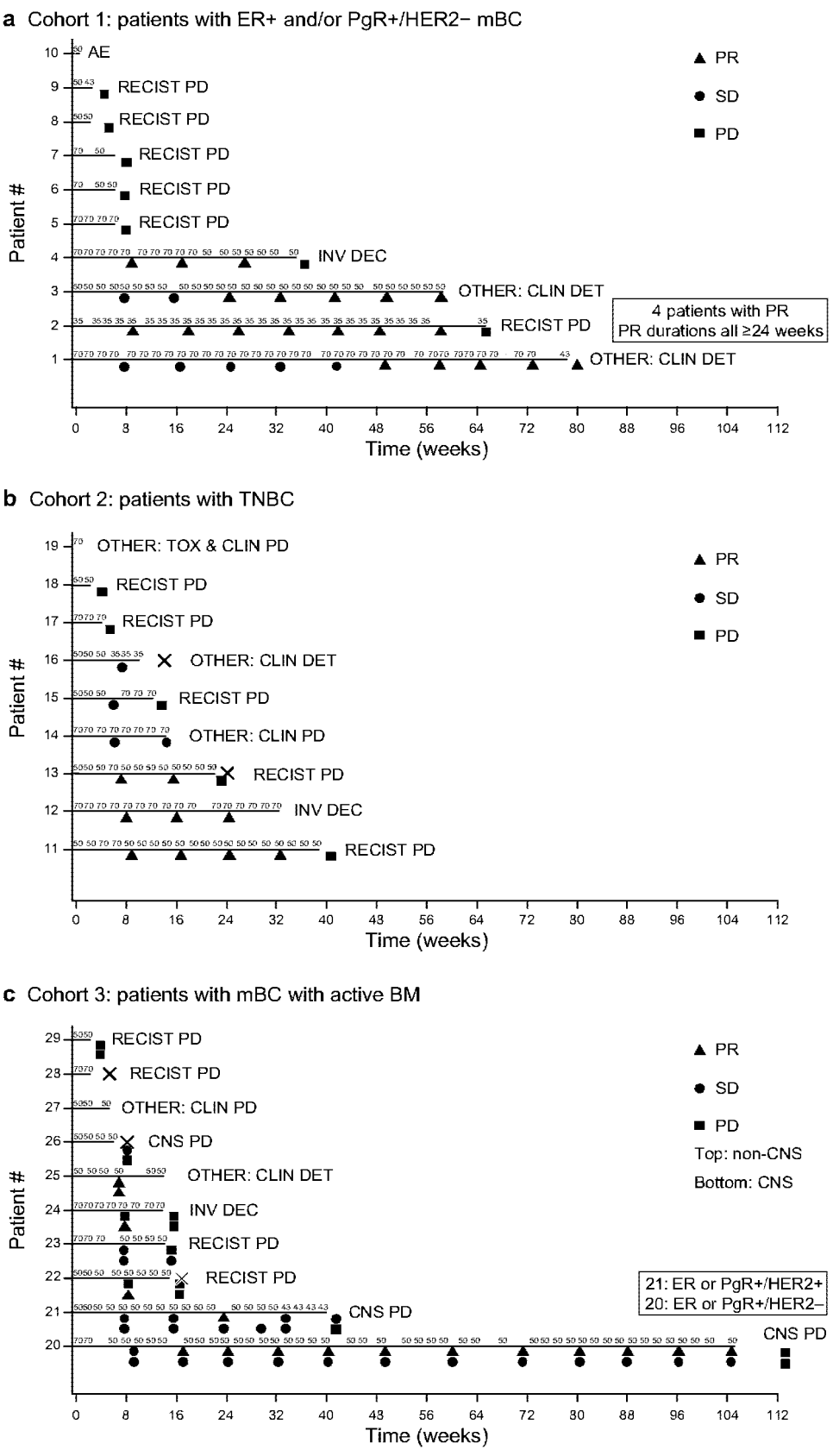

Fig. 2 Response to liposomal irinotecan over time until treatment discontinuation (liposomal irinotecan efficacy population, $n=29$). Individual doses of liposomal irinotecan are displayed above each patient's treatment timeline, and the values depict a 35, 43, 50, or 70 mg/m^2 free base intravenous infusion. One patient in cohort 2 was enrolled but discontinued before receiving treatment. Patient death is depicted by an 'X'. *AE* adverse event, *BM* brain metastases, *CLIN* clinical, *CNS* central nervous system, *DET* deterioration, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *INV DEC* investigator decision, *mBC* metastatic breast cancer, *PD* progressive disease, *PgR* progesterone receptor, *PR* partial response, *RECIST* Response Evaluation Criteria in Solid Tumors, *SD* stable disease, *TNBC* triple-negative breast cancer, *TOX* toxicity

CSPC Exhibit 1120
Page 94 of 447

Table 2 Response to treatment (evaluable efficacy population, $N=29$)

	Cohort 1 ($n=10$)	Cohort 2[a] ($n=9$)	Cohort 3		Total population (non-CNS) ($N=29$)
			non-CNS ($n=10$)	CNS ($n=10$)	
Best overall response, *n* (%)					
Complete response	0	0	0	0	0
Partial response	4 (40.0)	3 (33.3)	3 (30.0)	3 (30.0)	10 (34.5)
Stable disease	0	3 (33.3)	2 (20.0)	3 (30.0)	5 (17.2)
Progressive disease	5 (50.0)	2 (22.2)	3 (30.0)	2 (20.0)	10 (34.5)
Not evaluable	1 (10.0)	1 (11.1)	2 (20.0)	2 (20.0)	4 (13.8)
Objective response rate					
Patients with a complete or partial response, *n* (%)	4 (40.0)	3 (33.3)	3 (30.0)	3 (30.0)	10 (34.5)
95% CI	12.16–73.76	7.49–70.07	6.67–65.25	6.67–65.25	17.94–54.33
Clinical benefit rate					
Patients with a complete or partial response, or stable disease that lasted at least 24 weeks, *n* (%)	4 (40.0)	3 (33.3)	3 (30.0)	5 (50.0)	10 (34.5)
95% CI	12.16–73.76	7.49–70.07	6.67–65.25	18.71–81.29	17.94–54.33
Duration of objective response					
Number of months, median (range)	7.46 (6.4–13.0)	5.62 (3.7–7.4)	4.14 (0.0–22.2)	1.84 (0.0–1.9)	6.74 (0.0–22.2)
Progression-free survival					
Number of months, median (range)	1.9 (1.1–15.1)	4.3 (1.0–9.4)	3.2 (0.9–26.1)	3.6 (0.9–9.6)	3.2 (1.8–8.4)

CNS tumor response was evaluated according to modified RECIST

Percentages are subject to rounding

CI confidence interval, *CNS* central nervous system, *RECIST* Response Evaluation Criteria in Solid Tumors

[a]One patient was enrolled but not treated with liposomal irinotecan and is not included in any safety or efficacy assessments. Non-CNS tumor response was evaluated according to RECIST v1.1

Duration of response

In cohort 1 (ER+ and/or PgR+/HER2−), PR was reported in four patients; it lasted at least 24 weeks in three of the patients and more than 48 weeks in the fourth patient (Fig. 2a). In cohort 2 (TNBC), PR was reported in three patients; it lasted approximately 24 weeks in two of the patients and 40 weeks in the third patient (Fig. 2b). In cohort 3 (mBCBM), non-CNS PR was reported in three patients; CNS PR was reported in three patients (all of whom had TNBC) at week 8, but not at a subsequent assessment (Fig. 2c). One patient (TNBC) in cohort 3 had a non-CNS and a CNS PR at week 8, and another patient (ER+ and/or PgR+/HER2−) had a non-CNS PR from week 16 to 114 and a best CNS response of SD over the same time period).

Across all cohorts for non-CNS disease, median (range) DOR and PFS were 6.74 (0.0–22.2) months and 3.2 (1.8–8.4) months, respectively (Table 2). For CNS disease in cohort 3 (mBCBM), median (range) DOR and PFS were 1.84 (0.0–1.9) months and 3.6 (0.9–9.6) months, respectively (Table 2).

Tumor lesion size

There were 23 patients across all cohorts with measurable non-CNS disease with evaluable follow-up; seven patients in cohort 3 had measurable CNS disease and evaluable follow-up (Fig. 3). A reduction in tumor lesion size was observed in the majority of patients for both non-CNS disease (14 of 23 patients, 60.9%; Fig. 3a) and CNS disease (six of seven patients, 85.7%; Fig. 3b). In cohort 2 (TNBC) and for the non-CNS disease in cohort 3 (mBCBM), a reduction was observed in more than half of the evaluable patients. Compared with baseline measures, reductions varied from 5 to 90% for non-CNS lesions and from 7 to 55% for CNS lesions.

Safety

Median duration of exposure to liposomal irinotecan across all cohorts was 12.3 (0.1–105.3) weeks (Table 3). A dose reduction was recorded in six patients who initiated liposomal irinotecan at 70 mg/m^2 free base, and in three patients who initiated at 50 mg/m^2 free base (Fig. 2). A dose increase

CSPC Exhibit 1120
Page 95 of 447

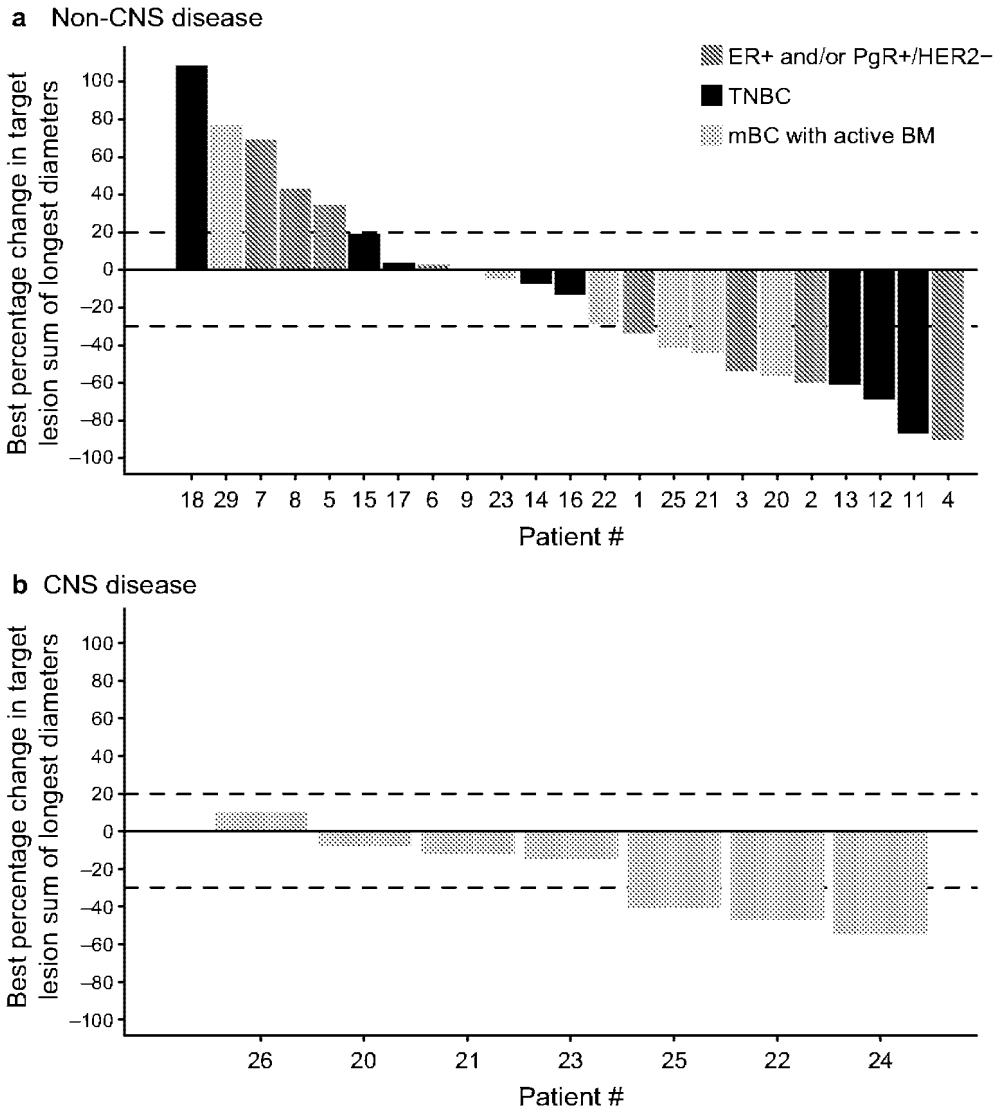

Fig. 3 Percentage reduction in tumor lesion size in patients with (**a**) non-CNS disease and (**b**) CNS disease[a]. [a]Only patients who had an evaluable post-baseline tumor assessment for designated target lesions are included in the waterfall plots. Horizontal dashed lines represent the range of stable disease (lower line, < 30% reduction in tumor size; upper line, < 20% increase in tumor size), as per RECIST v1.1 criteria. Patient numbers on the x axis relate to patient numbers on Fig. 2. *BM* brain metastases, *CNS* central nervous system, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *mBC* metastatic breast cancer, *PgR* progesterone receptor, *RECIST* Response Evaluation Criteria in Solid Tumors, *TNBC* triple-negative breast cancer

was recorded in a further three patients who initiated liposomal irinotecan at 50 mg/m^2 free base; of these, two patients had subsequent dose reductions (Fig. 2). All patients experienced TEAEs, with 28 patients (96.6%) experiencing TEAEs that were considered treatment related (Table 3). The most frequently reported TEAEs (reported in ≥ 25% of all patients) of any grade were diarrhea (89.7%), fatigue (62.1%), nausea (55.2%), vomiting (41.4%), hypokalemia (37.9%), and decreased appetite (31.0%). Serious TEAEs were reported in 17 patients (58.6%) overall and were considered treatment related in six patients (20.7%). Serious TEAEs reported in at least 10% of all patients were diarrhea (17.2%), nausea (10.3%), and asthenia (10.3%). In total, 21 patients (72.4%) experienced a TEAE with an NCI CTCAE grade of at least 3, with 12 patients (41.4%) experiencing a grade 3 or higher TEAE that was considered treatment related. TEAEs with an NCI CTCAE grade of at least 3 reported in at least 10% of all patients were diarrhea (27.6%), nausea (17.2%), fatigue (13.8%), asthenia (10.3%), and hypokalemia (10.3%); all grade 3. No grade 5 TEAEs were reported; no TEAEs resulted in death. One patient (3.4%) discontinued liposomal irinotecan monotherapy as a result of TEAEs (diarrhea, nausea, and vomiting) that were considered treatment related.

Based on laboratory abnormalities with an NCI CTCAE grade of 3 or 4, four patients had increased bilirubin, three had hypoglycemia, three had hypokalemia, three had hypophosphatemia, two had low hemoglobin, one had increased aspartate aminotransferase, one had leucopenia, and one had neutropenia (recorded as the MedDRA preferred term, neutrophil count decreased). Based on NCI CTCAE reports of grade 2 neutrophil count decreased, four additional patients had neutropenia, and all five reports of neutropenia were considered treatment related. Two further patients (6.9%) had an actual NCI CTCAE report of grade 2 neutropenia, one of which was considered treatment related.

Table 3 Patient safety analysis (liposomal irinotecan safety population, $N=29$)

	Cohort 1 ($n=10$)	Cohort 2[a] ($n=9$)	Cohort 3 ($n=10$)	Total population ($N=29$)
Exposure, median (range)				
Treatment duration, weeks	6.1 (0.1–78.4)	12.3 (0.1–38.9)	13.9 (2.1–105.3)	12.3 (0.1–105.3)
AEs, *n* (%)				
Any TEAE	10 (100.0)	9 (100.0)	10 (100.0)	29 (100.0)
TEAEs related to liposomal irinotecan	10 (100.0)	8 (88.9)	10 (100.0)	28 (96.6)
Serious TEAEs	6 (60.0)	4 (44.4)	7 (70.0)	17 (58.6)
Serious TEAEs related to liposomal irinotecan	4 (40.0)	1 (11.1)	1 (10.0)	6 (20.7)
TEAEs with NCI CTCAE grade ≥ 3	8 (80.0)	6 (66.7)	7 (70.0)	21 (72.4)
TEAEs with NCI CTCAE grade ≥ 3 related to liposomal irinotecan	6 (60.0)	3 (33.3)	3 (30.0)	12 (41.4)
TEAEs leading to liposomal irinotecan discontinuation	1 (10.0)	0	0	1 (3.4)
TEAEs leading to liposomal irinotecan discontinuation related to liposomal irinotecan	1 (10.0)	0	0	1 (3.4)
TEAEs leading to death	0	0	0	0
TEAEs leading to death related to liposomal irinotecan	0	0	0	0
TEAEs leading to dose adjustment	7 (70.0)	7 (77.8)	6 (60.0)	20 (69.0)
TEAEs leading to dose adjustment related to liposomal irinotecan	7 (70.0)	4 (44.4)	4 (40.0)	15 (51.7)
Commonly reported TEAEs (> 25% in any cohort)				
Diarrhea	10 (100.0)	9 (100.0)	7 (70.0)	26 (89.7)
Fatigue	6 (60.0)	5 (55.6)	7 (70.0)	18 (62.1)
Nausea	8 (80.0)	5 (55.6)	3 (30.0)	16 (55.2)
Vomiting	6 (60.0)	3 (33.3)	3 (30.0)	12 (41.4)
Hypokalemia	4 (40.0)	3 (33.3)	4 (40.0)	11 (37.9)
Decreased appetite	5 (50.0)	2 (22.2)	2 (20.0)	9 (31.0)
Back pain	4 (40.0)	1 (11.1)	2 (20.0)	7 (24.1)
Alanine aminotransferase increased	3 (30.0)	0	4 (40.0)	7 (24.1)
Anemia	3 (30.0)	2 (22.2)	2 (20.0)	7 (24.1)
Abdominal pain	3 (30.0)	3 (33.3)	1 (10.0)	7 (24.1)
Headache	3 (30.0)	1 (11.1)	2 (20.0)	6 (20.7)
Cough	1 (10.0)	2 (22.2)	3 (30.0)	6 (20.7)
Alopecia	4 (40.0)	2 (22.2)	0	6 (20.7)
Hypocalcemia	3 (30.0)	2 (22.2)	1 (10.0)	6 (20.7)
Asthenia	1 (10.0)	1 (11.1)	3 (30.0)	5 (17.2)
Constipation	3 (30.0)	0	2 (20.0)	5 (17.2)
Dyspnea	1 (10.0)	0	4 (40.0)	5 (17.2)

AE adverse event, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events, *TEAE* treatment-emergent adverse event

[a]One patient was enrolled but not treated with liposomal irinotecan and is not included in any safety or efficacy assessments

Metastatic tumor receptor status—exploratory, post hoc analyses

Among patients who received liposomal irinotecan and had evaluable on-study biopsies, metastatic tumor receptor status was discordant with cohort assignment for four of ten patients in cohort 1 (ER− and PR−, one patient [#8]; HER2+, three patients [#3, #5, #9]) and two of seven patients in cohort 2 (HER2+, one patient [#16]; ER+ and HER2+, one patient [#12]) (Supplementary Table S3).

Discussion

This study is the first to evaluate the efficacy and safety of liposomal irinotecan specifically in heavily pretreated adult patients with mBC, including those with active BM. Findings from the expansion phase of this open-label, phase I study demonstrate the antitumor activity of liposomal irinotecan monotherapy. Liposomal irinotecan was relatively well tolerated, with only one patient discontinuing because of TEAEs (diarrhea, nausea, and vomiting).

CSPC Exhibit 1120
Page 97 of 447

Despite recent improvements in survival rates, mBC remains an incurable disease, and new treatment options are needed, particularly because response rates in late lines of treatment and in patients with BM remain low. Typically, clinical trials of new agents exclude patients with active or untreated BM, and therefore CNS disease remains particularly challenging to treat. However, based on positive findings from the HER2CLIMB trial in patients with HER2+ mBC, which did include patients with BM [16], the HER2 inhibitor tucatinib, in combination with capecitabine and trastuzumab, recently received FDA-approval for the treatment of patients with advanced unresectable or metastatic HER2+ breast cancer, including patients with BM [4]. Neratinib and lapatinib are also small-molecule inhibitors of HER2 [17, 18], and have shown modest activity as single agents or in combination with capecitabine for treating HER2+ mBCBM. The present study evaluated heavily pretreated patients with mBC, including those with active BM; some patients have been living with mBC for more than 5 years. The study population is therefore representative of patients with high unmet need and for whom additional standard treatment options would not be expected to provide robust responses or durable benefit.

Endocrine, targeted, and cytotoxic systemic treatments used as monotherapy in pretreated patients with mBC have been reportedly associated with ORRs ranging from 14 to 32%; combination treatments are associated with improved ORRs [19]. Two small, single-arm clinical trials have specifically assessed the use of non-liposomal irinotecan monotherapy in patients with mBC, with reported ORRs of 5.6% and 23% [20, 21]. Studies of non-liposomal irinotecan in combination with a chemotherapeutic agent in patients with mBC have reported ORRs ranging from 11 to 58.3% [22–29]. In addition, in a small-scale pilot study that assessed the use of multi-omic profiling of target tumors to guide treatment selection in patients with mBC, the most frequently selected treatment was irinotecan based on identified topoisomerase I expression in 12 of 25 evaluated patients (7 received irinotecan combination therapy; 5 received irinotecan monotherapy) [30]. Of these 25 patients, 14 (56%) exhibited clinical benefit (defined as growth modulation index ≥ 1.3) [30]. One phase II study that assessed etirinotecan pegol, a long-acting formulation of irinotecan, reported an ORR of 29% [31]; however, the drug failed to demonstrate superiority to the physician's choice (single-drug treatment) for overall survival in the randomized phase III BEACON trial [32].

In the present study, the ORR observed with liposomal irinotecan (34.5%) was numerically higher than that historically reported with non-liposomal irinotecan monotherapy [20, 21]. This may be due to the prolonged plasma circulation and EPR effect observed with near-nanoscale liposomal irinotecan, both of which allow for improved tumor drug delivery. Nanoparticle deposition within patients' intracranial tumor lesions has previously been reported for ferumoxytol as assessed by MRI [15] and liposomes with comparable dimensions and lipid compositions to liposomal irinotecan as assessed by positron emission tomography [33]. The ability of liposomal irinotecan to penetrate the blood-tumor-barrier, in part owing to the small diameter of the liposomes (110 nm), and accumulate in CNS lesions has been demonstrated in non-clinical models of intracranial metastasis in breast cancer [13] and orthotopic glioblastoma models [8, 34]. Liposomes crossed the blood-tumor-barrier and accumulated in brain metastases, but not in normal brain tissue. Extended and preferential accumulation of irinotecan and the active metabolite, SN-38, were observed in these models compared to treatment with non-liposomal irinotecan [8, 13].

In the pilot phase of this study, total SN-38 levels and the ratio of total SN-38:total irinotecan were reportedly sixfold and eightfold higher in tumors than in plasma [12]. In the phase III NAPOLI-1 study in patients with mPDAC, average concentration and duration above threshold concentration for unencapsulated SN-38 in a population pharmacokinetics model were positively correlated with overall response rate, PFS and overall survival in patients receiving liposomal irinotecan with 5-fluorouracil/leucovorin [12]. Thus, the favorable pharmacokinetic characteristics of liposomal irinotecan likely contributed to the efficacy observed in the present study. The ORR with liposomal irinotecan was 30% for CNS disease in cohort 3 (mBCBM), and 50% of patients demonstrated clinical benefit. Two previous open-label, phase I studies that assessed liposomal irinotecan in patients with advanced solid tumors refractory to standard systemic chemotherapy included a small subset of patients with mBC [35, 36]. The observed BOR with liposomal irinotecan was PR in one of four patients with mBC in one study [35], and SD in one of two patients with mBC in the second study [36]. The present study provides additional evidence of the antitumor activity of liposomal irinotecan in a heavily pretreated population with mBC, including BM, supporting further investigation.

ORRs observed in this study were similar across all cohorts (ER+ and/or PgR+/HER2−, TNBC or mBCBM), demonstrating liposomal irinotecan activity in all subtypes of mBC. Notably, of the five patients in cohort 3 who had a PR (non-CNS PR, two patients; CNS PR, two patients; both non-CNS and CNS PR, one patient), three had TNBC (a total of four patients had TNBC in cohort 3), one patient had ER+ or PgR+/HER2+ mBC, and one patient had ER+ or PgR+/HER2− mBC. In these two patients with hormone-receptor-positive mBC with a PR, durable responses were noted for both CNS and non-CNS disease; lasting 40 weeks in the patient with HER2+ mBC, and 104 weeks in the patient with HER2− mBC. These findings warrant further

CSPC Exhibit 1120
Page 98 of 447

investigation of liposomal irinotecan in patients with mBC and BM, including those with TNBC for whom existing treatment options are extremely limited.

Our exploratory post hoc analyses of metastatic tumor receptor status were consistent with previous reports of the potential for discordance and receptor conversion between primary and metastatic tumors [37], highlighting the need to consider inter- and intra-tumor heterogeneity when selecting treatments [38].

The observed safety profile of liposomal irinotecan was consistent with that reported in earlier studies of non-liposomal and liposomal irinotecan, with gastrointestinal TEAEs, including diarrhea, nausea, and vomiting, being among the most commonly reported grade 3 or 4 TEAEs [20, 21, 24, 25, 28, 35, 36, 39, 40]; no new or unexpected TEAEs were reported. Perhaps the most noticeable difference between previous studies and the present findings is the absence of grade 3 or 4 neutropenia; however, it should be noted that neutropenia was observed in seven patients (NCI CTCAE records of grade 2 neutropenia in three patients, grade 2 neutrophil count decreased in three patients, and grade 3 neutrophil count decreased in one patient). This finding supports the suggestion that liposomal irinotecan monotherapy is associated with better tolerability than liposomal irinotecan combination therapy [41]. In the phase III NAPOLI-1 study, neutropenia was reported in 23.08% of patients receiving liposomal irinotecan 70 mg/m^2 free base every 2 weeks in combination with 5-fluorouracil/leucovorin [41]. The relatively low frequency of neutropenia observed in the current study may, in part, be due to the dose of liposomal irinotecan and/or the increased localization of liposomal irinotecan within target lesions (rather than in plasma) via the EPR effect [11, 12]. Improved tumor drug delivery via innovative therapeutic platforms, such as nanotherapeutics or antibody drug conjugates (ADCs), are major areas of research for increasing the efficacy of cytotoxic agents while minimizing toxicity. Sacituzumab govitecan-hziy is an ADC comprised of a Trop-2 monoclonal antibody linked to a SN-38 payload, that was recently approved for patients with metastatic TNBC who have received at least two prior lines of therapy for metastatic disease [42, 43]. This agent demonstrated an ORR of 33.3% in a population with a median of three prior lines of treatment, similar to the patient population in the present study [42]. However, this study excluded patients with active, symptomatic, or untreated BM. Thus, the CNS activity of sacituzumab govitecan-hziy is unknown at present. Future research will hopefully continue to elucidate optimal drug delivery mechanisms to maximize the therapeutic potential of irinotecan in mBC, particularly in patients with untreated BCBM.

The main strength of the present study is that liposomal irinotecan was assessed specifically in patients with mBC, including those with active BM. Our findings provide a springboard for further investigation of liposomal irinotecan in this population, in whom alternative therapies are still needed. Study limitations include a small sample size, the open-label study design, and the lack of a comparator group; however, this study showed encouraging antitumor activity in this heavily pretreated population who had experienced disease progression despite multiple lines of chemotherapy.

Conclusions

Among heavily pretreated patients with mBC with or without BM, liposomal irinotecan monotherapy every 2 weeks had a safety profile consistent with that previously reported for liposomal irinotecan in patients with solid tumors and was associated with an ORR of at least 30%. In future trials, proactive management of gastrointestinal toxicities, such as diarrhea, could improve the risk–benefit profile of liposomal irinotecan. These results suggest that further clinical assessment of liposomal irinotecan is warranted in mBC and active BM.

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Data availability If patient data can be anonymized, Ipsen will share all individual patient data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months, and ending 5 years, after publication; after this time, only raw data may be available.

Compliance with ethical standards

Conflict of interest Jasgit C. Sachdev has received research funding from Celgene, Genentech, and Pfizer; compensation for the role of adviser from Celgene, Ipsen, Novartis, Pfizer, Puma Biotechnology, TapImmune, Tempus, and TTC Oncology; and honorarium from Celgene, Ipsen, Novartis, Pfizer, Puma Biotechnology, and Tempus. Hyo Sook Han has received research funding from AbbVie, Bristol Myers Squibb, the Department of Defense, Horizon Therapeutics, Ipsen, Karyopharm Therapeutics, Novartis, Pfizer, Prescient, Seattle Genetics, TapImmune, and Tesaro; and compensation for a speaker's bureau from Eli Lilly. Cynthia Ma has received research funding from Pfizer, Puma Biotechnology, and Tempus; compensations for a consulting

CSPC Exhibit 1120
Page 99 of 447

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CSPC Exhibit H20
Page 100 of 447

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CSPC Exhibit 1120
Page 101 of 447

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CSPC Exhibit H20
Page 102 of 447

ORIGINAL RESEARCH

Real-World Cost of Care for Commercially Insured versus Medicare Patients with Metastatic Pancreatic Cancer Who Received Guideline-Recommended Therapies

Samantha Tomicki, MPH; Gabriela Dieguez, FSA, MAAA; Helen Latimer, MPH; Paul Cockrum, PharmD; George Kim, MD

BACKGROUND: Much of the literature about the costs of metastatic pancreatic cancer is focused on the Medicare population, but the cost in the commercially insured population is not well-documented. Differences in treatment patterns between commercially insured and Medicare patients with metastatic pancreatic cancer can provide insights into healthcare utilization and the total cost of care.

OBJECTIVE: To compare the total cost of care for commercially insured versus Medicare patients with metastatic pancreatic cancer who are receiving National Comprehensive Cancer Network (NCCN)-recommended treatment regimens.

METHODS: We identified 3904 patients (mean age at diagnosis, 56 years) with metastatic pancreatic cancer using *International Classification of Diseases, Ninth/Tenth Revision* diagnosis codes in claims data in the 2014-2018 MarketScan commercial database and 28,063 patients (mean age at diagnosis, 73 years) with metastatic pancreatic cancer in the 2014-2017 Medicare Parts A, B, and D 100% research identifiable data files. We calculated the total cost of care and resource utilization by NCCN-recommended (category 1) treatment regimen, including 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX); gemcitabine plus nab-paclitaxel; gemcitabine monotherapy; and liposomal irinotecan. All patients had ≥2 claims with a pancreatic cancer diagnosis more than 30 days apart and ≥1 subsequent claims with a secondary malignancy diagnosis for metastatic disease.

RESULTS: The mean total cost of care was 186% higher in the commercially insured cohort than in the Medicare cohort. Excluding gemcitabine monotherapy, the total cost of care for patients with metastatic pancreatic cancer was similar between the regimens used in each cohort, ranging from $95,426 to $116,325 in the commercial insurance group and from $39,777 to $40,390 in the Medicare group. The components of hospital-based inpatient and outpatient costs varied between similar regimens in both cohorts. The inpatient admission patterns of patients' regimens were consistent across the 2 cohorts, with patients receiving gemcitabine monotherapy or liposomal irinotecan having the lowest overall number of admissions in each cohort.

CONCLUSIONS: The treatment patterns varied across the regimens but were largely consistent between the commercially insured and the Medicare patients who received the same regimen for metastatic pancreatic cancer; the ratio of total cost of care was 3:1 (commercially insured to Medicare). The total costs of care were similar across the regimens in each cohort, but the components of the total cost varied. These results can inform clinical guidelines and pathways for pancreatic cancer therapy as new evidence and treatment options emerge, and in the context of increasing value-based care models.

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Supplemental material online

KEY WORDS: commercial insurance, cost of care, healthcare resource utilization, Medicare, metastatic pancreatic cancer, NCCN-recommended regimens, pancreatic cancer pathways

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GSPC Exhibit 1120
Page 103 of 447

KEY POINTS

- There is limited research comparing costs and resource utilization for patients with metastatic pancreatic cancer in Medicare versus patients with commercial insurance.
- This observational study compared the total cost of care and NCCN-recommended therapies for commercially insured and Medicare patients with metastatic pancreatic cancer.
- Patients received FOLFIRINOX, gemcitabine plus nab-paclitaxel, gemcitabine monotherapy, or liposomal irinotecan.
- The mean inpatient costs of patients with commercial insurance ($12,745-$20,247) were more than double those of patients with Medicare coverage ($5330-$9123) for all regimens.
- Commercially insured patients had 186% higher healthcare costs and lower mean hospital admission rates than Medicare patients.
- Excluding gemcitabine monotherapy, the total cost of care ranged from $95,426 to $116,325 for commercially insured patients versus $39,777 to $40,390 for Medicare patients.
- Patients who received gemcitabine monotherapy had the highest CCI scores and the oldest age at diagnosis of metastatic disease in both groups.
- These results can inform clinical guidelines and treatment pathways for pancreatic cancer as new therapies emerge and as value-based care models become more prevalent.

In 2020, the National Cancer Institute estimated that 57,600 adults in the United States would be diagnosed with pancreatic cancer.[1] Pancreatic cancer currently accounts for 3.2% of US cancer diagnoses and results in 7.8% of cancer deaths.[1] For 52% of patients with pancreatic cancer, the cancer has metastasized at the time of diagnosis.[2] A previous study comparing the total cost of care among frequently used treatment regimens for metastatic pancreatic cancer indicated that there are differences in the inpatient and outpatient cost components.

An analysis of Medicare fee-for-service patients with metastatic pancreatic cancer showed that the mean total cost of care for first-line gemcitabine monotherapy was $20,462, which was lower than the $40,392 for first-line treatment with gemcitabine plus nab-paclitaxel or the $40,325 for first-line treatment with the combination of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX).[3]

Patients who received second-line liposomal irinotecan had a higher mean total cost of care than patients who received third-line liposomal irinotecan ($41,600 vs $36,810, respectively), although the mean total cost of care was similar for first-line gemcitabine plus nab-paclitaxel and FOLFIRINOX.[3] Existing research has not assessed the differences in costs of care between commercially insured and Medicare patient populations with metastatic prostate cancer.

This current observational study compared the mean total cost of care for commercially insured patients and for Medicare patients with metastatic pancreatic cancer who received US Food and Drug Administration (FDA)-approved, category 1 National Comprehensive Cancer Network (NCCN)-recommended chemotherapy regimens. The NCCN Clinical Practice Guidelines in Oncology are recognized as a standard of care for 97% of cancers, including pancreatic cancer.[4,5] The FDA-approved category 1 NCCN-recommended treatment options for metastatic pancreatic adenocarcinoma include first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, first-line gemcitabine monotherapy, and second-line 5-FU plus leucovorin and liposomal irinotecan.[5] These recommendations are consistent with real-world treatment patterns seen in claims analyses of patients with metastatic pancreatic cancer.

Studies suggest a link between aggressive cancer treatments and overall survival.[6-9] A meta-analysis of randomized clinical trials of gemcitabine-based therapies indicates that gemcitabine monotherapy is associated with lower overall survival and less toxicity than combination therapies in patients with metastatic pancreatic cancer.[6] A study of patients with metastatic pancreatic cancer who received liposomal irinotecan after treatment with fluorouracil and a gemcitabine-based regimen showed a 2.2-month increase in survival if patients received liposomal irinotecan as a second-line therapy compared with the third-line setting or later.[7] In another study of patients with metastatic pancreatic cancer who received first-line category 1 NCCN-recommended treatment regimens, the median overall survival from diagnosis was 9.4 months in patients who received first-line FOLFIRINOX; 6.6 months in patients who received first-line gemcitabine plus nab-paclitaxel; and 3.7 months in patients who received first-line gemcitabine monotherapy.[8] In a similar study of patients with metastatic pancreatic cancer, those who received second- or third-line liposomal irinotecan had a median overall survival of 5.4 months and 4 months, respectively.[9]

In addition to cost and survival, outcome measures of healthcare utilization, including hospitalizations, readmissions, and emergency department visits, may influence the prescribing patterns of providers assuming risk in a value-

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GSPC Exhibit 1120
Page 104 of 447

based payment model, such as the Center for Medicare & Medicaid Innovation's Oncology Care Model (OCM) and its successor, the Oncology Care First (OCF) model. To curb the expenses associated with evolving cancer treatments, the Centers for Medicare & Medicaid Services (CMS) has developed episode-based models to incorporate high-value, high-quality oncology care.[10]

The OCF model was anticipated to begin in January 2021; however, because of the COVID-19 pandemic, the start date has been delayed indefinitely, while the OCM model continues into 2022.[11,12] Like its predecessor the OCM, the OCF proposes a similar episode-based methodology to balance the total cost of care with appropriate quality metrics, such as rates of hospital admissions, readmissions, and emergency department visits.[11]

The 2 payment structures proposed by the OCF model include a monthly population payment based on a prospective lump-sum payment, and a performance-based payment, which measures the total cost of care for 6-month episodes of care. These payment structures will provide further incentives for the adoption of therapies that can demonstrate high value in addition to better outcomes.[11]

The primary objective of our analysis was to characterize the mean total cost of care for commercially insured and Medicare-covered patients with metastatic pancreatic cancer who received FDA-approved, NCCN category 1–recommended regimens (first-line gemcitabine plus nab-paclitaxel, first-line FOLFIRINOX, first-line gemcitabine monotherapy, or second-line 5-FU plus leucovorin and liposomal irinotecan). A secondary objective was to compare the treatment patterns and components of the total cost of care across the treatment regimens and patient cohorts.

Methods

We used administrative claims to evaluate payers' costs for commercially insured patients and for those with Medicare fee-for-service coverage. We used *International Classification of Diseases, Ninth/Tenth Revision* diagnosis codes (**Appendix A**, available at **www.AHDBonline.com**) in claims data in the 2014-2018 MarketScan commercial database and the CMS 2014-2017 Medicare 100% research identifiable data files.

MarketScan is an annual database comprised of geographically diverse, private-sector health data from approximately 100 payers, and includes more than 28 million commercially insured lives. The data include person-specific clinical healthcare utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services from a selection of large employers, health plans, and governmental and public organizations.

The Medicare 100% research identifiable data files contain paid fee-for-service claims generated for all Medicare beneficiaries in the United States for Parts A, B, and D services. Information in the Medicare 100% research identifiable data files include diagnosis codes, procedure codes, site of service, and patient information, including age, eligibility status, and health maintenance organization enrollment. **Appendix B** (see **www.AHDBonline.com**) lists the study exclusions for Medicare and MarketScan data.

All study patients had at least 2 claims more than 30 days apart with a pancreatic cancer diagnosis and at least 1 claim with a secondary malignancy (ie, metastatic) diagnosis on or after the first pancreatic cancer diagnosis date. We defined the index date as the earliest metastatic pancreatic cancer diagnosis date and excluded patients with preindex malignancies that are not pancreatic cancer.

We excluded commercially insured patients who were not enrolled within the 3-month preindex or 1-month postindex period, and Medicare beneficiaries without enrollment in the 6-month preindex or 3-month (or until death, if earlier) postindex period. Because of variation in the monthly MarketScan enrollment, we have reduced the preindex period from 6 months to 3 months to preserve credible sample sizes for the commercially insured population.

The end date of a therapeutic regimen was defined as the day before a new chemotherapy began, 28 days after the last chemotherapy (if no new chemotherapy was recorded), or at death for the Medicare cohort (no reliable information was available for the commercial population). **Appendix C** (see **www.AHDBonline.com**) lists the chemotherapies and other related drugs included in this study.

The period from the start of the therapeutic regimen through the end date represents a line of therapy. Lines of therapy were assigned based on the order of therapies used: the first line of therapy was defined as the first occurrence of an eligible therapy initiated after or within the 14 days preceding the patient's index date, with the next line of therapy beginning on the day a patient switched to a new regimen. The end of the most recent line of therapy was defined as the earlier of 28 days after the most recent administration, visit date, or fill date for oral therapy (after the first date of chemotherapy), or the date of death. Liposomal irinotecan was most frequently used as a second-line or third-line therapy.

We calculated a Charlson Comorbidity Index (CCI) score for each regimen within every cohort. The CCI is a scale from 1 to 6, which weights patients' comorbidities to estimate the 10-year mortality risk.[13] The mean admissions per line of therapy were defined as the mean number of admissions per patient receiving 1 line of therapy. The mean length of stay was calculated as the mean number of days for each admission. The readmission rates, surgery rates, and intensive care unit (ICU) utiliza-

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CSPC Exhibit 1120
Page 105 of 447

tion rates were calculated as the proportion of admissions with a readmission, surgery, or ICU utilization, respectively. Each measurement was calculated per regimen and per line of therapy.

Cost Measures

The mean total cost of care was calculated as the sum of a payer's inpatient, outpatient, or pharmacy costs incurred during a line of therapy, divided by the number of patients within that line of therapy. Each measurement was calculated separately for all patients in the cohort who received the same regimen and the same line of therapy. The costs reflect the paid amounts (ie, payer liabilities, not including patient cost-sharing) by line of therapy and do not consider drug manufacturers' rebates.

Statistical Testing

All statistical tests were performed using SAS version 9.2 (SAS Institute, Inc; Cary, NC). Confidence intervals (CIs) were calculated for each outcome measure by treatment regimen and by line of therapy. The results with outcome measures where at least one 95% CI did not overlap with those from the other 3 regimens or lines of therapy were selected for additional statistical testing. A GENMOD procedure with negative binomial distribution for count outcomes and a MIXED procedure for cost outcomes were used to determine if an outcome for one regimen was significantly different from the other regimens. These procedures were selected to account for repeated measurements for patients who may have received more than 1 regimen during different lines of therapy.

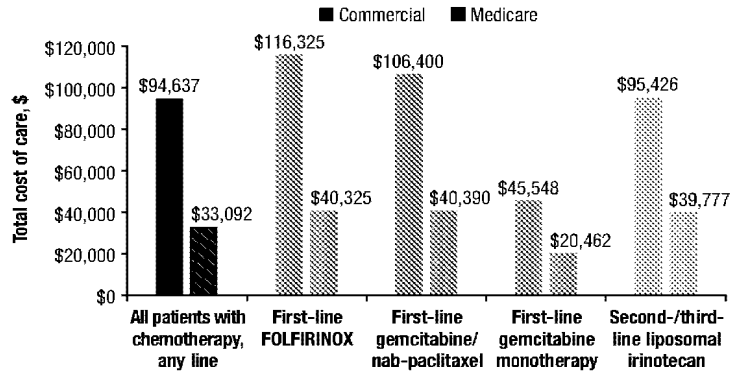
The regimen and line of therapy combinations within the cohorts often resulted in small cell sizes that produced wide CIs, which limited the testing significance of pair-wise comparisons. The results were considered significant if $P \leq .05$. The P values were reported for outcomes that were significantly different from other combinations of regimens or line of therapy.

Results

We identified 3904 patients with metastatic pancreatic cancer in the commercially insured population, with a mean age of 56 years at diagnosis, and 28,063 patients with metastatic pancreatic cancer in the Medicare population, with a mean age of 73 years at diagnosis. All patients received FOLFIRINOX, gemcitabine plus nab-paclitaxel, or gemcitabine monotherapy primarily as first-line regimens; liposomal irinotecan was the most often prescribed drug as a second- and third-line treatment for both patient populations.

Patients received multiple regimens more often in the commercially insured group than in the Medicare group, and patients in the commercially insured cohort were more likely to switch therapies earlier in their treatment process.

Figure 1 Mean Total Cost of Care[a] per Line of Therapy, by Regimen and Payer Cohort



[a]Mean total cost of care includes the service cost categories of inpatient facility, professional, chemotherapy (Part B and Part D claims for Medicare), chemotherapy-related procedures, antiemetic drugs, hematopoietic agents, other supportive drugs, outpatient facility, professional, skilled nursing facility/hospice/home health, surgery, and emergency department/observation costs.

FOLFIRINOX indicates 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

Source: Pelech D. Congressional Budget Office. An analysis of private-sector prices for physician services. Presented at the Academy Health Annual Research Meeting. June 26, 2017.

As expected, the patients in the commercially insured cohort were younger than those in the Medicare cohort; however, their CCI scores were higher, possibly indicating a higher risk profile. For the population with commercial insurance, the mean ages at diagnosis of metastatic pancreatic cancer were 55.4 years, 56.1 years, 56.6 years, and 55.3 years, and the CCI scores were 4, 4.1, 4.4, and 4.3 for patients who received first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, first-line gemcitabine monotherapy, and second- or third-line therapy liposomal irinotecan, respectively.

For the Medicare population, the mean ages at the diagnosis of metastatic pancreatic cancer were 69.8 years, 72.5 years, 75 years, and 72.2 years, and the CCI scores were 3, 3.3, 3.6, and 3.3 for patients receiving first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, first-line gemcitabine monotherapy, and second- or third-line liposomal irinotecan, respectively.

With any treatment regimen, patients with commercial insurance were diagnosed with pancreatic cancer at a mean 19.7-year younger age than patients with Medicare coverage (55.3 years vs 75 years, respectively).

The mean lengths of therapy by regimen in the commercially insured cohort were 165 days, 138 days, 133 days, and 97 days for patients receiving first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, first-line gemcitabine monotherapy, and second- or third-line liposomal irinotecan, respectively. The mean lengths of therapy by regimen in the Medicare cohort were 156

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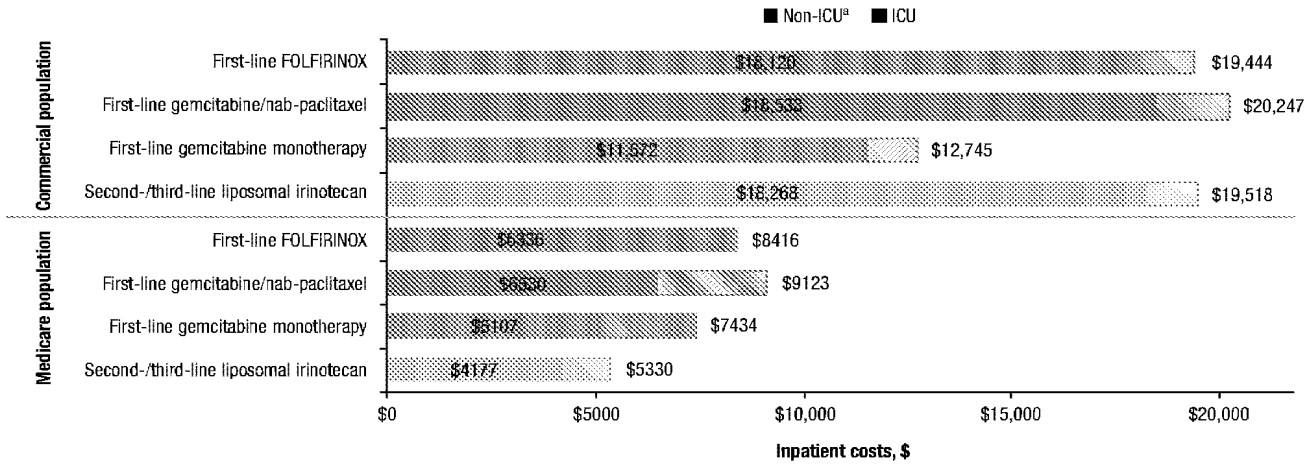
CSPC Exhibit 1120
Page 106 of 447

Figure 2 Mean Inpatient Costs per Line of Therapy, by Regimen and Payer Cohort



[a]Non-ICU includes inpatient facility, professional, and skilled nursing facility/hospice/home health costs.
FOLFIRINOX indicates 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; ICU, intensive care unit.

days, 142 days, 128 days, and 104 days for first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, first-line gemcitabine monotherapy, and second- or third-line liposomal irinotecan patients, respectively.

The mean total cost of care per line of therapy was 186% higher in the commercially insured cohort ($94,637) than in the Medicare cohort ($33,092; P <.05) for all chemotherapy regimens using any line of therapy, which resulted, in part, from the higher provider reimbursement rates of commercial payers (**Figure 1**).[14]

The mean total cost of care for first-line gemcitabine monotherapy was lower than for any other therapy: $45,548 for commercially insured patients and $20,462 for Medicare patients (P <.001). The differences in the mean total cost of care for all other regimens in the commercially insured and Medicare populations were not statistically significant.

The mean inpatient costs per line of therapy in the commercially insured cohort ($12,745-$20,247) were more than twice the Medicare cohort's costs ($5330-$9123) for all regimens (P <.05; **Figure 2**). In the commercially insured cohort, the mean inpatient costs per line of therapy for first-line gemcitabine plus nab-paclitaxel, first-line FOLFIRINOX, and second- or third-line liposomal irinotecan were not significantly different (P >.05). Patients who received first-line gemcitabine monotherapy had lower mean inpatient costs ($12,745) than those who received first-line gemcitabine plus nab-paclitaxel ($20,247; P <.05) or first-line FOLFIRINOX ($19,444; P <.05), but the mean inpatient costs were not statistically significant compared with the patients who received second- or third-line liposomal irinotecan (P >.10).

In the Medicare cohort, patients who received second- or third-line liposomal irinotecan had lower inpatient costs than patients who received all other regimens ($5330; P <.001). Patients who received second- or third-line liposomal irinotecan also had the lowest mean ICU costs in the Medicare cohort ($1153; P <.05).

Overall, the mean inpatient costs for commercially insured patients were from 71% to 266% higher than the costs for patients with Medicare coverage. Among the patients who received the same regimen, the mean hospital admissions per line of therapy were lower in the commercially insured patients than in the Medicare population (P <.05), with the exception of patients who received second- or third-line liposomal irinotecan (**Table 1**).

In the Medicare cohort, the patients who received first-line gemcitabine plus nab-paclitaxel had a higher mean number of admissions than patients who received any other regimen (0.95; P <.001). Patients receiving first-line gemcitabine monotherapy had the lowest mean number of admissions among the commercially insured cohort (0.54; P <.001).

Patients who received second- or third-line liposomal irinotecan had the lowest mean number of admissions among the Medicare beneficiaries (0.61; P <.001).

Patients who received first-line FOLFIRINOX or first-line gemcitabine plus nab-paclitaxel had a shorter length of hospital stay than patients who received first-line gemcitabine monotherapy (5.96, 6.01, and 6.88 days, respectively; P <.05) in the commercially insured cohort. Patients who received first-line gemcitabine plus nab-paclitaxel had a shorter length of hospital stay than the patients who received first-line gemcitabine monotherapy (6.62 vs 7 days, respectively; P <.001) in the Medicare cohort.

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GSPC Exhibit 1120
Page 107 of 447

Medicare beneficiaries receiving first-line FOLFIRINOX had similar rates of readmissions to those who received second- or third-line liposomal irinotecan, and a lower mean number of readmissions than patients receiving gemcitabine-based regimens (P <.05). In the Medicare cohort, patients receiving first-line FOLFIRINOX had the highest mean rate of surgical admissions (17%; P <.001), and patients receiving second- or third-line liposomal irinotecan had the lowest rate of surgical admissions (8%; P <.05).

The mean outpatient costs per line of therapy were 152% to 336% higher in the commercially insured cohort ($28,877-$89,716) than in the Medicare cohort ($6628-$28,754; P <.05; **Figure 3**). For first-line gemcitabine monotherapy in both cohorts, the mean outpatient costs were lowest (commercially insured: $28,877, P <.001; Medicare: $6628, P <.001). The mean outpatient costs per line of therapy were highest for second- or third-line liposomal irinotecan ($28,754; P <.001) in the Medicare cohort. The differences in mean outpatient costs per line of therapy for all other regimens in the commercially insured and Medicare populations were not statistically significant.

The mean outpatient cost ratios between the commercially insured and Medicare populations were approximately 15:1 for chemotherapy, 3:1 for growth factor, 4:1 for chemotherapy administration and associated drugs, and 6:1 for radiotherapy (**Table 2**).

Patients receiving first-line gemcitabine plus nab-paclitaxel or second- or third-line liposomal irinotecan had the highest mean chemotherapy costs in both cohorts: $45,256 and $40,180, respectively, for commercially insured patients; $14,510 and $18,635, respectively, for Medicare patients (P <.001).

Patients receiving first-line gemcitabine monotherapy had the lowest mean chemotherapy costs in both populations ($3043 for commercially insured patients, P ≤.001; $197 for Medicare patients, P <.05), and the lowest mean chemotherapy administration and supportive drug costs in the commercial insurance ($5906; P <.001) and Medicare ($2481; P <.001) cohorts.

Patients receiving first-line FOLFIRINOX had the highest mean growth factor costs in both study populations ($25,772 in commercially insured patients, P <.001; $11,964 in Medicare patients, P <.001) and also had higher mean chemotherapy administration and supporting drug costs in both populations ($24,322 in commercially insured patients, P <.001; $6845 in Medicare patients, P <.001).

Patients receiving first-line gemcitabine monotherapy had the lowest mean growth factor costs in both populations ($1274 in commercially insured patients, P <.05; $805 in Medicare patients, P <.001). For the commercial insurance cohort, second- or third-line liposomal irinotecan and first-line gemcitabine monotherapy had lower "other" outpatient (eg, outpatient facility, surgery, emergency department) costs than treatment with first-line gemcitabine plus nab-paclitaxel or with first-line FOLFIRINOX (P <.05). In the Medicare population, second- or third-line liposomal irinotecan had lower "other" outpatient costs than all of the other regimens (P <.05).

Table 1 Mean Hospital Readmissions, Admissions with ICU, and Length of Stay

Chemotherapy regimen	Mean admissions per line of therapy, N	Mean length of stay, days	Mean percent of total admissions		
			With readmissions, %	With ICU use, %	With surgery, %
Commercial analysis (MarketScan 2014-2018), N = 3904					
First-line FOLFIRINOX	0.70	5.96	23	21	16
First-line gemcitabine/nab-paclitaxel	0.78	6.01	24	22	13
First-line gemcitabine monotherapy	0.54	6.88	22	25	14
Second-/third-line liposomal irinotecan	0.60	6.90	17	21	5
Medicare analysis (Medicare 100% research identifiable data 2014-2017), N = 16,065					
First-line FOLFIRINOX	0.85	6.79	16	23	17
First-line gemcitabine/nab-paclitaxel	0.95	6.62	21	25	11
First-line gemcitabine monotherapy	0.75	7.00	20	26	12
Second-/third-line liposomal irinotecan	0.61	6.79	17	21	8

FOLFIRINOX indicates 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; ICU, intensive care unit.

Discussion

These findings highlight the similarities in treatment patterns for frequently prescribed FDA-approved and NCCN category 1–recommended regimens within commercially insured and Medicare fee-for-service populations with metastatic pancreatic cancer, as well as stark differences in the mean costs between the 2 groups. In this analysis, the patients who received first-line gemcitabine monotherapy had the highest CCI score (commercially insured patients, 4.4; Medicare patients, 3.6) and the oldest age at metastatic diagnosis (commercially insured patients, 56.6 years; Medicare patients, 75 years) in both populations.

For patients receiving gemcitabine monotherapy, older age and comorbidities are demographic trends supported by other research.[8,9] In a study of data from 2015 to 2019, patients with metastatic pancreatic cancer who were receiving first-line gemcitabine monotherapy were older at diagnosis and had higher Eastern Cooperative Oncology Group (ECOG) scores,[8] which is a similar diagnosis tool to the CCI.[15]

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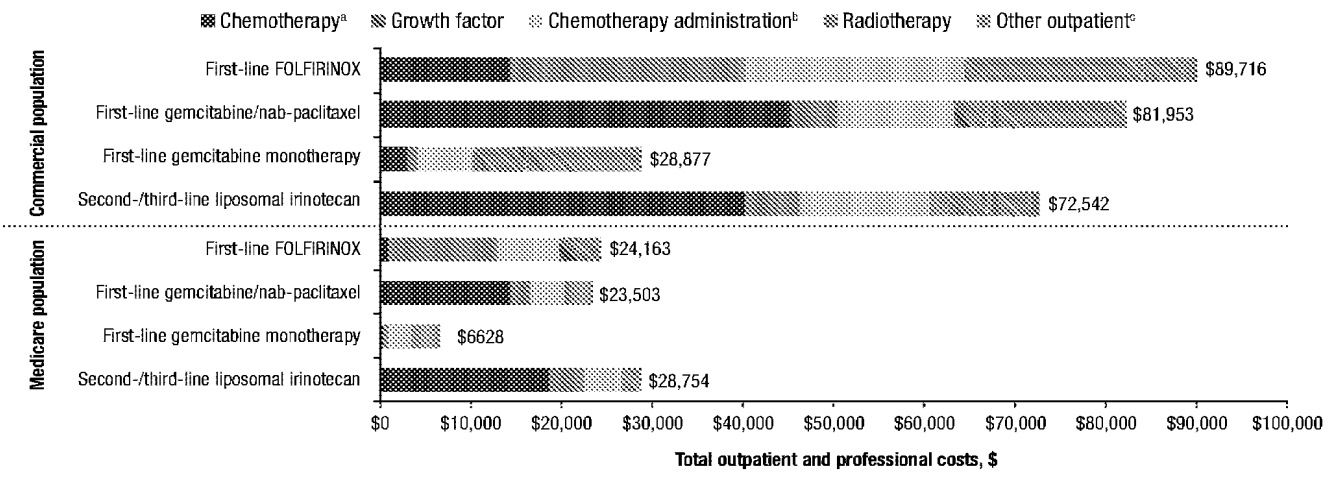
GSPC Exhibit 1120
Page 108 of 447

Figure 3 Mean Outpatient and Professional Costs



[a]Chemotherapy costs for Medicare include Part B and Part D claims.
[b]Contains chemotherapy-related procedures, antiemetic drugs, hematopoietic agents, and other supportive drugs.
[c]Includes outpatient facility, professional, and skilled-nursing facility/hospice/home health, surgery, and emergency department/observation costs.
FOLFIRINOX indicates 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

Table 2 Components of Mean Outpatient Costs

Chemotherapy regimen	Chemotherapy,[a] $	Growth factor, $	Chemotherapy administration and supportive drugs,[b] $	Radiotherapy, $	Other outpatient costs,[c] $
Commercial analysis (MarketScan 2014-2018), N = 3904					
First-line FOLFIRINOX	14,331	25,772	24,322	4888	20,404
First-line gemcitabine/nab-paclitaxel	45,256	5042	12,818	1597	17,238
First-line gemcitabine monotherapy	3043	1274	5906	5620	13,034
Second-/third-line liposomal irinotecan	40,180	5887	14,327	438	11,710
Medicare analysis (Medicare 100% research identifiable data 2014-2017), N = 16,065					
First-line FOLFIRINOX	1022	11,964	6845	1502	2830
First-line gemcitabine/nab-paclitaxel	14,510	1971	3852	477	2693
First-line gemcitabine monotherapy	197	805	2481	916	2229
Second-/third-line liposomal irinotecan	18,635	3842	4227	308	1742

[a]Chemotherapy costs for Medicare include Part B and Part D claims.
[b]Contains chemotherapy-related procedures, antiemetic drugs, hematopoietic agents, and other supportive drugs.
[c]Includes outpatient facility, professional, and skilled-nursing facility/hospice/home health, surgery, emergency department/observation costs.
FOLFIRINOX indicates 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

In the same study, patients who received first-line gemcitabine monotherapy had a shorter treatment duration and a lower median overall survival than patients who received first-line FOLFIRINOX or first-line gemcitabine plus nab-paclitaxel.[8]

Although more common in the commercial insurance cohort, some patients in each cohort in this study received multiple regimens; further analysis is needed to determine if patients who received gemcitabine monotherapy had transitioned from other therapies.

In recent studies of patients with metastatic pancreatic cancer, the patients who received regimens with a higher mean total cost of care (ie, first-line FOLFIRINOX, first-line gemcitabine plus nab-paclitaxel, and second- or third-line liposomal irinotecan) had longer overall survival, whereas patients receiving first-line gemcitabine monotherapy, which accounted for approximately 50% of the mean total cost of care of the other regimens, had a 39% to 56% lower overall survival rate.[8,9] Cost and survival, along with adverse events, are key components of value-based payment models that are gaining influence beyond Medicare's OCM.

Hospital resource utilization is an important component of value-based care models. In our analysis, com-

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CSPC Exhibit 1120
Page 109 of 447

mercially insured patients had generally lower mean admission rates (Table 1) than Medicare beneficiaries. In the Medicare cohort, first-line gemcitabine plus nab-paclitaxel had the highest mean admissions (0.95; P <.001), and patients receiving second- or third-line liposomal irinotecan had the lowest mean admissions (0.61; P <.05) of all regimens in the study. In addition, in the Medicare cohort, first-line FOLFIRINOX had the highest rate of surgical admissions (17%; P <.001), and patients receiving second- or third-line liposomal irinotecan had the lowest rate of surgical admissions (8%; P <.05).

In the Medicare cohort, patients who received first-line gemcitabine plus nab-paclitaxel had a shorter length of stay (6.62 days) than patients who received first-line gemcitabine monotherapy (7 days; P <.001).

In a similar study of commercially insured and Medicare patients with metastatic pancreatic cancer receiving category 1 NCCN-recommended regimens (ie, FOLFIRINOX, gemcitabine plus nab-paclitaxel, gemcitabine monotherapy, or liposomal irinotecan–based therapy), patients who received liposomal irinotecan in any line of therapy had the lowest mean admissions in the Medicare population (0.62) and was among the regimens with the lowest admission rate in the commercially insured population, along with gemcitabine monotherapy (0.56 and 0.54, respectively).[16] In the same study, commercially insured and Medicare patients who received liposomal irinotecan in any line of therapy had the lowest rates of readmissions (commercially insured, 14%; Medicare, 16%) and the lowest rate of surgical admissions (commercially insured, 6%; Medicare, 7%) versus patients who received other regimens.[16]

There were stark differences in the mean treatment costs between patients with commercial insurance and those with Medicare coverage, which are likely a result of higher provider reimbursement rates in the commercial insurance market; the mean commercial insurance costs were 2 to 3 times higher than with Medicare coverage. In a review of 19 recent cost analyses, the Kaiser Family Foundation observed that commercial insurers paid an average of 199% of Medicare rates for all services; for outpatient services, the difference between commercial insurance and Medicare rates was even larger, at an average of 264%.[17]

This ratio is consistent with the findings of the Congressional Budget Office's analysis of overall physician reimbursement differences among commercial insurance and Medicare markets.[14] However, our findings also indicated marked similarities in mean resource utilization for patients with metastatic pancreatic cancer who received the same chemotherapy regimen within the commercially insured and Medicare cohorts.

Limitations

This observational analysis was based on administrative claims data. The study has several limitations, because of the inherent restrictions of claims data. Patients in our study were not randomly assigned to each regimen. In addition, we were unable to adjust for individual dosing periods for regimens and did not include therapies administered before the metastatic pancreatic cancer diagnosis date.

Furthermore, because of the limited qualitative data in claims, we were not able to include quality-of-life measures. Because we were unable to track a patient's date of death in the MarketScan commercial claims files, we did not analyze survival in either cohort. Because the differences in emergency department utilization and emergency department costs were consistent, we decided to use emergency department costs in lieu of emergency department utilization.

The results have not been adjusted for differences in age, sex, CCI scores, or patient acuity. In addition, ECOG scores were not included in the data; thus, CCI scoring was used but was understood to not be as useful in describing the severity of illness in oncology.

Furthermore, this analysis does not consider other factors that may influence regimen performance, such as toxicity, tolerability, and side effects.

Because this analysis did not use health records data, we could not control for clinical covariates, nor were we able to determine cancer stage, although the studied regimens are indicated for metastatic pancreatic cancer. Patient characteristics and regimen performance may influence which regimens patients receive.

We also did not examine whether patients who received liposomal irinotecan also received concomitant 5-FU or previous gemcitabine-based therapy.

Also, later lines of therapy can be at a disadvantage when comparing the use of services and costs with earlier lines of therapy, particularly as a result of disease progression in patients with metastatic pancreatic cancer.

Commercial insurance claims data do not include reliable mortality information, and the Medicare and commercial insurance claims data do not include quality-of-life indicators. Although these data can be approximated with complex algorithms, this was not within the scope of our study.

Conclusions

Within each patient cohort, the mean treatment costs were similar among the therapeutic regimens, with the exception of first-line gemcitabine monotherapy. Previous studies show that patients who received first-line gemcitabine monotherapy had lower overall survival than patients who received FOLFIRINOX, gemcitabine

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GSPC Exhibit 1120
Page 110 of 447

plus nab-paclitaxel, or liposomal irinotecan–based therapy. The mean total cost of care was similar for patients who received second- or third-line liposomal irinotecan, and for those who received first-line gemcitabine plus nab-paclitaxel or first-line FOLFIRINOX, despite patients being more heavily pretreated and receiving treatment in a later line of therapy than patients who received treatment earlier in their disease.

The components of the mean treatment costs differed widely across the treatment regimens, with a difference observed between the commercially insured and Medicare cohorts. Healthcare resource utilization will have a greater impact on value-based care as public and private health plans increase their participation in alternative payment models. Considering these demographic and resource utilization differences can help inform clinical guidelines and pathways as they continue to evolve with new treatment options and emerging evidence, balancing costs, quality metrics, and overall survival.

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Author Disclosure Statement

Ms Tomicki, Ms Latimer, and Ms Dieguez are employees of Milliman, which provided consulting services to Ipsen Biopharmaceuticals. Dr Cockrum is an employee of and owns stock in Ipsen. Dr Kim is a consultant to and serves on the Speaker's Bureau of Ipsen.

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GSPC Exhibit 1120
Page 111 of 447

Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study

Changhoon Yoo, Kyu-pyo Kim, Jae Ho Jeong, Ilhwan Kim, Myoung Joo Kang, Jaekyung Cheon, Byung Woog Kang, Hyewon Ryu, Ji Sung Lee, Kyung Won Kim, Ghassan K Abou-Alfa, Baek-Yeol Ryoo

Summary

Background The prognosis of patients with advanced biliary tract cancer who have progressed on gemcitabine plus cisplatin is dismal. We aimed to investigate the efficacy and safety of second-line liposomal irinotecan plus fluorouracil and leucovorin in patients with metastatic biliary tract cancer that has progressed on gemcitabine plus cisplatin.

Methods This multicentre, open-label, randomised, phase 2b (NIFTY) study was done at five academic institutions in South Korea and included patients aged 19 years or older with histologically or cytologically confirmed metastatic biliary tract cancer that had progressed on first-line gemcitabine plus cisplatin and an Eastern Cooperative Oncology Group performance status of 0 or 1. By use of an interactive web-based response system integrated with an electronic data capture system, patients were randomly assigned (1:1) using permuted blocks (block size 4) to receive either intravenous liposomal irinotecan (70 mg/m² for 90 min) plus intravenous leucovorin (400 mg/m² for 30 min) and intravenous fluorouracil (2400 mg/m² for 46 h) every 2 weeks or leucovorin and fluorouracil only every 2 weeks, and were stratified by primary tumour site, previous surgery with curative intent, and participating centre. Study treatment was continued until the patient had disease progression or unacceptable toxicities, or withdrew consent. The primary endpoint was blinded independent central review (BICR)-assessed progression-free survival. The primary endpoint and safety were assessed in the full analysis set and the safety analysis set, respectively, both of which comprised all randomly assigned patients who received at least one dose of the study treatment. This trial is registered with ClinicalTrials.gov, NCT03524508, and enrolment is complete.

Findings Between Sept 5, 2018, and Feb 18, 2020, 193 patients were screened for eligibility, of whom 174 (88 in the liposomal irinotecan plus fluorouracil and leucovorin group and 86 in the fluorouracil plus leucovorin group) were enrolled and included in the full analysis and safety analysis sets. At a median follow-up of 11·8 months (IQR 7·7–18·7), the median BICR-assessed progression-free survival was significantly longer in the liposomal irinotecan plus fluorouracil and leucovorin group (7·1 months, 95% CI 3·6–8·8) than in the fluorouracil and leucovorin group (1·4 months, 1·2–1·5; hazard ratio 0·56, 95% CI 0·39–0·81; p=0·0019). The most common grade 3–4 adverse events were neutropenia (21 [24%] of 88 in the liposomal irinotecan plus fluorouracil and leucovorin group *vs* one [1%] of 86 in the fluorouracil and leucovorin group) and fatigue or asthenia (11 [13%] *vs* three [3%]). Serious adverse events occurred in 37 (42%) patients receiving liposomal irinotecan plus fluorouracil and leucovorin and 21 (24%) patients receiving fluorouracil and leucovorin. There were no treatment-related deaths.

Interpretation Adding liposomal irinotecan to fluorouracil and leucovorin significantly improved BICR-assessed progression-free survival in patients with advanced biliary tract cancer. Liposomal irinotecan plus fluorouracil and leucovorin could be considered a standard-of-care second-line therapy for advanced biliary tract cancer.

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Introduction

Biliary tract cancers are a group of heterogeneous diseases comprising intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.[1] Although surgery is the only curative treatment for patients with localised disease, only a third can undergo surgery with curative intent; moreover, the recurrence rate is high, with phase 3 trials reporting a median recurrence-free survival of 24–30 months.[2–3] Most studies of patients with unresectable or metastatic biliary tract cancers have reported a poor prognosis, with a median overall survival of less than 1 year, even with systemic chemotherapy.[4–6]

Gemcitabine plus cisplatin is the standard first-line treatment for patients with advanced biliary tract cancer according to the results of the pivotal ABC-02 trial and

CSPC Exhibit 1120
Page 112 of 447

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Research in context

Evidence before this study

We searched PubMed for reports of clinical trials published in English between database inception and Sept 1, 2018 (when this trial started patient enrolment), using the search terms "(biliary tract cancer OR cholangiocarcinoma) AND prospective AND randomised AND (chemotherapy OR drug therapy OR antineoplastic agent OR immunotherapy OR targeted therapy)". At the time, there were no adequately powered randomised phase 2 or phase 3 trials of patients with advanced biliary tract cancer who had progressed on previous chemotherapy. We therefore used the same search strategy to find relevant articles published between Sept 1, 2018, and May 1, 2021, which identified two large randomised trials: ClarIDHy and ABC-06. The ClarIDHy study (2020) reported that ivosidenib, an IDH1 inhibitor, significantly improved progression-free survival compared with placebo in patients with *IDH1*-mutated, chemotherapy-refractory biliary tract cancer. The ABC-06 study (2021) reported that second-line FOLFOX (fluorouracil, leucovorin, and oxaliplatin) plus active symptom control significantly improved overall survival compared with active symptom control alone in patients with advanced biliary tract cancer that had progressed on gemcitabine plus cisplatin.

Added value of this study

To our knowledge, the NIFTY trial is the first randomised study to show the superiority of combination chemotherapy over an active comparator (rather than a placebo or active symptom control) in the second-line setting for patients with advanced biliary tract cancer. Our study met its primary endpoint (blinded independent central review-assessed progression-free survival) and showed that the addition of liposomal irinotecan to fluorouracil and leucovorin significantly improved progression-free survival and overall survival in patients with metastatic biliary tract cancer that had progressed after first-line gemcitabine plus cisplatin. The addition of liposomal irinotecan had a clinically meaningful magnitude of benefit and an acceptable safety profile. Our quality of life analysis showed that the addition of liposomal irinotecan did not impair global health status.

Implications of all the available evidence

This adequately powered, multicentre, open-label, randomised, phase 2b trial provides high-level evidence that supports the use of liposomal irinotecan plus fluorouracil and leucovorin as a second-line treatment in patients with metastatic biliary tract cancer that has progressed on gemcitabine plus cisplatin. Based on the findings of the NIFTY trial, liposomal irinotecan plus fluorouracil and leucovorin could be considered as one of the standard-of-care second-line chemotherapy regimens for advanced biliary tract cancer.

subsequent studies in different populations.[4–6] Patients who show progression on gemcitabine plus cisplatin have a poor prognosis, with an overall survival of approximately 6 months.[7,8] A decade after the publication of the ABC-02 trial, there was still no globally accepted second-line therapy until the success of the ABC-06 trial.[9]

Fibroblast growth factor receptor (FGFR) inhibitors and isocitrate dehydrogenase-1 (IDH1) inhibitors have shown clinically meaningful efficacy outcomes in phase 2 and phase 3 trials for patients with cholangiocarcinoma harbouring *FGFR2* fusions or rearrangements and *IDH1* mutations, respectively.[10,11] However, only a subset of patients can benefit from these agents, as *FGFR2* fusions or rearrangements and *IDH1* mutations occur in about 15–20% of patients with intrahepatic cholangiocarcinoma.[12–14]

Advanced biliary tract cancers that progress on gemcitabine plus cisplatin have been widely managed with fluorouracil-based regimens in clinical practice; however, there is no high-level evidence based on randomised trials to support the use of these regimens and their efficacy is modest.[8,15] Meanwhile, the ABC-06 trial[9] showed a significant increase in overall survival with active symptom control plus FOLFOX (fluorouracil, leucovorin, and oxaliplatin) compared with active symptom control alone in patients with advanced biliary tract cancer who had previously been treated with gemcitabine plus cisplatin. The ABC-06 trial was the first randomised study to show the benefit of second-line chemotherapy in patients with advanced biliary tract cancer. However, despite its successful outcomes, further investigations are needed to develop effective chemotherapy regimens for patients with progressive biliary tract cancer.

Liposomal irinotecan is an intravenous liposomal formulation of irinotecan, a DNA topoisomerase I inhibitor.[16] Preclinical studies indicate that liposomal irinotecan is superior to conventional irinotecan in terms of enhanced tumour exposure to the active metabolite SN-38 and greater tumour growth inhibition.[16] In the NAPOLI-1 trial, a phase 3 randomised trial for metastatic pancreatic adenocarcinoma, liposomal irinotecan plus fluorouracil and leucovorin improved survival outcomes compared with fluorouracil plus leucovorin.[17] On the basis of this study, liposomal irinotecan plus fluorouracil and leucovorin has been approved by the US Food and Drug Administration and the European Medicines Agency for the management of metastatic pancreatic cancer after progression on gemcitabine-based therapy. Considering that biliary tract cancer has an enriched stroma[18] like pancreatic cancer and that our unpublished in-vitro work showed the activity of liposomal irinotecan and synergism between liposomal irinotecan and fluorouracil in a cholangiocarcinoma cell line, liposomal irinotecan might also be efficacious in biliary tract cancer.

Thus, we aimed to investigate the efficacy and safety of second-line liposomal irinotecan plus fluorouracil and

CSPC Exhibit 1120
Page 113 of 447

leucovorin in comparison with fluorouracil and leucovorin alone in patients with metastatic biliary tract cancer who showed disease progression after first-line gemcitabine plus cisplatin.

Methods

Study design and participants

The NIFTY trial is a multicentre, open-label, randomised, phase 2b study in which patients were recruited and treated at five tertiary referral academic institutions in South Korea (appendix 2 p 26). Eligible patients were aged 19 years or older and had histologically or cytologically confirmed biliary tract cancer, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer. Documented radiological disease progression graded by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) on previous first-line gemcitabine plus cisplatin, documented radiological metastatic disease at the time of enrolment, at least one measurable lesion defined by RECIST (version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate haematological, hepatic, and renal function were required, and no other previous chemotherapy except adjuvant therapy was allowed. Patients who had previously received adjuvant therapy were still eligible if there was at least a 6-month disease-free period after the completion of adjuvant therapy. Patients with any clinically significant gastrointestinal disorder or diarrhoea of more than a grade 2 or severe arterial thromboembolic events (ie, myocardial infarction, unstable angina pectoris, or stroke) within 6 months before the start of study treatment were ineligible.

The overall administrative process, site monitoring, and data management were conducted by the Academic Research Office at Asan Medical Center (Seoul, South Korea). This study was done according to the International Conference on Harmonisation of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol (appendix 2) received ethics approval from the institutional review boards of each participating centre, and all patients provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned (1:1) using permuted blocks (block size 4) to receive either liposomal irinotecan plus fluorouracil and leucovorin or fluorouracil plus leucovorin and were stratified by the primary tumour site (intrahepatic *vs* extrahepatic or gallbladder), previous surgery with curative intent (yes *vs* no), and participating centre. Previous surgery with curative intent was selected as a stratification factor because it was a statistically significant prognostic factor in our previous retrospective analysis of 740 patients with advanced biliary tract cancer.[6] Randomisation was done by use of an interactive web-based response system integrated with an electronic data capture system (Medrio, San Francisco, CA, USA). Site personnel (the principal investigator, sub-investigator, and study coordinator) accessed the interactive web-based response system through the electronic data capture system. The patient randomisation number and assignment to treatment groups were provided by this system. Treatment allocation was not masked for the investigators, the patients, and those analysing the data or assessing outcomes.

Procedures

Patients received 400 mg/m² of intravenous leucovorin for 30 min and 2400 mg/m² of intravenous fluorouracil for 46 h every 2 weeks. Patients assigned to the liposomal irinotecan plus fluorouracil and leucovorin group received 70 mg/m² of intravenous liposomal irinotecan for 90 min followed by leucovorin and fluorouracil. Study treatment was continued until the patient showed RECIST version 1.1-defined radiological disease progression, as determined by the investigator, unacceptable toxicities, or withdrew consent. 0·25 mg of palonosetron was administered intravenously 30 min before study treatment for the prevention of chemotherapy-induced nausea and vomiting in the liposomal irinitecan plus fluorouracil and leucovorin group. For every cycle after the first cycle of study treatment, patients were required to have a neutrophil count of at least $1·5\times10^9$ cells per L, a platelet count of at least 75×10^9 platelets per L, and non-haematological toxicity at grade 1 or less. According to the study protocol, dose modifications of liposomal irinotecan or fluorouracil were permitted for the management of adverse events. A maximum of two dose reduction levels per drug was allowed for grade 3–4 toxicities: level −1 represented a 25% reduction from the full initial dose of each drug and level −2 represented an additional 25% reduction. If liposomal irinotecan was discontinued due to toxicity, treatment could continue with fluorouracil and leucovorin if deemed appropriate by the investigator. For patients who required more than 3 weeks of treatment delay, the study treatment was discontinued unless the patient was regarded as having benefited from the study treatment by investigator assessment.

Assessment of radiological tumour response via CT or MRI was done every 6 weeks with a fixed schedule (window period 7 days) from day 1 of cycle 1; additional imaging was done if clinically indicated. The decision for the administration of study treatment was based on radiological assessment by the local investigator. Blinded independent central review (BICR) was not done for real-time confirmation of locally determined radiographic progression, but was done after data cutoff for the primary analysis. For the BICR, all imaging data were collected, anonymised, and centrally reviewed in a double-blinded manner by the central independent radiological review centre (appendix 2 pp 2–4). This procedure was managed by Asan Image Metrics at the Clinical Trial Centre of Asan Medical Centre (Seoul, South Korea). Tumour response was graded by use of

See Online for appendix 2

For more on Medrio see http://medrio.com/

CSPC Exhibit 1120
Page 114 of 447

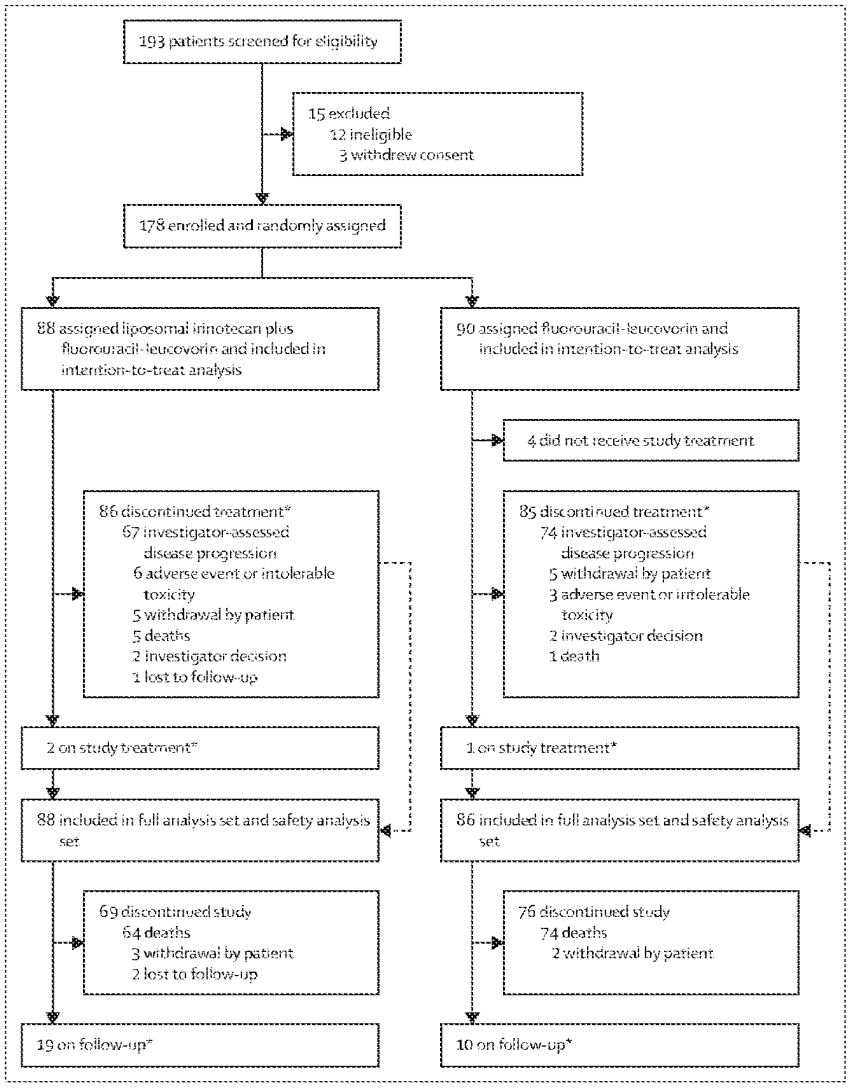


Figure 1: Trial profile
*As of the date of data cutoff: Sept 1, 2020.

RECIST, version 1.1. Patients who discontinued the study treatment for reasons other than disease progression or withdrawal of consent underwent response assessment every 6 weeks until disease progression or the start of a new cancer treatment. Quality of life was assessed from day 1 of cycle 1 to cycle 8 and then to the end of treatment by use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).[19] Patients completed the questionnaire themselves on paper. The EORTC QLQ-C30 has three independent domains: global health status, functional scales (ie, physical, role, cognitive, emotional, and social), and symptom or other scales (ie, appetite loss, constipation, diarrhoea, dyspnoea, fatigue, insomnia, pain, nausea and vomiting, and financial difficulty). The scores were standardised on a 0–100 scale by linear transformation of the raw scores. For the functional scales or global health status, higher scores represent better functioning, whereas, for the symptom or other scales, higher scores represent higher burden.

Safety and tolerability were assessed from the first dose of study treatment at each clinic visit every 2 weeks until the end of study treatment. During the clinic visits, physical examination, assessment of ECOG performance status, symptom monitoring, review of concomitant medication, and assessment of complete blood count, serum chemistry, and electrolytes, were done. CA19-9 concentration was measured every 6 weeks from day 1 of cycle 1 until disease progression. Adverse events were assessed at every visit according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Follow-up for survival status was carried out every 12 weeks for patients who showed disease progression during study treatment.

Outcomes

The primary endpoint was progression-free survival, as assessed by BICR per RECIST, version 1.1. Secondary endpoints were progression-free survival by investigator review per RECIST; overall survival; objective response rate per RECIST, by either BICR or investigator review; safety profile; quality of life per the EORTC QLQ-C30; and an exploratory biomarker analysis, which will be reported seperately. Progression-free survival was defined as the time from the date of randomisation to the date of disease progression or death from any cause, whichever occurred first, and overall survival was defined as the time from the date of randomisation to the date of death due to any cause. Objective response rate was defined as the proportion of patients who had a complete or partial response.

Statistical analysis

The study was designed to have an 80% power with a two-sided type I error of 5% for detecting a hazard ratio (HR) of 0·6 (expected median progression-free survival for the liposomal irinotecan plus fluorouracil and leucovorin group 3·3 months) for progression-free survival with the addition of liposomal irinotecan to fluorouracil and leucovorin. On the basis of our retrospective analysis of patients treated with second-line fluoropyrimidine,[8] the median progression-free survival with fluorouracil–leucovorin was assumed to be 2 months. We benchmarked the target HRs of 0·60–0·75 for metastatic pancreatic cancer previously suggested as clinically meaningful by the American Society of Clinical Oncology.[20] Considering the poor efficacy of second-line chemotherapy used in daily practice, an HR of 0·6 for the intervention versus control treatments was regarded as clinically meaningful. With an expected 10% loss to follow-up, 174 patients (87 per treatment group) were required in total. Accrual rate was assumed to be uniform. In total, 131 progression-free survival events were needed to analyse the primary endpoint. The data cutoff for our primary analysis was

CSPC Exhibit 1120
Page 115 of 447

scheduled for when the last enrolled patient completed 6 months of follow-up.

The efficacy analysis for progression-free survival, overall survival, and objective response rate was primarily done in the full analysis set, which comprised all randomly assigned patients who received at least one dose of the study treatment. Disease control rate, defined as the proportion of patients who had a complete response, a partial response, or stable disease, was also assessed post-hoc in the full analysis set. We also did efficacy analyses for progression-free survival, overall survival, objective response rate, and disease control rate in the intention-to-treat population, which comprised all randomly assigned patients. The reason we selected the full analysis set as the main analysis set was because we presumed that some patients assigned to the control group might drop out before the first dosing after they were made aware of their assignment. Patients in the control group, which involved an active treatment (fluorouracil plus leucovorin), who dropped out of the study treatment might have had poorer outcomes than those who continued the control treatment, as there is no proven effective treatment for biliary tract cancer in this setting. We analysed safety in the safety analysis set, which comprised all randomly assigned patients who received at least one dose of the study treatment. Quality of life analyses were done in the population in the full analysis set who had quality of life data. The discordance rates between the BICR and the investigator assessment for the date of progressive disease were calculated as the proportion of cases in the full analysis set for whom the date of progressive disease was different between the BICR and the investigator assessment. Post-hoc, we analysed 6-month progression-free survival and overall survival in the full analysis set.

We used the Kaplan-Meier method to calculate progression-free survival and overall survival, which were compared between the two treatment groups by use of the stratified log-rank test. The HRs, with 95% CIs, for progression-free survival and overall survival were estimated with a stratified Cox proportional hazards model using the randomisation stratification factors. Objective response rate and disease control rate were compared between treatment groups by use of the stratified Cochran-Mantel-Haenszel test. Patients without disease assessment after day 1 of cycle 1 were defined as not assessable for tumour response and were included as such in the denominator for the objective response rate calculation. Proportional hazard assumptions in the Cox models were evaluated by use of the Schoenfeld residual-based test.

Prespecified subgroup analyses of BICR-assessed progression-free survival, investigator-assessed progression-free survival, and overall survival were done according to sex, primary tumour site, age, ECOG performance status, duration of previous gemcitabine plus cisplatin treatment, baseline CA19-9 concentrations, sites of metastasis, and previous surgery with curative intent. Interactions between the study treatments and subgroups were evaluated by the stratified Cox proportional hazards model. For secondary analyses, there was no adjustment for multiplicity.

For the quality of life analysis, we analysed the mean changes in quality of life scores from baseline to each cycle using a restricted maximum likelihood-based repeated measures approach, combined with the Newton Raphson algorithm. Analyses of quality of life included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction. An unstructured covariance structure was used to model within-patient errors. The containment method was used to estimate denominator df. As we used a linear mixed model with a random intercept in a repeated measures analysis, we did not perform any statistical analysis for dealing with missing quality of life data.

All reported p values are two-sided, and statistical analyses were done by use of SAS, version 9.4. p values of less than 0·05 were considered an indication of significance.

	Liposomal irinotecan plus fluorouracil and leucovorin (n=88)	Fluorouracil and leucovorin (n=86)
Age, years	63 (38-84)	65 (37-80)
Sex		
Female	37 (42%)	38 (44%)
Male	51 (58%)	48 (56%)
Ethnicity		
Asian	88 (100%)	86 (100%)
ECOG performance status		
0	23 (26%)	15 (17%)
1	65 (74%)	71 (83%)
Primary tumour location		
Intrahepatic	35 (40%)	39 (45%)
Extrahepatic	22 (25%)	25 (29%)
Gallbladder	31 (35%)	22 (26%)
Metastatic disease at the time of screening	88 (100%)	86 (100%)
Site of metastatic lesion		
Liver	59 (67%)	64 (74%)
Lung	22 (25%)	16 (19%)
Lymph node	57 (65%)	48 (56%)
Peritoneum	25 (28%)	20 (23%)
Bone	5 (6%)	9 (10%)
Median duration of first-line gemcitabine plus cisplatin		
<5·1 months	48 (55%)	39 (45%)
≥5·1 months	40 (45%)	47 (55%)
≥6 months	31 (35%)	31 (36%)
Previous surgery with curative intent	26 (30%)	29 (34%)
Median serum CA19-9 concentration		
<172 U/mL	48 (55%)	39 (45%)
≥172 U/mL	40 (45%)	47 (55%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: Baseline characteristics in the full analysis set

CSPC Exhibit 1120
Page 116 of 447

	Liposomal irinotecan plus fluorouracil and leucovorin (n=88)	Fluorouracil and leucovorin (n=86)	HR (95% CI)	p value
Blinded independent central review				
Median progression-free survival, months	7·1 (3·6–8·8)	1·4 (1·2–1·5)	0·56 (0·39–0·81)	0·0019
6-month progression-free survival (95% CI)	55·7% (44·7–66·6)	26·2% (16·6–35·8)	..	..
Objective response rate (95% CI)	14·8% (8·1–23·9)	5·8% (1·9–13·0)	..	0·068
Complete response	0	0	..	..
Partial response	13 (15%)	5 (6%)	..	..
Stable disease	44 (50%)	25 (29%)	..	..
Progressive disease	26 (30%)	55 (64%)	..	..
Not evaluable	5 (6%)	1 (1%)	..	..
Disease control rate (95% CI)	64·8% (53·9–74·7)	34·9% (24·9–45·9)	..	0·0002
Investigator review				
Median progression-free survival, months	3·9 (2·7–5·2)	1·6 (1·3–2·2)	0·48 (0·34–0·69)	<0·0001
6-month progression-free survival (95% CI)	30·6% (20·6–40·5)	11·6% (4·9–18·4)	..	..
Objective response rate (95% CI)	19·3% (11·7–29·1)	2·3% (0·3–8·1)	..	0·0002
Complete response	0	0	..	..
Partial response	17 (19%)	2 (2%)	..	..
Stable disease	47 (53%)	41 (48%)	..	..
Progressive disease	19 (22%)	42 (49%)	..	..
Not evaluable	5 (6%)	1 (1%)	..	..
Disease control rate (95% CI)	72·7% (62·2–81·7)	50·0% (39·0–61·0)	..	0·0015
Overall survival				
Median overall survival, months	8·6 (5·4–10·5)	5·5 (4·7–7·2)	0·68 (0·48–0·98)	0·035
6-month overall survival (95% CI)	60·7% (50·3–71·2)	45·9% (35·3–56·5)	..	..

Data are median (95% CI) or n (%), unless otherwise specified. HR=hazard ratio.

Table 2: **Efficacy outcomes in the full analysis set**

Early safety review by an independent data monitoring committee was not planned to be done because of minimal critical safety concerns, as the investigational treatment (ie, liposomal irinotecan plus fluorouracil and leucovorin) had been approved by the US Food and Drug Administration, the European Medicines Agency, and the Korean Ministry of Food and Drug Safety for patients with pancreatic cancer. No interim analysis was planned. Data management was done by the Asan Research Office (Seoul, South Korea), an academic contract research organ-isation, using the electronic data capture system (Medrio). Data management planning and data validation specification were developed and used for data management. This study is registered with ClinicalTrials.gov, NCT03524508.

Role of the funding source

This study is an academic investigator-initiated trial. Servier supported this study by providing liposomal irinotecan and financing the study operation costs. HK inno.N provided palonosetron and financed its pharmacy cost. The funders of the study had no role in study design, data collection, data management, data analysis, data interpretation, or writing of the report.

Results

Between Sept 5, 2018, and Feb 18, 2020, 193 patients were screened for eligibility, of whom 178 were randomly assigned to receive either liposomal irinotecan plus fluorouracil and leucovorin (n=88) or fluorouracil and leucovorin only (n=90; figure 1). After excluding four patients in the fluorouracil and leucovorin group who did not receive any study treatment, 174 patients (88 in the liposomal irinotecan plus fluorouracil and leucovorin group and 86 in the fluorouracil and leucovorin group) were included in the full analysis and safety analysis sets (figure 1). The intention-to-treat population comprised all 178 patients who were randomly assigned.

The median age in the full analysis set was 64 years (IQR 38–84), and 99 (57%) of 174 patients were male. The primary tumour site was intrahepatic cholangiocarcinoma in 74 (43%) patients, extrahepatic cholangiocarcinoma in 47 (27%) patients, and gallbladder cancer in 53 (30%) patients. The median duration of previous first-line gemcitabine plus cisplatin treatment was 5·1 months (IQR 3·0–7·0). The baseline characteristics were well balanced between the two groups (table 1).

At data cutoff (Sept 1, 2020), median follow-up was 11·8 months (IQR 7·7–18·7) for patients in the full analysis set. 64 (73%) of 88 patients in the liposomal

CSPC Exhibit 1120

Page 117 of 447

irinotecan plus fluorouracil and leucovorin group and 74 (86%) of 86 patients in the fluorouracil and leucovorin group had died, and two patients in the liposomal irinotecan plus fluorouracil and leucovorin group and one patient in the fluorouracil and leucovorin group were still receiving study treatment (figure 1).

64 (73%) of 88 patients in the liposomal irinotecan plus fluorouracil and leucovorin group and 79 (92%) of 86 patients in the fluorouracil and leucovorin group had progression-free survival events according to BICR assessment, and 79 (90%) patients in the liposomal irinotecan plus fluorouracil and leucovorin group and 84 (98%) patients in the fluorouracil and leucovorin group had progression-free survival events according to investigator assessment. Median BICR-assessed progression-free survival was significantly longer in the liposomal irinotecan plus fluorouracil and leucovorin group (7·1 months, 95% CI 5·6–8·8) than in the fluorouracil and leucovorin group (1·4 months, 1·2–1·5; HR 0·56, 95% CI 0·39–0·81; p=0·0019; table 2; figure 2A). Results for the secondary efficacy outcomes and post-hoc analyses of disease control rate, 6-month progression-free survival, and overall survival in the full analysis set are shown in table 2, figure 2, and appendix 2 (p 31). The proportional hazards assumption was not met for BICR-assessed (p=0·0009) or investigator-assessed (p=0·016) progression-free survival (appendix 2 pp 9, 29), but there was no evidence of violation for overall survival (p=0·94). The discordance rate for the date of tumour progression between the investigator and the BICR assessments was 30% (52 of 174; appendix 2 pp 5–8). The most common cause of these discrepancies was differences in target lesion selection (19 [37%] of 52; appendix 2 pp 5–8). Prespecified subgroup analyses indicated no significant interactions between the study treatments and BICR-assessed progression-free survival (figure 3A), investigator-assessed progression-free survival (appendix 2 p 30), and overall survival (figure 3B) according to key baseline characteristics. Primary, secondary, and post-hoc efficacy outcomes in the intention-to-treat population are summarised in appendix 2 (pp 10, 32–33), and were generally consistent to those in the full analysis set.

All patients in the full analysis set were included in the safety analysis set. The median duration of study treatment was 3·04 months (IQR 1·45–6·59) for liposomal irinotecan plus fluorouracil and leucovorin and 1·45 months (1·15–2·92) for fluorouracil and leucovorin, and the median number of cycles administered was 6 (3–12) for the liposomal irinotecan plus fluorouracil and leucovorin group and 3 (3–6) for the fluorouracil and leucovorin group. Adverse events are summarised in table 3 and appendix 2 (pp 20–25). The most common grade 3–4 adverse events were neutropenia (21 [24%] of 88 in the liposomal irinotecan plus fluorouracil and leucovorin group *vs* one [1%] of 86 in the fluorouracil and leucovorin group) and fatigue or asthenia (11 [13%] *vs* three [3%]). Serious adverse events were reported in

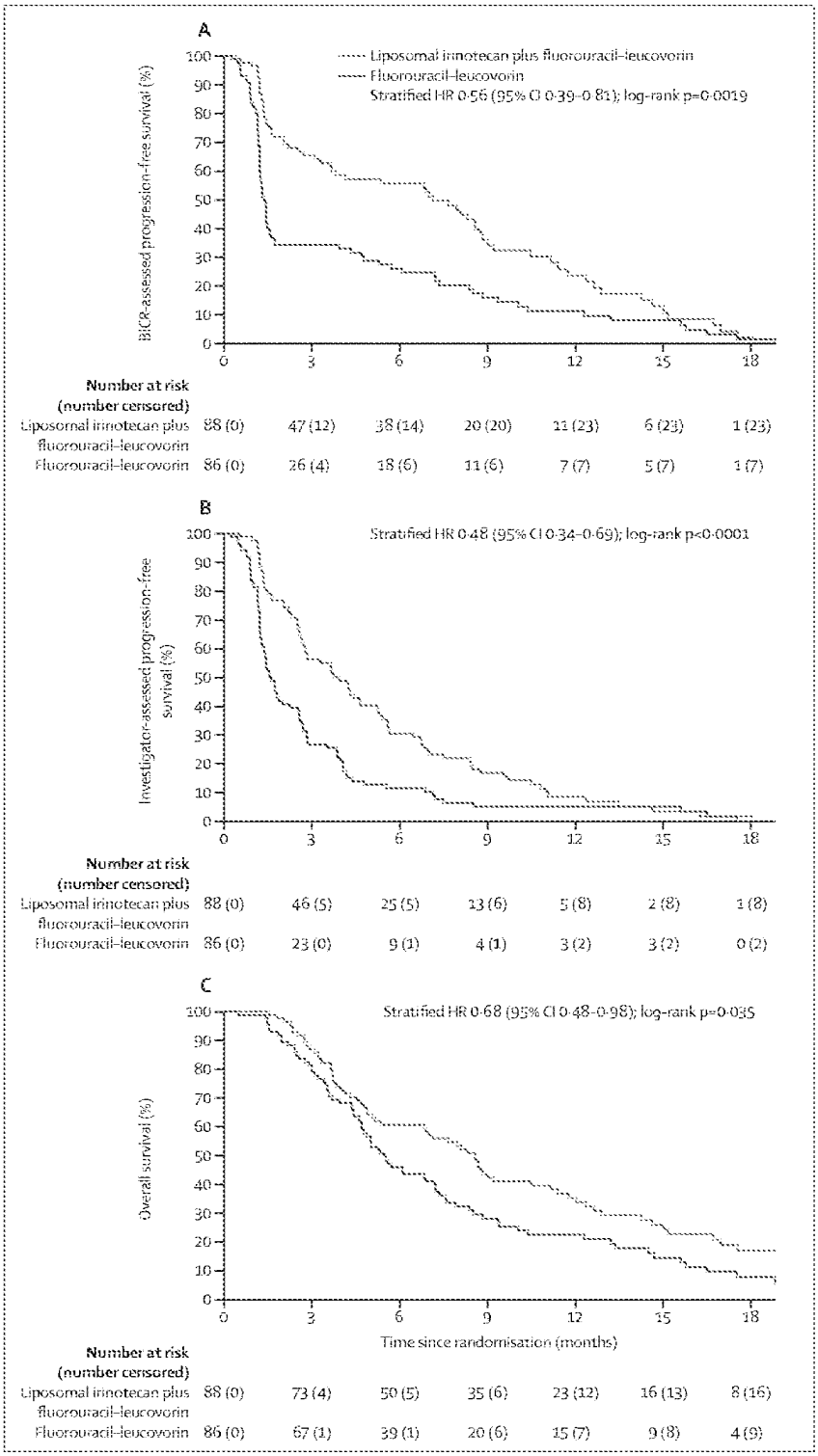


Figure 2: **Kaplan-Meier graphs for survival outcomes in the full analysis set**
(A) BICR-assessed progression-free survival. (B) Investigator-assessed progression-free survival. (C) Overall survival. BICR=blinded independent central review. HR=hazard ratio.

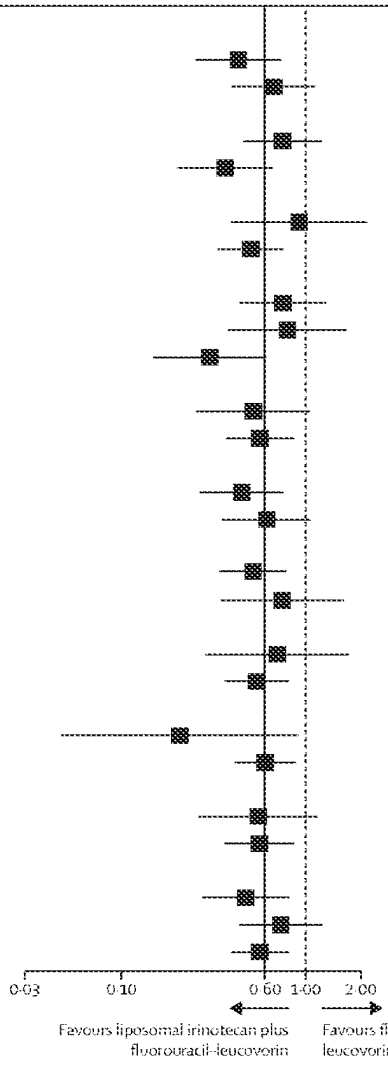
CSPC Exhibit 1120
Page 118 of 447

37 (42%) patients in the liposomal irinotecan plus fluorouracil and leucovorin group, of whom six (7%) had treatment-related serious adverse events (grade 4 pancytopenia [n=1], grade 3 febrile neutropenia [n=1], grade 3 diarrhoea [n=1], grade 3 fatigue [n=1], and grade 3 acute kidney injury [n=1]), and in 21 (24%) patients in the fluorouracil and leucovorin group, of whom one (1%) had a treatment-related serious adverse event (grade 3 colitis). Adverse events leading to death occurred in five (6%) patients receiving liposomal irinotecan plus fluorouracil and leucovorin (pneumonia [n=1], haemorrhage [n=1], sepsis [n=1], dyspnoea [n=1], and cerebrovascular infarction [n=1]) and one (1%) patient receiving fluorouracil and leucovorin (renal impairment), none of which were assessed by the investigator to be related to treatment. All other deaths (59 in the liposomal irinotecan plus fluorouracil and leucovorin group and 73 in the fluorouracil and leucovorin group) were related to progressive disease.

Study treatment was discontinued due to adverse events in six (7%) of 88 patients in the liposomal irinotecan plus fluorouracil and leucovorin group (grade 3 fatigue [n=3], grade 3 neutropenia [n=2], and grade 3 acute kidney injury [n=1]) and in three (3%) of 86 patients in the fluorouracil

A

	Number of events/ number of patients		Median BICR-assessed progression-free survival (95% CI), months		HR (95% CI)	$p_{interaction}$
	Liposomal irinotecan plus fluorouracil–leucovorin	Fluorouracil–leucovorin	Liposomal irinotecan plus fluorouracil–leucovorin	Fluorouracil–leucovorin		
Age (years)						0·25
<65	32/48	37/42	6·8 (1·6–8·6)	1·2 (1·2–1·3)	0·43 (0·25–0·73)	
≥65	32/40	42/44	8·6 (3·6–10·5)	1·6 (1·3–4·8)	0·67 (0·40–1·14)	
Sex						0·080
Male	39/51	43/48	5·4 (2·5–8·3)	1·4 (1·2–5·3)	0·75 (0·46–1·22)	
Female	25/37	36/38	8·6 (3·6–12·4)	1·3 (1·2–1·4)	0·37 (0·20–0·67)	
ECOG performance status						0·21
0	17/23	13/15	6·9 (1·2–14·6)	1·7 (1·3–8·8)	0·92 (0·40–2·16)	
1	47/65	66/71	7·1 (3·7–8·8)	1·3 (1·2–1·4)	0·50 (0·33–0·75)	
Primary tumour site						0·092
Intrahepatic	27/35	36/39	2·2 (1·3–8·1)	1·2 (1·1–1·4)	0·75 (0·44–1·29)	
Extrahepatic	16/22	21/25	8·8 (2·5–11·2)	1·6 (1·2–8·4)	0·79 (0·38–1·66)	
Gallbladder	21/31	22/22	9·0 (5·4–15·0)	1·4 (1·2–4·7)	0·30 (0·15–0·61)	
Previous surgery						0·84
Yes	17/26	26/29	10·5 (2·7–14·3)	1·4 (1·2–1·7)	0·52 (0·26–1·06)	
No	47/62	53/57	6·8 (3·1–8·1)	1·3 (1·2–1·6)	0·57 (0·37–0·87)	
Duration of previous gemcitabine-cisplatin (months)						0·43
<5·1	39/48	36/39	3·8 (1·6–8·3)	1·2 (1·1–1·6)	0·45 (0·27–0·75)	
≥5·1	25/40	43/47	8·8 (6·8–11·2)	1·4 (1·2–4·3)	0·61 (0·35–1·07)	
Metastatic site: liver						0·43
Yes	48/59	62/64	6·9 (3·3–8·6)	1·2 (1·2–1·4)	0·52 (0·34–0·79)	
No	16/29	17/22	7·1 (2·7–9·2)	3·2 (1·4–7·4)	0·74 (0·34–1·61)	
Metastatic site: lung						0·61
Yes	13/22	12/16	6·8 (1·6–9·0)	1·2 (1·2–10·1)	0·70 (0·29–1·71)	
No	51/66	67/70	7·1 (3·1–8·8)	1·4 (1·2–1·6)	0·54 (0·36–0·81)	
Metastatic site: bone						0·17
Yes	3/5	9/9	6·8 (NE–NE)	1·2 (0·5–1·2)	0·21 (0·05–0·91)	
No	61/83	70/77	7·7 (3·6–8·8)	1·4 (1·3–1·7)	0·60 (0·41–0·88)	
Metastatic site: peritoneum						0·98
Yes	18/25	19/20	3·6 (1·4–7·1)	1·3 (1·1–4·7)	0·55 (0·26–1·15)	
No	46/63	60/66	8·3 (3·8–9·0)	1·4 (1·2–1·7)	0·56 (0·37–0·86)	
Baseline CA19-9 concentration (U/mL)						0·26
<172	33/48	35/39	8·6 (6·9–12·4)	1·3 (1·2–5·3)	0·47 (0·27–0·81)	
≥172	31/40	44/47	3·6 (1·6–7·1)	1·4 (1·2–1·7)	0·73 (0·44–1·23)	
Overall	**64/88**	**79/86**	**7·1 (3·6–8·8)**	**1·4 (1·2–1·5)**	**0·56 (0·39–0·81)**	



(Figure 3 continues on next page)

CSPC Exhibit 1120
Page 119 of 447

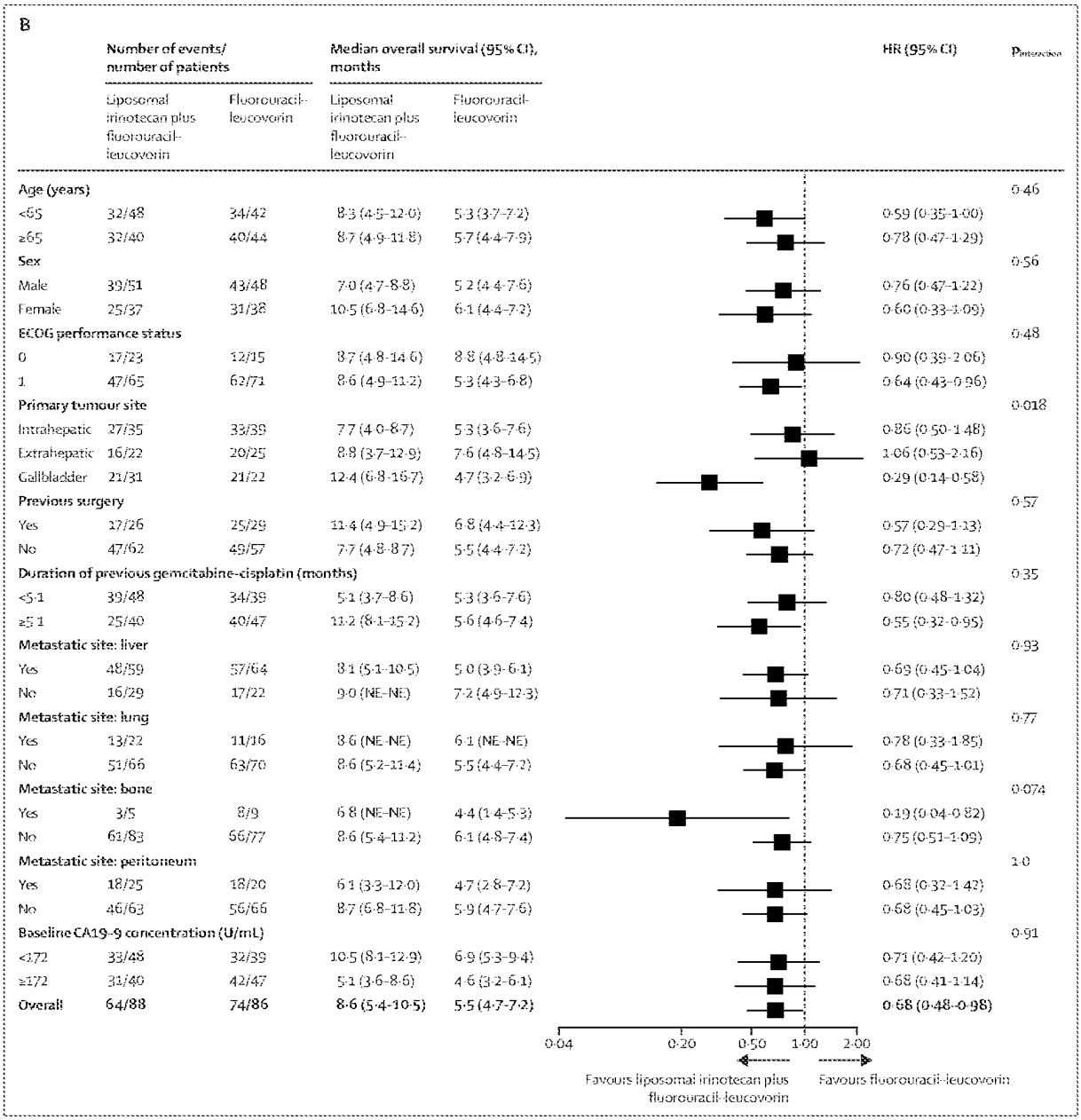


Figure 3: Forest plots of subgroup analyses

(A) Subgroup analysis of BICR-assessed progression-free survival. (B) Subgroup analysis of overall survival. BICR=blinded independent central review. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NE=not estimable.

and leucovorin group (grade 3 abdominal pain [n=1], grade 2 fatigue [n=1], and grade 1 interstitial pneumonitis [n=1]). Dose modifications occurred in 70 (80%) patients in the liposomal irinotecan plus fluorouracil and leucovorin group and in 26 (30%) patients in the fluorouracil and leucovorin group (appendix 2 pp 11–12).

For our quality of life assessment, all patients (n=88) in the liposomal irinotecan plus fluorouracil and leucovorin group and 85 (99%) of 86 patients in the fluorouracil and leucovorin group completed the EORTC QLQ-C30 at baseline (day 1 of cycle 1; appendix 2 pp 13–18). At all assessment timings, there was no significant difference between the treatment groups in the scores of all EORTC QLQ-C30 function and symptom subscales (appendix 2 pp 13–18).

30 (35%) of 86 patients who discontinued the study treatment in the liposomal irinotecan plus fluorouracil and leucovorin group and 27 (32%) of 85 patients who discontinued the study treatment in the fluorouracil and leucovorin group received systemic anticancer therapies

CSPC Exhibit 1120
Page 120 of 447

	Liposomal irinotecan plus fluorouracil–leucovorin (n=88)				Fluorouracil–leucovorin (n=86)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological								
Anaemia	5 (6%)	8 (9%)	0	0	2 (2%)	3 (3%)	0	0
Febrile neutropenia	NA	2 (2%)	0	0	NA	0	0	0
Neutropenia	8 (9%)	16 (18%)	5 (6%)	0	2 (2%)	1 (1%)	0	0
Thrombocytopenia	3 (3%)	0	0	0	0	1 (1%)	0	0
Non-haematological								
Nausea	17 (19%)	5 (6%)	0	0	13 (15%)	1 (1%)	0	0
Vomiting	9 (10%)	0	0	0	3 (3%)	1 (1%)	0	0
Abdominal pain	18 (20%)	4 (5%)	0	0	11 (13%)	3 (3%)	0	0
Constipation	26 (30%)	0	0	0	19 (22%)	0	0	0
Diarrhoea	16 (18%)	4 (5%)	0	0	9 (10%)	0	0	0
Dyspepsia	20 (23%)	0	0	0	12 (14%)	0	0	0
Stomatitis	12 (14%)	2 (2%)	0	0	10 (12%)	0	0	0
Fatigue or asthenia	16 (18%)	11 (13%)	0	0	14 (16%)	3 (3%)	0	0
Pyrexia	15 (17%)	0	0	0	7 (8%)	1 (1%)	0	0
Anorexia	23 (26%)	1 (1%)	0	0	16 (19%)	0	0	0
Acute kidney injury	0	2 (2%)	0	0	0	0	0	0
Pneumonia	0	2 (2%)	0	1 (1%)	0	2 (2%)	0	0
Haemorrhage	0	1 (1%)	0	1 (1%)	0	0	0	0
Dyspnoea	2 (2%)	0	0	1 (1%)	0	0	0	0
Renal impairment	0	0	0	0	0	0	0	1 (1%)
Cerebrovascular infarction	0	0	0	1 (1%)	0	0	0	0
Sepsis	0	0	0	1 (1%)	0	1 (1%)	0	0

Data are n (%). We report adverse events of grade 1–2 occuring in at least 10% of patients and all grade 3 or worse adverse events. NA=not applicable.

Table 3: Adverse events occurring in the safety analysis set regardless of causality

(appendix 2 p 19). Fluoropyrimidine plus cisplatin or oxaliplatin was the most commonly used therapy after study treatment discontinuation (15 [17%] patients in the liposomal irinotecan plus fluorouracil and leucovorin group and nine [11%] patients in the fluorouracil and leucovorin group).

Discussion

In this multicentre, open-label, randomised, phase 2b study, the addition of liposomal irinotecan to fluorouracil and leucovorin significantly improved BICR-assessed progression-free survival, investigator-assessed progression-free survival, and overall survival compared with fluorouracil and leucovorin alone for patients with metastatic biliary tract cancer who had disease progression after treatment with gemcitabine plus cisplatin. The HR for the median BICR-assessed progression-free survival was 0·56 (95% CI 0·39–0·81), achieving the target HR of 0·6 for intervention versus control treatments. The improvements in progression-free survival and overall survival with the addition of liposomal irinotecan to fluorouracil and leucovorin were clinically meaningful and generally consistent across various subgroups. The efficacy outcomes in the full analysis set were consistently observed in the intention-to-treat population.

Discrepancies between the values for BICR-assessed and investigator-assessed median progression-free survival were caused by discordance in the date of tumour progression between investigators and independent radiological reviewers. The independent radiological reviewers tended to select representative target lesions after reviewing all timepoint images from the baseline CT scan to the last CT scan, whereas investigators selected measurable target lesions after reviewing the baseline CT scan only. However, this was similar to findings in the phase 3 ClarIDHy trial (23% discordance rate).[11] As the number of BICR-assessed progression-free survival events was smaller than the number of investigator-assessed progression-free survival events, and given that progression-free survival events or censoring did not occur uniformly, the possibility of overestimation in the median progression-free survival by BICR assessment cannot be excluded. However, the number of events for BICR-assessed progression-free survival was sufficient for statistical comparison (minimum 131 events), and the HRs for median progression-free survival were similar between the BICR assessment and the investigator review.

In the ABC-06 trial,[9] which involved a similar therapeutic setting to our study (ie, patients with advanced biliary tract cancer that had previously progressed on

CSPC Exhibit 1120
Page 121 of 447

gemcitabine plus cisplatin, were molecularly unselected, and were given a second-line fluorouracil-containing regimen), second-line FOLFOX resulted in a median progression-free survival of 4·0 months (95% CI 3·2–5·0), a median overall survival of 6·2 months (95% CI 5·4–7·6), and an objective response rate of 5%. However, direct comparison of efficacy outcomes between the NIFTY and ABC-06 trials is difficult because of discrepancies in the intervals of disease evaluation (every 6 weeks *vs* every 3 months), disease status (all metastatic disease *vs* locally advanced disease in 19% of patients), and the presence of a measurable lesion (mandatary *vs* not necessary). Because liposomal irinotecan and oxaliplatin have different mechanisms of action and non-overlapping safety profiles, liposomal irinotecan plus fluorouracil and leucovorin and FOLFOX potentially could be sequentially used for medically fit patients with advanced biliary tract cancer without targetable genetic alterations in whom gemcitabine plus cisplatin treatment is not successful.

Although irinotecan has been investigated as a monotherapy or in combination with other chemotherapeutic agents, its role in advanced biliary tract cancer remains unclear because most studies examining irinotecan in this setting were small single-arm studies.[21–23] No previous prospective study has compared fluorouracil plus irinotecan versus fluorouracil monotherapy; however, in a multicentre, retrospective study, there were no significant differences in progression-free survival and overall survival between patients receiving the fluorouracil plus irinotecan combination and those receiving fluorouracil monotherapy after progressing on gemcitabine plus platinum.[24] Moreover, a randomised, phase 2 study did not meet its primary endpoint (6-month progression-free survival) and reported that FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) showed similar efficacy outcomes compared with gemcitabine plus cisplatin in the treatment of advanced biliary tract cancer in the first-line setting.[25] A phase 2 study showed that irinotecan plus capecitabine significantly improved progression-free survival compared with irinotecan monotherapy; however, no conclusion on irinotecan's efficacy in advanced biliary tract cancer could be drawn in this trial because there was no significant difference in objective response rate and overall survival between the two groups and only 60 patients were included.[26] Considering the scarcity of evidence regarding the clinically meaningful activity of irinotecan, our findings suggest that liposomal irinotecan might be useful for overcoming multiple biological barriers, such as the extracellular matrix in advanced biliary tract cancer, via enhanced drug delivery using nanoparticles.[27,28]

As molecular biomarker analysis was not mandatory for this study, we could not delineate the correlation between genetic alterations and efficacy outcomes. Considering the efficacy of pemigatinib for cholangiocarcinoma with *FGFR2* fusions or rearrangements (objective response rate 35·5%, 95% CI 26·5–45·4; median progression-free survival 6·9 months, 95% CI 6·2–9·6; and median overall survival 21·1 months, 95% CI 14·8–not estimable)[10] and ivosidenib for *IDH1*-mutated cholangiocarcinoma (objective response rate 2%; median progression-free survival 2·7 months, 95% CI 1·6–4·2, and median overall survival 10·8 months, 95% CI 7·7–17·6),[11] treatment with matched agents should be considered after disease progression on gemcitabine plus cisplatin for patients with these targetable genetic alterations. However, the accessibility and availability of molecular testing and targeted agents varies highly across different geographical regions in the management of biliary tract cancer.

The types and frequencies of adverse events from liposomal irinotecan plus fluorouracil and leucovorin in our study were in line with those reported in the NAPOLI-1 trial for patients with pancreatic adenocarcinoma.[17] Grade 3–4 adverse events were more common in the liposomal irinotecan plus fluorouracil and leucovorin group than in the fluorouracil and leucovorin group. Neutropenia and fatigue or asthenia were the most common grade 3–4 adverse events in the liposomal irinotecan plus fluorouracil and leucovorin group. Although the prevalence of grade 3–4 diarrhoea in the liposomal irinotecan plus fluorouracil and leucovorin group was lower in our study (four [5%] of 88 patients) than in the NAPOLI-1 trial (15 [13%] of 117),[17] our findings are in line with real-world data in the Korean population (2–5%) for liposomal irinotecan and the Asian subgroup analysis (one [3%] of 33) in the NAPOLI-1 study.[29–31] Despite an increase in adverse events due to the addition of liposomal irinotecan, there was no significant difference between the treatment groups in quality of life, suggesting that the adverse events of liposomal irinotecan plus fluorouracil and leucovorin were mostly manageable.

Because this trial was done in a single country and all patients were of east Asian ethnicity, its findings might have limited generalisability. However, previous studies of gemcitabine plus cisplatin for biliary tract cancer indicate that the benefit of chemotherapy is consistently observed across different geographical regions.[4,5] Furthermore, in the global NAPOLI-1 trial,[17] the efficacy of liposomal irinotecan plus fluorouracil and leucovorin for metastatic pancreatic adenocarcinoma was consistent regardless of ethnicity. Although our trial was adequately powered for the primary endpoint and had a sample size (n=174) larger than that of the phase 3 ABC-06 trial (n=162), it might be insufficient to fully show the impact of liposomal irinotecan in each subtype of biliary tract cancer. However, tumour response was carefully evaluated with imaging every 6 weeks by a BICR, thus allowing an accurate assessment of objective response rate, progression-free survival, and HRs of progression-free survival between two groups. The proportional hazards assumption was not met for progression-free survival by BICR or investigator review, mainly because most events for progression-free survival occurred within 6 months from

CSPC Exhibit 1120
Page 122 of 447

the initiation of study treatment. As this result implies that the HRs for progression-free survival might not be representative for the entire study period, further validation should be done in a large, phase 3 trial.

Taken together, the NIFTY trial shows the statistically significant and clinically meaningful benefit and manageable safety profile of second-line liposomal irinotecan plus fluorouracil and leucovorin for patients with metastatic biliary tract cancer who have progressed after gemcitabine plus cisplatin treatment. Based on these findings, liposomal irinotecan plus fluorouracil and leucovorin could be considered one of the standard-of-care second-line regimens. Further trials in the global patient population might be needed to validate our findings.

Contributors

CY designed the study, developed the protocol, and secured funding. JSL developed the protocol and statistical analysis plan. KWK developed the blinded imaging analysis plan. CY, K-pK, JHJ, IK, MJK, JC, BWK, HR, and B-YR participated in the recruitment of patients and collection of data. CY, JSL, and KWK analysed the data. All authors interpreted the data. CY, JSL, KWK, and GKA-A wrote the first draft of the manuscript. All authors contributed to the review and revision of the manuscript for important intellectual content and approved the final version for submission. CY, JSL, and KWK accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CY received honoraria from Servier, Bayer, AstraZeneca, Merck Sharp & Dohme, Eisai, Celgene, Bristol Myers Squibb, Debiopharm, Ipsen, Kyowa Kirin, Novartis, Boryung Pharmaceuticals, Merck Serono, Mundipharma, Roche, and Janssen, and received research grants from Servier, Bayer, AstraZeneca, Ono Pharmaceuticals, Celgene, Ipsen, Boryung Pharmaceuticals, Ildong Pharmaceuticals, CKD Pharmaceuticals, and HK inno.N. JHJ received honoraria from Boryung Pharmaceutical, Daewoong Pharmaceutical, Eisai, HK inno.N, Lilly, Novartis, Pfizer, and Roche. JC received honoraria from Roche, Bayer, Eisai, Ipsen, and Bristol Myers Squibb, and received research grants from Bayer and Dong-A Pharmaceuticals. GKAA reports research grants from Arcus, Agios, AstraZeneca, BioNtech, Bristol Myers Squibb, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Silenseed, and Yiviva, and personal consultation fees from Adicet, AstraZeneca, Alnylam, Autem, Bayer, Beigene, Berry Genomics, Cend, Celgene, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Merck, Nerviano, QED, Redhill, Rafael, Servier, Silenseed, Sillajen, Sobi, Surface Oncology, Therabionics, Vector, and Yiviva. All other authors declare no competing interests.

Data sharing

The data collected for this study will not be made available to the public. Investigators interested in the deidentified participant data are encouraged to contact the corresponding author at yooc@amc.seoul.kr after publication of this Article for data sharing and collaboration. The protocol and the statistical analysis plan can be found in appendix 2.

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CSPC Exhibit 1120

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CSPC Exhibit 1120
Page 124 of 447

frontiers in Oncology

ORIGINAL RESEARCH
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Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma Treated With Liposomal Irinotecan

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Background: The NAPOLI-1 trial demonstrated that liposomal irinotecan in combination with fluorouracil (5-FU) and leucovorin (LV) prolonged survival with a manageable safety profile in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy. Real-world data on clinical outcomes associated with liposomal irinotecan in NAPOLI-1-based regimens is needed to further substantiate this.

Methods: This real-world, retrospective chart review study included patients with mPDAC who received NAPOLI-1-based regimens from six academic centers in the United States. Liposomal irinotecan initiation defined the index date. Overall survival (OS) and progression-free survival (PFS) were assessed with Kaplan-Meier methodology.

Results: There were 374 patients evaluated; median age was 68 years, and 51% were female. Among 326 patients with baseline ECOG information, approximately 74% had ECOG score <2. Liposomal irinotecan was administered as a doublet with 5-FU in a NAPOLI-1-based regimen in the first line (1L; 16%), 2L (42%), and 3L+ (42%) of the metastatic setting. For patients treated in 1L, 2L, and 3L+, median [95% confidence interval (CI)] OS was 8.0 [5.1, 11.2], 7.3 [5.3, 8.8], and 4.6 [4.0, 5.7] months, and median [95% CI] PFS was 4.2 [2.2, 6.6], 3.0 [2.6, 3.7], and 2.0 [1.7, 2.2] months, respectively.

Conclusions: Patients in a real-world setting treated with NAPOLI-1-based liposomal irinotecan doublet regimens at academic centers were older with poorer performance status compared to trial patients yet had similar outcomes and efficacy. Furthermore, liposomal irinotecan was frequently used in the 3L+ setting where no treatment has been approved and provided clinical benefit.

Keywords: metastasis, pancreatic ductal adenocarcinoma, cancer management, pancreatic cancer, liposomal irinotecan

CSPC Exhibit 1120
Page 125 of 447

INTRODUCTION

Despite recent diagnostic and therapeutic advances, pancreatic cancer remains an aggressive and difficult to treat malignancy. Although it only comprises 3% of new cancer diagnoses, it is projected to be the second leading cause of cancer-related mortality by 2030 (1). Due to an absence of effective screening tools, pancreatic cancer is frequently diagnosed when locally advanced or widely metastatic. Delayed diagnosis contributes to treatment challenges as surgical resection is the only means to curative treatment and is a factor in the poor 5-year survival rate ranging from 3-8% (2).

In October 2015, the Food and Drug Administration (FDA) approved liposomal irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV) for the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) in patients that had previously progressed on gemcitabine-based chemotherapy following the results of the pivotal NAPOLI-1 trial. The NAPOLI-1 trial evaluated liposomal irinotecan in combination with 5-FU/LV compared to treatment with 5-FU/LV alone in patients with mPDAC previously treated with gemcitabine-based therapy (3). The results indicated that treatment with liposomal irinotecan in combination with 5-FU/LV compared to 5-FU/LV alone significantly prolonged the median overall survival (OS) (6.1 months *vs.* 4.2 months; hazard ratio [HR]: 0.67; p: 0.012) and median progression-free survival (PFS) (3.1 months *vs.* 1.5 months; HR: 0.56; p: 0.0001) in patients with mPDAC. Liposomal encapsulation prolongs the duration of circulating irinotecan prior to conversion to its active metabolite SN-38, thereby protecting irinotecan from hydrolysis and rapid metabolic conversion (4, 5). Liposomal irinotecan in combination with 5-FU/LV is the only category 1 treatment recommended by the National Comprehensive Cancer Network (NCCN) for patients with mPDAC after disease progression following gemcitabine-based therapy (6).

While the NAPOLI-1 trial results have expanded the treatment options for mPDAC, there are limited real-world data evaluating the use and outcomes of treatment with liposomal irinotecan. A single institution study conducted at Memorial Sloan Kettering Cancer Center (MSKCC) in 2017 assessed similar treatment outcomes among patients with mPDAC treated with liposomal irinotecan and reported similar results (median OS 5.3 months and median PFS 2.9 months) to NAPOLI-1 (7). To expand on the aforementioned study's findings, this real-world study incorporated patients from five additional cancer centers across the United States (US) in order to assess real-world outcomes, treatment patterns, and adverse events (AE) in patients with mPDAC treated with liposomal irinotecan in a NAPOLI-1-based doublet regimen.

METHODS

Study Design and Study Population

This was a non-interventional, retrospective, multi-center chart review study that was conducted using data from six academic cancer centers across the US. Participating centers included MSKCC, Cedars-Sinai Medical Center, Emory Winship Cancer Institute, Houston Methodist Cancer Center, Henry Ford Cancer Institute, and University of Pittsburgh Medical Center. Eligible patients were treated with liposomal irinotecan in a doublet with 5-FU between 2015 and 2020 and were diagnosed with mPDAC at any time before liposomal irinotecan initiation. Following IRB approval at each participating center, designated abstractors collected patient demographics, clinical characteristics and outcomes, and treatments from patient medical charts and electronic medical records using a standardized electronic case report form (eCRF). This study was conducted in two phases: a pilot phase and a full-launch phase. During the pilot phase, the eCRF was prepared and tested at one center using data from ten patient charts. Reviewers ensured that the eCRF accurately captured all relevant information and that data was collected as efficiently as possible. Based on feedback from the pilot phase, the eCRF was then updated and finalized for the full launch phase where data collection began at all centers.

Patient data were collected during the baseline and observation periods before and after the initiation of liposomal irinotecan, the index date. The baseline period captured data available prior to the index date (until the date of initial pancreatic cancer diagnosis if available). Study outcomes were assessed during the observation period, defined as the period from the index date to the end of data availability or death (**Figure 1**).

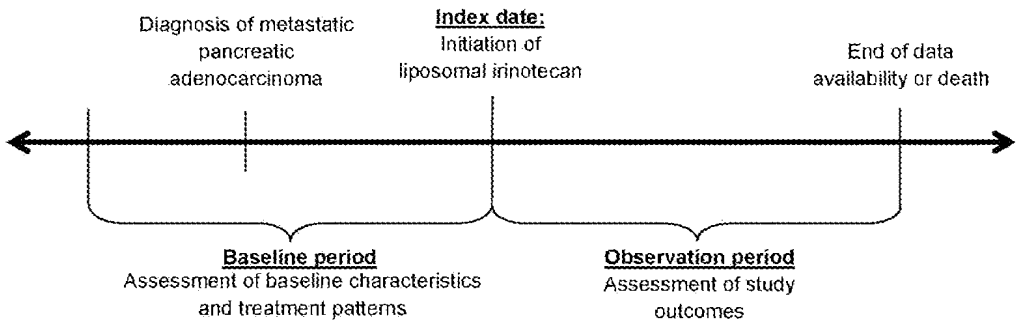

FIGURE 1 | Study Design

CSPC Exhibit 1120
Page 126 of 447

Study Variables and Outcomes

Patient demographics (e.g., age, region) and clinical characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status) were assessed during the baseline period or at index date. For patients with missing baseline ECOG performance status, their Karnofsky Performance Status (KPS) scores were converted to ECOG status.

Study outcomes included treatment patterns, real-world effectiveness (i.e., OS and PFS), and grade 3 or 4 AEs. Duration of liposomal irinotecan treatment was defined as the time from index date to discontinuation. Treatment patterns of therapies received in the metastatic setting prior to liposomal irinotecan were examined. Two definitions of OS were used: (1) OS from mPDAC diagnosis to death, and (2) OS from index date to death. PFS was calculated from index date to the earliest of disease progression or death. Clinically meaningful symptom-related grade 3 or 4 AEs were reported, based on the Common Terminology Criteria for Adverse Events (8).

Statistical Analyses

Summary statistics were presented as means, standard deviations (SDs), and medians for continuous variables or frequencies and proportions for categorical variables. Time to event analyses were conducted using Kaplan-Meier methodology. For OS, patients were censored at the end of data availability, and for PFS, patients were censored at liposomal irinotecan discontinuation or end of data availability. Time to event analyses were stratified by the line of therapy in the metastatic setting that patients received liposomal irinotecan [i.e., first-line (1L), second-line (2L), or third-line or later (3L+)].

The association between baseline characteristics and effectiveness outcomes [i.e., OS (from index), PFS] was analyzed using a Cox proportional hazards model. HRs, 95% confidence intervals (CIs), and p-values were reported. P-values from all statistical tests were reported based on an alpha level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics

374 patients met the study eligibility criteria and were included in this study (**Table 1**). The mean ± SD [median] age at index date was 67.8 ± 9.4 [68.6] years, and 51.3% of patients were female. Most patients were white (71.7%), from the Northeast (57.0%), and initiated liposomal irinotecan treatment in 2018 (32.6%) or 2019 (24.9%). The majority of patients (50.8%) had stage IV pancreatic cancer at initial diagnosis. Patients were treated with liposomal irinotecan in the 1L (17%), 2L (42%), or 3L+ (42%) of the metastatic setting. Among patients treated with liposomal irinotecan in 3L+, 57.0% were treated with a 5-FU-based regimen and 41.7% were treated with a gemcitabine-based regimen in 1L setting; 53.2% were treated with a gemcitabine-based regimen and 34.6% were treated with a 5-FU-based regimen in 2L setting. Among 326 patients with available performance status

TABLE 1 | Baseline demographic and clinical characteristics.

	N = 374
Demographic Characteristics	
Age (years) at index, mean ± SD [median]	67.8 ± 9.4 [68.6]
Female, n (%)	192 (51.3)
Race/Ethnicity, n (%)	
White	268 (71.7)
Black/African-American	48 (12.8)
Asian/Pacific Islander	26 (7.0)
Hispanic/Latino	13 (3.5)
Native American/American Indian	1 (0.3)
Unknown	18 (4.8)
Geographic location, n (%)	
Northeast	213 (57.0)
South	78 (20.9)
West	57 (15.2)
Midwest	26 (7.0)
Year of index, n (%)	
2015	1 (0.3)
2016	63 (16.8)
2017	82 (21.9)
2018	122 (32.6)
2019	93 (24.9)
2020	13 (3.5)
Clinical Characteristics	
Time from mPDAC diagnosis to index (months), mean ± SD [median]	10.9 ± 9.9 [8.4]
Cancer stage at first diagnosis of PDAC, n (%)	
I A	4 (1.1)
I B	6 (1.6)
II A	22 (5.9)
II B	52 (13.9)
III	72 (19.3)
IV	190 (50.8)
Unknown	28 (7.5)
Liposomal irinotecan line of therapy, n (%)	
1L	62 (16.6)
2L	156 (41.7)
3L+	156 (41.7)
Primary tumor location in pancreas, n (%)	
Head	207 (55.3)
Body	65 (17.4)
Tail	62 (16.6)
Body and tail	32 (8.6)
Neck	2 (0.5)
Neck and body	1 (0.3)
Unknown	5 (1.3)
Metastatic sites, n (%)[a]	
Liver	258 (69.0)
Lung	87 (23.3)
Peritoneum	79 (21.1)
Distant lymph nodes	51 (13.6)
Bone	16 (4.3)
Brain	3 (0.8)
Other[b]	25 (6.7)
Number of metastatic sites, n (%)	
1	280 (74.9)
2	57 (15.2)
3 or more	37 (9.9)
ECOG performance score, n (%)	
0	32 (8.6)
1	211 (56.4)
2	73 (19.5)
3	8 (2.1)

(Continued)

CSPC Exhibit 1120
Page 127 of 447

TABLE 1 | Continued

	N = 374
4	2 (0.5)
Unknown	48 (12.8)
Selected comorbidities, n (%)[a,c]	
Diabetes without end-organ damage	95 (25.4)
Peripheral vascular disease	16 (4.3)
Diabetes with end-organ damage	16 (4.3)
Chronic obstructive pulmonary disease	12 (3.2)
Moderate or severe renal disease	12 (3.2)
Congestive heart failure	10 (2.7)
Cerebrovascular disease	9 (2.4)

ECOG, eastern cooperative oncology group; mPDAC, metastatic pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

[a]Patients may have ≥1 value reported. Therefore, the sum of the percentages may be greater than 100%.

[b]Other metastatic sites included abdominal wall, adrenal glands, ascites, chest wall, diaphragm, gastric, gluteus muscle, kidney, ovary, pelvis, right adnexa, serosa, spleen, and thyroid.

[c]The listed comorbid conditions belong to the Charlson Comorbidity Index.

information, approximately 74% of patients had a baseline ECOG performance status of 0-1. Diabetes without end-organ damage was the most common comorbid condition, present in 25.4% of patients.

Table 2 provides information on 312 patients who received treatment in the metastatic setting prior to liposomal irinotecan. Gemcitabine-based therapy was received among 93.9% of patients. **Table 3** details liposomal irinotecan treatment characteristics. The overall median [95% CI] treatment duration of liposomal irinotecan was 1.6 [1.4, 1.9] months and was 2.8 [1.4, 5.6], 2.1 [1.6, 2.8], and 1.4 [1.3, 1.6] months for patients treated with liposomal irinotecan in 1L, 2L, and 3L+, respectively. Twenty three patients had treatment duration of liposomal irinotecan longer than 12 months, 82.6% of whom were treated with liposomal irinotecan in 1L or 2L. In addition, 9 patients had treatment duration of liposomal irinotecan longer than 18 months, and 5 patients had treatment duration of liposomal irinotecan longer than 24 months. Among 2L patients (n=156), 1.3% had prior irinotecan, and among 3L patients (n=156), 57.7% had prior irinotecan in the metastatic setting. Among 367 patients with dosing information, 29.4% patients had dose reduction at any time during liposomal irinotecan treatment. 7.0% of patients received granulocyte colony stimulating factor (GCSF) with their first administration of liposomal irinotecan.

TABLE 2 | Treatment patterns in the metastatic setting prior to liposomal irinotecan-based treatment.

	N = 374
Duration of metastatic treatments prior to liposomal irinotecan (months), mean ± SD [median][a]	9.4 ± 8.4 [7.0]
Treatment regimens prior to liposomal irinotecan, n (%)[b,c]	*312*
Gemcitabine (alone or in combination)	293 (93.9)
Gem + nab-P	226 (77.1)
Gemcitabine	48 (16.4)
Gem + nab-P + cisplatin	9 (3.1)
Gem + cisplatin	7 (2.4)
Gem + paclitaxel	5 (1.7)
5-FU (alone or in combination)	122 (39.1)
FOLFIRINOX	83 (68.0)
FOLFOX	37 (30.3)
FOLFIRI	32 (26.2)
5-FU/(LV)	15 (12.3)
Any irinotecan (alone or in combination), n (%)	92 (29.5)
Received irinotecan (alone or in combination) in the line of therapy prior to the first administration of liposomal irinotecan, n (%)	12 (3.8)

5-FU, 5-fluorouracil; FOLFIRI, 5-FU + leucovorin + irinotecan; FOLFIRINOX, 5-FU + leucovorin + irinotecan + oxaliplatin; FOLFOX, 5-FU + leucovorin + oxaliplatin; Gem, gemcitabine; LV, leucovorin or levoleucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; nab-P, nab-paclitaxel; PEGPH20, PEGylated recombinant human hyaluronidase; SD, standard deviation.

[a]Treatment duration was defined as cumulative duration of any treatment regimen. It was calculated among patients who had any treatment prior to liposomal irinotecan initiation.

[b]Patients may have ≥ 1 value reported. Therefore, the sum of the percentages may be greater than 100%.

[c]Treatment regimens were categorized by grouping together treatments that were initiated within 30 days of each other.

Real-World Effectiveness

Overall, 263 (70.3%) patients died, and 328 (87.7%) patients experienced disease progression or died over the observation period. The overall median (95% CI) OS from mPDAC diagnosis was 18.4 [16.1, 19.9] months and 9.6 (6.7, 14.3), 15.6 (13.5, 20.4), and 20.9 [19.1, 23.4] for patients treated with liposomal irinotecan in 1L, 2L, and 3L+, respectively (**Figure 2**). The overall median [95% CI]

TABLE 3 | Liposomal irinotecan treatment characteristics in the metastatic setting.

	N = 374
Duration of liposomal irinotecan (months), median [95% CI]	
All patients	1.6 [1.4, 1.9]
1L (n=62)	2.8 [1.4, 5.6]
2L (n=156)	2.1 [1.6, 2.8]
3L+ (n=156)	1.4 [1.3, 1.6]
Prior irinotecan in the metastatic setting, n (%)	
All patients	92 (29.5)
2L (n=156)	2 (1.3)
3L+ (n=156)	90 (57.7)
Liposomal irinotecan dosage, n (%)	
Patients with dose information available	*367*
Patients with dose modifications, n (%)	116 (31.6)
Patients with dose reduction, n (%)	108 (29.4)
Treatments concomitant with liposomal irinotecan, n (%)[a]	
5-FU/(LV)	358 (95.7)
Other	4 (1.1)
GCSF	80 (21.4)
Pegfilgrastim	75 (93.8)
Filgrastim	14 (17.5)
Tbo-filgrastim	3 (3.8)
Filgrastim-sndz	1 (1.3)
GCSF with first administration of liposomal irinotecan[b]	26 (7.0)
Any 5-FU (alone or in combination)	374 (100.0)

5-FU, 5-fluorouracil; CI, confidence interval; GCSF, granulocyte colony stimulating factor; LV, leucovorin; m, meter; mg, milligram; mPDAC, metastatic pancreatic ductal adenocarcinoma; SD, standard deviation.

[a]Patients may have ≥ 1 value reported. Therefore, the sum of the percentages may be greater than 100%.

[b]Patients that had GCSF administered between one and four days after index date are displayed, based on the NCCN Guidelines on Hematopoietic Growth Factors, Version 2.2020.

CSPC Exhibit 1120
Page 128 of 447

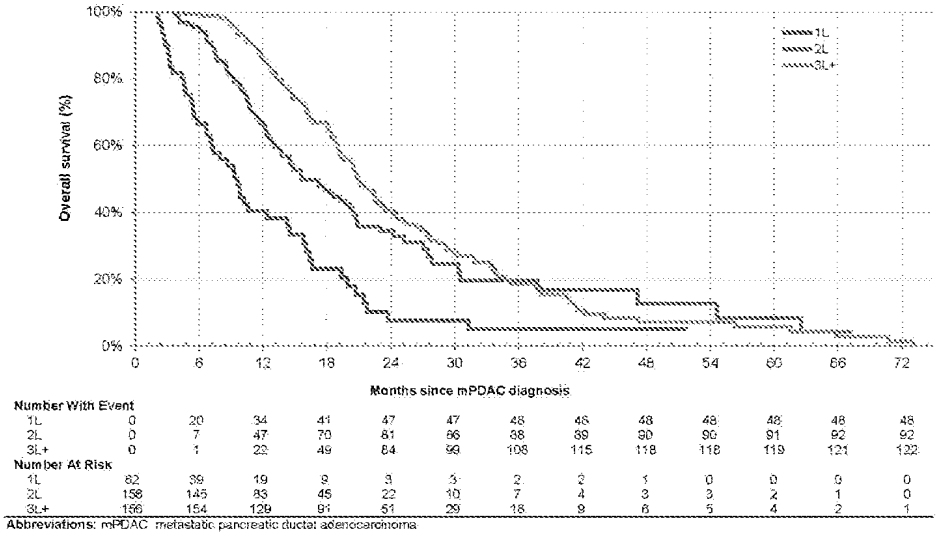

FIGURE 2 | Kaplan-Meier Analysis of Overall Survival from mPDAC Diagnosis among Patients with mPDAC Treated with Liposomal Irinotecan in a Doublet with 5-Fluorouracil

OS from the index date was 6.1 (5.1, 6.8) months and 8.0 (5.1, 11.2), 7.3 (5.3, 8.8), and 4.6 (4.0, 5.7) months for patients treated with liposomal irinotecan in 1L, 2L, and 3L+, respectively (**Figure 3**). The overall median [95% CI] PFS was 2.5 (2.2, 2.8) months and 4.2 (2.2, 6.6), 3.0 (2.6, 3.7), and 2.0 (1.7, 2.2) for patients treated with liposomal irinotecan in 1L, 2L, and 3L+, respectively (**Figure 4**).

The results of the multivariate Cox model analyzing the association between the baseline characteristics and effectiveness outcomes are presented in **Table 4**. In the model examining OS, patients treated with liposomal irinotecan in 3L+ *vs.* 2L had a significantly higher risk of death [HR: 1.90 (1.38, 2.63), p: < 0.001]. Patients with liver metastases [1.59 (1.19, 2.11), p: 0.002], brain metastases [6.53 (1.83, 23.29), p: 0.004], and congestive heart failure (3.01 [1.45, 6.26], p: 0.003) also had a significantly higher risk of death.

In the model examining PFS, patients treated with liposomal irinotecan in 3L+ *vs.* 2L also had a significantly higher risk of tumor progression/death [HR (95% CI): 1.99 (1.49, 2.65), p: < 0.001]. Consistent with OS, patients with liver metastases [1.63 (1.26, 2.10),

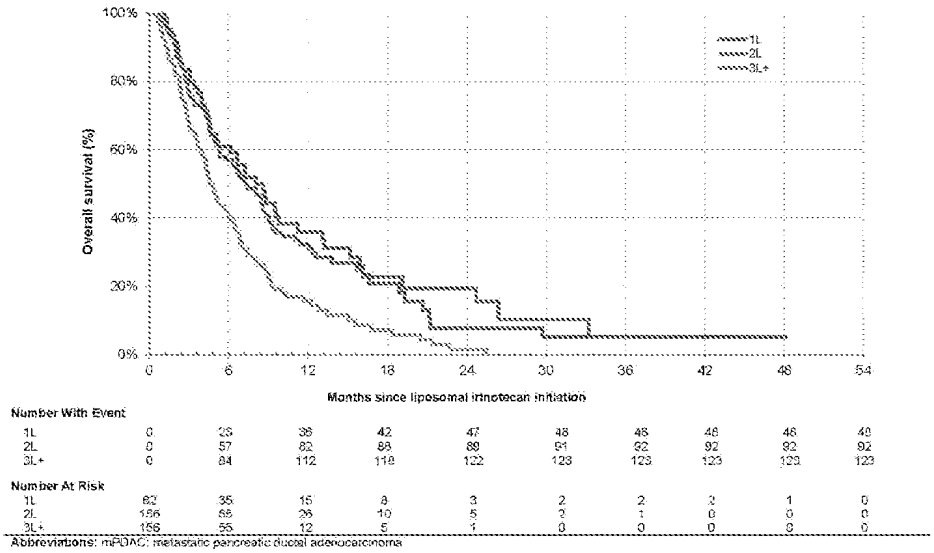

FIGURE 3 | Kaplan-Meier Analysis of Overall Survival from Initiation of Treatment with Liposomal Irinotecan among Patients with mPDAC Treated with Liposomal Irinotecan in a Doublet with 5-Fluorouracil

CSPC Exhibit 1120
Page 129 of 447

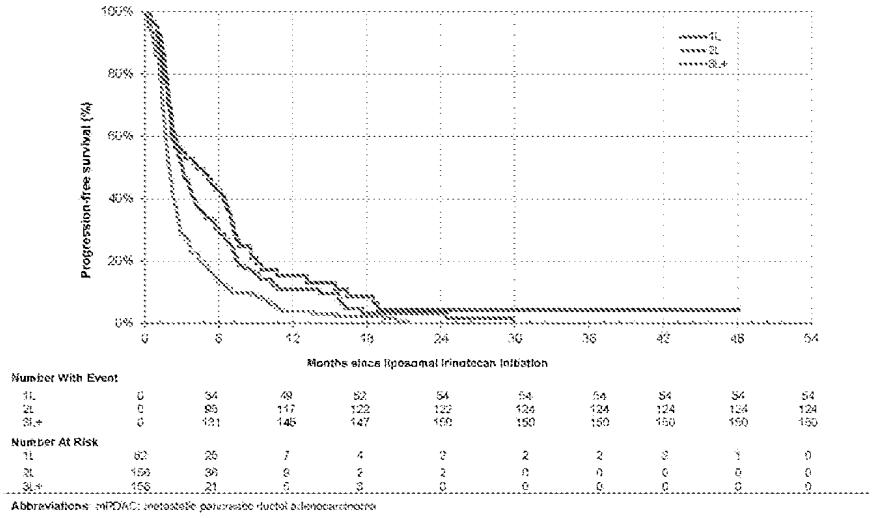

FIGURE 4 | Kaplan-Meier Analysis of Progression Free Survival among Patients with mPDAC Treated with Liposomal Irinotecan in a Doublet with 5-Fluorouracil.

p: < 0.001] and congestive heart failure [2.53 (1.29, 4.99), p: 0.007] had significantly higher risk of tumor progression/death.

Grade 3 or 4 Adverse Events

The most common grade 3 or 4 symptom-related AEs were fatigue/asthenia (4.0%), diarrhea (3.2%), and vomiting (1.6%). The most common grade 3 or 4 laboratory abnormalities were anemia (21.1%), lymphopenia (12.6%), and neutropenia (7.8%) (**Table 5**).

DISCUSSION

From six academic centers, 374 patients with mPDAC treated with liposomal irinotecan in a doublet with 5-FU were examined. The results of this retrospective, observational chart review study indicate that patients with mPDAC treated with liposomal irinotecan in the real-world setting compared to the pivotal phase 3 clinical trial (NAPOLI-1) (3) were older (median age: 69 *vs.* 63 years), had poorer ECOG performance status (ECOG <2: 74% *vs.* 91%), and had received more lines of therapy prior to liposomal irinotecan (2+ prior lines of therapy: 42% *vs.* 34%). Nonetheless, the median OS in this study was identical to data reported in the NAPOLI-1 trial (median OS: 6.1 months) (3). This study's results are also consistent with those from a real-world Flatiron study on patients with mPDAC treated with liposomal irinotecan in the community setting and reinforce the conclusions from the Glassman et al. study (7, 9).

Overall, liposomal irinotecan was effective for treatment of mPDAC in the study population, particularly among those receiving it in earlier lines of therapy. Patients treated with liposomal irinotecan in 1L, 2L, and 3L+ had median OS of 8.0 months, 7.3 months, and 4.6 months, respectively. This trend was similarly reported in the Flatiron study where patients treated with liposomal irinotecan in 1L, 2L, and 3L+ had median OS of 6.9, 5.4, and 4.0 months, respectively (9). Similarly, Glassman et al. reported an overall median OS of 5.3 months and longer OS in patients receiving liposomal irinotecan in earlier lines of therapy (7). Thus, the observed survival trends among patients treated with liposomal irinotecan in 1L, 2L and 3L+ are similar to other real world studies. In addition, this study found in adjusted analyses that patients treated with liposomal irinotecan in 3L+ *vs.* 2L had significantly higher risk of death. This study also reported that patients treated with liposomal irinotecan in earlier *vs.* later lines of therapy had better PFS. These results demonstrate the clinical benefit of being treated with liposomal irinotecan in earlier *vs.* later lines of therapy, which may be attributed to common resistance mechanisms, more severe disease, and worse prognosis/performance status in patients with each subsequent line of therapy.

To complement the OS and PFS benefit conferred by liposomal irinotecan, this study also described the safety profile of liposomal irinotecan in patients that were older and had poorer baseline performance status when compared to the pivotal NAPOLI-1 trial. It is noted that due to the real-world nature of this study, AEs may not have been recorded as often as AEs in clinical trials where patients are monitored more closely. Compared to other real-world settings, this study had a lower proportion of patients with grade 3 or 4 neutropenia than that previously reported in the community setting (8% *vs.* 11%) (9), and a slightly higher proportion of patients with various grade 3 or 4 AEs than in Glassman et al. (7). Overall, this study further supports the known safety profile and use of liposomal irinotecan.

Findings from this study may inform treatment recommendations for patients with mPDAC. Currently, the NCCN recommends liposomal irinotecan as a 2L therapy for patients with mPDAC and good performance status following treatment with a gemcitabine-based regimen (10). They do not list any recommended treatments for 1L or 3L+ for patients with mPDAC. This real-world study indicates promising survival among patients treated with liposomal irinotecan in 3L+, and

CSPC Exhibit 1120
Page 130 of 447

TABLE 4 | Associations between Baseline Characteristics and Effectiveness Outcomes of Liposomal Irinotecan - Multivariate Analysis.

	OS N = 374			PFS N = 374		
	HR	95% CI	P-value[3]	HR	95% CI	P-value[3]
Age at index date	1.00	(0.98, 1.01)	0.792	0.99	(0.98, 1.01)	0.248
Male (ref: female)	1.18	(0.92, 1.53)	0.189	1.05	(0.84, 1.32)	0.669
Race/Ethnicity (ref: white)						
Black/African-American	1.14	(0.72, 1.82)	0.569	0.92	(0.62, 1.36)	0.673
Hispanic/Latino	0.88	(0.43, 1.81)	0.736	1.03	(0.52, 2.05)	0.940
Asian/Pacific Islander and Native American/American Indian	0.80	(0.47, 1.37)	0.413	0.79	(0.50, 1.25)	0.316
Unknown	0.79	(0.45, 1.40)	0.424	0.63	(0.37, 1.07)	0.088
Geographic Location (ref: northeast)						
Midwest	0.79	(0.47, 1.35)	0.394	1.00	(0.62, 1.61)	0.999
South	0.60	(0.38, 0.94)	0.026*	0.98	(0.68, 1.42)	0.923
West	0.46	(0.29, 0.73)	<0.001*	0.65	(0.44, 0.96)	0.030*
Time from mPDAC diagnosis to index (months)	0.98	(0.96, 1.00)	0.013*	0.97	(0.96, 0.99)	0.001*
Cancer stage at first diagnosis of PDAC (ref: metastatic)						
Non-metastatic	0.84	(0.60, 1.18)	0.313	0.91	(0.67, 1.23)	0.525
Unknown	0.77	(0.41, 1.43)	0.406	0.60	(0.49, 1.31)	0.372
Line of therapy for liposomal irinotecan (ref: 2L)						
1L	0.60	(0.51, 1.27)	0.349	0.78	(0.52, 1.18)	0.246
3L+	1.90	(1.38, 2.63)	<0.001*	1.99	(1.49, 2.65)	<0.001*
Primary tumor location in pancreas (ref: head)						
Body	0.70	(0.49, 1.00)	0.048*	0.62	(0.45, 0.86)	0.004*
Body and tail	0.83	(0.53, 1.33)	0.443	0.72	(0.47, 1.10)	0.125
Neck or neck and body	0.61	(0.10, 6.23)	0.686	0.27	(0.04, 2.00)	0.199
Tail	1.01	(0.70, 1.45)	0.970	1.22	(0.89, 1.68)	0.222
Unknown	0.46	(0.06, 3.41)	0.448	0.65	(0.20, 2.15)	0.479
Metastatic sites						
Liver	1.59	(1.19, 2.11)	0.002*	1.63	(1.26, 2.10)	<0.001*
Brain	6.53	(1.83, 23.29)	0.004*	2.53	(0.73, 8.74)	0.144
Number of metastatic sites (ref: 1)						
2	0.99	(0.67, 1.45)	0.941	1.18	(0.85, 1.64)	0.316
3 or more	1.09	(0.65, 1.81)	0.744	1.05	(0.68, 1.62)	0.842
ECOG (ref: < 2)						
≥ 2	1.21	(0.87, 1.69)	0.254	1.01	(0.75, 1.34)	0.970
Unknown	1.09	(0.72, 1.65)	0.699	1.12	(0.77, 1.62)	0.555
Selected comorbidities						
Congestive heart failure	3.01	(1.45, 6.26)	0.003*	2.53	(1.29, 4.99)	0.007*

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mPDAC, metastatic pancreatic ductal adenocarcinoma; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression free survival.
**indicates p-value <0.05.*

TABLE 5 | Grade 3 or 4 symptom-related adverse events and laboratory abnormalities.

	N = 374
Symptom-related adverse events, n (%)	
Fatigue/asthenia	15 (4.0)
Diarrhea	12 (3.2)
Vomiting	7 (1.9)
Nausea	6 (1.6)
Laboratory abnormalities, n (%)	
Anemia	79 (21.1)
Lymphopenia	47 (12.6)
Neutropenia	29 (7.8)

may support using liposomal irinotecan in later lines of therapy when other treatment options are not available. Additionally, liposomal irinotecan was used as 1L therapy in a number of patients in this study despite not being indicated for front-line use; this could be due to several reasons: failure of adjuvant gemcitabine-based therapy, possible neuropathy, or patient/provider preferences based on toxicity profiles. This study therefore describes real-world use of liposomal irinotecan in circumstances where patients may not exactly fit clinical trial entry criteria.

There are several limitations to consider when interpreting findings from this study. Due to the non-randomized, retrospective nature of the study, residual confounding may impact the associations and conclusions identified. Specifically, residual confounding may have remained for the comparative analyses by line of therapy even after adjustment (e.g., patients receiving liposomal irinotecan in 3L may have been sicker than those receiving liposomal irinotecan in 1L). The results reported are based on data collected at academic cancer centers and may not be generalizable to patients with mPDAC treated in other

CSPC Exhibit 1120
Page 131 of 447

settings. Real-world evidence from medical charts is also limited by the availability of clinical data reported in the medical chart, although quality assurance procedures and data checks served to maximize data integrity. In addition, in analyses where less common conditions such as brain metastases or certain comorbidities are examined, the smaller number of patients with these conditions could limit the ability for robust conclusions. However, the findings from this study are corroborated by existing literature that report poorer prognostic outcomes among patients with pancreatic cancer who have brain metastases or comorbidities (11, 12). Furthermore, this study overall included a large number of patients to describe the current treatment landscape for mPDAC and evaluate NAPOLI-1-based liposomal irinotecan doublet regimens in the real-world setting. Baseline information on AEs were not collected, so it is unclear if the AE data reported are treatment emergent (i.e., associated with liposomal irinotecan). The assessments of disease progression and AE grading in real-world settings may be based on heterogeneous criteria and assessment schedules across subjects and centers. For example, PFS may be overestimated if the patient's visit and evaluation of progression was recorded in the patient's chart later than the actual date of progression itself.

Poor prognosis among patients with mPDAC necessitates continuous research on efficacious and better tolerated treatments to improve patient outcomes. This real-world study found that patients treated with liposomal irinotecan were older, sicker, and had more lines of therapy prior to liposomal irinotecan than those in the NAPOLI-1 registrational trial; however, real-world effectiveness was similar. Furthermore, patients were treated with liposomal irinotecan in 3L+, a setting with no currently approved options, and demonstrated clinical benefit.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Prior to commencing this study, each academic center that participated in this study received institutional review board (IRB) approval at their respective institution or received approval through a centralized IRB. Specific IRB approval details are listed below:

- Memorial Sloan Kettering Cancer Center IRB approval: #17-302
- Cedars-Sinai Medical Center IRB approval: Pro00057619
- Emory University IRB approval: #00111751
- Houston Methodist Research Institute IRB approval: Pro00023019
- Henry Ford Health System IRB approval: #13477
- Analysis Group - New England IRB Approved under Exempt Category: #1-8654-1
- University of Pittsburgh Medical Center - New England IRB Approved under Exempt Category: #1-8854-1

This study was implemented and reported in accordance with the ethical principles set forth in the Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KHY, AEH, OBA, AD, MA, EB, GK, and NB: Conceptualization, data curation, methodology, writing--review and editing. PC, Conceptualization, funding acquisition, writing-review and editing. MSD, MD, RHB, and CN: Conceptualization, formal analysis, methodology, project administration, writing - original draft. All authors contributed to the article and approved the submitted version.

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CSPC Exhibit 1120
Page 132 of 447

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CSPC Exhibit 1120
Page 133 of 447

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RESEARCH ARTICLE

Cancer Medicine WILEY

Real-world prognostic factors for survival among treated patients with metastatic pancreatic ductal adenocarcinoma

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Abstract

Background: Many real-world studies of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) are restricted to single centers, limiting the generalizability of their insights. This study aimed to identify important population-based predictors for survival in patients diagnosed with mPDAC in a broader setting.

Methods: Data between 1 January 2017 and 31 December 2019 were extracted from the Flatiron Health EHR database. Treatment-specific predictive models were generated for patients treated with first-line gemcitabine+nabpaclitaxel (GNP), FOLFIRINOX, gemcitabine monotherapy (gem-mono), and second-line liposomal irinotecan-based regimens. The holdout method was used for cross-validation. Age at diagnosis, sex, BMI, smoking status, and ECOG performance score were included in all models with additional demographic, clinical characteristics, and hematological function assessed for inclusion.

Results: Of the 3625 patients, 43% received GNP, 26% received FOLFIRINOX, 7% received gem-mono, and 23% received other regimens; 40% ($n = 1448$) advanced to the second line. Among all first-line patients, the following were included in the final model: prior surgery, white blood cell (WBC) counts, serum albumin (SA), liver function tests (LFTs), serum bilirubin, serum carbohydrate antigen 19–9, and ascites. Models for patients receiving specific therapies differed from the overall model, GNP (ascites removed), FOLFIRINOX (stage at initial diagnosis added), and gem-mono (LFTs omitted). Alkaline phosphatase (ALP), SA, and WBC counts were important predictors of survival among patients treated with second-line liposomal irinotecan. Across all regimens, the strongest predictors of survival were ECOG score, SA, and ALP.

Conclusions: In this real-world study of patients with mPDAC, important population prognostic factors of survival were identified in a large cohort of patients receiving systemic treatment.

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CSPC Exhibit 1120
Page 134 of 447

KEYWORDS
antineoplastic agents, electronic health records, pancreatic ductal adenocarcinoma, prognostic factors, real-world evidence, treatment options

1 | INTRODUCTION

Pancreatic cancer ranks in 11th place for cancer incidence in the United States in 2020, comprising about 3% of cases.[1,2] However, it is the third leading cause of cancer mortality. Specific early symptoms are generally lacking[3,4] contributing to delays in diagnosis with fewer than 20% of patients having resectable disease at diagnosis. The disease has aggressive biology characterized by early dissemination and intrinsic tumor resistance to radiation and chemotherapy. These together account for the poor prognosis of pancreatic cancer, which has an estimated 5-year survival rate of 10% for all diagnoses and as low as 3% for patients initially diagnosed with metastatic disease.[2,4] Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, comprising approximately 80% of new cases.[5] It is characterized by extensive stromal tissue that promotes a microenvironment for cancer progression[6] and resistance to chemotherapy and radiation treatment,[7] while also forming a barrier to drug delivery.[8]

Gemcitabine monotherapy (gem-mono) was shown in the late 1990s to result in longer survival compared with existing regimens. Subsequent to this, a combination of gemcitabine with nanoparticle albumin-bound paclitaxel (GNP) was found to produce further improvements in survival in metastatic PDAC (mPDAC).[9] A combination regimen consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) has also been shown to improve survival compared with gem-mono.[10,11] For second-line and later use in mPDAC, liposomal irinotecan in combination with 5-FU/leucovorin demonstrated improved overall survival (OS) when compared with 5-FU/leucovorin alone in the phase 3, NAPOLI-1 randomized trial.[12,13] These findings led to FDA approval for patients with mPDAC with documented progression after gemcitabine or gemcitabine-based therapy.[12] Furthermore, liposomal irinotecan is the only therapy so far to have National Comprehensive Cancer Network (NCCN) Category 1[14] and American Society of Clinical Oncology (ASCO)[15] recommendations as a post-gemcitabine therapy. No specific recommendations currently exist for third-line therapy.[16]

There are only limited data on real-world treatment outcomes in mPDAC, and data from clinical trials, which conform to strict eligibility criteria, are not representative of real-world practice. Real-world studies reported in the literature have included estimates of the prognostic impact of patient and disease characteristics in patients receiving systemic therapy for mPDAC.[17–21] Such studies have been limited in sample size due to a reliance on one or a limited number of study centers or a focus on patients receiving a particular drug regimen. This has limited their usefulness for guiding decision-making in the treatment of patients with mPDAC. Here, we report a large retrospective analysis of electronic health records of patients with mPDAC in the United States and the development of a validated predictive model for survival based on routinely collected data (demographic, clinical, and laboratory parameters), with the aim of improving the understanding of patient care in mPDAC in community oncology settings.

Lay summary

This study used Flatiron Health, a large research database of health records from patients with cancer across the United States. The records to not contain personal identifiers to ensure patient anonymity. The study analyzed all patients who began treatment for metastatic pancreatic cancer in between 1 January 2017 and 31 December 2019 and used information on medical history, test results, and cancer treatments received. This is the largest study of its kind to date and the findings that ECOG performance score, liver function, and serum albumin predict survival may help to inform clinical practicec.

2 | METHODS

2.1 | Data source and study design

This retrospective observational cohort analysis used data from the Flatiron Health database, a longitudinal, demographically diverse database derived from de-identified electronic health record data. The Flatiron database includes data from over 280 cancer clinics or approximately 800 sites of care, and the distribution of patients between community and academic practices largely reflects patterns of care in the United States.[22,23] Patient-level data include structured data such as laboratory values, treatments, and diagnosis codes. Documents

providing unstructured data in Flatiron are curated via technology-enabled abstraction; these include clinician notes, radiology reports, and death notices. Informed consent was waived as the study was retrospective and used only routinely collected data. To ensure patient privacy and confidentiality Flatiron de-identifies all data it collects and delivers, and this includes provisions to prevent re-identification.

2.2 | Study population

Patients included in the data source were those with a diagnosis code for pancreatic cancer (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM): 157.x or ICD-10-CM: C25.x), two documented clinical visits, on separate days, on or after 1 January 2014, had a pathology consistent with adenocarcinoma of the pancreas, and were diagnosed with stage IV disease or were diagnosed with earlier stage pancreatic cancer and subsequently developed recurrent or progressive disease on or after 1 January 2014. Patients were included based on a diagnosis of mPDAC between 1 January 2017 and 31 December 2019 as included in the January 2021 delivery of Flatiron data. To be eligible, patients also had pathology consistent with mPDAC. Other requirements were ≥18 years of age and a recorded activity such as a visit or treatment within 90 days on or after the diagnosis. Patients were also required to have received a treatment and to have a recorded activity after the start date of therapy. Patients were excluded if the date of death (uniformly assigned as the 15th of the month of death for OS) preceded the treatment start date.

2.3 | Lines of therapy

Lines of therapy in the Flatiron database are defined operationally and not necessarily the same as clinically defined lines of therapy. The index date for each patient was defined as the first day of the initial systemic therapy that began after diagnosis of mPDAC; any prior adjuvant or neoadjuvant therapies were not included in the definition. All additional components of therapy in the first 28 days were considered part of the same line of therapy. A treatment line was considered to have advanced to the next if a new drug was added after 28 days with the following exceptions, which could be made within 90 days of the start of therapy: 5-FU substituted for capecitabine or vice versa; leucovorin substituted for levoleucovorin or vice versa; LV/levoleucovorin added; or protein-bound paclitaxel added to a gemcitabine regimen or vice versa. Chemoradiation therapy was not included in the analysis.

2.4 | Variable definitions

Baseline variables were evaluated for this analysis, including demographics (age, height, weight, body mass index, smoking status, index year, sex, race, and region), clinical characteristics (stage, site of primary tumor, ECOG performance status (PS) score, prior surgery, ascites, sites, and number of metastases), and laboratory values (neutrophils, lymphocytes, WBC, serum albumin [SA], alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [AP], lactate dehydrogenase [LDH], serum bilirubin [SA], neutrophil–lymphocyte ratio, and serum carbohydrate antigen 19–9 [CA 19–9]). The presence of ascites and metastatic sites was identified based on diagnosis records in the EHR with relevant ICD-9-CM/ICD-10-CM codes. Lab values were categorized into normal, abnormal, and unknown based on their reported values and normal ranges. Clinical and laboratory characteristics were included if taken within +/-60 days of the index date and the reading closest to index date used for patients with multiple readings (the most severe was used for readings taken on the same day). The primary endpoint was OS, defined as the time between the index date and date of death. Censoring was applied at the last activity date if no death occurred. Univariate Cox proportional hazard models were used to estimate the association of OS with age category, sex, BMI category, prior or no/not known surgery, cancer stage (IV, I–III, and other), ECOG PS score, presence of ascites, number of metastases (0/not captured/1/≥2), and lab and hematologic values (normal/abnormal/unknown). All estimates were conducted for each line sequential line of therapy (first, second, and third lines) and for the regimens GNP, FOLFIRINOX, gem-mono, and (for second and third lines only) liposomal irinotecan/5-FU leucovorin. Categorical variables with missing data were included in the models.

2.5 | Statistical methods

All analyses were performed separately for first-, second-, and third-line treatments. Descriptive statistics were employed for continuous variables, including number of patients, mean, median, standard deviation, interquartile range, minimum, and maximum. Comparisons of continuous variables were made using the *t*-test of mean or nonparametric Wilcoxon rank-sum test of median as appropriate. Categorical variables were described as percentages and the Chi-squared tests or the Fisher exact tests were used for comparisons. The Kaplan–Meier methods were used to derive time to death and median time for OS with 95% confidence intervals (CIs). Univariate Cox proportional hazards models were used to derive hazard

ratios (HRs) and 95% CIs for death and time to treatment failure based on the listed variables, by determining whether an individual variable was associated with an outcome and assessing its magnitude and statistical significance. Key variables known to be important prognostic factors as well as any others found to be significant at a level of 0.2 were then carried forward to a multivariate Cox regression model. In the final models, variables were selected as covariates using a stepwise variable selection procedure to develop a good predictive model of OS. The model included important variables (HR <0.9 or >1.1) as well as any others according to a statistical significance threshold of <0.15 for inclusion and <0.1 for subsequent stepwise selection.

The log hazards (regression coefficients) or HRs with 95% CIs were determined. Proportional hazards testing of each of the risk factors in the multivariable model and log cumulative hazard curves by log of time were used to determine whether effects were constant over time.

A holdout model was used for cross-validation purposes, and data were divided into training (70%) and validation/test (30%) datasets. Predictive accuracy of the final OS model was assessed on the validation/test dataset based on Harrel's and Uno's concordance statistics and time-dependent receiver operating characteristic (ROC) curves for dealing with the right-censored data. Using the final model, the distribution of risk factors in the top 10% and bottom 10% of patients ranked by adjusted OS probabilities was also investigated with the aim of characterizing patients at the highest and lowest risk of death. All data analyses were performed using SAS 9.4 (Cary, NC) /R 4.0.0, and a p value of <0.05 was specified as the threshold for statistical significance.

3 | RESULTS

There were 3625 patients included in the study population. All received first-line therapy on or after diagnosis of metastatic disease. Of these, 1448 (40%) advanced to second-line therapy, including 230 (16%) who received liposomal irinotecan-based regimens. Of the second-line-treated patients, 504 (34.8%) received third-line therapy. Demographic and clinical characteristics of patients who began first-line therapy and patients who began second-line therapy with liposomal irinotecan/5-FU leucovorin are shown in Table 1. At diagnosis, 66% of patients in the overall sample had stage IV disease and 64% had ECOG PS scores of 0 or 1. Similar numbers of patients in enrollment years 2017, 2018, and 2019 entered first-line treatment; however, later-enrolled patients, especially those from 2019, were more likely to advance to a subsequent line of therapy. The most common racial categories in the overall sample were White (66%), Other (14%), and Black (8%), and similar proportions were found across regimens and treatment lines. All patient groups, whether by treatment line or therapy, included slightly more men than women.

3.1 | Treatment outcomes

Table 2 summarizes the regimens received. GNP was the most widely used first-line treatment, and FOLFIRINOX the second most widely used. The "other regimens" categories were the most common second- and third-line therapies, which included combinations regimens FOLFIRI and FOLFOX, and other systemic agents. Liposomal irinotecan was a first-line therapy in a few patients (2.3%) but was a more widely used second- or third-line therapy (16% and 23%, respectively). Median OS (95% CI) during first-line therapy was 6.5 months (6.1–7.0) with GNP, 9.5 months (8.6–10.3) with FOLFIRINOX, and 3.9 months (3.2–5.1) with gem-mono. Hazard ratios obtained from univariate and multivariate survival models are shown in Table S1. Clinical and laboratory variables showing prognostic significance for OS in most treatment categories included BMI, disease stage, prior surgery, ECOG PS score, presence of ascites, abnormal serum CA 19–9, and abnormal values for hematology variables and liver function markers. In the multivariate Cox regression model, which controlled for confounding between the variables retaining statistical significance and effect sizes were BMI (with underweight associated with a greater HR), ECOG PS score (2+ vs. 0), WBC, and SA (abnormal values for either associated with a greater HR). Baseline disease state did not have a prognostic effect in second lines of therapy. Prior regimen did not influence prognosis in patients receiving a second or third line of therapy (data not shown).

3.2 | Predictive accuracy of final models

The predictors of the final model for patients receiving first, second, and third lines of therapy are summarized in Figure 1. For patients receiving the four most common first-line therapies, the final model included the five variables selected for clinical significance plus prior surgery, WBC counts, SA, LFTs (ALP and ALT), serum bilirubin, CA 19–9, and ascites (c-statistic = 0.66). The model for patients treated with GNP differed from the overall model in that ascites was removed (c-statistic = 0.68). Stage at initial diagnosis was included in the model for patients treated with FOLFIRINOX, AST/ALT, and CA19-9, and prior surgery was removed (c-statistic = 0.68). Among patients treated with gem-mono, none of the three liver function LFTs, bilirubin, and CA1 9–9 were included in

TABLE 1 Baseline patient demographic characteristics

Characteristic	1L Gemcitabine+nabpaclitaxel, $N = 1569$	1L FOLFIRINOX, $N = 959$	1L Gemcitabine monotherapy, $N = 266$	2L Liposomal irinotecan, $N = 230$
Age at metastatic diagnosis, Mean (SD), median (IQR)	69 (9), 70 (63, 76)	64 (9), 64 (58, 70)	74 (9), 76 (68, 81)	69 (9), 70 (64, 76)
Age categories at metastatic diagnosis, *n* (%)				
<60 years old	245 (16%)	308 (32%)	22 (8.3%)	31 (13%)
60–69 years old	508 (32%)	390 (41%)	55 (21%)	81 (35%)
70–79 years old	607 (39%)	240 (25%)	98 (37%)	90 (39%)
>=80 years old	209 (13%)	21 (2.2%)	91 (34%)	28 (12%)
Body height (cm), Mean (SD), median (IQR)	169 (11), 168 (160, 178)	171 (11), 173 (163, 178)	168 (10), 168 (160, 175)	169 (10), 170 (163, 177)
Body weight (kg), Mean (SD), median (IQR)	74 (18), 72 (61, 85)	78 (19), 77 (64, 88)	71 (18), 69 (57, 80)	72 (16), 72 (61, 80)
BMI, *n* (%)				
Normal weight	645 (41%)	367 (38%)	126 (47%)	106 (46%)
Underweight	102 (6.5%)	38 (4.0%)	16 (6.0%)	14 (6.1%)
Overweight	470 (30%)	329 (34%)	73 (27%)	69 (30%)
Obese	327 (21%)	217 (23%)	40 (15%)	37 (16%)
Missing	25 (1.6%)	8 (0.8%)	11 (4.1%)	4 (1.7%)
Treatment initiation year, *n* (%)				
2017	488 (31%)	257 (27%)	84 (32%)	25 (11%)
2018	539 (34%)	289 (30%)	91 (34%)	78 (34%)
2019	495 (32%)	387 (40%)	81 (30%)	83 (36%)
2020	47 (3.0%)	26 (2.7%)	10 (3.8%)	44 (19%)
Gender, *n* (%)				
Male	827 (53%)	575 (60%)	144 (54%)	132 (57%)
Female	742 (47%)	384 (40%)	122 (46%)	98 (43%)
Race, *n* (%)				
White	1011 (64%)	628 (65%)	165 (62%)	153 (67%)
Black or African American	153 (9.8%)	67 (7.0%)	28 (11%)	21 (9.1%)
Asian	32 (2.0%)	15 (1.6%)	2 (0.8%)	6 (2.6%)
Other race	197 (12%)	163 (17%)	34 (13%)	31 (13%)
Unknown	176 (11%)	86 (9.0%)	37 (14%)	19 (8.3%)

(Continues)

CSPC Exhibit 1120
Page 138 of 447

TABLE 1 (Continued)

Characteristic	1L Gemcitabine+nabpaclitaxel, $N = 1669$		1L FOLFIRINOX, $N = 959$		1L Gemcitabine monotherapy, $N = 266$		2L Liposomal irinotecan, $N = 230$	
Region, *n* (%)								
Northeast	243	(15%)	134	(14%)	40	(15%)	38	(17%)
Midwest	184	(12%)	115	(12%)	34	(13%)	31	(13%)
South	722	(46%)	421	(44%)	121	(45%)	101	(44%)
West	235	(15%)	129	(13%)	41	(15%)	40	(17%)
Unknown	185	(12%)	160	(17%)	30	(11%)	20	(8.7%)

the model (c-statistic = 0.69). ALP, SA, AST, presence of ascites, HbA1C, and WBC counts were the variables retained in the model in patients treated with second-line liposomal irinotecan-based regimens (cstatistic = 0.81).

The bottom and top deciles of patients ranked by predicted OS probability based on characteristics at index date are shown in Table S2. Younger age, female sex, overweight BMI, and ECOG PS scores or 0–1, were all more prevalent in the top decile, whereas some older age categories, patients of underweight BMI, patients with baseline ECOG PS scores of 2, and patients with ascites comprised greater percentages of the bottom decile. Baseline history of surgery not involving the head of the pancreas or history of Whipple surgery was more frequent in the top decile. No consistent patterns were seen for any hematologic variables. Laboratory test results normal for SA, alkaline phosphatase, and glycosylated hemoglobin were more prevalent in the top decile compared with a greater prevalence of abnormal values for these in the bottom decile. First-line African American patients and patients of other races receiving first-line therapy were equally represented in the highest and lowest deciles of OS probability. However, for individual treatments, these racial groups comprised a relatively high percentage of the favorable prognosis patients in the GNP group compared to White patients, while in the groups receiving FOLFIRINOX and gem-mono, the opposite was the case.

Differences in the highest and lowest OS probability deciles in patients entering second-line therapy showed comparable differences to those for first-line therapy for the variables of BMI, sex, smoking history, disease stage, prior therapy, and ECOG PS score, presence of ascites, alkaline phosphatase, and SA. African American patients and patients of other races were overrepresented in the highest decile of OS probability compared to White patients.

4 | DISCUSSION

We performed a retrospective analysis of a large US nationally representative cohort of patients treated for mPDAC and identified prognostic factors for OS based on data from routinely collected electronic medical records. We believe this is the largest study of its kind covering the recent time span (2017–2019) in which all currently FDA-approved chemotherapeutic regimens, including second-line liposomal irinotecan-based regimens, have been in place. Because of the large size of the cohort, it was possible to overcome limitations imposed by subgroup size and to identify prognostic factors in patients receiving specific treatment regimens. In the current study, we found that patient characteristics of known clinical significance (age,

TABLE 2 Most common metastatic treatment regimens by line of therapy

Characteristic	First line N = 3625	Second line N = 1448	Third line N = 504
Regimen, *n* (%)			
Gemcitabine+nabpaclitaxel	1569 (43%)	477 (33%)	56 (11%)
FOLFIRINOX	959 (26%)	153 (11%)	36 (7.1%)
Gemcitabine monotherapy	266 (7.3%)	46 (3.2%)	12 (2.4%)
Liposomal irinotecan	84 (2.3%)	230 (16%)	118 (23%)
Other regimens	747 (21%)	542 (37%)	282 (56%)

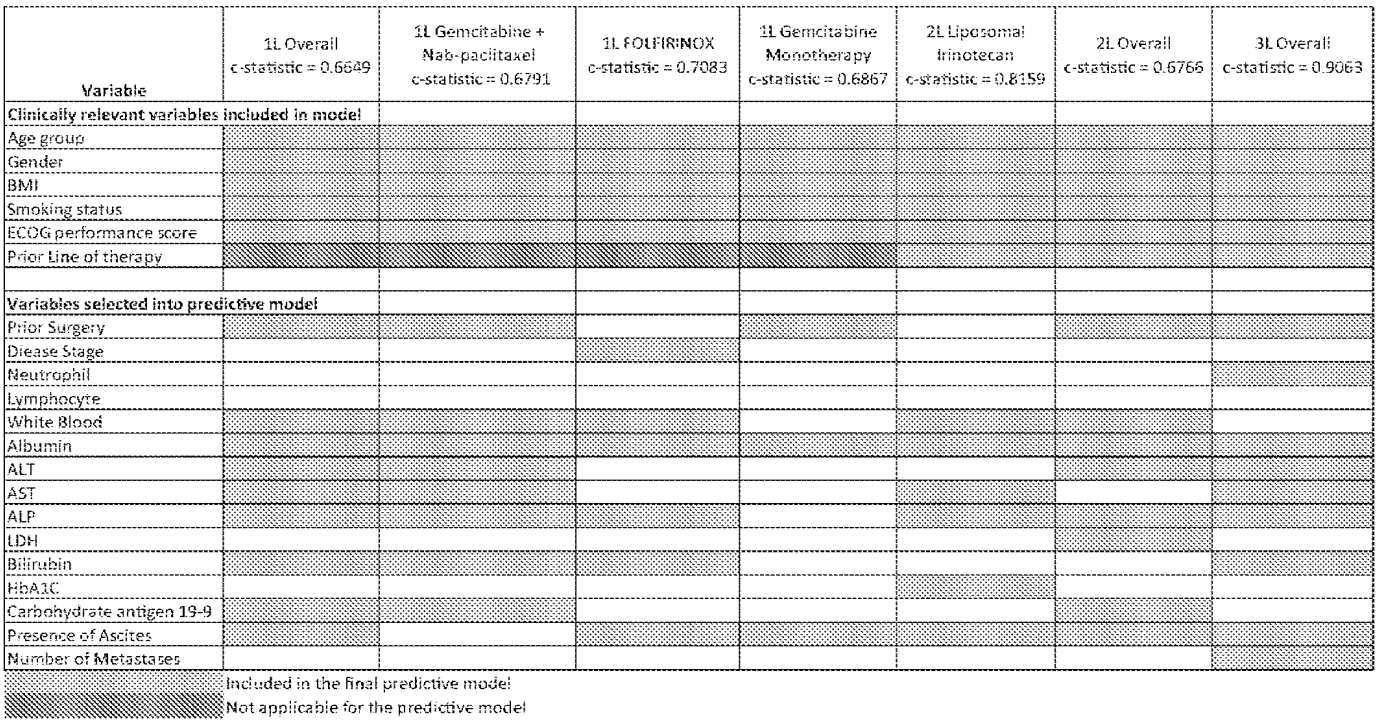

FIGURE 1 Prognostic models were obtained from multivariable Cox regression model. Models were selected based on univariable *p* value = 0.15 to allow a variable in the model and *p* value = 0.1 to keep a variable in the model. Exception: The 2L GNP cohort model was based on a *p* value =0.1 to allow a variable in the model and *p* value = 0.1 to keep the variable in the model. For models including ALT and AST simultaneously, final model included only ALT. 1L, 2L, and 3L first, second, and third lines of therapy; ALP alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; Hb1AC, glycosylated hemoglobin; LDH, lactate dehydrogenase; mPDAC, metastatic pancreatic ductal adenocarcinoma

sex, BMI, smoking status, and ECOG PS score) were independent prognostic factors in the large overall sample with 3625 patients who received first-line therapy. To our knowledge, this is the first study of its kind to investigate prognostic effects for OS in patients with mPDAC across multiple subgroups by treatment regimen received as given in real-world settings. Real-world median OS with first-line GNP, FOLFIRINOX, and second-line liposomal irinotecan-based therapy was, 6.5, 9.5, and 5.3 months, respectively, which was slightly less than the OS reported in phase 3 randomized controlled clinical trials of 8.5, 11.5, and 6.2 months, respectively, with these regimens.[9,10,12] The somewhat longer OS reported in clinical trials is not unexpected given the predefined inclusion and exclusion criteria that apply. We also found that baseline ECOG PS score, SA, and ALP were the strongest predictors of OS across almost all regimens.

Previously published real-world studies have identified some of the variables included in our comprehensive models. Serum C-reactive protein (CRP), performance status, and CA 19–9 have been identified by a number of small, retrospective real-world studies as strong predictors of OS.[24,25,28]

Age and PS were identified as independent prognostic variables in a chart review of 154 patients.[26] A small study of 94 patients in China receiving chemotherapy from 2009 to 2017[29] identified lymph node involvement, LDH, CA 19–9, CRP, and SA as independent prognostic factors

for OS. The type of treatment is often not accounted for in these studies. One study used prospectively collected data from five Japanese hospitals from 2001 to 2013 from patients receiving gemcitabine-based chemotherapy for nonresectable pancreatic cancer.[27] Based on univariate and multivariate analyses, they derived a predictive nomogram for survival probability that included age, sex, tumor size, regional lymph node metastasis, and distant metastasis. Song et al. conducted a large population-based study using the Surveillance, Epidemiology, and End Results (SEER) database to analyze 53,028 patients diagnosed with PDAC from 2004 to 2014.[30] They used significant prognostic factors for constructing a nomogram based on Cox regression analyses. Their nomogram identified the eight variables of age, race, tumor location, marital status, tumor size, TNM stage, tumor grade, and surgery for predicting cancer-specific survival. Taking a different approach, Rochefort et al. conducted a matched-pair analysis of 47 long-term (≥18 months) survivors of mPDAC with 47 control patients from the same center (Centre Leon Bérard, Lyon, France) between January 2010 and June 2015.[31] Multivariate analysis found that neutrophil–lymphocyte ratio was the only remaining prognostic factor for long-term OS in a logistic multivariate model that used backward selection. For prognostic estimates from clinical trials, an analysis of NAPOLI-1 showed that for patients treated with liposomal irinotecan, mostly as second line of therapy, PS, SA, time since most recent anticancer therapy, tumor stage at diagnosis, liver metastases, and baseline CA19-9 were prognostic for OS.[13] A systematic review also identified age, PS, and CA19-9 as the main prognostic factors across different clinical trials of systemic therapy regimens.[32]

Underweight by BMI, a history of smoking, and ECOG PS score >0 were associated with an adverse risk for OS. Female sex, age <70 years, and prior tumor resection were associated with favorable risk. In contrast, obesity at mPDAC diagnosis appeared to be favorable for OS in patients undergoing second-line therapy (HR 0.75, 95% CI 0.63–0.89). This is consistent with other reports of obesity as protective in advanced cancer and may be due to a greater nutritional reserve or to the exclusion of patients with baseline signs of cachexia. BMI may also be a surrogate measure of a loss of muscle mass suggestive of cachexia that would indicate a poor prognosis if present at baseline. Disease stage (I, II, and III vs. IV) did not appear as an independent prognostic factor in most treatment categories. SA (normal vs. low) was independently associated with OS for all treatment groups, and this is consistent with many other observational studies of cancer.[33] SA can be a marker of overall nutritional status, liver function, or a marker of a systemic response to malignant disease. As a prognostic factor, SA has the advantage of being inexpensive widely used in clinical practice. Elevated ALP was also associated with poor prognosis and was the most effective of the markers of metabolism assessed in this study. This enzyme plays a part in bone and liver metabolism.

We constructed prognostic models based on risk factors identified in the Flatiron cohort, which are all readily obtainable in the course of clinical practice. The c-statistics for the overall population who received first-, second-, and third-line treatments were 0.6649, 0.6766, and 0.7681, respectively, and were greater for the individual treatment categories. This would imply a greater prognostic accuracy than the c-statistic of 0.6 estimated for American Joint Committee on Cancer (AJCC) staging system (eighth edition).[34] This suggests that real-world data from electronic health records might be further developed as a way for physicians to be better informed for the prognosis of an individual patient at the time of diagnosis and be able to initiate more individualized management of mPDAC.

There are several limitations in a study of this type. The structured data are frequently in the form of diagnosis codes and may not capture all comorbid conditions. Real-world evidence also has a greater frequency of incorrect or missing data than would be the case in a clinical trial. Data collection frequency is not standardized, unlike in a clinical trial, which can lead to unavoidable statistical biases. Labs and performance scores may not be captured in the data due to lack of clinical importance (i.e., normal ECOG PS appear as missing) or site-specific practices and thus those with missing data may have their outcomes influenced by factors not directly related to their clinical characteristics. Data regarding ascites and sites of metastases were underreported and their role in patient outcomes may not be fully captured in our models. Care received outside of the oncology practice may not be reported back to the EHR and thus acute care episodes (e.g., hospitalizations, emergency room visits) are not accounted for in our models. Missing data were included in the models to account for these potential patterns of care. OS was slightly less than clinical trials of the same treatment, nevertheless, this is likely to be an expected estimate because some patients who would have been ineligible for clinical trials do get treated in clinical practice. The need to prevent re-identification can also obscure relevant data. For example, all patients ages >85 in the Flatiron databases are included as 85 years of age. Finally, we used only an internal sample from Flatiron for validation and did not compare using external data.

5 | CONCLUSIONS

In this large real-world study of patients with mPDAC we have identified prognostic factors of OS in patients receiving contemporary, systemic treatments. There was

evidence of variability in these predictors depending on the line of therapy, and the class of systemic therapy received. Prognostic variables identified may help to inform treatment selection and expectations for clinicians. Additional validation studies may be useful in understanding the generalizability of our results.

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CONFLICT OF INTEREST

KHY receives research funding from Ipsen and Bristol Myers Squibb; MO reports no conflict of interest; PC is an employee and has stock in Ipsen; AS and SW are employees of Genesis Research which receives research funding from Ipsen; BCC was an employee of Genesis Research at the time of the study.

ETHICS STATEMENT

The data accessed were de-identified in accordance with the HIPAA Privacy Rule, and no personal health information was extracted. Therefore, the study did not require informed consent or institutional review board approval.

PATIENT CONSENT

Informed consent was waived as this was a non-interventional study using routinely collected data. The data are de-identified and subject to obligations to prevent re-identification and protect patient confidentiality.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request, and are subject to a license agreement with Flatiron Health; interested researchers should contact <DataAccess@flatiron.com> to determine licensing terms.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Yu KH, Ozer M, Cockrum P, Surinach A, Wang S, Chu BC. Real-world prognostic factors for survival among treated patients with metastatic pancreatic ductal adenocarcinoma. *Cancer Med*. 2021;10:8934–8943. doi:10.1002/cam4.4415

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NOTICE OF ALLOWANCE AND FEE(S) DUE

153749 7590 04/21/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/21/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/664,976	07/31/2017	Keelung Hong	263266-416123	4323

TITLE OF INVENTION: Liposomes Useful for Drug Delivery

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/21/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
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P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153749 7590 04/21/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/664,976	07/31/2017	Keelung Hong	263266-416123	4323

TITLE OF INVENTION: Liposomes Useful for Drug Delivery

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/21/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
SHOMER, ISAAC	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

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Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/664,976	07/31/2017	Keelung Hong	263266-416123	4323

153749 7590 04/21/2021

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125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/21/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/664,976	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE on 12 January 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 185-192 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

As an initial matter, the claim amendments of claim 185 on 18 September 2020 are adequately supported in view of the instant specification at page 34, end of paragraph 0109. With regard to claim 192, which was previously newly added in the claim set on 1 May 2020, the recited size, as measured by quasi-elastic light scattering, is disclosed on page 116, paragraph 0280 of the instant specification. While this paragraph of the instant specification does not specifically disclose that the Gaussian model is used, this is disclosed elsewhere in the instant application, including but not limited to page 87, paragraph 0221. This is understood by the examiner to adequately support claim 192.

Additionally, with regard to claim 191, the examiner notes that the claim recites "one or more lipids" yet recites three different lipids. The examiner clarifies that the reason for this language is that claim 185, upon which claim 191 depends, recites the phrase "one or more lipids." In contrast, claim 191 further limits the "one or more lipids" previously recited by claim 185 to be the three lipids specifically recited by claim 191 in the specific ratio recited by the claim.

As close prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408), which was cited earlier in the prosecution history of the instant application. Chou et al. (hereafter referred to as Chou) is drawn to a liposome comprising irinotecan, as of Chou, page 405, title and abstract. This liposome for the treatment of cancer, as of Chou, page 405, left column, first

paragraph below abstract, which teaches antitumor activity of irinotecan. Chou teaches lipids such as phosphatidylcholines, as of Chou, page 405, title and abstract.

Chou differs from the claimed invention for at least the following reasons.

(a) First, Chou does not teach inositol hexaphosphate.

(b) Secondly, Chou does not teach that the concentration of encapsulated irinotecan in milimoles of irinotecan per gram of total liposome lipids is between 0.8 and 1.3. In contrast, the concentration of encapsulated irinotecan that is taught by prior art reference Chou is lower than what is required by the instant claims.

In view of at least these differences, the examiner takes the position that the instant claims are not prima facie obvious over Chou, either by itself or in view of another reference. The examiner presents the following reasoning below in support of the position that the amount of irinotecan in the liposome of Chou is lower than that required by the instant claims.

Chou teaches a maximum concentration of encapsulated drug of 0.254 milligrams of drug per milligram of lipid, as of Chou, page 407, right column, end of last full paragraph. The drug referred to by Chou at this portion in the text of Chou appears to be irinotecan. The examiner has provided the following calculation to convert this value into millimoles of irinotecan per gram of total liposome lipids, which are the units recited by instant claim 185, wherein this calculation is based upon an irinotecan molecular weight of 586.673 Daltons[1].

[1] In the above calculation, the examiner used the molecular weight of free irinotecan to perform the calculation. If, purely *en arguendo*, the examiner erred in estimating the molecular weight of irinotecan by failing to account for the counter-ion of irinotecan or waters of hydration of irinotecan, this would have resulted in a higher apparent molecular weight of irinotecan and therefore a lower concentration of irinotecan in terms of millimoles of irinotecan per gram of liposome lipids. If this were the case, the concentration of irinotecan in terms of millimoles per gram would be lower, which would further strengthen the examiner's position.

$$\left(\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid}\right) \times \left(\frac{1000\ mg\ lipid}{1\ gram\ lipid}\right) \times \left(\frac{1\ mmol\ irinotecan}{586.673\ g\ irinotecan}\right) \approx 0.433 \frac{mmol}{gram}$$

In view of the above calculation, Chou appears to teach a maximum amount of encapsulated irinotecan of 0.433 mmol of irinotecan per gram of liposome lipid. As such, the minimum amount of irinotecan encapsulated by the claimed liposome of 0.8 mmol irinotecan per gram of liposome lipid is almost twice the maximum amount of irinotecan encapsulated in a liposome by Chou.

The examiner takes the position that the increase in the amount of encapsulated irinotecan in the claimed invention as compared with the prior art is not a matter of routine optimization. This is because increasing the amount of irinotecan encapsulated in a liposome is not a matter of simply increasing the concentration of irinotecan, at least because successfully encapsulating[2] drug in a liposome is difficult. The difficulty of encapsulation of irinotecan is evidenced by Chou, at least in view of the fact that Chou needs to use a pH gradient comprising ammonium ions to load irinotecan into the liposome, as of Chou, page 405. Additionally, Chou appears to experience problems with drug leakage, as of Chou, page 406, right column, first full paragraph, which indicates that successfully encapsulating drug into a liposome and having it remain in the liposome is difficult.

Also, that a fairly specific protocol is needed to achieve drug encapsulation is evident through the instant specification. See the instant specification at page 32, paragraph 0108 at the bottom of the page and onto page 33, which appears to indicate that incubating the active agent with the liposome at a specific temperature above the

[2] As best understood by the examiner, the word “encapsulating” has the same meaning as the word “entrapping”, as used in instant claim 185. See the instant specification on page 1, last line, and page 2, first two lines in paragraph 0003.

phase transition of the lipids and with a specific ionic strength is needed to encapsulate the active agent.

As such, in view of the apparent difficulty of encapsulating irinotecan in a liposome, there would have been no reasonable expectation that the entrapped concentration of irinotecan could have successfully been increased from 0.433 mmol irinotecan per gram of liposome lipids, as in the prior art, to the range of between 0.8 and 1.3 mmol irinotecan per gram of liposome lipids, as required by the instantly claimed invention. Obviousness requires a reasonable expectation of success; however, in this case, the reasonable expectation of success appear to be lacking. See MPEP 2143.02.

In order to further explain this point, the examiner notes MPEP 2144.05(II)(A). A portion of text from this section of the MPEP is reproduced below.

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.);

The instantly claimed invention differs from the cited case because in the cited case, the amount of acid could have been increased from 10%, as in the prior art in the cited case, to 25-70%, as in the claimed invention in the cited case, simply by adding

more acid. In contrast, in the instant application, adding more irinotecan to a liposome preparation would not have been expected to have been sufficient to have resulted in greater encapsulation of irinotecan in a liposome due to the difficulty of encapsulating irinotecan in a liposome. As such, while there would have been a reasonable expectation that acid concentration could have successfully been increased to achieve the claimed range in the cited case, there would have been no reasonable expectation that the concentration of encapsulated irinotecan could have been successfully increased to achieve the claimed amounts in the instantly claimed invention.

The claimed invention also differs from the prior art of Chou in that the claimed invention recites inositol hexaphosphate, which is not taught by Chou. The examiner notes that an anti-cancer use of inositol hexaphosphate is taught by the prior art, specifically as of Vucenik et al. (The Journal of Nutrition, Volume 133, Issue 11, November 2003, Pages 3778S-3784S), which was previously cited on page 3 of the office action on 18 May 2020. Nevertheless, Vucenik does not appear to teach encapsulation of inositol hexaphosphate in liposomes. Furthermore, Vucenik does not teach that, had inositol hexaphosphate been encapsulated in liposomes with irinotecan, the concentration of encapsulated irinotecan could have been increased as compared with the concentration of irinotecan encapsulated in a liposome lacking inositol hexaphosphate. As such, there would have been no reasonable expectation that the combination of Chou and Vucenik would have been successfully capable of encapsulating or entrapping between 0.8 and 1.3 millimoles of irinotecan per gram of total liposome lipids.

As additional relevant art, the examiner cites two post-filing date references published well after the earliest effective filing date of the instant application. These references are Hattori et al. (Journal of Controlled Release, Vol. 136, 2009, pages 30-37) and Wei et al. (Asian Journal of Pharmaceutical Sciences, Vol. 8, 2013, pages 303-311). Both references were previously cited on the PTO-892 on 13 October 2020. Both references are drawn to liposomes comprising irinotecan, as of the titles and abstracts of both references. Hattori combines irinotecan with phytic acid, as of the title of Hattori, wherein phytic acid is a synonym for inositol hexaphosphate. Wei combines irinotecan with ammonium phytate, as of page 304, right column, section 2.3, wherein "ammonium phytate" is understood to refer to the ammonium salt of the conjugate base of phytic acid, wherein phytic acid is inositol hexaphsophate. However, as these references were published after the effective filing date of the instant application, they are not prior art, and no rejection has been written over these references.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Terminal Disclaimers

The terminal disclaimer filed on 8 March 2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of

US Patent 8,147,867

US Patent 8,329,213

US Patent 8,703,181

US Patent 8,992,970

US Patent 8,658,203

US Patent 9,717,723

US Patent 9,782,349

US Patent 9,737,528

US Patent 9,724,303 and

US Patent 9,703,891

has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on 8 March 2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of

US application 15/227,561

US application 15/227,631

US application 15/896,389 (now US Patent 10,722,508); and

US application 15/896,436

has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access

to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	263266-421428	5137

153749 7590 08/26/2021

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/26/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/809,815	Applicant(s) Bayever et al.	
	Examiner GOLLAMUDI S KISHORE	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 02-25-2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,4-15,18-19 and 21-23 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,4-15,18-19 and 21-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The RCE dated 2-25-2021is acknowledged.

Claims included in the prosecution are 1, 4-15, 18-19 and 21-23.

1. Claims 1, 5-8, 10 and 19 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi).

Bayever et al discloses a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan). Bayever further discloses 5-fluorouracil at a dose of 2400 mg/m^2 and leucovorin (*l* form administered at 200 mg/m^2 or the *l*+*d* racemic form administered at 400 mg/m^2). The method comprised at least one cycle of administration, wherein the cycle was a period of two weeks (page 3, last full paragraph).

In one embodiment, Bayever's population was patients undergoing treatment for metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10).

Bayever does not disclose oxaliplatin, as recited in claim 9.

Conroy discloses FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy discloses that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro* (page 1818, left column, second paragraph).

Conroy does not disclose that the irinotecan was liposomal irinotecan.

Since Bayever discloses treating metastatic pancreatic carcinoma with 5-fluorouracil and irinotecan, it would have been prima facie obvious to one of ordinary skill in the art to include oxaliplatin within Bayever's methods of treatment. An ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy (Conroy, page 1818, left column, second paragraph).

Regarding the claims 1 and 19 limitation of 60 mg/m^2 oxaliplatin, the combination of Bayever (e.g., Bayever taught 85 mg/m^2 oxaliplatin at the abstract), though not silent the claimed amount of oxaliplatin, does not specifically teach 60 mg/m^2 oxaliplatin.

However, Melis teaches [abstract] that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients.

As such, oxaliplatin, and its amount, is recognized to have different effects (treatment of advanced pancreatic adenocarcinoma) with changing amounts used. Thus, the general condition (the dosage) is known and the amount of this ingredient is recognized to be result effective. Therefore, result effective variables can be optimized

by routine experimentation, and it would have been prima facie obvious to optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis.

The combination of Bayever, Conroy and Melis reads on claims 1 and 19.

Claims 5-6 and 8 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes, and that leucovorin was administered prior to 5-FU (page 12, section IV).

Claim 7 is rendered prima facie obvious because Bayever disclosed that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle), because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Bayever disclosed irinotecan sucrose octasulfate liposomal irinotecan, where the irinotecan was entrapped within the liposome, at page 4, and the last paragraph.

Response to Arguments

Applicant's arguments filed 02-25-2021 have been fully considered but they are not persuasive.

Applicant argues that Bayever discloses treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2) in combination with 5-fluorocila (e.g., 2400 mg/m^2) and leucovorin (e.g., 400 mgm2 (l and d form) to a patient once every two weeks and Conroy describes administering a combination of 180 mg/m^2 of non-liposomal irinotecan, 85 mg/m^2 oxaliplatin, 5-FU and LV once every two weeks. According to applicant Melis is an abstract summarizing a phase I/II chemo-radiation study of continuous infusion of 200 mg/m^2 5-fluorouracil and escalating doses of oxaliplatin weekly for 5 weeks with concurrent radiation in patients with regionally advanced pancreatic cancer. Thus, according to applicant, Bayever, Conroy and Melis disclose treatment of pancreatic cancer with a different combination of therapeutic agents in different doses from that of the claimed invention.

These arguments are not persuasive since the rejection is made with combination of references using drugs which are routinely used in treating pancreatic cancer and the examiner sees no unexpected and surprising results using the art known pancreatic cancer treatment agents. With regard to the doses, if different, are routinely manipulatable parameters practiced by an artisan to obtain the best possible results. The Examiner also includes the previous responses by the previous Examiner in this regard.

With regard to applicant's arguments pertaining to Melis, as pointed out in the previous action, Melis was relied upon to show that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation (discussed above). Furthermore, cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); & MPEP 2145(IV)].

In response to Applicant's argument once again that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

2. Claims 4, 9, 18 and 23 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) further in view of Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) and further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy and Melis, has been discussed above.

Additionally, Bayever discloses that prior to each administration of liposomal irinotecan, the patient was pre-medicated with dexamethasone (e.g. corticosteroid) and another anti-emetic (page 4, fourth embodiment from the top of the page).

Further, Conroy discloses that a second active agent was given two hours after a first active agent (e.g., leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose oxaliplatin administration after liposomal irinotecan, as recited in claims 4, 18 and 23; liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming discloses that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy discloses administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration.

An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. The Examiner has already addressed Bayever et al (WO 2013/188586), Conroy et al (NEJM, 34(19), 2011, 1817) and Melis et al

Fleming is combined for its teaching of sequence of administration of drugs in general.

3. Claims 11-15 and 21-22 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817), further in view of Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) and as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever (2013), in view of Conroy and Melis, has been discussed above.

Although, Bayever (2013) discloses MM-398 liposome (at page 4, last paragraph and as discussed above), Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12 and 21-22.

However, Bayever (2016) evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE (page 30, section describing the drug product).

Thus, it is reasonable to assume that Bayever's (2013) MM-398 contained irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.

Claims 13-15 and 21-22 are rendered prima facie obvious because Bayever discloses that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes; liposomal irinotecan was administered prior to leucovorin; leucovorin was administered prior to 5-FU (page 12, section IV). Further, Bayever discloses that active agents were administered on day one of a two-week cycle, where cycles comprised at least one administration.

For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2-week cycle can also be administration on days 1 and 15 of a 28-day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Response to Arguments

Applicant's arguments filed have been fully considered but they are not persuasive. The Examiner has already addressed Bayever et al (WO 2013/188586), Conroy et al (NEJM, 34(19), 2011, 1817) and Melis et al. Bayever (WO 2016/094402) is combined for the teachings of MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE. Applicant provides no specific arguments.

Nonstatutory Double Patenting

A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26,

PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 1, 4-15, 18-19 and 21-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 9,492,442, in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Melis et al (The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi)

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin. The instant claims require oxaliplatin, and such an ingredient is not recited by the issued claims.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro* (page 1818, left column, second paragraph).

Melis taught [abstract] that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients.

Thus, it would have been prima facie obvious to use oxaliplatin in the issued method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro*. It would have been prima facie obvious to use oxaliplatin at 60 mg/m^2 because the said dosage is well tolerated in advanced pancreatic adenocarcinoma patients.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

The Applicants reiterated the above arguments regarding a failing to show a prima facie case of obviousness, to which the Examiner disagrees. A prima facie case of obviousness to combine each of the prior art was previously discussed.

5. Claims 1, 4-15, 18-19 and 21-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 10,980,795. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in both said patent and instant claims are drawn to treating metastatic adenocarcinoma of the pancreas using the same composition. Instant claims express the concentration of irinotecan in terms of free base and thus, claims in said patent and instant claims are obvious variants..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on Monday through Friday 6:30 AM - 4:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FRED KRASS can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

153749 7590 03/08/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 03/08/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/012,351	06/19/2018	Eliel Bayever	01208-0002-10US	3260

TITLE OF INVENTION: Methods For Treating Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$1000.00	$200	06/08/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

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If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153749 7590 03/08/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/012,351	06/19/2018	Eliel Bayever	01208-0002-10US	3260

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nonprovisional	UNDISCOUNTED	$1200	$0.00	$1000.00	$200	06/08/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
STRONG, TORI	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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153749 7590 03/08/2021

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125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 03/08/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/012,351	Applicant(s) Bayever et al.	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE filed 02 December 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-29 and 32-37 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/TORI STRONG/ Examiner, Art Unit 1629	/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 21-29 and 32-37 are pending in the instant application and are the allowable subject matter of the Office Action below.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on December 2, 2020 has been entered.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 12/02/2020, 02/04/2021, 02/05/2021 and 02/23/2021 were filed after the mailing date of the application on June 19, 2018. The submission is in compliance with the provisions of

37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Examination Considerations

Applicant's Amendments filed April 3, 2020 have been received and entered into the present application. Claims 21-29 and 32-37 are pending and are herein examined on the merits.

Applicant's Reply, filed April 3, 2020 has been fully considered and found persuasive. Rejections from previous Office Actions are hereby withdrawn.

Applicant's Terminal Disclaimers, both filed April 3, 2020, have been entered and approved.

Applicant has filed IDSs which has been entered and considered. The allowable subject matter remains and the reason for allowance is reiterated here within.

Statement of Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

None of the prior art teaches in a single disclosure, nor fairly suggest in any combination, Applicants' claimed method for treating metastatic adenocarcinoma of the pancreas in a human patient previously treated with gemcitabine comprising intravenously administering to the patient once every two weeks an antineoplastic therapy consisting of irinotecan sucrose octasulfate salt liposome injection (in a dose

equivalent of 70 mg/m^2 of free base irinotecan) in combination with (200 mg/m^2) of (l)-form of leucovorin (or 400 mg/m^2 of racemic form) and (2,400 mg/m^2) of 5-fluorouracil. Applicant further claims liposomal irinotecan injection formulated with components in the claimed ratio of 3:2:0.015. Applicant's claimed method administers a drug regimen sequentially once over a 46 hour period in two week cycles. Applicants have demonstrated a novel method with a novel composition in their disclosure as originally filed. Applicant discloses an embodiment of the claimed regimen commensurate in scope that provides for the unexpected result of improving clinical benefit of up to 80% and increasing the patient population survival of at least 6 months.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Allowable Subject Matter

Claims 21-29 and 32-37 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

153749 7590 02/11/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 02/11/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/012,372	06/19/2018	Eliel Bayever	01208-0002-11US	1003

TITLE OF INVENTION: Methods For Treating Pancreatic Cancer Using Combination Therapies

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	05/11/2021

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P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

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153749 7590 02/11/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
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Cambridge, MA 02140

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/012,372	06/19/2018	Eliel Bayever	01208-0002-11US	1003

TITLE OF INVENTION: Methods For Treating Pancreatic Cancer Using Combination Therapies

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	05/11/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
STRONG, TORI	1629	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/012,372	06/19/2018	Eliel Bayever	01208-0002-11US	1003

153749 7590 02/11/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 02/11/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/012,372	Applicant(s) Bayever et al.	
	Examiner TORI STRONG	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to reply filed 26 January 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 42-54 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/TORI STRONG/ Examiner, Art Unit 1629	/Kortney L. Klinkel/ Primary Examiner, Art Unit 1699

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status of Claims

Claims 42-54 are pending in the instant application and are the allowable subject matter of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 01/27/2021 and 01/29/2021 were filed after the mailing date of the application on June 19, 2018. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Examination Considerations

Applicant's Terminal Disclaimer, filed January 26, 2021, is entered and approved on January 28, 2021.

Applicant's Reply, filed January 26, 2021 has been fully considered and found persuasive. Rejections from previous Office Actions are hereby withdrawn.

Double Patenting – Withdrawn

Claims 42-54 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,339,497 B2; claims 1-29 of U.S. Patent No. 9,364,473 B2; claims 1-35 of U.S. Patent No. 9,452,162 B2; and claims 1-30 of U.S. Patent No. 9,492,442 B2; and claims 1-24 of U.S. Patent No. 9,717,724 B2 is ***withdrawn***.

Applicant has filed a terminal disclaimer thus obviating the rejection. Subsequent to filing, the rejection is withdrawn.

Claims 42-54 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-29 and 32-37 of copending Application No. 16/012,351; and claims 1-20 of copending Application 16/920,830 is ***withdrawn***.

Applicant has filed a terminal disclaimer thus obviating the rejection. Subsequent to filing, the rejection is withdrawn.

Statement of Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

None of the prior art teaches in a single disclosure, nor fairly suggest in any combination, Applicants' claimed method for treating metastatic adenocarcinoma of the pancreas previously treated with gemcitabine comprising intravenously administering

once every two weeks the antineoplastic therapeutic regimen that consist of liposomal irinotecan at a dosing of 70 mg/m^2; leucovorin (*l*-form) at a dose of 200 mg/m^2; and 5-fluorouracil at a dose of 2,400 mg/m^2. Applicants have demonstrated a novel method in their disclosure as originally filed. Applicants' disclosure includes embodiments built around administration the claimed combination, administered to patients previously treated with gemcitabine, increasing the median overall survival significantly (see specification, p.40, para. 1) providing the unexpected result of improving clinical benefit of up to 80% and the increasing the patient population survival of at least 6 months.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Allowable Subject Matter

Claims 42-54 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571)272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1699

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/302,050	11/15/2018	Bambang Adiwijaya	01208-0013-00US	4677

153749 7590 08/11/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/11/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 16/302,050	Applicant(s) Adiwijaya et al.	
	Examiner GOLLAMUDI S KISHORE	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5-26-2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-30 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

The RCE dated 1-29-2021 is acknowledged.

Claims included in the prosecution are 1-30.

1. Claims 1-30 are rejected under 35 U.S.C. 103 as being unpatentable over Tardi et al (US 2016/0058704), in view of Madden et al (USP 7,244,448 B2) optionally further in view of the FDA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf).

Tardi discloses irinotecan and cisplatin, co-administered in a blended liposome formulation, or administered as liposomal cisplatin alone or liposomal irinotecan alone, and given to mice bearing human small cell lung cancer solid tumors [0036-0038 and at Figures 7B-7C and Figure 8]. These compositions [0018] allowed the two agents to be delivered to the disease site in a coordinated fashion. This result was achieved whether the agents were co-encapsulated, or were separately encapsulated. The unilamellar liposomes taught by Tardi are of a diameter of less than 200 nm [0055], and formulated with DSPC, cholesterol [0034] and mPEG-DSPE [0054].

As such, Tardi teaches [0021] the delivery of a therapeutically effective amount of a platinum drug/therapeutic agent combination (e.g., preferred combinations were irinotecan and cisplatin or irinotecan and carboplatin, at [0020]), by administering a

platinum-based drug stably associated with a first blended delivery vehicle and an additional therapeutic agent stably associated with a second delivery vehicle. The first and second delivery vehicles were contained in separate vials, the contents of the vials being administered to a patient simultaneously or sequentially (reads on treating small cell lung cancer with irinotecan, following disease progression on or after first-line platinum therapy).

Although Tardi exemplifies the administration to mice, Tardi disclosed [0097] that the blended delivery vehicles may be administered to warm-blooded animals, including humans. For the treatment of human ailments, a qualified physician will determine dose, schedule and route of administration.

Although Tardi discloses that the dosage and schedule could be determined by a qualified physician, Tardi did not specifically disclose administering liposomal irinotecan every two weeks at 70 mg/m^2, as recited in claim 1. Tardi was silent as to the free base form of irinotecan, as recited in claim 1.

Madden discloses [title and abstract] liposomal antineoplastic agents (e.g., camptothecin) for treating neoplasia. Madden discloses that, for camptothecins (irinotecan disclosed at col 8, line 46) in the treatment of small cell lung cancer, the doses of active agent in humans are effective at ranges as low as from 0.015 mg/m^2, and are still tolerable at doses as high as 15 to 75 mg/m^2. Doses may be single or administered repeatedly, wherein preferred scheduling may employ a cycle of treatment that is repeated every two weeks, three weeks, four weeks, five weeks, six weeks or a combination thereof [col 9, line 63 to col 10, line 14].

Madden did not teach administering liposomal irinotecan following disease progression on or after first-line platinum-based therapy.

Since Tardi discloses liposomal irinotecan for the treatment of small cell lung cancer in humans, it would have been prima facie obvious to one of ordinary skill in the art to administer the active once every two weeks, at a dosage of 70 mg/m^2. An ordinarily skilled artisan would have been so motivated because, for camptothecins (e.g., irinotecan) in the treatment of small cell lung cancer, the doses of active agent in humans are effective at ranges as low as from 0.015 mg/m^2, and are still tolerable at doses as high as 15 to 75 mg/m^2. Doses may be single or administered repeatedly, wherein preferred scheduling may employ a cycle of treatment that is repeated every two weeks, three weeks, four weeks, five weeks, six weeks or a combination thereof [col 9, line 63 to col 10, line 14].

The combined teachings of Tardi and Madden are silent the free base form of liposomal irinotecan.

However, the FDA disclosed [page 11, first paragraph] that liposomal irinotecan is commercially available as irinotecan freebase.

The FDA does not teach the treatment of small cell lung cancer.

It would have been prima facie obvious to one of ordinary skill in the art to include free base irinotecan within the combined teachings of Tardi and Madden. An ordinarily skilled artisan would have been motivated to formulate the liposome with the commercially available form of the active [FDA, page 11, first paragraph].

The combination of Tardi, Madden and FDA reads on claims 1-2, 7-8, 11-12, 14-15.

Claim 1 recites administration of liposomal irinotecan once every two weeks at a dosage of 70 mg/m^2. Claim 15 recites at least three six-week cycles. The combined teachings of Tardi, Madden and FDA taught 15 to 75 mg/m^2 in a single dosage or administered repeatedly, wherein preferred scheduling may employ a cycle of treatment that is repeated every two weeks, three weeks, four weeks, five weeks, six weeks or a combination thereof. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A. Regarding claims 3 and 13, Tardi was silent the blood ANC of the human patients, as instantly recited. However, the FDA advised [page 4, section 5.1] that liposomal irinotecan should be administered when the ANC is 1500/mm^3 or above, as both a warning and a precaution against severe neutropenia.

It would be prima facie obvious to one of ordinary skill in the art to administer Tardi's liposomal irinotecan to humans when the patient's ANC was 1500/mm^3 or above, as advised by the FDA. An ordinarily skilled artisan would be motivated to avoid severe or life-threatening neutropenia and fatal neutropenic sepsis, as advised by the FDA at page 4, section 5.1.

Regarding claims 9, 16 and 21-22, although Tardi disclosed [0098] intravenous administration, Tardi was silent the preparation of liposomal irinotecan, as instantly recited. However, the FDA disclosed [pages 2-3, sections 2.2 and 2.4] that liposomal irinotecan is prepared as a pharmaceutical injection composition, by diluting 70 mg/m^2 of the agent in 500 mL dextrose or 0.9 % sodium chloride, and mixing, followed by administration as an intravenous infusion over 90 minutes.

It would have been prima facie obvious to one of ordinary skill in the art to prepare Tardi's liposomal irinotecan, as taught by the FDA. An ordinarily skilled artisan would have been motivated by the FDAs teachings of liposomal irinotecan in its commercially available formulation, as previously discussed [FDA, sections 2.2 and 2.4]. An ordinarily skilled artisan would have been motivated to administer the liposomal irinotecan as an infusion, as recommended by the FDA for human administration [FDA, sections 2.2 and 2.4].

Regarding claims 24-30, although Tardi taught (encapsulation previously discussed) unilamellar vesicles [0052] having a diameter of less than 200 nm [0055], and formulated with DSPC, cholesterol [0034] and mPEG-DSPE [0054], Tardi was not specific the liposomal formulation instantly recited, wherein the aqueous space encapsulated irinotecan in a gelated or precipitated state as the sucrose octasulfate salt, as recited in claim 24; the molecular weight of PEG, as recited in claims 26 and 29-30; amounts of phosphatidylcholine, cholesterol and mPEG, as recited in claims 26-28 and 30.

However, the FDA taught [page 11, 1st paragraph] that liposomal irinotecan is a dispersion, wherein the liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL.

It would have been prima facie obvious to one of ordinary skill in the art to formulate Tardi's liposomal irinotecan as taught by the guidance of the FDA. An ordinarily skilled artisan would be motivated to obtain liposomal irinotecan in its commercially available formulation, as previously discussed [FDA, page 11, 1st paragraph].

Claim 24 recites 110 nm diameter. Claim 27 recites one mPEG-2000-DSPE molecule per 200 phospholipid molecules. Claims 28 and 30 recite phosphatidylcholine, cholesterol and mPEG-2000-DSPE in a molar ratio of 3:2:0.015. Tardi taught liposomes at less than 200 nm; and, the FDA taught a vesicle approximately 110 nm in diameter, composed of DSPC 6.81 mg/mL, cholesterol 2.22 mg/mL, and MPEG-2000-DSPE 0.12 mg/mL. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant provides no specific arguments regarding this rejection.

2. Claims 4-6 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over Tardi et al (US 2016/0058704), in view of Madden et al (USP 7,244,448 B2), further in view of the FDA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf) and further in view of Mirtsching et al (Am J Med Sci, 2014, 347(2), 167-169).

The 35 U.S.C. 103 rejection over Tardi, Madden and the FDA was previously discussed. The combined teachings of the prior art were silent the platelet count of the human patient, as recited in claims 4 and 18; the blood hemoglobin value, as recited in claims 5 and 18; the serum creatinine value, as recited in claims 6 and 18.

Mirtsching taught [title] drug-induced immune thrombocytopenia, wherein [page 3, last paragraph] a human patient had become sensitized to irinotecan during treatment cycles with the active agent. Before treatment, the patient's platelet count was 143,000/μL. Said counts were maintained between 113,000-150,000/μL during therapy. However, after treatment, the patient had no platelet counts less than 100,000/μL, and no systemic symptoms during previous exposures to the active agent. Because cases of [page 3, last paragraph] acute, severe thrombocytopenia caused by irinotecan have now been identified, clinicians should consider this possible diagnosis in any patient who experiences an acute and isolated drop in the platelet levels after irinotecan administration. Other laboratory data included hemoglobin at 13.8 g/dL, and creatinine at 0.7 mg/dL [page 2, 2nd paragraph].

It would have been prima facie obvious to one of ordinary skill in the art to administer Tardi's liposomal irinotecan when the patient's blood platelet count was greater than 100,000/μL. An ordinarily skilled artisan would have been motivated to avoid a possible diagnosis of acute, severe thrombocytopenia [Mirtsching, page 3, last paragraph].

It would have been prima facie obvious to one of ordinary skill in the art to administer Tardi's liposomal irinotecan when the patient's blood hemoglobin was 13.8 g/dL, as taught by Mirtsching [page 2, 2nd paragraph]. An ordinarily skilled artisan would have been motivated to monitor the liver function, and the bone marrow reserve.

It would have been prima facie obvious to one of ordinary skill in the art to administer Tardi's liposomal irinotecan when the patient's serum creatinine was 0.7

mg/dL, as taught by Mirtsching [page 2, 2nd paragraph]. An ordinarily skilled artisan would have been motivated to monitor and ensure adequate renal function.

Claim 4 recites a platelet count greater than 100,000 cells per microliter. Claim 5 recites hemoglobin greater than 9 g/dL. Claim 6 recites creatinine less than or equal to 1.5xULN. Mirtsching taught a platelet count at 143,000/µL, hemoglobin at 13.8 g/dL and creatinine at 0.7 mg/dL, before treatment. A prima facie case of obviousness exists because of overlap, as previously discussed.

Further regarding claim 6, Mirtsching was silent the creatinine clearance, as instantly recited. However, it would be prima facie obvious to one of ordinary skill in the art to determine the creatinine clearance, as desired. An ordinarily skilled artisan would be motivated to monitor and ensure an adequate renal function.

Further, regarding claim 18, the claim instantly recites once every two weeks for a total of at least three six-week cycles. The combined teachings of Tardi and Madden taught administration in a single dosage, or repeatedly, wherein preferred scheduling may employ a cycle of treatment that is repeated every two weeks, three weeks, four weeks, five weeks, six weeks or a combination thereof. A prima facie case of obviousness exists because of overlap, as previously discussed.

Applicant provides no specific arguments regarding this rejection.

3) Claims 10 and 17 are rejected under 35 U.S.C. 103 as being unpatentable over Tardi et al (US 2016/0058704), in view of Madden et al (USP 7,244,448 B2), further in view of the FDA

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf) and further

in view of Cassileth et al (Arch Intern Med, 1983, 143(7), 1347-1349) and Drug and Therapeutics Bulletin, 43(8), 2005, 57-62.

The 35 U.S.C. 103 rejection over Tardi, Madden and the FDA was previously described. Additionally, the FDA generally advised [page 3, Premedication section] administration of a corticosteroid and an anti-emetic prior to liposomal irinotecan infusion.

However, the combined teachings of the prior art did not specifically teach dexamethasone and a 5-HT3 blocker, as instantly recited.

Nevertheless, Cassileth taught [title] antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy, wherein dexamethasone therapy has useful application in alleviating the emetic effects of cancer chemotherapy [abstract].

Moreover, the Drug and Therapeutics Bulletin taught [title] 5HT3-receptor antagonists as anti-emetics in cancer, wherein effective antiemetic therapy is crucial for patients undergoing chemotherapy or radiotherapy for cancer. Severe nausea and vomiting associated with such cancer treatment can lead to anxiety, anorexia, dehydration, electrolyte disturbance and renal failure, and may interrupt cancer therapy, demoralize patients or even cause them to abandon treatment [abstract].

Since the combined teachings of the prior art generally advised administration of a corticosteroid and an anti-emetic prior to liposomal irinotecan infusion, it would have been prima facie obvious to one of ordinary skill in the art to include dexamethasone and a 5-HT3 blocker within the combination of said teachings. An ordinarily skilled artisan would have been motivated to alleviate the emetic effects of cancer chemotherapy, since the severe nausea and vomiting associated with cancer treatment can lead to anxiety, anorexia, dehydration, electrolyte disturbance and renal failure, and

may interrupt cancer therapy, demoralize patients or even cause them to abandon treatment, as taught by the combined teachings of Cassileth and the Drug and Therapeutics Bulletin [abstracts and titles of each reference].

Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. See MPEP 2144.07. In the instant case, it is prima facie obvious to select both dexamethasone and a 5-HT3 blocker, for incorporation into a composition, based on their recognized suitability for the intended use as anti-emetics, as taught by the combined teachings of Cassileth and the Drug and Therapeutics Bulletin [abstracts and titles of each reference].

Applicant provides no specific arguments regarding this rejection.

4) Claims 19-20 and 23 are rejected under 35 U.S.C. 103 as being unpatentable over Tardi et al (US 2016/0058704), in view of Madden et al (USP 7,244,448 B2), further in view of the FDA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf), further in view of Mirtsching et al (Am J Med Sci, 2014, 347(2), 167-169), further in view of Cassileth et al (Arch Intern Med, 1983, 143(7), 1347-1349) and further in view of Drug and Therapeutics Bulletin, 43(8), 2005, 57-62.

The 35 U.S.C. 103 rejection over Tardi, Madden and the FDA was previously described. Additionally, the FDA generally advised [page 3, Premedication section] administration of a corticosteroid and an anti-emetic prior to liposomal irinotecan infusion. However, the combined teachings of the prior art did not specifically teach dexamethasone and a 5-HT3 blocker, as instantly recited.

Nevertheless, Cassileth taught [title] antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy, wherein dexamethasone therapy has useful application in alleviating the emetic effects of cancer chemotherapy [abstract]. Moreover, the Drug and Therapeutics Bulletin taught [title] 5HT3-receptor antagonists as anti-emetics in cancer, wherein effective antiemetic therapy is crucial for patients undergoing chemotherapy or radiotherapy for cancer. Severe nausea and vomiting associated with such cancer treatment can lead to anxiety, anorexia, dehydration, electrolyte disturbance and renal failure, and may interrupt cancer therapy, demoralize patients or even cause them to abandon treatment [abstract].

Since the combined teachings of the prior art generally advised administration of a corticosteroid and an anti-emetic prior to liposomal irinotecan infusion, it would have been prima facie obvious to one of ordinary skill in the art to include dexamethasone and a 5-HT3 blocker within the combination of said teachings. An ordinarily skilled artisan would have been motivated to alleviate the emetic effects of cancer chemotherapy, since the severe nausea and vomiting associated with cancer treatment can lead to anxiety, anorexia, dehydration, electrolyte disturbance and renal failure, and may interrupt cancer therapy, demoralize patients or even cause them to abandon treatment, as taught by the combined teachings of Cassileth and the Drug and Therapeutics Bulletin [abstracts and titles of each reference].

Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. See MPEP 2144.07. In the instant case, it is prima facie obvious to select both dexamethasone and a 5-HT3 blocker, for incorporation into a composition, based on their recognized

suitability for the intended use as anti-emetics, as taught by the combined teachings of Cassileth and the Drug and Therapeutics Bulletin [abstracts and titles of each reference].

Regarding claims 20 and 23, although Tardi disclosed [0098] intravenous administration, Tardi was silent the preparation of liposomal irinotecan, as instantly recited. However, the FDA disclosed [pages 2-3, sections 2.2 and 2.4] that liposomal irinotecan is prepared, as a pharmaceutical injection composition, by diluting 70 mg/m^2 of the agent in 500 mL dextrose or 0.9 % sodium chloride, and mixing, followed by administration as an intravenous infusion over 90 minutes.

It would have been prima facie obvious to one of ordinary skill in the art to prepare Tardi's liposomal irinotecan as taught by the FDA. An ordinarily skilled artisan would have been motivated by the FDAs teachings of liposomal irinotecan in its commercially available formulation, as previously discussed [FDA, sections 2.2 and 2.4]. An ordinarily skilled artisan would have been motivated to administer the liposomal irinotecan as an infusion, as recommended by the FDA for human administration [FDA, sections 2.2 and 2.4].

Applicant provides no specific arguments regarding this rejection.

5. Claims 1-30 are rejected under 35 U.S.C. 103 as being unpatentable over Morise in view of Chan (Experimental and Molecular therapeutics, AACR Annual Meeting, 2014), Drummond (Cancer Research, vol. 68(6), 2006) individually or in combination, optionally further in view of FDA cited above..

Morise et al disclose the low-dose irinotecan monotherapy as an effective second-line chemotherapy for recurrent small cell lung cancer. According to Morise irinotecan is a potent inhibitor of deoxyribonucleic acid topoisomerase 1 and a weekly schedule of 100-125 or 350 mg/ m^2 administration on day 1 every 3 weeks is recommended for recurrent small cell lung cancer. The study was conducted with 60 mg/m2 on days 1, 8 and 15 every 4 weeks. The study includes patients who underwent cisplatin based therapy (see entire publication including the table I). Morise teaches that irinotecan is a potent inhibitor of deoxynucleic acid topoisomerase 1 and is very toxic at the dose recommended in several phase 2 trials.

What is lacking in Morise is the use of liposome encapsulated irinotecan. Morise also does not disclose the nature of patient's condition in terms of claimed blood ANC, hemoglobin amounts, serum creatinine levels and creatinine clearance, platelet counts and claimed protocol of administration of liposomal irinotecan.

Chan teaches that liposome encapsulation of irinotecan greatly modifies the pharmacokinetic and biodistribution of irinotecan thereby improving its action in treating small cell lung cancers. Chan discloses the administration of 25 mg/kg/week or liposomal irinotecan at 30 and 50/mg/kg for three weeks (see entire publication).

Drummond teaches liposomal encapsulation of irinotecan to enhance its efficacy and ameliorate its toxicity. The liposomes contain DSPC, methoxypolyethylene glycol derivatized distearoylphosphatidylethanolamine and cholesterol in the mole ratio of 3:0.015: 2 (Abstract and entire publication).

As pointed out above, the FDA taught [page 11, 1st paragraph] that liposomal irinotecan is a dispersion, wherein the liposome is a unilamellar lipid bilayer vesicle,

approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL.

The use of liposome encapsulated irinotecan as the second-line chemotherapy at doses which are lesser than the recommended high doses for free irinotecan treatment of small cell lung cancer would have been obvious to one of ordinary skill in the because liposomes encapsulation enhances its therapeutic efficacy and reduce its toxicity as taught by Drummond and efficacy of liposomal encapsulation of irinotecan taught by Chan. One of ordinary skill in the art would be motivated further to use of liposomal irinotecan since FDA teaches that liposomal irinotecan is commercially available for administration. Although Morise does not disclose the nature of patient's condition in terms of claimed blood ANC, hemoglobin amounts, serum creatinine levels and creatinine clearance, platelet counts and claimed protocol of administration of liposomal irinotecan, it would have been obvious to one of ordinary skill in the art and the practitioner in the art to measure these parameters before the start of chemotherapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on Monday through Friday 6:30 AM - 4:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FRED KRASS can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

153749 7590 03/08/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 03/08/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/567,902	09/11/2019	Daryl C. Drummond	01208-0010-10US	3814

TITLE OF INVENTION: Stabilizing Camptothecin Pharmaceutical Compositions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/08/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153749 7590 03/08/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/567,902	09/11/2019	Daryl C. Drummond	01208-0010-10US	3814

TITLE OF INVENTION: Stabilizing Camptothecin Pharmaceutical Compositions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/08/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
SHOMER, ISAAC	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/567,902	09/11/2019	Daryl C. Drummond	01208-0010-10US	3814

153749 7590 03/08/2021

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	
ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 03/08/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/567,902	Applicant(s) Drummond et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE on 11 January 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 24-36,38-58 and 60-61 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Deborah Herzfeld on 25 February 2021.

The application has been amended as follows:

A) Claim 37 has been cancelled without prejudice or disclaimer.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Claim Interpretation: Claim 24, second line, recites a liposome comprising irinotecan sucrose octasulfate, cholesterol, and one or more phospholipids. However, on claim 24, 8th and 9th lines, the claim recites DSPC and methoxy terminated polyethylene glycol distearoyl phosphatidylethanolamine. These are both understood to be one or more phospholipids as required by the second line of claim 24. As such, the claim is understood to be definite and is understood to require a liposome comprising DSPC cholesterol, and methoxy terminated polyethylene glycol distearoyl phosphatidylethanolamine. A similar issue is recited as of claim 61.

Relevant Prior Art: The examiner has cited the following close prior art, and has provided an explanation as to why no rejection has been written over the cited prior art. The following is taken mostly from the corrected reasons for allowance in prior application 15/768,352 (now US Patent 10,456,360), mailed on 28 August 2019; the issues in the instant case are very similar to those in the '352 application.

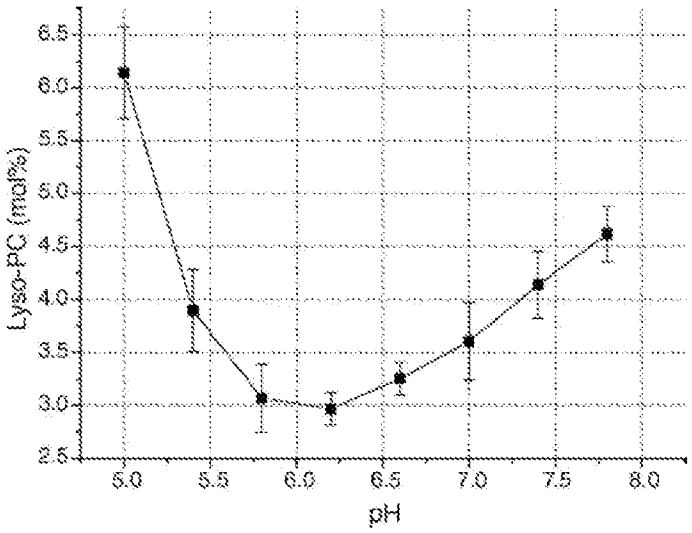
The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. As close and relevant prior art, the examiner cites Drummond et al. (US 2007/0110798 A1) and Hong et al. (US 2007/0116753 A1), which are also drawn to liposomes comprising sucrose octasulfate and irinotecan. Also cited by the examiner is Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80). All of these references have been previously cited in the prosecution history.

The following reasons are provided by the examiner explaining why the instant claims have not been rejected as anticipated by these references or obvious over these references.

Summary of Examiner's Position: Liposomes are known to suffer from degradation when in storage. One such form of degradation involves the hydrolysis of phosphatidylcholine, which is a phospholipid molecule with two hydrocarbon chains that makes up the structural of the bilayer of the liposome, to lysophosphatidylcholine, which has only one hydrocarbon chain. Such lysophosphatidylcholine is understood to have poor stability in the liposome bilayer, and a bilayer comprising sufficient amounts of lysophosphatidylcholine is subject to degradation. The instantly claimed invention is drawn to a liposome that has unexpectedly greater storage stability in that there is less degradation of phosphatidylcholine to lysophosphatidylcholine as compared with the liposomes of the Drummond and Hong prior art references cited above. The following reasons are presented by the examiner in support of this position.

A) pH Range: First, the instantly claimed liposome is stored in a medium wherein the pH is about 7.25 to about 7.50 (as in instant claim 24). Hong teaches that the liposome should be stored at a pH of between 6.0 and 7.5, with a pH of 6.5 as most optimal, as of Hong, paragraph 0115. However, additional relevant prior art shows that storage of a liposome in a pH of about 6.25 to 6.5 has the greatest storage stability, and that deviation from pH 6.25-6.5 results in more degradation during storage as compared to storage at pH 6.5. In support of this position, the examiner cites Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80). Saetern et al. (hereafter referred to as Saetern), teaches the following graph regarding degradation of

phosphatidylcholine to lysophosphatidylcholine, as of page 77, right column, Figure 5, which is reproduced below.



As such, the data of Saetern indicates that a pH of about 6.25 provides the greatest stability of a phosphatidylcholine containing liposome. The examiner also notes that the Saetern publication is especially relevant here because Saetern is drawn to encapsulating camptothecin as a drug, and the instant claims are drawn to a liposome that encapsulates irinotecan as a drug, wherein irinotecan is a derivative of camptothecin.

However, in the instant specification, applicant has presented data showing that a pH range of about 7.25 to about 7.50 unexpectedly provides increased stability as compared to a pH of about 6.5. In support of this position, the examiner cites table 1B on page 26 of the instant specification, which is reproduced below.

Table 1B: *Irinotecan Liposome Stability Ratio and Lyso-PC (after 6 months at 4 °C)*[b]

Sample	Molar (M) concentration of sulfate groups in the sucrosofate entrapped in the liposomes	Stability Ratio	pH	[mol% Lyso-PC] at 6 mos.
1	0.45	1047	6.5	19.5
2	0.475	992	6.5	17
3	0.5	942	6.5	26.5
4	0.6	785	6.5	30.2
5	0.45	1047	7.25	7.1
6	0.45	1047	6.5	14.6
7	0.45	1047	7.25	7.4
8	0.45	1047	7.5	5.4
9	0.6	785	6.5	29.8
10	0.6	785	7.25	24.1
11	0.6	785	7.5	22.8
13	0.45	1047	7.25	9.72

[b] Measured according to Method B, as described herein.

Instant table 1B discloses that a liposome at a pH of 6.5 and a sulfate group concentration of 0.45 M (Sample #1) shows 14.6 mol% or 19.5 mol% of lysophosphatidylcholine after 6 months, as of samples #6 and #1 respectively. In contrast, a sample with a pH of 7.25 and an identical sucrose octasulfate concentration of 0.45 M (Samples #5 and #7) shows only about 7.1 mol% or 7.4 mol% of lysophosphatidylcholine after 6 months of storage. As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the pH of a sucrose octasulfate containing irinotecan liposome is raised from 6.5 to 7.25.

This increase in stability with increase in pH is at odds with the teachings of the prior art, which indicate that a lower pH of 6.25 to 6.5 is optimal for achieving stability of the liposome. As applicant has shown that the claimed pH range is critical for achieving increased stability, this is understood to be evidence of non-obviousness. See MPEP 2144.05(III)(A). Additionally, proceeding contrary to accepted wisdom is evidence of

nonobviousness. See MPEP 2145(X)(D)(3), citing In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). In this case, applicant has proceeded contrary to the expected wisdom of the Saetern reference and has achieved beneficial results of increased stability.

B) Sucrose Octasulfate Loading Concentration: The instant claims were loaded at from 0.4 M to 0.5 M sucrose octasulfate. The following explanation is drawn to the reasons that this limitations is relevant to the examiner's decision not to reject the instant claims in view of this limitation.

B1 – Legal Information Regarding Product-by-Process Limitations: In the instantly claimed product-by-process, sucrose octasulfate was loaded in a concentration such that the sulfate groups are present in a concentration of 0.4 to 0.5 M based on sulfate groups, as of part (a) of claim 24.

As an initial matter, the examiner notes that, with regard to product-by-process claims, such claims are not limited to the manipulations of the recited steps, and are only limited to the structure implied by the steps. See MPEP 2113(I). Nevertheless, once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. See MPEP 2113(II). It is the examiner's position that applicant has provided such evidence to meet this burden. An explanation for why that is the case is provided below.

B2 – Explanation of Teachings of Hong Regarding Sucrose Octasulfate Concentration:

Hong teaches that the substituted ammonium and/or polyanion salt inside the liposome is in a concentration ranging from 10 mM to 1.0 M, with a preferred concentration range of about 0.65 M to about 1.0 M, as of Hong, paragraph 0104.

The examiner provides the following explanation of paragraph 0104 of Hong: Sucrose octasulfate is a polyanion (as it includes multiple sulfate anionic groups), and a salt of sucrose octasulfate is therefore a polyanion salt. Sucrose octasulfate as a substituted ammonium salt is taught in the examples of the Hong reference, e.g. as of paragraph 0138 in Example 7 of Hong and paragraph 0161 of Hong in Example 11. Paragraph 0161 of Hong teaches TEA-SOS, which is triethylammonium sucrose octasulfate.

As such, it is the examiner's best understanding that the "substituted ammonium and/or polyanion salt" in paragraph 0104 of Hong is a salt such as triethylammonium sucrose octasulfate (wherein triethylammonium is a substituted ammonium).

The examiner makes the following note regarding the chemistry of sucrose octasulfate. Sucrose octasulfate is a molecule comprising sucrose substituted with eight sulfate groups covalently attached thereto. Each sulfate group carries a formal charge of -1. As such, cations are needed to balance the negative formal charge in sucrose octasulfate. In the teachings of Hong, the most preferred cation is a substituted ammonium cation such as tetraethylammonium. The tetraethylammonium cation has a formal charge of +1, e.g. as of paragraph 0161 of Hong. As such, eight

tetraethylammonium cations are needed to balance the charge of one sucrose octasulfate anion.

The instant claims recites sucrose octasulfate concentration in terms of the sulfate concentration. Hong, in paragraph 0104, expresses polyanion (e.g. sucrose octasulfate) concentration in terms of the molarity of the substituted ammonium ion. These are equivalent concentrations, as one substituted ammonium ion is needed to balance the charge of one sulfate group.

As such, the value of 0.5 M in paragraph 0104 of Hong is within the range of 0.4 M to 0.5 M recited by instant claim 24. Nevertheless, a *prima facie* case of obviousness is overcome by unexpected results, as explained below.

B3 – Summary of Unexpected Results: In this case, any prima facie case of obviousness that may be present is overcome with unexpected results. See MPEP 716.01 and 716.02.

Data in the instant application show that loading with a level of sucrose octasulfate with a sulfate group concentration of 0.4 M to 0.5 M appears to provide a liposome with increased stability as compared with a liposome loaded at 0.60 to 0.65 M. In support of this position, the examiner cites table 1B on page 26 of the instant specification, which is reproduced above in section A of the reasons for allowance. Sample 10 of the instant specification shows loading at 0.60 M sucrose octasulfate and pH 7.25. In this example, there was 24.1 mol% lysophosphatidylcholine after 6 months of storage. In contrast, samples 5 and 7 are drawn to a liposome loaded with 0.45 M sucrose octasulfate and also a pH of 7.25, and these show 7.1% and 7.4% of lyosphosphatidylcholine respectively after 6 months of storage. Similar beneficial results

are shown in the instant specification upon comparing Sample 8, which discloses 0.45 M sucrose octasulfate and a pH of 7.5, with Sample 11, which discloses 0.6 M sucrose octasulfate and a pH of 7.5. Specifically, example 8 discloses 5.4% lysophosphatidylcholine after 6 months, whereas example 11 discloses 22.8% lysophosphatidylcholine after 6 months.

As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the concentration of sulfate groups from sucrose octasulfate is decreased from the preferred concentration in the prior art of 0.65 M to a lower concentration of 0.4 M to 0.5 M. This would not have been expected by the skilled artisan, and this also indicates that the concentration of sucrose octasulfate used in loading the liposome is critical to the liposome stability. This showing regarding the criticality of the claimed loading concentration of sucrose octasulfate is evidence of non-obviousness, and applicant's data show that the claimed range of sucrose octasulfate is critical with regard to the stability of the liposome that is ultimately formed. See MPEP 2144.05(III)(A).

B4 – Examiner's Statement Regarding MPEP 716.02(e) and the Prior Art: The examiner has included this section of the reasons for not rejection over prior art to make the case that applicant successfully compared the claimed invention to a comparative example that is at least as close as what is actually present in the prior art. See MPEP 716.02(e), especially 716.02(e)(II) and 716.02(e)(III). The following reasoning is presented by the examiner in support of this position.

The examiner notes here that while paragraph 0104 of Hong may teach sucrose octasulfate in amounts that overlap with the claimed amounts, most of the examples of

Hong teach sucrose octasulfate in amounts that are greater than the claimed amount or that differ from the claimed invention in other ways. For example, Hong, paragraph 0072, Example 13, teaches sucrose octasulfate in an amount of 0.643 N. The same teaching is present on Hong, Example 15, paragraph 0176. Example 16, paragraph 0183 of Hong teaches sucrose octasulfate at 0.65 M based upon triethylammonium. Hong teaches a higher concentration of 1.05 N sucrose octasulfate in Example 24, paragraph 0295.

Nevertheless, the closest example in Hong appears to be a teaching of a liposome comprising 0.47 M triethylammonium sucrose octasulfate in Example 23, paragraph 0204 of Hong. However, this example is for the drug topotecan, which differs from the claimed irinotecan. Also, this example has a pH that of 6.27, which differs as compared with the claimed pH range of about 7.25 to about 7.50.

As such, Hong does not appear to teach an example comprising a liposome with irinotecan and sucrose octasulfate in a concentration of 0.4 M to 0.5 M.

In the case of determination of a prima facie case of obviousness, whether sucrose octasulfate in a concentration of 0.4 M to 0.5 M is taught in the examples or in the broad disclosure of Hong is not particularly relevant. This is because, regardless of whether the teaching is in the examples or in the broad disclosure, there is a prima facie case of obviousness. See MPEP 2123. However, in this case, the relevant issue being discussed in this section of the reasons for allowance is in regards to unexpected results rather than a prima facie case of obviousness. For the relevant analysis regarding unexpected results, the examiner cites MPEP 716.02(e), which states that the claimed invention must be compared with the closest prior art.

Crucially, MPEP 716.02(e)(III) states that [a]lthough evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. In this case, the examiner understands that an irinotecan liposome comprising 0.4-0.5 M sucrose octasulfate and a pH of about 7.25 to about 7.50, thought potentially suggested by Hong through teachings at disparate portions of the reference, does not actually exist in Hong because it is not present in the examples of Hong.

As such, applicant's comparison of the claimed invention vs. a comparative example comprising 0.6 M sucrose octasulfate, as of Table 1B of the instant specification, which is reproduced above, is understood to successfully compare the claimed invention against a comparative example that is closer than the subject matter which actually exists in the prior art.

C) Combination of pH and Sucrose Octasulfate Concentration: The data shown above appear to indicate that it is not only the pH and the sucrose octasulfate concentration, but the combination of the pH and sucrose octasulfate concentration that lead to greater stability as compared with the prior art. For that matter, the only embodiments in Figure 1B, reproduced above, that form less than 10 mol% lysophosphatidylcholine after 6 months storage at 4°C have a pH of 7.25 or 7.5 and a sucrose octasulfate concentration of 0.45 M. Examples that differ by either pH, sucrose octasulfate concentration, or both, form a higher mol% of lysophosphatidylcholine after storage, which indicates lower stability.

As such, for at least these reasons, the examiner has not rejected the instant claims as prima facie obvious over Drummond et al. (US 2007/0110798 A1) or Hong et

al. (US 2007/0116753 A1). Also, for these reasons, the examiner has not written a double patenting rejection over patents issuing from the disclosures of either Drummond or Hong.

D) Additional Relevant Reference: The examiner also searched for lysophosphatidylcholine as an excipient in lipid particles. The art found by the examiner would appear to indicate that lysophosphatidylcholine is generally not desirable as an excipient, at least for structures comprising lipid bilayers. As relevant prior art in this regard, the examiner cites Israelachvili et al. (Quarterly Reviews of Biophysics, Vol. 13(2), 1980, pages 121-200), which was previously cited in the office action on 10 August 2020. Israelachvili teaches lysolecithin resulting in a hole forming in a lipid bilayer, as of page 175, figure 5.1, reproduced below.

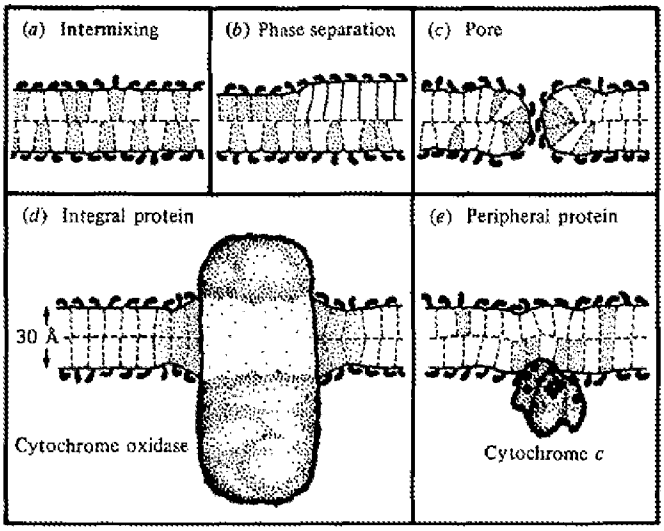


Fig. 5.1. Scaled drawings of mean packing conformations of mixed lipid and lipid–protein membranes. In each case the unperturbed bilayer hydrocarbon thickness is 30 Å. (*a*) Mixed lecithins of head-group area ~ 70 Å² but of different chain lengths, in the fluid state. (*b*) Solid-liquid phase separation in upper monolayer of a bilayer. Note that packing stresses must occur at the boundary. (*c*) Mixture of lecithin and lysolecithin where a transient local clustering of lysolecithin can produce a pore or channel. (*d*) Cytochrome oxidase in a lecithin bilayer. Note the perturbations at the protein boundary which may preferentially draw in certain lipids. Dimensions for cytochrome oxidase taken from Henderson *et al.* (1977); dimensions for lecithin are as discussed in Section IV. The detailed shape of cytochrome oxidase is still unknown. (*e*) Cytochrome *c* preferentially associating with charged lipids in a mixed-lipid bilayer via basic lysine residues of the protein surface. Dimensions for cytochrome *c* and positions of the haem and the five invariable lysine residues taken from Dickerson *et al.* (1971).

As best understood by the examiner, the above-reproduced diagram would appear to indicate that the presence of lysophosphatidylcholine (referred to as lysolecithin in the above-reproduced diagram) would appear to create a pore or hole in a lipid bilayer. The skilled artisan would have understood that such a pore or a hole would not have been desirable because it can result in drug leakage.

Therefore, the skilled artisan would have been motivated to have undertaken modifications to the liposome that would result in less degradation of phosphatidylcholine to lysophosphatidylcholine in order to have predictably reduced drug leakage. Nevertheless, the skilled artisan would not have known that the claimed lipids, product-by-process and sucrose octasulfate concentration would have resulted in less degradation of phosphatidylcholine to lysophosphatidylcholine as compared with the prior art.

As such, Israelachvili further speaks to the practical utility of reducing degradation of phosphatidylcholine to lysophosphatidylcholine and further bolster's the examiner's case for not rejecting the instant claims over prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Terminal Disclaimers

The terminal disclaimers filed on 11 January 2021 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of

US Patent 10,456,360; and

US application 17/011,617

have been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F Krass can be reached on (571)272-0580. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

Examiner-Initiated Interview Summary	**Application No.** 16/567,902	**Applicant(s)** Drummond et al.		
	Examiner ISAAC SHOMER	**Art Unit** 1612	**AIA (First Inventor to File) Status** Yes	**Page** **1 of 2**

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
ISAAC SHOMER	Primary Examiner	Telephonic
Deborah Herzfeld	Attorney of Record	

Date of Interview: 24 February 2021

Issues Discussed:

35 U.S.C. 112

Examiner called representative of applicant requesting cancellation of claim 37 in an examiner's amendment. Examiner explained that the reason cancellation is requested is because this claim appears to fail to further limit the claim it is dependent upon, and as such would be rejected under 35 U.S.C. 112(d). The examiner also explained that this claim would appear to be rejected under 35 U.S.C. 112(b) in view of the provisions of MPEP 2173.05(p)(II).

In response, representative of initially applicant took the position that claim 37 is definite because it is a product-by-process claim. The examiner verbally disagreed, and explained that the process recited in claim 37 is performed on the product is formed. In contrast, the the examiner took the position that the process steps in a product-by-process claim (such as claim 24) are process steps of making the claimed product, not process steps conducted on the claimed product after the claimed product is formed.

After this discussion, representative of applicant consulted with applicant. After said consultation with applicant, representative of applicant informed examiner that applicant agreed to the cancellation of claim 37 in an examiner's amendment. As such, this interview summary has been attached to a notice of allowance including an examiner's amendment canceling claim 37.

/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general

indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/711,072	12/11/2019	Eliel Bayever	01208-0003-04US	9819

153749 7590 12/10/2021

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
12/10/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 16/711,072	Applicant(s) Bayever et al.	
	Examiner BONG-SOOK BAEK	Art Unit 1611	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 7-23 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 7-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 8/7/2020 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Status of claims

Claims 1-6 have been canceled. Claims 7-23 are under examination in the instant office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 7-9, 12-13, 16, and 18-23 are rejected under 35 U.S.C. 103 as being unpatentable over US 20070110798 (cited in the IDS filed on 8/10/2020) in view of Hayashi *et al.* (Breast Cancer, 20:131-136, 2013, Epub, Nov. 29, 2011, cited in the IDS filed on 8/10/2020) in further view of Chen *et al.* (Journal of Clinical Oncology 26, no. 15_suppl, May 20 2008; cited in the IDS filed on 10/2/2020).

US 20070110798 discloses that a liposomal composition comprising a camptothecin compound such as irinotecan (CPT-11) has an anticancer activity at least two times, four times, or ten times higher than the camptothecin compound similarly administered in the absence of the composition, while the toxicity of the composition does not exceed, is at least two times, or at least four times lower than the toxicity of the camptothecin compound similarly administered in the absence of the composition ([0010]). US 20070110798 further discloses antitumor efficacy of CPT-11 liposomes (drug/phospholipid ratio 192 mg/mmol; average liposome size 86.8 nm) in the model of human breast carcinoma BT-474 and U87 tumors implanted within brain wherein greater anti-tumor activity with CPT-11 liposomes treatment were shown compared with free CPT-11 ([0184], [0185], [0330] and Fig. 3 and 49). US 20070110798 further discloses the liposome formulation of CPT-11 showed extended blood life, sustained release characteristics, and increased antitumor activity in the studied tumor model without an appreciable increase in toxicity ([0187] and Fig, 4). In addition, US 20070110798 discloses that the camptothecin compound encapsulated in a liposome provides an increased mean residence time of the camptothecin compound in the brain of a subject and the mean residence time of the liposomal drug in the healthy brain was at comparable infusate concentration (3 mg/mL) 24 times higher than that of the free CPT-11 (as a hydrochloride trihydrate salt, dissolved) and the mean residence time of the drug in the tumor

tissue, at equal drug concentration in the infusate, was 4 times higher than in the normal brain ([0016] and [0327]).

US 20070110798 specifically discloses unilamellar liposomes (lipid bilayer vesicles) loaded with CPT-11 (irinotecan as a hydrochloride trihydrate salt) in a gelated or precipitated state, yielding a final diameter of 95-110 nm and the drug/lipid ratio of about 500 mg/mmol phospholipid, wherein liposomes with entrapped triethylammonium sucrose octasulfate(TEA-SOS) (0.65 M TEA, pH 6.4, osmolality 485 mmol/kg) and lipid composition of 1,2-Distearoyl-SN-phosphatidylcholine (DSPC), Cholesterol, and poly(ethylene glycol) (MW 2000)-derivatized distearoylphosphatidylethanolamine (PEG-DSPE) such as N-(omega-methoxy-poly(ethylene glycol)-oxycarbonyl)-1,2-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) in a molar ratio of 3:2:0.015 were prepared (abstract, [0003], [0081], [0116], [0169], [0172], [0178], [0313], and [0327]). US 20070110798 further discloses that liposomal CPT-11 (Ls-CPT-11) was prepared, using lipid matrix of DSPC (M.W.790) 3 mol. parts, Cholesterol (M.W. 387) 2 mol. parts, PEG-DSPE (M.W. 2750) 1 mol. part; entrapped solution TEA-SOS having 0.65 M TEA, pH 6.4; drug loaded into liposomes in 5 mM HEPES buffer, 5% dextrose, pH 6.5, at 60.degree. C. for 30 min at the input drug/lipid ratio 500 mg drug/mmol of phospholipid and loading efficiency was greater than 99% and liposome size (volume average mean ±standard deviation by QELS): 101±37 nm. ([0116], [0150], [0169], [0172], and [0210]). Based on the disclosed molar ratios and molecular weights of DSPC, cholesterol and MPEG-2000-DSPE in liposome one of ordinary skilled artisan would arrive at the suitable amounts in mg/ml as claimed.

US 20070110798 further discloses that the liposome composition of the present invention can be administered in any way which is medically acceptable which may depend on the condition or injury being treated and possible administration routes include injections, by

parenteral routes such as intramuscular, subcutaneous, intravenous, intraarterial, intraperitoneal, intraarticular, intraepidural, intrathecal, or others ([0134]).

While US 20070110798 discloses antitumor activity of liposomal irinotecan in the model of human breast carcinoma and brain tumor, the reference does not specifically disclose administering once every two weeks at a dose of 60 mg/m^2 for the treatment of metastatic breast cancer with active brain metastasis or HER2 or triple negative metastatic breast cancer.

Hyashi *et al.* disclose phase II study of bi-weekly irinotecan for patients with previously treated HER2-negative metastatic breast cancer (MBC) including triple-negative breast cancer (TNBC), wherein eligible patients were HER2-negative, had a performance status of 0 to 2, and had been treated previously with either anthracyclines or taxanes for MBC (Title, Abstract and p133, Patient Charactersitics). Hyashi *et al.* further disclose that patients received irinotecan intravenously at 150 mg/ m^2 on days 1 and 15 every 4 weeks (once every two weeks) and biweekly administration of 150 mg/ m^2 irinotecan was feasible for patients with MBC treated previously with anthracyclines or taxanes (abstract).

Chen *et al*. discloses phase I study of liposome encapsulated irinotecan (PEP02), which is a novel nanoparticle liposome formulation of irinotecan aiming to enhance tumor localization and improve pharmacokinetic properties of irinotecan and its active metabolite-SN38, in advanced refractory solid tumor patients wherein PEP02 was given as 90 mins i.v. infusion, repeated every 3 weeks and the doses would have been escalated from 60, 120, 180 to 240 mg/m2 in a single-patient cohort accelerated titration design (Title, Methods, and Results).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use liposomal irinotecan taught by US 20070110798 for treating metastatic breast cancer with active brain metastasis because anti-

tumor efficacies of liposomal irinotecan in both breast and brain cancer models are already disclosed by US 20070110798 and irinotecan was taught to be effective for treating metastatic breast cancer such as HER2-negative metastatic breast cancer including TNBC as evidenced by Hyashi *et al*. Also, US 20070110798 teaches that liposomal irinotecan has extended blood life, sustained release characteristics, increased antitumor activity in breast cancer model, and higher residence time in brain without an appreciable increase in toxicity compared with free irinotecan. Thus, one of ordinary skill in the art would have been motivated to use the liposomal irinotecan taught by US 20070110798 in the treatment of breast cancer such as HER2-negative metastatic breast cancer and TNBC with active brain metastasis on the reasonable expectation that it would be more effective in the treatment of both breast cancer and brain metastasis than free irinotecan due to its increased residence time in brain and higher efficacy without an appreciable increase in toxicity compared with free irinotecan.

As to the dose of 60 mg/m^2, Hyashi *et al.* already disclose intravenously administering free irinotecan at 150 mg/m^2 once every two weeks in the treatment of HER2-negative metastatic breast cancer and US 20070110798 discloses that the liposomal composition comprising irinotecan (CPT-11) has an anticancer activity at least two times, four times, or ten times higher than free irinotecan (not in liposomal formulation). Thus, one of ordinary skill in the art would have been motivated to use liposomal irinotecan at a dose less than half the dose of free irinotecan taught by Hyashi *et al.* (e.g., less than 75 mg/ m^2) on the reasonable expectation that liposomal irinotecan at a dose less than half the dose of free irinotecan would provide anticancer activity comparable to free irinotecan. In addition, Chen *et al.* teaches titration of the dose of liposomal irinotecan (PEP02) from 60, 120, 180 to 240 mg/ m^2. Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the

claimed invention to optimize the dose of the liposomal irinotecan for getting desired effects based on the effective dosing ranges disclosed in the prior art in combination. Also, the claimed range falls within the range disclose in the prior art in combination. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Furthermore, "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). In addition, it is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ 33; *In re Russell*, 169 USPQ 426. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

As to claims 12-13, US 20070110798 does not specifically disclose that the patient has failed at least one prior platinum- based chemotherapy regimen, has failed prior treatment with gemcitabine, and/or has become resistant to gemcitabine. However, Hyashi *et al.* disclose that irinotecan was effective for patients previously treated with other chemotherapeutic agents such as anthracyclines or taxanes for MBC. Thus, one of ordinary skill in the art would have been motivated to use the liposomal irinotecan taught by US 20070110798 as an alternative treatment for patients who failed at least one prior platinum-based chemotherapy regimen or gemcitabine, and/or has become resistant to gemcitabine. It would have obvious to use alternative cancer

treatment for MBC such as liposomal irinotecan taught by US 20070110798 and Hyashi *et al.* when the other existing anticancer therapy was not working because irinotecan was taught to be effective for those cancers. This is what a person of ordinary skill in the corresponding art normally does.

Claims 10-11 are rejected under 35 U.S.C. 103 as being unpatentable over US 20070110798 (cited in the IDS filed on 8/10/2020) in view of Hayashi *et al.* (Breast Cancer, 20:131-136, 2013, Epub, Nov. 29, 2011, cited in the IDS filed on 8/10/2020) and Chen *et al.* (Journal of Clinical Oncology 26, no. 15_suppl, May 20 2008; cited in the IDS filed on 10/2/2020), in further view of Chang *et al.*(Neurosurgery, Volume 53, Issue 2, August 2003, Pages 272–281)

US 20070110798, Hayashi *et al. and* Chen *et al.* as applied *supra* are herein applied for the same teachings in their entirety.

US 20070110798 does not specifically teach that the active brain metastasis is at least one new or progressive brain metastasis after prior radiation therapy which is greater than or equal to 1 cm in longest diameter as recited in claim 10-11.

However, it was known in the art that tumor size in the radiosurgical management of patient with brain metastases in various cancers including breast cancer is measured using MRI and 1 cm in longest diameter is a cutoff size for radiosurgical control of small brain metastases (abstract and p273, table 1). Thus, one of ordinary skill in the art would have recognized that those patients with active brain metastasis the size of which is greater than or equal to 1 cm in longest diameter after prior radiation therapy would need alternative treatment and thus would have been motivated to use the liposomal irinotecan taught by US 20070110798 as an alternative

treatment for patients with new or progressive brain metastasis not controlled by radiation therapy. It would have obvious to use alternative cancer treatment for MBC such as liposomal irinotecan taught by US 20070110798 and Hyashi *et al.* when the prior radiation therapy was not working because irinotecan was taught to be effective for those cancers. This is what a person of ordinary skill in the corresponding art normally does.

Claims 14-15 are rejected under 35 U.S.C. 103 as being unpatentable over US 20070110798 (cited in the IDS filed on 8/10/2020) in view of Hayashi *et al.* (Breast Cancer, 20:131-136, 2013, Epub, Nov. 29, 2011, cited in the IDS filed on 8/10/2020) and Chen *et al.* (Journal of Clinical Oncology 26, no. 15_suppl, May 20 2008; cited in the IDS filed on 10/2/2020) in further view of US 2007/0219268 ((cited in the IDS filed on 8/10/2020).

US 20070110798, Hayashi *et al. and* Chen *et al.* as applied *supra* are herein applied for the same teachings in their entirety.

US 20070110798 does not specifically teach pre-medicating with at least one anti-emetic such as 5-HT3 antagonist or dexamethasone as recited in claims 14-15.

However, it was well known in the art that prior to chemotherapy, pre-medications such as anti-emetics and steroid such as dexamethasone are administered and at least one anti-emetic such as 5-HT3 antagonist is pre-medicated before the treatment with a chemotherapeutic agent including irinotecan for preventing vomiting (abstract, [0119] and [0142]). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to pre-medicate with dexamethasone or at least one anti-emetic such as 5-HT3 antagonist prior to administering liposomal irinotecan as taught by US 20070110798 in the treatment of metastatic breast cancer with active brain metastasis because providing pre-

medications such as anti-emetics and steroid such as dexamethasone was well known practice in the chemotherapy as evidenced by US 20070110798 and vomiting is a known adverse event related with irinotecan treatment as evidenced by Hayashi *et al.* (see p134, Toxicity section and Table 2). One of ordinary skill in the art would have been motivated to do so for preventing symptoms treatable with dexamethasone and vomiting caused by anti-cancer treatment.

Claim 17 is rejected under 35 U.S.C. 103 as being unpatentable over US 20070110798 (cited in the IDS filed on 8/10/2020) in view of Hayashi *et al.* (Breast Cancer, 20:131-136, 2013, Epub, Nov. 29, 2011, cited in the IDS filed on 8/10/2020) and Chen *et al.* (Journal of Clinical Oncology 26, no. 15_suppl, May 20 2008; cited in the IDS filed on 10/2/2020), in further view of US 2014/0170075 (cited in the IDS filed on 8/10/2020).

US 20070110798, Hayashi *et al. and* Chen *et al.* as applied *supra* are herein applied for the same teachings in their entirety.

US 20070110798 does not specifically teach administering a ferumoxytol infusion followed by an MRI scan prior to treatment with the liposomal irinotecan as recited in claim 17.

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent

(abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor, a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, or Ewing's sarcoma ([0068] and claims 14-16). US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]). The reference specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg and then were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0139], and Examples 9-10 and Figs. 6-8).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to administer ferumoxytol infusion followed by an MRI scan prior to treatment with the liposomal irinotecan because US 2014/0170075 teaches that

treatment with FMX followed by MRI prior to administration of nanoliposomal therapeutics such as liposomal irinotecan allows for selection patients who will (or will not) benefit from nanoliposomal therapy and identifies as having sites of pathology that are predicted to exhibit nanoparticle accumulation. Thus, one of ordinary skill in the art would have been motivated to do so on the reasonable expectation that treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy as taught by US 2014/0170075.

Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the

examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 7-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of US Patent 9895365 in view of US 20070110798.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '365 patent are drawn to a method of treating triple negative breast cancer by administering the same liposomal irinotecan once every two weeks as claimed.

The claims of the patent does not specifically teaches that the breast cancer has active brain metastasis. However, US 20070110798 discloses that a liposomal composition comprising a camptothecin compound such as irinotecan (CPT-11) has an anticancer activity at least two times, four times, or ten times higher than the camptothecin compound similarly administered in the

absence of the composition, while the toxicity of the composition does not exceed, is at least two times, or at least four times lower than the toxicity of the camptothecin compound similarly administered in the absence of the composition ([0010]). US 20070110798 further discloses antitumor efficacy of CPT-11 liposomes (drug/phospholipid ratio 192 mg/mmol; average liposome size 86.8 nm) in the model of human breast carcinoma BT-474 and U87 tumors implanted within brain wherein greater anti-tumor activity with CPT-11 liposomes treatment were shown compared with free CPT-11 ([0184], [0185], [0330] and Fig. 3 and 49). US 20070110798 further discloses the liposome formulation of CPT-11 showed extended blood life, sustained release characteristics, and increased antitumor activity in the studied tumor model without an appreciable increase in toxicity ([0187] and Fig, 4). In addition, US 20070110798 discloses that the mean residence time of the liposomal drug in the healthy brain was at comparable infusate concentration (3 mg/mL) 24 times higher than that of the free CPT-11 (as a hydrochloride trihydrate salt, dissolved) and the mean residence time of the drug in the tumor tisse, at equal drug concentration in the infusate, was 4 times higher than in the normal brain ([0327]).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use liposomal irinotecan for treating triple negative breast cancer with active brain metastasis or HER2 negative metastatic breast cancer because anti-tumor efficacies of liposomal irinotecan in both breast and brain cancer models are already disclosed by US 20070110798. Also, US 20070110798 teaches that liposomal irinotecan has extended blood life, sustained release characteristics, increased antitumor activity in breast cancer model, and higher residence time in brain without an appreciable increase in toxicity compared with free irinotecan. Thus, one of ordinary skill in the art would have been motivated to use the liposomal irinotecan taught by US 20070110798 in the treatment of breast cancer such

as TNBC with active brain metastasis on the reasonable expectation that it would be more effective in the treatment of both breast cancer and brain metastasis than free irinotecan due to its increased residence time in brain and higher efficacy without an appreciable increase in toxicity compared with free irinotecan. As to the dose of 60 mg/m^2, while the claims of the patent recite the dose of 70 mg/m^2, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to adjust the dose of the liposomal irinotecan for getting desired effects. A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

As such, the instant claims would have been obvious over the reference claims

Claims 7-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-37 of co-pending application 16/586609 in view of US 20070110798.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '609 application are drawn to a method of treating a solid tumor such as triple negative breast cancer by administering the same liposomal irinotecan once every two weeks as claimed.

The claims of the copending application does not specifically teaches that the breast cancer has active brain metastasis. However, US 20070110798 discloses that a liposomal composition

comprising a camptothecin compound such as irinotecan (CPT-11) has an anticancer activity at least two times, four times, or ten times higher than the camptothecin compound similarly administered in the absence of the composition, while the toxicity of the composition does not exceed, is at least two times, or at least four times lower than the toxicity of the camptothecin compound similarly administered in the absence of the composition ([0010]). US 20070110798 further discloses antitumor efficacy of CPT-11 liposomes (drug/phospholipid ratio 192 mg/mmol; average liposome size 86.8 nm) in the model of human breast carcinoma BT-474 and U87 tumors implanted within brain wherein greater anti-tumor activity with CPT-11 liposomes treatment were shown compared with free CPT-11 ([0184], [0185], [0330] and Fig. 3 and 49). US 20070110798 further discloses the liposome formulation of CPT-11 showed extended blood life, sustained release characteristics, and increased antitumor activity in the studied tumor model without an appreciable increase in toxicity ([0187] and Fig, 4). In addition, US 20070110798 discloses that the mean residence time of the liposomal drug in the healthy brain was at comparable infusate concentration (3 mg/mL) 24 times higher than that of the free CPT-11 (as a hydrochloride trihydrate salt, dissolved) and the mean residence time of the drug in the tumor tisse, at equal drug concentration in the infusate, was 4 times higher than in the normal brain ([0327]).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use liposomal irinotecan for treating triple negative breast cancer with active brain metastasis or HER2 negative metastatic breast cancer because anti-tumor efficacies of liposomal irinotecan in both breast and brain cancer models are already disclosed by US 20070110798. Also, US 20070110798 teaches that liposomal irinotecan has extended blood life, sustained release characteristics, increased antitumor activity in breast cancer model, and higher residence time in brain without an appreciable increase in toxicity

compared with free irinotecan. Thus, one of ordinary skill in the art would have been motivated to use the liposomal irinotecan taught by US 20070110798 in the treatment of breast cancer such as TNBC with active brain metastasis on the reasonable expectation that it would be more effective in the treatment of both breast cancer and brain metastasis than free irinotecan due to its increased residence time in brain and higher efficacy without an appreciable increase in toxicity compared with free irinotecan. As to the dose of 60 mg/m^2, while the claims of the '609 application recites the dose of 70 mg/m^2, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to adjust the dose of the liposomal irinotecan for getting desired effects, A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

As such, the instant claims would have been obvious over the reference claims

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00AM-6:00PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BONG-SOOK BAEK/
Primary Examiner, Art Unit 1611

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/07/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
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Office Action Summary	Application No. 16/906,601	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 28 January 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-31 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21-31 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21-31 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408) in view of Kirpotin (US Patent 6,110,491).

Chou et al. (hereafter referred to as Chou) is drawn to an irinotecan liposome and a method of preparing such a liposome via gradient loading, as of Chou, title and abstract. Chou teaches loading with dextran sulfate.

Chou does not teach polyphosphate with 13-18 phosphate units.

Kirpotin teaches a liposome composition comprising an encapsulated active compound, as of Kirpotin, title and abstract. Said liposome may be loaded with polyphosphate with 13-18 phosphate units, as of Kirpotin, column 13, Example 4, reproduced below.

EXAMPLE 4

Loading of Doxorubicin into Liposomes with Entrapped Sodium Salts of Sulfuric, Phosphoric, Polyvinylsulfuric, or Polyphosphoric Acid

Liposomes were prepared from egg phosphatidylcholine using the procedure identical to Example 1 but instead of polyacrylic acid, the inner buffers contained one of the following salts: sodium sulfate, sodium phosphate, sodium polyvinylsulfate (Fluka, Ronkonkoma, N.Y.; average chain length n=13), or sodium polyphosphate (Sigma Chemical Co.; average chain length n=13–18), at a concentration of 100 mill-equivalents of sodium/L. The liposomes were incubated with doxorubicin (300 nmol/μmol of phospholipid) overnight, free drug was removed from the liposomes, and the liposomes were assayed as described in Example 1. Drug incorporation into the liposomes was as follows (in nmol/μmol of phospholipid): sodium sulfate, 82.1±0.95; sodium phosphate, 76.8±2.3; sodium polyvinylsulfate, 109.8±0.25; sodium polyphosphate, 85.2±2.2; "blank" liposomes, containing 100 mM sodium chloride, 1.03±0.06.

Kirpotin also teaches a polyphosphate as a replacement for a polysulfate, as of Kirpotin, column 2 line 66 to column 3 line 5.

Kirpotin does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted the sodium polyphosphate of Kirpotin in place of the dextran sulfate of Chou to have been used in the liposome of Chou. Chou is drawn to a liposome comprising irinotecan and dextran sulfate, wherein dextran sulfate is used for gradient loading. Chou teaches that polyphosphate with 13-18 phosphate units is also useful with liposomes, apparently for gradient loading. As such, the skilled artisan would have been motivated to have substituted polyphosphate with 13-18 phosphate units, as of Kirpotin, in place of the dextran sulfate of Chou in order to have predictably provided gradient loading with a reasonable expectation of success.

As to claim 21, the claim requires a molar ratio of irinotecan to total lipids that is a minimum of about 0.15:1. Chou teaches a maximum of 0.254 mg drug (irinotecan)/mg lipid, as of Chou, page 407, right column, last full paragraph. The examiner has presented the following calculation to convert this to molar ratio below, using a molecular weight of 586 Daltons for irinotecan and 790.1 Daltons for distearoyl phosphatidylcholine, which is the most prominent lipid, and wherein the active is irinotecan.

$$\left(\frac{0.254\ mg\ active}{1\ mg\ lipid}\right)\times\left(\frac{1\ mmol\ active}{586\ mg\ active}\right)\times\left(\frac{790.1\ mg\ lipid}{1\ mmol\ lipid}\right)\approx 0.342\frac{mmol\ irinotecan}{mmol\ lipid}$$

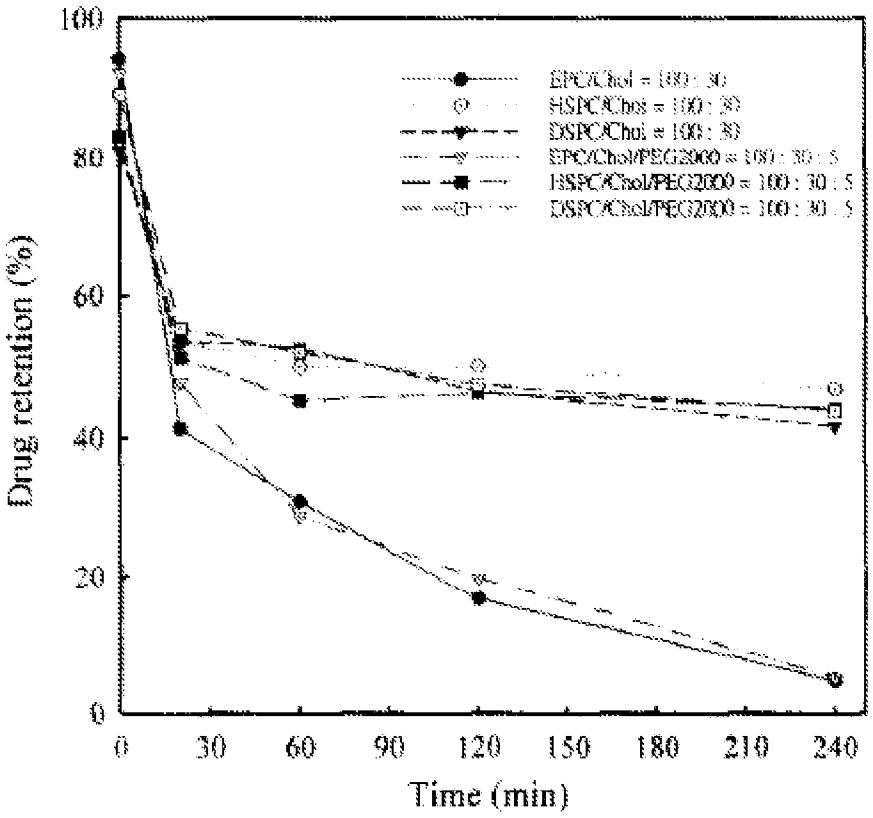
This value of 0.342 moles of irinotecan per moles of lipid is within the claimed range of 0.15:1 to 1.5:1 of irinotecan to total lipids by molar ratio.

As to claim 22, Chou teaches the following, as of page 406, right column, top paragraph.

> A pH gradient of 3.7 was subsequently used to improve the uptake of irinotecan. Figure 1 plots the leakage of irinotecan from liposomes that were composed of EPC/cholesterol, EPC/cholesterol/DSPE-PEG_{2000}, HSPC/cholesterol, HSPC/cholesterol/DSPE-PEG_{2000}, DSPC/cholesterol, and DSPC/cholesterol/DSPE-PEG_{2000} at 37°C as a function of time. Certain amounts of the encapsulated drug (approach-

The EPC, HSPC, and DSPC are understood to read on the required lecithin, as phosphatidylcholine and lecithin are synonyms. Chou also teaches cholesterol as of the above-reproduced text.

As to claims 23-24, Chou teaches the following, as of page 406, right column, figure 1, reproduced below.



Chou teaches a 100:30 ratio of DSPC to cholesterol in the above-reproduced chart. It is unclear whether this ratio would have been a mass ratio or a mole ratio. Nevertheless, even if, purely *en arguendo*, the ratio of DSPC to cholesterol in Chou differs from the claimed ratio, this is insufficient to overcome the applied obviousness rejection. This is because generally, differences in concentration between the prior art and claimed invention will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. See MPEP 2144.05(II)(A). In this case, no such evidence of criticality appears to have been presented. Additionally, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See MPEP 2144.05(II)(A). In this case, the general conditions of the instant claims are a liposome comprising phosphatidylcholine, cholesterol, and

irinotecan, and this is taught by the Chou reference. As such, it would not have been inventive for the skilled artisan to have discovered optimum or workable ranges of phosphatidylcholine and cholesterol via routine experimentation.

As to claims 25-27, Chou teaches DSPE-PEG_{2000}, as of Chou, page 406, right column, first full paragraph, reproduced above. This reads on the requirements of these claims.

As to claims 28-29, Chou teaches DSPC, cholesterol, and DSPE-PEG_{2000}, as explained above. It would not have been obvious for the skilled artisan to have optimized the concentrations of these ingredients to have achieved the claimed concentrations.

As to claims 30-31, these claims are drawn to specific ratios of irinotecan to encapsulating agent, which is polyphosphate in the case of the instant claims. Chou provides teachings on page 407, left column, bottom paragraph, and page 407, figure 4, which would appear to motivate the skilled artisan to have varied the concentration of dextran sulfate, which would have resulted in the ratio of irinotecan with respect to dextran sulfate having been varied. As it would have been obvious for the skilled artisan to have substituted polyphosphate in place of dextran sulfate, the skilled artisan would have similarly been motivated to have modified the ratio of irinotecan to polyphosphate. As such, the ratio of irinotecan to gradient loading material appears to be a result effective variable. The presence of a known result-effective variable would be one, but not the only, motivation for a person of ordinary skill in the art to experiment to reach another workable product or process; see MPEP 2144.05(II)(B), last line of last paragraph in section.

Examiner's Suggestion - Claim Amendment to Overcome Applied Rejection

The examiner provides the following suggestion regarding an examiner-proposed claim amendment to overcome the applied obviousness rejection.

Claim 21 (Proposed Amendment): A pharmaceutical composition comprising irinotecan liposomes encapsulating irinotecan and a polyphosphate having 13-18 phosphate units per polyphosphate molecule, said composition having a **[[** ~~molar~~ **]]** **mass** ratio of irinotecan to total lipids **entrapped in the liposome** ranging from **[[** ~~0.15:1 to 1.5:1~~ **]]** **0.35 mg irinotecan per mg lipid to 0.65 mg irinotecan per mg lipid**.

The proposed examiner's amendment appears to be supported in the manner required by 35 U.S.C. 112(a) as of the instant specification, pages 33-34, paragraph 0109, relevant text reproduced below from page 34.

> units by a routine calculation, as exemplified below. The weight ratio of an entity in the liposomes of the present invention is typically at least 0.05, 0.1, 0.2, 0.35, 0.5, or at least 0.65 mg of the entity per mg of lipid. In terms of molar ratio, the entity-to-lipid ratio according to

That the active agent (in this case irinotecan) is entrapped in the liposome is evidenced as of page 33, paragraph 0109. The term "entrapped" is understood by the examiner to have the same meaning as the term "encapsulated."

The "entity" in the above-reproduced text refers to the therapeutic active agent, which in this case is irinotecan.

The proposed examiner's amendment overcomes the applied rejection over Chou in view of Kirpotin. Chou teaches a maximum of 0.254 mg drug (irinotecan)/mg lipid, as of Chou, page 407, right column, last full paragraph. In contrast, the minimum encapsulation level in the proposed examiner's amendment is 0.35 mg irinotecan per mg lipid. As such, the instant claims require that a larger amount of irinotecan active agent be encapsulated as compared with what is taught by Chou.

The examiner further takes the position that it would not have been prima facie obvious for the skilled artisan to have optimized the composition of Chou to have encapsulated the amount of irinotecan recited by the claims of the proposed amendment. Even if, purely *en arguendo*, the skilled artisan would have been motivated to have modified Chou to have added more irinotecan, there would have been no reasonable expectation that the additionally added irinotecan would have been successfully encapsulated by the liposome. Chou appears to teach that 0.254 mg irinotecan per mg lipid is the maximum encapsulation level of irinotecan achievable, as of Chou, page 407, right column, last full paragraph. As such, there would have been no expectation that increasing the encapsulated amount of irinotecan would have been possible based upon the teachings of Chou. As applicant has encapsulated a greater amount of irinotecan than what was envisioned by Chou, the proposed examiner's amendment would appear to overcome the applied obviousness rejection.

The examiner clarifies that the proposed examiner's amendment, while sufficient to overcome the applied obviousness rejection, is not sufficient to overcome the applied double patenting rejections set forth below.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 10,350,201 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 10,413,510 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a composition comprising liposomes comprising irinotecan and a polyphosphate having 13-18 phosphate units. The claims require a range of irinotecan to total lipids of 0.15:1 to 1.5:1.

The conflicting claims are drawn to a composition comprising liposomes comprising irinotecan and either triphosphate (in the ‘510 patent) or pyrophosphate (in the ‘201 patent). The claims require a range of irinotecan to total lipids of 0.15:1 to 1.5:1.

The conflicting claims appear to differ from the instantly claimed invention because the conflicting claims do not require polyphosphate.

Kirpotin teaches a liposome composition comprising an encapsulated active compound, as of Kirpotin, title and abstract. Said liposome may be loaded with polyphosphate with 13-18 phosphate units, as of Kirpotin, column 13, Example 4, reproduced below.

EXAMPLE 4

Loading of Doxorubicin into Liposomes with Entrapped Sodium Salts of Sulfuric, Phosphoric, Polyvinylsulfuric, or Polyphosphoric Acid

Liposomes were prepared from egg phosphatidylcholine using the procedure identical to Example 1 but instead of polyacrylic acid, the inner buffers contained one of the following salts: sodium sulfate, sodium phosphate, sodium polyvinylsulfate (Fluka, Ronkonkoma, N.Y.; average chain length n=13), or sodium polyphosphate (Sigma Chemical Co.; average chain length n=13–18), at a concentration of 100 mill-equivalents of sodium/L. The liposomes were incubated with doxorubicin (300 nmol/μmol of phospholipid) overnight, free drug was removed from the liposomes, and the liposomes were assayed as described in Example 1. Drug incorporation into the liposomes was as follows (in nmol/μmol of phospholipid): sodium sulfate, 82.1±0.95; sodium phosphate, 76.8±2.3; sodium polyvinylsulfate, 109.8±0.25; sodium polyphosphate, 85.2±2.2; "blank" liposomes, containing 100 mM sodium chloride, 1.03±0.06.

Kirpotin also teaches a polyphosphate as of column 4 lines 20-34, reproduced below.

> In one general embodiment, the compound, when ionized, has a net positive charge, and the precipitating agent is a multivalent acid. The multivalent acid may be a polymer or non-polymer, organic or inorganic. For instance only, the multivalent acid may be a polysulfate, polysulfonate, polyphosphate or polycarboxylate. In an exemplary method, the compound is doxorubicin, or an analog thereof, and the precipitating agent is tartrate, citrate, sulfate, phosphate, diethylene thiamine pentacetate, or polyacrylate. is polyacrylate, chondroitin sulfate A, polyvinylsulfuric acid, or polyphosphoric acid. In other words, in this embodiment, the precipitating agent may be polymeric or non-polymeric. The polymeric compounds may be, for example, polyacrylate, chondroitin sulfate A, polyvinyl sulfuric acid, or polyphosphoric acid.

Kirpotin does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted the polyphosphate with 13-18 phosphate units of irinotecan in place of the triphosphate or polyphosphate of the conflicting claims to be combined with irinotecan in the liposome of the conflicting claims. Both polyphosphate, triphosphate, and pyrophosphate appear to comprise multiple repeating phosphate units. As such, these phosphates would have been useful for loading an active agent such as irinotecan. As such, the skilled artisan would have been motivated to have substituted the polyphosphate of Kirpotin with 13-18 phosphate units in place of the triphosphate or pyrophosphate of the conflicting claims in order to have predictably loaded the irinotecan of the conflicting claims into the liposome of the conflicting claims with a reasonable expectation of success. The simple substitution of one element (polyphosphate with 13-18 units) in place of another (triphosphate or pyrophosphate) to achieve predictable results is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 of U.S. Patent No. 9,737,528 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 9,717,723 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,724,303 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,730,891 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 9,782,349 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 10,722,508 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 11,052,079 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 10,456,360 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 10,993,914 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 11,071,726 in view of Kirpotin (US Patent 6,110,491).

Claims 21-31 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-159 of copending Application No. 17/325,337 in view of Kirpotin (US Patent 6,110,491). This is a provisional nonstatutory double patenting rejection.

The instant claims are drawn to a composition comprising liposomes comprising irinotecan and a polyphosphate having 13-18 phosphate units. The claims require a range of irinotecan to total lipids of 0.15:1 to 1.5:1.

The conflicting claims in all of the above applications are drawn to compositions or methods involving compositions comprising liposomes with irinotecan as the active agent and either sucrose octasulfate or inositol hexaphosphate in combination therewith.

The conflicting claims appear to differ from the instantly claimed invention because the conflicting claims do not require polyphosphate. The inositol hexaphosphate in the conflicting claims does not read on the claimed polyphosphate because the inositol hexaphosphate has only six phosphate units, whereas the instant claims require 13-18 phosphate units.

Kirpotin teaches a liposome composition comprising an encapsulated active compound, as of Kirpotin, title and abstract. Said liposome may be loaded with polyphosphate with 13-18 phosphate units, as of Kirpotin, column 13, Example 4, reproduced below.

EXAMPLE 4

Loading of Doxorubicin into Liposomes with Entrapped Sodium Salts of Sulfuric, Phosphoric, Polyvinylsulfuric, or Polyphosphoric Acid

Liposomes were prepared from egg phosphatidylcholine using the procedure identical to Example 1 but instead of polyacrylic acid, the inner buffers contained one of the following salts: sodium sulfate, sodium phosphate, sodium polyvinylsulfate (Fluka, Ronkonkoma, N.Y.; average chain length n=13), or sodium polyphosphate (Sigma Chemical Co.; average chain length n=13–18), at a concentration of 100 mill-equivalents of sodium/L. The liposomes were incubated with doxorubicin (300 nmol/μmol of phospholipid) overnight, free drug was removed from the liposomes, and the liposomes were assayed as described in Example 1. Drug incorporation into the liposomes was as follows (in nmol/μmol of phospholipid): sodium sulfate, 82.1±0.95; sodium phosphate, 76.8±2.3; sodium polyvinylsulfate, 109.8±0.25; sodium polyphosphate, 85.2±2.2; "blank" liposomes, containing 100 mM sodium chloride, 1.03±0.06.

Kirpotin also teaches a polyphosphate as of column 4 lines 20-34, reproduced below.

In one general embodiment, the compound, when ionized, has a net positive charge, and the precipitating agent is a multivalent acid. The multivalent acid may be a polymer or non-polymer, organic or inorganic. For instance only, the multivalent acid may be a polysulfate, polysulfonate, polyphosphate or polycarboxylate. In an exemplary method, the compound is doxorubicin, or an analog thereof, and the precipitating agent is tartrate, citrate, sulfate, phosphate, diethylene thiamine pentacetate, or polyacrylate. is polyacrylate, chondroitin sulfate A, polyvinylsulfuric acid, or polyphosphoric acid. In other words, in this embodiment, the precipitating agent may be polymeric or non-polymeric. The polymeric compounds may be, for example, polyacrylate, chondroitin sulfate A, polyvinyl sulfuric acid, or polyphosphoric acid.

Kirpotin does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted the polyphosphate with 13-18 phosphate units of irinotecan in place of the sucrose octasulfate or inositol hexaphosphate of the conflicting claims to be combined with irinotecan in the liposome of the conflicting claims. Both polyphosphate with 13-18 units, sucrose octasulfate, and inositol hexaphosphate appear to comprise multiple repeating anionic units. As such, these phosphates would have been useful for loading a cationic active agent such as irinotecan. As such, the skilled artisan would have been motivated to have substituted the polyphosphate of Kirpotin with 13-18 phosphate units in place of the sucrose octasulfate or inositol hexaphosphate of the conflicting claims in order to have predictably loaded the irinotecan of the conflicting claims into the liposome of the conflicting claims with a reasonable expectation of success. The simple substitution of one element (polyphosphate with 13-18 units) in place of another (sucrose octasulfate or inositol hexaphosphate) to achieve predictable results is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

With regard to the '726 patent, there do not appear to be common inventors between the '726 patent and the instant application. However, the '726 patent appears to have a common assignment with the instant application. As such, the double patenting rejection over the '726 patent is understood to be proper.

Additional Cited Art

As an additional relevant reference, the examiner cites Rahman et al. (WO 03/030864 A1). Rahman et al. (hereafter referred to as Rahman) is drawn to a

liposomal formulation of irinotecan, as of Rahman, title and abstract. However, Rahman does not teach polyphosphate with 13-18 phosphate units. As the composition of Rahman is not gradient loaded, it does not appear that the skilled artisan would have been motivated to have combined polyphosphate with 13-18 phosphate units with the liposome of Rahman.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached 7:30 AM to 5:00 PM Monday Through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

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ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Gollamundi S. KISHORE
Attorney Docket Number	01208-0007-01US

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	2	EP2861210: Proprietor's response to opponent's reply to proprietor's grounds of appeal following opposition, dated June 30, 2021, D37 (Declaration of Carla Schoonderbeek) including D37A (Directive 2001/20/EC of the European Parliament and of the Counsel of 4 April 2001 ("the Clinical Trials Directive" or CTD)), 26 total pages.	
	3	EP2861210: Proprietor's response to opponent's reply to proprietor's grounds of appeal following opposition, dated June 30, 2021, D38 (Declaration of Grant H. Castle, Ph.D.) including D38A (European Commission: "Communication from the Commission – Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)"), 23 total pages.	
	4	EP2861210: Communication of the Board of Appeals, Preliminary Opinion, dated August 9, 2021, 21 pages.	
	5	EP2861210: Proprietor Response to the Board of Appeals' Preliminary Opinion, dated December 21, 2021, 12 pages.	
	6	EP3266456: EPO Notice of Sandoz AG Opposition dated February 1, 2022, 6 pages.	
	7	EP3266456: Sandoz AG Opposition dated February 1, 2022, 23 pages.	
	8	EP3266456: EPO Notice of Teva Pharmaceuticals Industries Ltd. Opposition dated February 2, 2022, 6 pages.	
	9	EP3266456: Teva Pharmaceutical Industries Ltd. Opposition dated February 2, 2022, 12 pages.	
	10	EP3266456: EPO Notice of Generics [UK] Limited Opposition dated February 4, 2022, 5 pages.	

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	11	EP3266456: Generics [UK] Ltd. Opposition dated February 4, 2022, 13 pages.
	12	EP3266456: EPO Opposition Consolidated List of Citations, February 4, 2022, 2 pages.
	13	EP3266456: Consolidated Opposition dated February, 2022, D1 (CHEN L, et al., "Phase I Study of Liposome Irinotecan (PEP02) in Combination with Weekly Infusion of 5-FU/LV in Advanced Solid Tumors," J Clin Oncol. 28 (15_suppl):abstract e13024 (2010), 2 pages).
	14	EP3266456: Consolidated Opposition dated February, 2022, D2 (CHEN L, et al., "Phase I Study of Biweekly Liposome Irinotecan (PEP02, MM-398) in Metastatic Colorectal Cancer Failed on First-line Oxaliplatin-based Chemotherapy," J Clin Oncol. 30(4_suppl):Abstract 613 (2012), 2 pages).
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	17	EP3266456: Consolidated Opposition dated February, 2022, D5 ((Clinical Trials Identifier NCT01494506: 2012-05-29 version submitted, "A Randomized, Open Label Phase 3 Study of MM-398 Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer." 6 pages).
	18	EP3266456: Consolidated Opposition dated February, 2022, D5a ((Clinical Trials Identifier NCT01494506: 2012-08-08 submitted, "A Randomized, Open Label Phase 3 Study of MM-398, With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients with Metastatic Pancreatic Cancer Who Have Failed Prior Gemcitabine-based Therapy." 7 pages).
	19	EP3266456: Consolidated Opposition dated February, 2022, D6 ((Clinical Trials Identifier NCT01375816: 2011-06-16 version submitted, "A Randomized Phase II Study of PEP02 or Irinotecan in Combination with Leucovorin and 5-Fluorouracil in Second Line Therapy of Metastatic Colorectal Cancer." 6 pages).
	20	EP3266456: Consolidated Opposition dated February, 2022, D7 (TSAI C, et al., "Nanovector-Based Therapies in Advanced Pancreatic Cancer," J Gastroint Oncol 2(3):185-94 (2011)).
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	22	EP3266456: Consolidated Opposition dated February, 2022, D9 (FUSILEV package insert, 2008, 7 pages).
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	29	EP3266456: Consolidated Opposition dated February, 2022, D16 (EP2861210: Communication of the Board of Appeals, Preliminary Opinion, dated August 9, 2021, 21 pages).
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	33	EP3266456: Consolidated Opposition dated February, 2022, D20 (INFANTE J, et al., "Phase I and Pharmacokinetic Study of IHL-305 (PEGylated Liposomal Irinotecan) in Patients with Advanced Solid Tumors," Cancer Chemother Pharmacol. 70(5):699-705 (2012)).
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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2022-03-10
Name/Print	Mary R. Henninger	Registration Number	56992

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(54) Title: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN

(57) Abstract: Provided are methods for treating pancreatic cancer in a patient by administering liposomal irinotecan (MM-398) alone or in combination with additional therapeutic agents. In one embodiment, the liposomal irinotecan (MM-398) is co-administered with 5-fluorouracil and leucovorin.

METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 61/659,211 (filed June 13, 2012) and U.S. Provisional Application No. 61/784,382 (filed March 14, 2013), both of which are incorporated herein by reference.

BACKGROUND

Despite improvements in cancer treatments, there remains a critical need to further improve therapies so as to prolong patients' lives while maintaining quality of life, particularly in the case of advanced cancers such as pancreatic cancers that often are, or become, resistant to current therapeutic modalities.

Incidence of pancreatic cancer has markedly increased during the past several decades. It now ranks as the fourth leading cause of cancer death in the United States. Pancreatic cancer's high mortality rate is due to a dearth of effective therapies and a complete absence of reliably durable therapies. Because of the location of the pancreas, pancreatic cancer is typically not diagnosed until a tumor has become large enough to produce systemic symptoms. This, coupled with the absence of good screening tools and a limited understanding of risk factors, results in patients usually having advanced disease, often advanced metastatic disease, at the time of diagnosis. Metastatic pancreatic cancer has a dismal prognosis and is almost uniformly fatal, with an overall survival rate of less than 4% at 5 years.

Chemotherapy with one or more of 5-fluorouracil (5-FU) and gemcitabine has been shown to prolong survival in pancreatic cancer. Combination therapies including folinic acid (leucovorin or levoleucovorin), 5-fluorouracil, and irinotecan (FOLFIRI), folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX), or, less commonly, a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) are also used to treat some pancreatic cancers. Irinotecan is 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycampothecin, IUPAC name (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate. Irinotecan is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble

analog of the naturally-occurring alkaloid, camptothecin. Also known as CPT-11, irinotecan is currently marketed formulated as an aqueous solution as Camptosar® (irinotecan hydrochloride injection). Topoisomerase I inhibitors such as irinotecan work to arrest uncontrolled cell growth by inhibiting the unwinding of DNA and thereby preventing DNA replication.

The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug. Irinotecan is a prodrug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38. SN-38 is not recognized by P-glycoprotein, a drug transporter that plays an important role in acquired drug resistance by pumping certain drugs out of cells, so irinotecan is likely to be active in tumors resistant to other standard chemotherapies. In the body, SN-38 is cleared via glucuronidation, for which major pharmacogenetic variability has been described, and biliary excretion. These drug properties contribute to the marked heterogeneities in efficacy and toxicity observed clinically with irinotecan. Irinotecan hydrochloride injection is approved in the United States for treatment of metastatic colon or renal cancer and is also used to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

There are few approved treatment options for advanced or metastatic pancreatic cancers, particularly for those of exocrine origin. Single-agent gemcitabine is the current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma. In clinical trials, single-agent gemcitabine has consistently demonstrated a median prolongation of survival of 5 to 6 months and a 1-year survival rate of about 20%. Single agent gemcitabine was also approved as second line treatment for patients previously treated with but no longer responsive to 5-fluorouracil, with a median overall prolongation of survival of 3.9 months.

Based upon what is known of the biology of pancreatic cancer, a variety of targeted agents have been evaluated, but only erlotinib, a protein tyrosine kinase inhibitor targeted to EGFR, has been approved for first-line use in advanced pancreatic cancer, and the approval is only for use in combination with gemcitabine. The co-administration of erlotinib with gemcitabine resulted in a statistically significant benefit in survival, and improvements in median survival (6.4 months vs. 5.9 months), and 1-year survival rate (24% vs. 17%) compared to gemcitabine alone. Clinical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative. Thus, there is an

urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer. The disclosed invention addresses this need and provides other benefits.

SUMMARY

Provided are methods for treating pancreatic cancer in a patient (*i.e.*, a human patient) comprising administering to the patient liposomal irinotecan (e.g., irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398) alone or in combination with 5-fluorouracil (5-FU) and leucovorin (together, 5-FU/LV), according to a particular clinical dosage regimen. Compositions adapted for use in such methods are also provided.

In one aspect, a method for treatment (*e.g.*, effective treatment) of pancreatic cancer in a patient is provided, the method comprising: administering to the patient, and affective amount of liposomal irinotecan, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2. In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

In another aspect, a method for treatment of pancreatic cancer in a patient is provided, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle of administration, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2, and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m^2 to 80 mg/m^2 (*e.g.*, 60 mg/m^2 or 70 mg/m^2 or 80 mg/m^2);

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form, or levoleucovorin) or 400 mg/m^2 (*l* + *d* racemic form).

In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2. In one embodiment, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes.

In another embodiment, the 5-FU is administered intravenously over 46 hours.

In another embodiment, leucovorin is administered intravenously over 30 minutes.

In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

In another embodiment, the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In one embodiment, treating the patient results in a positive outcome, wherein the positive outcome is pathologic complete response (pCR), complete response (CR), partial response (PR) or stable disease (SD). In another embodiment, the combination therapy with liposomal irinotecan, 5-FU and leucovorin results in therapeutic synergy. In another embodiment, the liposomal irinotecan is formulated as irinotecan sucrose octasulfate salt liposome injection (MM-398). Irinotecan sucrose octasulfate salt liposome injection may also be referred to as irinotecan HCl liposome injection because irinotecan HCl is the active pharmaceutical ingredient that is used to load irinotecan into liposomes containing triethylammonium sucrose octasulfate to prepare MM-398 liposomes. This nomenclature may be used even though the hydrochloride ion of the irinotecan HCl reacts with the triethylammonium ion of the triethylammonium sucrose octasulfate to yield triethylammonium chloride (triethylamine hydrochloride), leaving irinotecan sucrose octasulfate salt as the entrapped pharmaceutical agent within the MM-398 liposomes. In another aspect, kits for treating pancreatic cancer in a patient are provided, the kit comprising a dose of liposomal irinotecan and instructions for using liposomal irinotecan as described herein.

In another aspect, kits for treating pancreatic cancer in a patient are provided, the kit comprising a dose of each liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, 5-FU, and leucovorin as described herein.

In one embodiment, the kit encompasses treating an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In one embodiment, the liposomal irinotecan is liposomal irinotecan sucrose octasulfate salt injection (MM-398).

In another aspect, a formulation of liposomal irinotecan for co-administration with 5-fluorouracil (5-FU) and leucovorin in at least one cycle is provided, wherein the cycle is a period of 2 weeks, the formulation of irinotecan is a liposomal formulation of irinotecan, and wherein:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form, or levoleucovorin) or 400 mg/m^2 (*l* + *d* racemic form).

In one embodiment, after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2. In another embodiment, the liposomal irinotecan is administered intravenously over 90 minutes.

In another embodiment, the 5-FU is administered intravenously over 46 hours.

In another embodiment, leucovorin is administered intravenously over 30 minutes.

In another embodiment, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

In another embodiment, the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma,

adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

In another embodiment, the liposomal formulation of irinotecan is irinotecan sucrose octasulfate salt liposome injection.

In another aspect is provided a method of improving chemotherapy outcomes by increasing tumor vascularity, the method comprising administering to a patient having a tumor an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and concomitantly administering an effective amount of a chemotherapy agent other than irinotecan to the patient.

In another aspect is provided irinotecan sucrose octasulfate salt liposome injection for concomitant administration to a patient having a tumor of 1) an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and 2) an effective amount of a chemotherapy agent other than irinotecan.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the anti-tumor activity of MM-398 in an orthotopic pancreatic tumor model expressing luciferase (L3.6pl).

Figure 2 is a graph showing accumulation of SN-38 in tumors following treatment with free irinotecan or liposomal irinotecan (MM-398).

Figure 3 is a graph showing the effect of MM-398 on Carbonic Anhydrase IX Staining in a HT29 Xenograft Model.

Figure 4 shows the effect of MM-398 on perfusion of small molecule Hoechst stain.

Figure 5 summarizes the pharmacokinetics of MM-398 in q3w (irinotecan, liposome + free drug).

Figure 6 summarizes the pharmacokinetics of MM-398 in q3w.

Figure 7 is a schematic illustration of a Phase 3 study design.

DETAILED DESCRIPTION

I. Definitions

As used herein, the term "subject" or "patient" is a human cancer patient.

As used herein, "effective treatment" refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder. A

beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of a cancer. Effective treatment may refer to alleviation of at least one symptom of a cancer. Such effective treatment may, e.g., reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a cancer tumor, and/or may slow growth of a cancer tumor.

The term "effective amount" refers to an amount of an agent that provides the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

The terms "combination therapy," "co-administration," "co-administered" or "concurrent administration" (or minor variations of these terms) include simultaneous administration of at least two therapeutic agents to a patient or their sequential administration within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

The term "monotherapy" refers to administering a single drug to treat a disease or disorder in the absence of co-administration of any other therapeutic agent that is being administered to treat the same disease or disorder.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (*e.g.*, per hour, per day, per week, per month, etc.) to a patient. Such parameters include, *e.g.*, the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, *e.g.*, taken at a single administration, *e.g.,* orally (*e.g.*, as one, two, three or more pills, capsules, etc.) or injected (*e.g.*, as a bolus). Dosage sizes may also relate to doses that are administered continuously (*e.g.*, as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

As used herein, "cancer" refers to a condition characterized by abnormal, unregulated, malignant cell growth. In one embodiment, the cancer is an exocrine pancreatic cancer. In another embodiment, the exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

The terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent.

II. Irinotecan sucrose sulfate liposome injection (MM-398; PEP02)

As provided herein, irinotecan is administered in a stable liposomal formulation as irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"), the formulation referred to herein as "MM-398" (also known as PEP02, see US 8,147,867). MM-398 may be provided as a sterile, injectable parenteral liquid for intravenous injection. The required amount of MM-398 may be diluted, *e.g.*, in 500mL of 5% dextrose injection USP and infused over a 90 minute period.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The

lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules.

This stable liposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process. The long circulating pharmacokinetics and high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR allows for deposition of the liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor.

Pharmacogenetics of Irinotecan Glucuronidation

The enzyme produced by the UGT1A1 gene, UDP-glucuronosyltransferase 1, is responsible for bilirubin metabolism and also mediates SN-38 glucuronidation, which is the initial step in the predominant metabolic clearance pathway of this active metabolite of irinotecan. Besides its anti-tumor activity, SN-38 is also responsible for the severe toxicity sometimes associated with irinotecan therapy. Therefore, the glucuronidation of SN-38 to the inactive form, SN-38 glucuronide, is an important step in the modulation of irinotecan toxicity.

Mutational polymorphisms in the promoter of the UGT1A1 gene have been described in which there is a variable number of thymine adenine (ta) repeats. Promoters containing seven thymine adenine (ta) repeats (found in the UGT1A1*28 allele) have been found to be less active than the wild-type six repeats, resulting in reduced expression of UDP-glucuronosyltransferase 1. Patients who carry two

deficient alleles of UGT1A1 exhibit reduced glucuronidation of SN-38. Some case reports have suggested that individuals who are homozygous for UGT1A1*28 alleles (referred to as having the UGT1A1 7/7 genotype, because both alleles are UGT1A1*28 alleles that contain 7 ta repeats, as opposed to the wild-type UGT1A1 6/6 genotype in which both alleles contain 6 ta repeats) and who have fluctuating elevation in serum bilirubin, (*e.g.*, Gilbert's Syndrome patients), may be at greater risk of toxicity upon receiving standard doses of irinotecan. This suggests that there is a link between homozygosity of the UGT1A1*28 allele, bilirubin levels and irinotecan toxicity.

The metabolic transformation of MM-398 to SN-38 (*e.g.*, in plasma) includes two critical steps: (1) the release of irinotecan from the liposome and (2) the conversion of free irinotecan to SN-38. While not intending to be limited by theory, it is believed that once irinotecan leaves the liposomes, it is catabolized by the same metabolic pathways as conventional (free) irinotecan. Therefore the genetic polymorphisms in humans predictive for the toxicity and efficacy of irinotecan and those of MM-398 can be considered similar. Nonetheless, due to the smaller tissue distribution, lower clearance, higher systemic exposure and longer elimination half-life of SN-38 of the MM-398 formulation compared to free irinotecan, the deficient genetic polymorphisms may show more association with severe adverse events and/or efficacy.

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) have been shown to be at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan (Camptosar®), in a study of 66 patients who received single-agent irinotecan (350 mg/m2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. Importantly, no grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype). In other studies, a lower prevalence of life threatening neutropenia is described. For this reason, patients who are enrolled in the phase 3 study described in the Examples herein and are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) will have MM-398 treatment initiated at

a lower dose than patients with one (*e.g.*, UGT1A1 6/7) or two (UGT1A1 6/6) wild-type alleles.

Additional genotypic modifiers of irinotecan metabolism

Although the UGT1A1*28 allele is relatively common in Caucasians (estimates 10%), the prevalence is varied in other ethnic groups. Furthermore, additional UGT1A1 genotypes are found with higher prevalence for example in Asian populations and these could be important for the metabolism of irinotecan in these populations. For example, the UGT1A1*6 allele is more prevalent in Asians. This allele is not associated with a ta repeat, but with a Gly71Arg mutation that reduces enzyme activity. In previous and ongoing studies of MM-398, pharmacogenetic information has been collected on patients being enrolled. In a study referred to as the PEP0203 study, the relationship of genetic polymorphism of UGT1A family and of DPYD (dihydropyrimidine dehydrogenase, an enzyme associated with catabolism of 5-FU) with pharmacokinetic parameters of MM-398 and toxicity did not provide a clear correlation with the small sample size of subjects evaluated. However, it was observed that patients with UGT1A1*6/*28 combined polymorphism had higher dose-normalized AUCs of SN-38 and experienced DLT.

III. 5-Fluorouracil (5-FU) and Leucovorin

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

Leucovorin (also called folinic acid) acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

Leucovorin has dextro- and levo-isomers, only the latter one being pharmacologically useful. As such, the bioactive levo-isomer ("levoleucovorin") has

also been approved by the FDA for treatment of cancer. The dosage of levoleucovorin is typically half that of the racemic mixture containing both dextro (*d*) and levo (*l*) isomers.

FU and leucovorin will be stored and handled according to the country specific package inserts.

IV. Administration

Liposomal irinotecan is administered intravenously, either alone or in combination with 5-fluorouracil (5-FU) and/or leucovorin. In one embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin. In another embodiment, leucovorin is administered prior to 5-FU. In another embodiment, liposomal irinotecan is administered intravenously over 90 minutes. In another embodiment, 5-FU is administered intravenously over 46 hours. In another embodiment, leucovorin is administered intravenously over 30 minutes. In various embodiments the liposomal irinotecan is MM-398.

V. Patient Populations

In one embodiment, a patient treated using the methods and compositions disclosed herein exhibits evidence of recurrent or persistent pancreatic cancer following primary chemotherapy.

In another embodiment, the patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

In one embodiment a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

In another embodiment, the pancreatic cancer of the patient undergoing treatment is advanced pancreatic cancer, which is a pancreatic tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor.

The compositions and methods disclosed herein are useful for the treatment of all pancreatic cancers, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments.

VI. Combination Therapy

In one embodiment, liposomal irinotecan is co-administered to patients having pancreatic cancer in combination with 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen, such as those described herein. In one embodiment, the liposomal irinotecan is MM-398.

As used herein, adjunctive or combined administration (coadministration) includes simultaneous administration of the compounds in the same or different dosage form, or separate administration of the compounds (e.g., sequential administration). For example, liposomal irinotecan can be simultaneously administered with 5-FU and leucovorin. Alternatively, liposomal irinotecan can be administered in combination with 5-FU and leucovorin, wherein liposomal irinotecan, 5-FU and leucovorin are formulated for separate administration and are administered concurrently or sequentially. For example, liposomal irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the 5-FU and leucovorin. Such concurrent or sequential administration preferably results in liposomal irinotecan, 5-FU, and leucovorin being simultaneously present in treated patients. In a particular embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin. In another particular embodiment, leucovorin is administered prior to 5-FU.

In another embodiment, liposomal irinotecan, 5-FU, and leucovorin are formulated for intravenous administration. In a particular embodiment, the patient is administered an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a) liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2; (b) 5-FU is administered at a dose of 2400 mg/m^2; and (c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form) In a particular embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2.

In one embodiment, liposomal irinotecan may be initially administered at a high dose and may be lowered over time. In another embodiment, liposomal

irinotecan is initially administered at a low dose and increased over time. In one embodiment, liposomal irinotecan is administered as a monotherapy.

In another embodiment, the dose of 5-FU is varied over time. For example, 5-FU may be initially administered at a high dose and may be lowered over time. In another embodiment, 5-FU is initially administered at a low dose and increased over time.

In another embodiment, the dose of leucovorin is varied over time. For example, leucovorin may be initially administered at a high dose and may be lowered over time. In another embodiment, leucovorin is initially administered at a low dose and increased over time.

VII. Treatment Protocols

Suitable treatment protocols include, for example, those wherein the patient is administered an effective amount of liposomal irinotecan, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2. In one embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

In another embodiment, the treatment protocol includes administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the treatment comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle: (a) liposomal irinotecan is administered on day 1 of the cycle at a dose of 80 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 60 mg/m^2; (b) 5-FU is administered at a dose of 2400 mg/m^2; and (c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form). In a particular embodiment, the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle to 80 mg/m^2.

VIII. Outcomes

Provided herein are methods for treating pancreatic cancer in a patient comprising administering to the patient liposomal irinotecan (MM-398), alone or in combination with 5-fluorouracil (5-FU) and leucovorin, according to a particular clinical dosage regimen.

Preferably, the combination therapy with liposomal irinotecan with 5-FU and leucovorin exhibits therapeutic synergy.

"Therapeutic synergy" refers to a phenomenon where treatment of patients with a combination of therapeutic agents manifests a therapeutically superior outcome to the outcome achieved by each individual constituent of the combination used at its optimum dose (T. H. Corbett et al., 1982, Cancer Treatment Reports, 66, 1187). In this context a therapeutically superior outcome is one in which the patients either a) exhibit fewer incidences of adverse events while receiving a therapeutic benefit that is equal to or greater than that where individual constituents of the combination are each administered as monotherapy at the same dose as in the combination, or b) do not exhibit dose-limiting toxicities while receiving a therapeutic benefit that is greater than that of treatment with each individual constituent of the combination when each constituent is administered in at the same doses in the combination(s) as is administered as individual components. In xenograft models, a combination, used at its maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its individual maximum tolerated dose, manifests therapeutic synergy when decrease in tumor growth achieved by administration of the combination is greater than the value of the decrease in tumor growth of the best constituent when the constituent is administered alone.

Thus, in combination, the components of such combinations have an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to monotherapy with liposome-encapsulated irinotecan alone or treatment with the chemotherapeutic(s) in the absence of liposomal irinotecan therapy. By "additive" is meant a result that is greater in extent (e.g., in the degree of reduction of tumor mitotic index or of tumor growth or in the degree of tumor shrinkage or the frequency and/or duration of symptom-free or symptom-reduced periods) than the best separate result achieved by monotherapy with each individual component, while "superadditive" is used to indicate a result that exceeds in extent the sum of such separate results. In one embodiment, the additive effect is measured as slowing or

stopping of pancreatic tumor growth. The additive effect can also be measured as, e.g., reduction in size of a pancreatic tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, increase in overall response rate, or increase in median or overall survival.

One non-limiting example of a measure by which effectiveness of a therapeutic treatment can be quantified is by calculating the log10 cell kill, which is determined according to the following equation:

log10 cell kill = T C (days)/3.32 × Td

in which T C represents the delay in growth of the cells, which is the average time, in days, for the tumors of the treated group (T) and the tumors of the control group (C) to have reached a predetermined value (1 g, or 10 mL, for example), and Td represents the time, in days necessary for the volume of the tumor to double in the control animals. When applying this measure, a product is considered to be active if log10 cell kill is greater than or equal to 0.7 and a product is considered to be very active if log10 cell kill is greater than 2.8. Using this measure, a combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose generally less than or equal to its maximum tolerated dose, exhibits therapeutic synergy when the log10 cell kill is greater than the value of the log10 cell kill of the best constituent when it is administered alone. In an exemplary case, the log10 cell kill of the combination exceeds the value of the log10 cell kill of the best constituent of the combination by at least 0.1 log cell kill, at least 0.5 log cell kill, or at least 1.0 log cell kill.

Responses to therapy may include:

Pathologic complete response (pCR): absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

Partial Response (PR): At least a 30% decrease in the sum of dimensions of target lesions, taking as reference the baseline sum diameters;

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) denotes at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression.

In exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of pancreatic cancer.

In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

In another embodiment, the patient so treated experiences tumor shrinkage and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as $\geq$10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target lesions, e.g., pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response

or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In some embodiments, administration of effective amounts of liposomal irinotecan, 5-FU and leucovorin according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a breast tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate (CBR = CR+ PR+ SD $\geq$ 6 months) better than that achieved by the same combinations of anti-cancer agents administered without concomitant MM-398 administration. In other embodiments, the improvement of clinical benefit rate is about 20% 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to the same combinations of anti-cancer agents administered without concomitant MM-398 administration.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1: Activity of MM-398 in an Orthotopic Pancreas Tumor Model Expressing Luciferase (L3.6pl)

The anti-tumor activity of MM-398 was assessed in an orthotopic pancreatic cancer model (L3.6pl), a highly hypoxic preclinical tumor model. Approximately 2.5 x 10^{-5} L3.6pl pancreatic tumor cells were implanted by direct injection into the pancreas. The bioluminescence images (BLI) were followed over time for tumor burden detection/quantitation. MM-398 and free irinotecan were dosed at a dose of 20 mg/kg/dose weekly for three weeks. As shown in Figure 1, MM-398 (liposomal CPT11) had significant anti-tumor activity, as compared to a control (HBS) and free CPT11.

Example 2: Accumulation of SN-38 in Tumors Following Treatment with Free Irinotecan or Liposomal Irinotecan (MM-398)

It was hypothesized that the anti-tumor activity observed in the orthotopic pancreatic cancer model is due to the effect of macrophages in converting irinotecan

to the more active SN-38 locally. To test this hypothesis, human colon cancer cells (HT-29) were injected subcutaneously into SCID mice, 40 mg/kg of free irinotecan or MM-398 was injected intravenously when the tumors reached 1000 mm^3 in size. Tumor-bearing mice were sacrificed at different time points, tumors from both groups were extracted and the concentrations of SN-38 were measured.

As shown in Figure 2, there was a 20-fold increase in the tumor AUC_{SN-38} for MM-398 as compared to free irinotecan. The long duration of exposure allows for prolonged exposure of the slow proliferating cancer cells to the active metabolite as they progress through the cell cycle. In addition, this activity was also hypothesized to result from a reduction in intra-tumoral hypoxia, and the subsequent downstream effects on angiogenesis, metastasis, and the immunosuppressive environment in tumors.

Example 3: Effect of MM-398 on Carbonic Anhydrase IX Staining in a HT29 Xenograft Model

To test whether MM-398 reduces markers of hypoxia, experiments were conducted in a human colon cancer cell (HT-29) model. Specifically, HT-29 cells were injected subcutaneously into nude mice, on day 13 either PBS control or 1.25, 2.5, 5, 10 or 20 mg/kg MM-398 was injected intravenously. MM-398 was dosed once a week for 4 weeks at the indicated doses. Tumors from both groups (n = 5) were extracted 24 hours after the last dose. Frozen tumor sections were used for immunohistochemical staining of Carbonic Anhydrase IX (CAIX). Quantification of CAIX staining was performed using Definiens® (Definiens AG, Munich) software.

As shown in Figure 3, MM-398 reduced markers of hypoxia. Specifically, the graphs in Figure 3 show the percentage of cells that stained with medium (middle third) or high (top third) intensity for CAIX. Representative samples from each group are shown as well as the group average (mean +/- stdev). MM-398 treatment modifies the tumor microenvironment by decreasing the percentage of both medium and high CAIX positive cells in a dose-dependent manner. As hypoxia is a hallmark of resistant and aggressive disease, a reduction in hypoxia is expected to make tumor cells more sensitive to chemotherapies.

Example 4: MM-398 Increases Perfusion of Hoechst Stain

In addition to changing the chemosensitivity of tumor cells through modification of the tumor microenvironment, lowering hypoxia can indicate improved tumor vascularization, which can facilitate delivery of small molecule therapies.

MM-398 treatment led to increased microvessel density 6 days after treatment as measured by CD31 (platelet endothelial cell adhesion molecule) staining in an HT29 xenograft study. To further assess the effect of MM-398 on small molecule tumor vascularization, a Hoechst 33342 perfusion experiment was conducted. Specifically, a primary pancreatic tumor was grown in NOD-SCID mice and given one dose of MM-398 (20mg/kg). After 24 hours, Hoechst 33342 stain was administered 20 minutes prior to sacrificing the animal. As shown in Figure 4, the increase in stain intensity in treated mice was statistically significant, $p < 0.001$. These data indicate that MM-398 modifies the tumor microenvironment in a manner that should make tumors more susceptible to agents such as 5-FU/LV, through decreasing tumor hypoxia and increasing small molecule perfusion.

Example 5: MM-398 Pharmacokinetics in Humans (Phase I)

The pharmacokinetic profile of MM-398 single agent was investigated in a phase I clinical study (PEP0201) in patients at 60, 120 or 180mg/m^2 dose levels and in a phase II clinical trial in gastric cancer patients (PEP0206) at 120mg/m^2. Plasma levels of total irinotecan, SN-38 and encapsulated irinotecan were measured in these studies.

The peak serum concentrations of total irinotecan (C_{max}) ranged from 48-79 μg/ml for 120mg/m^2 of MM-398, which was approximately 50 fold higher than 125mg/m^2 free irinotecan. The total irinotecan half-life ($t_{1/2}$) for MM-398 ranged from 21 to 48 hours, which was approximately 2-3 fold higher than 125mg/m^2 of free irinotecan. Overall, total irinotecan exposure at one week (AUC 0–T) ranged from 1200- 3000 (μg*h/ml) at a dose of 120 mg/m^2 of MM-398, approximately 50-100 fold higher than 300mg/m^2 of free irinotecan. In contrast, SN38 C_{max} levels at 120mg/m^2 of MM-398 ranged from 9 to 17 ng/ml, which was approximately 50% less than free irinotecan at 125mg/m^2. Overall, exposure of SN38 at one week (AUC 0-T) ranged from 474 to 997 ng*/ml and was only 1-2 fold higher than achieved by free irinotecan at 300mg/m^2. For both SN38 and total irinotecan, AUC increased less than proportionally with dose of MM-398. The PK parameters of encapsulated irinotecan almost matched that of total irinotecan indicates that most of irinotecan remained encapsulated in the liposomes during circulation. The MM-398 PK parameters were not significantly changed when combined with 5-FU/LV. Figures 5 and 6 summarize the PK findings in previous studies of MM 398.

Example 6: Phase 1 Dose Escalation Study

A regimen combining fluorouracil, leucovorin, and MM-398 was studied in a phase 1 trial of solid tumors in 16 subjects, of whom 5 were patients with pancreatic cancer. The objective tumor response rate, duration of response, and disease control rate were efficacy endpoints of the study. Among the 15 efficacy-evaluable patients, 2 (13.3%) had confirmed PR, 9 (60.0%) had SD, and 4 (26.7%) had PD. The overall disease control rate was 73.3%. Partial response was observed in one gastric cancer patient (at 80mg/m^2 dose level) and one breast cancer patient (at 100 mg/m2 dose level), with the duration of response of 142 and 76 days, respectively. Among the 6 patients who received the MTD dose of 80 mg/m^2, there were 1 PR, 4 SD and 1 PD. The tumor response rate and disease control rate were 16.7% and 83.3%, respectively. The main DLTs were grade 3 diarrhea, leucopenia, neutropenia and febrile neutropenia. The MTD for MM-398 was 80mg/m^2.

In the phase 1 dose-escalation study of MM-398 in combination with 5-FU/LV in advanced solid tumors (PEP0203), a total of 401 episodes of AE were reported from the 16 treated subjects (safety population), of which 74 (18.4%) were of CTC grade 3 or above. Among all AEs, 231 (57.6%) were considered by the investigators to be treatment-related. The most common treatment-related AEs, included nausea (81.3%), diarrhea (75.0%), vomiting (68.8%), fatigue (43.8%), mucositis (43.8%), leucopenia (37.5%), neutropenia (37.5%), weight loss (37.5%), anemia (31.3%), and alopecia (31.3%). Acute cholinergic diarrhea was rarely observed. Table 1 provides the incidence of treatment-emergent adverse events by maximum CTC grade and by causality (incidence ≥ 20%), as seen in the PEP0203 study. Table 2 provides the incidence of grade 3 or higher treatment-emergent adverse events seen in the 5 pancreatic cancer patients treated in the PEP0203 study.

Table 1: Incidence of treatment-emergent adverse events by maximum CTC grade and by causality (incidence ≥ 20%) in the PEP0203 Study

System organ class Preferred Term	Total (N = 16)	Severity (Grade)[1]				Causality[2]	
		I	II	III	IV	Yes	No
Blood and lymphatic system disorders							
Anemia	7 (43.8%)	3	2	2	0	5	2
Leucopenia	6 (37.5%)	0	3	2	1	6	0

CSPC Exhibit 1120
Page 297 of 447

System organ class Preferred Term	Total (N = 16)	Severity (Grade)[1]				Causality[2]	
		I	II	III	IV	Yes	No
Neutropenia	6 (37.5%)	0	2	3	1	6	0
Gastrointestinal disorders							
Abdominal pain	7 (43.8%)	3	2	2	0	3	4
Constipation	6 (37.5%)	3	3	0	0	0	6
Diarrhea	12 (75.0%)	3	4	5	0	12	0
Nausea	13 (81.3%)	6	6	1	0	13	0
Vomiting	12 (75.0%)	3	8	1	0	11	1
General disorders and administration site conditions							
Fatigue	8 (50.0%)	4	3	1	0	7	1
Mucosal inflammation	7 (43.8%)	4	3	0	0	7	0
Pyrexia	7 (43.8%)	3	4	0	0	2	5
Infections and infestations							
Infection	6 (37.5%)	0	3	3	0	2	4
Investigations							
ALT increased	5 (31.3%)	3	2	0	0	4	1
AST increased	4 (25.0%)	3	1	0	0	1	3
Weight decreased	8 (50.0%)	4	4	0	0	6	2
Metabolism and nutrition disorders							
Anorexia	4 (25.0%)	1	2	1	0	3	1
Hypoalbuminaemia	4 (25.0%)	0	3	1	0	0	4
Hypocalcaemia	5 (31.3%)	1	4	0	0	0	5
Hypokalaemia	8 (50.0%)	2	0	5	1	2	6
Hyponatraemia	4 (25.0%)	2	0	0	2	0	4
Nervous system disorders							
Dizziness	4 (25.0%)	4	0	0	0	1	3
Psychiatric disorders							
Insomnia	4 (25.0%)	4	0	0	0	1	3
Respiratory, thoracic and mediastinal disorders							
Cough	5 (31.3%)	3	1	1	0	0	5
Skin and subcutaneous tissue disorders							
Alopecia	5 (31.3%)	5	0	0	0	5	0

[1]: Severity grading used the highest grading ever rated for each subject if the subject had such adverse event reported

[2]: Defined as subject ever experienced AE related to the study drug in causality or not

Table 2: Incidence of Grade 3 or higher treatment-emergent adverse events in pancreatic cancer patients in the PEP0203 Study

	Overall N=5	60 mg/m2 N=1	80 mg/m2 N=3	120 mg/m2 N=1
Primary system organ class Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Any primary system organ class				
-Total	3 (60.0)	0	2 (66.7)	1 (100.0)
Infections and infestations				
-Total	3 (60.0)	0	2 (66.7)	1 (100.0)
Hepatitis viral	1 (20.0)	0	1 (33.3)	0
Infection	1 (20.0)	0	0	1 (100.0)
Pneumonia	1 (20.0)	0	1 (33.3)	0
Septic shock	1 (20.0)	0	1 (33.3)	0
Blood and lymphatic system disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Lymphopenia	1 (20.0)	0	0	1 (100.0)
Neutropenia	1 (20.0)	0	1 (33.3)	0
White blood cell disorder	1 (20.0)	0	0	1 (100.0)
Gastrointestinal disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Diarrhoea	2 (40.0)	0	1 (33.3)	1 (100.0)
Abdominal pain	1 (20.0)	0	0	1 (100.0)
Gastrointestinal haemorrhage	1 (20.0)	0	1 (33.3)	0
Investigations				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Blood bilirubin increased	1 (20.0)	0	1 (33.3)	0
Lipase increased	1 (20.0)	0	0	1 (100.0)
Neutrophil count decreased	1 (20.0)	0	0	1 (100.0)
White blood cell count decreased	1 (20.0)	0	0	1 (100.0)
Metabolism and nutrition disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Hypoalbuminaemia	1 (20.0)	0	1 (33.3)	0
Hypokalaemia	1 (20.0)	0	1 (33.3)	0
Hyponatraemia	1 (20.0)	0	0	1 (100.0)
Hypophosphataemia	1 (20.0)	0	0	1 (100.0)

	Overall N=5	60 mg/m2 N=1	80 mg/m2 N=3	120 mg/m2 N=1
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders				
-Total	2 (40.0)	0	1 (33.3)	1 (100.0)
Dyspnoea	1 (20.0)	0	0	1 (100.0)
Pleural effusion	1 (20.0)	0	1 (33.3)	0
General disorders and administration site conditions				
-Total	1 (20.0)	0	0	1 (100.0)
Death	1 (20.0)	0	0	1 (100.0)

Example 7: Phase 3 Trial

The promising efficacy and safety data from the Phase 1 Trial (described above) warrant the MM-398 and 5-FU plus leucovorin combination to be explored further in a phase 3 study.

A. Objectives

The primary objective of the Phase 3 trial is to compare overall survival following treatment with MM-398, with or without 5-fluorouracil plus leucovorin, versus 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer that have progressed on gemcitabine based therapy. The secondary objectives includes the following:

To compare time-to-event efficacy endpoints between the experimental and control arms (i.e., Progression-free survival (PFS) and Time to treatment failure (TTF));

- To compare the Objective Response Rate (ORR) between the treatment arms;
- To compare the tumor marker response of CA 19-9 between the treatment arms;
- To compare the Clinical Benefit Response (CBR) rate between the treatment arms;

- To assess patient-reported outcomes (PROs) between the treatment arms using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30);
- To compare the safety and adverse event profile between the treatment arms; and
- To determine the pharmacokinetic properties of MM-398, as a single agent and in combination with 5-FU and leucovorin.

A key exploratory objective of this study is to explore biomarkers associated with toxicity and efficacy following treatment with MM-398 and MM-398 plus 5-FU and leucovorin.

B. Study Design

This is an open label, randomized, three arm, Phase 3 trial of MM-398, with or without 5-FU and leucovorin, versus 5-fluorouracil (5-FU) and leucovorin (also known as folinic acid), in metastatic pancreatic cancer patients who have progressed on prior gemcitabine based therapy.

Approximately 405 eligible patients will be enrolled in this global study, under the protocol version 2 or later. All patients will participate in up to 28 days of screening, during which they will be assessed for eligibility and screened for the UGT1A1*28 allele. Eligible patients will be randomized, in a 1:1:1 ratio, to one of the following treatment arms:

Arm A (experimental arm): MM-398	MM 398 120 mg/m2 IV over 90 minutes, every 3 weeks. Patients who are homozygous for UGT1A1*28 allele will receive the first cycle of therapy at a reduced dose of 80 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased in increments of 20 mg/m^2 up to a maximum of 120 mg/m^2.
Arm B (control arm): 5-FU and leucovorin	**5-FU 2000 mg/m^2 IV over 24-hours (+/- 30 minutes), administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle.** **Levoleucovorin dosed at 200 mg/m^2 or the leucovorin *l* + *d* racemic mixture dosed at 400 mg/m^2, given IV over 30 minutes, administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle.**
Arm C (experimental arm): MM-398, 5-FU and	**MM-398 80 mg/m^2 IV over 90 minutes, every 2 weeks. Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of**

leucovorin	**therapy at a reduced dose of 60 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m^2.** **5-FU 2400 mg/m^2 IV over 46-hours, every 2 weeks.** **Levoleucovorin dosed at 200 mg/m^2 or the l + d racemic mixture dosed at 400 mg/m^2, IV over 30 minutes, every 2 weeks.** **MM-398 should be administered prior to 5-FU and leucovorin; leucovorin should always be administered prior to 5-FU. If the dosing of either MM-398 or 5-FU/leucovorin needs to be withheld, then the other drug in the combination should not be administered either.**

Patients will be evenly randomized to the treatment arms using an Interactive Web Response System (IWRS) at a central location. The randomization will be stratified based on the following prognostic factors:

- Baseline albumin levels ($\geq$ 4.0 g/dL *vs* < 4.0 g/dL)
- KPS (70 and 80 *vs* $\geq$ 90)
- Ethnicity (Caucasian *vs* East Asian *vs* All Others)

Therapy will be administered in cycles. Patients will be treated until disease progression (radiologic or clinical deterioration), intolerable toxicity or other reasons for study termination. Tumor responses will be assessed, using the RECIST guidelines (Eisenhauer, E.A., *et al.*, "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, 2009. 45:pp. 228-247) every 6 weeks or sooner if disease progression based on clinical signs and symptoms is evident. Tumor measurement images will be collected and stored on all patients throughout the study. However, all treatment decisions will be based on the local radiologist and/or PI assessment of disease status. An independent review of the scans may be performed in the event that an independent analysis of ORR and/or PFS is necessary.

Following treatment discontinuation a 30-day post therapy follow up visit is required. Subsequently, all patients will be followed-up every 1 month for overall survival (by phone or visit to the study site) until death or study closure, whichever occurs first. Patients, who withdraw from study treatment due to reasons other than objective disease progression, should continue to be assessed every 6 weeks during the follow-up period for radiologic progression (including patients who discontinue due to symptomatic deterioration).

All patients will be asked to complete a pain assessment and analgesic consumption diary throughout their participation in the study, which will document the patient's assessment of their pain intensity and daily analgesic consumption. Patient responses will be used for assessment of the clinical benefit response along with the other parameters. All patients will also be required to complete the EORTC-QLQ-C30 questionnaire for assessing quality of life.

In order to address the exploratory objectives of this study, all sites will be required to participate in the companion translational research (TR) protocol (MM-398-07-03-01.TR), unless prohibited by local regulations. Participation is this study will be optional for patients and they will be required to provide a separate consent for the translational research.

The primary analysis of OS will take place once at least 305 deaths events have occurred in patients enrolled under protocol version 2 or later. Patients receiving study treatment at the time of primary analysis for OS will continue to receive treatment until one of the criteria for discontinuation is met. During the course of the study, regular review of safety data will be conducted by an independent data safety monitoring board (DSMB). Figure 7 illustrates the study design.

C. Patient Selection and Discontinuation

Approximately 405 patients will be enrolled globally in this study, under the protocol version 2 or later. In order to be included in the study, patients must have/be:

1. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
2. Documented metastatic disease; disease status may be measurable or non-measurable as defined by RECIST v1.1 guidelines
3. Documented disease progression after prior gemcitabine or gemcitabine containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies include, but are not limited to:
    - Single agent gemcitabine
    - Any one gemcitabine-based regimen, with or without maintenance gemcitabine
    - Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added

- Gemcitabine administered in the adjuvant setting if disease recurrence occurred within 6 months of completing the adjuvant therapy

4. Karnofsky Performance Status (KPS) $\geq$ 70
5. Adequate bone marrow reserves as evidenced by:
    - ANC > 1,500 cells/µl without the use of hematopoietic growth factors; and
    - Platelet count > 100,000 cells/µl; and
    - Hemoglobin > 9 g/dL (blood transfusions are permitted for patients with hemoglobin levels below 9 g/dL)
6. Adequate hepatic function as evidenced by:
    - Serum total bilirubin within normal range for the institution (biliary drainage is allowed for biliary obstruction)
    - Albumin levels $\geq$ 3.0 g/dL
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 x ULN ($\leq$ 5 x ULN is acceptable if liver metastases are present)
7. Adequate renal function as evidenced by a serum creatinine $\leq$ 1.5 x ULN
8. Normal ECG or ECG without any clinically significant findings
9. Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy
10. At least 18 years of age
11. Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria:

1. Active CNS metastases (indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease)
2. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > grade 1
3. History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible.

CSPC Exhibit 1120
Page 304 of 447

Subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years.

4. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
5. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
6. Active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome
7. Known hypersensitivity to any of the components of MM-398, other liposomal products, fluropyrimidines or leucovorin
8. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study
9. Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results
10. Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a reliable method of birth control, during the study and for 3 months following the last dose of study drug.

The criteria for enrollment must be followed explicitly. Patients will be discontinued from the study treatment in the following circumstances:

- Patient has evidence of disease progression based on RECIST v1.1 criteria
- Patient shows symptomatic deterioration
- Patient experiences intolerable toxicity, or an adverse event which requires:
    - A third dose reduction

- Treatment to be withheld for more than 21 days from the start of next cycle, unless, in the opinion of the investigator, the patient is receiving benefit from study treatment

- Patient is significantly non-compliant with study procedures per PI assessment
- The patient or patient's attending physician requests that the patient be withdrawn from the study treatment
- The investigator or Sponsor, for any reason, but considering the rights, safety and well-being of the patient(s) and in accordance with ICH/GCP Guidelines and local regulations, stops the study or stops the patient's participation in the study

If a patient is lost to follow-up or withdraws from study treatment, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before considering the patient lost to follow-up. If a patient discontinues study treatment due to reasons other than objective disease progression, the patient should continue to have radiological disease assessment every 6 weeks until objective disease progression is observed.

All patients who discontinue study treatment should continue to be followed-up as required by the protocol. The only circumstance under which a patient should not be followed for study endpoints is when the patient has withdrawn consent. Withdrawal of consent should be a patient initiated decision and should mean, not only that the patient wishes to discontinue study treatment and follow-up visits but also that the investigator is no longer authorized to make further efforts to contact the patient, including any efforts to identify their survival status.

D. Method of Assigning Patients to Treatment Groups

After all screening assessments have been completed and UGT1A1*28 results are available, patients will be randomized using a computerized interactive web response system (IWRS), in a 1:1:1 ratio, to one of the following treatment arms:

- **Arm A** (experimental arm): MM-398
- **Arm B** (control arm): 5-FU and leucovorin
- **Arm C** (experimental arm): MM-398, 5-FU and leucovorin

Randomization must occur within 7 days of planned dosing. The randomization will be stratified based on the following prognostic factors:

- Baseline albumin levels (≥ 4.0 g/dL *vs* < 4.0g/dL)
- KPS (70 and 80 *vs* ≥ 90)
- Ethnicity (Caucasian *vs* East Asian *vs* All Others)

E. Description of MM-398

MM-398 is irinotecan (also known as CPT-11) encapsulated in a liposomal drug delivery system. It will be supplied as sterile, single-use vials containing 9.5 mL of MM-398 at a concentration of 5 mg/mL. The vials contain a 0.5 mL excess to facilitate the withdrawal of the label amount from each 10 mL vial.

MM-398 must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. MM-398 must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe.

MM-398 must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 6 hours if kept at room temperature (15-30°C).

Twenty vials of MM-398 will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements.

MM-398 will be dosed and administered as follows. All patients will be screened for UGT1A1*28 allele at baseline.

Arm A	• Patients who do not have the homozygous allele for UGT1A1*28 will receive MM-398 at a dose of 120 mg/m^2. • Any patient who is homozygous for UGT1A1*28 will receive the first cycle of therapy at a reduced dose of 80 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, their dose can be increased in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.
Arm C	• Patients who do not have the homozygous allele for UGT1A1*28 will receive MM-398 at a dose of 80 mg/m^2.

	• Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m^2. • MM-398 should be administered prior to 5-FU and leucovorin administration.

In Arm A, MM-398 will be administered by IV infusion over 90 minutes on the first day of each 3 week cycle, at the investigational site. In Arm C, MM-398 will be administered by an IV infusion over 90 minutes for the first cycle; the infusion time could be reduced to 60 minutes from cycle 2 onwards, if no acute infusion reaction has occurred in cycle 1. Cycle duration is 3 weeks for Arm A and 2 weeks for Arm C. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 3 days.

Prior to administration, the appropriate dose of MM-398 must be diluted in 5% Dextrose Injection solution (D5W) to a final volume of 500mL. Care should be taken not to use in-line filters or any diluents other than D5W. MM-398 can be administered using standard PVC-containing intravenous administration bags and tubing.

The actual dose of MM-398 to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since MM-398 vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

All patients must be premedicated prior to MM-398 infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics as per standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

F. Description of 5-FU and Leucovorin

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

FU and leucovorin will be stored and handled according to the country specific package inserts. Commercially available 5-FU and leucovorin will be provided to all patients in the study who are randomized to Arm B and Arm C.

5-FU and leucovorin will be dosed and administered as follows.

Arm B	• 5-FU will be administered at a dose of 2000 mg/m^2 as an IV infusion over 24-hours, (+/- 30 minutes), every week for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 week cycle • Leucovorin will be administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + d racemic form) as an IV infusion over 30 minutes, every week for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 week cycle
Arm C	• 5-FU will be administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours, (+/- 60 minutes), every 2 weeks • Leucovorin will be administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + d racemic form) as an IV infusion over 30 minutes, every 2 weeks

Leucovorin should be reconstituted per the instructions on the package inset or standard institutional guidelines for reconstitution of leucovorin. Leucovorin should be administered prior to the 5-FU infusion.

Actual dose of 5-FU and leucovorin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

After cycle 1, for the start of each new cycle, a window period of +/- 3 days will be permitted, and a window period of +/- 1 day will be permitted for the Day 8, 15 and 22 infusions.

All patients must be premedicated prior to 5-FU and leucovorin infusion with standard doses of dexamethasone, prochlorperazine or equivalent other anti-emetics as per standard institutional practices for 5-FU administration.

G. Important Treatment Considerations with MM-398

Data from previous MM-398 studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the treatment procedures for managing those toxicities are provided below.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous cycle of MM-398, prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide. Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia, with discretion. Patients, who are known to have experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

Care of Intravenous Site

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended.

Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal

glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

Other Toxicity Potential

MM-398, the new liposome formulation of irinotecan, is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

H. Dose Modification Requirements

Dosing may be held for up to 3 weeks from when it was due, to allow for recovery from toxicity related to the study treatments. If the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

Infusion reactions will be monitored. Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.0) definition of an allergic reaction/infusion reaction and anaphylaxis, as defined below:

Grade 1: Transient flushing or rash, drug fever <38° C (<100.4° F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <24 hrs
Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1 • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2 • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, premedicate with diphenhydramine hydrochloride 25-50 mg IV
Grade 3 • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary • No further treatment with MM-398 will be permitted
Grade 4 • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with MM-398 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), with discretion.

For patients who experience a second grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

I. MM-398 Dose Modifications for Hematological Toxicities

Prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq$ 1500/mm^3
- Platelet count $\geq$ 100,000/mm^3

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines in the tables below. If the patient had febrile neutropenia, the ANC must have resolved to $\geq$ 1500/mm^3 and the patient must have recovered from infection.

Table: MM-398 Dose Modifications for Neutrophil Count

ANC: cells/mm^3 (Worst CTCAE grade)	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28[d] Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28[d]
$\geq$ 1000 to 1999 (Grade 1 or 2)	100% of previous dose	100% of previous dose	100% of previous dose
< 1000 (Grade 3/4) or febrile neutropenia	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2[b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence[e, d]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study
[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

Table: MM-398 Dose Modifications for Other Hematologic Toxicity

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	Arm A: Patients Homozygous for UGT1A1*28 [d] Arm C: Patients Not Homozygous for UGT1A1*28	Arm C: Patients Homozygous for UGT1A1*28 [d]
≤ Grade 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3/4	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [e, d]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m2 must be withdrawn from the study
[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

J. MM-398 Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until diarrhea resolves to ≤ Grade 1, and for other Grade 3 or 4 non-hematological toxicities, until they resolve to Grade 1 or baseline. Guidelines for dose adjustment of MM-398 for drug related diarrhea and other Grade 3 or 4 non-hematological toxicities are provided below. Infusion reactions should be handled as described above.

Table: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28** [d] **Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28** [d]
Grade 1 or 2 (2-3 stools/day > pretreatment or 4-6 stools/day > pretreatment)	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence[c, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [e, d]

[a] All dose modifications should be based on the worst preceding toxicity

[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study

[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study

[d] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28

[e] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

Table: MM-398 Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia[d]

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28[e] Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28[e]**
Grade 1 or 2	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 or 4 (except nausea and vomiting)	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50mg/m^2 for the second occurrence [c, e]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [f, e]
Grade 3 or 4 nausea and or vomiting despite anti emetic therapy	Optimize anti-emetic therapy AND reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Optimize anti-emetic therapy **AND** reduce dose to 60 mg/m^2; if the patient is already receiving 60 mg/m^2, reduce dose to 50 mg/m^2 [c, e]	Optimize anti-emetic therapy **AND** reduce dose to 50 mg/m^2; if the patient is already receiving 50 mg/m^2, reduce dose to 40 mg/m^2 [f, e]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require a further dose reduction beyond 80 mg/m^2 must be withdrawn from the study
[c] Patients who require a further dose reduction beyond 50 mg/m^2 must be withdrawn from the study
[d] Asthenia and Grade 3 Anorexia do not require dose modification
[e] Patients who are homozygous for UGT1A1*28 and have had their dose increased should be dose reduced per guidelines for patients who are not homozygous for UGT1A1*28
[f] Patients who require a further dose reduction beyond 40 mg/m^2 must be withdrawn from the study

K. 5-FU and Leucovorin Dose Modifications (Arm B and Arm C)

Guidelines for 5-FU dose modifications are provided below. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for MM-398 infusion reaction management should be used.

L. 5-FU Dose Modifications for Hematological Toxicities

Prior to the next dose in a cycle or prior to initiating a new cycle of therapy, the patients must have:

- ANC $\geq 1500/mm^3$
- WBC $\geq 3500/mm^3$
- Platelet count $\geq 75,000/mm^3$ (according to the European summary of product characteristics for 5-FU, the platelets should have recovered to $\geq 100,000/mm^3$ prior to initiating therapy)

Treatment should be delayed to allow sufficient time for recovery and upon recovery, treatment should be administered according to the guidelines provided in the table below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table: 5-FU Dose Modifications for Hematological Toxicities (Arm B & C)

ANC ($cells/mm^3$)		Platelets ($cells/mm^3$)	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
≥ 1000	and	≥ 50,000	100% of previous dose	100% of previous dose
500 - 999	Or	<50,000 – 25,000	Hold; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]
< 500 or febrile neutropenia	Or	< 25,000 or thrombocytopenia with bleeding	Hold dose; when resolved, reduce dose by 25%[b]	Reduce dose by 25%[b]

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study

M. 5-FU Dose Modifications for Non-Hematological Toxicities

Treatment should be delayed until all Grade 3 or 4 non-hematological toxicities resolve to Grade 1 or baseline. Guidelines for dose adjustment of 5-FU related toxicities are provided below. The duration of the cycles is fixed at 6 weeks, and if a patient is unable to receive the D8, D15 or D22 dose due to toxicity, the dose will be considered as skipped.

Table: 5-FU Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[c] (Arm B & C)

Worst Toxicity CTCAE Grade	5-FU Dose for D8, D15, D22[a]	5-FU Dose for Next Cycle[a]
Grade 1 or 2	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 hand and foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity
Grade 2 hand foot syndrome	Reduce dose by 25%[b]	Reduce dose by 25%[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	Discontinue therapy	Discontinue therapy
Grade 3 or 4	Hold; when resolved, reduce dose by 25%[b], except for Grade 3 or 4 hand foot syndrome	Reduce dose by 25%[b],except for Grade 3 or 4 hand foot syndrome
Grade 3 or 4 hand foot syndrome	Discontinue therapy	Discontinue therapy

[a] All dose modifications should be based on the worst preceding toxicity
[b] Patients who require more than 2 dose reductions must be withdrawn from the study
[c] Asthenia and Grade 3 Anorexia do not require dose modification

N. Other Toxicities Requiring Special Attention

For both 5-FU and MM-398 treatment arms, QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated by with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhea as described above.

O. Concomitant Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

Antiemetic Medications

Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered to all patients as premedications unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.

Colony Stimulating Factors

Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever; prophylactic use of G-CSF will be permitted only in those patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy or have had documented grade 3 or 4 neutropenia or neutropenic fever while receiving prior anti-neoplastic therapy.

Therapy for Diarrhea

Acute diarrhea and abdominal cramps, developing during or within 24 hours after MM-398 administration, may occur as part of a cholinergic syndrome. The syndrome will be treated with atropine. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms during the study.

Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea are abstracted below.

Table: Recommendations for Management of Chemotherapy Induced Diarrhea

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

The synthetic octapeptide octreotide has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 micrograms twice daily to 500 micrograms three times daily, with a maximum tolerated dose of 2000 micrograms three times daily in a 5-day regimen. Patients should be advised to drink water copiously throughout treatment.

Other Treatments

Symptomatic treatment for other toxicities should be per institutional guidelines. Prevention of alopecia with cold cap or of stomatitis with iced mouth rinses is allowed.

P. Prohibited Therapy

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil. Treatment with these agents and any other that interact with irinotecan, should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Refer to the country specific package inserts of 5-FU and leucovorin for any other drug interactions.

The following therapies are not permitted during the trial:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies;
- Potentially curative radiotherapy; palliative radiotherapy is permitted; and
- Any other investigational therapy is not permitted.

Q. Laboratory Procedures

Complete Blood Count

A complete blood count (CBC) will be performed locally, and must include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

Serum Chemistry

Serum chemistry panel will be performed centrally. Additionally, chemistry may also be assessed locally, and local lab results may be used for enrollment and

treatment decisions, if central lab results are not available. If local lab results are used for enrollment, then local lab results must be used for all subsequent treatment decisions. Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

CA 19-9

CA 19-9 levels will be measured centrally for all patients.

Pregnancy Test

All women of child bearing potential must undergo a urine or serum pregnancy test.

UGT1A1*28 Allele

A whole blood sample will be collected from all patients at baseline and sent to the central lab to test for UGT1A1*28 allele status. Local lab results may be used if the central lab results are not available at the time of randomization.

Pharmacokinetic Assessments

PK analysis will be done centrally. Plasma PK samples will be collected in Cycle 1, from all patients randomized in this study, at the following timepoints:

- Arm A: just prior to infusion, during infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of infusion and on C1D8
- Arm B: one sample at the end of 5-FU infusion (C1D2)
- Arm C: just prior to MM-398 infusion, during MM-398 infusion (at 80 to 90 minutes after start of infusion), between 2 and a half and four hours after the start of MM-398 infusion, at the end of 5-FU infusion and on C1D8

In addition, a PK sample will be collected in Cycle 1, any time between 8 and 72 hours following administration of MM-398, from patients randomized to Arm A and Arm C, who provide an additional consent for collection of this sample.

R. Pain Assessment and Analgesic Consumption

Pain assessment and analgesic consumption diaries will be provided to the patients for recording their pain intensity daily on a visual analogue scale and to document their daily analgesic use.

S. EORTC-QLQ-C30

Quality of life will be assessed by the EORTC-QLQ-C30 instrument. The EORTC-QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included.

Patients will be required to complete the EORTC-QLQ-C30 questionnaire at timepoints outlined in the Schedule of Assessment. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients, for whom validated translations of the EORTC-QLQ-C30 questionnaire are available, will be required to complete the questionnaire.

T. Overall Survival/Post Study Follow-up

Overall survival data will be collected after a patient completes the 30 day follow-up visit, every 1 month (+/- 1 week) from the date of the 30 day follow-up visit. Post-discontinuation data to be collected will include: the date of disease progression (if not already documented; if patient discontinued from study treatment for reasons other than objective disease progression, patient should continue to undergo tumor assessment every 6 weeks, until commencement of new anti-neoplastic therapy or progressive disease); documentation of any anticancer treatment patient has received including the dates of any post-discontinuation systemic therapy, radiotherapy, or surgical intervention; and the date of death. All patients must be followed-up until death or study closure, whichever occurs first.

U. Determining the Severity and Relatedness of Adverse Events

Each adverse event will be graded according to the NCI CTCAE V 4.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal, which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;

- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event
- **Fatal**: an event that results in the death of the patient

The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

V. Analysis of the Overall Survival

Overall survival (OS) is the primary endpoint of this study. Overall survival is defined as the time from the date of patient randomization to date of death or the date last known alive. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data cut-off date.

The study primary analysis will involve two pair-wise comparisons of survival between the study treatments, in the ITT population using un-stratified Log Rank Test. The testing will be according to the Bonferroni-Holm procedure which strongly controls the family-wise error rate at 0.05 (two-sided) level [25]:

Reject $H_D^1 : S_A(t) = S_B(t)$, i.e. no effect of MM-398 monotherapy relative to control, if the logrank p-value for this test is less than 0.025 or if the logrank p-value for this test is less than 0.05 and the logrank p-value for the comparison between Arm B and Arm C is less than 0.025.

Reject $H_D^2 : S_C(t) = S_B(t)$, i.e. no effect of MM-398 combination therapy relative to control, if the logrank p-value for this test is less than 0.025 or if the logrank p-value for this test is less than 0.05 and the logrank p-value for the comparison between Arm A and Arm B is less than 0.025.

Kaplan-Meier analyses will be performed on each treatment group to obtain nonparametric estimates of the survival function and the median survival time. Corresponding 95% confidence intervals will be computed using the log-log method.

Cox proportional hazards modeling will be used to estimate hazard ratios and corresponding 95% confidence intervals.

The following additional sensitivity analyses will be carried out for overall survival on the ITT population (except as indicated) to evaluate the robustness of the primary analysis results:

log-rank comparisons of treatments on the PP population

stratified log rank analyses, using randomization stratification factors [with hazard ratio estimates from stratified Cox modeling]

Wilcoxon comparisons of treatments

Cox regression model with stepwise selection (p value to enter < 0.25, p-value to remain < 0.15) of model terms where treatment and the prognostic factors (noted below) are candidates for inclusion

univariate analyses to evaluate potential independent prognostic factors using Cox regression

subgroup analyses to examine differences in the effects of treatment in different segments of the study population.

Repeat all analyses (primary and sensitivity) with only patients who enrolled under protocol Version 2 (and later)

Prognostic factors to be examined include: baseline KPS, baseline albumin, ethnicity, geographic location, disease stage at diagnosis, original tumor location, number of prior chemotherapy treatments, prior radiotherapy, prior surgery, time since last treatment, best response on prior treatment, baseline CA 19-9, gender and age.

W. Secondary Efficacy Analyses

Progression Free Survival

PFS is defined as the number of months from the date of randomization to the date of death or progression, whichever occurred earlier (per RECIST 1.1). If neither death nor progression is observed during the study, PFS data will be censored at the last valid tumor assessment.

PFS will be compared between the treatment groups using paired un-stratified log-rank tests. The PFS curves will be estimated using Kaplan-Meier estimates. Estimates of the hazard ratios and corresponding 95% confidence intervals will be obtained using Cox proportional hazard models. Stratified analyses will also be carried

out using the randomization stratification factors. Treatment effects adjusting for stratification variables and other prognostic covariates will be explored. In addition, different censoring and missing data imputing methods may be used to perform sensitivity analyses on PFS. Methodology for the sensitivity analyses will be fully specified in the Statistical Analysis Plan.

The analyses will be performed for ITT, PP and EP populations.

Time to Treatment Failure

Time to treatment failure is defined as time from randomization to either disease progression, death or study discontinuation due to toxicity. Kaplan-Meier analyses as specified for analyses of progression free survival will be performed for time to treatment failure.

The analyses will be performed for ITT, PP and EP populations.

Objective Response Rate

The tumor assessment related to ORR will be determined using RECIST v1.1. If the Sponsor requires an independent review of the radiological assessments to support a new drug application or for any other reason, the response status of all patients may be reviewed by an independent panel of clinicians and may be reviewed by the Sponsor or its designee. In case of a discrepancy between the assessment of the independent panel and that of the investigator, the independent panel's assessment will take precedence.

Objective response rate (ORR) for each treatment group will be calculated combining the number of patients with a best overall response of confirmed CR or PR per RECIST. The ORR is the best response recorded from randomization until progression or end of study. The number and percentage of patients experiencing objective response (confirmed CR + PR) at the time of analysis will be presented and the 95% confidence interval for the proportion will be calculated. Objective response rates from the treatment arms will be compared using pair-wise Fisher's Exact Tests. The analyses will be performed for ITT, PP and EP populations.

Tumor Marker Response Analysis

CA 19-9 serum levels will be measured within 7 days before the start of treatment (baseline), and subsequently every 6 weeks. Tumor marker response of CA19-9 will be evaluated by the change of CA19-9 serum levels. Response is defined as a decrease of 50% of CA 19-9 in relation to the baseline level at least once during

the treatment period. Only patients with elevated baseline CA 19-9 value (> 30 U/mL) will be included in the calculation of tumor marker response rate.

Patient Reported Outcome Analyses

Analysis of the EORTC-QLQ-C30 questionnaires will be performed in accordance with the EORTC guidelines [22].

Safety Analysis

Treatment emergent adverse events will be presented by treatment arm, by patient, by NCI CTCAE grade and by MedDRA system organ class (SOC). Separate listings will be presented for total adverse events, serious adverse events, adverse events related to the study drugs and Grade 3 and 4 adverse events. Laboratory data will be presented by treatment arm and by visit. Abnormal laboratory values will be assessed according to NCI CTCAE grade, where possible. Evaluation of QTc will be done based upon Fridericia's correction method. CTCAE criteria will be applied to the QTc_F (i.e. Grade 3 = QTc > 500 msec). All the safety analyses will be performed by treatment arm, treatment cycle and week, where appropriate. Overall safety will also be evaluated by grade across cycles, SOC and extent of exposure. Additionally, safety analyses will include a comparison between the treatment arms in all patients in the Safety Population:

- Number of blood transfusions required
- Proportion of patients requiring G-CSF
- Adverse events resulting in dose delay or modification

Pharmacokinetics Analysis

Pharmacokinetic data will be collected on all patients randomized to either of the MM-398 arms. Plasma concentration-time data for MM-398 will be analyzed using population pharmacokinetic methods. Pharmacokinetic parameters will be estimated by Non-Linear Mixed Effects Modeling using NONMEM®, Version 7, Level 1.0 (ICON Development Solutions, Dublin, Ireland). PK parameters will include plasma C_{max}, T_{max}, AUC (area under the concentration curve), clearance, volume of distribution, and terminal elimination half-life. The effects of patient specific factors (age, race, gender, body weight, hepatic and renal function measures, ECOG value, etc.) on pharmacokinetic parameters will be evaluated. Population PK/PD methods will be used to assess the relationships between drug exposure and efficacy and/or toxicity (e.g. neutropenia, diarrhea) parameters. Additional

exploratory analysis may be performed on the PK samples, to help clarify any safety, efficacy or PK issues related to MM-398 that arise during the course of the study. Concentration levels of 5-FU will be summarized descriptively.

Endnotes

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein. The disclosure of each and every US, international, or other patent or patent application or publication referred to herein is hereby incorporated herein by reference in its entirety.

Claims

What is claimed is:

1. A method of treating pancreatic cancer in a human patient, the method comprising: administering to the patient an affective amount of liposomal irinotecan, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the liposomal irinotecan is administered on day 1 of the cycle at a dose of 120 mg/m^2, except if the patient is homozygous for the UGT1A1*28 allele, wherein liposomal irinotecan is administered on day 1 of cycle 1 at a dose of 80 mg/m^2.

2. The method of claim 1, wherein the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased after one cycle in increments of 20 mg/m^2, up to a maximum of 120 mg/m^2.

3. A method of treating pancreatic cancer in a human patient, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form).

4. The method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

5. The method of claim 3 or claim 4, wherein after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2.

6. The method of any one of the preceding claims, wherein the liposomal irinotecan is administered intravenously over 90 minutes.

7. The method of any one of claims 3-6, wherein the 5-FU is administered intravenously over 46 hours.

8. The method of any one of claims 3-7, wherein the leucovorin is administered intravenously over 30 minutes.

9. The method of any one of the preceding claims, wherein, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

10. The method of any one of the preceding claims, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

11. The method of any one of the preceding claims, wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection.

12. A formulation of irinotecan for co-administration with 5-fluorouracil (5-FU) and leucovorin in at least one cycle, wherein the cycle is a period of 2 weeks, the formulation of irinotecan is a liposomal formulation of irinotecan, and wherein:

(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m^2 (*l* + *d* racemic form).

13. The formulation of irinotecan of claim 12 wherein after cycle 1 the dose of liposomal irinotecan administered to the patient homozygous for the UGT1A1*28 allele is increased to 80 mg/m^2.

14. The formulation of claim 12 or claim 13, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.

15. The formulation of any one of claims 12-14, wherein the liposomal irinotecan is administered intravenously over 90 minutes.

16. The formulation of any one of claims 12-15, wherein the 5-FU is administered intravenously over 46 hours.

17. The formulation of any one of claims 12-16, wherein the leucovorin is administered intravenously over 30 minutes.

18. The formulation of any one of claims 12-17, wherein, prior to each administration of liposomal irinotecan, the patient is pre-medicated with dexamethasone and/or a 5-HT3 antagonist or another anti-emetic.

19. The formulation of any one of claims 12-18, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

20. The formulation of any one of claims 12-19 wherein the liposomal formulation of irinotecan is irinotecan sucrose octasulfate salt liposome injection.

21. A method of improving chemotherapy outcomes by increasing tumor vascularity, the method comprising administering to a patient having a tumor an

CSPC Exhibit 1120
Page 331 of 447

amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and concomitantly administering an effective amount of at least one anti-cancer agent other than irinotecan to the patient.

22. Irinotecan sucrose octasulfate salt liposome injection for concomitant administration to a patient having a tumor of 1) an amount of irinotecan sucrose octasulfate salt liposome injection effective to increase tumor vascularity and 2) an effective amount of at least one anti-cancer agent other than irinotecan.

23. A kit for treating pancreatic cancer in a human patient, the kit comprising a dose of liposomal irinotecan and instructions for using liposomal irinotecan in the method of claim 1 or 2.

24. A kit for treating pancreatic cancer in a human patient, the kit comprising a dose of each liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, and instructions for using liposomal irinotecan, 5-FU, and leucovorin in the method of claim 3 or 4.

25. The kit of claim 24, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

26. The kit of any one of claims 23-25, wherein the liposomal irinotecan is MM-398.

27. The method of any one of claims 1-11, or the formulation of any one of claims 13-21, wherein the co-administration results in therapeutic synergy or in a positive outcome in the patient, and wherein the positive outcome is pCR, CR, PR, or SD.

Activity of MM-398 (Ls-CPT11) in an Orthotopic Pancreas Tumor Model Expressing Luciferase (L3.6pl).

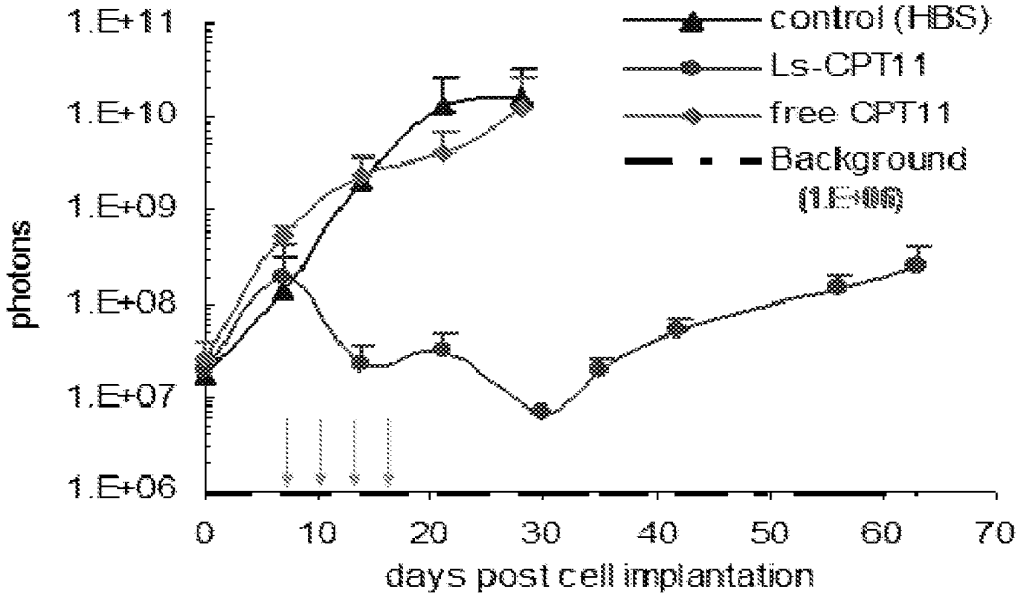


Fig. 1

Accumulation of SN-38 in Tumors Following Treatment with Free Irinotecan or Nanoliposomal Irinotecan (MM-398).

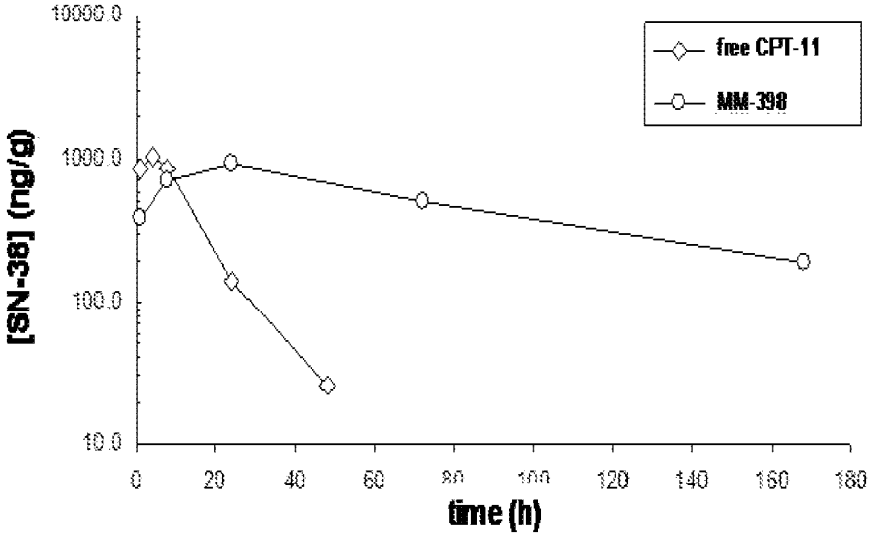


Fig. 2

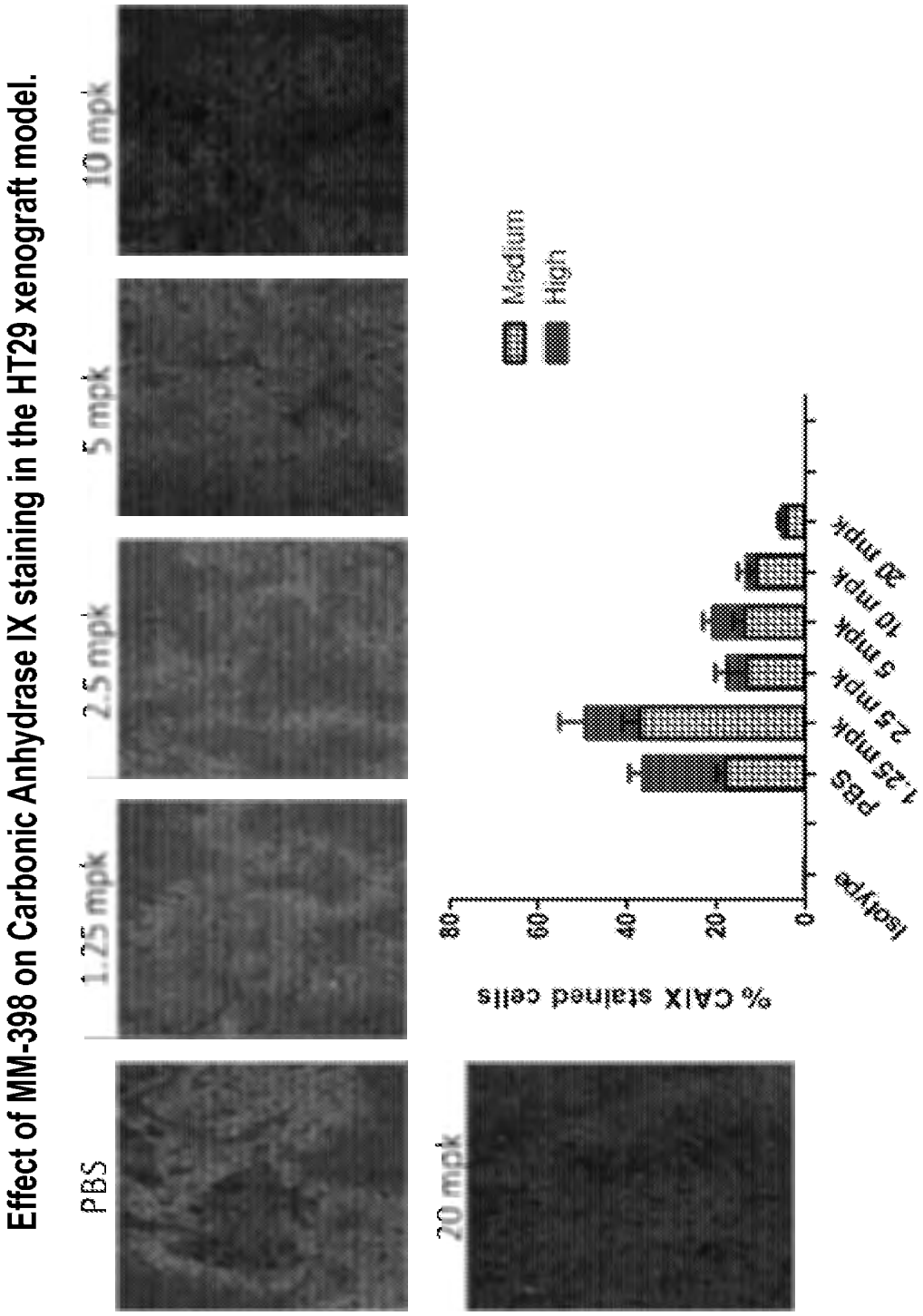

Effect of MM-398 on Carbonic Anhydrase IX staining in the HT29 xenograft model.
PBS
1.25 mpk
2.5 mpk
5 mpk
10 mpk
20 mpk
Medium
High
% CAIX stained cells
0
20
40
60
80
Isotype
PBS
1.25 mpk
2.5 mpk
5 mpk
10 mpk
20 mpk

Fig. 3

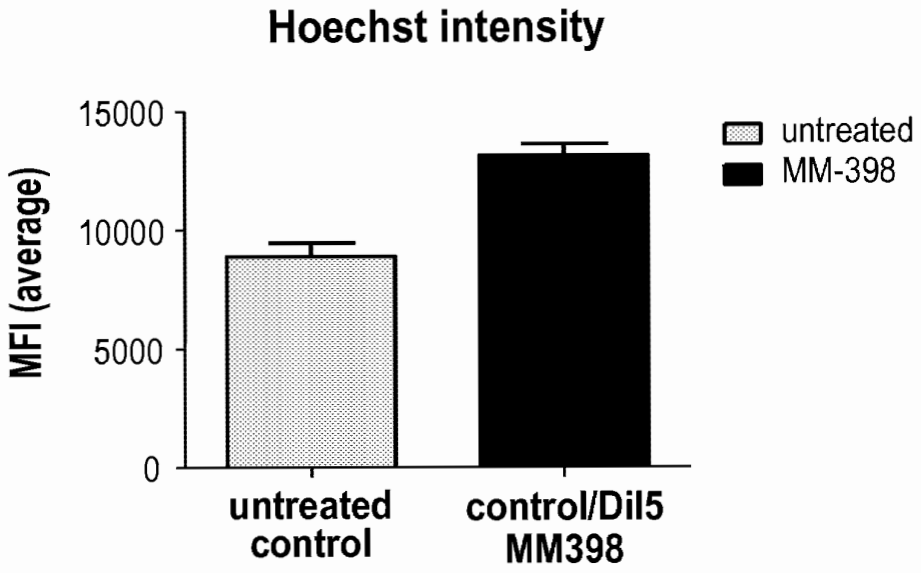

Hoechst intensity
MFI (average)
15000
10000
5000
0
untreated
MM-398
untreated control
control/Dil5 MM398

Fig. 4

MM-398 PK in q3w (irinotecan, liposome + free drug)

Dose (mg/m²) & Study	PEP0203			PEP0201		PEP0206		Camptosar® Package insert
	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Camptosar® 300 (n = 27)	125 mg/m² (N=64)	350 mg/m² (N=6)
Parameters										
C_{max} (µg/mL)	28.93 (± 15.75)	29.16 (± 5.24)	44.06 (± 7.65)	47.94 (± 16.24)	79.4 (± 13.9)	102 (± 17.6)	60.8 (± 36.6)	4.3 (± 1.2)	1.666 (± 0.797)	3.322 (± 0.874)
$t_{1/2}$ (h)	24.02 (± 16.76)	32.09 (± 18.21)	48.11 (± 17.41)	30.65 (± 5.32)	29.5 (± 17.2)	22.2 (± 11.5)	21.2 (± 18.3)	7.7 (± 4.4)	5.8 (± 8.7)	11.7 (± 1.6)
AUC_{0-T} (µg/mL•h)	1,047 (± 1,150)	1,116 (± 810)	2,193 (± 1,017)	1,117 (± 300)	2,835 (± 1,017)	1,945 (± 1,029)	1,651.5 (± 1,412.0)	24.2 (± 7.7)	18.2 (± 3.27)	29.60m (± 6.827)
$AUC_{0-\infty}$ (µg/mL•h)	1,114 (± 1,270)	1,211 (± 924)	2,472 (± 1261)	1,261 (± 300)	2,963 (± 1,947)	1,963 (± 1,035)	1,812.2 (± 1,601.9)	26.2 (± 9.0)	"	"
Cl (L/h/m²)	0.1269 (± 0.1650)	0.1164 (± 0.0 949)	0.0547 (± 0.0356)	0.1033 (± 0.0405)	0.0691 (± 0.0367)	0.119 (± 0.0703)	0.191 (± 0.260)	12.9 (± 4.7)	13.3 (± 6.01)	13.9 (± 4.6)
V_{ss} (L/m²)	2.6 (± 1.44)	2.93 (± 0.640)	2.63 (± 0.49)	3.16 (± 0.38)	1.8 (± 0.771)	1.97 (± 0.342)	2.23 (± 0.69)	98.5 (± 29.0)	118 (± 49.5)	234 (± 69.6)

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert,
T= 49.5 hours for Camptosar in the PEP0206 study and
T = 169.5 hours for MM-398.

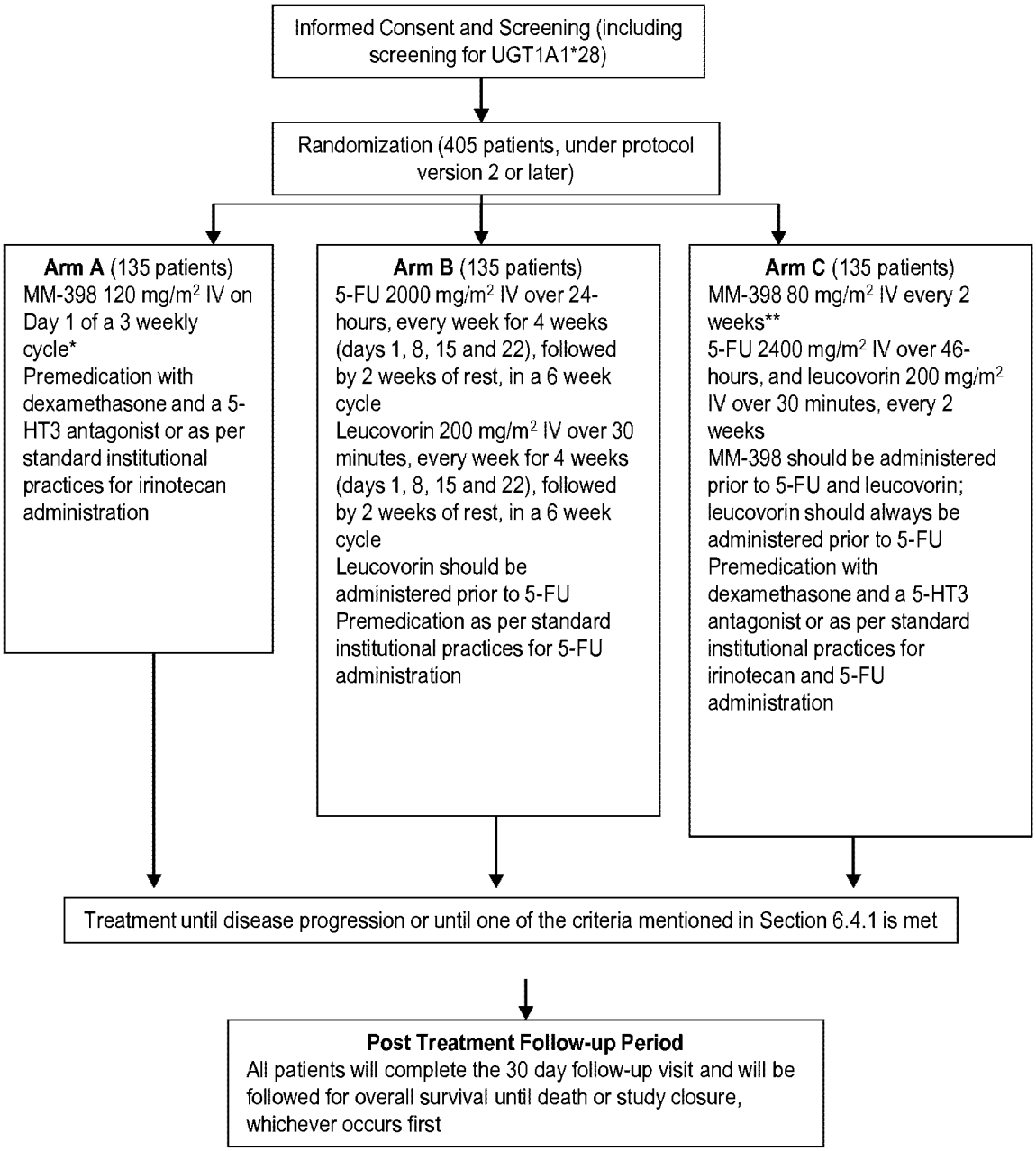
Fig. 5

MM-398 PK in q3w (SN-38)

Dose (mg/m²) & Study / Parameters	PEP0203				PEP0201		PEP0206		Camptosar® Package Insert	
	60 (n = 3)	80 (n = 6)	100 (n = 4)	120 (n = 2)	120 (n = 6)	180 (n = 4)	PEP02 120 (n = 37)	Campto® 300 (n = 27)	125 mg/m² (n = 61)	350 mg/m² (n = 61)
C_{max} (ng/mL)	7.02 (± 5.64)	7.58 (± 4.39)	7.39 (± 1.68)	16.64 (± 9.36)	9.2 (± 3.5)	14.3 (± 6.16)	8.79 (± 8.68)	44.1 (± 28.2)	26.3 (± 11.9)	56.0 (± 28.2)
$t_{1/2}$ (h)	183.81 (± 172.3)	53.75 (± 15.6)	73.41 (± 18.3)	26.23 (± 6.53)	75.4 (± 43.8)	58.0 (± 32.8)	88.8 (± 114.6)	22.8 (± 10.9)	10.4 (± 3.1)	21.0 (± 4.3)
AUC_{0-t} (ng·h/mL)	367.40 (± 227)	354.77 (± 145)	551.40 (± 331.8)	367.60 (± 155.7)	710 (± 395)	1,160 (± 969)	467 (± 310)	361 (± 125)	229 (± 108)	474 (± 245)
$AUC_{0-\infty}$ (ng·h/mL)	1,373.3 (± 1,119)	502.15 (± 153)	844.28 (± 444)	474.00 (± 209)	997 (± 680)	1,420 (± 1,134)	879 (± 1,426)	440 (± 162)	--	--

Note: AUC 0-T is defined as T = 24 hours for Camptosar package insert,
T= 49.5 hours for Camptosar in the PEP0206 study and
T = 169.5 hours for MM-398.

Fig. 6



* Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm A, will receive the first cycle of therapy at a reduced dose of 80 mg/m2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased in increments of 20 mg/m2, up to a maximum of 120 mg/m2.

** Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m2.

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/045495

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/4745 A61K31/513 A61K31/517 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Study of MM-398 Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer", , 11 December 2011 (2011-12-11), pages 1-3, XP055075223, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01494506/2011_12_16 [retrieved on 2013-08-14] the whole document ----- -/--	1,10-20, 23,26,27

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2013	22/08/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Haider, Ursula

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chang-Sung Tsai ET AL: "Nanovector-based therapies in advanced pancreatic cancer", Journal of Gastrointestinal Oncology, 1 September 2011 (2011-09-01), pages 185-194, XP055075231, DOI: 10.3978/j.issn.2078-6891.2011.034 Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3397610/pdf/jgo-02-03-185.pdf [retrieved on 2013-08-14]	1,6, 10-27
Y	page 189, right-hand column, paragraph 2	2-9
Y	J. M. HOSKINS ET AL: "UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters", JNCI JOURNAL OF THE NATIONAL CANCER INSTITUTE, vol. 99, no. 17, 5 September 2007 (2007-09-05), pages 1290-1295, XP055022025, ISSN: 0027-8874, DOI: 10.1093/jnci/djm115 the whole document	2
Y	HEDIA BRIXI-BENMANSOUR ET AL: "Phase II study of first-line FOLFIRI for progressive metastatic well-differentiated pancreatic endocrine carcinoma", DIGESTIVE AND LIVER DISEASE, W.B. SAUNDERS, GB, vol. 43, no. 11, 1 July 2011 (2011-07-01), pages 912-916, XP028296448, ISSN: 1590-8658, DOI: 10.1016/J.DLD.2011.07.001 [retrieved on 2011-07-07] page 915, right-hand column, paragraph 5	2-9
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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	"Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer", , 9 August 2012 (2012-08-09), pages 1-3, XP055075259, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01494506/2012_08_09 [retrieved on 2013-08-14] the whole document -----	1-27

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(54) **Title**: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING AN ANTI-ERBB3 ANTIBODY

(57) **Abstract**: Provided are methods for treating pancreatic cancer in a patient by co-administering combinations of an anti-ErbB3 antibody and one or more additional therapeutic agents. Further disclosed are the combinations of therapies which include: the an(i-ErbB3 antibody is coadministered with irinotecan, the anti-ErbB3 antibody is co-administered with paclitaxel (e.g., nab-paclitaxel), and the anti-ErbB3 antibody is coadministered with erlotinib and gemcitabine.

WO 2013/138371 A1

METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING AN ANTI-ERBB3 ANTIBODY

Background

Despite improvements in cancer treatments, there remains a critical need to further improve therapies so as to prolong patients' lives while maintaining quality of life, particularly in the case of advanced cancers such as pancreatic cancers that often are, or become, resistant to current therapeutic modalities.

The ErbB3 receptor is 148 kD transmembrane receptor that belongs to the ErbB/EGFR receptor tyrosine kinase family; it is the only family member known to lack intrinsic kinase activity. The ErbB receptors form homo- and heterodimeric complexes with other ErbB receptors that impact the physiology of cells and organs by mediating ligand-dependent (or rarely ligand independent) activation of multiple signal transduction pathways. Upon binding one of its physiological ligands (*e.g.,* heregulin), ErbB3 heterodimerizes with another ErbB family member, typically ErbB2 (HER2). ErbB3/ErbB2 dimerization results in phosphorylation of ErbB3 on tyrosine residues of the intracellular cytoplasmic region of the protein. ErbB3-containing heterodimers in tumor cells have been shown to be the most mitogenic and oncogenic receptor complexes of ErbB family members, and they strongly activate intracellular signaling pathways involved in tumorigenesis, such as those promoting cell survival, growth, and migration.

Incidence of pancreatic cancer has markedly increased during the past several decades. It now ranks as the fourth leading cause of cancer death in the United States. Pancreatic cancer's high mortality rate is due to a dearth of effective therapies and a complete absence of reliably durable therapies. Because of the location of the pancreas, pancreatic cancer is typically not diagnosed until a tumor has become large enough to produce systemic symptoms. This, coupled with the absence of good screening tools and a limited understanding of risk factors, results in patients usually having advanced disease, often advanced metastatic disease, at the time of diagnosis. Metastatic pancreatic cancer has a dismal prognosis and is almost uniformly fatal, with an overall survival rate of less than 4% at 5 years.

There are few approved treatment options for advanced or metastatic pancreatic cancers, particularly for those of exocrine origin. Single-agent gemcitabine is the current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma. In clinical trials, single-agent gemcitabine has consistently demonstrated a median prolongation of survival of 5 to 6 months and a 1-year survival rate of about 20%. Single agent gemcitabine was also approved as second line treatment for patients previously treated with but no longer responsive to 5-Fluorouracil, with a median overall prolongation of survival of 3.9 months.

Based upon what is known of the biology of pancreatic cancer, a variety of targeted agents have been evaluated, but only erlotinib, a protein tyrosine kinase inhibitor targeted to EGFR, has been approved for first-line use in advanced pancreatic cancer, and the approval is only for use in combination with gemcitabine. The co-administration of erlotinib with gemcitabine resulted in a statistically significant benefit in survival, and improvements in median survival (6.4 months vs. 5.9 months), and 1-year survival rate (24% vs. 17%) compared to gemcitabine alone. Clinical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative. Thus, there is an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer. The disclosed invention addresses this need.

Summary

Monotherapy with an anti-ErbB3 antibody significantly suppresses tumor growth in a dose-dependent manner in *in vivo* pancreatic adenocarcinoma xenograft models. It has now been discovered that co-administration of an anti-ErbB3 antibody with one or more additional therapeutic agents, such as paclitaxel (*e.g.*, nab-paclitaxel), irinotecan, or erlotinib (with or without concomitant gemcitabine), exhibits therapeutic synergy.

Accordingly, provided are methods of treating pancreatic cancer in a patient by co-administering therapeutically synergistic combinations of an anti-ErbB3 antibody and one or more additional therapeutic agents. These methods include a method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor. In some embodiments the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib. In some embodiments the one or more additional therapeutic agents is an EGFR inhibitor that is selected from MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab. In further embodiments the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor (e.g., formulated for intravenous administration) such a gemcitabine and the EGFR inhibitor (e.g., formulated for oral administration) is optionally erlotinib.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise 1) a nucleoside metabolic inhibitor such as gemcitabine, or 2) a microtubule stabilizing agent (e.g., formulated for intravenous administration) such as paclitaxel injection, nab-paclitaxel and docetaxel. Such co-administrations beneficially have an additive or superadditive effect on suppressing pancreatic tumor

growth, which effect on suppressing pancreatic tumor growth is measured, *e.g.*, in a mouse xenograft model using BxPC-3 or COLO-357 cells.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor and optionally wherein the topoisomerase 1 inhibitor is formulated for intravenous administration, such inhibitors are e.g., camptothecins selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, topotecan, lurtotecan, silatecan, and irinotecan and when the camptothecin is irinotecan or topotecan the irinotecan or topotecan may be liposomally encapsulated irinotecan or liposomally encapsulated topotecan. When the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan , the liposomally encapsulated irinotecan or liposomally encapsulated topotecan may each advantageously be contained in liposomes in the form of a sucrose octasulfate salt.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents is chosen from the group consisting of a bispecific anti-ErbB2/anti-ErbB3 antibody, an anti-IGF-1R/anti-ErbB3 antibody, an anti EGFR/anti-ErbB3 antibody, or a mixture of anti-EGFR and anti-ErbB3 antibodies.

Further provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one or more additional therapeutic agents comprises eribulin.

In each of the preceding methods the ErbB3 inhibitor may be an anti-ErbB3 antibody, *e.g.*, an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), or one comprising V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively. Anti-ErbB3 antibodies may further be selected from GE-huMab-HER3, MEDI3379, 8B8 (ATCC HB-12070), 1B4C3, 2D1D12, AMG888 and AV-203.

Further provided is a composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise 1) an orally available EGFR inhibitor, e.g., gefitinib, erlotinib, afatinib or lapatinib (frequently erlotinib), or a parenterally available EGFR inhibitor, e.g., MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab. In such combinations the one or more additional therapeutic agents may comprise a nucleoside metabolic inhibitor, e.g., gemcitabine; 2) a nucleoside metabolic inhibitor, e.g., gemcitabine; 3) a microtubule stabilizing agent, e.g., a taxane such as eribulin, paclitaxel injection, nab-paclitaxel or docetaxel (frequently nab-paclitaxel) – preferably co-administration of the anti-ErbB3 antibody and the taxane has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the taxane alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells; 4) a topoisomerase 1 inhibitor, e.g., a camptothecin such as 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, lurtotecan, silatecan, or (frequently) topotecan or irinotecan, *e.g.*, liposomally encapsulated irinotecan or liposomally encapsulated topotecan, each encapsulated, *e.g.*, in the form of a sucrose octasulfate salt. In one embodiment, the combination treatments are useful for inhibiting the spread of cancer cells from the pancreas to other tissues.

In each of the preceding methods and compositions the co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents preferably has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells. In certain embodiments of these methods, at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dosage that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy, *e.g.*, the reduced dosage is a dosage that is about half the dosage recommended by the manufacturer.

In each of the methods and compositions disclosed herein, the anti-ErbB3 antibody is advantageously formulated for intravenous administration. In each, the patient may have recurrent or persistent pancreatic cancer following primary chemotherapy and may have failed prior therapy with a

platinum-based therapeutic agent or have failed prior treatment with, or become resistant to treatment with one or more of a) a nucleoside analog therapeutic agent, b) a platinum-based therapeutic agent, c) a therapeutic agent, that is a topoisomerase 1 inhibitor and d) a therapeutic agent that is a tyrosine kinase inhibitor. In each of the additional therapeutic agent or agents may be administered following the administration of the anti-ErbB3 antibody; optionally, the topoisomerase 1 inhibitor may be administered before the administration of the anti-ErbB3 antibody or the topoisomerase 1 inhibitor and the anti-ErbB3 antibody are administered simultaneously. When a microtubule stabilizing agent is co-administered it may be administered before, after or concurrently with an anti-ErbB3 antibody. When EGFR inhibitor and nucleoside metabolic inhibitor are co-administered they may be administered before, after or concurrently with an anti-ErbB3 antibody.

In any of the foregoing methods and compositions the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is optionally gemcitabine. In the foregoing methods, the two or more additional therapeutic agents may be a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX), or a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), or a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

In any of the foregoing methods and compositions the anti-ErbB3 antibody may be formulated for intravenous administration and 1) is selected from the group comprising GE-huMab-HER3, MEDI3379, AMG888, AV-203, 8B8, 1B4C3 and 2D1D12, or 2) is selected from an antibody comprising V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively, or 3) comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

Furthermore, in any of the foregoing methods the pancreatic cancer may be an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors; or an adenocarcinoma that is a pancreatic ductal carcinoma; or an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome) – any of which may comprise a KRAS gene comprising a KRAS mutation such as KRAS G12S and may also or alternately comprise a BRAF mutation (e.g., BRAF V600E), in which case one of the one or more additional therapeutic agents is optionally a BRAF kinase inhibitor, frequently vemurafenib.

In any of the foregoing methods and compositions, the one or more additional therapeutic agents may comprise an mTOR inhibitor selected from the group consisting of temsirolimus, everolimus, sirolimus, and ridaforolimus, most commonly everolimus.

In any of the preceding methods and compositions, the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

In any of the foregoing compositions, the ErbB3 inhibitor may be an anti-ErbB3 antibody, e.g., an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively, or comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3). Alternately, the anti-ErbB3 antibody may be selected from 8B8, 1B4C3, 2D1D12, AMG888 and AV-203. Preferably co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells. In certain embodiments, at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dosage that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy, optionally the reduced dose is a dose that is about half the dosage recommended by the manufacturer.

In any of the preceding methods and compositions, the effective amount optionally 1) achieves a synergistic effect in reducing tumor volume in the patient; or 2) achieves tumor stasis in the patient.

Brief Description of the Drawings

Figure 1 shows suboptimal and optimal doses of MM-121 (**Figure 1A**) and irinotecan hydrochloride (CPT-11) (**Figure 1B**) for inhibiting tumor growth in a BxPC3 xenograft model.

Figure 2 shows tumor regression in a BxPC3 xenograft model after treatment with either CPT-11 or MM-398 in combination with the suboptimal (150 µg Q3D – **Figure 2A**) or optimal (600µg Q3D – **Figure 2B**) dose of MM-121.

Figure 3 shows tumor growth inhibition in a COLO-357 xenograft model after treatment with varying doses of MM-121.

Figure 4 shows tumor growth inhibition in a COLO-357 xenograft model after treatment with a suboptimal dose of MM-121 (300 μg Q3D) in combination with nab-paclitaxel **(Figure 4A)** or the same dose of MM-121 in combination with nab-paclitaxel with and without gemcitabine **(Figure 4B)**.

Figure 5 shows tumor growth inhibition in a COLO-357 xenograft model after treatment with MM-121 at 300 μg Q3D, erlotinib, and gemcitabine, either alone or in two-way or three-way combinations **(Figure 5A)**. **Figures 5B-E** depict each distinct dose combination shown in Figure **5A**.

Figure 6 shows tumor growth inhibition in a pancreatic primary tumor explant model after three-way combination treatment with MM-121, gemcitabine, and erlotinib.

Figure 7 shows the effect of MM-121 in combination with nab-paclitaxel and MM-398 in bioluminescent orthotopic pancreatic model using luciferase-labeled BxPC3 cells (BxPC3-Luc-2).

Figure 8 is a graph showing the effect of MM-121 on tumor cell migration to the lung (Figure 8A) or the liver (Figure 8B) in a pancreatic cancer orthotopic model.

Detailed Description

Methods of combination therapy and combination compositions for treating pancreatic cancer in a patient are provided. In these methods, the cancer patient is treated with both an anti-ErbB3 antibody and one or more additional therapeutic agents selected, *e.g.*, from irinotecan, paclitaxel, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and afatinib.

Definitions:

The terms "combination therapy," "co-administration," "co-administered" or "concurrent administration" (or minor variations of these terms) include simultaneous administration of at least two therapeutic agents to a patient or their sequential administration within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

The term "monotherapy" refers to administering a single drug to treat a disease or disorder in the absence of co-administration of any other therapeutic agent that is being administered to treat the same disease or disorder.

"Additional therapeutic agent" is used herein to indicate any drug that is useful for the treatment of a malignant pancreatic tumor other than a drug that inhibits heregulin binding to ErbB2/ErbB3 heterodimer.

"Antibody" describes a polypeptide comprising at least one antibody-derived antigen binding site (*e.g.*, VH/VL region or Fv, or complementarity determining region - CDR) that specifically binds to a specific antigen, *e.g.,* ErbB3. "Antibodies" include whole antibodies and any antigen binding fragment, *e.g.*, Fab or Fv, or a single chain fragment (*e.g.*, scFv), as well as bispecific antibodies and similar engineered variants, human antibodies, humanized antibodies, chimeric antibodies Fabs, Fab'2s, ScFvs, SMIPs, Affibodies®, nanobodies, or a domain antibodies, and may be of any of the following isotypes: IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgAsec, IgD, and IgE. The antibody may be a naturally occurring antibody or may be an antibody that has been altered (*e.g.*, by mutation, deletion, substitution, conjugation to a non-antibody moiety). For example, an antibody may include one or more variant amino acids (compared to a naturally occurring antibody) which change a property (*e.g.*, a functional property) of the antibody. For example, numerous such alterations are known in the art which affect, *e.g.*, half-life, effector function, and/or immune responses to the antibody in a patient. The term "antibody" thus includes whole antibodies and any antigen binding fragment (*i.e.*, "antigen-binding portion," *e.g.*, Fabs) or single chains thereof (*e.g.*, scFvs) as well as bispecific antibodies and similar engineered variants, provided that they retain the binding specificity of an antibody.

An "anti-ErbB3 antibody" is an antibody that immunospecifically binds to the ectodomain of ErbB3. Such binding to ErbB3 typically exhibits a binding affinity equal or greater than that indicated by a K_d of 50 nM (*i.e.*, a binding affinity corresponding to a K_d value of 50 nM, or a higher binding affinity as indicated by a lower K_d value such as 50 pM), *e.g.*, as measured by a surface plasmon resonance assay or a cell binding assay.

The terms "ErbB2," "HER2," and "HER2 receptor," as used interchangeably herein, refer to the protein product of the human neu oncogene, also referred to as the ErbB2 oncogene or the HER2 oncogene.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (*e.g.*, per hour, per day, per week, per month, etc.) to a patient. Such parameters include, *e.g.*, the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, *e.g.*, taken at a single administration, *e.g.,* orally (*e.g.*, as one, two, three or more pills, capsules, etc.) or injected (*e.g.*, as a bolus). Dosage sizes may also relate to doses that are administered continuously (*e.g.*, as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

"Effective treatment" refers to treatment producing a beneficial outcome, *e.g.*, amelioration of at least one symptom of a disease or disorder. A beneficial outcome can take the form of an improvement over baseline, which is generally an improvement over measurements, observations, or reported

symptoms made, *e.g.*, prior to, simultaneously with, or immediately following initiation of therapy. A beneficial outcome can also take the form of arresting, slowing, retarding, or stabilizing the progression of disease, *e.g.*, as indicated by changes in a biomarker. Effective treatment may also refer to improvement or alleviation of one or more symptoms of pancreatic cancer; *e.g.*, such treatment may reduce pain, increase patient mobility, reduce tumor size and/or number, increase longevity, reduce the rate of development of metastatic lesions, slow or reverse tumor growth, prevent or delay tumor recurrence, or inhibit, retard, slow or stop cancer cell infiltration into organs or tissues outside the pancreas.

"Effective amount" refers to an amount (administered in one or more doses) of an antibody, protein or additional therapeutic agent, which amount is sufficient to provide effective treatment.

The term "platinum-based therapeutic agent" refers to organoplatinum compounds (or treatment therewith), including for example oxaliplatin, carboplatin and cisplatin.

The disclosures if the following subsections should not be construed as limiting.

I. Anti-ErbB3 Antibody: An anti-ErbB3 antibody (*e.g.*, MM-121) is to be administered to a patient in a disclosed combination. MM-121 is a fully human anti-ErbB3 antibody currently undergoing Phase II clinical trials. MM-121 (also referred to as "Ab #6") and related human anti-ErbB3 antibodies are described in detail in U.S. patent No. 7,846,440, U.S. Patent Publication Nos. US 20100056761, and US 20100266584, and PCT Publication No. WO 2008/100624. Other anti-ErbB3 antibodies that may be used in a disclosed combination include any of the other anti-ErbB3 antibodies described in US patent No. 7,846,440, such as Ab #3 (SEQ ID NOs:14-21), Ab #14 (SEQ ID NOs:22-29), Ab #17 (SEQ ID NOs:30-37) or Ab #19 (SEQ ID NOs:38-45) or an antibody that competes with Ab #3, Ab #14, Ab #17 or Ab #19 for binding to ErbB3Additional examples of anti-ErbB3 antibodies that may be administered in accordance with the methods disclosed herein include antibodies disclosed in US patents and patent publications Nos. 7,285,649, 8,362,215, and 20100255010, as well as antibodies 1B4C3 (cat # sc-23865, Santa Cruz Biotechnology) and 2D1D12 (U3 Pharma AG), both of which are described in, *e.g.*, US Publication No. 20040197332 and are produced by hybridoma cell lines DSM ACC 2527 or DSM ACC 2517 (deposited at DSMZ) anti-ErbB3 antibodies disclosed in U.S. Patent No. 7,705,130 including but not limited to the anti-ErbB3 antibody referred to as AMG888 (U3-1287 -- U3 Pharma AG and Amgen), described in, *e.g.,* U.S. patent No. 7,705,130; the anti-ErbB3 antibody referred to as AV-203 (Aveo Pharmaceuticals) which is described in US patent publication No. 20110256154, and the monoclonal antibodies (including humanized versions thereof), such as 8B8 (ATCC® HB-12070™), described in U.S. patent No. 5,968,511. Additional examples include MEDI3379 (Medimmune), and GE-huMab-HER3 (Genentech), which is a glycoengineered anti-ErbB3 antibody. Other such examples include anti-ErbB3 antibodies that are multi-specific antibodies and comprise at least one anti-ErbB3 antibody (*e.g.*, one of the aforementioned anti-ErbB3 antibodies) linked to at least a second therapeutic antibody or to an

additional therapeutic agent. Examples of such antibodies include MM-141 and MM-111, described, e.g., in copending U.S. patent publication No. US 2011-0059076. Other suitable anti-ErbB3 antibodies also include pan-HER antibody compositions such as those disclosed, e.g., in PCT publication No. WO/2012/059857 (Symphogen) which describes antibody compositions targeting multiple ErbB family receptors. Yet other suitable anti-ErbB3 antibodies comprise either**: 1)** variable heavy (VH) and/or variable light (VL) regions encoded by the nucleic acid sequences set forth in SEQ ID NOs:1 and 3, respectively**, or 2)** VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively**, or 3)** CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and/or CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) as well as an antibody that binds to human ErbB3 and has at least 90% variable region sequence identity with the above-mentioned antibodies 1), 2), or 3). In one embodiment, the antibody has heavy and light chains comprising the amino acid sequences set forth in SEQ ID NOs 12 and 13, respectively. In another embodiment, the antibody competes for binding with and/or binds to the same epitope on human ErbB3 as any one of the above-mentioned antibodies. When the antibody is MM-121, the epitope typically comprises residues 92-104 of human ErbB3 (SEQ ID NO: 11). In other embodiments, the antibody is a fully human monoclonal antibody that binds to ErbB3 and, in living cells and either a) inhibits ErbB2/ErbB3 complex formation or b) prevents intracellular phosphorylation of ErbB3induced by any of the forms of each of the following: heregulin, EGF, TGFα, betacellulin, heparin-binding epidermal growth factor, biregulin, epigen, epiregulin, and amphiregulin, or does both a) and b).

Anti-ErbB3 antibodies described above, can be generated, *e.g.*, in prokaryotic or eukaryotic cells, using methods well known in the art, *e.g.*, in a cell line capable of glycosylating proteins, such as CHO cells.

II. Additional therapeutic agents:

Chemotherapy with one or more of 5-fluorouracil (5-FU) and gemcitabine has been shown to prolong survival in advanced pancreatic cancer. Many novel small molecules are being widely and actively researched as chemotherapeutic agents. These compounds include fluoropyrimidines, nucleoside analogues, platinum-based therapeutic agents, topoisomerase 1 inhibitors, antimicrotubule agents, BRAF inhibitors, proteasome inhibitors, vitamin D analogues, folinic acid (leucovorin or levoleucovorin), arachidonic acid pathway inhibitors, histone deacytylase inhibitors, farnesyltransferase inhibitors and epidermal growth factor receptor tyrosine kinase inhibitors. A combination therapy including folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI), folinic acid, 5-fluorouracil, irinotecan and oxaliplatin

(FOLFIRINOX), or, less commonly, a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) are also used to treat pancreatic cancer.

Additional therapeutic agents suitable for combination with anti-ErbB3 antibodies may further include: 1) EGFR inhibitors including but not limited to monoclonal antibody EGFR inhibitors (*e.g.* MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab), small molecule tyrosine kinase inhibitors (*e.g.*, afatinib, gefitinib, erlotinib, PKI-166, PD-158780, EKB-569, Tyrphostin AG 1478), dual inhibitors of EGFR and ErbB2 (*e.g.* afatinib and lapatinib), and pan-HER kinase inhibitors (*e.g.* CI-1033 (PD 183805), AC480, HM781-36B, AZD8931 and PF299804); 2) pyrimidine antimetabolites, *e.g.* the nucleoside metabolic inhibitor gemcitabine; 3) topoisomerase 1 inhibitors(*e.g.* irinotecan); 4) microtubule stabilizing agents (*e.g.* laulimalide, epothilone A, epothilone B, discodermolide, eleutherobin, sarcodictyin A, sarcodictyin B, cabazitaxel, paclitaxel, nab-paclitaxel or docetaxel); 5) BRAF inhibitors, (*e.g.* vemurafenib); 6) IGF1R inhibitors (e.g. dalotuzumab, XL228, BMS-754807 AMG-479, R1507, figitumumab, IMC-A12, and MM-141, a bispecific ErbB3/IGF1R inhibitor (further described in Lugovskoy *et al.*, copending commonly assigned U.S. Patent Application Serial No. 61/558,192, filed 11/10/2011, and PCT application No. PCT/US2012/034244) and molecule IGF1R inhibitors include XL228 and BMS-754807); 7) phosphoinositide-3-kinase (PI3K) inhibitors (e.g. CAL101 and PX-866); 8) mitogen activated kinase kinase (MEK) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib, and GSK1120212); and 9) mTOR inhibitors (*e.g.* everolimus, temsirolimus, sirolimus, or ridaforolimus). mTOR (mammalian target of rapamycin) is a serine/threonine protein kinase that regulates cell growth, proliferation, motility, survival, and protein synthesis and transcription. Rapamycin is now known as sirolimus, an mTOR inhibitor used as an immunosuppressant.

In certain combination therapy methods, one or more of the following therapeutic agents is co-administered to the patient with an anti-ErbB3 antibody.

Gemcitabine (Gemzar®) is indicated as first line therapy for pancreatic adenocarcinoma and is also used in various combinations to treat ovarian, breast and non-small-cell lung cancers. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (-isomer) (MW=299.66) and is administered parenterally, typically by i.v. infusion.

Irinotecan (Camptosar®) (irinotecan hydrochloride injection), also referred to as CPT-11, is administered parenterally, typically by i.v. infusion. CPT-11 is approved in the United States for treatment of metastatic colon or renal cancer. CPT-11 is also used to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

In one embodiment, CPT-11 is administered in a stable nanoliposomal formulation, *e.g.*, the formulation referred to herein as "MM-398" (also known as PEP02). MM-398 may be provided as a sterile, injectable parenteral liquid for intravenous injection. MM-398 may be administered, for example,

at a dosage of 120mg/m^2. The required amount of MM-398 may be diluted, *e.g.*, in 500mL of 5% dextrose injection USP and infused over a 90 minute period.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules. MM-398 recently achieved primary efficacy endpoints in Phase II clinical trials in metastatic pancreatic cancer and in gastric cancer, and is being investigated in the context of metastatic colorectal cancer.

Paclitaxel is administered parenterally, typically by i.v. infusion, and is formulated with polyethoxylated castor oil as "Taxol® (paclitaxel) injection" or with human serum albumin as "Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin bound)" also called nab-paclitaxel. Paclitaxel is used to treat, *e.g.*, breast cancer, non-small cell lung cancer (in combination with cisplatin), and AIDS-related Kaposi's sarcoma.

Erlotinib (Tarceva®) is orally administered and is used to treat, *e.g.*, locally advanced or metastatic non-small cell lung cancer (NSCLC) and locally advanced, unresectable or metastatic pancreatic cancer (in combination with gemcitabine).

Afatinib (Tomtovok®) is an orally administered tyrosine kinase inhibitor that irreversibly inhibits HER2 and EGFR kinases. It is not yet marketed and is being tested in the context of non-small cell lung carcinoma, breast, prostate, head and neck cancers, and glioma.

Temsirolimus (Torisel®) is an mTOR inhibitor that is administered parenterally, typically by i.v. infusion and is used to treat advanced renal cell carcinoma.

Everolimus (Afinitor®), a 40-O-(2-hydroxyethyl) derivative of sirolimus, is an mTOR inhibitor that is administered orally and is used to treat progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease.

Vemurafenib (Zelboraf®) is a BRAF enzyme inhibitor approved for the treatment of late-stage melanoma in patients whose cancer harbors a V600E BRAF mutation.

III. Combination Therapies

As herein provided, anti-ErbB3 antibodies (*e.g.,* MM-121) are co-administered with one or more additional therapeutic agents (*e.g.* irinotecan, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and/or afatinib), to provide effective treatment to human patients having a pancreatic cancer (*e.g.*, pancreatic adenocarcinoma).

The anti-ErbB3 antibody and one or more additional therapeutic agents for combination therapy may be administered to the patient in any suitable form. Typically, each of the anti-ErbB3 antibody and

the one or more additional therapeutic agents is provided in the form of a pharmaceutical composition, which comprises the antibody or additional therapeutic agent in a physiologically acceptable carrier. In certain embodiments, the one or more additional therapeutic agents are formulated for oral or intravenous administration. In another embodiment, the anti-ErbB3 antibody is formulated for intravenous administration.

In particular embodiments, the anti-ErbB3 antibody is administered at a dose selected from: 2-50 mg/kg (body weight of the patient) administered once a week, or twice a week or once every three days, or once every two weeks, and 1-100 mg/kg administered once a week, or twice a week or once every three days, or once every two weeks. In various embodiments, the anti-ErbB3 antibody is administered at a dosage of 3.2 mg/kg, 6 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg or 40 mg/kg at a timing of once a week, or twice a week or once every three days, or once every two weeks. Additional dosage ranges for the anti-ErbB3 antibody include: 1-1000 mg/kg, 1-500 mg/kg, 1-400 mg/kg, 1-300 mg/kg and 1-200 mg/kg. Suitable dosage schedules include once every three days, once every five days, once every seven days (*i.e.*, once a week), once every 10 days, once every 14 days (*i.e.*, once every two weeks), once every 21 days (*i.e.*, once every three weeks), once every 28 days (*i.e.*, once every four weeks) and once a month.

IV. Patient Populations

In one embodiment, a human patient for treatment using the methods and compositions disclosed herein exhibits evidence of recurrent or persistent disease following primary chemotherapy.

In another embodiment, such a human patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the human patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

As used herein the terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent. In one embodiment a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

In another embodiment, the pancreatic cancer undergoing treatment is advanced pancreatic cancer, which is a pancreatic tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor.

The combination therapies and methods disclosed herein are useful for the treatment of pancreatic cancers, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments. The methods can be used in the treatment of essentially any type of pancreatic cancer tumor that expresses ErbB3. Examples of types of pancreatic cancers to be treated include 1) exocrine pancreatic cancers, *e.g.,* acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell carcinoma of the pancreas, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, and serous cystadenocarcinoma, and 2) endocrine pancreatic cancers, *e.g.,* gastrinoma (Zollinger-Ellison Syndrome), insulinoma, nonfunctional islet cell tumor, somatostatinoma, vasoactive intestinal peptide-releasing tumor (VIPoma or Verner-Morrison Syndrome). In one embodiment, the pancreatic cancer is an adenocarcinoma (*i.e.*, pancreatic ductal carcinoma).

In one embodiment, the pancreatic cancer comprises one or more KRAS mutations (*e.g.,* a KRAS G12S mutation). "KRAS mutation" refers to oncogenic mutations found in certain cancers in KRAS, the human homolog of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene. It has been reported that KRAS mutations are found in 73% of pancreatic tumors. In another embodiment, the pancreatic cancer comprises a BRAF mutation (*e.g.,* a BRAF V600E mutation). "BRAF mutation" refers to oncogenic mutations in the BRAF (Serine/threonine-protein kinase B-Raf or "B-Raf") gene. When present, KRAS and BRAF mutations are typically found together in pancreatic tumors. Transgenomic, Inc., Omaha, Nebraska; Asuragen, Inc., Austin, Texas; EntroGen, Inc., Tarzana, California; and QIAGEN Gmbh, Hilden, Germany, are among the many companies that market both KRAS and BRAF testing kits. Multiple laboratories now offer KRAS and BRAF mutation testing of tumor biopsy samples as a commercial service. *e.g.,* GenPath, Elmwood Park, New Jersey and Clarient, Inc., Aliso Viejo, California.

V. Outcomes

As shown in the Examples herein, co-administration of an anti-ErbB3 antibody with one or more additional therapeutic agents (*e.g.* irinotecan, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and/or afatinib) provides improved efficacy compared to treatment with the antibody alone or with the one or more additional therapeutic agents in the absence of antibody therapy. Preferably, a combination of an anti-ErbB3 antibody with one or more additional therapeutic agents exhibits therapeutic synergy.

"Therapeutic synergy" refers to a phenomenon where treatment of patients with a combination of therapeutic agents manifests a therapeutically superior outcome to the outcome achieved by each individual constituent of the combination used at its optimum dose (T. H. Corbett et al., 1982, Cancer Treatment Reports, 66, 1187). In this context a therapeutically superior outcome is one in which the patients either a) exhibit fewer incidences of adverse events while receiving a therapeutic benefit that is equal to or greater than that where individual constituents of the combination are each administered as monotherapy at the same dose as in the combination, or b) do not exhibit dose-limiting toxicities while

receiving a therapeutic benefit that is greater than that of treatment with each individual constituent of the combination when each constituent is administered in at the same doses in the combination(s) as is administered as individual components. In xenograft models, a combination, used at its maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its individual maximum tolerated dose, manifests therapeutic synergy when decrease in tumor growth achieved by administration of the combination is greater than the value of the decrease in tumor growth of the best constituent when the constituent is administered alone.

Thus, in combination, the components of such combinations have an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to monotherapy with the anti-ErbB3 antibody or treatment with the chemotherapeutic(s) in the absence of antibody therapy. By "additive" is meant a result that is greater in extent (e.g., in the degree of reduction of tumor mitotic index or of tumor growth or in the degree of tumor shrinkage or the frequency and/or duration of symptom-free or symptom-reduced periods) than the best separate result achieved by monotherapy with each individual component, while "superadditive" is used to indicate a result that exceeds in extent the sum of such separate results. In one embodiment, the additive effect is measured as slowing or stopping of pancreatic tumor growth. The additive effect can also be measured as, e.g., reduction in size of a pancreatic tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, increase in overall response rate, or increase in median or overall survival.

One non-limiting example of a measure by which effectiveness of a therapeutic treatment can be quantified is by calculating the log10 cell kill, which is determined according to the following equation:

$$\log10 \text{ cell kill} = T\,C \text{ (days)}/3.32 \times Td$$

in which T C represents the delay in growth of the cells, which is the average time, in days, for the tumors of the treated group (T) and the tumors of the control group (C) to have reached a predetermined value (1 g, or 10 mL, for example), and Td represents the time, in days necessary for the volume of the tumor to double in the control animals. When applying this measure, a product is considered to be active if log10 cell kill is greater than or equal to 0.7 and a product is considered to be very active if log10 cell kill is greater than 2.8. Using this measure, a combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose generally less than or equal to its maximum tolerated dose, exhibits therapeutic synergy when the log10 cell kill is greater than the value of the log10 cell kill of the best constituent when it is administered alone. In an exemplary case, the log10 cell kill of the combination exceeds the value of the log10 cell kill of the best constituent of the combination by at least 0.1 log cell kill, at least 0.5 log cell kill, or at least 1.0 log cell kill.

VI. Kits and Unit Dosage Forms

Kits that include a pharmaceutical composition containing an anti-ErbB3 antibody, such as MM-121, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods are provided. The kits can optionally also include instructions, *e.g.*, comprising administration schedules, to allow a practitioner (*e.g.*, a physician, nurse, or patient) to administer the compositions contained therein to a patient having a pancreatic cancer. In one embodiment, the kit further comprises irinotecan. In another embodiment, the kit further comprises paclitaxel (*e.g.*, nab-paclitaxel). In another embodiment, the kit further comprises erlotinib and/or gemcitabine. In another embodiment the kit includes infusion devices such as needles, catheters, tubing, and the like. Optionally, the kits include multiple packages each containing a single dose amount of the antibody or of the chemotherapeutic (*e.g.*, in a unit dosage form distributed by the manufacturer) for administration in accordance with the methods provided herein.

VII. Treatment of Cancer Types other than Pancreatic Cancer

ErbB3 is a critical activator of phosphoinositide 3-kinase (PI3K) signaling in cancers that arise from dependence on the epidermal growth factor receptor, *e.g.*, pancreatic cancer, and reactivation of ErbB3 is a prominent method by which a cancer can become resistant to ErbB inhibitors. The methods and combination treatments described herein will thus be useful for treatment of types of cancer with a molecular pathology similar to that of pancreatic cancer in that they are EGFR-driven and, after anti-EGFR treatment, become resistant to such treatment through increased signaling in the PI3K pathway via ErbB3. Such cancer types include, but are not limited to, lung, colon, head and neck, and esophageal cancers.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

Incorporation By Reference: The disclosure of each and every US, International, or other patent or patent application or publication referred to herein is hereby incorporated herein by reference in its entirety.

Examples

Example 1 Combination Treatment with MM-121 and irinotecan Inhibits Tumor Growth in Pancreatic Cancer

The anti-tumor efficacy and tolerability of MM-121 and irinotecan (CPT-11 or in liposomal formulation (MM-398)), either alone (*i.e.*, as a monotherapy) or in combination, in tumor-bearing mice was evaluated using human pancreatic adenocarcinoma BxPC-3 cells (ATCC # CRL-1687) implanted as xenografts in nu/nu nude mice. BxPC-3 cells were derived from a human metastatic tumor and expressed

high levels of HRG and EGFR. In these xenograft studies, nu/nu nude mice were obtained from Charles River Laboratories International. The mice were housed in Tecniplast® Individually Ventilated polycarbonate (Makrolon®) Cages (IVC) set in climate-controlled rooms and had free access to food and acidified water. 8 x 10^6 cells were mixed 1:1 in reduced growth factor Matrigel™ (BD Biosciences, Cat # 354230) and implanted by subcutaneous injection into the left flank of female, 4-5 week old nu/nu mice. Tumors were allowed to reach 150 mm^3 in size before randomization.

Dose Escalation Study A dose escalation study was performed to determine suboptimal and optimal doses of MM-121 and CPT-11 in preparation for combination therapy using the BxPC-3 xenograft model.

Xenograft-bearing mice were randomized into 10 groups of 5 mice, containing mice with a similar size distribution of tumors. Four groups were treated with escalating intraperitoneal (i.p.) doses of MM-121 (75, 150, 300 or 600 µg, Q3D per group), 3 groups were treated with escalating doses of irinotecan (CPT-11) (6.25, 12.5, 25 or 50 mg/kg, Q7D, per group), one control group was treated with PBS, Q3D, and another control group was treated with 5% DMSO in PBS (CPT-11 vehicle), Q7D. Treatment continued for 3 weeks. Tumors were measured twice weekly, and tumor volume was calculated as $\pi/6 \times \text{length} \times \text{width}^2$, where the width is the shorter measurement.

Dose responses for inhibition of tumor growth were observed for MM-121 (Figure 1A) and CPT-11 (Figure 1B). The "suboptimal" doses for evaluation in combination therapy in BxPC-3 xenografts were identified as 150 µg Q3D for MM-121 and 12.5 to 25 mg/kg for CPT-11 Q7D. Meanwhile, the "optimal" doses for evaluation in BxPC-3 xenografts were identified as 600µg Q3D for MM-121 and 50 mg/kg for CPT-11.

Combination therapy study A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, irinotecan (CPT-11), and liposomal irinotecan (MM-398).

Mice were randomized as above into 9 groups of 5 mice each. Five groups were treated with i.p. doses of a single agent alone, as follows: (1) MM-121 (150 µg Q3D), (2) MM-121 (600 µg Q3D), (3) CPT-11 (25 mg/kg Q7D), (4) MM-398 (10 mg/kg Q3D), or (5) PBS (Q3D) alone (Control). Four groups were treated with a combination therapy of (1) MM-121 and CPT-11 or (2) MM-121 and MM-398 with the doses described above. Treatment continued for 4 weeks. Tumors were measured twice weekly and tumor volume calculated.

As shown in Figure 2A (MM-121 dose; 150 µg Q3D) and Figure 2B (MM-121 optimal dose; 600µg Q3D), MM-121 as a single agent significantly suppressed tumor growth in a dose-dependent manner. Moreover, while CPT-11 and MM-398 alone each inhibited tumor growth *in vivo*, combination treatments with MM-121 and CPT-11 or MM-121 and MM-398 exhibited an additive effect on tumor growth inhibition, as compared to tumor growth inhibition observed with each of the individual agents.

Furthermore, treatment with either CPT-11 or MM-398 in combination with the optimal dose of MM-121 (600μg Q3D) resulted in pronounced tumor regression.

Example 2 Combination Treatment with MM-121 and nab-paclitaxel Inhibits Tumor Growth in Pancreatic Cancer

The anti-tumor efficacy and tolerability of MM-121 and nab-paclitaxel (paclitaxel protein-bound particles for injectable suspension) combination treatment, with or without gemcitabine, was evaluated using COLO-357 cells (ECACC Cat # 94072245) implanted as xenografts in nu/nu nude mice. COLO-357 cells were derived from a lymph node metastasis of a human non-endocrine pancreatic cancer, and have been reported to harbor KRAS G12S and BRAF V600E mutations.

Xenograft-bearing mice were prepared as described except 5 x 10^6 COLO-357 cells were used.

Dose Escalation Study – MM-121 A dose escalation study was performed to determine optimal doses of MM-121 in preparation for combination therapy using the COLO-357 xenograft model.

Xenograft-bearing mice were randomized into seven groups of five mice, containing mice with a similar size distribution of tumors. Six groups were treated with escalating doses of i.p. MM-121 (18.75, 37.5, 75, 150, 300 or 600 μg, Q3D per group), and another control group was treated with PBS. Treatment continued for 4 weeks. Tumors were measured twice weekly, and tumor volume was calculated. As depicted in Figure 3, MM-121 suppressed tumor growth in a dose-dependent manner. The "suboptimal" doses for evaluation in combination therapy in COLO-357 cells xenografts were identified as 300 μg Q3D for MM-121, and the "optimal" dose was identified as 600μg Q3D.

Combination therapy study A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, nab-paclitaxel (Abraxis; Catalog # NDC68817-134-50), and gemcitabine (LC labs; Catalog # G1477).

Xenograft-bearing mice were randomized into 10 groups of 9-10 mice, containing mice with a similar size distribution of tumors. Four groups were treated with i.p. doses of a single agent alone, as follows: (1) 10 mg/kg Q3D i.p. of nab-paclitaxel, (2) 20 mg/kg Q3D i.p. of nab-paclitaxel (3) 300 μg Q3D i.p. of MM-121, (4) 150mg/kg Q7D i.p. of gemcitabine. Three groups were treated with duo combination therapy, as follows: (1) MM-121 and nab-paclitaxel (10 mg/kg), (2) MM-121 and nab-paclitaxel (20 mg/kg), and (3) MM-121 and gemcitabine (150mg/kg). Two groups were treated with triple combination therapy, as follows: (1) MM-121, nab-paclitaxel (10 mg/kg) and gemcitabine, and (2) MM-121, nab-paclitaxel (20 mg/kg) and gemcitabine. A control group was treated with PBS, Q3D, i.p.. Treatment continued for 7 weeks. Tumors were measured twice weekly, and tumor volume was calculated.

As shown in Figures 4A-B, MM-121 as a single agent, at the suboptimal dose of 300 μg Q3D, significantly suppressed tumor growth in a dose-dependent manner. However, the COL-357 xenograft

model responded poorly to nab-paclitaxel alone (Figure 4A) and moderately to gemcitabine alone (Figure 4B) for the doses tested.

With respect to the combination therapies, MM-121 in combination with nab-paclitaxel showed a dose-dependent additive effect on tumor growth suppression when compared to each drug alone (Figure 4A). Additionally, MM-121 in combination with gemcitabine shows little if any enhancement over MM-121 single therapy (Figure 4B) in COLO-357 tumors.

Moreover, while CPT-11 and MM-398 alone each inhibit tumor growth *in vivo*, treatment with the combinations of MM-121 and CPT-11 or MM-121 and MM-398 resulted in an additive effect on suppression of tumor growth, as compared to treatment with each of the individual agents. Furthermore, treatment with either CPT-11 or MM-398 in combination with the optimal dose of MM-121 (600µg Q3D) resulted in pronounced increase in cell death, as shown in figure 4.

The triple combination therapy of MM-121, nab-paclitaxel and gemcitabine suppressed tumor growth to a similar extent as the dual MM-121 and nab-paclitaxel combination, indicating that gemcitabine did not enhance the inhibitory effect of this dual combination (Figure 4B) in COLO-357 tumors.

Example 3 Triple Combination Treatment with MM-121, gemcitabine, and erlotinib Inhibits Tumor Growth in Pancreatic Cancer

A) A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, erlotinib (LC Laboratories – Catalog # E4007), and gemcitabine. Specifically, the anti-tumor efficacy of MM-121 and erlotinib in combination, with or without gemcitabine, on tumor-bearing mice was analyzed using COLO-357 cells. Xenograft bearing mice were prepared as described in the preceding Example.

Five groups were treated with single agents, as follows: (1) 50 mg/kg Q5D oral of erlotinib, (2) 100 mg/kg Q5D oral of erlotinib, (3) 300 µg Q3D i.p. of MM-121, (4) 150 mg/kg Q7D i.p. of gemcitabine, and (5) 300 mg/kg Q7D i.p. of gemcitabine. Additional groups were treated with double combination or triple combination therapy, as set forth in Table 1 below. A control group was treated with PBS, Q3D, i.p. Treatment continued for 7 weeks. Tumors were measured twice weekly and tumor volume was calculated.

Table 1

Group	Test Article	Dose	Route	Dose Schedule	Dose Volume	Mice (n)
1	Vehicle Control	NA	IP	Q3D X 12	0.1 ml	10
2	MM-121	300 µg	IP	Q3D X 12	0.1 ml	10

3	erlotinib	50 mg/kg	PO	QD (5x a week)	0.2 ml	10
4	erlotinib	100 mg/kg	PO	QD (5x a week)	0.2 ml	10
5	gemcitabine	150 mg/kg	IP	Q7D X 5	0.4ml	10
6	gemcitabine	300 mg/kg	IP	Q7D X 5	0.4ml	10
7	MM121 + erlotinib + gemcitabine	300µg+50mpk+150mpk	IP+PO+IP	Q3D X 12+ QD (5x a week)+ Q7D X 5	0.1 ml+0.2 ml+0.4ml	10
8	MM121 + erlotinib + gemcitabine	300µg+50mpk+300mpk	IP+PO+IP	Q3D X 12+ QD (5x a week)+ Q7D X 5	0.1 ml+0.2 ml+0.4ml	10
9	MM121 + erlotinib + gemcitabine	300µg+100mpk+150mpk	IP+PO+IP	Q3D X 12+ QD (5x a week)+ Q7D X 5	0.1 ml+0.2 ml+0.4ml	10
10	MM121 + erlotinib + gemcitabine	300µg+100mpk+150mpk	IP+PO+IP	Q3D X 12+ QD (5x a week)+ Q7D X 5	0.1 ml+0.2 ml+0.4ml	10
11	erlotinib + gemcitabine	50 mpk+150 mpk	PO+IP	QD (5x a week)+ Q7D X 5	0.2 ml+0.4ml	10
12	erlotinib + gemcitabine	100 mpk+300 mpk	PO+IP	QD (5x a week)+ Q7D X 5	0.2 ml+0.4ml	10
13	erlotinib + gemcitabine	50 mpk+300 mpk	PO+IP	QD (5x a week)+ Q7D X 5	0.2 ml+0.4ml	10
14	erlotinib + gemcitabine	100 mpk+150 mpk	PO+IP	QD (5x a week)+ Q7D X 5	0.2 ml+0.4ml	10

IP: interperitoneal administration - PO: oral administration

As shown in Figures 5A-E, the triple combination of MM-121, erlotinib and gemcitabine was superior in inhibiting tumor growth compared to all doses tested of the standard of care therapy (*i.e.*,

gemcitabine and erlotinib). These results indicate that the addition of MM-121 to the standard of care regimen is beneficial for tumor growth control.

B) To further demonstrate the effects of various combinations of MM-121, erlotinib and gemcitabine on pancreatic cancer, , a pancreatic primary tumor explant model (*i.e.*, low passage Champions Tumorgrafts™ CTG-0289 (PANC002), which is reported to harbor KRAS mutations) was used. Immunocompromised mice (Harlan®; nu/nu) between 4-6 weeks of age were implanted unilaterally on the right flank with tumor fragments harvested from 2-4 host animals each implanted from a specific passage lot. Pre-study tumor volumes were recorded for each experiment beginning approximately one week prior to its estimated start date. When tumors reach approximately 125-225 mm^3, animals were matched by tumor volume into treatment and control groups and dosing initiated (Day 0), as set forth in Table 2. Animals in all studies were tagged and followed individually throughout the experiment.

Beginning Day 0, tumor dimensions were measured twice weekly by digital caliper, and data including individual and mean estimated tumor volumes (Mean TV ± SEM) were recorded for each group. Tumor volume was calculated using the formula (1): $TV = width^2 \times length \times 0.52$. At study completion, percent tumor growth inhibition (%TGI) values was calculated and reported for each treatment group (T) versus control (C) using initial (i) and final (f) tumor measurements by the formula (2): $\%TGI = 1 - T_f - T_i \ / \ C_f - C_i$.

The results are set forth in Table 2 and Figure 6.

Table 2: *In Vivo* Evaluation of MM-121 in Pancreas Tumorgraft™ Model

Group	-n-	Agent	Dose (mg/kg/dose)	ROA/ Schedule*
1	9	Vehicle Control	--	i.p./ q3dx10
2	9	MM-121	30	i.p./ q3dx10
3	9	erlotinib	35	p.o./ qdx28
4	9	gemcitabine	60	i.p./ q3dx4
5	9	erlotinib	35	p.o./ qdx28
		gemcitabine	60	i.p./ q3dx4
6	9	MM-121	30	i.p./ q3dx10
		erlotinib	35	p.o./ qdx28
7	9	MM-121	30	i.p./ q3dx10
		gemcitabine	60	i.p./ q3dx4
8	9	MM-121	30	i.p./ q3dx10
		erlotinib	35	p.o./ qdx28
		gemcitabine	60	i.p./ q3dx4

*gemcitabine was dosed first and MM-121 was dosed second with administration occurring two hours apart from each other.

As shown in Figure 6, MM-121, gemcitabine or erlotinib treatment as single agents yielded suboptimal effects on tumor growth inhibition for the doses tested. Specifically, this pancreatic primary tumor explant model was moderately sensitive to gemcitabine and exhibited lesser responses to erlotinib or MM-121.

The combination of gemcitabine and erlotinib was no more efficacious than gemcitabine alone. Additionally, while MM-121 in combination with gemcitabine showed an additive effect as compared to the single agents, MM-121 in combination with erlotinib was not more efficacious than MM-121 alone in this model.

In contrast, the triple combination of MM-121, erlotinib, and gemcitabine had an additive effect on tumor growth inhibition, as compared to the agents alone or paired. In sum, the addition of MM-121 addition to the standard of care combination (erlotinib plus gemcitabine) in this primary pancreatic explant model provided enhanced tumor growth inhibition.

Example 4. Effect of MM-121 in combination with chemotherapies in an orthotopic model of pancreatic cancer

Luciferase-labeled human pancreatic cancer cells (BxPC-3-luc2 Bioware® Ultra, Caliper Life Sciences) were expanded in culture and inoculated orthotopically into nude mice (Charles River, nu/nu). Mice were anesthetized and a 0.5cm incision was made on the left flank region. The spleen and the tail of the pancreas were exteriorized. Cells were inoculated at $1x10^6$ cells/ 20µl into the sub-capsular space into the tail of the pancreas. The spleen and the pancreas were then placed back into the peritoneal cavity, and the cavity was sutured and skin closed with surgical staples.

In vivo whole body biophotonic imaging was performed weekly throughout the study. Seven days after inoculation of tumor cells the first bioluminescent imaging was performed and mice were randomized into 7 treatment groups (10 mice/group) and treated with PBS (Q3D, i.p.), MM121 600µg, 1200ug (Q3D, i.p.), MM398 10mg/kg (Q7D, i.v.), nab-paclitaxel 15mg/kg (Q3D, i.p.), or combination of MM121 600µg with either MM398 or nab-paclitaxel at the doses mentioned above.

Mice were treated via the regimen described above for 35 days; bioluminescent imaging was performed once every 7 days. At the end of the study, the mice were sacrificed 24 hours after the final dose of each treatment was administered, and final images were taken. The tumors were removed, imaged and placed in formalin for future evaluation. Selected organs such as lung, diaphragm, liver and gastrointestinal-associated lymph nodes were also removed at the end of study, placed in petri dishes and imaged for bioluminescence, as a measurement of tumor cell migration.

As shown in Figure 7, treatment with the combination of MM-121 and either MM-398 or nab-paclitaxel significantly decreased the tumor growth as compared to either drug treatment alone. In addition, MM-121 treatment significantly diminished tumor cell migration from pancreas to lung (Figure 8A) and liver (Figure 8B). Similar results were seen in the diaphragm and gastrointestinal-associated lymph nodes. Thus, these combination treatments are useful for inhibiting the spread of cancer cells from the pancreas to other organs.

SUMMARY OF SEQUENCES

MM-121 Heavy Chain Variable Region Nucleotide Sequence (SEQ ID NO:1)

gaggtgcagc tgctggagag cggcggaggg ctggtccagc caggcggcag cctgaggctg 60

tcctgcgccg ccagcggctt caccttcagc cactacgtga tggcctgggt gcggcaggcc 120

ccaggcaagg gcctggaatg ggtgtccagc atcagcagca gcggcggctg gaccctgtac 180

gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcac caggggcctg 300

aagatggcca ccatcttcga ctactggggc cagggcaccc tggtgaccgt gagcagc 357

MM-121 VH amino acid sequence (SEQ ID NO:2)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYVMAWVRQAPGKGLEWVSSISSSGGWTLYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGLKMATIFDYWGQGTLVTVSS

MM-121 Light Chain Nucleotide Sequence (SEQ ID NO:3)

cagtccgccc tgacccagcc cgccagcgtg agcggcagcc caggccagag catcaccatc 60

agctgcaccg gcaccagcag cgacgtgggc agctacaacg tggtgtcctg gtatcagcag 120

caccccggca aggcccccaa gctgatcatc tacgaggtgt cccagaggcc cagcggcgtg 180

agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg 240

cagaccgagg acgaggccga ctactactgc tgcagctacg ccggcagcag catcttcgtg 300

atcttcggcg agggaccaa ggtgaccgtc cta 333

MM-121 VL amino acid sequence (SEQ ID NO:4)
QSALTQPASVSGSPGQSITISCTGTSSDVGSYNVVSWYQQHPGKAPKLIIYEVSQRPSGVSNRFSG
SKSGNTASLTISGLQTEDEADYYCCSYAGSSIFVIFGGGTKVTVL

MM-121 VH CDR1 (SEQ ID NO:5)
HYVMA

MM-121 VH CDR2 (SEQ ID NO:6)
SISSSGGWTLYADSVKG

MM-121 VH CDR3 (SEQ ID NO:7)
GLKMATIFDY

MM-121 VL CDR1 (SEQ ID NO:8)
TGTSSDVGSYNVVS

MM-121 VL CDR2 (SEQ ID NO:9)
EVSQRPS

MM-121 VL CDR3 (SEQ ID NO:10)
CSYAGSSIFVI

ErbB3 (SEQ ID NO:11)
SEVGNSQAVCPGTLNGLSVTGDAENQYQTLYKLYERCEVVMGNLEIVLTGHNADLSFLQWIRE
VTGYVLVAMNEFSTLPLPNLRVVRGTQVYDGKFAIFVMLNYNTNSSHALRQLRLTQLTEILSGG
VYIEKNDKLCHMDTIDWRDIVRDRDAEIVVKDNGRSCPPCHEVCKGRCWGPGSEDCQTLTKTIC
APQCNGHCFGPNPNQCCHDECAGGCSGPQDTDCFACRHFNDSGACVPRCPQPLVYNKLTFQLEP
NPHTKYQYGGVCVASCPHNFVVDQTSCVRACPPDKMEVDKNGLKMCEPCGGLCPKACEGTGS
GSRFQTVDSSNIDGFVNCTKILGNLDFLITGLNGDPWHKIPALDPEKLNVFRTVREITGYLNIQSW
PPHMHNFSVFSNLTTIGGRSLYNRGFSLLIMKNLNVTSLGFRSLKEISAGRIYISANRQLCYHHSLN
WTKVLRGPTEERLDIKHNRPRRDCVAEGKVCDPLCSSGGCWGPGPGQCLSCRNYSRGGVCVTH
CNFLNGEPREFAHEAECFSCHPECQPMEGTATCNGSGSDTCAQCAHFRDGPHCVSSCPHGVLGA
KGPIYKYPDVQNECRPCHENCTQGCKGPELQDCLGQTLVLIGKTHLTMALTVIAGLVVIFMMLG
GTFLYWRGRRIQNKRAMRRYLERGESIEPLDPSEKANKVLARIFKETELRKLKVLGSGVFGTVH

KGVWIPEGESIKIPVCIKVIEDKSGRQSFQAVTDHMLAIGSLDHAHIVRLLGLCPGSSLQLVTQYL
PLGSLLDHVRQHRGALGPQLLLNWGVQIAKGMYYLEEHGMVHRNLAARNVLLKSPSQVQVAD
FGVADLLPPDDKQLLYSEAKTPIKWMALESIHFGKYTHQSDVWSYGVTVWELMTFGAEPYAGL
RLAEVPDLLEKGERLAQPQICTIDVYMVMVKCWMIDENIRPTFKELANEFTRMARDPPRYLVIK
RESGPGIAPGPEPHGLTNKKLEEVELEPELDLDLDLEAEEDNLATTTLGSALSLPVGTLNRPRGSQ
SLLSPSSGYMPMNQGNLGESCQESAVSGSSERCPRPVSLHPMPRGCLASESSEGHVTGSEAELQE
KVSMCRSRSRSRSPRPRGDSAYHSQRHSLLTPVTPLSPPGLEEEDVNGYVMPDTHLKGTPSSREG
TLSSVGLSSVLGTEEEDEDEEYEYMNRRRRHSPPHPPRPSSLEELGYEYMDVGSDLSASLGSTQS
CPLHPVPIMPTAGTTPDEDYEYMNRQRDGGGPGGDYAAMGACPASEQGYEEMRAFQGPGHQA
PHVHYARLKTLRSLEATDSAFDNPDYWHSRLFPKANAQRT

MM-121 Heavy Chain Amino Acid Sequence (SEQ ID NO:12)

1 EVQLLESGGG LVQPGGSLRL SCAASGFTFS HYVMAWVRQA PGKGLEWVSS
51 ISSSGGWTLY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCTRGL
101 KMATIFDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
151 YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSNFGTQTY
201 TCNVDHKPSN TKVDKTVERK CCVECPPCPA PPVAGPSVFL FPPKPKDTLM
251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV
301 VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP
351 PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG
401 SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK

MM-121 Light Chain Amino Acid Sequence (SEQ ID NO:13)

1 QSALTQPASV SGSPGQSITI SCTGTSSDVG SYNVVSWYQQ HPGKAPKLII
51 YEVSQRPSGV SNRFSGSKSG NTASLTISGL QTEDEADYYC CSYAGSSIFV
101 IFGGGTKVTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL VSDFYPGAVT
151 VAWKADGSPV KVGVETTKPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCRV
201 THEGSTVEKT VAPAECS

Ab # 3 VH amino acid sequence (SEQ ID NO:14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYNMRWVRQAPGKGLEWVSVIYPSGGATRYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGYYYYGMDVWGQGTLVTVSS

Ab # 3 VL amino acid sequence (SEQ ID NO:15)

QSVLTQPPSASGTPGQRVTISCSGSDSNIGRNYIYWYQQFPGTAPKLLIYRNNQRPSGVPDRISGS
KSGTSASLAISGLRSEDEAEYHCGTWDDSLSGPVFGGGTKLTVL

Ab # 3 VH CDR1 (SEQ ID NO:16)

AYNMR

Ab # 3 VH CDR2 (SEQ ID NO:17)

VIYPSGGATRYADSVKG

Ab # 3 VH CDR3 (SEQ ID NO:18

GYYYYGMDV

Ab # 3 VL CDR1 (SEQ ID NO:19)

SGSDSNIGRNYIY

Ab # 3 VL CDR2 (SEQ ID NO:20)

RNNQRPS

Ab # 3 VL CDR3 (SEQ ID NO:21)

GTWDDSLSGPV

Ab # 14 VH amino acid sequence (SEQ ID NO:22)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYGMGWVRQAPGKGLEWVSYISPSGGHTKYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVLETGLLVDAFDIWGQGTMVTVSS

Ab # 14 VL amino acid sequence (SEQ ID NO:23)

QYELTQPPSVSVYPGQTASITCSGDQLGSKFVSWYQQRPGQSPVLVMYKDKRRPSEIPERFSGSN
SGNTATLTISGTQAIDEADYYCQAWDSSTYVFGTGTKVTVL

Ab # 14 VH CDR1 (SEQ ID NO:24)

AYGMG

Ab # 14 VH CDR2 (SEQ ID NO:25)
YISPSGGHTKYADSVKG

Ab # 14 VH CDR3 (SEQ ID NO:26)
VLETGLLVDAFDI

Ab # 14 VL CDR1 (SEQ ID NO:27)
SGDQLGSKFVS

Ab # 14 VL CDR2 (SEQ ID NO:28)
YKDKRRPS

Ab # 14 VL CDR3 (SEQ ID NO:29)
QAWDSSTYV

Ab # 17 VH amino acid sequence (SEQ ID NO:30)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYGMGWVRQAPGKGLEWVSYISPSGGITVYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLNYYYGLDVWGQGTTVTVSS

Ab # 17 VL amino acid sequence (SEQ ID NO:31)
QDIQMTQSPSSLSASVGDRITITCQASQDIGDSLNWYQQKPGKAPRLLIYDASNLETGVPPRFSGS
GSGTDFTFTFRSLQPEDIATYFCQQSANAPFTFGPGTKVDIK

Ab # 17 VH CDR1 (SEQ ID NO:32)
WYGMG

Ab # 17 VH CDR2 (SEQ ID NO:33)
YISPSGGITVYADSVKG

Ab # 17 VH CDR3 (SEQ ID NO:34)
LNYYYGLDV

Ab # 17 VL CDR1 (SEQ ID NO:35)
QASQDIGDSLN

Ab # 17 VL CDR2 (SEQ ID NO:36)
DASNLET

Ab # 17 VL CDR3 (SEQ ID NO:37)
QQSANAPFT

Ab # 19 VH amino acid sequence (SEQ ID NO:38)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYGMWWVRQAPGKGLEWVSYIGSSGGPTYYVDS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGRGTPYYFDSWGQGTLVTVSS

Ab # 19 VL amino acid sequence (SEQ ID NO:39)
QYELTQPASVSGSPGQSITISCTGTSSDIGRWNIVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSG
SKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL

Ab # 19 VH CDR1 (SEQ ID NO:40)
RYGMW

Ab # 19 VH CDR2 (SEQ ID NO:41)
YIGSSGGPTYYVDSVKG

Ab # 19 VH CDR3 (SEQ ID NO:42)
GRGTPYYFDS

Ab # 19 VL CDR1 (SEQ ID NO:43)
TGTSSDIGRWNIVS

Ab # 19 VL CDR2 (SEQ ID NO:44)
DVSNRPS

Ab # 19 VL CDR3 (SEQ ID NO:45)
SSYTSSSTWV

What is claimed is:

1. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor.

2. The method of claim 1, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib.

3. The method of claim 1, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

4. The method of claim 1, wherein the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor.

5. The method of claim 4, wherein the nucleoside metabolic inhibitor is gemcitabine.

6. The method of claim 5, wherein the EGFR inhibitor is erlotinib.

7. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a nucleoside metabolic inhibitor.

8. The method of claim 7, wherein the one or more additional therapeutic agents is gemcitabine.

9. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents comprise a microtubule stabilizing agent.

10. The method of claim 9, wherein the microtubule stabilizing agent is selected from the group consisting of paclitaxel injection, nab-paclitaxel, cabazitaxel and docetaxel.

CSPC Exhibit 1120
Page 371 of 447

11. The method of claim 8, wherein the one or more additional therapeutic agents is nab-paclitaxel.

12. The method of claim 11, wherein co-administration of the anti-ErbB3 antibody and the nab-paclitaxel has an additive or superadditive effect on suppressing pancreatic tumor growth, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells implanted as xenografts in nude mice.

13. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor and optionally wherein the topoisomerase 1 inhibitor is formulated for intravenous administration.

14. The method of claim 13, wherein the wherein the topoisomerase 1 inhibitor is a camptothecin selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, topotecan, lurtotecan, silatecan, and irinotecan.

15. The method of claim 14, wherein the camptothecin is irinotecan or topotecan and the irinotecan or topotecan is liposomally encapsulated irinotecan or liposomally encapsulated topotecan.

16. The method of claim 15, wherein the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan and the liposomally encapsulated irinotecan or liposomally encapsulated topotecan is in the form of a sucrose octasulfate salt.

17. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents is chosen from the group consisting of a bispecific anti-ErbB2/anti-ErbB3 antibody, an anti-IGF-1R/anti-ErbB3 antibody, an anti EGFR/anti-ErbB3 antibody, or a mixture of anti-EGFR and anti-ErbB3 antibodies.

18. The method of claim any of claims 1 to 17, wherein the anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1,

CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

19. The method of claim 18, wherein the anti-ErbB3 antibody comprises V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

20. The method of claim any of claims 1 to 17, wherein the anti-ErbB3 antibody is selected from 8B8, 1B4C3, 2D1D12, GE-huMab-HER3, MEDI3379, AMG888 and AV-203.

21. The method of claim any one of claims 1 to 20, wherein co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357cells.

22. The method of any one of claims 1 to 20, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that comprises at least one reduced dose that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

23. The method of any one of claims 4 to 6 or 17 to 20, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that comprises at least one reduced dose that provides less of the one or more additional therapeutic agents than is provided by a dosage recommended by the manufacturer of the one or more additional therapeutic agents for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

24. The method of claim 22 or 23, wherein the reduced dose is about half the dose recommended by the manufacturer.

25. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein the antibody is formulated for intravenous administration.

26. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein the patient has recurrent or persistent pancreatic cancer following primary chemotherapy.

27. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein the patient has failed prior therapy with a platinum-based therapeutic agent.

28. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein the patient has failed prior treatment with, or become resistant to treatment with one or more of a) a nucleoside analog therapeutic agent, b) a platinum-based therapeutic agent, c) a therapeutic agent, that is a topoisomerase 1 inhibitor and d) a therapeutic agent that is a tyrosine kinase inhibitor.

29. The method of any one of claims 1 to 20, wherein each of the additional therapeutic agent or agents is administered following the administration of the anti-ErbB3 antibody.

30. The method of any one of 13 to 17 or 28, wherein the topoisomerase 1 inhibitor is administered before the administration of the anti-ErbB3 antibody.

31. The method of any one of claims 13 to 17 or 28, wherein the topoisomerase 1 inhibitor and the anti-ErbB3 antibody are administered simultaneously.

32. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is formulated for intravenous administration.

33. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is administered following the administration of the anti-ErbB3 antibody.

34. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is administered before the administration of the anti-ErbB3 antibody.

35. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent and the anti-ErbB3 antibody are administered simultaneously.

36. The method of any one of claims 1 to 6, wherein the EGFR inhibitor is formulated for oral administration.

37. The method of claim 7 or 8, wherein the nucleoside metabolic inhibitor is formulated for intravenous administration.

38. The method of claim 7 or 8, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered following the administration of the anti-ErbB3 antibody.

39. The method of claim 7 or 8, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered before the administration of the anti-ErbB3 antibody.

40. The method of claim 7 or 8, wherein the EGFR inhibitor, the nucleoside metabolic inhibitor and the anti-ErbB3 antibody are administered simultaneously.

41. The method of any one of claims 1 to 40, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents.

42. The method of any one of claims 1 to 6 and 9 to 41, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is gemcitabine.

43. The method of claim 41, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).

44. The method of claim 41, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

45. The method of claim 41, wherein the one or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

46. The method of any one of claims 1 to 45, wherein the anti-ErbB3 antibody is formulated for intravenous administration and is selected from the group comprising AMG888, AV-203, 8B8, 1B4C3 and 2D1D12.

47. The method of any one of claims 1 to 45, wherein the anti-ErbB3 antibody is formulated for intravenous administration and comprises V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

48. The method of any one of claims 1 to 47, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

49. The method of claim 48, wherein the adenocarcinoma is pancreatic ductal carcinoma.

50. The method of any one of claims 1 to 47, wherein the pancreatic cancer is an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome).

51. The method of any one of claims 1 to 47, wherein the pancreatic cancer comprises a KRAS gene comprising a KRAS mutation.

52. The method of claim 51, wherein the KRAS mutation is KRAS G12S.

53. The method of claim 50, wherein the one or more additional therapeutic agents comprise an mTOR inhibitor selected from the group consisting of temsirolimus, everolimus, sirolimus, and ridaforolimus.

54. The method of claim 53, wherein the mTOR inhibitor is everolimus.

55. The method of any one of claims 1 to 47, wherein the pancreatic cancer comprises a BRAF gene comprising a BRAF mutation and optionally wherein one of the one or more additional therapeutic agents is a BRAF kinase inhibitor, optionally vemurafenib.

56. The method of claim 55, wherein the BRAF mutation is BRAF V600E.

57. The method of any one of claims 1 to 56, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

58. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor.

59. The composition of claim 58, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib.

60. The composition of claim 58, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

61. The composition of claim 58, wherein the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor.

62. The composition of claim 61, wherein the nucleoside metabolic inhibitor is gemcitabine.

63. The composition of claim 62, wherein the EGFR inhibitor is erlotinib.

64. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a nucleoside metabolic inhibitor.

65. The composition of claim 64, wherein the one or more additional therapeutic agents is gemcitabine.

66. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a microtubule stabilizing agent.

67. The composition of claim 66, wherein the microtubule stabilizing agent is selected from the group consisting of paclitaxel injection, nab-paclitaxel and docetaxel.

68. The composition of claim 65, wherein the one or more additional therapeutic agents is nab-paclitaxel.

69. The composition of claim 68, wherein co-administration of the anti-ErbB3 antibody and the nab-paclitaxel has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the nab-paclitaxel alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells.

70. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor.

71. The composition of claim 70, wherein the wherein the topoisomerase 1 inhibitor is a camptothecin selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, topotecan, lurtotecan, silatecan, and irinotecan.

72. The composition of claim 71, wherein the camptothecin is irinotecan or topotecan and the irinotecan or topotecan is liposomally encapsulated irinotecan or liposomally encapsulated topotecan.

73. The composition of claim 72, wherein the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan and the liposomally encapsulated irinotecan or liposomally encapsulated topotecan is in the form of a sucrose octasulfate salt.

74. The composition of any of claims 58 to 73, wherein the ErbB3 inhibitor is an anti-ErbB3 antibody.

75. The composition of claim 74, wherein anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

76. The composition of claim 75, wherein the anti-ErbB3 antibody comprises V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

77. The composition of claim 74, wherein the anti-ErbB3 antibody is selected from 8B8, 1B4C3, 2D1D12, AMG888 and AV-203.

78. The composition of any one of claims 58 to 68 and 70 to 77, wherein co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells.

79. The composition of any one of claims 58 to 77, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dose that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

80. The composition of any one of claims 61 to 63 or 74 to 77, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dose that provides less of the one or more additional therapeutic agents than is provided by a dosage recommended by the manufacturer of the one or more additional therapeutic agents for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

81. The composition of claim 79 or 80, wherein the reduced dose is a dose that is about half the dosage recommended by the manufacturer.

82. The composition of any one of claims 58 to 81, wherein the patient has recurrent or persistent pancreatic cancer following primary chemotherapy.

83. The composition of any one of claims 58 to 77, wherein each of the additional therapeutic agent or agents is administered following the administration of the anti-ErbB3 antibody.

84. The composition of any one of claims 70 to 74, wherein the topoisomerase 1 inhibitor is administered before the administration of the anti-ErbB3 antibody.

85. The composition of any one of claims 70 to 74, wherein the topoisomerase 1 inhibitor and the anti-ErbB3 antibody are administered simultaneously.

86. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is formulated for intravenous administration.

87. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is administered following the administration of the anti-ErbB3 antibody.

88. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is administered before the administration of the anti-ErbB3 antibody.

89. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent and the anti-ErbB3 antibody are administered simultaneously.

90. The composition of any one of claims 58 to 63, wherein the EGFR inhibitor is formulated for oral administration.

91. The composition of claim 64 or 65, wherein the nucleoside metabolic inhibitor is formulated for intravenous administration.

92. The composition of claim 64 or 65, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered following the administration of the anti-ErbB3 antibody.

93. The composition of claim 64 or 65, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered before the administration of the anti-ErbB3 antibody.

94. The composition of claim 64 or 65, wherein the EGFR inhibitor, the nucleoside metabolic inhibitor and the anti-ErbB3 antibody are administered simultaneously.

95. The composition of any one of claims 58 to 97, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents.

96. The composition of any one of claims 58 to 63 and 66 to 96, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is gemcitabine.

97. The composition of claim 95, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).

98. The composition of claim 95, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

99. The composition of claim 95, wherein the one or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

100. The composition of any one of claims 58 to 99, wherein the anti-ErbB3 antibody is selected from the group comprising AMG888, AV-203, 8B8, 1B4C3 and 2D1D12.

101. The composition of any one of claims 58 to 99, wherein the anti-ErbB3 antibody comprises V_H and/or V_L regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

102. The composition of any one of claims 58 to 101, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous

cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

103. The composition of claim 102, wherein the adenocarcinoma is pancreatic ductal carcinoma.

104. The composition of any one of claims 58 to 101, wherein the pancreatic cancer is an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome).

105. The composition of any one of claims 58 to 101, wherein the pancreatic cancer comprises a KRAS gene comprising a KRAS mutation.

106. The composition of claim 105, wherein the KRAS mutation is KRAS G12S.

107. The composition of claim 104, wherein the one or more additional therapeutic agents comprise an mTOR inhibitor selected from the group consisting of everolimus, sirolimus, and ridaforolimus.

108. The composition of claim 107, wherein the mTOR inhibitor is everolimus.

109. The composition of any one of claims 58 to 101, wherein the pancreatic cancer comprises a BRAF gene comprising a BRAF mutation and optionally wherein one of the one or more additional therapeutic agents is a BRAF kinase inhibitor, optionally vemurafenib.

110. The composition of claim 109, wherein the BRAF mutation is BRAF V600E.

111. The composition of any one of claims 58 to 110, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

112. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents,

wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises erlotinib.

113. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises erlotinib and gemcitabine.

114. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises everolimus.

115. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises irinotecan.

116. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises everolimus and exemestane.

117. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises nab-paclitaxel.

118. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises cetuximab.

119. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises MM-151.

120. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises gemcitabine.

121. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises eribulin.

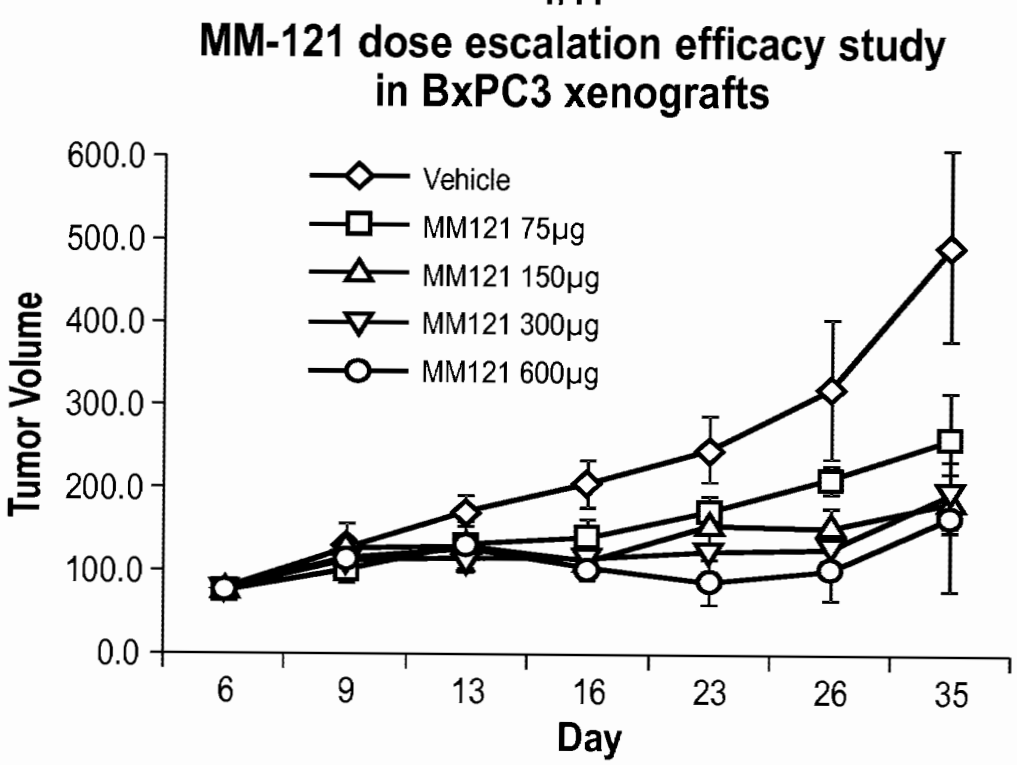

MM-121 dose escalation efficacy study
in BxPC3 xenografts
Vehicle
MM121 75µg
MM121 150µg
MM121 300µg
MM121 600µg
Tumor Volume
600.0
500.0
400.0
300.0
200.0
100.0
0.0
6
9
13
16
23
26
35
Day

Fig. 1A

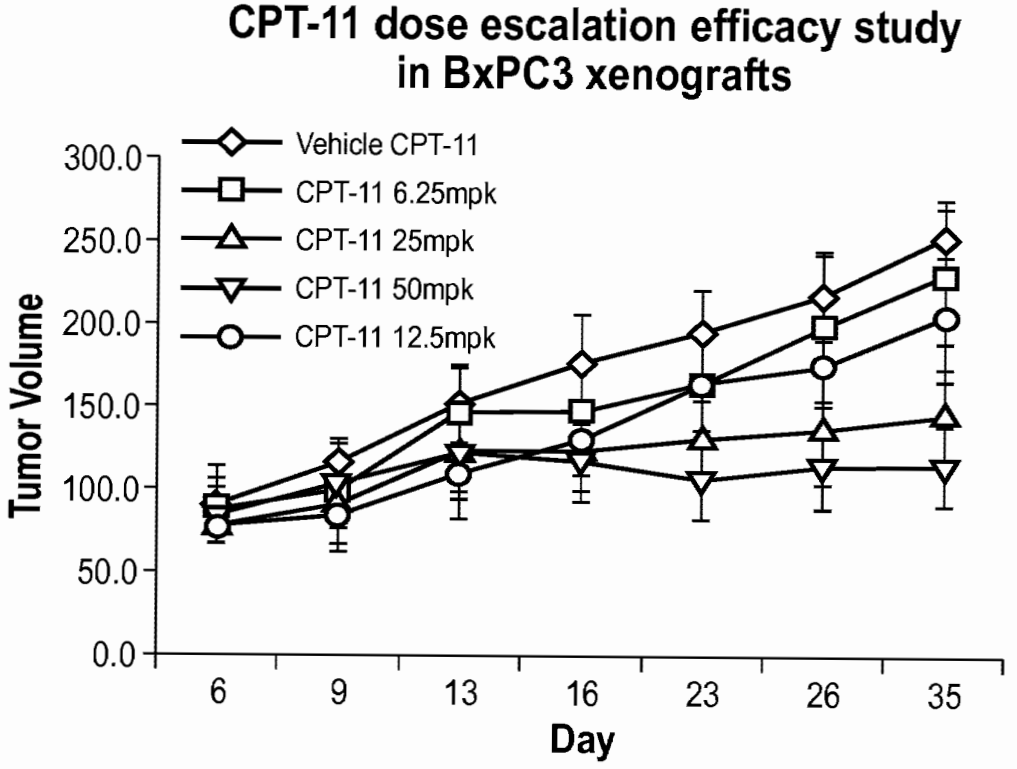

CPT-11 dose escalation efficacy study
in BxPC3 xenografts
Vehicle CPT-11
CPT-11 6.25mpk
CPT-11 25mpk
CPT-11 50mpk
CPT-11 12.5mpk
Tumor Volume
300.0
250.0
200.0
150.0
100.0
50.0
0.0
6
9
13
16
23
26
35
Day

Fig. 1B

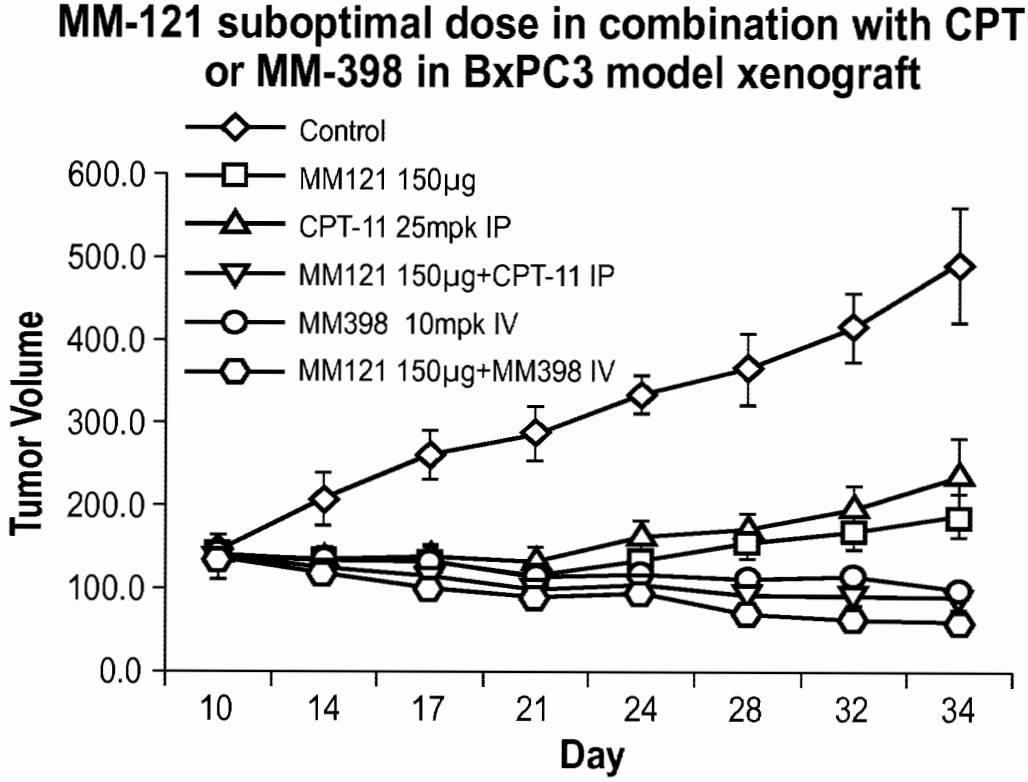

MM-121 suboptimal dose in combination with CPT11 or MM-398 in BxPC3 model xenograft
Control
MM121 150µg
CPT-11 25mpk IP
MM121 150µg+CPT-11 IP
MM398 10mpk IV
MM121 150µg+MM398 IV
Tumor Volume
600.0
500.0
400.0
300.0
200.0
100.0
0.0
10
14
17
21
24
28
32
34
Day

Fig. 2A

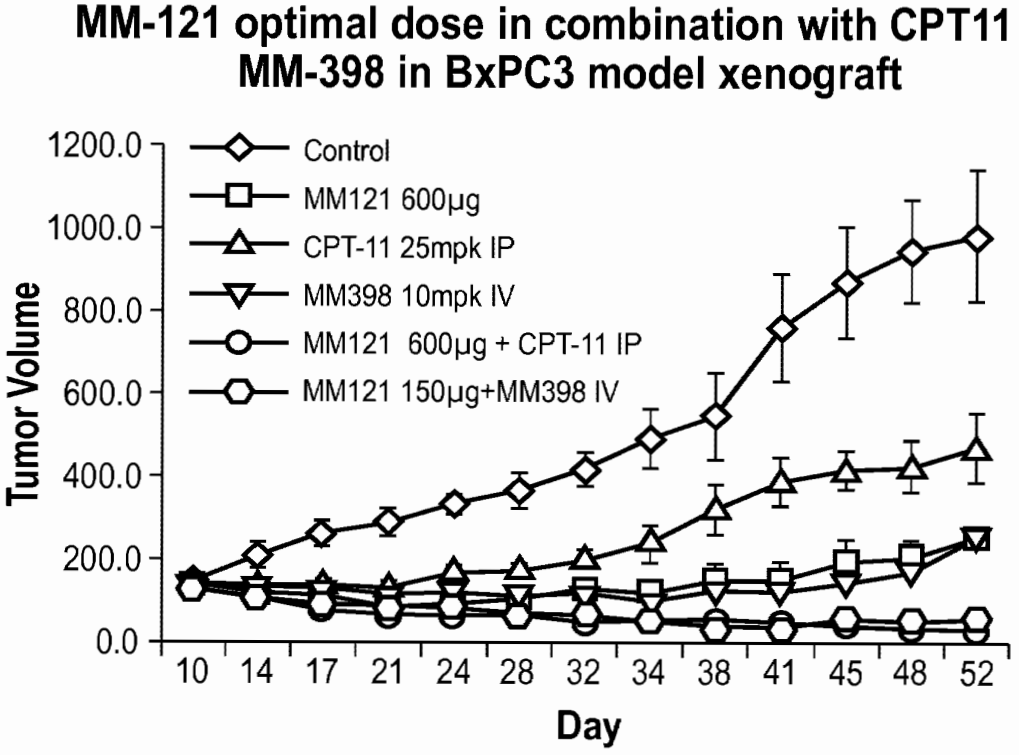

MM-121 optimal dose in combination with CPT11 or MM-398 in BxPC3 model xenograft
Control
MM121 600µg
CPT-11 25mpk IP
MM398 10mpk IV
MM121 600µg + CPT-11 IP
MM121 150µg+MM398 IV
Tumor Volume
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
10
14
17
21
24
28
32
34
38
41
45
48
52
Day

Fig. 2B

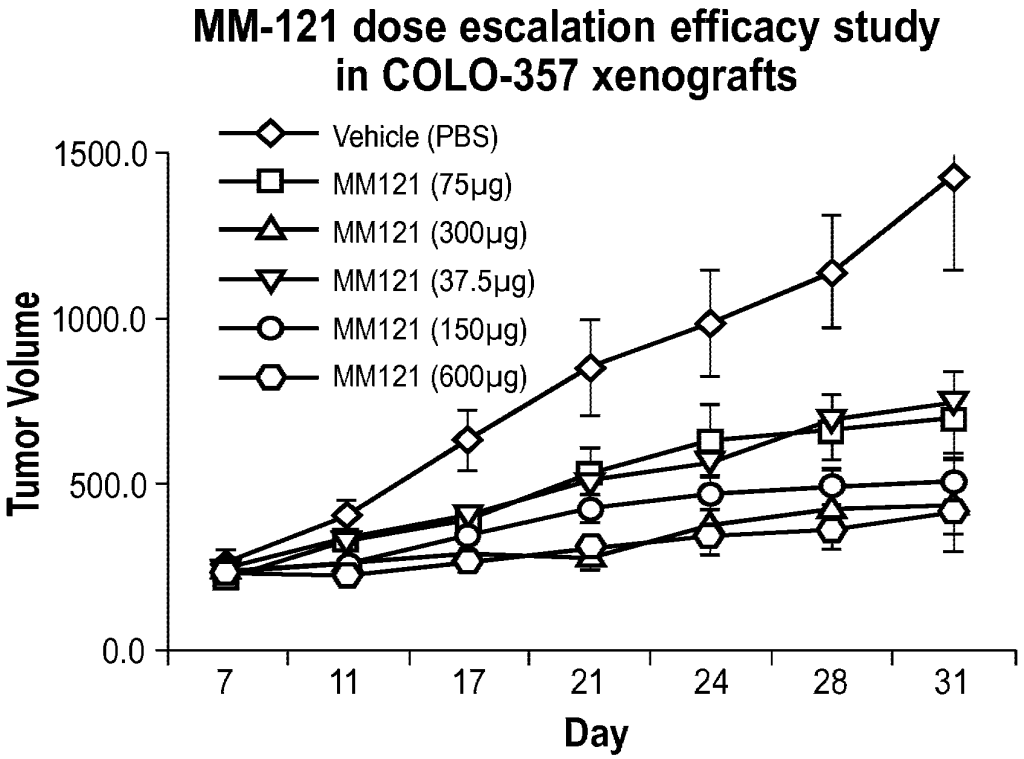

MM-121 dose escalation efficacy study
in COLO-357 xenografts
Vehicle (PBS)
MM121 (75µg)
MM121 (300µg)
MM121 (37.5µg)
MM121 (150µg)
MM121 (600µg)
Tumor Volume
1500.0
1000.0
500.0
0.0
7
11
17
21
24
28
31
Day

Fig. 3

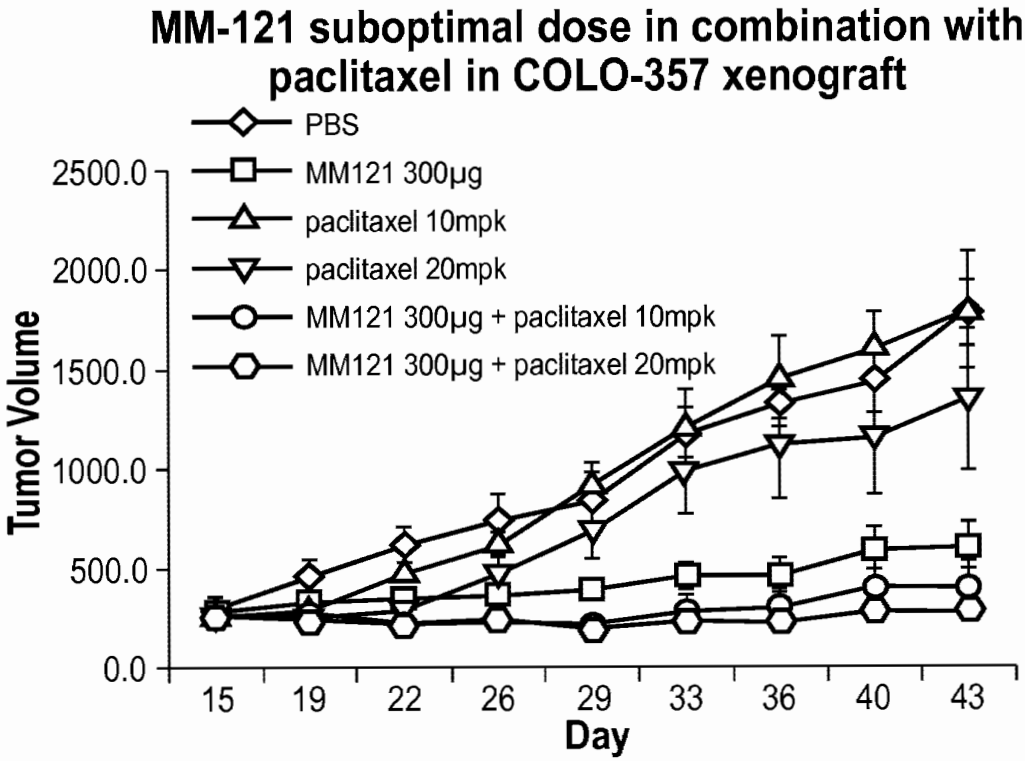

MM-121 suboptimal dose in combination with paclitaxel in COLO-357 xenograft
PBS
MM121 300µg
paclitaxel 10mpk
paclitaxel 20mpk
MM121 300µg + paclitaxel 10mpk
MM121 300µg + paclitaxel 20mpk
Tumor Volume
2500.0
2000.0
1500.0
1000.0
500.0
0.0
15
19
22
26
29
33
36
40
43
Day

Fig. 4A

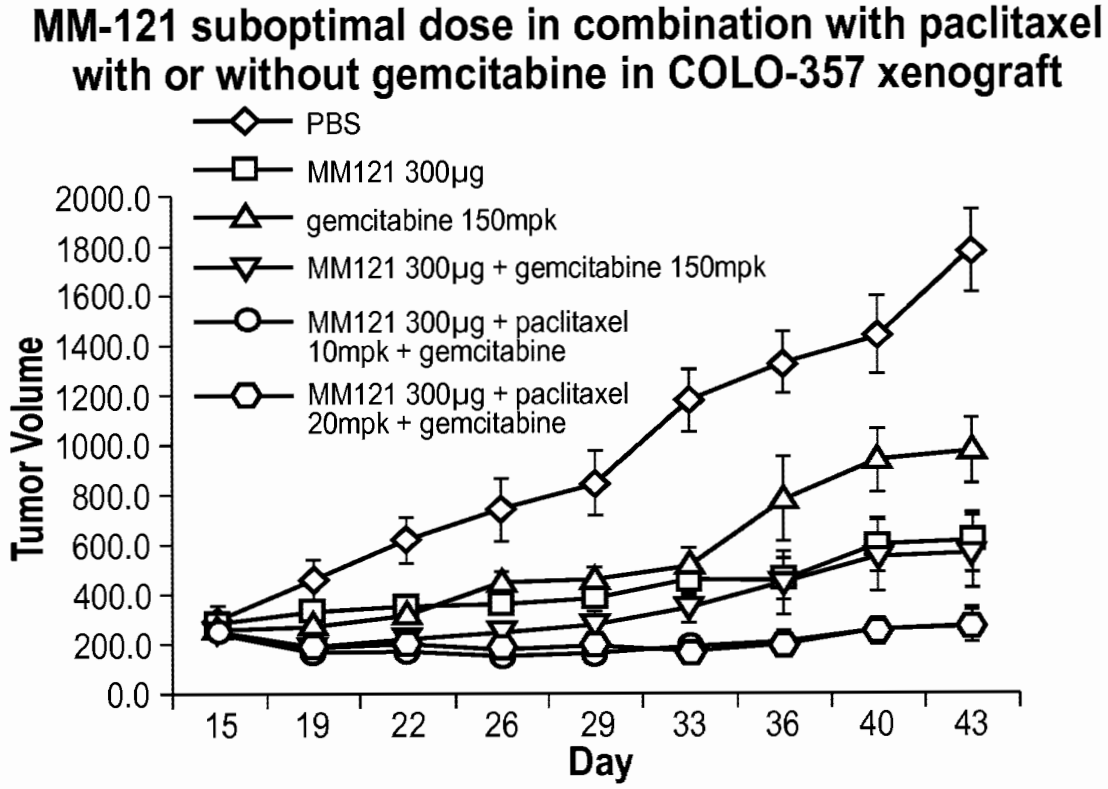
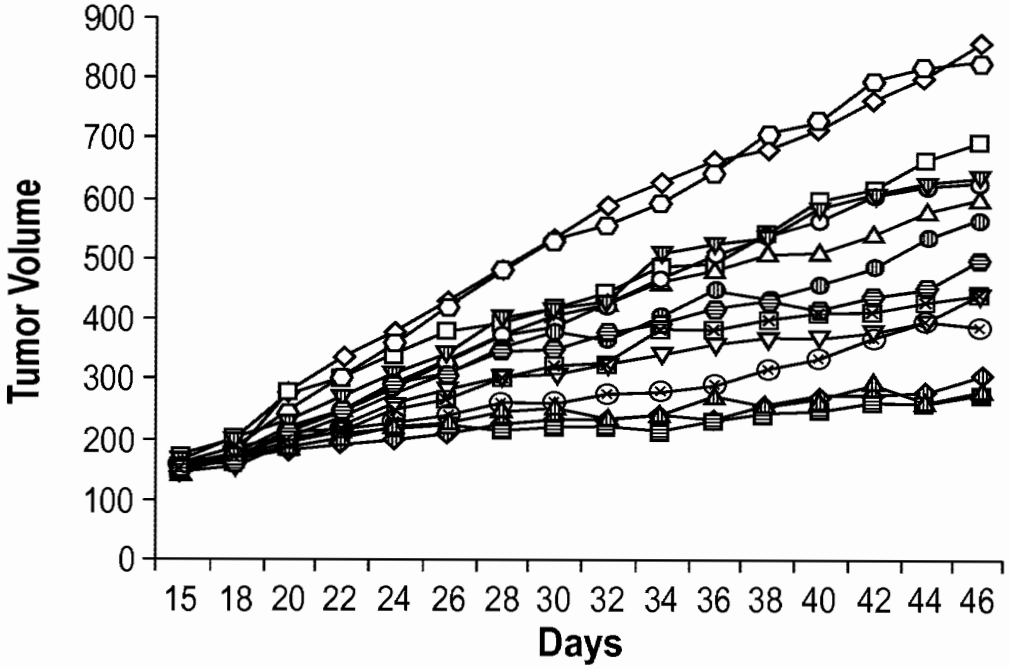

MM-121 suboptimal dose in combination with paclitaxel with or without gemcitabine in COLO-357 xenograft
PBS
MM121 300µg
gemcitabine 150mpk
MM121 300µg + gemcitabine 150mpk
MM121 300µg + paclitaxel 10mpk + gemcitabine
MM121 300µg + paclitaxel 20mpk + gemcitabine
Tumor Volume
2000.0
1800.0
1600.0
1400.0
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
15
19
22
26
29
33
36
40
43
Day

Fig. 4B

MM-121 suboptimal dose in combination with erlotinib and gemcitabine in COLO-357 xenograft (first graph with all groups included followed by graphs with each distinct dose combination)



- Group 1 - PBS Vehicle Control
- Group 2 - MM121 (300µg)
- Group 3 - erlotinib (50mpk)
- Group 4 - erlotinib (100mpk)
- Group 5 - gemcitabine (150mpk)
- Group 6 - gemcitabine (300mpk)
- Group 7 - MM121 (300µg), erlotinib (50mpk), gemcitabine (150mpk)
- Group 8 - MM121 (300µg), erlotinib (50mpk), gemcitabine (300mpk)
- Group 9 – MM121 (300µg), erlotinib (100mpk), gemcitabine (150mpk)
- Group 10 – MM121 (300µg), erlotinib (100mpk), gemcitabine (300mpk)
- Group 11 – erlotinib (50mpk), gemcitabine (150mpk)
- Group 12 – erlotinib (100mpk), gemcitabine (300mpk)
- Group 13 – erlotinib (50mpk), gemcitabine (300mpk)
- Group 14 – erlotinib (100mpk), gemcitabine (150mpk)

Fig. 5A

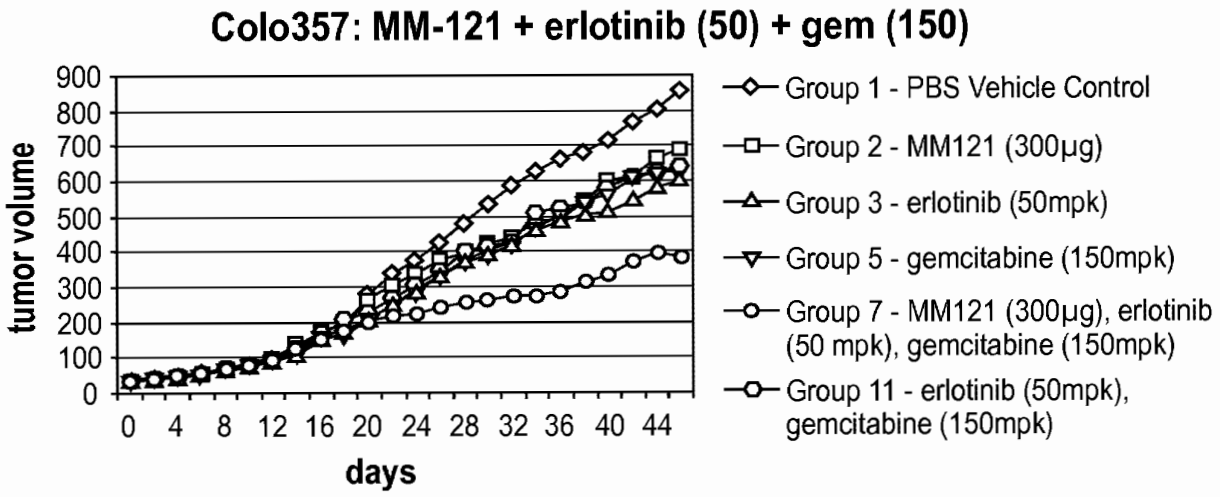

Colo357: MM-121 + erlotinib (50) + gem (150)
tumor volume
900
800
700
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44
days
Group 1 - PBS Vehicle Control
Group 2 - MM121 (300µg)
Group 3 - erlotinib (50mpk)
Group 5 - gemcitabine (150mpk)
Group 7 - MM121 (300µg), erlotinib (50 mpk), gemcitabine (150mpk)
Group 11 - erlotinib (50mpk), gemcitabine (150mpk)

Fig. 5B

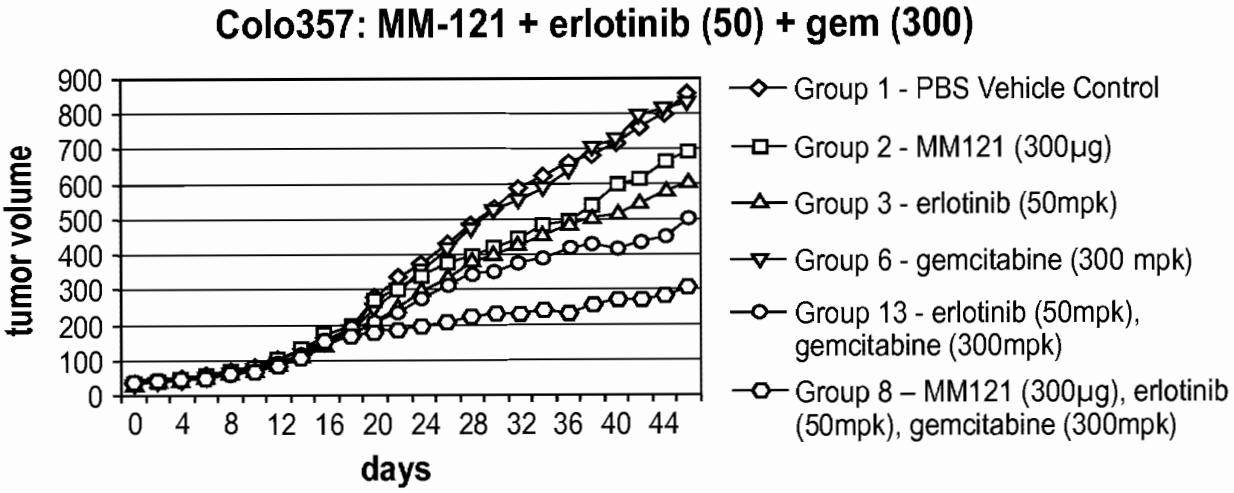

Colo357: MM-121 + erlotinib (50) + gem (300)
tumor volume
900
800
700
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44
days
Group 1 - PBS Vehicle Control
Group 2 - MM121 (300µg)
Group 3 - erlotinib (50mpk)
Group 6 - gemcitabine (300 mpk)
Group 13 - erlotinib (50mpk), gemcitabine (300mpk)
Group 8 – MM121 (300µg), erlotinib (50mpk), gemcitabine (300mpk)

Fig. 5C

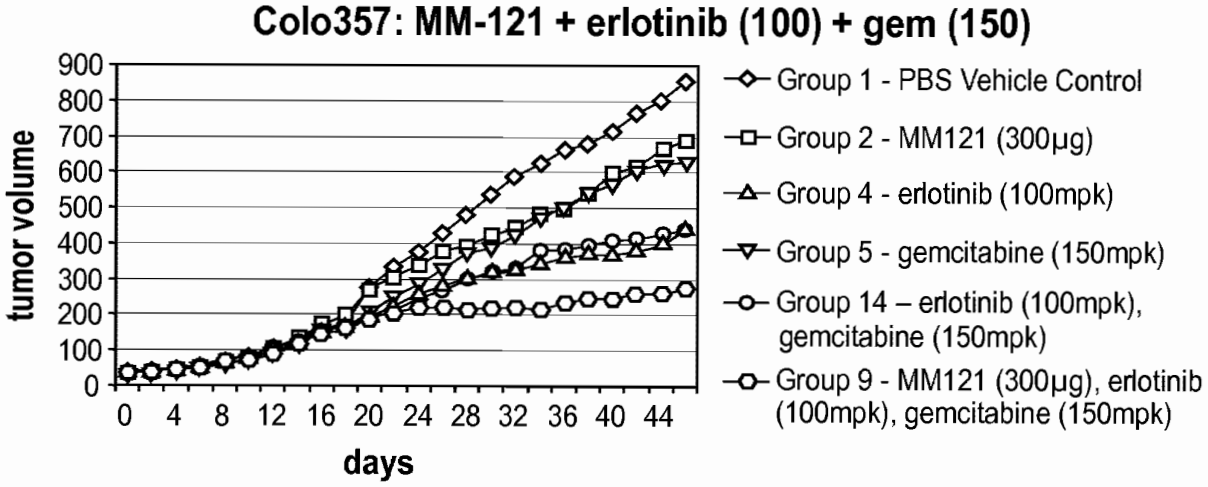

Colo357: MM-121 + erlotinib (100) + gem (150)
tumor volume
900
800
700
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44
days
Group 1 - PBS Vehicle Control
Group 2 - MM121 (300µg)
Group 4 - erlotinib (100mpk)
Group 5 - gemcitabine (150mpk)
Group 14 – erlotinib (100mpk), gemcitabine (150mpk)
Group 9 - MM121 (300µg), erlotinib (100mpk), gemcitabine (150mpk)

Fig. 5D

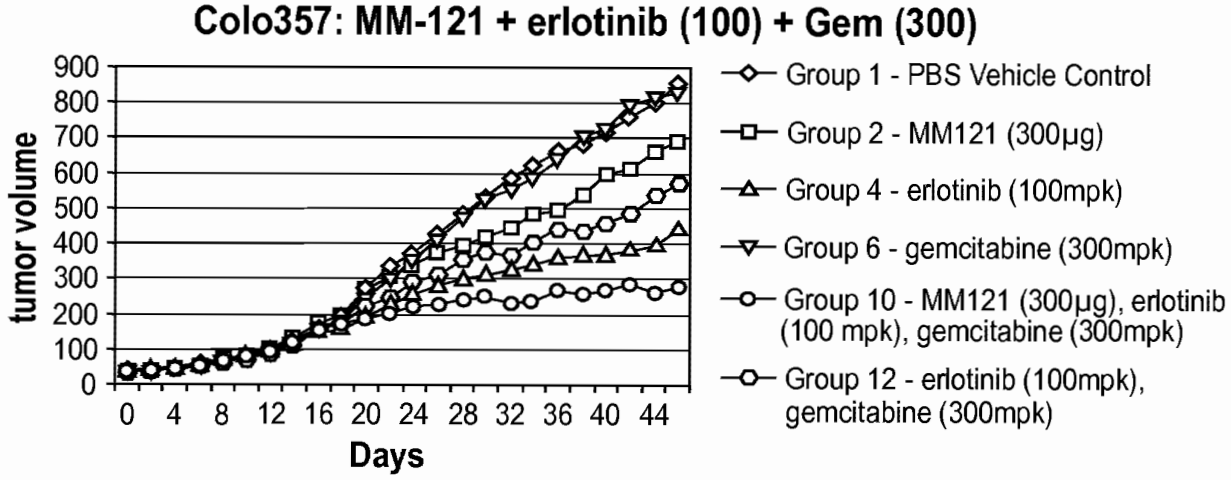

Colo357: MM-121 + erlotinib (100) + Gem (300)
tumor volume
900
800
700
600
500
400
300
200
100
0
0 4 8 12 16 20 24 28 32 36 40 44
Days
Group 1 - PBS Vehicle Control
Group 2 - MM121 (300µg)
Group 4 - erlotinib (100mpk)
Group 6 - gemcitabine (300mpk)
Group 10 - MM121 (300µg), erlotinib (100 mpk), gemcitabine (300mpk)
Group 12 - erlotinib (100mpk), gemcitabine (300mpk)

Fig. 5E

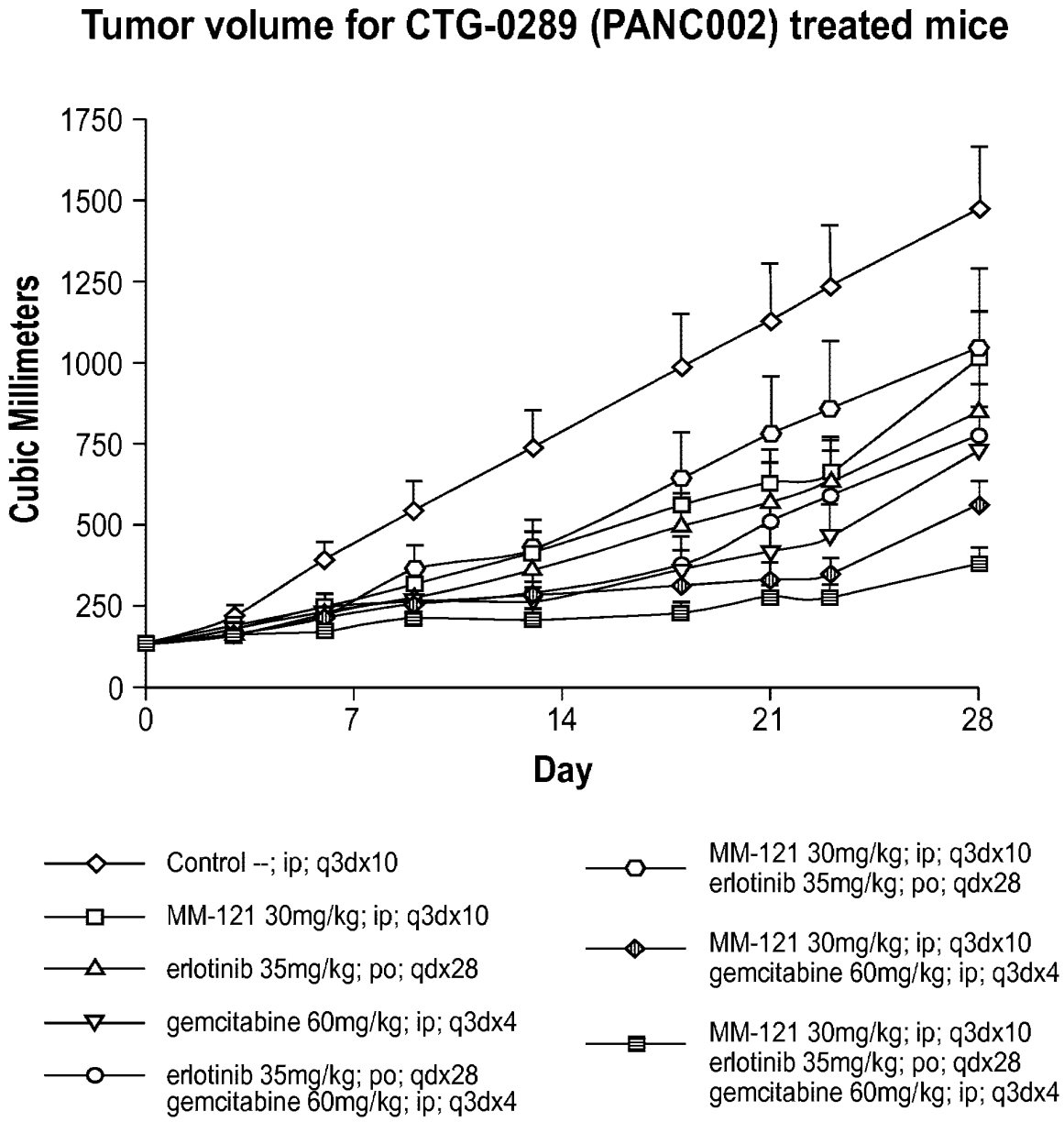

Tumor volume for CTG-0289 (PANC002) treated mice
Cubic Millimeters
1750
1500
1250
1000
750
500
250
0
0
7
14
21
28
Day
Control --; ip; q3dx10
MM-121 30mg/kg; ip; q3dx10
erlotinib 35mg/kg; po; qdx28
gemcitabine 60mg/kg; ip; q3dx4
erlotinib 35mg/kg; po; qdx28
gemcitabine 60mg/kg; ip; q3dx4
MM-121 30mg/kg; ip; q3dx10
erlotinib 35mg/kg; po; qdx28
MM-121 30mg/kg; ip; q3dx10
gemcitabine 60mg/kg; ip; q3dx4
MM-121 30mg/kg; ip; q3dx10
erlotinib 35mg/kg; po; qdx28
gemcitabine 60mg/kg; ip; q3dx4

Fig. 6

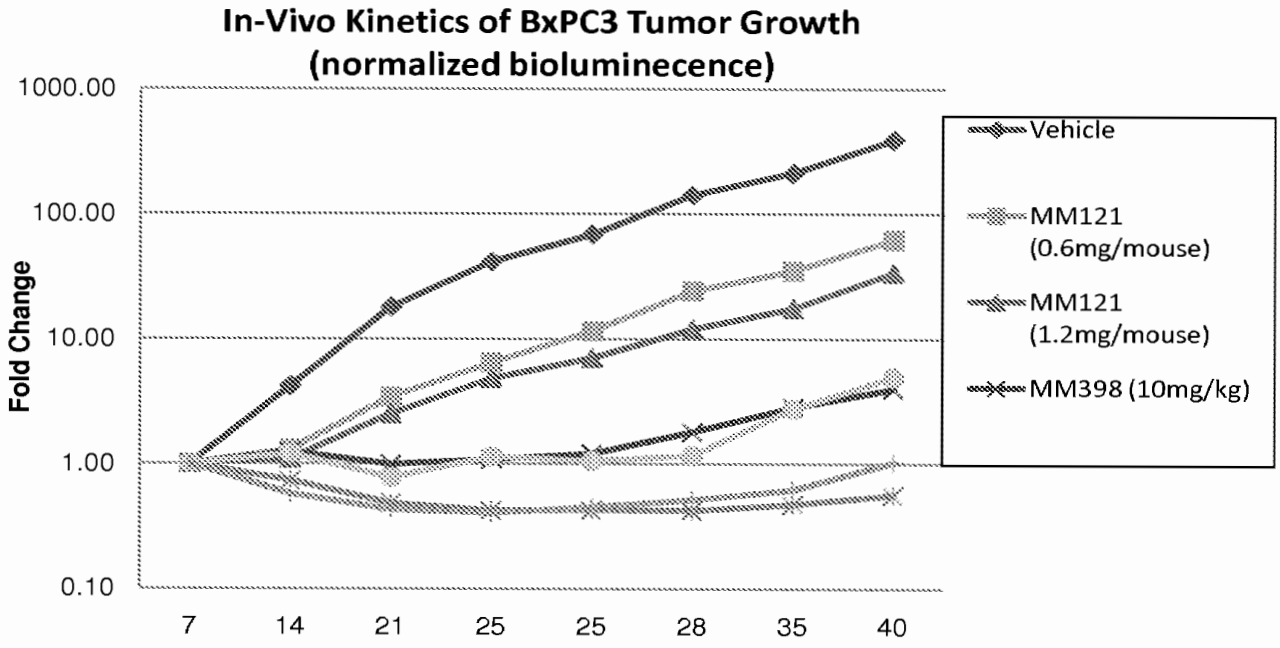

In-Vivo Kinetics of BxPC3 Tumor Growth
(normalized bioluminecence)
Fold Change
1000.00
100.00
10.00
1.00
0.10
7
14
21
25
25
28
35
40
Vehicle
MM121
(0.6mg/mouse)
MM121
(1.2mg/mouse)
MM398 (10mg/kg)

Fig. 7

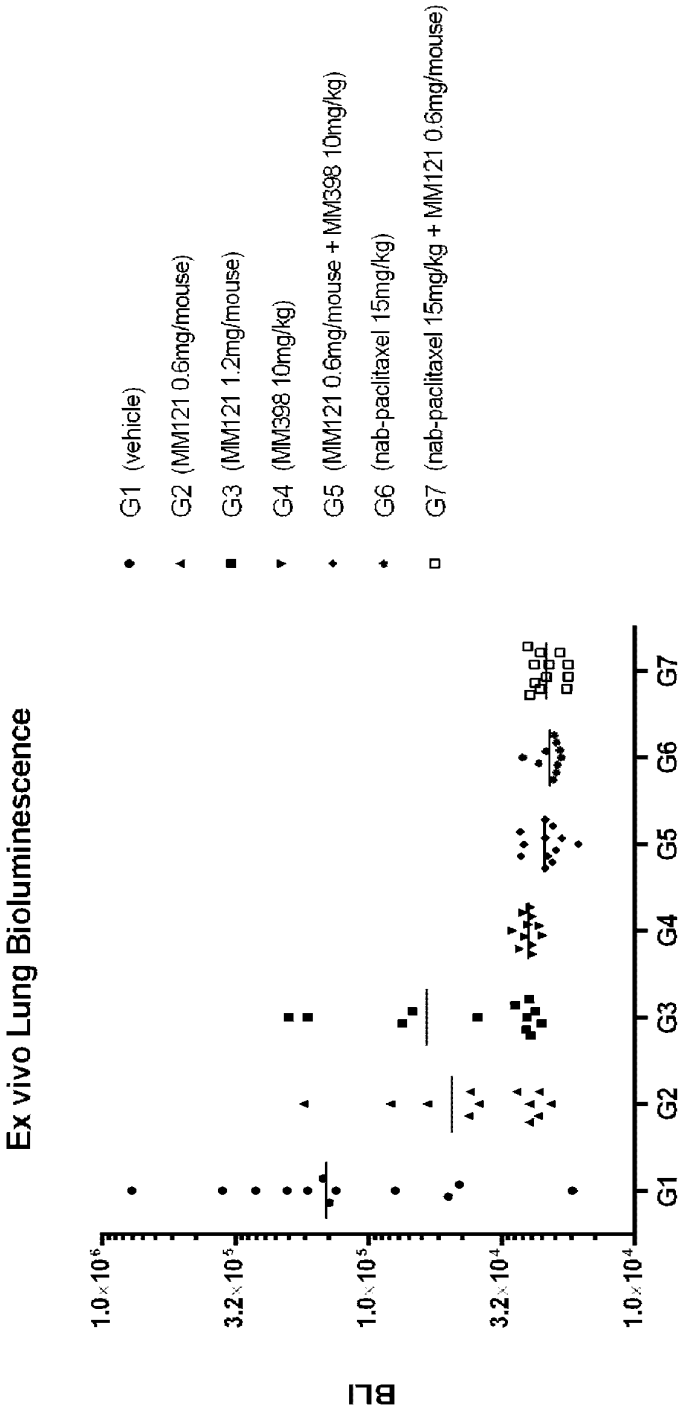

Ex vivo Lung Bioluminescence
BLI
1.0×10^6
3.2×10^5
1.0×10^5
3.2×10^4
1.0×10^4
G1
G2
G3
G4
G5
G6
G7
Treatment Groups
G1 (vehicle)
G2 (MM121 0.6mg/mouse)
G3 (MM121 1.2mg/mouse)
G4 (MM398 10mg/kg)
G5 (MM121 0.6mg/mouse + MM398 10mg/kg)
G6 (nab-paclitaxel 15mg/kg)
G7 (nab-paclitaxel 15mg/kg + MM121 0.6mg/mouse)

Fig. 8A

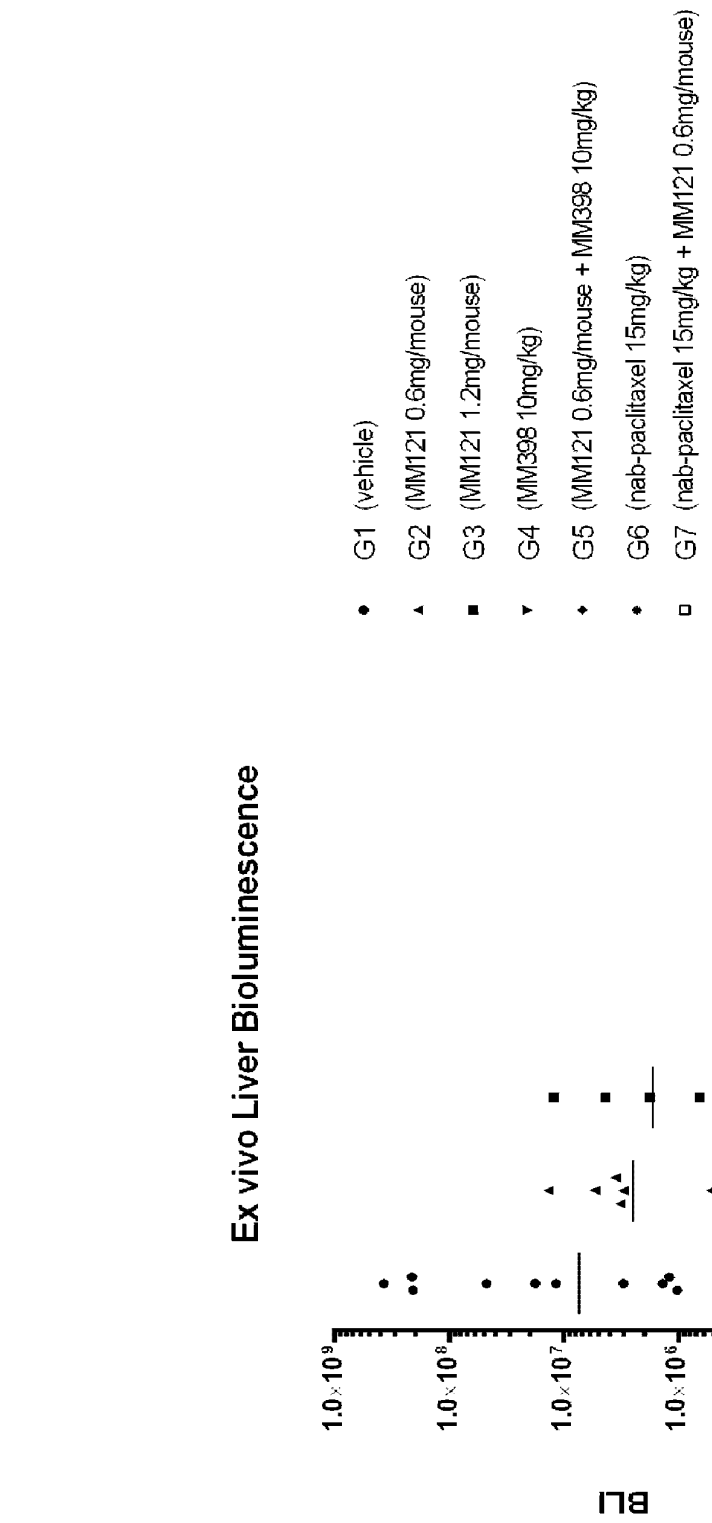

Ex vivo Liver Bioluminescence
G1 (vehicle)
G2 (MM121 0.6mg/mouse)
G3 (MM121 1.2mg/mouse)
G4 (MM398 10mg/kg)
G5 (MM121 0.6mg/mouse + MM398 10mg/kg)
G6 (nab-paclitaxel 15mg/kg)
G7 (nab-paclitaxel 15mg/kg + MM121 0.6mg/mouse)
BLI
1.0×10^9
1.0×10^8
1.0×10^7
1.0×10^6
1.0×10^5
1.0×10^4
G1
G2
G3
G4
G5
G6
G7
Treatment Groups

Fig. 8B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/30585

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; C12P 21/08 (2013.01)
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/00; C12P 21/08; A61K 39/395; C07K 16/00 (2013.01)
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9; 424/130.1, 424/141.1; 530/387.1, 530/388.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/00; C12P 21/08; A61K 39/395; C07K 16/00 (2013.01) - see keyword below
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9; 424/130.1, 424/141.1; 530/387.1, 530/388.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: anti-ErbB3, HER3, antibody, EGFR, inhibitor, antagonist, gefitinib, erlotinib, pancreatic, cancer, malignant, neoplastic, tumor, 8B8, 1B4C3, 2D1DI2, GE-huMab-HER3, MED13379, AMG888, AV-203, Heavy chain, light chain, CDR, variable region, administer, oral, co-administer, composition, treat, MM-

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0266584 A1 (SCHOEBERL et al.) 21 October 2010 (21.10.2010), para [0005], [0008], [0036], [0040], [0041], [0047], [0148], [0153], [0155], [0206], [0209], [0220], [0228], [0374], [0389], SEQ ID NO: 1 and SEQ ID NO: 2	1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112
A	KELLEY et al. Erlotinib in the treatment of advanced pancreatic cancer. Biologics. 2008, Vol.. 2(1), p. 83-95. Entire documentation, especially Abstract	1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112
A	MOHAMMED et al. The epidermal growth factor receptor inhibitor gefitinib prevents the progression of pancreatic lesions to carcinoma in a conditional LSL-KrasG12D/+ transgenic mouse model Cancer Prev Res (Phila). 2010, Vol. 3(11), p. 1417-26. Entire documentation, especially Abstract; pg 1421, col 2, lower para, and Fig 2; and pg 1424, col 2, top para	1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112
A	US 2011/0008327 A1 (CHENG et al) 13 January 2011 (13.01.2011), para [0221]	1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112
A	MATAR et al. Combined Epidermal Growth Factor Receptor Targeting with the Tyrosine Kinase Inhibitor Gefitinib (ZD1839) and the Monoclonal Antibody Cetuximab (IMC-C225): Superiority Over Single-Agent Receptor Targeting. Clin Cancer Res. 2004, Vol. 10(19), p. 6487-501. Entire documentation, especially Abstract	1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 2013 (26.06.2013)	11 JUL 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/30585

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 21-31, 41-57, 78-85, 95-111
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-20, 32-40, 58-77, 86-94, 112-121, drawn to methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an anti-ErbB3 antibody and one or more additional therapeutic agents; and compositions thereof. The first invention (claims 1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59)), is restricted to co-administering to the patient an anti-ErbB3 antibody and gefitinib (the first option for an EGFR inhibitor in claim 2), which will be searched without additional fee. Applicant is invited to elect additional therapeutic agents to be searched by paying an additional fee per additional therapeutic agent and clearly identifying the elected additional therapetuic agent(s) for co-administration. For example, applicant could elect EGFR inhibitor erlotinib (claims 1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112) with an additional fee; or applicant could elect a microtubule stabilizing agent (claims 9-12, 18-20/(9-12), 32-35, 66-69, 74-77/(66-69), 86-89, 117, 121) with an additional fee;

**********Continued in the the extra sheet**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-2, 18-20/(1-2), 36/(1-2), 58-59, 74-77/(58-59), 90/(58-59), 112, limited to gefitinib and erlotinib.

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Continuation of:
Boc No III (unity of invention is lacking)

(Continuation of Group I+) or applicant could elect EGFR inhibitor erlotinib and a nucleoside metabolic inhibitor [e.g. gemcitabine] (claims 1-2, 4-8, 18-20/(1-2, 4-8), 36/(1-2, 4-6), 37-40, 58-59, 61-65, 74-77(58-59, 61-65), 90/(58-59, 61-65), 91-94, 112, 113, 120) with 2X additional fees. The exact claims to be searched will depend on the election. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group will result in only the first claimed invention to be searched.

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I+ share the technical features of a composition for the treatment of pancreatic cancer comprising an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, and a method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents. Some claims within Group I+ (partial) also share the technical features of wherein the one or more additional therapeutic agents comprise an EGFR inhibitor. Some claims within Group I+ (partial) also share the technical features of an anti-ErbB3 antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4; or an anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1), SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO:8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3); and wherein anti-ErbB3 antibody is selected from 8B8, lB4C3, 2DIDI2, GE-huMab-HER3, MEDI3379, AMG888 and AV-203.

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2010/0266584 A1 to Schoeberl et al. (hereinafter 'Schoeberl') as follows:

Schoeberl discloses a method of treating pancreatic cancer in a patient (para [0040], [0148]) comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody (para [0005], [0040]- [0041], [0148]), and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor (claims 2 and 3; para ([0041]-[0058] - 'binding to ErbB1 ...and the inhibition of such binding by cetuximab').
Schoeberl further discloses an anti-ErbB3 antibody heavy chain and light chain variable sequences (para [0047] - 'an anti-ErbB3 antibody (Ab #6)'; para [0008] - 'a heavy chain variable region (V.sub.H) ... SEQ ID NO:1, ... a light chain variable region (V.sub.L) ... SEQ ID NO:2'; para [0389] - 'mapping of Ab #6 is performed ... the V.sub.H region (SEQ ID NO: 1) and the V.sub.L region (SEQ ID NO: 2)', wherein SEQ ID NO: 1 is 100% identical to the claimed SEQ ID NO: 2, and comprising a region between nucleotides 30-35, that is 100% identical to the claimed SEQ ID NO: 5 (CDRH1), a region between nucleotides 50-66, that is 100% identical to the claimed SEQ ID NO: 6 (CDRH2), and a region between nucleotides 99-108, that is 100% identical to the claimed SEQ ID NO: 7 (CDRH3); and wherein SEQ ID NO: 2 is 100% identical to the claimed SEQ ID NO: 4, and comprising a region between nucleotides 23-36, that is 100% identical to the claimed SEQ ID NO: 8 (CDRL1), a region between nucleotides 52-58, that is 100% identical to the claimed SEQ ID NO: 9 (CDRL2), and a region between nucleotides 91-101, that is 100% identical to the claimed SEQ ID NO: 10 (CDRL3)), and different anti-ErbB3 including anti -ErbB3 antibody selected from the group consisting of 2DIDI2, and AMG888 (Table I - Anti-ErbB3 antibodies Ab #14 described herein which bind different 1B4C3; 2D1D12 (U3 Pharma AG) epitopes U3-1287/AMG888 (U3 Pharma/Amgen)').

Without a shared special technical feature, the inventions lack unity with one another.

Therefore, inventions of Groups I+lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note re item 4: Claims 21-31, 41-57, 78-85, 95-111 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.

Note:

I) Claims 11 and 68 are objected to as lacking a proper antecedent basis for the "the one or more additional therapeutic agents comprise a microtubule stabilizing agent" limitation. It is assumed that claim 11 depends upon claim 9 and claim 68 depends upon claim 66 (Specification: pg 4, ln 9-10 'a microtubule stabilizing agent, e.g., a taxane such as eribulin, ... nab-paclitaxel'). For the purposes of this ISR, claims 11 and 68 are construed as follows:

11. The method of claim 9, wherein the one or more additional therapeutic agents is nab-paclitaxel.

68. The composition of claim 66, wherein the one or more additional therapeutic agents is nab- paclitaxel.

II) Claims 20 and 77 are objected to as using an improper Markush group. For the purposes of this ISR, the term 'selected from' in each claim is construed as 'selected from the group consisting of'.

EUROPEAN PATENT 2 861 210 B1

T2963/19 - 3.3.07 | DERIVING FROM 13731230.2 | O008029EP
Appellant / proprietor: IPSEN BIOPHARM LTD.
Respondent / opponent: TEVA PHARMACEUTICAL INDUSTRIES LTD

1 INTRODUCTION

1.1 In the respondent's reply to the proprietor's statement of grounds, thirteen (13) new documents (i.e. new pieces of evidence) were filed. These documents were not filed during the first instance proceedings before the OD. In addition, the respondent's reply includes several new facts and arguments which were not presented before the OD.

1.2 This submission is the appellant's first response in writing to these new facts, arguments, and evidence. This submission is being filed over nine months before the oral proceedings scheduled for 18th March 2022, so it is believed that there should be ample time for both the Board and the respondent to consider it and prepare for the oral proceedings accordingly.

2 REQUESTS

2.1 The requests made in paragraphs 2.1 - 2.5 of the statement of grounds of appeal are maintained. For the avoidance of doubt, we request that D23 (and its annexes) and D24 be admitted into the proceedings. Both of these documents were filed with the statement of grounds of appeal.

2.2 In addition, should the Board be minded to admit documents D15c, D35, and D36 into the proceedings, and the new facts and arguments which rely on these documents[1], we request that enclosed documents D37, D37A, D38, and D38A, summarised below, be admitted into the proceedings.

2.3 We also request that documents D25-D34 not be admitted into the proceedings.

3 ENCLOSURES

- D37 – Expert declaration of Carla Schoonderbeek
  - D37A – Directive 2001/20/EC ("the Clinical Trials Directive" or "CTD")
- D38 – Expert declaration of Grant H. Castle, Ph.D.
  - D38A – "*Communication from the Commission – Detailed Guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)*"

[1] See, for example, pages 17 and 20 of the reply to the appeal.

3.1 These documents should be admitted because they are filed in direct response to the new facts, arguments, and evidence which were filed by the respondent for the first time in its reply to the appeal.

3.2 During proceedings before the OD, the opponent relied on the disclosure of document D15b to support its inventive step attack. D15b is an extract from the website clinicaltrials.gov, and the document provides some information about a clinical trial having the brief title "*Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients with Metastatic Pancreatic Cancer*". The opponent argued that the disclosure of D15b alone was enough to render the Main Request obvious[2].

3.3 However, for the first time in its reply to the appeal, the respondent argues that the: "***key point*** *is that at the relevant date it was known to the skilled person that a Phase III clinical trial was underway involving over 400 patients… in over 70 sites in more than 10 different countries*" and that D15b "*is just one source of information concerning that trial*" (emphasis added)[3].

3.4 D15b does not mention that the clinical trial is taking place outside of the United States. Thus, the respondent is arguing for the first time in the appeal proceedings that, as well as D15b, one must also take into consideration the fact that the relevant clinical trial is taking place in other jurisdictions, most notably the United Kingdom and, more generally, the European Union. The respondent also cites for the first time a piece of UK national legislation in support of its arguments[4]. Documents D15c, D28, and D36 are cited as new evidence in support of these new facts and arguments.

3.5 D37 (and its annexes) and D38 are filed in direct response to these new facts, arguments, and evidence. Thus, should the Board be minded to admit these new facts, arguments, and evidence relied on by the respondent into the proceedings, D37, D37A, D38, and D38A must be admitted into the proceedings to ensure that the appellant's right to be heard under Article 113(1) EPC is respected.

3.6 Both D37 and D38 are *prima facie* highly relevant to the new facts, arguments, and evidence relied on by the respondent. In particular, both are expert declarations which show the respondent is wrong to suggest that explicit approval from a licensing authority would be required in the UK or, more generally, the EU, before the NAPOLI-1 trial could have begun. This has important implications for the question of whether the skilled person would have been led to the claimed subject matter with a reasonable expectation of success.

3.7 In addition, and as stated above, D37 and D38 are being filed over nine months before the oral proceedings, and so it is believed that both the Board and the respondent should have ample time to consider them and prepare for the oral proceedings accordingly.

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[2] See, for example, paragraph 5.5.2 of the OD's decision.
[3] Paragraph 7.45 of the reply to the appeal.
[4] See, for example, paragraph 7.53 of the reply to the appeal.

4 D23 AND D24 ARE ADMISSIBLE

4.1 The respondent is wrong to argue that D23 (and its annexes) and D24 should not be admitted into the proceedings pursuant to Article 12(4) of the RPBA 2007[5]. Both documents are highly relevant to the question of inventive step, and their filing with the statement of grounds of appeal constitutes a legitimate reaction to the first instance decision which does not constitute an abuse of procedure. Moreover, the respondent's right to be heard would not be compromised by admitting the documents into the proceedings.

4.2 D23 (and its annexes) and D24 are *prima facie* highly relevant because their content can reasonably be expected to influence the eventual result of the proceedings. Central to the OD's ruling that the Main Request lacked inventive step was the finding that, contrary to the arguments of the proprietor[6], "*the set-up of the clinical study of D15b thus inherently creates an expectation of success*"[7]. D23 is a declaration from an expert in the relevant technical field, and the document comes to the clear conclusion that the OD's finding on this key point was not correct[8]. Another central point to the OD's finding was the OD's belief that "*phase III clinical trials in particular are only authorised once it has been shown that the treatment under investigation has a high level of safety and efficacy in earlier preclinical and clinical studies*"[9]. D24 clearly demonstrates that this belief does not hold true in the present circumstances[10]. This point was made orally before the OD[11]. Thus, it is clear that both documents are *prima facie* extremely relevant to this case, and for this reason alone they should be admitted into the proceedings.

4.3 In addition, and as stated above, both D23 and D24 build on, and reinforce, arguments which were made by the proprietor during the first-instance proceedings. It is established case law that filing with the statement of grounds of appeal new documents which reinforce lines of argument taken before the department of first instance (in this case, the OD) represents the normal, legitimate behaviour of a losing party and does not constitute an abuse of procedure[12]. This provides a further reason why D23 and D24 should be admitted.

4.4 Furthermore, the admission of D23 (and its annexes) and D24 would not be detrimental to the respondent's right to be heard and/or necessitate the postponement of the oral proceedings. This is because, as can be seen from the respondent's reply to the appeal, the respondent has clearly had ample time to review both documents and provide detailed written arguments as to why they allegedly do not support the appellant's case[13].

4.5 Therefore, D23 (and its annexes) and D24 should be admitted into the proceedings.

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[5] The statement of grounds of appeal, D23 (plus annexes), and D24 were filed prior to 1st January 2020, so Article 12(4) – (6) RPBA 2020 do not apply to these documents following Article 25(2) of RPBA 2020.
[6] See, for example, the minutes of the oral proceedings, page 3, sixth paragraph.
[7] OD's decision, page 17, second paragraph.
[8] See, for example, paragraph 27 of D23.
[9] OD's decision, page 16, section 5.7.3, first sentence.
[10] D24, paragraphs 6 and 7.
[11] See the minutes of the oral proceedings, page 3, fourth paragraph; and page 4, third bullet point.
[12] Case Law of the Boards of Appeal, V.A.4.10.4, 9th Edition, page 1227 of English version.
[13] Reply to appeal, paragraphs 7.40 – 7.63.

5 D25 - D34 ARE INADMISSIBLE

5.1 Documents D25 – D34 were filed with the reply to the appeal. According to the respondent, these documents allegedly demonstrate that "*irinotecan sucrose octasulfate salt liposome injection*" was known in the art. According to the respondent, the reply to the appeal represented "*the first opportunity to file evidence*" in relation to these points[14]. This cannot be correct.

5.2 The Examining Division granted this patent with five claims. Granted claim 1 is an independent claim, and claims 2-5 were dependent on claim 1. The feature requiring the "*liposomal irinotecan*" to be "*irinotecan sucrose octasulfate salt liposome injection*" was present in granted claim 4. The opponent was clearly aware of granted claim 4 when preparing its original opposition statement, as claim 4 is explicitly referred to and attacked therein[15]. However, the opponent omitted to file any evidence demonstrating that the features of claim 4 were allegedly known in the art in its opposition statement or in its submission under Rule 116 EPC. Thus, it cannot be the case that the reply to the appeal represented "*the first opportunity to file evidence*" on this point. Therefore, the respondent's justification for filing D25-D34 now does not stand up to scrutiny, and thus these documents should not be admitted.

5.3 In addition, these documents appear to have been cited because they allegedly demonstrate that the "*MM-398*" referred to in D15b corresponds to "*irinotecan sucrose octasulfate salt liposome injection*". However, at least documents D26, D29, D33, and D34 are not *prima facie* relevant here because they do not mention "*MM-398*" at all. Further, whilst documents D31 and D32 do mention "*MM-398*", they are not *prima facie* relevant because, like D15b, they are silent as to what "*MM-398*" is. This is a further reason why these documents should not be admitted.

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6 RESPONSE TO THE NEW FACTS, ARGUMENTS, AND EVIDENCE

6.1 This section will respond to the new facts, arguments, and evidence provided for the first time in the respondent's reply to the appeal.

Inventive step

Reasonable expectation of success - D23, D37, and D38

6.2 As mentioned above, the respondent's reply to the appeal contains new facts, arguments, and evidence to support its position that the skilled person would have been led to the claimed subject matter with a reasonable expectation of success. Should the Board decide to admit these new facts, arguments, and evidence into the proceedings, it is explained below with reference to D37, D37A, D38, and D38A that it remains the case that the skilled person would not have been led to the subject matter of the Main Request with a reasonable expectation of success.

[14] Reply to appeal, paragraphs 2.3 and 2.4.
[15] Paragraph 24, second sentence.

6.3 The respondent attempts to undermine the credibility of Dr Amy McKee's testimony in D23 by arguing that her declaration concerns only the regulatory situation in the United States, and that the situation outside of the United States must also be taken into consideration. In particular, the respondent alleges that, in some countries such as the UK, where the NAPOLI-1 trial also took place, approval from both a licensing authority and an ethics committee/IRB would be required before commencing the clinical trial, and/or before adding Arm C to the trial by way of amendment. The respondent appears to be suggesting that this alleged additional requirement for approval by a licensing authority means that the clinical trial is subject to a higher degree of scrutiny from government bodies than it is in, for example, the United States. In view of this, the respondent seems to suggest that this provides further justification as to why the skilled person would have been led to the claimed subject matter with a reasonable expectation of success.

6.4 However, the respondent is wrong to argue that approval from a licensing authority would have been required before commencing the NAPOLI-1 clinical trial in the UK, or indeed anywhere else in the European Union. It is also wrong to argue that approval from a licensing authority would have been required before the addition of Arm C to the trial. This will be explained below with reference to enclosed documents D37 and D38.

6.5 As a starting point, it is indeed true that, as shown by D15c (section E.8.6.3), the NAPOLI-1 trial did not just take place in the United States. In particular, it also took place in several European countries, namely the Czech Republic, France, Germany, Hungary, Italy, Spain, and the UK. At the relevant date, all of these countries were EU Member States, meaning that they would have been required to adhere to Directive 2001/20/EC ("the Clinical Trials Directive" or "CTD", enclosed as D37A), and to implement the CTD into their national legislation. The "*Medicines for Human Use (Clinical Trials) Regulations (MHCTR) 2004 and 2006*" (hereafter the "UK Regulations") cited by the respondent implemented the CTD into UK national law[16].

6.6 Article 9 of the CTD lists the requirements that must be satisfied before a clinical trial may commence in an EU Member State. Article 9(1) of the CTD is reproduced below with emphasis added:

> "*Member States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.*
>
> *The sponsor may not start a clinical trial* ***until the Ethics Committee has issued a favourable opinion*** *and inasmuch as* ***the competent authority[17] of the Member State concerned has not informed the sponsor of any grounds for non-acceptance****. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.*"

6.7 Section 12 of the UK Regulations, cited by the respondent in paragraph 7.53 of the reply, implements Article 9 of the CTD into UK national law[18].

[16] D38, paragraph f.
[17] The UK Regulations use the term "*licencing authority*" rather than "*competent authority*". For present purposes, these two terms are synonymous.
[18] D38, paragraph j.

6.8 As is apparent from the underlined wording above, rather than giving its explicit approval for a clinical trial before a clinical trial can begin, the competent authority may only raise "*grounds for non-acceptance*" to prevent the trial from starting.

6.9 However, in actual fact, and as discussed in D38[19], Recital 11 of the CTD (reproduced below with emphasis added) states that, in the majority of circumstances, explicit, written approval from a competent authority should not be required before a trial can commence:

> "*As a rule, authorisation should be **implicit**, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials. In exceptional cases raising especially complex problems, explicit written authorisation should, however, be required.*"

6.10 The existence of this Recital demonstrates that the legislator did not intend for a competent authority to review and give its explicit authorisation to each and every clinical trial that takes place in the EU. In fact, once a request to begin a clinical trial has been filed with a competent authority, and no ground of non-acceptance has been raised within 60 days of the filing of the request, the clinical trial is authorised automatically via a so-called "*tacit authorisation*"[20]. Whilst not all clinical trials can benefit from "*tacit authorisation*", the information in D15c[21] makes it clear that the NAPOLI-1 trial could have received "*tacit authorisation*"[22]. Thus, it is entirely feasible, and consistent with the intention of the legislator expressed in Recital 11 of the CTD, that the NAPOLI-1 trial described in D15c did not receive any kind of explicit approval from a competent authority.

6.11 In any case, even if the trial did not receive "*tacit authorisation*", and did receive explicit approval from a competent authority (e.g. the MHRA in the UK, or another national agency in an EU Member State), this does not result in there being a reasonable expectation, or presumption, that the trial would be successful. This is made clear by, for example, paragraphs 22 and 25 – 30 of D37, paragraphs p - q of D38, and paragraph 18 (under heading "*2.1.3 Scope of authorisation*") of D38A.

6.12 The above discussion concerning the approval (or lack thereof) required to start the NAPOLI-1 trial also applies, *mutatis mutandis*, to the additional of Arm C to the trial by way of amendment[23]. In particular, it would not have been necessary to obtain explicit approval from a competent authority before adding Arm C to the trial, contrary to what the respondent suggests at paragraph 7.54 of the reply.

6.13 Thus, as is evidenced by D37 and D38, the respondent is wrong to argue that approval from a competent authority would have been required before commencing the NAPOLI-1 trial in the UK, nor would this have been required in any other of the European countries in which the

[19] D38, paragraph h.
[20] See D37, paragraph 21; D36, section 18(3) page 19, D38, paragraphs j-l.
[21] We also note that D28 has also been relied on by the respondent, seemingly because it states that "*Merrimack is currently recruiting participants for a randomized, open label Phase 3 study of MM-398 with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy*" (see page 3, sentence spanning left- and right-hand column). This disclosure adds nothing to that of D15b or D15c, so it will not be discussed further.
[22] D38, paragraph l.
[23] D38, paragraphs m-o.

trial was taking place. The respondent is also wrong to state that such approval would have been required before adding Arm C to the trial. If anything, the situation in Europe is similar to that in the United States explained in D23, in that the decisive factor in reality is the assessment that is conducted by the Ethics Committee/IRB[24].

6.14 It should be noted that D23, D37, and D38 are all declarations from experts who are experienced in the legal and scientific issues surrounding clinical trials. These experts come from a variety of clinical, scientific, and legal backgrounds. However, all three experts come to the same conclusion. That is, that the OD's finding that the mere fact that a clinical trial of a particular dosage regimen in a particular patient population is ongoing leads to a reasonable expectation or presumption of success is **not** consistent with the regulatory, legal, and technical framework within which clinical trials are authorised. Thus, the mere existence of an ongoing clinical trial would not have instilled in the skilled person a reasonable expectation that the therapeutic intervention being tested in that clinical trial would have been successful. No convincing evidence to the contrary has been provided by the respondent. What little evidence has been provided (e.g. D36 and the arguments in the reply concerning the same) has been shown to be based on an incorrect interpretation of the legal situation.

6.15 Therefore, it remains the case that the skilled person would not have looked to Arm C of D15b with a reasonable expectation of successfully providing a safe and effective therapy for gemcitabine-resistant pancreatic cancer.

D15b does not inherently/implicitly disclose "*irinotecan sucrose octasulfate salt liposome injection*"

6.16 In paragraphs 7.72 – 7.89, the respondent explains why "*irinotecan sucrose octasulfate salt liposome injection*" is allegedly implicitly disclosed in D15b. The respondent's arguments on this particular point are based on documents D25 – D34. Should the Board decide to admit these documents, they fail to prove the respondent's case.

6.17 As a starting point, whilst the skilled person will of course consider a document (e.g. D15b) in light of their common general knowledge, at no point has the respondent argued that any of documents D25 – D34 represent common general knowledge. Indeed, none of documents D25 – D34 is representative of the relevant common general knowledge because the documents are isolated publications from technical journals and/or publications from unrelated technical fields. Therefore, when considering what is explicitly or implicitly disclosed by D15b, it is not permissible to take any of documents D25 – D34 into consideration.

6.18 Even if some or all of D25-D34 are taken into consideration, they fail to advance the respondent's argument concerning the implicit disclosure of D15b. As the Board will be aware, the standard of proof required to establish that certain subject matter is *implicitly* disclosed in a document is a high one. In particular, it is established case law that:

> "*an alleged disclosure can only be considered "implicit" if it is immediately apparent to the skilled person than nothing other than the alleged implicit feature forms part of the subject-matter disclosed*"[25] [emphasis added]

[24] D37, paragraph 22.
[25] Case Law of the Boards of Appeal, I.C.4.3, 9th Edition, page 116 of the English version.

6.19 The arguments and evidence provided by the respondent come nowhere near this high standard.

6.20 The respondent begins by referring to documents D28 - D32 in paragraphs 7.78 – 7.82 of the reply, in an apparent effort to demonstrate that the link between "*MM-398*" and "*liposomal irinotecan*" was known at the relevant date. However, at least D29 and D31 do not mention "*MM-398*" at all, and so they fail to advance the respondent's case.

6.21 The respondent then considers the requirement in claim 1 for the liposomal irinotecan to be "*irinotecan sucrose octasulfate salt liposome injection*", and cites D25, D26, D27, D33, and D34. The respondent begins by referring to D25 and argues that, in view of D25, "*it was already known that MM-398 is a liposomal irinotecan sucrose octasulfate salt formulation*"[26]. The respondent attempts to support this with reference to D26. However, D26 discloses several different liposomal irinotecan formulations, and does not mention "*MM-398*" even once. D26 therefore fails to support the respondent's argument.

6.22 D33 and D34 also fail to mention "*MM-398*" even once. Therefore, like D26, these documents would not have assisted the skilled person in trying to establish what is meant by "*MM-398*" in D15b.

6.23 D27 does mention "*MM-398*". However, D27 states that "*MM-398*" is something other than "*irinotecan sucrose octasulfate salt liposome injection*". For example, D27 states that:

> "*PEP02, also known as MM-398 (Merrimack Pharmaceuticals, Inc.), is a highly stable liposomal nanocarrier formulation of irinotecan* ***hydrochloride*** *(CPT-11) [11]*"[27]
> [emphasis added]

6.24 Thus, not only would D27 have failed to disclose to the skilled person[28] at the relevant date that "*MM-398*" is "*irinotecan sucrose octasulfate salt liposome injection*", D27 would have led the skilled person at the relevant date to conclude that "*MM-398*" is something different and distinct from what is required by claim 1. The fact that the above passage cites D26 as reference "*[11]*" does not change this because, as stated above, D26 discloses several different liposomal irinotecan formulations, none of which are referred to as "*MM-398*".

6.25 It should also be noted that the statement in D27 that "*MM-398 is a … formulation of irinotecan hydrochloride*" is corroborated by the disclosure of D13[29].

6.26 Thus, even if they are taken into consideration (which they should not be as they are not common general knowledge), the documents relied on by the opponent fail to demonstrate that D15b implicitly discloses "*irinotecan sucrose octasulfate salt liposome injection*". In particular, the documents relied on fail to demonstrate that it would have been immediately apparent to the skilled person that the reference to "*MM-398*" in D15b means nothing other than "*irinotecan sucrose octasulfate salt liposome injection*". Therefore, the requirement in claim 1 of the Main Request that the liposomal irinotecan is "*irinotecan sucrose octasulfate*

[26] Reply to appeal, paragraph 7.85.
[27] D27, page 1568, left-hand column under heading "*PEP02*".
[28] As was stated in the statement of grounds of appeal (at, for example, paragraph 4.18), the skilled person in this case would be an oncologist, i.e. a clinician specialising in the treatment of cancer.
[29] See statement of grounds of appeal, paragraph 5.100.

salt liposome injection" constitutes a distinguishing feature vis-à-vis D15b (and the other prior art relied on by the respondent in its inventive step attacks).

6.27 In paragraph 7.90 of its reply to the appeal, the respondent argues that, even if the "*irinotecan sucrose octasulfate salt liposome injection*" feature in claim 1 is a distinguishing feature vis-à-vis D15b, the feature "*appears arbitrary*" and does not strengthen the appellant's position on inventive step. This point is dealt with in the statement of grounds of appeal and so will not be discussed in detail here[30]. However, in response to the final sentence of paragraph 7.90 of the reply, none of D25, D26, D33, or D34 considered in light of D15b would have led the skilled person to the subject matter of claim 1 with a reasonable expectation of providing a safe and effective treatment for gemcitabine-resistant pancreatic cancer.

6.28 As stated above, whilst D26, D33, and D34 do mention various liposomal irinotecan formulations, none of these documents discloses or suggests what the "*MM-398*" referred to in D15b is. In fact, none of these documents mentions "*MM-398*". Clearly then, none of these documents would have assisted the skilled person starting from D15b. D25 does mention "*MM-398*" and gives some discussion as to what "*MM-398*" is. However, this discussion is directly contradicted by the disclosure of other documents (e.g. D27 and D13), which state that "*MM-398*" is a formulation of liposomal irinotecan hydrochloride, so these documents would not have led to the claimed subject matter.

6.29 In any case, none of D25, D26, D33, or D34 teaches or suggests that "*irinotecan sucrose octasulfate salt liposome injection*" is, when administered in a dose of 80 mg/m^2 once every two weeks according to claim 1, able to safely and effectively treat gemcitabine-resistant pancreatic cancer. This is a further reason why the claimed subject matter involves an inventive step.

6.30 For the avoidance of doubt, the respondent's comments in the final sentence of paragraph 7.89 are wrong. In particular, the documents relied on by the opponent here do not represent anything like a "*convergent and consistent disclosure*". In fact, several of the documents contradict one another (see above).

"*economic considerations*" do not result in there being a "*reasonable expectation of success*"

6.31 In paragraphs 7.37 and 7.38, the respondent argues for the first time that "*economic considerations*" would have meant that the skilled person would have been led to the claimed subject matter with a reasonable expectation of success from D15b. This argument is allegedly supported by new facts[31] and evidence[32] presented for the first time in the reply to the appeal. Should the Board be minded to admit these new arguments, facts, and evidence, they fail to advance the respondent's case.

6.32 Specifically, the respondent argues that "*the skilled person would understand that a study sponsor would not embark on an expensive clinical trial programme without a reasonable expectation that it would be successful*". The respondent appears to suggest here that the costs associated with running the NAPOLI-1 trial would mean that the trial would only have

[30] See, statement of grounds of appeal, paragraphs 5.97 – 5.100.
[31] See, for example, footnote 8 on page 17 of the reply to the appeal
[32] E.g. D35.

been carried out had there been a reasonable expectation that the trial would have been successful.

6.33 However, there is no evidence on file which states how much it cost to run the NAPOLI-1 trial. Rather, it appears that the respondent is seeking to rely on D35 as a general reference which demonstrates the costs of clinical trials. As a starting point, D35 was published approximately 5 years after the patent's filing date, so it is not prior art and therefore irrelevant to the issue of inventive step. In any case, whilst D35 does state that "*high-cost trials occur*", the document also states that, in certain circumstances, clinical trials "*can be conducted at a lower cost*"[33]. So, as a matter of fact, it is not correct to assert that all clinical trials are very expensive, and certainly not so expensive that they would be commenced only if there is a reasonable expectation of success.

6.34 In any case, even if one does accept that clinical trials are always very expensive to carry out (which is not conceded), it cannot be correct to argue that the consequence of this is that a clinical trial would only be commenced if a reasonable expectation of success existed. If this were the case, very few (if any) clinical trials would ever take place, particularly in the field of oncology, and especially in the field of pancreatic cancer, where the clinical trial failure rate is very high[34]. Put another way, if a reasonable expectation of success were a prerequisite for commencing a clinical trial, pharmaceutical companies or other institutions would be very unlikely to invest the sums of money required to carry out the trial due to the high failure rate of clinical trials (particularly clinical trials in the field of pancreatic cancer).

6.35 In paragraph 7.38, the respondent makes numerous assertions about the company who sponsored the NAPOLI-1 trial. According to the respondent, this company (Merrimack Pharmaceuticals) were "*a relatively new company*" who were "*not one of the big established pharmaceutical companies*". No evidence to support this has been provided, and, in any case it is irrelevant to the issue of inventive step. In particular, even if "*economic considerations*" are relevant to the question of non-obviousness (which is not conceded), the fact that the trial sponsor is a relatively small and/or newly-established company says nothing at all about its financial situation and ability to fund clinical trials.[35]

6.36 The respondent ends paragraph 7.38 by arguing that the skilled person would have assumed that, even in the absence of any actual evidence, there was a "*robust technical rationale*" for carrying out the NAPOLI-1 trial. No evidence has been cited to demonstrate that such a "*robust technical rationale*" formed part of the state of the art at the relevant date. The respondent appears to be suggesting that there was some undisclosed and secret rationale, which would have been strong enough to instil a reasonable expectation of success, and which the skilled person would have been aware of, in spite of the fact that there is nothing to this effect in the state of the art. This argument must therefore fail because, following the respondent's own reasoning, "*the question of inventive step is addressed by the skilled*

[33] D35, central column, first complete paragraph.
[34] See, for example, Annexes A and B filed with D23.
[35] Even if, for the sake of argument, the respondent is correct to state that clinical trial sponsor was "*a relatively new company*" and "*not one of the big established pharmaceutical companies*", this would, if anything, have led the skilled person to be sceptical about the trial's chances of success (i.e. made the skilled person even less likely to have been instilled with a reasonable expectation of success).

person based on the state of the art" (emphasis added) and "*secret information* [such as the alleged "*robust technical rationale*"]... *is simply not relevant*"[36].

D5 as the closest prior art

6.37 The respondent argues for the first time in its reply to the appeal that D5 could be taken as the closest prior art, and that the Main Request lacks an inventive step if D5 is taken as the closest prior art. Should the Board be minded to admit this new argument, made for the first time in the reply to the appeal, the appellant provides the following arguments.

6.38 D5 is not a suitable choice of closest prior art. As explained in the statement of grounds of appeal, D13 should be taken as the closest prior art because it discloses actual treatment of pancreatic cancer in patients who have failed first-line gemcitabine-based therapy using liposomal irinotecan, and provides a more comprehensive disclosure than D12.[37] However, even if D5 is taken as the closest prior art, it remains the case that the claims of the Main Request involve an inventive step.

6.39 D5 describes a clinical trial in which 31 patients with metastatic pancreatic adenocarcinoma, who were previously treated with gemcitabine-based first-line chemotherapy[38], were administered a dosage regimen referred to as "*mFOLFIRI.3*". This regimen used two-week treatment cycles with the following steps[39]:

(1) 70 mg/m^2 non-liposomal irinotecan administered on day 1 of treatment over 1 hour;

(2) 400 mg/m^2 leucovorin administered on day 1 of treatment over 2 hours;

(3) 2000 mg/m^2 5-FU administered from day 1 of treatment over 46 hours;

(4) Another 70 mg/m^2 dose of non-liposomal irinotecan administered at the end of the 5-FU infusion on day 3, over 1 hour.

6.40 D5 concludes that this regimen "*could be safely used*" with "*modest anti-cancer activities*".[40] D5 does however concede that the study "*had small sample sizes*", and that the study was limited by "*the lack of assessment of clinical benefit or quality of life*"[41].

6.41 Claim 1 of the Main Request differs from D5 at least because claim 1 requires:

(i) the administration of "*liposomal irinotecan*", specifically, the administration of "*irinotecan sucrose octasulfate salt liposome injection*";

(ii) the administration of liposomal irinotecan on day 1 of each cycle;

(iii) the administration of 80 mg/m^2 of liposomal irinotecan to patients not homozygous for the UGT1A1*28 allele, and the administration of 60 mg/m^2 liposomal irinotecan to patients homozygous for the UGT1A1*28 allele on day 1 of cycle 1 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2; and

[36] Reply to appeal, paragraph 3.10.
[37] Statement of grounds of appeal, paragraphs 5.3 – 5.6 and paragraphs 5.41 – 5.51.
[38] D5, page 1659, left-hand column, first sentence under heading "*Patients*" and page 1660, Table 1.
[39] D5, page 1659, right-hand column, first sentence under heading "*Treatment dose and schedule*".
[40] D5, page 1662, left-hand column, second paragraph, first sentence.
[41] D5, page 1661, right-hand column, final sentence, and page 1662, left-hand column, first sentence.

(iv) the administration of 2400 mg/m^2 5-FU.

6.42 The technical effects of these differences are, at least, that a safe and effective treatment for gemcitabine-resistant pancreatic cancer is provided. The examples in the patent, particularly example 6, demonstrate that this technical effect is present. The disclosure of D19 (discussed at length in the statement of grounds of appeal[42]) backs-up the disclosure of the patent in this regard.

6.43 The objective technical problem can therefore be formulated as the provision of a safe and effective treatment for gemcitabine-resistant pancreatic cancer. The skilled person faced with this objective technical problem starting from D5 would not have been led to the claimed solution with a reasonable expectation of success.

6.44 There is no teaching or suggestion in D5 that would have motivated the skilled person to, for example, administer an active substance other than non-liposomal irinotecan, and certainly not anything to suggest that a very specific liposomal formulation comprising irinotecan sucrose octasulfate salt could be used to provide a safe and effective treatment. D5 teaches that therapeutic efficacy is observed when a total 140 mg/m^2 of non-liposomal irinotecan is administered in each two-week cycle, so the skilled person would not have arrived at the claimed dosage regimen, which requires the administration of a maximum of just 80 mg/m^2 liposomal irinotecan per two-week cycle (i.e. a much lower dose), with a reasonable expectation of providing an efficacious therapy. In addition, there is nothing in D5 which would have suggested that a safe therapy would have been provided by increasing the 5-FU dose by 20% from 2000 mg/m^2 to 2400 mg/m^2.

6.45 In paragraphs 7.125 and 7.126 of the reply to the appeal, the respondent argues that it would have been obvious to replace the non-liposomal irinotecan in D5 with "*MM-398*" in view of D7, D12, D13, D22, D29, D30, D31, and D32. However, these documents fail to assist the respondent's case. In particular, D7, D12, D22, D29, and D31 do not mention "*MM-398*" at all. The documents that do mention "*MM-398*" either refer vaguely to, for example, a "*nanoliposomal formulation of irinotecan*" (in the case of D30), or they go further and actually suggest the "*MM-398*" is something other than "*irinotecan sucrose octasulfate salt liposome injection*" (see D13 and 6.25 above). So these documents would not have led the skilled person to the claimed subject matter.

6.46 In paragraphs 7.127 - 7.128, the respondent refers to various doses disclosed in a variety of prior art documents, and then concludes in the following paragraph that "*it would have been obvious to use ... a dose of 80 mg/m^2*". The respondent's reasoning for arriving at this conclusion is not clear. However, it should be pointed out that the doses cited in paragraph 7.127 as being disclosed in D7, D13, D29, and D30 are different to those recited in claim 1, so they cannot render the claim obvious. D22 and D15b do mention a dose of "*80 mg/m^2*". However, this dose appears in connection with something called "*PEP02*" in D22 and something called "*MM-398*" in D15b. Neither "*PEP02*" nor "*MM-398*" is defined in either document. Moreover, in D22 this dose is administered once every three weeks[43] rather than once every two weeks as required by claim 1.

[42] Statement of grounds of appeal, paragraphs 5.12 – 5.20.
[43] D22, "*Methods*" section, second sentence.

6.47 The respondent also argues that the 5-FU dose in claim 1 would have been obvious in view of D15b considered in combination with D5. However, whilst a 2400 mg/m^2 dose of 5-FU is mentioned in D15b, it is mentioned in a combination regimen with something called "*MM-398*", which is not defined in D15b. The skilled person would not have been motivated by the disclosure in D15b of a 2400 mg/m^2 5-FU dose used in combination with an undefined agent ("*MM-398*") to take this dose and, for example, use it in combination with the specific dosage regimen of D5 with a reasonable expectation of providing a safe (and effective) therapy. In fact, even if the skilled person had been motivated to do this (which is denied), they would still have been no closer to the claimed subject matter because they would, for example, have arrived at a dosage regimen which requires the administration of non-liposomal irinotecan, not "*irinotecan sucrose octasulfate salt liposome injection*" as required by claim 1. Therefore, even if D5 is taken as the closest prior art, the main request involves an inventive step.

6.48 In fact, if one considers the results disclosed in D5 and compares them with the results obtained using the claimed dosage regimen[44], it is possible to formulate the objective technical problem more ambitiously as, for example, the provision of a treatment for gemcitabine-resistant pancreatic cancer *which is improved relative to D5*.

6.49 A comparison between the results described in D5 and those obtained using the claimed dosage regimen demonstrates that an improved treatment is present. This comparison therefore shows that the more ambitious objective technical problem formulated above is solved. For example, despite receiving a total dose of 140 mg/m^2 non-liposomal irinotecan in combination with leucovorin and 5-fluorouracil, D5 discloses a median overall survival of 16.6 weeks and a progression free survival of 8.3 weeks for patients who received the "*mFOLFIRI.3*" dosage regimen[45]. In contrast, the claimed dosage regimen demonstrated a median overall survival of 6.1 months and a median progression free survival of 3.1 months[46]. Comparing the results of D5 and the claimed subject matter by converting the reported PFS and OS values to estimated values in units of days (assuming a month is 30 days), patients who received the claimed dosage regimen had a 60% longer progression free survival (PFS)(i.e., a median PFS of 3.1 months or 93 days compared to 8.3 weeks or about 58 days for patients reciveing the "*mFOLFIRI.3*" regimen in D5) and a 58% greater overall survival (OS) (median overall survival of 6.1 months or 183 days, compared to 16.6 weeks or 116 days for patients receiving the "*mFOLFIRI.3*" regimen in D5). Thus, even if the Board unexpectedly finds that the solution to the problem formulated at 6.43 to be obvious, the solution to the more ambitious problem formulated above would not have been obvious. This is at least because there is nothing in D5, or the other prior art, that would have led the skilled person to the claimed subject matter with a reasonable expectation of providing a treatment for gemcitabine-resistant pancreatic cancer *which is improved relative to D5*. Therefore, the solution to the more ambitious technical problem involves an inventive step.

[44] These are described in, for example, the statement of grounds of appeal, paragraphs 5.12 – 5.20.
[45] D5, page 1661, left-hand column, first paragraph.
[46] Statement of grounds of appeal, table on page 11.

Priority

Claim 1 does not impermissibly combine two separate embodiments

6.50 In its reply to the appeal, the respondent argues for the first time that claim 1 is not entitled to the earliest priority date because it "*impermissibly combines two separate embodiments*"[47]. Should the Board be minded to take these new facts and arguments into consideration, they are not prejudicial to the priority claim.

6.51 The patient population being treated in claim 1 of the Main Request is a patient who (1) "*exhibits evidence of recurrent or persistent pancreatic cancer following primary chemotherapy*" and who has (2) "*failed prior treatment with gemcitabine or become resistant to gemcitabine*". As pointed out by the respondent, feature (1) finds basis on page 11, final paragraph, of PD1, and feature (2) finds basis on page 12, second paragraph, of PD2. However, the respondent is wrong to argue that the combination of these two features in claim 1 creates new subject matter which is not directly and unambiguously derivable from PD1.

6.52 Features (1) and (2) in PD1 are both disclosed in PD1 in a section entitled "*IV. Patient Populations*"[48], that is, the patient populations that may be treated according to the invention disclosed in PD1. Feature (1) is the first embodiment to be defined in this section, and is broadly defined as requiring the patient to "*exhibit evidence of recurrent or persistent pancreatic cancer following primary chemotherapy*". The skilled person would appreciate that gemcitabine therapy is a type of chemotherapy, as this would be consistent with their common general knowledge and the disclosure of page 1, lines 18-19, of PD1, which explicitly states that gemcitabine is a type of chemotherapy. With this in mind, the skilled person would look to the disclosure of feature (2) on page 12, and would understand that feature (2) is at least partially encompassed by feature (1), because gemcitabine falls within the scope of the "*primary chemotherapy*" required by feature (1). This is consistent with page 2, lines 13-14, of PD1, which states that "*gemcitabine is the current standard of care in first-line treatment* [i.e. the primary chemotherapy of] *advanced and metastatic pancreatic adenocarcinoma*".

6.53 Thus, rather than being separate features which cannot be combined, a combination of features (1) and (2) is consistent with the disclosure of PD1 as a whole and the skilled person's common general knowledge that the preferred "*primary chemotherapy*" (feature (1)) in this instance is gemcitabine (feature (2)). Therefore, there is a clear relationship between these two features meaning that their combination cannot create new subject matter. There is certainly no technical reason why these two features cannot be combined. Thus, the combination of features (1) and (2) would not have presented the skilled person with any subject matter which is not directly and unambiguously derivable from PD1.

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[47] Reply to appeal, paragraphs 6.2 – 6.5.
[48] PD1, page 11, line 27.

7 FURTHER COMMENTS ON THE REPLY TO THE APPEAL

7.1 In addition to the arguments made above, the appellant provides the following additional comments in response to various points raised in the reply.

Inventive step

D24 - Declaration of Dr Bruce Belanger

7.2 In paragraphs 7.40 to 7.43 the respondent argues that D24 is not relevant to the question of inventive step. Central to the respondent's argument is that, even if the claimed dosage regimen had not been tested in humans having pancreatic cancer whose disease had progressed following gemcitabine-based therapy prior to the NAPOLI-1 trial, this is not relevant because "*other evidence must have existed*". This evidence, the respondent suggests, would have led the skilled person to the claimed subject matter with a reasonable expectation of success. This cannot be correct.

7.3 In these proceedings, the respondent's position has previously been that the claimed dosage regimen would have shown "*a high level of safety and efficacy in earlier preclinical and clinical studies*" in patients whose pancreatic cancer had progressed following gemcitabine-based therapy prior to the beginning of the NAPOLI-1 trial[49]. There is now evidence on file which confirms that this is incorrect (D24). In spite of this, the respondent now argues that, in actual fact, it does not matter that the claimed dosage regimen had not shown "*a high level of safety and efficacy*", or even been tested at all, in the relevant patient population prior to the NAPOLI-1 trial. This is allegedly because "*other evidence must have existed*". However, the only piece of evidence cited by the respondent to support its arguments on this point is D19[50], which is not relevant to this point as it is not prior art. No other specific evidence is cited. Rather, the respondent merely alludes to "*methods in clinical pharmacology and pharmacometrics*".

7.4 The respondent's argument must fail here because it is not permissible to simply argue that "*other evidence must have existed*" that would have led the skilled person towards the claimed solution without stating what exactly this "*other evidence*" is. In fact, as the respondent himself has acknowledged, "*the question of inventive step is addressed by the skilled person based on the state of the art*"[51] (emphasis added). This reference to "*the state of the art*" should be contrasted with the respondent's vague and unsubstantiated "*other evidence*" which cannot be relied on in the problem-solution approach, whose very purpose is "*to ensure objective assessment of inventive step*"[52]. The fact that the trial sponsor may have been in possession of such "*other evidence*" which did not form part of the state of the art at the relevant date cannot change this conclusion[53].

D23 - Declaration of Dr Amy McKee

7.5 A large amount of the respondent's arguments concerning D23 and the NAPOLI-1 trial have been addressed above. In paragraphs 7.59 – 7.63, the respondent provides further

[49] See, for example, the OD's decision, paragraph 5.7.3.
[50] Reply to appeal, paragraph 7.41, final sentence.
[51] Reply to appeal paragraph 3.10.
[52] Case Law of the Board of Appeal, 9th Ed., I.D.2, page 176, 3rd paragraph.
[53] See, for example, T1868/16 – 3.3.01, Reasons 4.7, where it was stated that, albeit in the context of Article 83 EPC, "*it is not relevant what the respondent was aware of, but decided not to disclose*".

arguments stating that D23 is not relevant to this case. We will briefly comment on these arguments below.

7.6 In paragraph 7.59, the respondent argues that, in stating in D23 that there would have been "*no reasonable expectation that Arm C would be successful*", the term "*successful*" must be interpreted as "*outcomes necessary to facilitate the granting of a marketing authorisation*". This is not stated explicitly or implicitly in D23. Moreover, the respondent does not cite any evidence in support of this argument, and so it appears to be merely an unsupported assertion.

7.7 In any case, it is not correct to argue that "*success*" in this context equates to "*outcomes necessary to facilitate the granting of a marketing authorisation*". In particular, the "*outcomes necessary to facilitate the granting of a marketing authorisation*" are numerous and include "*outcomes*" which are not relevant to this case, for example, the requirement to provide confirmation that the medicinal product is manufactured in accordance with good manufacturing practice[54]. There is nothing in D15b, or in any of the documents on file, which would have led the skilled person to conclude that the results obtained from Arm C of D15b would have resulted in all of the "*outcomes necessary to facilitate the granting of a marketing authorisation*" being met, including those which are not relevant to this case. Clearly then it is not correct to equate "*success*" in this context to "*outcomes necessary to facilitate the granting of a marketing authorisation*".

7.8 In its arguments at paragraph 7.60, the respondent suggests that Dr McKee's conclusion might have been different had she been shown D2-D7, D12, D13, D22, and D29. As a starting point, the respondent's suggestion here appears to contradict its main argument that D15b alone is enough to create a reasonable expectation of success. In any case, the reasons why any one of D2-D7, D12, D13, D22, and D29 in combination with D15b would not have led the skilled person to the claimed subject matter has already been explained in the statement of grounds and in this submission, and so will not be repeated here.

The prior art teaches away from the claimed subject matter

7.9 In paragraphs 7.64 – 7.71, the respondent argues that the other prior art (i.e. prior art other than the D15 documents) would not have led the skilled person away from the claimed subject matter, and that the appellant has provided *"no evidence that the skilled person would be dissuaded from having a reasonable expectation of success for Arm C"*[55]. This is wrong not least because it was explained in detail in the statement of grounds of appeal why the evidence on file teaches away from the claimed subject matter[56]. These arguments will not be repeated here purely for the sake of brevity.

7.10 However, turning to the respondent's specific arguments on this point, the respondent argues that D22 would not have led the skilled person away from the claimed subject matter because the document is a "*single disclosure*" concerning a "*small study… in patients with a variety of*

[54] See, for example, Directive 2001/83/EC, Article 8(3)(ha).
[55] At paragraph 7.67 of the reply, the respondent argues that the arguments in the statement of grounds of appeal concerning D22 constitute a "*new point*". This is not correct because this argument was made in the oral proceedings before the OD. See the minutes of the oral proceedings (page 4, 3rd bullet point) and the decision (paragraph 5.7.3).
[56] Statement of grounds of appeal, paragraph 5.88 – 5.96.

solid tumours"[57]. As a starting point, it should be noted that the respondent's comments here, which essentially state that D22 is irrelevant, are at odds with the respondent's comments on sufficiency (see below), where a great deal of importance is attached by the respondent to the disclosure of D22.

7.11 In any case, the fact remains that D22 explicitly discloses to the skilled person that the maximum tolerated dose of "*PEP02*", defined in the "*Background*" section as a "*liposome formulation of irinotecan (CPT-11)*", is 80 mg/m^2 when administered every 3 weeks in combination with 5-FU/LV. The skilled person would have had no reason to doubt the accuracy of this conclusion, and thus the conclusion would have been accepted at face value.

7.12 The respondent also points to the disclosure in D30 of the maximum tolerated dose for "*PEP02*" being 100 mg/m^2 when administered. Should the Board be minded to admit D30, it fails to advance the respondent's argument on this point. In particular, D30 does not overcome the fundamental conflict between documents such as D7 and documents such as D22[58], and it still would not have motivated the skilled person to use an 80 mg/m^2 dose administered once every two weeks. Further, the study described in D30 took place in patients having a different cancer (colorectal) and who had previously been administered a different first-line chemotherapy (oxaliplatin-based chemotherapy) to the patients treated according to claim 1, so the skilled person would not have consulted D30 ahead of the more relevant disclosures of, for example, D7 or D22.

7.13 In addition, and with regard to paragraph 7.69 of the reply, D30's disclosure of a maximum tolerated dose of 100 mg/m^2 administered once every two weeks does not prove that the OD's assertion regarding dose reductions when combination therapies are used is correct[59]. Even if the skilled person would have looked to a reduced dose when using a combination therapy (which is not conceded), D30 provides no teaching as to how this might be done. Plus, even if the skilled person had for some reason thought to use an 80 mg/m^2 dose in a combination therapy (which, again, is not conceded), the skilled person would have known from D22 this this dose could only be administered safely once every three weeks, not once every two weeks as required by claim 1.

D12 as closest prior art

7.14 The respondents' arguments here (given in paragraphs 7.98 – 7.112 of the reply) begin with the argument that one must take the mention of the combination regimen in the "*Background*" section of D12 as the closest prior art embodiment. This cannot be correct.

7.15 Whilst we do not dispute that D12 *mentions* a combination regimen alongside a PEP02 monotherapy regimen, the question to be answered here is which of these two regimens constitutes the most promising starting point or most promising springboard towards the invention[60]. Clearly, the answer is that the monotherapy regimen is the most promising starting point or most promising springboard in D12 because only it is said to "*have both activity and tolerable side effects*" in the relevant patient population (see "*Conclusions*" section). In addition, and contrary to the respondent's arguments at paragraph 7.103 of the

[57] Paragraph 7.68 of the reply.
[58] See, for example, paragraph 5.94 of the statement of grounds of appeal.
[59] OD's decision, page 17, third sentence.
[60] Case Law of the Boards of Appeal, I.D.3.4, 9th Ed., English version, pages 182 – 183.

reply, D12 does not explicitly disclose any "*positive results*" which are specific to the combination regimen. Rather, the only positive results in D12 which are explicitly disclosed in connection with a specific dosage regimen appear in connection with the monotherapy.

7.16 The selection of the monotherapy regimen as the closest prior art does not, as the respondent suggests in paragraph 7.104, arise as a result of the combination regimen being "*ignored*". It simply arises as a consequence of considering what the most promising starting point or springboard is in D12, as is required by the problem-solution approach.

7.17 In paragraph 7.104 (final sentence), the respondent also suggests that the combination of both the combination regimen and the monotherapy regimen could together be taken as the closest prior art[61]. This approach is not consistent with a proper application of the problem-solution approach which requires that, when a document contains more than one embodiment (e.g. D12), one should select the closest prior art embodiment disclosed within the document[62]. It is certainly not correct to combine two embodiments disclosed separately in a document together in some way, and then take this combination as the closest prior art.

7.18 In paragraph 7.109, the respondent lists a number of prior art documents and various doses which are allegedly listed in these prior art documents. The relevance of this is not clear. However, in any case, it has already been explained above and in the statement of grounds of appeal that the skilled person would not have been led to the doses and administration frequencies recited in claim 1 with a reasonable expectation of success, and so these arguments will not be repeated here.

7.19 The respondent then argues at paragraph 7.110 that "*finding the optimum dosage is a matter of routine experimentation, which does not require inventive skill*". This argument is not relevant because, as explained above and in the statement of grounds of appeal, the objective technical problem does not relate to merely finding an optimal dosage.

7.20 In any case, even if the mention of the combination therapy trial in D12 is taken as the closest prior art, it remains the case that the claims are inventive. For example, claim 1 differs from this disclosure in D12 at least because it requires the administration of 80 mg/m^2 of irinotecan sucrose octasulfate salt liposome injection as part of a two-week administration cycle. The objective technical problem can be formulated as the provision a safe and effective treatment for gemcitabine-resistant pancreatic cancer. D12 would not have led the skilled person to the claimed solution with a reasonable expectation of success at least because it does not disclose or suggest the use of an 80 mg/m^2 dose every two weeks, nor does it disclose or suggest the use of irinotecan sucrose octasulfate salt liposome injection.

D13 as closest prior art

7.21 The arguments made above concerning the references to the mono- and combination regimens in D12 apply *mutatis mutandis* to D13 and so will not be repeated in full here.

[61] As the Board will be aware, within the problem-solution approach, the "*first consideration*" in selecting the "*closest prior art*" is that it is "*directed to a similar purpose or effect as the invention*". See, for example, the Guidelines, G-VII, 5.1.
[62] T1287/14 (Reasons 5.2.1 – cited in the statement of grounds of appeal), T72/07 (Reasons 2.3.1), T570/91 (Reasons 4.3), and T1194/00 (Reasons 3.1).

However, to reiterate and for the avoidance of doubt, the closest prior art embodiment should be taken as the disclosure of the monotherapy regimen in D13, not the combination regimen.

7.22 In response to the point made by the respondent in paragraph 7.117 of the reply, we note that that there is a large amount of case law which states that, contrary to the respondent's argument, the selection of the closest prior art is an exclusionary choice[63]. Thus, the respondent's arguments on this point are at odds with the relevant case law.

7.23 In paragraph 7.118, the respondent relied on D22 as evidence that 80 mg/m^2 of MM-398 "*had shown efficacy and acceptable safety*". As a starting point, D22 refers not to MM-398 but to something called "*PEP02*". In any case, and as stated previously, this fails to advance the respondent's case because in D22 the 80 mg/m^2 dose was administered once every three weeks, not once every two weeks as required by claim 1.

7.24 At paragraphs 7.119, the respondent argues that the reason why D13 does not describe a Phase II trial of the combination regimen is that the combination regimen was "*behind monotherapy in terms of development timelines*". No evidence has been given in support of this argument, and so it appears to be based purely on speculation. Thus, it is not prejudicial to inventive step.

7.25 In any case, even if the mention of the combination therapy trial in D13 is taken as the closest prior art, it remains the case that the claims are inventive, and the arguments made at 7.20 apply here *mutatis mutandis*.

Priority

The "*l-form*" of leucovorin is directly and unambiguously derivable from PD1

7.26 This point was addressed in detail in the statement of grounds of appeal[64]. These arguments are maintained, although purely for the sake of brevity they will not be repeated here. The respondent provides arguments on this point in paragraphs 6.6 – 6.27 of its reply. To assist the Board, the appellant provides the following brief additional comments.

7.27 As a starting point, the respondent suggests that the references to "*leucovorin*" in PD1 constitute direct and unambiguous references to "*racemic leucovorin*" or "*l+d leucovorin*" because this is "*in line with usual practice*" (i.e. consistent with the common general knowledge). The only evidence relied on by the respondent to support this point is D1b, cited in paragraph 6.7 of the reply. However, this document represents a single disclosure which is not representative of the common general knowledge. Moreover, it contains no general teaching on, for example, the nomenclature used for drugs which contain one or more chiral centres. Thus, the respondent's argument that the skilled person would interpret "*leucovorin*" in PD1 as "*racemic leucovorin*" or "*l+d leucovorin*" is not backed-up by the evidence or the common general knowledge.

7.28 The respondent does appear to agree that it was common general knowledge at PD1's filing date that "*leucovorin*" was available as "*l-leucovorin*" or "*racemic leucovorin*"[65]. Rather than being a generic term as suggested by the respondent, the term "*leucovorin*" would thus be

[63] Case Law of the Boards of Appeal, I.D.3.6, 9th Edition.
[64] Paragraphs 4.7 – 4.20.
[65] See, for example, paragraph 6.24, first sentence;

interpreted by the skilled person as merely a shorthand for "*l-leucovorin or racemic leucovorin*". In view of this, the case law cited in paragraph 6.20 is not relevant here. Like the case law relied on by the OD, in the cases cited in paragraph 6.20 there was nothing in the prior art or the common general knowledge to suggest to the skilled person that the claimed compound could exist in, for example, different optically-active forms. In this case, the situation is different because the existence of specific optically active forms of the claimed compound (i.e. "*l-leucovorin*" or "*racemic leucovorin*") forms part of the common general knowledge. As this information forms part of the common general knowledge it does not need to be laid out *expressis verbis* in PD1 in "*individualised form*" (to use the respondent's wording). Thus, and at worst for the appellant, it would be at least implicit, but nevertheless directly and unambiguously derivable, to the skilled person that the "*leucovorin*" in PD1 means "*l-leucovorin or racemic leucovorin*". A selection of one feature from two equally preferred alternatives cannot generate new subject matter, and so the priority claim is valid.

Sufficiency

7.29 The OD was correct to find that the Main Request complies with Article 83 EPC, and the appellant agrees with the majority of the reasoning given in the OD's decision[66]. The appellant's position on sufficiency was explained before the OD and outlined in the OD's decision and the minutes of the oral proceedings. These arguments are maintained, although they will not be repeated here for the sake of brevity. In addition, the appellant provides the following comments on the points raised in section 5 of the reply to the appeal.

7.30 The respondent's central argument in this case is that "*the claimed subject matter cannot meet the requirements of both Article 83 EPC and Article 56 EPC*"[67]. Aside from the fact that such a statement is, at best, dubious from a legal standpoint[68], it is also based on an incorrect interpretation of the application as filed and the prior art. When both are properly considered, it becomes apparent that the respondent is wrong to argue that the technical contribution of the invention resides in merely providing a dosage regimen for a known combination therapy in a known patient population[69]. Rather, the application as filed discloses for the first time that irinotecan sucrosofate salt liposome injection administered at a dose of 80 mg/m^2 in a combination dosage regimen according to claim 1 is able to treat pancreatic cancer in the patient population defined in claim 1. It has been explained in the statement of grounds of appeal and above that this is not disclosed or suggested in the prior art, and the OD correctly found that this is at least plausible. So, the respondent's argument must fail.

7.31 Turning to the respondent's specific arguments, its central legal argument is that "*it is necessary to positively demonstrate suitability*" of the claimed therapeutic effect in the

[66] For the avoidance of doubt, the appellant disagrees with some of the OD's findings. For example, the appellant does not agree with the OD's comment that "*the liposomal preparation of irinotecan according to the patent in suit is only directed to improve the therapeutic index*" (see page 8 of the OD's decision, first complete sentence).
[67] Reply to appeal, paragraph 5.1.
[68] Because, as was stated by the Board in T184/16, "the criteria for plausibility [i.e. Article 83 EPC] and obviousness [i.e. Article 56 EPC] are different" (Reasons 11), and it has been established that it is possible to, for example, rely on a prior art disclosure to establish compliance with Article 83 EPC and also establish inventive step in view of the same prior art under Article 56 EPC (e.g. T108/09).
[69] Reply to appeal, paragraph 5.9.

application as filed[70]. In making its arguments, the respondent is setting a relatively high bar for plausibility in a way which is inconsistent with recent case law.

7.32 For example, in T184/16 – 3.3.02, the appellant/opponent made similar arguments to the respondent in this case. Namely, it argued that the patent's medical use claims were insufficient because "*there was no evidence in the application as filed to show that the claimed compounds were suitable*" for treating the diseases listed in the claim (Reasons 2.1). The Board noted this but found that the plausibility threshold was met notwithstanding because "*there are no prima facie serious doubts that the effect can be obtained and conversely no a priori reason and indication in the common general knowledge that the effect cannot be obtained*" (Reasons 11). That is, in T184/16, the Board noted that the application as filed did not, to use the appellant's wording, "*positively demonstrate suitability*", but found that the requirements of Article 83 EPC were met in any case.

7.33 Similar guidance can be found in T2015/20 – 3.3.07 (Usuelli, Steendijk, Jimenez), where the Board acknowledged that the claimed therapeutic application of treating asthma was sufficiently disclosed in spite of the fact that there was no biological data relating to the treatment of asthma in application as filed. In coming to its decision, the Board found that the claimed therapeutic application was sufficiently disclosed because it "*does not go against any prevailing opinion in the prior art*", and found that the below passage of the application as filed represented a "*significant technical teaching, which is far from an invitation to perform a research programme and which does not prima facie lack plausibility. This teaching is as such falsifiable, in the sense that it is open to challenge, and is therefore considered to represent information in the form of a specific technical contribution which goes beyond some insufficient verbal statement.*"

> **[0003]** It is now surprisingly found that, for treatment of respiratory disorders, particularly asthma and COPD, in an adult human, aclidinium is most effective upon administration by inhalation in a dosage of about 400 µg metered nominal dose, typically a single dosage of about 400 micrograms per day metered nominal dose, (e.g., about 360 µg emitted dose, and about 120 µg Fine Particle dose) (weight corresponding to aclidinium bromide).

7.34 Thus, T2015/20 confirms that, rather than "*positively demonstrate suitability*" (whatever this may mean), it is enough for the purposes of Article 83 EPC that the therapeutic application does not go against any prevailing opinion in the art, and that the application as filed contains some sort of significant technical teaching which does not *prima facie* lack plausibility and which is falsifiable.

7.35 T2015/20 also shows that the respondent's argument that "*the requirement for "serious doubts" to substantiate insufficiency is not relevant to medical use claims*"[71] is wrong. In T2105/20, all of the claims considered by the Board were either medical use claims or Swiss claims. Notwithstanding this, the Board stated in Reasons 2 of the decision that:

> *"According to established jurisprudence of the Boards of Appeal of the EPO a convincing objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts, on the possibility for a skilled person to carry out the invention as claimed. (see Case Law of the Boards of Appeal*

[70] Reply to appeal, paragraphs 5.6 and 5.19 respectively.
[71] Reply to appeal, paragraph 5.19.

of the EPO, 9th Edition 2019, sections II.C.7.1.4 and II.C.9; see also Guidelines for the Examination in the EPO, October 2019, F-III,1)." (emphasis added)

7.36 Clearly, the Board would not have included this passage in its decision had the Board been of the view that the "*serious doubts*" requirement does not apply to medical use claims. In fact, the Board states explicitly later on in the decision that the "*serious doubts*" requirement does apply to medical use claims, and that T609/02 and the decisions on plausibility stemming from it do not change this:

"*Notably, neither T 609/02 nor the jurisprudence that developed from this decision signal a deviation from the established jurisprudence or an interpretation differing from the Guidelines* [F-III, 1]*, in particular with respect to the precondition of serious doubts for a convincing argument of lack of sufficiency.*" (Reasons 2.6, final sentence)

7.37 The case law discussed above is consistent with older case law such as T1616/09, where the Board held that the claimed therapeutic effect was plausible in the absence of any supporting data because there was "*no apparent reason to doubt*" that the claimed combination therapy would be effective (Reasons 6.2.2). It also appears that similar reasoning to that explained above was relied on by the Board in T1592/12 cited by the opponent. In particular, in that decision, central to the Board's finding of insufficiency was the conclusion that, on the basis of the evidence, the skilled person would have had "*serious doubts*" that the use of the dosing frequency recited in claim 1 would have been effective (Reasons 28 and 37).

7.38 Thus, the respondent is wrong to argue that the application as filed must "*positively demonstrate suitability*".

7.39 However, if one assumes purely for the sake of argument that the stricter standard put forward by the respondent is correct (which is not conceded), the application as filed does positively demonstrate that the claimed subject matter is able to treat pancreatic cancer in the patient population defined in claim 1. Thus, the plausibility threshold is met in any case. This is explained in the OD's decision (e.g., in paragraphs 3.3.1 and 3.3.2).

7.40 In attempting to argue that the application fails to positively demonstrate suitability/plausibility, the respondent argues that Example 6 of the application as filed cannot be relied on to support plausibility because certain features of claim 1 are not explicitly recited in Example 6. This cannot be right.

7.41 The skilled person considering the application as filed as a whole would note that there are two main embodiments described therein – a monotherapy embodiment which administers liposomal irinotecan as a single active agent (see, e.g., claim 1), and triple combination therapy embodiment (see, e.g., claim 3). Both of these embodiments are described throughout the application as filed in a consistent manner. For example, for the triple combination therapy embodiment, the skilled person would note that, every time specific doses and administration frequencies of 5-FU and leucovorin are mentioned, these doses and administration frequencies are those which appear in claim 1. This can be seen from, for example, page 3 (third complete paragraph), page 13 (third complete paragraph), page 14 (fourth complete paragraph), Example 7 (column labelled "*Arm C*" spanning pages 25 and 26), claim 1, claim 12, and Figure 7 of the application as filed. Thus, the skilled person would clearly understand from the application as filed taken as a whole that these doses and

administration frequencies were used in Example 6. Thus, there is no need for them to be recited *verbatim* in Example 6.

7.42 The same can be said for the order of administration of the three drugs in the triple combination therapy embodiment. Similar to the situation above, every time a specific order of administration for these three drugs is given in the application as filed, this order is that which appears in claim 1. This can be seen from, for example, page 4 (second sentence), Example 7 (row labelled "*Arm C*" of table spanning pages 25 and 26), claim 4, claim 14, and Figure 7. Thus, it is not necessary for this feature to be recited explicitly in Example 6 either.

7.43 The respondent's arguments essentially suggest that the skilled person would totally ignore the consistent disclosure of the application as filed when interpreting Example 6, and would instead consider Example 6 in isolation from the remainder of the application as filed. This is incompatible with a proper assessment of Article 83 EPC, which must be assessed on the basis of the application as filed as a whole through the eyes of the skilled person[72]. For the avoidance of doubt, D22 fails to assist the respondent's case at least because the document does not mention pancreatic cancer. Thus, the skilled person would not have taken D22 into consideration when considering whether or not the claimed combination dosage regimen is suitable/plausible for the treatment of pancreatic cancer in the patient population recited in claim 1.

7.44 For the avoidance of doubt, whilst Example 6 does not explicitly mention that the pancreatic cancer patients had "*failed prior treatment with gemcitabine or become resistant to gemcitabine*", this is not prejudicial to Article 83 EPC. However, as was correctly pointed out by the OD (paragraph 3.3.5 of the decision), it was known in the art at the relevant date that there was no cross-resistance between gemcitabine and irinotecan. Thus, the skilled person would have considered it at least plausible that the results obtained in Example 6 would work in patients who had "*failed prior treatment with gemcitabine or become resistant to gemcitabine*". Similar arguments apply to the differential dosing of patients based on whether or not they are homozygous for the UGT1A1*28 allele. In particular, the skilled person would have been aware that patients homozygous for the UGT1A1*28 allele should be administered a lower dose of irinotecan. Thus, the reference in claim 1 to patients homozygous for the UGT1A1*28 allele being administered a lower initial dose of liposomal irinotecan would not have taken away the skilled person's conclusion that the claimed combination dosage regimen is suitable or plausible for the treatment of pancreatic cancer in the patient population recited in claim 1.

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[72] This is illustrated well by T1046/97, relied on by the respondent in its priority arguments. In particular, Reasons 2.1.1.3 of T1046/97 state that "*the technical teaching of an example may be combined with general technical teaching disclosed elsewhere in the same document, in the absence of reasons to the contrary*".

EXPERT DECLARATION OF CARLA SCHOONDERBEEK
Filed in relation to the appeal against the revocation of EP 2 8610 210 (T2963/19 – 3.3.07)

A IDENTITY AND BACKGROUND

1. I graduated as a Master of Law at the University of Utrecht in the Netherlands in 1979 and was admitted to the Dutch Bar in 1980. I was a partner at the law firm CMS Derks Star Busmann until May 2005, at which time I joined the law firm NautaDutilh as a partner until July 2011 when I joined the law firm Hogan Lovells as a partner. In November 2012 I took up my present position as a partner in the law firm Hoyng Rokh Monegier.

2. My area of expertise is European Union ("**EU**") pharmaceutical and biopharmaceutical regulatory law and I have been active in that area of the law since 1985. I have extensive experience in EU law as it pertains to the regulation of medicinal products, both pharmaceuticals and biologicals. I have provided advice on EU and national marketing authorization procedures, regulatory exclusivities and EU clinical trial legislation to a large number of international pharmaceutical and biotechnological companies involved in the development and marketing of medicinal products in the EU. I have litigated, and regularly litigate, about pharmaceutical regulatory matters before the EU General Court and the Court of Justice of the EU and before the national Courts.

B INTRODUCTION

3. I have been asked by Carpmaels & Ransford LLP on behalf of Ipsen Biopharm Ltd. to provide my comments on the following case from a European regulatory law standpoint.

4. I understand that EP 2 861 210 was revoked by the EPO Opposition Division ("OD") as the claims allegedly lack an inventive step in view of document D15b (a clinicaltrials.gov entry for a clinical trial referred to as "NAPOLI-1"). I understand that the patent proprietor, Ipsen Biopharm Ltd. (hereafter "Ipsen"), has filed an appeal against this decision.

5. I have read document D23 (the Declaration of Amy McKee, M.D.) filed by Ipsen in support of its appeal. I agree with all of the statements made by Amy McKee, M.D. in her declaration.

6. I understand that the Opponent/Respondent in this case (Teva Pharmaceutical Industries Ltd., hereafter "Teva") has argued that D23 is not relevant because the points raised in it apply only to the regulatory situation in the United States. I understand that Teva has pointed out that the above-mentioned NAPOLI-1 trial took place in several other countries, including several EU countries – namely, the Czech Republic, France, Germany, Hungary, Italy, Spain, and the United Kingdom[1]. Teva appears to be suggesting here that the situation under EU law must also be taken into consideration.

[1] The United Kingdom was an EU Member State when the NAPOLI-1 trial was carried out (2011 - 2016).

C THE OD's DECISION

7. In their decision, in particular in paragraph 5.7.3 thereof, the OD appears to take the following position:

   - Clinical trials and phase III clinical trials in particular are only authorised once it has been shown that the treatment under investigation has a high level of safety and efficacy in earlier preclinical and clinical studies;

   - Consequently, the mere fact that a certain dosage regime is tested in an authorised clinical trial leads to an expectation or even a presumption of success, due to the fact that clinical studies are based on data obtained by preclinical testing both in vitro and in animals and require authority approval which takes ethical considerations into account:

   - This presumption of success is based on a careful risk/benefit evaluation by the authority. Ethical and economical considerations require that the "benefit" will arise with reasonable certainty and will not only "be hoped for". The set-up of the clinical study of D15b thus inherently creates an expectation of success.

8. On the basis of my many years of experience as a lawyer practicing in the field of EU pharmaceutical regulatory law, in my view the reasoning of the OD outlined above does not follow from the regulatory framework. In particular, I do not agree that the mere fact that a certain dosage regime of a medicinal product is being tested in a clinical trial leads to an expectation or even a presumption that this dosage regime would work. The fact that a request must be filed with an appropriate Competent Authority before the trial can begin does not change this conclusion.

9. This will be explained in more detail below, where I will set out the key features of clinical trial approval in the EU and in particular the nature and scope of the assessment and approval by the ethics committee and competent authority. On this basis I will explain that the so-called benefit / risk assessment that is conducted in the context of a clinical trial approval is not aimed at establishing or confirming the anticipated benefits of a medicinal product or dosage regime and cannot be the basis of a presumption or inherent expectation that the trial will be successful.

10. For ease of reference, a copy of Directive 2001/20/EC is enclosed as document D37A.

D LEGAL FRAMEWORK

General principles

11. According to Directive 2001/83/EC, all clinical trials conducted within the EU must comply with the requirements of Directive 2001/20/EC (the "Clinical Trial Directive or "CTD").

12. According to recital (2) of the CTD, the accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. It also provides that the clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical

trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

13. Article 1(4) of the CTD provides that all clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of Good Clinical Practice (GCP).[2]

14. These principles are laid down in Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products ("GCP Directive"). Article 3 of this directive provides that the available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

15. On this basis, insofar as it is relevant for this declaration, the following general principles of GCP have been developed:

- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

16. Accordingly, the CTD, which aims to implement the GCP principles, provides in its Article 9(1) that the sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the Competent Authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. As to the opinion of the Ethics Committee and the acceptance of the trial by the Competent Authority the CTD provides as follows.

Ethics Committee

17. Article 2(k) of the CTD defines Ethics Committee as "*an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.*"

18. Furthermore, Article 3(2) of the CTD provides that a clinical trial may be undertaken only if, in particular: "*the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may*

[2] According to Article 1(2) CTD, GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. In Article 1(3) the Commission is tasked with adopting the principles relating to GCP and detailed rules in line with those principles.

be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored".

19. According to Article 6(2) of the CTD the Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested. In this respect Article 6(3) provides that in preparing its opinion, the Ethics Committee shall consider, in particular (insofar relevant for this declaration)

    a. the relevance of the clinical trial and the trial design;
    b. whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified;
    c. the protocol;

        Note: According to Article 2(h), the protocol is a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol should include, inter alia, an evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of the CTD.

    d. the investigator's brochure;

        Note: According to Article 2(g) of the CTD, the investigator's brochure (IB) is 'a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects'.

Competent authority

20. In accordance with Article 9(1), in addition to having obtained a favourable opinion of the Ethics Committee, a clinical trial may only be started by a sponsor inasmuch the Competent Authority of the Member State concerned has not informed the sponsor of any grounds of non-acceptance. In this respect Article 9(2) provides that, before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial.

21. Article 9(4) of the CTD lays down time-lines for the validation of a request for authorisation of a trial. The Commission Communication[3] explains that if the request is valid, and by day 60 no ground for non-acceptance has been raised, the clinical trial is deemed to be authorised by the national competent authority of the Member State concerned (tacit authorisation). However, Articles 9(4), (5) and (6) of the CTD set out important exceptions to the rules on timelines and tacit authorisation as regards certain medicinal products, including medicinal products the active ingredient of which is a biological product of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components. Exceptions also apply to medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. In these situations, the CTD requires a written authorisation by the Competent Authorities as condition for the commencement of the trial.

22. Nevertheless, in my experience the approval of a trial with medicinal products will mainly rely on the substantive assessment that is conducted by the Ethics Committee and the authorisation by

[3] D38A

the Competent Authority will be marginal and focus on elements that the Ethics Committee may not have direct access to but the competent authority has, such as the European adverse reactions database (EudraVigilance) which the competent authority may consult to check if there are any previously reported suspected adverse reactions to the medicinal product which could lead to unacceptable risks to the participating research subjects.

National implementation

23. Because the CTD is a Directive, the implementation of the CTD is subject to national implementation which means that the rules and procedures concerning clinical trial approvals may differ according to national legislation (as long as these rules and procedures are not contrary to what is provided for in the CTD). Consequently, the roles of the Ethic Committee and the Competent Authority may be different between the Member States.

24. However, regardless of how the assessment is organised nationally, the scope and nature of the dual assessment (by the Ethics Committee and the National Competent Authority) that is conducted and that underlies a clinical trial approval in the EU shall be based on, and in conformity with, the criteria that are set out in the CTD. In light of the subject of this declaration I will focus on the assessment that is conducted in relation to:

    (i) the relevance of the clinical trial and the trial design; and

    (ii) on whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified (see points "a" and "b" in paragraph 19 above).

E ANALYSIS

25. It follows from the general principles set out above that the main purpose of the prior approval of clinical trials is to ascertain that the research respects the dignity, rights, safety and well-being of the people who are participating. According to these principles medical research must only be conducted if the importance of the findings outweigh the risks and burdens to the research subjects. This involves reflecting on the impact on the individuals participating, as well as the potential benefits to them and others who may be similarly affected by the disease. Risks must be monitored, mitigated, and if beginning to outweigh the potential benefits, the study must be immediately modified or stopped.

26. For this reason, the first part of the dual assessment that is performed concerns the question about the relevance of the scientific research (point (i) in paragraph 24 above). In this context it will be assessed if it is feasible that the scientific research will lead to the establishment of *new insights* in the field of medical science. It should be noted that even negative findings, e.g. a finding that a particular therapy is not efficacious for a particular sub population can establish new insights in medical science, because a negative finding would prevent physicians from exposing this sub population to adverse effects of the therapy without any benefit. By way of example: the underlying principle of the Paediatric Regulation (EC) 1901/2006 is that it is important to obtain information on the use of medicinal products in children and that such research should be conducted if this can be done safely, even if it is clear that the study may fail or will not support an authorisation of the product for use in children.

27. The assessment will then focus on the benefit / risk question (point (ii) of paragraph 24 above) by weighing the foreseeable risks and inconveniences of the trial subjects against the anticipated benefit (in terms of the feasible new insights discussed above) for the individual trial subject and future patients. In this context it will be assessed if it is feasible that the interests of the subject and other current or future patients to be served by the study are proportionate to the concerns and risks to the subject, also taking into account the circumstances of persons in the group to which the subject belongs. As stated in Article 3(2)(a) of the CTD, a clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks.

28. The assessment that is conducted is thus based on the fact that it is sufficiently justified that it is feasible that the trial will deliver new scientific insights which, if confirmed in the trial, will bring a benefit to trial subjects and, more in general, the relevant patient population. If a clinical trial is approved (by a favourable opinion of the Ethics Committee in combination with a tacit or explicit approval by the Competent Authority), this **does not** mean that this benefit is reasonably expected or that there is an inherent expectation that the anticipated benefit will be confirmed by the trial results. Rather, this dual approval system will ensure that the research is relevant in that it is feasible that the research will bring new insights in the field of medical science and that the anticipated benefit of those new insights, *if demonstrated*, outweighs the risks and burden for clinical trial subjects and that the methodology, design and power of the study is adequate in relation to the research question.

29. Although existing preclinical and (for Phase III trials) earlier clinical data and the other considerations relevant to justifying the initiation of a clinical trial as set out above may provide comfort for the applicant, the dual approval of the Ethics Committee and the Competent Authority**, does not, in any way, turn this comfort into an expectation or presumption of success** nor can it be considered as a confirmation by the competent authorities that based on available preclinical and clinical data the trial will likely be successful; it only means that from an ethical and medical perspective it is justifiable to conduct the research as proposed by the applicant.

30. As stated above, the approval of the trial means that the clinical trial is appropriate in terms of relevance, design and benefit/risk for patients to potentially demonstrate this anticipated benefit but is without prejudice of the likelihood of the outcome of the trial. In fact, there are many approved clinical trials that fail in late stage clinical development. Clinical trials with medicinal products offer many opportunities for failure. This is made clear by Annexes A and B filed with D23.

F CONCLUSION

31. On this basis I do not support the reasoning of the OD that the mere fact that a certain dosage regime of a medicinal product is being tested in a clinical trial leads to an expectation or even a presumption that this dosage regime is safe and effective for the treatment of the condition in question. The fact that a request must be filed with an appropriate Competent Authority before the trial can begin does not change this conclusion.

32. I declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true.

Declared in Amsterdam, the Netherlands, on 28 June 2021.

Carla Schoonderbeek

Enclosures

- D37A (Directive 2001/20/EC)

This document is meant purely as a documentation tool and the institutions do not assume any liability for its contents

►B DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

(OJ L 121, 1.5.2001, p. 34)

Amended by:

		Official Journal		
		No	page	date
►M1	Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006	L 378	1	27.12.2006
►M2	Regulation (EC) No 596/2009 of the European Parliament and of the Council of 18 June 2009	L 188	14	18.7.2009

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DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [4] requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products [5] lays down uniform rules on the compilation of dossiers including their presentation.

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when

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(1) OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.
(2) OJ C 95, 30.3.1998, p. 1.
(3) Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27). Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.
(4) OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
(5) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

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there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development of medicinal products should therefore be pursued through the appropriate fora, in particular the International Conference on Harmonisation.

(7) For medicinal products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], which include products intended for gene therapy or cell therapy, prior scientific evaluation by the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as the 'Agency'), assisted by the Committee for Proprietary Medicinal Products, is mandatory before the Commission grants marketing authorisation. In the course of this evaluation, the said Committee may request full details of the results of the clinical trials on which the application for marketing authorisation is based and, consequently, on the manner in which these trials were conducted and the same Committee may go so far as to require the applicant for such authorisation to conduct further clinical trials. Provision must therefore be made to allow the Agency to have full information on the conduct of any clinical trial for such medicinal products.

(8) A single opinion for each Member State concerned reduces delay in the commencement of a trial without jeopardising the well-being of the people participating in the trial or excluding the possibility of rejecting it in specific sites.

(9) Information on the content, commencement and termination of a clinical trial should be available to the Member States where the

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7)

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trial takes place and all the other Member States should have access to the same information. A European database bringing together this information should therefore be set up, with due regard for the rules of confidentiality.

(10) Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites, often in different Member States. Member States' current practices diverge considerably on the rules on commencement and conduct of the clinical trials and the requirements for carrying them out vary widely. This therefore results in delays and complications detrimental to effective conduct of such trials in the Community. It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned.

(11) As a rule, authorisation should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials. In exceptional cases raising especially complex problems, explicit written authorisation should, however, be required.

(12) The principles of good manufacturing practice should be applied to investigational medicinal products.

(13) Special provisions should be laid down for the labelling of these products.

(14) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned. The Directive should therefore take account of the special position of trials whose planning does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directives 75/319/EEC and 91/356/EEC, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation. Labelling of the investigational medicinal products intended for trials of this nature should be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational products and in Directive 91/356/EEC.

(15) The verification of compliance with the standards of good clinical practice and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.

(16) The person participating in a trial must consent to the scrutiny of personal information during inspection by competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available.

(17) This Directive is to apply without prejudice to Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [1].

[1] OJ L 281, 23.11.1995, p. 31.

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(18) It is also necessary to make provision for the monitoring of adverse reactions occurring in clinical trials using Community surveillance (pharmacovigilance) procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

(19) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1],

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Scope

1. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

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3. The Commission shall adopt the principles relating to good clinical practice and detailed rules in line with those principles and shall, if necessary, revise those principles and detailed rules to take account of technical and scientific progress. Those measures, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 21(3).

The principles and detailed rules shall be published by the Commission.

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4. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.

Article 2

Definitions

For the purposes of this Directive the following definitions shall apply:

(a) 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

[1] OJ L 184, 17.7.1999, p. 23.

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This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State;

(b) 'multi-centre clinical trial': a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries;

(c) 'non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

(d) 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

(e) 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;

(f) 'investigator': a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

(g) 'investigator's brochure': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

(h) 'protocol': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

(i) 'subject': an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

(j) 'informed consent': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

(k) 'ethics committee': an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

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(l) 'inspection': the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;

(m) 'adverse event': any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(n) 'adverse reaction': all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(o) 'serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

(p) 'unexpected adverse reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Article 3

Protection of clinical trial subjects

1. This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein. Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent.

2. A clinical trial may be undertaken only if, in particular:

(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;

(b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

(c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation;

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(e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent;

(f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

3. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.

4. The subject shall be provided with a contact point where he may obtain further information.

Article 4

Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Article 5

Clinical trials on incapacitated adults not able to give informed legal consent

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

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(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society; and

(i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

Article 6

Ethics Committee

1. For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.

2. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.

3. In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3;

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(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of subjects.

4. Notwithstanding the provisions of this Article, a Member State may decide that the competent authority it has designated for the purpose of Article 9 shall be responsible for the consideration of, and the giving of an opinion on, the matters referred to in paragraph 3(h), (i) and (j) of this Article.

When a Member State avails itself of this provision, it shall notify the Commission, the other Member States and the Agency.

5. The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned.

6. Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period laid down in paragraph 5 shall be suspended until receipt of the supplementary information.

7. No extension to the 60-day period referred to in paragraph 5 shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Article 7

Single opinion

For multi-centre clinical trials limited to the territory of a single Member State, Member States shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State.

In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trial.

Article 8

Detailed guidance

The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

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Article 9

Commencement of a clinical trial

1. Member States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.

The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial.

3. If the competent authority of the Member State notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

4. Consideration of a valid request for authorisation by the competent authority as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The competent authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.

No further extensions to the period referred to in the first subparagraph shall be permissible except in the case of trials involving the medicinal products listed in paragraph 6, for which an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy there shall be no time limit to the authorisation period.

5. Without prejudice to paragraph 6, written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of Directive 65/65/EEC and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components.

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

7. This authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms [1] and

[1] OJ L 117, 8.5.1990, p. 1. Directive as last amended by Directive 98/81/EC (OJ L 330, 5.12.1998, p. 13).

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90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms [1].

8. In consultation with Member States, the Commission shall draw up and publish detailed guidance on:

(a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol;

(c) the declaration of the end of the clinical trial.

Article 10

Conduct of a clinical trial

Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

(a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Articles 6 and 9.

On the basis of the details referred to in Article 6(3) and in accordance with Article 7, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the Ethics Committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment;

(b) without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time;

(c) within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has

[1] OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

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ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Article 11

Exchange of information

1. Member States in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the Agency and the Commission:

(a) extracts from the request for authorisation referred to in Article 9(2);

(b) any amendments made to the request, as provided for in Article 9(3);

(c) any amendments made to the protocol, as provided for in point a of Article 10;

(d) the favourable opinion of the Ethics Committee;

(e) the declaration of the end of the clinical trial; and

(f) a reference to the inspections carried out on conformity with good clinical practice.

2. At the substantiated request of any Member State, the Agency or the Commission, the competent authority to which the request for authorisation was submitted shall supply all further information concerning the clinical trial in question other than the data already in the European database.

3. In consultation with the Member States, the Commission shall draw up and publish detailed guidance on the relevant data to be included in this European database, which it operates with the assistance of the Agency, as well as the methods for electronic communication of the data. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

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4. By way of derogation from paragraph 1, the Agency shall make public part of the information on paediatric clinical trials entered in the European database in accordance with the provisions of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use [1].

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Article 12

Suspension of the trial or infringements

1. Where a Member State has objective grounds for considering that the conditions in the request for authorisation referred to in Article 9(2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

[1] OJ L 378, 27.12.2006, p. 1.

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2. Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.

Article 13

Manufacture and import of investigational medicinal products

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1. Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation.

The Commission shall lay down the minimum requirements which the applicant and, subsequently, the holder of the authorisation must meet in order to obtain the authorisation.

Those measures, designed to amend non-essential elements of this Directive, by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 21(3).

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2. Member States shall take all appropriate measures to ensure that the holder of the authorisation referred to in paragraph 1 has permanently and continuously at his disposal the services of at least one qualified person who, in accordance with the conditions laid down in Article 23 of the second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], is responsible in particular for carrying out the duties specified in paragraph 3 of this Article.

3. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 21 of Directive 75/319/EEC, without prejudice to his relationship with the manufacturer or importer, is responsible, in the context of the procedures referred to in Article 25 of the said Directive, for ensuring:

(a) in the case of investigational medicinal products manufactured in the Member State concerned, that each batch of medicinal products has been manufactured and checked in compliance with the requirements of Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use [2], the product specification file and the information notified pursuant to Article 9(2) of this Directive;

(b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 91/356/EEC, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

(c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that

[1] OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EC (OJ L 214, 24.8.1993, p. 22).
[2] OJ L 193, 17.7.1991, p. 30.

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each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to Article 9(2) of this Directive.

Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within the Community shall be drawn up pursuant to the good manufacturing practice guidelines, and in particular Annex 13 to the said guidelines. Such guidelines will be adopted in accordance with the procedure referred to in Article 21(2) of this Directive and published in accordance with Article 19a of Directive 75/319/EEC.

Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person.

4. In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions of this Article. The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member States concerned. This period shall in any event be not less than five years.

5. Any person engaging in activities as the qualified person referred to in Article 21 of Directive 75/319/EEC as regards investigational medicinal products at the time when this Directive is applied in the Member State where that person is, but without complying with the conditions laid down in Articles 23 and 24 of that Directive, shall be authorised to continue those activities in the Member State concerned.

Article 14

Labelling

The particulars to appear in at least the official language(s) of the Member State on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, shall be published by the Commission in the good manufacturing practice guidelines on investigational medicinal products adopted in accordance with Article 19a of Directive 75/319/EEC.

In addition, these guidelines shall lay down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials with the following characteristics:

— the planning of the trial does not require particular manufacturing or packaging processes;

— the trial is conducted with medicinal products with, in the Member States concerned by the study, a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directive 75/319/EEC;

the patients participating in the trial have the same characteristics as those covered by the indication specified in the abovementioned authorisation.

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Article 15

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.

The inspections shall be conducted by the competent authority of the Member State concerned, which shall inform the Agency; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. These inspections shall be coordinated by the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93. A Member State may request assistance from another Member State in this matter.

2. Following inspection, an inspection report shall be prepared. It must be made available to the sponsor while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the Agency, at their reasoned request.

3. At the request of the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with this Directive reveal differences between Member States.

4. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.

5. The detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Directive shall be adopted and revised in accordance with the procedure referred to in Article 21(2).

Article 16

Notification of adverse events

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

3. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These

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records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

Article 17

Notification of serious adverse reactions

1. (a) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

   (b) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

   (c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

   (d) The sponsor shall also inform all investigators.

2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

3. (a) Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access.

   (b) The Agency shall make the information notified by the sponsor available to the competent authorities of the Member States.

Article 18

Guidance concerning reports

The Commission, in consultation with the Agency, Member States and interested parties, shall draw up and publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

Article 19

General provisions

This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor.

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The Member States shall inform the Commission of such conditions.

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Article 20

The Commission shall adapt this Directive to take account of scientific and technical progress.

Those measures, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 21(3).

Article 21

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, referred to in Article 121(1) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use [1].

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period referred to in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

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Article 22

Application

1. Member States shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

They shall apply these provisions at the latest with effect from 1 May 2004.

When Member States adopt these provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field governed by this Directive.

Article 23

Entry into force

This Directive shall enter into force on the day of its publication in the Official Journal of the European Communities.

[1] OJ L 311, 28.11.2001, p. 67.

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Article 24

Addressees

This Directive is addressed to the Member States.