Utilization of Hospital Inpatient Services among Patients with Metastatic Pancreatic Cancer with Commercial and Medicare Insurance Treated with FDA-Approved/NCCN® Category 1 Regimens

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OBJECTIVE

To analyze rates of hospital inpatient utilization among patients with metastatic pancreatic cancer (m-PANC) with commercial insurance and Medicare fee-for-service (FFS), treated with the following FDA-Approved/NCCN® Category 1 therapeutic regimens: gemcitabine/nab-paclitaxel, gemcitabine monotherapy, FOLFIRINOX, liposomal irinotecan-based therapy.

DATA SOURCES

100% Medicare Research Identifiable (RIF) Claims Files (2014-2017)

- Contain all Medicare-paid fee-for-service Part A, B, and D claims for all beneficiaries in the U.S. for all services.
- Include diagnosis, procedure, and diagnosis-related group (DRG) codes; site of service information; and beneficiary information, including age, eligibility status, and HMO (Medicare Advantage) enrollment.

MarketScan® Commercial Data Files (2014-2018)

- Comprised of geographically diverse, private-sector health data from approximately 100 payers, and includes more than 28 million commercially-insured lives.
- Includes person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services from a selection of large employers, health plans, and governmental and public organizations.

METHODS

Patient Identification

- Patients were identified with m-PANC using ICD-9/10 diagnosis codes:
  - Two or more claims with a pancreatic cancer (PANC) diagnosis more than 30 days apart, and
  - One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first PANC diagnosis date.
- Index date was identified as the earliest metastasis diagnosis date.
- Patients were excluded based on:
  - Presence of pre-index non-pancreatic malignancies.

- In the Medicare population: lack of six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment.
- In the commercial population: lack of three-month pre-index and one-month or post-index commercial enrollment.

Hospital Inpatient Services by Any Line of Therapy (LOT)

- Hospital admission metrics were summarized by regimen for first, second, and third LOTs.
- LOTs were assigned based on the order of therapies used.
- First LOT defined as the first episode of an eligible therapy given after or in the 14 days preceding the beneficiary's index date.
- End of a LOT is defined as the earlier of:
  - The day before the start date of a new LOT, which begins when a beneficiary switches regimens.
  - If no switch, 28 days after the most recent administration, visit date, or fill for oral therapy after the first date of chemotherapy), or the date of death, if applicable in Medicare cohort.

Utilization Metrics

- Mean admissions per LOT were defined as the mean number of admissions per patient receiving one LOT.
- Mean length of stay (LOS) was calculated as the mean number of days for each admission.
- Readmission rates, surgery rates, and Intensive Care Unit (ICU) utilization rates were calculated as the proportion of admissions with a readmission, surgery, or ICU utilization, respectively.

Figures 1-3 show mean admissions, readmissions, ICU, and surgery rates per payer and m-PANC treatment regimen

Figure 1. Mean Admissions Per Patient on Any LOT by Payer and Regimen

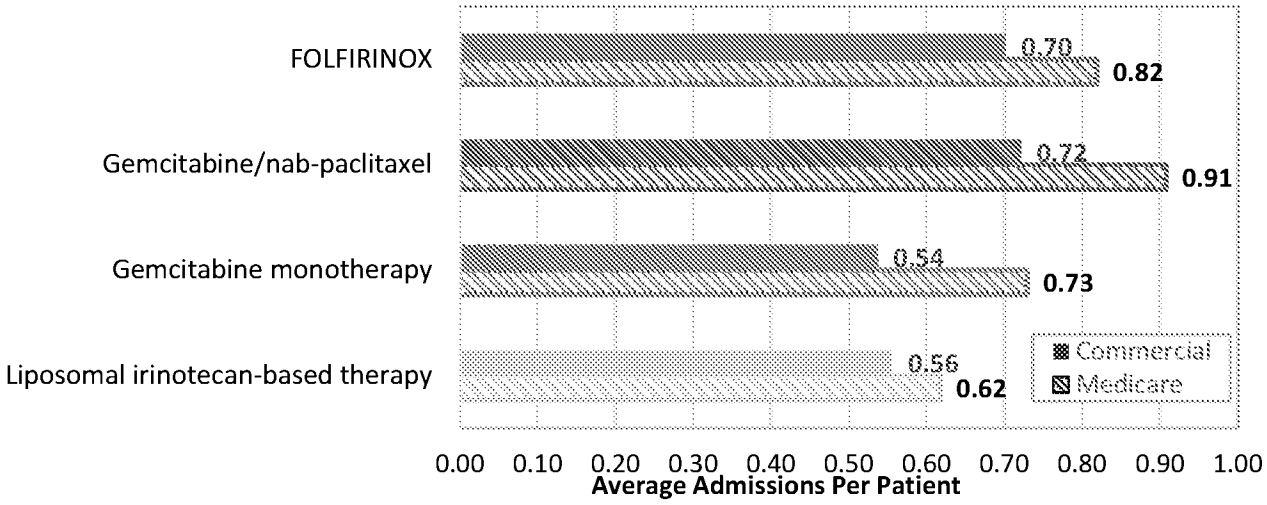


Figure 2. Mean Readmission, ICU, and Surgery Rates per Medicare Patient

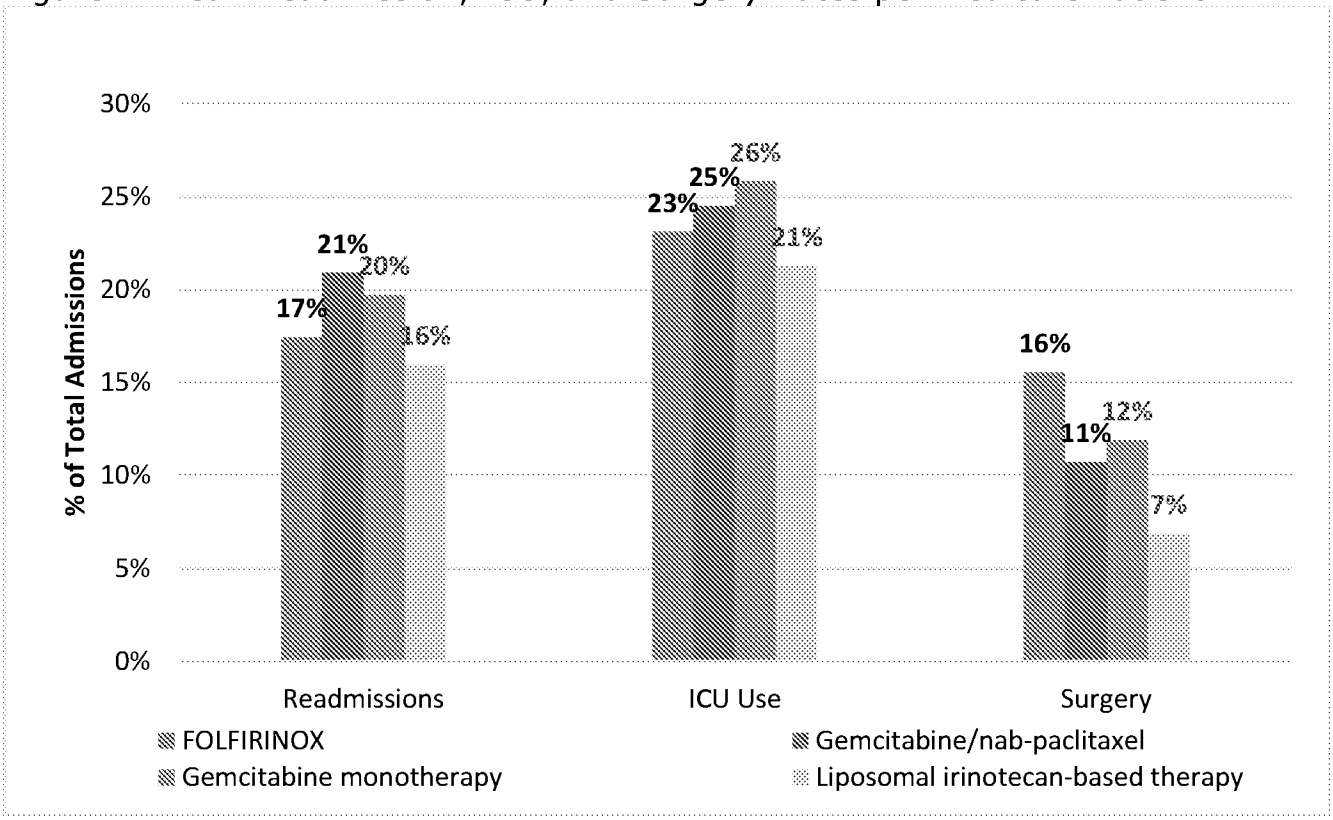
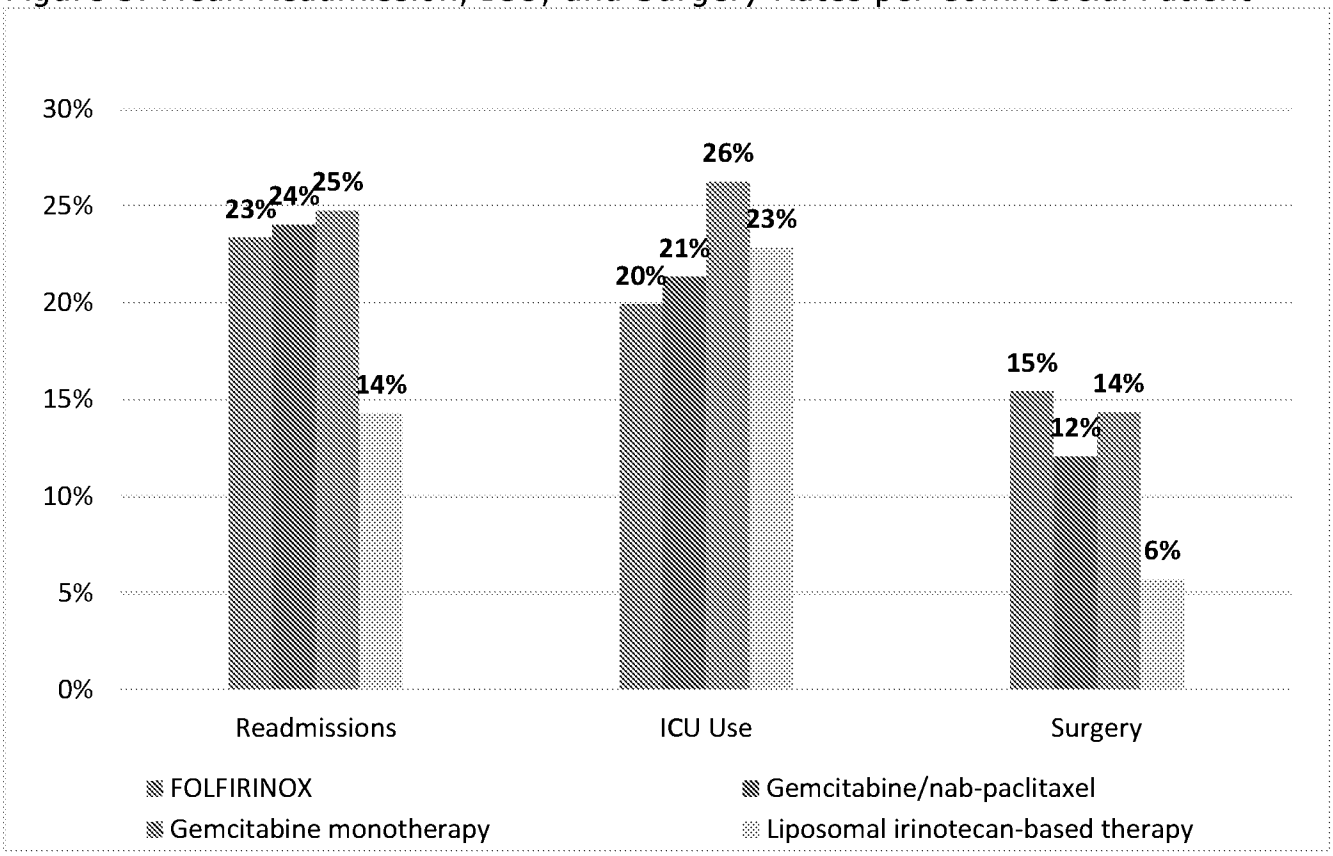


Figure 3. Mean Readmission, ICU, and Surgery Rates per Commercial Patient



RESULTS

- We identified 3,904 patients with m-PANC in the commercial population, with a mean age of 56 years at diagnosis, and 28,063 patients with m-PANC in the Medicare population, with a mean age of 75 years at diagnosis.
- Across all regimens, mean admission rates were higher for patients in the Medicare cohort than patients with commercial insurance. (Figure 1)
- Patients who received gemcitabine/nab-paclitaxel had the highest mean admission rate in both cohorts. Patients treated with liposomal irinotecan-based therapy had the lowest mean admission rate among Medicare patients; patients who received gemcitabine monotherapy or liposomal irinotecan-based therapy had the lowest mean admission rate in the commercial cohort. (Figure 1)
- Patients treated with gemcitabine-based regimens had the highest readmission rates in both cohorts. Patient treated with liposomal irinotecan-based therapy had the lowest mean readmission and surgery rates among both Medicare and commercial patients. Patients treated with FOLFIRINOX had the highest surgery rates in both cohorts. (Figures 2 & 3)
- In both cohorts, patients who received gemcitabine monotherapy had the highest mean ICU admit rate. (Figures 2 & 3)

CONCLUSIONS

- In both cohorts:
  - Gemcitabine-based regimens had the highest readmission rates while patients treated with liposomal irinotecan-based therapy had the lowest.
  - Mean admission rates were highest for patients treated with gemcitabine/nab-paclitaxel and lowest for patients treated with gemcitabine monotherapy or liposomal irinotecan-based therapy.
- As providers adopt value-based care payment models, balancing hospital resource utilization with therapy cost will become increasingly important for the population budget planning and management of m-PANC.

LIMITATIONS

The data analyzed includes the 2014 – 2017 Medicare FFS population and the 2014-2018 MarketScan® commercial population. Due to variation in monthly enrollment, we reduced the required pre-index period from 6 months in the Medicare cohort to 3 months in the commercial population to preserve credible sample sizes. Analysis of different populations or time periods will yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance may influence which regimens patients receive. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5FU or prior gemcitabine-based therapy.

DISCLOSURES

Samantha Tomicki, Helen Latimer, and Gabriela Dieguez are employed by Milliman and received consulting fees from Ipsen. Paul Cockrum is employed by Ipsen and owns Ipsen stock. George Kim is employed by George Washington University and received consulting fees from Ipsen.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [ST, HL, GD, PC, GK]; Drafting of the publication, or revising it critically for important intellectual content: [ST, HL, GD]; Final approval of the publication: [ST, GD, PC]. The authors thank Steven Metz and Sujith Peta at Milliman, Inc. for research assistance.
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AUTHOR CONTRIBUTIONS

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Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study

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Key words: pancreatic cancer, chemotehrapy, oxaliplatin, 5-FU, leucovorin

Summary

Study objectives: The present study was conducted to evaluate the efficacy and safety of the combination of Oxaliplatin, Leucovorin and 5-FU as second line therapy, following relapse to Gemcitabine, in patients with advanced adenocarcinoma of the pancreas. *Patients and methods*: Patients with advanced pancreatic cancer previously treated with Gemcitabine were included in the study. All patients had histologically or cytologically confirmed adenocarcinoma of the pancreas that was unresectable, locally advanced or metastatic. Treatment consisted of Oxaliplatin 50 mg/m^2 (2-hour iv infusion), followed by Leucovorin 50 mg/m^2 (i.v. bolus) and 500 mg/m^2 5-FU (1-hour iv infusion), administered weekly, until unacceptable toxicity or disease progression. Objective tumour response and toxicity were evaluated according to World Health Organisation (WHO) criteria. *Results*: A total of 30 patients, 20 men and 10 women, median age 63 years (range 52–71 years) and Karnofsky Performance Status (PS) of ≥50 entered the study. The majority of patients (96%) had locally advanced disease. A total of 380 doses of chemotherapy were delivered, a median of 12 doses per patient. Partial responses were observed in 7 patients (PR 23.3%), stable disease in 9 (SD 30.0%), while 14 patients progressed (PD 46.7%). Improved PS was observed in 18 (42.8%) patients. Patients that had responded to first-line Gemcitabine treatment were found more likely to respond or stabilize their disease with second-line treatment. The median duration of response was 22 weeks, and median overall survival was 25 weeks. Grade 3/4 toxicity expressed per chemotherapy dose included leukopenia 16%, anemia 3.2%, thrombocytopenia 3.2%, diarrhea 14.2%, fatigue 16.1% and neurotoxicity 4.2%. Eight patients (27%) suffered a febrile neutropenic event managed successfully with oral antibiotic home therapy, while 17 patients required G-CSF support. There were no treatment related deaths. *Conclusions*: The combination of Oxaliplatin, Leucovorin and 5-FU was tolerated with manageable toxicity, offering encouraging activity as second-line treatment of patients with advanced or metastatic pancreatic adenocarcinoma, previously treated with Gemcitabine. Additional studies are warranted with this regimen in Gemcitabine relapsed pancreatic cancer patients.

Introduction

The role of chemotherapy in pancreatic carcinoma remains so far limited. While pancreatic cancer is relatively rare, accounting for approximately 2% of all new cancer diagnoses, it represents about 5% of all cancer related deaths [1, 2]. The presentation in the majority of patients with unresectable and/or metastatic disease, the aggressiveness of the tumor and the current lack of effective systemic therapies, can in someway explain the poor 5-year survival figures for patients with pancreatic adenocarcinoma, that has remained at only 2–4% for many years [3, 4].

Only a small number of agents have demonstrated some activity against pancreatic cancer, and little improvement has been offered by multi-agent combination regimens. For patients with metastatic disease the prognosis is extremely poor, with response rates ranging from 5–15%, and median survival times rarely exceed 4–6 months [5–8] Chemotherapy has been proven superior to best supportive care, however, improvements in survival and response rates have only been marginal. As a

result, chemotherapy is primarily thought of as palliative [9, 10].

It is only recently that Gemcitabine has replaced 5-FU as the first-line choice for the treatment of advanced pancreatic carcinoma [11–13]. To date, no combination has proved superior to that of single agent Gemcitabine, with the possible exception of Gemcitabine/Cisplatin that in a recent large randomized trial has shown improved response rates but no survival advantage [14]. However, in general, overall response rates rarely exceed 20% [14–16], and therefore effective second-line therapies are currently warranted.

There is no established second-line treatment for advanced pancreatic cancer after gemcitabine failure. Only a limited number of combination chemotherapies have been investigated in patients relapsing following first-line Gemcitabine treatment [17–20]. Due to the efficacy of cisplatin in untreated patients, attention has been drawn to platinum-coordination compounds. Oxaliplatin appears to have significant differences from cisplatin and carboplatin; it is neither ototoxic nor nephrotoxic, and is believed to have activity in tumors marginally sensitive to other platinum analogues [21]. The combinations of gemcitabine/oxaliplatin (GEMOX) and oxaliplatin/5-FU/leucovorin have produced some interesting results in pancreatic cancer [22–25]. We conducted this phase II study to assess the safety and efficacy of the combination of Oxaliplatin, Leucovorin and 5-Fluorouracil as second-line treatment in advanced or metastatic pancreatic cancer, pre-treated with Gemcitabine.

Patients and methods

Patient selection

Patients with unresectable locally advanced or metastatic, histologically or cytologically confirmed pancreatic cancer were eligible to enter the study. All patients had received first-line treatment with Gemcitabine. Participants were required to have adequate bone marrow (WBC $>3.5 \times 10^9$/L, platelets $>100 \times 10^9$/L), hepatic (serum bilirubin ≤ 1.5 mg/dL and serum transaminases ≤ 3 times upper normal limit; or <5 times upper normal limit for patients with liver metastases) and renal function (serum creatinine ≤ 1.5 mg/dL). Patients aged ≥ 18 to ≤ 75 years, with a Karnofsky PS >50 were eligible. All patients had measurable disease, as defined by the presence of at least one lesion clearly measurable by computed tomography (CT) scan. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease. Exclusion criteria included: prior treatment with either of the study drugs, active secondary malignancy, psychiatric or addictive disorders, and pregnant or lactating women. The study was performed according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Approval was obtained from all local-institutional ethics committees, and written informed consent was obtained from all patients before initiation of study treatment.

Treatment schedule

Patients received Oxaliplatin 50 mg/m^2 as a 2-hour intravenous (i.v.) infusion, followed by Leucovorin 50 mg/m^2 delivered as an intravenous bolus and 5-FU 500 mg/m^2 as a one-hour infusion. Treatment was repeated every week / 6 weeks followed by a 2-week rest and then restarted. Responding patients (CR, PR and SD) continued to receive the regimen until progression, the appearance of unacceptable toxicity, or patient refusal. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not routinely used. Patients received as antiemetic therapy a single dose of tropisetron 5 mg combined with 8 mg dexamethasone i.v. Adequate treatment for control of pain and other symptoms were allowed and were recorded in detail during the study. Treatment was interrupted in all patients experiencing grade 3/4 toxicities, or persistent grade 2 toxicities.

Criteria for response and toxicity evaluation

Before study entry all patients had a detailed clinical history and physical examination, echocardiogram (ECG), evaluation of Karnofsky PS, full blood count, liver and kidney function tests, serum tumor markers and urinalysis. Chest X-ray (and a CT scan if indicated), CT scan of the abdomen and pelvis, bone scan if indicated and bone radiographs (following abnormal bone scan) were obtained within 3 weeks prior to study entry. Objective tumor assessments were repeated following cycle 8, following clinical signs indicative of disease progression, at the end of treatment and every 2 months until disease progression. Blood counts, urea, and serum creatinine were measured before each treatment administration.

Response and toxicity were evaluated according to World Health Organization (WHO) Criteria. All documented side effects were included, regardless of their relationship to study treatment.

Evaluation of response was performed following every 8 doses of therapy, unless clinical signs of overt recurrence were present. Patients experiencing toxic death despite objective responses at measurable sites would be categorized as treatment failures. Tumor responses were categorized as complete, partial, stable or progression. Complete response (CR) was defined as the disappearance of all signs and symptoms of disease for at least 1

month, with the documented disappearance of all known lesions by physical examination, X-rays, CT scans, bone scans, and the development of no new lesions. Partial response (PR) was indicated as a decrease of 50% or greater (compared with pre-treatment measurements) in the sum of the products of the two largest perpendicular diameters of all measurable lesions and no concomitant growth of new lesions for at least 1 month. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Stable disease (SD) was indicated as a decrease of less than 50% or an increase in tumor size less than 25% over the original measurements. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Progressive disease (PD) was defined as an increase of 25% or greater over the original measurements in the sum of the products of the two largest perpendicular diameters of any measurable lesions. Relapse was defined as occurring following a period of response when a former lesion reappeared or enlarged as above or a new lesion appeared. Follow-up disease evaluation was performed at 2-monthly intervals after the end of treatment. Standard treatment efficacy end points in relation to survival, objective response, time to disease progression and duration of response were determined. Duration of response was defined as the time from complete or partial response until first objective evidence of disease progression or death from any cause. Time to progression was defined as the time from enrollment onto study until progression or death. Toxicities were evaluated and graded according to the WHO toxicity criteria, on a per cycle basis.

Statistical analysis

Patients who received at least four doses of treatment were evaluable for response and patients who received one dose of the drugs were evaluable for toxicity. Toxicity analysis was carried out regarding the highest grade recorded. Summary statistics of continuous variables were based on central measures of disparity (mean, sd, percentiles, min, max). All categorical variables are summarised by frequency distribution tables. Statistical associations between categorical variables where investigated by chi square statistic. Response to treatment was correlated with Karnovsky performance status, CEA and CA-19.9 serum tumor marker changes after chemotherapy by the Kruskal Wallis test. Response duration was measured from the day of its initial documentation until confirmed disease progression; time to progression was calculated from study entry until evidence of progressive disease; overall survival was measured from the day of entry until last follow-up or death. Median duration of response, median TTP, and actuarial overall survival were estimated by the product-limit method of Kaplan-Meier. Survival distribution curves were statistically evaluated by log-rank test, whereas multivariate analysis was based on Cox's proportional hazard regression model. All statistical tests are 2-sided and the level of statistical significance was set at 5%. Statistical analysis was performed using the statistical package SAS V8.2.

Results

Patient characteristics

Thirty patients were enrolled in this study; all were evaluable for response and toxicity. The characteristics of the patients on the study are listed in Table 1. The median age at study entry was 63 years (range 52–71 years). There were 20 men (66%) and 10 women. Twenty-five patients (83.3%) had stage 3 or 4 disease at initial diagnosis and 29 (96.6%) had grade 2 or 3 tumors. At the time of study entry, only one patient had unresectable locally advanced disease, while all other patients had distant metastases. The metastatic sites are shown in Table 1, lymph nodes followed by liver metastases were the commonest sites.

Response to treatment

A total of 380 cycles of chemotherapy were delivered with a median of 12 per patient (range 3 to 30 cycles). Results of the study were analyzed on an intention-to-treat basis. Among the 30 patients eligible for response

Table 1. Patient characteristics

Eligible	30 (100%)
Male	20 (66.7%)
Female	10 (33.3%)
Age (years)	
Median	63
Range	52–71
Karnofsky performance status	
100–80	10 (33.4%)
70–50	20 (66.7%)
Previous response to Gemcitabine	
PR	8 (26.7%)
SD	13 (43.3%)
PD	9 (30.0%)
Primary site	
Head	20 (66.7%)
Body	8 (26.7%)
Tail	2 (6.6%)
Sites of Metastasis	
Liver	14 (46.7%)
Lymph nodes	25 (83.3%)
Lung	3 (10.0%)
Peritoneum	9 (30.0%)
Other	9 (30.0%)

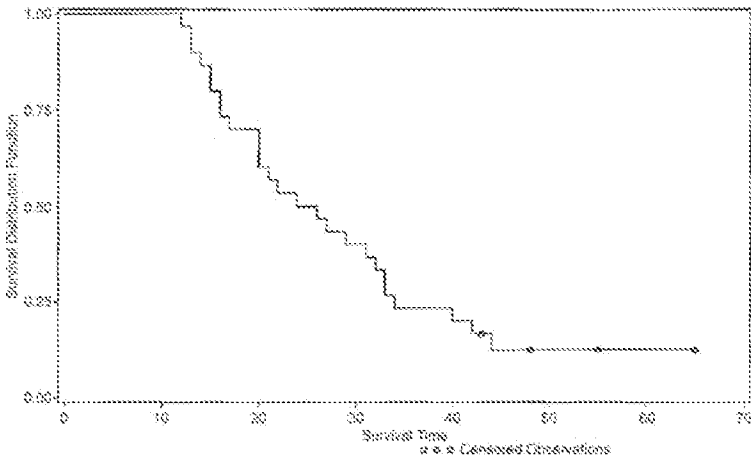

Figure 1. Overall survival.

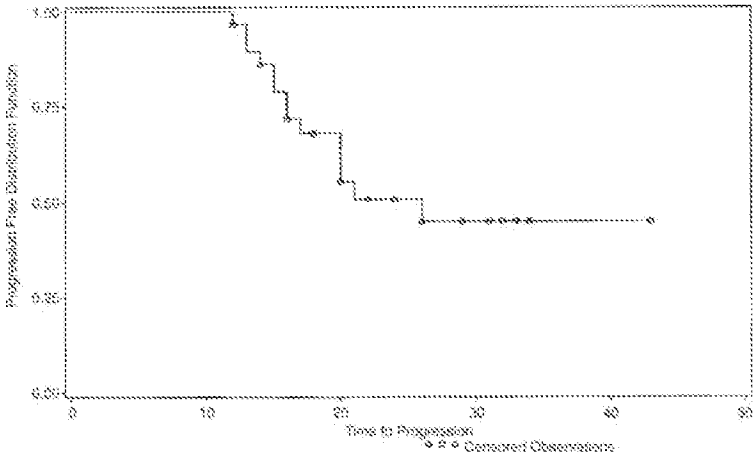

Figure 2. Time to progression.

evaluations there were 7 partial responses (PR 23.3%), and 9 patients with stable disease (SD 30.0%). The median response duration for all patients was 22 weeks (95% CI: 20–31%), and the median response duration for the 7 patients that demonstrated a partial response was 16 weeks. Treatment response to second-line combination chemotherapy is tabulated according to patient response to first line Gemcitabine in Table 3. The response rate is not significantly different between the two treatments ($p = 0.424$), with 5 patients deteriorating and 9 patients improving.

Survival

With a median follow-up of 25 weeks (range, 12–65 weeks) the median overall survival was 25 months (range, 20–33 months). The Kaplan-Meier estimate of survival is shown in Figure 1. The median survival for patients with progressive disease was 16 weeks and for those with stable disease 32 weeks and for patients with partial response 44 weeks.

Time to disease progression

The median time to progression for the on study population was 22 weeks (95% CI: 13–20 weeks) (Figure 2).

Toxicity

Major toxicities are listed in Table 2. Grade 3/4 neutropenia was observed in 61/380 (16%) of the administered doses, and no patient was hospitalized for febrile neutropenia. Seventeen patients received G-CSF during the

Table 2. Toxicities.

	Grade 1/2	Grade 3/4
Leukopenia	73 (19.1%)	61 (16.0%)
Thrombocytopenia	41 (10.7%)	12 (3.2%)
Anemia	108 (28.4%)	12 (3.2%)
Nausea/vomiting	22 (6.8%)	0
Fatigue	140 (36.8%)	0
Diarrhoea	171 (44.4%)	54 (14.2%)
Neurotoxicity	97 (25.6%)	16 (4.2%)
Treatment related deaths	0	0

course of the study. Other grade 3/4 events included anemia on 12/380 (3.2%), thrombocytopenia on 12 (3.2%), fatigue 61 (16%), neurotoxicity 16 (4.2%) and diarrhea (grade 3) 54 (14.2%). There were no treatment related deaths.

Prognostic factors

In a univariate analysis, for factors potentially affecting response and survival; age, gender, primary site (head, body, tail) and CEA tumor marker did not correlate with prognosis. The presence of liver metastasis was correlated with an increased likelihood for PD ($p = 0.017$). No other metastatic site correlated with response. Responding patients had a higher Karnofsky performance status than SD and PD patients. The same stands for alteration of PS, ($p < 0.0001$; PD patients had a reduction in score by at least 10 units, SD patients did not alter with respect to score, whereas PR patients had an increase in their PS). CA-19.9 serum tumor marker levels after treatment increased significantly in patients with PD as compared to the SD and PR patients that demonstrated decreased marker levels ($p < 0.0001$).

Discussion

A large number of chemotherapeutic regimens have been utilized for the treatment of pancreatic cancer. Only a few have demonstrated survival prolongation, and an improvement in quality of life compared to best supportive care [9, 10]. In general all regimens have been disappointing with median survival rarely exceeding 6 months, and response rates of less than 20% [5].

Of the new chemotherapeutic agents, only gemcitabine has proven superior to single-agent 5-FU [12]. More recently synergy has been demonstrated between gemcitabine and cisplatin. Based on some encouraging results in phase II trials a recent phase III trial indicated response rates of 25% [14]. The authors demonstrated a statistically significantly longer median time to disease progression of 8 vs 20 weeks for gemcitabine versus gemcitabine plus cisplatin, and a superior response rate of 9.2% vs 26.4%. Although, neither clinical benefit nor median overall survival was improved in the combination arm, it was suggested that this regimen warrants further investigation and may replace gemcitabine monotherapy.

Furthermore, in a phase III comparison of gemcitabine versus gemcitabine plus bolus 5-FU from ECOG [16], the combination did not offer significant improvement in median survival or progression free survival. The ECOG Group subsequently indicated that clinical resources should address other combinations and novel agents. One combination that is currently being compared to gemcitabine is gemcitabine/oxaliplatin.

To date, the phase III studies conducted have not demonstrated statistically significant improvements in survival with combination chemotherapy [14, 16, 26, 27], and therefore, more phase II studies are in progress for the identification of new clinically useful combinations. Many of these studies have indicated that combinations of gemcitabine are superior to gemcitabine monotherapy in terms of survival (5.7–8.4 months) and response rates 11–35%, but this has been at the expense of increased toxicity while it has been quite difficult to make comparisons between various studies (reviewed in [28]). However, these promising results with various gemcitabine combinations compared to gemcitabine monotherapy should be regarded with concern until results of planned or ongoing randomized phase III studies are available.

Since quality of life parallels the disease process in advanced pancreatic cancer, balancing toxicity and effective treatment remain central concerns in palliative treatment [29]. For this reason, and the fact that gemcitabine remains the standard of care for pancreatic cancer, second-line and subsequent palliative treatment modalities are urgently needed. To date, few studies have assessed second-line approaches primarily due to the poor prognosis, and the limited life expectancy in advanced pancreatic cancer after relapse following first-line chemotherapy.

In a phase II study of 38 patients that had relapsed following first-line treatment with gemcitabine, patients were randomized to either 3-weekly courses of raltitrexed (3 mg/m^2 d1) or irinotecan (200 mg/m^2 d1) plus raltitrexed (3 mg/m^2 d2). Ulrich-Pur et al. [17] reported a 16% response rate in the combination arm. Single-agent raltitrexed showed no responses, and the trial was stopped at the first stage. Clinical benefit response was superior in the combination arm (29 versus 8%) and treatment related toxicities were low; the authors suggested that further studies are warranted.

Kozuch et al. [19] reported second-line responses to a sequential regimen of Gemcitabine (500 mg/m^2), irinotecan (80 mg/m^2), leucovorin (300 mg/m^2), 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 infusional over 8 hours) administered on day 1; and leucovorin

(300 mg/m^2), 5-FU (400 mg/m^2 bolus), cisplatin (50–75 mg/m^2), 5-FU (600 mg/m^2 infusional over 8 hours) administered on day 2. In 34 patients who were previously treated with either gemcitabine or the combination of gemcitabine/5-FU/cisplatin partial responses were recorded in 8 patients (24%) and stable disease in 7 patients. The median time to progression for all 34 patients was 3.9 months and 5.9 for the PR patients. Median overall survival was 10.3 months. Grade 3–4 haematological toxicities included anemia (23%), thrombocytopenia (53%) and neutropenia (38%); non-haematological toxicities were rare.

Another study investigated the potential effectiveness of second or third-line therapy with paclitaxel following confirmed progression with a gemcitabine-containing schedule [20]. In this study only one patient presented with anemia and leukocytopenia of WHO grade III. Stable disease was observed in 5/18 patients enrolled, and one patient obtained a CR. The median survival time was 17.5 weeks.

Although there is limited data on second-line therapy following gemcitabine or gemcitabine containing regimens the response rates and overall survival times are hardly encouraging. Utilising the regimen of oxaliplatin, leucovorin and 5-FU we observed similar more favourable results to those of other second-line regimens, given the known limitations from inter-study comparisons. Among 30 eligible patients we report, 7 PRs (23.3%), and 9 patients with SD (30%) were observed. The median response duration for all patients was 22 weeks and the median time to progression in the 16 patients that demonstrated either a partial response or stable disease was 15.5 weeks. This represents a very meaningful improvement over current treatment. Responses in second-line with Oxaliplatin/5-FU/LV compared to first-line gemcitabine were not significantly different (Table 3), indicating that there is potentially non-cross resistance between first-line Gemcitabine and second-line Oxaliplatin/5-FU/LV chemotherapy. However, it should be pointed-out, that patients developing PD to first-line gemcitabine did never respond to second-line weekly oxaliplatin/5-FU/LV. This is also evident from the results of other second-line treatment regimens containing gemcitabine following relapse on gemcitabine containing regimens [19, 20].

Table 3. Response to treatment

	Response to Oxaliplatin			
Response to Gemcitabine	PR	SD	PD	Total
PR	4	2	2	8
SD	3	5	5	13
PD	0	2	7	9
Total	7	9	14	30

In a univariate analysis of response and survival according to metastatic site at presentation, patients with liver metastasis were correlated with increased likelihood of PD ($p = 0.017$). No other site of metastasis was related to response, however, the numbers were small with the exception of lymph node metastasis. Other studies have indicated the adverse prognostic significance of liver metastasis [30]. Performance status is by itself a recognized significant independent prognostic factor [31]. Similarly, in our study responding patients had a higher PS than SD and PD patients. The same holds true for alteration of PS ($p < 0.0001$): PD patients reduce the score by at least 10 units, SD patients did not alter the score, whereas PR patients increased the score. Although there was no statistical correlation between response and CEA levels, and the CA-19.9 levels after treatment were significantly higher in patients with PD. Various studies have indicated that CA-19.9 is an independent prognostic marker of prognosis and that monitoring of CA-19.9 may be useful in monitoring progression [32]. In this study, the CA-19.9 levels after treatment increased significantly in patients with PD as compared to patients with SD and PR, that demonstrated decreased marker levels ($p < 0.0001$). In respect to toxicity, hematological toxicities were the most severe, grade 3/4 events included anemia on 12 occasions (3.2%), thrombocytopenia on 12 occasions (3.2%) and neutropenia requiring G-CSF support occurred in 8 patients. These results indicate that a weekly schedule of oxaliplatin, 5-FU, leucovorin may be feasible as toxicities were mild. Weekly schedules have been shown to be well tolerated with several chemotherapeutic agents such as paclitaxel [20].

Our data indicate that additional studies are warranted for the second-line treatment of pancreatic cancer in order to identify agents and combinations that could meaningfully improve the prognosis of this dismal disease.

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ORIGINAL REPORT

Phase III Trial of Bevacizumab in Combination With Gemcitabine and Erlotinib in Patients With Metastatic Pancreatic Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

Treatment with gemcitabine provides modest benefits in patients with metastatic pancreatic cancer. The addition of erlotinib to gemcitabine shows a small but significant improvement in overall survival (OS) versus gemcitabine alone. Phase II results for bevacizumab plus gemcitabine provided the rationale for a phase III trial of gemcitabine-erlotinib plus bevacizumab or placebo.

Patients and Methods

Patients with metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine (1,000 mg/m^2/week), erlotinib (100 mg/day), and bevacizumab (5 mg/kg every 2 weeks) or gemcitabine, erlotinib, and placebo in this double-blind, phase III trial. Primary end point was OS; secondary end points included progression-free survival (PFS), disease control rate, and safety.

Results

A total of 301 patients were randomly assigned to the placebo group and 306 to the bevacizumab group. Median OS was 7.1 and 6.0 months in the bevacizumab and placebo arms, respectively (hazard ratio [HR], 0.89; 95% CI, 0.74 to 1.07; $P = .2087$); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved PFS (HR, 0.73; 95% CI, 0.61 to 0.86; $P = .0002$). Treatment with bevacizumab plus gemcitabine-erlotinib was well tolerated: safety data did not differ from previously described safety profiles for individual drugs.

Conclusion

The primary objective was not met. The addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS in patients with metastatic pancreatic cancer. PFS, however, was significantly longer in the bevacizumab group compared with placebo. No unexpected safety events were observed from adding bevacizumab to gemcitabine-erlotinib.

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INTRODUCTION

Adenocarcinoma of the pancreas is the fourth and fifth most common cause of cancer death in the United States and Europe, respectively, with an estimated 38,000 new cases in the United States and approximately 58,000 new cases in Europe occurring annually.[1,2] More than 90% of all patients will develop metastases. The outcome for patients with metastatic disease is particularly dismal, with an estimated survival time of only 2 to 4 months in the absence of treatment.[3] Meta-analyses have shown that chemotherapy improves median overall survival (OS) compared with best supportive care alone (hazard ratio [HR], 0.64; 95% CI, 0.42 to 0.98).[4]

Gemcitabine has been the reference treatment for patients with pancreatic cancer since 1997, when it was demonstrated that patients treated with gemcitabine had significantly improved survival compared with those treated with fluorouracil.[5] Subsequent trials aimed at improving survival have combined gemcitabine with various cytotoxic agents, including platinums; fluoropyrimidines; topoisomerase inhibitors; and various targeted agents including tipifarnib, marimastat, cetuximab, and erlotinib.[6,7] Only the combination of gemcitabine plus erlotinib significantly improved survival compared with gemcitabine alone.[6,8]

Clinical trials in patients with various malignancies, including colorectal, breast, and non–small-cell lung cancer, have shown a significant benefit from adding bevacizumab to a reference chemotherapy.[9-14] Bevacizumab combinations have shown promising results in phase II trials in patients with advanced pancreatic cancer, with response rates of 11% to 24%, median OS of 8.1 to 9.8

months, and median progression-free survival (PFS) of 3.6 to 5.8 months.[15-18] To date, however, these observations have not been confirmed in phase III trials. The Cancer and Leukemia Group B (CALGB) 80303 trial, which randomly assigned patients to bevacizumab (10 mg/kg every 2 weeks) or placebo in combination with gemcitabine, did not meet its primary objective of improvement in OS, nor were PFS or overall response rate (ORR) improved.[19] Although most studies included patients with metastatic as well as locally advanced disease, several studies have shown different outcomes in these two patient groups.[20,21] The primary objective of the present randomized, placebo-controlled, phase III trial was to show improved OS in patients with metastatic adenocarcinoma of the pancreas following treatment with bevacizumab plus gemcitabine-erlotinib compared with placebo plus gemcitabine-erlotinib.

PATIENTS AND METHODS

Patients

This multicenter (Appendix Table A1, online only), randomized, phase III trial included patients aged ≥ 18 years with histologically or cytologically documented metastatic adenocarcinoma of the pancreas. Patients with unresectable locally advanced disease without evidence of metastases elsewhere were not eligible. For inclusion in the study, patients were required to have Karnofsky performance status (KPS) ≥ 60%; adequate blood counts and liver and kidney function; proteinuria dipstick less than 2+ (≤ 1 g in 24-hour urine collection if proteinuria dipstick ≥ 2+). Patients were excluded if they had received prior adjuvant radiotherapy for pancreatic cancer (except for patients with progressive lesions outside the radiation port who completed radiotherapy ≥ 6 months before trial entry); adjuvant chemotherapy within 6 months before trial entry; adjuvant treatment with gemcitabine, epidermal growth factor receptor tyrosine kinase inhibitors, or anti–vascular endothelial growth factor–based therapy. Previous chemotherapy for metastatic disease was not allowed. Patients were also excluded if they had CNS metastases and tumor invasion of major blood vessels. Other exclusion criteria included major surgery within the preceding 28 days; clinically significant cardiovascular disease; nonhealing wounds or ulcers; pregnancy or lactation; concurrent or recent chronic use of aspirin (≥ 325 mg/day), anticoagulants, or thrombolytic agents; or pre-existing bleeding diathesis or coagulopathy with a risk of bleeding.

Ethics

All patients provided written informed consent. The trial protocol was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki, current US Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements.

Randomization and Treatment

Randomization was performed via an interactive voice recording service. Patients were stratified according to country, KPS (< 80% *v* ≥ 80%), and albumin (< 2.9 g/dL *v* ≥ 2.9 g/dL). Patients were randomly assigned 1:1 to gemcitabine-erlotinib-bevacizumab (bevacizumab arm) or gemcitabine-erlotinib-placebo (placebo arm). Gemcitabine 1,000 mg/m^2 was administered as an intravenous infusion weekly for 7 weeks followed by a 1-week rest in the first treatment cycle. In subsequent cycles, gemcitabine was administered weekly for 3 weeks followed by a 1-week rest, and erlotinib (100 mg/day orally ≥ 1 hour before or after food) was given continuously from day 1 of cycle 1. Bevacizumab/placebo (5 mg/kg intravenous infusion) was administered on days 1, 15, 29, and 43 of the first cycle and on days 1 and 15 thereafter. Bevacizumab/placebo was given before gemcitabine in the first treatment cycle and after gemcitabine in subsequent cycles to ensure the highest possible chemotherapy uptake.[22]

Bevacizumab/placebo doses were not modified and missed doses were not administered later. Bevacizumab was discontinued in patients who experienced gastrointestinal perforation, arterial thrombotic events, grade 3/4 hemorrhagic events, symptomatic grade 4 thrombosis, hypertensive crisis, or nephrotic syndrome. Bevacizumab was withheld for grade 2/3 hypertension (to allow initiation of appropriate antihypertensive therapy) and was discontinued in cases of uncontrolled hypertension or hypertensive crisis. Bevacizumab was also withheld in cases of 24-hour proteinuria more than 2 g until proteinuria returned to ≤ 2 g over 24 hours. Erlotinib doses were interrupted in patients with intolerable rash and were reduced or discontinued if symptoms persisted for ≥ 10 to 14 days. Erlotinib was withheld for patients with new or worsening respiratory symptoms and was discontinued in those with interstitial lung disease. Erlotinib doses were reduced for grade 2 diarrhea persisting for ≥ 48 to 72 hours and for grade 3 diarrhea following resolution to grade 1; erlotinib was discontinued for grade 4 diarrhea. The gemcitabine dose was reduced to 75% in patients with an absolute neutrophil count (ANC) of 0.5 to 0.99 × 10^9/L and was omitted in patients with an ANC ≤ 0.5 × 10^9/L; the dose was reduced to 50% or omitted for grade 3 nonhematologic toxicities and was omitted for grade 4 events.

Assessments

Patients underwent complete medical examination at baseline. Tumor assessments were made according to Response Evaluation Criteria in Solid Tumors guidelines at baseline, weeks 8, 16, 24, 32, 40, and every 12 weeks thereafter until disease progression. Patients were followed for survival and subsequent disease treatment until death, loss to follow-up, or trial termination. Assessments of KPS and body weight were collected weekly.

Adverse events were recorded at every visit using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v3). Hematology and coagulation tests were performed weekly; blood chemistry and urinalysis were performed every 2 weeks.

Blood samples for biomarker analyses were collected before trial treatment began, at bevacizumab steady-state (week 9), and at the time of disease progression.

Statistical Analyses

The primary end point was duration of survival, defined as the time between the date of randomization and the date of death from any cause. Patients without an event (death) were censored on the date they were last known to be alive. Secondary end points included PFS, defined as the time between the date of randomization and the date of documented disease progression or death from any cause, whichever occurred first. Patients without an event were censored on the date of last follow-up for disease progression or last available tumor assessment if no further follow-up for disease progression was performed. Other secondary end points were investigator-assessed ORR, defined as confirmed (within at least 4 weeks) complete response (CR) or partial response (PR) during the study treatment; disease control rate, defined as the combination of CR, PR, and stable disease at the first postbaseline tumor assessment; and tolerability.

Assuming a median survival of 6.9 months in the placebo arm and 9 months in the bevacizumab arm (corresponding to an HR of 0.767), 446 events were required to achieve 80% power for the log-rank test at a two-sided overall α level of 5%. In order to achieve the required number of events, 300 patients were randomly assigned per treatment arm.

The difference in duration of OS between the two treatment arms was tested with an unstratified two-sided log-rank test at the 5% α level. This was the primary analysis. A stratified log-rank test with all three stratification factors was also performed. PFS was analyzed similarly. The primary analysis of survival duration occurred after approximately 446 deaths, at which point all efficacy and safety parameters were analyzed.

Predefined prognostic factors included as covariates in a multiple Cox regression were: region (Asia/Pacific, Western Europe 1, Western Europe 2, and other), KPS (< 80%, ≥ 80%), baseline albumin (< 2.9 g/dL, ≥ 2.9 g/dL), gender (male, female), age, race (white, other), tumor location (pancreas head, body, and tail), jaundice at time of diagnosis (yes, no), baseline lactate dehydrogenase (LDH) (≤ upper limit of normal [ULN], > ULN), baseline alkaline phosphatase (≤ 484 U/L, > 484 U/L), baseline platelet count (≤ ULN, > ULN), baseline C-reactive protein (CRP; ≤ median, > median), baseline

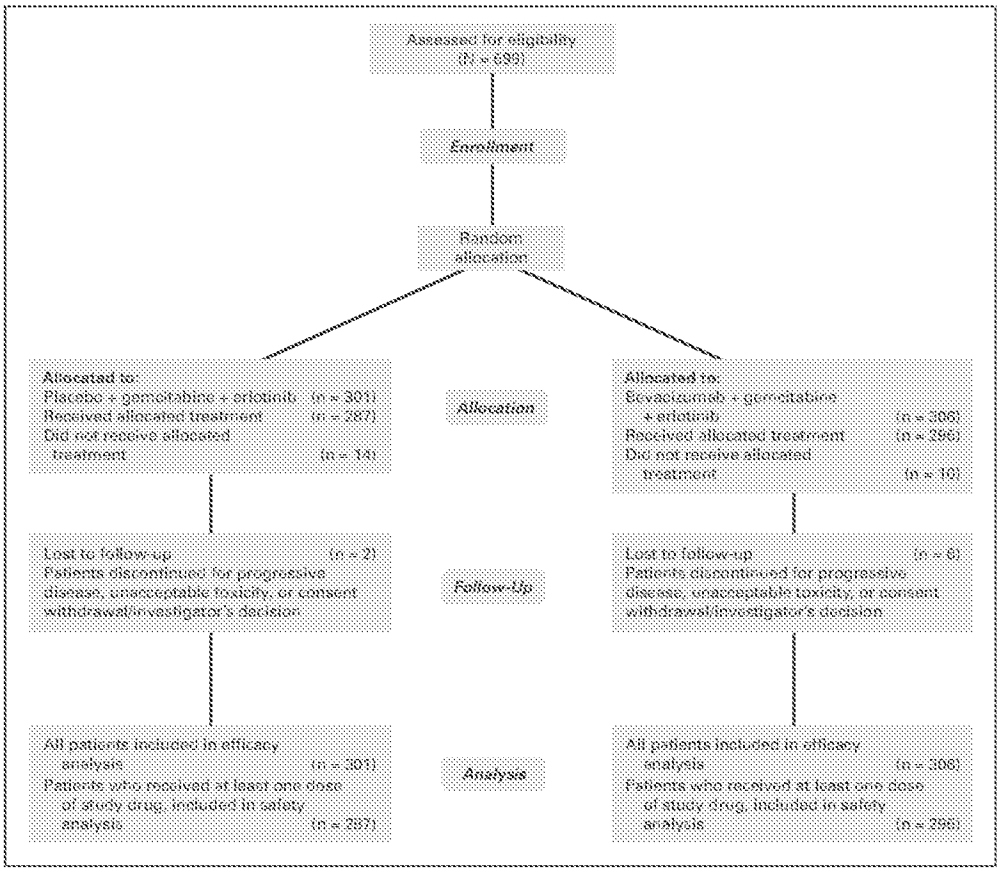

Fig 1. CONSORT diagram.

total bilirubin (≤ ULN, > ULN), baseline CA19.9 (≤ median, > median), baseline neutrophils (≤ ULN, > ULN), smoking status (yes, no), number of lesions at baseline (≤ 2, > 2), and liver lesions (yes, no).

Efficacy analyses were performed on the intention-to-treat population, which included all randomly assigned patients; patients were assigned to treatment arms based on the treatment to which they were randomly assigned. Safety analyses were performed on the safety population, which included all randomly assigned patients who received at least one dose of trial treatment; patients were assigned to treatment arms based on what they actually received.

RESULTS

Between July 2005 and September 2006, 607 patients were recruited at 92 institutions in 20 countries; 301 patients were randomly assigned to the placebo arm and 306 to the bevacizumab arm. In total, 24 patients did not receive any drug; 454 patients have died to date—233 (77.4%) in the placebo arm and 221 patients (72.2%) in the bevacizumab arm.

Patient flow is summarized in the CONSORT diagram (Fig 1), and patient characteristics are listed in Table 1; all 607 patients were evaluable for efficacy, and 583 patients were evaluable for safety.

The median duration of bevacizumab/placebo treatment was 99 days (range, 1 to 484 days) in the placebo arm and 106 days (range, 1 to 596 days) in the bevacizumab arm. Patients in the placebo arm received a median 91% (range, 9% to 110%) of the planned placebo dose, while those in the bevacizumab arm received a median 89% (range, 20% to 108%) of the planned bevacizumab dose.

Efficacy

The final analysis was conducted after 454 deaths (221 in the bevacizumab arm and 233 in the placebo arm). Median OS was 7.1 months in the bevacizumab arm and 6.0 months in the placebo arm, with an 11% reduction in the risk of death with bevacizumab; however, this difference did not reach statistical significance (HR, 0.89; 95% CI, 0.74 to 1.07; $P = .2087$; Fig 2A and Table 2).

PFS was significantly prolonged in the bevacizumab arm compared with the placebo arm (HR, 0.73; 95% CI, 0.61 to 0.86; $P = .0002$). Median PFS times were 4.6 months versus 3.6 months for bevacizumab and placebo (Fig 2B).

Results for subgroup analyses of OS by baseline stratification factors are shown in Appendix Figure A2, online only. Bevacizumab significantly prolonged OS in patients whose tumors were situated in the tail of the pancreas (9.0 *v* 5.5 months for bevacizumab and placebo; HR, 0.54; 95% CI, 0.36 to 0.81; $P = .0025$), those with a baseline CRP more than 1.4 mg/L (4.8 *v* 3.6 months; HR, 0.65; 95% CI, 0.51 to 0.84; $P = .0009$), and baseline LDH more than ULN (4.7 *v* 3.6 months; HR, 0.59, 95% CI, 0.43 to 0.82; $P = .0013$). In both treatment groups, patients experiencing skin rash had better survival than patients without skin rash (Appendix Figure A1, online only). In no subgroup was the placebo arm significantly superior to bevacizumab.

In total, 589 patients had measurable lesions and were evaluable for response: 297 in the bevacizumab arm and 292 in the placebo arm. Two CRs and 38 PRs were observed in the bevacizumab

Table 1. Patient Demographics and Clinical Characteristics at Baseline

Characteristic	Gemcitabine-Erlotinib + Placebo (n = 301)		Gemcitabine-Erlotinib + Bevacizumab (n = 306)	
	No.	%	No.	%
Age, years				
Median	61		62	
Range	33-85		29-85	
Sex				
Male	188	62	174	57
Female	113	38	132	43
Karnofsky performance status, %				
60	11	4	12	4
70	26	9	28	9
80	71	24	78	25
90	120	40	118	39
100	73	24	69	23
Primary pancreatic tumor location	297	99	304	99
Head	165	55	157	51
Body	65	22	79	26
Tail	67	22	68	22
Prior treatment for pancreatic cancer				
Antimetabolites	14	5	12	4
Previous radiotherapy	5	2	8	3

arm compared with 25 PRs and no CRs in the placebo arm (ORR, 13.5% *v* 8.6% for bevacizumab *v* placebo; $P = .0574$). The disease control rate was 62.1% in the bevacizumab arm and 58.5% in the placebo arm ($P = .3621$).

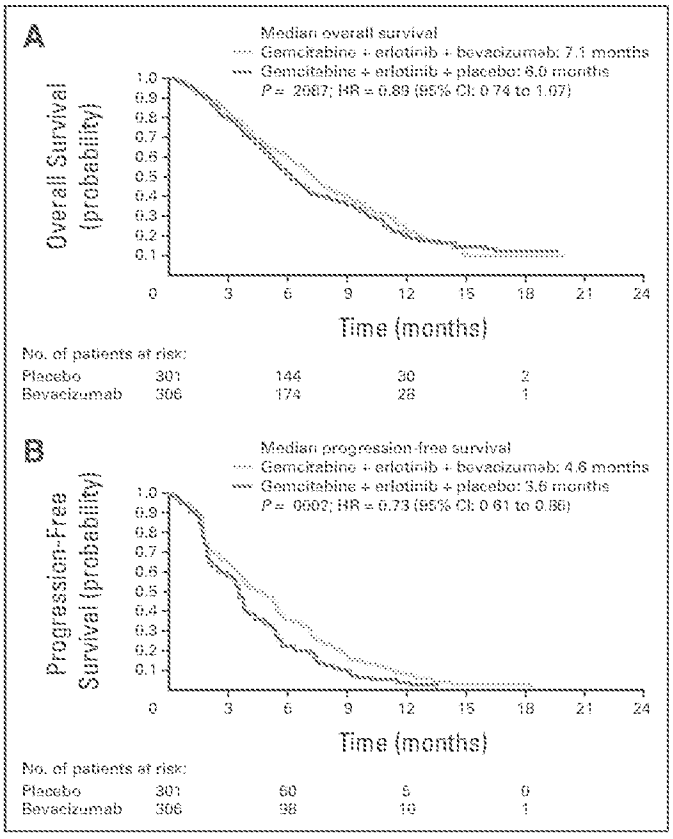

Fig 2. Duration of (A) overall survival and (B) progression-free survival in patients treated with placebo and bevacizumab.

Second-Line Therapy

Overall, 30% of patients in the bevacizumab arm and 39% in the placebo arm received second-line therapy. The most frequently used agents were antimetabolites (22% for bevacizumab and 31% for placebo) and platinum compounds (12% for bevacizumab and 16% for placebo).

Tolerability

Adverse events (occurring in ≥ 20% of patients) associated with treatment are summarized in Table 3. Grade 3 to 5 events were observed in 220 patients (74%) in the bevacizumab arm and in 202 patients (70%) in the placebo arm.

In the bevacizumab arm, 57 adverse events resulted in discontinuation of bevacizumab treatment, whereas 52 events in the placebo arm resulted in placebo treatment discontinuation. There was no between-group imbalance in the reasons given for treatment discontinuation.

Adverse events resulting in death were observed in 26 patients in the bevacizumab arm (9%) and 16 patients in the placebo arm (6%). Events occurring in more than one patient were pulmonary embolism (three patients in the bevacizumab arm and two patients in the placebo arm); gastrointestinal bleeding (four patients in the bevacizumab arm); cerebrovascular events (three patients in the bevacizumab arm and one patient in the placebo arm); septic shock/sepsis (one patient in the bevacizumab arm and three patients in the placebo arm); and respiratory failure (two patients in the placebo arm). Deaths within 30 days from last treatment dose (3% in each arm) and 60-day all cause mortality (10% in the bevacizumab arm and 12% in the placebo arm) were equally distributed between the arms.

Febrile neutropenia was observed in three patients in the bevacizumab arm and one patient in the placebo arm. All-grade adverse events of special interest for bevacizumab were observed in 61% of patients in the bevacizumab arm and in 45% of those in the placebo

Table 2. Efficacy Results

Efficacy Endpoint	Gemcitabine-Erlotinib + Placebo (n = 301)			Gemcitabine-Erlotinib + Bevacizumab (n = 306)			*P*	Hazard Ratio	95% CI
	No.	%	95% CI	No.	%	95% CI			
Overall survival, months									
Median		6.0			7.1		.2087	0.89	0.74 to 1.07
Range		0.1-19.5			0.0-19.8				
Progression-free survival, months									
Median		3.6			4.6		.0002	0.73	0.61 to 0.86
Range		0.0-13.6			0.0-18.3				
Best overall response*									
CR	0			2	0.7				
PR	25	8.6		38	12.8				
SD	132	45.2		146	49.2				
PD	71	24.3		59	19.9				
Missing	64	21.9		52	17.5				
Overall response rate (CR + PR)		8.6	5.6 to 12.4		13.5	9.8 to 17.9	.0574†		
Disease control rate (CR + PR + SD at first tumor assessment)		58.5	52.7 to 64.1		62.1	56.4 to 67.6	.3621†		

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*n = 292 for placebo; n = 297 for bevacizumab.
†χ^2 test.

arm (Table 4). This difference was mainly a result of epistaxis, hypertension, and proteinuria. Bleeding, proteinuria, and hypertension were more common in the bevacizumab arm than the placebo arm. The incidence of thrombotic events was similar in both arms. Gastrointestinal perforation was uncommon (1% in each arm).

Time to body weight reduction ≥ 7% was 6.7 months in the bevacizumab arm *v* 5.6 months in the placebo arm (HR, 1.04; 95% CI, 0.80 to 1.34; *P* = .786).

DISCUSSION

The outcome for patients with metastatic pancreatic cancer remains poor and represents an unmet need in daily clinical practice. Despite the extensive investigation of cytotoxic agents, little progress has been made—median survival consistently fails to exceed 6 months, and 1-year survival is only 20%. Several new targeted agents have been studied in phase III trials in combination with gemcitabine, including marimastat, tipifarnib, cetuximab, and erlotinib.[23,24] Only the combination of gemcitabine and erlotinib proved to be more active than gemcitabine alone.[8] The present trial is the first, to our knowledge, to build on this combination by adding a second targeted agent in an attempt to further improve outcomes in patients with metastatic pancreatic cancer. There is a biologic rationale for combining bevacizumab and erlotinib in this patient group. Retrospective studies demonstrated significantly reduced survival in patients with pancreatic cancer overexpressing epidermal growth factor receptor.[25] Similarly, shorter survival was observed in patients with moderate or high vascular endothelial growth factor overexpression.[26]

Table 3. Most Common All-Grade Adverse Events in Patients Treated With Placebo or Bevacizumab in Addition to Gemcitabine-Erlotinib

Adverse Event	Gemcitabine-Erlotinib + Placebo (n = 287)		Gemcitabine-Erlotinib + Bevacizumab (n = 296)	
	Any Grade Adverse Events, %	Grade 3-5 Adverse Events, %	Any Grade Adverse Events, %	Grade 3-5 Adverse Events, %
Anemia	33	9	27	7
Thrombocytopenia	26	6	30	8
Neutropenia	26	17	29	21
Diarrhea	51	6*	49	4
Nausea	51	3	46	4
Rash	44	3	49	8
Vomiting	42	3	37	5
Pyrexia	37	2	34	3
Fatigue	34	7	33	5
Anorexia	24	2	21	2
Constipation	23	< 1	27	1

NOTE. Adverse events with an incidence of ≥ 20% are shown.
*One patient had a grade 5 adverse event.

Table 4. Adverse Events of Special Interest

Adverse Event	Gemcitabine-Erlotinib + Placebo (n = 287)				Gemcitabine-Erlotinib + Bevacizumab (n = 296)			
	Any Adverse Events		Grade 3-5 Adverse Events		Any Adverse Events		Grade 3-5 Adverse Events	
	No.	%	No.	%	No.	%	No.	%
Bleeding	67	23	18	6	124	42	22	7
Epistaxis	31	11	—		87	29	2	< 1
Hypertension	26	9	3	1	60	20	10	3
Proteinuria	4	1	—		18	6	7	2
Arterial thromboembolic events	8	3	8	3	9	3	8	3
Venous thromboembolic events	53	18	28	10	43	15	17	6
Gastrointestinal perforations	4	1	4	1	2	< 1	2	< 1
Wound healing complications	3	1	1	< 1	6	2	2	< 1

In our study, adding bevacizumab to gemcitabine-erlotinib failed to meet the primary end point by not obtaining a statistically significant benefit for OS. However, there was a numerical difference in survival time (7.1 *v* 6.0 months), with a HR of 0.89 reflecting an 11% reduction in the risk of death (P = nonsignificant). This finding may have resulted from a limited but significant gain in PFS (HR, 0.75; 1-month improvement in the bevacizumab arm), suggesting that a subgroup of patients may derive a benefit from the bevacizumab combination. However, it is not possible to determine which patients may benefit from the addition of bevacizumab based on this study.

In the interests of optimizing outcomes, this study included only patients with metastatic disease because patients with locally advanced pancreatic cancer have a better outcome. Despite this approach, bevacizumab did not significantly improve OS in the overall population. Subgroup analyses indicate that perhaps patients with more aggressive disease, as indicated by elevated CRP or LDH, might derive a greater benefit from the bevacizumab combination. This suggests that well-defined patient populations might benefit from an approach that targets more than one of the pathways involved in pancreatic cancer. However, further trials are needed to better define which patient groups are likely to achieve the greatest benefit. Emerging biomarker data may also help to identify the patient populations most likely to respond to treatment with these agents. Biomarker analyses are planned in this trial in order to try to identify those patients who may benefit most from the addition of bevacizumab to standard therapy.

The combination of bevacizumab with gemcitabine-erlotinib was well tolerated, with a similar incidence in both arms of grade 3 to 5 adverse events, serious adverse events or events leading to discontinuation or death, and serious adverse events as the placebo arm. There were 26 patients in the bevacizumab arm and 16 patients in the placebo arm experiencing adverse events leading to death. However, deaths within 30-days from last treatment dose (3% in each arm) and 60-day all cause mortality (10% with bevacizumab *v* 12% with placebo) were equally distributed between arms. Bleeding, hypertension, and proteinuria were more frequent in the bevacizumab arm while gastrointestinal perforation and arterial and venous thromboembolic events were not increased. No new toxicity signals were observed in this study for this combination in pancreatic cancer.

In conclusion, the addition of bevacizumab to the active combination of gemcitabine-erlotinib is feasible and well tolerated in patients with metastatic pancreatic cancer. Although this combination did not significantly improve OS compared with gemcitabine-erlotinib, there are some indications of an additional benefit of adding bevacizumab, as reflected by the improved PFS in patients with metastatic pancreatic cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Aijing Shang, Roche (C); Jan Cosaert, Roche (C) **Consultant or Advisory Role:** Eric Van Cutsem, Roche (C); Jaafar Bennouna, Roche (C), Taiho (C); Yves Humblet, Roche (C); Sharlene Gill, Roche (C); Werner Scheithauer, Roche (C); Malcolm J. Moore, OSI Pharmaceuticals (C), Genentech (C) **Stock Ownership:** None **Honoraria:** Eric Van Cutsem, Roche; Sharlene Gill, Roche; Werner Scheithauer, Roche; Malcolm J. Moore, OSI Pharmaceuticals, Genentech **Research Funding:** Eric Van Cutsem, Roche **Expert Testimony:** None **Other Remuneration:** None

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Weekly high-dose 5-fluorouracil and folinic acid in metastatic pancreatic carcinoma: a phase II study of the EORTC GastroIntestinal Tract Cancer Cooperative Group

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Abstract

The aim of the study was to assess the response rate and toxicity of high-dose 24 h infusion of 5-fluorouracil (5FU) in metastatic adenocarcinoma of the pancreas. Patients with measurable disease, performance status 0–2, and no prior chemotherapy were registered to receive cycles of leucovorin (LV) 500 mg/m^2 (or l-LV 250 mg/m^2 over 1 h followed by 5FU 2.6 g/m^2 over 24 h, weekly for 6 weeks, followed by a 2-week rest. The main endpoints were the response rate and toxicity. From 37 patients, 36 were the analysed for toxicity, and 33 were eligible and analysed for response. The median age was 59 years (range 28–74 years), and the median performance status was 1. Partial response was observed in three patients (9%) (95% Confidential Interval (CI): [2–24]%). Main grade 3/4 National Cancer Institute (NCI) common toxicity criteria toxicities (patients) were diarrhoea ($n = 3$), vomiting ($n = 2$) and hand–foot syndrome ($n = 5$). Median time to progression was 7 weeks (95% CI: [6.4–11.7] weeks) and median survival 19 weeks (95% CI: [12–35] weeks). In conclusion, high-dose 5FU and folinic acid is well tolerated, but has only modest activity in pancreatic cancer.

Keywords: Pancreatic neoplasms/drug therapy; Fluorouracil; Leucovorin

1. Introduction

Pancreatic cancer is the fourth most common cause of death from malignant disease in Western countries. These tumours account for 3% of all malignancies, but for 5% of all cancer deaths. The disease carries a poor prognosis, the median survival of all patients with tumours of the exocrine pancreas being only 4–6 months. Only a few patients are candidates for surgical resection, which is the only possibility for cure [1]. All other patients may be considered for palliative chemotherapy or radiotherapy, the modality of treatment primarily being dependent on the stage of the disease. A large number of chemotherapeutic agents have been investigated in pancreatic cancer, but the results of both single-agents and combination chemotherapy in terms of response rate and overall survival have been disappointing [2,3]. The European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG) previously initiated studies with cisplatin, ifosfamide, epirubicin and epirubicin-based combination chemotherapy [4–8].

Especially in patients with metastatic pancreatic cancer, the toxicity of chemotherapy is of concern, as a decreased performance status and concomitant liver-,

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lung-, and cardiac disease are frequently present and may preclude a course of intensive therapy. When chemotherapy for pancreatic cancer is considered, single-agent 5-fluorouracil (5FU) and gemcitabine are probably the most frequently used regimens. Both bolus injections and prolonged infusions of 5FU, either alone or in combination with leucovorin, have been investigated [9–14]. The response rate in these studies varied between 0% and 19%. In a meta-analysis of randomised studies comparing bolus injections of 5FU with prolonged infusion in colorectal cancer, both the response rate and the survival times were significantly higher with prolonged infusions [15]. For the present study, aimed at assessing the activity of prolonged administration of 5FU in metastatic pancreatic cancer, a schedule using weekly administration of leucovorin followed by 5FU infusion over 24 h was selected. The schedule allows the delivery of a high dose-intensity, is associated with a favourable toxicity profile, and may achieve responses even in patients previously exposed to bolus 5FU [16,17].

2. Patients and methods

2.1. Study population

Patients eligible for the study were required to have histologically or cytologically confirmed adenocarcinoma of the pancreas, a performance status 0–2, an estimated life expectancy of 3 months or more, and bidimensionally measurable metastatic disease outside previously irradiated areas. Target lesions qualifying for measurable disease included lung metastases $\geqslant 1$ cm and liver, soft tissue or lymph node metastases $\geqslant 2$ cm. Lymph node and skin metastases $\geqslant 1$ cm were only allowed if their metastatic nature was proven by fine-needle aspiration. Prior chemotherapy was not allowed. Other eligibility criteria included age $\geqslant 18$ years, no other malignancy except adequately treated basal carcinoma of the skin, no overt cardiac disease or active infection, and no signs or symptoms of Central Nervous System (CNS) or leptomeningeal involvement. Excluded were major organ dysfunctions, indicated by white blood cell (WBC) $<3.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l, serum creatinine >120 μmol/l, and serum bilirubin >30 μmol/l. All patients had to be available for follow-up and to have given informed consent.

2.2. Treatment

Treatment consisted of weekly administration of racemic folinic acid 500 mg/m^2 over 1 h immediately followed by 5FU 2600 mg/m^2 as a 24-h infusion. The replacement of racemic folinic acid by L-folinic acid 250 mg/m^2 was allowed. Treatment was administered for 6 weeks, followed by a 2-week rest. This 8-week period was called a cycle.

Dose delays or adjustments were foreseen for toxicities. The grading of toxicities followed the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) guidelines. Treatment was skipped in case of WBC $<3 \times 10^9$/l or platelet count $<100 \times 10^9$/l at the day of scheduled retreatment. The dose of 5FU was reduced by 25% in subsequent courses in case of grade 3/4 leucopenia or thrombocytopenia, or when courses had to be delayed for one week or more due to insufficient recovery of the WBC or platelet count. The dose of 5FU was also reduced by 25% in case of grade $\geqslant 2$ mucositis, dermatitis, or diarrhoea, and was withheld in case of CTC organ toxicity >2, other than alopecia, nausea and vomiting. Pyridoxine was recommended for patients developing hand–foot syndrome. Treatment was administered until disease progression or unacceptable toxicity. Response assessment was planned every 8 weeks. In patients with stable disease, the continuation of treatment was left to the investigator's discretion.

2.3. Response assessment

Standard World Health Organisation (WHO) response criteria were used. A clinical complete response was defined as the disappearance of all clinically measurable and evaluable disease, and a partial response as a reduction of all measurable lesion of more than 50%, for a duration of at least 4 weeks. When measurable lesions increased less then 25% or decreased less than 50% for a duration of at least 6 weeks, this was called stable disease. Progressive disease was defined as an increase of measurable lesions more than 25% or the occurrence of new lesions. Early death was defined as death during the first 6 weeks after commencement of chemotherapy without severe toxicity, and a toxic death any death where drug toxicity was thought to have made a major contribution.

2.4. Statistics

The Simon one sample minimax design [18] was applied, with P_0 taken as 5%, P_1 (true response rate) as 20%, α as "0.1" and β as "0.1". The trial was to be prematurely closed if no responses were observed after 18 patients had been enrolled. Otherwise, accrual would continue until 32 eligible patients had been entered. If four or more responses were observed, the regimen would warrant further investigation.

3. Results

Thirty-seven patients from nine institutions were enrolled between December 1996 and August 1998. Thirty-

Table 1
Patient characteristics ($n = 37$)

Median age (range)	59 years (28–74)
WHO performance status	
0/1/2	11/20/6 pts
Male/Female	25/12 pts
Location of primary tumour	
Head/body/tail	21/9/7 pts
Prior surgery	13
Prior radiotherapy	0
Analgesic use	
None	9 (24%)
Nonopoids	8 (22%)
Weak opoids	9 (24%)
Strong opoids	11 (30%)

WHO, World Health Organisation ; pts, patients.

Table 2
Activity outcome ($n = 33$)

Partial response	3 (9%)	95% CI: [2–24]
No change	7 (21%)	
Progression	15 (46%)	
Early death	5 (15%)	
Not assessable	3 (9%)	
Median time to progression	7 weeks	95% CI: [6.4–11.7]
Median survival	19 weeks	95% CI: [12–35.2]

CI, confidence interval.

three patients were eligible and analysed for response, four patients were ineligible, three patients because of unsuitable target lesions and one patient due to enrollment after the treatment start. All patients enrolled were analysed for toxicity. Patient characteristics are summarised in Table 1. The median age of the patients was 59 years (range 28–74 years) and the median performance status was 1. Seventy-five percent of the patients used analgesics at study entry, evenly divided between nonopoids (usually non-steroidal anti-inflammatory drugs (NSAIDs)), weak opoids and strong opoids. Altogether 67 cycles of 8 weeks duration were administered. Twenty-four patients received 1 cycle, eight patients received 2 cycles, and five patients received 3 or more cycles, with a maximum of 13 cycles being given. The major reason for discontinuation of treatment was disease progression in 31 patients. Three patients stopped because of toxicities, namely angina pectoris, severe diarrhoea, and hand–foot syndrome, and three for other reasons.

Response to treatment is summarised in Table 2. Three patients (9%) achieved a partial response, and another 7 patients had stable disease. The median time to progression was 7 weeks, and the median survival 19 weeks (Fig. 1). Table 3 summarises the main non-haematological toxicities. The Grade 3 and 4 toxicities consisted of hand–foot syndrome (14%), diarrhoea (8%), lethargy (5%), nausea (5%), and stomatitis (3%). No leucocytopenia or thrombocytopenia in excess of grade 1 was observed, but mild to moderate anaemia occurred in 92% of patients.

4. Discussion

Over the years, a variety of administration schedules of 5FU have been explored, in which the drug was given either as a bolus injection or as a prolonged infusion, with or without biomodulation with leucovorin or other agents. Meta-analyses from the Advanced Colorectal Cancer Meta-analysis Project comparing various therapeutic strategies versus bolus 5FU showed a significantly

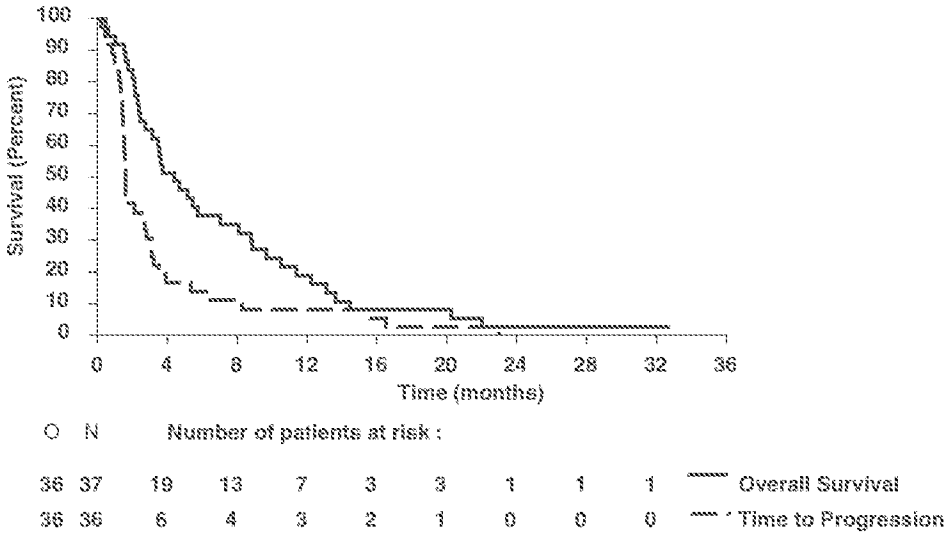

Fig. 1. Progression-free survival and overall survival of patients treated with high-dose 5-fluorouracil and leucovorin in metastatic pancreatic cancer. O, observed; N, number.

Table 3
Toxicities (worst adverse event)

Toxicity	Grades 1–2	Grade 3	Grade 4
Diarrhoea	13 (36%)	3 (5%)	1 (3%)
Nausea	26 (71%)	0	
Vomiting	13 (35%)	2 (5%)	
Hand–foot syndrome	3 (8%)	4 (11%)	1 (3%)
Stomatitis	11 (30%)	1 (3%)	
Lethargy	11 (31%)	2 (5%)	
Anaemia	34 (92%)	0	

improved response rate of leucovorin-modulated regimens (22.5% vs 11.1%) and continuous infusion schedules (22% vs 14%) in comparison with single-agent bolus 5FU [15,19]. Moreover, in colorectal cancer, responses have been observed with both low-dose continuous infusion and high-dose intermittent infusion over 24 h in patients previously treated with bolus injections [17,20,21]. In addition, toxicities of bolus and continuous infusion regimens differ. Leucocytopenia and mucositis are more frequently associated with bolus injections, hand–foot syndrome is more common in continuous infusion schedules [22]. This is also reflected in the toxicity pattern of the present trial. Leucocytopenia and thrombocytopenia were virtually absent, but hand–foot syndrome and stomatitis were regularly observed.

The improved response rate of protracted infusion that exists in colorectal cancer is not evident in pancreatic cancer. Typically, bolus injections are associated with a response rate of 0–17% [10–12]. Low-dose continuous infusion of 5FU 300 mg/m^2/day produced a response rate of 8.4% and a median survival time of 5.1 months in patients with locally advanced and metastatic disease [14]. More recently, a high-dose weekly infusion of 5FU has also been investigated in pancreatic cancer. The present trial showed a disappointing low response rate of 9%, which was below the preset level of interest (20%) of this schedule.

When considering the results of this trial, it should be taken into account that only patients with metastatic disease were eligible. In addition, the criteria for measurability were stringent, and deliberately required relatively large lesions in order to improve the accuracy of repeated measurements. Locally advanced disease was excluded, because the pancreatic primary was not considered a target for response assessment, as such lesions may contain a considerable amount of fibrosis. A set of studies using the gemcitabine and fluorouracil combination to treat pancreatic cancer show that the median survival increases with an increasing proportion of locally advanced disease. Median survival was 4.4, 6.7, 7, and 11 months, respectively, for proportions of patients with 0%, 11%, 46% and 64% of locally advanced disease [23–26]. The median survival of 19 weeks, as observed in the present study, is in agreement with what can be expected in a population of patients who all have metastatic disease. In another study of patients with locally advanced and metastatic disease treated with high-dose weekly 5FU, the response rate was 8%, and the median survival approximately 8 months [27]. The proportion of patients experiencing benefit from the treatment was larger and correlated with those patients who had stabilisation of their disease. These data are comparable to results achieved with single-agent gemcitabine, which is easier to administer. The high-dose weekly schedule might be useful in combination regimens, as it is associated with limited haematological toxicity.

In conclusion, the activity of high-dose infusional 5-FU/LV by itself to treat metastatic pancreatic cancer is insufficient. Whether improved results can be obtained by high-dose infusional 5-FU/LV in combination with other agents, such as CPT-11, oxaliplatin or the taxanes, will require further study.

Conflict of interest

None.

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Efficacy of nal-IRI and hypoxia modulation in orthotopic patient-derived pancreatic tumor models of high (OCIP51) and low (OCIP19) hypoxia.

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†Affiliation at the time of study.

Conflict of Interest: [(2)] employees of Merrimack Pharmaceuticals (at the time of study) received salaries and stock options from Merrimack Pharmaceuticals. University Health Network has received research funding as part of a sponsored research agreement from Merrimack Pharmaceuticals with Jinzi Zheng as the lead Principal Investigator.

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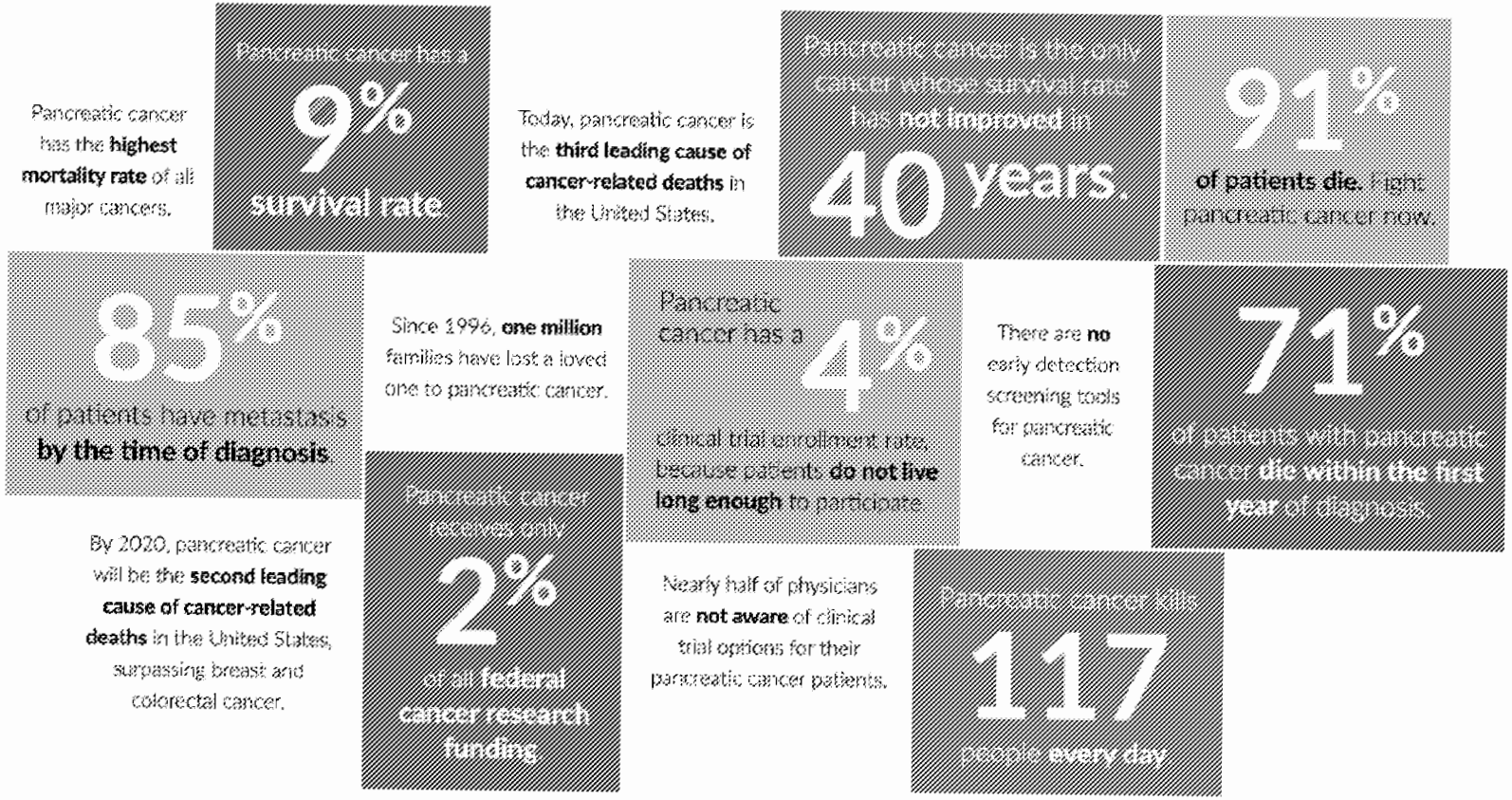
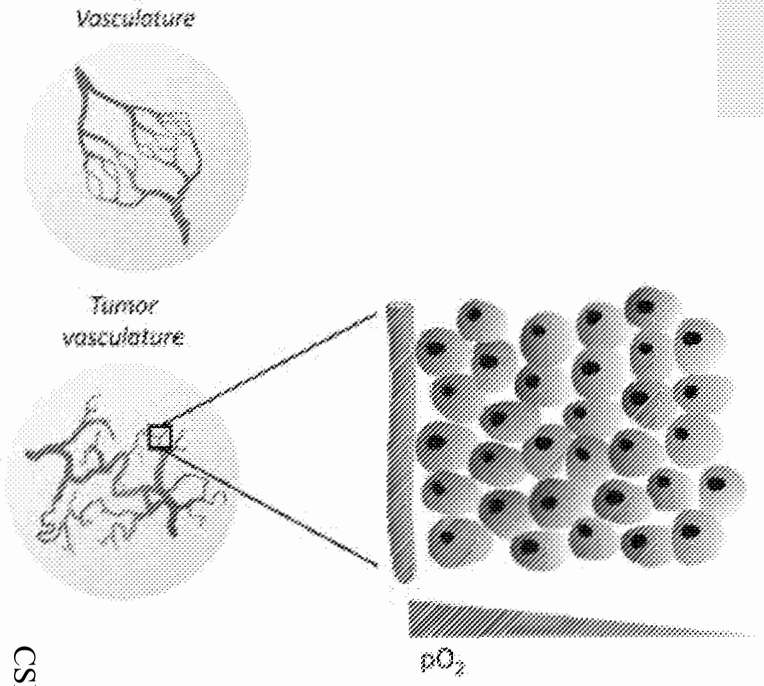
Pancreatic Cancer



Tumor Hypoxia



Tumor Hypoxia

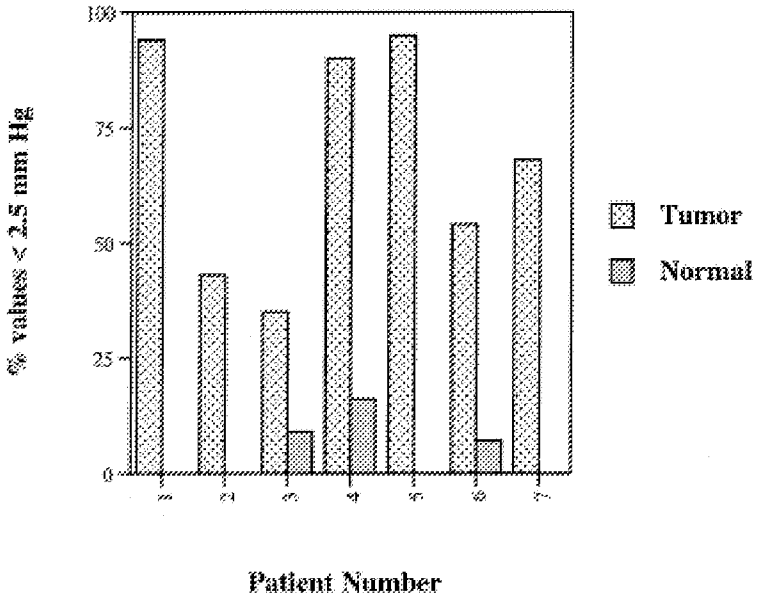
- Genomic instability
- Evasion of the immune system
- Activation of oncogenes
- Tissue invasion and metastasis

→ Chemo-resistance, Radio-resistance

→ **Poor clinical outcome**

Ramachandran S et al. Genes 2015

Hypoxia in pancreatic cancer



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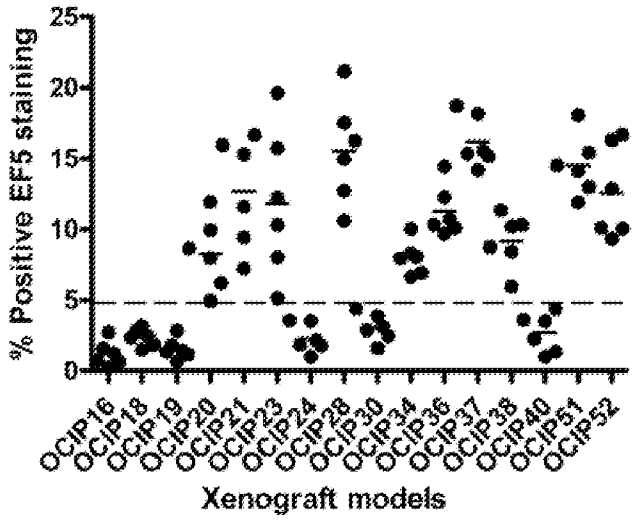
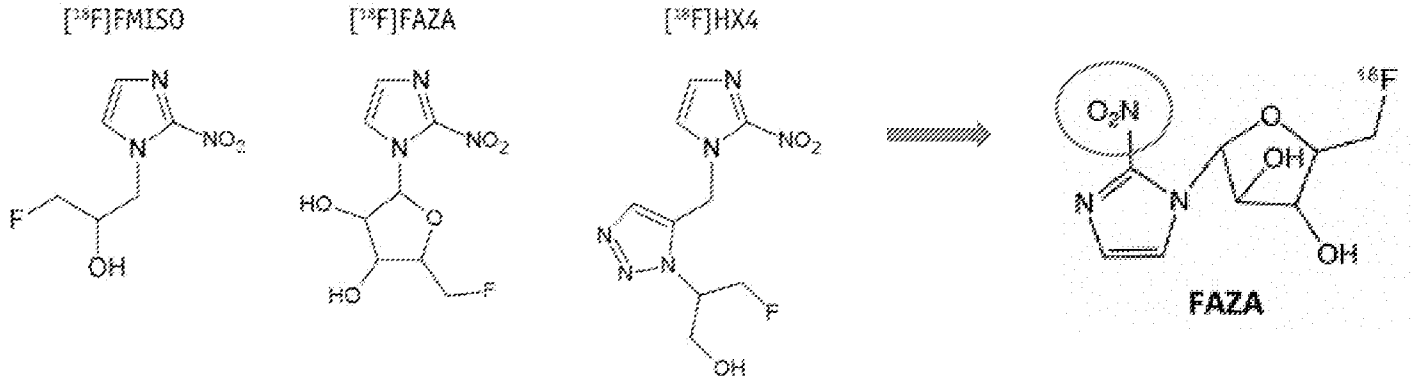
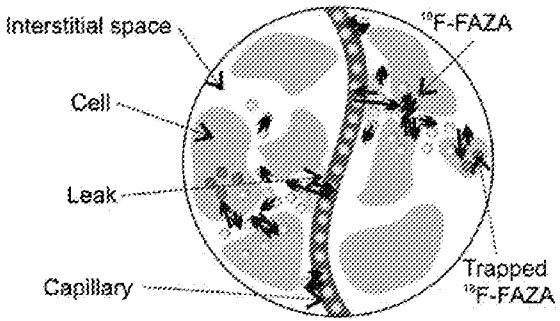


Chang Q et al. Cancer Res 2011.

Positive correlation among hypoxia levels, aggressive growth, and metastasis formation.

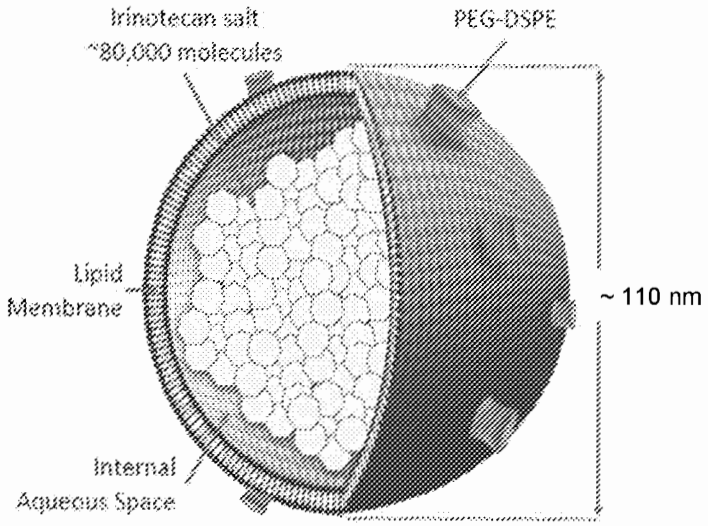
PET Imaging of Hypoxia





Lee ST et al. Semin Nucl Med 2007
Peeters SG et al. Int. J. Radiation Oncology Biol. Phys 2015

Liposomal Irinotecan (nal-IRI, Onivyde)



INDICATION (US)

ONIVYDE® (Irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

https://www.onivyde.com

Key Attributes:

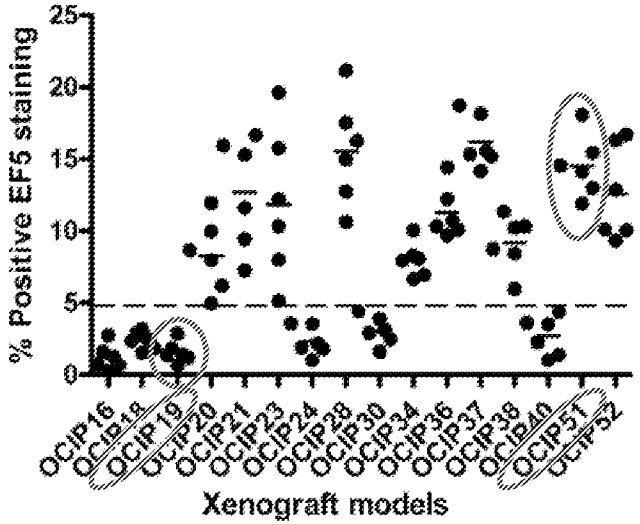
- Long circulation and sustained release
- Tumor accumulation via the enhanced permeability and retention (EPR) effect
- Improved treatment efficacy and reduced toxicity compared to non-encapsulated irinotecan (in animal models)

UHN TECHNA STTARR

Kalra AV et al., Cancer Research 2014.
Bernards N et al., Submitted 2017.

Aims of the study

- Evaluate the therapeutic activity of nal-IRI in orthotopic pancreatic cancer models.



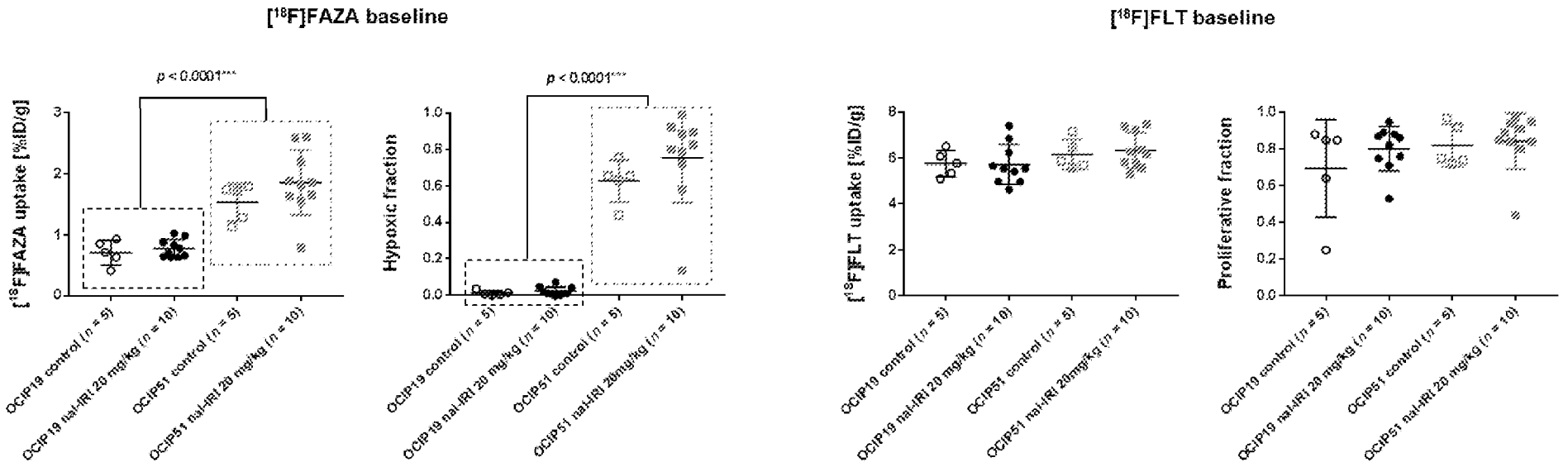
- Explore the value of longitudinal [^{18}F]FAZA-PET imaging following treatment with nal-IRI.

- Explore the ability of nal-IRI to modulate hypoxia in tumors with inherently high or low baseline hypoxia levels.

Methods

- Fragments of the patient-derived pancreatic tumors OCIP51 and OCIP19 (UHN Tumor Tissue Bank, Toronto) were implanted orthotopically into 6 to 8-week-old female NOD/SCID mice
- Tumor growth was monitored by 1T MRI until > 250 mm^3
- Mice were randomized into nal-IRI (20 mg/kg) treated and untreated control group
- Treatment efficacy:
  - 1T – MRI for tumor volume measurement
  - [^{18}F]FAZA – PET for tumor hypoxia quantification
  - [^{18}F]FLT – PET for tumor cell proliferation

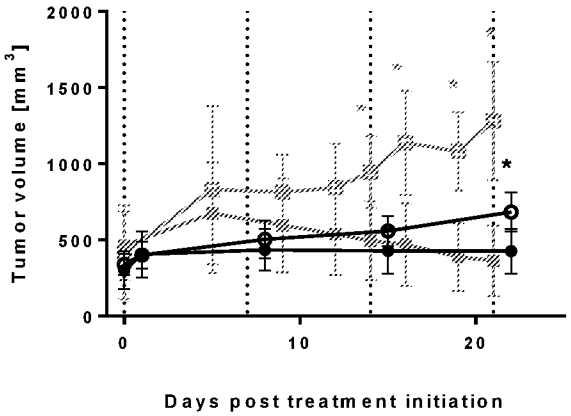
[18F]FAZA and [18F]FLT-PET uptake characteristics in OCIP51 and OCIP19 tumors at baseline



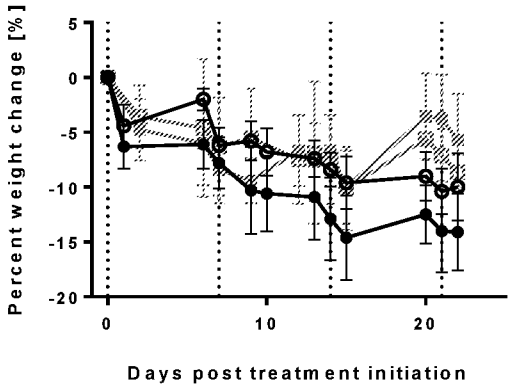
Hypoxic and proliferative fraction: A voxel was classified to be hypoxic, or highly proliferative, if its PET signal was higher than the threshold, defined as the mean + 3 standard deviations of the signal measured in the muscle region of the same animal.

Longitudinal monitoring of treatment and efficacy

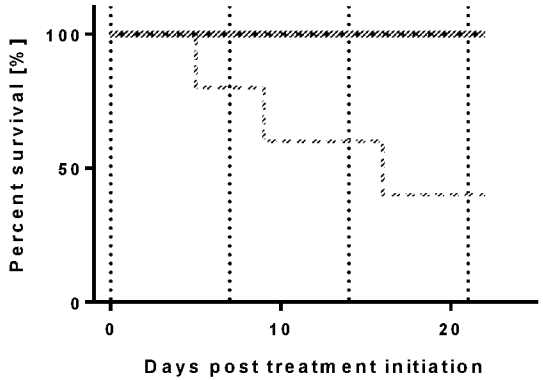
Nal-IRI treatment efficacy

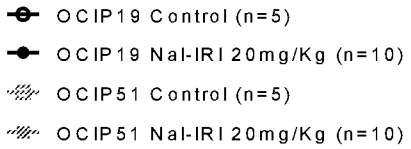


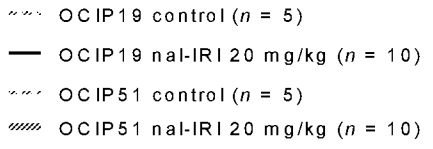
Nal-IRI treatment tolerability



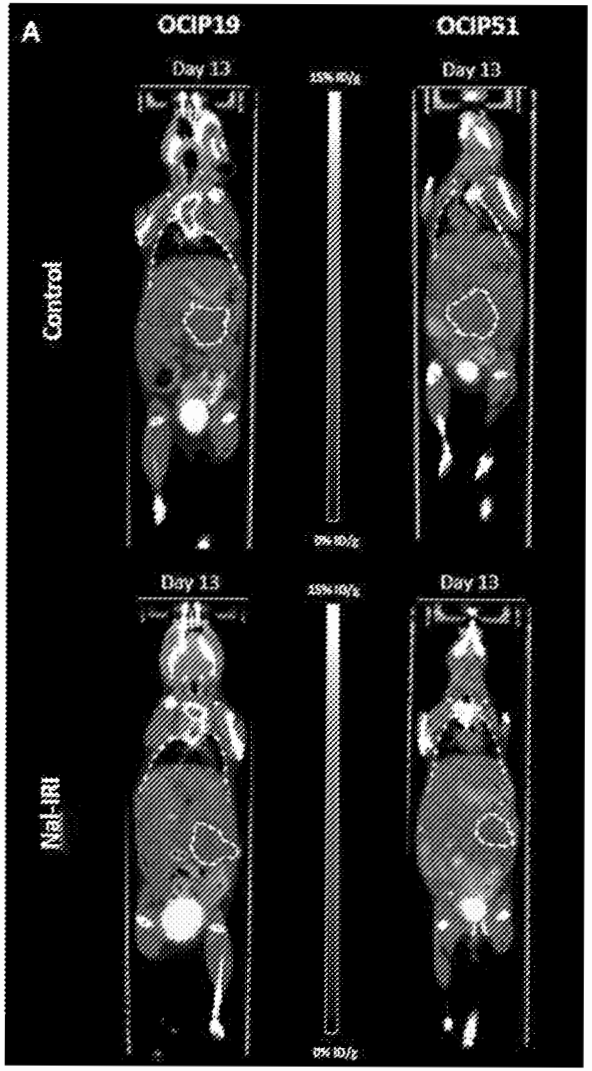
Percentage of survival



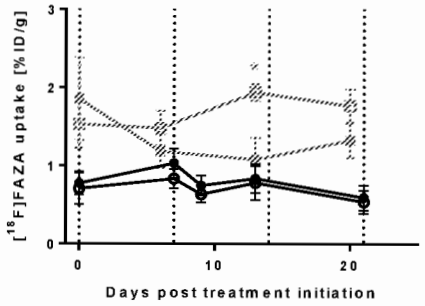


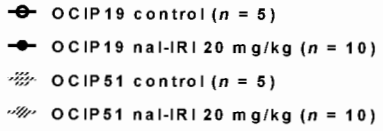


Nal-IRI mediated hypoxia modulation in tumor models of high and low baseline hypoxia

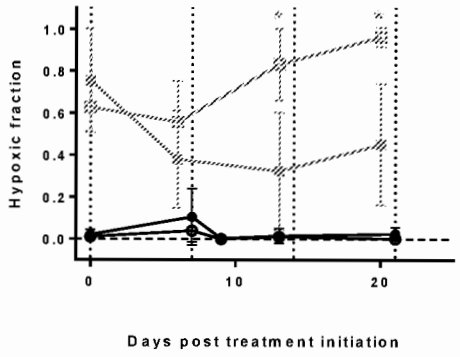


[18F]FAZA uptake (% ID/g)

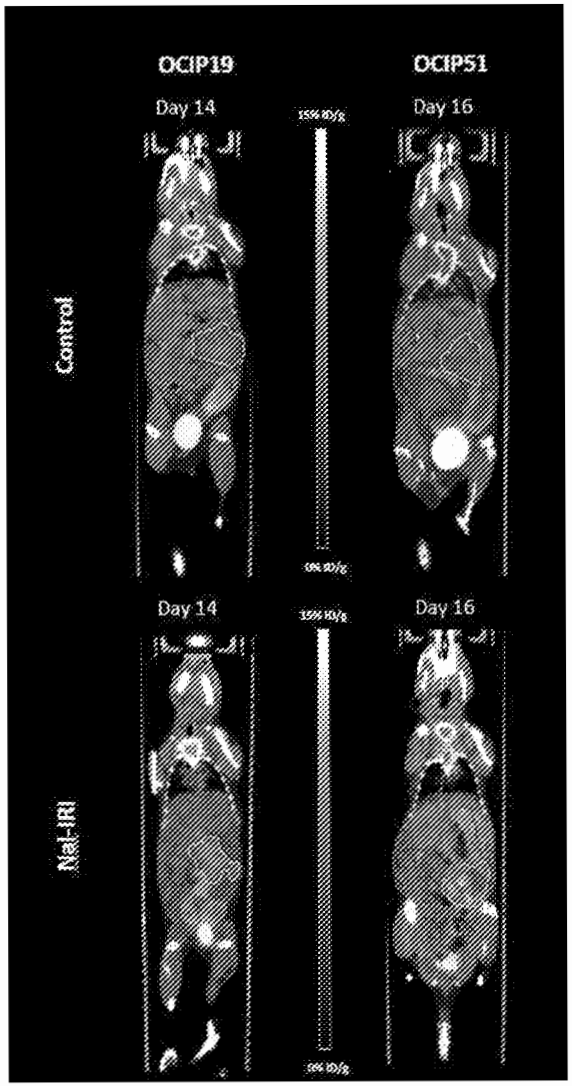


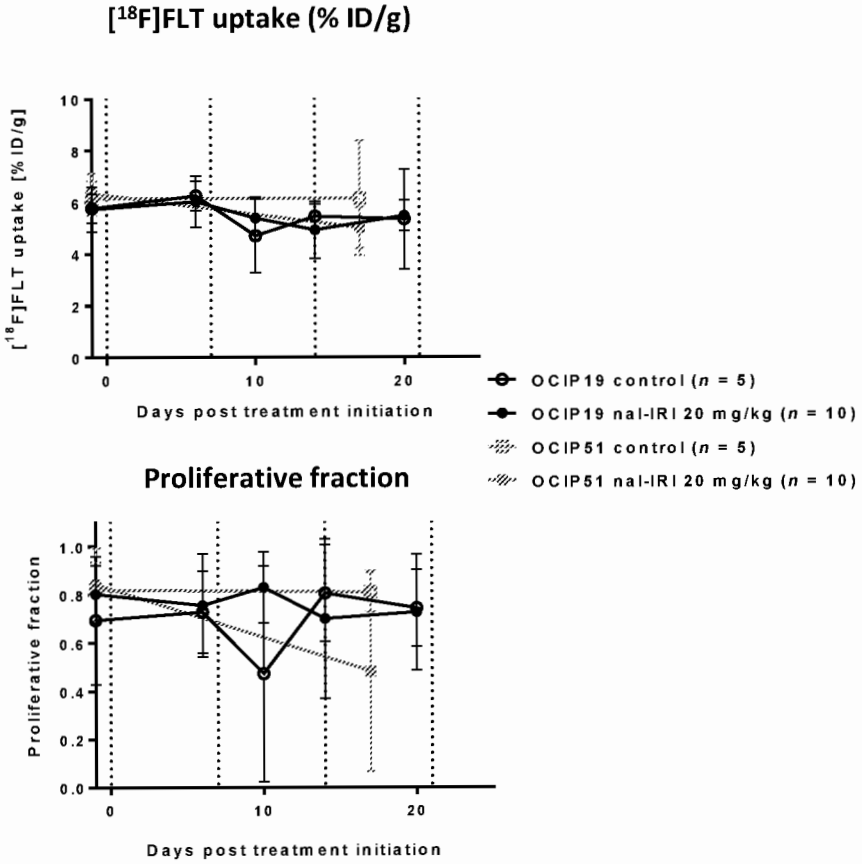


Hypoxic fraction

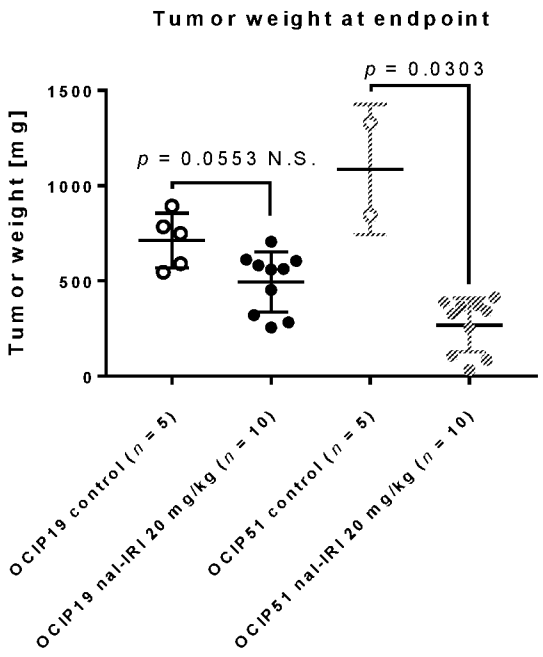


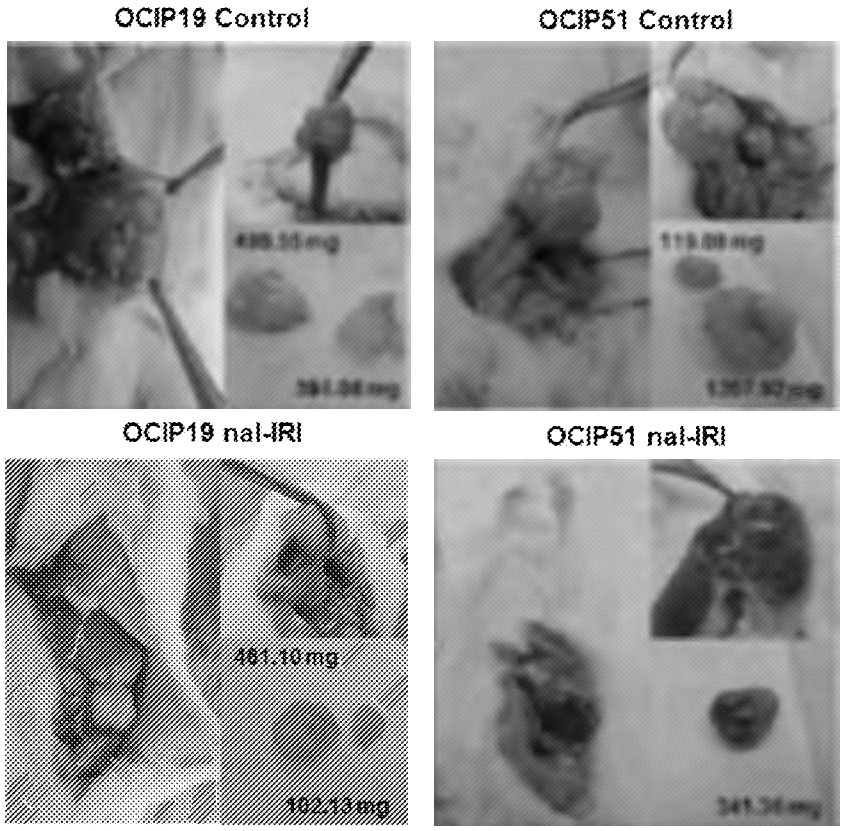
Longitudinal [^{18}F]FLT–PET imaging of nal-IRI treatment response





Tumor weight and morphology at the study endpoint





Summary and Conclusions:

We investigated the value of [^{18}F]FAZA-PET imaging in assessing the baseline levels of hypoxia in two orthotopic patient-derived tumor models of pancreatic cancer, OCIP19 and OCIP51, as well as in longitudinal monitoring of tumor hypoxia modulation following treatment with nal-IRI.

- [^{18}F]FAZA-PET confirmed EF5-based hypoxia measurements.
- Early prediction of treatment outcome for the high hypoxia OCP51 model is suggested by the Drop in tumor hypoxia detected 8 days before a significant decrease in tumor volume.
- [^{18}F]FLT-PET not ideal as surrogate imaging marker for treatment response assessment.

- [^{18}F]FAZA-PET hypoxia quantification as an early treatment response imaging biomarker following nal-IRI chemotherapy.
- Hypoxia modulation may be a key mechanism of action making nal-IRI more effective against highly hypoxic tumors.

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SESSION TITLE: Late Breaking Session 08: Oncology - Preclinical Imaging

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TITLE: Efficacy of nal-IRI and hypoxia modulation in orthotopic patient-derived pancreatic tumor models of high (OCIP51) and low (OCIP19) hypoxia.

PRESENTER: Manuela Ventura

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ABSTRACT BODY:

Abstract Body: Introduction: Despite the continuous advances in diagnostic tools and treatment regimens, the prognosis of pancreatic cancer remains very poor. High levels of hypoxia have been linked to aggressiveness, resistance to therapy, and poor prognosis of these tumors. Onivyde® (liposomal irinotecan, nal-IRI), in combination therapy with 5-fluorouracil and leucovorin, was recently approved for the treatment of patients with gemcitabine-refractory advanced and metastatic pancreatic cancer, and was previously shown to reduce hypoxia in preclinical tumor models. Our study evaluates the anti-tumor activity of nal-IRI and its ability to modulate hypoxia in patient-derived orthotopic models of pancreatic cancer with high (OCIP51) and low (OCIP19) hypoxia. Methods: Mice bearing orthotopic OCIP51 or OCIP19 tumors were randomized into: (i) control (n = 5 per tumor model) and (ii) treated, nal-IRI 20 mg/kg (n = 10 per tumor model) group. A total of four doses were administered and treatment efficacy was monitored by multiple MRI sessions. [^{18}F]FAZA imaging for tumor hypoxia quantification was performed on day 0, 7, 14, and 21 post treatment initiation. [^{18}F]FLT imaging for tumor cell proliferation evaluation was performed on day -1 and 16 for the OCIP51, and on days -1, 6, 13, and 20 for the OCIP19 model. Results: At baseline, OCIP51 mice exhibited significantly ($p < 0.0001$) higher tumor [^{18}F]FAZA uptake (1.75 ± 0.12 %ID/g) compared to the OCIP19 model (0.75 ± 0.04 %ID/g). More evident was the difference in tumor hypoxic fraction, 0.02 ± 0.01 for the OCIP19 versus 0.71 ± 0.06 for the OCIP51 ($p < 0.0001$), whereas [^{18}F]FLT uptake did not differ significantly between the two tumor models. OCIP51 mice treated with nal-IRI maintained significantly lower levels of hypoxia ($p = 0.0003$), smaller hypoxic fractions ($p = 0.003$), and smaller tumor volumes ($p = 0.03$) throughout the entire study, compared to the controls, and compared to the baseline characteristics. Differences in [^{18}F]FAZA uptake were detectable 8 days before any significant change in tumor volume. OCIP19 mice also responded to therapy, but significance was reached only after 4 doses of nal-IRI. Moreover, for this model, tumor volume was controlled, but not accompanied by any reduction in hypoxia or hypoxic fraction. [^{18}F]FLT uptake was comparable between both tumor models and between treated and untreated animals at any given time point. However, for OCIP51 the tumor response in treated animals was accompanied by a reduction in the proliferative fraction ($p = 0.0273$) compared to the baseline levels. Conclusions: In this study, nal-IRI reduced tumor volume in high hypoxic tumors (OCIP51) but not in low hypoxic tumors (OCIP19), suggesting that tumor hypoxia modulation might be a key mechanism through which nal-IRI acts, and potentially that tumors with a hypoxic microenvironment are more sensitive to nal-IRI. [^{18}F]FAZA imaging of hypoxia also provided early prediction of treatment response, showing a significant reduction in the levels of hypoxia 8 days prior to significant changes in tumor volume.

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Comorbidity, age and overall survival in patients with advanced pancreatic cancer – Results from NCIC CTG PA.3: A phase III trial of gemcitabine plus erlotinib or placebo

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ABSTRACT

Background: The effect of comorbidity, age and performance status (PS) on treatment of advanced pancreatic cancer is poorly understood. We examined these factors as predictors of outcome in advanced pancreatic cancer patients treated with gemcitabine +/− erlotinib.

Patients and methods: Comorbidity was evaluated by two physicians using the Charlson Comorbidity Index (CCI) and correlated with clinical outcome data from the NCIC Clinical Trials Group (NCIC CTG) PA.3 clinical trial.

Results: Five hundred and sixty-nine patients were included; 47% were ⩾65 years old, 36% had a comorbidity (CCI > 0). In multivariate analysis, neither age ($p = 0.22$) nor comorbidity ($p = 0.21$) were associated with overall survival. The baseline presence of better PS and lower pain intensity scores were associated with better overall survival ($p < 0.0001$ and $p = 0.01$, respectively). An improvement in survival with the addition of erlotinib therapy was seen in patients age <65 (adjusted hazard ratio (HR) 0.73, $p = 0.01$) or in the presence of a comorbidity (adjusted HR 0.72, $p = 0.03$). However, neither age nor CCI score were predictive of erlotinib benefit after test for interaction. Patients treated with gemcitabine plus erlotinib who were ⩾65 years of age or those with comorbidity had a higher rate of infections ⩾grade 3.

Conclusion: Low baseline pain intensity and better PS were associated with improved overall survival, while age and comorbidity were not independent prognostic factors for patients treated with gemcitabine-based therapy.

1. Introduction

Pancreatic cancer is a significant problem worldwide. It ranks ninth versus seventh in incidence, and fourth versus fifth in cancer-related mortality in the United States[1] and Europe,[2] respectively. Despite efforts to improve therapeutic strategies, prognosis is dismal with a 5 year overall survival (OS) of 5.5%.[3] Over the past decade, pancreatic cancer incidence has

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increased for both sexes and 53% of patients have metastatic disease at presentation.[3] Primarily a disease of the elderly, the median age at diagnosis is 72 years and 68% of patients are ⩾65 years of age.[3] With an aging population, pancreatic cancer incidence is expected to increase by 55% over the next 20 years.[4]

Despite their predominance among cancer patients generally, the elderly remain underrepresented in clinical trials.[5,6] Evidence suggests that patients aged ⩾65 years of age can benefit from experimental treatments and do not experience greater treatment-related mortality.[5,6] Though information is limited regarding the benefit and tolerance of chemotherapy in elderly patients with pancreatic cancer, small retrospective studies suggest that the elderly derive benefit from gemcitabine and do not experience greater toxicity.[7–9] In addition to advanced age, the influence of comorbidity on treatment effects is poorly understood. Elderly patients have a higher incidence of comorbidities, yet elderly patients included in clinical trials are generally free of significant comorbidity and therefore may not be representative of the wider population with cancer.[10]

Although various methods exist to measure comorbidity in cancer patients, the Charlson Comorbidity Index (CCI) is the most widely recognized and has been shown to have prognostic value in breast, head and neck, prostate, lung and colorectal cancers.[11–15] The index includes 19 medical conditions with weighted scores (1–6), which is based on the relative risk of death within 12 months. The total comorbidity score is represented by the sum of these weighted scores.[14] In pancreatic cancer, there has been little investigation into the interaction between comorbidity and outcome in patients receiving chemotherapy. Aside from the association between performance status (PS) and outcome, little is known about prognostic factors in advanced pancreatic cancer.[16–20]

The independent ability of age, comorbidity and PS to predict outcome in pancreatic cancer is poorly understood, but of clinical importance. Herein we explore this relationship in the NCIC Clinical Trials Group (NCIC CTG) PA.3 clinical trial.

2. Patients and methods

2.1. Patients

Five hundred and sixty-nine patients with locally advanced or metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine plus either erlotinib or a matched placebo as previously described.[21] Prior chemotherapy was not permitted, except for fluorouracil or gemcitabine given concurrently as a radiosensitizer with radiotherapy for local disease. Other eligibility included histologic or cytologic evidence of adenocarcinoma of the pancreas, measurable or evaluable disease, ECOG performance status 0, 1, or 2 and adequate hematologic, renal and hepatic function. Patients were randomly assigned to gemcitabine plus erlotinib (Gemcitabine 1000 mg/m^2 was given by 30-minute intravenous infusion on days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest in cycle one (8 weeks), and on days 1, 8 and 15 in all subsequent 4-week cycles; erlotinib was taken orally at 100 or 150 mg/d) (n = 285) or gemcitabine (identical schedule as above) plus placebo (n = 284). Treatment was continued until disease progression or unmanageable toxicity. The primary analysis has been reported, demonstrating a statistically significant prolongation of overall survival and progression free survival in favor of gemcitabine plus erlotinib.

2.2. Comorbidity, toxicity and response to therapy

A CCI score was retrospectively determined for each patient by two physician reviewers (independently) using baseline medical conditions and medications. Discrepancies in CCI scoring between the two reviewers were resolved by review of the patient chart and a generation of a consensus CCI score. A diagnosis of diabetes (insulin dependent, non-insulin dependent and diet controlled) and concomitant medications including statins and diabetic therapies were also recorded by chart review for each patient by one of the physician reviewers. Adverse events have been previously and prospectively graded using the National Cancer Institute Common Toxicity Criteria (CTC) toxicity scale, version 2. PS was graded using the Eastern Cooperative Oncology Group (ECOG) scale. Responses and progression were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST). Pain intensity was measured using a visual analog scale (0–100), with lower scores indicative of lower pain intensity.[22]

2.3. Statistical analysis

Overall survival was defined as the time from randomization until death from any cause and analyzed in an intent-to-treat fashion. Progression-free survival was defined as the time from randomization until the first objective observation of disease progression or death from any cause.

Variables of patient age and CCI score were dichotomized; age <65 versus ⩾65 and CCI score 0 (no comorbidity) versus >0 (comorbidity), with higher scores indicative of greater comorbidity. Chi-square test was used to assess the association between age groups and baseline patient, disease and treatment characteristics such as gender, race, ECOG PS, pain intensity and treatment allocation. Similar analyses were performed for the association between comorbidity groups and baseline patient, disease and treatment characteristics. The predictive effect of age and comorbidity on overall survival was assessed by log-rank test in univariate analysis and Cox regression models in multivariate analysis, respectively.

3. Results

3.1. Baseline age and comorbidity scoring

Of the 569 patients, 47% (N = 268) were ⩾65 years old and 36% (N = 202) had comorbidities (Tables 1 and 2). 31.1% had a CCI = 1 and 4.2% had a CCI = 2. Only one patient included in the analysis had a CCI > 2. The two physician reviewers differed in CCI scoring 51 patient charts and consensus scores were reached after review of these charts.

Table 1 – Baseline patient and disease characteristics by age.

Characteristics	Age < 65 (*n* = 301) no. (%)	Age ≥ 65 (*n* = 268) no. (%)	*p*-Value (univariate)
Treatment			
Erlotinib + gemcitabine	154 (51)	131 (49)	0.62
Gemcitabine	147 (49)	137 (51)	
Gender			
Female	138 (46)	133 (50)	0.40
Male	163 (54)	135 (50)	
Race			
White	256 (85)	244 (91)	0.13
Black	9 (3)	4 (2)	
Indian subcontinent	2 (1)	1 (0)	
Oriental	21 (7)	16 (6)	
Other	12 (4)	3 (1)	
Unknown	1 (0)	0 (0)	
ECOG PS			
0	102 (34)	68 (25)	0.009
1	136 (45)	156 (58)	
2	62 (21)	44 (16)	
Missing	1 (0)	0 (0)	
Pain intensity			
≤20	130 (43)	128 (48)	0.31
>20	163 (54)	133 (50)	
Missing	8 (3)	7 (3)	

Table 2 – Baseline patient and disease characteristics by comorbidity score.

Characteristics	Charlson Comorbidity Index (CCI) = 0 (*n* = 367) no. (%)	CCI > 0 (*n* = 202) no. (%)	*p*-Value (univariate)
Treatment			
Erlotinib + gemcitabine	185 (50)	100 (50)	0.86
Gemcitabine	182 (50)	102 (50)	
Gender			
Female	180 (49)	91 (45)	0.34
Male	187 (51)	111 (55)	
Race			
White	327 (89)	173 (86)	0.09
Black	6 (2)	7 (4)	
Indian subcontinent	1 (0)	2 (1)	
Oriental	26 (7)	11 (5)	
Other	6 (2)	9 (5)	
Unknown	1 (0)	0 (0)	
ECOG PS			
0	112 (31)	58 (29)	0.81
1	185 (50)	107 (53)	
2	70 (19)	36 (18)	
Missing	0 (0)	1 (1)	
Pain intensity			
≤20	162 (44)	96 (48)	0.53
>20	194 (53)	102 (51)	
Missing	11 (3)	4 (2)	
Age			
Years – median (range)	62.3 (36.4–88.9)	66.1 (36.1–92.4)	0.01
<65	209 (57)	92 (46)	
≥65	158 (43)	110 (54)	

Table 3 – Analysis of outcomes by age and comorbidity (all patients).

	Univariate analysis			Multivariate analysis*	
	Median survival (months) (95% confidence interval (CI))	Hazard ratio (95% CI)	Log-rank p-Value	Hazard ratio (95% CI)	p-Value from Cox regression
Overall survival					
<65 years (n = 301)	6.24 (5.45–7.13)	1.00 (NA–NA)	NA	1.00 (NA, NA)	NA
Age ⩾ 65 years (n = 268)	5.98 (5.42–6.60)	1.11 (0.93–1.32)	0.26	1.12 (0.93–1.35)	0.22
Comorbidity score = 0 (n = 367)	6.14 (5.78–7.00)	1.00 (NA–NA)	NA	1.00 (NA–NA)	NA
Comorbidity score > 0 (n = 202)	5.91 (4.90–6.87)	1.15 (0.95–1.38)	0.15	1.13 (0.93–1.37)	0.21
Performance status < 2 (n = 462)	6.64 (6.11–7.29)	1.00 (NA–NA)	NA	1.00 (NA–NA)	NA
Performance status = 2 (n = 106)	4.07 (3.12–4.60)	0.52 (0.42–0.65)	<0.0001	0.54 (0.43–0.68)	<0.0001
Baseline pain intensity status ⩽ 2 (n = 258)	6.77 (6.01–7.62)	1.00 (NA–NA)	NA	1.00 (NA–NA)	NA
Baseline pain intensity status > 20 (n = 296)	5.36 (4.80–6.18)	1.33 (1.11–1.60)	0.002	0.79 (0.65–0.95)	0.01

* Adjusting for treatment (erlotinib plus gemcitabine versus gemcitabine), gender (female versus male), race (white versus others), performance status (0 and 1 versus 2), baseline pain intensity (⩽20 versus >20). NA= Not applicable.

3.2. Baseline diabetes, metformin therapy, insulin therapy and statin therapy

Thirty percent (*N* = 175) of patients had a baseline diagnosis of diabetes mellitus, 26% (*N* = 46) were using metformin and 46% (*N* = 81) were using insulin therapy (Table 5). Ten percent (*N* = 60) of patients were using statin therapy at enrollment.

3.3. Association between age and comorbidity and other baseline characteristics

Significantly more older age patients (⩾65 years) had ECOG PS > 0 (odds ratio (OR) 1.51, $p = 0.009$) and had comorbidity (OR 1.58, $p = 0.01$) (Tables 1 and 2).

3.4. Age, comorbidity, PS and overall survival

Assessment of all patients in this trial revealed that age was not significantly associated with overall survival in univariate analysis (median 6.0 versus 6.2 months for ⩾65 versus <65; hazard ratio (HR) 1.11 [95% confidence interval (CI) 0.93–1.32], $p = 0.26$) or multivariate analysis (HR 1.12 for ⩾65 versus <65, [95% CI 0.93–1.35], $p = 0.22$) (Fig. 1, Table 3). Similarly, comorbidity was not significantly associated with overall survival in univariate analysis (median 5.9 versus 6.1 months for CCI > 0 versus 0; HR 1.15 [95% CI 0.95–1.38], $p = 0.15$) or multivariate analysis (HR 1.13 for CCI > 0 versus 0 [95% CI 0.93–1.37], $p = 0.21$) (Fig. 2, Table 3). Lower baseline PS (HR 0.54 for PS 0 or 1 versus 2, [95% CI 0.43–0.68], $p < 0.0001$) and pain intensity (HR 0.79 for intensity ⩽20 versus >20, [95% CI 0.65–0.95], $p = 0.01$) were significantly associated with better overall survival in multivariate analysis (Table 3).

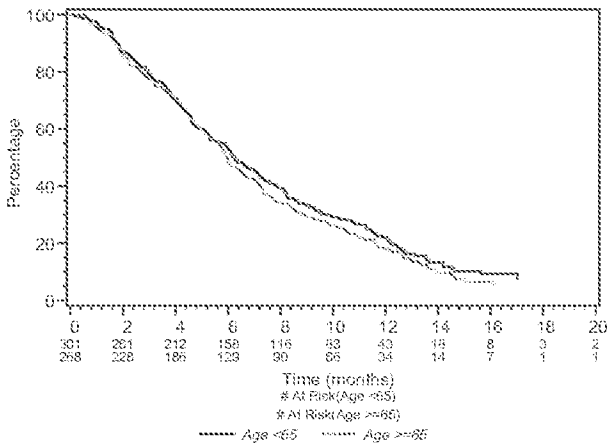

Fig. 1 – Kaplan–Meier curves for overall survival by age groups.

In multivariate analysis, the addition of erlotinib therapy was associated with improved overall survival in patients ⩽65 years old (median 6.4 versus 6.0 months; adjusted HR 0.73 [95% CI 0.56–0.94], $p = 0.01$), whereas a survival improvement from the addition of erlotinib therapy was not seen in patients >65 years (median 6.0 versus 5.9 months, adjusted HR 0.99 [95% CI 0.75–1.29], $p = 0.92$) (Table 4). Interaction testing showed a trend toward significance for age as a predictor of overall survival benefit from the addition of erlotinib therapy (adjusted HR 1.39 [95% CI 0.96–2.00], $p = 0.08$).

In multivariate analysis, the addition of erlotinib therapy was associated with improved overall survival for patients

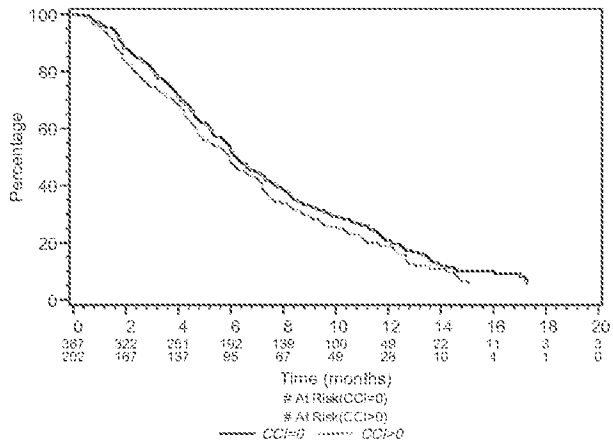

Fig. 2 – Kaplan–Meier curves for overall survival by comorbidity groups.

with comorbidity (median 6.5 versus 5.5 months, HR 0.72 [95% CI 0.53–0.97], $p = 0.03$), whereas a survival benefit from the addition of erlotinib was not demonstrated in patients with CCI = 0 (median 6.2 versus 6.1 months; adjusted HR 0.91 [95% CI 0.72–1.15], $p = 0.43$) (Table 4). However, as a predictive biomarker of overall survival benefit from erlotinib therapy, comorbidity did not achieve statistical significance from the test of interaction (adjusted HR 0.77 [95% CI 0.53–1.13], $p = 0.18$). In the gemcitabine plus erlotinib group a relative dose intensity higher than 90% was noted in 73.4% versus 78.3% of patients >65 versus ≤65 years of age, respectively ($p = 0.19$).

In multivariate analysis, the addition of erlotinib therapy was associated with improved survival in patients with a PS = 2 (median 4.6 versus 3.22 months; adjusted HR 0.60 [95% CI 0.40–0.91], $p = 0.02$) or those with a baseline pain intensity score of ≤20 (median 7.46 versus 6.21 months; adjusted HR 0.67 [95% CI 0.51–0.88], $p = 0.004$), while no significant association was found for patients with PS = 0 or 1 or with baseline intensity score >20 (Table 4). There was a trend to significance for PS or baseline pain intensity as a predictive factor for survival from the test of interaction (adjusted interaction $p = 0.07$ for both).

3.5. *Diabetes mellitus, therapy with metformin, insulin, or statins and overall survival*

In multivariate analysis, the presence of diabetes was not significantly associated with overall survival (HR 1.21 for presence versus absence of diabetes, [95% CI 0.99–1.47], $p = 0.058$) (Table 5). Statin usage was also not significantly associated with overall survival (HR 0.87 for statin use versus no statin use, [95% CI 0.64–1.17], $p = 0.35$).

In patients on the gemcitabine plus placebo arm, diabetes at baseline was associated with a worse overall survival (HR 1.33 for presence versus absence of diabetes, [95% CI 1.02–1.74]; $p = 0.04$), whereas diabetes was not significantly associated with OS in patients on the gemcitabine plus erlotinib arm (HR 1.05 for presence versus absence of diabetes, [95% CI 0.78 1.39]; $p = 0.76$) (Table 5). Diabetes at baseline was not a significant predictor of overall survival benefit from the addition of erlotinib therapy by interaction testing (adjusted HR 0.74 [95% CI 0.50–1.10], $p = 0.14$). In the patients with diabetes, neither metformin nor insulin therapy were significantly associated with OS (HR 0.78 for metformin use versus no metformin use, [95% CI 0.53–1.15], $p = 0.20$ and HR 1.08 for insulin use versus no insulin use, [95% CI 0.77–1.51], $p = 0.66$).

Table 4 – Analysis of outcomes by age, comorbidity and treatment.

Group	Erlotinib plus gemcitabine		Gemcitabine plus placebo			
	N	Median overall survival (OS) (months) (95% confidence interval (CI))	*N*	Median OS (months) (95% CI)	Hazard ratio (95% CI)	*p*-Value
Age < 65	154	6.37 (5.91, 7.92)	147	6.01 (4.63, 7.16)	0.73 (0.56, 0.94)	0.01
Age ≥ 65	131	6.01 (5.39, 7.20)	137	5.91 (4.83, 6.93)	0.99 (0.75, 1.29)	0.92
Comorbidity score = 0	185	6.24 (5.78, 7.36)	182	6.11 (5.29, 7.26)	0.91 (0.72, 1.15)	0.43
Comorbidity score > 0	100	6.54 (5.16, 7.49)	102	5.52 (4.24, 6.28)	0.72 (0.53, 0.97)	0.03
Performance status < 2	230	6.74 (6.01, 7.69)	232	6.54 (5.91, 7.29)	0.92 (0.75, 1.13)	0.42
Performance status = 2	54	4.60 (3.35, 5.95)	52	3.22 (2.37, 4.21)	0.60 (0.40, 0.91)	0.02
Baseline pain intensity ≤20	131	7.46 (6.08, 9.10)	127	6.21 (5.42, 7.33)	0.67 (0.51, 0.88)	0.004
Baseline pain intensity > 20	145	5.65 (4.83, 6.37)	151	5.11 (4.40, 6.54)	0.98 (0.77, 1.26)	0.89

Table 3 – Diabetes and concomitant medications and overall survival (OS)

Group	All patients				Gemcitabine plus erlotinib				Gemcitabine plus placebo			
	N	Median OS (months) (95% confidence interval (CI))	Hazard ratio (95% CI)	p-Value	N	Median OS (months) (95% CI)	Hazard ratio (95% CI)	p-Value	N	Median OS (months) (95% CI)	Hazard ratio (95% CI)	p-Value
Diabetes												
Yes	175	5.91 (4.70–6.87)	1.21 (0.99–1.47)	0.058	83	6.64 (5.42–8.21)	1.05 (0.78–1.39)	0.762	92	4.70 (4.04–6.28)	1.33 (1.02–1.74)	0.037
No	334	6.14 (5.78–7.00)			202	6.11 (5.75–7.20)			132	6.21 (5.36–7.26)		
Statins												
Yes	60	6.52 (4.90–8.12)	0.87 (0.64–1.17)	0.352	31	6.87 (5.22–11.5)	0.87 (0.57–1.32)	0.506	29	6.21 (3.58–8.12)	0.87 (0.57–1.33)	0.522
No	509	5.98 (5.65–6.60)			254	6.11 (5.75–7.20)			255	5.91 (5.09–6.60)		
Metformin												
Yes	46	6.52 (4.30–7.59)	0.78 (0.53–1.15)	0.206	24	7.41 (5.42–12.7)	0.61 (0.34–1.10)	0.100	22	4.17 (2.07–7.36)	1.18 (0.69–2.0)	0.550
No	129	5.91 (4.53–6.57)			59	6.08 (4.60–8.28)			70	4.93 (4.07–6.47)		
Insulin												
Yes	81	5.29 (4.27–6.57)	1.08 (0.77–1.51)	0.664	43	6.08 (4.44–8.28)	1.43 (0.85–2.41)	0.181	38	4.58 (2.53–6.47)	1.05 (0.65–1.71)	0.829
No	94	6.08 (4.83–7.20)			40	7.23 (5.65–9.10)			54	5.88 (3.71–7.06)		

Table 5 – Grade 3 to 4 adverse events of patients treated with gemcitabine and erlotinib or gemcitabine plus placebo by age group and comorbidity

Characteristic	Gemcitabine plus erlotinib						Gemcitabine plus placebo					
	Age < 65 (*n* = 152)	Age ≥ 65 (*n* = 130)	*p*-Value	Charlson Comorbidity Index (CCI) = 0 (*n* = 182)	CCI > 0 (*n* = 100)	*p*-Value	Age < 65 (*n* = 144)	Age ≥ 65 (*n* = 136)	*p*-Value	CCI = 0 (*n* = 180)	CCI > 0 (*n* = 100)	*p*-Value
Any	107 (70.4%)	103 (79.2%)	0.10	142 (78%)	68 (68%)	0.09	96 (66.7%)	97 (71.3%)	0.44	118 (65.6%)	75 (75%)	0.11
Diarrhea	7 (4.6%)	10 (7.7%)	0.32	12 (6.5%)	5 (5%)	0.80	1 (0.7%)	5 (3.7%)	0.11	3 (1.7%)	3 (3%)	0.67
Fatigue	26 (17.1%)	21 (16.2%)	0.87	28 (15.4%)	19 (19%)	0.50	29 (20.1%)	18 (13.2%)	0.15	25 (13.9%)	22 (22%)	0.10
Infection (any)	18 (11.8%)	29 (22.3%)	0.02	24 (13.1%)	23 (23%)	0.03	16 (11.1%)	23 (16.9%)	0.17	20 (11.1%)	19 (19%)	0.07
Rash	10 (6.6%)	6 (4.6%)	0.61	11 (6%)	5 (5%)	0.79	1 (0.7%)	2 (1.5%)	0.61	2 (1.1%)	1 (1%)	1.00
Stomatitis	0	1 (1%)	0.46	0	1 (1%)	0.36	0	0	NA	0	0	NA
	(0%)			(0%)			(0%)	(0%)		(0%)	(0%)	

NA = Not applicable

3.6. Age, comorbidity and toxicity

Adverse events greater or equal to grade 3 are reported in Table 6. In patients on the gemcitabine plus erlotinib arm, infections were more common in those with age ⩾65 years (22.3% versus 11.8%, $p = 0.02$) and those with a comorbidity (23.0% versus 13.1%, $p = 0.03$). Most infections were without neutropenia. No toxicity was found to be significantly different between age and comorbidity groups in patients on gemcitabine plus placebo.

4. Discussion

Since the relationship between advancing age, PS and comorbidity has not been adequately investigated in advanced pancreatic cancer, we undertook a retrospective analysis of the NCIC CTG PA.3 clinical trial to determine the role played by each of these factors as predictors of outcome. Our analysis revealed that in the total patient population on this trial, PS and baseline pain intensity were significantly correlated with survival, while neither age nor comorbidity were independent prognostic factors of overall survival in patients with advanced pancreatic cancer. Importantly, our study confirms that PS is of prognostic value even when age and comorbidity are considered. As predictive factors of benefit from the addition of erlotinib, there was a trend to significance for those patients with age <65 years, PS = 2 or pain intensity score ⩽20.

The prognostic importance of performance status and baseline pain intensity pancreatic cancer is expected and has been previously shown.[16–20,23,24] Why patients with a worse performance status may benefit more from the addition of erlotinib is not easily explained and counterintuitive. Younger patients (<65 years) also trended toward benefit from the addition of erlotinib and had fewer infections compared with older patients. Evaluation of erlotinib benefit in elderly patients with lung cancer has not revealed a differential effect based on age.[25] An analysis of the NCIC CTG Study BR.21, which compared erlotinib to placebo after failure of first or second line chemotherapy revealed that patients ⩾70 years had significantly more toxicity and less dose intensity compared with younger patients.[26] The elderly group in the gemcitabine plus erlotinib arm of our study received decreased but statistically not significant dose intensity, however this may have resulted in some dilution of the magnitude of benefit experienced by elderly patients.

The role of comorbidity (as measured by the CCI) has been assessed in multiple tumor sites and been shown to influence outcome in patients with lung cancer, colorectal cancer and head and neck cancer.[27–30] In pancreatic cancer, there has been limited exploration of the CCI as a prognostic factor. One study found that in the setting of pancreatic neoplasms, a higher adjusted CCI was predictive of not undergoing resection.[31] Nakai et al.[32] evaluated 237 consecutive patients with advanced pancreatic cancer and found that higher CCI was a poor prognostic factor in multivariate analysis, whereas age was not. In comparison to our study, the Nakai et al. study was significantly smaller, from a single institution, and population based, resulting in a higher proportion of patients with CCI ⩾2 (29.5% versus 4.2%). Patients with such high levels of

comorbidity may not have been considered for the NCIC CTG PA.3 trial or would not have met the eligibility criteria. It is important to note that the original validation cohort for the CCI only contained 7% with CCI ⩾2, yet CCI was still prognostic for overall survival.[14] More recently, Aldoss et al.[33] assessed the role of chemotherapy in the very elderly (>80 years) with metastatic pancreatic cancer using data from the Veterans Affairs Central Cancer Registry. Only 12% of the 440 patients identified received chemotherapy, however an improvement in median survival was noted in this group. After adjustment for baseline CCI, the administration of chemotherapy was still associated with and improved overall survival. This is in keeping with our findings that neither age nor comorbidity were predictors of response to gemcitabine-based chemotherapy. This study differs from ours in that it did not take into account the possible effect of performance status (or pain intensity) on outcomes and was population based and therefore patients had higher levels of comorbidity.

The CCI was developed using comorbidity data from 559 patients who were admitted to a medical service during a 1-month period and was initially validated in 685 breast cancer patients who were followed for ten years.[14] At 10 years, only 83 of the 685 patients had died of comorbid disease. Given the large difference in cancer specific mortality between advanced pancreatic cancer versus resected breast cancer, it is not surprising that comorbidity in our study did not influence survival. In the setting of malignancies with dismal prognoses, it is likely that lower levels of comorbidity (i.e. CCI 1 or 2) have no impact on survival. Although CCI has been validated in multiple tumor sites, it may also not be the ideal assessment of comorbidity for all tumor sites. For example, the presence of venothromboembolic disease (VTE) was shown to have prognostic value for overall survival in this trial as previously described.[34] The CCI does not include the presence of VTE as one of its weighted indices and therefore does not include all the relevant comorbidities for pancreatic cancer. Consequently, consideration should be given for the development of tumor site-specific comorbidity indices.

Due to its prevalence in pancreatic cancer and the interest in the influence of the insulin-like growth factor (IGF-1) pathway on cancer growth, we specifically assessed the affect of diabetes and diabetic therapy on overall survival. The rate of diabetes in this trial was 30%, which is consistent with other studies in pancreatic cancer patients.[35] In our study, the presence of baseline diabetes was not associated with overall survival in the entire study population, but the presence of diabetes did appear to adversely affect the outcome of patients treated with gemcitabine plus placebo. Interestingly, Okazaki et al.[35] have also shown that the presence of diabetes is a negative prognostic factor in pancreatic cancer patients receiving neoadjuvant chemotherapy (gemcitabine or gemcitabine plus cisplatin) and radiation. In a recent case-control study, the use of metformin was associated with a decreased risk of pancreatic cancer, while the use of insulin or insulin secretagogues was associated with an increased risk of pancreatic cancer.[36] In our study, use of metformin was not associated with better overall survival in patients treated with chemotherapy, nor insulin use with worse survival.

Due to reports of synergism between tyrosine kinase inhibitors against the epidermal growth factor receptor and statins, we also undertook a specific analysis of the influence of concomitant statin therapy on outcome of erlotinib treated patients in our study.[37] No difference in survival was noted in the patient population using statins and randomized to the gemcitabine plus erlotinib arm. These results should be interpreted cautiously as few patients were taking statins, decreasing the ability to detect a significant association.

The toxicity profile of the gemcitabine plus erlotinib arm was significantly different when age and CCI were assessed. In fact, the rate of grade 3 or worse infections doubled for patients age ⩾65 or in the presence of comorbidity. To our knowledge, the effect of age and comorbidity on infectious risk has not previously been reported and may have important implications for monitoring of patients in clinical practice or those on clinical trials where gemcitabine plus erlotinib is the control arm.

The retrospective assessment of comorbidity in our study may influence the accuracy of CCI scoring as information collected at study enrollment was not done specifically with the CCI in mind. Similarly, a diagnosis of diabetes was obtained by chart review and did not include laboratory verification, limiting conclusions from this analysis. Finally, the limited variability of CCI scores may also affect the generalizability of our results to non-clinical trial populations with advanced pancreatic cancer. The strengths of this study include the independent assessment of comorbidity by two physician investigators, the multiple centres included in this prospective clinical trial, and the large sample size, making it the largest assessment of comorbidity in pancreatic cancer.

This study confirms the prognostic influence of PS in pancreatic cancer in the setting of age and comorbidity. While younger age may predict benefit of gemcitabine plus erlotinib, comorbidity does not. Older age and higher comorbidity scores did predict higher risk of infectious complications.

Consequently, for patients deemed suitable for systemic therapy with gemcitabine-based chemotherapy, CCI between 0 and 2 and advanced age should not be considered contraindications to receipt of therapy.

Disclosure

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Conflict of interest statement

Michael Vickers, none; John Hilton, none; Wendy Parulekar, none; Chris O'Callaghan, none; Dongsheng Tu, none; Erin Powell, honoraria – Roche, Pfizer; Timothy Asmis, Consultant, Research funding, Honoraria – Roche; Derek Jonker, Consultant (unremunerated) – Roche; Malcolm Moore, Consultant – OSI Pharma.

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ORIGINAL REPORT

Gemcitabine Plus *nab*-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial

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Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
The trial objectives were to identify the maximum-tolerated dose (MTD) of first-line gemcitabine plus *nab*-paclitaxel in metastatic pancreatic adenocarcinoma and to provide efficacy and safety data. Additional objectives were to evaluate positron emission tomography (PET) scan response, secreted protein acidic and rich in cysteine (SPARC), and CA19-9 levels in relation to efficacy. Subsequent preclinical studies investigated the changes involving the pancreatic stroma and drug uptake.

Patients and Methods
Patients with previously untreated advanced pancreatic cancer were treated with 100, 125, or 150 mg/m^2 *nab*-paclitaxel followed by gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 every 28 days. In the preclinical study, mice were implanted with human pancreatic cancers and treated with study agents.

Results
A total of 20, 44, and three patients received *nab*-paclitaxel at 100, 125, and 150 mg/m^2, respectively. The MTD was 1,000 mg/m^2 of gemcitabine plus 125 mg/m^2 of *nab*-paclitaxel once a week for 3 weeks, every 28 days. Dose-limiting toxicities were sepsis and neutropenia. At the MTD, the response rate was 48%, with 12.2 median months of overall survival (OS) and 48% 1-year survival. Improved OS was observed in patients who had a complete metabolic response on [^{18}F]fluorodeoxyglucose PET. Decreases in CA19-9 levels were correlated with increased response rate, progression-free survival, and OS. SPARC in the stroma, but not in the tumor, was correlated with improved survival. In mice with human pancreatic cancer xenografts, *nab*-paclitaxel alone and in combination with gemcitabine depleted the desmoplastic stroma. The intratumoral concentration of gemcitabine was increased by 2.8-fold in mice receiving *nab*-paclitaxel plus gemcitabine versus those receiving gemcitabine alone.

Conclusion
The regimen of *nab*-paclitaxel plus gemcitabine has tolerable adverse effects with substantial antitumor activity, warranting phase III evaluation.

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INTRODUCTION

Metastatic pancreatic ductal adenocarcinoma (PDA) is a lethal disease with approximately 6 months of median survival.[1,2] Gemcitabine is the only approved single agent, with a median survival of 5.7 months and 20% 1-year survival.[3] Except for erlotinib, all phase III trials exploring gemcitabine-based combinations have failed to improve overall survival (OS).[4] Nevertheless, a recent meta-analysis of randomized trials revealed a general survival benefit for gemcitabine-based chemotherapies for patients with good performance status.[5] Because of the moderate activity of the current standard gemcitabine and gemcitabine-based regimens,[3-7] improved therapeutic options are greatly needed.

The selection of *nab*-paclitaxel, a 130-nm albumin-bound formulation of paclitaxel particles (Celgene, Summit, NJ), in combination with the standard gemcitabine was based on a molecular profiling of PDA tumor samples,[8] in which secreted protein acidic and rich in cysteine (SPARC), an albumin-binding protein, was noted to be overexpressed. *nab*-Paclitaxel has shown antitumor activity in various advanced cancer types that overexpress SPARC,[9-11] including breast,[12-14] lung,[15,16] and melanoma.[17]

The objectives of this trial were to identify the maximum-tolerated dose (MTD) of gemcitabine

plus *nab*-paclitaxel as first-line therapy in patients with metastatic PDA and to provide efficacy and safety data to permit the planning of a possible pivotal phase III trial. Additional exploratory objectives were to evaluate SPARC and CA19-9 levels and positron emission tomography (PET) scan response in relation to efficacy. Subsequent preclinical studies in human pancreatic cancer xenografts investigated the underlying biology of the substantial clinical activity seen in this phase I/II study.

PATIENTS AND METHODS

Phase I/II Clinical Study

The study was conducted at four centers in the United States in accordance with the Declaration of Helsinki and Good Clinical Practice, Guidelines of the International Conference on Harmonization. Written informed consent was obtained from all patients before entering the study. Eligibility criteria included age ≥ 18 years and histologically or cytologically confirmed metastatic PDA with measurable disease by computed tomography scan as defined by the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.0 guidelines.[18] Patients had no previous treatment for metastatic disease. Prior adjuvant treatment with fluorouracil or gemcitabine administered as a radiation sensitizer during and up to 4 weeks after radiation therapy was allowed. If a patient received adjuvant therapy, tumor recurrence must have occurred ≥ 6 months after the last treatment. Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 and had adequate hematologic, hepatic, and renal function.

Study Design

This was an open-label phase I/II study. In the phase I portion, the primary end point was to identify the MTD and dose-limiting toxicities (DLTs) of gemcitabine (1,000 mg/m^2) followed by *nab*-paclitaxel (100, 125, or 150 mg/m^2), administered intravenously (IV) on days 1, 8, and 15, every 28 days, using the standard 3 + 3 phase I dose-escalation design.[19] Per protocol, DLTs were treatment-related toxicities during cycle 1 per National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0, including any grade 4 hematologic toxicity; grade 3 thrombocytopenia with hemorrhage; grade ≥ 3 nausea, vomiting, or diarrhea despite prophylaxis; or any grade ≥ 3 treatment-related nonhematologic toxicity, excluding alopecia and fatigue. Dose escalation was stopped when ≥ one of three patients had DLTs, and the dose below was declared the MTD. Patients continued treatment until disease progression or unacceptable toxicity. In the phase II portion, accrual continued at the MTD to ≥ 42 patients to evaluate the efficacy and safety of the combination. This clinical study also evaluated PET scan response, CA19-9, and SPARC levels in relation to antitumor activity.

Assessments

All patients who received at least one dose of study drugs were evaluated for efficacy and safety. Response was assessed by computed tomography scans at baseline and every 4 weeks on day 1 of each cycle (per RECIST v1.0); an initial response (complete [CR] or partial response [PR]) had to be confirmed at least 4 weeks later. Metabolic activity was assessed by [^{18}F]fluorodeoxyglucose (FDG) PET scans at baseline and at 6 and 12 weeks on the basis of the European Organisation for Research and Treatment of Cancer criteria by an independent investigator.[20] Safety was assessed by the incidence of treatment-related adverse events (AEs), according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0, and incidence of patients experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug. CA19-9 levels were monitored by investigators at every cycle. Archived tumor blocks, if available, were collected for SPARC analysis.

Statistical Methods for Efficacy End Points and Biomarkers

With a total of 44 patients treated at the MTD, there was ≥ 95% power of observing a serious AE that had an incidence of ≥ 7%. The percentage of patients (with 95% CI) who achieved an objective CR or PR using RECIST criteria were summarized using descriptive statistics. Disease control rate was defined as the percentage of patients with CR, PR, and stable disease (SD) ≥ 16 weeks. Progression-free survival (PFS) was defined as the time from first dose of study drug to the start of disease progression or patient death, whichever occurred first. OS was defined as the time from first dose of study drug to patient death. PFS and OS were analyzed using Kaplan-Meier methods.

To assess possible relationships between CA19-9 and efficacy outcomes, the correlation of maximum decrease from baseline in CA19-9 with survival was analyzed. SPARC immunohistochemistry was performed using a monoclonal and a polyclonal antibody and proprietary methodology. Seven tissue components including tumor cells and stromal components such as fibroblast and inflammatory cells were evaluated. For each tissue component and each antibody, three measures were recorded by two board-certified pathologists at a Clinical Laboratory Improvement Amendments laboratory: maximum intensity, percentage of cells at the maximum intensity, and overall score, providing 42 variables. All variables were standardized across patients via z-score transformation and averaged between the two pathologists. For each patient, an average z-score was calculated across variables. On the basis of the average z-scores ≥ or less than 0, patients were classified into a high- or low-SPARC group, respectively. The difference in OS between the low- and high-SPARC groups was assessed by the log-rank test, and a multivariate Cox regression model was used to assess the independent predictive power of SPARC levels. All statistical analyses for SPARC were carried out in R version 2.12.0.[21]

Preclinical Study Methods

The objectives of these preclinical studies were to evaluate tumor progression, potential changes in the pancreatic stroma, and intratumoral drug penetration.

Xenograft Establishment and Treatment

Fresh pancreatic cancer tissues obtained from 11 chemotherapy-naive patients who underwent surgery at the Johns Hopkins (JH) Hospital were propagated as subcutaneous tumors in 6-week-old female athymic nude mice as a live PancXenoBank.[22] Mice with tumor size of ~200 mm^3 were randomly assigned to four treatment groups (seven to 10 tumors/group): (1) control, (2) gemcitabine 100 mg/kg intraperitoneally (IP) on days 1 and 5 weekly for 4 weeks, (3) *nab*-paclitaxel 30 mg/kg/d IV for 5 consecutive days, and (4) gemcitabine plus *nab*-paclitaxel in the preceding regimens for 4 weeks. A response was defined as a more than 50% regression in tumor size. Animals were killed on day 28. The experimental protocol was approved by the Animal Care and Use Committee at JH University.

Immunohistochemistry

Tumors obtained at euthanasia were immediately flash frozen, and a portion of each tumor was kept in 10% formalin for paraffin embedding. The extent of stromal desmoplasia was determined by an immunohistochemistry assay for collagen I (1:500; Abcam, Cambridge, MA).[23] Stromal vascularity was assessed using an anti-CD31 antibody (1:200; Santa Cruz Biotechnologies, Santa Cruz, CA).

Quantitative Real-Time PCR

Endothelial cell content was quantified by real-time polymerase chain reaction (qRT-PCR) for murine-specific nestin (mNestin) transcripts.[24] For qRT-PCR, total RNA was isolated (RNeasy Mini Kit, Qiagen, Santa Clarita, CA), followed by cDNA production (SuperScript III First Strand synthesis kit, Invitrogen, Carlsbad, CA). Relative fold expression of mNestin was calculated using the $2^{-\Delta\Delta Ct}$ method.[25]

Gemcitabine Uptake in Tumors

Mice harboring PANC265 xenograft were treated with gemcitabine at 100 mg/kg IP on day 5 or gemcitabine 100 mg/kg on day 5 plus *nab*-paclitaxel 30 mg/kg/d IV for 5 consecutive days. Animals were killed and tumors were harvested 1 hour after the last gemcitabine dose. Gemcitabine concentrations in tumors were measured in the JH Analytic Pharmacology Core. Briefly, tumor tissue homogenates were prepared. After liquid extraction and evaporation of homogenates, the sample was dissolved in 100 μL of methanol/water (10:90, volume/volume). The analytes were separated on a YMC Jsphr M80TM C18 column (Waters, Millford, MA), and gemcitabine and dFdU (a gemcitabine metabolite) were monitored by tandem mass spectrometry.

RESULTS

Patients

A total of 67 patients were enrolled and evaluated (Table 1). All patients have discontinued therapy either because of progressive disease (48%), unacceptable toxicity without progressive disease (18%), patient discretion (17%), investigator discretion (8%), AE (8%), or other (2%). The most common treatment-related AEs that led to treatment discontinuation were neuropathy and fatigue.

MTD and DLTs

Of the first six patients treated at dose level 1 (100 mg/m^2 *nab*-paclitaxel cohort), two patients had their day 8 treatment held: one patient with a possible history of ethanol abuse had asymptomatic neutropenia (absolute neutrophil count 0.85 × 10^9 cells/L), and a 79-year-old patient had asymptomatic thrombocytopenia (platelet count 60 × 10^9 cells/L). In three of those first six patients, radiologic responses were observed. Because of the confounding factors in two patients with dose delays, the potentially promising level of antitumor activity with this regimen, and the excellent tolerability in the remaining patients, the protocol was modified to allow for a total of 20 patients at dose level 1 rather than considering this dose level as having exceeded the MTD. Subsequently, dose escalation proceeded to dose level 2 and then 3. Of the three patients at dose level 3 (150 mg/m^2 of *nab*-paclitaxel), one patient died as a result of treatment-related systemic infection (neutropenia in the presence of a biliary stent) during cycle 1, and the MTD was established at dose level 2 (125 mg/m^2 of *nab*-paclitaxel). The other two patients at dose level 3 had grade 3 AEs that were resolved (leukopenia, fatigue, and neutropenia). A total of 44 patients were enrolled at dose level 2.

Table 1. Baseline Patient Demographics and Clinical Characteristics

	nab-Paclitaxel mg/m^2					
	100 (n = 20)		125 (n = 44)		150 (n = 3)	
Characteristic	No.	%	No.	%	No.	%
Age, years						
Median	62		61		69	
Range	30-86		28-78		53-72	
Female sex	9	45	25	57	1	33
ECOG						
0	9	45	22	50	2	67
1	11	55	22	50	1	33
Site of metastatic disease						
Abdomen/peritoneal*	16	80	38	86	2	67
Liver	11	55	34	77	2	67
Liver only	1	5	2	5	1	33
Lung	5	25	18	41	1	33
Lung only	1	5	5	11	1	33
Other	10	50	12	27	1	33
No. of metastatic sites						
1	6	30	8	18	1	33
2	8	40	18	41	2	67
≥ 3	6	30	18	41	0	
CA19-9 baseline levels, n	15		37		2	
Normal†	2	13	6	16	1	50
Elevated	13	87	31	84	1	50
CA19-9 baseline, μ/mL						
Median	1,148		881		181	
Range	14-180,082		1-96,990		23-339	
Previous treatment						
Prior chemotherapy‡	3	15	10	23	1	33
Prior adjuvant therapy	3	15	10	23	1	33
With gemcitabine	1	5	5	11	0	
With capecitabine	1	5	4	9	0	
With FU	2	10	1	2	0	
With docetaxel	0		2	5	0	
With erlotinib	0		0		1	33
Time since adjuvant therapy,§ months					5	
Median	84		12			
Range	9-81		1-23			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil; *nab*, albumin bound.
*Peritoneal was not collected separately.
†Cutoff for normal range was < 37 u/mL. Approximately 10% to 15% of patients with pancreatic cancer lack Lewis antigens and thus lack the ability to secrete CA19-9.
‡There were no prior neoadjuvant therapy regimens.
§Time from last dose of prior adjuvant therapy to metastatic disease.

Efficacy Results

Survival. In patients treated at the MTD of 125 mg/m^2 of *nab*-paclitaxel (n = 44), the median PFS was 7.9 months (95% CI, 5.8 to 11.0 months), median OS was 12.2 months (95% CI, 8.9 to 17.9 months; Fig 1A), and the 1-year survival was 48%. For all 67 patients, median PFS was 7.1 months (95% CI, 5.7 to 8.0 months), with median OS of 10.3 months (95% CI, 8.4 to 13.6).

Response rate. The overall response rate (ORR) was 46% for all patients (N = 67). In the 100 (n = 20) and 125 (n = 44) mg/m^2 *nab*-paclitaxel cohorts, the response rates were 45% and 48%, respectively (Table 2). The overall disease control rate was 60% and 68%, respectively.

PET scan analysis. FDG PET scans were available for 55 patients. The median decrease in metabolic activity was 79% for all three cohorts together at 12 weeks. In the 125 mg/m^2 *nab*-paclitaxel cohort (n = 38), the reduction in FDG uptake was greater compared with the 100 mg/m^2 cohort (n = 14; 68% *v* 53%; P = .044) at 6 weeks, but not at 12 weeks (74% *v* 76%; P = .13, respectively). When PET analyses from all three cohorts were combined, patients with a complete metabolic response, defined according to the European Organisation for Research and Treatment of Cancer criteria by the absence of FDG uptake, had a significantly improved OS compared with patients without a complete metabolic response (median 20.1 *v* 10.3 months, respectively; P = .01; Fig 1B).

Treatment Exposure

Across all *nab*-paclitaxel doses, patients received 81% of the planned dose and 85% of the planned gemcitabine dose. The median number of cycles administered was 6.0 (range, 1 to 24) for all patients. Twenty-five percent of patients had a *nab*-paclitaxel dose reduction, with 20% in the 125 mg/m^2 cohort. Thirty-one percent of patients had a gemcitabine dose reduction, with 43% in the 125 mg/m^2 cohort. For all patients and in the 125 mg/m^2 cohort, 72% and 70% of patients had a *nab*-paclitaxel dose delayed, respectively, mainly due to AEs. For all patients, 73% patients had a dose delay of gemcitabine sometime in their treatment, mainly because of AEs.

Safety Results

The DLTs were sepsis and neutropenia. The most common treatment-related AEs of any grade were anemia (98%), leukopenia (91%), neutropenia (89%), thrombocytopenia (83%), fatigue (76%),

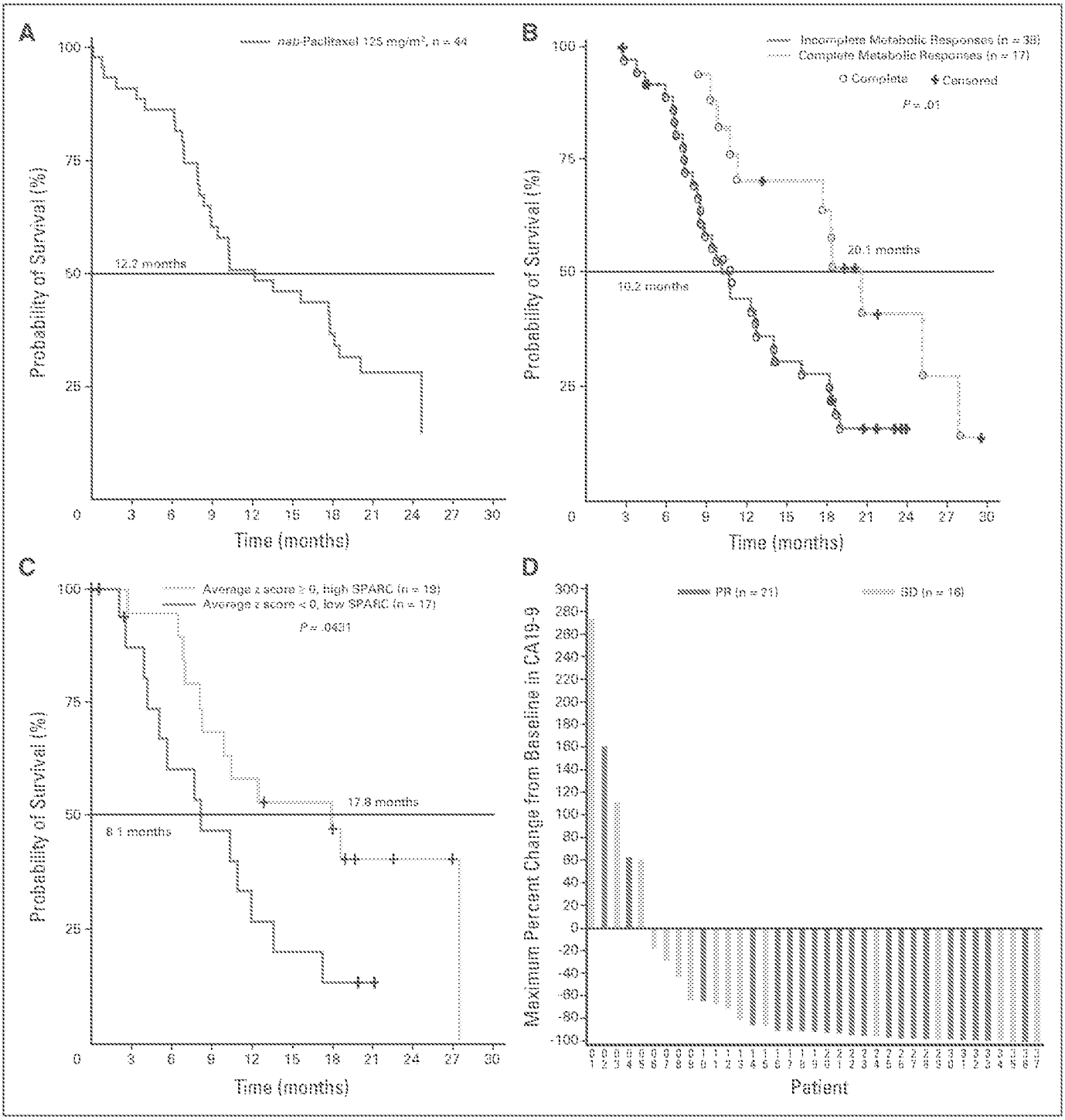

Fig 1. (A) Median overall survival in patients receiving 125 mg/m^2 of albumin-bound (*nab*) paclitaxel followed by 1,000 mg/m^2 of gemcitabine. (B) Median overall survival correlated with a complete metabolic response compared with baseline, defined according to the European Organisation for Research and Treatment of Cancer criteria by the absence of [^{18}F]fluorodeoxyglucose uptake (cohorts 1 and 2). (C) Median survival correlated with secreted protein acidic and rich in cysteine (SPARC; all cohorts). (D) Maximum percentage change in CA19-9 levels in patients receiving 125 mg/m^2 of *nab*-paclitaxel followed by 1,000 mg/m^2 of gemcitabine. PR, partial response; SD, stable disease.

alopecia (76%), sensory neuropathy (63%), and nausea (48%). Most of these treatment-related AEs were grade 1 and 2 (Table 3). Specifically, the most common grade ≥ 3 *nab*-paclitaxel–related nonhematologic AEs were fatigue (21%) and sensory neuropathy (15%). Of the grade ≥ 3 treatment-related hematologic AEs, neutropenia (67%), leukopenia (44%), and thrombocytopenia (23%) were the most common.

Biomarkers

SPARC. SPARC status was evaluated in 36 patients. Applying the average z-score algorithm to all 42 variables, patients were classified into high-SPARC (average z-scores ≥ 0, n = 19) and low-SPARC groups (average z-scores < 0, n = 17). A significant increase in OS was observed for patients in the high-SPARC group compared with patients in

Table 2. Response Rates, Disease Progression, and Disease Control Rates for All Patients and in the 125 mg/m^2 *nab*-Paclitaxel Cohort

	Dose Level 2 (n = 44)		All Dose Levels (n = 67)	
Response Result	No.	%	No.	%
Complete response	0		3	4
Partial response	21	48	28	42
Stable disease*	9	20	12	18
Progressive disease	7	16	15	22
Disease control rate†	30	68	43	64

*Stable disease was defined as ≥ 16 weeks.
†Disease control rate was defined as the percentage of patients with complete and partial response and stable disease ≥ 16 weeks.

Table 3. Selected Treatment-Related Adverse Events

	Dose Level 1 (n = 20)		Dose Level 2 (n = 44)		Dose Level 3 (n = 3)	
Adverse Events	No.	%	No.	%	No.	%
Nonhematologic events						
Diarrhea						
Grade 1	1	5	7	16	1	33
Grade 2	1	5	6	14	0	
Grade 3	3	15	1	2	0	
Grade 4	0		0		0	
Fatigue						
Grade 1	4	20	10	23	0	
Grade 2	9	45	13	30	1	33
Grade 3	1	5	12	27	1	33
Grade 4	0		0		0	
Nausea						
Grade 1	7	35	11	25	1	33
Grade 2	2	10	9	20	1	33
Grade 3	0		1	2	0	
Grade 4	0		0		0	
Sensory neuropathy						
Grade 1	5	25	15	34	0	
Grade 2	1	5	9	20	2	67
Grade 3	1	5	9	20	0	
Grade 4	0		0		0	
Vomiting						
Grade 1	1	5	10	23	1	33
Grade 2	2	10	3	7	1	33
Grade 3	0		3	7	0	
Grade 4	0		0		0	
Hematologic events						
Anemia						
Grade 1	7	35	10	23	2	67
Grade 2	11	55	27	63	1	33
Grade 3	1	5	6	14	0	
Grade 4	0		0		0	
Leukopenia						
Grade 1	2	10	6	14	1	33
Grade 2	12	60	9	21	1	33
Grade 3	4	20	16	37	1	33
Grade 4	0		8	19	0	
Neutropenia						
Grade 1	4	20	6	14	0	
Grade 2	3	15	1	2	1	33
Grade 3	8	40	11	26	2	67
Grade 4	2	10	21	49	0	
Febrile neutropenia						
Grade 1	0		0		0	
Grade 2	0		0		0	
Grade 3	1	5	1	2	0	
Grade 4	1	5	0		0	
Thrombocytopenia						
Grade 1	5	25	18	42	2	67
Grade 2	5	25	9	21	1	33
Grade 3	2	10	8	19	0	
Grade 4	1	5	4	9	0	

NOTE. One patient at dose level 3 had grade 5 sepsis.

the low-SPARC group (median OS, 17.8 *v* 8.1 months, respectively; $P = .0431$; Fig 1C). Furthermore, SPARC level remained a significant predictor for the OS in a multivariate Cox regression model after adjusting for clinical covariates, including sex, race, age, treatment, and baseline CA19-9 level ($P = .041$). Additionally, stromal SPARC was significantly correlated with OS ($P = .013$), but not SPARC in tumor cells ($P = .15$).

CA19-9 levels. Rapid decreases in CA19-9 levels were observed, with the median time to maximum decrease of 89 days. In the 125 mg/m^2 cohort, 92% evaluable patients (34 of 37) had a ≥ 20% decrease in CA19-9, 78% (29 of 37) had a ≥ 50% decrease, and 70% (26 of 37) had a ≥ 70% decrease in CA19-9. The median maximum percentage change in CA19-9 level was 91% for all patients and also for patients in the 125 mg/m^2 cohort (Fig 1D). CA19-9 levels were correlated with increased survival. Patients with ≥ 50% decrease in CA19-9 levels had a 62% ORR and 8.0 and 13.6 median months of PFS and OS, respectively, whereas those with less than 50% decrease in CA19-9 level had a 33% ORR and 3.6 and 6.5 months of PFS and OS, respectively ($P = .105$, $< .001$, and .004 for ORR, PFS, and OS, respectively).

Preclinical Study Results

Gemcitabine and *nab*-paclitaxel alone resulted in tumor regressions in two (18%) and four (36%) of 11 patient-derived xenografts, respectively. However, gemcitabine plus *nab*-paclitaxel chemotherapy resulted in tumor regressions in seven (64%) of 11 cases. The aggregate tumor regression response in individual xenografts derived from the 11 parental cases were 22 (24%) of 90, 34 (36%) of 95, and 53 (55%) of 96 for gemcitabine, *nab*-paclitaxel, and gemcitabine plus *nab*-paclitaxel, respectively (Fig 2A).

We analyzed the stromal content of two gemcitabine-resistant tumors in each of the treatment groups. Mice treated with vehicle or gemcitabine exhibited a profuse desmoplastic stroma, as demonstrated by the collagen type I fibers (Fig 2B). In contrast, *nab*-paclitaxel treatment depleted the desmoplastic stroma as evidenced by compact "back-to-back" arrangement of neoplastic glands separated by "wisps" of collagen. The reduction in stromal content was accompanied by dilated blood vessels in the tumor milieu, which were particularly prominent in the combination therapy cohort. An approximately three-fold increase in mNestin, marker of endothelial cells, was observed in xenografts receiving combination therapy as compared with control tumors, consistent with increased stromal endothelial cell content. The reduction in tumor stroma and the accompanied increase in vascularization facilitated the delivery of gemcitabine to these tumors.

The intratumor concentration of gemcitabine increased by 2.8-fold in the gemcitabine plus *nab*-paclitaxel treated tumors compared with gemcitabine-alone treated mice (Fig 2C).

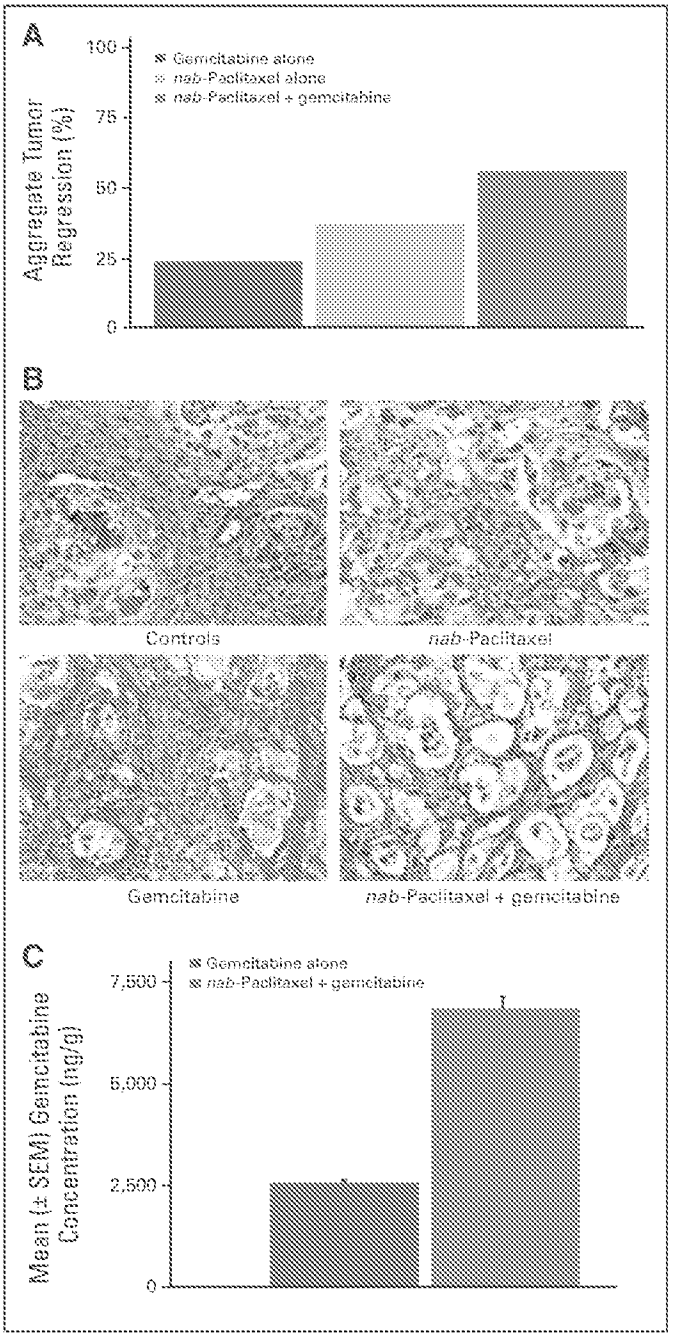

Fig 2. (A) Percentage incidence of aggregate tumor regression in response to gemcitabine, albumin-bound (*nab*) paclitaxel, and gemcitabine plus *nab*-paclitaxel in individual xenografts derived from the 11 parental cases. (B) Immunohistochemical assay for collagen type 1 fibers in a gemcitabine-resistant human pancreatic cancer xenograft treated with *nab*-paclitaxel, gemcitabine, or gemcitabine plus *nab*-paclitaxel. (C) Intratumor concentration of gemcitabine in human pancreatic cancer xenografts.

DISCUSSION

The MTD (the recommended dose for phase II) was 1,000 mg/m^2 of gemcitabine plus 125 mg/m^2 of *nab*-paclitaxel administered weekly for 3 weeks, repeated every 4 weeks. The 48% ORR, 12.2 months of OS, and 1-year survival of 48% at the MTD is among the highest reported for a phase II study in patients with PDA, including the fluorouracil, leucovorin, irinotecan, and oxaliplatin regimen,[26] which in a recent randomized phase III trial produced significantly improved survival compared with gemcitabine alone.[27] Additionally, this current study is among the first to formally assess PET scan responses in pancreatic cancer. Results showed that a complete loss of FDG metabolic activity was associated with favorable survival. In accordance with published results showing that CA19-9 is a prognostic marker for both PFS and OS,[28] decrease from baseline CA19-9 in the present study was an independent prognostic factor for OS. Overall, SPARC expression was not correlated with baseline CA19-9 levels, indicating that SPARC is a predictive marker independent of CA19-9 levels. Although an increase in SPARC level was correlated with improved OS, the significant increase was specific to elevated stromal SPARC and not SPARC in tumor cells. This is particularly important because historically, SPARC expression in the stroma, but not in the tumor, has been associated with poor survival,[29,30] suggesting that a unique mechanism of action of the present regimen may play a role in this reverse outcome. Together these observations indicate that stromal SPARC expression may be an important marker of early activity of gemcitabine plus *nab*-paclitaxel combination regimens in advanced pancreatic cancer.

The preclinical studies were subsequently initiated on the basis of the encouraging responses seen in the clinical trial. In the present preclinical study, *nab*-paclitaxel alone and in combination with gemcitabine depleted the peritumoral desmoplastic stroma, and intratumoral concentration of gemcitabine increased in mice treated with *nab*-paclitaxel versus those receiving gemcitabine alone. We speculate that reducing the dense tumor stroma, a histologic hallmark of PDA, may allow the chemotherapeutics to reach the tumor tissue more efficiently. Although these preclinical results were compelling in the athymic mouse, it has been noted that the mouse stromal cells may be transformed in the presence of human xenograft.[31,32] Other existing models of PDA (eg, *Kras* mutations that harbor similar precancerous lesions as humans) may be needed to confirm the stromal depletion seen in this model. The stromal depletion and the increased survival with SPARC expression observed in this study indicate that, in addition to intrinsic antitumor effects against the cancer cell, *nab*-paclitaxel may target stromal SPARC and facilitate delivery of chemotherapy. These data are consistent with a recent preclinical study targeting the hedgehog pathway in pancreatic cancer[23] and suggest that stroma-directed treatments may be a new treatment strategy. In particular, the antitumor activity of gemcitabine plus *nab*-paclitaxel combination therapy may, in part, be explained by the use of the albumin receptor(gp60)--caveolin-1--caveolae--SPARC pathway to increase intratumoral drug concentrations.[33]

Although the results of this clinical phase I/II study are promising, as with any nonrandomized study, patient selection may have influenced the outcome, and validation by a larger randomized trial is necessary. Given the favorable safety profile and the encouraging antitumor activity of the *nab*-paclitaxel plus gemcitabine regimen, a phase III study comparing gemcitabine plus *nab*-paclitaxel and gemcitabine alone has been initiated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked

with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

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ABSTRACT

BACKGROUND

In a phase 1–2 trial of albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine, substantial clinical activity was noted in patients with advanced pancreatic cancer. We conducted a phase 3 study of the efficacy and safety of the combination versus gemcitabine monotherapy in patients with metastatic pancreatic cancer.

METHODS

We randomly assigned patients with a Karnofsky performance-status score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status) to nab-paclitaxel (125 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter) on days 1, 8, and 15 every 4 weeks or gemcitabine monotherapy (1000 mg per square meter) weekly for 7 of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks (cycle 2 and subsequent cycles). Patients received the study treatment until disease progression. The primary end point was overall survival; secondary end points were progression-free survival and overall response rate.

RESULTS

A total of 861 patients were randomly assigned to nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median overall survival was 8.5 months in the nab-paclitaxel–gemcitabine group as compared with 6.7 months in the gemcitabine group (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 35% in the nab-paclitaxel–gemcitabine group versus 22% in the gemcitabine group at 1 year, and 9% versus 4% at 2 years. The median progression-free survival was 5.5 months in the nab-paclitaxel–gemcitabine group, as compared with 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were neutropenia (38% in the nab-paclitaxel–gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups. In the nab-paclitaxel–gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.

CONCLUSIONS

In patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased. (Funded by Celgene; ClinicalTrials.gov number, NCT00844649.)

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Pancreatic cancer is the fourth leading cause of cancer-related death in Europe and the United States.[1,2] Since 1997, gemcitabine therapy has been the standard first-line treatment for patients with unresectable locally advanced or metastatic pancreatic cancer.[3] Among patients with metastatic disease, the 5-year survival rate is only 2%,[1] and 1-year survival rates of 17 to 23% have been reported with gemcitabine.[3-5] Numerous phase 2 studies involving patients with advanced pancreatic cancer have shown promising results; however, most subsequent large phase 3 studies have not shown significantly improved survival,[6-16] with the exception of a study involving patients who received combination therapy with gemcitabine plus erlotinib, which was associated with a significant improvement in overall survival (median increase, 2 weeks),[5] and a phase 2–3 trial conducted by a French consortium study group involving patients who received oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) therapy, which was associated with a median increase in overall survival of 4.3 months.[4]

In preclinical studies, albumin-bound paclitaxel particles (nab-paclitaxel [Abraxane], Celgene) showed antitumor activity as a single agent and synergistic activity in combination with gemcitabine in murine models of pancreatic cancer.[17,18] In particular, nab-paclitaxel improved the intratumoral concentration of gemcitabine.[17,18] On the basis of preclinical evidence, a phase 1–2 clinical trial was conducted that involved previously untreated patients with metastatic pancreatic adenocarcinoma. In that study, the maximum dose of nab-paclitaxel that was associated with an acceptable level of adverse events was 125 mg per square meter of body-surface area, which was administered in combination with gemcitabine, at a dose of 1000 mg per square meter, on days 1, 8, and 15 every 4 weeks.[17] The efficacy was promising, with a median survival of 12.2 months and a manageable safety profile. In a phase 3 study, we investigated the efficacy and safety of this combination therapy.

METHODS

STUDY OVERSIGHT

The study was approved by the independent ethics committee at each participating institution and was conducted in accordance with the International Conference on Harmonisation E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki.[19] All the patients provided written informed consent before the initiation of the study.

All the authors vouch for the adherence of the study to the protocol (available with the full text of this article at NEJM.org). The first draft of the manuscript was written by the first author, with input from the trial investigators, and by clinical researchers and a biostatistician employed by the sponsor (Celgene), all of whom are authors. The authors were assisted by a medical writer who was employed by the sponsor. No one who is not an author or who is not otherwise acknowledged contributed to the manuscript. The first author made the decision to submit the manuscript for publication, which was agreed on by all the authors.

The sponsor monitored the study and provided the study drugs at no charge. The protocol was designed by the first author in collaboration with the sponsor. Data were collected by the investigators and analyzed by a statistician, employed by the sponsor, who is also an author and who vouches for the accuracy and completeness of the data reported.

PATIENTS

Eligible adults (≥18 years of age) had a Karnofsky performance-status score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status), had not previously received chemotherapy for metastatic disease, and had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas that was measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[20] Metastatic disease had to have been diagnosed within 6 weeks before randomization.

Eligible patients could have received treatment with fluorouracil or gemcitabine as a radiation sensitizer in the adjuvant setting if the treatment had been received at least 6 months before randomization. Patients who had received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting and those with islet-cell neoplasms or locally advanced disease were excluded. Patients had to have adequate he-

matologic, hepatic, and renal function (including an absolute neutrophil count of ≥1.5×10⁹ per liter, a hemoglobin level of ≥9 g per deciliter, and a bilirubin level at or below the upper limit of the normal range, according to the standards at the central laboratory).

STUDY DESIGN AND TREATMENT

In this international, multicenter, open-label, randomized, phase 3 study, we randomly assigned eligible patients, in a 1:1 ratio, to receive a 30-to-40–minute intravenous infusion of nab-paclitaxel at a dose of 125 mg per square meter, followed by an infusion of gemcitabine according to the gemcitabine label at a dose of 1000 mg per square meter, on days 1, 8, 15, 29, 36, and 43, or to receive gemcitabine alone at a dose of 1000 mg per square meter weekly for 7 of 8 weeks (cycle 1). In subsequent cycles, all patients were administered treatment on days 1, 8, and 15 every 4 weeks.

Patients were stratified according to performance status, presence or absence of liver metastases, and geographic region. Treatment continued until disease progression or until there was an unacceptable level of adverse events. Per protocol, crossover was not allowed at any time after randomization.

ASSESSMENTS

The investigators evaluated the tumor response in patients every 8 weeks by means of spiral computed tomography or magnetic resonance imaging. In addition, all scans were independently assessed by two readers and one adjudicator, all of whom were unaware of the treatment assignments, with the use of RECIST, version 1.0. Serial measurements of the carbohydrate antigen 19-9 (CA19-9) level were performed at baseline and every 8 weeks thereafter.

Safety was monitored by means of an assessment by the investigators of treatment-related adverse events and serious adverse events, weekly laboratory testing performed at a central laboratory, and the rates of dose modifications, dose delays, and premature discontinuations of the study drug. Patients were followed for survival until death or study closure.

STUDY END POINTS

The primary efficacy end point was overall survival. The secondary end points were progression-free survival and the response rate as assessed by means of independent radiographic review. Progression-free survival and response rates were also analyzed by means of investigator assessments. Additional efficacy end points included the rate of disease control (defined as stable disease for ≥16 weeks, confirmed complete response, or confirmed partial response) and the time to treatment failure. The percentages of patients with a maximum reduction in the CA19-9 level of at least 20% and at least 90% were also calculated for each treatment group.

Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and were coded and summarized according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 15.0.

STATISTICAL ANALYSIS

All efficacy analyses were carried out in the intention-to-treat population (i.e., all patients who underwent randomization). Overall survival, which was the primary efficacy end point, was analyzed with the use of the Kaplan–Meier method and a stratified log-rank test. We calculated that with a sample of 842 patients with 608 events the study would have 90% power to detect a hazard ratio for death with nab-paclitaxel plus gemcitabine versus gemcitabine monotherapy of 0.769 at a two-sided alpha level of 0.049. The power was increased from 80 to 90% in a protocol amendment before any interim analyses were performed. One planned interim efficacy analysis to assess futility was performed when at least 200 patients had been followed for 6 months or more. For the final analysis, the survival status of all patients was updated within 1 month before the data-cutoff date (September 17, 2012). Data from patients who were alive were censored for the survival analysis (see the statistical analysis plan, which is available with the protocol).

A multivariate analysis of survival was performed with the use of a Cox proportional-hazard model to evaluate the treatment effect with adjustment for stratification factors. The comparison of the response rates between the treatment groups was performed with the use of the chi-square test. The correlation between changes in

serum levels of CA19-9 and survival was evaluated by means of a Cox regression model.

RESULTS

PATIENTS AND TREATMENT GROUPS

A total of 861 patients in North America (63%), eastern Europe (15%), Australia (14%), and western Europe (9%) underwent randomization during the period from May 2009 through April 2012 at 151 community and academic centers in 11 countries. A total of 431 patients were randomly assigned to nab-paclitaxel plus gemcitabine, and 430 to gemcitabine alone (intention-to-treat population). A total of 421 patients received nab-paclitaxel plus gemcitabine, and 402 received gemcitabine (treated population) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). All demographic and clinical characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

Overall Survival

The survival analysis was based on 692 deaths (80% of patients), including 333 in the nab-paclitaxel–gemcitabine group (77%) and 359 in the gemcitabine group (83%). In the intention-to-treat population, the median survival was 8.5 months (95% confidence interval [CI], 7.89 to 9.53) with nab-paclitaxel plus gemcitabine, as compared with 6.7 months (95% CI, 6.01 to 7.23) with gemcitabine

Table 1. **Characteristics of the Patients at Baseline.***

Characteristic	nab-Paclitaxel plus Gemcitabine (N = 431)	Gemcitabine Alone (N = 430)	Total (N = 861)
Age			
No. of yr			
Median	62	63	63
Range	27–86	32–88	27–88
Distribution — no. (%)			
<65 yr	254 (59)	242 (56)	496 (58)
≥65 yr	177 (41)	188 (44)	365 (42)
Sex — no. (%)			
Female	186 (43)	173 (40)	359 (42)
Male	245 (57)	257 (60)	502 (58)
Race or ethnic group — no. (%)†			
Asian	8 (2)	9 (2)	17 (2)
Black	16 (4)	16 (4)	32 (4)
White	378 (88)	375 (87)	753 (87)
Hispanic	25 (6)	26 (6)	51 (6)
Other	4 (1)	4 (1)	8 (1)
Region — no. (%)			
Australia	61 (14)	59 (14)	120 (14)
Eastern Europe	64 (15)	62 (14)	126 (15)
North America	268 (62)	271 (63)	539 (63)
Western Europe	38 (9)	38 (9)	76 (9)
Karnofsky performance-status score — no./total no. (%)‡			
100	69/429 (16)	69/429 (16)	138/858 (16)
90	179/429 (42)	199/429 (46)	378/858 (44)
80	149/429 (35)	128/429 (30)	277/858 (32)
70	30/429 (7)	33/429 (8)	63/858 (7)
60	2/429 (<1)	0/429	2/858 (<1)

Table 1. (Continued.)

Characteristic	nab-Paclitaxel plus Gemcitabine (N=431)	Gemcitabine Alone (N=430)	Total (N=861)
Pancreatic tumor location — no. (%)			
Head	191 (44)	180 (42)	371 (43)
Body	132 (31)	136 (32)	268 (31)
Tail	105 (24)	110 (26)	215 (25)
Unknown	3 (1)	4 (1)	7 (1)
Site of metastatic disease — no. (%)			
Liver	365 (85)	360 (84)	725 (84)
Lung	153 (35)	184 (43)	337 (39)
Peritoneum	19 (4)	10 (2)	29 (3)
No. of metastatic sites — no. (%)			
1	33 (8)	21 (5)	54 (6)
2	202 (47)	206 (48)	408 (47)
3	136 (32)	140 (33)	276 (32)
>3	60 (14)	63 (15)	123 (14)
Level of carbohydrate antigen 19-9 — no./total no. (%)			
Normal§	60/379 (16)	56/371 (15)	116/750 (15)
ULN to <59× ULN	122/379 (32)	120/371 (32)	242/750 (32)
≥59× ULN	197/379 (52)	195/371 (53)	392/750 (52)
Carbohydrate antigen 19-9 — U/ml¶			
Median	2293.7	2759.2	2469.7
Range	1.0–6,159,233.0	0.3–12,207,654.2	0.3–12,207,654.2
Previous therapy — no. (%)			
Radiation therapy	19 (4)	11 (3)	30 (3)
Chemotherapy	23 (5)	12 (3)	35 (4)
Whipple procedure	32 (7)	30 (7)	62 (7)
Biliary stent	80 (19)	68 (16)	148 (17)

* There were no significant between-group differences at baseline. The term nab-paclitaxel denotes 130-nm albumin-bound paclitaxel, and ULN upper limit of the normal range.
† Race or ethnic group was self-reported.
‡ Karnofsky performance-status scores range from 0 to 100, with higher scores indicating better performance status. Two patients in the nab-paclitaxel–gemcitabine group had a score of 70 or more at the screening visit but a score of 60 at the baseline visit on day 1 of cycle 1.
§ The normal range was 0 to 35 U per milliliter. Approximately 10 to 15% of patients with pancreatic cancer do not have Lewis antigens and thus do not have the ability to secrete carbohydrate antigen 19-9.
¶ Data were missing for 52 patients in the nab-paclitaxel–gemcitabine group and for 59 in the gemcitabine group.

(hazard ratio for death, 0.72; 95% CI, 0.62 to 0.83; P<0.001) (Fig. 1A).

At the time point at which 25% of the patients were alive, survival was longer in the nab-paclitaxel–gemcitabine group than in the gemcitabine group (14.8 months vs. 11.4 months). Data were censored if the patients were alive at the time of the analysis or had been lost to follow-up. Data for 23% of the patients were censored for survival in the nab-paclitaxel–gemcitabine group, as compared with data for 17% of the patients in the gemcitabine group, with a median follow-up of 9.1 months (range, 0.1 to 36.9) and 7.4 months (range, 0.0 to 31.3), respectively.

The 1-year and 2-year survival rates were significantly higher with nab-paclitaxel plus gemcitabine than with gemcitabine (Table 2). A Cox regression analysis of survival with the stratifi-

cation factors as covariates was performed. In addition to a significant treatment effect with nab-paclitaxel plus gemcitabine, with a hazard ratio for death of 0.71 (95% CI, 0.61 to 0.83; P<0.001), the Karnofsky performance-status score and the presence or absence of liver metastases were independent predictors of survival.

Figure 1 (facing page). **Kaplan–Meier Curves for Survival and Progression-free Survival in the Intention-to-Treat Population.**

The dashed line indicates the median and the solid line the time point at which 25% of the patients were alive. The term nab-paclitaxel denotes 130-nm albumin-bound paclitaxel.

Second-Line Therapy

The rate of the use of subsequent anticancer therapy was balanced between the treatment groups: 38% in the nab-paclitaxel–gemcitabine group and 42% in the gemcitabine group. A total of 27 patients (6%) in the gemcitabine group crossed over to receive a regimen that included nab-paclitaxel. When the data for survival were censored at the time of the initiation of subsequent therapy, there was significantly longer survival with nab-paclitaxel plus gemcitabine than with gemcitabine (median survival, 9.4 months vs. 6.8 months; hazard ratio for death, 0.68; 95% CI, 0.56 to 0.82; P<0.001).

Progression-free Survival

In the analysis of progression-free survival according to independent assessment, 542 patients (63%) had progression of disease or died, including 64% of the patients in the nab-paclitaxel–gemcitabine group and 62% in the gemcitabine group. There was significantly longer progression-free survival in the nab-paclitaxel–gemcitabine group than in the gemcitabine group, with a median of 5.5 months (95% CI, 4.5 to 5.9) versus 3.7 months (95% CI, 3.6 to 4.0) (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001) (Fig. 1B and Table 2). The rate of progression-free survival at 1 year was 16% in the nab-paclitaxel–gemcitabine group, as compared with 9% in the gemcitabine group. The median progression-free survival according to investigator assessment was 5.3 months (95% CI, 4.4 to 5.5) with nab-paclitaxel plus gemcitabine versus 3.5 months (95% CI, 3.2 to 3.6) with gemcitabine (hazard ratio for disease progression or death, 0.61; 95% CI, 0.52 to 0.71; P<0.001) (Fig. 1C) — a finding that was similar to that for progression-free survival according to independent review.

Time to Treatment Failure

The median time to treatment failure, according to independent review, was 5.1 months (95% CI, 4.1 to 5.5) in the nab-paclitaxel–gemcitabine group, as compared with 3.6 months (95% CI, 3.5 to 3.9) in the gemcitabine group (hazard ratio, 0.70; 95% CI, 0.60 to 0.80; P<0.001).

Overall Response Rates

The response rate according to independent review was significantly higher with nab-paclitaxel plus gemcitabine than with gemcitabine (23% [95% CI, 19 to 27] vs. 7% [95% CI, 5 to 10]; P<0.001; response-rate ratio, 3.19 [95% CI, 2.18 to 4.66]) (Table 2). Similarly, the response rate that was based on investigator assessment was significantly higher with nab-paclitaxel plus gemcitabine than with gemcitabine (29% [95% CI, 25 to 34] vs. 8% [95% CI, 5 to 11]; P<0.001; response-rate ratio, 3.81 [95% CI, 2.66 to 5.46]).

The rate of disease control (confirmed response or stable disease for ≥16 weeks), according to independent assessment, was 48% (95% CI, 43 to 53) in the nab-paclitaxel–gemcitabine group and 33% (95% CI, 28 to 37) in the gemcitabine group (rate ratio for disease control, 1.46; 95% CI, 1.23 to 1.72; P<0.001) (Table 2).

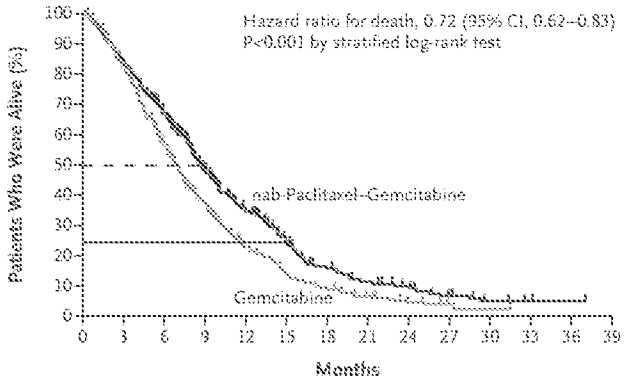
Subgroup Analyses

The treatment effect consistently favored the nab-paclitaxel–gemcitabine group across the majority of prespecified subgroups. In general, the patients with more advanced disease — those with poorer performance status (Karnofsky performance-status score of 70 or 80), the presence of liver metastasis, more than three sites of metastatic disease, metastatic pancreatic cancer at the initial diagnosis, or a CA19-9 level that was 59 times the upper limit of the normal range or higher — had the greatest reduction in the risk of death (Fig. 2A). Similar trends were observed for progression-free survival according to subgroup (Fig. 2B).

CA19-9

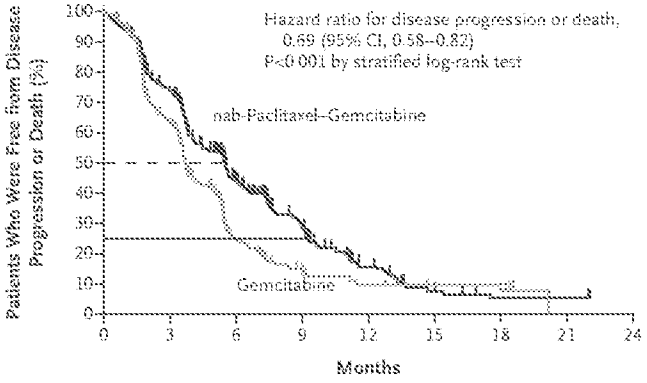
A total of 379 patients in the nab-paclitaxel–gemcitabine group and 371 patients in the gemcitabine group had a baseline CA19-9 measure-

A Overall Survival



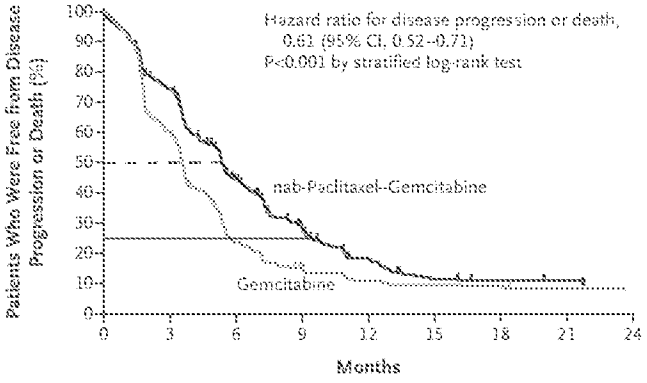
No. at Risk														
nab-Paclitaxel–Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

B Progression-free Survival, According to Independent Review



No. at Risk									
nab-Paclitaxel–Gemcitabine	431	281	122	62	24	8	4	2	0
Gemcitabine	430	209	51	23	10	6	4	0	0

C Progression-free Survival, According to Investigator Review



No. at Risk									
nab-Paclitaxel–Gemcitabine	431	288	132	64	26	8	5	3	0
Gemcitabine	430	213	54	24	9	5	4	1	0

Table 2. **Overall Survival, Progression-free Survival, and Response Rates in the Intention-to-Treat Population.**

Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N = 431)	Gemcitabine Alone (N = 430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
Overall survival				
Median overall survival — mo (95% CI)	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	<0.001
Survival rate — % (95% CI)				
6 mo	67 (62–71)	55 (50–60)		<0.001
12 mo	35 (30–39)	22 (18–27)		<0.001
18 mo	16 (12–20)	9 (6–12)		0.008
24 mo	9 (6–13)	4 (2–7)		0.02
Progression-free survival				
Median progression-free survival — mo (95% CI)	5.5 (4.5–5.9)	3.7 (3.6–4.0)	0.69 (0.58–0.82)	<0.001
Rate of progression-free survival — % (95% CI)				
6 mo	44 (39–50)	25 (20–30)		
12 mo	16 (12–21)	9 (5–14)		
Response				
Rate of objective response				
Independent review				
No. of patients with a response	99	31	3.19 (2.18–4.66)	<0.001
% (95% CI)	23 (19–27)	7 (5–10)		
Investigator review				
No. of patients with a response	126	33	3.81 (2.66–5.46)	<0.001
% (95% CI)	29 (25–34)	8 (5–11)		
Rate of disease control†				
No. of patients	206	141	1.46 (1.23–1.72)	<0.001
% (95% CI)	48 (43–53)	33 (28–37)		
Best response according to independent review — no. (%)				
Complete response	1 (<1)	0		
Partial response	98 (23)	31 (7)		
Stable disease	118 (27)	122 (28)		
Progressive disease	86 (20)	110 (26)		
Could not be evaluated‡	128 (30)	167 (39)		

* The hazard ratio for death is provided for overall survival, and the hazard ratio for progression or death is provided for progression-free survival, with a hazard ratio of less than 1 favoring the nab-paclitaxel–gemcitabine group. The response-rate ratios are provided for the response rates, with a response-rate ratio of more than 1 favoring the nab-paclitaxel–gemcitabine group. The 95% confidence interval for response-rate ratios was calculated according to the asymptotic 95% confidence interval of the relative risk in the nab-paclitaxel–gemcitabine group, as compared with the gemcitabine group.

† Disease control included confirmed complete response, confirmed partial response, and stable disease for 16 weeks or more.

‡ Included are 72 patients (17%) in the nab-paclitaxel–gemcitabine group and 87 (20%) in the gemcitabine group who did not have an assessment after the baseline visit.

ment. A total of 61% of the patients in the nab-paclitaxel–gemcitabine group, as compared with 44% of those in the gemcitabine group, had a decrease from baseline of at least 20% (P<0.001), and 31% versus 14% had a decrease of at least 90% (P<0.001). Patients in the two treatment groups who had a decrease of at least 90% in the CA19-9 level had a median survival of 13.5 months,

as compared with 8.2 months among those with a decrease of less than 90% (hazard ratio for death, 0.53; 95% CI, 0.43 to 0.67; P<0.001).

TREATMENT EXPOSURE

The median duration of treatment was 3.9 months (range, 0.1 to 21.9) in the nab-paclitaxel–gemcitabine group and 2.8 months (range, 0.1 to 21.5) in the gemcitabine group, with 32% and 15% of patients, respectively, receiving treatment for at least 6 months. In the nab-paclitaxel–gemcitabine group, 41% of the patients had reductions in the nab-paclitaxel dose and 47% had reductions in the gemcitabine dose. In total, 71% of all nab-paclitaxel doses administered during the study were at the full dose of 125 mg per square meter. The median relative dose intensity (the proportion of the administered cumulative dose relative to the planned cumulative dose) in the nab-paclitaxel–gemcitabine group was 81% for nab-paclitaxel and 75% for gemcitabine.

In the gemcitabine group, 33% of patients had dose reductions, resulting in a median relative dose intensity of 85%. The median cumulative dose of gemcitabine delivered was greater in the nab-paclitaxel–gemcitabine group than in the gemcitabine group (11,400 mg per square meter vs. 9000 mg per square meter); this difference was related to the increased duration of treatment in the nab-paclitaxel–gemcitabine group.

SAFETY

In the nab-paclitaxel–gemcitabine group, the most frequently reported nonhematologic adverse events related to treatment were fatigue (in 54% of patients), alopecia (in 50%), and nausea (in 49%). Treatment-related adverse events of grade 3 or higher that were reported more often in the nab-paclitaxel–gemcitabine group than in the gemcitabine group were neutropenia, leukopenia, fatigue, and peripheral neuropathy (Table 3). The incidences of anemia and thrombocytopenia were similar in the two groups. The incidence of febrile neutropenia was low and was similar in the two treatment groups. The incidence of peripheral neuropathy (all grades) leading to the discontinuation of nab-paclitaxel was 8%, and the incidence leading to a dose reduction was 10%.

None of the patients had grade 4 neuropathy. Among patients who received treatment for 4 months (the average treatment duration), the rate of grade 3 neuropathy was 7%. In the nab-paclitaxel–gemcitabine group, the median time to the first occurrence of grade 3 neuropathy was 140 days, and the median time to improvement from grade 3 to grade 2 was 21 days and to grade 1 or resolution of the event was 29 days. Of the patients who had grade 3 peripheral neuropathy, 44% resumed treatment at a reduced dose of nab-paclitaxel within a median of 23 days after the onset of a grade 3 event.

The proportion of patients with serious adverse events was similar in the two treatment groups (50% with nab-paclitaxel plus gemcitabine and 43% with gemcitabine). Fatal events were reported for 4% of the patients in each treatment group. Sepsis (all grades) was reported more often in the nab-paclitaxel–gemcitabine group than in the gemcitabine group (5% vs. 2%), as was pneumonitis (4% vs. 1%).

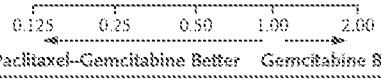
DISCUSSION

This large, randomized, international, phase 3 study showed that nab-paclitaxel plus gemcitabine led to a significant improvement in survival at all time points. In particular, the survival curves separated early, with a median improvement of 1.8 months and an improvement of 3.4 months at the time point when 25% of the patients were alive (Fig. 1A). The rate of survival was significantly higher in the nab-paclitaxel–gemcitabine group than in the gemcitabine group — by 59% at 1 year (35% vs. 22%) and by more than 100% at 2 years (9% vs. 4%). A sensitivity analysis of survival showed that the difference between the treatment groups could not be attributed to the use of second-line therapy. The treatment effect consistently favored the nab-paclitaxel–gemcitabine group across the majority of prespecified subgroups.

With respect to the secondary end points (progression-free survival and response rate) and all other efficacy end points, there were consistent, significant improvements with nab-paclitaxel plus gemcitabine, supporting the results of the primary analysis of overall survival. The improvement in progression-free survival corresponded to a 31% reduction in the risk of progression or death with nab-paclitaxel plus gemcitabine, as compared with gemcitabine. The response rate

A Overall Survival

Subgroup	nab-Paclitaxel–Gemcitabine	Gemcitabine	Hazard Ratio for Death (95% CI)
	no. of events/no. of patients		
All patients	333/431	359/430	0.72 (0.62–0.83)
Age			
<65 yr	188/254	209/242	0.65 (0.53–0.79)
≥65 yr	145/177	150/188	0.81 (0.63–1.03)
Sex			
Female	138/186	141/173	0.72 (0.57–0.93)
Male	195/245	218/257	0.72 (0.59–0.88)
Karnofsky performance-status score			
70–80	142/179	146/161	0.61 (0.48–0.78)
90–100	187/248	212/268	0.75 (0.62–0.92)
Primary tumor location			
Head	142/191	155/180	0.53 (0.46–0.75)
Other	188/237	201/246	0.80 (0.65–0.98)
Liver metastases			
Yes	290/365	309/360	0.69 (0.59–0.81)
No	43/66	50/70	0.86 (0.56–1.33)
No. of metastatic sites			
1	21/33	16/21	0.41 (0.19–0.88)
2	159/202	163/206	0.75 (0.60–0.95)
3	104/136	121/140	0.79 (0.61–1.04)
>3	49/60	59/63	0.30 (0.33–0.76)
Level of CA19-9			
Normal	47/60	43/56	1.07 (0.69–1.66)
<59× ULN	96/122	95/120	0.83 (0.61–1.12)
≥59× ULN	153/197	171/195	0.61 (0.48–0.77)
Region			
Australia	30/61	53/59	0.67 (0.44–1.01)
Eastern Europe	62/64	59/62	0.84 (0.58–1.23)
Western Europe	14/38	17/38	0.72 (0.38–1.47)
North America	207/268	230/271	0.68 (0.56–0.82)



B Progression-free Survival

Subgroup	nab-Paclitaxel–Gemcitabine	Gemcitabine	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
All patients	277/431	265/430	0.69 (0.58–0.82)
Age			
<65 yr	172/254	149/242	0.69 (0.55–0.87)
≥65 yr	105/177	116/188	0.69 (0.52–0.91)
Sex			
Female	114/186	100/173	0.79 (0.60–1.05)
Male	163/245	165/257	0.62 (0.49–0.78)
Karnofsky performance-status score			
70–80	125/179	112/161	0.65 (0.50–0.84)
90–100	150/248	146/268	0.68 (0.53–0.86)
Primary tumor location			
Head	118/191	110/180	0.53 (0.40–0.71)
Other	158/237	155/246	0.74 (0.59–0.94)
Liver metastases			
Yes	242/365	238/360	0.65 (0.54–0.78)
No	35/66	27/70	0.92 (0.54–1.58)
No. of metastatic sites			
1	17/33	17/21	0.38 (0.16–0.89)
2	130/202	118/206	0.73 (0.57–0.95)
3	89/136	88/140	0.78 (0.57–1.06)
>3	41/60	42/63	0.35 (0.21–0.59)
Level of CA19-9			
Normal	37/60	37/56	0.80 (0.47–1.36)
<59× ULN	84/122	68/120	0.71 (0.50–1.01)
≥59× ULN	126/197	133/195	0.59 (0.46–0.77)
Region			
Australia	42/61	45/59	0.60 (0.38–0.94)
Eastern Europe	47/64	49/62	0.84 (0.55–1.29)
Western Europe	21/38	19/38	0.78 (0.40–1.51)
North America	167/268	152/271	0.64 (0.51–0.80)

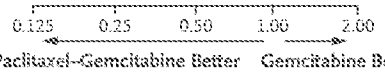


Figure 2 (facing page). **Forest Plots of the Treatment Effect on Survival and Progression-free Survival in Prespecified Subgroups.**

Karnofsky performance-status scores range from 0 to 100, with higher scores indicating better performance status. CA19-9 denotes carbohydrate antigen 19-9, and ULN upper limit of the normal range.

according to independent review was tripled with nab-paclitaxel plus gemcitabine. The results with respect to progression-free survival and response rate as assessed by the investigators were consistent with those as assessed by independent review. A higher percentage of patients in the nab-paclitaxel–gemcitabine group than in the gemcitabine group had a reduction of at least 90% in the CA19-9 level, which has been reported to be associated with an improvement in survival.[21]

Adherence to treatment and dose intensity were high with both agents and in both treatment groups. The addition of nab-paclitaxel to gemcitabine increased the cumulative delivery of gemcitabine. The longer treatment duration and greater cumulative dose in the nab-paclitaxel–gemcitabine group, as compared with the gemcitabine group, showed that this combination can be administered effectively. The suitability of the dosing regimen was confirmed by the observations that the majority of patients did not require a dose reduction and that 71% of the nab-paclitaxel doses were delivered at the starting dose of 125 mg per square meter.

The safety profile for both regimens was consistent with that in previous reports.[3,17,22] The rate of serious life-threatening adverse events was not increased with nab-paclitaxel plus gemcitabine, as compared with gemcitabine alone; adverse events were generally grade 3 or lower and resolved without specific treatment. The most notable difference in adverse events between the two treatment groups was observed

Table 3. **Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.***

Event	nab-Paclitaxel plus Gemcitabine (N = 421)	Gemcitabine Alone (N = 402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

* NA denotes not applicable, and NR not reached.
† Assessment of the event was made on the basis of laboratory values.
‡ Assessment of the event was made on the basis of investigator assessment of treatment-related adverse events.
§ Peripheral neuropathy was reported on the basis of groupings of preferred terms defined by standardized queries in the *Medical Dictionary for Regulatory Activities*.

with respect to peripheral neuropathy, which was cumulative and rapidly reversible in most patients with temporary discontinuation of nab-paclitaxel and a subsequent reduction in the dose. The incremental risks of sepsis and pneumonitis were managed by protocol amendments to increase awareness; early diagnosis and treatment of these events reduced the risk of fatal outcomes. A limitation of the study was that quality of life was not measured.

This international study was carried out at academic and community centers in North America, Europe, and Australia. The dose used in this trial was established in the phase 1–2 trial on the basis of the greatest efficacy and an acceptable adverse-event profile, and all efficacy analyses presented here were prespecified and were carried out in the intention-to-treat population. The use of randomization and the large sample resulted in well-balanced treatment groups, both overall and within strata. The estimated medians for overall survival, progression-free survival, and the response rates that were observed in the gemcitabine group fell within the ranges reported in large, phase 3 studies that have evaluated chemotherapy for the treatment of adenocarcinoma of the pancreas.[3-6,8-10,13,15,16]

Many agents that have shown promising results in phase 2 trials of pancreatic cancer fail to improve survival in phase 3 trials.[9-16] Although this phase 3 trial showed a clinically significant improvement in survival, the median survival in the nab-paclitaxel–gemcitabine group in the current trial was more than 3 months shorter than the survival observed at the same dose level in the phase 1–2 trial.[17] It should be noted that the preceding phase 1–2 study was conducted in only 4 U.S. treatment centers, whereas this multinational, phase 3 study enrolled patients at 151 centers in 11 countries.

The phase 2–3 trial of FOLFIRINOX versus gemcitabine[4] also showed a clinically meaningful improvement in survival among patients with pancreatic adenocarcinoma. The FOLFIRINOX study differed from the current study in several aspects. It pooled data from the phase 2 and 3 portions and excluded patients older than 75 years of age. In our study, 10% of the patients were at least 75 years of age. The FOLFIRINOX study also excluded patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 (on a scale from 0 to 5, with 0 indicating no symptoms and full activity and higher scores indicating increasing levels of disability), whereas 8% of the patients in our trial had a poor performance status, corresponding to an ECOG performance status of 2.[2,3] The relevance of these differences is highlighted by the results of a multivariate Cox regression analysis, in which performance status was an independent predictor of survival. Nevertheless, FOLFIRINOX improved median survival by 4.3 months over gemcitabine and is clearly an active regimen.

In conclusion, nab-paclitaxel combined with gemcitabine is superior to gemcitabine alone but causes more myelosuppression and peripheral neuropathy; however, these side effects appear to be reversible.

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First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

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Abstract LBA-1

Disclosures

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Liposomal irinotecan in patients with mPDAC

There is a need for therapies that prolong survival and are well tolerated for patients with PDAC,[1] who typically present with metastatic disease and have a poor prognosis[2]

- Established first-line treatment options for mPDAC include:
  - Gem/nab (gemcitabine + albumin-bound paclitaxel particles)[3]
  - FOLFIRINOX (non-liposomal irinotecan + 5-FU + LV + OX)[4]
- Non-liposomal irinotecan is an established component of the FOLFIRINOX combination but has a complex and rapid metabolism,[5] a short half-life,[6] and its toxicity is dose-limiting[5]
- Liposomal irinotecan (ONIVYDE® pegylated liposomal[a]) may provide additional benefits over the non-liposomal formulation
  - During circulation, 95% of irinotecan remains contained within the liposome[7]
  - The active metabolite persisted in tumours for longer following administration of liposomal irinotecan (168 h) than with non-liposomal irinotecan (< 48 h) in a preclinical setting[8]
  - Preclinical data suggest that prolonged exposure may be more important than high concentrations for cytotoxic activity[9]
- Liposomal irinotecan is indicated, in combination with 5-FU and LV, for the treatment of adults with mPDAC after disease progression following gemcitabine-based therapy[7]

[a]Historical names include nal-IRI, MM-398 and PEP02. 5-FU, 5-fluorouracil; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; OX, oxaliplatin; PI, prescribing information; SmPC, summary of product characteristics. 1. Hall BR *et al. Oncotarget* 2018;9:19396–405. 2. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. Cancer stat facts: pancreatic cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html (Accessed Jun 2020). 3. Von Hoff DD *et al. N Engl J Med* 2013;369:1691–703. 4. Conroy T *et al. N Engl J* Med 2011;364:1817–25; 5. de Man FM *et al. Clin Pharmacokinet* 2018;57:1229–54. 6. CAMPTOSAR US PI, Jan 2020. 7. ONIVYDE EU SmPC May 2020. 8. Kalra AV *et al. Cancer Res* 2014;74:7003–13. 9. Gerrits CJ *et al. Br J Cancer* 1997 76:952–62

Study objectives

This phase 1/2 study assessed liposomal irinotecan in combination with 5-FU/LV and OX ('NALIRIFOX') in treatment-naïve[a] patients with locally advanced or mPDAC

Primary objectives

- Evaluate the safety and tolerability of NALIRIFOX
- Characterize DLTs associated with NALIRIFOX and determine the recommended dose for future development

Secondary efficacy objectives

Antitumour activity

RECIST v1.1 assessment at screening (baseline), every 8 weeks until PD and at EoT

- PFS and OS
- Other clinical responses: best overall response, overall response rate, DCR at week 16, duration of response

Exploratory objectives included

Biomarkers – genomic profiling

When available, archival tumour samples were analysed for patients who had given additional consent

- Subtyped as classical or basal-like (Moffitt schema,[1] as used in COMPASS trial[2]) using PurIST[SM] RNAseq assay[3]
- PFS and best change from baseline in sum of target-lesion diameter

[a]Not previously treated in the metastatic setting.

5-FU, 5-fluorouracil; DCR, disease control rate; DLT, dose-limiting toxicity; EoT, end of treatment; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; OS, overall survival; OX, oxaliplatin; PD, progressive disease; PFS, progression-free survival; PurIST, Purity Independent Subtyping of Tumors; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid.

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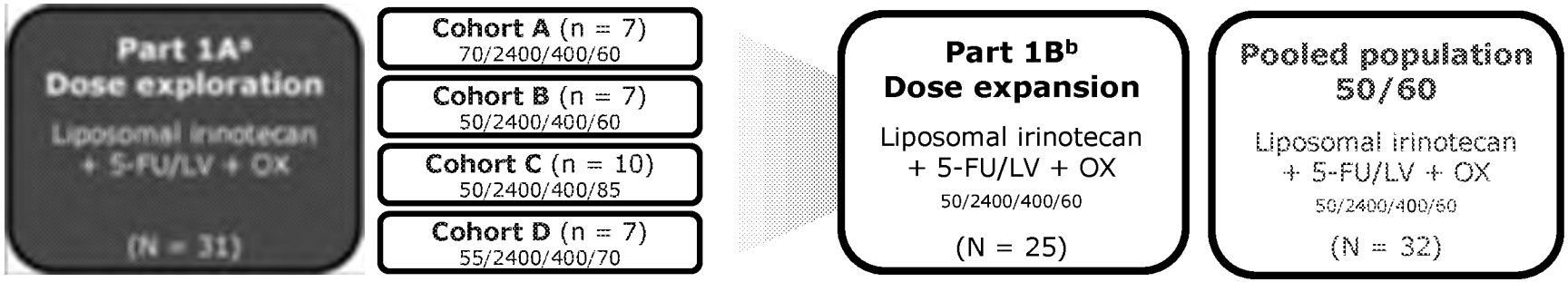
Study methods

Open-label, two-part phase 1/2 trial enrolled patients at 15 sites
Australia (1 site), Spain (4 sites) and the USA (10 sites)



- **Dose-exploration**: safety run-in (traditional 3 + 3 design) performed to confirm an appropriate dose for NALIRIFOX in the **dose-expansion** part
- **Pooled population 50/60**: all patients who received liposomal irinotecan, 50 mg/m^2 (free base), 5-FU 2400 mg/m^2, LV 400 mg/m^2 and OX 60 mg/m^2
- **Long-term follow-up results**: data cut-off 26 Feb 2020

Study drugs were administered on days 1 and 15 of each 28-day cycle
[a]Enrolled between 26 Oct 2015 and 28 Mar 2018. [b]Enrolled between 11 Jun 2018 and 29 Oct 2018.
5-FU, 5-fluorouracil; LV, leucovorin; NALIRIFOX, liposomal irinotecan+ 5-FU/LV + OX; OX, oxaliplatin

Study population

Inclusion criteria

- ≥ 18 years of age
- Histologically/cytologically confirmed PDAC
- Unresectable, locally advanced or metastatic disease
- Diagnosed ≤ 6 weeks before screening
- ≥ 1 measurable lesion using CT or MRI, defined by RECIST v1.1
- Adequate haematologic parameters and liver function
- ECOG Performance Status score 0 or 1
- KPS ≥ 70 (dose-expansion only)

Exclusion criteria

- Prior treatment of locally advanced or mPDAC (palliative radiotherapy or biliary-stent placement permitted)
- Any second malignancy in the prior 3 years
- Use of strong CYP3A4 inhibitors/inducers
- Known contraindications/hypersensitivity to any study drug
- Clinically significant GI disorder, active infection or unexplained fever > 38.5°C at screening/first dose
- Concurrent illnesses/other conditions deemed likely to interfere with the study

CT, computed tomography; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; KPS, Karnofsky Performance Score; mPDAC, metastatic pancreatic ductal adenocarcinoma; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors

Demographics, characteristics and disposition

	Dose-exploration cohorts				Dose-expansion cohort N = 25	Pooled population (50/60[a,b]) N = 32
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)		
Age (years)						
Median (range)	64 (58–78)	57 (44–74)	66.5 (57–73)	61 (54–73)	58 (39–76)	58 (39–76)
Age group, n (%)						
< 65 Years	4 (57.1)	4 (57.1)	3 (30.0)	4 (57.1)	19 (76.0)	23 (71.9)
Sex, n (%)						
Men	1 (14.3)	3 (42.9)	8 (80.0)	5 (71.4)	11 (44.0)	14 (43.8)
Race, n (%)						
White	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Tumour stage at diagnosis						
IIA[c]	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
Baseline ECOG Performance Status score						
Fully active (ECOG 0)	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
Restricted activity (ECOG 1)	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)
Disposition						
Discontinued treatment,[d] n (%)	7 (100)	7 (100)	10 (100)	7 (100)	24 (96.0)	31 (96.9)

[a]Dose of liposomal irinotecan (free base)/dose of OX expressed in mg/m^2 to be administered in combination with 5-FU 2400 mg/m^2 and LV 400 mg/m^2 every 2 weeks.
[b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and OX 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.
[c]One patient in dose-expansion cohort was diagnosed as stage IIA, but entered the treatment phase as stage IV. [d]At time of data cut-off (26 Feb 2020).
5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin; OX, oxaliplatin

Safety – overview of DLTs and TEAEs

	Dose-exploration cohorts				Dose-expansion cohort (50/60) (N = 25)	Pooled population (50/60) (N = 32)
	A (70/60) (n = 7)	B (50/60) (n = 7)	C (50/85) (n = 10)	D (55/70) (n = 7)		
Dose-limiting toxicities (DLTs)	Not tolerable (DLTs) DLTs in 2 patients: neutropaenia infection (1 patient), neutropaenic sepsis (1)	Tolerable (DLTs and cumulative safety data) DLT in 1 patient: febrile neutropaenia (1 patient)	Not tolerable (DLTs) DLTs in 2 patients: diarrhoea (2 patients), vomiting (1), anal fissure (1), anal inflammation (1), proctalgia (1)	Not tolerable (cumulative safety data: TEAEs of grade ≥ 3) No DLTs; cumulative safety data are not shown here	NA	NA
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Leading to dose discontinuation[a]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Leading to dose adjustment[a]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	6 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)[b]
Treatment-related[c]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)[d]
Treatment-related TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Treatment-related of grade ≥ 3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Treatment-related TEAE of grade ≥ 3 in at least 5% of the pooled population						
Neutropaenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Febrile neutropaenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Neutrophil count decreased	0	0	1 (10.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	2 (8.0)	3 (9.4)
Nausea	0	0	2 (20.0)	0	3 (12.0)	3 (9.4)
Vomiting	1 (14.3)	0	3 (30.0)	0	2 (8.0)	2 (6.3)
Hypokalaemia	1 (14.3)	2 (28.6)	2 (20.0)	2 (28.6)	2 (8.0)	4 (12.5)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
Alanine aminotransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
GGT increased	0	0	0	0	2 (8.0)	2 (6.3)
Lymphocyte count decreased	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

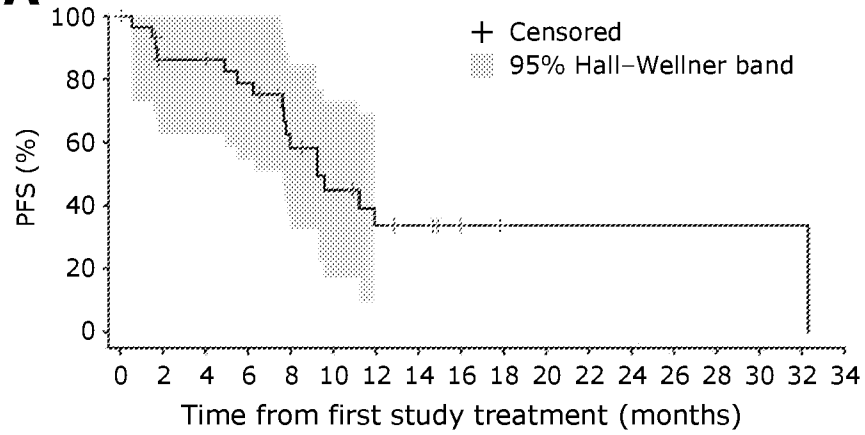
Treatment-related grade ≥ 3 peripheral sensory neuropathy present only in cohort C (1 patient); fatigue present only in cohort A (1 patient)

Data are number (%) of patients from the safety population unless otherwise stated. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. [a]Refers to discontinuation or adjustment in dose for any of the four treatments administered. [b]Malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage and disease progression, none were considered related to treatment. [c]Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing. [d]Most common were febrile neutropenia and nausea, each reported in 3 patients (9.4%). DLT, dose-limiting toxicity; GGT, gamma-glutamyltransferase; grd, grade; NA, not applicable; TEAE, treatment-emergent adverse event; TR, treatment related

Clinical response (I)

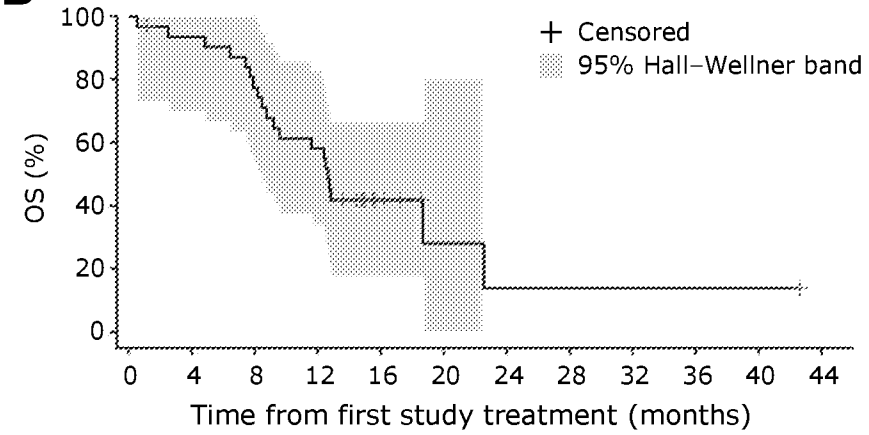
Kaplan–Meier curves for PFS (A) and OS (B): pooled population 50/60 (N = 32)

A



Median PFS: 9.2 months
[95% CI: 7.69–11.96]

B



Median OS: 12.6 months
[95% CI: 8.74–18.69]

Data are from the safety population. PFS and OS were analysed using the Kaplan–Meier method. Median [95% CI] values were calculated using the Brookmeyer–Crowley method. One patient with minimal progressive disease per RECIST v1.1 was approved for treatment continuation as the investigator believed there was a benefit from treatment. Data from this patient were censored at PD date.
CI, confidence interval; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Clinical response (II)

	Dose-exploration cohorts				Dose-expansion cohort (50/60) (N = 25)	Pooled population (50/60) (N = 32)
	A (70/60) (n = 7)	B (50/60) (n = 7)	C (50/85) (n = 10)	D (55/70) (n = 7)		
Best overall response[a]						
CR	0	0	0	0	1 (4.0)	1 (3.1)[b]
PR	0	3 (42.9)	3 (30.0)	1 (14.3)	7 (28.0)	10 (31.3)
SD	2 (28.6)	3 (42.9)	1 (10.0)	3 (42.9)	12 (48.0)	15 (46.9)
PD	1 (14.3)	0	2 (20.0)	1 (14.3)	3 (12.0)	3 (9.4)
Non-PD/non-CR[c]	1 (14.3)[c]	0	0	0	0	0
NE	3 (42.9)	1 (14.3)	4 (40.0)	2 (28.6)	2 (8.0)	3 (9.4)
Overall response rate						
(CR + PR), rate [95% CI][d]	0 [0 –41.0]	42.9 [9.9–81.6]	30.0 [6.7–65.2]	14.3 [0.4–57.9]	32.0 [14.9–53.5]	34.4 [18.6–53.2]
Disease control rate at 16 weeks						
(CR + PR + SD), rate [95% CI][e]	42.9 [9.9–81.6]	71.4 [29.0–96.3]	40.0 [12.2–73.8]	28.6 [3.7–71.0]	72.0 [50.6–87.9]	71.9 [53.3–86.3]
Duration of response[f]	(n = 0)	(n = 3)	(n = 3)	(n = 1)	(n = 8)	(n = 11)
Median, months [95% CI]	NE [NE–NE]	28.4 [3.52–NE]	NE [NE–16.39]	NE [NE–NE]	9.4 [2.20–NE]	9.4 [3.52–NE]
Rate, % [95% CI], at:						
6 months	NE [NE–NE]	66.7 [9.4–99.2]	100 [29.2–100]	0 [0–97.5]	62.5 [24.5–91.5]	63.6 [30.8–89.1]
12 months	NE [NE–NE]	33.3 [0.8–90.6]	100 [29.2–100]	0 [0–97.5]	25.0 [3.2–65.1]	27.3 [6.0–61.0]
24 months	NE [NE–NE]	33.3 [0.8–90.6]	0 [0–70.8]	0 [0–97.5]	0 [0–36.9]	9.1 [0.2–41.3]

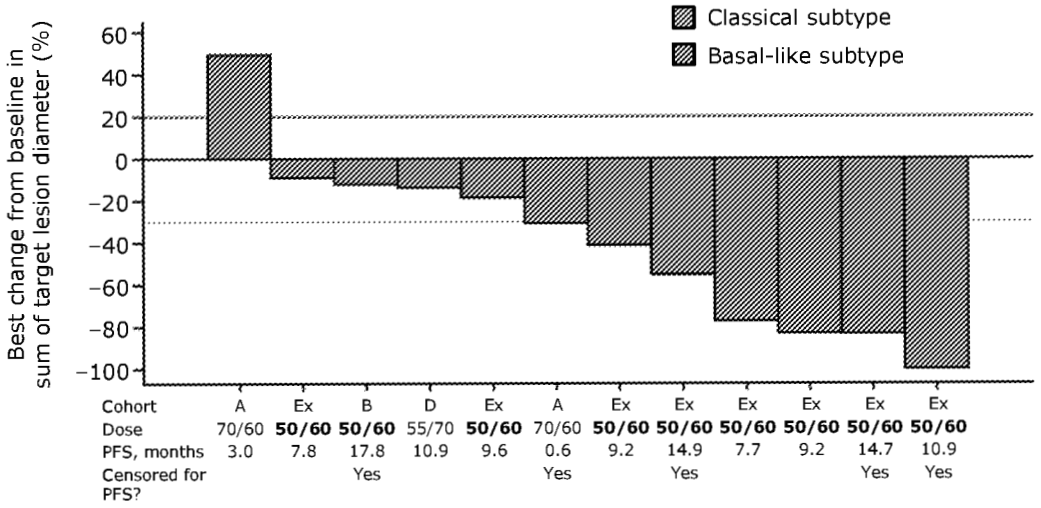
Data are from the safety population and with responses determined using RECIST v1.1 [a]Best response recorded from start of study treatment until disease progression or start of new anticancer therapy. [b]Patient received a diagnosis of locally advanced stage III disease. [c]As per the protocol at the time of their screening (version 1.0), one patient had a measurable lymph node lesion at screening that was too small to be considered a target lesion per RECIST 1.1 criteria. Consequently, this patient was only followed for NT lesions (hence non PD/non CR) but is considered in the summary of overall response. The protocol was later amended to require the presence of target lesion(s). [d]Proportion of patients with a CR or PR as the best overall response; 95% CIs were calculated using the Clopper–Pearson method. [e]Proportion of patients with CR, PR or SD at the week-16 assessment; patients who died, whose tumours were no longer assessed or who started new anticancer treatment before the week-16 assessment were not considered to have achieved disease control at week 16. [f]Time from the first date of response (CR or PR) to date of first documented radiologically determined PD per RECIST v1.1; duration of response was not calculated for patients who started a new anticancer treatment before the first response. CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Biomarkers – genomic profiling

Tumour samples were analysed for 16 patients

- Pooled population 50/60, n = 11
  - 10 in dose expansion, one in cohort B
- Cohort A (70/60), n = 3
- Cohort D (55/70), n = 1
- Plus one patient who gave consent for archived sample analysis but did not pass screening for the main study

Tumour response data were available for 12 patients



PFS in the pooled population 50/60

- Classical subtype: range 7.7–17.8 months (n = 8)
- Basal-like subtype: 9.6 months (n = 1)

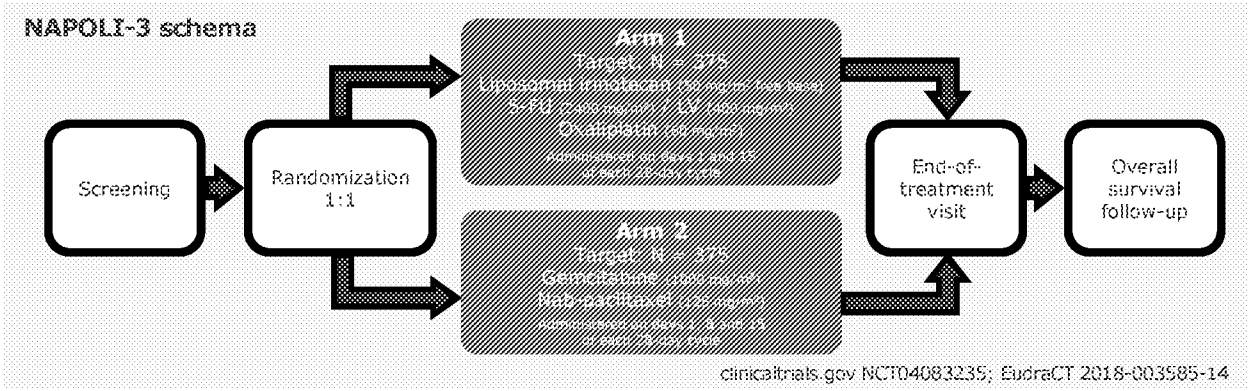
Ex, dose-expansion part; PFS, progression-free survival

Conclusions

Findings from this phase 1/2 study suggest that NALIRIFOX is tolerable for patients with previously untreated locally advanced or mPDAC

Regimen: liposomal irinotecan, 50 mg/m² (free base), 5-FU 2400 mg/m², LV 400 mg/m², OX 60 mg/m² on days 1 and 15 of each 28-day cycle

- No new safety signals were identified
- Antitumour activity (secondary outcome) was promising
  - Median PFS of 9.2 months (95% CI: 7.69–11.96)
  - Median OS of 12.6 months (95% CI: 8.74–18.69)
- The observed antitumour activity warrants further investigation
- Efficacy is the primary objective of the ongoing NAPOLI-3 phase 3 study in adults with previously untreated mPDAC



CI, confidence interval; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; NALIRIFOX, liposomal irinotecan + 5-FU/LV + OX; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; OX, oxaliplatin; PFS, progression-free survival

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First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

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BACKGROUND

- FOLFIRINOX (non-liposomal irinotecan + 5-fluorouracil [5-FU] + leucovorin [LV] + oxaliplatin)[1] is an established first-line treatment for patients with metastatic pancreatic ductal adenocarcinoma (PDAC).[2]
  - However, non-liposomal irinotecan has a complex and rapid metabolism,[3] and a short half-life,[4] and its toxicity is dose-limiting.[3]
- Liposomal irinotecan (ONIVYDE® pegylated liposomal) may provide additional benefits over the non-liposomal formulation.
  - During circulation, 95% of irinotecan remains contained within the liposome.[5]
  - The active metabolite persisted in tumours for longer following administration of liposomal irinotecan (168 h) than with non-liposomal irinotecan (< 48 h) in a preclinical setting.[6]
  - Preclinical data suggest that prolonged exposure may be more important than high concentrations for cytotoxic activity.[7]
- Liposomal irinotecan is indicated, in combination with 5-FU and LV, for the treatment of adults with metastatic PDAC after disease progression following gemcitabine-based therapy.[5]

OBJECTIVE

- To evaluate the safety, tolerability and efficacy of the NALIRIFOX regimen (liposomal irinotecan + 5-FU/LV + oxaliplatin) as a first-line treatment for patients with locally advanced or metastatic PDAC.

METHODS

Study design

- This open-label phase 1/2 study (EudraCT 2015-003086-28; NCT02551991) was conducted in two parts:
  - dose exploration using a traditional 3 + 3 design
  - dose expansion.

Study population

- Patients were adults (≥ 18 years old) with:
  - unresectable, locally advanced, or metastatic PDAC
  - diagnosis ≤ 6 weeks before screening and who were not treated previously in the metastatic setting
  - Eastern Cooperative Oncology Group Performance Status score of 0 or 1
  - Karnofsky Performance Status score ≥ 70 (dose-expansion part only)
  - adequate organ function.

Treatment regimen

- During dose exploration, patients in four cohorts were treated on days 1 and 15 of each 28-day cycle with 5-FU 2400 mg/m^2 and LV 400 mg/m^2 in combination with the following doses of liposomal irinotecan (free base) and oxaliplatin, respectively:
  - cohort A, 70 mg/m^2 and 60 mg/m^2
  - cohort B, 50 mg/m^2 and 60 mg/m^2
  - cohort C, 50 mg/m^2 and 85 mg/m^2
  - cohort D, 55 mg/m^2 and 70 mg/m^2.
- The dose selected for expansion was based on dose-limiting toxicities and cumulative safety data from dose exploration.

Endpoints and analyses

- Safety (primary objective): treatment-emergent adverse events (TEAEs); dose-limiting toxicities (dose exploration only).
- Efficacy (secondary objective): progression-free survival (PFS; primary efficacy endpoint), overall survival (OS), best overall response, overall response rate, disease control rate at week 16, and duration of response.
  - Disease was assessed using Response Evaluation Criteria in Solid Tumours v1.1 at screening, every 8 weeks thereafter, and at the end of study treatment.
  - Assessments continued until radiologically determined progressive disease; for the analyses, data could be censored before progression or death was recorded (e.g. on initiation of a new anticancer therapy).
- Exploratory objective: response data according to tumour subtype (classical or basal-like; Moffitt schema[8]) were assessed using genomic profiling of archival samples (PurIST^{SM} RNAseq assay,[9] GeneCentric Therapeutics, Inc.).
- The long-term follow-up results reported here focus on the patients who received the selected dose (pooled population receiving liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2; pooled population 50/60); data cut-off 26 February 2020.

RESULTS

Patient disposition and baseline characteristics

- Overall, 31 patients were treated during dose exploration, and the pooled population 50/60 comprised 32 patients (seven from dose exploration cohort B and 25 from dose expansion) (Table 1).
  - One patient was still receiving treatment at data cut-off.
- In the pooled population 50/60, the median age was 58 years, 43.8% of patients were men, 87.5% had metastatic disease at baseline, and 56.3% had an Eastern Cooperative Oncology Group Performance Status score of 1 (Table 1).
- Mean (standard deviation) durations of treatment in the pooled population 50/60 were: liposomal irinotecan, 223.4 (202.49) days; oxaliplatin, 209.3 (197.96) days; 5-FU, 225.5 (202.59) days; and LV, 223.4 (202.49) days.

Dose selection

- The 50/60 dose received by cohort B was selected for expansion (Table 2).

Pooled population 50/60

Safety

- Treatment-related TEAEs of grade 3 or higher occurred in 22 patients (68.8%), and the most common were neutropaenia, febrile neutropaenia and hypokalaemia (Table 2).
  - No patients in the pooled population 50/60 experienced treatment-related grade ≥ 3 peripheral sensory neuropathy or fatigue.
  - Treatment-related grade ≥ 3 peripheral sensory neuropathy and fatigue were observed in cohort C (one patient) and cohort A (one patient), respectively.
- Three TEAEs led to death (malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage and disease progression), but none were considered to be treatment related.
- Serious treatment-related TEAEs were reported for 10 patients (31.3%). The most common were febrile neutropaenia and nausea (three patients, 9.4%, in each case).

Efficacy

- Median PFS was 9.2 months (95% confidence internal [CI]: 7.69–11.96) and OS was 12.6 months (95% CI: 8.74–18.69) (Figure 1).
- The best overall responses were complete response in one patient (3.1%; the patient had locally advanced PDAC), stable disease in 15 patients (46.9%) and partial response in 10 patients (31.3%).
- Overall response rate was 34.4% (95% CI: 18.6–53.2%).
- Disease control rate at week 16 was 71.9% (95% CI: 53.3–86.3%).
- Median duration of response was 9.4 months (95% CI: 3.52–not estimable).

Genomic profiling

- Tumour subtype and tumour-response data were available for nine patients (eight had the classical subtype and one had the basal-like subtype) (Figure 2).
  - PFS values were 7.7–17.8 months and 9.6 months, respectively.

Table 1. Baseline demographic and clinical characteristics

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Age (years), median (range)	64.0 (58–78)	57.0 (44–74)	66.5 (57–73)	61.0 (54–73)	58.0 (39–76)	58.0 (39–76)
Age group, n (%) ≥ 65 years	4 (57.1)	2 (57.1)	3 (30.0)	4 (57.1)	19 (76.0)	23 (71.9)
Men, n (%)	1 (14.3)	3 (42.9)	8 (80.0)	5 (71.4)	11 (44.0)	14 (43.8)
Race, n (%) white	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Tumour stage at diagnosis, n (%)						
IIA[c]	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
ECOG Performance Status, n (%)						
Fully active (score = 0)	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
Restricted activity (score ≥ 1)	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)

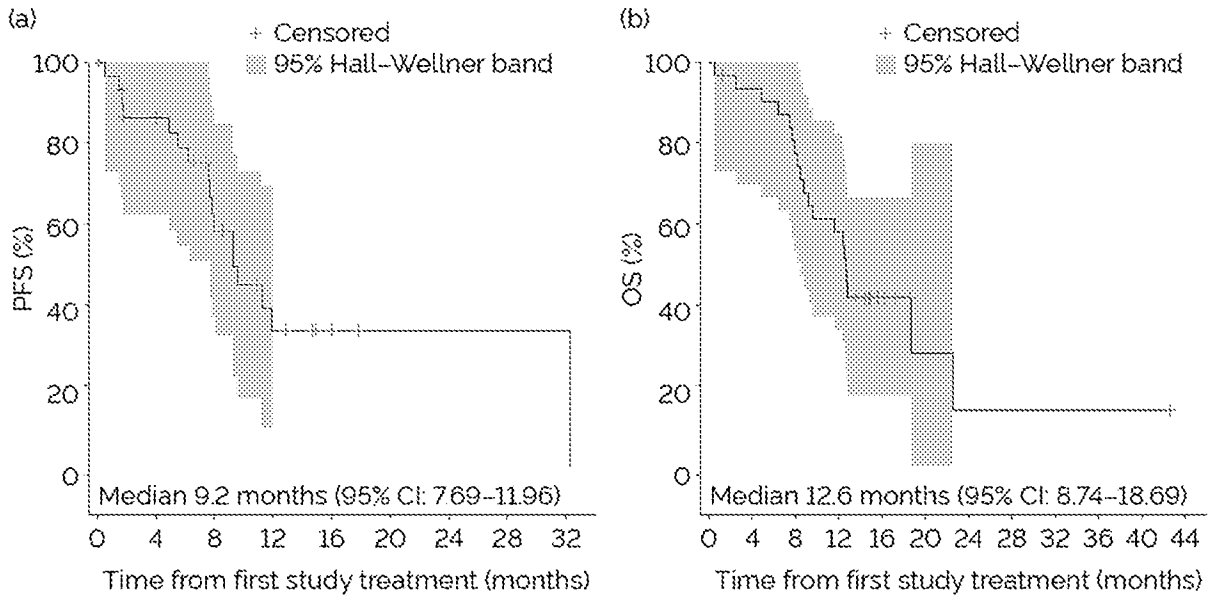
[a]Dose of liposomal irinotecan (free base)/dose of oxaliplatin expressed in mg/m² administered in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m² on days 1 and 15 of each 28-day cycle. [b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m² and oxaliplatin 60 mg/m² during the dose-exploration or dose-expansion parts of the study. [c]One patient in the dose-expansion cohort had a diagnosis of stage IIA but entered the treatment phase with a diagnosis of stage IV.
ECOG, Eastern Cooperative Oncology Group

Table 2. Dose selection and treatment-emergent adverse events

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Tolerability assessment during dose exploration	Not tolerable	Tolerable	Not tolerable	Not tolerable		
Reason	DLT(s) in > 1 patient	DLT and assessment of cumulative safety data	DLT(s) in > 1 patient	Assessment of cumulative safety data, including TEAEs of grade < 3 (not shown)		
DLTs (number of patients)	DLTs in 2 patients: neutropaenia infection (1), neutropaenic sepsis (1)	DLT in 1 patient: febrile neutropaenia (1)	DLTs in 2 patients: diarrhoea (2), vomiting (1), anal fissure (1), anal inflammation (1), proctalgia (1)	None		
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Leading to dose discontinuation[c]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Leading to dose adjustment[c]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	5 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)
Treatment-related[d]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)
Any treatment-related TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Grade ≥ 3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Treatment-related TEAEs[e] of grade ≥ 3 in ≥ 5% of the pooled population						
Neutropaenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Febrile neutropaenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Neutrophil count decreased	0	0	1 (10.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	2 (8.0)	3 (9.4)
Nausea	0	0	2 (20.0)	0	3 (12.0)	3 (9.4)
Vomiting	1 (14.3)	0	3 (30.0)	0	2 (8.0)	2 (6.3)
Hypokalaemia	1 (14.3)	2 (28.6)	2 (20.0)	2 (25.6)	2 (8.0)	4 (12.5)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
Alanine aminotransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Gamma-glutamyltransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Lymphocyte count decreased	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

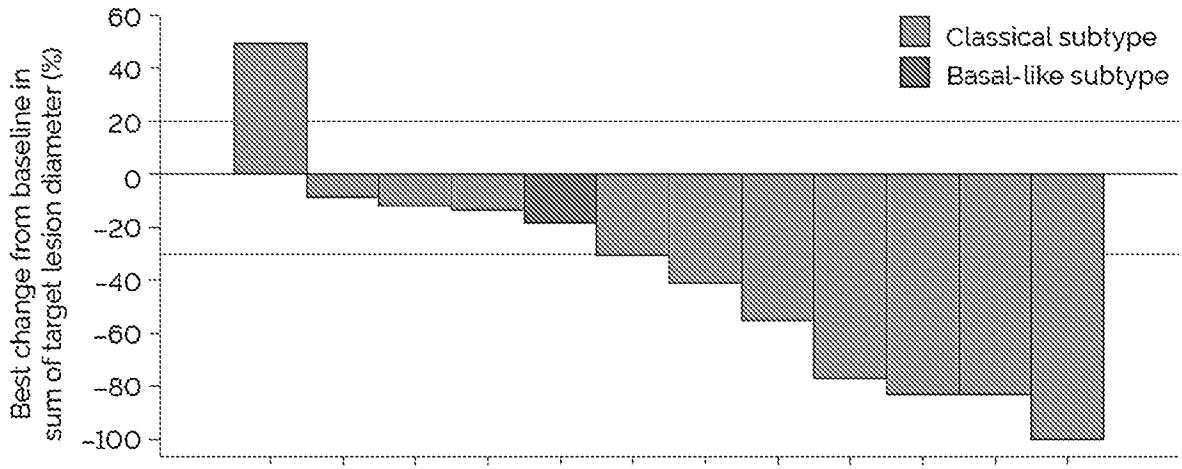
Data are number (%) of patients from the safety population unless stated otherwise. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, v20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.
[a]Dose of liposomal irinotecan (free base)/dose of oxaliplatin expressed in mg/m² administered in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m² on days 1 and 15 of each 28-day cycle. [b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m² and oxaliplatin 60 mg/m² during the dose-exploration or dose-expansion parts of the study. [c]Refers to discontinuation or adjustment in dose for any of the four treatments administered. [d]Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing.
DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event

Figure 1. PFS (a) and OS (b) in the pooled population 50/60[a]



Data are from the safety population. Disease progression was assessed according to RECIST v1.1. PFS and OS were analysed using the Kaplan–Meier method. Median (95% CI) values were calculated using the Brookmeyer–Crowley method. One patient with minimal progressive disease as per RECIST v1.1 was approved for treatment continuation because the investigator believed there was a benefit from treatment. PFS time for this patient ended at the date of progressive disease. [a]Comprises cohorts assigned to receive liposomal irinotecan (free base) 50 mg/m² and oxaliplatin 60 mg/m², in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m², on days 1 and 15 of each 28-day cycle during either the dose-exploration or dose-expansion parts of the study.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 2. Tumour-response and PFS data



Cohort	A	Ex	B	D	Ex	A	Ex	Ex	Ex	Ex	Ex	Ex
Dose	70/60	**50/60**	**50/60**	55/70	**50/60**	70/60	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**
PFS, months	3.0	7.8	17.8	10.9	9.6	0.6	9.2	14.9	7.7	9.2	14.7	10.9
Censored for PFS?			Yes			Yes		Yes			Yes	Yes

Patients in the pooled population (n = 9) are those for whom dose is given as 50/60 (liposomal irinotecan (free base) 50 mg/m² and oxaliplatin 60 mg/m², in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m², on days 1 and 15 of each 28-day cycle in the dose-exploration or dose-expansion parts of the study).
A–D, cohorts from the dose-exploration part of the study; Ex, dose-expansion cohort; PFS, progression-free survival.

Conclusions

- No new safety signals were observed with first-line NALIRIFOX in patients with locally advanced or metastatic PDAC, and anti-tumour activity was promising.
- The ongoing phase 3 NAPOLI-3 study (EudraCT 2018-003585-14, NCT04083235) will compare first-line NALIRIFOX with gemcitabine + nab-paclitaxel in adults with metastatic PDAC.

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Author contributions

All authors have contributed to study conception/design, drafting the publication or revising it critically for scientific accuracy and important intellectual content, and final approval of the publication.

Disclosures

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First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

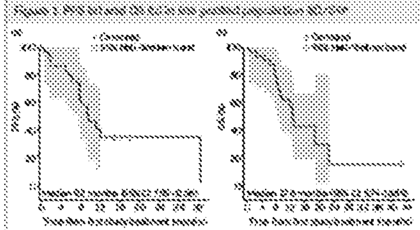
LBA-001

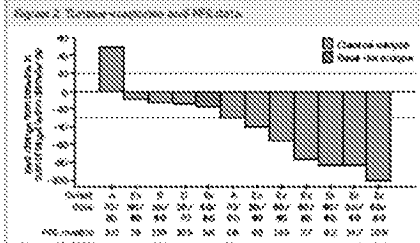
BACKGROUND

OBJECTIVES

METHODS

RESULTS





CONCLUSIONS

NAPOLI-3: an open-label, randomized, phase 3 study of first-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma

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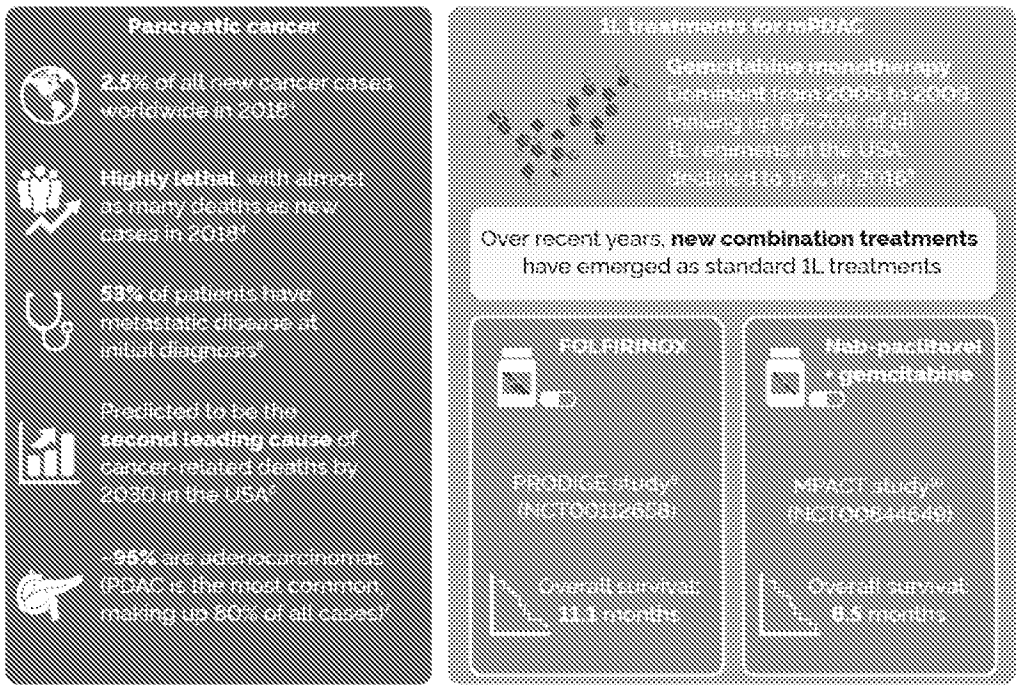
BACKGROUND

- Liposomal irinotecan (ONIVYDE, ONIVYDE pegylated liposomal) + 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA for the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy.[1]
- Approval was based on findings from the phase 3 NAPOLI-1 study (NCT01494506), in which liposomal irinotecan + 5-FU/LV showed significantly improved overall survival (OS) compared with 5-FU/LV alone (6.1 months vs 4.2 months; hazard ratio [HR] 0.67; $p = 0.012$).[2]
- An ongoing phase 2 study (NCT02551991) of liposomal irinotecan + 5-FU/LV + oxaliplatin (NALIRIFOX) in patients with previously untreated locally advanced/metastatic PDAC has shown promising anti-tumor activity with NALIRIFOX as first-line (1L) therapy.[3]
  - Given the poor prognosis and survival rates of less than 1 year with current 1L therapies,[4-10] new treatment options are needed for mPDAC (**Figure 1**).
- Here, we present the design of the phase 3 NAPOLI-3 study (NCT04083235) investigating the efficacy and safety of the NALIRIFOX regimen as 1L therapy in patients with mPDAC.

Figure 1. Pancreatic cancer overview and treatment options for mPDAC



1L, first-line; FOLFIRINOX, 5-fluorouracil + leucovorin + irinotecan + oxaliplatin; PDAC, pancreatic ductal adenocarcinoma; mPDAC, metastatic pancreatic ductal adenocarcinoma.

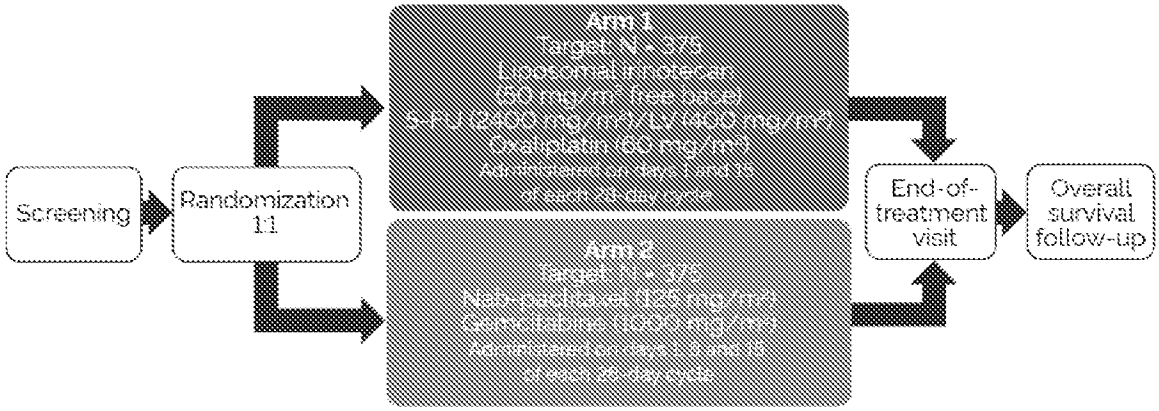
STUDY DESIGN

- NAPOLI-3 is an ongoing, open-label, randomized, multicenter, phase 3 study to evaluate the efficacy and safety of 1L NALIRIFOX (arm 1) compared with 1L nab-paclitaxel + gemcitabine (arm 2) in adult patients with mPDAC who have not been previously treated in the metastatic setting (**Figure 2**).

Study objectives

- The primary objective is to evaluate the efficacy of NALIRIFOX in improving OS in patients who have not previously received chemotherapy for mPDAC (**Table 1**).
- Secondary and exploratory objectives are listed in **Table 1**.

Figure 2. Study design overview



5-FU, 5-fluorouracil; LV, leucovorin

Table 1. NAPOLI-3 study objectives

Primary objective	
OS	Time from the date of randomization to the date of death by any cause
Secondary objectives	
PFS	Time from randomization to the first documented objective disease progression as per RECIST v1.1 or death by any cause, whichever comes first
ORR	The proportion of patients with a BOR of complete or partial response as per RECIST v1.1. BOR is defined as the best response from treatment initiation to disease progression
Safety	Severity of AEs and SAEs graded according to NCI-CTCAE v5.0. AEs leading to treatment discontinuation and/or death, AEs related to study treatment, laboratory abnormalities, incidence of patients experiencing dose modifications (including infusion interruptions, dose omissions and dose delays) and/or premature treatment discontinuation (including reason for discontinuation)
Exploratory objectives	
Health status	Deterioration or worsening of physical functioning, disease-related symptoms and treatment-related symptoms of interest using patient-reported outcome data
PK	Evaluation of the PK of arm 1, and the relationship between PK exposure and associated efficacy and safety
TTF	Time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death
DOR	Time of initial response (complete response or partial response as per RECIST v1.1) until documented tumor progression
TTR	Time from randomization to the first objective tumor response as per RECIST v1.1

AE, adverse event; BOR, best overall response; DOR, duration of objective response; NCI-CTCAE v5.0, National Cancer Institute – Common Terminology Criteria for Adverse Events version 5.0; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; TTF, time to treatment failure; TTR, time to response.

Study population

- Eligible patients are adults with untreated mPDAC (key inclusion and exclusion criteria are shown in **Table 2**).
- Patients will be stratified according to Eastern Cooperative Oncology Group Performance Status (0 or 1), region (North America, East Asia, other) and liver metastases (yes or no).

Data collection and follow-up

- Anonymized data will be collected using an electronic case-report form.
- Thirty days after permanent discontinuation of study treatment, patients will undergo a follow-up assessment and will be observed for survival status every 2 months until death or study end (when all patients have died or withdrawn consent, or are lost to follow-up).

Table 2. Key inclusion and exclusion criteria

Key inclusion criteria
• Aged ≥ 18 years
• Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting
• Initial diagnosis of metastatic disease must have occurred ≤ 6 weeks before screening
• At least one metastatic tumor measurable by CT scan or MRI according to RECIST v1.1
• ECOG Performance Status of 0 or 1 at screening and in the 7 days before randomization
• Adequate hematologic, hepatic and renal functions
• ECG without clinically significant findings
Key exclusion criteria
• Previous treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational product – Palliative radiotherapy and placement of biliary stent/tube are permitted
• Previous treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except if ≥ 12 months have elapsed since completion of the last dose and no persistent treatment-related toxicities are present
• Only localized advanced disease
• History of CNS metastases – Patients who are receiving a stable or decreasing dose of steroids and whose disease is deemed clinically stable are eligible
• Clinically significant gastrointestinal disorders
• History of any second malignancy in the past 2 years – Patients with a history of *in situ* cancer or basal- or squamous-cell skin cancer are eligible – Patients who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are eligible
• Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma

CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- All patients will receive 28-day cycles of treatment until disease progression, treatment toxicity or withdrawal from the study.
- Tumor assessments will be performed by computed tomography or magnetic resonance imaging every 8 weeks (± 1 week) using Response Evaluation Criteria in Solid Tumors version 1.1.

Dose modifications

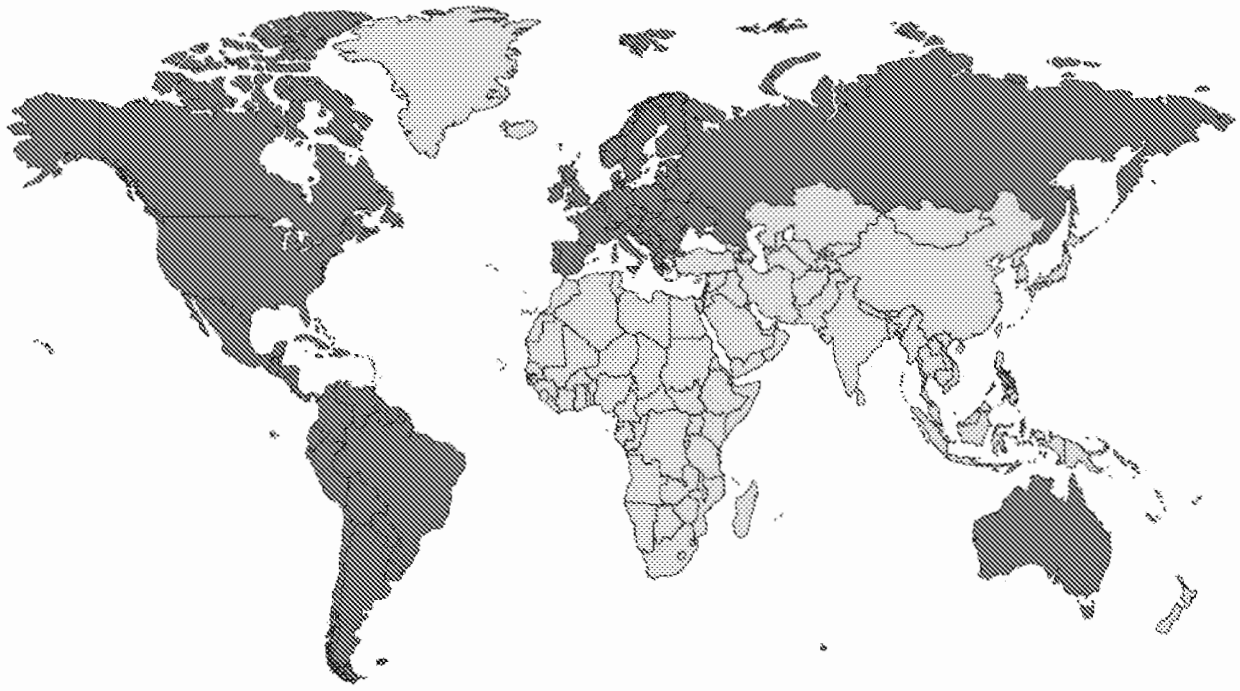
- Treatment dose may be reduced owing to toxicity, and re-escalation will generally not be permitted.

- In arm 1, no more than three dose reductions are permitted and, in arm 2, no more than two dose reductions are permitted.
- To allow time for recovery from toxicity, the treatment dose may also be delayed.
  - Doses may be delayed for up to 28 days in arm 1 and for up to 21 days in arm 2.
  - Dose delays that are longer than the prespecified timeframe will be recorded as an omission, and discontinuation will be considered unless overall benefit to the patient is demonstrated.
- At the investigator's discretion, oxaliplatin may be discontinued if not well tolerated, and patients can continue treatment with liposomal irinotecan + 5-FU/LV.
  - Discontinuation of any other treatment will result in discontinuation from the study.

Analyses

- Efficacy analyses will be performed on the 'intent-to-treat' population, defined as all randomized patients who have given informed consent.
- Safety analyses will be performed on patients who received at least one dose of any study treatment.
- OS will be assessed using Kaplan–Meier methodology, and differences between treatment arms will be assessed using a stratified log-rank test.

Figure 3. Countries involved in the NAPOLI-3 study



- The estimated treatment effect for arm 1 will be summarized by the HR from stratified Cox regression analysis.
- Progression-free survival (PFS) and objective response rate (ORR) (secondary endpoints) will only be compared between treatment arms if arm 1 shows superiority in OS.
  - PFS comparisons will be analyzed similarly to OS.
  - ORR comparisons will be analyzed using the Cochran–Mantel–Haenszel method and adjusted by randomization strata.

Recruitment update

- Recruitment is ongoing or planned in North America, South America, Europe and Australia (Figure 3).

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Author contributions

All authors have contributed to study conception/design, drafting the publication or revising it critically for scientific accuracy and important intellectual content, and final approval of the publication.

Disclosures

ZAW: AstraZeneca, Daiichi-Sankyo, Five Prime, Ipsen, Lilly, Merck, Novartis, Plexxikon; TB-S: IGlobe Health Institute, AbGenomics, Amgen, Array BioPharma, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Biomedical, Bristol-Myers Squibb, Celgene, Clovis Oncology, Exelixis, Genentech, Immuneering, Imugene, Incyte, Ipsen, Lilly, Merck, PanCan, Seattle Genetics, Sobi, Sun BioPharma, Treos Bio; RH: Bayer, Bristol-Myers Squibb BTG, Eisai, Ipsen, priME Oncology, Roche; TM: Aglos, AstraZeneca, ASLAN Pharmaceuticals, Baxalta, Bayer, BeiGene, Celgene, Genentech, Genzyme, Halozyme, H3 Biomedicine, Immunomedics, Incyte, Ipsen, Lilly, Merck, Merrimack Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Novocure, OncoMed, Pfizer, Pharmacyclics, ODE, Roche, Sanofi, Servier, Shire, Tesaro, SP; Actinium, Advanced Accelerator Applications, Amgen, Aptose Biosciences, AstraZeneca, Bristol-Myers Squibb, Cardinal Health, Eisai, Exelixis, Hutchinson, Immunomedics, Incyte, Ipsen, Lilly Seattle Genetics, Taiho Pharmaceutical; EVC: Array BioPharma, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Halozyme, GlaxoSmithKline, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Pierre Fabre, Roche, Server, Sirtex, Taiho Pharmaceutical; EMO: Acta Biologica, AstraZeneca, Bayer, BioLineRx, Bristol-Myers Squibb, CytomX, Genentech, Ipsen, Loxo Oncology, MabVax Therapeutics, Merck, Polaris Pharma, Roche, Silenseed, Targovax.

FM, YM, TW and BZ are employees of Ipsen.

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NAPOLI-3: an open-label, randomized, phase 3 study of first-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma

BACKGROUND

STUDY DESIGN

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

LATE-BREAKING ABSTRACTS

LBA-1 First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study

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Background: Liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) is approved for adults with metastatic pancreatic ductal adenocarcinoma (PDAC) following progression with gemcitabine-based therapy. We report long-term follow-up results (data cut-off 26 Feb 2020) from an open-label phase 1/2 study (NCT02551991; EudraCT 2015-003086-28) of adults with previously untreated, unresectable, locally advanced/metastatic PDAC receiving liposomal irinotecan + 5-FU/LV + oxaliplatin (NALIRIFOX).

Methods: Following dose exploration (Part 1A), the dose selected for expansion (Part 1B), based on dose-limiting toxicities and cumulative safety data, was liposomal irinotecan 50 mg/m2 (free base), 5-FU 2400 mg/m2, LV 400 mg/m2, oxaliplatin 60 mg/m2 on days 1 and 15 of each 28-day cycle. The analyses included patients receiving the selected dose (pooled population 50/60): 7 patients from Part 1A and 25 from Part 1B. Patients were aged $\geq$ 18 years with ECOG performance status score $\leq$ 1 and adequate organ function. The primary endpoint was safety and tolerability; secondary efficacy endpoints were progression-free survival (PFS; primary efficacy endpoint), overall survival (OS), best overall response, overall response rate (ORR), disease control rate at 16 weeks (DCR16) and duration of response (DoR); exploratory endpoints included tumour subtype. Disease was assessed (RECIST v1.1) at screening, end of treatment and every 8 weeks. Archival tumour samples were subtyped (Moffitt schema) using the PurISTSM RNAseq assay (GeneCentric Therapeutics, Inc).

Results: The PP 50/60 comprised 32 patients (median age 58.0 years [range 39-76]; 14 [43.8%] men; 28 [87.5%] with metastatic disease at diagnosis; 18 [56.3%] with ECOG performance status score 1; 1 receiving study treatment at data cut-off). In total, 22 of these patients had grade $\geq$ 3 treatment-related treatment-emergent adverse events (TEAEs); the most common were neutropaenia (31.3%), febrile neutropaenia (12.5%), hypokalaemia (12.5%), diarrhoea (9.4%), nausea (9.4%) and decreased neutrophil count (9.4%); vomiting occurred in 6.3% of patients, while fatigue and peripheral neuropathy were not reported. Serious TEAEs (SAEs) were reported in 17 patients; 10 of these patients had SAEs considered related to treatment, most commonly nausea (9.4%) and febrile neutropaenia (9.4%). TEAEs leading to death occurred in 3 patients (malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage, disease progression); none were considered related to treatment. TEAEs led to dose adjustment in 26 patients and discontinuation (of oxaliplatin or all four study drugs) in 8. Median PFS (95% CI) was 9.2 months (7.69, 11.96) and median OS was 12.6 months (8.74, 18.69). Complete response was observed in 1 patient (with locally-advanced disease), partial response in 10, and stable disease in 15. ORR (95% CI) was 34.4% (18.6, 53.2), DCR16 was 71.9% (53.3, 86.3) and median DoR was 9.4 months (3.52, NE). Tumour subtype and response data were available for 9 patients in the PP 50/60 (classical, n=8, PFS range 7.7-17.8 months; basal-like, n=1, PFS 9.6 months).

Conclusion: No new safety signals were observed with first-line NALIRIFOX in patients with locally advanced/metastatic PDAC, and anti-tumour activity was promising. The ongoing randomized phase 3 NAPOLI-3 study (NCT04083235; EudraCT 2018-003585-14) will compare NALIRIFOX with gemcitabine + nab-paclitaxel.

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LBA-2 A two arm randomized prospective superiority phase II multicentric clinical trial to evaluate the efficacy of capecitabine-irinotecan (CAPIRI) versus irinotecan in advanced gall bladder cancer progressing on first line chemotherapy

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Background: There is limited data with regard to second line chemotherapeutic options (CT2) in advanced gallbladder cancer (GBC) post progression on gemcitabine-based1st line chemotherapy (CT1). Using a combination or monotherapy as CT2 is an important question in this context.

Methods: Patients diagnosed with disease progression or recurrence post CT1 were randomized (1:1) to either capecitabine-Irinotecan (CAPIRI) or single agent Irinotecan (IRI). Patients with ECOG PS 0-1, and adequate end organ function were eligible. Primary endpoint was percentage overall survival (OS) at 6 months. Sample size was 98 patients with requirement of 68 events for analysis (80% power; 10% two-sided alpha), assuming median 6-month OS for IRI was 55% and 70% for CAPIRI, respectively.

Results: 98 patients (49 in each arm) were randomized (August 18 to Jan 20); median age 51 years (range: 29-70); gender: Women 60 (61%), Men 38 (39%). There were no significant differences in baseline characteristics between both groups. After sixty-nine OS events, the Hazard Ratio (HR) was 0.98 (95% CI: 0.61 — 1.57; p= 0.93: CAPIRI vs. IRI). Six months (mo.) OS (%), median OS and median progression free survival were 38.4%, 5.16 mo., and 2.27 mo. for CAPIRI arm and 54.2%, 6.28 mo. and 3.12 mo. for IRI arm, respectively. Thirteen patients (27%) required dose modifications in CAPIRI arm and 4 patients (9%) in IRI arm and this difference was statistically significant (p=0.03). No chemotherapy related deaths were seen.

Conclusion: Monotherapy with Irinotecan appears as efficacious as CAPIRI in terms of OS with lesser requirement for dose modifications in patients with GBC after progression on first line gemcitabine-based chemotherapy. Irinotecan mono therapy may be considered as a standard of care in this scenario.

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LBA-3 CheckMate 459: Long-term (minimum follow-up 33.6 months) survival outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma

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Background: Patients with advanced hepatocellular carcinoma (aHCC) not amenable to surgical resection or locoregional therapy may be treated with multitargeted kinase inhibitors or immuno-oncology—based combination therapy. Sorafenib is approved as first-line (1L) therapy but provides only a modest survival benefit. Despite approved 1L therapies for aHCC, there remains an unmet need to prolong survival while improving treatment tolerability. The phase 3 CheckMate 459 study compared 1L nivolumab versus sorafenib in patients with aHCC; initial efficacy and safety data were previously presented (Yau et al. ESMO 2019; NCT02576509). The protocol-defined statistical significance threshold for overall survival (OS) was not met. Although

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

NAPOLI-3: An open-label, randomized, phase III study of first-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma.

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Show Less

Abstract Disclosures

Abstract

TPS4661

Background: Liposomal irinotecan administered with 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA for metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy. A phase 1/2 study in previously untreated locally advanced/metastatic PDAC showed promising anti-tumor activity with liposomal irinotecan 50 mg/m^2 free base + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 + oxaliplatin (OX) 60 mg/m^2 on days 1 and 15 of a 28-day cycle (Wainberg *et al. Ann Oncol*2019;30 Suppl 4: SO-005). Herein, we present the design of the phase 3 NAPOLI-3 study investigating the efficacy and safety of this regimen as first-line therapy in patients with mPDAC. **Methods:** NAPOLI-3 (NCT04083235) is a phase 3, open-label, randomized, global study in adults with histologically/cytologically confirmed pancreatic adenocarcinoma not previously treated in the metastatic setting. Patients are required to have one or more metastatic tumors measurable with computed tomography/magnetic resonance imaging and an Eastern Cooperative Oncology Group performance status score of 0–1. Site activation began in Dec 2019 and enrollment is ongoing. Random allocation (1:1) of 750 patients is planned to liposomal irinotecan + 5-FU/LV + OX (regimen as per phase 1/2 study) or

nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle. The primary endpoint is overall survival (OS). Secondary endpoints (progression-free survival [PFS] and overall response rate assessed with Response Evaluation Criteria in Solid Tumors v1.1 criteria) will be compared only if the primary endpoint shows superiority for liposomal irinotecan + 5-FU/ LV + OX over nab-paclitaxel + gemcitabine. Safety assessments include adverse-event monitoring. Patients will continue treatment until disease progression, unacceptable toxicity or study withdrawal, and will then be followed for survival every 2 months until death or study end (when all patients have died, withdrawn consent or are lost to follow-up). Clinical trial information: NCT04083235.

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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Beyond first-line chemotherapy for advanced pancreatic cancer: An expanding array of therapeutic options?

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Abstract

While an increasing number of therapeutic options are now available for the first-line treatment of locally advanced or metastatic pancreatic cancer, the optimal choice for treatment in the second-line setting and beyond is less well defined. A variety of cytotoxic agents, either alone or in combination, have been evaluated, although primarily in the context of small single-arm or retrospective studies. Most regimens have been associated with median progression-free survival rates in the range of 2-4 mo and overall survival rates between 4-8 mo, highlighting the very poor prognosis of patients who are candidates for such treatment. Targeted therapies studied in this chemotherapy-refractory setting, meanwhile, have produced even worse efficacy results. In the current article, we review the clinical evidence for treatment of refractory disease, primarily in patients who have progressed on front-line gemcitabine-based chemotherapy. In the process, we highlight the limitations of the available data to date as well as some of the challenges in designing appropriate clinical trials in this salvage setting, including how to select an appropriate control arm given the absence of a well-established reference standard, and the importance of incorporating predictive biomarkers and quality of life measures whenever possible into study design.

Key words: Pancreatic cancer; Refractory; Second-line chemotherapy; Gemcitabine

Core tip: No standard of care exists for patients with advanced pancreatic cancer who have progressed on front-line chemotherapy. To date, most available evidence has come from small non-randomized studies, with efficacy results that have been fairly dismal. In this review, we discuss both traditional and novel cytotoxic and targeted therapies that have been evaluated in this refractory setting and how they may (or may not) be applicable to clinical practice; and raise considerations for clinical trial design in the future, particularly in this current era of both expanding chemotherapeutic options and molecular/"precision" medicine.

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INTRODUCTION

More than 80% of patients diagnosed with pancreatic adenocarcinoma have metastatic or locally advanced inoperable disease at the time of initial presentation[1], at which point systemic therapy becomes the mainstay of care. Over the past decade-plus, gemcitabine alone or in combination with other drugs (most commonly a fluoropyrimidine, a platinum analogue, or the epidermal growth

factor receptor inhibitor erlotinib) have represented the most commonly used front-line treatment options. The treatment landscape is gradually shifting, however, with recent positive results from a couple of phase III studies establishing two new standards of care for first-line treatment, FOLFIRINOX [infusional 5-fluorouracil (FU), leucovorin, irinotecan, oxaliplatin] and the doublet of gemcitabine plus *nab*-paclitaxel.

Invariably, regardless of choice of front-line therapy, patients with advanced/metastatic disease will progress, and at that point the choice of treatment becomes considerably murkier. According to results from one United States cooperative group trial (CALGB 80303), fewer than half of patients with advanced pancreatic cancer went on to receive any additional therapy after progressing on front-line study treatment[2]. This reflects, in part, the fact that patients in this setting frequently demonstrate significant clinical deterioration and a decline in performance status, and are no longer deemed appropriate candidates for further anti-cancer therapy. However, it also highlights the fact that no second-line regimen(s) has consistently and unequivocally been shown to confer a survival benefit for patients, and as such providers are left grasping for best available evidence to inform treatment decisions, especially for patients who wish to remain proactive with some form of therapy.

In this review, we summarize the various therapeutic options that have been evaluated to date in the second-line (and beyond) setting for advanced pancreatic cancer. In so doing, we raise a number of important issues regarding appropriate clinical trial design, what (if any) should be considered a correct reference standard and benchmark of success in this setting, and how the expanding armamentarium of available agents and established regimens for this disease both expands our array of therapeutic options and adds to the complexity in decision-making.

GEMCITABINE-CONTAINING REGIMENS

Gemcitabine emerged as the standard of care for first-line treatment of advanced pancreatic cancer following its FDA approval in 1996[3]. Once patients develop resistance following front-line gemcitabine-based therapy, the natural question arises as to whether continuing with this same drug while adding novel agents can confer, or restore, clinical activity by overcoming drug-specific chemotherapeutic resistance and/or through synergistic effects.

Kozuch *et al*[4] first demonstrated the feasibility of this approach in a retrospective analysis of 34 consecutive patients with metastatic pancreatic cancer receiving irinotecan/gemcitabine/5-FU/leucovorin/cisplatin (G-FLIP), 32 of whom had previously progressed on gemcitabine and 31 who had progressed specifically on gemcitabine/5-FU/cisplatin (GFP). Of these 31 patients, whose regimen was altered only by the addition of irinotecan, 7 (23%) achieved partial responses (PR) and 7 (23%) achieved stable disease (SD). Notably, 8 of these 14 patients demonstrating disease control had previously experienced progressive disease as a best response to GFP alone. Median progression-free and overall survival (OS) for all 34 patients receiving second-line G-FLIP was 3.9 and 10.3 mo, respectively.

Another multidrug regimen that has been evaluated in the refractory setting is cisplatin/epirubicin/5-FU/gemcitabine (PEFG). This combination was initially tested in the front-line setting in an Italian phase III trial by Reni *et al*[5], and showed improved 4-mo PFS and 2-year survival rates compared to gemcitabine monotherapy, albeit with significant rates of hematologic toxicity. PEFG was subsequently studied by the same research group as second-line therapy in patients with progressive or metastatic disease refractory to gemcitabine-based treatment. In this 46-patient study, subjects receiving either classic or dose-intense PEFG had a median OS of 8.3 mo, with no significant difference between the different doses of PEFG tested[6]. Again, marked toxicities were noted, including Grade 3-4 neutropenia and thrombocytopenia in 26 (56%) and 10 (22%) patients, respectively.

Building upon observations from prior phase III trials demonstrating improvements in response rate (RR), progression free survival (PFS), and clinical benefit response (CBR) of gemcitabine/platinum doublets compared to gemcitabine monotherapy in the front-line setting[7,8], a similar strategy has also been explored in the gemcitabine-refractory setting in a variety of contexts. Demols *et al*[9] investigated the combination of gemcitabine plus oxaliplatin (GemOx) in a single-arm phase II study involving 33 patients with gemcitabine-refractory advanced pancreatic cancer. A partial response was observed in 7 patients (21%) with an additional 12 patients (36%) achieving SD. Median OS was 6 mo. Importantly, 17 patients (52%) were reported as having a clinical benefit response. One more recent approach has involved testing the potential for enhanced chemotherapeutic efficacy at higher temperatures[10], by which basis Tschoep-Lechner *et al*[11] conducted a study of gemcitabine and cisplatin combined with regional hyperthermia (RHT) in the second-line setting. Median time to progression for the 23 patients treated with this strategy was 4.3 mo, with a median overall survival of 12.9 mo. These results have spurred an ongoing prospective phase II trial offering second-line Gem/Cis/RHT (EudraCT: 2005-003855-11).

Other doublet regimens that have been evaluated in the salvage setting include gemcitabine plus the oral fluoropyrimidine S-1[12] and gemcitabine plus *nab*-paclitaxel[13] with median times to progression of 2.8 and 3.2 mo, respectively. More details of these and other gemcitabine-based combinations are summarized in Table 1.

NOVEL MONOTHERAPEUTIC REGIMENS

An alternative approach to second-line therapy involves administration of a completely non-cross-resistant regimen; using such a strategy, previous agents (such as

Table 1 Clinical results of gemcitabine-refractory pancreatic cancer treatment regimens

Ref.	Regimen	Sample size	RR[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Kozuch *et al*[69], 2003	G-FLIP	34	24%	3.9	10.3	47%
Reni *et al*[70], 2008	PEFG	46	24%	5.0	8.3	26%
Demols *et al*[71], 2006	GEMOX	33	21%	4.2	6.0	NR
Fortuna *et al*[72], 2009	GEMOX	17	24%	2.6	6.4	29%
Stathopoulos *et al*[73], 2006	Gem, Lipoplatin	24	8.3%	NR	4.0	NR
Tschoep *et al*[74], 2012	Gem, Cisplatin, RHT	23	4.3%	4.3	NR	NR
Morizane *et al*[75], 2012	Gem, S-1	40	18%	2.8	7.0	18%
Ernani *et al*[76], 2012	Gem, *nab*-Paclitaxel	30	20%	3.2	NR	NR

[1]Intent-to-treat analysis. G-FLIP: Gemcitabine, 5-fluorouracil, leucovorin, cisplatin; PEFG: Cisplatin, epirubicin, 5-fluorouracil, gemcitabine; GEMOX: Gemcitabine, oxaliplatin; Gem: Gemcitabine; RHT: Regional hyperthermia; *Nab*-paclitaxel: Albumin-bound nanoparticle paclitaxel; NR: Not reported; PFS: progression free survival; OS: Overall survival; TTP: Time to progression.

gemcitabine) are discontinued and an entirely new drug or drug combination is given. In terms of monotherapy, several topoisomerase inhibitors have been investigated in patients refractory to gemcitabine-based front-line treatment. The orally active camptothecin rubitecan, for example, showed sufficient single-agent activity in two separate studies of gemcitabine-refractory disease[14,15] to warrant a randomized phase III trial in which 409 pretreated patients (70% of whom had received two or more prior regimens) were randomized to receive either rubitecan monotherapy or "best choice (BC)" alternative therapy as determined by treating physicians (most commonly gemcitabine, 5-FU, mitomycin C, capecitabine, or docetaxel). Presented as an abstract at the 2004 ASCO annual meeting but never subsequently published, the trial did not show a statistically significant difference in overall survival between groups (108 d *vs* 94 d, respectively, $P = 0.63$), although significant improvements were observed with rubitecan in terms of progression-free survival (58 d *vs* 48 d, $P = 0.01$) and response rate (6.1% *vs* 0.5%, $P = 0.01$)[16].

More recently, a phase II study of liposomal irinotecan sucrosofate (PEP02, MM-398), a drug formulation with improved pharmacokinetics and tumor bioavailability relative to free irinotecan, was performed in patients with metastatic pancreatic cancer refractory to front-line gemcitabine-based therapy[17]. Ko *et al*[17] reported a disease control rate of 50% (including 7.5% with an objective response) as well as a 50% or greater CA19-9 decline in 31% of evaluable subjects, with a median overall survival of 5.2 mo. Toxicities were manageable, with cytopenias, asthenia, and diarrhea representing the most common grade 3/4 adverse events. These results prompted the launch of an international randomized phase III trial (NAPOLI-1, NCT01494506) that has been recently completed, comparing MM-398 with or without 5-FU/leucovorin to 5-FU/leucovorin alone.

Inhibitors of microtubule dynamics, including taxanes (docetaxel, paclitaxel, *nab*-paclitaxel) and eribulin mesylate, have also been investigated in small retrospective and single-arm phase II studies[18-22]. Given the unique formulation of *nab*-paclitaxel that may allow it to more successfully traverse the blood-stroma barrier, in addition to the positive results from the phase III MPACT trial establishing the combination of *nab*-paclitaxel/gemcitabine as a viable option for first-line therapy[23], there has been natural interest in evaluating this agent in the salvage setting. To date, we only have results from a small phase II study of *nab*-paclitaxel as a single agent for refractory pancreatic cancer, in which there was a single objective response (with an additional 6 achieving disease stabilization) amongst 19 patients, with a median PFS of 1.7 mo. Estimated median OS in this cohort was 7.3 mo[22].

Fluoropyrimidines have also been studied in the advanced refractory disease setting. Boeck *et al*[24] studied second-line capecitabine monotherapy after gemcitabine failure and observed disease stabilization in 39% of patients (no objective responses), with a median time to progression and overall survival of 2.3 mo and 7.6 mo, respectively. Another oral fluoropyrimidine, S-1, widely used in Asia and other parts of the world for gastric and pancreatic cancer, has also been evaluated in several phase II studies as monotherapy for gemcitabine-refractory patients; response rates associated with this agent range from 4%-15%, with a median PFS almost uniformly in the 2 mo range[25-28]. See Table 2 for additional data from these studies.

CYTOTOXIC COMBINATION REGIMENS (NON-GEMCITABINE-BASED)

Patients who maintain a good performance status after progressing on front-line therapy may also be candidates for non-gemcitabine-based combination chemotherapy regimens.

Platinum-based combinations

To date, the majority of studies have concentrated on the combination of a fluoropyrimidine plus a platinum analogue, most notably 5-FU, leucovorin, and oxaliplatin administered in various dosing schedules. One of the earliest studies, a non-randomized phase II trial conducted in Greece by Tsavaris *et al*[29], showed encouraging clinical activity of these drugs when administered weekly in bolus fashion, with the best response including partial responses in 7 of 30 patients (23%) and stable disease in an additional 9 (30%). More traditional FOLFOX regimens, with biweekly dosing schedules and prolonged 5-FU infusion

Table 2 Clinical results of second-line single-agent chemotherapy trials

Ref.	Regimen	Sample size	RR[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Jacobs *et al*[116], 2004	Rubitecan	198	11%	1.9	3.5	NR
Burris *et al*[117], 2005	Rubitecan	58	5.2%	2.0	3.1	9%
Yi *et al*[118], 2009	Irinotecan	33	9%	2.0	6.6	NR
Takahara *et al*[119], 2013	Irinotecan	56	3.6%	2.9	5.3	NR
Ko *et al*[93], 2013	Nanoliposomal irinotecan	40	7.5%	2.4	5.2	25%
Oettle *et al*[98], 2000	Paclitaxel	18	5.6%	NR	4.1	NR
Maeda *et al*[98], 2011	Paclitaxel	30	10%	NR	6.7	NR
Cereda *et al*[99], 2008	Docetaxel	10	0%	1.5	4.0	0%
Hosein *et al*[13], 2013	*Nab*-Paclitaxel	19	5%	1.7	7.3	37%
Boeck *et al*[100], 2007	Capecitabine	39	0%	2.3	7.6	NR
Bodoky *et al*[101], 2012	Capecitabine	38	7.9%	2.2	5.0	NR
Morizane *et al*[121], 2009	S-1	40	15%	2.0	4.5	14%
Todaka *et al*[102], 2010	S-1	52	3.8%	2.1	5.8	12%
Mizuno *et al*[28], 2013	S-1	67	6%	1.9	5.9	NR
Ioka *et al*[103], 2013	Best fluoropyrimidine[2]	40	10%	3.8	7.5	NR
Fukahori *et al*[108], 2012	Gemcitabine[3]	27	14%	2.6	8.0	NR
Androulakis *et al*[104], 2005	Oxaliplatin	18	0%	NR	3.5	NR
Boeck *et al*[105], 2007	Pemetrexed	52	3.8%	1.6	4.7	NR
Ulrich-Pur *et al*[106], 2003	Raltitrexed	19	0%	2.5	4.3	0%
Kindler *et al*[107], 2008	Arsenic trioxide	13	0%	1.6	3.8	0%

[1]Intent-to-treat analysis, [2]S-1 (67.5%), uracil-tegafur (20%), or 5-fluorouracil (12.5%); [3]S-1 refractory disease. *Nab*-paclitaxel: Albumin-bound nanoparticle paclitaxel; NR: Not reported; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression.

times similar to that given in colorectal cancer, have also been examined with demonstrable evidence of activity in this setting. Yoo *et al*[30] conducted a randomized phase II trial comparing modified versions of FOLFOX and FOLFIRI (5-FU, leucovorin, irinotecan) for gemcitabine-refractory advanced pancreatic cancer. However, in this study, response rates to both regimens were low (7% and 0%) with associated PFS times of 6.0 and 8.3 wk, respectively. A more recent phase II trial of FOLFOX4 from Korea reported modestly better results, with an objective response rate of 11%, a tumor stabilization rate of 41%, and a median time to progression of 9.9 wk[31]. Single-arm studies of capecitabine plus oxaliplatin (CapOx) have also been performed by several Asian groups, with fairly comparable results[32,33].

The most convincing evidence supporting a fluoropyrimidine/platinum-based combination comes from Germany, using a regimen termed OFF, in which 5-FU (given as a 24-h infusion) plus folinic acid are given weekly x 4 in 6-wk cycles, with the addition of oxaliplatin during weeks 2 and 4. Prompted by promising results from a phase II trial using this regimen (disease control rate lasting 12 wk or better in 43% of study patients), a phase III randomized trial was designed by Charité Onkologie (CONKO-003) in which patients were randomized to receive either the OFF regimen or best supportive care (BSC). A sample size of 165 was planned, but the study was stopped due to poor accrual (likely from the possibility of randomization to a BSC arm) after enrolling 46 patients[36]. Even with the limited sample size, overall survival in patients receiving OFF was 4.8 mo compared to 2.3 mo in those receiving BSC ($P = 0.008$)[37]. The investigators sought to build on these results with another randomized phase III trial comparing OFF to weekly 5-FU/folinic acid (FF) alone. The results of this 168-patient trial were presented in abstract form at the 2008 ASCO meeting[38]. As compared to the FF regimen, patients receiving OFF demonstrated improved PFS (13 wk *vs* 9 wk, $P = 0.012$) and median OS (26 wk *vs* 13 wk, $P = 0.014$). This trial marks the largest phase III study to date showing a survival benefit of second-line therapy for pancreatic cancer; as such, the OFF regimen (or iterations thereof) has become accepted as the de facto standard treatment of refractory disease.

With the emergence of FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) as a front-line standard for patients with advanced pancreatic cancer and good performance status[39], there has naturally been interest in investigating this regimen in the second-line setting. To date, we only have data from one small retrospective series that included 27 patients[40]. Seventeen (63%) demonstrated stable disease or better, including 5 with partial responses, with an associated median TTP of 5.4 mo. Importantly, treatment was generally well-tolerated with manageable and predictable toxicities. Further evaluation of this regimen clearly needs to be performed in prospectively designed studies.

While fluoropyrimidine/platinum combinations have been studied most extensively, single-arm studies of platinum-based agents partnered with other classes of agents, including oxaliplatin in combination with irinotecan[41,42], raltitrexed[43], and pemetrexed[44], have also been examined. Results of these small series are shown in Table 3.

Non-platinum-based combinations

In addition to the previously described phase II trial by Yoo *et al*[30] in which gemcitabine-refractory patients were randomized to receive modified versions of either FOLFOX or FOLFIRI, other smaller prospective and retrospective studies of FOLFIRI have been conducted,

Table 2 Clinical results of second-line systemic chemotherapy trials in refractory pancreatic cancer

Ref.	Regimen	Sample size	RR[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
	Platinum based regimens					
Tsavaris *et al*[59], 2005	FOLFOX	30	23%	5.1	5.8	NR
Mitry *et al*[84], 2006	FOLFOX	18	0%	0.9	1.3	NR
Gebbia *et al*[85], 2007	FOLFOX	42	14%	4	6.7	NR
Novarino *et al*[86], 2009	FOLFOX	23	0%	2.7	4.6	NR
Yoo *et al*[87], 2009	FOLFOX	30	6.7%	1.4	3.5	NR
Chung *et al*[88], 2013	FOLFOX	44	11%	2.3	7.3	NR
Berk *et al*[89], 2012	FOLFOX	46	17%	3.7	5.8	NR
Sancho *et al*[58], 2008	CapOx[2]	18	5.6%	3.9	5.8	NR
Xiong *et al*[83], 2008	CapOx	41	2.4%	2.3	5.4	21%
Casetti-Blesa *et al*[90], 2009	CapOx	15	6.7%	NR	5.3	NR
Berk *et al*[89], 2012	CapOx	39	18%	3.7	4.9	NR
Pelzer *et al*[91], 2009	OFF	37	5.4%	2.8	5.1	NR
Pelzer *et al*[92], 2011	OFF	23	0%	NR	4.8	NR
Pelzer *et al*[93], 2008	OFF	76	NR	3	6.3	NR
Assaf *et al*[94], 2011	FOLFIRINOX	27	19%	5.4	8.5	NR
Togawa *et al*[95], 2007	Cisplatin, S-1	17	29%	NR	10	32%
Kim *et al*[96], 2012	Cisplatin, S-1	11	0%	1.5	2.7	NR
Takahara *et al*[97], 2013	Oxaliplatin, S-1	30	10%	3.4	5.0	NR
Cantore *et al*[83], 2004	Oxaliplatin, irinotecan	30	10%	4.1	5.9	23%
Oh *et al*[42], 2010	Oxaliplatin, irinotecan	14	21%	1.4	4.1	7.1%
Reni *et al*[98], 2006	Oxaliplatin, raltitrexed	41	24%	1.8	5.2	12%
Mazzer *et al*[99], 2009	Oxaliplatin, pemetrexed	16	56%	3.3	NR	NR
	Non-platinum based regimens					
Yoo *et al*[100], 2009	FOLFIRI	31	0%	1.9	3.9	NR
Gebbia *et al*[101], 2010	FOLFIRI	40	15%	3.7	6.0	0%
Cereda *et al*[102], 2010	FOLFIRI or XELIRI	34	0%	2.0	4.2	5.6%
Zaniboni *et al*[103], 2012	FOLFIRI	50	8%	3.2	5.0	NR
Neuzillet *et al*[104], 2012	FOLFIRI	63	7.9%	3.0	6.6	NR
Mizuno *et al*[105], 2013	S-1, irinotecan	60	18%	3.6	6.9	NR
Blaya *et al*[106], 2007	Capecitabine, docetaxel	24	13%	NR	NR	NR
Kalopodis *et al*[107], 2011	Capecitabine, docetaxel	31	9.7%	2.4	6.4	15%
Kim *et al*[51], 2009	5-FU, paclitaxel	28	10%	2.5	7.6	NR
Lee *et al*[108], 2009	Conti-FAM[3]	31	12%	2.3	6.7	NR
Shi *et al*[109], 2012	Capecitabine, thalidomide	31	6.5%	2.7	6.1	NR
Saif *et al*[110], 2009	Capecitabine, PHY906	25	5.3%	NR	NR	NR
Ulrich-Pur *et al*[111], 2003	Irinotecan, raltitrexed	19	16%	4.0	6.8	NR
Reni *et al*[112], 2004	MDI	15	0%	1.7	6.1	0%
Cereda *et al*[113], 2011	Mitomycin, ifosfamide	21	4.8%	1.7	3.7	9.5%
Ko *et al*[114], 2008	Irinotecan, docetaxel	14	0%	1.2	4.5	21%

[1]Intent-to-treat analysis; [2]Pooled analysis of pancreatic (50%), biliary (22%), gallbladder (22%) and ampullary (6%) cancer; [3]Pooled analysis of pancreatic (48%), biliary (35%) and gallbladder (16%) cancer. FOLFOX: Oxaliplatin, 5-fluorouracil, folinic acid, biweekly; CapOx: Capecitabine, oxaliplatin, OFF: Oxaliplatin, 5-fluorouracil, leucovorin, in 6-wk cycles, FOLFIRINOX: Oxaliplatin, leucovorin, 5-fluorouracil, irinotecan; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan; XELIRI: Capecitabine, irinotecan; 5-FU: 5-Fluorouracil; Conti-FAM: 5-Fluorouracil, doxorubicin, mitomycin-c; MDI: Mitomycin, docetaxel, irinotecan; NR: Not reported; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression.

with response rates ranging between 8%-15% and median progression-free survival in the 3-4 mo range[45-47]. Another fluoropyrimidine/irinotecan combination termed IRIS (irinotecan plus S-1) was compared to S-1 alone in a randomized phase II trial from Japan of 127 patients who had progressed on gemcitabine[48]. The combination produced a response rate of 18%, compared to 6% with S-1 alone ($P = 0.03$). Median PFS and OS also favored the IRIS combination, although these improvements did not reach statistical significance (107 and 208 d, compared to 58 and 176 d for S-1, respectively). Irinotecan has also been tested in combination with the folate antimetabolite raltitrexed in a randomized phase II trial *vs* raltitrexed monotherapy[98]. In this 38-patient study, the doublet was associated with a higher rate of objective response (16% *vs* 0%) and prolonged PFS (4.0 mo *vs* 2.5 mo) and OS (6.5 mo *vs* 4.3 mo), albeit with higher rates of clinically relevant toxicities including gastrointestinal symptoms and alopecia.

Taxanes represent the other most frequently studied class of agents evaluated in the salvage setting for pancreatic cancer. Combination regimens including capecitabine/docetaxel[49,50] and 5-FU/paclitaxel[51] have been studied in small phase II trials, with response rates in the 10% range and median PFS centered around 2 mo. A small phase II study looking at the combination of irinotecan/docetaxel was discontinued early due to excess toxicity, with no responses observed in 14 evaluable patients[52]. Table 3 highlights other non-platinum-based combinations that have been explored, mostly in the context of single-arm phase II studies.

Table 4 Ongoing randomized phase II/III trials of refractory pancreatic cancer therapy

Clinical trial	Design	Study arms	Goal enrollment	Primary measure	Previous therapy	Status
NCT00674973	Phase II	Erlotinib *vs* placebo	207	PFS, biomarkers	1 prior CT regimen	Active, not recruiting
NCT01074996	Phase II	S-1 *vs* S-1, leucovorin	96	OS	Gem-based	Recruiting
NCT01417000	Phase II	GVAX pancreas, cyclophosphamide, CRS-207 *vs* GVAX pancreas, cyclophosphamide	90	OS	≥ 1 prior CT regimen	Active, not recruiting
NCT01423604	Phase II	Capecitabine, ruxolitinib *vs* capecitabine, placebo	138	OS	Gem-based	Active, not recruiting
NCT01658943	Phase II	Selumetinib, MK2206 *vs* FOLFOX	133	OS, PFS	Gem-based	Recruiting
NCT01796782	Phase II	QYHJ granules *vs* Capecitabine	60	OS	Non-capecitabine containing CT	Active, not recruiting
NCT01121848	Phase III	Capecitabine or 5-FU, leucovorin *vs* XELOX or mFOLFOX-6	128	PFS	Gem-based	Active, not recruiting
NCT01494506	Phase III	MM-398 *vs* MM-398, 5-FU, leucovorin *vs* 5-FU, leucovorin	405	OS	Gem-based	Active, not recruiting
NCT01954992	Phase III	Glufosfamide *vs* 5-FU	430	OS	Gem-based	Recruiting
NCT01956812	Phase III	Gemcitabine, IMMU-107 *vs* Gemcitabine, placebo	440	OS	2 prior CT regimens, ≥ 1 Gem-based	Not yet open for recruitment

GVAX pancreas: Allogeneic pancreatic cancer cell vaccine, induces GM-CSF production; CRS-207: Attenuated listeria monocytogenes vaccine, induces immune response to mesothelin; MK2206: Akt inhibitor; FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin; QYHJ: Qingyihuaji formulation; 5-FU: 5-Fluorouracil; XELOX: Capecitabine, oxaliplatin; mFOLFOX-6: Modified schedule 5-fluorouracil, leucovorin, oxaliplatin; MM-398: Liposomal irinotecan; IMMU-107: Yttrium-90 radiolabeled humanized monoclonal antibody against mucin1 (CD227); PFS: Progression free survival; OS: Overall survival; CT: Chemotherapy; Gem-based: Gemcitabine-containing chemotherapy regimen.

TARGETED THERAPIES

In recent years, an improved understanding of cancer biology has led to the development of targeted therapies intended to inhibit tumor-specific proteins or pathways instrumental in cellular proliferation and survival. These include small molecule inhibitors, which inhibit a specific intracellular protein or pathway; or engineered antibodies, designed to target proteins expressed preferentially on the tumor cell surface. In pancreatic cancer, a number of potentially actionable oncogenic pathways have been identified for which such targeted therapies have been developed and tested, many in the chemo-refractory setting, either alone or in combination with other targeted or cytotoxic agents.

Small molecule inhibitors that bind the intracellular tyrosine kinase (TK) domain of the human epidermal growth factor receptor (HER1/EGFR) block signaling through this pathway that controls aspects of DNA synthesis, cell proliferation, adhesion, and migration. Erlotinib, one such anti-EGFR TK inhibitor (TKI), was approved in the front-line setting for advanced pancreatic cancer based on a small but statistically significant improvement in median survival when added to gemcitabine in a randomized phase III trial led by the National Cancer Institute of Canada[53]. When tested as monotherapy in the setting of gemcitabine-refractory disease in a (non-published) phase II trial, erlotinib produced prolonged disease control (greater than 8 wk) in 10/40 evaluable patients, with a median time to progression of 1.6 mo and a median survival of 4.1 mo[54]. A randomized trial of erlotinib *vs* placebo (NCT00674973) has completed accrual with the goal of identifying biomarkers predictive of benefit to this agent (Table 4); data are not yet available. Another phase II study tested erlotinib in combination with capecitabine in the refractory setting and produced somewhat better results, including a 10% objective response rate, a median PFS of 3.4 mo, and a median OS of 6.5 mo, with no associated grade 4 toxicities[55].

Downstream of EGFR is the protein encoded by the *KRAS* oncogene, which is mutated and hence constitutively activated in the vast majority of pancreatic cancers[56-58]. While KRAS itself has proved to be challenging as a druggable target, KRAS effector pathways such as the MAP (RAF/MEK/ERK) signaling cascade may be more amenable to pharmacologic inhibition. Bodoky *et al*[59] investigated selumetinib, a selective MEK1/2 inhibitor, in a randomized phase II trial *vs* capecitabine for gemcitabine-resistant pancreatic cancer. Selumetinib, though well tolerated, did not improve survival relative to capecitabine monotherapy, with median PFS and OS times of 2.1 and 5.4 mo compared to 2.2 and 5.0 mo, respectively. Two of 32 patients on the selumetinib arm (6.3%) did achieve a (unconfirmed) partial response.

Several lines of preclinical evidence indicate that inhibition of MEK induces compensatory hyperactivation of a semi-parallel EGFR signaling pathway, the PI3K/AKT cascade[60], and that simultaneous blockade of multiple nodes leads to better anti-tumor activity. Ko *et al*[61] tested this approach of dual inhibition for refractory pancreatic cancer in a multicenter phase II study, using the combination of selumetinib plus erlotinib. Although no objective responses were observed, 12 of 46 patients (26%) achieved stable disease for a minimum of 12 wk, and 38% of evaluable patients had a biomarker response (CA19-9 decline > 50%). Median OS on this study was 7.5 mo. An ongoing randomized phase II study led by the Southwest Oncology Group (SWOG 1115) is comparing the combination of selumetinib plus the AKT inhibitor MK2206 to standard FOLFOX chemotherapy in patients who have progressed on front-line gemcitabine-based treatment (NCT01658943) (Table 4).

Table 3 Clinical results of second-line chemotherapy trials

Ref.	Regimen	Sample size	RR[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Ignatiadis *et al*[67], 2006	Gefitinib, docetaxel	26	0%	2.1	2.9	NR
Brell *et al*[68], 2009	Gefitinib, docetaxel	41	2.4%	1.8	4.5	0%
Kulke *et al*[69], 2007	Erlotinib, capecitabine	30	10%	3.4	6.5	26%
Tang *et al*[58], 2009	Erlotinib	30	0%	1.6	4.1	6 m = 39%[2]
Iyer *et al*[59], 2010	Erlotinib	18	0%	1.4	3.3	NR
Bodoky *et al*[70], 2012	Selumetinib	32	6.3%	2.1	5.4	NR
Ko *et al*[71], 2013	Selumetinib, erlotinib	46	0%	2.6	7.5	NR
Wolpin *et al*[62], 2009	Everolimus	33	0%	1.8	4.5	NR
Garrido-Laguna *et al*[63], 2010	Sirolimus	31	0%	NR	NR	6 m = 26%[2]
Javle *et al*[64], 2010	Everolimus, erlotinib	16	0%	1.6	2.9	NR
Javle *et al*[65], 2010	Temsirolimus	5	0%	0.6	1.5	NR
Dragovich *et al*[66], 2008	Vatalinib	65	NR%	6 m = 14%[2]	6 m = 31%[2]	NR
O'Reilly *et al*[60], 2010	Sunitinib	77	1.4%	1.3	3.7	NR
Ko *et al*[61], 2010	Bevacizumab, erlotinib	36	2.8%	1.3	3.4	6 m = 22%[2]
Astsaturov *et al*[106], 2011	Bevacizumab	16	0%	1.4	5.5	NR
Astsaturov *et al*[106], 2011	Bevacizumab, docetaxel	16	0%	1.6	4.2	NR
Milella *et al*[72], 2004	Celecoxib, 5-FU	17	12%	1.9	3.5	NR
Pino *et al*[73], 2009	Celecoxib, capecitabine[3]	35	8.6%	4.0	4.4	NR
Starling *et al*[107], 2012	Imatinib, gem, oxaliplatin	27	7.4%	4.6	5.6	28%
Carvajal *et al*[108], 2009	Flavopiridol, docetaxel	10	0%	1.9	4.2	0%
Nallapareddy *et al*[109], 2010	Sarcatinib	19	0%	1.6	2.5	NR

[1]Intent-to-treat analysis; [2]Pooled analysis of pancreatic (86%) and biliary (14%) cancer; [3]6 m: 6 mo survival rate. 5-FU: 5-Fluorouracil; Gem: Gemcitabine; NR: Not reported; PFS: Progression free survival; OS: Overall survival; TTP: Time to progression.

Among other effects, the EGFR/PI3K/AKT signaling cascade results in activation of the mammalian target of rapamycin (mTOR) protein kinase. mTOR plays a central role in cell growth and cell-cycle control, integrating mitogenic signals from various extracellular ligands including EGF, insulin, and insulin-like growth factor (IGF-1/2). Wolpin *et al*[62] tested the direct mTOR inhibitor everolimus in gemcitabine-resistant disease, but observed no objective responses and a disease control rate of only 21%, with a median PFS of 1.8 mo. A trial of sirolimus monotherapy, in which 75% of patients had received prior chemotherapy, similarly revealed minimal to no clinical activity[63]. Javle *et al*[64] tested a dual inhibition strategy of everolimus in combination with erlotinib in a small phase II study, but this study was closed early due to futility.

In a separate (but not unrelated) category, anti-angiogenic strategies, primarily targeting vascular endothelial growth factor (VEGF) and its corresponding receptor (VEGFR), have been extensively studied in pancreatic cancer in both the front-line and salvage settings. The anti-VEGF monoclonal antibody bevacizumab, which did not improve survival when added to either gemcitabine[105] or erlotinib/gemcitabine[106] as first-line therapy in two large randomized phase III studies, has also been explored in the refractory setting, with fairly minimal activity. A phase II trial by Ko *et al*[61] examined the combination of bevacizumab and erlotinib in gemcitabine-refractory patients and reported a progression-free survival rate of 1.3 mo, with a median OS of only 3.4 mo. Oral TKIs directed against VEGFR have also been explored, including fairly large single-arm phase II studies of vatalinib[66] and sunitinib[60]. Sunitinib, tested in the context of a cooperative group study (CALGB 80603), reported a single objective response amongst 77 patients (1.3%), a disease control rate of 22%, and progression-free and overall survival times of 1.3 and 3.7 mo, respectively. Interestingly, recent evidence suggests that pancreatic cancer, despite VEGF/VEGFR upregulation, is poorly vascularized relative to other tumors[107]. These data may help explain the minimal efficacy of anti-angiogenic therapy in pancreatic cancer.

Several other potential oncogenic pathways have been targeted in the second-line setting. Cyclooxygenase-2 (COX-2) is upregulated in pancreatic cancer[71], and its product prostaglandin-E can transactivate EGFR and promote tumor survival[72]. Celecoxib, a selective COX-2 inhibitor, has been tested in combination with fluoropyrimidines (5-FU or capecitabine) in second-line regimens and found to produce response rates of 9%-12% with very mild side effect profiles[72,74]. Ruxolitinib, an oral inhibitor of Janus kinase (JAK) signaling that is approved for use in myelofibrosis, has been evaluated as second-line therapy in combination with capecitabine in a randomized phase II trial in patients with refractory pancreatic cancer (NCT01423604); this study has completed accrual as of mid-2013 and results are currently being awaited (Table 4). Data from other studies of targeted therapies are shown in Table 5.

DISCUSSION

There is presently no universally accepted standard of care for patients with advanced pancreatic cancer who have progressed on front-line therapy. As described above, with a few notable exceptions, the vast majority of studies conducted in this setting have been single-arm, single-institution trials with relatively modest sam-

ple sizes. Such non-randomized trials need to be carefully interpreted in light of their inherent selection bias; certainly, those patients who are well enough to consider salvage treatment may already have more favorable tumor biology that influences patient outcomes, including survival rates, independent of the specific choice of therapy.

This argument certainly lends itself in support of randomized phase II / III trials; studies that fit this category and remain open or are still actively recruiting (as of December 2013) are presented in Table 4. However, it should be recognized that the design and performance of randomized studies in this setting is particularly challenging. As the CONKO investigators observed, a control arm of best supportive care alone, while perhaps appropriate in many cases, is not a particularly attractive option to patients and may hinder study enrollment. But deciding on what the appropriate reference standard should be in a randomized study design, absent compelling evidence to support one regimen over another, is not a straightforward issue. For example, can a fluoropyrimidine alone (capecitabine, S-1, or 5-FU) be considered adequate as a control arm? Some might argue that there are adequate data indicating that a (fluoropyrimidine plus oxaliplatin) combination is clearly superior, and thus represents a more appropriate (and ethical) comparator for a randomized trial. But for a novel agent being evaluated in this setting, does comparing it alone to a reference standard of, for example, FOLFOX, provide adequate study equipoise?

It should also be noted that almost all of the studies detailed above were conducted in the pre-FOLFIRINOX era; as such, they primarily included patients who received a gemcitabine-based regimen as front-line therapy. It would seem logical that for a patient in the present time who receives FOLFIRINOX as first-line therapy, the next step would be to try a gemcitabine-based regimen (monotherapy, gemcitabine/*nab*-paclitaxel, or perhaps another gemcitabine-based combination). However, prospective randomized studies are still required to support this recommendation. Moreover, such FOLFIRINOX-treated patients would obviously not be appropriate for enrollment onto a study in which (s)he might be randomized to receive any of these same drugs, alone or in combination, as part of the control arm. Thus, looking ahead, one must consider the possibility that separate clinical trials should be developed in the second-line setting depending on patients' first-line treatment exposure.

These conundrums highlight only some of the challenges in designing clinical trials in this refractory setting for pancreatic cancer. The other major obstacle hindering progress is the lack of validated predictive biomarkers for this disease that could help inform treatment decisions, whether for conventional cytotoxics or for targeted agents. The track record for targeted agents in chemorefractory pancreatic cancer is particularly dismal, bringing to light the fact that, in the future, we need to be superselective in identifying the patients most likely to benefit from a particular novel therapy, and to develop patient enrichment schemes in clinical trial design accordingly. However, obtaining adequate tumor tissue in this patient population for identifying and validating predictive molecular markers represents a substantial ongoing challenge.

We also propose that certain uniform study benchmarks be established to define "success" for a particular regimen and justify moving on to a larger phase III study. A recent systematic review of 34 studies found a median survival for any second line regimen of 6 mo, compared to 2.8 mo for best supportive care alone[75]. With this in mind, thresholds of at least 6 mo for median OS, at a bare minimum, and 4 mo for median PFS, represent reasonable starting points that could be considered clinically meaningful and reflect treatment efficacy that matches or is superior to most historic data reported to date.

Additionally, cost-effectiveness analysis represents an important element to consider embedding within trial design, especially in larger studies, to help inform broader health care decisions in this clinical context in which the magnitude of survival benefit of any novel agent or regimen is likely to be measurable in extra months, if not only weeks. Finally, and perhaps even more importantly, we recommend that every effort should be made to incorporate quality of life (QoL) endpoints/patient-reported outcomes into study design, as these measures are of paramount importance for patients in this late-stage setting.

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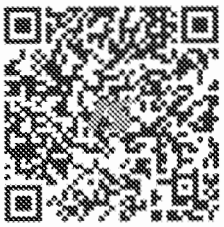

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Poster #293

Characteristics of Long-term Survivors in a Randomized Phase 3 Trial (NAPOLI-1) of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Treated With Liposomal Irinotecan (nal-IRI; MM-398) + 5-FU/LV

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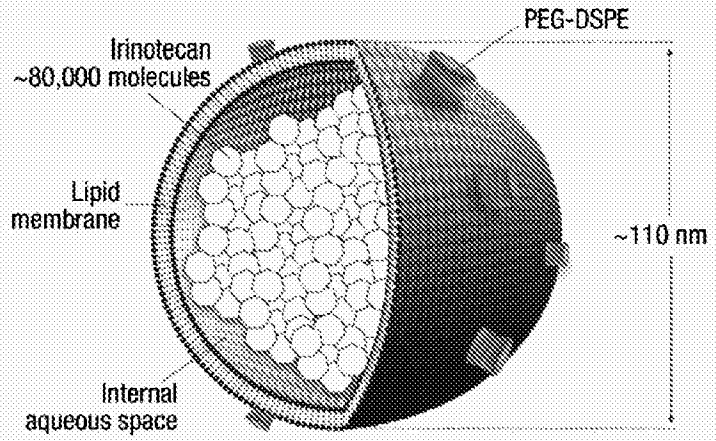
BACKGROUND

- Pancreatic cancer is the third leading cause of cancer death in the United States, the fifth leading cause in Europe, and the seventh leading cause globally[1,2]
- Treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) remains a significant unmet need; studies have shown a 1-year survival rate of approximately 20% to 50% after diagnosis, depending on first-line treatment[3-5]
- nal-IRI (liposomal irinotecan; MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (**Figure 1**)[6]

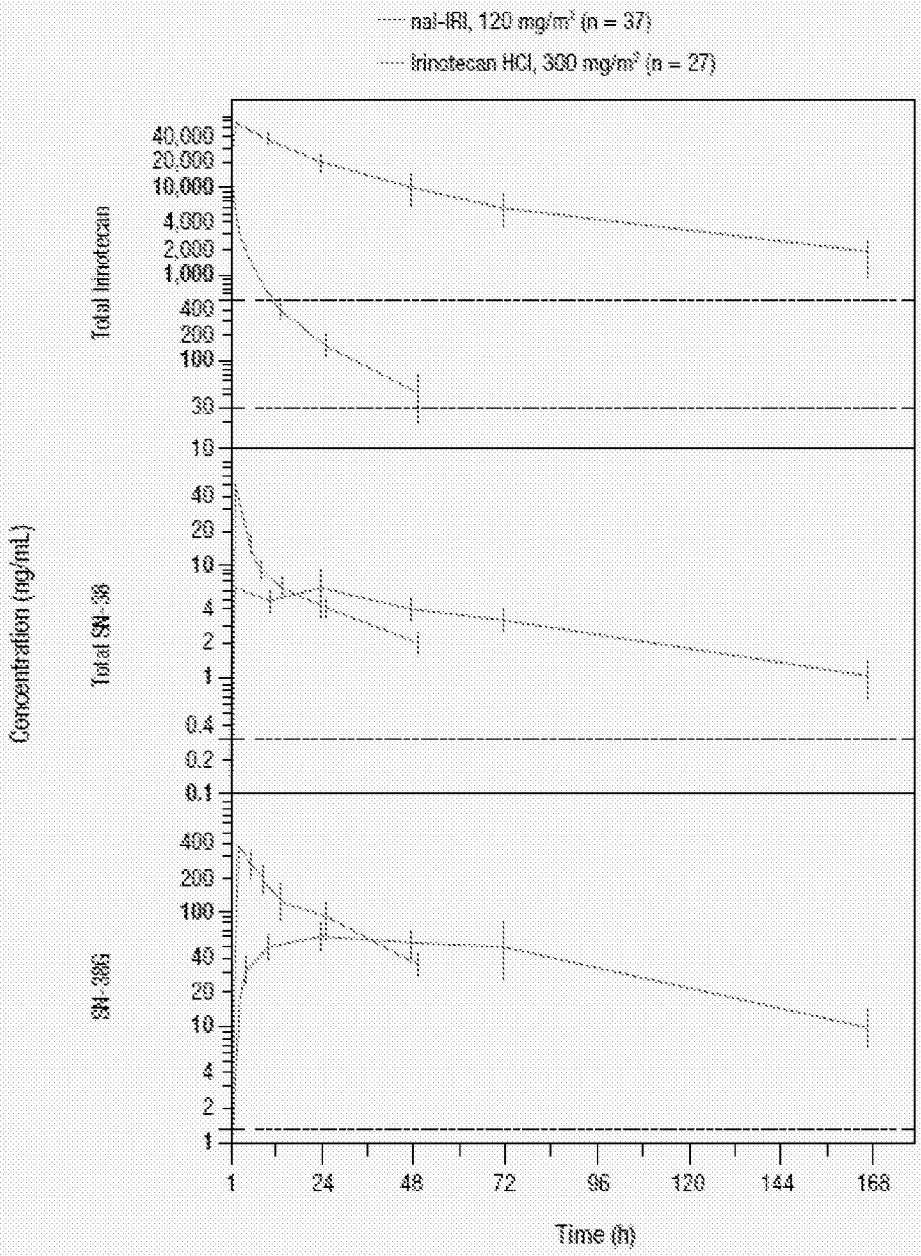
Figure 1. nal-IRI Design[6]



nal-IRI, liposomal irinotecan; PEG-DSPE, polyethylene glycol)–distearoylphosphatidylethanolamine.

- Pharmacokinetic analyses performed in patients with gastric cancer who were treated with either nal-IRI (120 mg/m^2) or conventional irinotecan hydrochloride trihydrate salt (300 mg/m^2) showed extended circulation of irinotecan within the liposome (**Figure 2**)[7,8]

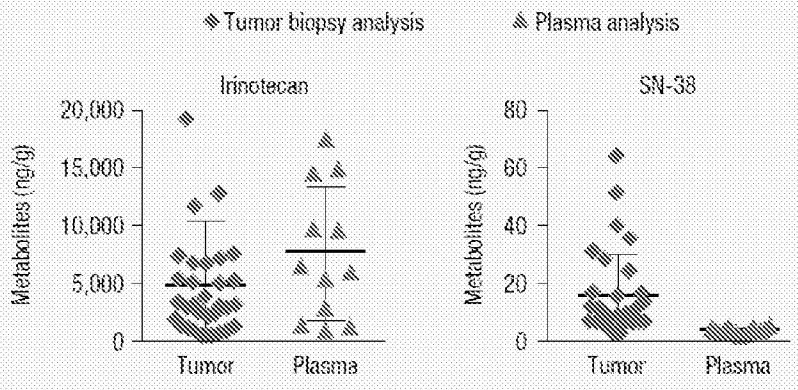
Figure 2. Sustained Circulation of nal-IRI[7,8]



nal-IRI, liposomal irinotecan; AUC, area under the curve; C_{max}, maximal concentration; HCl, hydrochloride trihydrate salt; SN-38, active metabolite of irinotecan; SN-38G, SN-38 glucuronide.
Comparing nal-IRI with irinotecan HCl, total irinotecan AUC was 4.8 times greater and total irinotecan C_{max} was 13.4 times greater; SN-38 AUC was 1.4 times greater, and SN-38 C_{max} was 0.19 times as great. The peak of SN-38 metabolite was lower with nal-IRI vs irinotecan HCl, without an increase in SN-38 plasma AUC.

- A mouse xenograft model of human colon carcinoma demonstrated that the liposomal formulation facilitates intratumoral drug deposition through the enhanced permeability and retention effect[6]
- Preliminary data from a pilot study in various cancers showed higher levels of SN-38 (the active metabolite of irinotecan) in tumor biopsies compared with plasma at 72 hours, suggesting local metabolic conversion (and thus activation) of irinotecan to SN-38 (**Figure 3**)[6]

Figure 3. Irinotecan and SN-38 Levels 72 Hours After nal-IRI Treatment[6]



LC/MS/MS, liquid chromatography-tandem mass spectrometry; LLoQ, lower limit of quantification; nal-IRI, liposomal irinotecan.
Drug metabolite quantification in tumor biopsies and plasma analyses from a study of patients (N = 14) with advanced solid tumors. Tumor biopsy material averaged 10.5 mg (range, 3.3-21.9 mg); metabolite detection was in an LC/MS/MS TSQ Vantage instrument, with LLoQ of 50 pg/mL for irinotecan and 100 pg/mL for SN-38.
Plasma analysis was performed at QPS according to validated procedures, with LLoQ of 140 ng/mL for irinotecan and 500 pg/mL for SN-38.

- Results from the primary analysis of the large (N = 417), phase 3 NAPOLI-1 trial (NCT01494506) led to the approval of nal-IRI (in the United States, Taiwan, Australia, and the EU) for use in combination with 5-fluorouracil and leucovorin (5-FU/LV) for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy[10]
  - Median overall survival (OS; the primary endpoint) was significantly improved with nal-IRI+5-FU/LV vs 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio [HR], 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$)
  - Median progression-free survival (PFS) was significantly improved with nal-IRI+5-FU/LV vs 5-FU/LV (3.1 vs 1.5 months; unstratified HR, 0.56 [95% CI, 0.41-0.75]; $P = 0.0001$)
  - Objective response rate (ORR) was significantly improved with nal-IRI+5-FU/LV vs 5-FU/LV (16% vs 1%; $P < 0.0001$)
  - The grade ≥3 treatment-emergent adverse events (TEAEs) most commonly reported with nal-IRI+5-FU/LV were neutropenia, fatigue, diarrhea, and vomiting
  - Quality-of-life measures at 6 and 12 weeks did not differ appreciably from baseline measures with nal-IRI+5-FU/LV or with 5-FU/LV; quality of life was maintained in patients treated with nal-IRI+5-FU/LV, despite the addition of another chemotherapeutic agent[11]

OBJECTIVES

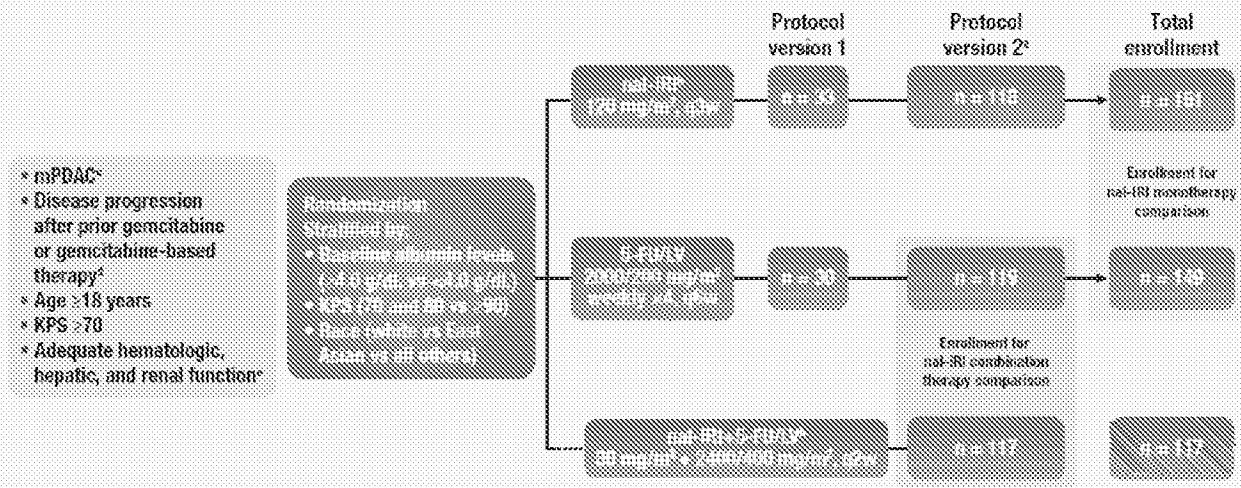
- This was a post hoc analysis of the NAPOLI-1 trial to:
  - Evaluate the characteristics of long-term survivors (patients who survived ≥1 year) in NAPOLI-1
  - Report efficacy and safety/tolerability of nal-IRI+5-FU/LV in this population

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (**Figure 4**)[10]

Figure 4. NAPOLI-1 Study Design[10]



5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; nal-IRI, liposomal irinotecan; q2w, every 2 weeks; q3w, every 3 weeks; q6w, every 6 weeks.
[a]Patients were initially randomized to nal-IRI monotherapy or 5-FU/LV. The protocol was amended to add a third arm (nal-IRI+5-FU/LV) after safety data on the combination became available from a concurrent study in metastatic colorectal cancer; 63 patients were enrolled under protocol version 1 before all sites switched to version 2. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm.
[b]The above nal-IRI doses are expressed as the irinotecan hydrochloride (HCl) trihydrate salt. Converting the dose from irinotecan HCl trihydrate to irinotecan free base is accomplished by substituting the molecular weight of irinotecan HCl trihydrate (677.19 g/mol) with that of irinotecan free base (586.68 g/mol), which results in a conversion factor of 0.866. The above nal-IRI doses of 120 and 80 mg/m² approximate to 100 and 70 mg/m² irinotecan free base.
[c]Histologically or cytologically confirmed mPDAC, with documented measurable or non-measurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1).
[d]In a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
[e]Including absolute neutrophil count >1500 cells/µL, normal serum total bilirubin, and albumin levels ≥3.0 g/dL. Additionally, patients with an active central nervous system metastasis, a clinically significant gastrointestinal disorder, or a severe arterial thromboembolic event <6 months before study entry were excluded.

Long-term Survivor Analysis

- This post hoc analysis (data cutoff, November 16, 2015) focuses on the 46 patients assigned (under protocol version 2) to either nal-IRI+5-FU/LV every 2 weeks (n = 29) or 5-FU/LV weekly for weeks 1-4 of 6-week cycles (n = 17) who survived ≥1 year
- For comparison, baseline characteristics and efficacy for all 117 patients assigned to treatment with nal-IRI+5-FU/LV and all 119 patients assigned to the combination control arm (treatment with 5-FU/LV under protocol version 2) are included
- Efficacy endpoints are reported in the intent-to-treat population and safety/tolerability endpoints are reported in the safety population, in which patients are categorized as treated
- These analyses are limited by small sample sizes

RESULTS

Patient Characteristics

- A total of 29 (25%) patients in the nal-IRI+5-FU/LV arm and 17 (14%) patients in the 5-FU/LV arm survived ≥1 year
- The baseline characteristics of these long-term survivors, as well as those in the nal-IRI+5-FU/LV arm and the 5-FU/LV arm of the overall patient population, are summarized in **Table 1**

Table 1. Baseline Characteristics of All Patients and Long-term Survivors[a]

	All Patients		Long-term Survivors	
	nal-IRI+5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+5-FU/LV (n = 29)	5-FU/LV (n = 17)
Age				
Mean (SD), years	62 (9)	61 (9)	60 (10)	56 (12)
Median (IQR), years	63 (57-70)	62 (55-69)	59 (55-66)	57 (44-63)
≤65 years	66 (56)	91 (68)	21 (72)	14 (82)
>65 years	51 (44)	38 (32)	8 (28)	3 (18)
Sex				
Female	48 (41)	52 (44)	13 (45)	9 (53)
Race				
White	72 (62)	76 (64)	19 (66)	8 (47)
East Asian	34 (29)	36 (30)	10 (34)	7 (41)
Black	4 (3)	3 (3)	0	2 (12)
Other	7 (6)	4 (3)	0	0
Region				
Asia	34 (29)	35 (29)	10 (34)	6 (35)
Europe	47 (40)	49 (41)	13 (45)	5 (29)
North America	19 (16)	19 (16)	2 (7)	4 (24)
Other	17 (15)	16 (13)	4 (14)	2 (12)
KPS				
≥90	66 (56)	67 (56)	22 (76)	13 (76)
<90	51 (44)	52 (44)	7 (24)	4 (24)
Neutrophil-to-lymphocyte ratio				
≤5	93 (71)	81 (68)	26 (86)	10 (59)
>5	33 (28)	38 (32)	3 (10)	7 (41)
Albumin				
≥40 g/L	53 (45)	54 (45)	16 (55)	13 (76)
<40 g/L	64 (55)	65 (55)	13 (45)	4 (24)
CA19-9 level[b]				
Median (IQR), U/mL	1278 (120-9001)	1292 (99-16,381)	334 (18-2264)	108 (16-475)
≥40 U/mL, n/N (%)	92/114 (81)	91/114 (80)	19/27 (70)	10/16 (63)
<40 U/mL, n/N (%)	22/114 (19)	23/114 (20)	8/27 (30)	6/16 (38)
<59 x ULN, n/N (%)	64/114 (56)	61/114 (54)	20/27 (74)	14/16 (88)
Pancreatic tumor location				
Head	76 (65)	69 (58)	20 (69)	12 (71)
Not head	41 (35)	50 (42)	9 (31)	5 (29)
Site of metastatic lesions				
Liver	75 (64)	84 (71)	12 (41)	8 (47)
Lung	36 (31)	36 (30)	9 (31)	8 (47)
Distant lymph nodes	32 (27)	31 (26)	10 (34)	5 (29)
Regional lymph nodes	13 (11)	14 (12)	6 (21)	2 (12)
Peritoneum	28 (24)	32 (27)	11 (38)	3 (18)
Pancreas	75 (64)	72 (61)	18 (62)	7 (41)
Other	27 (23)	39 (33)	7 (24)	5 (29)
Measurable metastatic lesions				
1	19 (16)	22 (18)	7 (24)	8 (47)
2	49 (42)	58 (49)	10 (34)	3 (18)
3	22 (19)	15 (13)	4 (14)	2 (12)
>3	7 (6)	8 (7)	1 (3)	0
Prior therapy				
Gemcitabine monotherapy only	53 (45)	55 (46)	13 (45)	9 (53)
Gemcitabine in combination	64 (55)	64 (54)	16 (55)	8 (47)
5-FU	50 (43)	52 (44)	14 (48)	6 (35)
Platinum	38 (32)	41 (34)	10 (34)	5 (29)
Irinotecan	12 (10)	17 (14)	0	2 (12)
Radiotherapy	24 (21)	27 (23)	9 (31)	7 (41)
Whipple procedure	30 (26)	33 (28)	8 (28)	9 (53)
Biliary stent	15 (13)	8 (7)	3 (10)	1 (6)
Prior lines of metastatic therapy				
0[c]	15 (13)	15 (13)	1 (3)	3 (18)
1	62 (53)	67 (56)	18 (62)	9 (53)
>1	40 (34)	37 (31)	10 (34)	5 (29)

5-FU, 5-fluorouracil; CA19-9, carbohydrate antigen 19-9; IQR, interquartile range; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan; SD, standard deviation; ULN, upper limit of normal (37 U/mL for CA19-9).

[a]Data are n (%) unless otherwise specified.

[b]Includes only patients who had a measured CA19-9 value before treatment, with denominators as shown.

[c]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but had no previous therapy for metastatic disease.

Treatment Exposure

- The mean duration of treatment (time from first to last study drug administration) in all patients was 17 weeks (median, 7 weeks; range, 0.4-126 weeks) in the nal-IRI+5-FU/LV arm and 9 weeks (median, 3 weeks; range, 0.3-67 weeks) in the 5-FU/LV arm
- The mean duration of treatment in the long-term survivors was 41 weeks (median, 40 weeks; range, 2-126 weeks) in the nal-IRI+5-FU/LV arm and 25 weeks (median, 17 weeks; range, 0.3-67 weeks) in the 5-FU/LV arm
- In all patients, the mean (median) relative dose intensity of nal-IRI was 83% (86%), and the mean (median) relative dose intensities of 5-FU were 83% (88%) and 96% (100%) in the nal-IRI+5-FU/LV and 5-FU/LV arms, respectively; in the long-term survivors, the mean (median) relative dose intensity of nal-IRI was 72% (71%), and the mean (median) relative dose intensities of 5-FU were 72% (72%) and 97% (98%) in the nal-IRI+5-FU/LV and 5-FU/LV arms, respectively

Efficacy

- Efficacy parameters for the long-term survivors and for all patients in the nal-IRI+5-FU/LV arm and the 5-FU/LV arm are shown in **Table 2**
- Among long-term survivors, the median OS was numerically longer for patients who received 5-FU/LV (25.1 months [95% CI, 16.5-33.3 months]) vs nal-IRI+5-FU/LV (19.1 months [95% CI, 15.3-21.3 months]), which may be explained by small numbers of patients and/or administration of post-study therapy; however, no statistical comparisons were performed
  - A higher proportion of long-term survivors in the 5-FU/LV arm vs the nal-IRI+5-FU/LV arm received any post-study drug (76% vs 59%)

Table 2. Summary of Efficacy in All Patients and Long-term Survivors

	All Patients		Long-term Survivors	
Endpoint	nal-IRI+5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+5-FU/LV (n = 29)	5-FU/LV (n = 17)
OS, months, median (95% CI)[a]	6.2[b] (4.8-8.4)	4.2[b] (3.3-5.3)	19.1[b] (15.3-21.3)	25.1[b] (16.5-33.3)
PFS, months, median (95% CI)[a]	3.1 (2.7-4.2)	1.5 (1.4-1.8)	9.9 (7.0-14.2)	8.1 (1.4-16.5)
TTF, months, median (95% CI)[a]	2.3 (1.6-2.8)	1.4 (1.3-1.4)	9.7 (5.4-13.6)	4.7 (1.3-9.6)
ORR, % (95% CI)[c]	17 (10-24)	1 (0-2)	31 (14-48)	0 (0-0)
Best overall response, n (%)				
PR[c]	20 (17)	1 (1)	9 (31)	0
SD[d]	38 (32)	26 (22)	15 (52)	10 (59)
Non-CR/non-PD[e]	3 (3)	2 (2)	1 (3)	1 (6)
PD	34 (29)	56 (47)	3 (10)	4 (24)
Not evaluable	22 (19)	34 (29)	1 (3)	2 (12)
DCR (CR + PR + SD + non CR/non-PD), % (95% CI)[c,d]	52 (43-61)	24 (17-32)	86 (74-99)	65 (42-87)
CA19-9				
50% reduction from baseline, n/N[f] (%)	27/95 (28)	8/82 (10)	13/20 (65)	6/9 (67)

5-FU, 5-fluorouracil; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; CR, complete response; DCR, disease control rate; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; TTF, time to treatment failure.
[a]Kaplan-Meier estimate.
[b]In the 4 patient groups shown, 36%, 42%, 59%, and 76%, respectively, received any post-study drug.
[c]Designation of response did not require confirmation and was based solely on the investigator's assessment using RECIST v1.1.
[d]Minimum time from baseline for designation of SD (for patients with measurable disease at baseline) and non-CR/non-PD (for patients with non-measurable disease at baseline) was 6 weeks after starting treatment.
[e]N = patients with baseline CA19-9 >30 U/mL.

Safety/Tolerability

- The most common grade ≥3 TEAEs in patients who survived ≥1 year are summarized in **Table 3**

Table 3. Treatment-Emergent Adverse Events in Long-term Survivors (Based on Grade ≥3 Events Reported for ≥10% of Patients in Either Subgroup of the Safety Population)

	nal-IRI+5-FU/LV (n = 29)		5-FU/LV (n = 16)	
TEAE, %	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	29 (100)	28 (97)	16 (100)	7 (44)
Neutropenia[a]	18 (62)	15 (52)	7 (44)	5 (31)
Decreased WBC count	10 (34)	5 (17)	1 (6)	0
Diarrhea	22 (76)	5 (17)	3 (19)	1 (6)
Fatigue	14 (48)	4 (14)	6 (38)	1 (6)
Vomiting	18 (62)	4 (14)	4 (25)	0
Anemia	12 (41)	1 (3)	4 (25)	2 (13)

5-FU, fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event; WBC, white blood cell.
TEAEs are ordered by grade ≥3 frequency in the nal-IRI+5-FU/LV arm.
[a]Neutropenia includes agranulocytosis (nal-IRI+5-FU/LV, 0% any grade; 5-FU/LV, 0% any grade), febrile neutropenia (3%; 0%), granulocytopenia (0%; 0%), neutropenia (41%; 31%), neutropenic sepsis (3%; 0%), decreased neutrophil count (21%; 13%), and pancytopenia (0%; 0%).

- Dose modifications (dose delays, reductions, and discontinuations) for TEAEs were required in 97% of long-term survivors in the nal-IRI+5-FU/LV arm (93%, 55%, and 7%, respectively) and 56% of long-term survivors in the 5-FU/LV arm (56%, 6%, and 13%, respectively)

- The most common TEAEs that required dose modifications in the long-term survivors of the nal-IRI+5-FU/LV and 5-FU/LV arms were neutropenia (55% and 19%, respectively), diarrhea (31% and 6%), decreased white blood cell count (24% and 6%), pyrexia (14% and 6%), fatigue (14% and 0%), vomiting (10% and 6%), and dehydration (0% and 13%)

CONCLUSIONS

- **A greater proportion of patients receiving nal-IRI+5-FU/LV (25%; 29/117) vs 5-FU/LV (14%; 17/119) survived ≥1 year**

- **The most common grade ≥3 TEAEs in the long-term survivors (reported in ≥10% of patients in either arm) were neutropenia (52%, nal-IRI+5-FU/LV; 31%, 5-FU/LV), decreased white blood cell count (17%; 0%), diarrhea (17%; 6%), fatigue (14%; 6%), vomiting (14%; 0%), and anemia (3%; 13%)**

- **While no statistical comparisons were performed, it was observed that patients in the nal-IRI+5-FU/LV arm who survived ≥1 year were (at baseline): more likely to be ≤65 years of age, more likely to have Karnofsky performance status ≥90, neutrophil-to-lymphocyte ratio ≤5, and CA19-9 level <59 x upper limit of normal, and less likely to have liver metastases when compared with all patients in the nal-IRI+5-FU/LV arm**

- **The clinical significance of the prognostic factors identified in this exploratory analysis should be validated in future studies**

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Dose modifications of liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) in NAPOLI-1: impact on efficacy

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Background

- Pancreatic cancer is the third leading cause of cancer-associated mortality in the United States; however, it represents only 3.2% of new cancer diagnoses. Despite surgery, locoregional therapy, chemotherapy, and molecular therapies, the 5-year survival rate is only 8.2%.[1]
- Chemotherapeutic approaches to the management of patients with metastatic pancreatic cancer are varied, with the National Comprehensive Cancer Network guidelines recommending 5-fluorouracil-oxaliplatin-irinotecan (FOLFIRINOX) or nab-paclitaxel plus gemcitabine as first-line therapy.[2]
- Second-line therapy for patients with pancreatic cancer is not standardized, and is dependent on a number of factors including the patient's performance status, current comorbidities, previous first-line treatments, and residual treatment toxicities.[2]
- Liposomal irinotecan (nal-IRI, ONIVYDE®) is approved in the US, EU, and other countries in combination with 5-fluorouracil/leucovorin for treatment of adult patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy.
- NAPOLI-1 (NCT01494506) was a randomized phase 3 study of nal-IRI in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, in combination with 5-fluorouracil (5-FU) and leucovorin (LV).[3]
- The NAPOLI-1 study protocol allowed for up to 2 dose reductions for nal-IRI and 5-FU, and for a dosing delay of up to 3 weeks to allow for recovery from toxicity-related adverse events.

Objective

- This exploratory analysis of NAPOLI-1 examined the impact of dose reductions or dose delays, when used to manage adverse events, on OS.

Methods

NAPOLI-1

- NAPOLI-1 (NCT01494506) was a large (N = 417), global, phase 3 clinical trial that evaluated nal-IRI alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, for patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy. Results have been previously published.[3]

- Patients were initially randomized to receive nal-IRI (120 mg/m^2 every 3 weeks, expressed as irinotecan HCl salt, equivalent to 100 mg/m^2 expressed as irinotecan free base) or 5-FU/LV (2000/200 mg/m^2 weekly for 4 weeks) of each 6-week cycle.

- After n = 63 patients were enrolled, a third treatment arm, nal-IRI (80 mg/m^2 every 2 weeks, expressed as irinotecan HCl salt, equivalent to 70 mg/m^2 expressed as irinotecan free base) + 5-FU/LV (2400/400 mg/m^2 every 2 weeks), was added (protocol version 2).

- Treatment was continued until disease progression or unacceptable toxicity.

- The primary endpoint was OS, with key secondary endpoints including progression-free survival (PFS), objective response rate, and safety.[3]

Exploratory Post Hoc Analysis

- This was an exploratory post hoc analysis of patients in NAPOLI-1 who received study drug and who required a dose reduction or dose delay for nal-IRI in the nal-IRI+5-FU/LV arm to manage adverse events within the first 6 weeks of the study.
  - A dose reduction was defined as any reduction in the scheduled dose from the initial administered dose.
  - A dose delay was defined as any delay in dosing greater than 3 days from the targeted dosing date.

- To evaluate the impact of a dose modification (i.e., a delay or dose reduction) on patient outcomes, OS was compared within the nal-IRI+5-FU/LV arm and with the 5-FU/LV arm.

- All comparisons were made using the population cohort of patients randomized to receive either 5-FU/LV or nal-IRI+5-FU/LV and who enrolled under protocol version 2.
- OS was calculated using the Kaplan-Meier method.
- Hazard ratios (HRs) were calculated to assess the impact of dose modifications or delays used to manage adverse events on OS in the individual and pooled treatment arms.
  - HRs were estimated by Cox regression analysis.
  - Fisher's exact test was used for comparisons.
  - All *P* values that were calculated were descriptive in nature.

Results

NAPOLI-1 Results

- A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013.[3]
- Patient demographic and baseline clinical characteristics were well balanced between the nal-IRI+5-FU/LV arm (n = 117) and the 5-FU/LV control arm (n = 119).
- Median OS increased significantly in patients with nal-IRI+5-FU/LV compared with patients who received 5-FU/LV alone (6.1 vs 4.2 months; unstratified HR = 0.67 [95% confidence interval (CI): 0.49–0.92]; *P* = 0.012).
- Median PFS (3.1 vs 1.5 months; unstratified HR = 0.56 [95% CI: 0.41–0.75]; *P* = 0.0001) and objective response rate (16% vs 1%; *P* <0.0001) were also significantly improved with nal-IRI+5-FU/LV compared with 5-FU/LV.
- Treatment with nal-IRI+5-FU/LV demonstrated a manageable safety and tolerability profile, with the most frequently reported (≥10% of patients) grade ≥3 treatment-emergent adverse events (TEAEs) being neutropenia, fatigue, diarrhea, and vomiting.
- More patients in the nal-IRI+5-FU/LV treatment group experienced adverse events that required dose delay and/or reduction than in the 5-FU/LV treatment group (62% vs 33%).

Exploratory Post Hoc Analysis Results

- A total of n = 53 (45%) patients who received nal-IRI+5-FU/LV received a dose modification during the first 6 weeks of treatment in the NAPOLI-1 clinical trial.
  - Patients requiring dose delay: n = 49
  - Patients requiring dose reduction: n = 34
    - 4 patients who received a dose reduction did not require a dose delay.

- Baseline characteristics of patients who received nal-IRI+5-FU/LV and required a dose modification during the first 6 weeks of treatment are presented in Table 1.

Table 1. Baseline Demographic Characteristics of Patients Who Received nal-IRI+5-FU/LV and Required a Dose Modification During the First 6 Weeks of Treatment

	nal-IRI+5-FU/LV Dose Modification (n = 53)	nal-IRI+5-FU/LV No Dose Modification (n = 64)	5-FU/LV Control (n = 105)
Gender, n (%)			
Male	33 (62.3)	34 (53.1)	59 (56.2)
Age (yrs), mean (SD)	62.2 (9.53)	63.9 (8.81)	61.2 (9.52)
Weight (kg), mean (SD)	63.0 (13.71)	67.6 (15.82)	66.6 (19.07)
BMI (kg/m²), mean (SD)	23.70 (4.211)	23.82 (4.033)	23.78 (5.188)
Race, n (%)			
White	26 (49.1)	47 (73.4)	70 (66.7)
Black/African American	1 (1.9)	3 (4.7)	3 (2.9)
Asian	22 (41.5)	11 (17.2)	30 (28.6)
Other	4 (7.5)	3 (4.7)	2 (1.9)
Region, n (%)			
Asia	22 (41.5)	11 (17.2)	29 (27.6)
Europe	17 (32.1)	31 (48.4)	45 (42.9)
North America	5 (9.4)	13 (20.3)	17 (16.2)
Other	9 (17.0)	9 (14.1)	14 (13.3)
Baseline Albumin (g/dL), mean (SD)	4.03 (0.431)	3.93 (0.479)	3.99 (0.471)
Baseline CA 19-9 (U/mL), mean (SD)	14481.6 (31689.33)	24341.8 (84436.54)	26200.6 (67613.39)
Baseline KPS Level, n (%)			
60	0	2 (3.1)	0
70	5 (9.4)	2 (3.1)	10 (9.5)
80	22 (41.5)	17 (26.6)	48 (45.7)
90	20 (37.7)	30 (46.9)	36 (34.3)
100	6 (11.3)	13 (20.3)	11 (10.5)
Prior gemcitabine monotherapy, n (%)	23 (43.4)	31 (48.4)	50 (47.6)
Prior gemcitabine in combination, n (%)	30 (56.6)	33 (51.6)	55 (52.4)
Prior 5-FU, n (%)	22 (41.5)	28 (43.8)	42 (40.0)
Prior irinotecan, n (%)	4 (7.5)	8 (12.5)	14 (13.3)
Prior platinum, n (%)	18 (34.0)	19 (29.7)	34 (32.4)

BMI, Body Mass Index; CA 19-9, Cancer Antigen 19-9; KPS, Karnovsky Performance Score; 5-FU, Fluorouracil.

- The most common Grade 3/4 adverse events (n = ≥5) in patients who required a dose modification in the first 6 weeks of nal-IRI+5-FU/LV were:
  - Patients requiring dose delay: white blood cell decrease (n = 11), neutrophil count decrease (n = 9), neutropenia (n = 8), diarrhea (n = 6), platelet count decrease (n = 5)
  - Patients requiring dose reduction: neutrophil count decrease (n = 7), neutropenia (n = 5), white blood cell decrease (n = 5)

Impact of Dose Modification in the First 6 Week of Treatment on Overall Survival

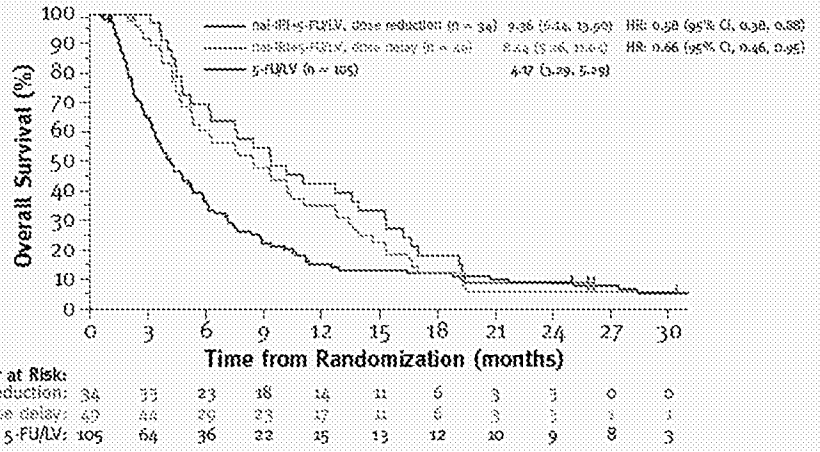
- In the between-treatment arm analysis, which assessed the impact of nal-IRI dose delays or dose reductions in the first 6 weeks of treatment on OS between the nal-IRI+5-FU/LV and the 5-FU/LV arms, OS was greater in the nal-IRI+5-FU/LV treatment arm, regardless of whether the modification was a delay or dose reduction (Table 2, Figure 1).

Table 2. Between Group Analysis of the Impact of Dose Modification During the First 6 Weeks of Treatment on Overall Survival

	Median Overall Survival (months)	Hazard Ratio (95% CI)
nal-IRI Dose Delay		
nal-IRI 5-FU/LV (n = 49)	8.44	0.66 (0.46, 0.95)
5-FU/LV (n = 105)	4.17	
nal-IRI Dose Reduction		
nal-IRI+5-FU/LV (n = 34)	9.36	0.58 (0.38, 0.88)
5-FU/LV (n = 105)	4.17	

5-FU, fluorouracil; LV, leucovorin.

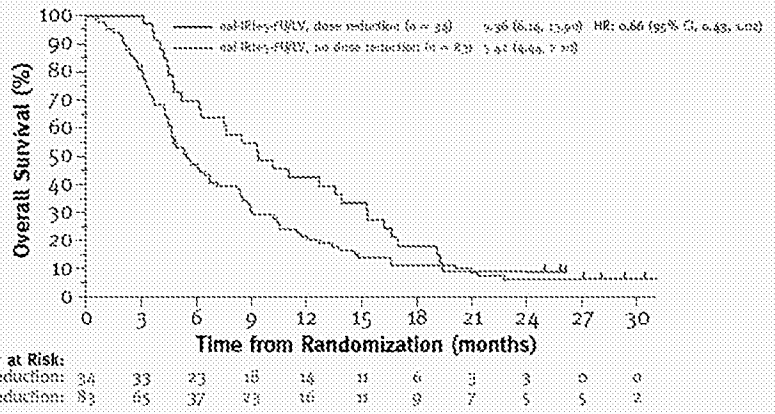
Figure 1. Impact of nal-IRI Dose Delay or Dose Reduction on Overall Survival Between Treatment Arms



OS analysis includes all patients randomized after implementation of a protocol amendment that added the nal-IRI+5-FU/LV combination arm. nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HR, hazard ratio; CI, confidence interval.

- In the analysis to assess any differences in OS within the nal-IRI+5-FU/LV treatment arm due to a reduction in nal-IRI dose during the first 6 weeks of treatment, median OS was numerically, but not significantly, different between patients who did (n = 34) versus did not (n = 83) have a dose reduction (9.4 vs 5.4 months; HR = 0.66 [95% CI: 0.43, 1.02]) (Figure 2).

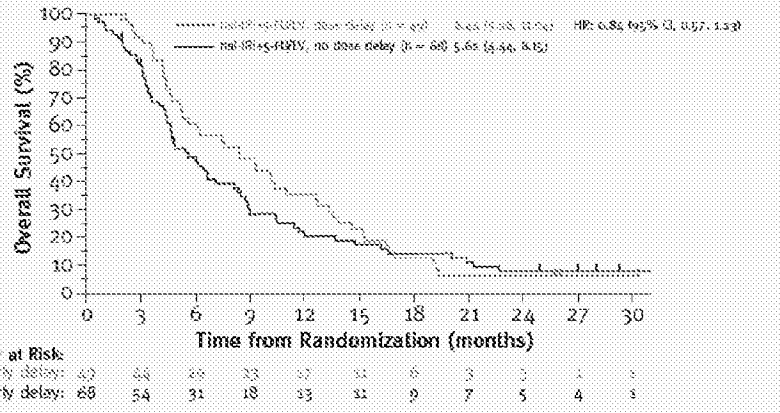
Figure 2. Impact of nal-IRI Dose Reduction vs No Dose Reduction on Overall Survival Within the nal-IRI+5-FU/LV Treatment Arm



OS analysis includes all patients randomized after implementation of a protocol amendment that added the nal-IRI+5-FU/LV combination arm. nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HR, hazard ratio; CI, confidence interval.

- In the analysis of the impact of a nal-IRI dose delay on OS within the nal-IRI+5-FU/LV treatment arm, median OS was numerically, but not significantly, different between patients who did (n = 49) versus did not (n = 68) have a nal-IRI dose delay (8.4 vs 5.6 months; HR = 0.84 [95% CI: 0.57, 1.23]) (Figure 3).

Figure 3. Impact of nal-IRI Dose Delay vs No Dose Delay on Overall Survival Within the nal-IRI+5-FU/LV Treatment Arm



OS analysis includes all patients randomized after implementation of a protocol amendment that added the nal-IRI+5-FU/LV combination arm. nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HR, hazard ratio; CI, confidence interval.

Conclusions

- In the NAPOLI-1 trial of patients with metastatic pancreatic ductal adenocarcinoma following gemcitabine-based therapy, treatment with nal-IRI+5-FU/LV significantly improved OS and PFS compared with 5-FU/LV control.[3]
- Consistent with the overall OS results in NAPOLI-1, OS was greater in patients who received nal-IRI+5-FU/LV but required a dose reduction or a dosing delay compared with those who received 5-FU/LV.
- There was no significant impact on OS in the nal-IRI+5-FU/LV arm between patients who required a dose reduction or dose delay and those who did not.
- This analysis suggests that an appropriate dose modification of nal-IRI+5-FU/LV, either a dose reduction or a dose delay during the 1st 6 weeks of treatment, does not adversely affect the clinical outcome on OS achieved with nal-IRI+5-FU/LV treatment.

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Dose modifications of liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) in NAPOLI-1: impact on efficacy

Author block

Background

- Pancreatic cancer is the most lethal cause of cancer-associated mortality in the United States; however, it represents only 3.2% of new cancer diagnoses. Despite surgery, locoregional therapy, chemotherapy, and molecular therapies, the 5-year survival rate is only 8.2%.
- Comprehensive perspective on the management of patients with metastatic pancreatic cancer (mPC) treated with first-line (1L) chemotherapy, National Network Cancer Network guidelines recommending 5-fluorouracil/leucovorin-irinotecan (FOLFIRINOX) or nab-paclitaxel plus gemcitabine as first-line therapy.[1]
- Secondline therapy for patients with pancreatic cancer is not standardized, and is dependent on a number of factors including the patients performance status, disease manifestations, previous first-line treatments, and available treatment options.[2]
- Liposomal irinotecan (nal-IRI; ONIVYDE®) is approved across the US, EU, and other countries in combination with 5-fluorouracil/leucovorin, for treatment of adult patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy.
- NAPOLI-1 (NCT01494506) was a randomized phase 3 study of nal-IRI in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy in combination with 5-fluorouracil (5-FU) and leucovorin (LV).[3]
- The NAPOLI-1 study reported clinically meaningful benefit for nal-IRI, with 5-FU, and 5-FU alone, along with key safety findings to allow for recovery from toxicity-related adverse events.

Objective

- This exploratory analysis of NAPOLI-1 examined the impact of dose reductions on dose delays, dose cuts to manage adverse events, on OS.

Methods

NAPOLI-1

- NAPOLI-1 (NCT01494506) was a large (N = 417), global, phase 3 clinical trial that evaluated nal-IRI alone and in combination with 5-FU/LV compared with 5-FU/LV alone, for patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy. Results have been previously published.[3]
- Patients were initially randomized to receive nal-IRI 120 mg/m² every 2 weeks, approved as effective as IRI, equivalent to 100 mg/m² approved as irinotecan free base) or 5-FU/LV (2000 mg/m² weekly for 4 weeks) of each 6-week cycle.
- After ~ 12 months were enrolled, a third treatment arm, nal-IRI 80 mg/m² every 2 weeks, approved as irinotecan free base) + 5-FU/LV (2000 mg/m² weekly for 4 weeks) was added as irinotecan free base) + 5-FU/LV (2000 mg/m² weekly for 4 weeks) was added to the study.[4]
- Treatment was continued until disease progression or unacceptable toxicity.
- The primary endpoint was OS, with key secondary endpoints including progression free survival (PFS), objective response rate, and safety.

Exploratory Post Hoc Analysis

- We now an exploratory post hoc analysis of patients in NAPOLI-1 who received nal-IRI + 5-FU/LV and required a dose modification during the first 6 weeks of treatment, to investigate the impact of dose reductions on clinical outcomes within the first 6 weeks of the study.
- A dose reduction was defined as any reduction in the scheduled dose from the initial administered dose.
  - A dose delay was defined as one delay in dosing greater than 3 days from the assigned dosing date.
- To evaluate the impact of a dose modification (i.e., a delay or dose reduction) on patient outcomes, OS was compared within the nal-IRI + 5-FU/LV arm and with the 5-FU/LV arm.
- All comparisons were made using the investigator cohort of patients (dose/dosed by investigator) and likely 5-FU/LV arm who received cycle 2 onward.
- OS was calculated using the Kaplan-Meier method.
- Hazard ratios (HRs) were calculated to assess the impact of dose modifications or delays used to manage adverse events on OS in the treatment and pooled treatment arms.
  - HRs were estimated by the regression analysis.
  - Patient data was used for comparisons.
  - All p values that were considered were descriptive in nature.

Results

NAPOLI-1 Results

- A total of 75 sites in 15 countries enrolled 417 patients between January 2012 and September 2013.[3]
- Patient demographic and baseline clinical characteristics were well balanced between the nal-IRI + 5-FU/LV (n = 151) and 5-FU/LV control arm (n = 151).
- Median OS increased significantly in patients who received nal-IRI + 5-FU/LV compared with patients who received 5-FU/LV alone (6.1 vs 4.2 months; unstratified HR = 0.67 [95% CI, 0.49–0.92]; 1-sided p = 0.0077; 2-sided p = 0.0154).
- Median PFS (6.1 vs 3.1 months; unstratified HR = 0.56 [95% CI, 0.42–0.75]; 2-sided p < 0.0001) and objective response rate (ORR; 16% vs 1%; 2-sided p < 0.0001) were also significantly improved with nal-IRI + 5-FU/LV.
- Treatment with nal-IRI + 5-FU/LV demonstrated a manageable safety and tolerability profile with the most frequently reported Grade ≥3 (≥5%) grade 3/4 abnormal neutropenia, anemia, fatigue, diarrhea, and vomiting.
- Most patients in the nal-IRI + 5-FU/LV treatment group experienced adverse events that required dose delay and/or reduction from the nal-IRI + 5-FU/LV treatment group (93% vs 33%).

Exploratory Post Hoc Analysis Results

- A total of 131 (93.6%) patients who received nal-IRI + 5-FU/LV required a dose modification during the first 6 weeks of treatment on the nal-IRI + 5-FU/LV arm.
  - Patients requiring dose reduction: n = 74
  - Patients requiring dose delay: n = 94
  - 5 patients received a dose reduction did not require a dose delay.
- Baseline characteristics of patients who received nal-IRI + 5-FU/LV and required a dose modification during the first 6 weeks of treatment on the nal-IRI + 5-FU/LV arm were consistent with the overall nal-IRI + 5-FU/LV arm.

Table 1. Baseline Demographic Characteristics of Patients Who Received nal-IRI + 5-FU/LV and Required a Dose Modification During the First 6 Weeks of Treatment

	nal-IRI + 5-FU/LV (n = 151)	5-FU/LV (n = 151)	Total (N = 302)
Median age, years (range)	64 (34–84)	63 (34–84)	64 (34–84)
Age, n (%)			
<65 years	84 (55.6)	84 (55.6)	168 (55.6)
≥65 years	67 (44.4)	67 (44.4)	134 (44.4)
Sex, n (%)			
Male	87 (57.6)	87 (57.6)	174 (57.6)
Female	64 (42.4)	64 (42.4)	128 (42.4)
Race, n (%)			
White	126 (83.4)	126 (83.4)	252 (83.4)
Asian	15 (9.9)	15 (9.9)	30 (9.9)
Other	10 (6.6)	10 (6.6)	20 (6.6)
Region, n (%)			
US	39 (25.8)	39 (25.8)	78 (25.8)
Canada	12 (7.9)	12 (7.9)	24 (7.9)
Australia	10 (6.6)	10 (6.6)	20 (6.6)
Eastern Europe (EU) countries	90 (59.6)	90 (59.6)	180 (59.6)
Baseline ECOG PS, n (%)			
0	57 (37.7)	57 (37.7)	114 (37.7)
1	94 (62.3)	94 (62.3)	188 (62.3)
Prior surgery for primary tumor, n (%)	39 (25.8)	39 (25.8)	78 (25.8)
Prior radiotherapy, n (%)	49 (32.5)	49 (32.5)	98 (32.5)
Prior biliary stent, n (%)	11 (7.3)	11 (7.3)	22 (7.3)
Prior metastases, n (%)	6 (4.0)	6 (4.0)	12 (4.0)
Prior gemcitabine-based therapy, n (%)	151 (100)	151 (100)	302 (100)
Prior gemcitabine-based therapy for metastatic disease, n (%)	151 (100)	151 (100)	302 (100)
Prior 5-FU/LV, n (%)	151 (100)	151 (100)	302 (100)
Prior oxaliplatin, n (%)	151 (100)	151 (100)	302 (100)
Prior irinotecan, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Prior nab-paclitaxel, n (%)	47 (31.1)	47 (31.1)	94 (31.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU/LV, 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan.

- The most common Grade ≥3 adverse events (≥ 5%) in patients who required a dose modification in the first 6 weeks of nal-IRI + 5-FU/LV were:
  - Patients receiving dose delay: anemia (nal-IRI + 5-FU/LV: 11% vs 5-FU/LV: 3%), neutropenia (nal-IRI + 5-FU/LV: 10% vs 5-FU/LV: 3%), fatigue (nal-IRI + 5-FU/LV: 6% vs 5-FU/LV: 3%), diarrhea (nal-IRI + 5-FU/LV: 6% vs 5-FU/LV: 1%), and vomiting (nal-IRI + 5-FU/LV: 5% vs 5-FU/LV: 1%).
  - Patients receiving dose reduction: neutropenia (nal-IRI + 5-FU/LV: 8% vs 5-FU/LV: 2%), anemia (nal-IRI + 5-FU/LV: 6% vs 5-FU/LV: 2%), and diarrhea (nal-IRI + 5-FU/LV: 5% vs 5-FU/LV: 1%).

Impact of Dose Modification in the First 6 Week of Treatment on Overall Survival

- In the intent-to-treat analysis, when assessed the impact of nal-IRI dose delays or dose reductions in the first 6 weeks of treatment on OS between the nal-IRI + 5-FU/LV and the 5-FU/LV arms, OS was pooled in the nal-IRI + 5-FU/LV treatment arm, regardless of whether the modification was a delay or dose reduction (Table 2; Figure 1).

Table 2. Between Group Analysis of the Impact of Dose Modification During the First 6 Weeks of Treatment on Overall Survival

	nal-IRI + 5-FU/LV	5-FU/LV
Median OS (95% CI), mo	7.24	4.92 (4.04–5.62)
OS rate (95% CI), %		
6 mo	61.7	44.8 (36.9–52.5)
12 mo	31.6	19.8 (13.9–26.4)
Unstratified HR (95% CI)	0.67 (0.49–0.92)	
Unstratified p value	0.0077	

Figure 1. Impact of nal-IRI Dose Delay or Dose Reduction on Overall Survival Between Treatment Arms

Figure 2. Impact of nal-IRI Dose Reduction on Overall Survival Within the nal-IRI + 5-FU/LV Treatment Arm

Figure 3. Impact of nal-IRI Dose Delay on the Dose Rate on Overall Survival Within the nal-IRI + 5-FU/LV Treatment Arm

- In the analysis of the impact of a nal-IRI dose delay on OS within the nal-IRI + 5-FU/LV treatment arm, median OS was numerically, but not significantly, shorter in patients who received a dose delay (6.1 vs 8.3 months; HR = 1.24 [95% CI, 0.93–1.65]; 2-sided p = 0.1433; 1-sided p = 0.0717).

Figure 4. Impact of nal-IRI Dose Delay on the Dose Rate on Overall Survival Within the nal-IRI + 5-FU/LV Treatment Arm

- In the analysis to assess any differences in OS within the nal-IRI + 5-FU/LV treatment arm, due to a reduction in nal-IRI dose during the first 6 weeks of treatment, median OS was numerically, but not significantly, shorter in patients who had (n = 74) versus did not (n = 76) have a dose reduction (6.0 vs 8.3 months; HR = 1.36 [95% CI, 0.99–1.85]; 2-sided p = 0.0552; 1-sided p = 0.0276).

Figure 5. Impact of nal-IRI Dose Reduction on Overall Survival Within the nal-IRI + 5-FU/LV Treatment Arm

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Nomogram for predicting overall survival in patients treated with liposomal irinotecan (nal-IRI) ± 5-fl uorouracil/leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy in NAPOLI-1

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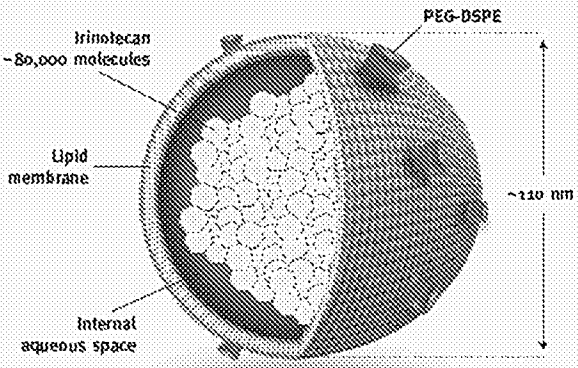
Background

- Liposomal irinotecan (nal-IRI, MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (Figure 1). This formulation was designed to utilize the enhanced permeability and retention effect to increase drug concentration in the tumor.[1,2] Pharmacokinetic analyses have demonstrated prolonged circulation of the irinotecan-containing liposome.[3]

Figure 1. Liposomal Structure of nal-IRI



- Results from NAPOLI-1 (NCT01494506), a phase 3 study in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who were previously treated with gemcitabine-based therapy, demonstrated a significant improvement in overall survival (OS; *primary endpoint*), progression-free survival (PFS), and objective response rate with nal-IRI+5-FU/LV vs 5-FU/LV alone.[4]

- The use of nomograms has become of greater clinical interest in oncology[5-8] because they provide an opportunity to evaluate multiple patient-based characteristics factors and predict a patient's individualized risk for a prespecified event – such as survival, death, or an adverse event of interest.[9-10]
  - A nomogram is a simple graphical representation of a statistical predictive model that generates a numerical probability of a clinical event.[11]

Objective

- This exploratory post hoc analysis of the baseline patient characteristics and other variables from NAPOLI-1 aimed to develop a nomogram to predict OS in patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine based therapy.
  - Specifically, the nomogram was developed to predict OS at 6 and 12 months for patients treated with nal-IRI+5-FU/LV based on NAPOLI-1 data.

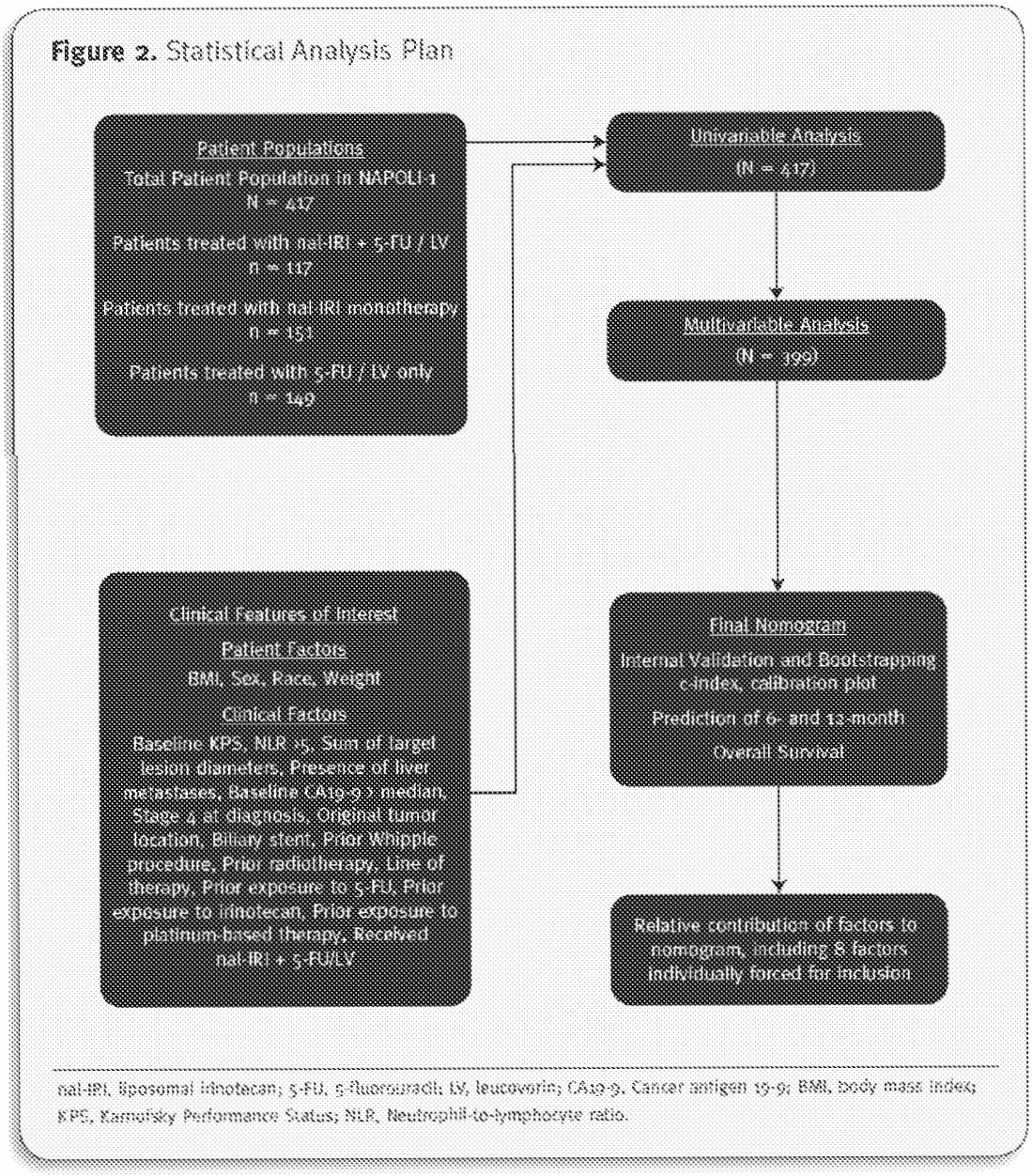
Methods

Patients

- The methods of NAPOLI-1 have been previously described.[4]
- All analyses were based on the final, completed data set for the NAPOLI-1 clinical study, which was conducted from January 11, 2012, through February 14, 2014.

Statistical Analyses

- A statistical analysis plan was developed, based on the use of univariable and multivariable analyses to determine the factors within the NAPOLI-1 clinical study that were significantly predictive of OS (Figure 2).
- A multivariable Cox model on OS was developed using baseline factors that were significantly predictive of OS by univariable analysis (P <0.10) or considered clinically important and retained in the model after stepwise selection (P <0.10).
- The final set of identified factors was used to create a nomogram that assigned points equal to the weighted sum of the relative significance of each factor.
  - The most predictive factor was assigned a maximum point value of 100.
  - Points for other factors were determined based on comparison with this most influential factor.
- Validation of the final model was assessed by the concordance index (c-index), which was bias-corrected using bootstrap (2000 iterations) methodology.
- The total patient population was divided into low-, intermediate-, and high-risk groups by allocating the total points from all patients into tertiles and survival by risk group is displayed via Kaplan-Meier plots.



Results

Patient Characteristics

- Baseline patient characteristics in NAPOLI-1 were balanced between each treatment arm and have been previously reported.[4]

Prognostic Factors of Overall Survival

- Data from the univariate analysis (n = 417) and multivariate analysis (n = 399, with n = 18 patients excluded for missing baseline data) were utilized to evaluate predictive value of factors on OS.
- The univariate analysis identified 21 independent factors that contributed to OS, with 8 factors found to be significantly associated with OS (Table 1).
- The clinically relevant variables found to be significantly associated with OS (or within close proximity to the prespecified α level) in the univariate analysis were used in the multivariate analysis (all $P < 0.01$, except body mass index [$P = 0.03$]) (Table 2).

Table 1. Univariate Cox Regression of Overall Survival (N = 417)

Parameter	n	Wald *P*-value	Hazard Ratio (95% CI)
Baseline Karnofsky score ≥90	417	<0.0001	0.527 (0.421, 0.660)
Baseline albumin ≥4 g/dL	417	<0.0001	0.643 (0.515, 0.802)
Neutrophil/lymphocyte ratio >5	415	<0.0001	0.582 (0.458, 0.741)
Sum of longest diameter of target lesions (mm)	417	<0.0001	1.005 (1.003, 1.007)
Presence of liver metastases	417	<0.0001	1.688 (1.314, 2.168)
Baseline CA19-9 > median (1542 U/mL)	404	<0.0001	1.620 (1.291, 2.032)
Stage 4 disease at diagnosis	413	<0.0001	1.774 (1.413, 2.226)
Primary tumor location: Head of pancreas	417	0.19	0.860 (0.685, 1.079)
Prior biliary stent	417	0.90	0.973 (0.651, 1.455)
Prior Whipple procedure	417	0.021	0.739 (0.573, 0.955)
Prior radiotherapy	417	0.0046	0.668 (0.506, 0.883)
Line of therapy	417	0.71	1.033 (0.870, 1.227)
Prior exposure to 5-FU	417	0.43	1.095 (0.874, 1.370)
Prior exposure to irinotecan	417	0.13	1.324 (0.922, 1.902)
Prior exposure to platinum-based therapy	417	0.44	1.099 (0.867, 1.394)
Received nal-IRI + 5-FU/LV	417	0.0008	0.640 (0.493, 0.830)
Age (years)	417	0.13	1.009 (0.997, 1.020)
Body mass index >25 kg/m^2	417	0.020	0.746 (0.584, 0.954)
Race: White	417	0.30	1.129 (0.900, 1.416)
Race: Asian	417	0.20	0.857 (0.677, 1.085)
Sex: Female	417	0.86	0.979 (0.782, 1.227)
Weight (kg)	417	0.065	0.993 (0.987, 1.000)

CI, confidence interval; nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; CA19-9, Cancer antigen 19-9

Table 2. Multivariate Cox Regression of Overall Survival (N = 399)[a]

Parameter	Wald *P*-value	Hazard Ratio (95% CI)
Karnofsky Performance Status (KPS) ≥90	<0.0001	0.58 (0.45, 0.73)
Albumin ≥4 g/dL	0.0031	0.70 (0.55, 0.89)
Neutrophil-to-lymphocyte ratio (NLR) >5	0.0001	0.61 (0.47, 0.78)
Presence of liver metastases	<0.0001	1.72 (1.33, 2.24)
CA19-9 >median (1542 U/mL)	<0.0001	1.59 (1.26, 2.01)
Stage 4 at diagnosis	<0.0001	1.61 (1.27, 2.04)
Received nal-IRI + 5-FU/LV	0.0001	0.60 (0.46, 0.78)
Body mass index (BMI)	0.0792	0.98 (0.95, 1.00)

[a]Stepwise multivariate analysis with $P < 0.10$ for model entry and $P < 0.10$ for model retention.

CI, confidence interval; nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin.

- Based on the findings of the original Multivariable analysis, the Multivariate Cox Regression analysis was repeated using various stratification criteria to ensure clinical relevance

Table 3. Stratified Multivariate Cox Regression of Overall Survival (N = 399)[a]

Parameter	Patients (n)	Parameter Estimate (β)	Wald *P*-value	Hazard Ratio (95% CI)
Baseline Karnofsky score ≥90 vs 60–80	219/180	−0.545	<0.0001	0.58 (0.46, 0.74)
Baseline albumin ≥4 vs <4 g/dL	221/178	−0.382	0.0013	0.68 (0.54, 0.86)
Neutrophil/lymphocyte ratio >5 vs ≤5	284/115	−0.493	0.0001	0.61 (0.47, 0.79)
No liver metastasis vs liver metastases	124/275	−0.534	<0.0001	0.59 (0.45, 0.76)
Baseline CA19-9 ≤1542 vs >1542 U/mL	199/200	−0.462	<0.0001	0.63 (0.50, 0.79)
Stage <4 vs Stage 4 at diagnosis	190/209	−0.483	<0.0001	0.62 (0.49, 0.78)
Body mass index >25 vs ≤25 kg/m^2	121/278	−0.283	0.030	0.75 (0.58, 0.97)
nal-IRI+5-FU/LV vs 5-FU/LV or nal-IRI	112/287	−0.523	0.0001	0.59 (0.45, 0.77)

[a]Model excludes 18 patients with missing value of one or more parameters.

CI, confidence interval; nal-IRI, liposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; CA19-9, Cancer antigen 19-9.

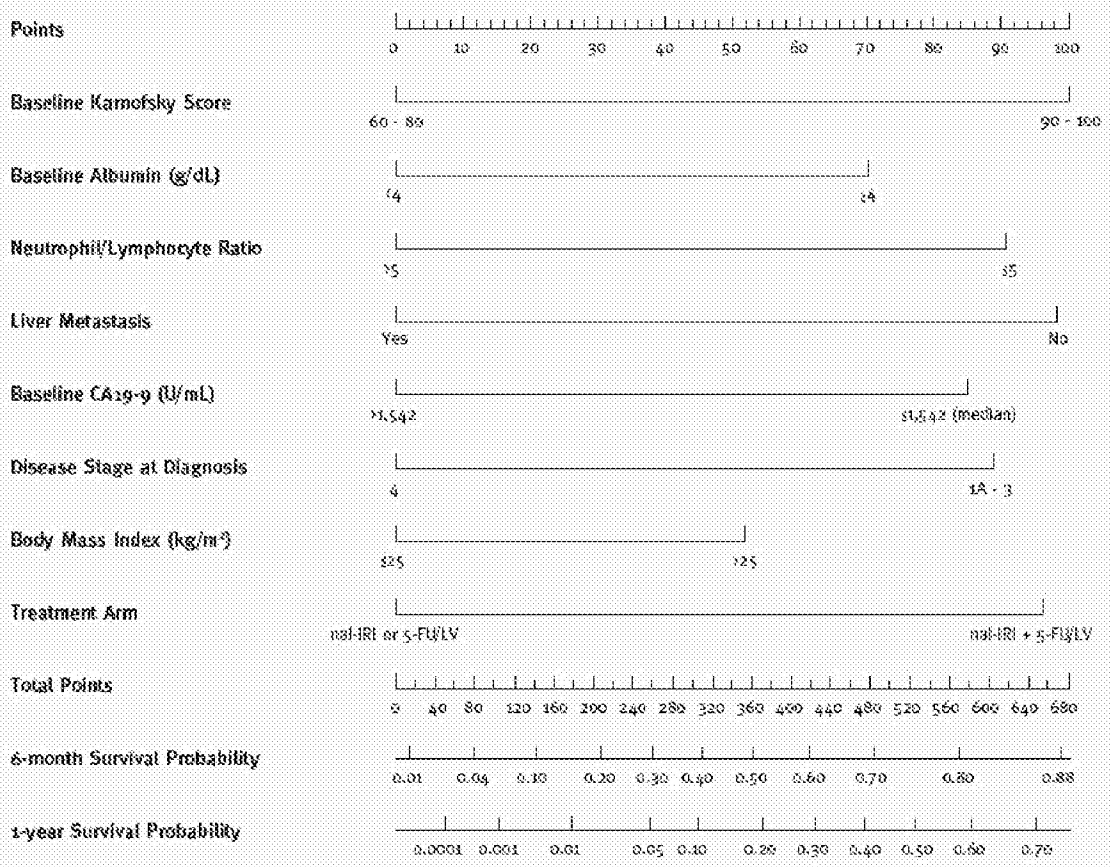
Safety

- Grade 3/4 adverse events in this post-hoc analysis population were consistent with the overall population

Nomogram for Overall Survival

- Karnofsky score contributed the largest number of points (100) to the predicted OS, followed by presence of liver metastasis (98) and randomized treatment arm (96).

Figure 3. Nomogram to Predict Overall Survival in Patients with Metastatic Pancreatic Cancer Treated with nal-IRI+5-FU/LV in the NAPOLI-1 Study



CA19-9, Cancer antigen 19-9.

Utilizing the Nomogram for Overall Survival

- Each clinical factor in the nomogram was assigned a numerical value point by drawing a line upward from the observed value through to the Points line.
- The total sum of points from each of the clinical factors was tabulated, and plotted on the Total Points line.
- The corresponding prediction for 6- and 12-month survival probability was read by dropping a vertical line down.
- The larger the value of Total Points on the nomogram corresponds to a greater 6- and 12-month survival probability.

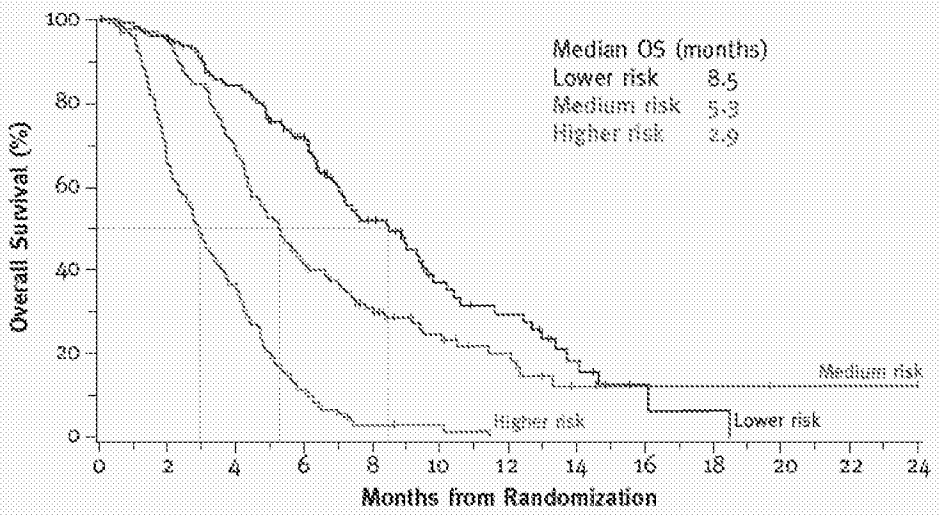
Model Validation

- The nomogram for survival in the nal-IRI+5-FU/LV population utilized for this analysis (n = 399) was able to distinguish lower (n = 131), intermediate (n = 137), and higher (n = 131) risk groups which have median OS values of 8.5, 5.3, and 2.9 months, respectively. (Figure 4).

- The estimate of the bias-corrected c-index for the final nomogram for OS was 0.70 (95% CI: 0.67 – 0.73).

- Figure 4 shows the discrimination of OS between low, (n = 131), intermediate (n = 137), and high (n = 131) risk groups based on the nomogram. The mean absolute errors between the observed and predicted probabilities for OS at 3, 6, and 9 months were 0.07, 0.08, and 0.07, respectively.

Figure 4. Overall Survival of Lower-Risk, Medium-Risk, and Higher-Risk Patients[a]



[a] Low-, intermediate-, and high-risk groups were determined allocating the total points from all patients and dividing the total patient population into tertiles.

Discussions & Limitations

- Previous analyses of the NAPOLI-1 clinical trial identified similar baseline characteristic factors associated with OS.
  - There was some variability compared with the current analysis in the sets of factors examined.
  - The multivariable analyses did not allow for individualized patient prediction.
- A limitation of this analysis was the lack of an external validation group. However, the large patient population in the NAPOLI-1 clinical study assisted in overall validation in the analysis.

Conclusions

- Through univariable and multivariable analyses, 8 baseline patient and disease characteristics from patients in the NAPOLI-1 clinical trial were identified that formed the basis of a nomogram to assist in predicting the OS of patients treated with nal-IRI+5-FU/LV.
- Treatment with nal-IRI+5-FU/LV was identified as an important factor in the nomogram.
- This nomogram distinguishes between risk groups and may aid in clinical decision making.

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Nomogram for predicting overall survival in patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy in NAPOLI-1

Background

Objective

Methods

Results

Discussion & Limitations

Poster #417

Updated Overall Survival Analysis of NAPOLI-1: Phase 3 Study of Nanoliposomal Irinotecan (nal-IRI; MM-398), with or without 5-Fluorouracil and Leucovorin (5-FU/LV), versus 5-FU/LV in Metastatic Pancreatic Cancer (mPAC) Previously Treated with Gemcitabine-based Therapy

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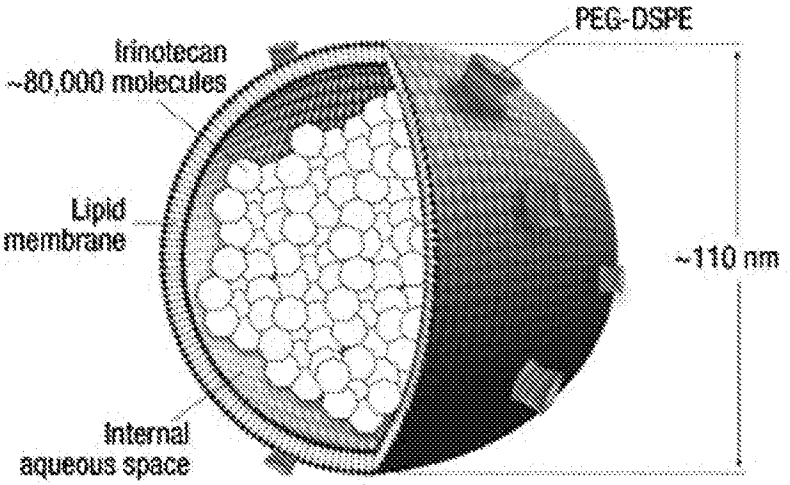
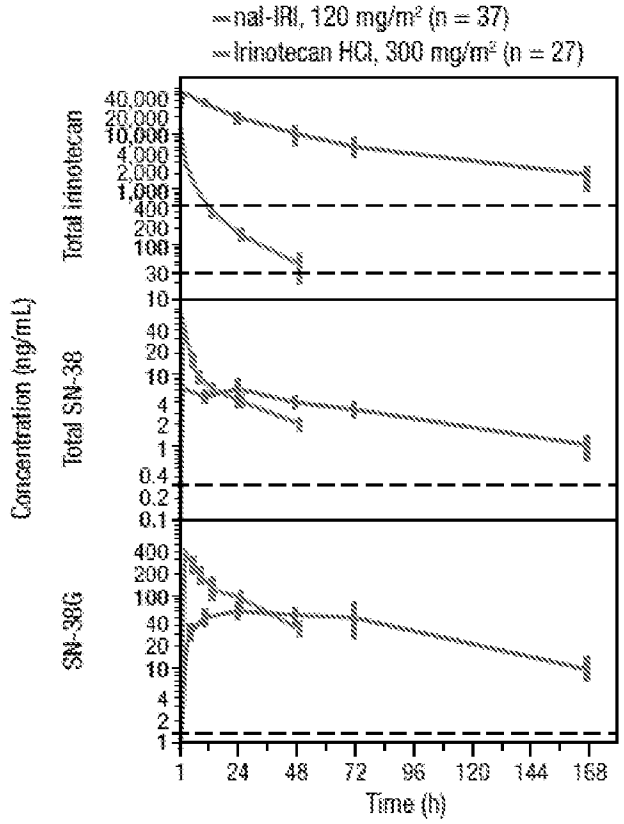
BACKGROUND

- Pancreatic cancer is the fourth leading cause of cancer death in the United States and in Europe.[1,2]
- mPAC represents a significant unmet need, with approximately 80% of patients with mPAC succumbing to disease within 12 months.[3]
- nal-IRI (ONIVYDE™ [irinotecan liposome injection]; MM-398) is a nanoliposomal formulation of irinotecan, a topoisomerase inhibitor, for intravenous use (**Figure 1**[4]).
  - Pharmacokinetic analyses showed extended circulation of irinotecan within the liposome in patients with gastric cancer treated with nal-IRI at a different dose (120 mg/m^2) and schedule compared with the approved dose and schedule (**Figure 2**).[5,6]
  - The liposome facilitates intratumoral drug deposition through the enhanced permeability and retention effect.[7]
  - Preliminary data from a small pilot study across different cancer types showed higher levels of SN-38 found in tumor biopsies compared with plasma at 72 hours, suggesting local metabolic activation of irinotecan, which was contained in the liposomal nanoparticles, to SN-38 (**Figure 3**).[4]



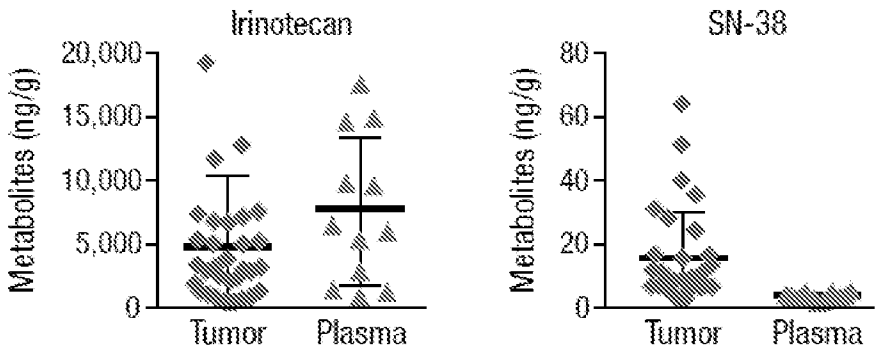
nal-IRI, nanoliposomal irinotecan.

Figure 1. nal-IRI design[3]



nal-IRI, nanoliposomal irinotecan; AUC, area under the curve; C_{max}, maximal concentration.
Comparing nal-IRI with irinotecan HCl, total irinotecan AUC was 46 times greater and total irinotecan C_{max} was 13.4 times greater; SN-38 AUC was 1.4 times greater, and SN-38 C_{max} was 0.19 times greater. The peak of SN-38 metabolite was lower with nal-IRI versus irinotecan HCl, without an increase in SN-38 plasma AUC.

Figure 2. Sustained circulation of nal-IRI[3,4]



nal-IRI, nanoliposomal irinotecan; LLoQ, lower limit of quantification.
Drug metabolite quantification in tumor biopsies and plasma analyses from a study of patients (N = 14) with advanced solid tumors.
Tumor biopsy material averaged 10.5 mg (range, 3.3–21.9 mg); metabolite detection was in an LC/MS/MS TSQ Vantage instrument, with LLoQ of 50 pg/mL for irinotecan and 100 pg/mL for SN-38.
Plasma analysis was performed at GPS according to validated procedures, with LLoQ of 140 ng/mL for irinotecan and 600 pg/mL for SN-38.

Figure 3. Irinotecan and SN-38 levels 72 hours after nal-IRI treatment[7]

- nal-IRI was recently approved by the US Food and Drug Administration for use in combination with 5-FU/LV for the treatment of patients with mPAC after disease progression following gemcitabine-based therapy, based in part on results from the primary analysis of the large (N = 417), Phase 3 NAPOLI-1 trial in this setting.[8]
  - Median overall survival (OS) increased significantly with nal-IRI + 5-FU/LV relative to 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio [HR] = 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$).
  - Median OS did not differ between patients assigned nal-IRI monotherapy and those allocated to 5-FU/LV (4.9 vs 4.2 months; unstratified HR = 0.99 [95% CI, 0.77-1.28]; $P = 0.94$).
  - Median progression-free survival (PFS; 3.1 vs 1.5 months; unstratified HR = 0.56 [95% CI, 0.41-0.75]; $P = 0.0001$) and objective response rate (ORR; 16% vs 1%; $P < 0.0001$) were also improved with nal-IRI + 5-FU/LV compared with 5-FU/LV alone.
  - nal-IRI + 5-FU/LV demonstrated a predictable and manageable safety profile; the most frequently reported grade ≥3 treatment-emergent adverse events (TEAEs) were neutropenia, fatigue, diarrhea, and vomiting.

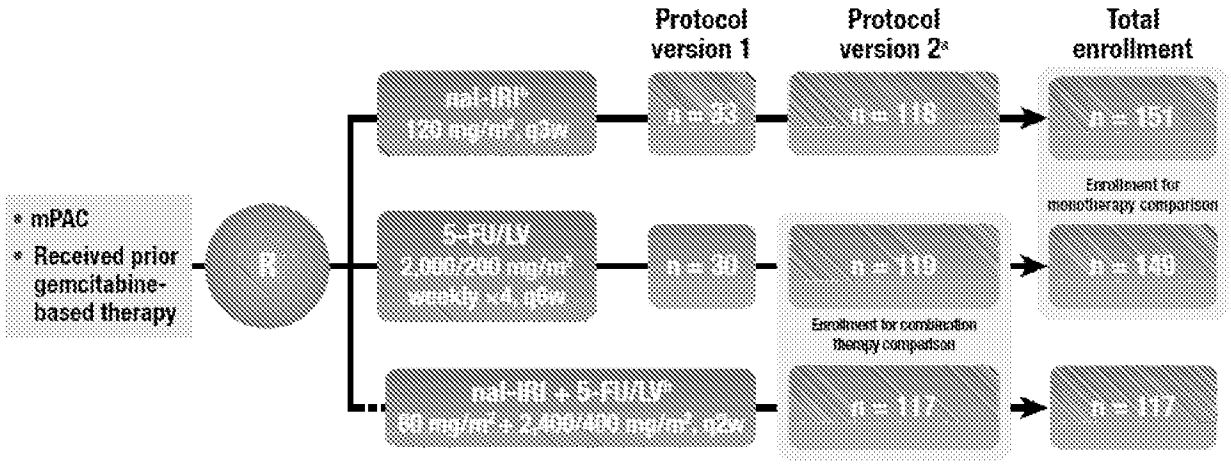
OBJECTIVE

- The objectives of the current descriptive analysis of the NAPOLI-1 trial are to
  - Evaluate the robustness of the previously observed OS treatment effect for nal-IRI + 5-FU/LV versus 5-FU/LV control using data from longer follow-up; and
  - Assess the long-term safety and tolerability of nal-IRI regimens.

NAPOLI-1 METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, Phase 3 trial (**Figure 4**).
  - Patients were initially randomized to nal-IRI monotherapy or 5-FU/LV.
  - The protocol was amended to add a third arm of the combination of nal-IRI + 5-FU/LV once safety data of the combination became available from a concurrent study in metastatic colorectal cancer. The decision to add the third arm was made shortly after the trial was initiated, and 63 patients were enrolled under protocol version 1 before all sites switched to version 2.
  - Randomization was stratified by baseline albumin levels, Karnofsky performance status (KPS), and ethnicity.



nal-IRI, nanoliposomal irinotecan; mPAC, metastatic pancreatic cancer; 5-FU, 5-fluorouracil; LV, leucovorin.
[a]NAPOLI-1 was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm.
[b]The above nal-IRI doses are expressed as the irinotecan HCl trihydrate, whereas doses in the US prescribing information are expressed as the irinotecan free base. Converting the dose is accomplished by substituting the molecular weight of irinotecan HCl trihydrate (677.19 g/mol) with that of irinotecan free base (586.68 g/mol), which results in a conversion factor of 0.866. The above nal-IRI doses of 120 and 80 mg/m² approximate to 100 and 70 mg/m², respectively, based on irinotecan free base.

Figure 4. NAPOLI-1 study design

- Analysis of the primary endpoint (OS) compared each treatment arm to its corresponding 5-FU/LV control by unstratified log-rank test; family-wise type I error rate was controlled at the 2-sided 0.05 level using the Bonferroni-Holm method.
  - The primary analysis was planned for when ≥305 OS events had occurred, in order to have 85% power to detect an HR of 0.67 in the nal-IRI arm and 98% power to detect an HR of 0.50 in the nal-IRI + 5-FU/LV arm.
  - A supportive stratified analysis that accounted for the randomization strata was also performed.

- Results presented in this poster are based on unaudited data from an updated data snapshot on May 25, 2015, after 378 OS events.

Key Inclusion Criteria

- Metastatic pancreatic ductal adenocarcinoma (measurable or non-measurable)
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting
- KPS ≥70
- Adequate hematologic (including absolute neutrophil count >1,500/μL), hepatic (including normal serum total bilirubin and albumin levels ≥3.0 g/dL), and renal function
- Adults ≥18 years of age

RESULTS

Patient Characteristics

- A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013.
- Patient demographic and baseline clinical characteristics were well balanced across treatment arms (**Table 1**).

Treatment Exposure

- The mean duration of treatment exposure was 18.5 weeks (median, 8.7 weeks; range, 2-115 weeks) in the nal-IRI + 5-FU/LV arm, 12.3 weeks (median, 8.9 weeks; range, 3-69 weeks) in the nal-IRI arm, and 10.8 weeks (median, 6.0 weeks; range, 1-68 weeks) in the 5-FU/LV control arm.
- The mean relative dose intensity of nal-IRI was 83% in the combination arm and 90% in the monotherapy arm.

Table 1. Patient Demographic and Baseline Clinical Characteristics

Parameter	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV combination control (n = 119)	nal-IRI monotherapy (n = 151)	5-FU/LV monotherapy control (n = 149)
Median age (IQR), y	63 (57-70)	62 (55-69)	65 (58-70)	63 (55-69)
KPS, %				
100	15	14	15	15
90	44	34	42	36
80	32	43	33	41
70	6	8	10	7
50-60	3	0	0	0
Race, %				
Caucasian	62	64	59	62
East Asian	29	30	34	34
Other	9	6	7	5
CA19-9 ≥40 U/mL, %[a]	81	80	86	81
Pancreatic head tumor, %	65	58	66	54
Prior lines of metastatic therapy, %				
0[b]	13	13	11	13
1	53	56	57	58
2	34	31	32	30

nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; IQR, interquartile range; KPS, Karnofsky performance status; CA19-9, carbohydrate antigen 19-9.

[a]Includes only patients who had a measured CA19-9 value prior to treatment. Data were missing for 3 patients in the nal-IRI + 5-FU/LV group and 5 patients each in the nal-IRI monotherapy and 5-FU/LV groups.

[b]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but had no previous therapy for metastatic disease.

Efficacy

- After 378 OS events, nal-IRI + 5-FU/LV retained an OS advantage relative to 5-FU/LV (6.2 vs 4.2 months; **Table 2** and **Figure 5A**).
  - With OS events in nearly all patients, the Kaplan-Meier OS curves converge at approximately 20 months, with 19 (16.2%) patients surviving beyond 20 months.
- No OS advantage was observed with nal-IRI monotherapy versus 5-FU/LV (4.9 vs 4.2 months; **Figure 5B**).
- Median PFS was 3.1 months for nal-IRI + 5-FU/LV versus 1.5 months for the 5-FU/LV combination control, and was 2.7 months for nal-IRI monotherapy compared with 1.6 months for the 5-FU/LV monotherapy control (**Table 2** and **Figure 6**).
- ORR was higher than 5-FU/LV control for both nal-IRI + 5-FU/LV (difference of 16% [95% CI, 9-24]) and nal-IRI monotherapy (difference of 5% [95% CI, 1-9]; **Table 2**).

Safety/Tolerability

- The safety profiles of nal-IRI + 5-FU/LV and nal-IRI monotherapy described in the current updated analysis did not change appreciably from those reported in the primary analysis.[6]
- The most frequently reported grade ≥3 TEAEs in the nal-IRI–containing arms were neutropenia, diarrhea, vomiting, and fatigue (**Table 3**).
- TEAEs led to dose delay, reduction, and/or discontinuation in 73% of patients in the nal-IRI + 5-FU/LV arm, 56% of patients in the nal-IRI monotherapy arm, and 37% of patients in the 5-FU/LV control arm.
  - The most common reasons for dose reduction in the nal-IRI + 5-FU/LV and nal-IRI monotherapy arms were gastrointestinal events (12% and 17%, respectively) and neutropenia (18% and 10%, respectively).
  - The rate of treatment discontinuation due to a TEAE was 12% with nal-IRI + 5-FU/LV, 14% with nal-IRI monotherapy, and 8% with 5-FU/LV; neutropenia, diarrhea, and vomiting were the most common reasons for discontinuation in the nal-IRI–containing arms.
  - Grade ≥3 febrile neutropenia occurred in 2 (2%) patients receiving nal-IRI + 5-FU/LV and 6 (4%) patients receiving nal-IRI monotherapy; 1 and 5 patients, respectively, required a dose reduction, but no patient discontinued treatment due to febrile neutropenia.
- No additional deaths due to treatment-related TEAEs have been reported since the primary analysis.

Table 2. Summary of Updated Efficacy

Endpoint	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)	Treatment effect[a]	nal-IRI (n = 151)	5-FU/LV (n = 149)	Treatment effect[a]
Median OS (95% CI), months	6.2 (4.8-8.4)	4.2 (3.3-5.3)	HR = 0.75 *P* = 0.042	4.9 (4.2-5.6)	4.2 (3.6-4.9)	HR = 1.08 *P* = 0.513
OS rate at 6 months (95% CI), %	53 (44-62)	38 (29-47)	–	–	–	–
OS rate at 12 months (95% CI), %	26 (18-35)	16 (10-24)	–	–	–	–
Median PFS (95% CI), months	3.1 (2.7-4.2)	1.5 (1.4-1.8)	HR = 0.56 *P* <0.0001	2.7 (2.1-2.9)	1.6 (1.4-1.8)	HR = 0.81 *P* = 0.111
ORR (95% CI), %[b]	17 (10-24)	1 (0-2)	*P* <0.0001	6 (2-10)	1 (0-2)	*P* = 0.020
Best overall response, %[c]						
Partial response	17	1	–	6	1	–
Stable disease[e]	33	22	–	36	24	–
Progressive disease	29	47	–	34	48	–
Other[d]	3	2	–	2	1	–
Not evaluable	19	29	–	23	27	–

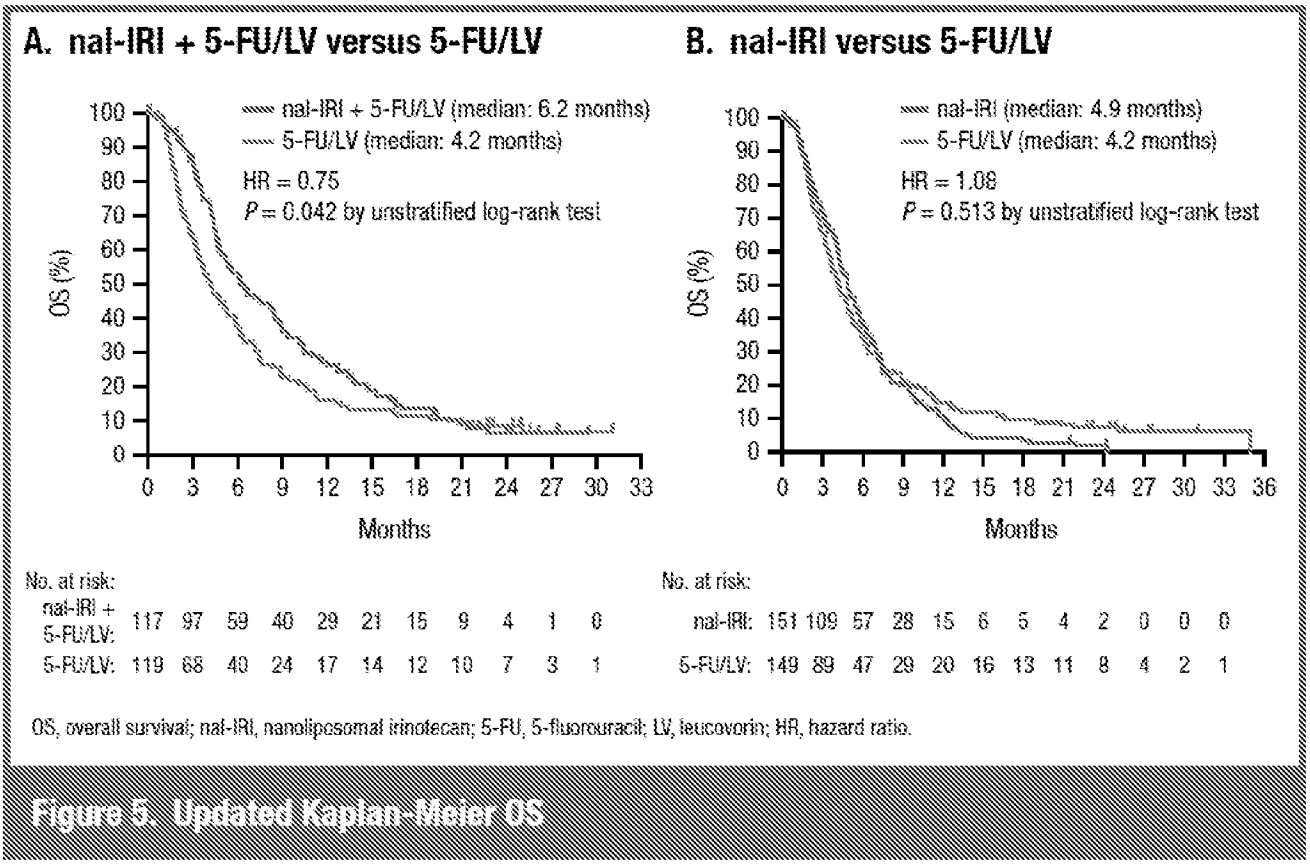
nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Unstratified HR and log-rank *P* value.

[b]Designation of response did not require confirmation and was based solely on the investigator's assessment using RECIST v1.1 criteria.

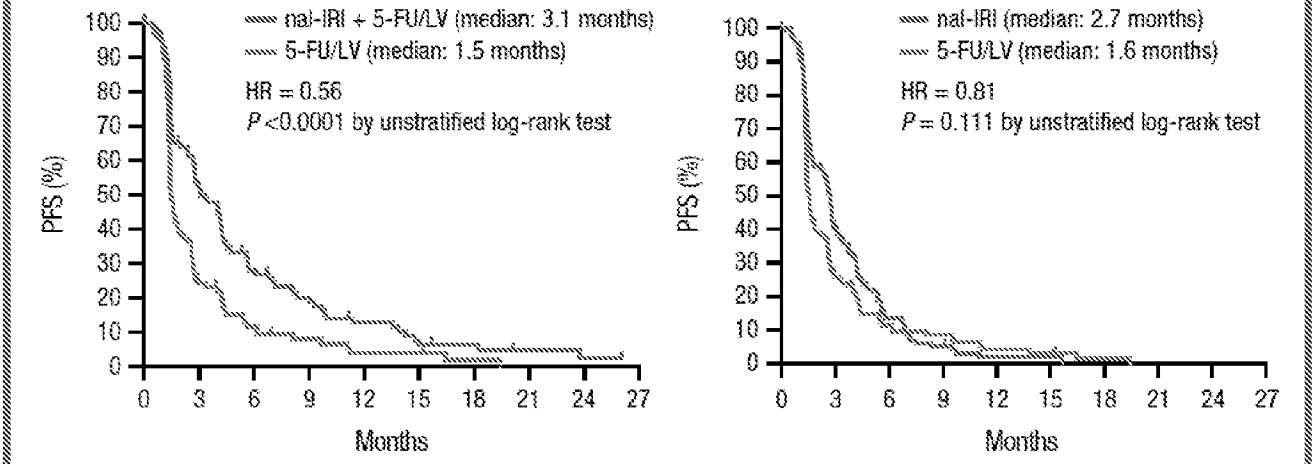
[c]Minimum duration for stable disease from baseline is 6 weeks from the date of randomization.

[d]Patients without measurable (target) disease at baseline may have a best overall response of non–complete response/non–partial response.



OS, overall survival; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HR, hazard ratio.

Figure 5. Updated Kaplan-Meier OS



PFS, progression-free survival; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; HR, hazard ratio.

Figure 6. Updated Kaplan-Meier PFS

Table 3. Grade ≥3 TEAEs

Grade ≥3 TEAE, %	nal-IRI + 5-FU/LV (n = 117)	nal-IRI monotherapy (n = 151)	5-FU/LV (n = 134)
Any TEAE	80	76	56
Neutropenia[a]	28	15	2
Fatigue	14	6	4
Diarrhea	13	21	5
Vomiting	12	14	4
Anemia	9	11	7
Asthenia	8	7	7
Nausea	8	5	3
Abdominal pain	7	8	7
Decreased appetite	5	9	2
Hypokalemia	3	12	2
Hyponatremia	3	6	2
Hyperglycemia	2	5	2

TEAE, treatment-emergent adverse event; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin.
The table includes all grade ≥3 TEAEs reported for ≥5% of patients in any treatment arm.
[a]Neutropenia includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

CONCLUSIONS

- **In this analysis of updated data from the NAPOLI-1 trial, the previously described OS and PFS benefits were maintained for nal-IRI + 5-FU/LV compared with 5-FU/LV alone.**
- **Convergence of the OS curves at 20 months (with 19 [16%] patients surviving beyond 20 months) is likely a reason for the observed attenuation of the OS HR estimate and unstratified log-rank *P* value.**
- **No new safety concerns were detected with nal-IRI as monotherapy or in combination with 5-FU/LV.**
- **nal-IRI + 5-FU/LV may represent a new standard of care for patients with mPAC following treatment with gemcitabine-based therapy.**

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Poster #437

Updated Overall Survival Analysis of MAPCALL: A Phase 3 Study of Nanoliposomal Irinotecan (nal-IRI, MM-398), with or without 5-Fluorouracil and Leucovorin (5-FU/LV), versus 5-FU/LV in Metastatic Pancreatic Cancer (mPAC) Previously Treated with Gemcitabine-based Therapy

Baselle

Pamela Kunz, Craig D. Shriver, Jeffrey Moser, Jeffrey Meyerhardt, Thomas Buchschacher, Jr., Jeffrey Lipton, Jeffrey Weber, Jeffrey Infante, Jeffrey Bendell, Jeffrey Berlin, Jeffrey Goldberg, Jeffrey Drebin, Jeffrey Sosman, Jeffrey Clark, Jeffrey Meyer, Jeffrey Hoffman, Jeffrey Ford, Jeffrey Gold, Jeffrey Saltz, Jeffrey Weitz, Jeffrey Kirkwood, Jeffrey Whitehead, Jeffrey Ross, Jeffrey Cohen, Jeffrey Fisher, Jeffrey Markowitz, Jeffrey Wolpin, Jeffrey Abrams, Jeffrey Mamon, Jeffrey Saif, Jeffrey Seufferlein, Jeffrey Giantonio, Jeffrey Kindler, Jeffrey Sharma, Jeffrey Peppercorn, Jeffrey Weinberg, Jeffrey Flaherty, Jeffrey Wong, Jeffrey Ko, Jeffrey Swanson, Jeffrey Bekaii-Saab, Jeffrey Picozzi, Jeffrey Hochster, Jeffrey Wade, Jeffrey Narayan, Jeffrey Chiorean, Jeffrey Strickler, Jeffrey Uboha, Jeffrey Starr, Jeffrey Grem, Jeffrey Hwang, Jeffrey Hall, Jeffrey Cardin, Jeffrey Bullock, Jeffrey Noel, Jeffrey Fountzilas, Jeffrey Steen, Jeffrey Ghalib, Jeffrey Reilley, Jeffrey Scott, Jeffrey Uronis, Jeffrey Mahaseth, Jeffrey Starling, Jeffrey Dotan, Jeffrey Matin, Jeffrey Feliciano, Jeffrey Cates, Jeffrey Gong, Jeffrey Stanley, Jeffrey Finney, Jeffrey Guthrie, Jeffrey Christensen, Jeffrey Hendifar, Jeffrey Tuli, Jeffrey Fishbein, Jeffrey Gong, Jeffrey Kim, Jeffrey Wu, Jeffrey Pishvaian, Jeffrey Brody, Jeffrey Berlin, Jeffrey Carpenter, Jeffrey Lowy, Jeffrey Gong, Jeffrey Shah, Jeffrey Hochster, Jeffrey Wade, Jeffrey Narayan, Jeffrey Chiorean, Jeffrey Strickler, Jeffrey Uboha, Jeffrey Starr, Jeffrey Grem, Jeffrey Hwang, Jeffrey Hall, Jeffrey Cardin, Jeffrey Bullock, Jeffrey Noel, Jeffrey Fountzilas, Jeffrey Steen, Jeffrey Ghalib, Jeffrey Reilley, Jeffrey Scott, Jeffrey Uronis, Jeffrey Mahaseth, Jeffrey Starling, Jeffrey Dotan, Jeffrey Matin, Jeffrey Feliciano, Jeffrey Cates, Jeffrey Gong, Jeffrey Stanley, Jeffrey Finney, Jeffrey Guthrie, Jeffrey Christensen, Jeffrey Hendifar, Jeffrey Tuli, Jeffrey Fishbein, Jeffrey Gong, Jeffrey Kim, Jeffrey Wu, Jeffrey Pishvaian, Jeffrey Brody, Jeffrey Berlin, Jeffrey Carpenter, Jeffrey Lowy, Jeffrey Gong, Jeffrey Shah

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Poster #4126

Updated overall survival analysis of NAPOLI-1: Phase 3 study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin, vs 5-fluorouracil and leucovorin in metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine

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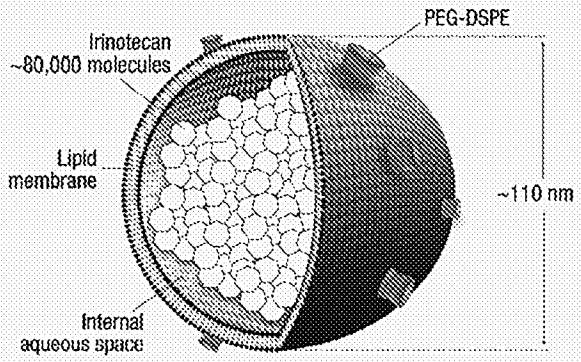
BACKGROUND

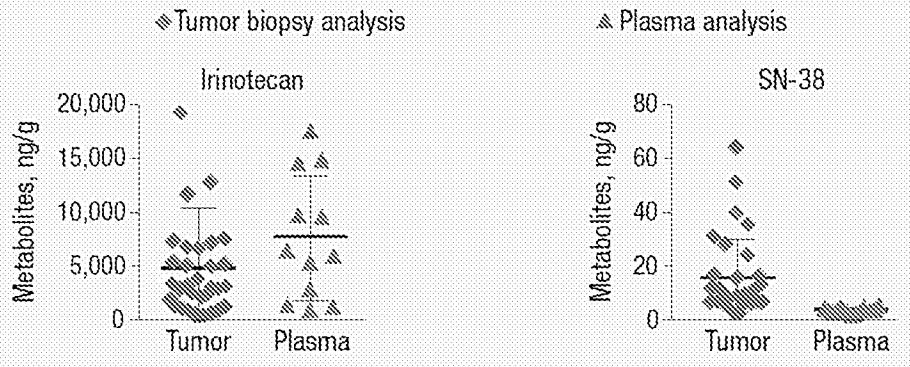
- Pancreatic cancer is the third leading cause of cancer-related death in the United States and the seventh leading cause in Europe[1,2]
- Treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) represents a significant unmet need, with approximately 80% of patients with mPAC succumbing to disease within 12 months[3]
- nal-IRI (liposomal irinotecan; MM-398) is a nanoliposomal formulation of irinotecan, a topoisomerase inhibitor, for intravenous use (**Figure 1**)[4]
  - Pharmacokinetic analyses in patients with gastric cancer treated with either nal-IRI (120 mg/m^2 irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m^2 irinotecan free base) or irinotecan (300 mg/m^2) showed extended circulation of irinotecan within the liposome in patients treated with nal-IRI[5,6]
  - The liposome facilitates intratumoral drug deposition through the enhanced permeability and retention effect[7]
  - Preliminary data from a pilot study across different cancer types showed higher levels of SN-38 (the active metabolite of irinotecan) in tumor biopsies compared with plasma at 72 hours, suggesting local metabolic activation of irinotecan to SN-38 (**Figure 2**)[8]

Figure 1. nal-IRI design.[6]



nal-IRI, liposomal irinotecan; PEG-DSPE, poly(ethylene glycol)–distearoylphosphatidylethanolamine.

Figure 2. Irinotecan and SN-38 levels 72 hours after nal-IRI treatment.[8]



LC/MS/MS, liquid chromatography-tandem mass spectrometry; LLoQ, lower limit of quantification; nal-IRI, liposomal irinotecan.
Drug metabolite quantification in tumor biopsies and plasma analyses from a study of patients (N = 14) with advanced solid tumors.
Tumor biopsy material averaged 10.5 mg (range, 3.3-21.9 mg); metabolite detection was in an LC/MS/MS TSQ Vantage instrument, with LLoQ of 50 pg/mL for irinotecan and 100 pg/mL for SN-38.
Plasma analysis was performed at QPS according to validated procedures, with LLoQ of 140 ng/mL for irinotecan and 600 pg/mL for SN-38.

- nal-IRI is approved by the US Food and Drug Administration for use in combination with 5-fluorouracil and leucovorin (5-FU/LV) for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy, based on results from the primary analysis of the large (N = 417), phase 3 NAPOLI-1 trial in this setting (data cutoff, February 14, 2014)[4,9]
  - Median overall survival (OS) increased significantly with nal-IRI + 5-FU/LV relative to 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio [HR], 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$)[9]
  - Median OS did not differ between patients assigned nal-IRI monotherapy and those allocated to 5-FU/LV 4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77-1.28]; $P = 0.94$)[9]
  - Median progression-free survival (PFS; 3.1 vs 1.5 months; unstratified HR, 0.56 [95% CI, 0.41-0.75]; $P = 0.0001$) and objective response rate (ORR; 16% vs 1%; $P < 0.0001$) were also improved with nal-IRI + 5-FU/LV compared with 5-FU/LV alone[9]
  - Among patients with baseline CA 19-9 >30 U/mL (nal-IRI + 5-FU/LV, n = 97; 5-FU/LV, n = 81), CA 19-9 response (≥50% decline from baseline level) was significantly higher with nal-IRI + 5-FU/LV than with 5-FU/LV alone (29% vs 9%; $P = 0.0006$)[9]
  - A greater treatment effect of nal-IRI + 5-FU/LV on OS and PFS relative to 5-FU/LV was observed with higher baseline CA 19-9 levels[10]
  - nal-IRI + 5-FU/LV demonstrated a predictable and manageable safety profile; the most frequently reported Grade ≥3 treatment-emergent adverse events (TEAEs) were neutropenia, fatigue, diarrhea, and vomiting[9]

OBJECTIVES

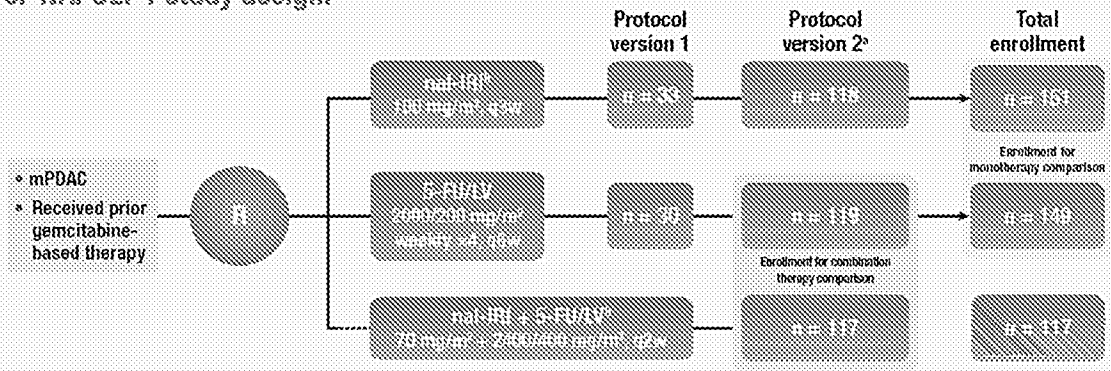
- The objectives of the current descriptive analysis of the NAPOLI-1 trial are to
  - Evaluate the robustness of the previously observed OS treatment effect for nal-IRI + 5-FU/LV versus 5-FU/LV control using data from longer follow-up
  - Assess the long-term safety and tolerability of nal-IRI regimens

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (**Figure 3**)
  - Patients were initially randomized to nal-IRI monotherapy (100 mg/m² irinotecan free base every 3 weeks, equivalent to 120 mg/m² irinotecan hydrochloride trihydrate salt) or 5-FU/LV (200 mg/m² LV and 2000 mg/m² 5-FU, every week for the first 4 weeks of 6-week cycles)
  - The protocol was amended to add a third arm of the combination of nal-IRI + 5-FU/LV (70 mg/m² irinotecan free base every 3 weeks, equivalent to 80 mg/m² irinotecan hydrochloride trihydrate salt; 400 mg/m² LV and 2400 mg/m² 5-FU every 2 weeks) once safety data of the combination became available from a concurrent study in metastatic colorectal cancer. The decision to add the third arm was made shortly after the trial was initiated, and 63 patients were enrolled under protocol version 1 before all sites switched to version 2
  - Randomization was stratified by baseline albumin levels (≥ 4.0 g/dL vs < 4.0 g/dL), Karnofsky performance status (KPS; 70 and 80 vs ≥ 90), and race (white vs East Asian vs all others)

Figure 3. NAPOLI-1 study design.



5-FU, 5-fluorouracil; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; nal-IRI, liposomal irinotecan; q2w, every 2 weeks; q3w, every 3 weeks; q6w, every 6 weeks; R, randomization.
[a]NAPOLI-1 was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm.
[b]The above nal-IRI doses are expressed as the irinotecan free base, as is the dose in the US prescribing information. Converting the dose from irinotecan HCl trihydrate to irinotecan free base is accomplished by substituting the molecular weight of irinotecan HCl trihydrate (677.19 g/mol) with that of irinotecan free base (586.68 g/mol), which results in a conversion factor of 0.866. The above nal-IRI doses of 100 and 70 mg/m² approximate to 120 and 80 mg/m² irinotecan HCL trihydrate.

Statistical Analyses

- Analysis of the primary end point (OS) compared each treatment arm with its corresponding 5-FU/LV control by unstratified log-rank test; family-wise type I error rate was controlled at the 2-sided 0.05 level using the Bonferroni-Holm method
  - The primary analysis was planned for when ≥305 OS events had occurred, in order to have 85% power to detect an HR of 0.67 in the nal-IRI arm and 98% power to detect an HR of 0.50 in the nal-IRI + 5-FU/LV arm
  - A supportive stratified analysis that accounted for the randomization strata was also performed
- Results presented in this poster are based on unaudited data from an updated data snapshot on May 25, 2015, after 378 OS events had occurred in the intention-to-treat (ITT) population

Key Inclusion Criteria

- Adults ≥18 years of age
- mPDAC (measurable or nonmeasurable as defined by RECIST version 1.1)
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting
- KPS ≥70
- Adequate hematologic (including absolute neutrophil count >1500/μL), hepatic (including normal serum total bilirubin and albumin levels ≥3.0 g/dL), and renal function

Key Exclusion Criteria

- Active central nervous system metastasis
- Clinically significant gastrointestinal disorders
- Severe arterial thromboembolic event <6 months before inclusion
- New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias, or uncontrolled blood pressure
- Active infection or uncontrolled fever

RESULTS

Patient Characteristics

- A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013
- Patient demographic and baseline clinical characteristics were well balanced across treatment arms (**Table 1**)

Table 1. Patient Demographic and Baseline Clinical Characteristics

Parameter	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV combination control (n = 119)	nal-IRI monotherapy (n = 151)	5-FU/LV monotherapy control (n = 149)
Age, years, median (IQR)	63 (57-70)	62 (55-69)	65 (58-70)	63 (55-69)
KPS, %				
100	15	14	15	15
90	44	34	42	36
80	32	43	33	41
70	6	8	10	7
50-60	3	0	0	0
Race, %				
White	62	64	59	62
East Asian	29	30	34	34
Other	9	6	7	5
CA 19-9 ≥40 U/mL, %[a]	81	80	86	81
Pancreatic head tumor, %	65	58	66	54
Prior lines of metastatic therapy, %				
0[b]	13	13	11	13
1	53	56	57	58
2	34	31	32	30

5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; IQR, interquartile range; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Includes only patients who had a measured CA 19-9 value prior to treatment. Data were missing for 3 patients in the nal-IRI + 5-FU/LV group and 5 patients each in the nal-IRI monotherapy and 5-FU/LV groups.
[b]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but had no previous therapy for metastatic disease.

Treatment Exposure

- The mean duration of treatment exposure was 18.5 weeks (median, 8.7 weeks; range, 2-115 weeks) in the nal-IRI + 5-FU/LV arm, 12.3 weeks (median, 8.9 weeks; range, 3-69 weeks) in the nal-IRI arm, and 10.8 weeks (median, 6.0 weeks; range, 1-68 weeks) in the 5-FU/LV control arm
- The mean relative dose intensity of nal-IRI was 83% in the combination arm and 90% in the monotherapy arm

Efficacy

- After 378 OS events, nal-IRI + 5-FU/LV retained an OS advantage relative to 5-FU/LV (6.2 vs 4.2 months; **Table 2** and **Figure 4A**)
  - With OS events in nearly all patients, the Kaplan-Meier OS curves converge at approximately 20 months, with 19 (16.2%) patients surviving beyond 20 months
- No OS advantage was observed with nal-IRI monotherapy versus 5-FU/LV (4.9 vs 4.2 months; **Figure 4B**)
- Median PFS was 3.1 months for nal-IRI + 5-FU/LV versus 1.5 months for the 5-FU/LV combination control, and was 2.7 months for nal-IRI monotherapy compared with 1.6 months for the 5-FU/LV monotherapy control (**Table 2** and **Figure 5**)

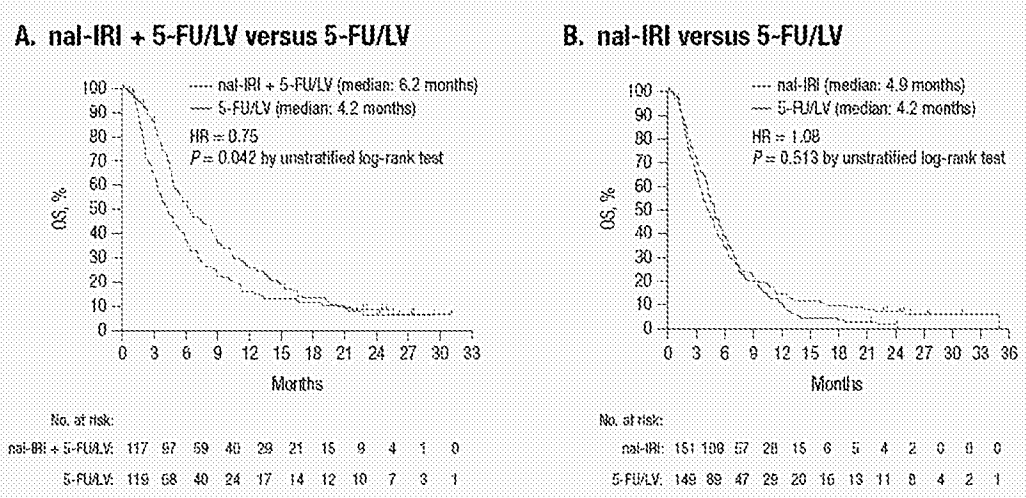
- ORR was higher for both nal-IRI + 5-FU/LV (difference of 16% [95% CI, 9%-24%]) and nal-IRI monotherapy (difference of 5% [95% CI, 1%-9%]; **Table 2**) compared with the 5-FU/LV control

Table 2. Summary of Updated Efficacy

End point	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)	Treatment effect[a]	nal-IRI (n = 151)	5-FU/LV (n = 149)	Treatment effect[a]
OS, months, median (95% CI)	6.2 (4.8-8.4)	4.2 (3.3-5.3)	HR = 0.75 *P* = 0.042	4.9 (4.2-5.6)	4.2 (3.6-4.9)	HR = 1.08 *P* = 0.513
OS rate at 6 months (95% CI), %	53 (44-62)	38 (29-47)	–	–	–	–
OS rate at 12 months (95% CI), %	26 (18-35)	16 (10-24)	–	–	–	–
PFS, months, median (95% CI)	3.1 (2.7-4.2)	1.5 (1.4-1.8)	HR = 0.56 *P* < 0.0001	2.7 (2.1-2.9)	1.6 (1.4-1.8)	HR = 0.81 *P* = 0.111
ORR (95% CI), %[b]	17 (10-24)	1 (0-2)	*P* < 0.0001	6 (2-10)	1 (0-2)	*P* = 0.020
Best overall response, %[b]						
Partial response	17	1	–	6	1	–
Stable disease[c]	33	22	–	36	24	–
Progressive disease	29	47	–	34	48	–
Other[c]	3	2	–	2	1	–
Not evaluable	19	29	–	23	27	–

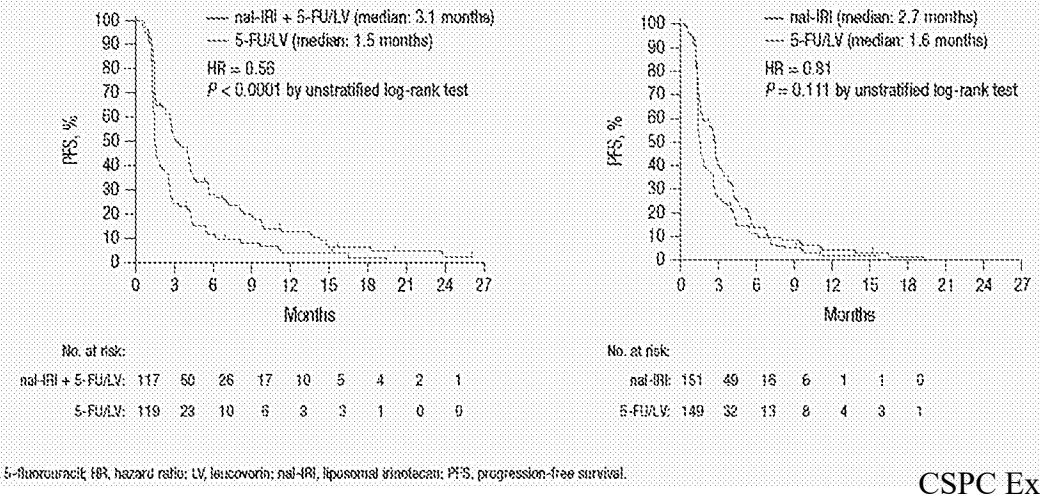
5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Unstratified HR and log-rank *P* value.
[b]Designation of response did not require confirmation and was based solely on the investigator's assessment using RECIST v1.1 criteria.
[c]Minimum duration for stable disease from baseline is 6 weeks from the date of randomization.
[d]Patients without measurable (target) disease at baseline may have a best overall response of non-complete response/non-partial response.

Figure 4. Updated Kaplan-Meier OS.



5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; OS, overall survival.

Figure 5. Updated Kaplan-Meier PFS.



5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; PFS, progression-free survival.

Safety/Tolerability

- The safety profiles of nal-IRI + 5-FU/LV and nal-IRI monotherapy described in the current updated analysis did not change appreciably from those reported in the primary analysis[9]
- The most frequently reported Grade ≥3 TEAEs in the nal-IRI–containing arms were neutropenia, diarrhea, vomiting, and fatigue (**Table 3**)
- TEAEs led to dose delay, reduction, and/or discontinuation in 73% of patients in the nal-IRI + 5-FU/LV arm, 56% of patients in the nal-IRI monotherapy arm, and 37% of patients in the 5-FU/LV control arm
  - The most common reasons for dose reduction in the nal-IRI + 5-FU/LV and nal-IRI monotherapy arms were gastrointestinal events (12% and 17%, respectively) and neutropenia (18% and 10%, respectively)
  - The rate of treatment discontinuation due to a TEAE was 12% with nal-IRI + 5-FU/LV, 14% with nal-IRI monotherapy, and 8% with 5-FU/LV; neutropenia, diarrhea, and vomiting were the most common reasons for discontinuation in the nal-IRI–containing arms
  - Grade ≥3 febrile neutropenia occurred in 2 (2%) patients receiving nal-IRI + 5-FU/LV and 6 (4%) patients receiving nal-IRI monotherapy; 1 and 5 patients, respectively, required a dose reduction, but no patient discontinued treatment because of febrile neutropenia
- No additional deaths due to TEAEs have been reported since the primary analysis

Table 3. Grade ≥3 TEAEs Reported for ≥5% of Patients in Any Treatment Arm

Grade ≥3 TEAE, %	nal-IRI + 5-FU/LV (n = 117)	nal-IRI monotherapy (n = 151)	5-FU/LV (n = 134)
Any TEAE	80	76	56
Neutropenia[a]	28	15	2
Fatigue	14	6	4
Diarrhea	13	21	5
Vomiting	12	14	4
Anemia	9	11	7
Asthenia	8	7	7
Nausea	8	5	3
Abdominal pain	7	8	7
Decreased appetite	5	9	2
Hypokalemia	3	12	2
Hyponatremia	3	6	2
Hyperglycemia	2	5	2

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
The table includes all Grade ≥3 TEAEs reported for ≥5% of patients in any treatment arm.
[a]Neutropenia includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

CONCLUSIONS

- **In this analysis of updated data from the NAPOLI-1 trial, the previously described OS and PFS benefits were maintained for nal-IRI + 5-FU/LV compared with 5-FU/LV alone**
- **Convergence of the OS curves at 20 months (with 19 [16%] patients surviving beyond 20 months) is likely a reason for the observed attenuation of the OS HR estimate and unstratified log-rank *P* value**
- **No new safety concerns were detected with nal-IRI as monotherapy or in combination with 5-FU/LV**
- **nal-IRI + 5-FU/LV may represent a new standard of care for patients with mPAC following treatment with gemcitabine-based therapy**

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Updated overall survival analysis of NAPOLI-1: Phase 3 study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin, vs 5-fluorouracil and leucovorin in metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine

CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Characteristics of long-term survivors in a randomized phase III trial (NAPOLI-1) of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan (nal-IRI; MM-398) + 5-FU/LV.

Andrea Wang-Gillam, Chung-Pin Li, Gyorgy Bodoky, Andrew Dean, Kyung-Hun Lee, David Cunningham, Richard Hubner, Jens T. Siveke, Fadi S. Braiteh, J. Marc Pipas, Bruce Belanger, Floris de Jong, Purvi D. Mody, Li-Tzong Chen, Daniel D. Von Hoff

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Abstract Disclosures

Abstract

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Background: nal-IRI, a liposomal formulation of irinotecan, plus 5-FU/LV is approved in the United States and Taiwan for patients (pts) with mPDAC previously treated with gemcitabine-based therapy. Primary analysis of the NAPOLI-1 trial (NCT01494506) showed that nal-IRI+5-FU/LV significantly improved median overall survival vs 5-FU/LV (6.1 vs 4.2 months; HR, 0.67; 95% CI, 0.49-0.92; $P = 0.012$; Wang-Gillam et al, *Lancet*. 2016). Herein we report baseline characteristics of pts surviving ≥1 year (data cutoff, Nov 2015). **Methods:** This analysis includes 117 pts assigned to treatment with nal-IRI 70 mg/m^2 (free base) + 5-FU/LV 2400/400 mg/m^2 q2w, and 119 pts assigned to treatment with 5-FU/LV 2000/200 mg/m^{2}weekly for weeks 1-4 q6w. **Results:** A total of 29 (25%) pts in the nal-IRI+5-FU/LV arm and 17 (14%) in the 5-FU/LV arm survived ≥1 year. These pts typically had better performance status, lower CA19-9 (U/mL) levels, and were less likely to have liver metastases at baseline, compared with the overall population (Table). For long-term survivors in the nal-IRI+5-FU/LV arm, a higher proportion of pts

had neutrophil-to-lymphocyte ratio (NLR) >5, a marker of poor prognosis, suggesting that higher NLR may potentially be predictive of survival outcome with nal-IRI+5-FU/LV. **Conclusions:** More pts receiving nal-IRI+5-FU/LV versus 5-FU/LV were alive beyond 1 year. The most prominent prognostic markers of survival ≥1 year included lower CA19-9, KPS ≥90 and absence of liver metastases. These analyses may be limited by small sample sizes. Clinical trial information: NCT01494506.

Baseline characteristics of long-term survivors (data are n [%] unless specified)

	All patients		Long-term survivors	
	Nal-IRI+5-FU/LV n = 117	5-FU/LV n = 119	Nal-IRI+5-FU/LV n = 29 (25)	5-FU/LV n = 17 (14)
Ethnic origin				
East Asian	34 (29)	36 (30)	10 (34)	7 (41)
Black	4 (3)	3 (3)	0	2 (12)
White	72 (62)	76 (64)	19 (66)	8 (47)
Other	7 (6)	4 (3)	0	0
KPS ≥90	66 (56)	67 (56)	22 (76)	13 (76)
NLR >5	83 (71)	81 (68)	25 (86)	10 (59)
Albumin (g/L) ≥40	53 (45)	54 (45)	16 (55)	13 (76)
Presence of liver metastases	75 (64)	84 (71)	12 (41)	8 (47)
CA19-9 level				
Median (U/mL)	1278	1292	334	108
<59 × ULN	64 (55)	61 (51)	20 (69)	14 (82)

CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Dose modifications of liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) in NAPOLI-1: Impact on efficacy.

Andrea Wang-Gillam, Richard Hubner, Beloo Mirakhur, Floris A de Jong, Bruce Belanger, Li-Tzong Chen

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Washington University School of Medicine in St. Louis, St. Louis, MO; Christie NHS Foundation Trust, Manchester, United Kingdom; Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ; Shire GmbH, Zug, Switzerland; Ipsen Bioscience, Inc., Cambridge, MA; National Health Research Institutes/ National Institute of Cancer Research, Tainan, Taiwan;

Abstract Disclosures

Abstract

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Background: In NAPOLI-1 (NCT01494506), a randomized phase 3 study in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, nal-IRI+5-FU/LV improved overall survival (OS; primary endpoint) vs 5-FU/LV (6.1 mos vs 4.2 mos; HR = 0·67, 95% CI 0.49□0.92; *P* = 0.012). This exploratory analysis examined the impact of dose modifications or delays used to manage adverse events (AEs) on OS. The study protocol allowed ≤2 dose reductions for nal-IRI and 5-FU and for up to 3 weeks. **Methods:** Patient who had a dose delay or reduction within the planned first 6 weeks of the study were included. Delays were defined as any delay in dosing > 3 days from target dosing date and dose reductions were defined as any reduction in dose from initial administered dose. OS was compared within the nal-IRI+5-FU/LV arm and with the 5-FU/LV arm. Comparisons were made using the cohort of 5-FU/LV and nal-IRI+5-FU/LV patients enrolled under protocol version 2. Median OS was based on Kaplan-Meier estimates and Cox regression analysis was used to calculate HRs. **Results:** More patients in the nal-IRI+5-FU/LV treatment group experienced AEs that required dose delay and/or reduction than in the 5-FU/LV treatment group (62% vs 33%). Within the nal-IRI+5-FU/LV arm, median OS was numerically but not significantly different between patients who did (n = 34) vs did not (n = 83) have a dose reduction (9.3 vs 5.4 mos; HR = 0.66 [95% CI 0.43, 1.01]) and for those who did (n = 49) vs did not (n = 68) have a dose delay (8.4 vs 5.6 mos; HR = 0.71 [95% CI 0.46,

1.23]). Between treatment arms, OS was greater in the nal-IRI+5-FU/LV arm regardless of dose delay or reduction (Table). **Conclusions:**Dose modifications in the nal-IRI+5-FU/LV arm did not significantly impact OS compared with those who did not need a dose modification, and OS remained greater than in 5-FU/LV-treated patients. This suggests that appropriate dose modification of nal-IRI+5-FU/LV for AEs may not adversely affect outcomes. Clinical trial information: NCT01494506.

	Median OS, mos	Hazard Ratio (95% CI)
nal-IRI Dose Delay		
nal-IRI+5-FU/LV (n = 49)	8.4	0.66 (0.46, 0.94)
5-FU/LV (n = 105)	4.2	
nal-IRI Dose Reduction		
nal-IRI+5-FU/LV (n = 34)	9.4	0.58 (0.38, 0.88)
5-FU/LV (n = 105)	4.2	

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Updated overall survival (OS) analysis of NAPOLI-1: Phase 3 study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin (5-FU/LV), vs 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine (gem)-based therapy.

Andrea Wang-Gillam, Chung-Pin Li, Gyorgy Bodoky, Andrew Dean, Yang-Shen Shan, Gayle S. Jameson, Teresa Macarulla, Kyung-Hun Lee, David Cunningham, Jean-Frédéric Blanc, Richard Hubner, Chang-Fang Chiu, Gilberto Schwartsmann, Jens T Siveke, Fadi S. Braiteh, Victor M. Moyo, Bruce Belanger, Eliel Bayever, Daniel D. Von Hoff, Li-Tzong Chen

Siteman Cancer Center, Washington University, Saint Louis, MO; Taipei Veterans General Hospital, Taipei, Taiwan; St. László Teaching Hospital, Budapest, Hungary; St. John of

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Abstract Disclosures

Abstract

4126

Background: NAPOLI-1 is a global, randomized Phase 3 study evaluating nal-IRI—a nanoliposomal irinotecan—with or without 5-FU/LV vs 5-FU/LV in 417 mPAC patients previously treated with gem-based therapy. Primary survival analysis was based on 313 events. nal-IRI+5-FU/LV significantly improved OS (primary endpoint), 6.1 months (mo) vs 4.2 mo; with 5-FU/LV (unstratified hazard ratio [HR] = 0.67; P = 0.012). The primary endpoint was supported by improved progression-free survival, time to treatment failure, objective response and CA19-9 response rates, and manageable toxicities. An updated analysis of OS, 6- and 12-month-survival estimates, and safety is presented. **Methods:** The updated descriptive analysis of OS, based on 378 events (25 May 2015), includes data from all randomized patients across the 3 arms. The final OS analysis will also be presented. **Results:** After 378 OS events, nal-IRI+5-FU/LV (n = 117) retained an OS advantage relative to 5-FU/LV (n = 119): 6.2 mo (95% confidence interval [CI], 4.8–8.4) vs 4.2 mo (95% CI, 3.3–5.3) with an

unstratified HR of 0.75 (P = 0.0417). In contrast, there was no OS advantage with nal-IRI monotherapy (n = 151) vs 5-FU/LV (n = 149): 4.9 mo [95% CI, 4.2–5.6] vs 4.2 mo [95% CI, 3.6–4.9], HR = 1.08; P = 0.5. Six-month survival estimates were 53% (95% CI, 44–62%) for nal-IRI+5-FU/LV vs 38% (95% CI, 29–47%) for 5-FU/LV; 12-month survival estimates were 26% (95% CI, 18–35%) for nal-IRI+5-FU/LV vs 16% (95% CI, 10–24%) for 5-FU/LV. With events in nearly all patients, the OS curves converge at ~20 mo with 19 patients (16.2%) surviving beyond 20 mo. This is a reason for attenuation of the HR estimate and unstratified log rank p-value. The most common ≥ grade 3 adverse events occurring at a ≥ 2% incidence in nal-IRI-containing arms were neutropenia, diarrhea, vomiting, and fatigue. **Conclusions:** In an updated analysis, the median OS benefit for nal-IRI+5-FU/LV over 5-FU/LV was maintained with a similar safety profile. nal-IRI+5-FU/LV may be a new standard of care for mPAC patients previously treated with gem-based therapy. Clinical trial information: NCT01494506.

HER2–, Node-Positive, High-Risk, Early Breast Cancer (monarchE)
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Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer
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CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

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Abstract Disclosures

Abstract

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Electronic Acknowledgement Receipt

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Confirmation Number:	5137
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First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/Richard King
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6	Non Patent Literature	Siveke_ASCO_GI_2018_abstract.pdf	111289 88a24f93c65ff26c23a6b1647034f115ba26bd7f	no	2
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7	Non Patent Literature	Siveke_DDK_2016_abstract.pdf	50396 a6e59ab8834b339a52b452d869494b986161cd37	no	1
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8	Non Patent Literature	Siveke_DGHO_2016_abstract.pdf	51131 0fbdcca708d8f8815218f85266f10e009ee32676	no	1
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9	Non Patent Literature	Soares_2014.pdf	107855 859f83b91e6a40779584aebd158b45c52436463b	no	7
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11	Non Patent Literature	Sohal_2016.pdf	512557 e791584ef19d736641b49eb95381091b50f3c72f	no	56
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12	Non Patent Literature	Sohal_2016b.pdf	85315 68a4fd60bd2ae38845a3f7bd2c9053ef1358f544	no	2
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16	Non Patent Literature	Stathis_2010.pdf	368667 5f8d78a62664512718e9b3d50e7101b904a72ab7	no	10
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17	Non Patent Literature	Stathopoulos_2006.pdf	102593 d494a7f6f36812e027b5e365781c57ebd0b1de70	no	6
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18	Non Patent Literature	Stathopoulos_2006a.pdf	92561 f9b648c252b02ddaff7ca0e3cccb862f32407830	no	4
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21	Non Patent Literature	Tempero_1_2012.pdf	721255 fd66b1e587e5f2a8323fdcc40af30b53c9f0a498	no	79
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22	Non Patent Literature	Tempero_2_2012.pdf	1626015 f32b62285477d52ad70c5fe219c29b3cfa0da6b4	no	94
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23	Non Patent Literature	Tempero_2_2014_1of4.pdf	10175878 164c8f642e5a4ab7a5b882841ecdfec3dca4ccdd	no	30
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46	Non Patent Literature	Wang-Gillam_ASCO_GI_2017_poster.pdf	3713423 5a889ab50c6e821922aa089ea6c9f2660cbbe342	no	9
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47	Non Patent Literature	Wang-Gillam_ASCO_GI_2018_poster.pdf	5390243 542c11bed71dfe5fbcff327cfcc65095160d6682	no	8
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48	Non Patent Literature	Wang-Gillam_ASCO_GI_2018_1_poster.pdf	4247817 f58c9db9234f1f062a0515330430e9a3c16d829b	no	9
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51	Non Patent Literature	Wang-Gillam_ASCO_GI_2017_abstract.pdf	119681 ef5682d8cadebf300a91adf12f78f44029e2ede0	no	2
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53	Non Patent Literature	Wang-Gillam_ASCO_2016_abstract.pdf	1876638 8c56a6d4faf518b7a323a3193d93fb26fadb5e07	no	5
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APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/25/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(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	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	10456360	B2	2019-10-29	Drummond et al.	
	2	10478428	B2	2019-11-19	Blanchette et al.	
	3	10722508	B2	2020-07-28	Hong et al.	
	4	5543152	A	1996-08-06	Webb et al.	
	5	6511676	B1	2003-01-28	Boulikas	
	6	6787132	B1	2004-09-07	Gabizon et al.	
	7	7244448	B2	2007-07-17	Madden et al.	
	8	7842676	B2	2010-11-30	Janoff et al.	

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	Attorney Docket Number	01208-0007-01US

	9	7850990	B2	2010-12-14	Tardi et al.	
	10	9511155	B2	2016-12-06	Drummond et al.	
	11	9616081	B2	2017-04-11	Taiho Pharmaceutical Co., Ltd.	

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	1	20020035091	A1	2002-03-21	Govindarajan et al.	
	2	20040071768	A1	2004-04-15	Sarris et al.	
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	7	20160303264	A1	2016-10-20	Hendricks et al.	
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	1	2412790	CA	A1	2002-01-10	Ahkong et al.		
	2	101878229	CN	A	2010-11-03	Rochlitz et al.	See WO 2009040426 (cited below for English language)	☒
	3	1829741	CN	A	2006-09-06	William Fyfe	See WO 2005000900 (cited below for English language)	☒

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	4	1980637	CN	B	2014-02-19	Hermes Biosciences, Inc.	See WO 2005107712 (cited below for English language)	☒
	5	2000023052	WO	A1	2000-04-27	Alza Corporation		☐
	6	2004017940	WO	A3	2004-04-29	Neopharm, Inc.		☐
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	11	2012031293	WO	A1	2012-03-08	Kabanov et al.		☐
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	14	2016168451	WO	A1	2016-10-20	Merrimack Pharmaceuticals, Inc.		☐

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	15	2017066726	WO	A1	2017-04-20	Merrimack Pharmaceuticals, Inc.		☐
	16	2017172678	WO	A1	2017-10-05	Merrimack Pharmaceuticals, Inc.		☐
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	19	2005107712	WO	A1	2005-11-17	Hermes Biosciences, Inc.		☐

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	Art Unit	1612
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	Attorney Docket Number	01208-0007-01US

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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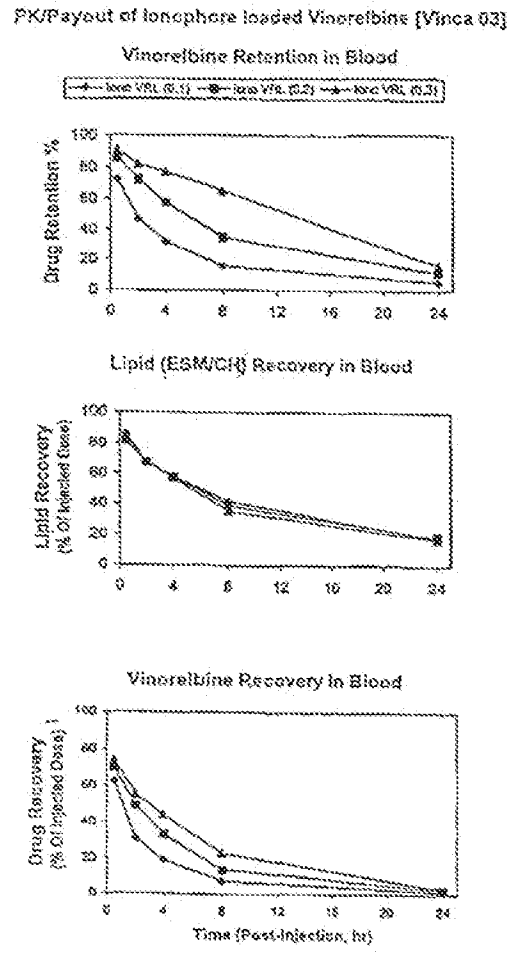
(54) MEDICAMENTS ANTINEOPLASIQUES LIPOSOMAUX ET LEURS UTILISATIONS
(54) LIPOSOMAL ANTINEOPLASTIC DRUGS AND USES THEREOF

(57)
This invention relates to liposomal antineoplastic agents (e.g., camptothecin) compositions and methods of using such compositions for treating neoplasia and for inhibiting angiogenesis. The compositions and methods are useful for modulating the plasma circulation half-life of an active agent.



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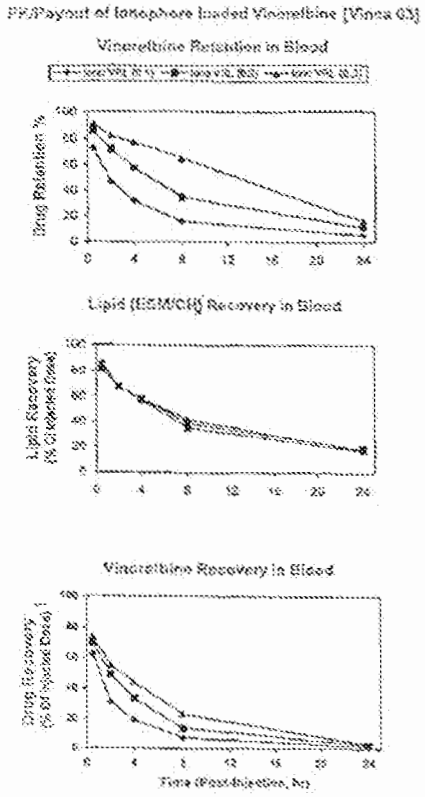

(57) Abrégé/Abstract:
This invention relates to liposomal antineoplastic agents (e.g., camptothecin) compositions and methods of using such compositions for treating neoplasia and for inhibiting angiogenesis. The compositions and methods are useful for modulating the plasma circulation half-life of an active agent.

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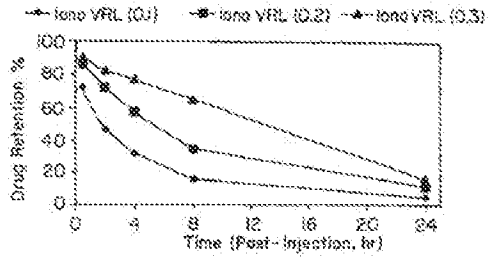

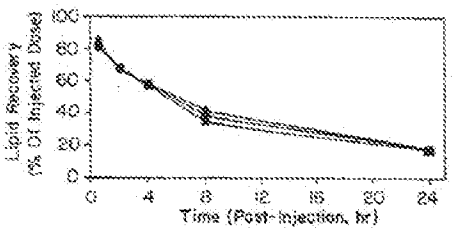

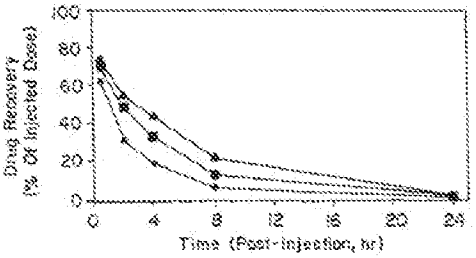

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