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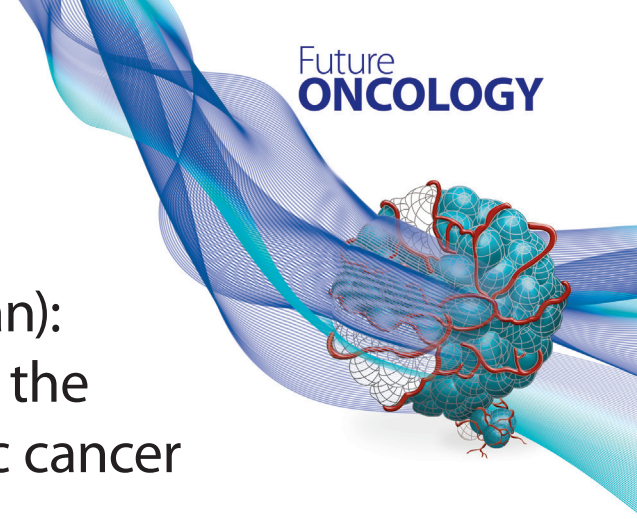

MM-398 (nanoliposomal irinotecan): emergence of a novel therapy for the treatment of advanced pancreatic cancer

Julia Carnevale[1] & Andrew H Ko*[,1]

While progress in the treatment of advanced pancreatic cancer has accelerated in recent years, this malignancy continues to have an exceedingly poor prognosis, with no standard of care options beyond front-line chemotherapy. Currently, there are a number of new therapeutic agents in varying stages of clinical development, including molecularly targeted agents, immunotherapies, and modified versions of cytotoxics. MM-398, a novel nanoliposomal formulation of irinotecan, was designed to maximize tumor exposure while minimizing systemic toxicity due to its favorable pharmacokinetic profile. Overall, across multiple clinical trials in multiple disease indications, MM-398 has been shown to have a favorable safety and tolerability profile compared with standard irinotecan. Recent results of the Phase III NAPOLI-1 trial in patients with metastatic pancreatic cancer refractory to gemcitabine-based chemotherapy have shown a significant improvement in overall survival of MM-398 when combined with 5-fluorouracil/leucovorin, compared with 5-fluorouracil/leucovorin alone. This review focuses on the development and pharmacokinetic properties of MM-398, followed by evaluation of its safety and efficacy with a primary emphasis on clinical trials in advanced pancreatic cancer.

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Notorious for its late presentation at diagnosis as well as its poor prognosis, pancreatic cancer continues to be one of the most deadly of all human diseases. The estimated incidence rate of pancreatic cancer in the USA is 48,960, with most patients expected to succumb to their disease, even those with early stage disease who are able to undergo resection [1]. Globally, pancreatic cancer is the eighth leading cause of cancer deaths in men (138,100 deaths annually) and the ninth in women (127,900 deaths annually) [2]. While progress in the therapeutic development of this disease has historically taken a slow and painstaking course, littered with numerous negative trial results, over the past 5 years several new treatment options have emerged and research is accelerating in this area. This review will focus on the development and clinical evaluation of MM-398, a novel nanoliposomal irinotecan, which, based on recent clinical results, is now being incorporated into standard treatment paradigms for patients with advanced pancreatic cancer.

Overview of the market: currently available therapeutics

Following the approval of gemcitabine for advanced pancreatic cancer in 1996, there followed well over a decade of numerous negative Phase III clinical trials, most of which compared gemcitabine monotherapy to gemcitabine combined with either a second cytotoxic or a molecularly targeted agent

[1]Division of Hematology & Oncology, University of California San Francisco, San Francisco, CA, USA
*Author for correspondence: andrewko@medicine.ucsf.edu

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in the front-line setting. During this period, only one major randomized study demonstrated an improvement in survival in this patient population [3]; while it did lead to the approval of the EGFR inhibitor erlotinib as an option to add to gemcitabine, the degree of clinical benefit, and hence its widespread usage for this indication, is relatively modest.

This stretch of failed or clinically inconsequential trials changed in 2010, when results of the PRODIGE 4/ACCORD 11 trial demonstrated that the combination of 5-fluorouracil (5-FU), leucovorin (LV), irinotecan and oxaliplatin (FOLFIRINOX) led to a significant improvement in median overall survival (OS; 11.1 vs 6.8 months; hazard ratio [HR]: 0.57; $p < 0.001$) when compared with gemcitabine for advanced pancreatic cancer patients with good performance status in the first-line setting [4]. Subsequently, in 2013, the combination of gemcitabine with nanoparticle albumin-bound paclitaxel (nab-paclitaxel; Abraxane, Celgene, NJ, USA) was also approved as an acceptable regimen for the first-line treatment of advanced pancreatic cancer patients. This approval was based on the results from the Phase III MPACT trial that showed an improvement in median OS of this doublet when compared with gemcitabine monotherapy (8.5 vs 6.7 months; HR: 0.72; $p < 0.001$) [5]. Therefore, for patients with advanced pancreatic cancer and good performance status, FOLFIRINOX and gemcitabine plus nab-paclitaxel both represent viable options in the first-line setting. These two regimens have not been directly compared head-to-head, and absent any predictive biomarker that allows for selection of one versus the other, the choice depends on clinical and practical factors such as age, medical co-morbidities and patient preference.

Upon progression following first-line treatment, the appropriate choice of therapy (for those who remain well enough to continue with some form of active treatment) becomes less clear. Before the introduction of FOLFIRINOX, most studies were designed to assess the efficacy of second-line therapy following progression on gemcitabine or a gemcitabine-based regimen. A prior systematic review of 34 clinical trials evaluating the efficacy of different second-line regimens after gemcitabine-based therapy concluded that there does appear to be a survival advantage of continuing with some form of therapy as opposed to best supportive care [6]. However, whether combination therapy is superior to monotherapy in this setting is uncertain. A randomized Phase III trial from Germany, CONKO-003, showed that oxaliplatin when combined with folinic acid and fluorouracil (OFF) significantly extended median OS (5.9 vs 3.3 months; HR: 0.66; log-rank $p = 0.010$) compared with folinic acid and fluorouracil (FF) in patients with gemcitabine-resistant pancreatic cancer [7]. Conversely, a similar trial conducted in Canada called PANCREOX did not find any benefit of FOLFOX over 5-FU/LV alone [8].

Now that both FOLFIRINOX and gemcitabine/nab-paclitaxel are being commonly used as first-line treatment, there is considerable interest in evaluating how well each of these regimens works in patients who have already received the other. Randomized clinical trial data sequencing these regimens one after the other are still lacking, although some small series (primarily retrospective) and case reports do indicate modest efficacy of each in the second-line setting [7,9–13]. Recognizing the limitations of available data, current consensus guidelines [14] recommend that patients who have progressed on first-line gemcitabine-based therapy could be offered a 5-FU-based regimen, albeit without offering clearer direction as to whether and when it should be offered as part of combination therapy. On the other hand, for those who have started with a 5-FU-based regimen such as FOLFIRINOX, a gemcitabine-based regimen would be the next logical step – although again, without certainty as to the magnitude of benefit of using such a sequencing approach.

Overview of the market: competitor compounds in the clinic/late development

Despite the significant clinical advances that have been made recently for patients with advanced pancreatic cancer, overall prognosis remains poor, with only around 2% of patients surviving 5 years [15]. Thankfully, a number of research efforts are ongoing evaluating new therapeutic agents for this disease, including some in later stages of clinical development. For organizational purposes, each of these drugs can be placed into one of four broad categories: cytotoxics, stromal targeting agents, targeted signaling inhibitors and immune modulators, although many may actually mediate effects across multiple of these categories [16].

The two main cytotoxic agents furthest along in clinical development include nanoliposomal irinotecan (MM-398, Merrimack

Pharmaceuticals, MA, USA), the main focus of this article, and evofosfamide (TH-302, Merck/EMD Serono, Rockland, MA, USA). MM-398 is a novel nanoparticle/liposome construct containing irinotecan designed to improve drug delivery to the tumor while minimizing toxic effects to the rest of the body. By changing the pharmacokinetic properties of irinotecan, MM-398 enhances tumor retention and increases the therapeutic window [17]. As will be discussed in detail below, Phase III clinical data has led to the recent approval of this agent by the US FDA that should lead to incorporation of this agent into our treatment algorithms for pancreatic cancer patients. Evofosfamide, meanwhile, is a prodrug of the cytotoxic alkylating agent, bromo-isophosphoramide mustard. This drug is activated under hypoxic conditions, providing a strong rationale for its evaluation in pancreatic cancer, an exceedingly hypoxic tumor. A randomized Phase II study comparing gemcitabine versus gemcitabine plus evofosfamide in patients with advanced pancreatic cancer demonstrated an improvement in median progression-free survival (PFS) with the addition of evofosfamide (5.6 vs 3.6 months; HR: 0.63; p = 0.005) [18], prompting a Phase III study, the MAESTRO trial, for this same patient population, results of which are pending.

Due to the impressive desmoplastic stroma that characterizes most pancreatic cancers, there has been considerable interest in targeting the stroma to alter the biology and the therapeutic accessibility of the tumor. Most advanced in clinical development is an agent termed PEGPH20 (Halozyme, CA, USA), a pegylated form of recombinant human hyaluronidase, which acts by breaking down hyaluronic acid, a major stromal component. Interim analysis of the Phase II HALO-109-202 study, a study of gemcitabine/nab-paclitaxel with or without PEGPH20 in previously untreated stage IV pancreatic cancer patients, showed intriguing early results. In a subset of patients with high levels of hyaluronic acid in their tumor specimens, overall response rate (71 vs 29%) and median PFS (9.2 vs 4.3 months) were significantly improved in the PEGPH20-containing arm [19]. These results have prompted the development of a global Phase III randomized controlled trial of gemcitabine/nab-paclitaxel with or without PEGPH20 specifically in patients with high intratumoral levels of hyaluronic acid, scheduled to start in 2016. Other ongoing studies are evaluating this same agent in combination with different chemotherapy backbones, including FOLFIRINOX.

A number of agents targeting specific signaling pathways that drive the growth, proliferation and survival of pancreatic cancer are also fairly far along in clinical development for advanced pancreatic cancer. Ruxolitinib (Jakafi, InCyte Pharmaceuticals, NY, USA), a small molecule inhibitor of the JAK1 and JAK2 kinases, may act both through direct anti-oncogenic mechanisms as well as by reducing the cytokine burden that contributes to pancreatic cancer-related cachexia. This agent was evaluated in combination with capecitabine in patients who had failed gemcitabine-based chemotherapy in the Phase II RECAP trial. In a preplanned analysis of patients with elevated levels of C-reactive protein (CRP), reflecting high levels of systemic inflammation, median survival was significantly longer in those patients who received the ruxolitinib/capecitabine combination as opposed to capecitabine alone (83 vs 55 days; HR: 0.47; p = 0.01) [20]. Based on these encouraging results, two Phase III trials (JANUS 1 and JANUS 2) have been initiated to evaluate this agent specifically in pancreatic cancer patients with high CRP levels. Another recently opened randomized Phase II trial, this one in the frontline setting, is evaluating MM-141, a bispecific IGFR/HER3 monoclonal antibody, in combination with gemcitabine plus nab-paclitaxel for patients with metastatic pancreatic cancer who have high serum levels of free IGF-1. The use of IGF-1 as a selection biomarker was informed by results from a preceding Phase I trial that showed that patients with higher circulating levels of this growth factor were able to stay on MM-141 approximately twice as long [21].

Finally, while pancreatic cancer has historically been considered an immune-privileged tumor, there have been a number of attempts to stimulate an immune attack in this disease, with different immune modulatory agents currently in various stages of clinical testing. Vaccination-based strategies represent one such approach far along in clinical development. For example, CRS-207 (Aduro Biosciences, Berkeley, CA, USA) is a live-attenuated *Listeria monocytogenes* vaccine vector genetically engineered to express mesothelin, a tumor-associated antigen expressed in the majority of pancreatic cancers. CRS-207 was shown to prolong survival when combined with the cellular vaccine GVAX in a

Phase II trial of patients with chemorefractory metastatic pancreatic cancer, as compared with GVAX alone (median OS: 6.0 vs 3.4 months; HR: 0.4477; p = 0.0057) [22]. These results have led to successor trials comparing this vaccine-based strategy to standard cytotoxic therapy, as well as evaluating it in combination with immune checkpoint blockade (nivolumab). Other immune modulatory agents currently under evaluation in pancreatic cancer include monoclonal antibodies directed against PD-1, PDL-1 and CTLA-4; IDO inhibitors; CD40 agonist antibodies; and Bruton tyrosine kinase inhibitors. One very novel approach still in pilot stages of clinical evaluation in pancreatic cancer (as well as other solid tumors) consists of adoptive T-cell transfer, using a patient's own (autologous) T cells that are genetically engineered to express chimeric antigen receptors (CAR) that then recognize tumor-specific proteins such as mesothelin.

Introduction to MM-398

MM-398 (also known as nal-IRI; previously referred to as PEP02) is a novel nanoparticle/liposome construct containing irinotecan, which has been engineered to optimize drug delivery and retention in the tumor while minimizing systemic toxicity [17]. First approved in 1996, irinotecan is a semisynthetic analog of the natural alkaloid camptothecin that is currently used widely for a variety of solid tumor indications. By stabilizing the complex between topoisomerase I and bound DNA, irinotecan induces stalling of replication forks which ultimately leads to DNA strand breaks and inhibits replication [23,24].

While it has been used in the treatment of many different malignancies, irinotecan has historically been most heavily used in the treatment of colon cancer, typically in combination with 5-FU and LV (FOLFIRI) [25]. Based on results of the PRODIGE 4/ACCORD 11 trial, irinotecan is also frequently used in combination with oxaliplatin, fluorouracil and LV (FOLFIRINOX) as first-line treatment in patients with pancreatic cancer and good performance status [4]. The primary dose limiting toxicities of irinotecan include diarrhea and myelosuppression. By improving accumulation and activation specifically within the tumor, MM-398 was designed to increase the therapeutic window of irinotecan to achieve maximum efficacy while minimizing these toxicities.

Chemistry

Liposomal-based systems have been used to improve the delivery of other cytotoxic agents, such as the example of PEGylated liposomal doxorubicin, which is presently used for the treatment of breast cancer, Kaposi sarcoma and other anthracycline-sensitive malignancies. However, development of liposomal constructs for other chemotherapeutics has proven more challenging. In 2006, Drummond and colleagues developed a new intraliposomal drug stabilization technique to successfully encapsulate irinotecan into liposomal nanoparticles [17]. To achieve this, they used highly charged anions of sucrose octasulfate to trap the irinotecan in the liposome (see **Figure 1**). The triethylammonium component of this salt compound is thought to provide a source of cations that exchange for the influx of the irinotecan molecules. The sucrose octasulfate forms a stable complex with the irinotecan and the triethylammonium crosses the lipid bilayer as triethylamine. This leads to an extremely efficient loading system, ultimately packaging 109,000 drug molecules per particle, which far exceeds liposomal formulations of other chemotherapies [17].

Pharmacokinetics & pharmacodynamics

Irinotecan is a prodrug that is converted by nonspecific carboxylesterases into its active metabolite, SN-38, which is about 100- to 1000-fold more potent [26]. In addition, irinotecan exists in an equilibrium between its active lactone form (acidic conditions) and an inactive carboxylate form (basic conditions). SN-38 is glucuronidated in the liver by UGT1A1 and then cleared by biliary excretion.

Genetic variants of UGT1A1 produce significant variability in the metabolism and excretion of irinotecan, which contributes substantially to interpatient differences in tolerability of this agent, particularly hematologic toxicity (see Pharmacogenomics section below). The liposomal carrier system of MM-398 offers a way to protect irinotecan from premature activation, allowing a longer duration in circulation and improved biodistribution. It is thought that these nanoliposomes passively accumulate preferentially in the tumor due in part to what is known as the enhanced permeability and retention (EPR) effect [27]. The EPR effect in tumors is attributed to a combination of irregular and permeable blood vessels along with an impaired lymphatic system that leads

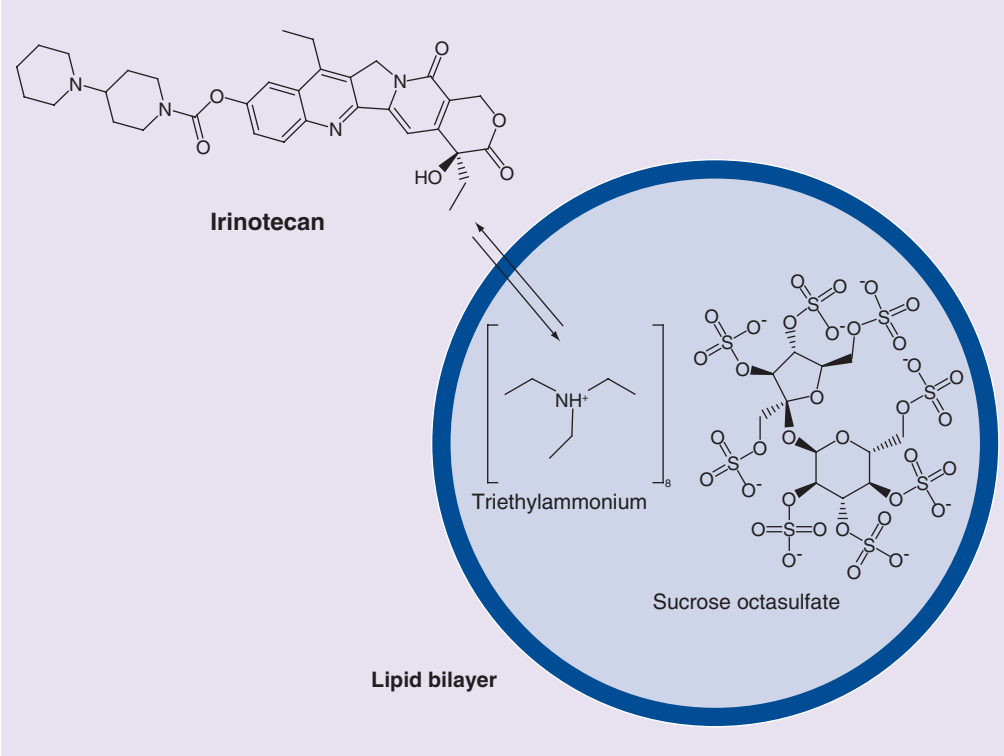

Figure 1. Depiction of exchange of triethylamine for irinotecan, which forms a stable complex with sucrose octasulfate inside the liposome.

to increased cumulative trapping of macromolecules in tumors relative to other tissues. Once deposited in the tumor, liposomes can be taken up by tumor-resident macrophages, which release the bound irinotecan and convert it to active SN-38 [17,28].

Preclinical pharmacokinetic (PK) analyses in rodents demonstrated a significant increase in the half-life of MM-398 in circulation compared with standard irinotecan, by a factor of 40. Standard irinotecan was rapidly cleared from the circulation, with only 2% of the injected dose remaining at 30 min and 35% present in the inactive carboxylate form. By comparison, 23.2% of MM-398 was detectable in circulation at 24 h, with no conversion of the irinotecan to either SN-38 or the carboxylate form in the blood [17]. These preclinical studies suggest that the nanoliposomal carrier could successfully provide protection from lactone hydrolysis or activation to the toxic SN-38 metabolite in circulation, thus increasing circulation time and tumor delivery. Additional studies of breast and colon cancer xenograft models in mice furthered the notion that this novel drug formulation can translate into improved antitumor activity. Specifically, when compared with standard irinotecan, nanoliposomal irinotecan led to greater inhibition of tumor growth and higher rates of complete tumor regressions, with less associated toxicity (transient weight loss representing the primary side effect) [17].

Two published studies in humans have reported on the phamacokinetics of MM-398. In a Phase I study of MM-398 in advanced solid tumor patients [29], the maximal tolerated dose (MTD) was determined to be 120 mg/m^2 every 3 weeks, with the primary toxicities including myelosuppression and diarrhea. In this study, the slow release of irinotecan from MM-398 resulted in a small volume of distribution and a prolonged terminal half-life of total irinotecan in circulation, while the active metabolite of irinotecan, SN-38, demonstrated a lower C_{max} and longer terminal half-life than respective values of these measures reported in the literature for standard irinotecan. Furthermore, the area under the curve (AUC) of SN-38 after 120 mg/m^2 MM-398 was in the same range as that achieved with 300–350 mg/m^2 of standard irinotecan described in the literature, suggesting that MM-398 confers an improved therapeutic window and may be a better choice for combination with other cytotoxic agents.

Meanwhile, a randomized Phase II trial of MM-398 compared with either irinotecan or docetaxel as second-line treatment for patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma [30] afforded the opportunity to directly compare the PK properties of MM-398 with those of standard irinotecan. PK values were analyzed for MM-398 dosed at 120 mg/m^2 and for irinotecan dosed at 300 mg/m^2. The dose-normalized PK results of these PK parameters evaluated are displayed in **Table 1**. Compared with standard irinotecan, MM-398 demonstrated a higher AUC, a lower clearance and smaller volume of distribution for total and encapsulated irinotecan. The active metabolite SN-38 showed a longer mean T_{max} (10.2 vs 2.1 h after infusion of 120 mg/m^2 MM-398 and 300 mg/m^2 irinotecan, respectively). After administration of MM-398, the dose-normalized C_{max} value for the formation of SN-38 was about 50% less than after infusion of standard irinotecan, indicating less premature activation of the prodrug irinotecan in the circulation in its encapsulated form. Additionally, the dose-normalized AUC_{0-t} and $AUC_{0-\infty}$ values of SN-38 following MM-398 administration were 3.3- and five-times higher, respectively, than those seen with standard irinotecan [30]. These favorable PK parameters confirmed that liposomally encapsulated irinotecan can stably circulate in plasma significantly longer than free irinotecan, enabling a slow release of irinotecan over time and increasing the likelihood of exposure of the tumor to the active SN-38 metabolite.

Pharmacogenetics

As discussed above, SN-38 is detoxified by *UGT1A1* to its inactive form SN-38 glucuronide (SN-38G), which is subsequently excreted via bile and urine. More than 60 genetic variants in the promoter region and exon 1 of *UGT1A1* have been identified, most of which are associated with reduced or absent enzymatic activity. This results in higher levels and prolonged exposure to SN-38, and consequently, a higher risk for irinotecan-associated toxicity, including neutropenia and diarrhea. The most well-studied among these *UGT1A1* genetic variants is the *28 polymorphism [31–33], which produces seven repeats of the two-base insertion TA in TATA box in the promoter region of the gene. Individuals who are homozygous for this *UGT1A1*28* allele (also known as 7/7) are more than threefold likely to develop severe neutropenia compared with those with wild genotype (reviewed in [34]).

In the above referenced Phase I trial of MM-398, the study investigators were only able to analyze *UGT1A1* genetic polymorphisms in three study patients. Interestingly, the one

Table 1. Pharmacokinetic values from the Phase II trial by Roy *et al.*

Parameter	Unit	Drug given	Total irinotecan	MM-398/ irinotecan	SN-38	MM-398/ irinotecan
C_{max}	ng/ml	MM-398	60,842	36	9	0.498
		Irinotecan	4265		44	
T_{max}	h	MM-398	2.1	1.31	10.2	4.9
		Irinotecan	1.6		2.1	
AUC_{0-t}	h·ng/ml	MM-398	1,651,508	171	476	3.3
		Irinotecan	24,155		361	
$AUC_{0-\infty}$	h·ng/ml	MM-398	1,812,221	173	879	4.99
		Irinotecan	26,159		440	
Vss	ml/m^2	MM-398	2234	0.0227	NA	NA
		Irinotecan	98,527		NA	NA
CL	ml/h/m^2	MM-398	191	0.0148	NA	NA
		Irinotecan	12,886		NA	NA
$T_{½}$	h	MM-398	21.2	2.75	88.8	3.9
		Irinotecan	7.7		22.8	
$MRT_{0-\infty}$	h	MM-398	30.1	3.58	128.7	5
		Irinotecan	8.4		26	

AUC_{0-t}: Area under the curve at T_{max}; AUC0-∞: Area under the curve extrapolated to infinite time; CL: Clearance; C_{max}: maximum concentration; MRT0-∞: Mean residence time; SN-38: Active metabolite of irinotecan; T½: Half-life; T_{max}: Time at which Cmax is reached; Vss: Volume of distribution at steady state.

Data taken from [30].

Table 2. List of clinical trials evaluating MM-398.

Year	Title	First author	Ref.
2010	Phase I study of liposome irinotecan (PEP02) in combination with weekly infusion of 5-FU/LV in advanced solid tumors	Chen *et al.*	[38]
2012	Phase I study of biweekly liposome irinotecan (PEP02, MM-398) in metastatic colorectal cancer failed on first-line oxaliplatin-based chemotherapy	Chen *et al.*	[39]
2013	A randomized Phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma	Roy *et al.*	[30]
2013	A multinational Phase II study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer	Ko *et al.*	[35]
2015	Phase I study of nanoliposomal irinotecan (PEP02) in advanced solid tumor patients	Chang *et al.*	[29]
2015	PEPCOL: a randomized noncomparative Phase II study of PEP02 (MM-398) or irinotecan in combination with leucovorin and 5-fluorouracil as second-line therapy in patients with unresectable metastatic colorectal cancer – A GERCOR Study	Chibaudel *et al.*	[41]
2015	A Phase I trial of intravenous liposomal irinotecan in patients with recurrent high-grade gliomas	Clarke *et al.*	[42]
2015	Phase III study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy	Wang-Gillam *et al.*	[40]

patient experiencing treatment-related death due to myelosuppression on this study was heterozygous for both UGT1A1*6 and UGT1A1*28, and showed a higher $AUC_{0-\infty}$ and C_{max} of SN-38 (two- to three-fold higher than those of the other three patients treated at the same dose level) [29]. In the Phase II gastric cancer study, UGT1A1 variants were observed to correlate with toxicity; specifically, among patients treated with MM-398, a significantly higher frequency of grade 3–4 neutropenia was seen in patients heterozygous for UGT1A1*6 compared with wild-type patients [30]. A separate nonrandomized Phase II study of MM-398 monotherapy in gemcitabine-resistant metastatic pancreatic cancer patients included analysis of polymorphisms in both UGT1A1 and UGT1A9; however, no correlation was identified with either nonhematologic or hematologic toxicity [35].

It is worth noting a prior PK and dose-finding study performed by Innocenti and colleagues evaluating the MTD and dose-limiting toxicities in patients who were either homozygous or heterozygous carriers of the UGT1A1*28 variant. These results suggested that doses of irinotecan could be individualized based on *UGT1A1* genotype [36]. Despite these and other studies demonstrating differences in PK and toxicity based on *UGT1A1* genotype, there are currently not well-established guidelines on testing for *UGT1A1* polymorphisms in clinical practice. The package insert for irinotecan notes that a reduction in the starting dose of this drug should be considered for patients known to be homozygous for the UGT1A1*28 allele, although the appropriate dose reduction is not known [37]. It is reasonable to expect that similar fairly general recommendations will extend to MM-398 unless and until further larger-scale pharmacogenetic studies with this agent are conducted.

Clinical efficacy

A number of Phase I, II and III clinical trials of MM-398 have been conducted across many different solid tumors (listed in **Table 2**) [29,30,35,38–42]. As noted previously, Chang *et al.* [29] published a multicenter, first-in-human, open-label, Phase I, dose-escalation study of MM-398 in patients with advanced refractory solid tumors, including one patient with pancreatic cancer who had been refractory to gemcitabine and FOLFOX. Best response by RECIST criteria was partial response in 20% of the evaluable study cohort (including the patient with pancreatic cancer); with an overall disease control rate of 50%. The maximum tolerated dose was 120 mg/m^2.

Specific to pancreatic cancer, Ko *et al.* conducted a multinational Phase II study of MM-398 in patients with metastatic pancreatic cancer refractory to gemcitabine-based front-line chemotherapy [35]. Forty patients were enrolled and received MM-398 at a dose of 120 mg/m^2 every 3 weeks, with the option of dose-escalating to 150 mg/m^2 if the first cycle was tolerated well. The study met its primary end point with a 3-month OS rate of 75%, and median PFS and OS was 2.4 and 5.2 months, respectively. An objective response was noted in 7.5% of patients and disease control (partial response + stable disease) in 50%. Additionally, of the patients with an elevated CA19-9 level at baseline, 31.3% showed a decline in this tumor marker by greater

than 50%.

Based on these results, an international randomized Phase III trial called NAPOLI-1 was developed to evaluate the efficacy of MM-398 for this same disease indication, with OS serving as the primary end point [40]. Patients were stratified according to albumin levels (less than or greater than 4.0 g/dl), Karnofsky Performance Status (70–80 vs 90–100) and ethnicity (Caucasian vs east Asian vs other). The study was originally designed with two arms only, comparing MM-398 (120 mg/m^2 every 3 weeks) to a control arm of 5-FU (administered as a weekly 24-h infusion at 2000 mg/m^2) plus LV (200 mg/m^2), for 4 out of 6 weeks. Subsequently, after the first 63 patients were enrolled, a third arm consisting of biweekly MM-398 (80 mg/m^2) plus 46-h infusion of 5-FU (2400 mg/m^2) and LV (400 mg/m^2) was added. The impetus for inclusion of this additional arm stemmed not only from the historical precedent of combining irinotecan with 5-FU in gastrointestinal malignancies, but also from preclinical evidence suggesting a biologic rationale to evaluate liposomal irinotecan in combination with other therapies. Specifically, studies of Irinophore-C (another liposomal irinotecan formulation) in subcutaneous and orthotopic mouse models showed that this agent increased microvessel density and thereby increased delivery of small molecule chemotherapies [43,44]. In a randomized Phase II trial of MM-398 in advanced colorectal cancer (PEPCOL), patients receiving MM-398 in combination with 5-FU and leuvocorin demonstrated not only promising antitumor activity, but also an improved safety profile in comparison to subjects on the irinotecan + 5-FU/LV arm [41].

Overall, the three arms on NAPOLI-1 were well balanced according to age (median age 63 years), sex (54–59% male) and Karnofsky performance status (56% Karnofsky performance status 90–100). In the entire (intention to treat) cohort (n = 417), patients on the MM-398 + 5-FU/LV arm had an improved median survival compared with the 5-FU/LV alone arm (6.1 vs 4.2 months; HR: 0.67; p = 0.0122). Forest plot analyses showed that survival benefit for the MM-398-containing combination was retained across all subgroups, including according to Karnofsky performance status, age, ethnicity, baseline CA19-9 level and line of therapy (second-line or beyond). The combination arm also showed significant improvements in median PFS (3.1 vs 1.5 months; HR: 0.56, p = 0.0001), PFS at 12 weeks (57 vs 26%), objective response rate (16 vs 1%) and CA19-9 decline ≥50% (36 vs 12%). In a subsequent analysis of the per-protocol population (defined as those patients who received greater than 80% of their planned doses during the first 6 weeks of study treatment), improvement in median OS associated with MM-398 + 5-FU/LV was even more pronounced (8.9 vs 5.1 months; HR: 0.47; p = 0.0018). Notably, there was no statistically significant difference in median survival between patients receiving MM-398 monotherapy and those receiving 5-FU/LV alone (4.9 vs 4.2 months; HR: 0.99; p = 0.94). The main efficacy findings of NAPOLI-1 are summarized in **Table 3**.

Safety & tolerability

The primary adverse effects seen with MM-398, including bone marrow suppression and diarrhea, are similar to those typically associated with irinotecan. In the Phase II trial of MM-398 monotherapy in patients with gemcitabine-refractory metastatic pancreatic cancer, 15% of patients experienced grade 3 or 4 diarrhea and 30% developed grade 3–4 neutropenia (defined as an absolute neutrophil count less than 1000 cells/μl). Importantly, three of the 40 patients on this study had deaths attributable to treatment-related neutropenia [35]. Other notable grade 3–4 side

Table 3. Efficacy results of the Phase III trial, NAPOLI-1, of MM-398 ± 5-fluorouracil/leucovorin compared with 5-fluorouracil/leucovorin alone.

Parameter	MM-398 + 5-FU/LV	5-FU/LV	MM-398
n	117	149	151
Median OS	6.1 months	4.2 months	4.9 months
Median PFS	3.1 months	1.5 months	2.7 months
PFS at 12 weeks	57%	28%	47%
ORR	16%	1%	6%
CA19-9 reduction ≥50%	36%	12%	31%

5-FU: 5-fluorouracil; LV: Leucovorin; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

Table 4. Adverse events ≥grade 3 in trials evaluating MM-398.

	Ko *et al.* (2013) [35]	Roy *et al.* (2013) [30]	Chang *et al.* (2015) [29]	Chibaudel *et al.* (2015) [41]	Wang-Gillam *et al.* (2015) [40]	
Study phase	II	II	I	II	III	III
Dosing regimen	MM-398 120 mg/m^2 q3 weekly	MM-398 120 mg/m^2 q3 weekly	MM-398 60–180 mg/m^2 q3 weekly	MM-398 80 mg/m^2 plus LV 400 mg/m^2 and 46-h infusion 5-FU 2400 mg/m^2 q2 weekly	MM-398 80 mg/m^2 plus LV 400 mg/m^2 and 46-h infusion 5-FU 2400 mg/m^2 q2 weekly	MM-398 120 mg/m^2 q3 weekly
Sample size	40	44	11	28	117	151
Nonhematologic toxicity (%)						
Diarrhea	15	27	33	33	13	21
Nausea	10	11	33	4	8	5
Vomiting	N/A	5	67	4	11	14
Fatigue	20	5	17	N/A	14	6
Hyponatremia	15	N/A	N/A	N/A	3	6
Anorexia	10	7	0	N/A	N/A	N/A
Hematologic toxicity (%)						
Neutropenia	30	7	17	11	20	16
Anemia	15	5	0	N/A	6	7
Thrombocytopenia	N/A	2	N/A	N/A	2	1

5-FU: 5-fluorouracil; LV: Leucovorin; N/A: Not applicable; q2 weekly: Once every 2 weeks; q3 weekly: Once every 3 weeks.

effects included fatigue (20%), anemia (15%), hyponatremia (15%), anorexia (10%) and nausea (10%). Meanwhile, in the Phase III NAPOLI-1 study, grade 3–4 diarrhea was reported in 13% of patients receiving the combination of MM-398 plus 5-FU/LV, and grade 3–4 neutropenia in an additional 20%. Other grade 3–4 toxicities associated with this combination included fatigue (14%), vomiting (11%), anemia (6%) and thrombocytopenia (2%).

In considering the toxicities of MM-398 in the future context in which it will be most commonly used in pancreatic cancer, perhaps the most appropriate comparison would be of (MM-398 + 5-FU/LV) to FOLFIRI. The previously discussed Phase II PEPCOL study, in which patients with advanced colorectal cancer received either MM-398 plus 5-FU/LV or FOLFIRI (including both FOLFIRI-1 and modified FOLFIRI-3 regimens), is instructive in that regard. This study utilized the same dose of 5-FU in all arms, and 80 mg/m^2 of MM-398 compared with 180 mg/m^2 total of irinotecan. In terms of grade 3–4 toxicity, lower levels of both neutropenia (10.7 vs 29.6%) and diarrhea (21.4 vs 33.3%) were observed in the MM-398 + 5-FU/LV arm compared with the FOLFIRI arm [41].

Taken together, the safety and toxicity profile of MM-398 appears to be comparable to, if not better than, that of irinotecan. Although administration of MM-398 as monotherapy is associated with substantial cytopenias, including several deaths associated with neutropenic complications in the Phase II pancreatic cancer trial, this does not appear to be as a major issue when using the biweekly dosing schedule of MM-398 with 5-FU/leuvocorin. Therefore, primary prophylaxis with granulocyte colony-stimulating factors is not necessarily indicated, except perhaps for patients with a prior history of neutropenia on prior antineoplastic agents. **Table 4** provides a summary of the primary toxicity profile of MM-398 reported in various clinical studies, both as a single agent and in combination with 5-FU/LV.

Regulatory affairs

In 2011, MM-398 received orphan drug designation from both the US FDA and the EMA for the treatment of advanced pancreatic cancer. Based on the positive results of the NAPOLI-1 trial, in November 2014 the FDA granted MM-398 a Fast Track designation as second-line therapy, in combination with 5-FU and LV, for patients with metastatic pancreatic cancer who have progressed on a gemcitabine-based regimen. Merrimack Pharmaceuticals, in partnership with Baxter International, completed rolling submission of

the New Drug Agreement (NDA) to the FDA in April 2015, where it was subsequently assigned priority review designation. This priority review assignment indicates that the FDA will take action on the marketing application within 6 months from the date of assignment (June 2015). In parallel, the EMA also accepted for review a Marketing Authorization Application (MAA) for the same indication.

In October 2015, MM-398 received official FDA approval, under the name Onivyde, for use in combination with fluorouracil and LV for the treatment of metastatic pancreatic cancer in patients who have previously received gemcitabine-based chemotherapy.

Conclusion

MM-398 is a novel nanoliposomal formulation of irinotecan designed to increase the drug payload to the tumor while minimizing systemic toxicity. There is now evidence from multiple clinical trials demonstrating improvement in the pharmacokinetic properties of MM-398 compared with standard irinotecan. Furthermore, at the maximum tolerated dose MM-398 appears to be as safe as, if not safer than, standard irinotecan. MM-398 is currently being tested across a range of different solid tumors, but has now completed Phase III evaluation in advanced pancreatic cancer. Based on results from the Phase III NAPOLI-1 trial of pancreatic cancer patients refractory to gemcitabine-based therapy, MM-398 monotherapy appears to perform similarly to 5-FU/LV, but significantly better in terms of OS and other clinical outcome measures when administered in combination with 5-FU/LV.

Future perspective

Based on the positive results of NAPOLI-1, MM-398 in combination with 5-FU/LV is the first therapeutic agent to gain approval specifically for second-line use in patients with metastatic pancreatic cancer. This regimen might now be expected to be used commonly in patients who have progressed on gemcitabine plus nab-paclitaxel, a first-line standard of care combination. It is also of interest whether the optimized PK and safety profile of MM-398 over standard irinotecan would make it an ideal substitute for irinotecan in the first-line FOLFIRINOX

EXECUTIVE SUMMARY

Mechanism of action

- MM-398 is a nanoliposomal formulation of irinotecan, designed to maximize tumor delivery and minimize systemic toxicity via optimized pharmacokinetic properties.

Pharmacokinetic properties

- Compared with standard irinotecan, MM-398 demonstrates a significantly increased area under the curve and half-life when both total irinotecan and SN-38 (the active metabolite) are measured in the blood.
- MM-398 also demonstrates a decreased clearance and decreased volume of distribution.
- Overall, this suggests a longer time in circulation and increased tumor exposure.

Clinical efficacy

- MM-398 has now been assessed in Phase I–III clinical trials in advanced pancreatic cancer patients.
- Based on results from the Phase III NAPOLI-1 trial of pancreatic cancer patients refractory to gemcitabine-based therapy, MM-398 significantly improves overall survival when combined with 5-fluorouracil/leucovorin compared with 5-fluorouracil/leucovorin alone.

Safety & tolerability

- The primary adverse effects of standard irinotecan are bone marrow suppression and diarrhea.
- Across studies, it appears that the safety and tolerability of MM-398 compares favorably to standard irinotecan.

Dosage & administration

- The maximum tolerated dose of MM-398 monotherapy has been determined to be 120 mg/m^2 every 3 weeks.
- When given in combination with 5-fluorouracil/leucovorin, MM-398 is dosed at 70 mg/m^2 every 2 weeks (this is the free base equivalent to the 80 mg/m^2 dose of the salt form used in the NAPOLI-1 trial), with 5-fluorouracil dosed at 2400 mg/m^2 (as a continuous infusion over 46 h) and leucovorin at 400 mg/m^2, every 2 weeks.

regimen. This might represent a natural extension of MM-398's role in metastatic pancreatic cancer. Future clinical trials of MM-398, whether in the first-line setting or beyond, should also assess its combinability with other cytotoxics, including gemcitabine and nab-paclitaxel; as well as with novel therapeutics currently in development. It would also be instructive if such trials were to incorporate tumor biomarker evaluation as well as the pharmacodynamic effects of MM-398 on the tumor and its microenvironment. For instance, pre- and post-treatment evaluation of tumor stroma and microvasculature, macrophage composition and resultant small molecule penetrance, would be of great interest given the predicted modulation of MM-398 on these compartments based on preclinical studies.

Financial & competing interests disclosure

AH Ko has previously served as an advisory board member for Merrimack Pharmaceuticals, and currently receives funding support (paid to his institution) from Merrimack for the conduct of pancreatic cancer-specific clinical trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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