REVIEW

Options for the Treatment of Gemcitabine-Resistant Advanced Pancreatic Cancer

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Summary

Context Pancreatic cancer is noteworthy in that the number of patients dying from the disease is roughly equal to the number diagnosed. For more than a decade, gemcitabine has constituted the standard of care for the palliative treatment of the majority of patients who present with metastatic or relapsed disease, although the survival gains are limited. Despite a median survival of less than 6 months, there is a significant proportion of advanced pancreatic cancer patients who progress on gemcitabine that remains fit and these patients are candidates for second-line treatment. **Methods** The OVID MEDLINE database was searched from 1950 to present using the MeSH terms "pancreatic neoplasms", "drug treatment" and "gemcitabine". After excluding non-relevant results, 31 published studies were identified. These results were supplemented by searching the last three (2007-2009) American Society of Clinical Oncology (ASCO) Proceedings of Annual Meetings for studies published only in abstract form and reviewing reference lists of published articles. **Results and discussion** The evidence for second line treatments of metastatic pancreatic cancer consists mostly of single arm, small phase II studies. Oxaliplatin-fluoropyrimidine combinations appear promising and have shown increased survival compared to best supportive care. As the molecular pathways governing pancreatic cancer are unravelled, novel targeted therapies may offer the greatest promise for this disease either given alone, combined with one another, or with cytotoxic agents. The need for further, collaborative research is emphasised.

Introduction

According to Surveillance Epidemiology and End Results (SEER) estimates, more than 42,000 patients will be diagnosed with pancreatic cancer in the United States in 2009 [1]. With 35,000 deaths attributed to the disease over the same time period, pancreatic cancer constitutes the 4th most common cause of death from malignancy. The situation is similar in Europe, where just over 60,000 patients were diagnosed with pancreatic cancer in 2006 and almost the same number died from their disease [2]. More than 80% of patients present with unresectable, locally advanced or metastatic disease, the prognosis of which remains dismal with a median survival of approximately 6 months and fewer than 2% of patients surviving for 5 years [1].

Gemcitabine has been the standard of care for the first line treatment of metastatic pancreatic cancer since 1997, when it was shown to improve survival compared to 5-fluorouracil (5-FU). In the pivotal trial reported by Burris *et al.*, treatment with gemcitabine resulted in a median survival of 5.65 months compared to 4.41 months with bolus 5-FU, together with an improvement in clinical benefit response of 23.8% compared with 4.8%. More impressively, 1-year survival increased from 2% to 18%, establishing gemcitabine as the preferred initial treatment option [3]. Over the past decade multiple phase II and III studies have attempted to improve on the above results with various combinations of gemcitabine with traditional cytotoxic or novel targeted agents. A phase III trial has shown a modest improvement in overall survival with the addition of erlotinib [4] to standard gemcitabine chemotherapy, whereas the initially

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Abbreviation ASCO: American Society of Clinical Oncology, COX-2: cyclo-oxygenase 2; EGFR: epidermal growth factor receptor; FAM: 5-fluorouracil, doxorubicin, mitomycin-C; FF: folinic acid, 5-fluorouracil; FOLFIRI.3: irinotecan, folinic acid, infusional 5-fluorouracil; FOLFOX: oxaliplatin, folinic acid, infusional 5-fluorouracil; GEMOX: gemcitabine, oxaliplatin; G-FLIP: gemcitabine, irinotecan, folinic acid, 5-fluorouracil, cisplatin; IROX: irinotecan, oxaliplatin; KRAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; mTOR: mammalian target of rapamycin; NCCN: National Comprehensive Cancer Centre, OFF: oxaliplatin, folinic acid, 5-fluorouracil, OS: overall survival, PDGFR: platelet-derived growth factor receptor; PEFG: cisplatin, 5-fluorouracil, epirubicin, gemcitabine; PFS: progression-free survival; PS: performance status, TKI: tyrosine kinase inhibitor; TTP: time to progression; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; XELOX: oxaliplatin, capecitabine

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reported survival advantage from the addition of capecitabine [5], was no longer evident with more complete follow up [6]. A third study has reported improved progression-free survival with the addition of bevacizumab to a combination of gemcitabine and erlotinib [7]. However, currently, there remains a lack of convincing evidence that any single or combination drug regimen yields consistent, clinically meaningful, survival benefits compared with single agent gemcitabine.

While the standard of care in the first line setting is established, there is limited data available to guide treatment decisions in patients whose disease has progressed following gemcitabine treatment. This is exemplified by the National Comprehensive Cancer Centre (NCCN) pancreatic cancer guidelines that suggest participation in a clinical trial as the preferred treatment option for patients who have previously received gemcitabine [8]. Given the short life expectancy with advanced pancreatic cancer, many patients deteriorate quickly after disease progression, rendering further active treatment inappropriate. However, perhaps as many as 1 in 3 patients are fit enough for consideration of a second line option. Generally, this group includes patients with good performance status (WHO 0-1) and adequate haematological, renal and hepatic function who wish to proceed with treatment after an informed discussion regarding the potential benefits of such an option. The earlier detection of disease progression or relapse with the use of advanced imaging technologies and serum tumour markers is likely to expand the pool of suitable patients.

In this review article, we present an overview of the available published data on second line therapy for advanced disease. In order to identify relevant studies, the OVID Medline database was searched from 1950 to present using the MeSH terms "pancreatic neoplasms", "drug treatment" and "gemcitabine". After excluding non-relevant results, 31 published studies were identified. These results were supplemented by searching the last 3 (2007-2009)

Table 1. Prospective single arm phase II chemotherapy trials in gemcitabine-resistant metastatic pancreatic cancer.

Study	Regimen	No. of patients	Partial response + complete response (PR+CR: %)	Median progression-free survival (PFS: months)	Median overall survival (OS: months)
Pelzer *et al.* [9]	OFF	37	6	2.8	5.1
Tsavaris *et al.* [12]	OFF	30	23	n/a	5.8
Novarino *et al.* [13]	OFF	23	0	2.7	4.0
Xiong *et al.* [16]	XELOX	41	2	2.3	5.3
Gasent Blesa *et al.* [17]	XELOX	15	7	n/a	5.3
Sancho *et al.* [18]	XELOX	18	5	4.0	5.8
Androulakis *et al.* [19]	Oxaliplatin	18	0	n/a	n/a
Demols *et al.* [21]	GEMOX	33	21	4.2	6.0
Mazzer *et al.* [25]	Oxaliplatin, pemetrexed	16	19	3.2	n/a
Reni *et al.* [26]	Oxaliplatin, raltitrexed	41	24	n/a	5.2
Cantore *et al.* [24]	IROX	30	10	4.1	5.9
Morizane *et al.* [27]	S-1	40	15	2.0	4.5
Boeck *et al.* [29]	Capecitabine	39	0	2.3	7.6
Togawa *et al.* [30]	Cisplatin, S-1	17	29	n/a	9.0
Kim *et al.* [33]	5-FU, paclitaxel	28	7	2.5	7.6
Lee *et al.* [34]	FAM	15	0	2.3	6.7
Blaya *et al.* [35]	Capecitabine, docetaxel	24	12.5	n/a	n/a
Pino *et al.* [38]	Capecitabine, celecoxib	35	9	n/a	4.4
Millela *et al.* [37]	5-FU, celecoxib	17	12	1.9	3.5
Saif *et al.* [39]	Capecitabine, PHY906	25	4	n/a	n/a
Yi *et al.* [40]	Irinotecan	33	9	2.0	6.0
Ko *et al.* [41]	Docetaxel, irinotecan	14	0	1.2	4.4
Reni *et al.* [42]	Mitomycin C, docetaxel, irinotecan	15	0	1.7	6.1
Burris *et al.* [44]	Rubitecan	58	5	1.9	3.0
Cereda *et al.* [46]	Docetaxel	10	0	1.5	4.0
Carvajal *et al.* [47]	Docetaxel, flavopiridol	10	0	n/a	n/a
Oettle *et al.* [48]	Paclitaxel	18	6	n/a	4.1
Boeck *et al.* [49]	Pemetrexed	52	4	1.6	4.7
Moore *et al.* [50]	Eribulin	15	0	n/a	n/a
Stathopoulos *et al.* [51]	Lipoplatin, gemcitabine	24	8	3.0	n/a
Tschoep *et al.* [52]	Regional hyperthermia, gemcitabine, cisplatin	22	9	4.2	n/a

FAM: 5-fluorouracil, doxorubicin, mitomycin C; GEMOX: gemcitabine, oxaliplatin; IROX: irinotecan, oxaliplatin, OFF: oxaliplatin, folinic acid, 5-fluorouracil; XELOX: capecitabine, oxaliplatin

n/a: not available

Table 2. Prospective randomised phase II and III trials in gemcitabine-resistant metastatic pancreatic cancer

Study	Regimen	No. of patients	Partial response + complete response (PR+CR; %)	Median progression-free survival (PFS; months)	Median overall survival (OS; months)
Oettle *et al.* [10]	OFF	46	n/a	n/a	4.9
	Best supportive care	(total)			2.3
					(P=0.008)
Pelzer *et al.* [11]	OFF	76	n/a	3.0	6.0
	FF	84		2.1	3.0
				(P=0.012)	(P=0.014)
Hwang *et al.* [15]	FOLFOX	30	n/a	1.4	4.0
	FOLFIRI.3	30		1.9	4.0
				(P>0.05)	(P>0.05)
Ulrich-Pur *et al.* [43]	Irinotecan, raltitrexed	19	16	4.0	6.5
	Raltitrexed	19	0	2.5	4.3
Jacobs *et al.* [45]	Rubitecan	198	11	1.9	3.5
	Best care [a]	211	1	1.6	3.1
			(P<0.001)	(P=0.003)	(P=0.626)
Astsaturov *et al.* [64]	Bevacizumab	15	0	1.4	5.9
	Bevacizumab, docetaxel	15	7	1.5	4.0
				(P=0.5)	(P=0.8)

FF: folinic acid, 5-fluorouracil; FOLFIRI.3: irinotecan, folinic acid, infusional 5-fluorouracil; FOLFOX: oxaliplatin, folinic acid, infusional 5-fluorouracil, OFF: oxaliplatin, folinic acid, 5-fluorouracil
[a] clinician's choice of chemotherapy or best supportive care
n/a: not available

American Society of Clinical Oncology (ASCO) Proceedings of Annual Meetings for studies published only in abstract form and reviewing reference lists of published articles. The evidence for second line treatments of metastatic pancreatic cancer consists mostly of single arm, small phase II studies, testing a variety of drug combinations in a heterogeneous population. Therefore, a descriptive approach was adopted, as any attempt at statistical analysis using meta-analytic approaches would be inappropriate.

Oxaliplatin-Fluoropyrimidine Combinations

The combination of oxaliplatin with a fluoropyrimidine appears promising in phase II second line trials and is one of only a handful of regimens evaluated in the phase III setting (Tables 1 and 2). In an initial phase II study, Pelzer *et al.* [9] reported on the efficacy of the OFF (oxaliplatin, folinic acid, 5-FU) regimen, combining oxaliplatin 85 mg/m^2 on days 8 and 22, folinic acid 500 mg/m^2 and 5-FU 2,600 mg/m^2 as a 24-h infusion on days 1, 8, 15 and 22. The regimen was repeated every 42 days and toxicity was apparently quite acceptable, with grade 3 non-haematologic adverse events occurring in 32% of patients and no reported grade 4 non-haematologic toxicities. Thirty seven gemcitabine-pretreated patients were enrolled and the median time to progression (TTP) and overall survival (OS) were 12 and 22 weeks, respectively. Two patients (6%) showed radiological responses, while a further 16 (43%) had stable disease for more than 12 weeks.

These results prompted a phase III study (Charité Onkologie; CONKO 003). The initial study design was a comparison of the OFF regimen (modifying the 5-FU dose to 2,000 mg/m^2 and the folinic acid dose to 200 mg/m^2) with best supportive care. Eligibility criteria included progression on previous gemcitabine-based chemotherapy, adequate haematological, renal, cardiac and hepatic function and a Karnofsky performance status greater than 70. Unfortunately, the control arm was closed after 46 of the planned 165 patients were enrolled due to clinician reluctance to enroll in a no-treatment arm. The results of this initial cohort of the trial were presented at the 2005 ASCO Annual Meeting [10]. Median survival was 22 weeks in the experimental arm and 10 weeks in the best supportive care arm (P=0.0077).

Given this impressive survival difference, the trial design was altered to include an alternative relevant comparator arm, comprising 5-FU plus folinic acid chemotherapy (FF regimen) at the same doses and the trial therefore became a randomised comparison of OFF *versus* FF. A further 165 patients were enrolled and results for the 160 assessable patients were presented at the 2008 ASCO Annual Meeting [11]. Toxicity was acceptable with few grade 3-4 adverse events. Median progression-free survival (PFS) and overall survival were significantly better in the OFF arm (13 *vs.* 9 weeks, P=0.012, and 26 *vs.* 13 weeks, P=0.014, respectively).

Two further single arm phase II studies using oxaliplatin plus bolus 5-FU/folinic acid have been reported. Tsavaris *et al.* [12] administered weekly oxaliplatin (50 mg/m^2), bolus folinic acid (50 mg/m^2) and 5-FU as a 1-h infusion (500 mg/m^2). Thirty gemcitabine-pretreated patients were enrolled, 29 of whom had locally advanced disease. Seven patients showed a partial response and a further 9 had stable disease for a disease control rate (partial response plus stable disease) of 53%. The median duration of response was 22 weeks and median survival was 25 weeks. Of note, 27% of patients experienced febrile neutropenic events but there were no treatment related fatalities.

Novarino *et al.* [13] also utilised a weekly oxaliplatin/5-FU/folinic acid regimen (oxaliplatin 40 mg/m^2, folinic acid 250 mg/m^2, and 5-FU 500 mg/m^2 on a 3 week-on/1 week-off schedule). Twenty three patients were enrolled, 17 were assessable and no objective responses were seen. Four patients had stable disease for a median duration of stable disease of 14 weeks. The median TTP was 11.6 weeks and median survival was 17.1 weeks. Grade 3-4 toxicity occurred in 7 (30%) patients.

Using a combination regimen more familiar to colorectal cancer specialists, FOLFOX4 (oxaliplatin 85 mg/m^2 on day 1, levo-folinic acid 100 mg/m^2 over 2 h, 5-FU 400 mg/m^2 i.v. bolus then 600 mg/m^2 over 22 h on days 1 and 2 every two weeks), Gebbia *et al.* reported a retrospective case series of 42 patients [14]. Six (14%) partial responses and 16 (38%) cases of stable disease were seen. Twenty seven patients reported subjective improvement; the median TTP was 4 months and the median survival was 6.7 months. Although encouraging, these results are subject to the usual limitations of a retrospective design, with unclear selection criteria.

Hwang *et al.* [15] presented the first results of a small randomised phase II trial of the FOLFOX (oxaliplatin, folinic acid, infusional 5-fluorouracil) regimen at the 2009 ASCO Annual Meeting (Table 2). Sixty patients with advanced pancreatic cancer and previous progression on gemcitabine were randomised to modified FOLFOX (oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, and 5-FU 2,000 mg/m^2 over 46 hours every two weeks) or FOLFIRI.3 (the same 5-FU/folinic acid regimen but with irinotecan 70 mg/m^2 every two weeks). Thirty patients were enrolled in each arm and median survival was identical at 4 months. The median PFS was 1.4 and 1.9 months for FOLFOX and FOLFIRI.3, respectively (P>0.05); slightly more patients in the latter (28% *vs.* 20%) achieved disease control (defined as partial response or stable disease).

Finally, three small single arm phase II studies have investigated the efficacy of oxaliplatin-capecitabine combinations. Xiong *et al.* [16] enrolled 41 gemcitabine-pretreated patients on a single arm study of XELOX (oxaliplatin and capecitabine) in advanced pancreatic cancer (oxaliplatin 130 mg/m^2, capecitabine 1,000 mg/m^2 *po bid* days 1-14, every 3 weeks). One (2%) patient showed a partial response and a further 10 (24%) had stable disease. The median PFS was 10 weeks and the median survival 23 weeks. Grade 3 or worse non-haematologic toxicities were uncommon with only fatigue and diarrhoea occurring in more than 1 patient. Two more, smaller, studies have been presented in abstract format only. The first, by Gasent-Blesa *et al.* [17] enrolled 15 patients. Treatment was with a modified XELOX regimen in which the oxaliplatin dose was reduced to 100 mg/m^2. One patient had a complete response and a further 5 had stable disease. Median survival from initiation of second-line treatment was 163 days (23 weeks) and the regimen was well tolerated with no grade 3-4 adverse events. Sancho *et al.* [18] also performed a study of XELOX in advanced gemcitabine-resistant pancreatic and biliary adenocarcinoma. Eighteen patients (9 with pancreatic cancer) were enrolled and the median PFS and OS were 17 and 25 weeks respectively. There was no information on the outcomes of the pancreatic cancer patients separately. It should be noted that the toxicity of the full dose XELOX regimen was higher than that reported by Xiong *et al.* and Gasent-Blesa *et al.*, with 11 grade 3 adverse events.

In summary, oxaliplatin-fluoropyrimidine combinations appear to show some promising activity in gemcitabine-pretreated patients. The OFF regimen has been shown to be superior to best supportive care or 5-FU/folinic acid in a randomised study and might be considered as an emerging standard of care in this setting. To date, it remains the only regimen that has achieved a survival advantage in a randomised trial, a position recognised by the NCCN guidelines that recommend the use of oxaliplatin and fluoropyrimidine combination if enrolment in a clinical trial is not possible [8]. Although direct comparisons are lacking, the XELOX regimen shows comparable efficacy and offers the advantage of oral fluoropyrimidine treatment, obviating the need for infusion pumps with associated complications and more frequent hospital attendances. Even so, more large scale, well designed, randomised controlled trials are required in this setting before a new standard of care can be established.

Other Oxaliplatin Based Combinations

Studies of oxaliplatin as single agent or in combination with a non-fluoropyrimidine are summarised in Table 1. As might be predicted from both preclinical and clinical studies in colorectal cancer, single agent oxaliplatin (130 mg/m^2 every 3 weeks) was shown to be inactive in a small study involving 18 patients [19]. No responses were seen, with just 3 (17%) patients achieving stable disease for more than 2 months.

Based upon initial data suggesting that fixed-dose-rate gemcitabine (10 mg/m^2/min) results in higher intracellular accumulation of active gemcitabine metabolites and higher response rates (although at the cost of increased toxicity) [20], Demols *et al.* [21] tested the hypothesis that the addition of oxaliplatin to fixed-dose-rate gemcitabine in patients whose disease had previously progressed on standard single agent gemcitabine would restore chemosensitivity. They enrolled 33 patients to a phase II study of GEMOX (gemcitabine 1,000 mg/m^2 over 100 min on day 1, oxaliplatin 100 mg/m^2 on day 2 every 2 weeks). Toxicity was considerable, with one patient fatality from neutropenic sepsis and 48% experiencing at least one grade 3 toxic event. The regimen showed evidence of activity with 7 (21%) of patients showing partial response and a further 11 (33%) stable disease for more than 8 weeks. Median TTP and OS were 4.2 and 6 months respectively. Recently, Fortune *et al.* [22] reported their institutional experience with the

GEMOX regimen, again utilising fixed-dose-rate gemcitabine. Seventeen patients that had progressed on previous gemcitabine treatment were retrospectively identified. There were 4 (24%) partial responses and 5 (29%) cases of stable disease. The median PFS was 2.6 months whereas the median survival was 6.4 months. The toxicity of GEMOX is significant and, in view of the findings of the phase III E6201 study [23] in the first-line setting, further evaluation for the second-line treatment of pancreatic cancer does not appear to be worthwhile. E6201 was a randomised study of gemcitabine *versus* fixed-dose-rate gemcitabine *versus* GEMOX in previously untreated patients with advanced pancreatic cancer. More than 800 patients were enrolled and although toxicity was increased in both experimental arms, no survival or clinical benefit was noted [23].

Oxaliplatin has also been investigated in combination with irinotecan (IROX) with some preliminary evidence of efficacy [24]. Thirty patients were treated with oxaliplatin (60 mg/m^2 days 1 and 15) and irinotecan (60 mg/m^2 days 1, 8 and 15 every 4 weeks); 3 (10%) partial responses were noted and the disease remained stable in a further 7 (23%) patients. The regimen was well tolerated and median TTP and survival were 4.1 and 5.9 months, respectively.

The combination of oxaliplatin (120 mg/m^2) with pemetrexed (500 mg/m^2 every 3 weeks) may have some activity. Initial results of a phase II study presented at the 2009 ASCO Annual Meeting showed 3 partial and 6 minor responses in 15 evaluable patients. The median PFS was 14 weeks and grade 3 toxicities appeared uncommon [25]. Oxaliplatin (130 mg/m^2) has also been combined with another novel antifolate, raltitrexed (3 mg/m^2). Forty one patients were treated in a phase II trial and the partial response rate was an encouraging 24% [26]. Significant toxicity was uncommon, but, disappointingly, median survival was only 5.2 months.

Single-Agent Fluoropyrimidines

Two single arm phase II studies and a retrospective series have addressed the role of a fluoropyrimidine as a single agent following disease progression on gemcitabine. Morizane *et al*. [27] reported on the use of S-1, a novel oral fluoropyrimidine prodrug, in this setting. S-1 consists of ftorafur, a 5-FU prodrug, combined with the dihydropyrimidine dehydrogenase (DPD) inhibitor, chloro-dihydroxypyridine, and the orotate phosphoribosyltransferase inhibitor potassium oxonate. In the study by Morizane *et al*., 40 patients received S-1 at a dose of 40 mg/m^2 daily for 28 days followed by a 14-day rest period. Six (15%) patients had a partial response and 17 (43%) had stable disease. Median PFS and OS were 2 and 4.5 months, respectively. Nakai *et al*. [28] reported their institutional experience with S-1 in the second line treatment of gemcitabine-resistant pancreatic cancer at the University of Tokyo Hospital. Twenty nine patients were treated with 5 (17%) responding. Median PFS and OS were 2.5 and 7.8 months, respectively.

Capecitabine (1,250 mg/m^2 *po bid* for 2 weeks every 3 weeks) was administered to 39 patients by Boeck *et al*. [29]. No objective responses were seen and 13% of patients experienced grade 3 palmar-plantar erythema. Median TTP was 2.3 months and median survival was 7.6 months in this study, indicating some efficacy, even in the absence of objective responses.

Cisplatin-Fluoropyrimidine Combinations

Evidence regarding the use of cisplatin in patients with gemcitabine-resistant disease is limited (Table 1). A small single arm Japanese phase II study tested the combination of cisplatin and S-1 [30]. The regimen consisted of S-1 80 mg/m^2 daily for 21 days, followed by a 14-day rest period, and cisplatin 40 mg/m^2 on day 8. Seventeen patients were enrolled with 5 (29%) showing partial response and a further 2 (12%) stable disease. The median survival was an impressive 9 months and 32% were still alive at 12 months. Treatment was well tolerated with only a single episode of grade 3 toxicity (leukopaenia). However, of note, in this study all patients had received gemcitabine adjuvantly and treatment with cisplatin and S-1 was in the first line metastatic setting, which most probably explains the prolonged median survival compared to other studies in this review.

A four drug combination of cisplatin, 5-FU, epirubicin and gemcitabine (PEFG) was tested by Reni *et al*. [31]. This was an observational study with two cohorts of gemcitabine-resistant patients treated either with "classic" (cisplatin and epirubicin 40 mg/m^2 day 1, gemcitabine 600 mg/m^2 days 1 and 8, 5-FU 200 mg/m^2/day continuous infusion days 1-28) or "dose-intense" PEFG (cisplatin and epirubicin 30 mg/m^2, gemcitabine 800 mg/m^2 every 14 days; 5-FU 200 mg/m^2/day continuous infusion days 1-28). Dose intensification led to more common grade 3 and 4 haematological toxicity but non-haematological toxicity was generally mild with both regimens. There were no significant differences in efficacy between the "classic" and the "dose-intense" cohort. Response rates, median PFS and OS for the 46 enrolled patients were 24%, 5 months and 8.3 months, respectively.

Another intensive regimen incorporating both cisplatin and 5-FU is G-FLIP. The regimen consists of gemcitabine (500 mg/m^2 day 1), irinotecan (80 mg/m^2 day 1), folinic acid (300 mg days 1 and 2), 5-FU (400 mg/m^2 i.v. bolus followed by 600 mg/m^2 over 8 hours days 1 and 2) and cisplatin (50-75 mg/m^2 day 2). In a retrospective series, Kozuch *et al*. [32] reported their experience with 34 gemcitabine-resistant patients. Grade 3-4 haematological toxicities were common and 8 (24%) patients experienced a partial response. The median PFS was 3.9 months, whereas the median survival was an impressive 10.3 months.

These two observational studies appear to show that improved efficacy can be achieved by combining multiple non-crossresistant agents. However, the toxicity of the regimens appears high, potentially limiting their use in a select subset of patients. It remains to be seen whether comparative efficacy is

achieved in prospectively designed, preferably randomised, studies.

Other Fluoropyrimidine-Based Combinations

Studies have also been conducted combining a fluoropyrimidine with a non-platinum agent (Table 1). Kim *et al*. combined 5-FU (1,000 mg/m^2/day on days 1-3) with paclitaxel (175 mg/m^2). Twenty eight patients were enrolled, of which 2 (7%) showed a partial response to treatment. Median TTP and OS were 2.5 and 7.6 months, respectively [33]. Another small Korean study tested the combination of 5-FU, doxorubicin, and mitomycin-C (FAM) in a mixed population of patients with gemcitabine-refractory pancreatic and biliary tumours [34]. Fifteen of the 31 enrolled patients had pancreatic cancer. The results were reported for all patients combined and the median TTP and OS were 2.3 and 6.7 months, respectively. In another study, Blaya *et al*. [35] combined capecitabine (800 mg/m^2 *po bid* days 1-14) with docetaxel (30 mg/m^2 days 1 and 8). There were 3 (12.5%) responses among 24 treated patients and 11 patients showed a decrease in CA 19-9 levels; further results are awaited.

The cyclo-oxygenase 2 (COX-2) pathway is frequently upregulated in pancreatic cancer and treatment with COX-2 inhibitors has shown promising activity in preclinical studies [36]. Two studies have tested the combination of a fluoropyrimidine with the COX-2 inhibitor celecoxib in gemcitabine pretreated patients. In the first study, Milella *et al*. [37] administered 5-FU (200 mg/m^2/day) and celecoxib (400 mg *bid*) continuously until progression. Two of the 17 enrolled patients showed a patient response and the median TTP was 8 weeks. Median survival in this study was 17 weeks and the regimen was well tolerated although 4 patients discontinued celecoxib due to upper gastrointestinal tract toxicity. Pino *et al*. administered capecitabine (1,000 mg/m^2 *po bid* for 2 weeks every 3 weeks) with celecoxib (200 mg *bid* continuously) to 35 patients with gemcitabine-resistant pancreatic or biliary tract cancer [38]. The primary endpoint of the trial was 3-month PFS. This was achieved by 60% of the patients and the median survival was 19 weeks.

Saif *et al*. presented preliminary results of a study of PHY906, a Chinese herbal medicine, in combination with capecitabine at the 2009 ASCO Annual Meeting [39]. Capecitabine was administered at a dose of 1,500 mg *po bid* on days 1-7 and PHY906 at 800 mg *po bid* on days 1-4 on a 14-day cycle. Of the first 25 patients enrolled, 1 (4%) showed a partial response and 4 have survived for more than 6 months. Of note, 7 patients died within a month of enrolment (6 from progressive disease) and one was withdrawn because of severe palmar-plantar erythema. More mature outcome data are awaited.

Camptothecins

Irinotecan is the most commonly used camptothecin analogue in advanced pancreatic cancer (Table 1). Two studies incorporating irinotecan in the IROX [24] and G-FLIP [32] regimens have already been mentioned. The efficacy of irinotecan (150 mg/m^2 every 2 weeks) as a single agent was reported by Yi *et al*. [40]. Thirty three gemcitabine-resistant patients were treated and 3 (9%) partial responses were seen. Median PFS and OS were 2 and 6.6 months and toxicity was acceptable.

A pilot study combining irinotecan (160 mg/m^2) and docetaxel (65 mg/m^2) in a three-weekly schedule had to be abandoned after only 14 patients were enrolled due to excess toxicity, mainly neutropenia, diarrhoea, nausea and vomiting [41]. No responses were seen and the median time to treatment failure was a disappointing 36 days (5.1 weeks). Similarly disappointing results were reported from a dose escalation study of mitomycin-C, docetaxel and irinotecan [42]. No responses were seen among 15 patients treated at the maximum tolerated dose and median PFS and OS were 1.7 and 6 months, respectively. Therefore, despite encouraging preclinical evidence, the combination of irinotecan and docetaxel appears inactive in gemcitabine-resistant pancreatic cancer.

The addition of irinotecan to raltitrexed, was tested in a randomised phase II study by Ulrich-Pur *et al*. [43]. Thirty eight patients were randomised to receive raltitrexed (3 mg/m^2) with or without irinotecan (200 mg/m^2) every 3 weeks. The combination arm was clinically superior with median PFS and OS being 4 and 6.5 months, respectively, compared to 2.5 and 4.3 months in the raltitrexed arm (Table 2). No tests of statistical significance were reported, although the small number of patients enrolled would probably preclude any valid inferences. Toxicity was increased with combination treatment, but grade 3 toxicity was uncommon in this small study and the regimen was well tolerated.

Rubitecan, an orally bioavailable camptothecin derivative, was the subject of the largest study conducted in gemcitabine-resistant pancreatic cancer. Burris *et al*. [44] reported the results of an initial single arm study in which 58 heavily pretreated patients were enrolled. Rubitecan (1.5 mg/m^2 *po* 5 days per week) was reasonably well tolerated, although 34% of the patients required a dose reduction due to toxicity. Median TTP and OS were a modest 1.9 and 3 months, respectively. Subsequently, a large phase III study was launched (Table 2), the results of which have only been reported in abstract form [45]. Four-hundred and nine patients were randomised to treatment with rubitecan or physician's best choice (chemotherapy 89%, supportive care only 11%). There were more responses in the rubitecan arm (11% *vs*. 1%) and the difference in median PFS, although clinically modest, reached statistical significance (1.9 *vs*. 1.6 months). There was no significant difference however, in OS which was 3.5 months in the rubitecan arm compared to 3.1 months in the control arm. The drug manufacturer, SuperGen (Dublin, CA, USA), withdrew an FDA new drug application for rubitecan in 2005 and has since halted clinical development of the agent.

Taxanes

The lack of clinical activity of the docetaxel-irinotecan combination has already been mentioned [41, 42]. These results were echoed in a small study of single agent weekly docetaxel (30 mg/m^2) that enrolled 10 patients and reported no objective responses [46]. Median PFS and OS were 2.5 and 4 months respectively. Similarly, a study of weekly docetaxel (35 mg/m^2) and flavopiridol (80 mg/m^2) was closed early due to excess toxicity and lack of any objective responses in gemcitabine-resistant patients [47].

Paclitaxel has shown some activity in combination with 5-FU (see "Other fluoropyrimidine-based combinations"). A study of weekly paclitaxel (90 mg/m^2) as a single agent in 18 gemcitabine-resistant patients showed good tolerability. One (6%) response was seen and median survival was 17.5 weeks [48]. In summary, the activity of taxanes in this setting appears to be negligible and docetaxel-based regimens, in particular, have been associated with unacceptable levels of toxicity.

Other Chemotherapeutic Combinations

Pemetrexed, lipoplatin, eribulin and regional hyperthermia modulation of cisplatin have all been investigated in gemcitabine-resistant pancreatic cancer (Table 1). Pemetrexed has shown promising activity in combination with oxaliplatin [25] and has also been tested as a single agent. In a study by Boeck *et al.* [49], 52 patients received pemetrexed (500 mg/m^2) every 3 weeks. Two (4%) of patients had a partial response to treatment and toxicity was manageable with a quarter of the patients experiencing grade 3-4 gastrointestinal toxicity. Median PFS and OS were however only 7 and 20 weeks, respectively.

Eribulin is a microtubule-stabilising halichondrin B analogue. Moore *et al.* [50] conducted a small phase II study of eribulin (1.4 mg/m^2 days 1 and 8 every 3 weeks) in gemcitabine-resistant advanced pancreatic cancer. Three (20%) patients showed prolonged stable disease, lasting in excess of 9 months. However, there were no responses among 15 enrolled patients and the study was therefore terminated.

A liposomal formulation of cisplatin, lipoplatin, was originally developed to improve the toxicity profile of cisplatin. Stathopoulos *et al.* [51] performed a dose escalation study of biweekly lipoplatin (25-125 mg/m^2) in combination with gemcitabine (1,000 mg/m^2) in patients whose disease had progressed on previous gemcitabine-based chemotherapy. Two (8%) of the 24 patients showed a partial response and a further 14 (58%) had stable disease for a median duration of 3 months. Non-haematological toxicity was minimal and further evaluation of the combination is planned.

Tschoep *et al.* [52] presented the results of a study of regional hyperthermia combined with biweekly cisplatin (25 mg/m^2 days 1 and 2) and gemcitabine (1,000 mg/m^2) in 22 gemcitabine-refractory patients. Toxicity was minimal with only 3 cases of grade 3 anaemia and no non-haematological toxicity greater than grade 2. The study reached its primary endpoint with a median TTP of 4.2 months and a phase III study of regional hyperthermia-modulated cisplatin-gemcitabine is planned.

Biological Agents

Multiple growth pathways are activated in pancreatic adenocarcinomas. These include the EGFR-RAS-MEK-ERK, the PI3K-AKT-mTOR and the VEGF-VEGFR pathways [53]. Since around 80% of pancreatic adenocarcinomas possess mutations in v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) [54], molecular targeted therapy has always been considered to hold potential for this highly chemoresistant form of cancer. Even so, studies conducted with tipifarnib, a farnesyltransferase inhibitor designed to inhibit KRAS, proved remarkably disappointing [55]. Subsequently, at least in first line therapy, the addition of erlotinib and bevacizumab to standard gemcitabine-based chemotherapy has resulted in only very modestly improved outcomes [4, 7]. Still, it is hoped that, as other key pathways governing the malignant process are identified, new biological agents, such as inhibitors of the Hedgehog [56] and Notch [57] pathways, will be developed which might achieve greater clinical improvements, both in the first and second line setting. Table 3 summarises the available data regarding the use of targeted agents in patients with gemcitabine-refractory metastatic disease.

Table 3. Prospective single arm phase II biological agent trials in gemcitabine-resistant metastatic pancreatic cancer.

Study	Regimen	No. of patients	Partial response + complete response (PR+CR; %)	Median progression-free survival (PFS; months)	Median overall survival (OS; months)
Ignatiadis *et al.* [62]	Gefitinib, docetaxel	26	0	2.1	2.9
Brell *et al.* [63]	Gefitinib, docetaxel	41	2	1.8	4.5
Kulke *et al.* [58]	Erlotinib, capecitabine	30	10	3.4	6.5
Javle *et al.* [59]	Erlotinib, everolimus	16	0	n/a	n/a
Ko *et al.* [60]	Erlotinib, bevacizumab	26	4	1.3	3.4
Dragovich *et al.* [65]	Vatalinib	65	n/a	6-month PFS: 14%	6-month OS: 31%
O'Reilly *et al.* [66]	Sunitinib	77	0	1.3	3.2
Javle *et al.* [59]	Temsirolimus	5	0	n/a	n/a
Garrido-Laguna *et al.* [67]	Sirolimus	n/a	n/a	1.5	n/a
Wolpin *et al.* [68]	Everolimus	33	0	1.8	4.5

n/a: not available

The evidence that erlotinib, an oral tyrosine kinase inhibitor (TKI) inhibiting the epidermal growth factor receptor (EGFR) is effective against pancreatic cancer is far from convincing. In the phase III PA.3 trial conducted in previously untreated metastatic pancreatic cancer, the addition of erlotinib to gemcitabine generated a statistically significant improvement in median survival, although the actual gain was under 2 weeks (6.24 *vs.* 5.91 months, P=0.038) [4]. In gemcitabine-pretreated patients, Kulke *et al.* [58] tested the combination of capecitabine (1,000 mg/m^2 *po bid* days 1-14 every 3 weeks) and erlotinib (150 mg *po od* continuously). Toxicity was significant with mostly grade 3 diarrhoea and skin toxicity leading to dose modifications and delays in two thirds of the 30 enrolled patients. However, 3 partial responses were observed and the median PFS and OS were an encouraging: 3.4 and 6.5 months, respectively.

Erlotinib has also been tested in combination with other biological agents, in the absence of chemotherapy. In a study of erlotinib and everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, no evidence of efficacy was seen [59]. Out of 16 patients, 7 experienced grade 3 or worse toxicity and progressive disease was noted at the first evaluation point in 15. Similarly, a combination of erlotinib (150 mg *po* daily) and the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (15 mg/kg i.v. every 3 weeks) only showed modest activity. One (4%) of 26 patients showed a partial response in a small phase II study with a further 7 (27%) having stable disease for at least 6 weeks [60]. Median TTP and OS were only 1.3 and 3.4 months, respectively.

Gefitinib is another TKI targeting the EGFR. In preclinical studies it showed evidence of activity, inhibiting pancreatic cell growth, invasion and colony formation [61]. However, two phase II studies of gefitinib combined with docetaxel in gemcitabine-refractory patients showed limited efficacy. Ignatiadis *et al.* [62] administered docetaxel (75 mg/m^2 every 3 weeks) and gefitinib (250 mg *po od* continuously) to 26 patients. No responses were seen, the median TTP was 2.1 months and the median survival a disappointing 2.9 months. Brell *et al.* evaluated the same regimen in 41 patients [63]. They reported unacceptably high levels of febrile neutropenia and disappointing efficacy with median TTP and OS of 1.8 and 4.5 months respectively. These studies reflect the poor results seen in other taxane-based regimens tested in gemcitabine-refractory pancreatic cancer; whether combining gefitinib with a more active agent will improve outcomes is currently unknown.

Bevacizumab has also been evaluated in a small randomised study with docetaxel in gemcitabine-resistant disease [64]. Thirty patients were randomised to bevacizumab (10 mg/kg every 2 weeks) with or without weekly docetaxel (35 mg/m^2). Five patients experienced serious adverse events (3 thromboembolic episodes and 2 bowel perforations). Efficacy was minimal with only one response seen in the combination arm. Median PFS was 1.4 and 1.5 months for bevacizumab and bevacizumab-docetaxel respectively. The corresponding median OS was 5.9 and 4 months (P=0.8). Recruitment was halted after the first stage as the target median PFS of 4 months in either arm was not reached.

Similar modest efficacy has been noted with other VEGF targeting agents. Vatalinib, an oral VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) TKI, was evaluated in a single arm phase II study. Sixty-five patients received vatalinib in doses up to 750 mg *po bid* with good tolerability. The 6-month PFS and OS rates were 14% and 31%, respectively, which met the study's primary endpoint and was considered promising [65]. Sunitinib is a multi-targeted TKI that primarily inhibits VEGFR and PDGFR. In a phase II study in patients that had previously received gemcitabine, either in the adjuvant or metastatic setting, and had relapsed or progressive disease, sunitinib (50 mg *po od* 4weeks on/2 weeks off schedule) was administered to 77 patients [66]. The majority (86%) of patients received only a single 6-week cycle of treatment, mainly due to rapid disease progression. Median PFS and OS were disappointing at 1.3 and 3.2 months, respectively.

mTOR inhibitors, when used as single agents appear to be inactive in gemcitabine-resistant pancreatic cancer. A trial of temsirolimus (25 mg i.v. weekly) was halted after only 5 patients were enrolled. No responses were seen and 2 patients died within a month of enrolment, one from a haemorrhagic stroke that could be related to the study medication [59]. Sirolimus was associated with a median PFS of 1.5 months and a 6-month survival rate of 20% in a study by Garrido-Laguna *et al.* [67]. Finally, everolimus (10 mg *po od*) also exhibited minimal activity a 33-patient phase II study with median PFS and OS of 1.8 and 4.5 months, respectively [68].

In summary, although limited by small patient numbers, enrolment of heavily pretreated patients and use of combinations with inactive agents such as docetaxel, the available evidence regarding biological agents tested to date in gemcitabine-resistant pancreatic cancer is mostly disappointing.

Performance Status and Toxicity Considerations

It should be kept in mind that almost all the studies summarised in this review restricted eligibility to patients with good performance status (PS). The majority of enrolled patients had a WHO PS of 0 or 1, with a minority having a PS of 2. Unfortunately, the small number of patients in each study precludes any analysis of differential efficacy or toxicity in patients with a PS of 2 compared to patients with better PS and such data have not been reported. It should be noted however, that poor PS is an established adverse prognostic factor in gemcitabine-refractory pancreatic cancer [69]. At present, best supportive care should be

the preferred option in such patients, a position endorsed by professional guidelines [8].

Conclusions and Future Directions

Pancreatic cancer remains a highly chemoresistant malignancy carrying an extremely poor prognosis. For the past decade gemcitabine has been the standard of care for first line treatment of metastatic disease, offering a modest prolongation in survival. However, improvements in diagnosis and earlier intervention with chemotherapy, alongside better supportive care measures over the same time period, have resulted in increasing numbers of patients that remain fit and request second-line treatment following progression on gemcitabine. The needs of these patients remain essentially unmet. Dozens of small studies have shown some hints of activity, with oxaliplatin-fluoropyrimidine combinations appearing the most promising. Second line trials conducted to date are fraught with problems of small patient numbers, while comparisons between trials are made impossible by incomplete information regarding performance status and disease stage, factors that are well known to impact on survival irrespective of treatment. Further randomised trials are much needed. In considering the design of such trials, experience in testing the OFF regimen demonstrated well the difficulties of randomisation where the standard arm is best supportive care.

As the molecular pathways governing pancreatic cancer are unravelled, novel targeted therapies may offer the greatest promise for this disease either given alone, combined with one another, or with cytotoxic agents. Of all human cancers, pancreatic adenocarcinoma has the highest incidence of KRAS mutation (more than 80%) and there is evidence to suggest that signalling through KRAS dominates tumourigenesis. The two key signalling pathways downstream of KRAS are Raf/MEK/ERK and PI3K/AKT/mTOR. Dual blockade of these pathways is now possible with new small molecule inhibitors available, by combining for example a MEK1/2 inhibitor and an mTOR kinase inhibitor. In addition, other pathways such as those involved in notch and hedgehog signalling are implicated in pancreatic carcinogenesis and are the focus of novel drug discovery programmes. The first studies testing some of these targeted agents either alone or in combination are now underway and their results eagerly awaited to determine whether mechanism-driven treatment will offer much needed improved outcomes for this chemoresistant cancer.

Conflict of interest The authors have no potential conflicts of interest.

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The cost-effectiveness of liposomal Irinoticanand 5-Fluorouracil (5-FU)/ Leucovorin (LV) for the treatment of patients with metastatic adenocarcinoma of pancreas who have progressed following the use of gemcitabine-related therapies in Greece.

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Introduction

- Pancreatic cancer (PC) is strongly associated with age and constitutes a major burden in more developed countries [1].
- Mortality rate associated with PC is very close to the incidence rate, possibly due to the late stage at which the disease is usually diagnosed, reflecting its the fatal nature [2, 3].
- In Greece, PC represents 3.2% of new cancer cases and 6.1% of cancer deaths, and it was estimated to be the 7th most commonly diagnosed cancer site and the 4th commonest cause of cancer death, with 2,175 new cases and 2,031 deaths annually [4, 5].
- Despite the advances in PC treatments, most of the therapeutic options have been established in the first-line setting were very limited data to support standard of care for the second-line chemotherapy in metastatic pancreatic cancer (mPDAC) [6-8].
- The results of NAPOLI-1 clinical trial [9], showed improved overall survival (OS) (OS: 6.1 months vs. 4.2 months, P=0.012) and progression free survival (PFS) (PFS: 3.1 months vs. 1.5 months, P<0.001) for nanoliposomal irinotecan (nal-IRI) plus 5-Fluorouracil/Leucovorin (5-FU/LV) over 5-FU/LV alone, as second-line treatment of mPDAC.
- ESMO [10] and NCCN [11] guidelines, include nal-IRI as "Treatment of mPDAC, in combination with 5-FU and LV, in adult patients who have progressed following gemcitabine based therapy".

Objective

To evaluate the cost-effectiveness of the nal-IRI+5-FU/LV compare to 5-FU/LV alone in the treatment of patients mPDAC who have previously received gemcitabine-based regimens in Greece.

Methods

- A partitioned survival model was locally adapted from a public payer's perspective over a 10-year time horizon.
- Based on a recent update of ESMO guidelines, the nal-IRI+5-FU/LV combination is the only available option for the management of patients with mPDAC who were previously treated with a gemcitabine-based therapy, although the off-label use of chemotherapies such as FOLFIRINOX FOLFIRI or OFF schemes is a common practice in Greece, in the absence of any other recommendation.
- However, neither direct nor indirect comparisons are available between the nal-IRI plus 5-FV/LV and the aforementioned off-label therapies. As such, for the purposes of cost-effectiveness analysis, the comparator chosen was the 5-FV/LV, for which direct comparison data were retrieved from the NAPOLI-1 phase 3, clinical trial.
- The clinical inputs considered in the model were the PFS, OS, time on treatment (ToT) and the incidence rate of adverse events (AEs) for IRI plus 5-FU/LV and 5-FU/LV alone, as obtained from NAPOLI-1 clinical trial [9].
- Utility values in pre- and post-progression states were extracted from the literature [12, 13]. Disutility due to AEs was also considered in the model and were extracted from literature [14-16] (Table 1).
- Cost inputs considered in the model included, drug acquisition and drug administration cost, monitoring costs-split into initial monitoring costs and monitoring costs during follow-up, AEs management costs, palliative care cost, post-progression treatment costs and end-of-life care cost. (Table 2). All costs reflect the year 2019 in euro (€). Both costs and outcomes were discounted at 3.5% per annum.

- Primary outcomes were patients' life years (LYs), quality-adjusted life years (QALYs), total costs and incremental cost-effectiveness ratio (ICER) per QALY and LY gained.
- A one-way sensitivity analysis (OWSA) was performed to test the robustness of the results.
- A probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model.
- Additional scenarios with two subgroups of patient population were also considered, IRI- naïve population (patients without prior IRI treatments), and NLR ≤ 5 patients (patients who received treatments and with NLR ≤ 5 in the baseline period).

Table 1. Utility values considered in the model

Baseline utility value	5-FU/LV	nal-IRI+5-FU/LV	Source
Pre-progression	0.742	0.742	Romanus et al. (2012) [12, 13]
Post-progression	0.672	0.672	
Decrement due to AE			
Pre-progression	0.007	0.014	Calculated based on AE durations and utility decrements for each AE [14-16]
Post-progression	0.017	0.021	
Final utility value			
Pre-progression	0.735	0.728	Baseline values adjusted by decrements
Post-progression	0.655	0.651	

5-FU/LV: 5-Fluorouracil/Leucovorin, nal-IRI+5-FU/LV: nanoliposomal Irinotican plus 5-Fluorouracil/Leucovorin, AE: Adverse events

Table 2. Overview of cost inputs considered in the model

Description	Unit cost (€) considered in the model	Source
Drug acquisition cost (per cycle)		
nal-IRI+5-FU/LV	€1.000	Price bulletin issued by the Greek Ministry of Health [17]
5-FU/LV	€16.44	
Monitoring cost (per cycle)		
Initial monitoring costs (only 1st cycle)	€108.18	Government gazette (FEK A' 262/16-12-2011) and the official website of EOPYY
*Monitoring costs during follow-up**	€23.84	
Adverse events cost (per cycle)		
nal-IRI+5-FU/LV	€19.74	Calculation of the model and Gourzoulidis, G., et al [18]
5-FU/LV	€11.33	
Palliative care cost (cost per cycle)		
nal-IRI+5-FU/LV[1]	€21.03	Greek Ministry of Health (drug price bulletin issued) [17] and the official website of EOPYY [19]
5-FU/LV	€23.57	
Post-progression treatment costs (per patient)		
nal-IRI+5-FU/LV[1]	€45.57	Price bulletin issued by the Greek Ministry of Health [17], Local experts
5-FU/LV	€359.87	
End-of-life care cost		
Terminal care cost (one-off)	€695.30	Gourzoulidis, G., et al [18]

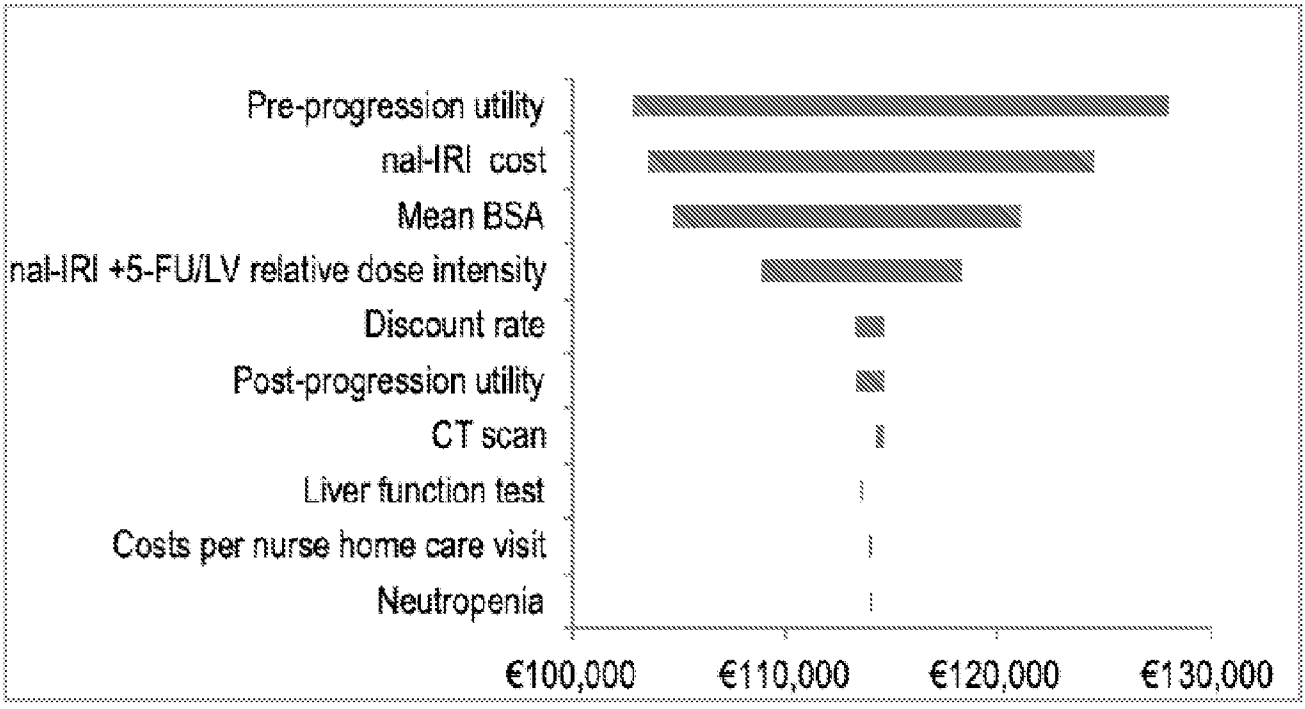
Nal-IRI+5-FU/LV: nanoliposomal Irinotican plus 5-Fluorouracil/Leucovorin; EOPYY: National Healthcare Fund

Table 3. Base case analysis results

Breakdown cost	nal-IRI+ 5-FU/LV	5-FU/LV	Difference
Drug costs	€17,215	€132	€17,083
Administration cost	€1,863	€1,176	€687
Monitoring cost	€518	€302	€216
Adverse Events cost	€356	€114	€242
Palliative care/ End of life cost	€1,289	€1,188	€100
Post-progression treatment cost	€227	€1,847	-€1,620
Total cost	**€21,468**	**€4,758**	**€16,710**
Total LYs	**0.85**	**0.64**	**0.21**
Total QALYs	**0.58**	**0.43**	**0.15**
ICER per LY gained			**€79,799**
ICER per QALY gained			**€114,153**

LYs: life years, QALYs: quality-adjusted life years, ICER: incremental cost- effectiveness ratio, nal-IRI+5-FU/LV: nanoliposomal Irinotican plus 5-Fluorouracil/Leucovorin

Figure 1: Cost-effectiveness analysis: Tornado diagram of nal-IRI+5-FU/LV vs 5-FU/LV



nal-IRI+5-FU/LV: nanoliposomal Irinotican plus 5-Fluorouracil/Leucovorin

Results

- The total cost per patient was estimated to be €21,468 and €4,758 for nal-IRI+5-FU/LV and 5-FU/LV, respectively (Table 3).
- In terms of health outcomes, nal-IRI+5-FU/LV was associated with 0.15 increment in QALYs and 0.21 in LYs compared with 5-FU/LV (Table 3).
- The incremental analysis showed that nal-IRI+5-FU/LV was more effective and more costly than 5-FU/LV alone, leading to an ICER of €114,153 per QALY gained and €79,799 per LY gained versus 5-FU/LV alone (Table 3).
- The results of OWSA indicated that the most influential parameter on the model was utility values assigned to the pre-progression state and the drug acquisition cost of nal-IRI (Figure 2).
- PSA confirmed the deterministic results, as showed that nal-IRI+5-FU/LV was a more expensive and more effective treatment option compared 5-FU/LV alone.

Scenario analysis

- Both scenario analyses, of IRI naïve population and NLR≤ 5 population, showed that nal-IRI+5-FU/LV compared to 5-FU/LV alone, was more effective and more costly.
- In terms of QALYs and LYs, when the IRI naïve population was considered in the analysis, nal-IRI+5-FU/LV was associated with 0.26 and 0.18 increment in LYs and QALYs, respectively, compared with 5-FU/LV alone. When the NLR≤ 5 population was considered in the analysis, nal-IRI+5-FU/LV was associated with 0.26 increment in QALYs compared with 5-FU/LV alone.

- The total cost per patient, when the IRI naïve population was considered in the analysis, was estimated to be €22,645 and €4,760, for nal-IRI+5-FU/LV and 5-FU/LV alone, respectively. As for NLR≤ 5 population, an additional cost of €21,909 was estimated.
- When the IRI naïve population was considered in the analysis, nal-IRI+5-FU/LV versus 5-FU/LV alone yields ICERs of €100,740 per QALY gained and €69,241 per LY gained. As for NLR≤ 5 population, nal-IRI+5-FU/LV versus 5-FU/LV alone resulted in an ICER of €85,562 per QALY gained and €59,802 per LY gained.

Conclusions

The study results indicate that nal-IRI plus 5-FU/LV, a therapy covering the unmet medical need of patients with mPDAC after disease progression following gemcitabine-based therapy, was estimated to be a good value for money treatment option in Greece.

Acknowledgments

Authors would like to thank Servier Hellas for sponsoring this study.

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VIRTUAL ISPOR EUROPEAN CONGRESS, 16-19 NOVEMBER 2020, MILAN, ITALY

The cost-effectiveness of liposomal irinotecan and 5-Fluorouracil (5-FU)/ Leucovorin (LV) for the treatment of patients with metastatic adenocarcinoma of pancreas who have progressed following the use of gemcitabine-related therapies in Greece.

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Introduction

- Pancreatic cancer (PC) is strongly associated with age and constitutes a major burden in more developed countries [1].
- Mortality rate associated with PC is very close to the incidence rate, possibly due to the late stage at which the disease is usually diagnosed, reflecting its the fatal nature [2, 3].
- In Greece, PC represents 3.2% of new cancer cases and 5.1% of cancer deaths, and it was estimated to be the 7th most commonly diagnosed cancer site and the 4th commonest cause of cancer death, with 2,175 new cases and 2,051 deaths annually [4, 5].
- Despite the advances in PC treatments, most of the therapeutic options have been established in the first-line setting were very limited data to support standard of care for the second-line chemotherapy in metastatic pancreatic cancer (mPDAC) [6-8].
- The results of NAPOLI-1 clinical trial [9], showed improved overall survival (OS) (OS: 6.1 months vs. 4.2 months, P=0.012) and progression free survival (PFS) (PFS: 3.1 months vs. 1.5 months, P<0.001) for nanoliposomal irinotecan (nal-IRI) plus 5-Fluorouracil/Leucovorin (5-FU/LV) over 5-FU/LV alone, as second-line treatment of mPDAC.
- ESMO [10] and NCCN [11] guidelines, include nal-IRI as "Treatment of mPDAC, in combination with 5-FU and LV, in adult patients who have progressed following gemcitabine based therapy".

Objective

To evaluate the cost-effectiveness of the nal-IRI+5-FU/LV compare to 5-FU/LV alone in the treatment of patients mPDAC who have previously received gemcitabine-based regimens in Greece.

Methods

- A partitioned survival model was locally adapted from a public payers' perspective over a 10-year time horizon.
- Based on a recent update of ESMO guidelines, the nal-IRI+5-FU/LV combination is the only available option for the management of patients with mPDAC who were previously treated with a gemcitabine-based therapy, although the off-label use of chemotherapies such as FOLFIRINOX, FOLFIRI or OFF schemes is a common practice in Greece, in the absence of any other recommendation.
- However, neither direct nor indirect comparisons are available between the nal-IRI plus 5-FU/LV and the aforementioned off-label therapies. As such, for the purposes of cost-effectiveness analysis, the comparator chosen was the 5-FU/LV, for which direct comparison data were retrieved from the NAPOLI-1 phase 3, clinical trial.
- The clinical inputs considered in the model were the PFS, OS, time on treatment (ToT) and the incidence rate of adverse events (AEs) for IRI plus 5-FU/LV and 5-FU/LV alone, as obtained from NAPOLI-1 clinical trial [9].
- Utility values in pre- and post-progression states were extracted from the literature [12, 13]. Disutility due to AEs was also considered in the model and were extracted from literature [14-16] (Table 1).
- Cost inputs considered in the model included, drug acquisition and drug administration cost, monitoring costs- split into initial monitoring costs and monitoring costs during follow-up, AEs management costs, palliative care cost, post-progression treatment costs and end-of-life care cost. (Table 2). All costs reflect the year 2019 in euro (€). Both costs and outcomes were discounted at 3.5% per annum.
- Primary outcomes were patients' life years (LYs), quality-adjusted life years (QALYs), total costs and incremental cost-effectiveness ratio (ICER) per QALY and LY gained.
- A one-way sensitivity analysis (OWSA) was performed to test the robustness of the results.
- A probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model.
- Additional scenarios with two subgroups of patient population were also considered, IRI- naïve population (patients without prior IRI treatments), and NLR ≤ 5 patients (patients who received treatments and with NLR ≤ 5 in the baseline period).

Table 1. Utility values considered in the model

Baseline utility value	5-FU/LV	nal-IRI+5-FU/LV	Source
Pre-progression	0.742	0.742	Konstantakis et al. (2013) [12], 3.5
Post-progression	0.672	0.672	
Decrement due to AE			
Pre-progression	0.003	0.016	Calculated based on AE durations and utility decrements for each AE [14-16]
Post-progression	0.037	0.031	
Age utility values			
Pre-progression	0.736	0.736	Baseline values adjusted by decrements
Post-progression	0.635	0.651	

5-FU/LV: 5-Fluorouracil/Leucovorin, nal-IRI+5-FU/LV: nanoliposomal irinotecan plus 5-Fluorouracil/Leucovorin, AE: Adverse events

Table 2. Overview of cost inputs considered in the model

Description	Unit cost (€) considered in the model	Source
Drug acquisition cost (per cycle)		
nal-IRI+5-FU/LV	€1,205	Price bulletin issued by the Greek Ministry of Health [17]
5-FU/LV	€15.44	
Monitoring cost (per cycle)		
Initial monitoring cost	€102.12	Customized gamma (FEP in 2007/16-12-2011) and the official website of EOPYY
Monitoring costs during follow-up*	€23.84	
Adverse events management cost		
nal-IRI+5-FU/LV	€19.74	Calculation of the mentioned Gkouvatsiotis, G., et al. [18]
5-FU/LV	€11.33	
Palliative care cost (per cycle)		
nal-IRI+5-FU/LV*	€21.83	Greek Society of Health Economics (HAYE) and the official website of EOPYY [19]
5-FU/LV	€23.87	
Post-progression treatment cost (per patient)		
nal-IRI+5-FU/LV*	€437.87	Price bulletin issued by the Greek Ministry of Health [17], Local experts
5-FU/LV	€219.87	
End of life care cost		
Terminal care cost (one-off)	€945.00	Gkouvatsiotis, G., et al. [18]

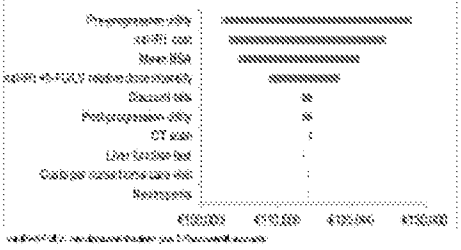
nal-IRI+5-FU/LV: nanoliposomal irinotecan plus 5-Fluorouracil/Leucovorin, EOPYY: National Healthcare Fund

Table 3. Base case analysis results

Budget impact	nal-IRI+5-FU/LV	5-FU/LV	Difference
Drug costs	€17,215	€135	€17,080
Administration cost	€1,865	€1,178	€687
Monitoring cost	€319	€205	€114
Adverse Events cost	€385	€114	€262
Palliative care cost	€1,259	€1,166	€100
End of life cost			
Post-progression treatment cost	€927	€1,847	-€1,020
Total costs	€21,969	€3,788	€18,218
Total LYs	0.95	0.44	0.51
Total QALYs	0.69	0.32	0.36
ICER per LY gained			€35,709
ICER per QALY gained			€50,553

LYs: life years, QALYs: quality-adjusted life years, ICER: incremental cost-effectiveness ratio, nal-IRI+5-FU/LV: nanoliposomal irinotecan plus 5-Fluorouracil/Leucovorin, 5-FU/LV: 5-Fluorouracil/Leucovorin

Figure 1: Cost-effectiveness analysis: Tornado diagram of nal-IRI+5-FU/LV vs 5-FU/LV



Results

- The total cost per patient was estimated to be €21,468 and €4,758 for nal-IRI+5-FU/LV and 5-FU/LV, respectively (Table 3).
- In terms of health outcomes, nal-IRI+5-FU/LV was associated with 0.15 increment in QALYs and 0.21 in LYs compared with 5-FU/LV (Table 3).
- The incremental analysis showed that nal-IRI+5-FU/LV was more effective and more costly than 5-FU/LV alone, leading to an ICER of €314,183 per QALY gained and €79,799 per LY gained versus 5-FU/LV alone (Table 3).
- The results of OWSA indicated that the most influential parameter on the model was utility values assigned to the pre-progression state and the drug acquisition cost of nal-IRI (Figure 2).
- PSA confirmed the deterministic results, as showed that nal-IRI+5-FU/LV was a more expensive and more effective treatment option compared 5-FU/LV alone.

Scenario analysis

- Both scenario analyses, of IRI naïve population and NLR≤ 5 population, showed that nal-IRI+5-FU/LV compared to 5-FU/LV alone, was more effective and more costly.
- In terms of QALYs and LYs, when the IRI naïve population was considered in the analysis, nal-IRI+5-FU/LV was associated with 0.26 and 0.18 increment in LYs and QALYs, respectively, compared with 5-FU/LV alone. When the NLR≤ 5 population was considered in the analysis, nal-IRI+5-FU/LV was associated with 0.26 increment in QALYs compared with 5-FU/LV alone.
- The total cost per patient, when the IRI naïve population was considered in the analysis, was estimated to be €22,645 and €4,760, for nal-IRI+5-FU/LV and 5-FU/LV alone, respectively. As for NLR≤ 5 population, an additional cost of €21,909 was estimated.
- When the IRI naïve population was considered in the analysis, nal-IRI+5-FU/LV versus 5-FU/LV alone yields ICERs of €100,740 per QALY gained and €68,243 per LY gained. As for NLR≤ 5 population, nal-IRI+5-FU/LV versus 5-FU/LV alone resulted in an ICER of €85,560 per QALY gained and €59,802 per LY gained.

Conclusion

The study results indicate that nal-IRI plus 5-FU/LV, a therapy covering the unmet medical need of patients with mPDAC after disease progression following gemcitabine-based therapy, was estimated to be a good value for money treatment option in Greece.

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The Cost-Effectiveness of Liposomal Irinotecan and 5-Fluorouracil (5-FU)/ Leucovorin (LV) for the Treatment of Patients with Metastatic Adenocarcinoma of Pancreas WHO Have Progressed Following the Use of Gemcitabine-Related Therapies in Gre ...

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OBJECTIVES: To evaluate the cost-effectiveness of the liposomal Irinotecan (nal-IRI) plus 5-Fluorouracil (5-FU)/ Leucovorin (LV) compare to 5-FU/LV alone for the treatment of patients with metastatic pancreatic cancer (mPDAC) who have previously received gemcitabine-based regimens in Greece.

METHODS: A partitioned survival model was locally adapted from a public payer perspective over a 10-year time horizon. Utility values, efficacy and safety data applied in the model, were extracted from the literature. Resource consumption data were obtained from local experts using a questionnaire, developed for the purposes of the study, and were combined with unit costs (in €2019) obtained from official sources. Primary outcomes were patients' life years (LYs), quality-adjusted life years (QALYs), total-costs, and incremental cost-effectiveness ratio (ICER) per QALY and LY gained. Both costs and outcomes were discounted at 3.5% per annum. A one-way sensitivity analysis (OWSA) was undertaken to test the robustness of the results and a probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model.

RESULTS: The analysis revealed that, the total cost per patient was estimated to be €21,468 and €4,758 for nal-IRI+5-FU/LV and 5-FU/LV respectively. In terms of health outcomes, nal-IRI+5-FU/LV was associated with 0.58 QALYs and 0.85 LYs, while patients who received 5-FU/LV alone

accrued 0.43 QALYs and 0.64 LYs. The incremental analysis showed that nal-IRI+5-FU/LV resulted in an ICER of €114,153 per QALY gained and €79,799 per LY gained versus 5-FU/LV alone. OWSA results indicated that the most influential parameter on the model was utility values assigned to the pre-progression state. PSA confirmed the deterministic results.

CONCLUSIONS: The present economic evaluation suggests that nal-IRI+5-FU/LV, a therapy that provides survival benefits to patients with mPDAC after disease progression following gemcitabine-based treatment, was estimated to be a good value for money treatment option for the Greek patients.

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NEW PARADIGMS IN THE TREATMENT OF PANCREAS CANCER

CHEMOTHERAPY FOR ADVANCED PANCREATIC CANCER

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Achieving substantial and meaningful improvements in the response and survival rates for advanced pancreatic cancer has proved to be an elusive goal for many years. 5-Fluorouracil (5-FU)–based chemotherapy has typically produced discouraging response rates or improved clinical benefit for patients, and attempts to improve these results by altering 5-FU dosages, administration schedules, or using a variety of drugs in combination with 5-FU have been unrewarding. A clinical benefit, however, was identified when gemcitabine first generated improvements in symptom control in patients with advanced disease. In a subsequent randomized trial, gemcitabine demonstrated superiority to 5-FU with respect to response rate, time to progression, and median survival. These improvements were also associated with improvement in clinical benefit. The findings of subsequent randomized Phase III trials have suggested a survival benefit for gemcitabine compared with several single agents or combinations. Gemcitabine has thus become the de facto standard of care for advanced pancreatic cancer, and current efforts are directed toward finding strategies that can capitalize on and extend these clinical benefits.

Pancreatic cancer, Treatment, Gemcitabine, 5-Fluorouracil.

INTRODUCTION

Adenocarcinoma of the pancreas represents 95% of the malignant neoplasms of pancreatic origin and is an aggressive disease with an extremely poor prognosis (1). In the United States, in 2003, an estimated 30,700 new cases of pancreatic cancer will have been diagnosed, and approximately 30,000 deaths will have resulted (2). For all stages combined, the 1-year survival rate for pancreatic cancer is approximately 21% and the 5-year survival rate is approximately 5%. The median survival time is 3–6 months and 6–10 months for patients with metastatic disease and local disease, respectively (2).

Pancreatic cancer spreads early to the regional lymph nodes and the liver, resulting in most patients presenting with advanced disease at diagnosis. In addition to these poor survival rates, such symptoms as weight loss, weakness, fatigue, pain, nausea, vomiting, and anorexia become more prominent as the disease progresses and are the cause of substantial morbidity. Given the unlikely probability of cure in locally advanced or metastatic disease and symptoms that become progressively more intense as the disease advances, the goal of chemotherapy in the setting of advanced pancreatic cancer is symptom palliation. Despite this palliative goal, the overwhelming majority of chemotherapy trials that have been conducted during the past two decades have typically measured traditional clinical trial end points such as tumor response and survival rates to evaluate efficacy. It has been only in recent years that trials in advanced pancreatic cancer patients have also incorporated symptom improvement end points as additional evidence of clinical benefit.

5-FLUOROURACIL

5-Fluorouracil (5-FU) was previously considered the standard treatment for advanced pancreatic cancer, with early encouraging results according to clinical examination findings, before the widespread availability of more objective imaging such as CT that could more precisely measure the size and extent of tumor involvement (3). In trials using CT assessment of tumor response, the reported response rates for single-agent 5-FU ranged from 0% to 19% (1). Before 1995, other chemotherapy agents had been studied for advanced pancreatic cancer; however, 5-FU was the only drug with a response rate with an upper 95% confidence limit exceeding 20% (4). The median survival time for patients treated with single-agent 5-FU ranged from 4.2 to 5.5 months (3). One early study (5) indicated that 5-FU used in combination could improve the response rate and median survival, but these findings could not be reproduced in subsequent studies, suggesting little improvement over single-agent 5-FU (3). Except for one study (6), most trials

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using 5-FU did not report on other measures of patient benefit, such as symptom improvement.

GEMCITABINE

Single-agent Phase II trial

On the basis of promising clinical observations of the benefits of gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN) in early Phase I trials, a Phase II trial of gemcitabine in patients with advanced cancer of the pancreas produced a response rate of 11%, within the range of what had been achieved in single-agent trials of 5-FU (7). In this trial, decreased pain severity, a decreased requirement for analgesics, an increased appetite and weight gain, and improved functional status appeared to be associated with response, as well as occurring in some patients who had stable disease.

Randomized Phase III trials of single-agent gemcitabine

A randomized trial (3) was conducted to determine whether gemcitabine provided any advantages compared with a control arm of 5-FU with respect to clinical benefit or objective response. The study randomized 126 chemotherapy-naive patients to potentially equitoxic treatment regimens, with either 5-FU 600 mg/m^2 or gemcitabine 1000 mg/m^2. Both drugs were administered as a 30-min i.v. infusion weekly for 7 weeks followed by 1 week of rest, and then weekly for 3 of every 4 weeks thereafter.

To assess the nontraditional measures of treatment effects more accurately, the concept of clinical benefit response (CBR) was developed. Pain and Karnofsky performance status (KPS) were the primary components of this measurement. Pain was measured subjectively by reports of pain intensity and objectively by quantifying the amount of analgesic used. Weight was a secondary component of the CBR. To be classified as having a positive response, the patient had to have exhibited sustained (at least 4 weeks) improvement in at least one of the CBR components, without deterioration in any of the other components of the CBR (3). The number of patients experiencing a CBR (n = 15, 23.8%) was significantly greater in the group randomized to gemcitabine than in the 5-FU-treated group (n = 3, 4.8%; p = 0.0022), with a small, but statistically significant, survival advantage favoring gemcitabine (5.65 months compared with 4.41 months, p = 0.0025). The median time to progressive disease for gemcitabine was 9 weeks compared with 4 weeks for 5-FU (p = 0.0002). Despite these differences in CBR, median survival, and median time to progression, no statistically significant difference was found in the overall response rate between the two groups (5.4% for gemcitabine and 0% for 5-FU), supporting the observation that the traditional measure of success in Phase II and III trials, the response rate, may be a poor marker of cytotoxicity in pancreatic cancer. Additional randomized studies have confirmed the efficacy of single-agent gemcitabine (8–13) (Table 1).

Table 1. Pancreas cancer

Status of disease at time of presentation
<20% macroscopically confined to pancreas
~40% locally advanced
~40% visceral metastases
~35% peritoneal implants
Therapeutic staging
Resectable
Locally unresectable
Metastatic

Moore *et al.* (8) compared gemcitabine with BAY12-9566, a matrix metalloproteinase inhibitor, in chemotherapy-naive patients with unresectable recurrent or metastatic adenocarcinoma of the pancreas. Gemcitabine 1000 mg/m^2 was given weekly for 7 weeks, followed by 1 week of rest and then on Days 1, 8, and 15 every 28 days. BAY12-9566 1600 mg was administered in divided doses b.i.d. on a continuous basis. The gemcitabine group had 6 partial responses (4%) and the matrix metalloproteinase inhibitor group had only a single partial response (1%). In addition, 45% of gemcitabine-treated patients had disease stabilization. Progression-free and overall survival was significantly longer for patients treated with gemcitabine, 6.7 months compared with 4.3 months, respectively. The 1-year survival rate was also greater in the gemcitabine group, 25%, compared with 10% in the BAY12-9566 group.

In a dose-ranging study with marimastat, a matrix metalloproteinase inhibitor, patients with unresectable pancreatic cancer were randomized to one of three doses of marimastat or to gemcitabine 1000 mg/m^2 given weekly for 7 weeks followed by 1 week of rest (9). Treatment was then resumed and given weekly for 3 of 4 weeks thereafter. The median survival time for the marimastat 5, 10, and 25 mg and gemcitabine groups was 111, 105, 125, and 167 days, and the corresponding 1-year survival rate was 14%, 14%, 20%, and 19%, respectively. Although these data suggested a dose–response relationship for marimastat, no statistically significant difference was found in overall survival between gemcitabine and the highest dose of marimastat.

Single-agent gemcitabine was then compared with the combination of gemcitabine and marimastat in a randomized Phase III trial (10) as first-line treatment for advanced pancreatic cancer. Gemcitabine 1000 mg/m^2, alone and in combination with marimastat 10 mg b.i.d., was administered on the same schedule used in the earlier randomized trial (9). No statistically significant differences in overall response rates (11% with the combination and 16% for gemcitabine) were found. The median survival for the gemcitabine/marimastat combination was 165.5 days compared with 164 days for single-agent gemcitabine (p = .95) and the 1-year survival was 18% for the combination and 17% for single-agent treatment.

Another randomized Phase III trial compared single-agent gemcitabine with the combination of gemcitabine plus cisplatin (11). In an intent-to-treat analysis, the overall response rate was 9.2% for single-agent gemcitabine vs. 26.4% for the gemcitabine/cisplatin combination (p = 0.02).

The CBR was greater, 52.6% vs. 49%, for the gemcitabine/cisplatin group but the difference was not statistically significant. Although the difference in the time to progression favoring the combination, 20 weeks, compared with 8 weeks for the single agent was statistically significant ($p = 0.04$), the median survival was not significantly longer statistically ($p = 0.43$) in the gemcitabine/cisplatin group. Grade 3–4 diarrhea occurred in 4% of the patients treated with the combination but in none of the patients treated with single-agent gemcitabine. As expected, the toxicity of the combination regimen was greater than for single-agent therapy, although not prohibitively so.

Additional randomized trials have also compared gemcitabine alone to a gemcitabine-based combination regimen (12, 13) in patients who had had no prior chemotherapy for advanced disease. These combinations included gemcitabine plus 5-FU (12) and gemcitabine plus R115777, a farnesyltransferase inhibitor (13). Except for significantly longer progression-free survival (3.4 vs. 2.2 months, $p = 0.022$) for the combination of gemcitabine and 5-FU, no statistically significant differences were found in any other efficacy measures in these two comparative trials. These trials, and the randomized study of gemcitabine with marimastat compared with single-agent gemcitabine (1), have yet to demonstrate that the addition of novel agents or other chemotherapeutic drugs to gemcitabine do not significantly improve efficacy, when measured by traditional measures of success, such as tumor response rate, time to tumor progression, or improvement in median survival. This observation leads directly to the conclusion that both new agents and newer methods of assessing treatment efficacy are required to move forward in the treatment of patients with pancreatic cancer.

Single-agent gemcitabine in 5-FU–refractory pancreas cancer

Rothenberg *et al.* (14) designed a Phase II study to assess the effect of gemcitabine in patients with metastatic pancreas cancer whose disease had progressed despite previous 5-FU–based therapy. Gemcitabine at a dose of 1000 mg/m^2 was administered weekly as a 30-minute infusion to 63 patients with advanced pancreas cancer. Most (87.3%) patients had distant organ metastases, and the median interval between the end of a 5-FU–containing regimen and the start of gemcitabine therapy was 4 weeks. A CBR of 27%, median time to disease progression of 2.5 months, and median survival of 3.9 months was observed in this refractory population. The overall objective partial response rate was 10.5%, and 29.8% of patients had stable disease. Among those patients who achieved a CBR, the median survival was 7 months compared with 3.1 months for patients without a CBR. Gemcitabine therapy was generally well tolerated in this second-line study, which is particularly important in patients with this disease (Table 2).

Both the first-line comparative trial (3) and the second-line Phase II trial (14) demonstrated that gemcitabine was associated with clinical benefit for treating advanced pancreas cancer and provided the basis for the U.S. Food and Drug Administration to approve gemcitabine in May 1996.

Table 2. Clinical trials issues in pancreas cancer

Research issues:
Measures of success
Response rate and TTP
Overall survival
Clinical benefit
When do we integrate new therapies?
First- or second-line?
Compared to, or combined with, gemcitabine?
Stage? (the earlier, the better?)
Role of radiation therapy

Abbreviation: TTP = time to progression.

Treatment Investigational New Drug program

Because of the findings of the previous two studies (3, 14), gemcitabine was made available through an Investigational New Drug (IND) treatment program to patients with locally advanced or metastatic pancreatic cancer before Food and Drug Administration approval of the new drug application (15). The Treatment IND program enrolled 3023 patients between March 1995 and June 1996, when gemcitabine became commercially available. The Treatment IND program retrospectively assessed disease-related symptom improvement using data that are routinely collected in the medical records of patients with pancreatic cancer. Patients considered to be disease-related symptom improvement responders had improvement in at least one of three parameters (pain, class of analgesic used, and at least a 20-point improvement in KPS), with no deterioration in any parameter, or stability in all three parameters accompanied by a minimal weight increase of 7%.

Of the 3023 patients enrolled, 80% had Stage IV disease at entry and 84% had a KPS $\geq$70. By Cycle 5 of therapy, the cumulative percentage of patients classified as disease-related symptom improvement responders was 18.4%. Median survival data were available for 2380 patients (censored for 57%), and disease progression data were available for 2012 patients (censored for 31%). The median survival was 4.8 months, and the median time to progression was 2.7 months. Tumor response data by investigator review were available for 982 patients and indicated an overall response rate of 12.0%; these data were consistent with those seen in the much smaller randomized trial.

Subgroup analyses indicated that the median survival and median time to progression was significantly longer for patients with a KPS $\geq$70 than for those with a KPS $<$70. Patients with earlier stage disease, Stage II-III, also had a median survival that was longer than the median survival of patients with Stage IV disease, emphasizing the need to understand the patient selection and eligibility for both reported and planned clinical trials when assessing results that are thought to be treatment related.

These single-agent gemcitabine trials and other small-

sample-size, single-agent gemcitabine trials (16–20) (Table 2) have encouraged additional investigations to assess whether other strategies can be used to make the de facto standard treatment, gemcitabine, more effective for patients with pancreatic cancer.

GEMCITABINE DOSE AND SCHEDULE

One such strategy is to use different doses and schedules of gemcitabine administration, investigated in a randomized Phase II study by Tempero *et al.* (21). The concept of a fixed-dose-rate infusion of gemcitabine was prompted by pharmacokinetic data suggesting that the active metabolite, gemcitabine triphosphate, could be accumulated more effectively by a longer infusion, allowing for greater inhibition of DNA synthesis. This trial randomized 67 patients to dose-intense treatment with 2200 mg/m^2 of gemcitabine administered as a standard 30-min infusion or to fixed-dose-rate treatment with 1500 mg/m^2 of gemcitabine at a rate of 10 mg/m^2/min, with both arms projected to be equitoxic. Pharmacokinetic analysis of 7 patients in the dose-intense treatment group and 10 patients in the fixed-dose-rate group revealed higher mononuclear cell concentrations of gemcitabine triphosphate in the fixed-dose-rate group than in the dose-intense group (336 μM and 114 μM, respectively; $p = 0.003$). Furthermore, preliminary analysis of clinical end points showed more objective responses, longer median survival, and greater 1-year survival in the fixed-dose-rate group than in the dose-intense, 30-min infusion group. The mature results of this study have not yet been reported, but a large Phase III Eastern Cooperative Oncology Group trial is underway, designed to confirm these results, with a third comparative treatment of fixed-dose-rate gemcitabine plus oxaliplatin.

OTHER GEMCITABINE COMBINATIONS

Gemcitabine–5-FU combination trials

Series of Phase III trials were conducted examining the potential of the combination of gemcitabine and 5-FU. Some used continuous infusion 5-FU and others used bolus therapy. For example, a Phase I-II trial (22) evaluated gemcitabine 1000 mg/m^2 with leucovorin 250 mg/m^2 weekly in combination with escalating doses (1400, 2000, and 2600 mg/m^2) of 5-FU as a weekly 24-h continuous infusion. Overall, 25 patients were treated: 9 at the 1400 mg/m^2 dose, 6 at the 2000 mg/m^2 dose, and 10 at the highest dose level. The overall response rate was 8%. The overall median survival was 9.6 months, and the median time to progression was 4 months. The CBR and median survival in this trial appeared to be superior than had been achieved in previous single-agent trials of either agent, although the response rates were similar.

Using a 600 mg/m^2 i.v. bolus dose of 5-FU in combination with 1000 mg/m^2 i.v. of gemcitabine on Days 1, 8, and 15 every 28 days produced a median survival of 7.5 months in one trial (23) and 7 months in a second trial (24). The second trial also reported a CBR rate of 51%. Again, these measures appeared to exceed the CBR and median survival reported in the earlier single-agent studies of gemcitabine (3, 8). Additional Phase II trials are described in Table 3.

Table 3. Synergy between gemcitabine and radiation

—Ways to exploit synergy without decreasing tolerance
- Full-dose radiation (5040 cGy) with low-dose gemcitabine: enhance local control
  —Cancer and Leukemia Group B: 40 mg/m^2 biweekly
- Full-dose gemcitabine (1000 mg/m^2/wk) with low-dose radiation: enhance chemotherapeutic potential
  —University of Michigan: 4200 cGy
- Sequential gemcitabine and radiation/5-FU
  —Radiation Therapy Oncology Group R9704 adjuvant trial

Abbreviation: 5-FU = 5-fluorouracil.

The largest Phase III randomized trial (12) with 5-FU was performed by the Eastern Cooperative Oncology Group and compared single-agent gemcitabine with gemcitabine plus 5-FU. Patients were randomized to receive gemcitabine 1000 mg/m^2 weekly for 3 of every 4 weeks or to receive the same dose of gemcitabine followed by 5-FU, 600 mg/m^2/wk. Among the 322 eligible patients, 162 received single-agent gemcitabine and 160 received the combination regimen. The median survival was 6.7 months with the combination therapy and 5.4 months with single-agent gemcitabine, a difference that was not statistically significant ($p = 0.11$). Both therapies were well tolerated, although the incidence of Grade 3-4 leukopenia (29%), thrombocytopenia (19%), and diarrhea (10%) was greater in the combination therapy arm than in the single-agent gemcitabine arm (16%, 11%, and 4%, respectively). Although the trend toward improved survival was encouraging, the interest in 5-FU–based combinations is generally waning, in part because of encouraging data from other cytotoxic and noncytotoxic drugs, either alone or in combination with gemcitabine.

Gemcitabine-cisplatin combination trials

Gemcitabine combined with cisplatin has been used in another poor-prognosis disease, non–small-cell lung cancer (33). Therefore, it has been considered reasonable to investigate whether this combination could provide similar benefit in patients with advanced pancreas cancer, although the single-agent Phase II data for cisplatin and other cytotoxic drugs in pancreatic cancer are generally quite limited. Two nonrandomized studies (34, 35) have been done of gemcitabine 1000 mg/m^2 administered as a 30-min infusion on Days 1, 8, and 15 of a 28-day cycle and i.v. cisplatin 50 mg/m^2 administered on Days 1 and 15 after the gemcitabine infusion. Only patients who had no prior cytotoxic chemotherapy were eligible to participate in the first study (34). The second study excluded patients who had received prior gemcitabine therapy, but other prior cytotoxic therapy was allowed (35).

In the first trial (34), the median survival in the chemotherapy-naive patients was 8.3 months, with a 1-year sur-

vival rate of 28%. The group of 35 patients assessable for tumor response had an overall response rate of 11.5%. In the study that allowed prior chemotherapy with agents other than gemcitabine (35), the median survival was 7.4 months, with an overall response rate of 36.4%.

A randomized Phase II study compared a 30-min i.v. infusion of 1000 mg/m^2 gemcitabine administered on Day 1 to a regimen with the same dose of gemcitabine, followed by i.v. cisplatin at a dose of 25 mg/m^2 in 103 patients with advanced pancreatic cancer (36). The preliminary results indicated that the combination therapy was more effective at producing tumor responses than single-agent gemcitabine, but additional follow-up is indicated to determine whether potential response, survival, and CBR data are confirmed, and whether the additional toxicities of cisplatin-based combination therapies are warranted, and in which patient populations.

Gemcitabine-irinotecan combination trials

Irinotecan is a newer cytotoxic chemotherapy agent, a topoisomerase I inhibitor proved efficacious in the treatment of GI cancers. Two multicenter Phase II trials have evaluated the combination of gemcitabine and irinotecan in advanced pancreatic cancer patients who had received no prior chemotherapy.

Using i.v. gemcitabine at a dose of 1000 mg/m^2 in a 30-min infusion followed immediately by i.v. irinotecan 100 mg/m^2 for 90 min on Day 1 and Day 8 every 3 weeks, Rocha Lima *et al.* (37) reported a 20% tumor response rate, a median survival of 6 months, and a median time to progression of 2.9 months among 45 patients with locally advanced or metastatic pancreatic cancer, with modest toxicity. More significant toxicities were reported among 28 chemotherapy-naive patients who received a different combination dose of gemcitabine and irinotecan (38). In this second Phase II trial, i.v. gemcitabine was administered at a dose of 900 mg/m^2 as a 30-min infusion on Days 1 and 8 and i.v. irinotecan was administered at a dose of 300 mg/m^2 as a 1-h infusion on Day 8 every 3 weeks. At this dose, Grade 3 or 4 neutropenia was reported in 36% of patients. Neutropenic fever developed in 4 of 10 patients who experienced Grade 3 or 4 neutropenia, and 1 patient died of sepsis. A large Phase III trial comparing gemcitabine alone to the first combination of gemcitabine and irinotecan has been completed.

Gemcitabine-docetaxel combination

Jacobs *et al.* (39) reported the results of a Phase I–II study using gemcitabine with docetaxel. Initially, patients were treated with gemcitabine 800 mg/m^2 on Days 1, 8, and 15 and docetaxel 75 mg/m^2 on Day 1, repeated every 28 days (n = 18). However, because of excessive hematologic toxicity, subsequent patients were treated with gemcitabine 1000 mg/m^2 and the dose of docetaxel was reduced to 40 mg/m^2 (n = 11). Overall, 7 patients (28%) achieved a partial response, and the median time to progression was 5.25 months. With the dose modifications, no Grade 3 or 4 toxicities were reported. At a median follow-up of 5 months for both cohorts, the median survival had not yet been reached. To explore these gemcitabine doublets further, the Cancer and Leukemia Group B, for example, is conducting a randomized Phase II study of four gemcitabine-based treatments for pancreatic cancer (see Fig. 1). This study randomized patients to treatment with gemcitabine plus cisplatin, single-agent gemcitabine at a fixed-dose-rate of 10 mg/m^2/min, gemcitabine plus docetaxel, or gemcitabine plus irinotecan.

Gemcitabine and oxaliplatin

Oxaliplatin has preclinical and clinical activity in a number of GI cancers, particularly colorectal cancer, for which it is a widely used drug in Europe and has recently been approved in the United States. A number of combination regimens with gemcitabine and oxaliplatin are being reported. Recently, a multicenter Phase II trial of previously untreated patients with metastatic and locally advanced unresectable pancreatic adenocarcinoma treated with gemcitabine and oxaliplatin was reported by the GERCOR group in France (40). Patients received gemcitabine 1000 mg/m^2 at a fixed-dose rate of 10 mg/m^2/min infusion on Day 1 and oxaliplatin 100 mg/m^2 as a 2-h infusion on Day 2, every 2 weeks. The response rate for the 62 patients with measurable disease was 30.6% (95% confidence interval 19.7–42.3%). Among 58 assessable patients, 40% had clinical benefit (improved pain and/or performance status for at least 4 consecutive weeks). The median progression-free survival and median overall survival was 5.3 and 9.2 months, respectively, with 36% of patients alive at 1 year. The median survival for patients with metastatic disease and locally advanced disease was 8.7 and 11.5 months, respectively. This group is currently enrolling patients into a randomized Phase III trial of gemcitabine alone compared with gemcitabine and oxaliplatin. Similarly, the Eastern Cooperative Oncology Group is also planning a three-arm Phase III trial evaluating standard dose-rate gemcitabine, fixed-dose-rate gemcitabine, and gemcitabine and oxaliplatin.

Gemcitabine-pemetrexed combination

Pemetrexed (Alimta, LY231514, Eli Lilly) is a pyrrolopyrimidine-based multitargeted antifolate that undergoes intracellular polyglutamation, resulting in prolonged intracellular retention (41). Phase I studies suggested activity in pancreatic cancer, and a Phase II trial in patients with unresectable or metastatic pancreatic cancer was subsequently performed (42). Forty-two previously untreated patients received 600 mg/m^2 of pemetrexed every 21 days. The overall response rate among 35 patients assessable for response was 5.7%. The median progression-free survival was 4 months, median survival was 6.5 months, and the 1-year survival rate was 28%. Toxicity was generally manageable; however, 41% of patients experienced Grade 3–4 neutropenia.

Because of the activity of both gemcitabine and pem-

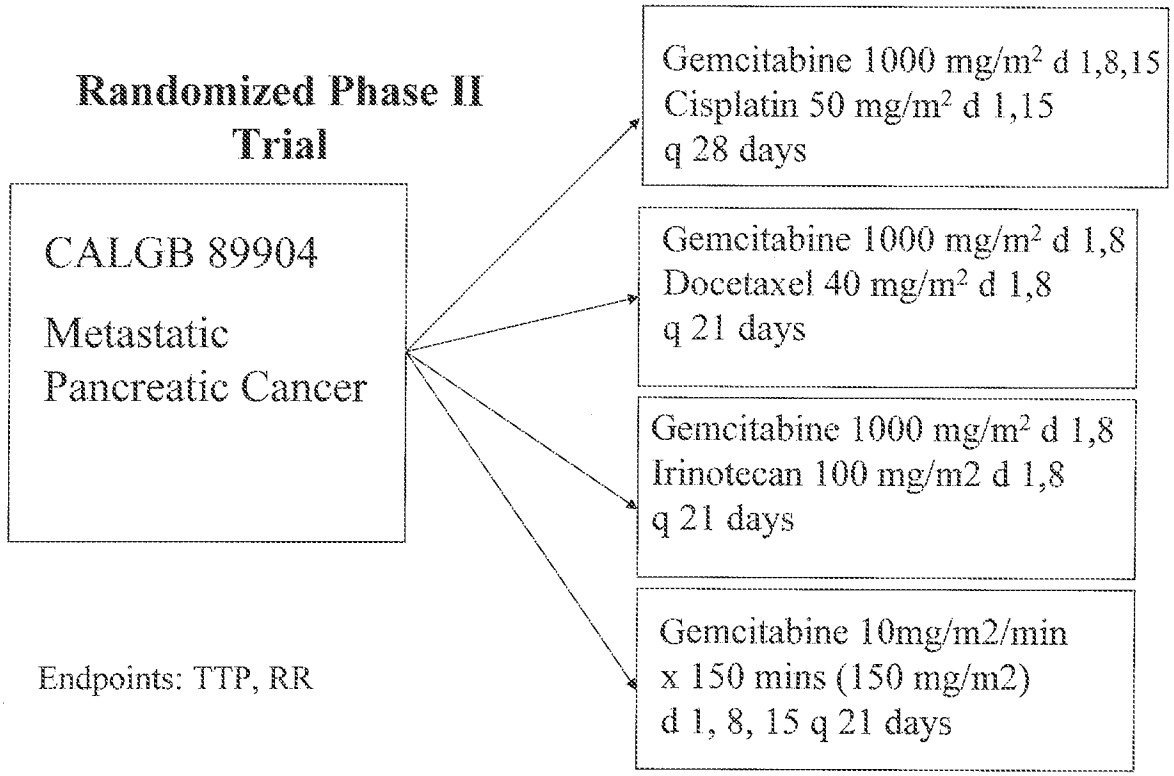

Fig. 1. Cancer and Leukemia Group B Phase II trial in metastatic pancreatic cancer.

etrexed in pancreatic cancer, investigators at the University of Chicago (Chicago, IL) initiated a multicenter Phase II trial of gemcitabine plus pemetrexed. Patients received 1250 mg/m^2 of gemcitabine on Days 1 and 8 of a 21-day cycle and 500 mg/m^2 of pemetrexed on Day 8 after gemcitabine. When safety data determined that pemetrexed toxicity could be reduced with vitamin supplementation, all patients were given 350–1000 μg of folic acid daily, and 1600 μg B_{12} every 9 weeks beginning at least 1 week before pemetrexed administration. On the basis of the promising results of this trial (43), an international Phase III randomized trial in 520 patients comparing the pemetrexed plus gemcitabine combination with single-agent gemcitabine, was initiated, completing accrual in February 2003.

FUTURE DIRECTIONS

On the basis of demonstrated superior survival, time to progression, and CBR compared with 5-FU, gemcitabine has become the standard chemotherapy for locally advanced and metastatic adenocarcinoma of the pancreas, both as a practice standard and as a regulatory and clinical trial standard. Gemcitabine, in addition to its clinical effectiveness, has a manageable toxicity profile, making it an attractive agent to investigate in combination with newer agents. Not surprisingly, additional ongoing clinical trials are evaluating methods to combine other treatment modalities and newer agents with gemcitabine. When combined with 5-FU, radiotherapy can significantly increase survival in patients with unresectable pancreatic cancer. Adjuvant chemoradiotherapy is considered by many to be successful in conferring a survival advantage to patients who undergo pancreaticoduodenectomy. Preclinical studies indicate that gemcitabine radiosensitizes a wide variety of tumor cells in culture. Although the precise mechanism of sensitization has not been clearly elucidated, laboratory evidence suggests that gemcitabine lowers the threshold for radiation-induced apoptosis (44). Novel gemcitabine-based chemoradiotherapy approaches are currently being evaluated in advanced/metastatic pancreatic cancer (see articles by Willett and McGinn in this Supplement), with the goal that such treatment strategies in these patients will improve long-term outcome. Other authors will also address the role of novel targets for therapy, including those directed at cancer cells, such as tumor antigens, growth receptors, and altered genetic or biochemical pathways, as well as those directed more toward host factors such as the immune response. Although early trials of some agents, such as R115777, have not strongly supported a role for some classes of agents, other preliminary work with antibodies to epidermal growth factor receptor and vascular endothelial growth factor may prove more fruitful. Designing trials that can properly select and evaluate these new agents, alone and in combination with chemotherapy, will prove to be the greatest challenge for the innovative treatment of pancreatic cancer in the next decade. It is unlikely that newer targeted therapies individ-

nally will answer these questions or completely supplant the traditional antitumor treatment, such as cytotoxic chemotherapy, but individualized treatment determined by rational drug and patient selection will likely hold more promise.

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Cancer Research

Experimental and Molecular Therapeutics

Lipidic nanoparticle CPT-11 in a bioluminescent orthotopic pancreas cancer model

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Abstract

5648

Efforts to treat pancreas cancer have been hampered by a lack of effective therapeutic options as well as predictive preclinical models. We hypothesized that nanoparticle agents encapsulating potent cytotoxic compounds may be useful against pancreatic cancer; and that antibody-targeted versions directed against EGFR may further increase efficacy against EGFR-overexpressing pancreatic cancers. We applied a liposome-based drug loading and stabilization technique to generate nanoliposomal CPT-11, a novel lipidic nanoparticle agent containing the prodrug CPT-11 (irinotecan) that has entered clinical trials. In addition, Fab' fragments of C225 were conjugated to nanoliposomal CPT-11 to generate EGFR-targeted immunoliposomal CPT-11.

Another objective of this study was to develop a bioluminescent-based orthotopic xenograft model of pancreas cancer with EGFR-overexpression to test this therapeutic approach. COLO357, a human pancreatic cell line, was passaged multiple times in vivo to generate the sub-line L3.6pl. This cell line was subsequently modified by lentiviral transduction to generate a firefly luciferase-expressing cell line, L3.6pl-T. L3.6pl-T cells were injected, during surgery, directly into the pancreas of a nude mouse to generate a tumor xenograft. Following ip administration of luciferin, animals were immediately imaged using a Xenogen IVIS 100 bioluminescent imager, and subsequently imaged at weekly intervals. Tumor burden was quantified by measuring luminescence. The signal was quantified by defining regions of interest (ROIs) and measuring photons/sec/str.

Agents evaluated in this model included EGFR-targeted immunoliposomal CPT-11, nanoliposomal CPT-11, free drug or vehicle control. All treatments were administered i.v. by tail vein beginning at 7 days post- tumor implantation and continued weekly for a total of three treatments. Both nanoliposomal CPT-11 and immunoliposomal CPT-11 showed potent antitumor activity, including durable tumor regressions, and were markedly superior to the equivalent dose of free drug. While both nanoparticle constructs were highly potent, the immunoliposome agent appeared to provide more prolonged duration of responses than the non-targeted version. Systemic toxicity was not observed with any treatment.

We conclude that nanoparticle-mediated delivery of CPT-11 via nanoliposomal CPT-11 or anti-EGFR immunoliposomal CPT-11 greatly enhances antitumor efficacy in the orthotopic COLO357 pancreatic xenograft model. This therapeutic approach offers potential advantages for pancreatic cancer treatment, and this type of model system may be useful in preclinical evaluation.

Footnotes

- 98th AACR Annual Meeting-- Apr 14-18, 2007; Los Angeles, CA

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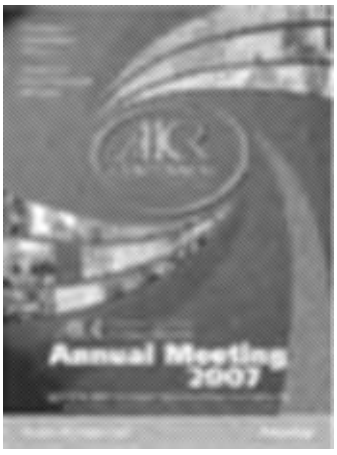

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ORIGINAL REPORT

Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared With Gemcitabine Alone in Advanced Pancreatic Cancer

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To compare the effectiveness and tolerability of gemcitabine plus cisplatin with single-agent gemcitabine as first-line chemotherapy for locally advanced or metastatic pancreatic cancer.

Patients and Methods
Patients with advanced adenocarcinoma of the pancreas were randomly assigned to receive either gemcitabine 1,000 mg/m^2 and cisplatin 50 mg/m^2 given on days 1 and 15 of a 4-week cycle (GemCis arm) or gemcitabine alone at a dose of 1,000 mg/m^2 on days 1, 8, and 15 of a 4-week regimen (Gem arm). The primary end point was overall survival; secondary end points were progression-free survival, response rate, safety, and quality of life.

Results
One hundred ninety-five patients were enrolled and showed baseline characteristics well balanced between treatment arms. Combination treatment in the GemCis arm was associated with a prolonged median progression-free survival (5.3 months *v* 3.1 months; hazard ratio [HR] = 0.75; P = .053). Also, median overall survival was superior for patients treated in the GemCis arm as compared with the Gem arm (7.5 *v* 6.0 months), an advantage which did not, however, reach statistical significance (HR = 0.80; P = .15). Tumor response rates were comparable between treatment arms (10.2% *v* 8.2%). The rate of stable disease was, however, greater in the combination arm (60.2% *v* 40.2%; P < .001). Grade 3 to 4 hematologic toxicity did not exceed 15% in both treatment arms.

Conclusion
These results support the efficacy and safety of an every-2-weeks treatment with gemcitabine plus cisplatin. Median overall survival and progression-free survival were more favorable in the combination arm as compared with gemcitabine alone, although the difference did not attain statistical significance.

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INTRODUCTION

Cancer of the exocrine pancreas remains a fatal disease for most patients. Because of its predominantly late diagnosis, most patients present with advanced disease.[1,2] Without effective treatment, these patients have a median survival of 3 to 4 months. Systemic chemotherapy with single-agent gemcitabine has evolved as a moderately active standard of care for treatment of locally advanced and metastatic pancreatic cancer.[3,4] Its wide acceptance is based not only on good tolerability but also on its potential to improve clinical benefit response.[5,6] In patients receiving gemcitabine, Karnofsky performance status (KPS) and stage of disease have been identified as important prognostic factors for treatment outcome.[7]

In an effort to improve therapeutic efficacy, numerous clinical studies have investigated gemcitabine (Gem) -based combination regimens. Some trials showed an improvement of overall response rates (ORR) and progression-free survival (PFS). However, a significant prolongation of overall survival (OS) has not been demonstrated when Gem was combined with platinum analogs,[8,9] antimetabolites,[10-13] or topoisomerase inhibitors.[14,15] This may be explained by the notably low chemosensitivity of pancreatic cancer,

but it may also relate to the fact that knowledge on adequate patient selection for different treatment strategies is limited so far.

The rationale for a combined use of Gem and cisplatin (Cis) is based on the preclinical evidence that Gem not only increases Cis-induced DNA cross links, but also effectively inhibits their repair. Synergistic cytotoxicity observed in vitro clearly relates to this drug interaction.[16-19] In pancreatic cancer, several clinical studies suggest that the combination of Gem and Cis is active and may improve ORR, PFS, and OS.[8,20-22] The present trial compares a biweekly application of Gem and Cis to a regimen where single-agent Gem was administered weekly for 3 weeks in a 4-week regimen.

PATIENTS AND METHODS

Patient Population

This trial included patients with pathologically confirmed, locally advanced or metastatic pancreatic cancer (adenocarcinoma or poorly differentiated) not amenable to surgical resection. Tumor lesions had to be bidimensionally measurable with a minimum size of 1 cm × 1 cm. Prior chemotherapy was not allowed. Prior radiotherapy was permitted only when the irradiated lesion was not the target lesion. Other eligibility criteria included age at least 18 years, life expectancy at least 12 weeks, and KPS at least 70%. Patients must have had adequate bone marrow and organ function tests.

Patient Assignment

Written informed consent was provided by all patients before study entry. Central random assignment was performed before the start of treatment, and patients were assigned to one of the treatment arms.

Treatment

In this open-label multicenter trial, treatment was applied in an out- or inpatient setting according to the decision of the respective medical facility. In the experimental arm, patients received Gem (1,000 mg/m^2, 30-minute intravenous [IV] infusion) plus Cis (50 mg/m^2, 1 hour IV infusion). Both agents were administered on days 1 and 15 of a 4-week cycle. In the control arm, patients received single-agent Gem (1,000 mg/m^2, 30-minute IV infusion) administered on days 1, 8, and 15 of a 4-week cycle. Doses could be adjusted according to prespecified dose reduction tables to maintain an acceptable toxicity profile.

Efficacy Evaluation

The intent-to-treat population was defined by the recruited patients. The efficacy-analyzable population was defined by all recruited patients who had completed at least one cycle of Gem-based chemotherapy. The primary outcome measure was OS, which was determined for all randomly assigned patients from the date of random assignment to the date of death or last contact. Patients alive and patients lost to follow-up were censored at the last date of contact. Among secondary outcome measures, PFS was defined as the time from random assignment until death or evidence of tumor progression. Patients who discontinued treatment on the study without documented progression were censored at their last date of tumor assessment. ORR (according to WHO criteria) was defined as the best tumor response during treatment. Assessment of ORR was carried out every two cycles (every 8 weeks) applying the initially used imaging procedure.

Safety Evaluation

Before entering the study, patients had a full blood count and analysis of blood chemistry, including liver and renal function tests. A full blood count was taken each day of treatment, and blood chemistry at the start of each cycle. According to the protocol, the safety analysis included all patients who had received at least one dose of Gem.

Quality-of-Life Evaluation

Before and during the course of treatment, quality of life was determined using the quality-of-life (QOL) index according to Spitzer et al.[23] QOL was assessed by the patients before start of treatment on study and at each new cycle of therapy.

Statistical Methods

The study was designed to detect a 60% improvement in median survival from 5 to 8 months with a power of 80% and an overall significance level of 5%. Time-to-event curves were estimated according to the method of Kaplan and Meier and were compared using the log-rank test. Results from Peto's adaptation of the Wilcoxon test variant for censored data are provided for comparison, in case of distinct deviation from the proportional hazard assumption. Fisher's exact test was used to compare categoric characteristics and response rates. The midrank Wilcoxon test was applied to compare the distributions of dose-intensity, toxicity, and quality of life between treatment arms. The Cox proportional hazards model was applied for multivariate analysis. All *P* values result from two-sided tests.

RESULTS

Patient Characteristics

Between December 1997 and January 2002, a total of 195 patients (intent-to-treat population) were enrolled onto the study from 34 different centers (see Online Only Appendix). Five patients (three in the GemCis arm and two in the Gem arm) did not receive treatment per protocol and further follow-up was omitted. According to the protocol, 190 patients (95 in the GemCis arm and 95 in the Gem arm) were assessable and were included into the population of analyzable patients.

Median follow-up for patients treated in the GemCis arm was 7.4 months (range, 0.2 to 48.6 months), whereas it was 6.0 months (range, 0.3 to 48.5 months) for those in the Gem arm. At the time of final analysis, 92.3% of patients had died. Patient characteristics are shown in Table 1.

Treatment Administration

Median duration of treatment was longer in the GemCis arm compared with the Gem arm (4.1 *v* 3.3 months). Accordingly, patients in the combination arm received a median of 4 cycles (range, 0 to 20) of chemotherapy as compared to a median of 3 cycles documented for the single-agent arm (range, 0 to 15).

Adherence to the treatment protocol was comparable in both treatment arms. In the GemCis arm, 1,013 cycles were analyzed; dose reductions were performed in 5.3%, dose delays in 2.7%, and omissions of doses in 1.5% of cycles. In the Gem arm, a total of 772 cycles were applied; dose reductions, delays, and omissions were reported in 7.5%, 4.6%, and 2.3%, respectively. The analysis of relative dose-intensity during a range of 1 to 10 treatment cycles indicated that more than 90% of chemotherapy doses were applied as scheduled with no significant difference between treatment arms. The median relative dose-intensity was 93% to 99% for Gem and 92% to 99% for Cis in the GemCis arm, whereas it was 92% to 97% in the Gem arm.

Second-Line Therapy

After failure of first-line treatment, 31 patients (16.1%; 15.8% in the GemCis arm and 16.5% in the Gem arm) received second-line therapy. Fifteen patients (8%) received fluoropyrimidine-based therapy, 12 patients (6%) single-agent Gem, and 4 patients (2%) were treated with GemCis.

Safety Results

The overall tolerability of both regimens was equally acceptable (Table 2). Hematologic toxicity was low, and WHO grade 3 to 4 events remained below 15% for both arms. Also, nonhematologic toxicity

Table 1. Baseline Patient Characteristics

Patient Characteristic	GemCis Arm (n = 98) No	GemCis Arm (n = 98) %	Gem Arm (n = 97) No	Gem Arm (n = 97) %
Age, years				
Median	64		66	
Range	37-82		43-85	
Sex				
Male		65.3		61.9
Female		34.7		38.1
Karnofsky performance status, %	79		82	
100	20	25.3	18	23.2
90	24	30.4	21	25.6
80	27	34.2	29	35.4
70	8	10.1	13	15.8
Stage				
Locally advanced		20		21.1
Metastatic		80		78.9
Primary tumor site				
Head		58.3		56.9
Body		19.5		24.5
Tail		24.1		18.6
Histologic degree of differentiation				
Well		8.4		11.0
Moderate		48.2		41.5
Poor		43.4		47.5
Liver metastasis		84.3		70.1
Number of sites of metastasis				
1		67.1		76.0
2		22.4		14.7
3		3.9		6.7

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone.

Table 2. Summary of Maximum WHO Grades for Toxicity

Adverse Event	Patients (%) GemCis Grade 1-2	GemCis Grade 3-4	Gem Grade 1-2	Gem Grade 3-4
Leucopenia	35.6	10.0	37.6	8.3
Anemia	64.5	13.3	37.0	10.6
Thrombopenia	25.5	4.4	23.4	10.6
Infection	12.2	1.1	12.9	2.4
Bleeding	2.2	2.2	1.2	3.6
Bilirubin	13.4	7.8	15.3	8.3
Transaminase	42.3	2.2	45.7	8.3
Alkaline phosphatase	43.3	5.5	48.3	4.8
Serum creatinine	33.3	0.0	13.1	0.0
Proteinuria	31.1	0.0	29.4	0.0
Hematuria	24.4	0.0	18.8	0.0
Nausea/vomiting	66.7	22.2*	49.4	5.9
Diarrhea	30.0	3.3	14.1	4.7
Mucositis	18.8	4.4	15.3	2.4
Pain	40.0	12.2	40.0	8.3
Alopecia	43.3	2.2	20.0	1.2
Allergy	5.6	0.0	7.1	1.2
Rash	11.1	0.0	7.0	1.2
Drug-related fever	7.8	2.2	17.6	1.2
Sensory neuropathy	0	0	0	0
Pulmonary	14.4	1.1	10.6	3.5
Peripheral edema	3.3	0.0	5.9	0.0

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone. *Grade 3-4 nausea and vomiting significantly more frequent in the GemCis arm compared with Gem alone ($P = .0002$).

was predominantly mild to moderate, and WHO grade 3 to 4 adverse events were observed in less than 15% of patients. Only nausea and vomiting were significantly more frequent in the GemCis arm (22.2% *v* 5.9%; $P = .0002$; Table 2).

Efficacy Results

A detailed analysis of treatment efficacy is shown in Tables 3 and 4.

Response rate. Response to treatment was evaluated by intent-to-treat for the whole population of randomly assigned patients. The rate of partial responses was comparable between treatment arms amounting to 10.2% (95% CI, 4.2 to 16.2) in the GemCis arm and 8.2% (95% CI, 2.8 to 13.7) in the Gem arm. A significant improvement was, however, observed in the stable disease rate when patients received GemCis (60.2%; 95% CI, 50.5% to 69.9%) as compared with Gem (40.2%; 95% CI, 30.5% to 50%). Median duration of response for GemCis and Gem was 7.3 months (range, 2.0 to 10.8 months) versus 7.8 months (range, 2.1 to 11.4 months), and median duration of stable disease was 6.0 months (range, 1.1 to 28 months) versus 4.4 months (range, 1.2 to 37.4 months), respectively. Disease control rate (DCR) summarizes partial response and stable disease, thereby accounting for the overall benefit from treatment. DCR was significantly ($P < .001$) greater in the GemCis arm (70.4%, 95% CI, 61.4% to 79.5%) as compared with the Gem arm (DCR = 48.5%, 95% CI, 38.5% to 58.4%). The relevance of this observation is underlined by nonoverlapping CIs and is reflected by a 2.4-fold lower rate of progressive disease (PD) in the GemCis arm.

PFS. GemCis caused a superior PFS (5.3 *v* 3.1 months; $P = .053$) compared with Gem (Fig 1). In a post hoc subset analysis, the superiority of GemCis was even more pronounced in locally advanced disease (8.6 *v* 3.2 months; $P = .0053$), whereas only a moderate advantage was detected in patients with metastatic disease (4.2 *v* 3.1 months; $P = .31$). A further subset analysis revealed that GemCis was

Table 3. Summary of Efficacy Results: Response Rate

	% GemCis	% Gem	*P*
Best response			—
Enrolled patients	98	97	
Assessable patients	87	89	
ITT analysis			
CR	0	0	—
PR	10.2	8.2	—
SD	60.2	40.2	< .001
DCR (PR + SD)	70.4	48.5	< .001
PD	18.4	43.3	< .001
Assessable patients			
ORR	11.5	9.0	< .001
DCR (PR + SD)	79.3	52.5	< .001

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone; ITT, intent to treat; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; PD, progressive disease; ORR, overall response rate.

Table 4. Summary of Efficacy Results: Overall Survival and Progression-Free Survival

	No. of Patients	% GemCis	% Gem	HR	Log-Rank *P*
Median OS					
All patients	190	7.5	6.0	0.80	.15
Locally advanced	39	10.3	10.4	0.65	.29
Metastatic	151	7.2	4.7	0.82	.23
KPS 70%-80%	76	4.9	4.8	1.13	.64
KPS 90%-100%	84	10.7	6.9	0.62	.051*
6-month survival		59.0	50.5		.45
12-month survival		25.3	24.7		.21
Median PFS					
All patients	190	5.3	3.1	0.75	.053
Locally advanced	39	8.6	3.2	0.30	.0053
Metastatic	151	4.2	3.1	0.84	.31
KPS 70%-80%	76	2.8	2.9	0.91	.69
KPS 90%-100%	84	7.7	2.8	0.54	.013†

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone; HR, hazard ratio; OS, overall survival; KPS, Karnofsky performance status; PFS, progression-free survival.
*Peto-Wilcoxon-Test $P = .0079$.
†Peto-Wilcoxon-Test $P = .0020$.

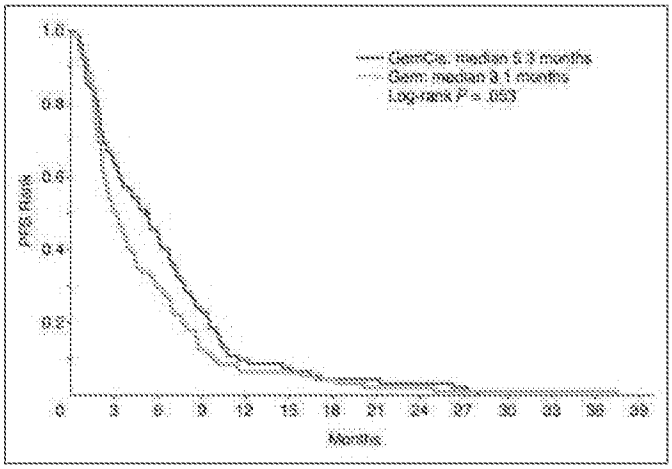

Fig 1. Kaplan-Meier estimates of progression-free survival (PFS). GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone.

superior to Gem in patients with a KPS of 90% to 100% (7.7 *v* 2.8 months; $P = .013$), whereas no advantage was observed in patients with a KPS of 70% to 80%.

Overall Survival

Although GemCis was superior to Gem, inducing a 25% increase of median survival (7.5 *v* 6.0 months), the study was not sufficiently powered to reach statistical significance (hazard ratio [HR] = 0.80, $P = .15$; Fig 2). In patients with metastatic disease only, median survival was markedly prolonged (7.2 *v* 4.7 months). This was not the case in locally advanced pancreatic cancer (10.3 *v* 10.4 months). In patients with KPS 90% to 100%, GemCis induced an increase of median survival time from 6.9 to 10.7 months ($P = .051$), but no improvement of survival (4.9 *v* 4.8 months) was noted in patients with KPS 70% to 80%.

Uni- and Multivariate Analysis of Prognostic Factors

In the univariate analysis, stage of disease (HR = 1.55, $P = .0048$) and KPS (HR = 0.52, $P = .0006$) had a significant prognostic impact on survival, whereas treatment arm, age, sex, and tumor grading did not. A subsequently performed multivariate analysis (Table 5) confirmed stage of disease (HR = 1.65; $P = .022$) and KPS (HR = 0.59; $P = .0051$) as independent determinants of overall survival.

Table 5. Multivariate Analysis of Potential Prognostic Factors Associated With Survival

Parameter	HR	95% CI	*P*
Treatment arm	0.92	0.66 to 1.28	.62
Age	1.02	1.00 to 1.04	.079
Stage (metastatic disease)	1.65	1.08 to 2.52	.022
Tumor grading			
G2	1.66	0.92 to 3.01	.094
G3	1.76	0.97 to 3.19	.064
KPS 90-100%	0.59	0.41 to 0.85	.0051

Abbreviations: HR, hazard ratio; KPS, Karnofsky performance status.

QOL Results

QOL was assessed at treatment start and was followed for up to six cycles of therapy (Table 6). The analysis of the five-item QOL index[23] suggests a trend for an improvement during the first two cycles of chemotherapy. Thereafter, the QOL index remained stable and, at no time point, showed a significant difference between treatment arms. Pain intensity as rated by a visual analog scale decreased during the first two cycles of chemotherapy, where a plateau was reached. No significant difference was apparent between the treatment arms.

DISCUSSION

The optimal regimen for the combined use of gemcitabine and cisplatin has not been defined. In several clinical studies, cisplatin has been applied once every 3 to 4 weeks, biweekly, or even weekly. In a previous phase II trial performed in the first-line treatment of advanced pancreatic cancer, Gem (1,000 mg/m^2) was administered on days 1, 8, and

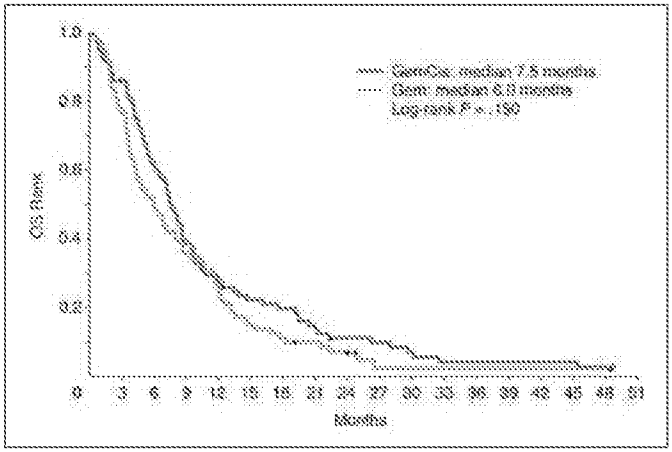

Fig 2. Kaplan-Meier estimates of overall survival (OS). GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone.

Table 6. Summary of Quality of Life: Spitzer[23] 5-Item Index and Pain Intensity

	No. of Treatment Cycles						
	0	1	2	3	4	5	6
Spitzer index*							
GemCis	7.3 ± 1.3	8.2 ± 1.0	8.6 ± 0.6	8.6 ± 0.8	8.5 ± 0.9	8.0 ± 1.0	8.1 ± 1.1
Gem†	7.4 ± 1.3	7.4 ± 1.2	8.5 ± 1.0	7.9 ± 1.2	8.6 ± 1.0	8.1 ± 1.4	8.5 ± 0.7
Pain intensity‡							
GemCis	3.4 ± 1.2	2.9 ± 1.0	2.8 ± 0.9	2.8 ± 0.8	3.1 ± 0.9	2.9 ± 0.9	3.0 ± 1.1
Gem†	4.4 ± 1.2	3.7 ± 1.0	3.0 ± 0.8	3.4 ± 0.9	3.1 ± 0.9	3.0 ± 1.0	3.2 ± 0.8

Abbreviations: GemCis, gemcitabine plus cisplatin; Gem, gemcitabine alone.
*Quality of life rated by the Spitzer five-item index, including activity, daily living, health perception, support, and outlook on life with a score ranging from 0 to 10.
†No significant difference between treatment arms.
‡Pain intensity assessed by means of a visual analog score ranging from 1 to 10.

15 of a 4-week schedule, whereas cisplatin (50 mg/m^2) was administered on days 1 and 15.[21] Median survival in this trial was 8.2 months. Although tolerability of this regimen was deemed acceptable, hematotoxicity with grade 3 to 4 neutropenia (29% of patients) and thrombocytopenia (13% of patients) were the main reasons for dose reductions or omissions documented in more than 30% of cycles. To improve on feasibility and to ensure the application of cisplatin and gemcitabine on day 15, the treatment schedule was modified, and the application of gemcitabine on day 8 was generally omitted. In the present trial, the experimental arm consisted of Gem and cisplatin both administered on days 1 and 15 of a 4-week regimen, whereas in the comparator regimen, patients received single-agent Gem on days 1, 8, and 15 every 4 weeks. The more intensive treatment in the combination arm was therefore in part balanced by a more frequent drug application in the control arm. According to the protocol, the relative dose-intensity of Gem for the Gem versus the GemCis arm was 1.5.

In the randomized trial, tolerability was acceptable in both treatment arms, which is reflected by a high relative dose-intensity (> 90%). In view of the low number of reduced, delayed, or omitted doses (< 10%, respectively) the presently used biweekly regimen of Gem and cisplatin showed a better tolerability than the previously used schedule (Gem administered on days 1, 8, 15 plus cisplatin administered on days 1 and 15 every 4 weeks).[21] Compared with the GemOx regimen (fixed-dose rate Gem plus oxaliplatin) previously reported by Louvet et al,[9] toxicity associated with GemCis was comparable with the exception of nausea and vomiting observed at a higher rate in the cisplatin-based regimen and peripheral sensory neuropathy occurring more frequently with oxaliplatin-based therapy.

QOL has gained acceptance as a surrogate end point of treatment efficacy due to the trials reported by Burris and Rothenberg.[5,6] Their work on clinical benefit response as a composite parameter of pain, performance status, and weight not only demonstrated that Gem was superior over bolus fluorouracil, but also showed that this end point related to a significantly improved survival. Using the five-item QOL index described by Spitzer al,[23] it could be shown in this trial that treatment with GemCis, despite a higher overall incidence of adverse effects, did not impair QOL when compared with treatment with Gem alone. A trend toward an improved QOL score was equally observed in both treatment arms during the initial two cycles of therapy.

It is a general notion that response evaluation by imaging is difficult in pancreatic cancer and may be limited by desmoplastic and inflammatory reactions of the tumor. For this reason, DCR may give a more reliable reflection of drug efficacy than ORR alone. Previous reports had indicated that Gem induced a DCR of 42% to 44%,[5,8] whereas the combination of Gem and Cis consistently increased DCR to a range of 55% to 68%.[8,20–22] These data are essentially confirmed by the present randomized trial where in the intent-to-treat analysis a DCR of 70.4% was reached in the GemCis arm, whereas DCR in the Gem arm was 48.5%. From the viewpoint of preventing initial PD, GemCis was 2.4-fold more effective than Gem (PD = 18.4% *v* 43.3%; $P < .001$).

Patients treated in the GemCis arm showed a marked (71%) prolongation of PFS compared with Gem alone (5.3 *v* 3.1 months). Although this improvement suggests a distinctly greater efficacy of the GemCis combination, it failed to reach the level of significance when all patients were evaluated. A significantly superior effect of the GemCis regimen was, however, demonstrated in a post hoc analysis of patients with locally advanced pancreatic cancer (8.6 *v* 3.2 months; $P = .0053$). So far, there is no good explanation as to why the PFS advantage observed in locally advanced disease did not translate into a corresponding survival benefit (10.3 *v* 10.4 months). Comparable results have also been reported by Louvet et al[9]; their GemOx regimen improved PFS but had no effect on survival compared with standard-dose Gem. A further hypothesis-generating subset analysis suggests that patients with a good KPS (90% to 100%) may be those who benefit most from a relevant prolongation of PFS in the GemCis as compared with the Gem arm (7.7 *v* 2.8 months; HR = 0.54; $P = .013$).

The primary end point of this trial was OS. The 25% (7.5 *v* 6.0 months) increase of OS induced by GemCis compares with a 50% (7.5 *v* 5.0 months) increase observed by the Italian group[8] and also relates to the 27% (9.0 *v* 7.1 month) increase reported for the GemOx regimen by the French/Italian group.[9] Although it appears that platinum-based regimens consistently prolonged survival, none of the trials so far showed a statistically significant superiority of the combination. Most likely, this is a result of the underpowered design of the trials. In view of the consistency of results, the question of whether the outcome of the aforementioned trials should rightfully be considered a negative one needs to be asked. Not only a meta-analysis of the available studies, but also the upcoming data from an Eastern Cooperative Oncology Group

(ECOG) trial comparing GemOx with fixed-dose rate and standard-dose Gem may help to clarify this topic.

The interpretation of trial results may also depend on subgroups of patients with different prognosis. A multivariate analysis performed in this trial suggests that not only stage of disease, but also performance status are independent prognostic factors for survival. Moreover, evidence from a post hoc analysis leads to the hypothesis that specifically patients with a good KPS (90% to 100%) will draw the greatest benefit from combination therapy with Gem and Cis, whereas those patients with a worse performance status should receive single-agent therapy with Gem.

Also, second-line therapy evolves as an important confounder of survival analysis. So far, second-line therapy has not been established in pancreatic cancer. Although in this trial, centers were encouraged to allow cross-over when treatment failed in one arm, only 16% of patients actually received second-line therapy, which did not have an impact on outcome. By comparison, already 55% of patients received further treatment in the French/Italian trial.[9]

In conclusion, the combination of Gem with Cis has significantly improved disease control rate and induced an improved, but not statistically significant, prolongation of PFS and OS. The perspective for further development in pancreatic cancer therapy is set by the development of targeted agents. First results indicate the superiority of gemcitabine in combination with erlotinib.[24] Future trials must define those subgroups of patients who will benefit most from targeted therapy alone or in conjunction with single-agent or combination chemotherapy.

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Appendix

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®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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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LUNG CANCER

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Budget Impact in the USA of Liposomal Irinotecan as a Post-Gemcitabine Treatment Option for Patients With Metastatic Pancreatic Adenocarcinoma (mPC)*

Authors: Oscar Herrera-Restrepo[1], Cheryl P Ferrufino[1], S. Pinar Bilir[2], Paul Cockrum[3], Adriana Valderrama[4]

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BACKGROUND

- Pancreatic cancer is a very aggressive disease, with an overall 5-year survival rate of 9%.[1] Pancreatic cancer was anticipated to affect 55,440 new patients in the United States (US) in 2018,[2] with 85% having the most common form, pancreatic adenocarcinoma.[3]
- Although US statistics indicate that pancreatic cancer is ranked 11th in expected cancer incidence for 2018, only lung and colorectal cancers lead to more deaths; 44,330 were anticipated to die of pancreatic cancer in 2018.[4]
- Mortality is particularly grim for patients in stages III/IV, with less than 3% surviving five years.[1,2,3,5,6]
- For patients with locally advanced or metastatic pancreatic cancer, treatment options are limited.
- 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 (AmPC) after disease progression following gemcitabine (gem)-based therapy.[7]
- 5-FU + LV + nal-IRI significantly improved median overall survival (OS) versus 5-FU + LV alone (6.1 months vs 4.2 months; hazard ratio [HR]: 0.68; P=0.014); improvement was also seeing in progression-free survival (PFS; 3.1 months vs 1.5 months; HR: 0.55).[8]

OBJECTIVE

- This analysis estimated the budget impact of adding or increasing access to nal-IRI for the treatment of patients with metastatic adenocarcinoma of the pancreas (mPC) after disease progression following gemcitabine-based therapy in first-, second-, and third-line (1L, 2L, 3L) of therapy from a US commercial payer perspective.
- The BIM was developed following AMCP (Academy of Managed Care Pharmacy) and ISPOR (International Society for Pharmacoeconomics and Outcomes Research) best modeling practice recommendations.[9,10]

METHODS

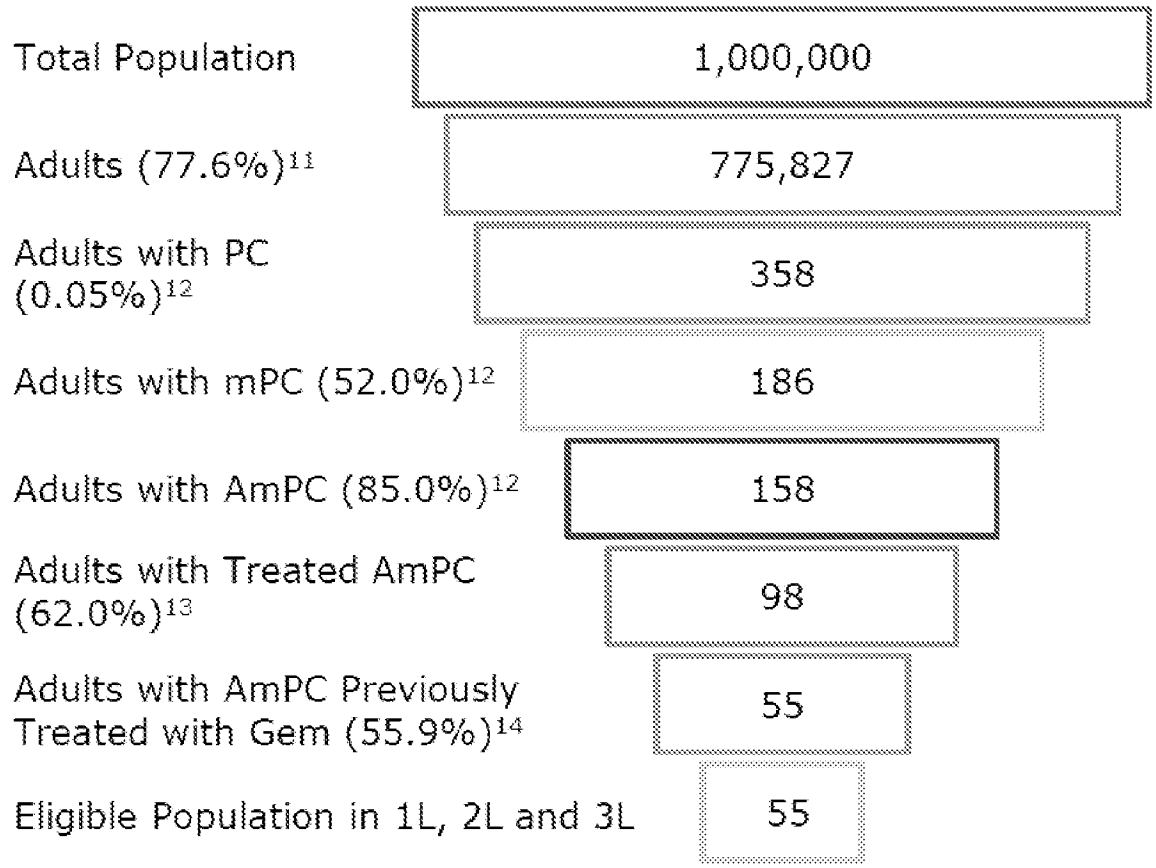
Model Approach

- The BIM employed a comparative cost determination framework to estimate the budget impact of adding nal-IRI to a payer formulary.
  - Annual costs were calculated for the baseline scenario (i.e., a "world with *current* nal-IRI utilization") and for the projected scenario (i.e., "world with *increasing* nal-IRI utilization") to estimate the incremental annual budget of nal-IRI from an US commercial payer perspective.

Population

- Epidemiology inputs were applied to a hypothetical plan population of 1M members to calculate the number of patients eligible for nal-IRI (Figure 1).
- The base case eligible population was defined as patients 18+ years old with mPC after disease progression following gemcitabine-based therapy.
  - Default epidemiology inputs were sourced from official and publicly available literature, reflecting US-representative mPC population.[11,12,13,14]

Figure 1. Population Cascade



Market Shares

- The base case market basket included only the most common treatment options for mPC and irinotecan regimens, they were: 5-FU+LV+nal-IRI, FOLFIRI, FOLFOX, FOLFIRINOX, gem+Abraxane, and gemcitabine.
- The current market shares of treatment options available in the US market were calculated based on estimated treatment usage from Flatiron data[15] (data derived from Q2-2018 counts of patients receiving treatment for mPC in 1L, 2L, 3L therapy). See Table 1.
  - The projected scenario assumed that nal-IRI uptake is equiproportionally sourced from other treatment options available in the market. The nal-IRI uptake was based on manufacturer market research data.

Table 1. Market Share Assumptions						
	1L		2L		3L	
Treatment Options in First-Line	Baseline Scenario	Projected Scenario	Baseline Scenario	Projected Scenario	Baseline Scenario	Projected Scenario
5-FU + LV + nal-IRI	**1.2%**	**1.4%**	**20.5%**	**21.5%**	**34.1%**	**40.2%**
FOLFIRI	0.6%	0.6%	0.9%	0.8%	0.0%	0.0%
FOLFIRINOX	33.2%	33.2%	14.5%	14.4%	13.6%	12.4%
FOLFOX	3.9%	3.9%	19.7%	19.4%	25.0%	22.7%
Gemcitabine	7.3%	7.2%	3.4%	3.4%	0.0%	0.0%
Gemcitabine + Abraxane	53.8%	53.7%	41.0%	40.5%	27.3%	24.8%

Dosage

- Product prescribing information and published literature on drug dosing and administration schedule were used to establish drug dosing for each treatment option[16,17,18,19,20,21]
- Treatment duration for each treatment regimen was based on published real-world or clinical trial data. See Table 2

Drug and Administration Costs

- Calculated costs per cycle and course are shown in Table 2 for the treatment options included in the model
  - Treatment duration was retrieved from prescribing information or clinical trials publications of treatment options (see references in Table 2)
  - For drugs administered based on body surface area (BSA) calculations from the NAPOLI-1 Trial[22]
  - Drug unit costs reflect Wholesale Acquisition Costs [WAC] from Medi-Span PriceRx,[23] and administration costs were derived from the 2019 Medicare Physician and Laboratory Fee Schedules[24]

Table 2. Treatment Cost and Duration

Treatment Options	Per Cycle		Per Course of Therapy		Duration of Therapy
All Lines	Drug Costs	Admin Costs	Drug Costs	Admin Costs	All Lines
5-FU + LV + nal-IRI	$6,123	$747	$27,554	$3,362	4.5 cycles, 14 days per cycle[16]
FOLFIRI	$98	$448	$624	$2,868	6.4 cycles, 14 days per cycle[20]
FOLFIRINOX	$215	$895	$2,148	$8,953	10.0 cycles, 14 days per cycle[21]
FOLFOX	$159	$789	$1,071	$5,327	6.8 cycles, 14 days per cycle[19]
Gem	$192	$455	$432	$1,024	2.3 cycles, 28 days per cycle[18]
Gem+ Abraxane	$9,143	$675	$38,206	$2,821	3.2 cycles, 28 days per cycle[17]

G-CSF (granulocyte-colony stimulating factor) Use and Costs (Table 3)

- Prophylactic G-CSF use data per treatment option and G-CSF type were derived from Flatiron analyses on patients diagnosed with mPC.[25] Therapeutic G-CSF use was assumed to be accounted into adverse event management costs.
- G-CSF dosing from Neulasta and Neupogen prescribing information[26,27] was used to calculate the G-CSF dose per treatment cycle and course. The latter was estimated based on the treatment duration of each treatment.
- The model assumed that Neulasta is given via subcutaneous (SC) injection. With respect Neupogen, an IV administration was assumed.
- G-CSF WAC costs were retrieved from Medispan PriceRx ($6,231.10 for Neulasta SC injection 6mg/0.6ml, and $501.30 for Neupogen IV 480mcg/1.6ml)[23] G-CSF administration costs were derived from the 2019 Medicare Physician Fee Schedule ($16.94 for SC injection, CPT code 96372).[24]

Table 3. G-CSF Use and Costs per Cycle and Course of Therapy

	G-CSF Use			Per Cycle		Per Course of Therapy	
Regimen	1L	2L	3L	G-CSF Drug Costs	G-CSF Admin Costs	G-CSF Drug Costs	G-CSF Admin Costs
5-FU + LV + nal-IRI	9.5%	8.6%	8.1%	$5,700	$10.77	$25,651	$48.45
FOLFIRI	7.6%	7.4%	7.6%	$5,700	$10.77	$36,481	$68.91
FOLFIRINOX	12.8%	12.2%	9.9%	$5,700	$10.77	$57,001	$107.67
FOLFOX	6.1%	5.8%	6.1%	$5,700	$10.77	$38,476	$72.68
Gem	3.2%	2.8%	8.8%	$7,440	$10.77	$16,740	$24.23
Gem + Abraxane	6.9%	7.4%	7.2%	$7,440	$10.77	$31,088	$44.99

Monitoring Resource Use and Costs

- Resource use per treatment option was retrieved from published product PIs.[16,17,18,28,29,30,31]
- For combination therapy, the highest resource use of an individual drug was used to avoid double counting.
- Resource use costs were derived from the 2019 Medicare Physician and Laboratory Fee Schedules.[24]

Adverse Event (AE) Rates and Management Costs (Table 4)

- AE rates and management costs were derived from real-world Medicare FFS claims data in beneficiaries diagnosed with mPC.[32]
- AEs costs were assumed to be managed in an inpatient setting.
- Proteinuria costs were reported overall, not by line.
- Incremental costs were not reported for lymphopenia.

Table 4. Adverse Event Rates and Costs

AEs	5-FU + LV+ nal-IRI	FOLFIRI	FOLFI-RINOX	FOLFOX	Gem	Gem + Abrax-ane	Incr. Unit Cost
Abdominal pain or cramping	22.4%	18.4%	28.2%	22.0%	19.5%	23.1%	**$841**
Anemia	32.2%	29.4%	33.8%	27.1%	34.4%	40.2%	**$3,593**
Diarrhea	25.6%	18.4%	28.4%	14.7%	13.5%	16.1%	**$1,550**
Fatigue/ asthenia	26.5%	26.4%	30.3%	26.3%	25.9%	29.3%	**$1,105**
Lymphopenia	0.0%	0.0%	0.0%	NR	NR	NR	**$0**
Nausea	13.8%	12.1%	19.2%	13.5%	11.2%	13.4%	**$1,134**
Neuropathy	24.3%	22.4%	18.7%	15.0%	5.7%	15.1%	**$686**
Neutropenia	17.7%	17.8%	32.2%	18.8%	16.0%	20.0%	**$2,447**
Proteinuria	0.0%	NR	NR	0.0%	0.5%	0.3%	**$3,333**
Throm-bocytopenia	9.1%	7.4%	17.2%	13.5%	11.8%	15.3%	**$2,775**
Vomiting	13.8%	12.1%	19.2%	13.5%	11.2%	13.4%	**$1,134**
Total Costs per Course in 1L, 2L, or 3L	**$3,198**	**$2,858**	**$4,055**	**$2,921**	**$2,909**	**$3,533**	

Note: % AE does not reflect time on therapy but proportion of patient experiencing event

Scenario Analyses

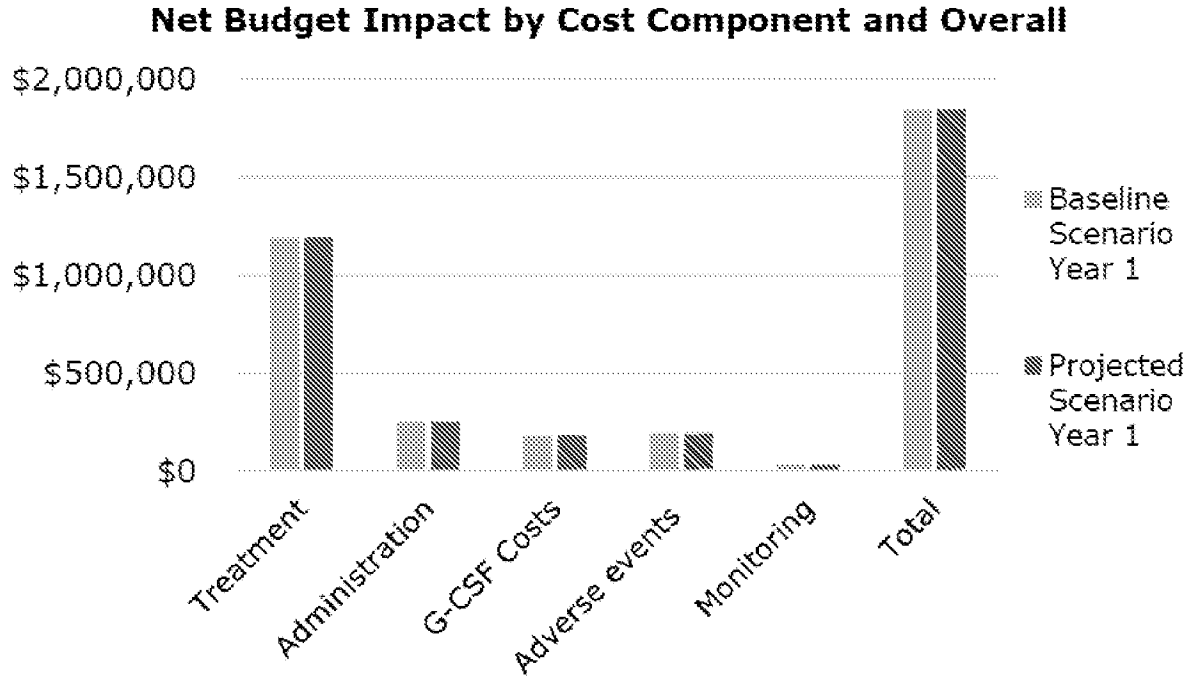
- Scenario 1 considers only patients in 2L therapy
- Scenario 2 excludes administration and monitoring costs
- Scenario 3 excludes G-CSF and adverse event management costs
- Scenario 4 explores a Medicare perspective which utilizes ASP (average sales price) drug prices
- Note: For all scenarios, all other inputs and assumptions remaining the same as in the base case analysis

RESULTS

Base Case Analysis

- In a 100% commercial plan with a population of 1M patients, and with an increasing nal-IRI uptake of 1.4% in first-, 21.5% in second-, and 40.2% in third-line relative to current utilization, the net budget impact in Year 1 was estimated to be $0.0003 PMPM (see Figure 2)
  - A total of 6.56 patients received nal-IRI in the projected scenario
  - The introduction of naI-IRI resulted in a net budget impact of $3,076. The incremental cost can be attributed to a $4,480 (0.4%) increase in drug costs
  - However, the incremental treatment cost of nal-IRI was offset by savings in administration $724 (-0.3%), G-CSF $464 (-0.3%), adverse event management $126 (-0.1%) and monitoring costs $90 (-0.3%)

Figure 2. Base Case Results



Scenario Analyses

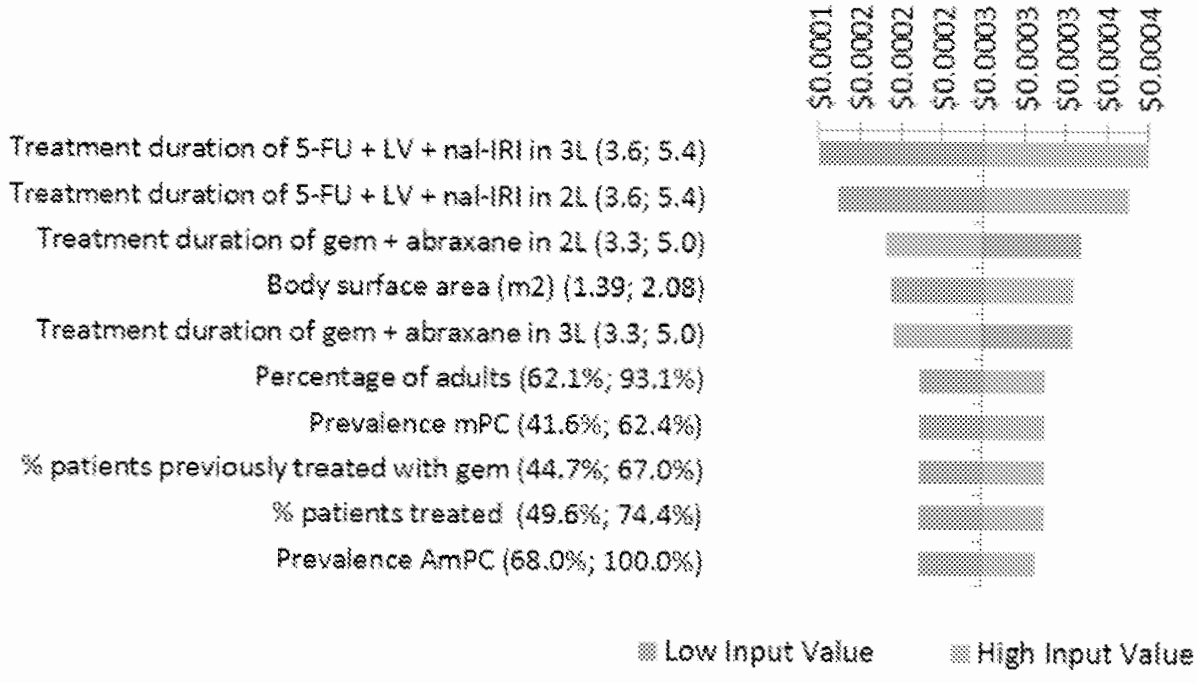
- Scenario 1: Considering only 2L patients decreased the incremental PMPM to $0.0001

- Scenario 2: Excluding administration and monitoring costs increased the incremental PMPM to $0.0003
- Scenario 3: Excluding G-CSF and adverse event costs increased the incremental PMPM to $0.0003
- Scenario 4: Exploring a Medicare perspective with ASP cost inputs increased the incremental PMPM to $0.0011 due to lower drug prices for the comparators and more eligible patients (i.e., higher concentration of older population with higher prevalence and incidence of pancreatic cancer)

OWSA

- Despite input value uncertainty (+/- 20%), the cost PMPM values remained similar to those of the model base case of $0.0003 (variation range: +/- $0.0002). See Figure 3
  - The top 10 most influential variables across results options (in order of impact on incremental PMPM) related to treatment duration, body surface area and epidemiological inputs
  - As published list costs were not variable, the OWSA did not vary drug acquisition costs

Figure 3. OWSA Results



LIMITATIONS

- Results depend on the quality and accuracy of model inputs, and known data limitations exist, including those around published data for commercial payers (i.e., uncertainty surrounding model inputs for G-CSF use and adverse events rates and costs). The results of this analysis should be interpreted with consideration of these limitations.
- Any particular payer may experience a different budget impact if negotiated prices differ from published prices.
- Lastly, this analysis is limited to a US healthcare setting; results are not generalizable to other patient subgroups, disease indications, or geographies.

CONCLUSIONS

- Overall, increasing access to nal-IRI, in agreement with recent NCCN guidelines for treatment of post-gemcitabine mPC, is **budget neutral** due to cost-offsets driven by lower: (1) administration costs, (2) G-CSF use, and (3) real-world rate of AEs compared to common alternatives
  - In the base case analysis, increasing utilization of nal-IRI resulted in an incremental PMPM of $0.0003 in Year 1. This results assumed that the increasing utilization of nal-IRI is equi-proportionally drawn from the most common mPC treatment options and irinotecan regimens in the US market

*Results shown in this poster differ from those reported at the moment of abstract submission. Differences pertain to 2019 cost updates as well as the inclusion of G-CSF Use and Costs

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Presented at ISPOR | New Orleans, LA, USA | May 18th-22nd 2019

This study was sponsored by Ipsen

Budget Impact in the USA of Liposomal Irinotecan as a Post-Gemcitabine Treatment Option for Patients With Metastatic Pancreatic Adenocarcinoma (mPC)*

Authors: [redacted]

BACKGROUND

OBJECTIVE

METHODS

METHODS (continued)

RESULTS

LIMITATIONS

CONCLUSION

stay (p<0.01), health insurance type (p<0.01), and hospital level (p<0.01). **Conclusions:** Compared with urban per capita disposable income in China from 2012 to 2016 (24565 RMB, 26955 RMB, 29381 RMB, 31790 RMB, 33616 RMB), the direct medical expenditures for inpatients with MM were high. And the drug expense was the main component of total medical expenses. The geography disparity of medical expenses of MM were associated with different reimbursement policy and the unbalance distribution of medical resource, which implicated that effective measures include reducing the length of hospital stay and controlling spending at tertiary hospitals could lower medical expenditure of MM patients in China.

PCN77
HEALTH SERVICES UTILIZATION AND EXPENDITURES AMONG PROSTATE CANCER PATIENTS WITH AND WITHOUT DEPRESSION IN THE UNITED STATES FROM 2010 TO 2015: A PROPENSITY SCORE-MATCHED CROSS-SECTIONAL STUDY

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Objectives: To compare the estimated utilization of health services and expenditures between prostate cancer patients with and without depression using propensity score matching (PSM). **Methods:** This was a cross-sectional study. Data were obtained from the publicly available Medical Expenditure Panel Survey (MEPS) from 2010 to 2015. We included adult patients with prostate cancer in our study while other types of cancers were excluded. We used 1:1 PSM for cohort formation. Health care utilization and expenditures analyzed included emergency room visits (ER), hospitals inpatient stay (IP), outpatient clinical visits (OP), office-based medical provider visits (OB), and prescribed medicines (RX). All costs were adjusted to 2018 U.S dollars. **Results:** A total of 136 individuals (weighted N=308,602) were identified with prostate cancer after applying PSM. There were 68 patients in each group. The total expenditure of emergency room visits was $149 million in individuals with prostate cancer and depression while around $50 million for individuals with prostate cancer that did not have a diagnosis of depression. The average expenditure of emergency room visits between prostate cancer patients with depression was $3,092.3 and $1,330.6 for patients without depression (p = 0.0382). For other health care services, there were no statistical mean differences of expenditure between prostate cancer patients with and without depression which included IP (p=0.7473), OP (p=0.6810), OB (p=0.7988), and RX (p=0.2427). Moreover, there were no significant mean differences observed in the utilization of all health care services such as ER (p=0.1337), IP (p=0.7398), OP (p=0.5596), OB (p=0.7008), and RX (p=0.1035) between both groups. **Conclusions:** The total expenditure of emergency room visits was higher in patients with documentation of depression than those without depression. Further research is warranted to understand this finding.

PCN78
COST EFFECTIVENESS OF MIDOSTAURIN IN ADDITION TO STANDARD CARE VERSUS STANDARD CARE ALONE IN FIRST LINE TREATMENT OF ACUTE MYELOD LEUKEMIA WITH FLT3 MUTATION FROM THE PERSPECTIVE OF CHILEAN HEALTH SYSTEM

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Objectives: The aim of this analysis was to estimate the cost-effectiveness of Midostaurin in addition to standard care as first line treatment for acute myeloid leukemia in patients with FLT3 mutation from the perspective of Chilean health system. **Methods:** A partitioned cohort model was adapted in order to represent the natural evolution of the disease. Estimation of resource usage and costs was performed from the perspective of public payer. Expected costs were measured in Chilean pesos (1 USD = 650 CLP) and benefits in quality adjusted life years (QALYs). Other outcomes represented were rate of response and life years. Health related quality of life was estimated from published literature. A lifetime time horizon was used and a 3% discount rate was considered for costs and outcomes. A probabilistic sensitivity analysis was performed to account for uncertainty. **Results:** The total expected costs of treating acute myeloid leukemia with Midostaurin plus standard therapy are higher than standard therapy alone (USD148,128 and USD76,909 respectively). Similarly, the expected incremental health benefit is higher in Midostaurin group (1.57 incremental QALYs). The base case scenario (current market prices for all treatments) shows an average ICER of Midostaurin in addition to standard care versus standard therapy of USD 45,470/QALY. The ICER is reduced to USD 38,904 when the base price of Midostaurin is reduced a 25%. Both ICERs are between the cost effectiveness threshold range suggested by WHO of 1 to 3 GDPs per capita. Deterministic sensitivity analysis shows a high impact of price, hazard ratio, rate of stem cell therapy and maintenance therapy duration as drivers of change of incremental cost-effectiveness ratio. **Conclusions:** Estimates of cost effectiveness ratio of Midostaurin can be considered as cost effective for Chilean health system. The assessed intervention delivers high gains in life years and quality adjusted life years in comparison with standard care.

PCN79
COST EFFECTIVENESS OF OSIMERTINIB VERSUS CHEMOTHERAPY IN SECOND LINE TREATMENT OF NON SMALL CELL LUNG CANCER WITH EPIDERMAL GROWTH FACTOR AND 790M MUTATION IN CHILEAN HEALTH SYSTEM

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Objectives: The aim of this analysis is to estimate the cost effectiveness of Osimertinib versus standard chemotherapy for patients with non-small cell lung cancer (NSCLC) with epidermal growth factor and 790m mutation who have failed to first line tirosin-kinase inhibitor treatment. **Methods:** A partitioned cohort model with 3 health states (Pre progression, progression and death) was adapted in order to represent the natural evolution of the disease. Estimates of resource usage and costs were performed from the perspective of public payer. Expected costs were measured in Chilean pesos (1 USD = 650 CLP) and benefits in quality adjusted life years (QALYs). Health related quality of life was estimated from AURA-3 trial study. A lifetime time horizon was used, and a 3% discount rate was considered for costs and outcomes. A probabilistic sensitivity analyses was performed to account for uncertainty. **Results:** The total expected costs of treating NSCLC with Osimertinib are higher than standard chemotherapy (USD122,500 and USD13,000 respectively). Similarly, the expected incremental health benefit is higher in Osimertinib group (1.07 incremental QALYs). The base case scenario (current market prices for all treatments) shows an average ICER of Osimertinib versus standard chemotherapy of USD 101,777/QALY. The ICER is reduced to USD 78,206/QALY when the base price of Osimertinib is reduced a 25%. Both ICERs are above the cost effectiveness threshold range suggested by WHO of 1 to 3 GDPs per capita (USD15,000 to USD45,000). Deterministic sensitivity analysis shows a high impact of the price of treatment as a driver for incremental cost-effectiveness ratio. **Conclusions:** Osimertinib delivers high gains in life years and quality adjusted life years in comparison with standard chemotherapy. Higher costs driven by the price of the intervention under analysis should be a matter of negotiation in order to provide financial coverage to Chilean population.

PCN80
BUDGET IMPACT IN THE USA OF LIPOSOMAL IRINOTECAN AS A POST-GEMCITABINE TREATMENT OPTION FOR PATIENTS WITH METASTATIC PANCREATIC ADENOCARCINOMA (MPC)

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Objectives: Liposomal irinotecan (nal-IRI; Onivyde), in combination with fluorouracil (5-FU)+leucovorin (LV), is the only category-1 NCCN recommendation for treating post–gemcitabine adult patients with mPC. Given expected increases in nal-IRI use based on guidelines, it may be valuable to understand fiscal implications to US health plans. This study estimates the budgetary consequences of increasing nal-IRI use for treating post–gemcitabine mPC adult patients from a US commercial payer perspective. **Methods:** A Microsoft® Excel budget impact model was developed to estimate the one-year fiscal impact for a hypothetical 1–million-member health plan. The treatment-eligible population included mPC patients receiving first-, second-, or third-line post-gemcitabine therapy. Inputs (epidemiology, dosing, direct costs [drug, administration, and monitoring]) were derived from published literature, product labels/clinical trials, Medispan PriceRx, CMS fee schedules, and a de novo real-world study of Medicare AE rates and costs (aligning to the FDA Framework for Real-World Evidence Program). Costs reflect 2018 USD. Market distributions for current and projected scenarios were provided by the manufacturer, including most common mPC treatment options and irinotecan regimens. The budget impact (total annual costs, cost per member per month [PMPM]) was calculated as the difference between current and projected markets. Sensitivity analyses examined the impact of uncertainty (±20% variation) on results. **Results:** Increased nal-IRI use (*1.4%, 21.5%, and 40.2% in first-, second-, and third-line therapy, respectively*) in year 1 would cost $0.0001 PMPM (total cost difference of $1,132). Sensitivity analyses across all parameters did not change conclusions (+/- $0.0001 PMPM variation). AE cost offsets are achieved given the lower real-world rate of AEs for nal-IRI versus the most common regimens (FOLFIRINOX and Gemcitabine+Abraxane; e.g., anemia, fatigue, neutropenia, and thrombocytopenia). **Conclusions:** Increasing access to nal-IRI, in agreement with recent NCCN guidelines for treatment of post–gemcitabine mPC, is budget neutral given the lower real-world rate of AEs compared to common alternatives.

PCN81
POLYPHARMACY IS ASSOCIATED WITH INCREASED DIRECT HEALTHCARE EXPENDITURE AMONG CANCER SURVIVORS IN THE UNITED STATES.

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Objectives: We sought to determine if polypharmacy is associated with increased healthcare expenditures among cancer survivors in the U.S. **Methods:** A cross-

REVIEW ARTICLE

MEDICAL PROGRESS

Pancreatic Cancer

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DEATHS FROM PANCREATIC DUCTAL ADENOCARCINOMA, ALSO KNOWN AS pancreatic cancer, rank fourth among cancer-related deaths in the United States. In 2008, the estimated incidence of pancreatic cancer in the United States was 37,700 cases, and an estimated 34,300 patients died from the disease.[1] Pancreatic cancer is more common in elderly persons than in younger persons, and less than 20% of patients present with localized, potentially curable tumors. The overall 5-year survival rate among patients with pancreatic cancer is <5%.[1,2]

The causes of pancreatic cancer remain unknown. Several environmental factors have been implicated, but evidence of a causative role exists only for tobacco use. The risk of pancreatic cancer in smokers is 2.5 to 3.6 times that in nonsmokers; the risk increases with greater tobacco use and longer exposure to smoke.[3] Data are limited on the possible roles of moderate intake of alcohol, intake of coffee, and use of aspirin as contributing factors. Some studies have shown an increased incidence of pancreatic cancer among patients with a history of diabetes or chronic pancreatitis, and there is also evidence, although less conclusive, that chronic cirrhosis, a high-fat, high-cholesterol diet, and previous cholecystectomy are associated with an increased incidence.[4-7] More recently, an increased risk has been observed among patients with blood type A, B, or AB as compared with blood type O.[8]

Approximately 5 to 10% of patients with pancreatic cancer have a family history of the disease.[9] In some patients, pancreatic cancer develops as part of a well-defined cancer-predisposing syndrome for which germ-line genetic alterations are known (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In addition, in some families with an increased risk of pancreatic cancer, a genetic rather than an environmental cause is suspected. The risk of pancreatic cancer is 57 times as high in families with four or more affected members as in families with no affected members.[10] The genetic bases for these associations are not known, although a subgroup of such high-risk kindred carry germ-line mutations of DNA repair genes such as *BRCA2* and the partner and localizer of *BRCA2* (*PALB2*).[11-13]

In recent years, there have been important advances in the understanding of the molecular biology of pancreatic cancer as well as in diagnosis, staging, and treatment in patients with early-stage tumors. Minimal progress has been made, however, in prevention, early diagnosis, and treatment in patients with advanced disease. This review summarizes recent progress in the understanding and management of pancreatic cancer.

THE BIOLOGY OF PANCREATIC CANCER

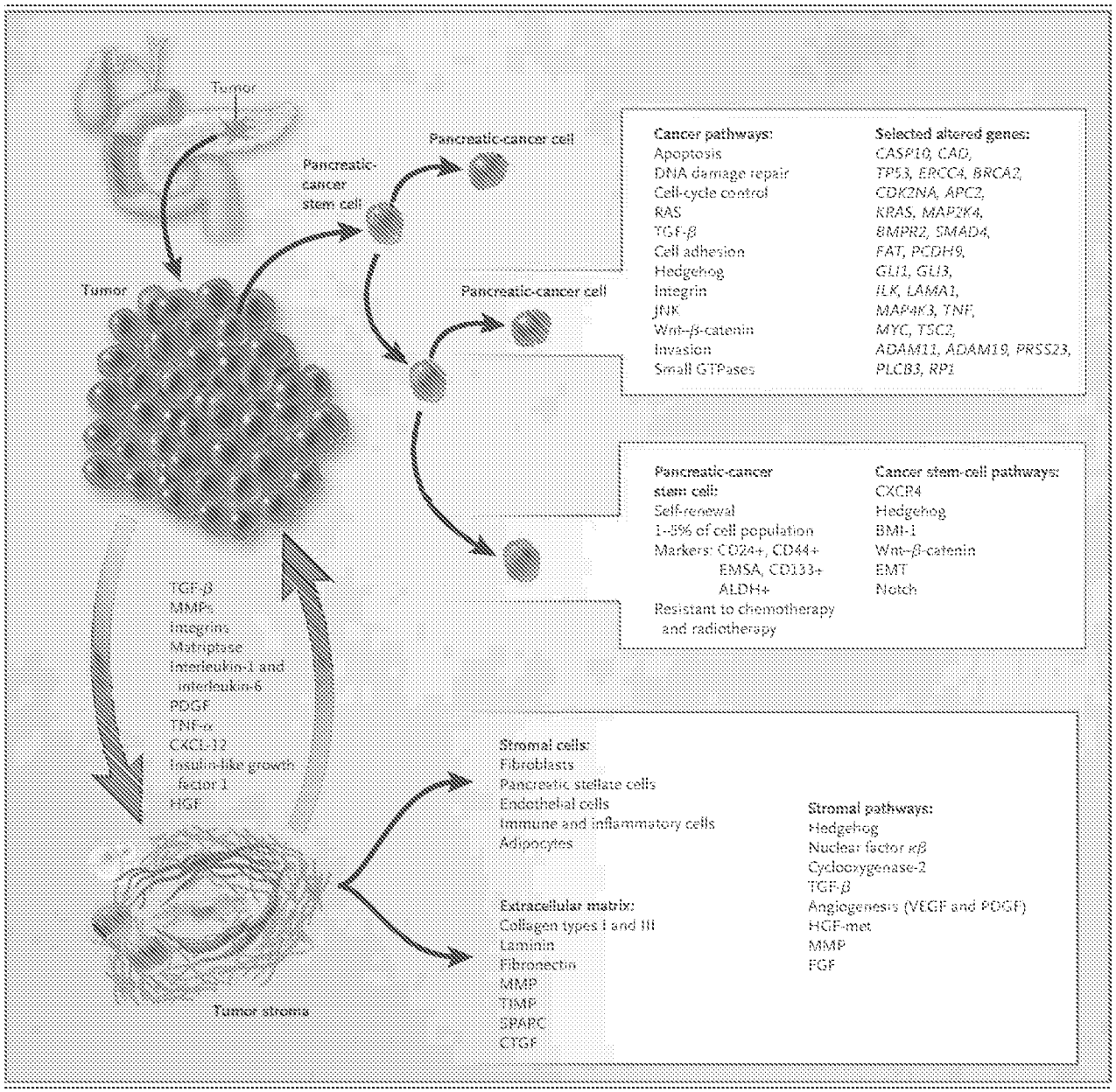
Data suggest that pancreatic cancer results from the successive accumulation of gene mutations.[14] The cancer originates in the ductal epithelium and evolves from premalignant lesions to fully invasive cancer. The lesion called pancreatic intraepithe-

lial neoplasia is the best-characterized histologic precursor of pancreatic cancer.[15] The progression from minimally dysplastic epithelium (pancreatic intraepithelial neoplasia grades 1A and 1B) to more severe dysplasia (pancreatic intraepithelial neoplasia grades 2 and 3) and finally to invasive carcinoma is paralleled by the successive accumulation of mutations that include activation of the *KRAS2* oncogene, inactivation of the tumor-suppressor gene *CDKN2A* (which encodes the inhibitor of cyclin-dependent kinase 4 [*INK4A*]), and, last, inactivation of the tumor-suppressor genes *TP53* and deleted in pancreatic cancer 4 (*DPC4*, also known as the SMAD family member 4 gene [*SMAD4*]).[16] This sequence of events in pancreatic carcinogenesis is supported by studies in genetically engineered mouse models in which targeted activation of *Kras2* with concomitant inactivation of *Trp53* or *Cdkn2A*/*Ink4A* results in the development of pancreatic cancer that is identical to the cognate human disease.[17-19] Other premalignant lesions of the pancreas, which are less well characterized, include intrapancreatic mucinous neoplasia and mucinous cystic neoplasia.[20]

Almost all patients with fully established pancreatic cancer carry one or more of four genetic defects.[21] Ninety percent of tumors have activating mutations in the *KRAS2* oncogene. Transcription of the mutant *KRAS* gene produces an abnormal Ras protein that is "locked" in its activated form, resulting in aberrant activation of proliferative and survival signaling pathways. Likewise, 95% of tumors have inactivation of the *CDKN2A* gene, with the resultant loss of the p16 protein (a regulator of the G1–S transition of the cell cycle) and a corresponding increase in cell proliferation. *TP53* is abnormal in 50 to 75% of tumors, permitting cells to bypass DNA damage control checkpoints and apoptotic signals and contributing to genomic instability. *DPC4* is lost in approximately 50% of pancreatic cancers, resulting in aberrant signaling by the transforming growth factor β (TGF-β) cell-surface receptor. A recent comprehensive genetic analysis of 24 pancreatic cancers showed that the genetic basis of pancreatic cancer is extremely complex and heterogeneous.[11] In that study, an average of 63 genetic abnormalities per tumor, mainly point mutations, were classified as likely to be relevant. These abnormalities can be organized in 12 functional cancer-relevant pathways (Fig. 1). However, not all tumors have alterations in all pathways, and the key mutations in each pathway appear to differ from one tumor to another.

Figure 1 (facing page). **Components of Pancreatic Cancer.** Pancreatic cancers are composed of several distinct elements, including pancreatic-cancer cells, pancreatic-cancer stem cells, and the tumor stroma. A recent analysis of 24 pancreatic cancers suggested that the mature pancreatic-cancer cell carries on average 63 genetic alterations per cancer; these alterations can be grouped in 12 core signaling pathways.[11] These results, if confirmed in larger studies, would indicate that pancreatic cancer is genetically very complex and heterogeneous. Thus, effective treatments will probably need to attack several targets (with combination regimens) and may require individualized therapy. A small group of cells (≤5%) appear to have cancer stem-cell features that render them capable of asymmetric division, enabling them to generate mature cells as well as cancer stem cells. These stem cells may be identified by the expression of specific membrane markers and can regenerate into full tumors on implantation in immunodeficient animals. Pancreatic-cancer stem cells are resistant to conventional treatment, but they have alterations in developmental pathways such as Notch, hedgehog, and wingless in drosophila (Wnt)–β-catenin that may result in new therapeutic targets. Pancreatic cancer is characterized by a dense, poorly vascularized stroma; this microenvironment contains a mixture of interacting cellular and noncellular elements. Autocrine and paracrine secretion of growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β) and cytokines results in continuous interaction between the stromal and cancer cells. Pancreatic stellate cells are a key cellular element in the stroma. They are characterized by the expression of desmin, glial fibrillary acidic protein, and intracellular fat droplets. On stimulation by growth factors, pancreatic stellate cells express α–smooth-muscle actin and produce abundant collagen fibers that contribute to tumor hypoxia. ALDH+ denotes aldehyde dehydrogenase, CTGF connective-tissue growth factor, CXCL-12 chemokine 12 ligand, EMSA electrophoretic mobility-shift assay, EMT epithelial-to-mesenchymal transition, FGF fibroblast growth factor, GTPase guanosine triphosphatase, HGF hepatocyte growth factor, HGF-met hepatocyte growth factor mesenchymal–epithelial transition factor, JNK jun N-terminal kinase, MMP matrix metalloproteinase, SPARC secreted protein, acidic, cysteine-rich, TIMP tissue inhibitor of MMP, TNF-α tumor necrosis factor α, and VEGF vascular endothelial growth factor.

A characteristic of pancreatic cancer is the formation of a dense stroma termed a desmoplastic reaction (Fig. 1).[22,23] The pancreatic stellate cells (also known as myofibroblasts) play a critical role in the formation and turnover of the stroma. On activation by growth factors such as TGFβ1, platelet-derived growth factor (PDGF), and fibroblast growth factor, these cells secrete



collagen and other components of the extracellular matrix; stellate cells also appear to be responsible for the poor vascularization that is characteristic of pancreatic cancer.[24,25] Furthermore, stellate cells regulate the reabsorption and turnover of the stroma, mainly through the production of matrix metalloproteinases.[26] The stroma is not just a mechanical barrier; rather, it constitutes a dynamic compartment that is critically involved in the process of tumor formation, progression, invasion, and metastasis.[22,23] Stromal cells express multiple proteins such as cyclooxygenase-2, PDGF receptor, vascular endothelial growth factor, stromal cell–derived factor, chemokines, integrins, SPARC (secreted protein, acidic, cysteine-rich), and hedgehog pathway elements, among others, which have been associated with a poor prognosis and resistance to treatment. However, these proteins may also represent new therapeutic targets.[27,28]

The role of angiogenesis in pancreatic cancer remains controversial. Although early data suggested that pancreatic cancer is angiogenesis-dependent, as are most solid tumors, treatment

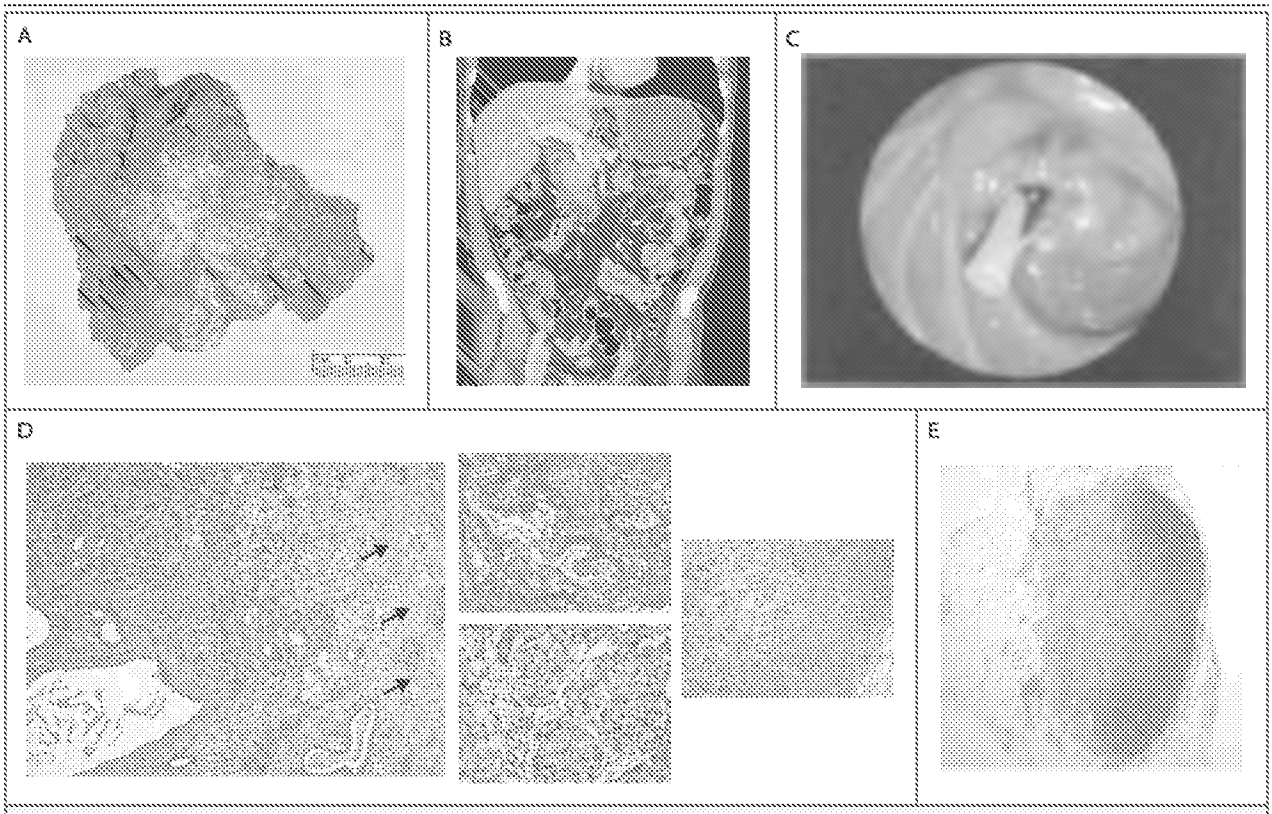


Figure 2. Pathological, Radiologic, and Histologic Features of Pancreatic Cancer.

Panel A shows a macroscopical view of a resected tumor affecting the head of the pancreas. Panel B shows a contrast-enhanced computed tomographic scan from a patient with a T3 pancreatic mass. The tumor invades the splenic superior mesenteric vein–portal vein axis. Panel C shows endoscopic retrograde cholangiopancreatographic imaging of a plastic stent through the ampulla of Vater in a patient with a tumor in the head of the pancreas. Panel D (hematoxylin and eosin) shows microscopical adenocarcinoma of the pancreas with abundant tumor stroma (black arrows). Smaller images show the tumor stroma at low, medium, and high magnification. Panel E shows a peripancreatic lymph node involved with metastatic adenocarcinoma (hematoxylin and eosin, high magnification). (Courtesy of Emilio de Vicente, M.D., and Elena García, M.D.)

with angiogenesis inhibitors has failed in patients with pancreatic cancer. A recent study in a mouse model showed that targeting the stromal hedgehog pathway increases tumor vascularization, resulting in increased delivery of chemotherapeutic agents to pancreatic tumors and greater efficacy.[29]

In addition, a subgroup of cancer cells with cancer stem-cell properties such as tumor initiation have been identified within the tumor.[30,31] These cells, which compose just 1 to 5% of the tumor, are capable of unlimited self-renewal, and through asymmetric division, they give rise to more-differentiated cells (Fig. 1). Pancreatic-cancer stem cells are resistant to chemotherapy and radiation therapy, which may explain why these treatments do not cure the disease and why there is much interest in targeting these specific cells.[31,32]

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The presenting symptoms of pancreatic cancer depend on the location of the tumor within the gland, as well as on the stage of the disease. The majority of tumors develop in the head of the pancreas and cause obstructive cholestasis (Fig. 2A). Vague abdominal discomfort and nausea are also common. More rarely, a pancreatic tumor may also cause duodenal obstruction or gastrointestinal bleeding. Pancreatic cancer often causes dull, deep upper abdominal pain that broadly localizes to the tumor area.

Obstruction of the pancreatic duct may lead to pancreatitis. Patients with pancreatic cancer often have dysglycemia. Indeed, pancreatic cancer should be considered in the differential diagnoses of acute pancreatitis and newly diagnosed diabetes.

At presentation, most patients also have systemic manifestations of the disease such as asthenia, anorexia, and weight loss. Other, less common manifestations include deep and superficial venous thrombosis, panniculitis, liver-function abnormalities, gastric-outlet obstruction, increased abdominal girth, and depression.

Physical examination may reveal jaundice, temporal wasting, peripheral lymphadenopathy, hepatomegaly, and ascites. Results of routine blood tests are generally nonspecific and may include mild abnormalities in liver-function tests, hyperglycemia, and anemia.[2,21]

Evaluation of a patient in whom pancreatic cancer is suspected should focus on diagnosis and staging of the disease, assessment of resectability, and palliation of symptoms. Multiphase, multidetector helical computed tomography (CT) with intravenous administration of contrast material is the imaging procedure of choice for the initial evaluation.[33] This technique allows visualization of the primary tumor in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein and also in relation to distant organs (Fig. 2B). In general, contrast-enhanced CT is sufficient to confirm a suspected pancreatic mass and to frame an initial management plan. Overall, contrast-enhanced CT predicts surgical resectability with 80 to 90% accuracy.[34] Positron-emission tomography can be useful if the CT findings are equivocal.

Some patients require additional diagnostic studies. Endoscopic ultrasonography is useful in patients in whom pancreatic cancer is suspected although there is no visible mass identifiable on CT. It is the preferred method of obtaining tissue for diagnostic purposes. Although a tissue diagnosis is not needed in patients who are scheduled for surgery, it is required before the initiation of treatment with chemotherapy or radiation therapy. Endoscopic retrograde cholangiopancreatography (ERCP) shows the pancreatic and bile-duct anatomy and can be used to guide ductal brushing and lavage, which provides tissue for diagnosis. The ERCP technique is especially useful in patients with jaundice in whom an endoscopic stent is required to relieve obstruction (Fig. 2C).[35] In patients who have large tumors, especially in the body and tail of the pancreas, as well as other indications of advanced disease such as weight loss, an elevated level of carbohydrate antigen 19-9 (CA 19-9), ascites, or equivocal CT findings, a staging laparoscopy can accurately determine metastatic and vascular involvement.[36]

There are many potential serum biomarkers for diagnosis, stratification of a prognosis, and monitoring of therapy.[37] CA 19-9 is the only biomarker with demonstrated clinical usefulness and is useful for therapeutic monitoring and early detection of recurrent disease after treatment in patients with known pancreatic cancer.[37-41] However, CA 19-9 has important limitations. It is not a specific biomarker for pancreatic cancer; the level of CA 19-9 may be elevated in other conditions such as cholestasis. In addition, patients who are negative for Lewis antigen a or b (approximately 10% of patients with pancreatic cancer) are unable to synthesize CA 19-9 and have undetectable levels, even in advanced stages of the disease. Although measurement of serum CA 19-9 levels is useful in patients with known pancreatic cancer, the use of this biomarker as a screening tool has had disappointing results.

Universal primary screening for pancreatic cancer is currently not recommended, given the tools available and their performance.[42] Single-institution studies focusing on surveillance of patients at high risk, such as those with a strong family history or cancer-predisposition syndromes, have used serial endoscopic ultrasonography and CT. Pancreatic lesions associated with benign intrapancreatic mucinous neoplasia or pancreatic intraepithelial neoplasia have been detected in approximately 10% of these high-risk patients. However, the cost-effectiveness of this approach is unclear, and its use is investigational.[43]

STAGING OF PANCREATIC CANCER

Pancreatic cancer is staged according to the most recent edition of the American Joint Committee on Cancer tumor–node–metastasis classification, which is based on assessment of resectability by means of helical CT.[44] T1, T2, and T3 tumors are potentially resectable, whereas T4 tumors, which involve the superior mesenteric artery or celiac axis, are unresectable (Table 1). Tumors involving the superior mesenteric veins, portal veins, or

Table 1. Staging of Pancreatic Cancer.*

Stage	Tumor Grade	Nodal Status	Distant Metastases	Median Survival†	Characteristics
				mo	
IA	T1	N0	M0	24.1	Tumor limited to the pancreas, ≤2 cm in longest dimension
IB	T2	N0	M0	20.6	Tumor limited to the pancreas, >2 cm in longest dimension
IIA	T3	N0	M0	15.4	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
IIB	T1, T2, or T3	N1	M0	12.7	Regional lymph-node metastasis
III	T4	N0 or N1	M0	10.6	Tumor involves the celiac axis or the superior mesenteric artery (unresectable disease)
IV	T1, T2, T3, or T4	N0 or N1	M1	4.5	Distant metastasis

* N denotes regional lymph nodes, M distant metastases, and T primary tumor.
† Data are from Bilimoria et al.[45]

splenic veins are classified as T3, since these veins can be resected and reconstructed, provided that they are patent.

MANAGEMENT OF EARLY DISEASE

Patients with pancreatic cancer are best cared for by multidisciplinary teams that include surgeons, medical and radiation oncologists, radiologists, gastroenterologists, nutritionists, and pain specialists, among others.[46,47] For patients with resectable disease, surgery remains the treatment of choice.[48] Depending on the location of the tumor, the operative procedures may involve cephalic pancreatoduodenectomy (the Whipple procedure), distal pancreatectomy, or total pancreatectomy. A minimum of 12 to 15 lymph nodes should be resected, and every attempt should be made to obtain a tumor-free margin. Data from several randomized clinical trials indicate that a more extensive resection does not improve survival but increases postoperative morbidity. Recent studies show that the results of vein resection and vascular reconstruction in patients with limited involvement of the superior mesenteric vein and portal vein are similar to the results in patients without vein involvement.[49] Poor prognostic factors include lymph-node metastases, a high tumor grade, a large tumor, high levels of CA 19-9, persistently elevated postoperative levels of CA 19-9, and positive margins of resection.[38,40,50,51]

Up to 70% of patients with pancreatic cancer present with biliary obstruction, which can be relieved by percutaneous or endoscopic stent placement. Decompression is appropriate for patients in whom surgery is delayed, such as patients who are treated with neoadjuvant therapy before resection or who are referred to other centers for treatment.[52] Patients with symptoms of cholangitis require decompression as well as antibiotic treatment before surgery.

Even if the tumor is fully resected, the outcome in patients with early pancreatic cancer is disappointing. The results of three large randomized clinical trials, summarized in Table 2 in the Supplementary Appendix, have established the role of postoperative treatment in patients with resected pancreatic cancer.[53-55] The results of the European Study Group for Pancreatic Cancer Trial 1 and Charité Onkologie 1 trial show that postoperative administration of chemotherapy with either fluorouracil and leucovorin or gemcitabine, a nucleotide analogue commonly used to treat advanced pancreatic cancer, improves progression-free and overall survival. In addition, the Radiation Therapy Oncology Group trial 97-04 showed that the combination of gemcitabine with fluorouracil administered as a continuous infusion and radiation therapy resulted in a trend toward increased overall survival, although the increase was not significant, among patients with tumors in the head of the pancreas. These results are similar to those of large single-institution series that incorporated radiation therapy.[56]

Notwithstanding differences in patient populations and therapies, the outcome in patients treated in these trials was similar, with a median survival of 20 to 22 months. Large tumor size, high differentiation grade, and involvement of the lymph nodes are risk factors for recurrent disease. The effect of positive resection margins, however,

is more controversial.[57] Thus, gemcitabine alone or gemcitabine in combination with fluorouracil-based chemoradiation can be considered the standard of care in this setting. The unequivocal demonstration that postoperative treatment improves the outcome in these patients is one of the most important advances that has been made in the management of pancreatic cancer.

An emerging strategy in patients with resectable pancreatic cancer is the use of preoperative (neoadjuvant) treatment. Nonrandomized, phase 2 studies suggest that this approach is at least as effective as postoperative treatment and may decrease the rate of local failures and positive resection margins after surgery.[58] These findings are particularly relevant for patients who have so-called borderline-resectable tumors with limited vascular involvement; in these patients, preoperative treatment may result in tumor-free resection margins.[59]

MANAGEMENT OF LOCALLY ADVANCED AND SYSTEMICALLY ADVANCED DISEASE

Approximately 30% of patients with pancreatic cancer receive a diagnosis of advanced locoregional disease, and an additional 30% of patients will have local recurrence of tumors after treatment for early disease. The treatment of patients with advanced locoregional disease is palliative; with current treatments, the median overall survival ranges only from 9 to 10 months. Management options range from systemic chemotherapy alone to combined forms of treatment with chemoradiation therapy and chemotherapy. A series of randomized trials conducted over the past two decades established that chemoradiation therapy was superior to radiation therapy alone in these patients.[60,61] The results of more recent studies, summarized in Table 3 in the Supplementary Appendix, suggest that chemotherapy is indeed the critical component in the treatment approach and that combined treatment with chemotherapy and chemoradiation therapy is an effective, though more toxic, approach. However, randomized clinical trials of such combined treatments have had low enrollment, precluding a firm conclusion.[60,62,63]

The majority of patients with pancreatic cancer either present with metastatic disease or metastatic disease develops in them, mainly in the liver and peritoneal cavity. The treatment of patients with advanced disease remains palliative, although these patients should be offered the opportunity to participate in clinical trials evaluating new treatments when available. A meta-analysis of published findings from clinical trials showed an improvement in survival among patients who received chemotherapy; these findings suggest that active treatment is beneficial.[64] For more than a decade, gemcitabine has been the treatment of choice on the basis of the results of the randomized trial of gemcitabine versus fluorouracil, summarized in Table 3 in the Supplementary Appendix.[64] Multiple new agents with diverse mechanisms of action in combination with gemcitabine have been tested in randomized clinical trials, with no improvement in outcome.[2,65,66]

The only agent that, in combination with gemcitabine, has shown a small, but statistically significant improvement in survival among patients with advanced pancreatic cancer is erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR) (Table 3 in the Supplementary Appendix).[67] As shown in other studies of agents targeting the EGFR, patients in whom drug-induced rashes developed had a better outcome. However, the high frequency of *KRAS2* mutations in pancreatic cancer probably limits the benefits of an EGFR inhibitor; this limitation is similar to that observed in other cancers such as colon cancer. As compared with erlotinib alone, the combination of gemcitabine and erlotinib has more toxicity, particularly gastrointestinal symptoms. Together with the rather modest improvement in survival, the toxicity of this combination has limited its wide acceptance as the standard of care. A recent meta-analysis of randomized trials showed that patients with minimal disease-related symptoms and otherwise good health may benefit from combination chemotherapy with gemcitabine and either a platinum agent or a fluoropyrimidine.[60,68] Thus, at the present time, the accepted treatment approach for patients with advanced disease is either gemcitabine given alone or gemcitabine combined with a platinum agent, erlotinib, or a fluoropyrimidine.

Once the disease progresses, there is no accepted standard of care; most patients at that point are too sick to receive any other treatment. In a highly selected group of patients with minimally symptomatic disease, second-line chemotherapy has modest efficacy, and it can be offered to patients with good functional reserve (i.e., pa-

Table 2. **Commonly Used Treatment Regimens in Pancreatic Cancer.***

Drug	Mechanism of Action	Dose	Serious Toxic Effects Occurring in >10% of Patients	Reference
First-line therapy				
Gemcitabine (2′,2′-dFdC)	Nucleoside analogue metabolized to triphosphate moiety (dFdC triphosphate) by deoxycytidine kinase is incorporated into the nascent DNA and blocks DNA replication	1000 mg/m^2 given as 30-min IV infusion either weekly for 7 wk, followed by 1 wk rest, then weekly for 3 of every 4 wk, or weekly for 3 of every 4 wk	Neutropenia (26%), elevated alkaline phosphatase level (16%), thrombocytopenia (10%), elevated AST level (10%)	Burris et al.[64]
Fixed-dose infusion of gemcitabine	Prolonged exposure to gemcitabine increases accumulation of dFdC triphosphate	1500 mg/m^2 given as 10 mg/m^2/min IV infusion weekly for 3 of every 4 wk	Neutropenia (49%), thrombocytopenia (37%), anemia (23%), nausea and vomiting (21%)	Tempero et al.[71]
Gemcitabine plus oxaliplatin	Oxaliplatin is a diaminocyclohexane platinum analogue that binds and alkylates DNA	Gemcitabine: 1000 mg/m^2 given as 10 mg/m^2/min IV infusion on day 1 every other wk; plus oxaliplatin: 100 mg/m^2 given as 120-min IV infusion on day 2, every other wk	Neutropenia (20%), peripheral sensory neuropathy (19%), thrombocytopenia (14%), nausea (10%)	Louvet et al.[72]
Gemcitabine plus cisplatin	Cisplatin is a DNA-binding alkylating agent	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion every other wk; cisplatin: 50 mg/m^2 given as IV infusion every other wk	Nausea and vomiting (22%), anemia (13%), pain (12%), leukopenia (10%)	Heinemann et al.[73]
Gemcitabine plus capecitabine	Capecitabine is converted in the tumor to fluorouracil and inhibits thymidylate synthetase	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion weekly for 3 of every 4 wk; plus capecitabine: 1300 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses	Neutropenia (23%)	Bernhard et al.[74]
Gemcitabine plus erlotinib	Erlotinib is a small-molecule inhibitor of the epidermal growth factor receptor	Gemcitabine: 1000 mg/m^2 given as 30-min IV infusion, either weekly for 7 wk followed by 1 wk rest, then weekly for 3 of every 4 wk, or weekly for 3 of every 4 wk; plus erlotinib: 100 mg/day orally daily	Neutropenia (24%), infection (17%), fatigue (15%), elevated AST level (11%), thrombocytopenia (10%)	Moore et al.[67]

Second-line therapy				
Modified FOLFOX (combination regimen including oxaliplatin, fluorouracil, and leucovorin)	Fluorouracil is an inhibitor of thymidilate synthetase, and leucovorin potentiates the inhibition of thymidilate synthetase by fluorouracil	Oxaliplatin: 85 mg/m^2 given as 120-min IV infusion every other wk; leucovorin: 400 mg/m^2 on day 1, every other wk; and fluorouracil: 2000 mg/m^2 given as 46-hr infusion every other wk	Neutropenia (20%), asthenia (13%), vomiting (10%)	Li and Saif[73]
Modified FOLFIRI.3 (combination regimen of irinotecan with fluorouracil and leucovorin)	Fluorouracil is an inhibitor of thymidilate synthetase, and irinotecan is a topoisomerase I inhibitor; leucovorin potentiates the inhibition of thymidilate synthetase by fluorouracil	Irinotecan: 70 mg/m^2 given as 60-min IV infusion on day 1; leucovorin: 400 mg/m^2 given as given as 120-min IV infusion on day 1; and fluorouracil: 2000 mg/m^2 given as 46-hr IV infusion on day 1; and irinotecan: 70 mg/mg^2 given as 60-min IV infusion at the end of the infusion of fluorouracil, every 2 wk	Neutropenia (22%), vomiting (10%)	Li and Saif[73]
Oxaliplatin plus capecitabine	Oxaliplatin is a diaminocyclohexane platinum analogue that binds and alkylates DNA; capecitabine is converted in the tumor to fluorouracil and inhibits thymidilate synthetase	Oxaliplatin: 130 mg/m^2 given as 120-min IV infusion every 3 wk; and capecitabine: 2000 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses	Oxaliplatin: fatigue (13%), diarrhea (5%), vomiting (3%); capecitabine: hand–foot syndrome (3%), abdominal pain (3%)	Xiong et al.[69]
Capecitabine plus erlotinib	Capecitabine is converted in the tumor to fluorouracil and inhibits thymidilate synthetase; erlotinib is a small-molecular inhibitor of the epidermal growth factor receptor	Capecitabine: 2000 mg/m^2 daily, orally for 14 days every 3–4 wk, divided in two daily doses; and erlotinib: 150 mg orally daily	Capecitabine: diarrhea (17%), rash (13%), hand–foot syndrome (13%), mucositis (10%); erlotinib: fatigue (3%), elevated bilirubin level (3%), elevated alkaline phosphatase level (3%)	Kulke et al.[70]

* AST denotes aspartate aminotransferase; dFdC difluorodeoxycytidine; FOLFIRI.3 regimen of fluorouracil, leucovorin, and irinotecan; FOLFOX regimen of folinic acid, fluorouracil, and oxaliplatin; and IV intravenous.

Table 3. Selected Strategic Targets in Pancreatic Cancer.*

Target	Agent	Drug Class	Mechanism of Action	Trial Phase	Reference
SPARC	Nanoparticle albumin-bound paclitaxel	Cytotoxic agent	SPARC, expressed in cancer cells and stroma in the pancreas, binds nanoparticle albumin-bound paclitaxel, increasing local drug delivery	3	Li and Saif[75]
IGF-1R	MK-0646, AMG 479, R1507	Monoclonal antibody	Inhibits ligand binding activation of the IGF-1R and cell proliferation	3	Hewish et al.[78]
Death receptor	AMG 655, CS1008	Monoclonal antibody	Agonist antibodies to membrane death receptors induce apoptosis	2	Li and Saif,[75] Derosier et al.[79]
Mucin-1	90Y-hPAM4	Radioimmunoconjugate	Targets mucin-1 expressed in pancreatic-cancer cells and delivers radiation load	1–2	Gold et al.[80]
Hedgehog pathway	GDC-0449, IPI-926	Small-molecule inhibitor	Inhibits smoothened receptor, resulting in inhibition of cell proliferation; targets cancer stroma and cancer stem cells in the pancreas	1	Olive et al.,[76] Jimeno et al.[32]
c-kit, PDGFR, FGFR	Masitinib	Small-molecule inhibitor	Multikinase inhibitor targets c-kit, PDGFR, and FGFR3 and affects the FAK pathway; masitinib was shown to enhance the antiproliferative effects of gemcitabine in preclinical studies	3	Li and Saif[75]
MEK	AZD6244	Small-molecule inhibitor	Targets and inhibits MEK, decreasing cell proliferation	2	Chung et al.[81]
Src	AZD0530, dasatinib	Small-molecule inhibitor	Targets and inhibits Src kinase, resulting in inhibition of cell proliferation and invasion	2	Rajeshkumar et al.[77]
RAS	Sarilasib	Small-molecule inhibitor	Dislodges all forms of RAS from the plasma membrane, inhibiting RAS signaling	2	Hakimi et al.[82]
PSCA	AGS-1C4D4	Monoclonal antibody	Binds membrane PSCA; specific mechanisms of cell killing undetermined	2	Wente et al.[83]
Mesothelin	MORAb-009	Monoclonal antibody	Binds membrane mesothelin; specific mechanisms of cell killing undetermined	2	Hassan et al.[84]
TNF-α	TNFerade	Gene therapy	Adenoviral gene therapy increases intratumoral concentration of TNF-α	3	Murugesan et al.[85]

* The abbreviation c-kit denotes stem-cell factor receptor, FAK focal adhesion kinase, FGFR fibroblast growth factor receptor, IGF-1R type I insulin-like growth factor receptor, MEK mitogen-activated protein kinase–extracellular-signal–regulated kinase, PDGFR platelet-derived growth factor, PSCA prostate stem-cell antigen, SPARC secreted protein, acidic, cysteine-rich, and TNF-α tumor necrosis factor α.

tients who are ambulatory and minimally symptomatic).[69,70] Table 2 lists commonly used first-line and second-line therapeutic regimens.

FUTURE DIRECTIONS

There is much room for improvement in all aspects of treatment for pancreatic cancer. Screening of high-risk persons by means of either innovative imaging methods or measurements of serum biomarkers for early diagnosis is critical.[42,49,76] A better understanding of the biology of pancreatic cancer is opening new avenues for treatment, and an increasing number of new targeted agents are in clinical development (Table 3). These agents include small-molecule inhibitors of oncogenes and signaling pathways such as RAS, Src, and MEK, monoclonal antibodies targeting cell-membrane proteins such as mesothelin and the so-called death receptors, and new nanotechnology and adenoviral agents. The recognition that the tumor microenvironment and cancer stem cells are critical components of pancreatic cancer has led to the development of agents, such as the hedgehog inhibitors, that target these components.[23,29,31,32] The availability of preclinical models that recapitulate the complexity of this disease will probably help in establishing priorities and strategies for the development of new treatments.[77,86] The complexity of the genome of pancreatic cancer indicates that it is a heterogeneous cancer and that methods to individualize therapy will be required.[11,87]

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Comparing total costs of care for Medicare fee-for-service patients with pancreatic cancer, by chemotherapy regimen

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BACKGROUND

- It was predicted that pancreatic cancer would be the third leading cause of cancer-related death in the USA in 2019.[1]
  - Despite accounting for only 3.2% of new cancer diagnoses in 2019, pancreatic cancer was the cause of an estimated 45,750 deaths.[1]
- More than half (approximately 53%) of patients in the USA with pancreatic cancer have metastatic disease at the time of diagnosis.[2]
- In addition to the morbidity and mortality burden associated with pancreatic cancer, the costs of care are high and increasing.[3]

OBJECTIVE

- The aim of this study was to evaluate the total cost of care associated with three licensed treatment regimens for pancreatic cancer using Medicare fee-for-service (FFS) claims data.

METHODS

Data sources

- Data were extracted from the following two Medicare claims data sets covering 2014–2016, which included diagnosis, procedure and diagnosis-related group codes, site-of-service information and beneficiary information (e.g. age, eligibility status and health maintenance organization [Medicare Advantage] enrollment):
  - 100% limited data set (LDS): all Medicare (paid) FFS Part A and Part B claims, except those for professional services and durable medical equipment (DME) claims, for 45 million beneficiaries.
  - Medicare 5% LDS: all Medicare paid FFS claims, including those for professional services and DME claims, for a random 5% sample of beneficiaries.
- Oncology Care Model documentation:
  - contained initiating cancer therapies and codes, and performance and baseline-period lists
  - was used as a comprehensive reference of all chemotherapies and to identify eligible beneficiaries.

Treatment regimens

- Total care costs were evaluated for the following three drugs or regimens for pancreatic cancer, which have been approved by the US Food and Drug Administration and are National Cancer Care Network Category 1 regimens:
  - Liposomal-irinotecan-based therapy.
  - Gemcitabine + nab-paclitaxel (gem/nab).
  - Folinic acid + 5-fluorouracil + irinotecan + oxaliplatin (FOLFIRINOX).

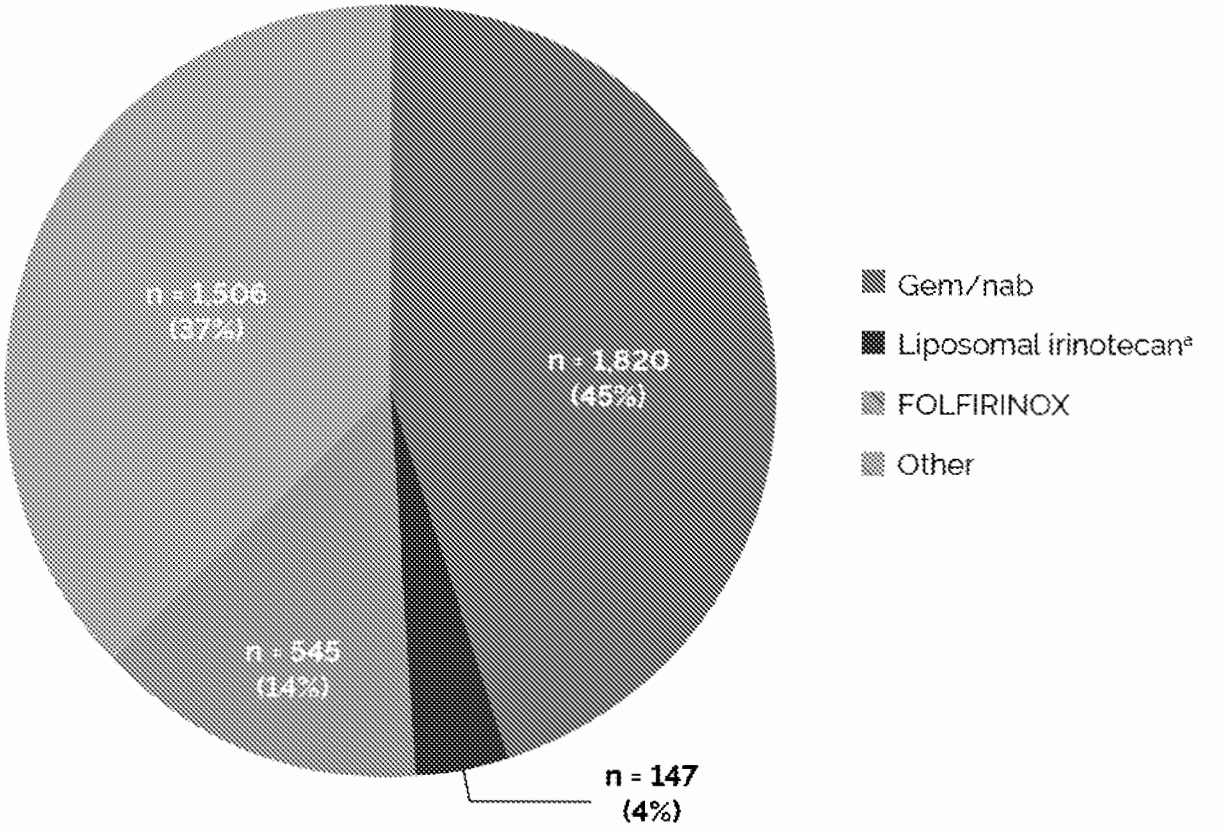
Analysis

- Cancer type was identified by the diagnostic codes from the International Classification of Diseases and Related Health Problems, 9th and 10th revisions, Clinical Modification, with pancreatic cancer being assigned if it was the most frequently coded cancer type during the episode.
  - If equal numbers of claims were coded for pancreatic and other cancers, a logic algorithm was applied based on the most recently coded diagnosis and cancer type eligible for reconciliation.
- Cancer care costs were calculated for pancreatic cancer episodes, defined as the 6-month period immediately following an index date at which a chemotherapy claim for pancreatic cancer occurred.
- Eligible episodes occurred during 2016 and required patients to be enrolled in the Medicare FFS database for at least 6 months before, and 3 months after, the index date or until the date of death (i.e. the earlier of the two).
- Cost calculations
  - Mean episode costs were calculated from claim paid amounts.
  - For each treatment regimen, means were calculated for total episode costs, which comprised: Part B chemotherapy and other Part B costs; DME; inpatient and outpatient costs; emergency department and observation costs; hospice, skilled nursing facility or home health costs; professional costs; and radiation costs.
    - DME and other Part B spending were evaluated for episodes identified in the 5% LDS and extrapolated to provide DME and other Part B cost estimates for episodes identified in the 100% LDS.

RESULTS

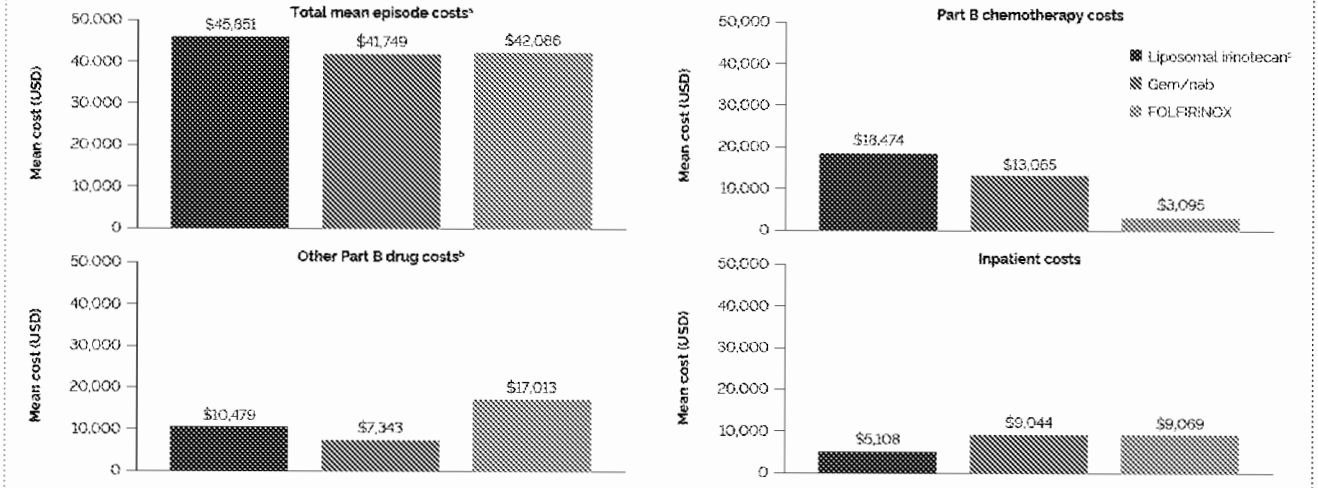
- In total, 110,618 cancer episodes were identified in 2016, of which 4,018 (4%) were for pancreatic cancer and eligible for inclusion.
  - The mean age of patients receiving treatment for pancreatic cancer was 71.3 years.
- The most commonly prescribed pancreatic cancer regimen of interest was gem/nab, which was used in 45% of episodes (n = 1,820), followed by FOLFIRINOX in 14% (n = 545) and liposomal-irinotecan-based therapy in 4% (n = 147) (Figure 1).
- Total mean episode costs were: US$45,851 for liposomal-irinotecan-based therapy; US$41,749 for gem/nab; and US$42,086 for FOLFIRINOX (Figure 2).
  - The main cost drivers across all treatment regimens were mean costs for: Part B chemotherapy; other Part B drugs; and inpatient services (Figure 2).

Figure 1. Distribution of pancreatic cancer episodes (N = 4,018) by treatment regimen



[a]Liposomal-irinotecan-based therapy.
Gem/nab, gemcitabine + nab-paclitaxel; FOLFIRINOX, folinic acid + 5-fluorouracil + irinotecan + oxaliptatin.

Figure 2. Mean costs of care for pancreatic cancer episodes (N = 4,018) by treatment regimen and cost type



[a]Includes DME and other Part B drug costs based on episodes in 5% LDS and extrapolated to provide estimates for eligible 100% LDS episodes. [b]Based on episodes in 5% LDS and extrapolated to provide estimates for eligible 100% LDS episodes. [c]Liposomal-irinotecan-based therapy.
DME, durable medical equipment; FOLFIRINOX, folinic acid + 5-fluorouracil + irinotecan + oxaliptatin; gem/nab, gemcitabine + nab-paclitaxel; LDS, limited data set; USD, US dollars.

LIMITATIONS

· These findings are specific to Medicare FFS episodes occurring in 2016. Analyses of different populations and of other time periods may yield different results.

· Given that this analysis used claims data, rather than electronic health records, it was not possible to control for potential confounders or relevant clinical covariates (e.g. line of therapy).

Conclusions

· In this analysis of 4,018 pancreatic cancer episodes in a Medicare FFS population:
  - total episode costs were similar for liposomal-irinotecan-based therapy, gem/nab and FOLFIRINOX, but the relative contribution of the different cost drivers varied
  - episodes with liposomal-irinotecan-based therapy had the largest Part B chemotherapy costs and the lowest inpatient service costs compared with gem/nab and FOLFIRINOX
  - inpatient service costs were similar for gem/nab and FOLFIRINOX episodes
  - episodes with FOLFIRINOX had the highest other Part B drug costs compared with liposomal-irinotecan-based therapy and gem/nab.

· The variation in drivers of total care costs observed between regimens highlights the importance of taking all cost drivers into account when conducting cost-effectiveness analyses.

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Conflicts of interest

JH and GD are employees of Milliman, Inc., and received consultation fees from Ipsen Biopharmaceuticals, Inc.

PC is an employee of Ipsen Biopharmaceuticals, Inc., and holds stock or stock options.

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Comparing total costs of care for Medicare fee-for-service patients with pancreatic cancer, by chemotherapy regimen
BACKGROUND
OBJECTIVE
METHODS
RESULTS
CONCLUSIONS
LIMITATIONS
Total mean episode costs
Other Part B drug costs
Part B chemotherapy costs
Inpatient costs
% Generic
% POEM/NOS
% Other

Comparing Total Costs of Care for Medicare Fee-For-Service (FFS) Patients with Metastatic Pancreatic Cancer by Chemotherapy Regimen

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OBJECTIVE

The aim of this study is to evaluate the total cost of care for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer (m-PANC) treated with the following FDA-approved/NCCN® Category 1 therapies: gemcitabine/nab-paclitaxel, FOLFIRINOX, and 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.

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,
  - Lack of six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment.

Total Costs by Any Line of Therapy (LOT)

- Total costs of care 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.

- Next LOT began the day after a beneficiary switched to a new regimen.
- End of most recent LOT was defined as the earlier of:
  - 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.

Cost Analysis

- Average total costs of care were evaluated for the following three drugs or regimens for pancreatic cancer, which have been approved by the US Food and Drug Administration and are National Cancer Care Network Category 1 drugs or regimens:
  - Liposomal irinotecan + 5FU (see limitations)
  - Gemcitabine + nab-paclitaxel
  - Folinic acid + 5-fluorouracil + irinotecan + oxaliplatin (FOLFIRINOX)

Average total costs of care reflect claim paid amounts (excluding patient cost sharing) for any line of therapy for each treatment regimen. Costs of care were calculated as the sum of Part B chemotherapy, Part B growth factor, and inpatient (intensive care unit –ICU-, radiotherapy, and surgery) costs.

Figures 1-3 show regimen frequencies, average total cost of care and cost components by m-PANC treatment regimen

Figure 1. Frequency of m-PANC Treatment Regimens Across All LOTs

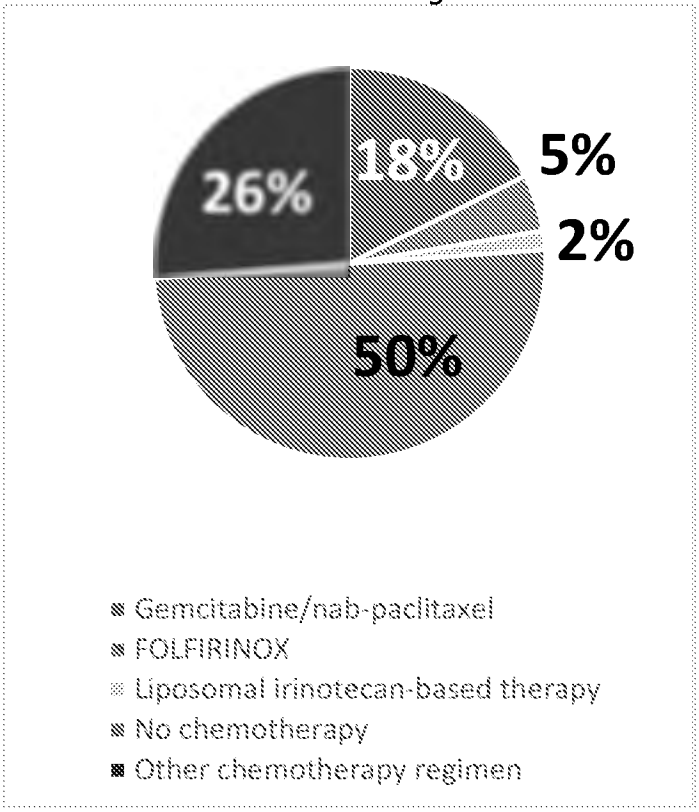


Figure 2. Average Total Costs of Care by m-PANC Treatment

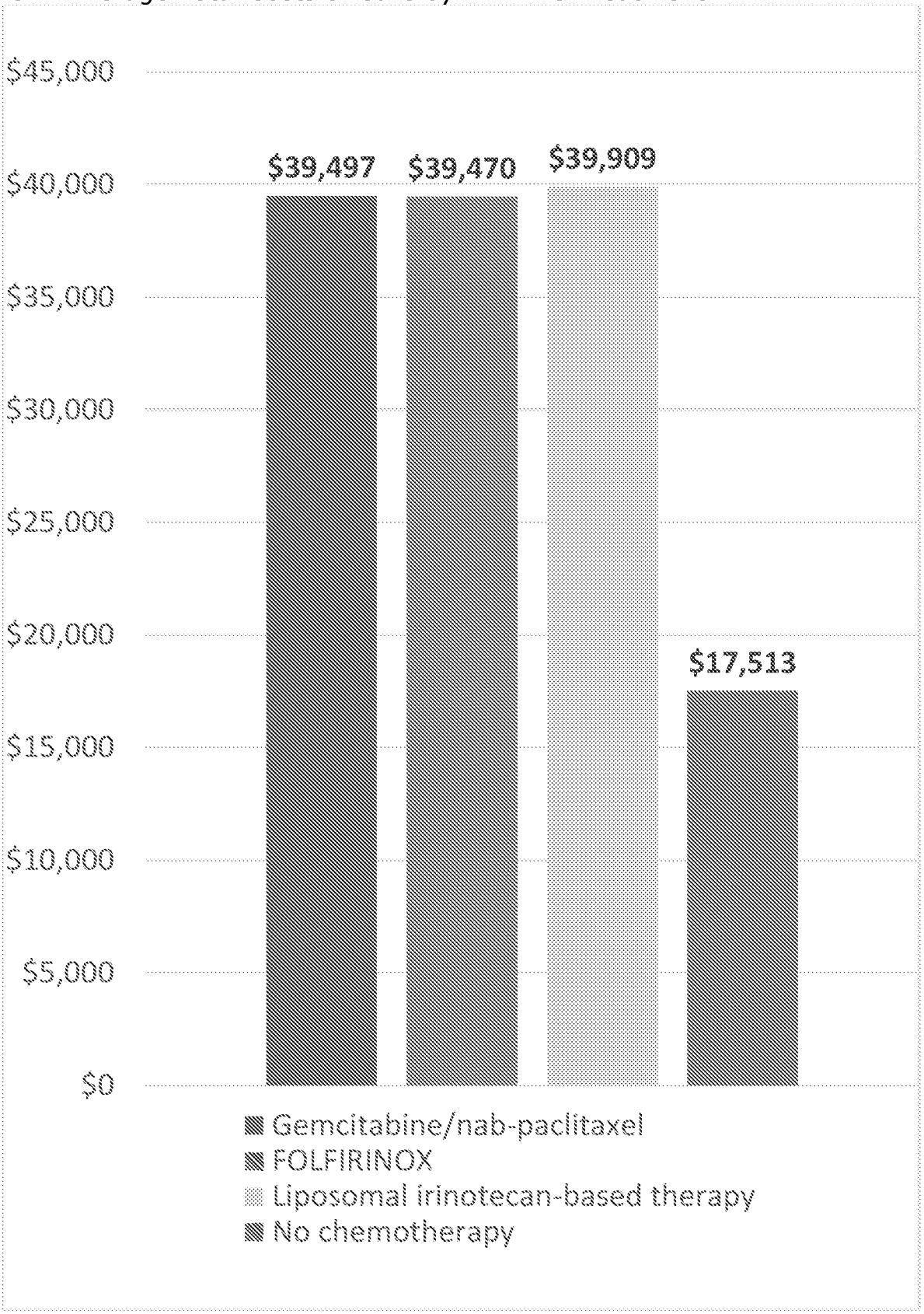
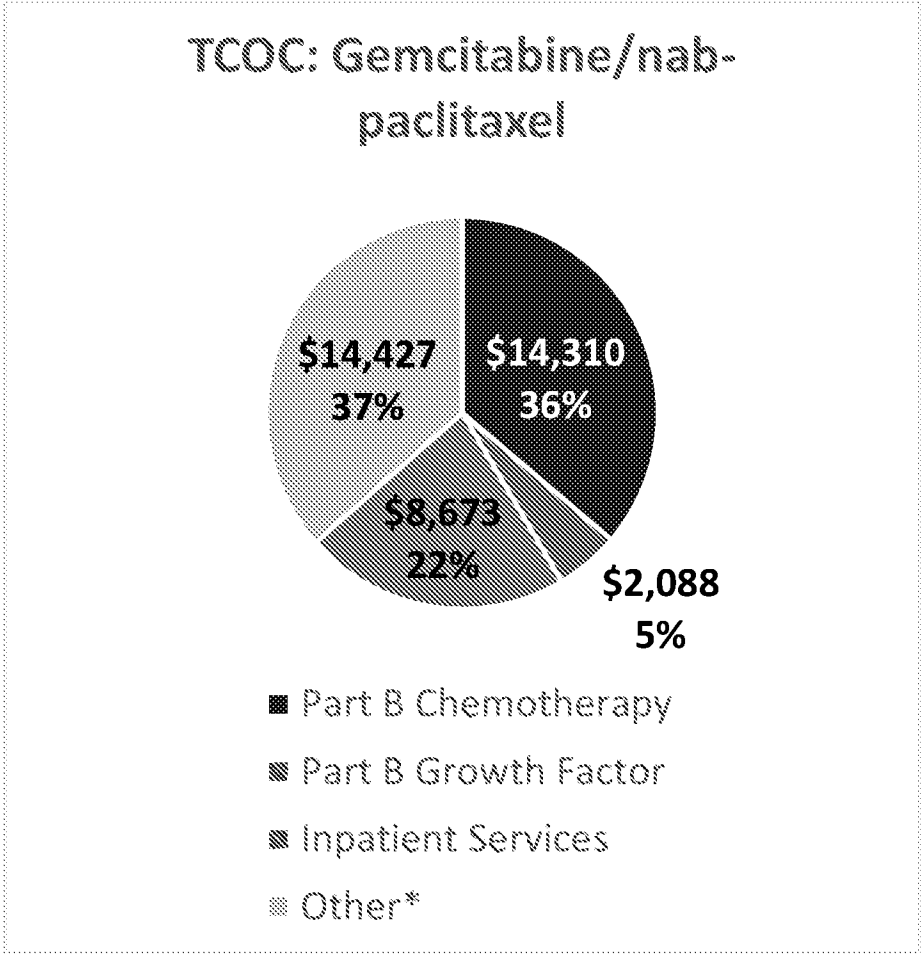
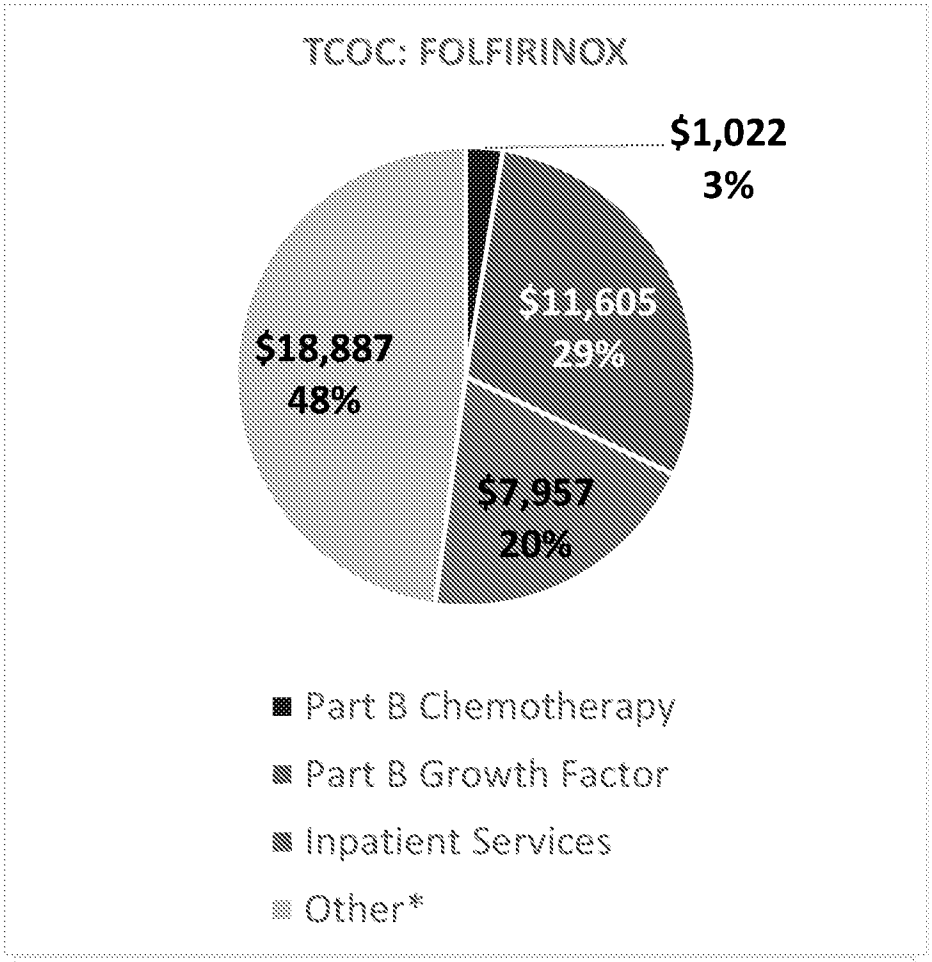
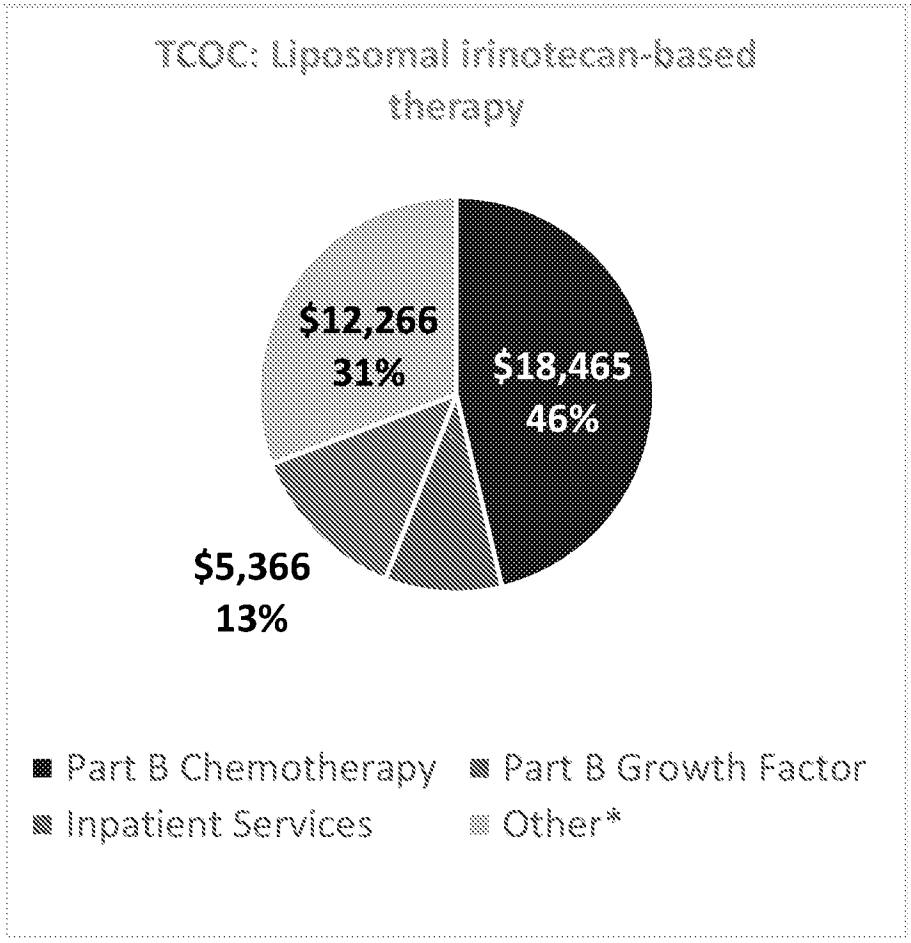


Figure 3. Proportions of Total Cost of Care (TCOC) By Select NCCN® Category 1 Treatment: Mean Part B Chemotherapy, Part B Growth Factor, and Inpatient Costs




TCOC: FOLFIRINOX
$1,022
3%
$11,605
29%
$7,957
20%
$18,887
48%
Part B Chemotherapy
Part B Growth Factor
Inpatient Services
Other*


TCOC: Liposomal irinotecan-based therapy
$18,465
46%
$5,366
13%
$12,266
31%
Part B Chemotherapy
Part B Growth Factor
Inpatient Services
Other*

*Includes: Part B Surgery, Radiotherapy, and Other Services; ED and Observation; Outpatient Services; DME; Hospice; SNF/Home Health; and Part D Chemotherapy, Growth Factor, and Other Services

RESULTS

- We identified 28,063 Medicare fee-for-service (FFS) patients with m-PANC with a mean age of 74.5 years at index and a mean Charlson comorbidity score of 3.4.
- The most commonly prescribed pancreatic cancer drug or regimen of interest was gemcitabine/nab-paclitaxel, which was used by 18% of the study population (n = 8,237), followed by FOLFIRINOX in 5% (n = 2,717) and liposomal irinotecan-based therapy in 2% (n = 730) on all lines of therapy. (Figure 1)
- Total cost of care for m-PANC patients was similar across regimens. On any line of therapy, the total cost of care was $39,497 for patients on gemcitabine/nab-paclitaxel, $39,470 for patients on FOLFIRINOX, and $39,909 for patients on liposomal irinotecan-based therapy. Total cost of care for m-PANC patients that received no chemotherapy was $17,513. (Figure 2)
- The service categories for the primary cost drivers across all regimens were Part B chemotherapy, Part B growth factor, and inpatient services (ICU, inpatient radiotherapy, and inpatient surgery) (Figure 3):
  - Part B Chemotherapy costs were 36% of total costs for gemcitabine/nab-paclitaxel, 3% of total costs for FOLFIRINOX, and 46% of total costs for liposomal irinotecan-based therapy.
  - Part B Growth Factor costs were 5% of total costs for gemcitabine/nab-paclitaxel, 29% of total costs for FOLFIRINOX, and 10% of total costs for liposomal irinotecan-based therapy.
  - Inpatient service costs were 22% of total costs for gemcitabine/nab-paclitaxel, 20% of total costs for FOLFIRINOX, and 13% of total costs for liposomal irinotecan-based therapy.

LIMITATIONS

The data analyzed covers the Medicare FFS population from 2014 - 2017. Analysis of different populations or time periods will yield different results. Our study used claims data and not electronic health records (EHRs), and we could not control for clinical covariates. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5FU or prior gemcitabine-based therapy.

CONCLUSIONS

- The mean total Part A, B, and D costs of care for the three FDA-Approved/NCCN® Category 1 regimens studied were similar, however, the main drivers of cost differed across regimen.
- Gemcitabine/nab-paclitaxel had the lowest Part B Growth Factor costs (5%), but the highest inpatient Services (22%) costs.
- FOLFIRINOX had the lowest Part B Chemotherapy costs (3%), but the highest Part B Growth Factor costs (29%).
- Liposomal irinotecan-based therapy had the lowest Inpatient Services costs (13%), but the highest Part B Chemotherapy costs among the regimens studied (46%).
- These results are consistent with other claims data demonstrating lower inpatient and growth factor costs for liposomal irinotecan-based therapy compared to other NCCN® Category 1 regimens.

DISCLOSURES

Jared Hirsch and Gabriela Dieguez are employed by Milliman and received consulting fees from Ipsen. Paul Cockrum is employed by Ipsen and owns Ipsen stock.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [JH, GD, PC]; Drafting of the publication, or revising it critically for important intellectual content: [JH, GD, PC]; Final approval of the publication: [JH, GD, PC]. The authors thank Samantha Tomicki and Helen Latimer at Milliman, Inc. for research assistance.
For questions, please contact Gabriela.Dieguez@Milliman.com

Presented at AMPC Nexus 2020 Virtual | October 2020
This study was sponsored by Ipsen

Comparing Total Costs of Care for Medicare Fee-For-Service (FFS) Patients with Metastatic Pancreatic Cancer by Chemotherapy Regimen

ABSTRACT

DATA SOURCES

METHODS

RESULTS

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CONCLUSIONS

DISCLOSURES

AUTHOR CONTRIBUTIONS

The cost of adverse events for FDA-Approved/NCCN® Category 1 treatments for Medicare fee-for-service patients with metastatic pancreatic cancer

Hirsch J[1], DieguezG[1], CockrumP[2]
[1]Milliman, Inc., New York, NY; [2]Ipsen Biopharmaceuticals, Cambridge, MA

OBJECTIVE

To analyze mean incremental costs of adverse events (AEs) by line of therapy (LOT) for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer (m-PANC) treated with the following FDA-approved/NCCN® Category 1 therapies: gemcitabine/nab-paclitaxel, gemcitabine monotherapy, FOLFIRINOX, and liposomal irinotecan. This study focuses on the most common LOTs for these regimens in clinical practice for the treatment of m-PANC.

DATA SOURCES

Medicare 100% Limited Data Set Claims Files (2013 - 2017)

- Contain all Medicare FFS Part A and B claims, except professional services and durable medical equipment, for 45 million beneficiaries.
- Include diagnosis, procedure, and diagnosis-related group (DRG) codes; site of service information; and beneficiary information such as age, eligibility status, and Medicare Advantage enrollment.

METHODS

Patient Identification

- Patients were identified with m-PANC using ICD-9/10 diagnosis codes:
  - Two or more claims with a pancreatic cancer 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,
  - Lack of six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment.

Line of Therapy Determination

- 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.
- Next LOT began when a beneficiary switched regimens.
- End of most recent LOT was defined as the earlier of:
  - 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy),
  - The date of death, if applicable.
- Other LOT end dates are defined as the day before the start date of the next LOT (which begins when a beneficiary switches regimens).

Estimation of Mean Incremental Costs of Adverse Events

- Adverse events (AEs) were identified using ICD-9/10 diagnosis codes occurring during LOTs.
- Control patients in the same LOT and regimen without an AE were randomly sampled and assigned shadow AE dates.
- 30-day costs were calculated, starting on the day of AE onset or shadow AE date.
  - For LOTs and regimens with at least 80 patients (cases and controls), we estimated 30-day AE incremental costs using log-link generalized linear models and gamma-distributed errors.
  - We predicted mean 30-day AE incremental costs relative to controls using recycled projections and bootstrapped 95% confidence intervals to determine statistical significance relative to zero.

Figures 1-3 show cohort attrition, mean rates of AEs, and average cost by regimen

Figure 1. Patient Identification Cascade Chart

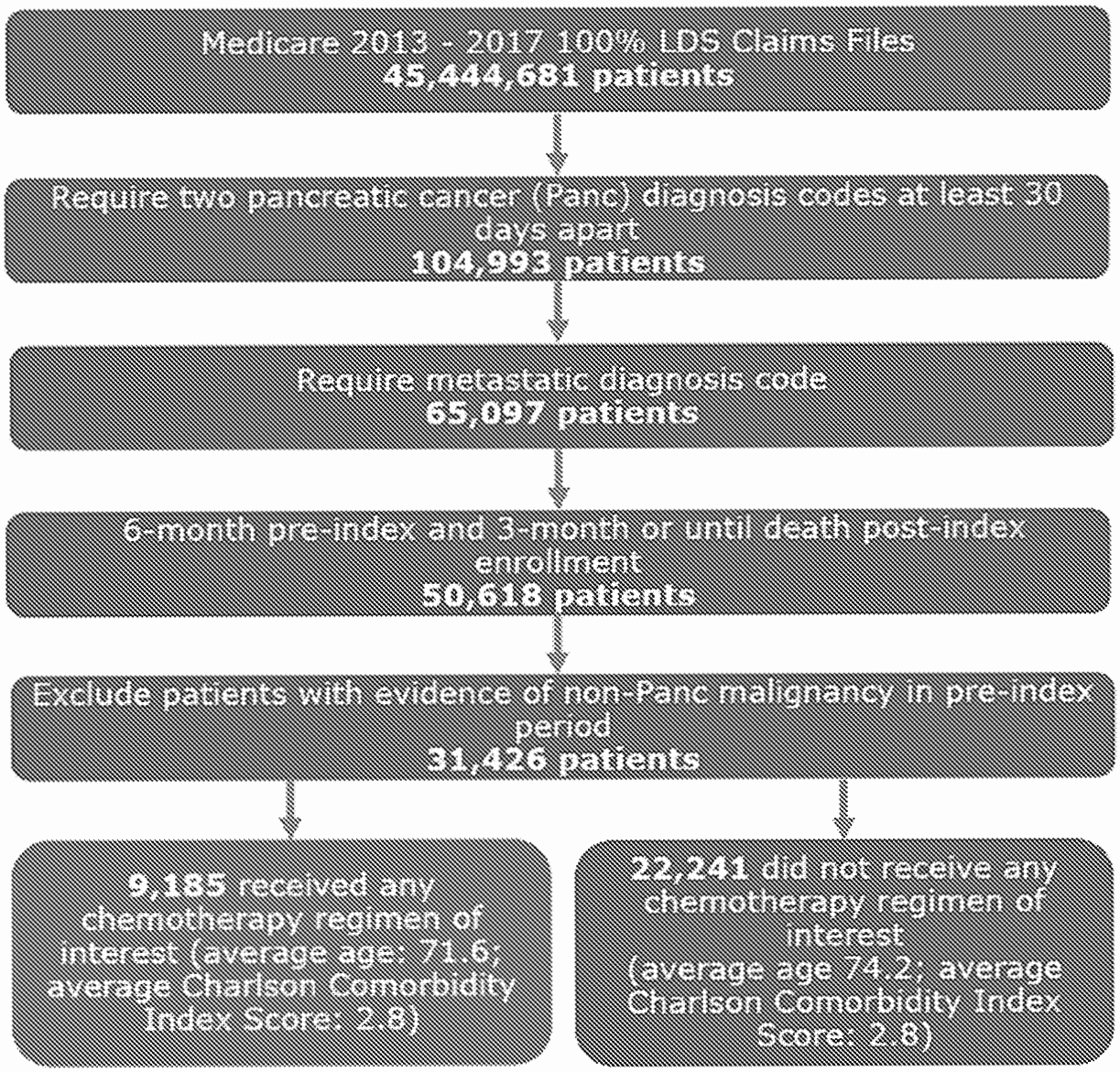


Figure 2. Mean Rates of Observed Adverse Events by Chemotherapy Regimen

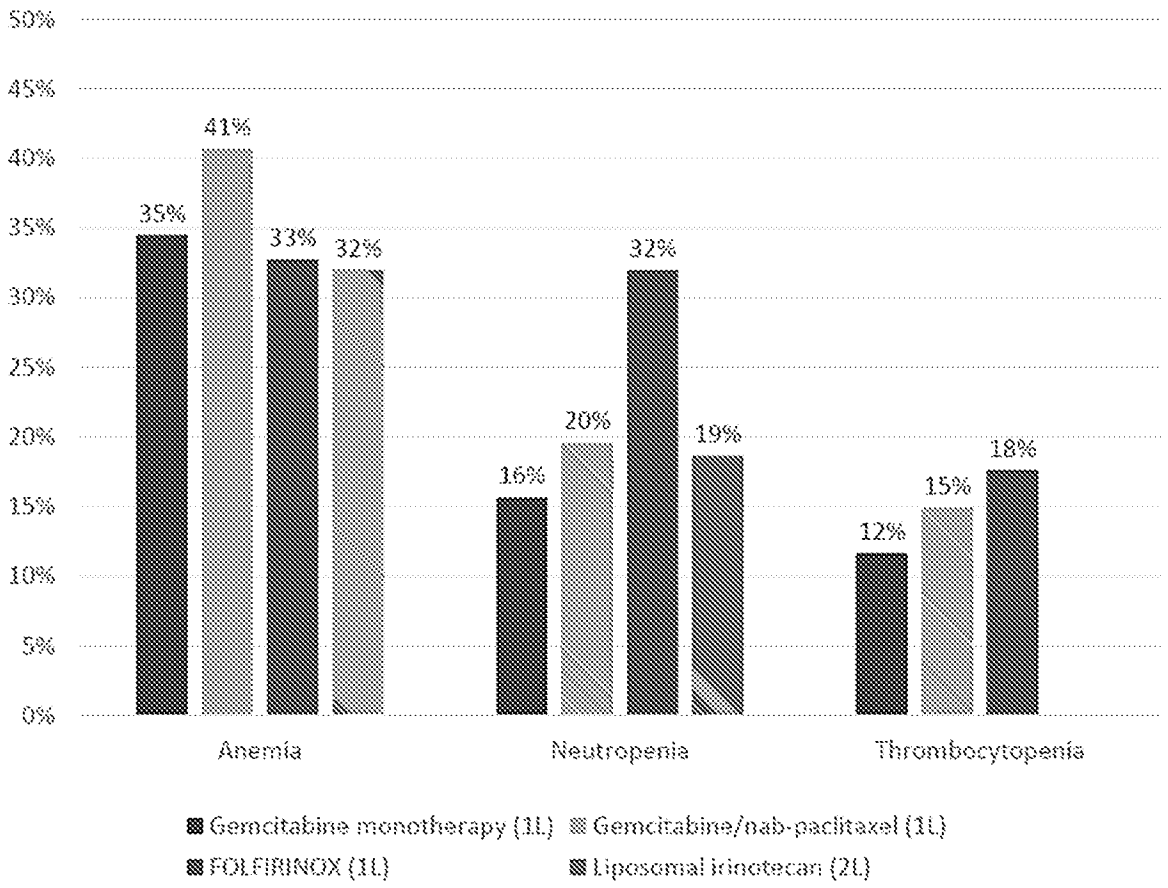
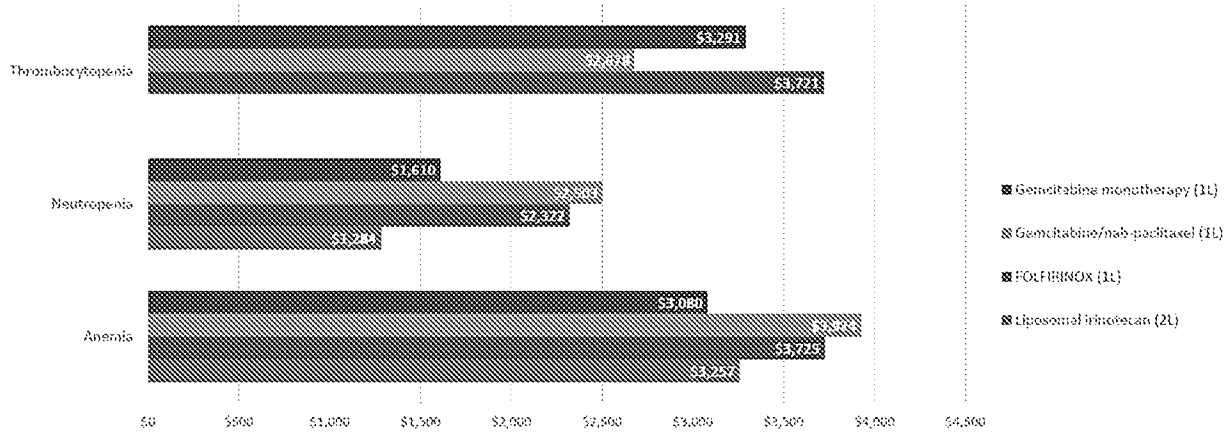


Figure 3. Mean 30-Day Incremental Costs of Adverse Events By Chemotherapy Regimen and LOT



RESULTS

- We identified 31,426 target patients with m-PANC. (Figure 1)
- Mean rates of observed AEs and 30-day incremental costs of AEs are summarized by the most common LOT among therapies: Gemcitabine monotherapy, gemcitabine/nab-paclitaxel, and FOLFIRINOX were most commonly used as first line (1L) and liposomal irinotecan was most commonly used as second line (2L).
- Anemia was the most common AE, ranging from 32% of patients receiving second line (2L) liposomal irinotecan to 41% of patients receiving first line (1L) gemcitabine/nab-paclitaxel. (Figure 2)
- Neutropenia rates ranged from 16% of patients receiving 1L gemcitabine monotherapy to 32% of those receiving 1L FOLFIRINOX. (Figure 2)
- The occurrence of thrombocytopenia ranged from 12% in patients receiving 1L gemcitabine monotherapy to 18% in those receiving 1L FOLFIRINOX. (Figure 2)
- We observed the following mean 30-day incremental costs relative to controls by AE: (Figure 3)
  - Anemia incremental costs ranged from $3,080 for 1L gemcitabine monotherapy to $3,924 for 1L gemcitabine/nab-paclitaxel; all values were statistically different from zero.
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LIMITATIONS

The data analyzed covers the Medicare FFS population from 2013 - 2017. Analysis of different populations or time periods will yield different results. Our study used claims data and not EHRs, and we could not control for clinical covariates. We did not study whether liposomal irinotecan patients received concomitant 5FU or prior gemcitabine-based therapy.

CONCLUSIONS

- AEs impose substantial costs for Medicare FFS patients with m-PANC receiving FDA-Approved/NCCN® Category 1 treatments
- For 1L regimens, we observed statistically significant incremental costs associated with three of the most common m-PANC AEs:
  - Anemia (mean incremental cost: $3,080-$3,924),
  - Neutropenia (mean incremental cost: $1,610-$2,503), and
  - Thrombocytopenia (mean incremental cost: $2,678-$3,721)
- Among 2L liposomal irinotecan patients, only anemia incremental costs ($3,257) were statistically significant; neutropenia incremental costs were not statistically different from zero, and there were insufficient thrombocytopenia cases to estimate incremental costs.

DISCLOSURES

Jared Hirsh and Gabriela Dieguez are employed by Milliman and received consulting fees from Ipsen. Paul Cockrum is employed by Ipsen and owns Ipsen stock.

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Presented at HOPA Annual Conference | Tampa, FL | March 2020

The cost of adverse events for FDA-Approved/NCCN Category 1 treatments for Medicare fee-for-service patients with metastatic pancreatic cancer

OBJECTIVE

DATA SOURCES

METHODS

RESULTS

LIMITATIONS

CONCLUSIONS

DISCLOSURES

AUTHOR CONTRIBUTIONS

The cost of adverse events for FDA-Approved/NCCN Category 1 treatments for Medicare fee-for-service patients with metastatic pancreatic cancer

Hirsch J[1], Dieguez G[1], Cockrum P[2]
[1]Milliman, Inc., New York, NY; [2]Ipsen Biopharmaceuticals, Cambridge, MA

OBJECTIVE

To analyze mean incremental costs of adverse events (AEs) by line of therapy (LOT) for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer (m-PANC) treated with the following FDA-approved/NCCN Category 1 therapies: gemcitabine/nab-paclitaxel, gemcitabine monotherapy, FOLFIRINOX, and liposomal irinotecan. This study focuses on the most common LOTs for these regimens in clinical practice for the treatment of m-PANC.

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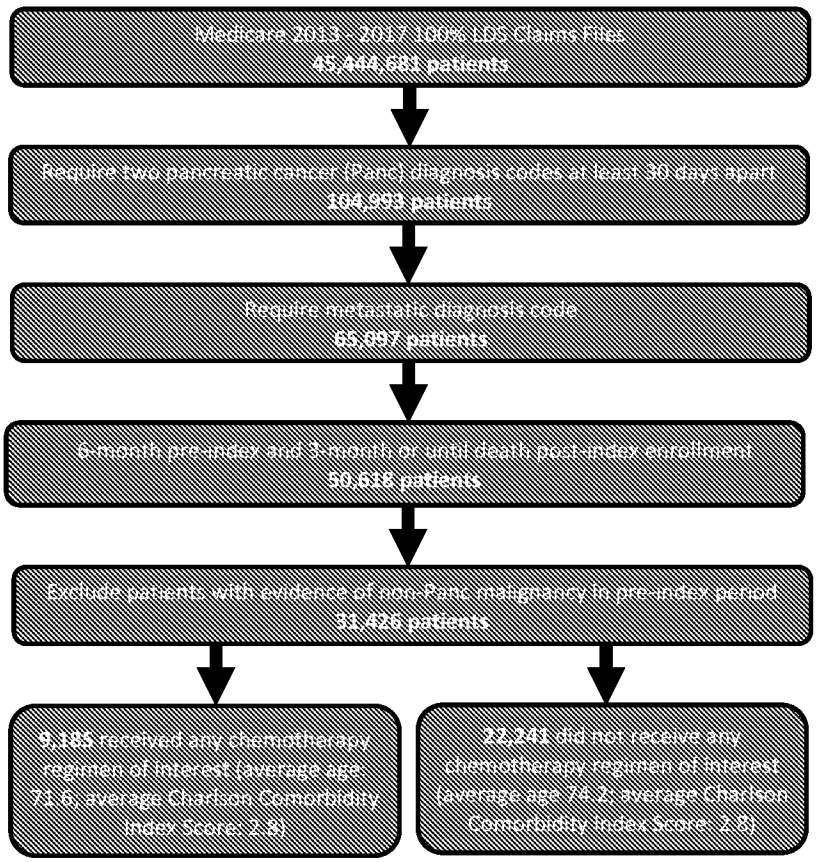


Figure 2. Mean Rates of Observed Adverse Events by Chemotherapy Regimen

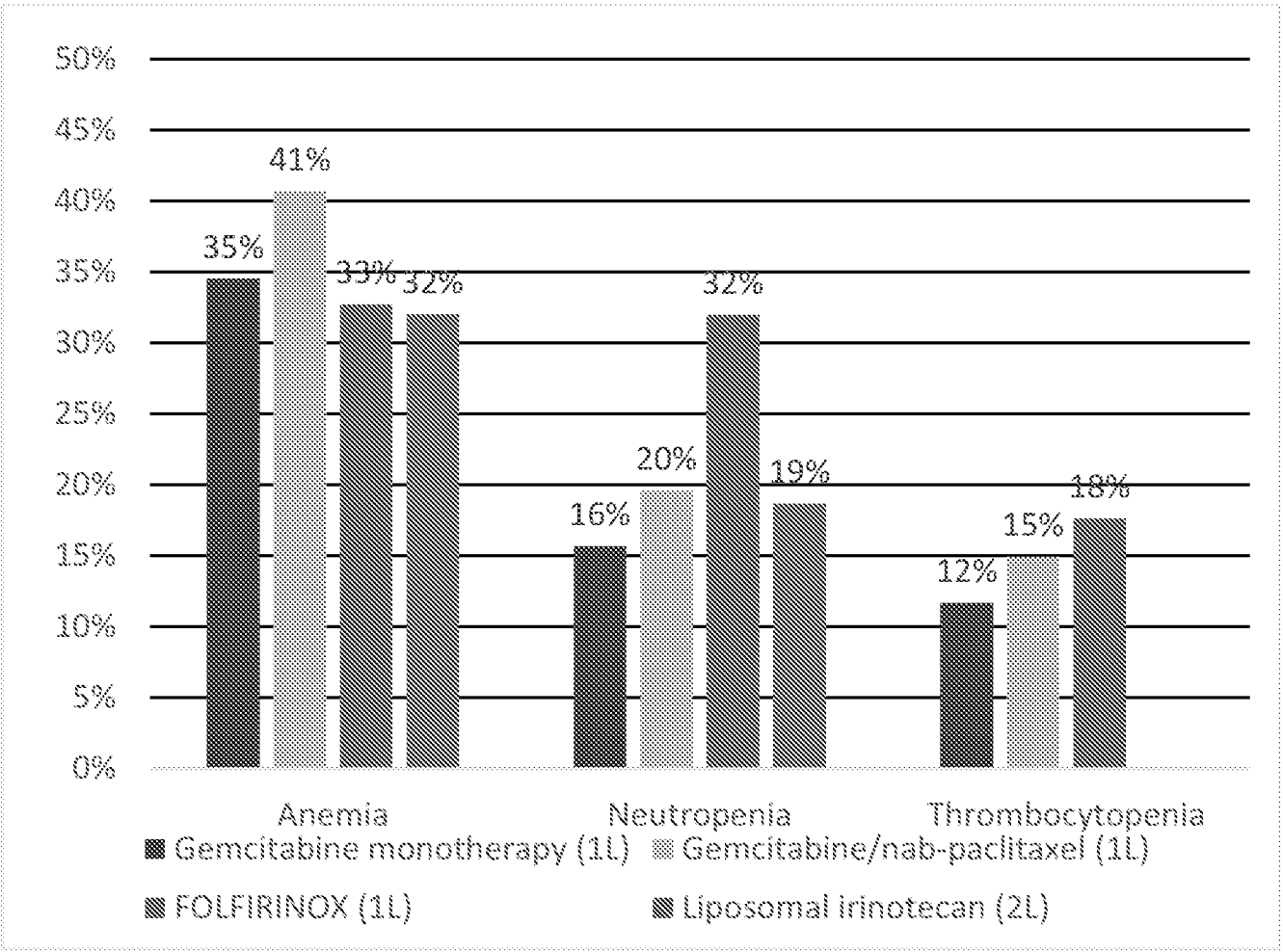
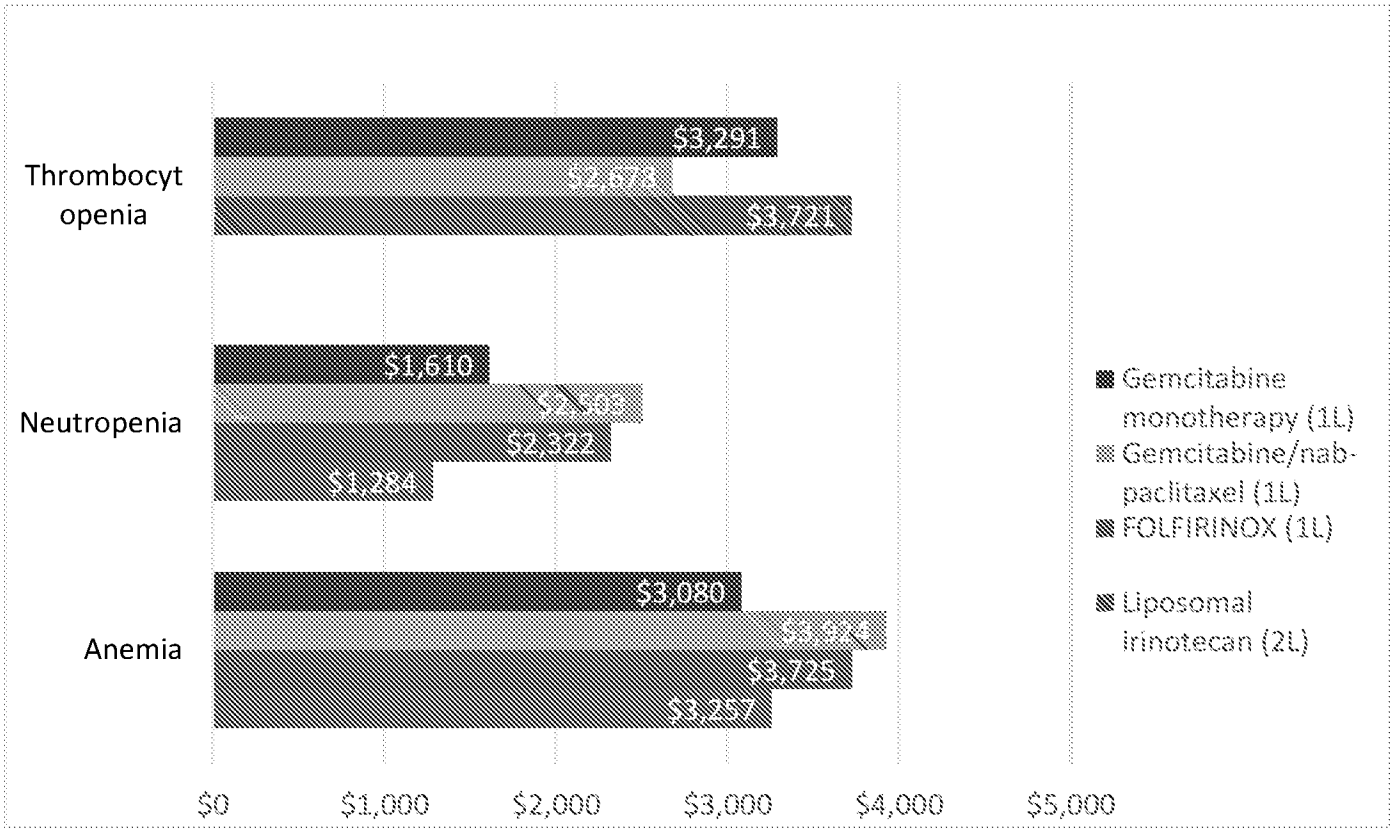


Figure 3. Mean 30-Day Incremental Costs of Adverse Events By Chemotherapy Regimen and LoT



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- AEs impose substantial costs for Medicare FFS patients with m-PANC receiving FDA-Approved/NCCN Category 1 treatments
- For 1L regimens, we observed statistically significant incremental costs associated with three of the most common m-PANC AEs:
  - Anemia (mean incremental cost: $3,080-$3,924),
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Jared Hirsh and Gabriela Dieguez are employed by Milliman and received consulting fees from Ipsen. Paul Cockrum is employed by Ipsen and owns Ipsen stock.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [JH, GD, PC]; Drafting of the publication, or revising it critically for important intellectual content: [JH, GD]; Final approval of the publication: [PC]. The authors thank Samantha Tomicki and Helen Latimer at Milliman, Inc. for research assistance.

Presented at ASHP Midyear 2019 | Las Vegas, NV | December 2019
This study was sponsored by Ipsen

The cost of adverse events for FDA-Approved/NCCN Category 1 treatments for Medicare fee-for-service patients with metastatic pancreatic cancer

OBJECTIVE

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Patient Identification

Index Date

Measures of Healthcare Resource Use

Cost of Healthcare Resource Use

Statistical Analysis

Subgroup Analyses

Sensitivity Analyses

Figure 1. Patient Identification Cohort Chart

Figure 2. Mean Rates of Observed Adverse Events by Chemotherapy Regimen

Figure 3. Mean 28-Day Unadjusted Costs of Adverse Events by Chemotherapy Regimen and Type

RESULTS

LIMITATIONS

CONCLUSIONS

RISK DISPARITIES

FUNDING CONTRIBUTIONS

2019 ASHP Midyear Clinical Meeting
Professional Poster Abstracts

Session-Board # - 4-138

Poster Title: The cost of adverse events for FDA-approved/NCCN category 1 treatments for medicare fee-for-service patients with metastatic pancreatic cancer

Poster Type: Descriptive Report

Submission Category: Oncology /Hematology

Primary Author: Jared Hirsch, Milliman Inc.; **Email:** jared.hirsch@milliman.com

Additional Authors:
Gabriela Dieguez
Paul Cockrum

Purpose: Adverse events (AEs) related to cancer therapy reduce patients' quality of life and generate substantial healthcare costs. There is limited real-world evidence regarding the AE costs for patients with metastatic pancreatic cancer (m-PANC) who receive FDA-Approved/NCCN Category 1 treatments. We analyzed the costs of three of the most common AEs for patients receiving FDA-Approved/NCCN Category 1 treatments: neutropenia, anemia, and thrombocytopenia in the Medicare fee-for-service (FFS) population by chemotherapy regimen and line of therapy (LOT).

Methods: We identified patients with m-PANC using ICD-9/10 diagnosis codes in the 2013-2017 Medicare 100% Limited Data Set claims, which include all Medicare FFS Part A and B claims, except professional services, for 45 million beneficiaries. Patients in our study had multiple claims with a pancreatic cancer (PANC) diagnosis more than 30 days apart and one+ claim(s) with a secondary malignancy (metastasis) diagnosis on/after the first PANC diagnosis date. We defined the index date as the earliest metastasis diagnosis date. We excluded patients with pre-index non-PANC malignancies and those without six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment. LOTs were assigned based on the order of therapies used. LOTs ended when a new regimen began, 28 days after the last chemotherapy (if no new regimen), or upon death.
We identified AEs using ICD-9/10 diagnosis codes occurring during LOTs. We randomly sampled control patients in the same LOT and regimen without an AE and assigned them shadow AE dates. We calculated 30-day costs after the AE onset or shadow AE date. For LOTs and regimens with at least 80 patients (cases and controls), we estimated 30-day AE incremental costs using

log-link generalized linear models and gamma-distributed errors. We predicted mean 30-day AE incremental costs relative to controls using recycled projections and bootstrapped 95% confidence intervals to determine statistical significance relative to zero.

Results: Anemia was the most common AE, ranging from 41% of patients receiving first line (1L) gemcitabine/nab-paclitaxel to 32% of patients receiving second line (2L) liposomal irinotecan. Mean 30-day anemia incremental costs were $3,924 for 1L gemcitabine/nab-paclitaxel, $3,080 for 1L gemcitabine monotherapy, $3,725 for 1L FOLFIRINOX, and $3,257 for 2L liposomal irinotecan, all of which were statistically significant.
Neutropenia was observed for 20% of patients receiving 1L gemcitabine/nab-paclitaxel, 16% of those receiving 1L gemcitabine monotherapy, 32% of those receiving 1L FOLFIRINOX, and 19% of patients receiving 2L liposomal irinotecan. Mean 30-day neutropenia incremental costs were $2,503 for 1L gemcitabine/nab-paclitaxel, $1,610 for 1L gemcitabine monotherapy, and $2,322 for 1L FOLFIRINOX, all of which were statistically significant. The mean 30-day neutropenia incremental costs for (2L) liposomal irinotecan were $1,284, which was not statistically significant, possibly because there were few cases (42).
The occurrence of thrombocytopenia ranged from 18% of patients receiving 1L FOLFIRINOX to 8% of those receiving 2L liposomal irinotecan. Mean 30-day thrombocytopenia incremental costs were $2,678 for 1L gemcitabine/nab-paclitaxel, $3,291 for 1L gemcitabine monotherapy, and $3,721 for 1L FOLFIRINOX, all of which were statistically significant. There were too few 2L liposomal irinotecan patients with thrombocytopenia to estimate incremental costs.

Conclusion: AEs impose substantial costs for Medicare FFS patients with m-PANC receiving FDA-Approved/NCCN Category 1 treatments. For 1L regimens, we observed statistically significant incremental costs associated with three of the most common m-PANC AEs: anemia (mean incremental cost: $3,080-$3,924), neutropenia (mean incremental cost: $1,610-$2,503), and thrombocytopenia (mean incremental cost: $2,678-$3,721). Among 2L liposomal irinotecan patients, only anemia incremental costs ($3,257) were statistically significant; neutropenia incremental costs were not statistically different from zero, and there were insufficient thrombocytopenia cases to estimate incremental costs.

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

PANCREATIC CANCER

Comparing total cost of care for Medicare FFS patients with pancreatic cancer by chemotherapy regimen.

Jared Hirsch, Gabriela Dieguez, Paul Cockrum

Show More

Abstract Disclosures

Abstract

721

Background: To analyze total cost of care for patients with pancreatic cancer by FDA-Approved/NCCN Category 1 regimen. **Methods:** Cancer episodes were identified using a

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

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methodology similar to the Medicare Oncology Care Model (OCM) in the 2014-2016 100% Medicare Limited Data Set (LDS) claims files. Index dates were established for chemotherapy claims that did not occur within 6 months of another chemotherapy claim for all Medicare fee-for-service beneficiaries. Cancer episodes were defined as the 6-month period following an index date. Each episode was assigned a cancer type based on the plurality of cancer ICD 9/10 diagnosis codes that occurred on chemotherapy claims in the episode. Episode costs were calculated from claim paid amounts, and DME and other Part B spending was estimated using episodes created in the 5% Medicare LDS files using the same methodology. We analyzed total episode costs for three FDA-Approved/NCCN Category 1 pancreatic cancer regimens: gemcitabine plus nab-paclitaxel (gem-nab), FOLFIRINOX (FFX), and liposomal irinotecan (nal-IRI). **Results:** We identified 110,618 cancer episodes in 2016, of which 4,018 were for pancreatic cancer (average age at index: 71.3 years). Pancreatic cancer patients in these episodes were treated with gem-nab (45% of episodes), FFX (14%), and nal-IRI (4%). The main cost drivers across all regimens were Part B chemotherapy, other Part B drugs and inpatient services. Episode costs were $41,749, $42,086, and $45,851 for patients receiving gem-nab, FFX, and nal-IRI, respectively. Part B chemotherapy costs were $13,065 (gem-nab), $3,095 (FFX), and $18,472 (nal-IRI); other Part B drug costs were $7,343 (gem-nab), $17,013 (FFX), and $10,479 (nal-IRI); and inpatient service costs were $9,044 (gem-nab), $9,069 (FFX), and $5,108 (nal-IRI). **Conclusions:** Total episode costs for pancreatic cancer care were similar among three FDA-Approved/NCCN Category 1 regimens, but the components of cost varied. Episodes with Nal-IRI had the largest Part B chemotherapy costs and the lowest inpatient service costs. Episodes with FFX and gem-nab had similar inpatient service costs, which were higher than episodes

with nal-IRI. Episodes with FFX had the highest other Part B drug costs.

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HEALTH SERVICES RESEARCH AND QUALITY IMPROVEMENT

Comparing total cost of care for Medicare FFS patients with pancreatic cancer by chemotherapy regimen.

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Abstract Disclosures

Abstract

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Background: To analyze total cost of care for patients with pancreatic cancer by common therapeutic regimens. **Methods:** Cancer episodes were identified using a methodology similar to the Medicare Oncology Care Model (OCM) in the 2014-2016 100% Medicare Limited Data Set (LDS) claims files. Index dates for chemotherapy claims could not occur within 6 months of another chemotherapy claim for all Medicare FFS beneficiaries. Cancer episodes were defined as the 6-month period following an index date. Each episode was assigned a cancer type based on the plurality of cancer ICD 9/10 diagnosis codes that occurred on chemotherapy claims in the episode. Episode costs were calculated from claims paid amounts. DME and other Part B spending was estimated using episodes from the 5% Medicare LDS files using the same methodology. We analyzed total episode costs for five pancreatic cancer treatment regimens: gemcitabine plus nab-paclitaxel (gem-nab), FOLFIRINOX, liposomal irinotecan, FOLFOX, and FOLFIRI. **Results:** We identified 110,618 cancer episodes in 2016, of which 4,018 were pancreatic cancer. Pancreatic cancer patients in these episodes were treated with gem-nab (45% of episodes), FOLFIRINOX (14%), FOLFOX (8%), FOLFIRI (6%), and liposomal irinotecan (4%). The main drivers of episode costs among regimens were Part B chemotherapy, other Part B drugs, and inpatient services. Episode costs were $41,749, $42,086, $35,601, $36,169, and $45,851 for patients receiving gem-nab, FOLFIRINOX, FOLFOX, FOLFIRI, and liposomal irinotecan, respectively. Part B chemotherapy costs were $13,065 (gem-nab), $3,095 (FOLFIRINOX), $4,853 (FOLFOX), $3,204 (FOLFIRI), and $18,474 (liposomal irinotecan); other Part B drug costs were $7,343 (gem-nab), $17,013 (FOLFIRINOX), $11,131 (FOLFOX), $15,377

(FOLFIRI), and $10,479 (liposomal irinotecan); and inpatient service costs were $9,044 (gem-nab), $9,069 (FOLFIRINOX), $7,701 (FOLFOX), $5,838 (FOLFIRI), and $5,108 (liposomal irinotecan). **Conclusions:** Total episode costs for pancreatic cancer care ranged from $35,601 (FOLFOX) to $45,851 (liposomal irinotecan), but the cost components varied by regimen. Episodes with liposomal irinotecan had the largest Part B chemotherapy costs but the lowest inpatient service costs. Episodes with FOLFIRINOX and gem-nab had similar inpatient service costs, which were higher than episodes with liposomal irinotecan, FOLFOX, or FOLFIRI. Episodes with FOLFIRINOX and FOLFIRI had higher other Part B drug costs than episodes with FOLFOX, liposomal irinotecan, or gem-nab.

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Nanovectors for anti-cancer drug delivery in the treatment of advanced pancreatic adenocarcinoma

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Abstract

Liposome, albumin and polymer polyethylene glycol are nanovector formulations successfully developed for anti-cancer drug delivery. There are significant differences in pharmacokinetics, efficacy and toxicity between pre- and post-nanovector modification. The alteration in clinical pharmacology is instrumental for the future development of nanovector-based anticancer therapeutics. We have reviewed the results of clinical studies and translational research in nanovector-based anti-cancer therapeutics in advanced pancreatic adenocarcinoma, including nanoparticle albumin-bound paclitaxel and nanoliposomal irinotecan. Furthermore, we have appraised the ongoing studies incorporating novel agents with nanomedicines in the treatment of pancreatic adenocarcinoma.

Key words: Pancreatic adenocarcinoma; Nanovector; Nanoparticle albumin-bound paclitaxel; Nanoliposomal irinotecan; Biomarker

Core tip: The nanovector-based anti-cancer therapeutics play important role in the treatment of advanced pancreatic adenocarcinoma. Data from completed clinical trials are reviewed, and important ongoing studies are presented. Biomarkers for patient selection and personalized medicine are discussed.

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INTRODUCTION

Nanomedicines are pharmaceuticals prepared by manipulating matter at the nanoscale (< 1000 nm); *i.e.,* manipulations at less than 1000th of a millimeter. The vast majority of nanomedicines are the result of the packaging of pharmacologically active compounds within nanovectors (5-800 nm). The chemical compounds used to construct these nanomedicines include low molecular weight self-assembling amphiphilic polymers, polymer-drug conjugates, water insoluble polymers/cross-linked polymers, dendrimers, inorganic chemistries and carbon nanotubes. Targeting of solid tumors by most of the nanomedicines is achieved by passive means known as enhanced permeability and retention (EPR) effect. Because of their size and surface properties, nanomedicines can easily travel through leaky blood vessel walls in the tumors, with enhanced retention due to impaired lymphatic drainage. This gives rise to a significant increase in the accumulation of attached drug by nanovectors in tumor tissue compared to that achieved with the free-form drug[1]. Nanovector formulation of anticancer compounds has several potential advantages over the free-form drugs: protecting drugs from being degraded in the body before they reach their target, enhancing uptake of drugs into tumor, allowing for better control over the timing and distribution of drugs to tumor tissue, and preventing drugs from interacting with normal cells thus decreasing the toxicities.

Adenocarcinoma of pancreas is the fourth most common cause of cancer-related death among United States men and women, and the seventh leading cause of cancer mortality worldwide, causing more than 300000 deaths globally every year[2]. Due to lack of specific symptoms and effective screening modality, about 80% of cases are diagnosed at an advanced stage with locally advanced or metastatic disease. Surgery remains the only curative therapy; however, most patients die within two years of diagnosis, and the 5-year survival rate is less than 5%[3].

Gemcitabine was approved for advanced pancreatic adenocarcinoma in late 1990. Further studies have confirmed a 2-wk gain of overall survival (OS) by adding erlotinib, a tyrosine kinase inhibitor of epidermal growth factor receptor, to gemcitabine[4], and a 7-wk gain of survival with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine *vs* gemcitabine[5]. The combination of 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, and oxaliplatin (FOLFIRINOX) has also demonstrated improved overall survival by 4 to 5 mo *vs* gemcitabine alone in a phase Ⅲ study (ACCORD11/PRODIGE4) involving more than 340 patients with metastatic pancreatic cancer[6]. In October 2015, nanoliposomal irinotecan (nal-IRI, MM-398) has been approved by the United States Food and Drug Administration (FDA) to be used in combination with 5-FU and LV in patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Carbohydrate antigen 19-9 (CA 19-9) is currently used as a marker for following patients during treatment for pancreatic adenocarcinoma. Only about 80% to 85% of patients with pancreatic adenocarcinoma can demonstrate an elevated CA 19-9 level[7]. Retrospective analyses of clinical trials have shown that pretreatment serum CA 19-9 concentration is an independent prognostic factor for survival. In patients with advanced pancreatic cancer receiving either gemcitabine or gemcitabine and capecitabine, median OS for patients with baseline CA 19-9 level $\geqslant$ the median value [59 × upper limit of normal (ULN)] was significantly shorter than that for patients whose baseline CA 19-9 level < median (5.8 mo *vs* 10.3 mo, $P < 0.0001$)[8]. Retrospective analysis of CA 19-9 decrease in patients with metastatic pancreatic adenocarcinoma treated with FOLFIRINOX or gemcitabine in ACCORD11/PRODIGE4 indicated that an 8-wk CA 19-9 decrease $\geqslant$ 20% was correlated with an improved OS compared to an 8-wk CA 19-9 decrease < 20% (10.3 mo *vs* 7.8 mo, $P = 0.002$)[9].

Here, we have reviewed the mechanism of action and clinical studies of the 2 United States FDA approved nanomedicines in pancreatic adenocarcinoma and the utility of biomarkers such as CA 19-9 in correlation with clinical outcomes and population pharmacokinetic studies in different ethnic groups. Furthermore, we have examined ongoing investigations incorporating novel agents with nab-paclitaxel and gemcitabine platform. We have also looked back at previous nanomedicines studied in pancreatic adenocarcinoma.

NANOPARTICLE ALBUMIN-BOUND PACLITAXEL

Mechanism of action and SPARC

Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) is a Cremophor EL-free, albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers, and is the first in its class of biologically interactive albumin-bound forms of chemotherapy[10]. This formulation results in enhanced intra-tumoral concentration of paclitaxel by a receptor-mediated transport process. This albumin-specific receptor mediated process involves the binding of a specific receptor, gp60, on the endothelial cell wall, yielding the activation of a protein caveolin-1, which initiates an opening in the endothelial wall with transport

of the albumin-bound chemotherapeutic complex to the underlying tumor interstitium[11].

Secreted protein acidic and rich in cysteine (SPARC), a calcium-binding glycoprotein also known as osteonectin, is a nonstructural matricellular protein, secreted by the tumor and involved in cell-matrix interaction during tissue remodeling, embryonic development, cell migration, and angiogenesis[12]. SPARC has an affinity for binding albumin[13]. It has been postulated that SPARC binds and entraps the albumin, and may help to accumulate nab-paclitaxel inside tumor interstitium, allowing release of the hydrophobic drug to the tumor cell membrane. The transport of nab-Paclitaxel *via* this gp-60/caveolin-1/caveolae/SPARC pathway potentially increases intratumoral concentration of drug while reducing toxicity to normal tissue. Preclinical studies comparing nab-paclitaxel to paclitaxel demonstrated lower toxicities, with a maximum tolerated dose approximately 50% higher for nab-paclitaxel compared to paclitaxel. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma[14].

Overexpression of SPARC in many cancer types such as squamous cell carcinoma of head and neck, esophageal and urothelial cancers is associated with poor prognosis[15]. Interestingly, in certain tumor types such as non-small cell lung cancer and pancreatic adenocarcinoma, strong expression of SPARC has been detected predominantly in the stroma adjacent to the cancer cells[16,17]. In a retrospective analysis of patients with resectable pancreatic adenocarcinoma, Infante *et al*[18] found that the presence of SPARC in stromal fibroblasts was associated with worse OS and the presence of SPARC in tumor cells did not significantly impact OS. A subgroup analysis from CONKO-001, a phase Ⅲ trial showing improved survival from adjuvant gemcitabine therapy in patients with resectable pancreatic adenocarcinoma, confirmed the prognostic significance of SPARC expression after resection of pancreatic cancer; however, the negative prognostic impact was restricted to patients who received adjuvant treatment with gemcitabine, suggesting SPARC as a predictive marker for response to gemcitabine[19].

In preclinical studies of combination of nab-paclitaxel and gemcitabine in mice bearing human tumor xenograft, nab-paclitaxel depleted the desmoplastic stroma of pancreatic adenocarcinoma, and increased intratumoral concentration of gemcitabine by 2.8-fold when compared to gemcitabine alone[20]. Moreover, nab-paclitaxel reduced the levels of cytidine deaminase protein in cultured tumor cells through reactive oxygen species-mediated degradation, resulting in the increased stabilization and levels of gemcitabine[21]. Early-phase clinical studies of nab-paclitaxel and gemcitabine in metastatic pancreatic adenocarcinoma have shown that overexpression of SPARC correlated with increased RR and OS[20].

MPACT trial and analyses of biomarkers

A randomized phase Ⅲ study, MPACT, in 861 patients with metastatic pancreatic adenocarcinoma has demonstrated an increased median OS with nab-paclitaxel plus gemcitabine *vs* gemcitabine (8.5 mo *vs* 6.7 mo, $P < 0.001$)[5]. For patients who received nab-paclitaxel/gemcitabine *vs* gemcitabine, the median progression-free survival (PFS) was 5.5 mo compared to 3.7 mo ($P < 0.001$), and the overall RR was 23% *vs* 7% ($P < 0.001$), respectively. Patients who received nab-paclitaxel/gemcitabine had more grade 3 or higher toxicities in neutropenia, fatigue, and neuropathy but similar incidences of grade 3 toxicities in anemia and thrombocytopenia, when compared with gemcitabine.

Retrospective analysis of SPARC levels in the phase Ⅲ MPACT trial showed no association between stromal SPARC level and OS in either treatment arm. Neither tumor epithelial SPARC nor plasma SPARC was associated with OS[22]. This exploratory analysis does not support making treatment decisions regarding nab-paclitaxel plus gemcitabine or gemcitabine alone in metastatic pancreatic adenocarcinoma based on SPARC expression.

Goldstein *et al*[23] have performed a post hoc analysis of the MPACT trial with data collected by May 9, 2013. In this extended follow-up study, they found that the median OS for nab-paclitaxel plus gemcitabine group was more than 2 mo longer than gemcitabine alone (8.7 mo *vs* 6.6 mo, HR = 0.72, $P < 0.001$); 4% of nab-paclitaxel plus gemcitabine compared to 0% of gemcitabine alone survived more than 36 mo. They further identified baseline CA 19-9 level and neutrophil-to-lymphocyte ratio (NLR) as prognostic markers for OS. An elevated NLR, which is a marker of systemic inflammation, has been associated with angiogenesis and metastasis resulting in adverse outcomes in many solid tumor malignancies including pancreatic cancer[24]. Retrospective analyses have demonstrated baseline NLR greater than five predicts worse OS in patients with advanced pancreatic cancer receiving palliative chemotherapy[25-27]. In the pooled treatment arm analysis of the MPACT trial, 543 patients with baseline NLR $\leqslant 5$ had a significantly longer OS than 309 patients whose baseline NLR > 5 (9.1 mo *vs* 5.0 mo, HR = 1.839, $P < 0.001$). In patients with baseline NLR $\leqslant 5$, better OS was noted in the nab-paclitaxel and gemcitabine group compared to gemcitabine alone (10.9 mo *vs* 7.9 mo, HR = 0.67, $P < 0.001$); however, there was no significant OS difference in patients whose baseline NLR > 5, treated with nab-paclitaxel plus gemcitabine or gemcitabine alone (5.6 mo *vs* 4.3 mo, HR = 0.81, $P = 0.079$).

The median baseline CA 19-9 level for all patients in MPACT trial was 2470 U/mL; 15% of patients had normal baseline CA 19-9 level, and 52% of patients had baseline CA 19-9 level $\geqslant 59 \times$ ULN, equally distributed between 2 treatment arms. In patients with

Table 1 Advanced ongoing trials with nab-paclitaxel in pancreatic adenocarcinoma

Trial	Trial phase	Treatment regimen	Primary endpoint	Planned patients number
NCT01964430 (APACT) after resection	III	Adjuvant nab-paclitaxel and gemcitabine *vs* gemcitabine alone	Disease-free survival	800
NCT02562716 (SWOG 1505) in resectable disease	II	Perioperative nab-paclitaxel and gemcitabine *vs* FOLFIRINOX	2-yr overall survival	112
NCT02047513 (NEONAX) in resectable disease	II	Perioperative nab-paclitaxel and gemcitabine *vs* adjuvant nab-paclitaxel and gemcitabine	Disease-free survival	166
NCT01921751 (RTOG 1201) in locally advanced disease	II	Upfront nab-paclitaxel and gemcitabine followed by standard *vs* high intensity radiation	2-yr overall survival	346
NCT02301143 (LAPACT) in locally advanced disease	II	Upfront treatment with nab-paclitaxel and gemcitabine	Time to treatment failure	110
NCT02436668 (RESOLVE) in metastatic disease	III	1st-line with nab-paclitaxel and gemcitabine ± ibrutinib	Progression-free survival	326
NCT02715804 (HALO-301) in metastatic disease	III	1st-line with nab-paclitaxel and gemcitabine ± PEGPH20	Progression-free and overall survival	420
NCT02399137 (CARRIE) in metastatic disease	II	1st-line with nab-paclitaxel and gemcitabine ± istiratumab	Progression-free survival	260
NCT02551991 in metastatic disease	II	1st-line nab-paclitaxel and gemcitabine, *vs* nal-IRI/LV/5-FU ± oxaliplatin	Progression-free survival rate at 24 wk	168

a baseline CA 19-9 level ⩾ median, the nab-paclitaxel plus gemcitabine arm had a significantly longer OS than the gemcitabine arm (HR = 0.612, $P < 0.001$). In the gemcitabine arm, OS was longer in patients whose baseline CA 19-9 level < median compared to patients whose baseline CA 19-9 level ⩾ median (HR = 0.773, $P = 0.001$); however OS was similar regardless of baseline CA 19-9 level in patients treated with nab-paclitaxel and gemcitabine. A higher proportion of patients with baseline CA 19-9 level ⩾ 59 × ULN survived 2 years or longer in the nab-paclitaxel and gemcitabine group than in the gemcitabine group (55% *vs* 15%). Thus, nab-paclitaxel may reduce the negative impact of elevated baseline CA 19-9 level on OS for patients with metastatic pancreatic adenocarcinoma receiving nab-paclitaxel and gemcitabine as upfront treatment.

Chiorean *et al*[28] further examined the CA 19-9 decrease at 8 wk as a predictor of OS in the MPACT study. Combining both treatment arms for analysis, patients with any CA 19-9 decline *vs* those without (20% of combined treatment patients) had improved OS (median 11.1 mo *vs* 8.0 mo, $P = 0.005$). In the nab-paclitaxel plus gemcitabine arm, patients with *vs* without (18% of this treatment arm) any CA 19-9 decrease at week 8 had a confirmed overall RR of 40% *vs* 13%, and a median OS of 13.2 mo *vs* 8.3 mo ($P = 0.001$), respectively. In the gemcitabine arm, patients with *vs* without (21% of this treatment arm) CA 19-9 decrease at week 8 had a confirmed ORR of 15% *vs* 5%, and median OS of 9.4 mo *vs* 7.1 mo ($P = 0.404$), respectively. This analysis demonstrated that in patients with pancreatic adenocarcinoma receiving nab-paclitaxel and gemcitabine as front-line treatment, any CA 19-9 decrease at week 8 can be a predictive marker for chemotherapy efficacy and improved clinical outcomes including survival benefit.

Current investigation

Nab-paclitaxel and gemcitabine is currently under active investigation in neoadjuvant and adjuvant settings for patients with resectable pancreatic adenocarcinoma (Table 1). Furthermore, many studies in different phases have explored the combination of novel therapeutics with nab-paclitaxel/gemcitabine in the metastatic setting. These novel agents include Bruton tyrosine kinase inhibitor (ibrutinib, NCT02436668), pegylated recombinant human hyaluronidase (PEGPH20, NCT02715804), antibody against programmed death receptor 1 (PD-1) (nivolumab, NCT02309177), cancer stemness inhibitor (BBI-608, NCT02231723), phosphatidylinositol 3-kinase (PI3K) inhibitor (BYL719, NCT02155088), antibody against IGF-1R and ErbB3 (istiratumab, NCT02399137), *etc*. The combination of nab-paclitaxel and gemcitabine has become the platform of research for combining targeted agents in advancing the management of pancreatic adenocarcinoma.

PEGPH20 removes hyaluronan or hyaluronic acid (HA). HA is a glycosaminoglycan, which is the major component of extracellular matrix. Many solid tumors including pancreatic adenocarcinoma, have been shown to secrete high levels of HA, which can lead to unusually elevated interstitial fluid pressure collapsing the tumor's blood vessels. This in turn attenuates the delivery of chemotherapeutic agents into tumor tissues[29]. In preclinical studies, PEGPH20 removed HA from tumors, reduced tumor interstitial fluid pressure, and enhanced the effects of chemotherapy in mouse models of pancreatic adenocarcinoma[30,31].

In a randomized phase II study in metastatic pancreatic adenocarcinoma investigating nab-paclitaxel/gemcitabine with or without PEGPH20 as a first-line therapy, patients with HA-high tumors showed significant improvement in PFS and a trend toward

improved OS after receiving nab-paclitaxel/gemcitabine and PEGPH20 combination[32]. This study enrolled 135 patients, 74 received the 3-drug combination while 61 received nab-paclitaxel and gemcitabine. Forty-four patients had HA-high tumors; PFS was 9.2 mo in 23 patients treated with the 3-drug combination *vs* 4.3 mo in 21 patients treated with nab-paclitaxel/gemcitabine (HR = 0.39, P = 0.05). The global phase Ⅲ study has been launched in early 2016 to assign patients with HA-high metastatic pancreatic adenocarcinoma to nab-paclitaxel/gemcitabine with or without PEGPH20 as first-line treatment (NCT02715804).

NANOLIPOSOMAL IRINOTECAN (NAL-IRI, PEP02, MM-398)

Mechanism of action

Irinotecan has a complicated pharmacology that causes it to have a narrow therapeutic index. Irinotecan exists in a pH and serum protein dependent equilibrium between the active lactone form (stable in acidic pH) and the inactive carboxylate form (stable in neutral to basic pH)[33]. Therefore, in normal physiologic pH, the lactone form rapidly hydrolyzes and is inactivated. This instability of the active drug molecule at physiological pH is a major obstacle in attaining efficacy. Moreover, only a small fraction of irinotecan is converted to its more potent metabolite SN-38, which requires metabolism by carboxylesterases (CES) in the liver with variability among patients. It has been shown that more than 50% of pancreatic adenocarcinoma express CES, and high CES2 expression in tumor tissue was associated with longer overall survival in resectable and borderline resectable patients who underwent neoadjuvant FOLFIRINOX treatment[34].

SN-38 is eliminated by the biliary system, after glucuronidation from the uridine diphosphate glucuronosyltransferase (UGT)1A1 enzyme. The glucoronidated SN-38 can be converted back to SN-38 by beta-glucoronidase enzymes secreted from the intestinal flora in the gut. Retrospective analyses have demonstrated that individuals who are homozygous for UGT1A1*28 are at an increased risk of developing irinotecan-related neutropenia and diarrhea toxicities[35,36]. This UGT1A1*28 polymorphism is characterized by the presence of an additional TA repeat in the TATA sequence of the UGT1A1 promoter, causing markedly decreased expression of UGT1A1, which leads to slower SN-38 glucuronidation, and a greater SN-38 plasma concentration over time. It is estimated that about 10% of Caucasians may be homozygous for UGT1A1*28, and the prevalence is lower in Asians. Other variants have been reported and characterized; UGT1A1*6 which occurs at exon 1 and reduces catalytic function of UGT1A1 by 60% is more commonly seen in Asians and can cause severe neutropenia after irinotecan treatment[37].

In an attempt to overcome these pharmacological limitations of irinotecan with the goals of improved efficacy and decreased toxicity, nal-IRI was developed[38]. This is a novel formulation that encapsulates irinotecan in an approximately 100 nm spherical liposome with high drug load (approximately 80000 molecules of irinotecan per liposome) and high stability that surpasses previously developed liposomal formulations (including liposomal anthracyclines). This is done using novel gradient based drug loading technology with a highly charged, nonpolymeric anion sucrose octasulfate. The liposome formulation allows for protection of irinotecan in its lactone form from hydrolysis in the serum until it reaches the tumor site. The end result of this nanoliposomal formulation on irinotecan pharmacology is slower drug elimination, lower plasma concentration, and enhanced accumulation of the drug into the tumor site. The formulation of nal-IRI has been shown to improve the pharmacokinetics and tumor bio-distribution of both irinotecan and its active metabolite SN-38 with less toxicity in mouse xenograft study[39-41]. Moreover, nal-IRI demonstrated increased efficacy compared to free irinotecan in pancreatic cancer xenograft study[42].

Clinical studies

The first-in-human phase Ⅰ study conducted in advanced refractory solid tumors confirmed the favorable pharmacokinetics of the liposomal formulation of irinotecan[43]. The maximum tolerated dose (MTD) of nal-IRI intravenously for 90 min every 3 wk was 120 mg/m^2 (equivalent to 100 mg/m^2 of free irinotecan); the toxicity profile remained similar to that of free-form irinotecan, with diarrhea and myelosuppression being the dose limiting toxicities. This study observed slow release of irinotecan from liposomes, small volume of distribution in plasma, slow clearance, prolonged terminal half-life of circulating total irinotecan, and a favorable pharmacokinetics of the active metabolite SN-38. Two patients achieved partial response, including one patient with pancreatic cancer who failed prior gemcitabine-based treatment. This promising result was further observed in another phase Ⅰ trial in advanced solid tumors studying dose-escalating nal-IRI in combination with weekly 24-h infusion of high-dose LV/5-FU[44]. The MTD of nal-IRI in combination with weekly 24-h infusion of high-dose LV/5-FU given every-3-wk was 80 mg/m^2 (equivalent to 70 mg/m^2 free irinotecan). In these two phase Ⅰ trials, 7 pancreatic cancer patients who failed gemcitabine-based regimen received nal-IRI with or without weekly 24-h infusion of high-dose LV/5-FU. There was 1 patient with partial response, 4 patients with stable disease, and 2 patients with progressive disease. This indicated a potential activity of nal-IRI as a second-line treatment in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma[45].

Based on the promising activity from phase Ⅰ and preclinical studies, a phase Ⅱ study of nal-IRI was conducted in 40 patients with metastatic pancreatic

adenocarcinoma following progression on gemcitabine-based therapy[46]. Patients were given nal-IRI 120 mg/m^2 every 3 wk with a primary end point of 3-mo OS. The study met its primary endpoint with 75% of patients surviving at least 3 mo and 25% reaching 1 year. The median PFS was 2.4 mo and OS was 5.2 mo. Three patients (7.5%) achieved an objective response, with an additional 17 (42.5%) demonstrating stable disease. Ten (31.3%) of 32 patients with an elevated baseline CA 19-9 had a > 50% biomarker decline. In terms of safety, nal-IRI was generally well tolerated with gastrointestinal and hematologic toxicities being the most common toxicities, as well as fatigue and abdominal pain. Twenty-six patients (65%) experienced at least one grade 3 or higher adverse event. Dose modification due to adverse events was required in 11 patients (27.5%). The results implied the feasibility and activity of nal-IRI in gemcitabine-refractory advanced pancreatic adenocarcinoma.

The combination of nal-IRI and LV/5-FU was compared to free-form irinotecan and LV/5-FU (FOLFIRI) in a multicenter, open-label, noncomparative, randomized phase Ⅱ study (PEPCOL) as second-line treatment in patients with metastatic colorectal cancer[47]. Patients who had failed one prior oxaliplatin-based first-line therapy were randomized to every 14-d FOLFIRI or nal-IRI with LV/5-FU (nal-IRI 80 mg/m^2 IV over 90 min, followed by LV 400 mg/m^2 iv over 2 h, then 5-FU 2400 mg/m^2 continuous infusion over 46 h). Bevacizumab (5 mg/kg every 14 d) was allowed in both arms. The primary endpoint was 2-mo response rate (RR). Fifty-five patients were randomized (FOLFIRI, n = 27; nal-IRI/LV/5-FU, n = 28), and the 2-mo RR was 7.4% and 10.7% in the FOLFIRI and nal-IRI/LV/5-FU, respectively. The most common grade 3-4 adverse events reported in the FOLFIRI and nal-IRI/LV/5-FU were diarrhea (33% *vs* 21%), neutropenia (30% *vs* 11%), mucositis (11% *vs* 11%), and grade 2 alopecia (26% *vs* 25%). The results of the PEPCOL study suggested that the nal-IRI/LV/5-FU regimen was more active than the standard FOLFIRI regimen in patients with oxaliplatin-pretreated metastatic colorectal cancer with an acceptable safety profile. Based on the preliminary results of the PEPCOL study, the nal-IRI/LV/5-FU combination regimen was added as the third arm of the phase Ⅲ NAPOLI-1 study in metastatic pancreatic cancer.

The pivotal NAPOLI-1 study was an open label, randomized, international phase Ⅲ study that enrolled 417 patients across 76 sites in 14 countries worldwide[48]. In version 1 of the protocol, it assigned patients with metastatic pancreatic adenocarcinoma that progressed on first-line gemcitabine-based therapy in a 1:1 ratio to receive either nal-IRI 120 mg/m^2 alone over 90 min every 3 wk, or the control arm with LV 200 mg/m^2 infused over 30 min followed by 5-FU 2000 mg/m^2 over 24 h, every week for the first 4 wk of each 6-wk cycle. Sixty-three patients were enrolled on version 1 of the protocol: 33 in nal-IRI and 30 in the control arm. After the PEPCOL study demonstrated the feasibility of nal-IRI/LV/5-FU (nal-IRI 80 mg/m^2 IV over 90 min, followed by LV 400 mg/m^2 IV over 2 h, then 5-FU 2400 mg/m^2 continuous infusion over 46 h, every 14 d), this combination regimen was added as a third arm in version 2 of the protocol. There were 117 patients assigned to nal-IRI/LV/5-FU, 119 patients assigned to the control arm, and 118 patients assigned to nal-IRI alone on version 2 of the protocol. For all the efficacy comparisons, the 117 patients assigned to the combination arm were compared to 119 patients assigned to the control arm on version 2 of the protocol, whereas patients assigned to nal-IRI were compared to the control arm under both version 1 and 2 of the protocol. It demonstrated a statistically significant increase in OS for the combination of nal-IRI/LV/5-FU (6.1 mo) *vs* the control arm (4.2 mo) (HR=0.57, 95%CI: 0.41-0.80, and P = 0.0009).

The objective RR was 7.7% *vs* 0.8%, for the combination and control, respectively. For those with baseline CA 19-9 levels of > 30 U/mL at baseline (84% in the combination arm), there was a ⩾ 50% reduction in the marker for 29% of patients treated with the nal-IRI/LV/5-FU *vs* 9% in the control arm (P = 0.0006). Nal-IRI monotherapy did not demonstrate superior efficacy compared with LV/5-FU. The rates of diarrhea were 12.8% *vs* 21.1% and the rates of vomiting were 11.1% *vs* 13.6% for the nal-IRI combination *vs* single-agent, respectively. Additionally, febrile neutropenia occurred in 1.7% of patients in the combination arm compared with 4.1% with nal-IRI alone, and not at all with the control arm. Nal-IRI alone was associated with more adverse events compared with the nal-IRI/LV/5-FU, indicating that nal-IRI should only be used in combination with LV/5-FU in pancreatic adenocarcinoma.

An expanded analysis was conducted in the per-protocol population, which was defined as patients who received ⩾ 80% of the protocol defined dose and were able to remain on treatment for at least 6 wk[49]. This analysis further validated the initial data results with a median OS of 8.9 mo for the combination arm *vs* 5.1 mo for the control (HR = 0.47 95%CI: 0.29-0.77, and P = 0.0018). Moreover, there was a significant increase in PFS (overall and at 3 mo), overall RR, and CA 19-9 response for the combination *vs* the control. The safety profile was manageable with most frequent grade 3 or 4 adverse effects being neutropenia, fatigue, and GI effects (diarrhea and vomiting) in the combination arm. Based on the NAPOLI-1, nal-IRI in combination with 5-FU/LV has been approved by United States FDA in October 2015 for patients with metastatic pancreatic adenocarcinoma who have progressed from gemcitabine-based treatment.

An open-label phase Ⅱ comparative study is currently underway to explore the safety and efficacy of adding oxaliplatin to nal-IRI/LV/5-FU as 1st-line treatment in metastatic pancreatic adenocarcinoma

Table 2 Advanced nanomedicines studied in clinical trials for pancreatic adenocarcinoma

Nanomedicine	Nanoplatform	Status	Reference/trial information
Nanoplatin (NC-6004)	Polymeric nanoparticle (PEG-polyaspartate) of cisplatin	Phase Ⅲ on going in advanced disease as 1st-line; 290 patients expected	NCT02043288; gemcitabine ± NC6004
EndoTAG-1	Cationic liposome encapsulated paclitaxel	Phase Ⅱ (with gemcitabine *vs* gemcitabine) published in 2012	Löhr *et al*[56] 2012/NCT00377936
Genexol-PM	Methoxy-PEG-poly(D,L-lactide) based formulation of paclitaxel	Phase Ⅱ monotherapy published in 2010	Saif *et al*[65] 2010/NCT00111904
Rexin-G	Pathotropic nanoparticle with cytocidal cyclin G1 construct	Phase Ⅰ/Ⅱ monotherapy published in 2010	Chawla *et al*[66] 2010/NCT00504998
Lipoplatin	Liposomal formulation of cisplatin	Phase Ⅰ/Ⅱ (with gemcitabine) published in 2006	Stathopoulos *et al*[67] 2006
Caelyx/Doxil	Liposomal formulation of doxorubicin	Phase Ⅱ monotherapy published in 1995 and 2001	Schwartz *et al*[68] 1995; Halford *et al*[69] 2001

(NCT02551991)[50]. This study will initiate part 1 as a safety and tolerability run-in of nal-IRI/LV/5-FU/LV and oxaliplatin combination. About 6 to 18 patients are enrolled on a traditional dose escalation design to confirm the target dose of oxaliplatin. Part 2 is a randomized, efficacy study to assign approximately 160 patients to 3 treatment arms: (1) nal-IRI/LV/5-FU and oxaliplatin; (2) nal-IRI/LV/5-FU; and (3) nab-paclitaxel and gemcitabine (control arm). The primary endpoint is PFS rate at 24 wk, and secondary endpoints are OS, PFS, and RR. Additionally, pharmacokinetic data will be collected in part 1 of the study.

Analyses of biomarker and pharmacokinetics

A biomarker analysis at the 2016 ASCO GI Cancers Symposium looked specifically at the impact of CA 19-9 levels on the efficacy in NAPOLI-1[51]. In this analysis, there was a greater treatment effect from nal-IRI/LV/5-FU on OS with higher CA 19-9 level relative to the control 5-FU/LV. Median OS was similar between the nal-IRI/LV/5-FU combination arm and the control for those with CA 19-9 levels < 120 U/mL (7.6 mo *vs* 7.2 mo; HR = 1.12). As CA 19-9 levels increased, the benefit with nal-IRI combination became more dramatic. In those with CA 19-9 levels ≥ 12815 U/mL, median OS was 4.6 *vs* 1.9 mo in the nal-IRI/LV/5-FU (n = 26) *vs* the control arm (n = 26; HR = 0.35; 95%CI: 0.19-0.64). The CA 19-9 serum level provided important information with regards to overall survival in NAPOLI-1.

The population pharmacokinetics and exposure-safety relationship of nal-IRI were evaluated in 353 patients with advanced solid tumors receiving nal-IRI 60-120 mg/m^2 on 6 clinical studies[52]. Both age (28 to 87 years) and gender after adjusting for body surface area (BSA) had no clinically meaningful effect on the exposure of irinotecan and SN-38. Mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. SN-38 maximum plasma concentration (Cmax) was associated with incidence of severe neutropenia and anemia (grade 3 or higher), and IRI Cmax was associated with incidence of severe diarrhea (grade 3 or higher). Compared to Caucasians, Asians had a 0.5-fold lower IRI Cmax, corresponding to a 5% lower predicted severe diarrhea. In contrast, Asians had a 1.5-fold higher SN-38 Cmax than Caucasians, corresponding to a 7% higher predicted severe neutropenia. Compared to patients with bilirubin < 1 mg/dL, patients with bilirubin 1-2 mg/dL had a 1.4-fold higher SN-38.

OTHER NANOMEDICINES

We have summarized 6 frequently mentioned nanomedicines that have been clinically studied in pancreatic adenocarcinoma (Table 2). Among these 6 compounds, only nanoplatin (NC-6004) is still under active investigation in pancreatic adenocarcinoma. Nanoplatin is a novel cisplatin-incorporating polymeric micelle formulation that retains the activity but avoids the renal toxicity and neurotoxicity caused by the high peak Cmax concentrations of cisplatin[53,54]. A phase Ⅰ/Ⅱ trial of nanoplatin in combination with gemcitabine in patients with advanced pancreatic adenocarcinoma was conducted in Asia and reported in 2012 ESMO congress. Among 19 patients enrolled, partial response was found in 1 (5.9%) and stable disease in 10 (58.8%) patients; the disease control rate was 64.7%. The combination of nonoplatin and gemcitabine was well tolerated and demonstrated modest efficacy in patients with advanced pancreatic adenocarcinoma. Therefore a phase Ⅲ study in advanced pancreatic adenocarcinoma comparing nanoplatin with gemcitabine *vs* gemcitabine alone as front-line therapy was launched in 2014 with expected accrual of 290 patients and completion in 2017.

EndoTAG-1 is a formulation in which paclitaxel is embedded in a cationic liposome membrane. The positively charged liposomes have a high affinity to the endothelial cells of tumor blood vessels, leading to selective targeting and delivery of paclitaxel to the tumor microenvironment[55]. An open-label, randomized, controlled multicenter phase Ⅱ trial was conducted in order to evaluate the safety and efficacy of EndoTag-1 in treatment naïve patients with locally

advanced or metastatic pancreatic adenocarcinoma[56]. Two hundred and twelve patients were randomly assigned to one of four treatment arms: gemcitabine monotherapy or a combination of gemcitabine and EndoTAG-1 administered at 3 different dose levels: 11 mg/m^2 (Endo11), 22 mg/m^2 (Endo22) and 44 mg/m^2 (Endo44). Median overall survival rates were higher in the combination arms at 8.1 mo for Endo11 (HR = 0.93), 8.7 mo for Endo22 (HR = 0.69), and 9.3 mo for Endo44 (HR = 0.66) *vs* 6.8 mo for gemcitabine alone. Similarly, PFS times were longer in the combination arms with PFS of 4.1 mo for Endo11 (HR = 0.84), 4.6 mo for Endo22 (HR = 0.58), and 4.4 mo for Endo44 (HR = 0.74) *vs* 2.7 mo for gemcitabine monotherapy. The 12-mo survival rates were also higher at 21%, 35%, and 30% for Endo11, Endo22, and Endo44, respectively, compared to 15% for gemcitabine alone. In terms of safety, there were marginal additive adverse reactions in the combination groups compared to gemcitabine monotherapy. Combination therapy resulted in a dose dependent increase in the severity of thrombocytopenia as well as the frequency of infusion-related reactions (mainly pyrexia and chills). There was no evidence of clinically relevant organ toxicity or neurotoxicity or deaths relating to the study medication. Moreover, there was no cumulative toxicity of EndoTAG-1 in combination with gemcitabine after repeated treatment cycles or additive effects to gemcitabine's liver toxicity. This randomized phase Ⅱ study demonstrated a better efficacy for the combination of gemcitabine and EndoTag-1 with acceptable toxicity profiles. A phase Ⅲ trial has been planned to confirm these results and identify a potential role for EndoTAG-1 in combination with gemcitabine in advanced pancreatic adenocarcinoma[57].

CONCLUSIONS AND PLACE IN THERAPY

The systemic treatment of pancreatic adenocarcinoma remains a daunting task but improved survival has been more obvious since early 2010 when FOLFIRINOX and nab-paclitaxel/gemcitabine have become standard first-line treatment options. Since October 2015, nal-IRI/LV/5-FU has been approved as second-line therapy in advanced pancreatic adenocarcinoma after failing gemcitabine-based treatment. Retrospective analysis of MPACT trial showed second-line treatment was feasible and extended patients' survival after failing front-line therapy[58]. Patients who received any second-line therapy after progression had a median OS of 12.8 mo if their initial treatment was nab-paclitaxel and gemcitabine compared with 9.9 mo if they received gemcitabine alone in the first line setting. This has echoed the recommendation from NCCN guideline in metastatic pancreatic adenocarcinoma for patients with good performance status, *i.e.*, ECOG 0-1 with adequate pain control and nutritional status and without obstructive jaundice, to continue on systemic treatment after failing first-line treatment. The keys to successful second-line treatment are patient selection and regimen selection. Therefore clinical trials with novel therapeutics/strategies will be ideal for patients to participate in if there is no standard of care such as progression after FOLFIRINOX. A phase Ⅱ study reported by French investigators with nab-paclitaxel/gemcitabine as second-line treatment showed promising activity in patients with rapid progression (PFS less than 248 d) from FOFIRINOX as first-line treatment[59].

Identification of prognostic and predictive markers can personalize treatment and select patients for target-driven therapy. CA 19-9, NLR, HA and CES2 seem to provide useful predictive information for systemic treatment in pancreatic adenocarcinoma, but require perspective study to confirm. Elevated C-reactive protein (CRP) levels in the plasma at diagnosis correlate with higher tumor stage and grading and poorer clinical outcome in pancreatic adenocarcinoma[60]. The CRP level could be a useful marker for patient stratification, and the JAK inhibitor ruxolitinib may improve clinical outcome in patients with elevated CRP. An ongoing phase Ⅲ study, known as JANUS 2, is examining the role of a JAK inhibitor as a second-line treatment option in patients with advanced pancreatic adenocarcinoma[61].

A hallmark of pancreatic adenocarcinoma is the presence of a dense desmoplastic stroma that consist largely of fibroblasts, immune cells, endothelial cells, pancreatic stellate cells, extracellular matrix proteins, *etc.*[62]. This provides an excellent milieu to test novel therapeutics including nanomedicines (with EPR effect) and immune checkpoint inhibitors such as antibody against PD-1. The PD-1 is primarily expressed by activated T-cells as negative co-stimulatory receptor; binding of PD-1 to its ligands, PD-L1 and PD-L2, downregulates T-cells and the immune system[63]. Many tumor cells express PD-L1 and PD-L2 which is a mechanism which allows escape from immune destruction of the tumor cells. The combination of nanomedicine and antibody against PD-1 seems to provide a good stroma targeting effect and will be tested in pancreatic adenocarcinoma (NCT02309177)[64].

Besides delivery through EPR effect, nanomedicines can be harnessed with targeting system to reach the malignant tissue or cells more promptly and precisely. With the advance of technology and better understanding of cancer biology, we are confident that the next-generation nanomedicines will greatly advance cancer treatment and improve patients' outcome.

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Effects of nal-IRI (MM-398) ± 5-Fluorouracil on Quality of Life (QoL) in NAPOLI-1: A Phase 3 Study in Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy

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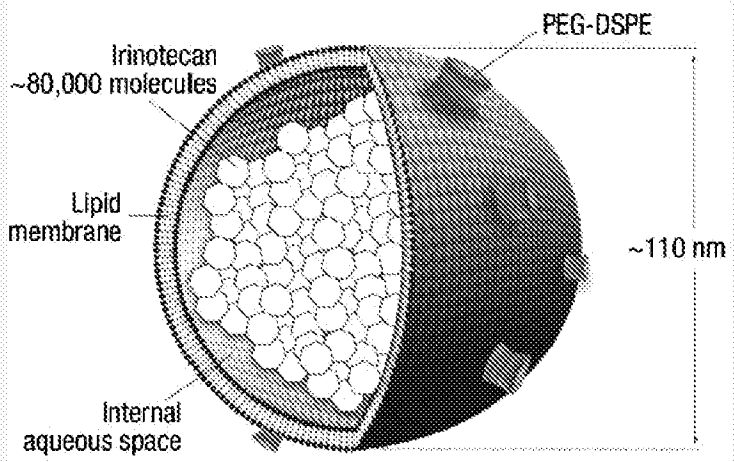
BACKGROUND

- Pancreatic cancer is the fourth leading cause of cancer-related death in Europe, and the seventh leading cause of cancer-related death worldwide[1,2]
- Survival rates for pancreatic cancer are poor because of rapid disease progression and difficulties in diagnosis[3]
  - 1-year survival, 15%
  - 5-year survival, 4%
- Gemcitabine-based therapies and FOLFIRINOX are the standard first-line treatments for pancreatic cancer; however, there is no standard treatment for patients with metastatic disease who have progressed on first-line therapy[4]
- nal-IRI (MM-398) is a novel liposomal formulation of irinotecan that exhibits extended circulation and enhanced intratumoral drug deposition when compared with nonliposomal (ie, conventional) irinotecan (**Figure 1**)[5,6]
- nal-IRI is approved by the US Food and Drug Administration, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), for use following disease progression in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy[7]

Figure 1. nal-IRI design.



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

- NAPOLI-1 was a phase 3 trial evaluating the efficacy and safety of nal-IRI, as monotherapy and in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with mPDAC previously treated with gemcitabine-based therapy[6]
  - As of the data cutoff of February 14, 2014 (primary analysis) 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]; $P = 0.012$), but did not differ significantly between nal-IRI monotherapy and 5-FU/LV (4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77-1.28]; $P = 0.94$)
  - Median PFS was significantly longer with nal-IRI + 5-FU/LV compared with 5-FU/LV (3.1 vs 1.5 months; unstratified HR, 0.56; 95% CI, 0.41-0.75; $P = 0.0001$)
  - Median ORR was significantly higher with nal-IRI + 5-FU/LV compared with 5-FU/LV (16% vs 1%; $P < 0.0001$)
  - nal-IRI + 5-FU/LV exhibited a manageable safety profile; grade 3/4 adverse events (AEs) occurring more frequently with nal-IRI + 5-FU/LV vs 5-FU/LV included neutropenia (27% vs 1%), fatigue (14% vs 4%), diarrhea (13% vs 4%), and vomiting (11% vs 3%)

OBJECTIVES

- To assess the quality of life (QoL) in patients receiving nal-IRI + 5-FU/LV and 5-FU/LV from the NAPOLI-1 study

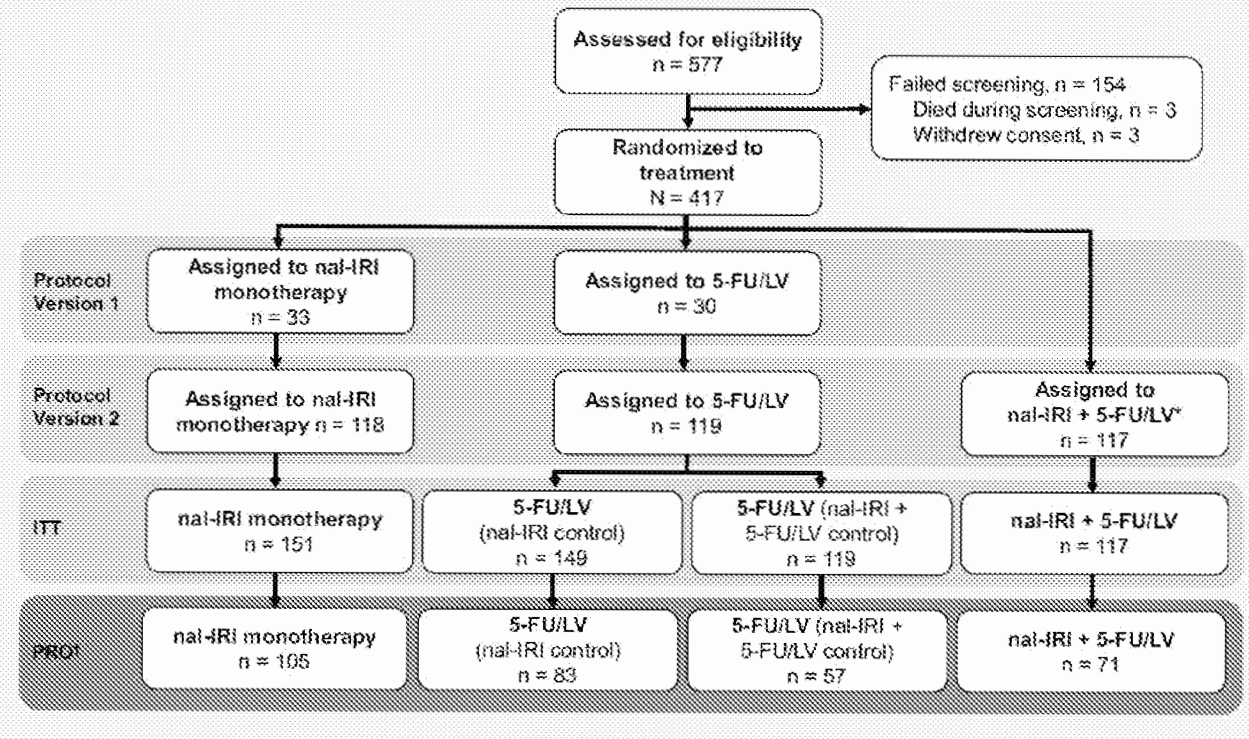
METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (**Figure 2**)
  - Patients were initially randomized to nal-IRI monotherapy (120 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 100 mg/m^2 irinotecan free base every 3 weeks) or 5-FU/LV (200 mg/m^2 LV and 2000 mg/m^2 5-FU, every week for the first 4 weeks of each 6-week cycle; protocol version 1)
  - Once safety data for the combination treatment became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a third arm, nal-IRI + 5-FU/LV (80 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 70 mg/m^2 irinotecan free base every 2 weeks; 400 mg/m^2 LV and 2400 mg/m^2 5-FU every 2 weeks; protocol version 2)
- QoL was assessed at baseline, every 6 weeks, and at the 30-day post–follow-up visit, using the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (EORTC-QLQ-C30) version 3.0[9]
  - QoL was assessed in all patients in the intention-to-treat (ITT) population who provided baseline and ≥1 subsequent QoL assessment (patient-reported outcome [PRO] population); patients were classified by the treatment arm to which they were randomized (**Figure 2**)
  - QoL was assessed in 3 independent domains (global health status, functionality, and symptomatology) across 15 scales
  - Linear transformations were applied to raw scores so that the reported score ranged from 0-100 for each scale
  - Patients were classified into 1 of 3 categories:
    - Improved: Patient had scores ≥10% above baseline and remained above baseline value for ≥6 weeks
    - Stable: Patient did not meet criteria for improved or worsened
    - Worsened: Patient did not meet improvement criteria and died, or had scores that decreased by 10%

— Pairwise treatment group comparisons were performed using Cochran-Mantel-Haenszel testing adjusted for multiplicity with a Benjamini-Hochberg correction to control false discovery rate at 0.05 level for the 15 comparisons

Figure 2. Trial profile.



*Study was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination became available; 63 patients had already been enrolled in the original 2-arm study at the time of amendment.
†Used for QoL analyses; included all patients in the ITT population who provided a baseline and ≥1 subsequent QoL assessment.
5-FU, fluorouracil; ITT, intention-to-treat; LV, leucovorin; nal-IRI, liposomal irinotecan; PRO, patient-reported outcome population; QoL, quality of life

Eligibility Criteria

Key Inclusion Criteria

- Adults ≥18 years of age
- Histologically or cytologically confirmed PDAC
- Documented measurable or nonmeasurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, 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
- Karnofsky performance status (KPS) score ≥70
- Adequate hematologic (including absolute neutrophil count >1.5 × 10^9 cells per L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function

Key Exclusion Criteria

- Active central nervous system metastasis
- Clinically significant gastrointestinal disorders
- Severe arterial thromboembolic events <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

- 71 patients (61% of the ITT population randomized under protocol version 2) in the nal-IRI + 5-FU/LV arm and 57 patients (48% of the ITT population randomized under protocol version 2) in the 5-FU/LV arm provided baseline and ≥1 subsequent EORTC assessment (PRO population)
- Patient demographics and baseline characteristics were similar between the treatment arms (**Table 1**)

Table 1. Demographics and Baseline Characteristics (PRO Population)

Parameter	nal-IRI + 5-FU/LV n = 71	5-FU/LV n = 57
Sex, n (%)		
Male	43 (60.6)	31 (54.4)
Female	28 (39.4)	26 (45.6)
Age, median (range), years	63.0 (41-81)	63.0 (41-80)
Ethnicity, n (%)		
White	42 (59.2)	39 (68.4)
East Asian	22 (31.0)	16 (28.1)
Other	7 (9.9)	2 (3.5)
KPS score, n (%)		
100	12 (16.9)	8 (14.0)
90	31 (43.7)	23 (40.4)
80	24 (33.8)	22 (38.6)
70	3 (4.2)	4 (7.0)
60	1 (1.4)	0

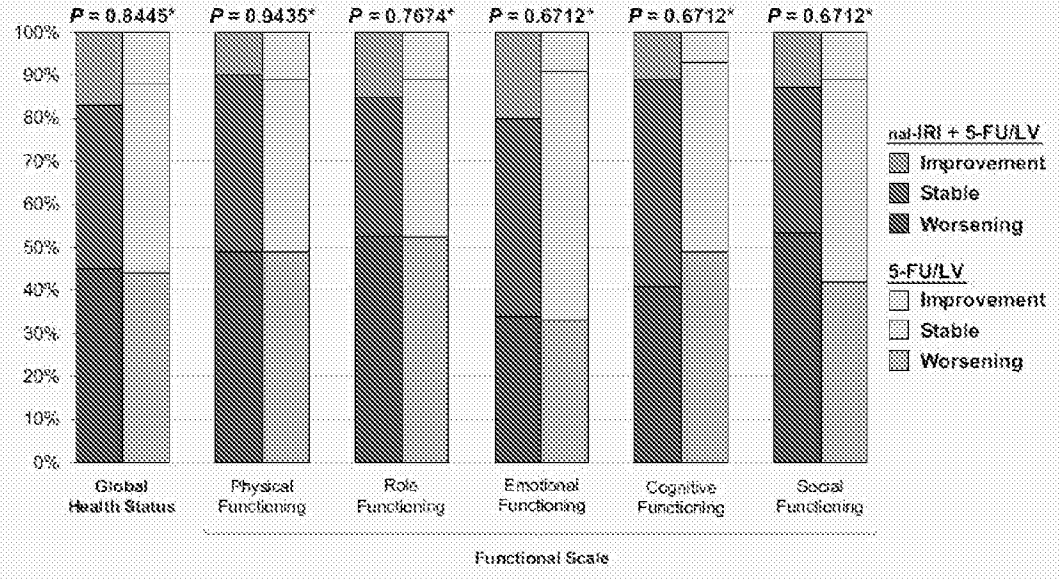
5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan

Quality of Life

- No substantial differences were identified in the proportion of patients exhibiting improved, stable, or worsening QoL in the domains of global health status or functional scale scores between the nal-IRI + 5-FU/LV and 5-FU/LV arms (**Figure 3**)

BACKGROUND

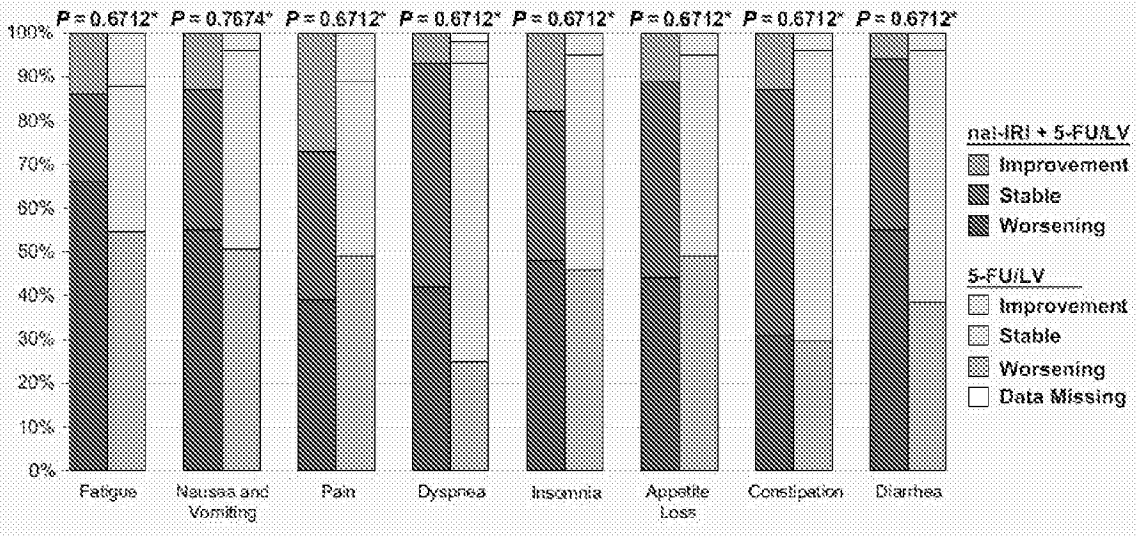
Figure 3. Proportion of patients demonstrating improvement, stability, or worsening in global health status and functional scale scores (nal-IRI + 5-FU/LV, n = 71; 5-FU/LV, n = 57).



*Benjamini–Hochberg–adjusted *P* values. The adjustment was conducted across the 15 domains of the QoL questionnaire to control the overall false discovery rate (FDR).

- No substantial differences were identified in the proportion of patients exhibiting improved, stable, or worsening QoL in symptom scale scores between the nal-IRI + 5-FU/LV and 5-FU/LV arms (**Figure 4**)

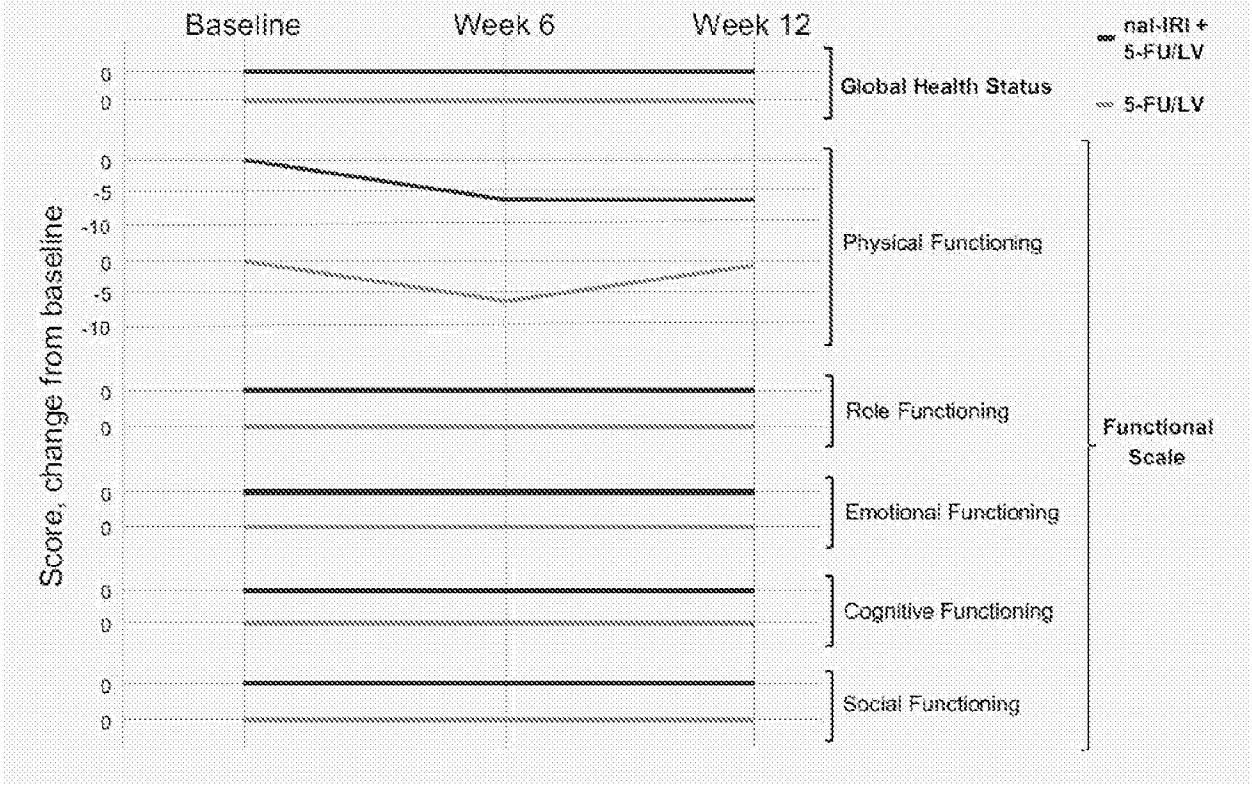
Figure 4. Proportion of patients demonstrating improvement, stability, or worsening in symptom scale scores (nal-IRI + 5-FU/LV, n = 71; 5-FU/LV, n = 57).



*Benjamini–Hochberg–adjusted *P* values. The adjustment was conducted across the 15 domains of the QoL questionnaire to control the overall FDR.

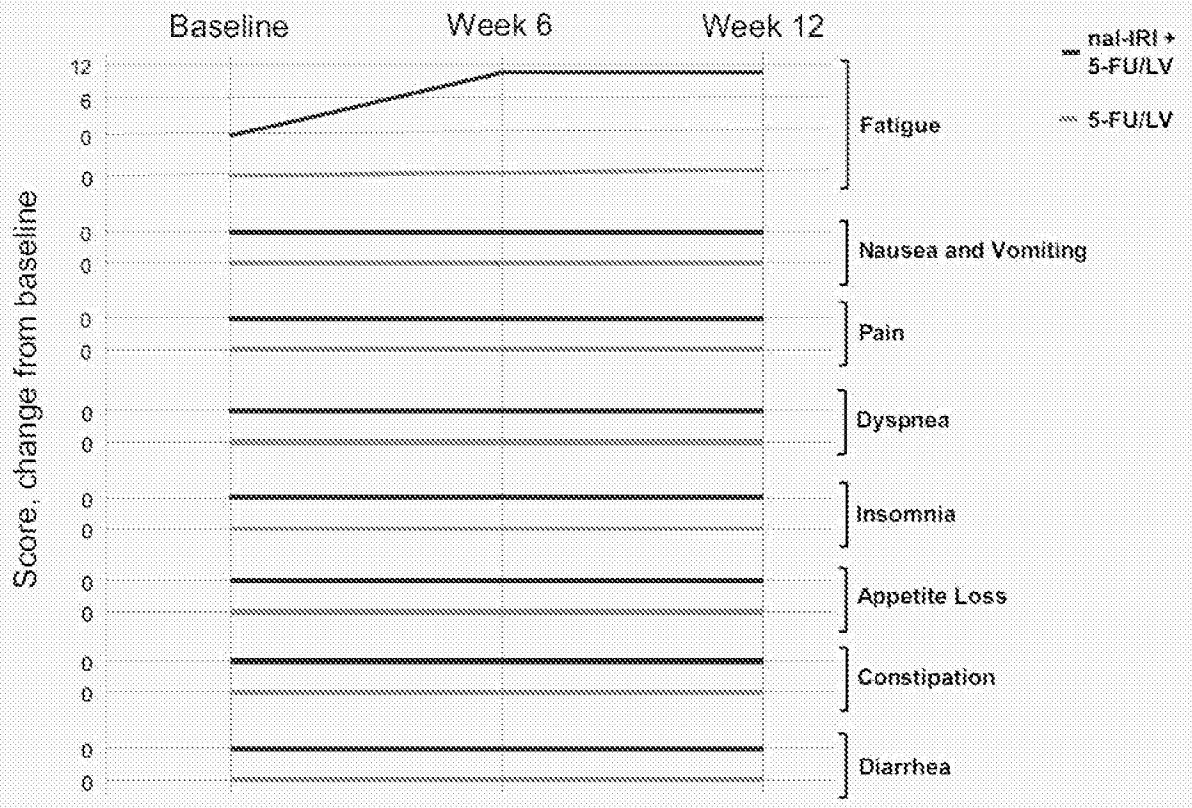
- Baseline global health status and functional scale scores ranged from 58-83 and were similar between the treatment arms
- Overall, there were no appreciable changes from baseline in global health status and functional scale scores between the nal-IRI + 5-FU/LV and 5-FU/LV arms (**Figure 5**)
  - The observed median change from baseline to week 6 in physical functioning score was 6.7 points in both arms; which corresponds to "a little" decrease[10]

Figure 5. Median change from baseline to week 12 in global health status and functional scale scores (nal-IRI + 5-FU/LV, n = 71 at baseline; 5-FU/LV, n = 57 at baseline).



- Baseline symptom scale scores ranged from 0-33 and were similar between the treatment arms
- Overall, there were no appreciable changes from baseline in symptom scale scores between the nal-IRI + 5-FU/LV and 5-FU/LV arms (**Figure 6**)
  - The observed median change from baseline to week 6 in fatigue score was approximately 11 points in the nal-IRI + 5-FU/LV arm, which corresponds to a "moderate" increase[10]

Figure 6. Median change from baseline to week 12 in symptom scale scores (nal-IRI + 5-FU/LV, n = 71 at baseline; 5-FU/LV, n = 57 at baseline).



CONCLUSIONS

- nal-IRI + 5-FU/LV significantly improves OS in patients with mPDAC previously treated with gemcitabine-based therapy compared with 5-FU/LV
- Overall, patients treated with nal-IRI + 5-FU/LV had no deterioration in QoL over 12 weeks, despite the addition of a second chemotherapeutic agent
  - Global health status and functional scale scores were not significantly different between treatment arms at baseline, and showed no appreciable change over 12 weeks
  - Median symptom scale scores at baseline ranged from 0-33 (low levels of symptomatology), and showed no appreciable change over 12 weeks
- Study limitations included limited proportions of patients with QoL data, open-label design, and inherent variability in PROs
- nal-IRI + 5-FU/LV provides a new treatment option that does not compromise QoL in patients with mPDAC previously treated with gemcitabine-based therapy

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Effects of nal-IRI (MM-398) ± 5-Fluorouracil on Quality of Life (QoL) in NAPOLI-1: A Phase 3 Study in Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy

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[1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13]

Background

Methods

Results

Conclusions

References

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Effects of nal-IRI (MM-398) ± 5-fluorouracil on quality of life (QoL) in NAPOLI-1: a phase 3 study in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

Richard Hubner,[1] Antonio Cubillo,[2] Jean-Frédéric Blanc,[3] Davide Melisi,[4] Daniel D. Von Hoff,[5] Andrea Wang-Gillam,[6] Li-Tzong Chen,[7] Claus Becker,[8] Khalid Mamlouk,[8] Bruce Belanger,[8] Yoojung Yang,[9] Floris de Jong,[10] Jens T. Siveke[11]

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Disclosures

- Celgene, advisory board, and conference attendance

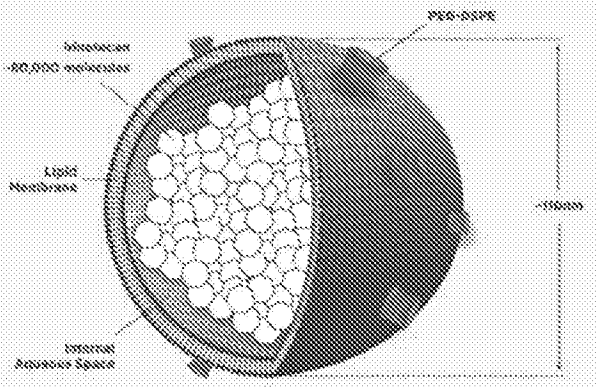
Introduction

mPDAC

- 4th leading cause of cancer-related deaths in Europe; 7th leading cause worldwide[1,2]
  - 1-year survival: 15%
  - 5-year survival: 4%
- Gemcitabine-based therapies and FOLFIRINOX are standard first-line treatments
- No standard treatment for patients with metastatic disease who have progressed on first-line therapy

nal-IRI (MM-398)

- Novel liposomal formulation of irinotecan
- Approved in the United States, in combination with 5-FU and LV, for the treatment of metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy[3]



1. Malvezzi M, et al. *Ann Oncol*. 2016;27:725-731. 2. Ferlay J, et al. *Int J Cancer*. 2015;136:E359-E386. 3. Onivyde [package insert]. Cambridge, MA: Merrimack Pharmaceuticals, Inc.; 2015.

NAPOLI-1 Study Design

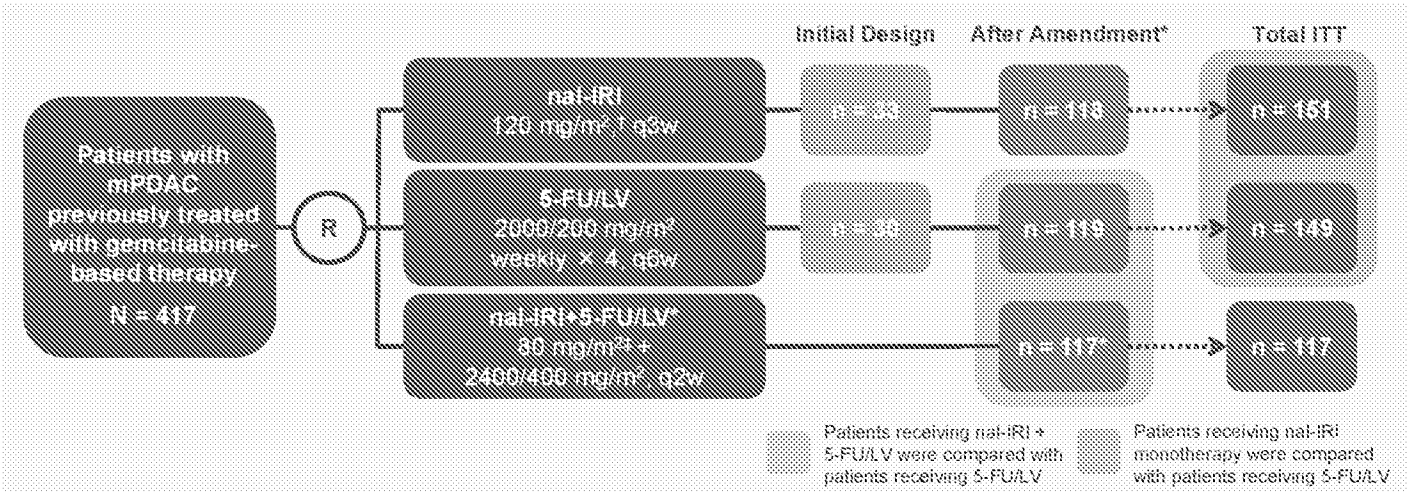
Objective: Assess efficacy and safety of nal-IRI, alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with mPDAC previously treated with gemcitabine-based therapy

Study design: Global, multicenter, open-label, phase 3 (76 sites in 14 countries)

Stratification factors: Albumin (≥40 g/L vs <40 g/L); KPS (70 and 80 vs ≥90); ethnicity (white vs East Asian vs others)

Primary end point: OS

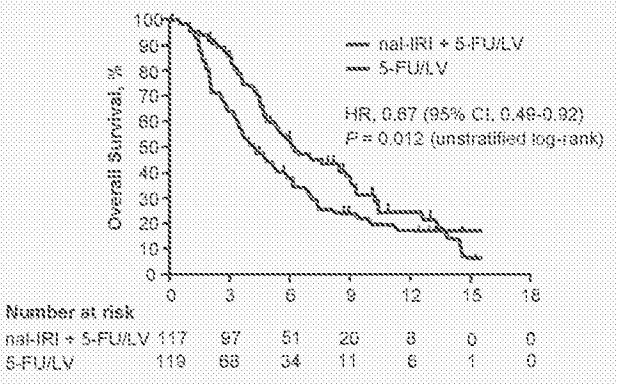
Secondary end points: PFS, TTF, ORR, CA19-9 response, CBR, QoL, safety



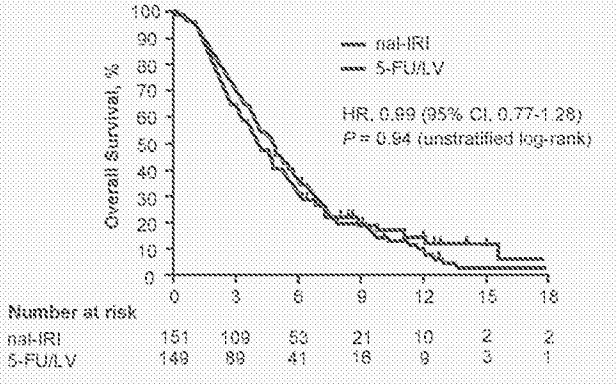
*Study was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination became available; 83 patients already had been enrolled in the original 2-arm study at the time of amendment.
†120-mg/m² dose expressed as the irinotecan hydrochloride trihydrate salt (equivalent to 100 mg/m² irinotecan free base).
‡80-mg/m² dose expressed as the irinotecan hydrochloride trihydrate salt (equivalent to 70 mg/m² irinotecan free base).
Wang-Gillam A, et al. *Lancet*. 2016;387:545-557

NAPOLI-1 Primary Results

Median OS was improved with nal-IRI + 5-FU/LV vs 5-FU/LV (6.1 vs 4.2 months)



Median OS was not improved with nal-IRI vs 5-FU/LV (4.9 vs 4.2 months)



- Median **PFS** was 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)
- **ORR** was significantly higher with nal-IRI + 5-FU/LV vs 5-FU/LV (16% vs 1%; *P* < 0.0001)
- nal-IRI + 5-FU/LV exhibited a manageable safety profile
  - Grade 3/4 AEs occurring more frequently with nal-IRI + 5-FU/LV vs 5-FU/LV included neutropenia (27% vs 1%), fatigue (14% vs 4%), diarrhea (13% vs 4%), and vomiting (11% vs 3%)

Data cutoff, February 14, 2014.
Wang-Gillam A, et al. *Lancet*. 2016;387:545-557.

NAPOLI-1 QoL Analyses

- PRO population included all patients in the ITT population who provided a baseline and ≥1 subsequent QoL assessment, and are classified by the arm they were randomized to

  nal-IRI + 5-FU/LV arm: n = 71 (62% of ITT†)

  5-FU/LV control arm: n = 57 (48% of ITT†)

- Assessed at baseline, every 6 weeks, and at the 30-day post–follow-up visit
- Linear transformations applied to raw scores so that the reported score ranged from 0-100 for each scale
- Patients classified into 1 of 3 categories:

  Improved: Patient had scores ≥10% relative to baseline & remained above the baseline value for ≥6 weeks

  Stable: Patient did not meet criteria for improved or worsened

  Worsened: Patient did not meet improvement criteria and died OR had scores that decreased by 10%

- Pairwise treatment group comparisons were performed using Cochran-Mantel-Haenszel testing adjusted for multiplicity with a Benjamini-Hochberg correction to control false discovery rate at the 0.05 level for the 15 comparisons

EORTC-QLQ-C30 Questionnaire*

Scores computed in the following domains:

- Global health status — **Global HRQoL**

- Physical functioning
- Role functioning
- Emotional functioning
- Cognitive functioning
- Social functioning

— **Functional Scales**

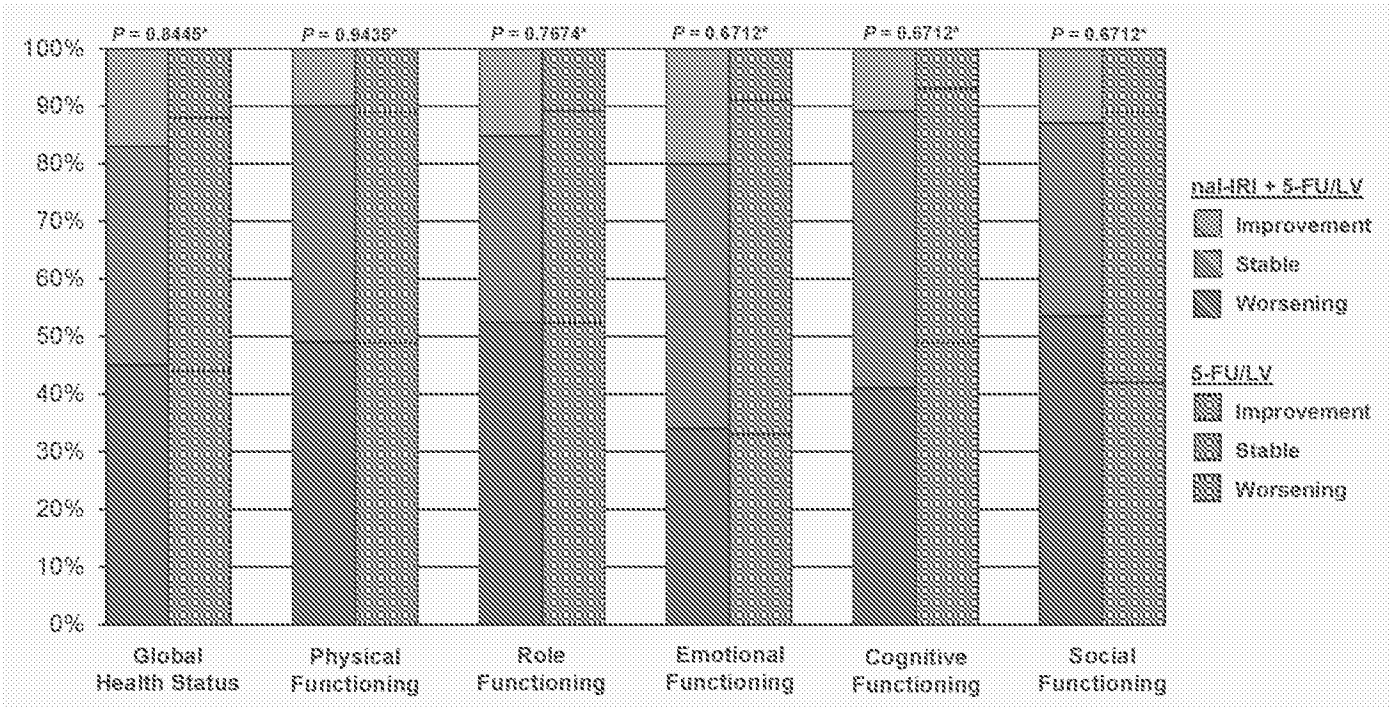
- Fatigue
- Nausea and vomiting
- Pain
- Dyspnea
- Insomnia
- Appetite loss
- Constipation
- Diarrhea
- Financial difficulties

— **Symptom Scales**

*Scored according to the EORTC QLQ-C30, version 3.0, scoring manual.[1]
†Includes patients randomized under protocol version 2.
1. Aaronson NK, et al. *J Natl Cancer Inst.* 1993;85:365-376.

NAPOLI-1 Global Health Status and Functional Scale Scores

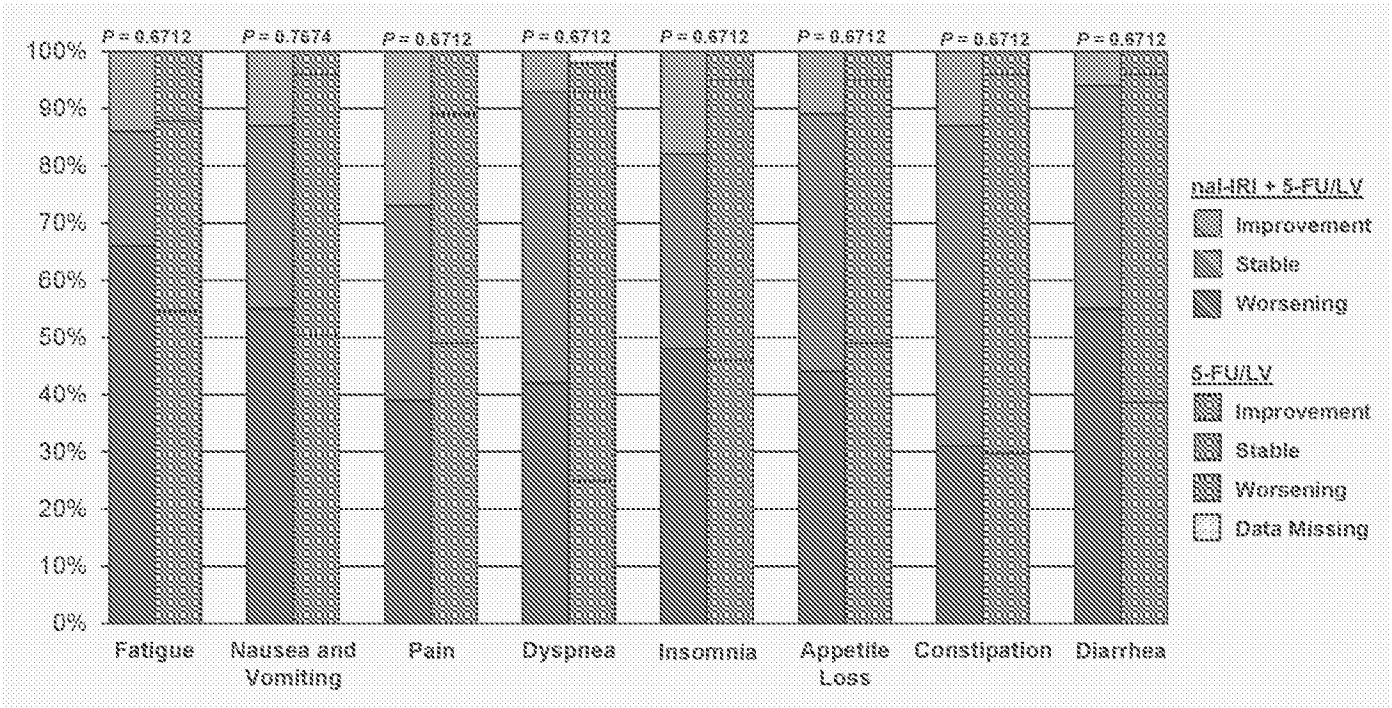
No substantial differences seen in global health status and functional scale scores between the nal-IRI + 5-FU/LV (n = 71; left bar) and 5-FU/LV (n = 57; right bar) arms



*Benjamini-Hochberg–adjusted *P* values. The adjustment was conducted across the 15 domains of the QoL questionnaire to control the overall false discovery rate (FDR).

NAPOLI-1 Symptom Scale Scores

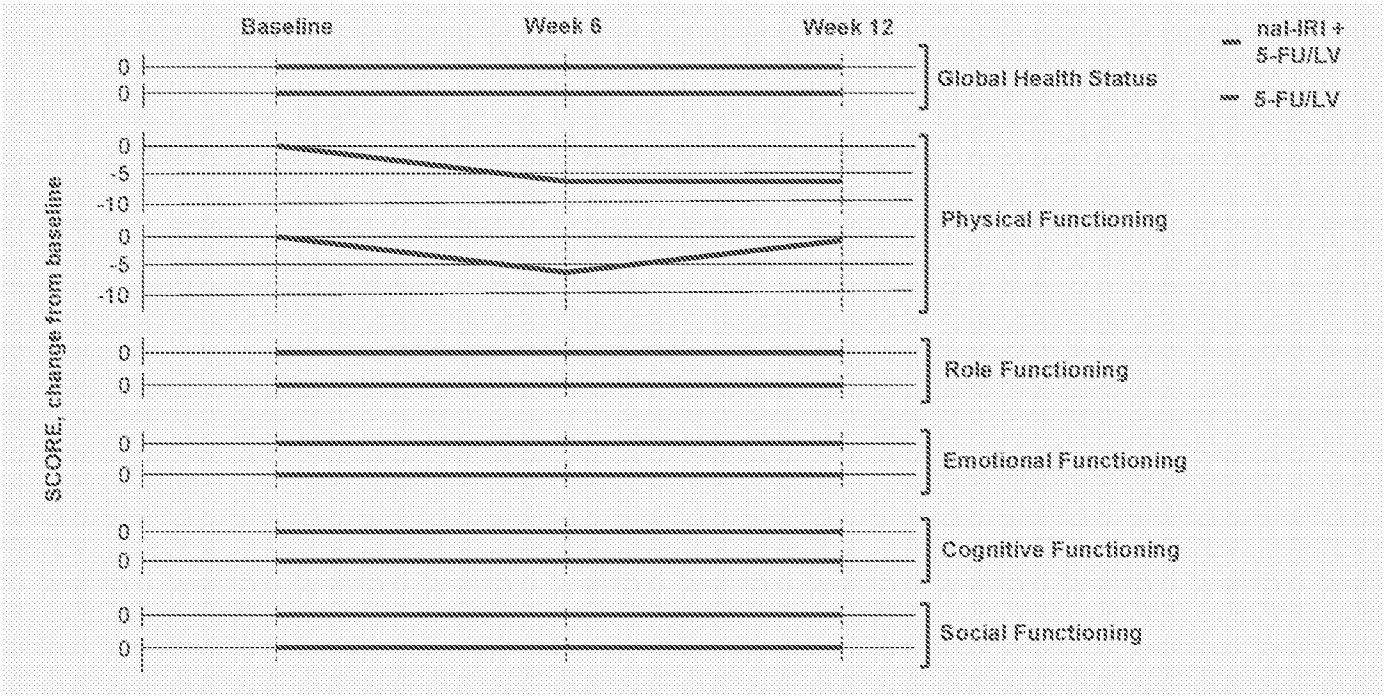
No substantial differences seen in symptom scale scores between the nal-IRI + 5-FU/LV (n = 71; left bar) and 5-FU/LV (n = 57; right bar) arms



*Benjamini-Hochberg–adjusted *P* values. The adjustment was conducted across the 15 domains of the QoL questionnaire to control the overall FDR.

NAPOLI-1 Global Health Status and Functional Scale Scores: Median Change Over Time

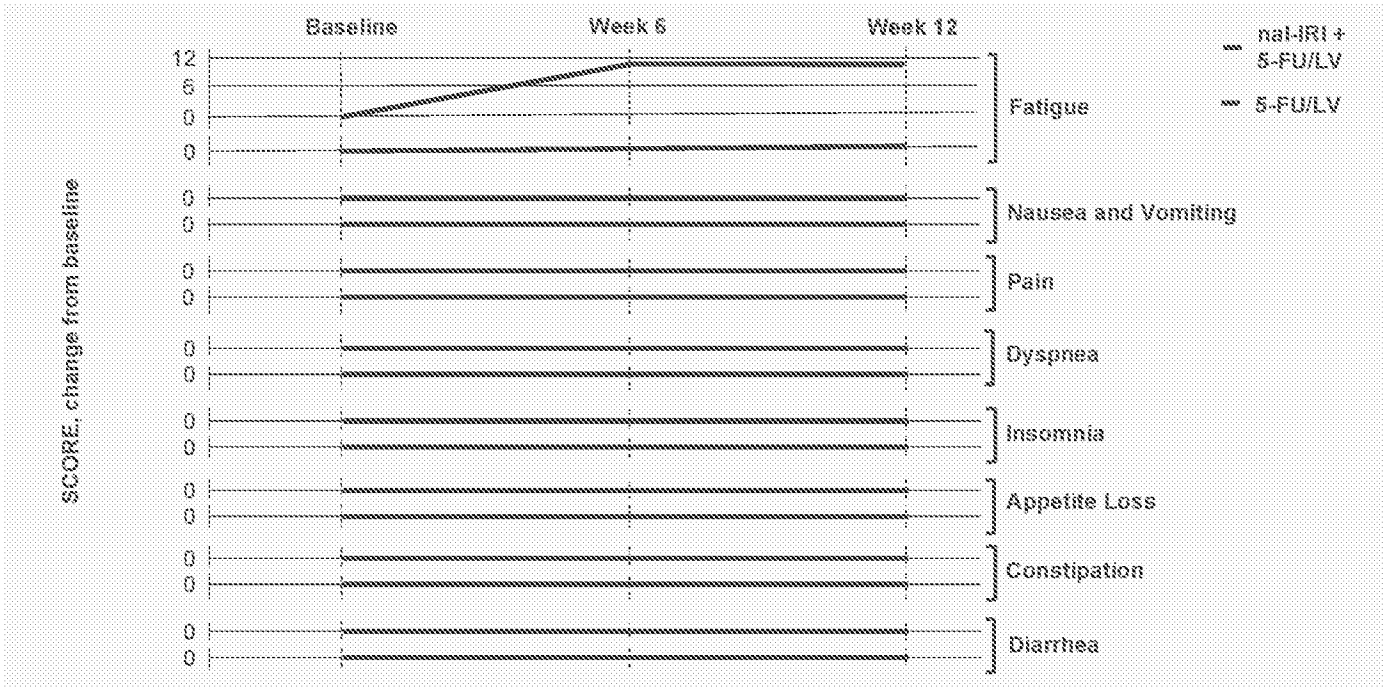
- Baseline global health status and functional scale scores ranged from 58-83 and were similar between arms
- No appreciable change from baseline in global health status and functional scale scores between the nal-IRI + 5-FU/LV (n = 71 at baseline) and 5-FU/LV (n = 57 at baseline) arms
  - Observed median change from baseline to week 6 in physical functioning score was 6.7 points in both arms; corresponding to "a little" decrease[1]



1. Osoba D, et al. *J Clin Oncol*. 1998;16:139-144.

NAPOLI-1 Symptom Scale Scores: Median Change Over Time

- Baseline symptom scale scores ranged from 0-33 and were similar between arms
- No appreciable change from baseline in symptom scale scores between the nal-IRI + 5-FU/LV (n = 71 at baseline) and 5-FU/LV (n = 57 at baseline) arms
  - Observed median change from baseline to week 6 in fatigue score was ~11 points in the nal-IRI + 5-FU/LV arm; corresponding to "moderate" increase[1]



1. Osoba D, et al. *J Clin Oncol*. 1998;16:139-144.

Summary

- nal-IRI + 5-FU/LV significantly improves OS in patients with mPDAC previously treated with gemcitabine-based therapy compared with 5-FU/LV
- Overall, patients treated with nal-IRI + 5-FU/LV had no deterioration in QoL over 12 weeks, despite the addition of a second chemotherapeutic agent
  - Global health status and functional scale scores were not significantly different between treatment arms at baseline, and showed no appreciable change over 12 weeks
  - Median symptom scale scores at baseline ranged from 0-33 (low levels of symptomatology), and showed no appreciable change over 12 weeks
- Study limitations included limited proportions of patients with QoL data, open-label design, and inherent variability in PROs
- **nal-IRI + 5-FU/LV provides a new treatment option that does not compromise QoL in patients with mPDAC previously treated with gemcitabine-based therapy**

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- This study (ClinicalTrials.gov: NCT01494506) was supported by Merrimack Pharmaceuticals, Inc. (Cambridge, Massachusetts, USA)
- Editorial assistance was provided by Jemimah Walker, PhD, and Payal Gandhi, PhD, of ApotheCom (Yardley, Pennsylvania, USA) and was supported by Merrimack Pharmaceuticals, Inc.

Abbreviations

5-FU = fluorouracil

AE = adverse event

CA = carbohydrate antigen

CBR = clinical benefit response

EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire (core questionnaire)

FOLFIRINOX = oxaliplatin, irinotecan, 5-FU, and leucovorin

HR = hazard ratio

HRQoL = health-related quality of life

ITT = intention-to-treat

KPS = Karnofsky performance status

LV = leucovorin

mPDAC = metastatic pancreatic ductal adenocarcinoma

nal-IRI = liposomal irinotecan

ORR = objective response rate

OS = overall survival

PEG-DSPE = poly(ethylene glycol)–distearoylphosphatidylethanolamine

PFS = progression-free survival

PRO = patient-reported outcome

q2w = every 2 weeks

q3w = every 3 weeks

q6w = every 6 weeks

R = randomization

TTF = time to treatment failure

QoL = quality of life

741P

Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone

Richard Hubner[1], Li-TzongChen[2], Chung-Pin Li[3], GyörgyBodoky[4], Andrew Dean[5], Kyung-Hun Lee[6], David Cunningham[7], Jens T. Siveke[8], FadiBraiteh[9], Floris A. de Jong[10], Bruce Belanger[11], Beloo Mirakhur[11], Purvi D. Mody[11], Daniel D. Von Hoff[12], Andrea Wang-Gillam[13]

[1]The Christie NHS Foundation Trust, Manchester, UK; [2]National Health Research Institutes -National Institute of Cancer Research, Tainan, Taiwan; [3]Taipei Veterans General Hospital, Taipei, Taiwan; [4]Saint Laszlo Teaching Hospital, Budapest, Hungary; [5]St John of God Hospital, Subiaco, Australia; [6]Seoul National University Hospital, Seoul, Republic of Korea; [7]Royal Marsden Hospital, Sutton, UK; [8]West German Cancer Center, University Hospital Essen, Essen, Germany; [9]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [10]Ipsen GmbH, Zug, Switzerland; [11]Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA; [12]Translational Genomics Research Institute and Honorhealth Research Institute, Phoenix and Scottsdale, AZ, USA; [13]Washington University School of Medicine, St Louis, MO, USA

Introduction

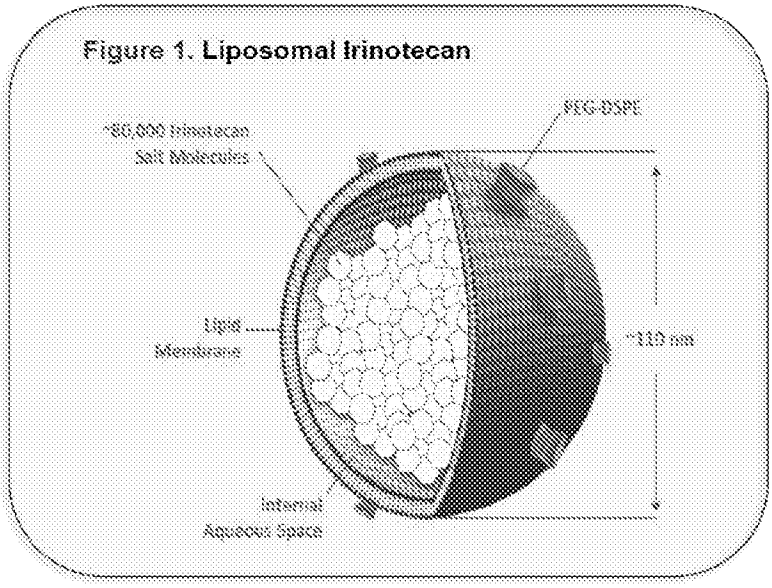
Neutrophil-to-Lymphocyte Ratio (NLR)

- Cell-mediated inflammation has been shown to play a role in the development of tumors and cancer progression[1]
- Neutrophils have been shown to inhibit the activity of T cells, which has been associated with a poor prognosis, whereas tumor-infiltrating lymphocytes have been shown to be associated with better outcomes in a variety of cancers[1]
- High peripheral blood NLR is associated with a poor outcome in patients with pancreatic cancer[1-5]

Liposomal Irinotecan

- Liposomal irinotecan (nal-IRI, MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (Figure 1)
- Pharmacokinetic analyses in patients with gastric cancer showed extended circulation of irinotecan within the liposome[6]
- 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[7]

Figure 1. Liposomal Irinotecan



Methods

NAPOLI-1

- NAPOLI-1 was a large (N = 417; NCT01494506), phase 3 trial that evaluated liposomal irinotecan alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy[8]
- Patients were initially randomized to receive nal-IRI (120 mg/m^2 every 3 weeks) or 5-FU/LV (2000/200 mg/m^2 weekly for 4 weeks of each 6-week cycle). After 63 patients were enrolled, a third arm, nal-IRI (80 mg/m^2 every 2 weeks) + 5-FU/LV (2400/400 mg/m^2 every 2 weeks), was added. Treatment was continued until disease progression or unacceptable toxicity[8]
  - 120-mg/m^2 dose based on irinotecan HCl trihydrate is equivalent to 100 mg/m^2 irinotecan free base and the 80-mg/m^2 dose of nal-IRI based on irinotecan HCl trihydrate salt is equivalent to 70 mg/m^2 irinotecan free base
- Primary endpoint was overall survival (OS); key secondary endpoints included progression-free survival (PFS), objective response rate, and safety[8]

Exploratory Post Hoc Analysis

- This was an exploratory post hoc analysis of patients in NAPOLI-1 who were enrolled in the study after the addition of the third arm, who received nal-IRI+5-FU/LV or 5-FU/LV, and who had baseline NLR data available to assess the relationship between NLR and OS and PFS (data cutoff, November 16, 2015; 382 OS events) using a cutoff ratio of 5[4,5]
- OS was calculated by the Kaplan-Meier method
- Hazard ratios (HRs) for OS comparisons based on high (>5) or low (≤5) baseline NLR in individual and pooled treatment arms were estimated by Cox regression analysis, and Fisher's exact test was used for comparisons; *P* values were descriptive

Results

NAPOLI-1 Results

- A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013[8]
- nal-IRI+5-FU/LV therapy resulted in a longer median OS (6.1 vs 4.2 months; HR for death = 0.67 [95% confidence interval (CI) 0.49, 0.92]; *P*=0.012) and PFS (3.1 vs 1.5 months; HR = 0.56 [95% CI 0.41, 0.75]; *P*=0.001)[8]

NLR Post Hoc Analysis Patient Characteristics

- 222 patients met the criteria of enrolling in the study after the third arm was added and received study drug; 221 (99%) of these had baseline NLR available (Table 1)

Table 1. **Patient Characteristics in Post-hoc Analysis**

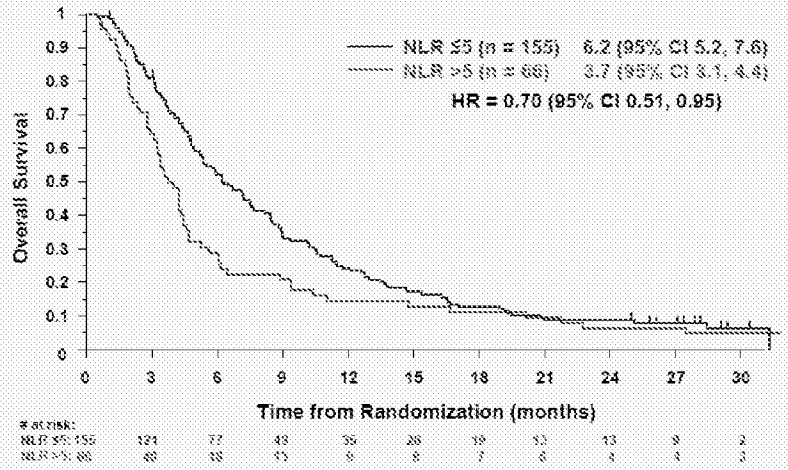
	Pooled Population		nal-IRI+5-FU/LV		5-FU/LV	
	≤5 (n = 155)	>5 (n = 66)	≤5 (n = 82)	>5 (n = 34)	≤5 (n = 73)	>5 (n = 32)
Age, mean (SD), y	62.2 (9.1)	62.2 (9.8)	62.8 (8.9)	63.8 (9.8)	61.6 (9.5)	60.4 (9.7)
Men, %	56.1	59.1	57.3	58.8	59.4	56.1
Race, %						
Caucasian	62.6	68.2	59.8	67.6	65.8	68.8
Asian	31.0	22.7	34.1	14.7	27.4	31.3
Other	6.4	9.1	6.1	17.7	6.8	0
Albumin, mean (SD), g/dL	4.0 (0.5)	3.9 (0.5)	4.0 (0.5)	3.9 (0.4)	3.9 (0.5)	4.0 (0.5)
KPS, %						
<90	42.6	59.1	32.9	58.8	53.4	59.4
≥90	57.4	40.9	67.1	41.2	46.6	40.6
Prior lines of metastatic therapy, %						
0	14.2	10.6	14.6	8.8	13.7	12.5
1	56.1	54.5	54.6	52.9	57.5	56.3
2 or more	29.7	34.8	30.5	38.2	28.8	31.3

5-FU/LV, 5-fluorouracil/leucovorin; KPS, Karnofsky Performance Scale; nal-IRI, liposomal irinotecan; SD, standard deviation; y, years.

NLR Post Hoc Analysis: OS, PFS, and Safety

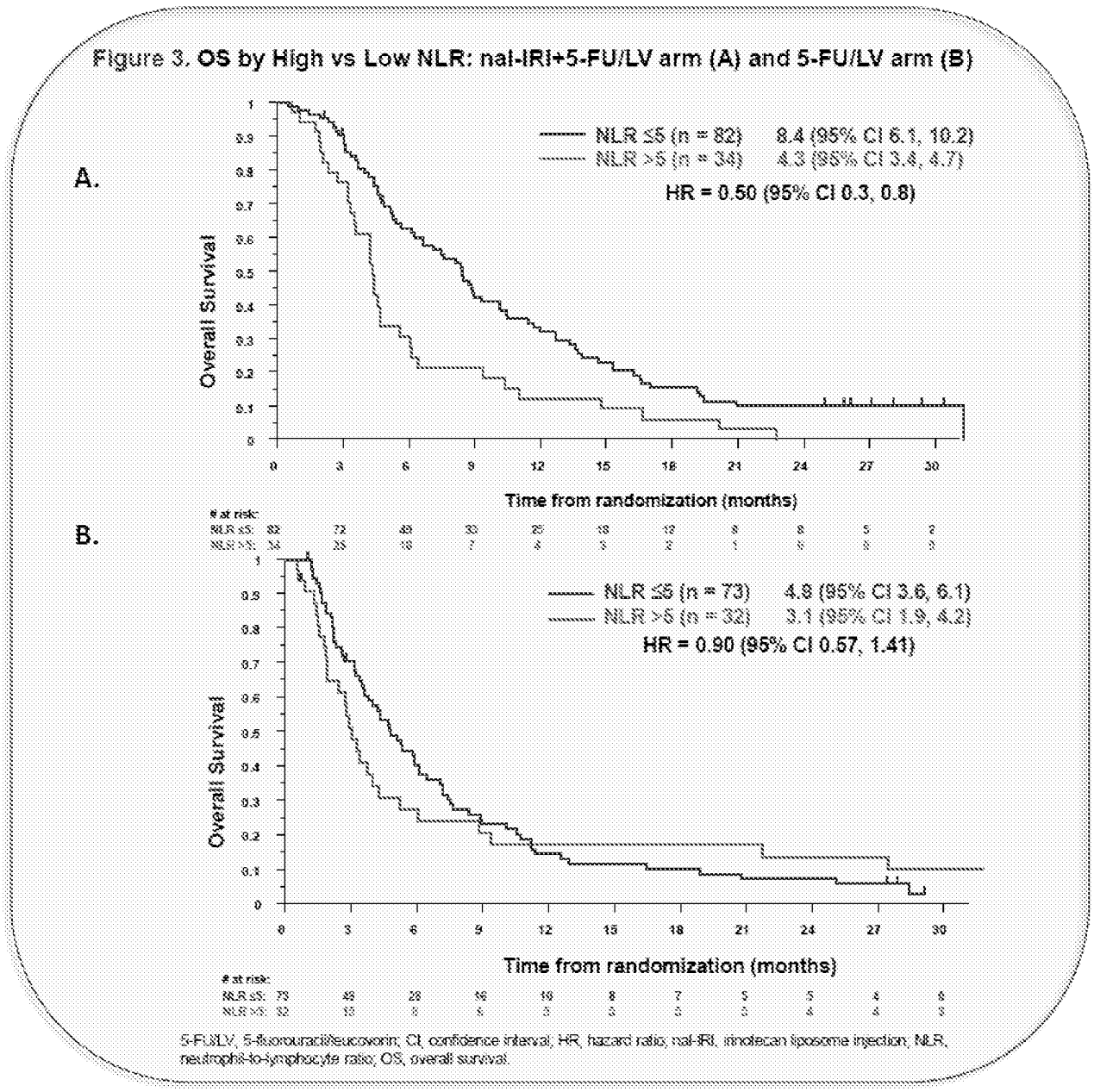
- After pooling treatment arms, the NLR ≤5 group had significantly increased OS compared with the NLR >5 group (6.2 vs 3.7 months, HR = 0.7; *P*=0.02; Figure 2)
- In the nal-IRI+5-FU/LV arm, the NLR ≤5 group had significantly increased OS compared with the NLR >5 group (8.4 vs 4.3 months, HR = 0.5; *P*=0.001; Figure 3A); the difference in the 5-FU/LV arm was not significant (4.8 vs 3.1 months, HR = 0.9; *P*=0.6; Figure 3B)
- PFS was significantly increased in patients with NLR ≤5 vs NLR >5 in the pooled (2.7 vs 1.4 months; HR = 0.7, *P*=0.05) and nal-IRI+5-FU/LV (4.2 vs 1.4 months, HR = 0.5; *P*=0.002) treatment arms, but not the 5-FU/LV arm (1.5 vs 1.4 months, HR = 1.1; *P*=0.6)
- Grade 3/4 adverse events in this post hoc analysis population were consistent with the overall population

Figure 2. OS by High vs Low NLR: Pooled Treatment Arms



CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

Figure 3. **OS by High vs Low NLR: nal-IRI+5-FU/LV arm (A) and 5-FU/LV arm (B)**



5-FU/LV, 5-fluorouracil/leucovorin; CI, confidence interval; HR, hazard ratio; nal-IRI, irinotecan liposome injection; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

Conclusions

- nal-IRI+5-FU/LV significantly improved OS and PFS compared with 5-FU/LV control in the NAPOLI-1 trial of patients with mPDAC following gemcitabine-based therapy[1]
- Based on these post hoc analyses, median OS and PFS were significantly increased in patients with low (vs high) baseline NLR in the nal-IRI+5-FU/LV arm but not in the 5-FU/LV arm
- These data are consistent with previous reports supporting the prognostic value of baseline NLR in mPDAC, and extend it to the post-gemcitabine setting
- Adverse events in this population were consistent with the overall population[1]
- These analyses may be limited by the small sample size of post hoc analysis subgroups

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Time Course of Selected Treatment-Emergent Adverse Events in NAPOLI-1: A Phase 3 Study of Liposomal Irinotecan (nal-IRI; MM-398) ± 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy

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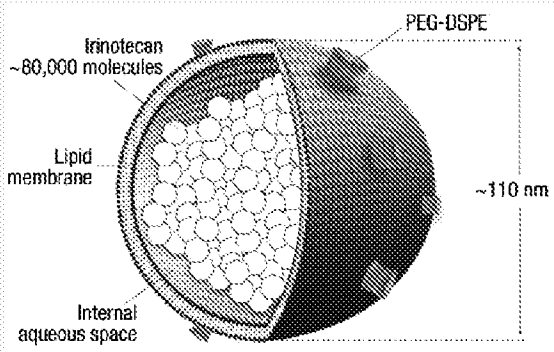
BACKGROUND

- Pancreatic cancer is the sixth most commonly diagnosed cancer and the fifth most common cause of cancer-related death in Europe[1]
- Liposomal irinotecan (nal-IRI) is a topoisomerase I inhibitor that, in combination with 5-fluorouracil and leucovorin (5-FU/LV), has been approved in the United States and received a positive opinion in Europe from the Committee for Medicinal Products for Human Use for the treatment of patients with metastatic adenocarcinoma of the pancreas (mPAC) after disease progression following gemcitabine-based therapy[2] (**Figure 1**)
  - Approval was based on the primary results of the phase 3 NAPOLI-1 trial (data cutoff, February 14, 2014) in which a significant survival advantage was observed for nal-IRI+5-FU/LV compared with 5-FU/LV alone (overall survival [OS], 6.1 vs 4.2 months; unstratified hazard ratio [HR], 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$). In contrast, OS in patients receiving nal-IRI monotherapy was similar to that of patients receiving 5-FU/LV (4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77-1.28]; $P = 0.94$)[3]
  - Additionally, nal-IRI+5-FU/LV versus 5-FU/LV demonstrated:
    - Improved progression-free survival (3.1 vs 1.5 months; unstratified HR, 0.56 [95% CI, 0.41-0.75]; $P = 0.0001$)
    - Improved objective response rate (16% vs 1%; difference, 15.4% [95% CI, 8.5%-22.3%]; $P < 0.0001$)
    - Similar quality of life (QOL) between treatment groups, suggesting that the addition of nal-IRI did not negatively affect QOL[4]
  - nal-IRI+5-FU/LV had a predictable and manageable safety profile in NAPOLI-1; the most commonly occurring grade 3 or 4 treatment-emergent adverse events (TEAEs) included neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%)[3]

Figure 1. nal-IRI design.[3]



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

OBJECTIVES

- To further characterize the safety profile of nal-IRI+5-FU/LV by investigating the incidence and prevalence of TEAEs of special interest over time in the phase 3 NAPOLI-1 trial

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (for additional details regarding study design, see poster 3707)
  - Patients were initially randomly assigned to nal-IRI monotherapy (120 mg/m^2 irinotecan hydrochloride trihydrate salt [equivalent to 100 mg/m^2 irinotecan free base] every 3 weeks) or 5-FU/LV (2000 mg/m^2 5-FU and 200 mg/m^2 LV, every week for the first 4 weeks of each 6-week cycle; protocol version 1)
  - Once safety data for combination nal-IRI+5-FU/LV became available from a concurrent metastatic colorectal cancer trial, the protocol was amended to include a third arm; combination nal-IRI+5-FU/LV (80 mg/m^2 irinotecan hydrochloride trihydrate salt [equivalent to 70 mg/m^2 irinotecan free base] every 2 weeks; 2400 mg/m^2 5-FU and 400 mg/m^2 LV every 2 weeks; protocol 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)

Dose Modifications

- Dosing may be held for up to 3 weeks to allow for recovery from adverse events (AEs). If the time required for recovery from toxicity exceeded 3 weeks, study treatment was generally discontinued
- In general, dose reductions were not required for AEs ≤grade 2. For grade 3/4 AEs:
  - Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 in the nal-IRI monotherapy arm
  - Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence in the nal-IRI+5-FU/LV arm

Post hoc Analysis

- Within this post hoc analysis, the incidence and prevalence of selected TEAEs was analyzed over 3 time periods:
  - Weeks 1-6
  - Weeks 6-12
  - Week 12 to the end of the study period (data cutoff, February 14, 2014)
- The treatment-emergent period for AEs is from time of first administration of study drug to 30 days after administration of the last dose of study drug
- Incidence was used as a measure of the first occurrence of a TEAE within a specified time interval; the numerator was the number of patients reporting the TEAE of interest for the first time during the period, and the denominator was the number of patients still on treatment during that period who had not yet experienced the TEAE of interest
- Prevalence was used as a measure of the ongoing frequency of the TEAE of interest within a specified time interval; the numerator included all patients who were experiencing the TEAE of interest during the period, and the denominator included all patients who were evaluable for safety for that period

Key Inclusion Criteria

- Adults aged ≥18 years
- Histologically or cytologically confirmed mPAC
- Documented measurable or nonmeasurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1])
- Disease progression after previous gemcitabine or gemcitabine-based 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 >1.5 × 10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function

Key Exclusion Criteria

- Active central nervous system metastasis
- Clinically significant gastrointestinal disorders
- History of any second malignancy in the past 5 years
- Severe arterial thromboembolic events <6 months before inclusion

RESULTS

Patient Characteristics

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

Table 1. Patient Demographics and Baseline Characteristics Based on the Safety Population

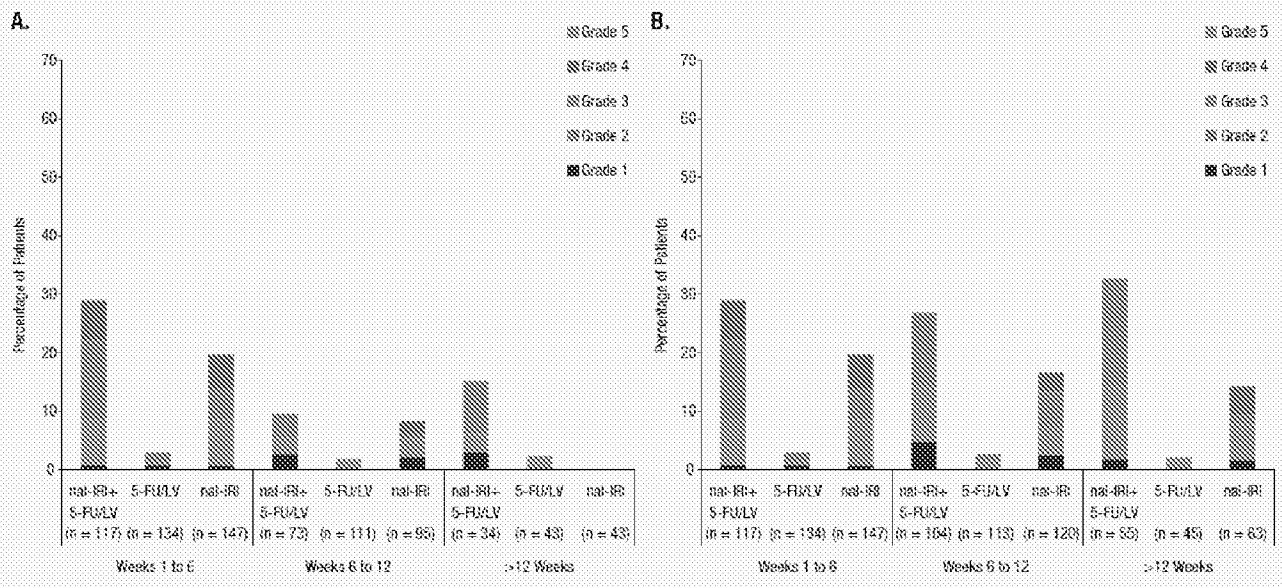
Parameter	nal-IRI+5-FU/LV (n = 117)	nal-IRI Monotherapy (n = 147)	5-FU/LV Monotherapy Control (n = 134)
Sex, %			
Male	57	57	54
Female	43	43	46
Age, years, median (range)	63 (41-81)	65 (31-87)	63 (39-83)
Race, %			
White	62	58	63
East Asian	28	35	33
Other	9	7	4
KPS, %			
100	16	14	12
90	43	43	37
80	33	33	43
70	6	10	8
50-60	2	0	0
Prior lines of metastatic therapy, %			
0[a]	13	12	13
1	54	56	59
2	33	33	28
Previous anticancer therapy,[b] %			
Gemcitabine alone	46	44	46
Gemcitabine combination	54	56	54
Fluorouracil	43	46	40
Irinotecan	10	11	10
Platinum	32	36	28

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease.
[b]Columns add to >100% because some patients received more than 1 line of therapy, and regimens may include multiple drug classes.

Incidence and Prevalence of Any-Grade TEAEs by Time Period

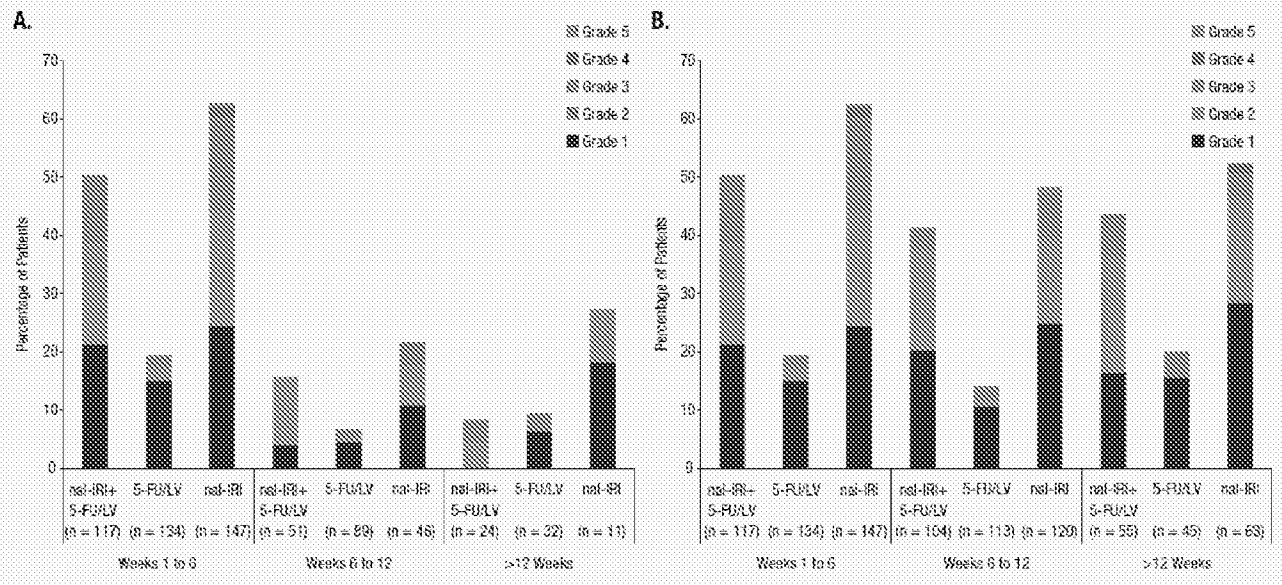
- In the nal-IRI+5-FU/LV arm, the incidence of neutropenia was highest during the first 6 weeks of treatment with lower incidence in subsequent periods; in some cases, the first occurrence of grade 3 neutropenia occurred at >12 weeks (**Figure 2A**). Prevalence of neutropenia increased slightly from weeks 1-6 to >12 weeks, but grade 4 neutropenia resolved within 6 weeks (**Figure 2B**)
- The incidence of diarrhea in the nal-IRI+5-FU/LV arm was highest during weeks 1-6 and tended to persist throughout the treatment course based on relatively stable prevalence (**Figure 3**). However, the majority of persisting events were grade 1/2, and the proportion of patients with discontinuation due to diarrhea was low (1.7%)
- Nausea and vomiting showed a similar pattern in the nal-IRI+5-FU/LV arm, with the incidence of both AEs being highest in weeks 1-6 and decreasing over time; the prevalence decreased from weeks 1-6 to >12 weeks, suggesting a short duration for these AEs (**Figures 4** and **5**)

Figure 2. Incidence[a] (A) and prevalence[b] (B) of all-grade neutropenia[c] over time by treatment arm.



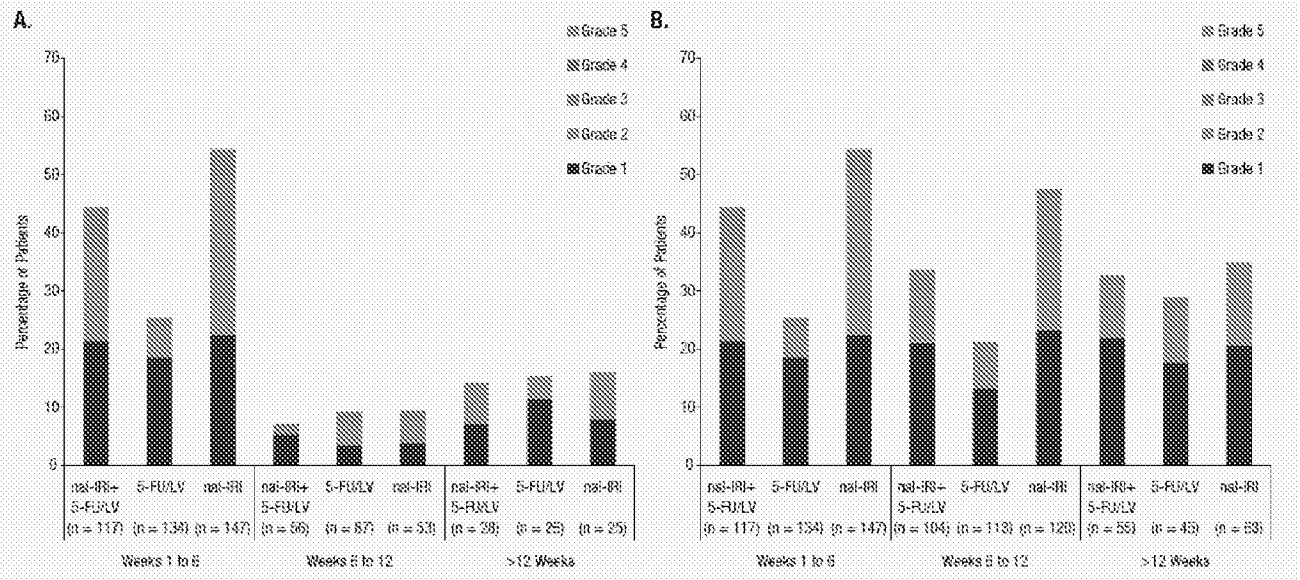
5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.
[c]Neutropenia encompasses agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

Figure 3. Incidence[a] (A) and prevalence[b] (B) of all-grade diarrhea over time by treatment arm.



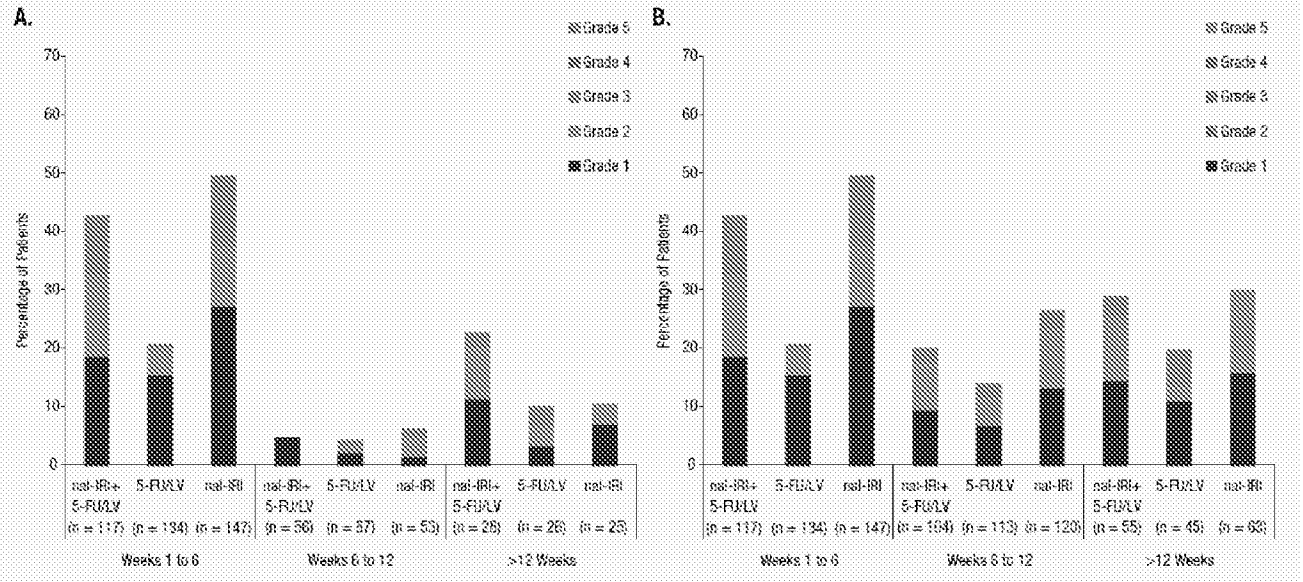
5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

Figure 4. Incidence[a] (A) and prevalence[b] (B) of all-grade nausea over time by treatment arm.



5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

Figure 5. Incidence[a] (A) and prevalence[b] (B) of all-grade vomiting over time by treatment arm.



5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

- The incidence of peripheral neuropathy was low in all treatment arms, at 1.7% (n = 2) in the nal-IRI+5-FU/LV arm, 0.7% (n = 1) in the nal-IRI monotherapy arm, and 2.2% (n = 3) in the 5-FU/LV arm
- In the nal-IRI+5-FU/LV arm, 1 patient in weeks 1-6 and 1 patient at >12 weeks experienced grade 3 febrile neutropenia, and 1 patient in weeks 1-6 experienced grade 3 neutropenic sepsis; these were managed by dose reduction and/or interruption. In the nal-IRI arm, 5 patients experienced febrile neutropenia in weeks 1-6 (4 with grade 3 febrile neutropenia and 1 with grade 4), and 1 experienced grade 3 febrile neutropenia in weeks 6-12; these were managed by dose reduction and/or interruption. No patients in the 5-FU/LV arm experienced febrile neutropenia

Duration of Adverse Events

- Across treatment arms, the median duration of AEs ranged from 2 to 18 days and was typically within the range of 5-14 days, whether for any grade or for grade ≥3 (**Table 2**)

Table 2: Duration of Adverse Events in Days[a]

Adverse Event, Days, Median (25th percentile, 75th percentile)[b]	nal-IRI+5-FU/LV (n = 117)		5-FU/LV (n = 134)		nal-IRI (n = 147)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Diarrhea	6 (3, 19)	8 (5, 17)	3 (2, 11)	6 (2, 11)	8 (3, 16)	10 (7, 15)
Nausea	11 (5, 42)	10 (6, 14)	6 (2, 53)	8 (5, 11)	14 (5, 58)	7 (4, 10)
Vomiting	5 (2, 17)	10 (7, 13)	2 (1, 9)	4 (2, 9)	4 (2, 12)	7 (3, 14)
Neutropenia[c]	9 (6, 15)	9 (8, 15)	8 (6, 13)	18 (15, 21)	8 (7, 15)	10 (7, 19)
Neutropenic fever/sepsis[c]	8 (5, 11)	6 (4, 10)	13 (13, 13)	NA	7 (6, 10)	7 (6, 7)

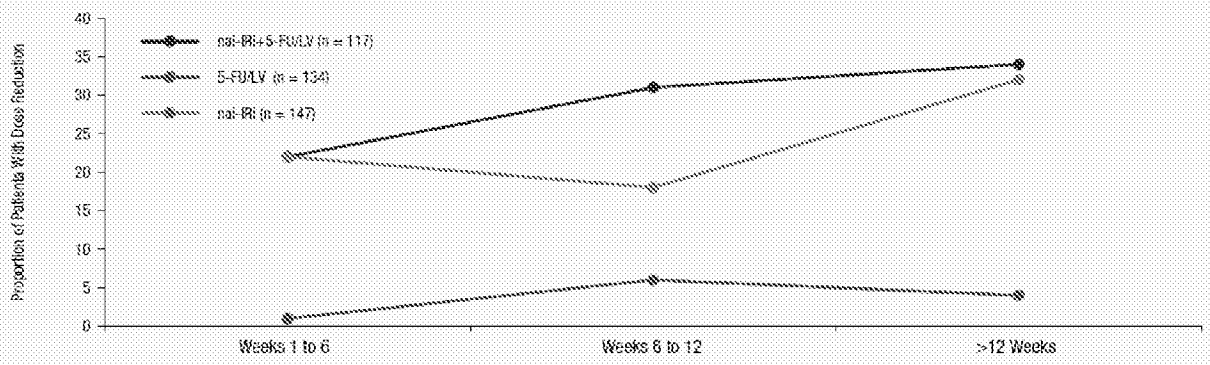
NA, not applicable
[a]For events without end date, duration is censored at the earliest of death date, last study drug + 30 days.
[b]Median and quartiles from Kaplan-Meier estimation.
[c]Neutropenia and neutropenic fever/sepsis are based on umbrella terms.

Dose Reductions or Delays

- The proportion of patients with dose reductions or delays increased over the course of treatment in the nal-IRI+5-FU/LV arm (**Figure 6A** and **B**). It is possible that dose reductions and delays may have contributed to the observed decrease in the incidence and severity of AEs over time
  - The 25th percentile and median time to first dose reduction were 36 and 70 days, respectively, for nal-IRI+5-FU/LV, not applicable (NA) and NA for 5-FU/LV, and 33 and 86 days for nal-IRI
  - The 25th percentile and median time to first dose delay were 29 and 50 days, respectively, for nal-IRI+5-FU/LV, 429 and 429 days for 5-FU/LV, and 50 and 103 days for nal-IRI

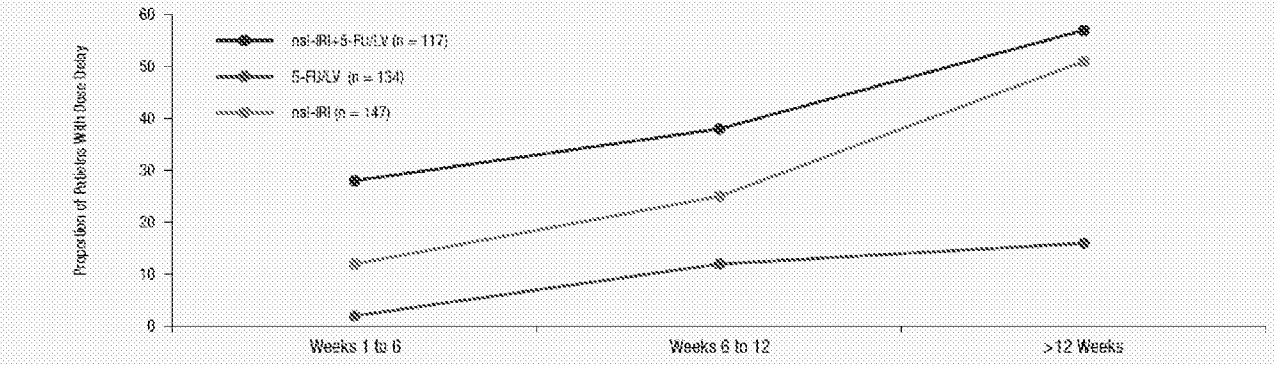
Figure 6. Dose modifications over time by treatment arm based on dose reduction (A) or dose delay (B).

A.



n value per period			
nal-IRI+5-FU/LV	117	65	44
5-FU/LV	134	53	25
nal-IRI	147	73	41

B.



n value per period			
nal-IRI+5-FU/LV	117	65	44
5-FU/LV	134	52	25
nal-IRI	147	73	41

Denominators for the dose modification figures reflect the numbers of patients who received study drug during the period.
5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.

CONCLUSIONS

- **In the nal-IRI+5-FU/LV treatment arm, the incidence of neutropenia, diarrhea, nausea, and vomiting typically was highest early during the course of treatment, with fewer incident events later in time**
- **For patients treated with nal-IRI+5-FU/LV, the prevalence of nausea and vomiting was highest in the first 6 weeks of treatment and decreased thereafter. The prevalence of neutropenia was largely similar across the entire assessment period, but a decrease in severity occurred as all grade 4 cases resolved within the first 6 weeks of treatment. The prevalence of diarrhea, mostly grade 1/2, remained relatively stable across treatment periods**
- **The median duration of AEs, grade ≥3 or any, was within 5-11 days in the nal-IRI+5-FU/LV treatment arm**
- **Dose modifications, including reductions and interruptions/delays, were commonly used to manage AEs throughout the course of treatment and may have, in some instances, accounted for the decreased incidence and/or severity of AEs over time**

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POSTER PRESENTED AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) ANNUAL CONGRESS; OCTOBER 7-11, 2016; COPENHAGEN, DENMARK

Time Course of Selected Treatment-Emergent Adverse Events in NAPOLI-1: A Phase 3 Study of Liposomal Irinotecan (nal-IRI; MM-398) + 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy

POSTER PRESENTED AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) ANNUAL CONGRESS. OCTOBER 7–11, 2016. COPENHAGEN, DENMARK

Methods: In this prospective observational study, metastatic gall bladder cancer patients with performance status ≤2, who progressed on two-lines of therapy, were enrolled from May 2012 to july 2016. Single agent nab-paclitaxel (dose 125mg/m^2) was administered on Day 1, 8 and 15 in a cycle of 28 days and i.e. until progression or unacceptable toxicity. Response evaluation was done after 2 cycles of chemotherapy.

Results: A total of 34 patients were enrolled in this study. The median age of patients was 62 years (31--71 years), of which 20 (58.82%) were males and 14 (41.17%) were females. The median number of cycles could be given were 3.5 (0.5 – 9.6). 20 patients (58.82%) could be given more than 3 cycles of chemotherapy and only 3 patients (8.82%) in this study received more than 6 cycles of chemotherapy. Disease control rate was seen in 24 (70.58%) patients, with complete response in none, partial response in 13 (38.23%), stable disease in 11 (32.35%) and progressive disease in 10 (29.41%) patients. The median progression free survival was 3.12 months. The median overall survival was 4.9 months. The main Grade 3/4 side effects seen were hematological in 32.35% (n = 11). 8 patients (23.52%) had Grade 1/2 peripheral neuropathy.

Conclusions: Nab-paclitaxel is an effective and well-tolerated agent as a third-line option in metastatic gall bladder cancer patients. Further studies are required, especially in the Indian subcontinent.

Legal entity responsible for the study: N/A.

Funding: RGCI&RC.

Disclosure: All authors have declared no conflicts of interest.

242P Effects of nal-IRI (MM-398) ± 5-fluorouracil on quality of life (QoL) of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine based therapy: Results from NAPOLI-1

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Background: The randomized phase 3 NAPOLI-1 study showed that nal-IRI + 5-fluorouracil/leucovorin (5-FU/LV) significantly improved overall survival vs 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio 0.67; P = 0.012) in patients with mPDAC previously treated with gemcitabine-based therapy (Wang-Gillam et al., Lancet 2016). QoL was a secondary end point of NAPOLI-1.

Methods: Patients were to complete the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (EORTC-QLQ-C30) at baseline, every 6 weeks, and 30 days after follow-up visit. The population analyzed included patients with a baseline and ≥1 post-baseline assessment. In a responder analysis, patients were classified as improved (≥10% improvement from baseline score maintained for ≥6 weeks), worsened (did not meet improvement criteria and died or had ≥10% worsening from baseline score), or stable (not improved or worsened) for each subscale. Pairwise treatment arm comparisons on response classification were performed for each subscale using Cochran-Mantel-Haenszel testing adjusted for multiplicity with a Benjamini-Hochberg correction.

Results: Of 154 evaluable patients in this population, 69% (49/71) of patients in the nal-IRI + 5-FU/LV arm and 53% (44/83) in the 5-FU/LV arm had data at 12 weeks. Median baseline scores for Global Health Status (GHS), Functional and Symptom Scales were similar between arms. The median change in score at 12 weeks was 0 for both treatment arms for GHS and for all Functional and Symptom Scales except for physical functioning and fatigue. The between-arm differences for physical functioning and fatigue were not substantial. Also, there were no significant between-arm differences in the proportion of improved, worsened, or stable patients.

Conclusions: In NAPOLI-1, nal-IRI + 5-FU/LV--treated patients with data through 12 weeks tended to maintain their baseline QoL over the period, and no significant differences versus the 5-FU/LV--treated patients were observed. Study results are limited by the small number of patients and variability in QoL subscale scores.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: Shire

Funding: Shire

Disclosure: J-F. Blanc: Received honoraria from Baxalta. D. Melisi: Served on advisory board for Eli Lilly and received honoraria from Celgene and Roche. D.D. von Hoff: Served as consultant for AlphaMed. A. Wang-Gillam: Received research funding from Newlink, EMD, Pfizer, AstraZeneca, Pricision Biological, BioMed Valley, Halozyme, ChemoCentryx, OncoMed, ADURO, Millennium, Merrimack, Prometheus, and CTI, and served on ad boards for Pfizer and Merrimack. L.-T. Chen: Received data monitoring board, statistician, and support of medical writer from Merrimack and honorarium from PharmaEngine, Inc. C. Becker: Employee of Merrimack. K. Mamlouk, B. Belanger: Employee of, own stock in, and have received reimbursement for travel/accommodations/ expenses from Merrimack. Y. Yang: Employee of and hold stock options in Baxalta Inc. F. de Jong: Employee of and own stock in Shire. J.T. Siveke: Served on ad board for Merrimack. All other authors have declared no conflicts of interest.

243P The effects of genomic polymorphisms in one-carbon metabolism pathways on survival of gastric cancer patients received fluorouracil-based adjuvant therapy

T. Zhao

Department of Oncology Nanjing First Hospital Nanjing Medical University, Nanjing First Hospital, Nanjing, China

Background: Objective: 5-fluorouracil (5-FU) is widely used to treat patients with gastric cancer (GC). However, the response rate is quite heterogeneous. The single nucleotide polymorphisms (SNPs) and their interactions of genes in the one-carbon metabolism (OCM) pathway, including Methylenetetrahydrofolate reductase (MTHFR), Methionine synthase reductase (MTRR), Methionine synthase (MTR), and Thymidylate synthase (TS), significantly affect 5-FU metabolism.

Methods: In this study, 650 stage II-III patients were recruited from 1998 to 2006. Among them, 251 received 5-FU-based chemotherapy and other 399 patients were untreated. The Cox regression analysis, log-rank tests and Kaplan–Meier plots were adopted in our study.

Results: In the chemotherapy cohort, MTRR 66 GA + GG genotypes decreased the risk of death (HR = 0.657, 95% CI = 0.446-0.967, p = 0.031); however, the protect effect of MTRR 66 GA + GG disappeared when GC patients simultaneously had MTHFR 677TT + TC or MTR 2756GG + GA genotypes (HR = 0.871, 95% CI = 0.443-1.713; HR = 0.761, 95% CI = 0.451-1.287). TS 5′-UTR 2R3R + 3R3R genotypes also prolonged overall survival of patients treated with 5-FU (HR = 0.498, 95% CI = 0.259-0.960, p = 0.032). And this favorable prognosis obviously enhanced when GC patients simultaneously had TS 3′-UTR DD + DI and TS 5′-UTR 2R3R + 3R3R genotypes (HR = 0.332, 95% CI = 0.154-0.822, p = 0.046).

Conclusions: Our findings showed that the polymorphisms of MTRR 66 A > G and TS 5′-UTR 3R > 2R may be potential prognostic factors for GC patients receiving 5-FU-based regimens.

Legal entity responsible for the study: N/A.

Funding: This work was partly supported by National 973 Basic Research Program of China (Grant No. 2013CB911300), Grants from National Natural Science Foundation of China (Grant No. 81572928) to Dr. Jinfei Chen.

Disclosure: All authors have declared no conflicts of interest.

244P NOP14 promotes invasion and metastasis by maintaining mutant p53-induced oncogenic signaling in pancreatic cancer

Y. Du[1], L. You[1], Z. Li[1], C. Liu[2], Z. Liu[1], Y. Zhao[1]

[1]*General Surgery, Peking Union Medical College Hospital, Beijing, China,* [2]*Biochemistry and Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China*

Background: Mutant p53 (mutp53) proteins accumulate and promote invasion and metastasis in pancreatic ductal adenocarcinoma (PDAC). However, the mechanism underlying the sustained activation of mutp53 oncogenic signaling is currently unclear. Here, we investigate the function of NOP14 in PDAC metastasis by enhancing the mRNA stability of mutp53, thereby leading to blunted microRNA-17-5p/P21 signaling.

Methods: NOP14 expression was evaluated in paired PDAC samples by immunohistochemistry analysis. Wound-healing, in vitro transwell and invasion assays were employed to investigate the impact of NOP14 on PDAC cell movement. In vivo invasion assays were conducted on established subcutaneously/orthotopically/ intravenously injected tumor mouse models to examine the function of NOP14 in PDAC metastasis. In addition, the functional targets of NOP14 were identified by RNA sequencing and quantitative real-time PCR analyses. Further, the correlations among NOP14, mutp53, and the related signaling molecules were assessed by RNA stability, chromatin immunoprecipitation, and immunoblotting assays.

Results: Increased NOP14 expression was associated with PDAC progression. NOP14 overexpression promoted cell movement, whereas NOP14 inhibition decreased the invasive capacity of PDAC cells. In vivo invasion assays indicated NOP14 as a promoter

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Annals of Oncology

Official Journal of the European Society for Medical Oncology and the Japanese Society of Medical Oncology

Volume 27, 2016 Supplement 9

ESMO Asia Congress

16–19 December 2016, Singapore

ABSTRACT BOOK

Guest Editors:

ESMO Asia 2016 Scientific Committee

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Electronic Acknowledgement Receipt

EFS ID:	42017616
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/Richard King
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	263266-421428
Receipt Date:	25-FEB-2021
Filing Date:	10-NOV-2017
Time Stamp:	20:27:18
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	2021-02-25_01208-0007-01US_SB08_2_OF_6_as_filed.pdf	1058165 20a430bb9c9723001fb60e4611d8e5361fe8fca3	no	8

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/30EFS (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15/809,815	Filing Date	2017-11-10	Docket Number (if applicable)	01208-0007-01US	Art Unit	1612
First Named Inventor	Eliel Bayever			Examiner Name	Celeste A. RONEY		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 506488

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

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Signature of Registered U.S. Patent Practitioner			
Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-02-25
Name	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 01208-0007-01US

Application Number: 15/809,815

Filed: November 10, 2017

For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

Art Unit: 1612

Examiner: Celeste A. Roney

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☐ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$
☑ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$ 2,320
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

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I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration number 56,992.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Mary R. Henninger/ — Signature

February 25, 2021 — Date

Mary R. Henninger — Typed or printed name

404-891-1400 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Inventors:	
	Group Art Unit: 1612
Eliel BAYEVER et al.	
	Examiner: Celeste A. RONEY
Application No.: 15/809,815	
Filed: November 10, 2017	
	Confirmation No.: 5137
Title: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

VIA EFS WEB

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicant brings to the attention of the Examiner the documents listed on the enclosed IDS Forms PTO/SB/08. This Information Disclosure Statement is being filed concurrently with a Request for Continued Examination.

Copies of the listed non-US patent publication documents are enclosed.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they have been considered by making appropriate notations on the enclosed form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed documents are material or constitute "prior art." If the Examiner applies a cited document against any claim of the application and Applicant determines that the cited document does not constitute "prior art," Applicant reserves the right to present to the Office the relevant facts and law regarding the appropriate status of the document.

Applicant further reserves the right to take appropriate action to establish the patentability of the claimed invention over the cited documents, should the Examiner apply one or more of the documents against any of the claims of the present application.

Please charge any fee required for entry of this Information Disclosure Statement, or credit any overpayment, to Deposit Account No. 506488.

Respectfully submitted,

McNeill Baur PLLC

Dated: February 25, 2021

By: /Mary R. Henninger/
Mary R. Henninger
Reg. No. 56,992
Telephone: 404-891-1400

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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 Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2017-11-10
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	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

	1	ClinicalTrials.gov search results for ONIVYDE, retrieved from clinicaltrials.gov website on January 27, 2021, 27 pages.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

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

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-02-25
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ClinicalTrials.gov Search Results 01/27/2021

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
1	NCT03207724	Study of Onivyde and 5-FU in Combination With Xilonix for Pancreatic Cancer With Cachexia	Completed	No Results Available	• Pancreatic Cancer • Cachexia • Weight Loss	• Drug: Xilonix plus Onivyde and 5FU	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Number of Participants With Dose Limiting Toxicities (DLT) in the First Cycle for the determination of the Maximum Tolerated Dose (MTD) • Maximum Tolerated Dose (MTD) of onivyde, 5-fluorouracil/folinic acid in combination with Xilonix • Weight stability • Lean Body Mass • Overall Survival • Progression Free Survival • Mean change in global quality of life (QOL) score (EORTC Pan26) • Mean change in global score of patient-reported response to therapy (FAACT questionnaire- Functional Assessment of Anorexia/ Cachexia Therapy)	Enrollment: 16	• Andrew Hendifar, MD • Ipsen • Janssen Research & Development, LLC • Cedars-Sinai Medical Center	Study Start: October 16, 2017 Last Update Posted: December 30, 2020	• Cedars-Sinai Medical Center, Los Angeles, California, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
2	NCT01770353	MM-398 (Nanoliposomal Irinotecan, Nal-IRI) to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages and to Predict Patient Response to Treatment	Completed	Has Results	• Solid Tumors • ER/PR Positive Breast Cancer • Triple Negative Breast Cancer • Metastatic Breast Cancer With Active Brain Metastasis	• Drug: Ferumoxytol • Drug: MM-398	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Pilot Phase: Tumour Levels of Irinotecan and SN-38 at Cycle 1 Day 4 • Expansion Phase: Impact of the Quality of MRI Scan on Tumour Evaluation • Expansion Phase: Best Overall Tumour Response (BOR) by Tumour FMX Uptake Classification at 16 - 24 Hours Post-FMX Dose • Pilot Phase + Expansion Phase: Median Progression-free Survival (PFS) (Non-CNS Assessment) • Expansion Phase: Median PFS for Cohort 3 (CNS Assessment) • Pilot Phase + Expansion Phase: BOR (Non-CNS Assessment) • Expansion Phase: BOR for Cohort 3 (CNS Assessment) • Pilot Phase + Expansion Phase: Objective Response Rate (ORR) (Non-CNS Assessment) • Expansion Phase: ORR for Cohort 3 (CNS Assessment) • Pilot Phase + Expansion Phase: Median Duration of Objective Response (DOR) (Non-CNS Assessment) • and 14 more	Enrollment: 45	• Ipsen	Study Start: November 2012 Last Update Posted: November 27, 2019	• Mayo Clinic, Scottsdale, Arizona, United States • HonorHealth, Scottsdale, Arizona, United States • UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, United States • Moffitt Cancer Center, Tampa, Florida, United States • University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, United States • Washington University, Saint Louis, Missouri, United States • UNC- Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
3	NCT03446872	Post Marketing Surveillance Study for ONIVYDE® in South Korea	Recruiting	No Results Available	• Metastatic Pancreatic Cancer	• Drug: ONIVYDE • Drug: 5-fluorouracil • Drug: Leucovorin	Study Type: Observational Phase: Outcome Measures: • Number of Adverse Events (AEs) • Grade 3 and 4 neutropenia cases • Visit Information: Number of Visit Types • Visit Information: Reason for Visits • Median Dose of ONIVYDE • Median Dose of fluorouracil • Median Dose of Leucovorin • Overall response • Overall Survival • Progression free survival • Quality of Life assessment (EQ-5D-5 L Health Questionnaire)	Enrollment: 78	• Institut de Recherches Internationales Servier • ADIR, a Servier Group company • Servier	Study Start: March 8, 2018 Last Update Posted: May 22, 2020	• Konyang University Hospital, Daejeon, Korea, Republic of • National Cancer Center, Gyeonggi-do, Korea, Republic of • Severance Hospital, Yonsei University Health System - Gastroenterology, Seoul, Korea, Republic of • Severance Hospital, Yonsei University Health System - Oncology, Seoul, Korea, Republic of • ASAN Medical Center, Seoul, Korea, Republic of • Gangnam Severance Hospital, Yonsei University Health System, Seoul, Korea, Republic of • Samsung Medical Center - Oncology, Seoul, Korea, Republic of • The Catholic University of Korea Seoul St.Mary's Hospital, Seoul, Korea, Republic of • Korea University Guro Hospital, Seoul, Korea, Republic of • Ajou University Hospital, Suwon, Korea, Republic of

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
4	NCT03088813	Study of Irinotecan Liposome Injection (ONIVYDE®) in Patients With Small Cell Lung Cancer	Recruiting	No Results Available	• Small Cell Lung Cancer	• Drug: Irinotecan liposome injection • Drug: Topotecan	Study Type: Interventional Phase: • Phase 2 • Phase 3 Outcome Measures: • Overall survival (OS) • Progression-free survival • Objective Response • Proportion of Patients with Symptom Improvement • Incidence of treatment-emergent adverse events, serious adverse events and laboratory abnormalities	Enrollment: 480	• Ipsen	Study Start: April 25, 2018 Last Update Posted: December 19, 2020	• Sutter Cancer Center, Sacramento, California, United States • National Jewish Health, Denver, Colorado, United States • Rocky Mountain Cancer Centers, Denver, Colorado, United States • Florida Cancer Specialists (South Region), Fort Myers, Florida, United States • Adventist Health System/Sunbelt, Inc., Orlando, Florida, United States • Florida Cancer Specialists, Saint Petersburg, Florida, United States • Florida Cancer Specialists, West Palm Beach, Florida, United States • Winship Cancer Institute of Emory University, Atlanta, Georgia, United States • Northwest Georgia Oncology Centers, Marietta, Georgia, United States • Cancer Treatment Centers of America-Georgia, Newnan, Georgia, United States • and 135 more
5	NCT02013336	Phase 1 Study of MM-398 Plus Cyclophosphamide in Pediatric Solid Tumors	Recruiting	No Results Available	• Recurrent or Refractory Solid Tumors • Ewing Sarcoma • Rhabdomyosarcoma • Neuroblastoma • Osteosarcoma	• Drug: MM-398 (Irinotecan Sucrosofate Liposome Injection) plus cyclophosphamide	Study Type: Interventional Phase: Phase 1 Outcome Measures: • To determine the Maximum Tolerated Dose (MTD) of MM-398 in combination with intravenous cyclophosphamide by assessing the occurrence of dose limiting toxicities • Measurement of plasma levels of study drug to determine the pharmacokinetic properties of MM-398 in combination with cyclophosphamide	Enrollment: 30	• South Plains Oncology Consortium	Study Start: December 2013 Last Update Posted: September 18, 2019	• Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States • University Of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States • UT Southwestern, Dallas, Texas, United States • Houston, Texas, United States • Texas Tech University Health Sciences Center, Lubbock, Texas, United States • Midwest Children's Hospital, Milwaukee, Wisconsin, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
6	NCT03524508	Nal-IRI(Nanoliposomal Irinotecan) Plus 5-FU/LV in Metastatic Biliary Tract Cancer	Active, not recruiting	No Results Available	• Metastatic Biliary Tract Cancer	• Drug: Onivyde • Drug: 5-FU/LV	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression Free Survival by independent central reviewer • Overall Survival • Response rates determined by the investigator according to the RECIST(Response Evaluation Criteria in Solid Tumors) v1.1 • EORTC-QLQ (European Organization for Research and Treatment of Cancer - Quality of life Questionnaire) C30 (version 3.0) • Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability] • Progression Free Survival by investigator assessment	Enrollment: 178	• Changhoon Yoo • Ulsan University Hospital • Chungnam National University Hospital • Kyungpook National University Chilgok Hospital • Inje University • Asan Medical Center	Study Start: September 4, 2018 Last Update Posted: December 11, 2020	• Asan Medical Center, Seoul, Korea, Republic of
7	NCT01494506	Study of MM-398 With or Without 5-FU/LV, Versus 5-FU/LV in Patients With Metastatic Pancreatic Cancer	Completed	Has Results	• Metastatic Pancreatic Cancer	• Drug: MM-398 • Drug: 5 Fluorouracil • Drug: Leucovorin	Study Type: Interventional Phase: Phase 3 Outcome Measures: • Overall Survival • Progression Free Survival • Objective Response Rate • Time to Treatment Failure • Percentage of Patients With Clinical Benefit Response • Percentage of Patients With Tumor Marker (CA 19-9) Response • EORTC-QLQ-C30 • Pharmacokinetic Measurements of Total Irinotecan	Enrollment: 417	• Merrimack Pharmaceuticals	Study Start: November 2011 Last Update Posted: June 17, 2016	• Gilbert, Arizona, United States • Glendale, Arizona, United States • Scottsdale, Arizona, United States • Burbank, California, United States • Duarte, California, United States • Fresno, California, United States • LaVerne, California, United States • San Luis Obispo, California, United States • Boyton Beach, Florida, United States • Atlanta, Georgia, United States • and 69 more

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
8	NCT03810742	Nanoliposomal Irinotecan (Nal-IRI, ONIVYDE®) in Combination With TAS-102 (LONSURF®) in Refractory Solid Tumors	Recruiting	No Results Available	• Refractory Solid Tumors	• Drug: Nanoliposomal Irinotecan	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Determination of Dose Limiting Toxicities (DLT) • Evaluation of Safety profile of nal-IRI and TAS-102 - Incidence of Treatment-Emergent Adverse Events • Evaluation of objective tumor response as per Response Evaluation Criteria in Solid Tumors (RECIST) • Pharmacokinetics study - (Cmax) • Pharmacokinetics study - (Tmax) • Pharmacokinetics study - (T1/2) • Pharmacokinetics study - (AUC0#t) • Pharmacokinetics study - (AUC0##) • Pharmacokinetics study - (CL)	Enrollment: 57	• PharmaEngine	Study Start: March 5, 2019 Last Update Posted: January 5, 2021	• China Medical University Hospital, Taichung, Taiwan • National Cheng Kung University Hospital, Tainan, Taiwan
9	NCT02640365	A Dose Escalation Study of MM-398 Plus Irinotecan in Patients With Unresectable Advanced Cancer	Completed	No Results Available	• Unresectable Advanced Cancer	• Drug: MM-398 • Drug: Irinotecan • Drug: Leucovorin (LV) • Drug: 5-fluorouracile (5-FU) • Drug: bevacizumab	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Adverse Event (AE) • Dose Limiting Toxicities (DLT) • Maximal tolerated dose (MTD) • Response Rate (RR) • Best overall Response (BOR) • Overall survival (OS) • Progression free survival (PFS) • Pharmacokinetic of MM-398 plus irinotecan combination therapy	Enrollment: 10	• GERCOR - Multidisciplinary Oncology Cooperative Group • Merrimack Pharmaceuticals	Study Start: November 18, 2015 Last Update Posted: January 31, 2017	• Hôpital Saint Antoine, Paris, France

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
10	NCT03119064	BrUOG 329 Onivyde & Metronomic Temozolomide in Recurrent Glioblastoma	Completed	No Results Available	• Glioblastoma Multiforme • Glioblastoma • GBM	• Drug: Nanoliposomal Irinotecan • Drug: Temozolomide	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • MTD • Response • PFS • Toxicities	Enrollment: 12	• Heinrich Elinzano, MD • Merrimack Pharmaceuticals • Rhode Island Hospital • Brown University	Study Start: November 30, 2017 Last Update Posted: August 26, 2020	• Rhode Island Hospital, Providence, Rhode Island, United States
11	NCT03739801	MK-3475 and Ramucirumab in Treating Patients With Gastric Cancer or Gastroesophageal Junction Adenocarcinoma	Withdrawn	No Results Available	• Locally Advanced Unresectable Gastric Adenocarcinoma • Metastatic Gastroesophageal Junction Adenocarcinoma • Metastatic Unresectable Gastric Adenocarcinoma • Unresectable Gastroesophageal Junction Adenocarcinoma • Gastric Adenocarcinoma • Gastroesophageal Junction Adenocarcinoma	• Drug: Liposomal Irinotecan • Other: Quality-of-Life Assessment • Other: Questionnaire Administration • Biological: Ramucirumab	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • Dose limiting toxicity (DLT) (Phase I) • Progression-free survival (PFS) (Phase II) • Best overall response (BOR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria • Incidence of adverse events graded according to CTCAE version 4.0	Enrollment: 0	• University of Southern California • National Cancer Institute (NCI) • Ipsen	Study Start: April 6, 2020 Last Update Posted: March 27, 2020	• USC / Norris Comprehensive Cancer Center, Los Angeles, California, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
12	NCT02826486	Study Assessing Safety and Efficacy of Combination of BL-8040 and Pembrolizumab in Metastatic Pancreatic Cancer Patients (COMBAT/KEYNOTE-202)	Active, not recruiting	No Results Available	• Metastatic Pancreatic Adenocarcinoma	• Drug: BL-8040 • Drug: Pembrolizumab • Drug: Chemotherapy of Onivyde	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Objective response rate (ORR) assessed by imaging according to RECIST 1.1 criteria • Objective response rate (ORR) assessed by imaging according to irRECIST • Overall survival • Progression-free survival (PFS) by imaging (RECIST 1.1) • Disease Control	Enrollment: 80	• BioLineRx, Ltd. • Merck Sharp & Dohme Corp.	Study Start: September 2016 Last Update Posted: June 9, 2020	• Mayo Clinic, Phoenix, Arizona, United States • Honor Health, Scottsdale, Arizona, United States • Ochsner Medical Center, New Orleans, Louisiana, United States • Massachusetts General Hospital (MGH), Boston, Massachusetts, United States • Beth Israel Deaconess Medical Center (BIDMAC), Boston, Massachusetts, United States • DF/HCC, Boston, Massachusetts, United States • Karmanos Cancer Center, Wayne State University, Detroit, Michigan, United States • Washington University of St Louis, Saint Louis, Missouri, United States • Atlantic Medical Group, Morristown, New Jersey, United States • NYU Langone Health, New York, New York, United States • and 21 more
13	NCT03719924	Nal-iri/tv5-fu Versus Paclitaxel as Second Line Therapy in Patients With Metastatic Oesophageal Squamous Cell Carcinoma	Recruiting	No Results Available	• Squamous Cell Carcinoma	• Drug: Onivyde • Drug: Paclitaxel	Study Type: Interventional Phase: Phase 2 Outcome Measures: • survival at 9 months • Progression-free survival • Overall survival (OS) • Best response rate during treatment • Toxicity (NCI-CTC v4) • Quality of life (questionnaires)	Enrollment: 106	• Federation Francophone de Cancerologie Digestive • Shire	Study Start: March 7, 2019 Last Update Posted: March 30, 2020	• Chu Amiens, Amiens, France • Institut Sainte Catherine, Avignon, France • Hopital Européen, Marseille, France • Ch Le Raincy, Montfermeil, France • Chu Saint Louis, Paris, France • Ch Perpignan, Perpignan, France • Chu de Poitiers, Poitiers, France • Chu Rouen, Rouen, France • Ch Duchenne, Saint-Malo, France

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
14	NCT03528785	A Study of Nal-IRI With 5-FU, Levofolinic Acid and Oxaliplatin in Patients With Resectable Pancreatic Cancer	Unknown status	No Results Available	• Pancreatic Adenocarcinoma	• Drug: Irinotecan Liposomal Injection [Onivyde]; oxaliplatin, 5-FU; Levofolinic Acid	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Number of patients achieving R0 resection after preoperative nanoliposomal irinotecan (nal-IRI), Oxaliplatin, Leucovorin (LV), 5-FluoroUracil (5-FU) • To determine 2-year overall survival (OS) • determine disease-free survival (DFS) • estimate frequency and severity of adverse events associated with chemotherapy • determine overall response rate (ORR) following preoperative chemotherapy • estimate proportion of patients going to surgery for resection after preoperative chemotherapy • estimate pathologic response rate (pCR) • assess lymph node status • assess surgical mortality • assess surgical morbidity	Enrollment: 67	• Centro Ricerche Cliniche di Verona	Study Start: January 1, 2018 Last Update Posted: May 18, 2018	• Centro Ricerche Cliniche, Verona, Italy
15	NCT03712397	Nanoliposomal Irinotecan in Head & Neck and Esophagus After Prior Platinum-based Chemotherapy or Chemoradiotherapy	Unknown status	No Results Available	• Head & Neck Cancer	• Drug: nanoliposomal irinotecan	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Objective tumor response rate • Progression-Free Survival (PFS) • Treatment toxicities and safety profiles • UGT1A family - UGT1A1 and UGT1A9 with toxicity • cytokine and chemokine before and after treatment	Enrollment: 52	• National Health Research Institutes, Taiwan • China Medical University Hospital • Tri-Service General Hospital • Taipei Veterans General Hospital, Taiwan • National Cheng-Kung University Hospital	Study Start: October 15, 2018 Last Update Posted: October 19, 2018	• China Medical University Hospital, Taichung, Taiwan • National Cheng Kung University Hospital, Tainan, Taiwan • Taipei Veterans General Hospital, Taipei, Taiwan • Tri-Service General Hospital, Taipei, Taiwan

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
16	NCT03483038	A Study of the Safety and Activity of Liposomal Irinotecan in Combination With the 5-FU and Oxaliplatin in the Preoperative Treatment of Pancreatic Adenocarcinoma	Recruiting	No Results Available	• Pancreatic Adenocarcinoma	• Drug: Liposomal Irinotecan • Drug: FOLFOX regimen	Study Type: Interventional Phase: Phase 2 Outcome Measures: • 30 day post operative complication rate • Treatment Completion Rate • Rate of complete surgical resection • Objective Response Rate • Biochemical Response Rate • Patient-Reported Quality of Life • Rate of other pathologic downstaging • To determine the safety of liposomal irinotecan in combination with 5-fluorouracil, oxaliplatin, and leucovorin as assessed by the number of treatment-related adverse events as assessed by CTCAE v 4.0	Enrollment: 53	• University of Florida • Ipsen	Study Start: December 13, 2018 Last Update Posted: January 13, 2021	• University of Florida, Gainesville, Florida, United States • Orlando Health UF Health Cancer Center, Orlando, Florida, United States • Tallahassee Memorial Health Care, Tallahassee, Florida, United States • Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indiana, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
17	NCT03837977	Second-line Therapy for Patients With Progressive Poorly Differentiated Extra-pulmonary Neuroendocrine Carcinoma	Recruiting	No Results Available	• Oncology • Neuroendocrine Carcinoma	• Drug: Liposomal Irinotecan • Drug: Fluorouracil • Drug: Folinic Acid • Drug: Docetaxel	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression-free survival defined as a binary outcome (progression-free or not) • Progression-free survival defined as time from randomisation to progression or death from any cause. • Overall survival defined as time from randomisation to death from any cause. • Objective response rate defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. • Toxicity defined as the number of participants with treatment-related adverse events as assessed by common terminology criteria for adverse events (CTCAE) v5.0. • Quality of life assessed according to the patient reported outcome measures; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 • Neuron-specific enolase (NSE) measurements. • Quality of life assessed according to the patient reported outcome measures; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) GINET21.	Enrollment: 102	• The Christie NHS Foundation Trust • University of Leeds • Servier • National Institute for Health Research, United Kingdom	Study Start: November 13, 2018 Last Update Posted: February 28, 2019	• The Beaston West of Scotland Cancer Center, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom • Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom • The Christie NHS Foundation Trust, Manchester, United Kingdom • Weston Park Hospital, Sheffield Teaching Hospitals, NHS Trust, Sheffield, United Kingdom

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
18	NCT02551991	Study of Nanoliposomal Irinotecan (Nal-IRI)-Containing Regimens Versus Nab-paclitaxel Plus Gemcitabine in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma	Active, not recruiting	No Results Available	• Pancreatic Cancer	• Drug: nal-IRI • Drug: 5 fluorouracil • Drug: Leucovorin • Drug: Oxaliplatin	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • Safety by reporting the adverse events and serious adverse events • Determine dose limiting toxicities (DLT) • Pharmacokinetic Cmax of total irinotecan, SN-38 and oxaliplatin • Pharmacokinetic Cavg of total irinotecan, SN-38 and oxaliplatin • Pharmacokinetic Cmin of total irinotecan, SN-38 and oxaliplatin • Pharmacokinetic AUCt of total irinotecan, SN-38 and oxaliplatin • Pharmacokinetic CL of total irinotecan, SN-38 and oxaliplatin • Pharmacokinetic Vd of total irinotecan, SN-38 and oxaliplatin • Progression Free Survival (PFS) • Overall Survival (OS) • and 3 more	Enrollment: 56	• Ipsen	Study Start: September 2015 Last Update Posted: November 27, 2020	• University of South Alabama, Mobile, Alabama, United States • University of South Alabama - Mobile, Mobile, Alabama, United States • Arizona Center for Cancer Care, Avondale, Arizona, United States • Mayo Clinic Cancer Center, Scottsdale, Arizona, United States • University of California Irvine Medical Center (UCIMC) - Chao Family Comprehensive Cancer Center, Orange, California, United States • University of California, Los Angeles (UCLA) Medical Center - Santa Monica Cancer Center, Santa Monica, California, United States • University of Colorado (CU) Cancer Center - Anschutz Cancer Pavilion, Aurora, Colorado, United States • Mayo Clinic Cancer Center - Jacksonville, Jacksonville, Florida, United States • Mayo Clinic Cancer Center - Rochester, Rochester, Minnesota, United States • US Oncology - Comprehensive Cancer Centers of Nevada (CCCN), Las Vegas, Nevada, United States • and 14 more
19	NCT00062842	Study of Irinotecan on a Weekly Schedule in Children	Completed	No Results Available	• Cancer	• Drug: Irinotecan	Study Type: Interventional Phase: Phase 1 Outcome Measures:	Enrollment: 23	• Baylor College of Medicine	Study Start: September 9, 1998 Last Update Posted: March 4, 2020	• Texas Children's Hospital, Houston, Texas, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
20	NCT02231723	A Study of BBI608 in Combination With Standard Chemotherapies in Adult Patients With Pancreatic Cancer	Completed	No Results Available	• Metastatic Pancreatic Adenocarcinoma	• Drug: BBI608 • Drug: Nab-paclitaxel • Drug: Gemcitabine • Drug: Oxaliplatin • Drug: Leucovorin • Drug: Irinotecan • Drug: Fluorouracil • Drug: MM-398	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Safety by reporting the adverse events and serious adverse events • Determination of the Recommended Phase 2 Dose by assessing dose-limiting toxicities (DLTs) • Assess the preliminary anti-tumor activity of BBI608 when administered in combination with standard chemotherapies by performing tumor assessments every 8 weeks • Assess the preliminary anti-tumor activity of BBI608 when administered in combination with standard chemotherapies by performing serum CA 19-9 level measurement • Assess pharmacokinetic profile of BBI608 when administered in combination with standard chemotherapies • Assess pharmacodynamic activity of BBI608 when administered in combination with standard chemotherapies	Enrollment: 139	• Sumitomo Dainippon Pharma Oncology, Inc	Study Start: August 2014 Last Update Posted: July 21, 2020	• Mayo Clinic Arizona, Phoenix, Arizona, United States • Emory University Winship Cancer Institute, Atlanta, Georgia, United States • Parkview Research Center, Fort Wayne, Indiana, United States • Indiana University Health Goshen Center for Cancer Care, Goshen, Indiana, United States • Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indiana, United States • Comprehensive Cancer Centers of Nevada, Henderson, Nevada, United States • The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, United States • The University of Tennessee Medical Center, Knoxville, Tennessee, United States • Texas Oncology - Austin Midtown, Austin, Texas, United States • Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, Texas, United States • Texas Oncology - SAT&BC, San Antonio, Texas, United States • Virginia Oncology Associates, Norfolk, Virginia, United States
21	NCT02631733	Liposomal Irinotecan and Veliparib in Treating Patients With Solid Tumors	Suspended	No Results Available	• Malignant Solid Neoplasm	• Drug: Ferumoxytol • Drug: Irinotecan Sucrosofate • Other: Laboratory Biomarker Analysis • Procedure: Magnetic Resonance Imaging • Drug: Veliparib	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Incidence of adverse events • Maximum tolerated dose and recommended phase II dose of liposomal irinotecan in combination with veliparib • Tumor response • Objective response rate • Clinical benefit rate defined as complete response, partial response, or stable disease • Progression free survival	Enrollment: 48	• National Cancer Institute (NCI)	Study Start: July 15, 2016 Last Update Posted: January 8, 2021	• Johns Hopkins University/Sidney Kimmel Cancer Center, Baltimore, Maryland, United States • National Institutes of Health Clinical Center, Bethesda, Maryland, United States • NCI - Center for Cancer Research, Bethesda, Maryland, United States • Mayo Clinic in Rochester, Rochester, Minnesota, United States • NYP/Columbia University Medical Center/Herbert Irving Comprehensive Cancer Center, New York, New York, United States • Cleveland Clinic Foundation, Cleveland, Ohio, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
22	NCT03468335	Second-line Therapy With Nal-IRI After Failure Gemcitabine/Nab-paclitaxel in Advanced Pancreatic Cancer - Predictive Role of 1st-line Therapy	Recruiting	No Results Available	• Locally Advanced Pancreatic Cancer • Metastatic Pancreatic Cancer	• Drug: Irinotecan Liposomal Injection [Onivyde]	Study Type: Interventional Phase: Phase 3 Outcome Measures: • Time to Treatment Failure of second-line treatment (TTF2) • Overall survival (OS) • Progression Free Survival (PFS) • AEs / SAEs • Quality of Life (QoL) EORTC QLQ-C30 • Quality of Life (QoL) EORTC QLQ-PAN26 • Quality of Life (QoL) EORTC EQ-5D-5L • Evaluation of time to definitive deterioration of QoL (TDD) • Growth modulation index (GMI)	Enrollment: 270	• AIO-Studien-gGmbH • Crolll Gmbh • Servier	Study Start: March 31, 2018 Last Update Posted: August 7, 2019	• Klinikum St. Marien Amberg, Amberg, Germany • HELIOS Klinikum Bad Saarow, Bad Saarow, Germany • "St.Josef-Hospital Klinikum der Ruhr-Universität Bochum ", Bochum, Germany • Städtisches Klinikum Brandenburg, Brandenburg, Germany • MVZ Klinikum Coburg GmbH, Coburg, Germany • BAG Onkologische Gemeinschaftspraxis Dresden, Dresden, Germany • MVZ Onkologische Kooperation Harz, Goslar, Germany • Universitätsmedizin Göttingen, Göttingen, Germany • Facharztzentrum Eppendorf, Hamburg, Germany • Medi Projekt, Hannover, Germany • and 25 more
23	NCT03665441	Study of Eryaspase in Combination With Chemotherapy Versus Chemotherapy Alone as 2nd-Line Treatment in PAC	Recruiting	No Results Available	• Pancreatic Adenocarcinoma	• Drug: eryaspase • Drug: Gemcitabine plus Abraxane • Drug: Irinotecan plus 5-FU plus leucovorin	Study Type: Interventional Phase: Phase 3 Outcome Measures: • Overall Survival (OS) • Progression Free Survival (PFS) • Objective Response Rate (ORR) • Duration of Response (DoR) • Disease Control Rate (DCR) • Incidence of treatment emergent adverse events as assessed by CTCAE v5.0 • Assess quality of life for global health status, functional scale and symptom scale using questionnaire EORTC QLQ-C30	Enrollment: 500	• ERYtech Pharma	Study Start: September 15, 2018 Last Update Posted: September 30, 2020	• Arizona Cancer Center, Scottsdale, Arizona, United States • St. Joseph Heritage Healthcare, Fullerton, California, United States • University of California Davis Medical Center, Sacramento, California, United States • Georgetown University Hospital, Washington, District of Columbia, United States • Boca Raton Regional Hospital, Boca Raton, Florida, United States • Ochsner Clinic Foundation, New Orleans, Louisiana, United States • Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States • University of Minnesota Health Clinics and Surgery Center, Minneapolis, Minnesota, United States • Roswell Park Cancer Institute, Buffalo, New York, United States • Weill Cornell Medicine, New York, New York, United States • and 6 more

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
24	NCT02022644	Study of Convection-Enhanced, Image-Assisted Delivery of Liposomal-Irinotecan in Recurrent High Grade Glioma	Recruiting	No Results Available	• High Grade Glioma	• Drug: nanoliposomal irinotecan	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Maximum tolerated dose • Tumor Response Rate • Time to Progression (TTP) • Overall Survival (OS)	Enrollment: 30	• University of California, San Francisco • National Institutes of Health (NIH) • Ipsen • National Cancer Institute (NCI)	Study Start: October 16, 2014 Last Update Posted: May 5, 2020	• University of California, San Francisco, San Francisco, California, United States
25	NCT03703063	Alternative Neoadjuvant Chemotherapy in Resectable and Borderline Resectable Pancreatic Cancer	Recruiting	No Results Available	• Pancreatic Adenocarcinoma	• Drug: Gemcitabine • Drug: nab paclitaxel • Drug: Onivyde • Drug: Leucovorin • Drug: 5-fu	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Treatment safety as assessed by CTCAE v4.03 • Overall survival • Progression free survival (PFS) • Response rate	Enrollment: 30	• Benaroya Research Institute	Study Start: September 17, 2018 Last Update Posted: January 27, 2021	• Virginia mason medical Center, Seattle, Washington, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
26	NCT02697058	Phase II of BAX2398/5-FU/Calcium Levofolinate in Pancreatic Cancer	Completed	No Results Available	• Metastatic Pancreatic Cancer	• Biological: BAX2398 + 5-FU/ calcium levofolinate • Drug: 5-FU/calcium levofolinate	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression Free Survival (PFS) in Part 2 of Study • Progression Free Survival (PFS) in Part 1 of Study • Overall Survival (OS) • Time to Treatment Failure (TTF) • Objective Response Rate (ORR) • Disease Control Rate (DCR) • Tumor Marker Response • Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Scores • Change From Baseline in Pain • Change from Baseline in Analgesic use • and 30 more	Enrollment: 84	• Institut de Recherches Internationales Servier • ADIR, a Servier Group company • Servier	Study Start: March 30, 2016 Last Update Posted: July 21, 2020	• Hirosaki University School of Medicine & Hospital, Hirosaki-shi, Aomori-Ken, Japan • Chiba Cancer Center, Chiba-shi, Chiba-Ken, Japan • National Cancer Center Hospital East, Kashiwa-shi, Chiba-Ken, Japan • NHO Shikoku Cancer Center, Matsuyama-shi, Ehime-Ken, Japan • NHO Kyushu Cancer Center, Fukuoka-shi, Fukuoka-Ken, Japan • Kyushu University Hospital, Fukuoka-shi, Fukuoka-Ken, Japan • Hokkaido University Hospital, Sapporo-shi, Hokkaido, Japan • Kanagawa Cancer Center, Yokohama, Kanagawa -ku, Japan • Yokohama City University Medical Center, Yokohama-shi, Kanagawa-Ken, Japan • Kyoto University Hospital, Kyoto-shi, Kyoto-Fu, Japan • and 6 more
27	NCT03785873	Phase Ib/II Trial of Nal-Irinotecan and Nivolumab as Second-Line Treatment in Patients With Advanced Biliary Tract Cancer	Recruiting	No Results Available	• Biliary Tract Cancer	• Drug: Nivolumab • Drug: Nanoliposomal-Irinotecan • Drug: 5-Fluorouracil • Drug: Leucovorin	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • Phase Ib: Incidence of dose-limiting toxicities (DLTs) of drug combination nanoliposomal-Irinotecan, 5-fluorouracil, leucovorin and nivolumab • Phase II: Median Progression-Free Survival (PFS) • Incidence of adverse events • Overall Response Rate (ORR) • Median Overall Survival (OS)	Enrollment: 40	• University of Michigan Rogel Cancer Center • Ipsen • Bristol-Myers Squibb	Study Start: May 22, 2019 Last Update Posted: November 3, 2020	• University of Michigan Rogel Cancer Center, Ann Arbor, Michigan, United States • Cancer and Hematology Centers of Western Michigan, Grand Rapids, Michigan, United States • University of Utah, Salt Lake City, Utah, United States • Virginia Mason, Seattle, Washington, United States • University of Wisconsin, Madison, Wisconsin, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
28	NCT04514497	Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer	Not yet recruiting	No Results Available	• Metastatic Lung Small Cell Carcinoma • Metastatic Malignant Solid Neoplasm • Metastatic Neuroendocrine Carcinoma • Metastatic Pancreatic Adenocarcinoma • Stage III Lung Cancer AJCC v8 • Stage III Pancreatic Cancer AJCC v8 • Stage IIIA Lung Cancer AJCC v8 • Stage IIIB Lung Cancer AJCC v8 • Stage IIIC Lung Cancer AJCC v8 • Stage IV Lung Cancer AJCC v8 • and 7 more	• Drug: Elimusertib • Drug: Irinotecan Sucrosofate • Drug: Topotecan Hydrochloride	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Maximum tolerated dose (MTD) (Dose Escalation Phase) • Occurrence of grade 4 hematologic AEs (Dose Expansion Phase) • Objective response rate (ORR) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Maximum concentration (Cmax) • Area under the concentration-time curve (AUC) • Changes in tumor expression patterns of gamma-H2AX • Changes in tumor expression patterns of pS343-NBS1	Enrollment: 87	• National Cancer Institute (NCI)	Study Start: January 15, 2021 Last Update Posted: December 28, 2020	

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
29	NCT02785068	Evaluation of MM-151 + Nal-IRI + 5-FU + Leucovorin in RAS/RAF Wild-type Metastatic Colorectal Cancer	Withdrawn	No Results Available	• Colorectal Cancer	• Drug: MM-151 • Drug: nal-IRI • Drug: Leucovorin • Drug: 5-FU	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • To find the phase II dose of MM-151 based on safety and tolerability of MM-151 + nal-IRI + 5-FU + Leucovorin that will be assessed through evaluation of dose limiting toxicity reporting. • To correlate disease response according to RECIST with levels of irinotecan and SN-38 in tumor tissue • The number of participants with adverse events (AE) related to treatment with MM-151 + nal-IRI + 5-FU + leucovorin, assessed according to NCI CTCAE v4.0 • The PK parameters of MM-151 and nal-IRI will be described per Cmax • The PK parameters of MM-151 and nal-IRI will be described per AUC • Objective response based on RECIST • Measure pre-treatment and on-treatment levels of EGFR ligands • Presence of anti-drug antibodies will be assessed	Enrollment: 0	• Merrimack Pharmaceuticals	Study Start: July 2016 Last Update Posted: January 11, 2017	

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
30	NCT03721744	A Study of Napabucasin in Combination With Weekly Paclitaxel and Low-dose Gemcitabine in Patients With Pancreatic Cancer	Recruiting	No Results Available	• Metastatic Pancreatic Cancer	• Drug: Napabucasin • Drug: Paclitaxel • Drug: Gemcitabine • Other: Standard of care treatment options	Study Type: Interventional Phase: Phase 3 Outcome Measures: • Overall survival (OS) • Progression free survival (PFS) • Objective response rate (ORR) • Disease control rate (DCR) • Number of Patients with Adverse Events • Quality of Life (QoL)	Enrollment: 230	• 1Globe Health Institute LLC • 1Globe Biomedical Co., Ltd.	Study Start: October 25, 2018 Last Update Posted: June 18, 2019	• The 81st Hospital of Chinese PLA, Nanjing, Jiangsu, China
31	NCT03487016	First-line Therapy in Metastatic PDAC	Recruiting	No Results Available	• Metastatic Pancreatic Cancer	• Drug: Gemcitabine • Drug: Nab-paclitaxel • Drug: 5-FU • Drug: Irinotecan Liposomal Injection • Drug: Oxaliplatin	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression-free survival • Overall survival • Objective response rate • Disease control rate • Duration of study treatment • Type, incidence, causal relationship and severity of adverse events according to NCI CTCAE version 4.03 • Efficacy of second-line chemotherapy • Choice of second-line chemotherapy • Duration of second-line chemotherapy • Quality of life as assessed by EORTC-QLQ-C30	Enrollment: 270	• Ludwig-Maximilians - University of Munich	Study Start: February 15, 2019 Last Update Posted: February 18, 2019	• Klinikum der Universitaet Muenchen - Campus Grosshadern, Munich, Germany
32	NCT04258072	Vactosertib With Nal-IRI/FL in Metastatic Pancreatic Ductal Adenocarcinoma	Not yet recruiting	No Results Available	• Pancreas Cancer	• Drug: Vactosertib	Study Type: Interventional Phase: Phase 1 Outcome Measures: Progression-Free Survival (PFS)	Enrollment: 24	• Samsung Medical Center	Study Start: December 1, 2020 Last Update Posted: October 22, 2020	• Samsung Medical Center, Seoul, Korea, Republic of

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
33	NCT03554707	SGT-53 in Children With Recurrent or Progressive CNS Malignancies	Not yet recruiting	No Results Available	• Childhood CNS Tumor	• Genetic: SGT-53 • Radiation: Radiation • Drug: Irinotecan • Drug: Temozolomide • Drug: Bevacizumab	Study Type: Interventional Phase: Early Phase 1 Outcome Measures: • Incidence of Adverse Events • Response Rate • Duration of Response • Overall Survival • Progressive-Free Survival (PFS) • Characterization of Phenotype of Patients • Feasibility of Droplet PCR Assays to Monitor for Tumor Burden	Enrollment: 6	• SynerGene Therapeutics, Inc.	Study Start: June 2021 Last Update Posted: November 16, 2020	• Children's National Medical Center, Washington, District of Columbia, United States
34	NCT04371224	NalCap (Irinotecan Liposome (Nal-IRI)/Capecitabine) vs. NAPOLI (Nal-IRI/5-FU/LV) in Advanced Pancreatic Cancer	Recruiting	No Results Available	• Pancreatic Cancer	• Drug: Irinotecan Liposomal Injection [Onivyde] • Drug: Capecitabine • Drug: 5-fluorouracil • Drug: Leucovorin	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression-free survival • Objective response rate • Overall survival • Adverse events • QOL: eortc qlq-c30	Enrollment: 200	• Seoul National University Hospital	Study Start: June 23, 2020 Last Update Posted: November 2, 2020	• Seoul National University Bundang Hospital, Seongnam-si, Korea, Republic of • Seoul National University Hospital, Seoul, Korea, Republic of

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
35	NCT03336216	A Study of Cabiralizumab Given With Nivolumab With and Without Chemotherapy in Patients With Advanced Pancreatic Cancer	Active, not recruiting	No Results Available	• Advanced Pancreatic Cancer	• Biological: Cabiralizumab • Drug: Nab-paclitaxel • Drug: Onivyde • Biological: Nivolumab • Drug: Fluorouracil • Drug: Gemcitabine • Drug: Oxaliplatin • Drug: Leucovorin • Drug: Irinotecan Hydrochloride	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Progression free survival (PFS) by Blinded Independent Central Review (BICR) • Progression Free Survival (PFS) by Investigator Assessment • Progression Free Survival Rate (PFSR) • Objective response rate (ORR) • Duration of response (DOR) • Overall Survival (OS) • Overall survival rate (OSR) • Incidence of Adverse Events (AE) • Incidence of Serious Adverse Events (SAE) • Incidence of Adverse Events (AE) leading to discontinuation • and 4 more	Enrollment: 179	• Bristol-Myers Squibb	Study Start: December 15, 2017 Last Update Posted: September 10, 2020	• Mayo Clinic - PPDS, Phoenix, Arizona, United States • HonorHealth Research Institute, Scottsdale, Arizona, United States • Ucla Medical Center, Los Angeles, California, United States • University Of Colorado, Aurora, Colorado, United States • Florida Cancer Specialists - South, Fort Myers, Florida, United States • Florida Cancer Specialists - North, Saint Petersburg, Florida, United States • Johns Hopkins University, Baltimore, Maryland, United States • Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States • Dana Farber Cancer Institute., Boston, Massachusetts, United States • Massachusetts General Hospital, Boston, Massachusetts, United States • and 31 more

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
36	NCT04083235	A Study to Assess the Effectiveness and Safety of Irinotecan Liposome Injection, 5-fluorouracil/Leucovorin Plus Oxaliplatin in Patients Not Previously Treated for Metastatic Pancreatic Cancer, Compared to Nab-paclitaxel+Gemcitabine Treatment	Recruiting	No Results Available	• Metastatic Adenocarcinoma of the Pancreas	• Drug: Irinotecan Liposomal Injection • Drug: Oxaliplatin • Drug: 5Fluorouracil • Drug: Leucovorin • Drug: Nab-paclitaxel • Drug: Gemcitabine	Study Type: Interventional Phase: Phase 3 Outcome Measures: • Overall survival (OS) • Progression free survival (PFS) • Overall Response Rate (ORR)	Enrollment: 750	• Ipsen	Study Start: February 19, 2020 Last Update Posted: December 19, 2020	• University of Alabama at Birmingham, Birmingham, Alabama, United States • Clearview Cancer Institute, Huntsville, Alabama, United States • University of South Alabama - Division of Clinical Research, Mobile, Alabama, United States • Banner Health- MD Anderson Cancer Center, Gilbert, Arizona, United States • Mayo Clinic - Scottsdale, Phoenix, Arizona, United States • Comprehensive Blood And Cancer Center, Bakersfield, California, United States • Presbyterian Intercommunity Hospital (PIH), Costa Mesa, California, United States • City of Hope National Medical Center, Duarte, California, United States • University of California, Los Angeles (UCLA), Los Angeles, California, United States • St. Jude Hospital Yorba Linda dba St. Joseph Heritage Healthcare, Orange, California, United States • and 229 more

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
37	NCT03883919	Liposomal Irinotecan Plus 5-FU / LV Combined With Paricalcitol in Patients With Advanced Pancreatic Cancer Progressed on Gemcitabine-based Therapy	Recruiting	No Results Available	• Pancreatic Cancer • Pancreas Cancer • Cancer of the Pancreas	• Drug: 5-FU • Drug: Leucovorin • Drug: Liposomal Irinotecan • Drug: Paricalcitol • Procedure: Serum and plasma blood samples • Procedure: Tumor biopsy	Study Type: Interventional Phase: Phase 1 Outcome Measures: • Tolerability between two different dose levels of paricalcitol added to the combo regimen of liposomal irinotecan plus 5-FU / LV as measured by the occurrence of grade 3 and 4 toxicities • Overall response rate (ORR) • Progression-free survival (PFS) • Overall survival (OS) • CA19-9 biochemical response rate • Duration of overall response • Duration of complete response • Duration of stable disease	Enrollment: 20	• Washington University School of Medicine • Ipsen	Study Start: July 11, 2019 Last Update Posted: November 10, 2020	• Washington University School of Medicine, Saint Louis, Missouri, United States
38	NCT03693677	First Line Metastatic Pancreatic Cancer : 5FU/LV+Nal-IRI, Gemcitabine+Nab-paclitaxel or a Sequential Regimen of 2 Months 5FU/LV+Nal-IRI	Recruiting	No Results Available	• Metastatic Pancreatic Cancer	• Drug: Irinotecan Liposomal Injection • Drug: 5-FU/LV • Drug: Nab-Paclitaxel • Drug: Gemcitabine	Study Type: Interventional Phase: Phase 2 Outcome Measures: • The progression free survival at 6 months according to the RECIST 1.1 criteria • Progression free survival at 6 months (according to central review) • Best objective response rate • Overall survival • Time to treatment failure • Treatment safety	Enrollment: 288	• Federation Francophone de Cancerologie Digestive	Study Start: November 16, 2018 Last Update Posted: July 19, 2019	• Clinique privée de l'Europe, Amiens, France • CHU Hôtel Dieu, Angers, France • Hôpital privé, Antony, France • CH, Auxerre, France • CH de la Côte Basque, Bayonne, France • CHU Avicenne, Bobigny, France • CH Duchenne, Boulogne-sur-Mer, France • Hôpital Privé Sainte Marie, Chalon-sur-Saône, France • CHU Estaing, Clermont-Ferrand, France • Hopitaux civils de Colmar, Colmar, France • and 26 more

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
39	NCT03328884	Evaluation of the Efficacy and Safety of Nal-IRI for Progressing Brain Metastases in Breast Cancer Patients	Recruiting	No Results Available	• Breast Cancer Metastatic	• Drug: Irinotecan Hydrochloride	Study Type: Interventional Phase: Phase 2 Outcome Measures: • CNS Overall Response Rate (ORR) • CNS disease stabilization on week 12 • ORR, according to a volumetric parameter, and to the RECIST v.1.1 criteria • CBR • Safety profile of nal-IRI in this population by Common Terminology Criteria for Adverse Events version 4 (CTCAE v.4) criteria • Progression-Free Survival (PFS) • Overall Survival (OS)	Enrollment: 63	• MedSIR	Study Start: May 2, 2017 Last Update Posted: November 27, 2020	• ICO, Badalona, Spain • MedSIR Site, Barcelona, Spain • IOB Institute of Oncology - Quirón Barcelona, Barcelona, Spain • Hospital San Pedro Alcántara, Cáceres, Spain • ICO, Girona, Spain • H. Ruber Juan Bravo, Madrid, Spain • Hospital Clínico San Carlos, Madrid, Spain • Hospital Doce de Octubre, Madrid, Spain • Hospital Universitario Ramón y Cajal, Madrid, Spain • MD Anderson Madrid, Madrid, Spain • and 9 more
40	NCT04617457	Chemotherapy and Surgical Resection in Patients With Hepatic Oligometastatic Adenocarcinoma of the Pancreas	Not yet recruiting	No Results Available	• Pancreatic Cancer • Metastasis • Surgery • Oligometastatic Disease	• Drug: nal-irinotecan (nal-iri) (Onyvide), oxaliplatin (ox), 5-fluouracil (5-FU), folinic acid (FA)	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Overall survival after R0/R1 resection (OS-res) • R0/R1 resection rate after neoadjuvant chemotherapy • Overall survival (OS) • Progression-free survival (PFS) after R0/R1 resection according to RECIST v1.1 • Type, frequency and severity of adverse events (AE) with severity (SAE) according to NCI CTCAE version 5.0 • HR-QoL according to EORTC QLQ-C30 • Quality of life (QoL) according to EORTC QLQ-PAN-26 • QoL-adjusted OS	Enrollment: 150	• University of Cologne • Servier	Study Start: January 1, 2021 Last Update Posted: December 8, 2020	

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
41	NCT04037241	Study of Anti-CEA CAR-T + Chemotherapy VS Chemotherapy Alone in Patients With CEA +Pancreatic Cancer & Liver Metastases	Not yet recruiting	No Results Available	• Malignant Tumor of Pancreas Metastatic to Liver	• Biological: Anti-CEA CAR-T cells • Drug: gemcitabine/ nab paclitaxel • Drug: NLIR+FU/FA • Drug: Capecitabine	Study Type: Interventional Phase: • Phase 2 • Phase 3 Outcome Measures: • Assess efficacy by overall survival • Assess safety by monitoring adverse events • Assess efficacy by within-liver progression free survival (PFS) • Assess efficacy by progression free survival (PFS) • Assess efficacy by within-liver time to progression (TTP) • Assess efficacy by time to progression (TTP) • Assess efficacy by within-liver radiographic response rate using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) • Assess efficacy by overall whole-body radiographic response rate using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) • Assess efficacy by duration of response within-liver in accordance with RECIST v 1.1 criteria • Assess efficacy by duration of response of overall whole-body in accordance with RECIST v 1.1 criteria • and 5 more	Enrollment: 167	• Sorrento Therapeutics, Inc.	Study Start: November 1, 2021 Last Update Posted: July 15, 2020	

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
42	NCT03368963	TAS102 in Combination With MAL-IRI in Advanced GI Cancers	Recruiting	No Results Available	• Colorectal Adenocarcinoma • Gastric Adenocarcinoma • Metastatic Pancreatic Adenocarcinoma • Non-Resectable Cholangiocarcinoma • Stage IV Colorectal Cancer • Stage IV Gastric Cancer • Stage IV Pancreatic Cancer • Stage IVA Colorectal Cancer • Stage IVB Colorectal Cancer • Stage III Colorectal Cancer • and 4 more	• Drug: Nanoliposomal Irinotecan • Drug: Trifluridine and Tipiracil Hydrochloride	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • Incidence of adverse events of trifluridine/ tipiracil hydrochloride combination agent TAS-102 in combination with nanoliposomal irinotecan • Overall response rate based on modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 • Progression free survival • Response duration • Response rate	Enrollment: 64	• Emory University • Taiho Oncology, Inc. • Ipsen	Study Start: January 30, 2018 Last Update Posted: August 19, 2020	• Emory University Hospital Midtown, Atlanta, Georgia, United States • Emory University Hospital/Winship Cancer Institute, Atlanta, Georgia, United States • Emory Saint Joseph's Hospital, Atlanta, Georgia, United States
43	NCT03736720	Liposomal Irinotecan, Fluorouracil and Leucovorin in Treating Patients With Refractory Advanced High Grade Neuroendocrine Cancer of Gastrointestinal, Unknown, or Pancreatic Origin	Recruiting	No Results Available	• Locally Advanced Digestive System Neuroendocrine Carcinoma • Locally Advanced Pancreatic Neuroendocrine Carcinoma • Metastatic Digestive System Neuroendocrine Carcinoma • Metastatic Pancreatic Neuroendocrine Carcinoma • Refractory Digestive System Neuroendocrine Carcinoma • Refractory Pancreatic Neuroendocrine Carcinoma • Unresectable Digestive System Neuroendocrine Carcinoma • Unresectable Pancreatic Neuroendocrine Carcinoma	• Drug: Fluorouracil • Drug: Leucovorin • Drug: Liposomal Irinotecan • Procedure: Quality-of-Life Assessment	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Objective response rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • Overall survival • Progression-free survival assessed by RECIST 1.1 • Time-to treatment failure • Proportion of patients achieving an objective response based on prior response to platinum etoposide • Clinical benefit response • Quality of life (QOL) as assessed by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) • Incidence of adverse events	Enrollment: 37	• Roswell Park Cancer Institute • National Cancer Institute (NCI) • Ipsen	Study Start: June 17, 2019 Last Update Posted: August 10, 2020	• Roswell Park Cancer Institute, Buffalo, New York, United States • Stony Brook Cancer Center, Stony Brook, New York, United States

	NCT Number	Title	Status	Study Results	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Dates	Locations
44	NCT03337087	Liposomal Irinotecan, Fluorouracil, Leucovorin Calcium, and Rucaparib in Treating Patients With Metastatic Pancreatic, Colorectal, Gastroesophageal, or Biliary Cancer	Recruiting	No Results Available	• Metastatic Biliary Tract Carcinoma • Metastatic Colorectal Carcinoma • Metastatic Gastroesophageal Junction Adenocarcinoma • Metastatic Malignant Digestive System Neoplasm • Metastatic Pancreatic Adenocarcinoma • Stage IV Colorectal Cancer AJCC v7 • Stage IV Pancreatic Cancer AJCC v6 and v7 • Stage IVA Colorectal Cancer AJCC v7 • Stage IVB Colorectal Cancer AJCC v7	• Drug: Fluorouracil • Other: Laboratory Biomarker Analysis • Drug: Leucovorin Calcium • Drug: Liposomal Irinotecan • Drug: Rucaparib	Study Type: Interventional Phase: • Phase 1 • Phase 2 Outcome Measures: • Number of participants with dose limiting toxicities (Phase I) • Objective response (Phase Ib) • Best response rate (Phase II) • Disease control rate (DCR) • Overall survival (Phase II) • Progression-free survival (Phase II) • Incidence of adverse events (Phase II)	Enrollment: 110	• Academic and Community Cancer Research United • National Cancer Institute (NCI)	Study Start: November 2, 2018 Last Update Posted: January 22, 2021	• Mayo Clinic in Arizona, Scottsdale, Arizona, United States • Emory University Hospital/Winship Cancer Institute, Atlanta, Georgia, United States • Mayo Clinic, Rochester, Minnesota, United States
45	NCT04233866	Comparing Two Treatment Combinations, Gemcitabine and Nab-Paclitaxel With 5-Fluorouracil, Leucovorin, and Liposomal Irinotecan for Older Patients With Pancreatic Cancer That Has Spread	Recruiting	No Results Available	• Metastatic Pancreatic Adenocarcinoma • Stage IV Pancreatic Cancer AJCC v8	• Drug: Fluorouracil • Drug: Gemcitabine • Drug: Gemcitabine Hydrochloride • Drug: Leucovorin • Drug: Leucovorin Calcium • Drug: Liposomal Irinotecan • Drug: Nab-paclitaxel • Other: Quality-of-Life Assessment • Other: Questionnaire Administration	Study Type: Interventional Phase: Phase 2 Outcome Measures: • Overall survival (OS) • Instrumental Activities of Daily Living (IADL)	Enrollment: 184	• ECOG-ACRIN Cancer Research Group • National Cancer Institute (NCI) • Eastern Cooperative Oncology Group	Study Start: June 18, 2020 Last Update Posted: June 25, 2020	• Saint Alphonsus Cancer Care Center-Boise, Boise, Idaho, United States • Saint Alphonsus Cancer Care Center-Caldwell, Caldwell, Idaho, United States • Kootenai Medical Center, Coeur d'Alene, Idaho, United States • Walter Knox Memorial Hospital, Emmett, Idaho, United States • Idaho Urologic Institute-Meridian, Meridian, Idaho, United States • Saint Alphonsus Medical Center-Nampa, Nampa, Idaho, United States • Kootenai Cancer Center, Post Falls, Idaho, United States • Kootenai Cancer Clinic, Sandpoint, Idaho, United States • Community Hospital of Anaconda, Anaconda, Montana, United States • Billings Clinic Cancer Center, Billings, Montana, United States • and 33 more

REMARKS

I. Status of Claims

Claims 1, 4-15, 18-19, and 21-23 are pending in the application. Claims 2, 3, 16, 17, and 20 were previously canceled without prejudice or disclaimer. Applicant expressly reserves the right to pursue the subject matter of those claims in the future. Claims 1, 8, and 19 are amended to even more clearly recite the subject matter being claimed. Support for the amendments can be found throughout the specification and originally filed claims. The amendments add no new matter.

II. Rejections Under 35 U.S.C. § 103

Rejection of claims 1, 5-8, 10 and 19

The Examiner maintains the rejection of claims 1, 5-8, 10 and 19 under 35 U.S.C. 103 as allegedly being unpatentable over WO 2013/188586 ("Bayever"), in view of Conroy et al., N Engl J Med., 364(19):1816-25, 2011) ("Conroy"), and further in view of Melis et al., The Society for Surgery of the Alimentary Tract, 2011; http://meetings.ssat.com/abstracts/11ddw/P57.cgi) ("Melis"). Office Action at p. 2. The Examiner asserts that Bayever discloses treatment of metastatic pancreatic cancer comprising "co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan)," a dose of 2400 mg/m^2 5-fluorouracil, and a dose of 200 mg/m^2 1 form or 400 mg/m^2 l+d form leucovorin for at least one cycle of two weeks. *Id.* at pp. 2-3. The Examiner also alleges that Conroy discloses treatment of metastatic pancreatic cancer with oxaliplatin, irinotecan, leucovorin, and fluorouracil. *Id.* at p. 3. Furthermore, the Examiner alleges that "it would have been prima facie obvious to one of ordinary skill in the art to include oxaliplatin within Bayever's methods of treatment" and that "[a]n ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy… ." *Id.*

Regarding the 60 mg/m^2 oxaliplatin dose recited in claims 1 and 19, the Examiner alleges that Conroy teaches 85 mg/m^2 oxaliplatin[1], but not 60 mg/m^2 oxaliplatin. *Id.* at p. 4. The Examiner then points to Melis for allegedly teaching "that a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients." *Id.* The Examiner alleges that the dosage of oxaliplatin is "recognized to be result effective" and that "it would have been prima facie obvious to optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis." *Id.*

Applicant respectfully traverses. Bayever discloses treatment of pancreatic cancer by administering a combination of liposomal irinotecan (e.g., 60 or 80 mg/m^2), in combination with 5-fluorouracil (5-FU) (e.g., 2400 mg/m^2) and leucovorin (LV) (e.g., 400 mg/m2 l+d form) to a patient once every two weeks. Conroy describes administering a combination of 180 mg/m^2 non-liposomal irinotecan, 85 mg/m^2 oxaliplatin, 5-FU, and LV once every two weeks. Melis is an abstract summarizing a phase I/II chemo-radiation (CRT) study of continuous infusion of 200 mg/m^2 5-fluorouracil and escalating doses of oxaliplatin (30 mg/m^2 in 10 mg intervals up to 60 mg/m^2) weekly for 5 weeks with concurrent radiation in patients with regionally advanced pancreatic cancer. Thus, Bayever, Conroy, and Melis disclose treatment of pancreatic cancer with a different combination of therapeutic agents in different doses from that of the claimed invention.

Applicant incorporates by reference the arguments presented in the January 7, 2020 Non-Final Office Action Response explaining the lack of a *prima facie* case of obviousness of the claimed methods and impermissible reliance on hindsight. Namely, a person of ordinary skill in the art would not have been motivated to select and combine the weekly 60 mg/m^2 dose of oxaliplatin referenced in Melis with the teachings of Bayever and Conroy to reach the claimed methods with a reasonable expectation of success for numerous reasons. First, the Melis Study involved patients with locally advanced pancreatic cancer and ***excluded*** patients with metastatic disease, which is the patient population recited in the pending claims. *See also* Amodeo et al, "Can we downstage locally advanced pancreatic cancer to resectable? A phase I/II study of induction oxaliplatin and 5-FU chemoradiation," J Gastrointest Oncol, 9(5):922-935, 2018

[1] Applicant assumes that the Examiner's statement that Bayever teaches 85 mg/m^2 oxaliplatin was meant to refer to Conroy. *See* Office Action at p. 4. Applicant responds accordingly.

("Amodeo") (cited in the January 7, 2020 IDS) at p. 924. Second, in contrast to the "once every two weeks" coadministration schedule recited in the pending claims, the Melis Study involved ***weekly*** administration of 60 mg/m^2 oxaliplatin. Third, the Melis Study included ***continuous infusion*** of 200 mg/m^2 5-fluorouracil compared to the claimed coadministration of 2,400 mg/m^2 5-fluorouracil once every two weeks. Fourth, the Melis treatment regime did not result in improved outcomes compared to other combination therapies for locally advanced pancreatic cancer. *See* Amodeo at p. 933. Fifth, patients who remained unresectable for cure but did not progress continued on a modified FOLFOX6 regime involving a higher 85 mg/m^2 dose of oxaliplatin every two weeks. *See* Melis abstract and Amodeo at p. 924. If anything, the teachings of Melis would have discouraged treatments of metastatic adenocarcinoma of the pancreas involving a 60 mg/m^2 dose of oxaliplatin once every two weeks.

The Examiner responds alleging that Melis is relied upon to show that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation. Office Action at pp. 6 and 7.

Applicant respectfully maintains that the cited references do not teach or suggest a combination or composition comprising 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 5-FU, and LV for use in treating metastatic pancreatic cancer in a patient who has not previously received chemotherapy for the cancer and that is administered once every two weeks. As discussed in the January 7, 2020 Non-Final Office Action Response, the Examiner's rejection fails to account for the many factors, such as drug combination, dose, dosing schedule, drug-drug interactions, and overlapping toxicities, that each affect in unpredictable ways the tolerability and efficacy of a particular cancer treatment. The Examiner responds by alleging that "the skilled artisan would be led by Bayever's guidance of study design and patient selection [pages 25-31], at the discretion of the investigator, to account for factors affecting tolerability and efficacy of the protocol." Office Action at p. 7.

Even if a prima facie case of obviousness were to be established regarding any of the pending claims, which Applicant fervently traverses, one or more objective indicia of nonobvious would support a finding of nonobviousness. "Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing '(1) [t]hat the prior art taught away from the claimed invention… or (2) that there are new and unexpected results relative to the prior art.' Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392

F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004)." MPEP § 2144.05 III B. Other objective evidence of nonobviousness includes evidence of criticality, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc. See MPEP §§ 716.01(a) and 2145.

Respectfully, and to provide additional background that may help distinguish the claimed methods from the cited disclosures, in 2015, ONIVYDE® (irinotecan liposome injection) was approved by the US FDA at a recommended dose of 80 mg/m^2 in combination with fluorouracil and leucovorin once every two weeks, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy—i.e., a second-line therapy for metastatic pancreatic cancer. *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf and the present Specification at page 2, lines 19-22. This liposomal irinotecan, 5-FU, LV regimen is described in Bayever.

The FOLFIRINOX regimen described in Conroy has been recommended by the National Comprehensive Cancer Network (NCCN) as a preferred option for first-line metastatic pancreatic cancer since 2011. *See* the present Specification at page 2, lines 9-11. Conroy reports at page 1817 that for the FOLFIRINOX group, the median overall survival (OS) was 11.1 months, the median progression free survival (PFS) was 6.4 months, and the objective response rate (ORR) was 31.6%.

The Examiner alleges that the dosage of oxaliplatin is a result effective variable that can be optimized by routine experimentation and that the skilled artisan would be led to account for factors affecting tolerability and efficacy. *See* Office Action at pp. 6 and 7. However, combining 85 mg/m^2 oxaliplatin of Conroy with the lower 60 mg/m^2 dose of liposomal irinotecan, 5 FU, and LV of Bayever is ***not tolerable*** in patients with metastatic pancreatic cancer. Likewise, the higher 80 mg/m^2 dose of liposomal irinotecan, 5 FU, and LV of Bayever combined with a lower 60 mg/m^2 oxaliplatin dose is ***not tolerable***. Surprisingly, however, the claimed lower dose combinations and compositions of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 5-FU, and LV are tolerable and despite the lower combined dose achieved unexpected therapeutic effects over that of the standard first-line FOLFIRINOX regimen as reported in Conroy.

The 2020 Wainberg abstract, poster, and presentation[2] provided herewith report data resulting from the clinical protocol described in Example 3 of the instant application. Specifically, four cohorts of patients with unresectable, locally advanced or metastatic pancreatic ductal adenocarcinoma 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 and oxaliplatin[3]:

- Cohort A: 80 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("80/60");
- Cohort B: 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin ("60/60");
- Cohort C: 60 mg/m^2 liposomal irinotecan and 85 mg/m^2 oxaliplatin ("60/85"); and
- Cohort D: 65 mg/m^2 liposomal irinotecan and 70 mg/m^2 oxaliplatin ("65/70").

Each of the therapies of Cohorts A (80/60), C (60/85), and D (65/70) were not tolerable, whereas Cohort B (60/60) was tolerable. *See* Table 2 of the Wainberg poster and slide 8 of the Wainberg presentation. Accordingly, the maximum tolerated dose of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin was used for the dose expansion study. Hence, the results of Cohort B and the dose expansion group are relevant to the methods of the pending claims.

The cohort of patients treated with the only tolerable dose of oxaliplatin and liposomal irinotecan tested (60/60) unexpectedly resulted in primary efficacy outcomes ***higher*** than that of the currently preferred FOLFIRINOX regimen as reported in Conroy. Specifically, the median overall survival (OS) was 12.6 months, the median progression free survival (PFS) was 9.2

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[2] Wainberg Z, et al., "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," Ann Oncol. 31(Suppl 3):S241 doi.org/10.1016/j.annonc.2020.04.076 (2020) ("Wainberg abstract"), and corresponding poster ("Wainberg poster") and presentation ("Wainberg presentation") presented at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, virtual format, July 1-4, 2020. The 2020 Wainberg abstract, poster, and presentation are appended hereto and included in the information disclosure statement filed herewith and correspond to cite numbers 39, 37, and 36 of SB08 5 of 6, respectively.

[3] The 50, 55, and 70 mg/m^2 free base doses of liposomal irinotecan referenced in the Wainberg abstract, poster, and presentation are equivalent to 60, 65, and 80 mg/m^2 doses, respectively, of liposomal irinotecan based on the molecular weight of irinotecan hydrochloride trihydrate. *See* present Specification at page 8, lines 12-19 and page 67, lines 10-14.

months, and the objective response rate (ORR) was 34.4 % for the 32 patients[4] from both the Cohort B and dose-expansion study. *See* Results section of the Wainberg abstract and poster and slides 9 and 10 of the Wainberg presentation. These primary efficacy outcomes are each ***higher*** than those reported in Conroy for FOLFIRINOX (i.e., compared to OS of 11.1 months, PFS of 6.4 months, and ORR of 31.6%).

In summary, the administration of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 5-FU, and LV as claimed showed superior primary efficacy outcome measures compared to that of the currently preferred first-line FOLFIRINOX treatment regimen as reported in Conroy. While the right to present additional objective evidence of nonobviousness is reserved, Applicant respectfully asserts that the evidence of unexpected results presented above negates any prima facie case of obviousness. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over Bayever, in view of Conroy, and in further view of Melis.

Rejection of claims 4, 9, 18 and 23

The Examiner maintains the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. 103 as allegedly being unpatentable over Bayever, in view of Conroy, and further in view of Melis and Fleming et al. found at htttp://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-inchemotherapy-administration/article/378072/ ("Fleming"). Office Action at pp. 7-8. The Examiner alleges that Fleming discloses at the last sentence of the first paragraph that "the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics." *Id.* at p. 8. The Examiner alleges that in view of Fleming, one of ordinary skill in the art would have been motivated to vary the order of administration of the combined methods of Bayever and Conroy. *Id.*

Applicant respectfully traverses for at least the reasons discussed above and in the January 7, 2020 Non-Final Office Action Response with respect to claims 1 and 19, from which claims 4, 9, 18, and 23 depend. As discussed, the Examiner has failed to establish a prima facie

[4] Of the 32 patients in the pooled population of patients from Cohort B and the dose-expansion group, 29 had metastatic disease (i.e., stage IV) at initial treatment. *See* Wainberg presentation at slide 7 pooled patient population column and footnote c.

case of obviousness at least with respect to the claimed treatment of metastatic adenocarcinoma of the pancreas comprising, in-part, co-administration of a dose of 60 mg/m^2 oxaliplatin once every two weeks. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy.

Accordingly, claims 4, 9, 18, and 23, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, leucovorin (200 mg/m^2 l-form or 400 mg/m^2 l+d form), and 2,400 mg/m^2 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, and/or Fleming. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 4, 9, 18, and 23 under 35 U.S.C. § 103 over Bayever in view of Conroy, and further in view of Melis and Fleming.

Rejection of claims 11-15 and 21-22

The Examiner maintains the rejection of claims 11-15 and 21-22 under 35 U.S.C. § 103 as allegedly being obvious over Bayever in view of Conroy, further in view of Melis, and as evidenced by WO 2016/094402 ("Bayever II"). *Id.* at pp. 9-10. The Examiner alleges that while "Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12 and 21-22," Bayever II "evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE." *Id.* at p. 10. The Examiner also alleges that claims 13-15 and 21-22 are rendered obvious because of the administration durations and cycles disclosed in Bayever. *Id.*

Applicant respectfully traverses for at least the reasons discussed above and in the January 7, 2020 Non-Final Office Action Response with respect to claims 1 and 19, from which claims 11-15 and 21-22 depend. As discussed, the Examiner has failed to establish a prima facie case of obviousness at least with respect to the claimed treatment of metastatic adenocarcinoma of the pancreas comprising, in-part, co-administration of a dose of 60 mg/m^2 oxaliplatin once every two weeks. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy.

Accordingly, claims 11-15 and 21-22, which, in part, incorporate treatment of metastatic adenocarcinoma of the pancreas comprising co-administration of 60 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, leucovorin (200 mg/m^2 l-form or 400 mg/m^2 l+d form), and 2,400 mg/m^2 5-fluorouracil once every two weeks are nonobvious over Bayever, Conroy, Melis, and/or Bayever II. Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 11-15 and 21-22 under 35 U.S.C. § 103 over Bayever in view of Conroy, further in view of Melis, and as evidenced by Bayever II.

III. Nonstatutory Double Patenting

The Examiner maintains the rejection of claims 1, 4-15, 18-19, and 21-23 on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-18 of U.S. Patent No. 9,492,442 ("the '442 Patent") in view of Conroy, and further in view of Melis. *Id.* at pp. 12-13. The Examiner alleges that the "issued claims recite all of the features instantly recited for the method of treatment except for the administration of oxaliplatin." *Id.* The Examiner further alleges that "it would have been prima facie obvious to use oxaliplatin in the issued method, because oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro*." *Id.* at p. 13. The Examiner argues that Melis allegedly teaches that "a dosage of 60 mg/m^2 oxaliplatin was well tolerated in advanced pancreatic adenocarcinoma patients" and that "[i]t would have been prima facie obvious to use oxaliplatin at 60 mg/m^2 because the said dosage is well tolerated in advanced pancreatic adenocarcinoma patients." *Id.*

Applicant respectfully traverses. Coadministration of a dose of 60 mg/m^2 oxaliplatin once every two weeks for the treatment of metastatic adenocarcinoma of the pancreas would not have been an obvious variation of any of claims 1-18 of the '442 Patent for at least the reasons discussed above and in the January 7, 2020 Non-Final Office Action Response. Further, any prima facie case of obviousness has been overcome by the unexpected therapeutic effects the lower claimed combined dose achieved over that of the standard first-line FOLFIRINOX regimen as reported in Conroy. Accordingly, the pending claims are not obvious variations of issued claims 1-18 of the '442 Patent.

Applicant respectfully requests reconsideration and withdrawal of the nonstatutory double patenting rejection over claims 1-18 of the '442 Patent, in view of Conroy, and further in view of Melis.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

MCNEILL BAUR PLLC.

Dated: February 25, 2021

By: /Mary R. Henninger/
Mary R. Henninger
Reg. No. 56,992
404-891-1400

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace the prior versions and listings of claims in the application. Please amend the claims as follows:

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~:
   a. 60 mg/m^2 of liposomal irinotecan,
   b. 60 mg/m^2 oxaliplatin,
   c. 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
   d. 2,400 mg/m^2 5-fluorouracil;

   to treat the metastatic adenocarcinoma of the pancreas in the human patient.

2. (Canceled)

3. (Canceled)

4. (Original) The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

5. (Original) The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

6. (Original) The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

7. (Original) The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

8. (Currently Amended) The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over ~~a total of~~ about 90 minutes.

9. (Original) The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

10. (Original) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

11. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

12. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

13. (Previously Presented) The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

14. (Previously Presented) The method of claim 19, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

15. (Previously Presented) The method of claim 14, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered

prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

16. (Canceled)

17. (Canceled)

18. (Previously Presented) The method of claim 19, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

19. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient ~~a total of~~ once every two weeks, the antineoplastic therapy consisting of ~~administering to the patient a total of~~:

    a. 60 mg/m^2 of liposomal irinotecan,
    b. 60 mg/m^2 oxaliplatin,
    c. 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
    d. 2,400 mg/m^2 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

20. (Canceled)

21. (Previously Presented) The method of claim 1, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

22. (Previously Presented) The method of claim 19, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

23. (Previously Presented) The method of claim 1, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Eliel BAYEVER et al. Application No.: 15/809,815 Filed: November 10, 2017 For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	Group Art Unit: 1612 Examiner: Celeste A. Roney Confirmation No.: 5137

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Via EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner Roney:

Applicants respond to the Final Office Action mailed February 27, 2020. A Notice of Appeal and request for extension of three months were filed on August 25, 2020. This response is filed with a Request for Continued Examination and an Information Disclosure Statement. The period for response has been extended by four months, to February 25, 2021, by request for extension and payment of extension fees herewith. Please amend the above-identified application as follows:

Amendments to the Claims begin at page 2.

Remarks begin at page 6.

Attachments include Wainberg 2020 abstract, poster, and presentation.

2020 Wainberg Abstract

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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

Z. Wainberg[1], T. Bekaii-Saab[2], P. Boland[3], F. Dayyani[4], T. Macarulla[5], K. Mody[6], B. Belanger[7], F. Maxwell[8], Y. Moore[7], A. Thiagalingam[7], T. Wang[7], B. Zhang[7], A. Dean[9]

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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.

Editorial acknowledgement: Medical writing support provided Oxford PharmaGenesis, Oxford, UK, which was sponsored by Ipsen Biopharmaceuticals, Inc., in accordance with Good Publication Practice guidelines.

Legal entity responsible for the study: Ipsen.

Funding: This study is funded by Ipsen.

Disclosure: Zev Wainberg has an affiliation with Grant/Research Support: Ipsen, Novartis; Consultant: Ipsen, Merck, Lilly.

https://doi.org/10.1016/j.annonc.2020.04.076

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.

Legal entity responsible for the study: The authors.

Funding: The Terry Fox Foundation.

Disclosure: The presenting author has declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.04.077

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

2020 Wainberg Poster

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

Zev A Wainberg,[1] Tanios Bekaii-Saab,[2] Patrick M Boland,[3] Farshid Dayyani,[4] Teresa Macarulla,[5] Kabir Mody,[6] Bruce Belanger,[7] Fiona Maxwell,[8] Yan Moore,[7] Arunthathi Thiagalingam,[7] Tiffany Wang,[7] Bin Zhang,[7] Andrew Dean[9]

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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)	4 (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)

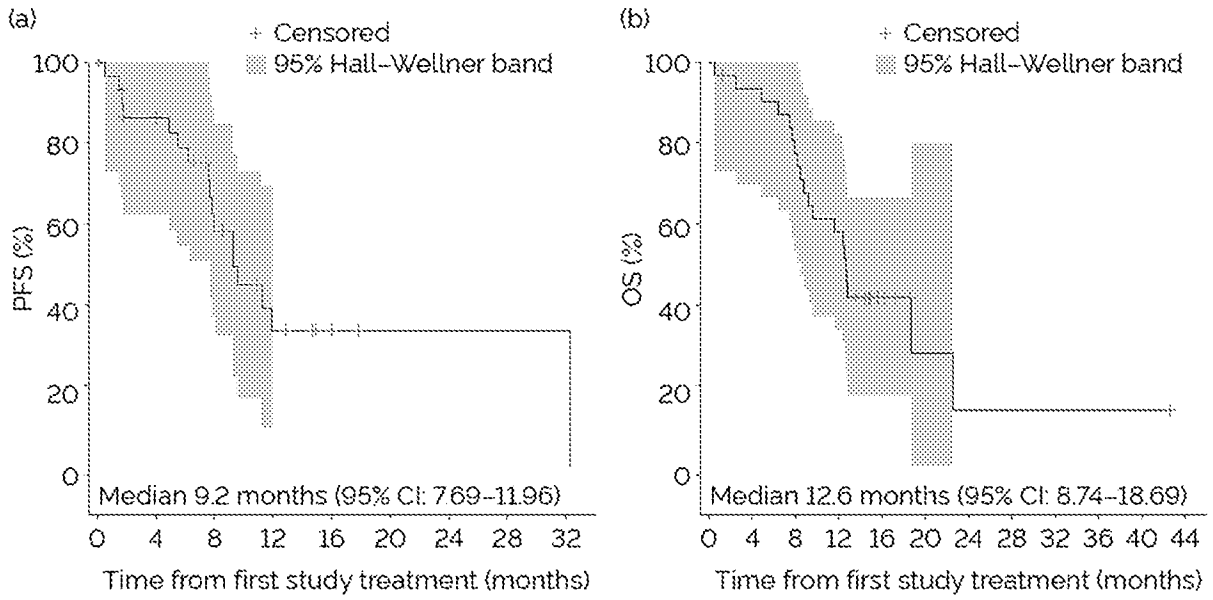
[a]Dose of liposomal irinotecan (free base)/dose of oxaliplatin expressed in mg/m² administered in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m² on days 1 and 15 of each 28-day cycle. [b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m² and oxaliplatin 60 mg/m² 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	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)
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)

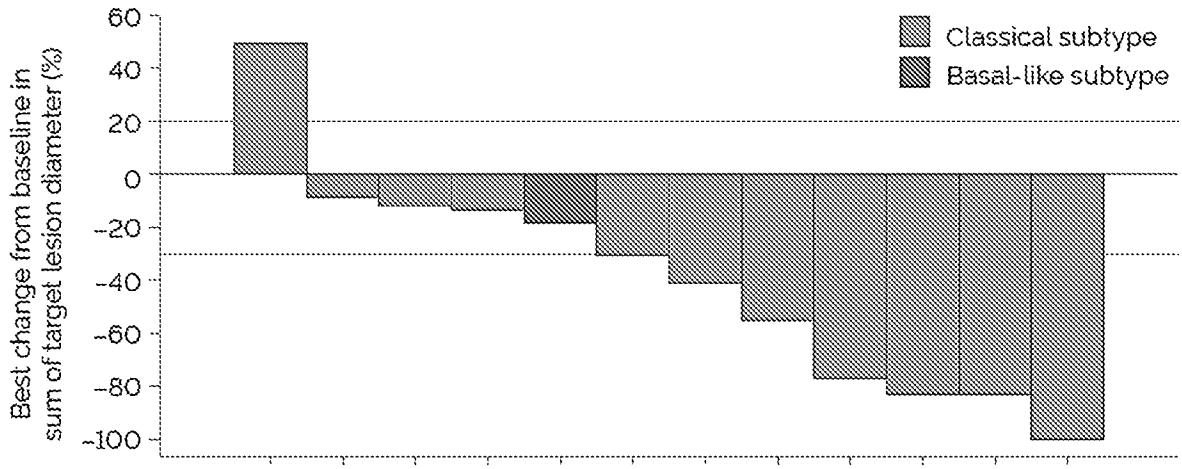
Data are number (%) of patients from the safety population unless stated otherwise. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, v20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.
[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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9. Rashid NU *et al. Clin Cancer Res* 2020;26:82–92.

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

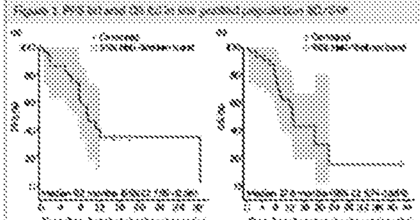
LBA-001

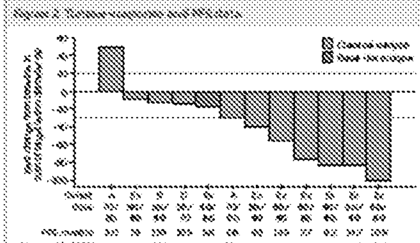
BACKGROUND

OBJECTIVES

METHODS

RESULTS





CONCLUSIONS

2020 Wainberg Presentation

ESMO WORLD CONGRESS ON Gastrointestinal Cancer | 2020 VIRTUAL

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

Author	Disclosure
Zev A. Wainberg	Research support (to institution): Five Prime Therapeutics, Ipsen, Novartis, Plexxikon; Consulting: AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Ipsen, Merck, QED Therapeutics
Tanios Bekaii-Saab	1Globe Health Institute, AbGenomics, Amgen, Array BioPharma, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Biomedical, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Exelixis, Genentech, Immuneering, Imugene, Incyte, Ipsen, Merck, Pancreatic Cancer Action Network (PanCAN), Seattle Genetics, Sobi, Sun BioPharma, Treos Bio
Patrick M. Boland	Research support: Advaxis, Bayer, Boehringer Ingelheim, Boston Biomedical, Cascadian Therapeutics, Genentech, Merck; Consulting: Bayer, Merrimack Pharmaceuticals; Honoraria: Sirtex Medical
Farshid Dayyani	Research support (to institution): Amgen, AstraZeneca, Bristol-Myers Squibb, Exelixis, Ipsen, Taiho Pharmaceutical; Consultant: Eisai, Exelixis, Foundation Medicine, Genentech, Ipsen, Natera, QED Therapeutics; Speakers' bureau: Amgen, Deciphera Pharmaceuticals, Eisai, Exelixis, Ipsen, Natera, Sirtex Medical; Spouse employee: Roche Diagnostics
Teresa Macarulla	Research support: AstraZeneca, Agios, Aslan Pharmaceuticals, Bayer, Biogen, Celgene, Eli Lilly, Genentech, Halozyme Therapeutics, Immonomedics, Merrimack Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Novocure, OncoMed Pharmaceuticals, Pfizer, Pharmacyclics, Roche; Honoraria: Eli Lilly, Ipsen, Roche, Sanofi, Sanofi Genzyme, Shire, Tesaro; Consulting: Baxalta, Celgene, H3 Biomedicine, Incyte, QED Therapeutics, Sanofi Genzyme, Shire, Servier; Speakers' bureau: Celgene, Sanofi, Shire; Travel/accommodation/expenses: Bayer, H3 Biomedicine, Merck, Sanofi
Kabir Mody	Research support: Agios, ArQule, AstraZeneca, Genentech, Incyte, Puma Biotechnology, Senwa Biosciences, Taiho Pharmaceutical, NCI of the NIH award # NCI/NIH P50 CA210964; Consulting: AstraZeneca, Bayer, Celgene, Eisai, Exelixis, Ipsen, Merrimack Pharmaceuticals, Vicus Therapeutics
Bruce Belanger	Employment: Ipsen
Fiona Maxwell	Employment and stock/other ownership: Ipsen
Yan Moore	Employment, leadership and stock/other ownership: Ipsen
Arunthathi Thiagalingam	Employment and stock ownership: Ipsen
Tiffany Wang	Employment and stock/other ownership: Ipsen
Bin Zhang	Employment, stock/other ownership and patents/royalties/other intellectual property: Ipsen
Andrew Dean	Non-paid consulting: Shire, Specialised Therapeutics; Travel/accommodation/expenses: Amgen

NCI, National Cancer Institute; NIH, National Institutes of Health

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

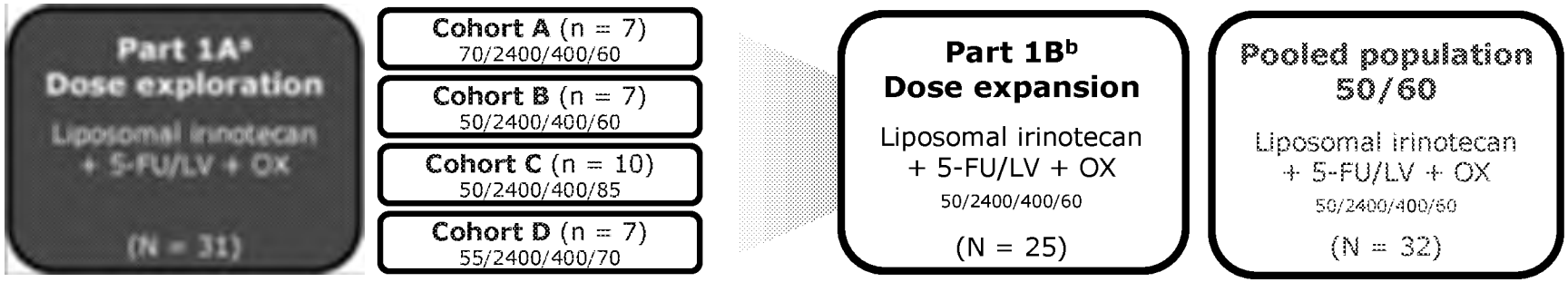
[a]Not previously treated in the metastatic setting.

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.

1. Moffitt RA *et al*. *Nat Genet* 2015;47:1168–78. 2. Aung KL *et al*. *Clin Cancer Res* 2018;24:1344–54. 3. GeneCentric Therapeutics, Inc; Rashid NU *et al*. *Clin Cancer Res* 2020;26:82–92

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

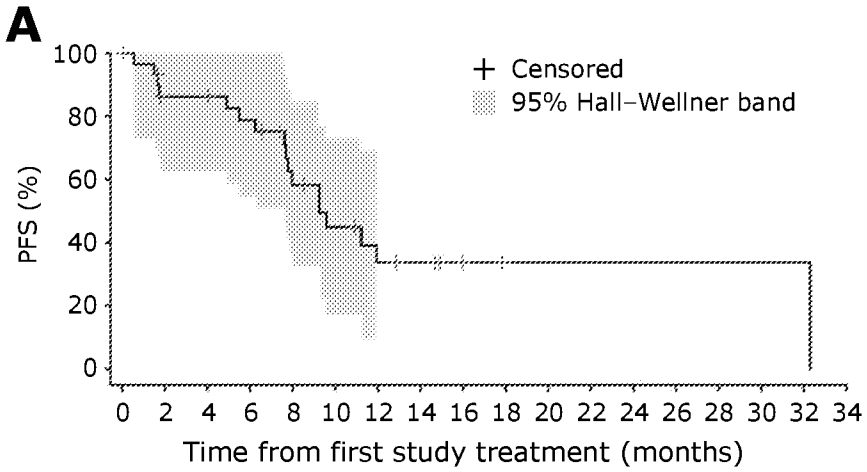
	Dose-exploration cohorts				Dose-expansion cohort (50/60) (N = 25)	Pooled population (50/60) (N = 32)
	A (70/60) (n = 7)	B (50/60) (n = 7)	C (50/85) (n = 10)	D (55/70) (n = 7)		
DLT, safety assessment during dose exploration (regimen) and details of DLTs	Not tolerable (DLTs) DLTs in 2 patients: neutropaenia 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)

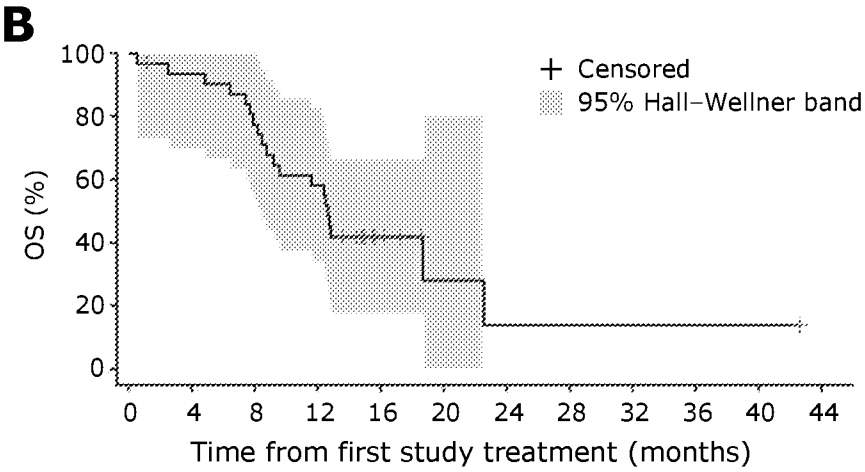
Data are number (%) of patients from the safety population unless otherwise stated. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events 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)



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



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 = 5)	(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]

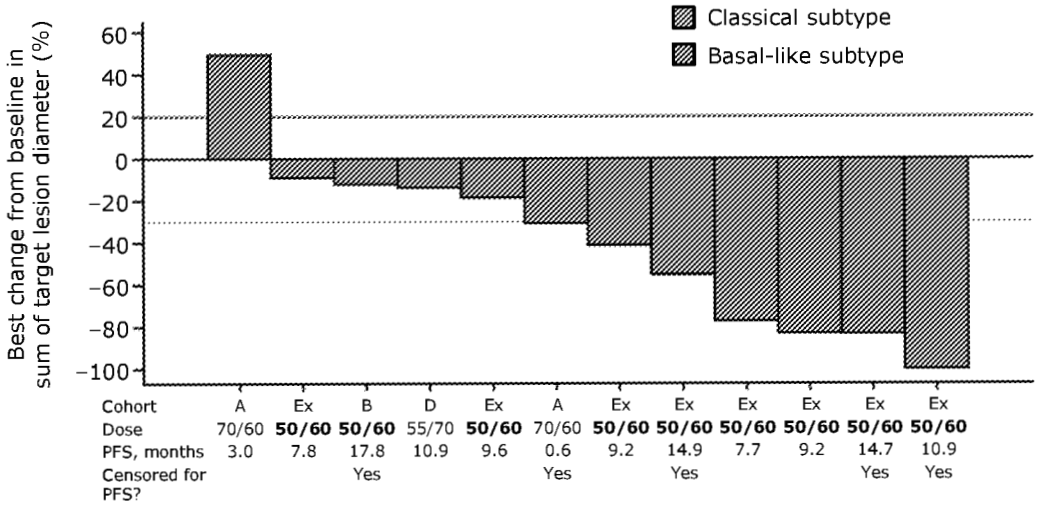
Data are from the safety population and with responses determined using RECIST v1.1 [a]Best response recorded from start of study treatment until disease progression or start of new anticancer therapy. [b]Patient received a diagnosis of locally advanced stage III disease. [c]As per the protocol at the 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)

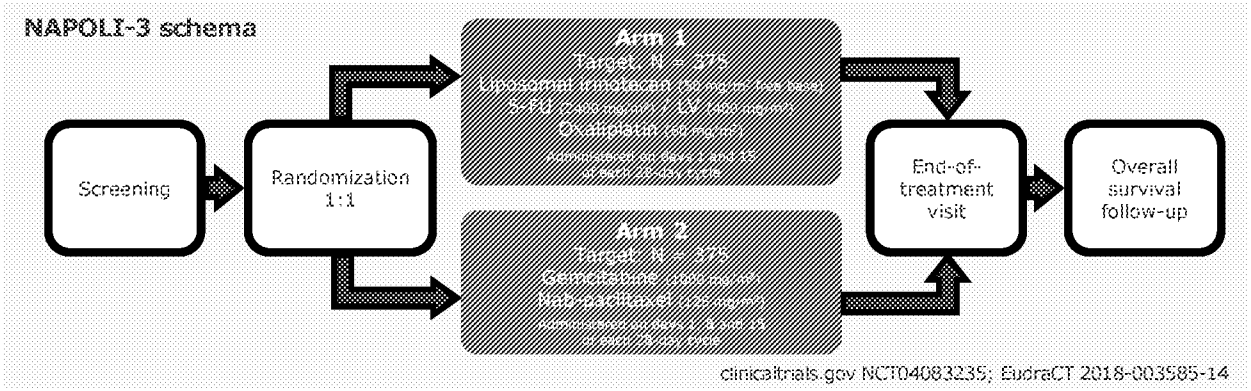
Ex, dose-expansion part; PFS, progression-free survival

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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Electronic Patent Application Fee Transmittal

Application Number:	15809815
Filing Date:	10-Nov-2017
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Filer:	Mary Rucker Henninger/Richard King
Attorney Docket Number:	263266-421428

Filed as Large Entity

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Miscellaneous-Filing:				
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Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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		Total in USD ($)		**4320**

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EFS ID:	42027780
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/Richard King
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	263266-421428
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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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	1	ABRAMS T, et al., "Patterns of Chemotherapy Use in a U.S.-Based Cohort of Patients with Metastatic Pancreatic Cancer," Oncologist. 22(8):925–933 (2017).
	2	ABUSHAHIN L, et al., "Multivariable Analysis of Real-World Clinical Outcomes Associated With Dose Reductions (DRs) for Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with Liposomal Irinotecan." Poster presented at the European Society for Medical Oncology Virtual Congress September 19-21, 2020, 6 pages.
	3	ABUSHAHIN L, et al., Abstract 1534P. "Multivariable Analysis of Real-World Clinical Outcomes Associated With Dose Reductions (DRs) for Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with Liposomal Irinotecan" Ann Oncol. 31(Suppl_4):S881-S897 10.1016/annonc/annonc285 (2020), 2 printed pages.
	4	ABUSHAHIN L, et al., Abstract e16780. "Real-World Dosing, Management, and Clinical Outcomes of Patients (pts) With Metastatic Pancreatic Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan," J Clin Oncol. 38 (15_Suppl):e16780 DOI: 10.1200/JCO.2020.38.15_suppl.e16780 (2020), 2 printed pages.
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	7	AMZAL B, et al., "Imputing Missing Values to Estimate Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer Treated With 5-Fluorouracil and Leucovorin, With and Without Liposomal Irinotecan (nal-IRI)." Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, Boston, MA, May 20-24, 2017, 6 pages.
	8	AMZAL B, et al., Abstract PCN179. "Imputing Missing Values to Estimate Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer (mpc) Treated With 5-Fluorouracil and Leucovorin, With and Without Liposomal Irinotecan (nal-IRI)," Value in Health. 20(5):A119 (2017).
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	10	ATKINS K, et al., "A Phase I Study of Nanoliposomal Irinotecan and 5-Fluorouracil/Folinic Acid in Combination With Interleukin-1-alpha Antagonist for Advanced Pancreatic Cancer Patients With Cachexia (OnFX)." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 23-25, 2020, 1 page.
	11	ATKINS K, et al., Abstract TPS780. "A Phase I Study of Nanoliposomal Irinotecan and 5-Fluorouracil/Folinic Acid in Combination With Interleukin-1-alpha Antagonist for Advanced Pancreatic Cancer Patients With Cachexia (OnFX)," J Clin Oncol. 38(4_Suppl):TPS780 DOI: 10.1200/JCO.2020.38.4_suppl.TPS780 (2020), 2 printed pages.

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	12	BARBIER S, et al., Abstract e16724. "Differentiation of Liposomal Irinotecan From Dose-Dense Non-Liposomal Irinotecan in Patient-Derived Pancreatic Cancer Xenograft Tumor Models," J Clin Oncol. 38(15_Suppl):e16724 DOI: 10.1200/JCO.2020.38.15_suppl.e16724 (2020), 5 printed pages.
	13	BARZI A, et al., Abstract e16229. "Real World Outcomes of Metastatic Pancreatic Cancer (mPC) Patients (pts) Treated With Liposomal Irinotecan (nal-IRI) in the US," J Clin Oncol. 36(15_Suppl):e16229 DOI: 10.1200/JCO.2018.36.15_suppl.e16229 (2018), 2 printed pages.
	14	BECKER C, et al., "Multivariate Analysis of Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer Treated with 5-Fluorouracil and Leucovorin (5-FU/LV), With and Without Liposomal Irinotecan (nal-IRI)." Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, Boston, MA, May 20-24, 2017, 7 pages.
	15	BECKER C, et al., Abstract PCN182. "Multivariate Analysis of Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer (mPC) Treated with 5- Fluorouracil and Leucovorin, With and Without Liposomal Irinotecan (nal-IRI)," Value in Health. 20(5):A120 (2017).
	16	BECKER C, et al., Abstract PCN58. "Budget Impact Analysis of Nanoliposomal Irinotecan for Treatment of Pancreatic Cancer Following Progression on Gemcitabine - A US Payer Perspective," Value in Health. 19(7):A718-A719 (2016).
	17	BLANC J, et al., "Subgroup Analysis by Prior Non-Liposomal Irinotecan Therapy in NAPOLI-1: A Phase 3 Study of nal-IRI ± 5-Fluorouracil/Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated with Gemcitabine-Based Therapy." Poster presented at the European Society for Medical Oncology Asia 2017 Congress, Singapore, November 17-19, 2017, 8 pages.
	18	BLANC J, et al., Abstract 228P. "Subgroup Analysis by Prior Non-Liposomal Irinotecan Therapy in NAPOLI-1: A Phase 3 Study of nal-IRI ± 5-Fluorouracil/Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated with Gemcitabine-Based Therapy," Ann Oncol. 28(Suppl_10):x67-x68 doi:10.1093/annonc/mdx660 (2017).
	19	BLANC J, et al., Abstract PD-18. "Subgroup Analysis by Prior Non-Liposomal Irinotecan Therapy in NAPOLI-1: A Phase 3 Study of nal-IRI ± 5-Fluorouracil/Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy," Ann Oncol. 28(Suppl_3):7 doi:10.1093/annonc/mdx263 (2017).
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Gastrointestinal Cancer

Patterns of Chemotherapy Use in a U.S.-Based Cohort of Patients with Metastatic Pancreatic Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Anticancer drug combinations • Carcinoma • Chemotherapy • Pancreatic ductal

Abstract

Purpose. Few population studies have examined patterns of systemic therapy administration in metastatic pancreatic cancer (MPC) or the predictors associated with specific treatment choices.

Patients and Methods. We assessed 4,011 consecutive MPC patients who received chemotherapy between January 2005 and December 2015 at academic, private, and community-based oncology practices subscribing to a U.S.-wide chemotherapy order entry system capturing disease, patient, provider, and treatment data. Multivariate analyses of these prospectively recorded characteristics identified significant predictors of specific therapeutic choices.

Results. Overall, 100 different regimens were used in first-line treatment of MPC. First-line gemcitabine monotherapy usage fell steadily from 72% in 2006 to 16% in 2015. This steep decline mirrored increases in first-line usage of both 5 fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) and gemcitabine + nab-paclitaxel. Younger male patients were more likely to receive FOLFIRINOX as first-line treatment, whereas patients treated at community practices and by oncologists with lower MPC patient volume were more likely to receive gemcitabine plus nab-paclitaxel (all $p \leq .05$). Among all patients receiving first-line chemotherapy for MPC, 49% went on to receive second-line therapy and 19% received third-line therapy; administration of second- and third-line therapies increased steadily over the time course of follow-up. Younger patients and those treated by oncologists with higher MPC patient volume were more likely to receive second- and third-line therapies.

Conclusion. This population-based study provides insight into treatment patterns of MPC in the U.S. Usage patterns varied greatly according to patient and provider characteristics. ***The Oncologist*** 2017;22:925–933

Implications for Practice: This study examined real world metastatic pancreatic cancer treatment patterns in the United States with the goals of understanding changes in chemotherapy treatment frequencies over time and determining the individual predictors that underlie the chemotherapy choices oncologists make for their patients. Our data set is unique in that it captured not only patient-level data, but also oncologist-level data. It also captured data from private and community practices as well as academic centers. To our knowledge, this is the only data set that can give this degree of insight into oncologist decision making practices.

Introduction

Of the approximately 53,070 people diagnosed with pancreatic cancer (PC) in the U.S. in 2016, more than 41,000 will succumb to the disease [1]. In 2015, PC overtook breast cancer as the third leading cause of cancer-related deaths in the U.S. During the past decade, randomized clinical trials in metastatic pancreatic cancer (MPC) patients have established new chemotherapeutic standards of care for treatment of the disease, and these regimens, including 5 fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) [2] and gemcitabine + nab-paclitaxel [3], have altered the MPC treatment landscape. Optimal use and sequencing of these approved regimens remain uncertain, and data describing how these agents are used in routine clinical practice have proven difficult to procure.

Few studies have examined administration frequencies of specific chemotherapeutic regimens and the predictors of their usage in MPC [4–14]. Existing literature consists of research conducted in limited practice settings [8, 11, 12] or studies with data derived from retrospective medical record extraction [10], patient and physician surveys [9], or insurance claims to ascertain use [5, 13, 14]. To understand factors influencing treatment decisions, we analyzed data from a nationwide, commercially available chemotherapy order entry (COE) system that provided tumor stage, disease status and treatment indication.

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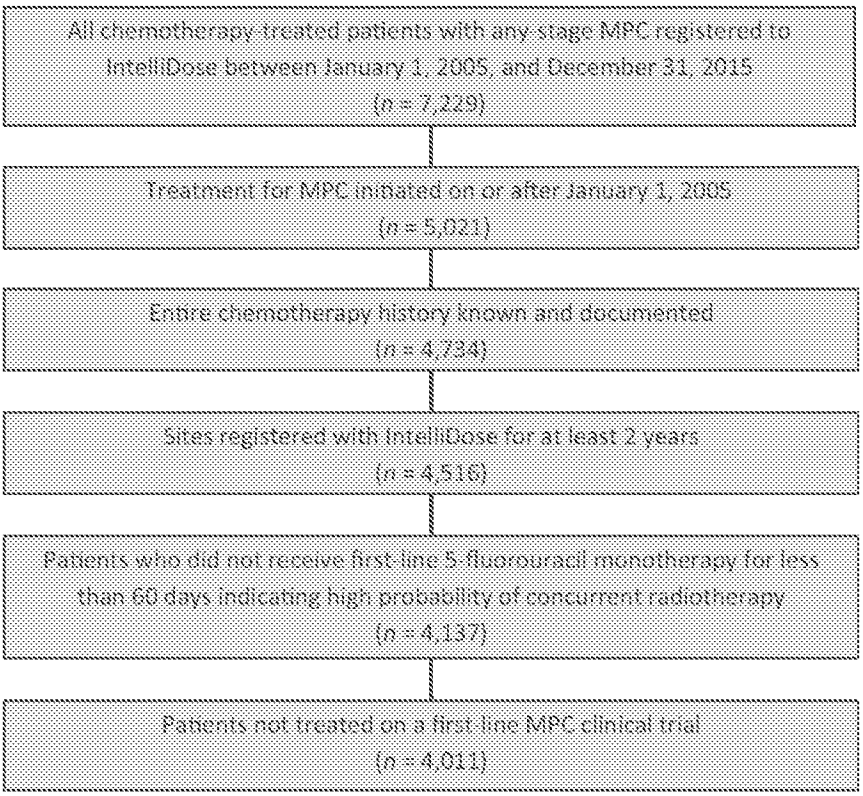

Figure 1. Derivation of cohort size.
Abbreviation: MPC, metastatic pancreatic cancer.

Within this database, we identified temporal trends for prescribing patterns across the continuum of MPC therapy and identified patient and provider characteristics influencing treatment selection across multiple lines of therapy.

Materials and Methods

Data Source and Study Cohort

Our study cohort was composed of 4,011 MPC patients who initiated systemic therapy at academic, private practice, and nonacademic hospital-based centers across the U.S. between January 2005 and December 2015. Participating medical oncology practices used the IntelliDose (IntrinsiQ Specialty Solutions, Frisco, TX, http://www.intrinsiq.com/) COE system as their exclusive method of outpatient chemotherapy ordering for the entire study period (139 medical oncology practice settings in 40 U.S. states for a total of 684 unique medical oncologists). Of the 139 participating centers, 11% were academic medical centers (accounting for 26% of all eligible patients in the analysis), 59% were physician-owned private practices (accounting for 51% of patients), and 30% were community hospital- or clinic-based cancer facilities not owned by the practicing physicians (accounting for 23% of all patients).

Physicians registering new patients into IntelliDose were prompted to enter patient demographic data, including sex, age, diagnosis, date of diagnosis, American Joint Committee on Cancer stage, and previous cancer treatment history, including chemotherapy, surgery, and/or radiotherapy. Clinicians were also required to enter all chemotherapeutic agents and doses, as well as patient data such as height, weight, and date of birth. Use of oral chemotherapy was captured either by direct physician entry or by IntrinsiQ staff nurses entering the data into IntelliDose after having been provided with duplicate hard copy prescriptions.

Data inputted from practice sites were electronically delivered in real time to a mainframe computer housed on-site at IntrinsiQ headquarters (Burlington, MA). IntrinsiQ staff nurses reviewed incoming data that failed built-in consistency tests to assess for data entry inaccuracies or deviations from standard practice.

Within the database, we identified ($n = 7,229$) unique patients who began chemotherapy treatment for any-stage PC between January 1, 2005, and December 31, 2015. We restricted analysis to patients with documented MPC ($n = 5,021$), including patients initially diagnosed with early-stage PC but who eventually developed MPC. We limited analysis to patients whose entire chemotherapy history was documented ($n = 4,734$) and those treated at sites registered with IntelliDose for at least 2 years ($n = 4,516$). We excluded 379 patients treated with first-line 5 fluorouracil or capecitabine monotherapy for less than 60 days to eliminate the possibility of counting patients treated with concurrent chemotherapy and radiotherapy ($n = 4,137$). We also excluded those patients treated on a first-line clinical trial for MPC ($n = 126$), resulting in a final study cohort of 4,011 patients (supplemental online Fig. 1).

Chemotherapeutic Line Determination

We used predefined rules to assign chemotherapy treatments to particular therapeutic lines (i.e., first-line, second-line, and so on). If treatment was changed for progression of disease, lack of response, or treatment intolerance, the patient was

Table 1. Baseline characteristics of cohort with respect to first-line chemotherapy category

Characteristic, *n* (%)	Gem monotherapy (*n* = 1,818)	Gem doublet[a] (*n* = 488)	Gem + nab- paclitaxel (*n* = 543)	FOLFIRINOX (*n* = 609)	Other regimens[b] (*n* = 553)	*p*[c]
Median age, years (range)	69 (29–95)	65 (23–87)	68 (36–94)	61 (33–85)	66 (31–91)	<.001[d]
Sex						.02
Male	959 (52.8)	273 (55.9)	308 (56.8)	367 (60.3)	294 (53.2)	
Female	858 (47.2)	215 (44.1)	234 (43.2)	242 (39.7)	259 (46.8)	
Practice site type						<.001
Private practice	900 (49.5)	267 (54.6)	282 (51.9)	326 (53.6)	279 (50.4)	
Community-based	450 (27.8)	62 (12.8)	180 (33.2)	136 (22.3)	105 (19.0)	
Academic	468 (25.7)	159 (32.6)	81 (14.9)	147 (24.1)	169 (30.6)	
U.S. practice region[e]						<.001
Central	679 (37.4)	172 (35.2)	214 (39.4)	251 (41.2)	175 (31.7)	
East	877 (48.2)	233 (47.8)	239 (44.0)	250 (41.1)	322 (58.2)	
West	262 (14.4)	83 (17.0)	90 (16.6)	108 (17.7)	56 (10.1)	
Annual no. of MPC patients treated per practice site, median (range)	127 (2–485)	122 (2–485)	116 (1–485)	129 (1–485)	129 (3–485)	<.001[d]
Annual no. of MPC patients treated per physician, median (range)	15 (1–239)	16 (1–239)	13 (1–239)	15 (1–239)	21 (1–239)	<.001[d]
Chemo start year						<.001[d]
2005–06	207 (11.4)	41 (8.4)	0	0	43 (7.8)	
2007–08	427 (23.5)	113 (23.2)	0	2 (0.3)	82 (14.8)	
2009–10	458 (25.2)	139 (28.4)	12 (2.2)	17 (2.8)	84 (15.2)	
2011–12	417 (22.9)	133 (27.2)	32 (5.9)	219 (36.0)	157 (28.4)	
2013–14	226 (12.4)	52 (10.7)	306 (56.4)	221 (36.3)	111 (20.1)	
2015	83 (4.6)	10 (2.1)	193 (35.5)	150 (24.6)	76 (13.7)	

[a]Gem doublet refers to any gemcitabine containing regimen except for gemcitabine + nab-paclitaxel

[b]Other regimens include fluorouracil-based regimens other than FOLFIRINOX, taxane monotherapy, or other unclassifiable regimens

[c]*P* value calculated using Likelihood Ratio chi-square test unless otherwise noted

[d]*P* value calculated using Kruskal–Wallis test.

[e]States included in U.S. practice regions: Central: IL, IN, IA, KS, KY, LA, MI, MN, MO, NE, ND, OH, OK, SD, TX, WI; East: AL, AR, CT, DE, FL, GA, ME, MA, MD, MS, NC, NH, NJ, NY, PA, RI, SC, TN, VA, VT, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.

Abbreviations: FOLFIRINOX, 5 fluorouracil, leucovorin, irinotecan and oxaliplatin; Gem, gemcitabine; mono, monotherapy; MPC, metastatic pancreatic cancer.

considered to have advanced to the next line of treatment. However, if treatment was modified by the elimination of one or more drugs from a multidrug regimen, such as FOLFIRINOX, the patient was not considered to have advanced to a subsequent treatment line. Chemotherapy re-initiation after a treatment suspension of more than 90 days also constituted progression to a subsequent line regardless of the reason for the suspension. These line determination criteria were set prior to data analysis and are consistent with those from several peer-reviewed patterns-of-care studies published previously in metastatic colorectal cancer [15–17].

Institutional Review Board Approval

All patient data were submitted electronically to IntrinsiQ without personal identifiers, and an Excel database was then created at IntrinsiQ from the de-identified data for our analysis. The Dana-Farber/Harvard Cancer Center Institutional Review Board granted approval for the study.

Statistical Analysis

We measured the frequencies of specific chemotherapy and biologic usage with respect to treatment line. The distribution of baseline patient and physician characteristics across stage and specific treatment regimens was evaluated using likelihood ratio chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. We performed univariate and multivariable logistic regressions to evaluate the associations between patient and provider characteristics and use of specific chemotherapeutic regimens. Because standards of care evolved significantly over the entirety of our study, these analyses were conducted over appropriate time periods only.

To avoid the possibility of selecting cut-points that could maximize the associations between any continuous variable and specific chemotherapy delivered, statistical analyses were also performed modeling the relevant characteristic as a continuous variable. To maintain the normality assumption, practice volume variables were modeled with a square-root

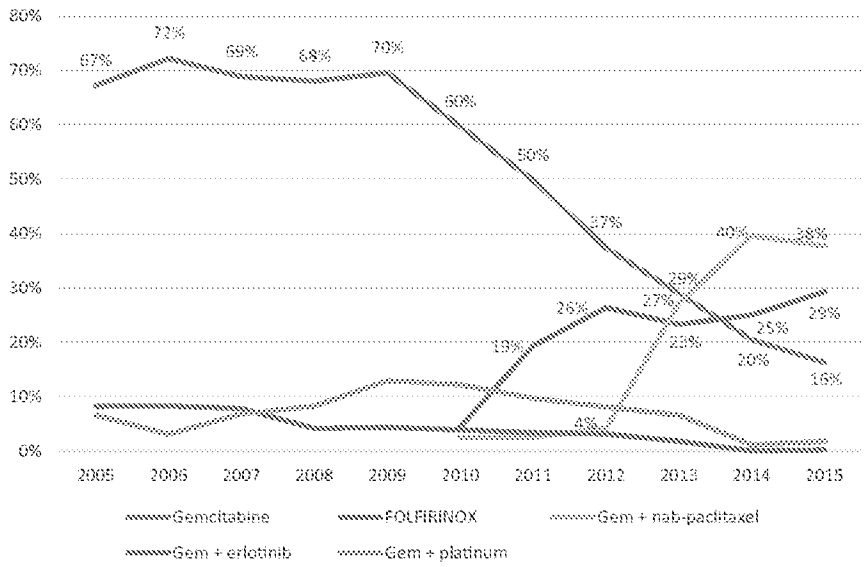

Figure 2. First-line metastatic pancreatic cancer chemotherapy treatments (January 2005 to December 2015).
Abbreviation: FOLFIRINOX, 5 fluorouracil, leucovorin, irinotecan and oxaliplatin.

transformation. However, modeling without transforming MPC patient volume did not change the results. Stratified analyses were conducted to determine whether the influence of MPC treatment volume was modified by various co-variables. We used SAS 9.4 software (SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html) for all statistical analyses. All statistical tests were two-sided.

Results

Baseline Characteristics of the Cohort

Between January 1, 2005, and December 31, 2015, we identified 4,011 eligible patients who received first-line chemotherapy for MPC. Of the 3,374 of those who completed first-line treatment prior December 31, 2014, 1,666 (49%) went on to receive second-line treatment, 590 (17%) received third-line treatment, and 247 (7%) received fourth-line treatment. Despite the paucity of effective, evidence-based treatment regimens for MPC [18], 100 distinct first-line regimens, including 31 different chemotherapeutic and biologic agents, were administered, and 242 different regimens were utilized across all lines of therapy.

Baseline characteristics of the cohort according to the administered first-line regimen of therapy are displayed in Table 1. Younger male patients were more likely to receive first-line FOLFIRINOX ($p < .001$), whereas patients treated at academic centers were less likely to receive first-line gemcitabine and nab-paclitaxel ($p < .001$).

Secular Trends in First-Line MPC Chemotherapy Regimens (2005–2014)

Gemcitabine monotherapy was the dominant regimen administered in first-line treatment of metastatic pancreas cancer from 2005 through 2009, ranging from 67%–70% of all first-line regimens during that period. After 2009, first-line gemcitabine monotherapy use declined rapidly, with only 16% receiving gemcitabine monotherapy in 2015 (Fig. 1). Following the initial report in 2010 of a phase III trial demonstrating improved survival for first-line FOLFIRINOX as compared with gemcitabine [19], FOLFIRINOX use increased from 4% in 2010 to a peak of 29% in 2015. Thereafter, following the first report in 2013 of a phase III trial demonstrating improved survival for the first-line combination of gemcitabine and nab-paclitaxel as compared with gemcitabine [20], gemcitabine and nab-paclitaxel use increased from 4% in 2012 to 40% in 2014.

Predictors of First-Line Chemotherapy Regimen Choice

In a multivariate model, we examined influences of patient and provider characteristics on the usage of first-line gemcitabine monotherapy relative to all other combination chemotherapy regimens in first-line MPC treatment (supplemental online Table 1). Advancing age, receiving care at a community-based practice, or receiving care in the central U.S. was associated with greater use of gemcitabine monotherapy (p_{trend} for age $< .001$). In contrast, treatment administration in time periods following 2006 was independently associated with a decreasing likelihood of gemcitabine monotherapy administration ($p_{trend} < .001$). Additionally, receipt of care from an oncologist with higher MPC patient volume appeared to be inversely associated with the likelihood of gemcitabine monotherapy administration, although the trend was not statistically significant.

We similarly assessed for independent predictors of receiving first-line FOLFIRINOX. For this analysis, we limited the timeframe to the period following the first report of the phase III trial for this regimen (2011 through 2015). Younger age and male gender were each associated with significantly increased use of FOLFIRINOX. Treatment in the western U.S. was also associated with a statistically significant increased likelihood of FOLFIRINOX usage.

We similarly conducted a multivariate model to identify significant independent predictors of receiving first-line gemcitabine and nab-paclitaxel during the time period of 2013 through 2015. Later time periods during study conduct were associated with a significantly increased likelihood of gemcitabine and nab-paclitaxel use; moreover, receipt of care in a community-based practice was associated with greater gemcitabine and nab-paclitaxel use when compared with other practice settings.

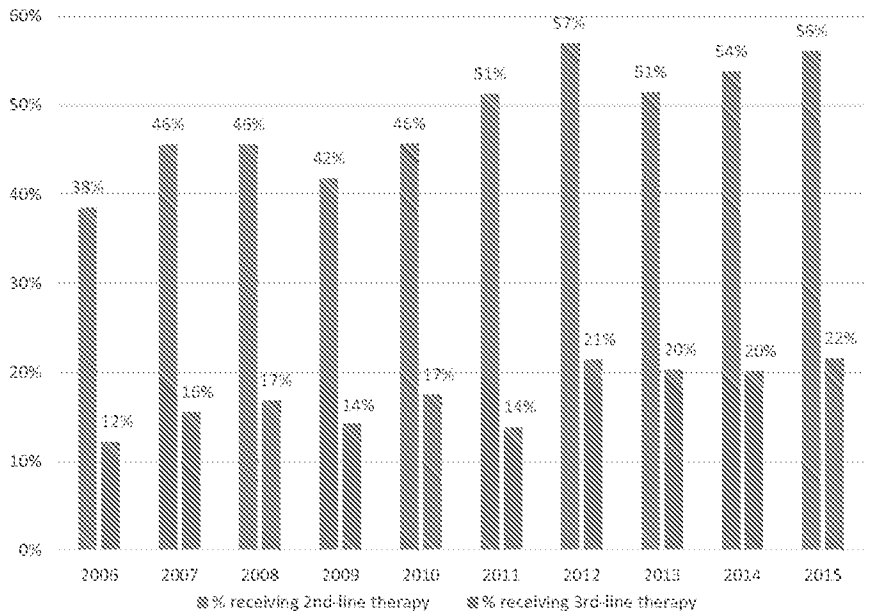

Figure 3. Rates of second- and third-line metastatic pancreatic cancer chemotherapy treatment (January 2006 to September 2015).

Finally, oncologists with higher MPC-treatment volume were less likely to prescribe first-line gemcitabine and nab-paclitaxel for their MPC patients.

First-Line Chemotherapy Treatment Duration

We examined duration of treatment of all first-line regimens initiated from January 2011 through September 2015. FOLFIRINOX and gemcitabine + nab-paclitaxel were both associated with significantly longer first-line treatment durations (median = 100 and 98.5 days, respectively) compared with gemcitabine monotherapy, which was associated with a median treatment duration of 91 days (FOLFIRINOX: odds ratio [OR] = 1.51; 95% confidence intervals [CI], 1.20–1.89; gemcitabine + nab-paclitaxel: OR = 1.62; 95% CI, 1.29–2.05). Moreover, in a multivariate logistic regression model, MPC patients treated with either first-line FOLFIRINOX or gemcitabine and nab-paclitaxel were significantly more likely to receive treatment for more than 90 days than patients receiving gemcitabine monotherapy (FOLFIRINOX: OR = 1.84; 95% CI, 1.38–2.45; gemcitabine + nab-paclitaxel: OR = 1.99; 95% CI, 1.47–2.69). No other patient or physician characteristics independently influenced treatment duration. Of note, we limited our treatment duration analysis to patients who received at least 28 days of first-line therapy.

Subsequent Lines of Therapy

Usage of second-line chemotherapy increased from 38% in 2006, peaking at 57% in 2012 and remaining >50% through 2015 (Fig. 2). Third-line chemotherapy usage also increased during this timeframe from 12% in 2006 to 22% in 2015.

A diverse group of regimens were employed in the treatment of second-line MPC, including the combination of fluorouracil, leucovorin, and oxaliplatin (FOLFOX, 19.6%), gemcitabine monotherapy (16.9%), fluorouracil or capecitabine monotherapy (10.3%), gemcitabine + nab-paclitaxel (13.9%), and FOLFIRINOX (8.5%).

We examined independent predictors of receiving second-line chemotherapy in a multivariate model. Significant predictors of second-line chemotherapy administration included younger age (multivariate OR = 1.61; 95% CI, 1.19–2.18, when comparing age <60 to age ≥80 years) and receipt of care from an oncologist treating more than 20 MPC patients per year (OR = 1.42; 95% CI, 1.19–1.68, compared with <10 patients per year; Tables 2, 3, and 4). In addition, patients who received any first-line regimen containing multiple agents were significantly more likely to go on to receiving second-line treatment when compared with patients who received first-line gemcitabine monotherapy. Specifically, the OR for receiving second-line therapy was 3.06 (95% CI, 2.50–3.75) for FOLFIRINOX and 1.33 (95% CI, 1.07–1.66) for gemcitabine + nab-paclitaxel.

Discussion

Using data from a COE system that included academic, community-based, and private practice sites across the U.S. from January 1, 2005, to December 31, 2015, we examined how practicing oncologists interpret and assimilate the available literature to make treatment decisions for MPC patients. During this time period, we identified 102 different first-line regimens administered. Of this group of distinct regimens, 75.2% of patients received either gemcitabine monotherapy, gemcitabine + nab-paclitaxel, FOLFIRINOX or 5-fluorouracil/capecitabine monotherapy, 17.9% received regimens such as FOLFOX, FOLFIRI, gemcitabine + 5-fluorouracil/capecitabine, gemcitabine + cisplatin, gemcitabine + erlotinib, and gemcitabine + oxaliplatin, 3.6% received therapies including three or more of the above agents (i.e., gemcitabine + nab-paclitaxel + 5-fluorouracil/capecitabine), and 3.3% received regimens including agents not usually associated with MPC treatment, such as bevacizumab, cetuximab, carboplatin, docetaxel, cyclophosphamide, and doxorubicin. We considered excluding the 3.3% of patients who received a nonstandard therapeutic agent for first-line MPC treatment from our analysis, as we were concerned about the possibility of diagnosis entry error. Ultimately, we did not feel we had enough evidence to doubt the database's accuracy and were reassured by IntrinsiQ's internal

Table 2. Significant independent predictors of receiving gemcitabine monotherapy in first-line MPC treatment

Characteristic	No. patients	% given gem monotherapy	Univariate OR (95% CI)	Multivariate OR (95% CI[a])	p_{trend}[b]
Age, categories					<.001
<60	1,100	37.4%	Referent	Referent	
60–69	1,311	41.8%	1.20 (1.02–1.42)	1.41 (1.17–1.69)	
70–79	1,161	49.9%	1.67 (1.41–1.97)	2.03 (1.68–2.45)	
≥80	439	63.8%	2.95 (2.35–3.72)	4.08 (3.14–5.28)	
Sex					
Male	2,201	43.6%	Referent	Referent	
Female	1,808	47.5%	1.17 (1.03–1.33)	1.18 (1.03–1.36)	
Chemo start year					<.001
2005–06	291	71.1%	Referent	Referent	
2007–08	624	68.4%	0.88 (0.65–1.19)	0.90 (0.66–1.23)	
2009–10	710	64.5%	0.74 (0.55–0.99)	0.75 (0.55–1.02)	
2011–12	958	43.5%	0.31 (0.24–0.42)	0.30 (0.23–0.41)	
2013–14	916	24.7%	0.13 (0.10–0.18)	0.11 (0.08–0.15)	
2015	512	16.2%	0.08 (0.06–0.11)	0.06 (0.04–0.09)	
Practice site type					
Private practice	2,054	43.8%	Referent	Referent	
Community-based	933	48.2%	1.20 (1.02–1.40)	1.56 (1.29–1.88)	
Academic	1,024	45.7%	1.08 (0.93–1.26)	0.87 (0.73–1.04)	
U.S. practice region[c]					
Central	1,491	45.5%	Referent	Referent	
East	1,921	45.7%	1.01 (0.88–1.15)	0.74 (0.63–0.87)	
West	599	43.7%	0.93 (0.77–1.13)	0.63 (0.50–0.79)	
Annual no. of patients with MPC treated per physician					.14
<10	1,284	46.2%	Referent	Referent	
10–19	1,057	43.6%	0.90 (0.77–1.06)	0.94 (0.78–1.13)	
≥20	1,670	45.8%	0.98 (0.85–1.14)	0.84 (0.71–1.01)	

[a]Adjusted for age (<60, 60–69, 70–79, ≥80), gender, practice site type (academic, community-based, or private practice), year of MPC chemotherapy initiation (2005–06, 2007–08, 2009–10, 2011–12, 2013–14, 2015), U.S. practice region (Central, East or West), and annual number of MPC patients treated per physician (<10, 10–19, ≥20).

[b]*P* trend derived from multivariate regression.

[c]States included in U.S. practice regions: Central: IL, IN, IA, KS, KY, LA, MI, MN, MO, NE, ND, OH, OK, SD, TX, WI; East: AL, AR, CT, DE, FL, GA, ME, MA, MD, MS, NC, NH, NJ, NY, PA, RI, SC, TN, VA, VT, WV, West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.

Abbreviations: CI, confidence interval; gem, gemcitabine; MPC, metastatic pancreatic cancer; OR, odds ratio.

quality control measures, which require staff nurses to review incoming data that deviate from standard practice. Therefore, we elected to keep these patients in our analysis (supplemental online Table 2). However, we made an a priori decision to exclude MPC patients enrolled on first-line clinical trials ($n = 126$; 2.5%) from our analysis, as our study aim from the outset was to ascertain practice patterns independent of clinical trials. Nonetheless, we re-ran our analyses with clinical trial patients and found their inclusion produced no significant changes to our results.

Our observed 2.5% clinical trial enrollment rate was in line with a widely cited estimate that <3% of U.S. cancer patients enroll in clinical trials [21]. It was less than the 4.57% rate observed by Hoos et al. in their study of PC trial accrual in the U.S., but that study included all-stage MPC patients and counted patients who had been enrolled on trials in subsequent lines of therapy, as well [22]. While our observed rates of clinical trial enrollment were roughly in line with previous studies, we are extremely disappointed by the very low observed rate and support national efforts to improve rates of MPC clinical trial enrollment.

While gemcitabine monotherapy was the most commonly administered first-line chemotherapy regimen during the entirety of our study, its usage decreased significantly after 2009, reflecting the development of new, more effective regimens during the study period. First-line FOLFIRINOX emerged as a treatment option following the report of a phase III trial in 2010 [2]. Subsequently, following the report of a phase III trial in 2012 [23], first-line administration of gemcitabine and nab-paclitaxel increased sharply, emerging as the most commonly used first-line regimen in the U.S. in 2014.

Few studies have examined patterns of care in MPC. Previous studies were conducted in limited practice settings or relied on retrospective medical record extraction, physician surveys,

Table 3. Significant independent predictors of receiving gem + nab-paclitaxel in first-line MPC treatment (2013–15 only)

Characteristic	No. patients	% given gem + nab-paclitaxel	Univariate OR (95% CI)	Multivariate OR (95% CI[a])	p_{trend}[b]
Age, categories					<.001
<60	343	28.0%	Referent	Referent	
60–69	486	32.1%	1.22 (0.90–1.65)	1.24 (0.91–1.68)	
70–79	435	43.2%	1.96 (1.45–2.65)	1.99 (1.46–2.71)	
≥80	164	36.0%	1.45 (0.97–2.15)	1.47 (0.98–2.20)	
Sex					
Male	785	36.3%	Referent	Referent	
Female	641	33.2%	0.87 (0.70–1.09)	0.86 (0.69–1.08)	
Chemo start year					.006
2013	456	27.2%	Referent	Referent	
2014	460	39.6%	1.75 (1.33–2.32)	1.78 (1.34–2.37)	
2015	512	37.7%	1.62 (1.23–2.13)	1.44 (1.08–1.91)	
Practice site type					
Private practice	798	33.8%	Referent	Referent	
Community-based	411	41.9%	1.41 (1.10–1.80)	1.38 (1.04–1.83)	
Academic	219	26.0%	0.69 (0.49–0.96)	0.76 (0.53–1.09)	
U.S. practice region[c]					
Central	588	32.7%	Referent	Referent	
East	627	35.7%	1.15 (0.90–1.45)	1.14 (0.87–1.49)	
West	213	39.0%	1.32 (0.95–1.82)	1.05 (0.73–1.53)	
Annual no. of patients with MPC treated per physician					.04
<10	485	39.0%	Referent	Referent	
10–19	415	35.7%	0.87 (0.66–1.14)	0.87 (0.66–1.15)	
≥20	528	30.7%	0.69 (0.54–0.90)	0.68 (0.52–0.90)	

[a] Adjusted for age (<60, 60–69, 70–79, ≥80), gender, practice site type (academic, community-based, or private practice), year of MPC chemotherapy initiation (2013, 2014, or 2015), U.S. practice region (Central, East or West), and annual number of MPC patients treated per physician (<10, 10–19, ≥20).

[b] *P* trend derived from multivariate regression.

[c] States included in U.S. practice regions: Central: IL, IN, IA, KS, KY, LA, MI, MN, MO, NE, ND, OH, OK, SD, TX, WI; East: AL, AR, CT, DE, FL, GA, ME, MA, MD, MS, NC, NH, NJ, NY, PA, RI, SC, TN, VA, VT, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.

Abbreviations: CI, confidence interval; gem, gemcitabine; MPC, metastatic pancreatic cancer; OR, odds ratio.

or insurance claims data to ascertain use. In contrast, our study represents the largest MPC practice patterns analysis, including academic, private, and hospital-based practice settings across the U.S., and was conducted over a nine-year period of considerable MPC practice evolution. We were able to examine chemotherapeutic usage across multiple lines of therapy and patient and provider characteristics associated with those practice patterns.

We concurrently assessed predictors of first-line chemotherapy choice in our cohort. In general, FOLFIRINOX was more commonly administered to younger and male patients. In contrast, gemcitabine monotherapy was more commonly given as a first-line treatment to older subjects and those patients treated at community-based practice settings.

We observed an increasing use of subsequent lines of therapy for MPC in our cohort. Patients treated with multiple agents in the first-line and those who received their care from oncologists with higher MPC treatment volume were more likely to receive second-line therapy.

We recognize several potential limitations of our study. Data on performance status, race, insurance coverage, and socioeconomic status were unavailable for inclusion. Moreover, the database has no information about patient survival or treatment-associated adverse events. However, we were able to calculate therapy duration and identify predictors for likelihood of remaining on treatment long term and receiving second-line therapy. We found that combination treatments with FOLFIRINOX and gemcitabine + nab-paclitaxel were associated with significant improvements in these indirect measures of treatment outcome. Notably, we elected to forgo an analysis of chemotherapy dose reductions given the database's inability to provide information regarding the rationale for these dose reductions.

We also recognize that our patient cohort may not be representative of the larger MPC patient population treated in the U.S. However, the 2012 American Society of Clinical Oncology National Census of Oncology Practices [24] found the distribution of practice settings relatively consistent with outpatient cohort (ASCO practice survey: academic = 9.5%, private practice = 56%, community hospital = 24% vs. our study: academic = 8%, private practice = 54% and community hospitals = 38%), suggesting that our patient cohort may indeed be representative of the larger U.S. MPC patient population.

Table 4. Significant independent predictors of receiving FOLFIRINOX in first-line MPC treatment (2011–15 only)

Characteristic	No. patients	% given FOLFIRINOX	Univariate OR (95% CI)	Multivariate OR (95% CI[a])	p_{trend}[b]
Age, categories					<.001
<60	630	38.7%	Referent	Referent	
60–69	808	27.2%	0.57 (0.46–0.71)	0.56 (0.44–0.70)	
70–79	684	15.5%	0.28 (0.22–0.36)	0.27 (0.20–0.35)	
≥80	264	5.3%	0.09 (0.05–0.15)	0.08 (0.05–0.15)	
Sex					
Male	1,306	27.4%	Referent	Referent	
Female	1,078	21.5%	0.73 (0.60–0.88)	0.71 (0.58–0.86)	
Chemo start year					<.001
2011	476	19.3%	Referent	Referent	
2012	482	26.4%	1.49 (1.10–2.02)	1.63 (1.19–2.24)	
2013	456	23.3%	1.26 (0.92–1.73)	1.46 (1.05–2.02)	
2014	460	25.0%	1.39 (1.02–1.90)	1.65 (1.19–2.28)	
2015	512	29.3%	1.73 (1.29–2.33)	2.10 (1.53–2.89)	
Practice site type					
Private practice	1,317	24.4%	Referent	Referent	
Community-based	585	23.3%	0.94 (0.75–1.18)	0.82 (0.63–1.07)	
Academic	484	27.5%	1.18 (0.93–1.49)	1.10 (0.85–1.43)	
U.S. practice region[c]					
Central	950	25.8%	Referent	Referent	
East	1,089	21.9%	0.81 (0.66–0.99)	0.87 (0.69–1.09)	
West	347	30.8%	1.28 (0.98–1.68)	1.46 (1.06–2.00)	
Annual no. MPC patients treated per physician					.17
<10	761	24.8%	Referent	Referent	
10–19	679	27.4%	1.14 (0.90–1.45)	1.26 (0.98–1.61)	
≥20	946	22.7%	0.89 (0.71–1.11)	1.03 (0.81–1.32)	

[a]Adjusted for age (<60, 60–69, 70–79, ≥80), gender, practice site type (academic, community-based, or private practice), year of MPC chemotherapy initiation (2011, 2012, 2013, 2014 or 2015), U.S. practice region (Central, East or West), and annual number of MPC patients treated per physician (<10, 10–19, ≥20).

[b]*P* trend derived from multivariate regression.

[c]States included in U.S. practice regions: Central: IL, IN, IA, KS, KY, LA, MI, MN, MO, NE, ND, OH, OK, SD, TX, WI; East: AL, AR, CT, DE, FL, GA, ME, MA, MD, MS, NC, NH, NJ, NY, PA, RI, SC, TN, VA, VT, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY.

Abbreviations: CI, confidence interval; FOLFIRINOX, 5 fluorouracil, leucovorin, irinotecan and oxaliplatin; gem, gemcitabine; OR, odds ratio; MPC, metastatic pancreatic cancer.

The potential for data misclassification always represents a concern. Our data relied on a COE system designed for safety purposes to ensure accurate entry of drugs, doses, patient characteristics, disease indication, and stage in a manner readily available for quality audits and analysis. To further ensure data quality, nurses employed by IntrinsiQ routinely reviewed data from all sites to assess for data entry inaccuracies or deviation from standard practice.

In summary, our analysis offers insight into patterns of care in MPC across the U.S. during a period of considerable change in MPC therapy. Recent improvements in the efficacy of first-line therapy may account for the observed increase in second-line therapy.

Conclusion

Our data suggest that FOLFIRINOX and gemcitabine + nab-paclitaxel are currently being prescribed at similar rates among patients with MPC, with a preference for FOLFIRINOX in patients <70 years old and gemcitabine + nab-paclitaxel in those aged 70 and older. Studies that rely on FOLFIRINOX as the control arm may encounter difficulty in accruing elderly patients, and those that rely on gemcitabine + nab-paclitaxel may encounter difficulty in accruing younger, fitter patients with MPC. Moreover, as biologic and immunotherapeutic agents are investigated alongside the current arsenal of therapies for patients with MPC, ongoing patterns-of-care research will be vital to ensuring successful recruitment to clinical trials. Perhaps more importantly, these studies will also provide data to help policy makers and the medical community understand how these agents are incorporated into routine practice.

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are solely the responsibility of the authors and do not necessarily represent views of Celgene or IntrinsiQ Specialty Solutions. The research presented in this manuscript is original. A poster reflecting these data was presented at the ASCO 2014 Annual Meeting in Chicago, IL on June 2, 2014.

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Disclosures

Thomas A. Abrams: Aduro, Bristol-Myers Squibb (C/A), Celgene (C/A, RF); **Gary Meyer:** IntrinsiQ Specialty Solutions, an AmerisourceBergen Specialty Group Company (E); **Brian M. Wolpin:** Celgene (RF); **Charles S. Fuchs:** Merrimack, Celgene, Sanofi, Genentech, Taiho, Merck, Eli Lilly, Entrinsic Health (C/A). The other authors indicated no financial relationships.

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Multivariable analysis of real-world clinical outcomes associated with dose reductions (DRs) for patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan

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BACKGROUND

- Pancreatic cancer is projected to account for 47,050 deaths in the United States in 2020, making it the 4th deadliest cancer[1]
- Patients with pancreatic cancer often present at an advanced stage. 30% of newly diagnosed patients present with regional spread to lymph nodes and 52% present with metastases[2]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[2]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only U.S. Food and Drug Administration and European Medicines Agency approved, in combination with fluorouracil and leucovorin, second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network® (NCCN) Category 1 [3,4]
- Post-hoc analyses of the pivotal phase 3 registrational trial, NAPOLI-1, suggest that dose reductions (DRs) do not impact the efficacy of liposomal irinotecan[5,6]

OBJECTIVE

- To evaluate the survival outcomes associated with dose reductions among patients with mPDAC treated with liposomal irinotecan in the real-world setting

METHODS

Study Design and Data Source

A retrospective descriptive analysis was performed using the Flatiron Health® longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data which includes data from over 280 cancer clinics representing more than 2.4 million active US cancer patients

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC and treated with liposomal irinotecan between November 1, 2015 and October 31, 2019
- Eligible patients were those who:
  - Were treated with a liposomal irinotecan based regimen in the metastatic setting
  - were at least 18 years old at treatment initiation
  - had at least one recorded activity after the start of treatment
  - Patients whose initial dose was within either of the following ranges: 65mg/ m^2 – 75mg/ m^2 or <65mg/ m^2
  - received at least 3 cycles of liposomal irinotecan

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, starting liposomal irinotecan dose, and real-world overall survival (OS) were assessed

Measures and Statistical analyses (cont'd)

- The starting dose of liposomal irinotecan component of the regimen was derived from body surface area (derived from patients' height and weight) and the first recorded administered dose
  - Patients were categorized into two starting dose groups: 70mg/ m^2 (indicated dose) or <65mg/ m^2
  - A dose reduction was defined as a reduction of at least 7mg/ m^2 from the starting dose in any subsequent administration
- Median OS was determined via Kaplan-Meier analysis
- Patients without a death recorded in their follow-up were censored on the date of their last recorded activity
- Unadjusted and multivariable time-dependent Cox proportional hazards models were used to assess the impact of dose reductions on OS. The presence of a dose reduction was treated as time-dependent covariate
- The following variables were included in the multivariable model:
  - Age at treatment initiation
  - Gender
  - Year of treatment initiation
  - ECOG Performance status
  - Stage at initial diagnosis
  - Number of prior lines of therapy
  - Baseline serum albumin

- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Patient Characteristics

- 348 Patients with mPDAC treated with liposomal irinotecan for at least 3 cycles were included in the study
- (33%) Patients had two or more prior lines of therapy, 209 (60%) had an ECOG score of 0-1, 48 (14%) had an ECOG score of 2+, and 91 (26%) had missing scores (Table 1)
- The median age at treatment initiation was 69 years (IQR: 62.5 – 75)
- 220 (63%) initiated treatment at 70mg/m² and 128 (37%) initiated at <65mg/m²
- 83 (38%) 70mg/m2 and 26 (20%) <65mg/m2 patients experienced a DR

Overall Survival

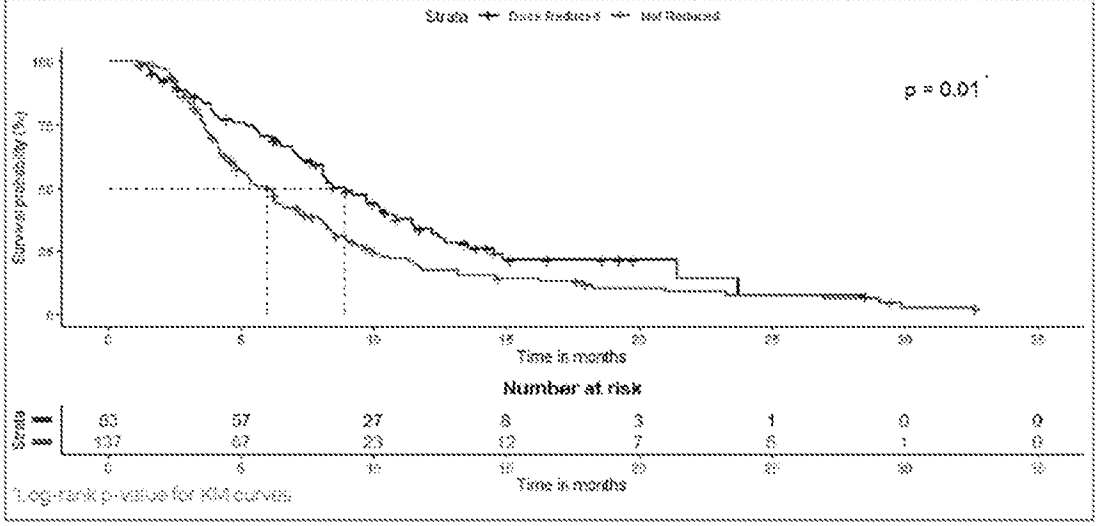
- Among patients who initiated at 70mg/m², those with a dose reduction had an median OS (95% CI) of 8.9 months (7.3 – 10.8) and those without a DR had an mOS of 6.0 months (4.8 – 7.2) [HR: 0.78 (0.56 – 1.09), adjusted HR: 0.77 (0.55 – 1.08)] (Figure 1)
- For patients who initiated at <65mg/m², mOS was 7.7 months (5.0 – 14.9) for patients with a DR and 6.0 mos (4.7 – 7.2) for patients without [HR: 0.93 (0.55 – 1.56), adjusted HR: 0.83 (0.46 – 1.49)] (Figure 2)

Table 1: Patient characteristics at the start of liposomal irinotecan treatment

Characteristics	Overall N = 348	Indicated Dose (70mg/m2) N = 220	Low Dose (<65mg/m2) N = 128
Age at index, years, median (Q1-Q3)	69 (62.5 - 75)	68 (62 - 73)	71 (64 - 78)
Male, n (%)	183 (52.59)	115 (52.3%)	68 (53.13%)
Stage at initial diagnosis, n (%)			
Stage IV	188 (54.02%)	120 (54.55%)	68 (53.13%)
Other	160 (45.98%)	100 (45.45%)	60 (46.88%)
Index Year, n (%)			
Prior to 2018	155 (44.54%)	98 (44.55%)	57 (44.53%)
On or after 2018	193 (55.46%)	122 (55.45%)	71 (55.47%)
Geographic Region, n (%)			
Northeast	60 (17.24%)	40 (18.18%)	20 (15.63%)
Midwest	49 (14.08%)	31 (14.09%)	18 (14.06%)
South	161 (46.26%)	98 (44.55%)	63 (49.22%)
West	56 (16.09%)	36 (16.36%)	18 (14.06%)
Unknown	22 (6.32%)	13 (5.91%)	9 (7.03%)
ECOG PS, n (%)			
0	64 (18.39%)	36 (16.36%)	28 (21.88%)
1	145 (41.67%)	95 (43.18%)	50 (39.06%)
2+	48 (13.79%)	28 (12.73%)	20 (15.63%)
Missing	91 (26.15%)	61 (27.73%)	30 (23.44%)
Baseline serum albumin, n (%)			
<40 g/L	247 (70.98%)	157 (71.36%)	90 (70.31%)
>= 40g/L	73 (20.98%)	49 (22.27%)	24 (18.75%)
Unknown / Not tested	28 (8.05%)	14 (6.36%)	14 (10.94%)
Practice Type, n (%)			
Academic	21 (6.03%)	13 (5.91%)	8 (6.25%)
Community	327 (93.97%)	207 (94.09%)	120 (93.75%)
Previous lines of therapy, n (%)			
0	52 (14.94%)	36 (16.36%)	16 (12.5%)
1	180 (51.72%)	116 (52.73%)	64 (50%)
2 or more	116 (33.33%)	68 (30.91%)	48 (37.5%)

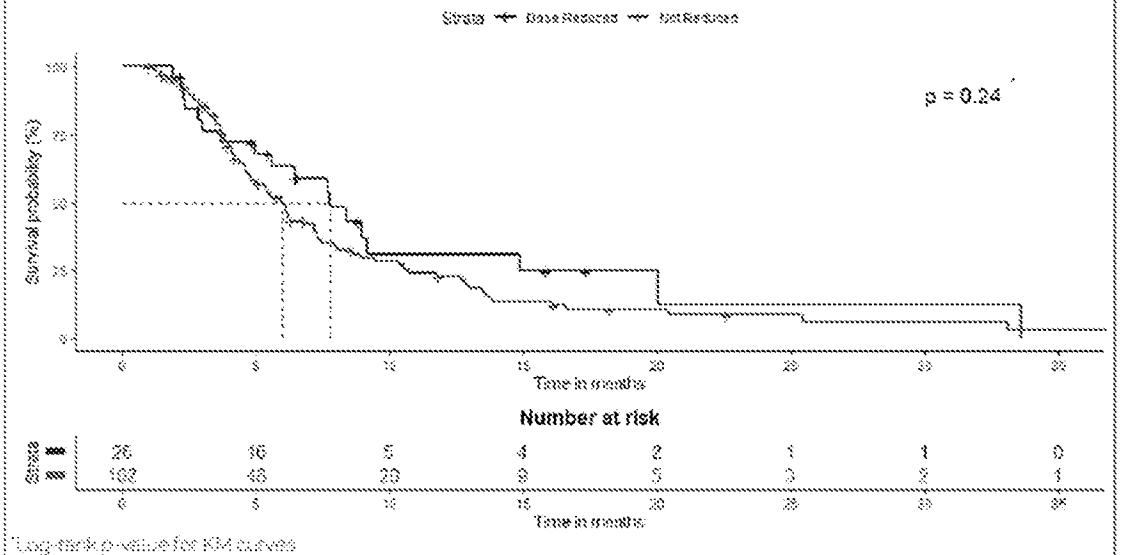
ECOG PS: Eastern Cooperative Oncology Group Performance score

Figure 1. Overall survival by dose reduction, starting dose 65mg/m2 – 75mg/m2



*Log-rank p-value for KM curves

Figure 2. Overall survival by dose reduction, starting dose <65mg/m2



*Log-rank p-value for KM curves

Conclusions

- In this real-world study of patients with mPDAC treated with a liposomal irinotecan-based regimen for ≥3 cycles, DRs were associated with lower risks of death, though not statistically significant, consistent with post-hoc analyses of the phase III trial, NAPOLI-1
- Dose reductions were more beneficial for patients who were able to initiate at the indicated dose of 70mg/m^2 than for patients who were able to initiate at <65mg/m^2
- Dose reductions appear to be an effective option for managing adverse effects while maintaining treatment efficacy
- Further studies are needed to characterize factors that influence clinical outcomes among liposomal irinotecan pts who receive DRs

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- There are no data available on reasons for dose reduction or treatment discontinuation which could further characterize and influence the treatment patterns observed in this study
- Age was limited to 85 years and younger for de-identification reasons therefore the true age of the older patients of the population and true average age of the overall population is unknown.

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Conflicts of interest

L.A receives consulting fees from Bionest. A.S. is an employee of Genesis Research, which receives consulting fees from Ipsen. P.C. and S.B. are employees of Ipsen

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Multivariable analysis of real-world clinical outcomes associated with dose reductions (DR) by patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) initiating gemcitabine (Gem)-based therapy

1534P

BACKGROUND

OBJECTIVE

METHODS

RESULTS

Conclusions

Limitations

MULTIVARIABLE ANALYSIS OF REAL-WORLD CLINICAL OUTCOMES ASSOCIATED WITH DOSE REDUCTIONS (DRS) FOR PATIENTS (PTS) WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC) TREATED WITH LIPOSOMAL IRINOTECAN

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Presenters
Laith Abushahin

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More

Resources

Abstract 1534P

Background

Pancreatic cancer is the fourth most lethal cancer in Europe. Liposomal irinotecan is indicated, in combination with 5-fluorouracil and leucovorin, for pts with mPDAC following disease progression with gemcitabine-based therapy. This study examines the survival outcomes associated with DRs among pts with mPDAC treated with liposomal irinotecan.

Methods

This retrospective observational study utilized the Flatiron Health EHR-derived de-identified database from over 280 cancer clinics in the US. Data were analyzed for adult pts with mPDAC treated with liposomal irinotecan based regimens between Nov 2015 and Oct 2019. Pts were categorized into two starting dose groups: 70mg/m^2 (indicated dose) or <65mg/m^2 (cut off for DR). Pt characteristics, overall survival (OS), and impact of DRs (reduction ≥ 7mg/m^2) were assessed among pts who received ≥3 cycles of treatment (tx). Unadjusted and multivariable time-dependent Cox proportional hazards models were used to assess the impact of DRs on OS.

Results

Of 348 pts (median age 60y, 43 – 85), 116 (33%) pts had two or more prior lines of tx, 209 (60%) had an ECOG score of 0-1, 48 (14%) had an ECOG score of 2+, and 91 (26%) had missing scores. 220 (63%) initiated tx at 70mg/m^2 and 128 (37%) initiated at <65mg/m^2. 83 (38%) 70mg/m^2 and 26 (20%) <65mg/m^2 pts. experienced a DR. Among pts who initiated at 70mg/m^2, those with a DR had an mOS (95% CI) of 8.9 mos (7.3 – 10.8) and those without a DR had an mOS of 6.0 mos (4.8 – 7.2) [HR: 0.78 (0.56 – 1.09), adjusted HR: 0.77 (0.55 – 1.08)]. For pts who initiated at <65mg/m^2, mOS was 7.7 mos (5.0 – 14.9) for pts with a DR and 6.0 mos (4.7 – 7.2) for pts without [HR: 0.93 (0.55 – 1.56), adjusted HR: 0.83 (0.46 – 1.49)]. ECOG score (2+) and prior lines of tx (≥2) were associated with reduced survival among pts receiving 70mg/m^2 or <65mg/m^2, respectively.

Conclusions

In this real-world study of patients with mPDAC treated with a liposomal irinotecan based regimen for ≥3 cycles, DRs were associated with lower risks of death, though not statistically significant. Further studies are needed to characterize factors that influence clinical outcomes among liposomal irinotecan pts who receive DRs.

Clinical trial identification

Funding

Ipsen.

Disclosure

L. Abrahamsen: Advisory/Consultancy: Bionest. P. Cockrum, B. Belanger: Shareholder/Stockholder/Stock options, Full/Part time employment: Ipsen. A. Surinach: Advisory/Consultancy, Work for Genesis Research which receives funding from Ipsen: Ipsen.

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Real-world dosing, management, and clinical outcomes of patients (pts) with metastatic pancreatic adenocarcinoma (mPDAC) treated with liposomal irinotecan.

Laith I. Abushahin, Paul Cockrum, Andy Surinach, Bruce Belanger

Show Less

Ohio State University, Comprehensive Cancer Center, Columbus, OH; Ipsen, Cambridge, MA; Genesis Research, Hoboken, NJ

Abstract Disclosures

Abstract

e16780

Background: Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 10%. Liposomal irinotecan is a topoisomerase inhibitor indicated, in combination with 5-fluorouracil and leucovorin, for pts with mPDAC following disease progression on gemcitabine-based therapy. This study examines the real-world use and therapeutic management of pts with mPDAC treated with liposomal irinotecan. **Methods:** This retrospective observational study utilized the Flatiron Health EHR-derived de-identified database from over 280 cancer clinics in the US. Data were analyzed for adult pts with mPDAC treated with liposomal irinotecan based regimens between Nov 2015 and Oct 2019. Pts were categorized into two starting dose groups: 70mg/m^2 and < 65mg/m^2. Pt characteristics, overall survival (OS), duration of treatment (DOT), and impact of dose reductions (DR, reduction ≥ 7mg/m^2) were assessed among pts who received ≥3 cycles of treatment (tx). **Results:** Of the 532 pts (median age: 69y, IQR: 62-75) included in the study, 95 (18%) had an ECOG score of 2+ at tx initiation. Of the 184 pts (69y, 42 – 84) that did not receive 3 cycles of tx, 47 (25%) had an ECOG score of 2+ and 83 (45%) had two or more prior lines of tx. 348 pts (69y, 43 – 85) received ≥3 cycles of tx. 116 (33%) pts had two or more prior lines of tx, 209 (60%) had an ECOG score of 0-1, 48 (14%) had an ECOG score of 2+, and 91 (26%) had missing scores. 220 (63%) initiated tx at 70mg/m^2 and 128 (37%) initiated at < 65mg/m^2. 83 (38%) 70mg/m^2 and 26 (20%) < 65mg/m^2 pts experienced a DR during tx. 43 (52%) and 14 (54%) of the DRs occurred within the first 6 wks of

tx in the 70mg/m^2 and < 65mg/m^{2}cohorts, respectively. Median DOT was 12.6 weeks for 70mg/mg^2 and 9.1 wks for < 65mg/m^2 pts; DOT was longer among pts with a DR: 19.0 wks and 16.1 wks, respectively. Median OS (mOS) was 7.2 months (95% CI: 6.2 – 8.1) and 6.2 mos (5.0 – 7.4) for pts receiving 70mg/m^2 and < 65mg/m^2, respectively. mOS for pts with a DR was 8.9 mos (7.3 – 10.8) and 7.7 mos (5.0 – 14.9) for pts receiving 70mg/m^2 and < 65mg/m^2, respectively. mOS for pts with no DR was 6.0 mos (4.8 – 7.2) and 6.0 mos (4.7 - 7.2) for those receiving 70mg/m^2 and < 65mg/m^2, respectively. **Conclusions:** In this descriptive study among pts who were able to receive ≥3 cycles of liposomal irinotecan and remain on tx for ≥4 wks, DRs were effective in extending DOT and OS, independent of starting dose. The longest DOT and OS were observed in the pts who received 70mg/m^2 with DRs. Pts who received 70mg/m^2 and < 65mg/m^{2}had similar OS in the absence of DRs.

Research Sponsor:

Ipsen Biopharmaceuticals

735P

Real-world dosing patterns of patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in US oncology clinics

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BACKGROUND

- Pancreatic cancer accounts for about 3% of all cancers and is the third leading cause of cancer related death in the United States, surpassing breast cancer.[1]
- Due to limited treatment options and the aggressive nature of the cancer, 5-year survival remains very low at 8.5%.[2]
- Liposomal irinotecan (nal-IRI) is a topoisomerase inhibitor indicated, in combination with 5-fluorouracil and leucovorin, for the treatment of metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.[3]
- Used in combination with fluorouracil and folinic acid, nal-IRI has been proven to extend median overall survival to 6.1 months compared to 4.2 months in patients treated with fluorouracil and folinic acid.[4]
- Dose intensity over 6 weeks and duration of exposure for combination therapy with nal-IRI in the NAPOLI-1 trial was 167.5 mg/m^2 (SD 44.8) and 8.7 weeks (IQR: 5.4 – 22.0), respectively.[4]
  - Hazard ratios reported in NAPOLI-1 included overall survival [0.67 (95% CI 0.49 – 0.92)] and progression-free survival [0.56 (95% CI 0.41 – 0.75)].[4]

OBJECTIVE

- To describe the real-world dosing patterns of patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI).

METHODS

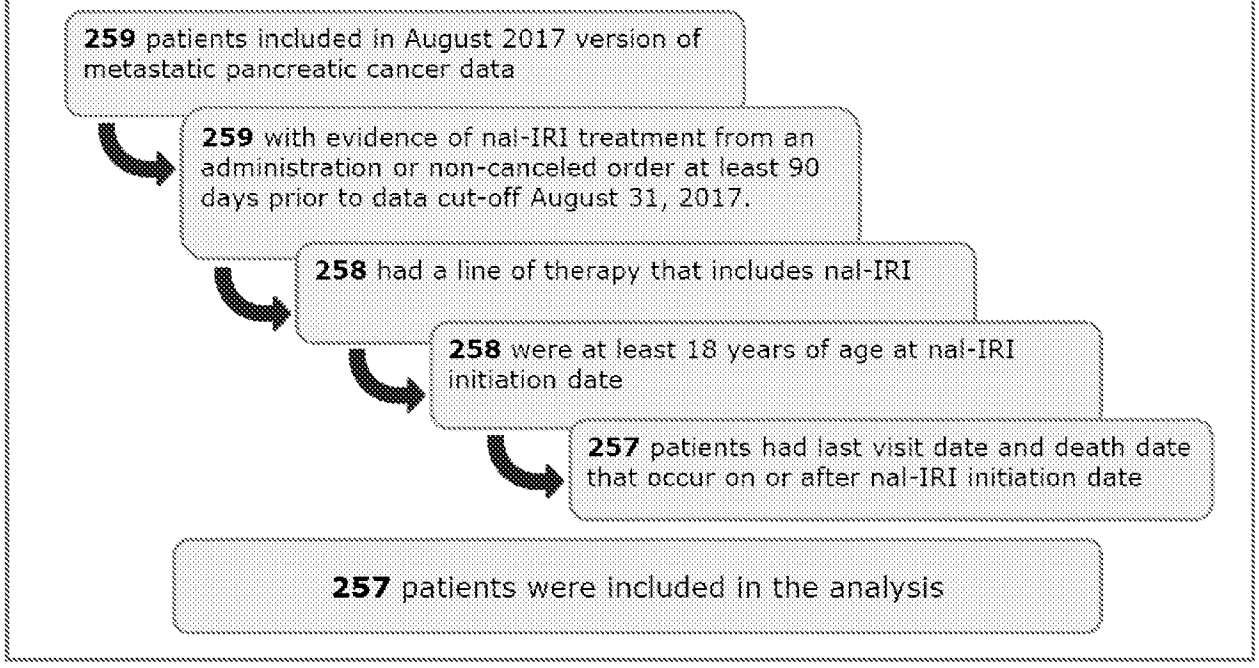
Study Design and Data Source

- A retrospective descriptive analysis was performed using the Flatiron Health longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data which includes data from over 265 cancer clinics representing more than 2 million active US cancer patients for analysis.[5]
- Patient-level data include structured and unstructured data, curated via technology-enabled abstraction.
- Data provided for study were de-identified with provisions in place to prevent re-identification and protect patients' confidentiality.

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPC between 1/1/2014 and 8/31/2017 and treated with nal-IRI between 11/1/2015 and 8/31/2017.
- Eligible patients were those who initiated nal-IRI treatment at least 90 days prior to 8/31/2017, were at least 18 years old, had last visit date and death date that occurred on or after nal-IRI initiation date.

Figure 1. Cohort Attrition



Measures and Statistical Analyses

- Baseline demographics and clinical characteristics, dose intensity (DI), dose modification, and duration of exposure (DOE) (on or after index date), grade 3-4 adverse events (AE), growth factor usage, and reasons for discontinuation were determined.
- Dose intensity was the total dose (in mg/m^2) of nal-IRI given to patients within the first 6 weeks of initiating a nal-IRI regimen.
- Dose modification was defined as a difference of ≥7 mg/m^2 amid consecutive administrations (or orders if missing administration).
- Grading of adverse events was only possible for lab values and used the NCI CTCAE grading scheme between nal-IRI initiation and discontinuation.
  - Grade 3 and 4 neutropenia was calculated as neutrophil counts <1000-500/μL and <500/μL, respectively.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Population

- The study sample included 257 patients; demographic and clinical characteristics are summarized in **Table 1**.

Table 1. Demographics and Clinical Characteristics

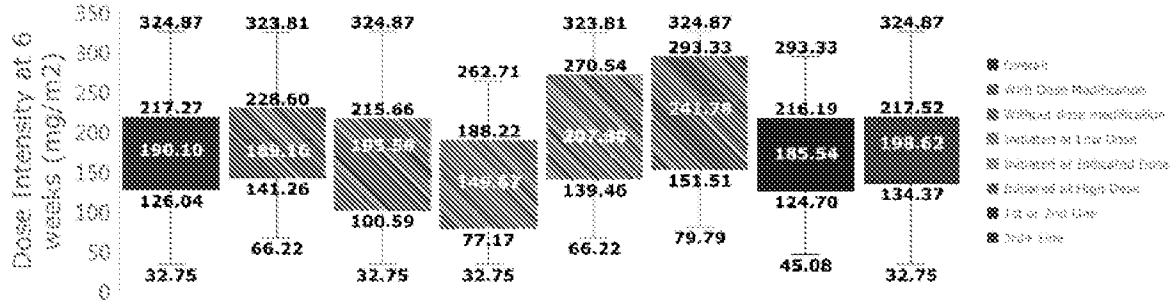
Demographics	
Total Cohort	257 (100%)
Male (n=132)	132 (51.3%)
Age at index, median (IQR) years (n=257)	68 (61-74)
Clinical Characteristics	
BMI, median (IQR) kg/m^2 (n=225)	23.2 (20.7-26.5)
Tumor Location, n(%)	
Head	132 (51.4%)
Body	68 (26.5%)
Tail	35 (13.6%)
Overlapping	20 (7.8%)
Pancreas, NOS	2 (0.8%)
ECOG Score, n(%)	
0-1	128 (49.8%)
2-4	33 (12.8%)
Missing	96 (37.4%)
Charlson Comorbidity Index, n(%)	
2 or more	257 (100%)
Neutrophil to Lymphocyte Ratio (NLR), median (IQR) (n=160)	3.9 (2.5-5.7)
Number of lines prior to nal-IRI, n(%)[a]	
0[b]	38 (14.8%)
1	107 (41.6%)
2	85 (33.1%)
3	21 (8.2%)
4+	6 (2.3%)
Initial Dose, n(%)	
Low (30 - <65 mg/m^2)	67 (26.1%)
Indicated (65 - <75 mg/m^2)	152 (59.1%)
High (≥70 mg/m^2)	11 (4.3%)
Missing	27 (10.5%)

[a] 94.1% of patients received prior gemcitabine
[b] Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease

Dose Intensity

- Overall mean DI was 177.8 mg/m^2 (SD 74.9 mg/m^2) with median DI for subgroups indicated in **Figure 2.**
- Stratified into groups based on median DI (190 mg/m^2), more patients below (<) median DI initiated at a low dose compared to those at or above (≥) median DI (44.4% vs 13.8%, respectively).

Figure 2. Dose Intensity at 6 weeks



Duration of Exposure

- The median DOE for all patients was 7.3 weeks (IQR 3.4 – 17.1). **Table 3** contains a summary for each subgroup.
- In 1st or 2nd line patients, median DOE was 8.9 (IQR 3.1 – 19.0) weeks compared to 6.4 (IQR 3.4 – 12.1) weeks in 3rd+ line patients.
- Stratified by initial dose, patients initiated at the indicated dose had a median DOE of 8.1 weeks (IQR 3.4 – 18.3).
- Low dose and high dose DOE was 7.1 and 6.1 weeks, respectively.
- Patients with a dose modification experienced a longer DOE (13.1 weeks) compared to those without a dose modification (6.1 weeks).

Table 3. Duration of Exposure

Characteristic	n	Median (IQR), weeks
Overall	257	7.3 (3.4 – 17.1)
Below Median Dose Intensity	115	3.1 (0.1 – 8.1)
With Dose Modification	70	13.1 (7.1 – 24.9)
Initiated at Low Dose	67	7.1 (2.1 – 13.4)
Initiated at Indicated Dose	152	8.1 (3.4 – 18.3)
Initiated at High Dose	11	6.1 (2.1 – 24.3)
1st or 2nd Line	145	8.9 (3.1 – 19.0)
Below Median Dose Intensity	66	2.1 (0.1 – 8.9)
With Dose Modification	47	14.1 (7.1 – 25.1)
3rd+ Line	112	6.4 (3.4 – 12.1)
Below Median Dose Intensity	49	3.4 (0.7 – 7.1)
With Dose Modification	23	11.0 (7.1 – 24.1)

Dose Modification

- Overall, 27.2% of patients experienced a dose modification **(Table 4)**; when stratified by median DI similar rates were seen for below median DI and at or above median DI.
  - Across all subgroups, dose reductions were more common compared to dose escalations.

Table 4. Dose Modifications

Category	All Patients, n(%)	< Median DI, n(%)	≥ Median DI, n(%)
Overall	257 (100%)	115 (100%)	116 (100%)
Modified Dose	70 (27.2%)	35 (30.4%)	35 (30.2%)
Increased Dose	25 (9.7%)	11 (9.6%)	14 (12.1%)
Decreased Dose	58 (22.6%)	29 (25.2%)	29 (25.0%)
1st or 2nd Line	145 (56.4%)	66 (57.4%)	65 (56.0%)
Modified Dose	47 (32.4%)	24 (36.4%)	23 (35.4%)
Increased Dose	18 (12.4%)	7 (10.6%)	11 (16.9%)
Decreased Dose	37 (25.5%)	20 (30.3%)	17 (26.2%)
3rd+ Line	112 (43.6%)	49 (42.6%)	51 (44.0%)
Modified Dose	23 (20.5%)	11 (22.4%)	12 (23.5%)
Increased Dose	7 (6.3%)	4 (8.2%)	3 (5.9%)
Decreased Dose	21 (18.8%)	9 (18.4%)	12 (23.5%)

Adverse Events

- Neutropenia was the only AE with labs to measure grading during and before the nal-IRI containing regimen.
  - Grade 3 and 4 neutropenia during baseline was observed in 21.4% and 8.2% of all patients, respectively **(Table 5)**.

Table 5. Grade 3 or 4 Neutropenia

	Baseline*, n(%)	During 90-day baseline, n(%)	During nal-IRI treatment, n(%)
Grade 3			
All Patients	55 (21.4%)	17 (6.6%)	18 (7.0%)
1st or 2nd line	26 (17.9%)	11 (7.6%)	8 (5.5%)
3rd+ line	29 (25.9%)	6 (5.7%)	10 (8.9%)
Below Median DI	22 (19.1%)	8 (7.0%)	8 (7.0%)
At or above Median DI	27 (23.3%)	7 (6.0%)	7 (6.0%)
Grade 4			
All Patients	21 (8.2%)	5 (2.0%)	5 (2.0%)
1st or 2nd line	8 (5.5%)	1 (0.7%)	3 (2.1%)
3rd+ line	13 (11.6%)	4 (3.6%)	2 (1.8%)
Below Median DI	9 (7.8%)	2 (1.7%)	2 (1.7%)
At or above Median DI	10 (8.6%)	3 (2.6%)	3 (2.6%)

*Time period for baseline was from mPC diagnosis to nal-IRI initiation

Growth Factor Usage

- For all groups, a higher proportion of patients were on growth factors prior to nal-IRI treatment compared with during treatment.

Reasons for Discontinuation

- Progression was the most common reason for discontinuation across all groups and was followed by disease-related symptoms not due to therapy **(Table 6)**.

Table 6. Reasons for Discontinuation*

End Reason	Overall, n(%)	< Median DI, n(%)	≥ Median DI, n(%)
Completed treatment	3 (1.17%)	1 (0.87%)	2 (1.72%)
Death	14 (5.45%)	5 (4.35%)	6 (5.17%)
Disease-related symptoms not due to therapy	32 (12.45%)	19 (16.52%)	12 (10.34%)
Other	3 (1.17%)	2 (1.74%)	1 (0.86%)
Patient request	14 (5.45%)	12 (10.43%)	1 (0.86%)
Progression	106 (41.25%)	34 (29.57%)	60 (51.72%)
Toxic effect of therapy	27 (10.51%)	17 (14.78%)	8 (6.90%)
Missing	66 (25.68%)	29 (25.22%)	31 (26.72%)
Total Unique Patients	257 (100.00%)	115 (100.00%)	116 (100.00%)

*Patients may have multiple end reasons, categories are not mutually exclusive, and therefore percentages in each column may sum to more than 100%.

LIMITATIONS

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values.
- Age was limited to 85 years and younger for de-identification reasons therefore the true age of the older patients of the population and true average age of the overall population is unknown.
- Diagnosis codes from the structured data were captured at the oncology clinic. Conditions not relevant to cancer may not have been captured, potentially leading to an underestimate of the true comorbidity burden.

CONCLUSIONS

- Compared to the NAPOLI-1 trial, this real-world analysis demonstrated similar DI results, however patients had fewer dose modifications and were slightly older, with worse performance status than those in the trial.
  - Similarly, rates of treatment related reasons for discontinuation were comparable: 10.5% in this analysis vs. 11.1% in NAPOLI-1.
- Below median DI was associated with an increased proportion of patient discontinuation due to side effects and patient request, as opposed to progression in the ≥ median DI group, suggesting that median DI reflect tolerability.
- Larger patient cohort analyses will further elucidate dosing patterns and outcomes in patients treated with nal-IRI.

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Real-world dosing patterns of patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in US oncology clinics

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735P Real-world dosing patterns of patients (pts) with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in US oncology clinics

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Background: nal-IRI + 5FU/LV therapy demonstrated significant survival improvement in mPC pts previously treated with gemcitabine-based therapy (NAPOLI-1). The generally recommended nal-IRI initiation dose is 70 mg/m^2 (free base, equivalent to 80 mg/m^2 salt based dosing). This retrospective observational analysis describes the real-world dosing patterns of nal-IRI.

Methods: Using the Flatiron Health® longitudinal database, data was extracted and analyzed for adult pts with mPC treated with nal-IRI between Nov 2015 to Aug 2017. Dose intensity (DI) over the first 6 weeks of treatment, dose modifications anytime (mods), and overall duration of exposure (DOE) to nal-IRI were assessed. All dosing is expressed in terms of the free base.

Results: 257 mPC pts (median age: 67y; IQR 61–74) treated with nal-IRI were identified; DI was calculated for 231 pts with available dose, height, and weight data. Mean DI was 177.8 mg/m^2 (SD: 74.9 mg/m^2). Median DOE was 7.3 (IQR: 3.4 – 17.1) weeks (wks). Median dose at initiation was 69.4 (IQR 56.7–70.2) mg/m^2. Stratified into groups based on median DI (150 mg/m^2), more pts below median DI initiated at a lower dose (LD) (30 – 65 mg/m^2) compared to the pts at/above the median DI (44.4% vs 13.8%). Pts below median DI were also older: median age 70y (IQR 63 - 76) vs 65y (IQR 61 - 72). Mean DI was similar for pts who initiated nal-IRI in 1st/2nd line (176.4 mg/m2; n = 131) vs later lines (179.6 mg/m2; n = 100). In 1st/2nd line pts, median DOE was 8.9 (IQR: 3.1 – 19) wks vs 6.3 (IQR: 3.4 – 12.1) wks in 3rd+ line. Median DOE in pts initiated at the recommended dose of 65-75 mg/m^2 (n = 152) was 8.1 wks. DOE in LD (n = 67) and higher dose (75–90 mg/m^2; n = 11) pts was 7.1 and 6.1 wks, respectively. 27.2% of pts experienced a dose mod (18.3% in 1st/2nd line; 8.9% in 3rd+ line). Pts with dose mods had a median DOE of 13.1 vs 6.1 wks in pts without mods.

Conclusions: This real-world analysis showed similar DI results to the NAPOLI-1 trial, while dose mods were slightly lower. Pts with higher DI had longer DOE. Pts who experienced a dose mod, initiated nal-IRI in 1st/2nd line, were at/above median DI had, on average, longer DOE. Larger pt cohort analyses will elucidate dosing patterns and outcomes in nal-IRI treated pts.

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Disclosure: D. Ahn: Advisory board: Eisai. A. Surinach, F.A. Corvino: Employee: Genesis Research that received funding from Ipsen Biopharmaceuticals to conduct study. A. Valderrama, S. Puigar: Employee: Ipsen Biopharmaceuticals. K. Mamlouk: Consultant: Ipsen Biopharmaceuticals. All other authors have declared no conflicts of interest.

Imputing Missing Values to Estimate Health-Related Quality of Lifee (HR-QoL) in Metastatic Pancreatic Cancer Treated with 5-fluorouracil and Leucovorin (5-FU/LV), with and without Liposomal Irinotecan (nal-IRI)

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Background and Objective

- Irinotecan Liposome (nal-IRI) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. non-liposomal irinotecan. [1-3]
- NAPOLI-1, a global, phase 3 study, demonstrated, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy, that nal-IRI in combination with 5-FU/LV significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio = 0.67; P = 0.012) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified hazard ratio = 0.56; P = 0.0001) compared with 5-FU/LV alone. [4]
- The most frequent Grade ≥ 3 treatment-emergent adverse events (TEAEs) in patients treated with nal-IRI+5-FU/LV were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%). [4]
- Quality of life was not compromised in patients treated wtih nal-IRI + 5-FU/LV as demonstrated by the proportions of patients with improved, stable, or worsening EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer quality-of-life core questionnaire) symptom, global health status - quality of life (GHS-QL) and functional scale scores (secondary end-point).[4]
- Furthermore, post hoc analysis of EORTC QLQ-C30 measures suggests that post-treatment change in HR-QoL was improved with nal-IRI + 5-FU/LV compared to 5-FU/LV alone.[5] However, a limited number of patients had HR-QoL data.
- We investigated how imputation of missing values would affect initial findings.

Methods

- In NAPOLI-1, patients were initially randomized to nal-IRI monotherapy or 5-FU/LV (protocol version 1). Once safety data for the combination treatment became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a nal-IRI + 5-FU/LV arm (protocol version 2). This trial is registered at ClinicalTrials.gov, number NCT01494506.
- A principal component (PC) analysis was performed on EORTC QLQ-C30 scale week-6 change from baseline retaining PC explaining about 60% of the variance.
- Patients randomized to 5-FU/LV alone or to nal-IRI + 5-FU/LV (protocol version 1, or 2), and who had EORTC QLQ-C30 scale measurements at baseline and week-6 were included in the PC analysis.
- For patients with missing information, imputation of PC scores was performed based on clinical baseline characteristics using either regression predictors or median value of study population-matched controls.
- PC score predictions and population match selection were performed using the following clinical baseline characteristics: Karnofsky performance status ≥ 90, albumin level ≥ 4g/dL, carbohydrate antigen (CA) 19-9 ≥ 40 U/mL, stage IV cancer at diagnosis, presence of liver metastases, and time since prior anticancer therapy ≥ 40 days.
- Before and after each imputation method, *P*-values for univariate or multivariate between-group differences in scores were obtained using parametric tests.

Results

- A total of 266 patients were assigned to receive 5-FU/LV alone (n=149 including 30 patients randomized prior to protocol amendment) or 5-FU/LV + nal-IRI (n=117).
- Of these, 122 (45.9%) had both baseline and week-6 EORTC QLQ-C30 scale measures; 52 (44.4%) among those assigned to 5-FU/LV + nal-IRI and 70 (47.0%) among assigned to 5-FU/LV alone.
- Four PCs, explaining 59.3% of the variance were retained. With positive weights on functioning and GHS/QL scales, and negative weights on symptoms and financial difficulties scales, the first PC (explained variance: 34%) was found to reflect general HR-QoL, higher scores revealing better HR-QoL increments.

- Table 1 show clinical characteristics at baseline for in each group. These were similar in patients with and without missing PC scores.
- Figure 1 illustrates the estimated densities for associations between baseline clinical characteristics and PC scores for week-6 change in EORTC QLQ-C30 scales. Presence of liver metastases was the strongest predictors of the PC scores followed by albumin level ≥ 4g/dL, Karnofsky performance status ≥ 90, time since prior anticancer therapy ≥ 40 days, stage IV cancer at diagnosis and amount of CA 19-9 ≥ 40U/mL.
- Imputation of HR-QoL change from baseline PC scores was performed with 5 of these clinical baseline characteristics. Amount of CA 19-9 was not included as it did not provide sufficient additional information after other clinical factors were accounted for. With 5 covariates, 94% of patients without EORCT QLQ-C30 change from baseline measures were matched to at least one 1 patient with same clinical characteristics.
- In 11 patients with missing baseline clinical characteristic(s), imputation was performed based on available factors.
- Table 2 shows the results of PC score comparisons between patients treated with or without nal-IRI obtained with or without imputation of missing values.
- Prior to imputation, patients treated with nal-IRI had better increments in EORTC QLQ-C30 scale change PC scores than non-users, indicating better post-treatment HR-QoL increments (1st PC: +0.45 vs –0.34, $P = 0.0478$; 4 PCs multivariate comparison: $P = 0.0051$)[8].
- Comparable results were found after imputation of missing values using either
  - Predictive model (1st PC: +0.30 vs –0.14, P=0.0214; 4 PCs multivariate comparison: $P = 0.0015$)
  - Population-matched values (1st PC: +0.34 vs –0.10, $P = 0.0271$; 4 PCs multivariate comparison: $P = 0.0007$).

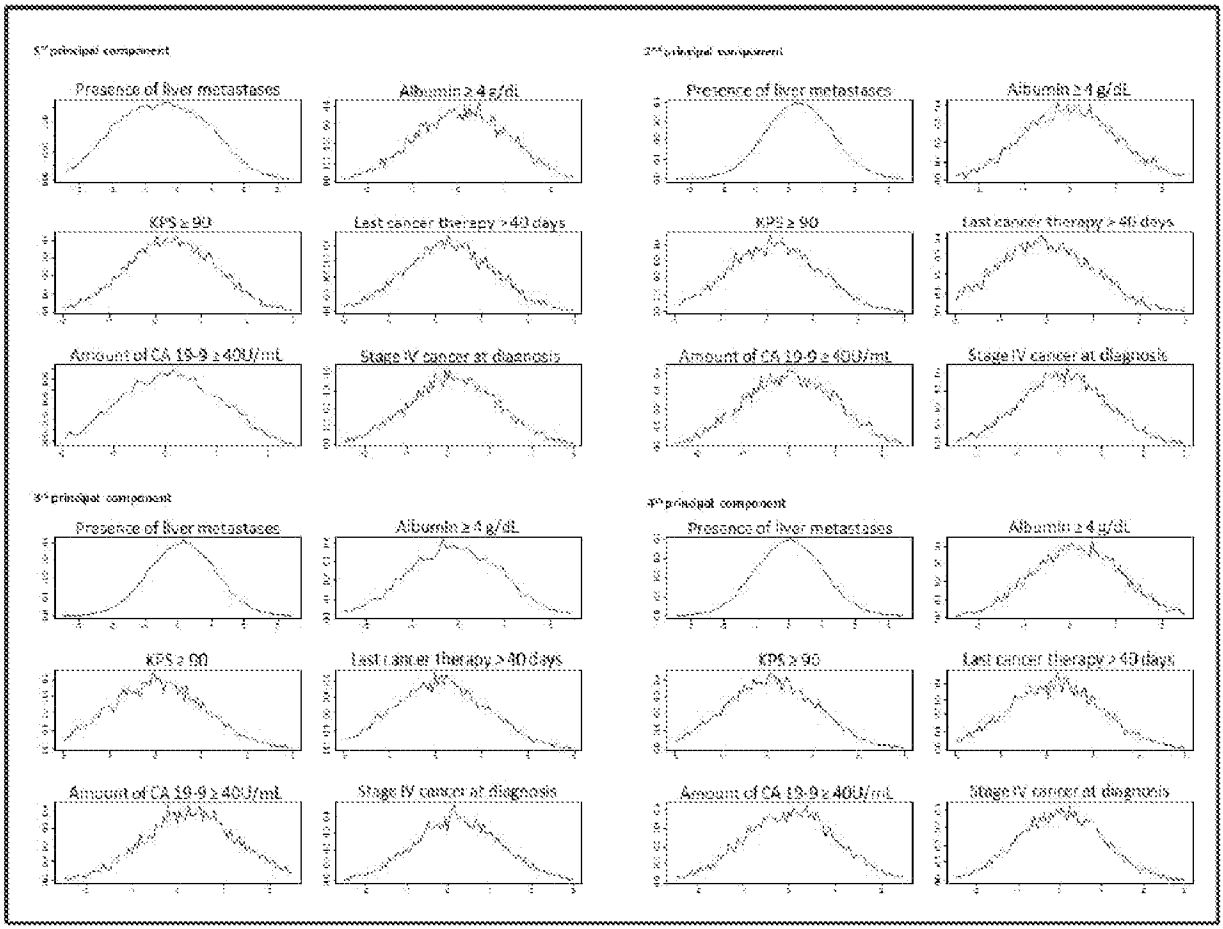
Tables and Figure

Table 1. Baseline characteristics in patients with and without EORCT QLQ-C30 scales week-6 change from baseline measures

Clinical baseline characteristics, % (n) *	EORCT QLQ-C30 scales change measures			
	Missing (n = 144)		Not missing (n = 122)	
Karnofsky performance status ≥ 90	83.6	(107)	77.0	(94)
Albumin level ≥ 4g/dL	50.0	(68)	47.5	(58)
Amount of CA 19-9 ≥ 40U/mL	56.6	(77)	59.0	(72)
Stage IV cancer at diagnosis	42.6	(58)	48.4	(59)
At least 40 days since last anticancer therapy	55.6	(74)	51.6	(63)
Presence of liver metastases	66.2	(90)	72.1	(88)

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire ; CA, carbohydrate antigen

Figure 1. Estimated densities of the associations between baseline clinical characteristics and principal component scores for EORCT QLQ-C30 scale week-6 change from baseline



EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire ; KPS, Karnofsky performance status; CA, carbohydrate antigen

Table 2. Comparison of principal components scores for week-6 change from baseline in EORCT QLQ-C30 scales according to missing value imputation method: 5-FU/LV + nal-IRI vs. 5-FU/LV alone

Principal components, by imputation method	Anticancer therapy group comparison							
	nal-IRI + 5-FU/LV		5-FU/LV		Group difference		P-value for group difference	
	mean	(SD)	mean	(SD)	mean	[95% CI]	Univariate	Multivariate
Without Imputation								
1st PC	0.45	(1.97)	-0.34	(2.38)	0.79	[0.01 ; 1.57]	0.0478	0.0051
2nd PC	-0.38	(1.18)	0.28	(1.17)	-0.66	[-1.08 ; -0.23]	0.0028	
3rd PC	0.16	(1.13)	-0.12	(1.12)	0.27	[-0.14 ; 0.68]	0.1874	
4th PC	-0.02	(1.18)	0.02	(0.97)	-0.04	[-0.44 ; 0.36]	0.8421	
Regression predictors								
1st PC	-0.14	(1.71)	0.30	(1.44)	0.45	[0.07 ; 0.83]	0.0214	0.0015
2nd PC	0.14	(0.84)	-0.22	(0.83)	-0.36	[-0.56 ; -0.16]	0.0006	
3rd PC	-0.03	(0.79)	0.08	(0.77)	0.11	[-0.08 ; 0.30]	0.2464	
4th PC	0.00	(0.67)	0.01	(0.79)	0.01	[-0.17 ; 0.19]	0.9297	
Population matching								
1st PC	-0.10	(1.74)	0.34	(1.48)	0.44	[0.05 ; 0.83]	0.0271	0.0007
2nd PC	0.18	(0.86)	-0.18	(0.85)	-0.36	[-0.57 ; -0.15]	0.0008	
3rd PC	-0.08	(0.82)	0.10	(0.82)	0.18	[-0.02 ; 0.38]	0.0785	
4th PC	0.00	(0.68)	-0.03	(0.81)	-0.03	[-0.21 ; 0.15]	0.7543	

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; PC, principal component.

Conclusion

- Data missingness was not at random and induces potential biases due to e.g. differential mortality between treatment groups.
- The improvement in HR-QoL with nal-IRI + 5-FU/LV vs. 5-FU/LV observed in the post hoc analysis of NAPOLI-1 results was strengthened after imputation of missing values.
- Results were comparable regardless of the imputation method considered (regression vs. matching).

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Imputing Missing Values to Estimate Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer Treated with 5-fluorouracil and Leucovorin (5-FU/LV), with and without Liposomal Irinotecan (nal-IRI)

PCN 179

Oncology R&D, Pfizer Ltd, Sandwich, Worldwide Pharmaceuticals, Inc., Cambridge, MA

Background and Objective

- Irinotecan liposome (nal-IRI) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. non-liposomal irinotecan.[1-3]
- NAPOLI-1, a global, phase 3 study, demonstrated, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy, that nal-IRI in combination with 5-FU/LV significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio = 0.67; $P = 0.012$) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified hazard ratio = 0.56; $P = 0.0001$) compared with 5-FU/LV alone.[4]
- The most frequent Grade ≥ 3 treatment-emergent adverse events (TEAEs) in patients treated with nal-IRI+5-FU/LV were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%).[4]
- Quality of life was not compromised in patients treated with nal-IRI + 5-FU/LV as demonstrated by the proportions of patients with improved, stable, or worsening EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer quality-of-life core questionnaire) symptom, global health status / quality of life (GHS-QL) and functional scale scores (secondary end-point).[4]
- Furthermore, post hoc analysis of EORTC QLQ-C30 measures suggests that post-treatment change in HR-QoL was improved with nal-IRI + 5-FU/LV compared to 5-FU/LV alone.[5] However, a limited number of patients had HR-QoL data.
- We investigated how imputation of missing values would affect initial findings.

Methods

- In NAPOLI-1, patients were initially randomized to nal-IRI monotherapy or 5-FU/LV (protocol version 1). Once safety data for the combination treatment became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a nal-IRI + 5-FU/LV arm (protocol version 2). This trial is registered at ClinicalTrials.gov, number NCT01494506.
- A principal component (PC) analysis was performed on EORTC QLQ-C30 scale week-8 change from baseline retaining PC explaining about 80% of the variance.
- Patients randomized to 5-FU/LV alone or to nal-IRI + 5-FU/LV (protocol version 1 or 2), and who had EORTC QLQ-C30 scale measurements at baseline and week-8 were included in the PC analysis.
- For patients with missing information, imputation of PC scores was performed based on clinical baseline characteristics using either regression predictors or median value of study population-matched controls.
- PC score predictions and population match selection were performed using the following clinical baseline characteristics: Karnofsky performance status ≥ 90, albumin level ≥ 4g/dL, carbohydrate antigen (CA) 19-9 ≥ 40 U/mL, stage IV cancer at diagnosis, presence of liver metastases, and time since prior anticancer therapy ≥ 40 days.
- Before and after each imputation method, *P*-values for univariate or multivariate between-group differences in scores were obtained using parametric tests.

Results

- A total of 266 patients were assigned to receive 5-FU/LV alone (n=149 including 30 patients randomized prior to protocol amendment) or 5-FU/LV + nal-IRI (n=117).
- Of these, 127 (45.9%) had both baseline and week-8 EORTC QLQ-C30 scale measures: 52 (44.4%) among those assigned to 5-FU/LV + nal-IRI and 79 (47.0%) among assigned to 5-FU/LV alone.
- Four PCs, explaining 59.3% of the variance were retained. With positive weights on functioning and GHS/QL scales, and negative weights on symptoms and financial difficulties scales, the first PC (explained variance: 34%) was found to reflect general HR-QoL, higher scores revealing better HR-QoL increments.
- Table 1 shows clinical characteristics at baseline for in each group. These were similar in patients with and without missing PC scores.
- Figure 1 illustrates the estimated densities for associations between baseline clinical characteristics and PC scores for week-8 change in EORTC QLQ-C30 scales. Presence of liver metastases was the strongest predictors of the PC scores followed by albumin level ≥ 4g/dL, Karnofsky performance status ≥ 90, time since prior anticancer therapy ≥ 40 days, stage IV cancer at diagnosis and amount of CA 19-9 ≥ 40U/mL.
- Imputation of HR-QoL change from baseline PC scores was performed with 5 of these clinical baseline characteristics. Amount of CA 19-9 was not included as it did not provide sufficient additional information after other clinical factors were accounted for. With 5 covariates, 94% of patients without EORTC QLQ-C30 change from baseline measures were matched to at least one 1 patient with same clinical characteristics.
- In 11 patients with missing baseline clinical characteristic(s), imputation was performed based on available factors.

Results (cont'd)

- Table 2 shows the results of PC score comparisons between patients treated with or without nal-IRI obtained with or without imputation of missing values.
- Prior to imputation, patients treated with nal-IRI had better increments in EORTC QLQ-C30 scale change PC scores than non-users, indicating better post-treatment HR-QoL increments (1st PC: +0.45 vs −0.34, $P = 0.0479$; 4 PCs multivariate comparison: $P = 0.0052$)[F].
- Comparable results were found after imputation of missing values using either
  - Predictive model (1st PC: +0.30 vs −0.14, P=0.0214; 4 PCs multivariate comparison: $P = 0.0035$)
  - Population-matched values (1st PC: +0.34 vs −0.10, $P = 0.0272$; 4 PCs multivariate comparison: $P = 0.0007$).

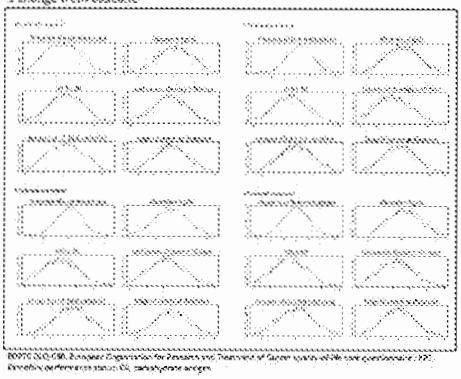
Tables and Figure

Table 1. Baseline characteristics in patients with and without EORTC QLQ-C30 scales week-8 change from baseline measures

Clinical baseline characteristics, N (%)	EORTC QLQ-C30 scale change measures			
	Missing (n = 268)		Non-missing (n = 127)	
Karnofsky performance status ≥ 90	83.6	(169)	77.9	(99)
Albumin level ≥ 4g/dL	50.0	(98)	55.2	(56)
Amount of CA 19-9 ≥ 40U/ml	60.2	(77)	58.1	(52)
Stage IV cancer at diagnosis	42.6	(108)	42.8	(59)
At least 40 days since last anticancer therapy	55.6	(74)	53.4	(63)
Presence of liver metastases	66.2	(98)	72.2	(88)

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; CA, carbohydrate antigen.

Figure 1. Estimated densities of the associations between baseline clinical characteristics and principal component scores for EORTC QLQ-C30 scale week-8 change from baseline



EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; KPS, Karnofsky performance status; CA, carbohydrate antigen.

Table 2. Comparison of principal components scores for week-8 change from baseline in EORTC QLQ-C30 scales according to missing value imputation method: 5-FU/LV + nal-IRI vs. 5-FU/LV alone

Imputation method	Number of patients	Mean (SE)	Number of patients	Mean (SE)	Mean difference (SE)	95% CI	P-value
No imputation							
1st PC	52	0.45 (0.20)	79	−0.34 (0.16)	0.79 (0.26)	0.28 ; 1.30	0.0026
2nd PC	52	−0.08 (0.12)	79	0.05 (0.10)	−0.13 (0.16)	−0.45 ; 0.19	0.4208
3rd PC	52	0.16 (0.10)	79	−0.10 (0.08)	0.26 (0.13)	0.00 ; 0.52	0.0496
4th PC	52	−0.03 (0.10)	79	0.02 (0.08)	−0.04 (0.13)	−0.30 ; 0.21	0.7426
Regression prediction							
1st PC	268	0.30 (0.07)	149	−0.14 (0.09)	0.44 (0.11)	0.23 ; 0.65	0.0002
2nd PC	268	0.10 (0.05)	149	0.02 (0.06)	0.08 (0.08)	−0.08 ; 0.24	0.3304
3rd PC	268	0.02 (0.04)	149	−0.01 (0.05)	0.03 (0.06)	−0.09 ; 0.15	0.6004
4th PC	268	0.00 (0.04)	149	0.00 (0.04)	0.00 (0.05)	−0.10 ; 0.10	0.9967
Population matching							
1st PC	268	0.34 (0.07)	149	−0.10 (0.09)	0.44 (0.11)	0.23 ; 0.65	0.0002
2nd PC	268	0.10 (0.05)	149	0.02 (0.06)	0.08 (0.08)	−0.08 ; 0.24	0.3304
3rd PC	268	0.02 (0.04)	149	−0.01 (0.05)	0.03 (0.06)	−0.09 ; 0.15	0.6004
4th PC	268	0.00 (0.04)	149	0.00 (0.04)	0.00 (0.05)	−0.10 ; 0.10	0.9967

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; PC, principal component.

Conclusion

- Data missingness was not at random and induces potential biases due to e.g. differential mortality between treatment groups.
- The improvement in HR-QoL with nal-IRI + 5-FU/LV vs. 5-FU/LV observed in the post hoc analysis of NAPOLI-1 results was strengthened after imputation of missing values.
- Results were comparable regardless of the imputation method considered (regression vs. matching).

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PCN176

EFFECT OF ENZALUTAMIDE ON SPECIFIC SYMPTOMS AND FUNCTIONAL AREAS IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: A NOVEL ANALYTIC APPROACH

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OBJECTIVES: Enzalutamide has a positive impact on outcomes assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument, including slower overall decline in total FACT-P scores among patients with metastatic castration-resistant prostate cancer (mCRPC). This research aimed to describe specific benefits of enzalutamide through novel exploratory analyses of individual symptom and functioning items of FACT-P in mCRPC clinical trials. **METHODS:** FACT-P was administered at baseline and every 12 weeks during placebo-controlled trials of enzalutamide in chemotherapy-treated (AFFIRM) and chemotherapy-naïve (PREVAIL) mCRPC patients. Scores on FACT-P 0–4 scales were transformed to 0–100% to facilitate interpretation; higher scores indicated reduced symptoms and better functioning. Descriptive analyses were performed on change from baseline scores. **RESULTS:** In both trials, the impact of enzalutamide on items related to pain was relatively robust compared with other symptom items. In AFFIRM, at week 25, men receiving enzalutamide reported a median decrease (deterioration) of 3% across all FACT-P pain items, compared with a 16% decrease in those receiving placebo. Throughout both studies, enzalutamide delayed worsening in various aspects of social, physical, and emotional functioning versus placebo, including ability to work and enjoy life, worrying about dying, and feeling sad. Throughout both trials, there was little impact of enzalutamide on symptom and functioning items assessing urinary and sexual symptoms compared with placebo. **CONCLUSIONS:** The exploratory analysis indicates enzalutamide preserves mCPRC patients' level of symptomatology and physical functioning, supporting overall health-related quality-of-life scores previously reported. The analyses suggest enzalutamide may prevent a progression in pain and preserve patients' standard of living, ability to work, and emotional views of their disease. Given a lack of decline in the context of a chronic condition, patients may deem these effects as positive. Analyses of individual items are an innovative and valuable approach to interpreting treatment effects from broad patient-reported outcome measures.

PCN177

UNDERSTANDING KEY SYMPTOMS, SIDE EFFECTS AND IMPACTS OF HR+ AND HER2- ADVANCED BREAST CANCER: LITERATURE REVIEW AND EXPERT INTERVIEWS

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OBJECTIVES: While patients with HR+/HER2- advanced breast cancer experience a wide range of disease-related symptoms, side effects, and impacts, identifying the most important and relevant concepts of interest can allow for generalization of the patient experience. This study sought to describe these commonalities based on a review of the literature and interviews with therapeutic experts. **METHODS:** Literature reviews were conducted in MEDLINE®, Embase, and PsycINFO® to identify articles relevant to study goals (search terms included "breast cancer," "metastatic," "advanced," and "symptoms OR side effects OR impacts"; articles published from March 2005 to February 2016 were considered for inclusion). Individual telephone interviews were conducted with five US-based breast cancer oncologists. **RESULTS:** Literature reviews identified 13 eligible studies. Disease-related symptoms were described for six metastatic sites. Six treatment types and their side effects were described. Nausea/vomiting, pain, weight changes, and diarrhea were reported in at least half of these treatments. Emotional and physical impacts of cancer and treatment were reported most frequently. Interviews with experts identified disease-related symptoms for 10 metastatic sites. Pain, fatigue, loss of appetite, and nausea were reported as symptoms generalizable to all HR+/HER2- breast cancer patients, regardless of location of metastasis. Pain and fatigue were reported by three experts as both the most severe and most bothersome disease-related symptoms. Four types of treatment were discussed. Fatigue was reported by three experts as generalizable to all metastatic sites discussed, and relevant to all treatments discussed. The majority of reported impacts focused on physical functioning. **CONCLUSIONS:** Literature and expert perspectives suggest that patients with HR+/HER2- advanced breast cancer commonly experience pain and fatigue as disease-related symptoms; nausea/vomiting, pain, weight changes, diarrhea, and fatigue as treatment-related side effects; and impacts on physical functioning, regardless of the location of their metastases.

PCN178

EXPERIENCES OF TREATMENT-RELATED SIDE EFFECTS AND SUPPORTIVE CARE WITH KOREAN MEDICINE IN WOMEN WITH BREAST CANCER - A FOCUS GROUP STUDY

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OBJECTIVES: In some countries, clinical practice guidelines have included acupuncture as supportive care for breast cancer survivors (BCS). This study aimed to explore experiences of treatment-related side effects and supportive care among Korean BCS. **METHODS:** Focus group interview was conducted with six Korean women with breast cancer at stage I-III. Participants were recruited through snowballing. Interview was audio-recorded and transcribed verbatim. NVivo-11 was used to code the data into themes. **RESULTS:** Two major themes were identified: (1) experiences of the Western-medicine, including side effects, communication with doctors, and costs; (2) experiences of Korean-medicine, including the same as above. Participants had mean age of 48.7 (SD 6.8) years and had survived for 1-7 years without recurrence. All participants experienced Western-medicine in treatment phase and reported impairment of physical, emotional, and social functioning during and after Western-medicine treatment. Korean-medicine was used after treatments ended. The negative responses from Western-medicine doctors were the most important factor keeping participants from accessing Korean-medicine when treatment-related side effects occurred. For this reason, some participants used Korean-medicine without disclosure. Participants usually acquired information about Korean-medicine from online community or other BCS, which was another important factor because it raised concerns about side effects and credibility of Korean-medicine. High cost of Korean-medicine was also reported as barrier in using Korean-medicine. When getting the cancer treatment, participants tended to endure their treatment-related side effects rather than to resolve them or express needs. Needs of information about effective and economical supportive care were identified. **CONCLUSIONS:** Korean BCS may be at risk of greater physical or emotional distress during treatment period. Findings suggest that there is a high need for supportive care to relieve treatment-related side effects and improve patients' quality-of-life. Furthermore, developing a systematic guidance or credible information sources is warranted to help patients find the best supportive care options.

PCN179

IMPUTING MISSING VALUES TO ESTIMATE HEALTH-RELATED QUALITY OF LIFE (HR-QOL) IN METASTATIC PANCREATIC CANCER (MPC) TREATED WITH 5-FLUOROURACIL AND LEUCOVORIN, WITH AND WITHOUT LIPOSOMAL IRINOTECAN (NAL-IRI)

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OBJECTIVES: The survival benefits of nal-IRI+5-fluorouracil/leucovorin vs fluorouracil/leucovorin in mPC patients who progressed after prior gemcitabine-based therapy were demonstrated in a phase 3 study (NAPOLI-1); preplanned analyses of QoL demonstrated no differences between treatment groups. Post hoc analysis of NAPOLI-1 EORTC-QLQ-C30 questionnaire results showed that HR-QoL change was improved with nal-IRI+5-fluorouracil/leucovorin. However, about half of randomized patients had missing scores. We investigated how imputation of missing values would affect initial findings. **METHODS:** A principal component (PC) analysis was performed on EORTC-QLQ-C30 scales week-6 changes. For patients with missing information, clinical data-based imputation was performed using either regression predictors or median value of study population-matched controls. **RESULTS:** Of 266 randomized patients, 122 had baseline and week-6 EORTC-QLQ-C30 scale measures and were used for PC analysis and imputation model development. Four PCs explaining 59% of variance were retained. With positive weights on Global Health Status/Quality of Life (GHS/QL) and functioning scales and negative weights on financial difficulties and symptoms scales, the first PC (PC1: variance explained 34%) reflected general HR-QoL. Prior to imputation, patients treated with nal-IRI+5-fluorouracil/leucovorin had better HR-QoL PC score week-6 increments vs 5-fluorouracil/leucovorin (PC1: +0.45 vs −0.34, P=0.0478; 4-PC multivariate comparison: P=0.0051). The baseline predictors included in the imputation model were Karnofsky performance status ≥90, albumin ≥4g/dL, CA19-9 ≥403U/mL, stage IV cancer at diagnosis, presence of liver metastases, and ≥40 days since prior anticancer therapy. The population was matched using these predictors, excluding CA 19-9 (94% patients with ≥1 match). Comparable results were found using either predictive model (PC1: +0.30 vs −0.14, P=0.0214; 4-PC multivariate comparison: P=0.0015) or population-matched values (PC1: +0.34 vs −0.10, P=0.0271; 4-PC multivariate comparison: P=0.0007). **CONCLUSIONS:** The improvement in HR-QoL with nal-IRI+5-fluorouracil/leucovorin observed in the post hoc analysis of NAPOLI-1 results remained comparable after imputation of missing values in this imputation exercise.

PCN180

NON-PROGRESSION ON TREATMENT WITH AVELUMAB CONTRIBUTES TO GAINS IN HEALTH UTILITY SCORES IN PATIENTS WITH METASTATIC MERKEL CELL CARCINOMA

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OBJECTIVES: Patient-reported outcomes are an important component of drug benefit/risk and reimbursement evaluation, but limited data are available from patients with rare tumors, such as Merkel cell carcinoma (MCC). This study aimed to assess differences in health utility scores between non-progressing and progressing patients with metastatic MCC treated with anti-PD-L1 avelumab. **METHODS:** EQ-5D data collected from a phase 2 single-arm trial (NCT02155647) of 88 patients with chemotherapy-treated metastatic MCC were analyzed. The EQ-5D was assessed at baseline, week 7, every 6 weeks thereafter, and at the end-of-treatment visit. At each assessment, tumor response was determined by radiologically by an independent review committee per RECIST v1.1 performed within approximately 7 days of the EQ-5D assessment. EQ-5D utilities were calculated based on US and UK value sets. Linear mixed models were fitted to EQ-5D data, including progressive disease (vs complete response/partial response/stable disease) as a single time-varying covariate. In sensitivity analyses, estimates were adjusted for grade 3-4 adverse events (AEs) ongoing at EQ-5D assessment and treatment-related AEs of any grade. **RESULTS:** Among 70 evaluable patients, 247 observations were analyzed. Utility based on the US (UK) value sets was 0.8058 (0.8327) in the non-progression health state and 0.7120 (0.7130) in the

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ORIGINAL ARTICLE

Biweekly Low-Dose Sequential Gemcitabine, 5-Fluorouracil, Leucovorin, and Cisplatin (GFP): A Highly Active Novel Therapy for Metastatic Adenocarcinoma of the Exocrine Pancreas[#]

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ABSTRACT

Phase II studies have suggested an improved response rate and acceptable toxicity profile associated with gemcitabine combinations compared to gemcitabine alone for treatment of metastatic adenocarcinoma of the pancreas. The GFP regimen (gemcitabine, 5-fluorouracil, leucovorin, and cisplatin) is based on laboratory evidence of disease-specific chemotherapy interaction.[8] This retrospective analysis examined the outcome of 49 consecutive patients with histologically confirmed metastatic pancreatic adenocarcinoma treated between July 1998 and September 2000. Day 1 treatment consisted of gemcitabine 500 mg/m^2 over 30 minutes and then leucovorin 300 mg bolus, 5-fluorouracil (5-FU) 400 mg/m^2 bolus, followed by infusional 5-FU 600 mg/m^2 over 8 hours. Day 2 consisted of leucovorin 300 mg bolus, 5-FU 400 mg/m^2 bolus, followed by cisplatin 50–75 mg/m^2 over 30 minutes and then infusional 5-FU 600 mg/m^2 over 8 hours. Treatment was administered every 2 weeks. Median patient age was 61.5 years, 74% were men, and 20 patients had refractory disease (11 patients had disease progression upon gemcitabine-based therapy). Grade 3–4 toxic effects (% patients) consisted of neutropenia (30%), thrombocytopenia (14%), anemia (8%), and neutropenic fever (2%). Grade 3–4 nonhematological toxicities (% patients) consisted of neuropathy (14%), ototoxicity (8%), nephrotoxicity (6%), nausea/vomiting (14%), and mucositis (10%). The majority of dose reductions were made for neuropathy or cytopenias. Filgrastim and erythropoietin were given as needed to promote dose intensity. Eight patients attained a partial response (PR) by RECIST criteria. Fourteen had stable disease (SD). Two patients attaining PR and two attaining SD had progressive disease with prior

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gemcitabine-based therapy. The median time to disease progression (TTP) from GFP start was 9 weeks. For all 49 patients, the median overall survival (OS) from GFP start was 10.6 months, 12-month survival was 46%, and 24-month survival was 30%. Notably, upon disease progression, 31 patients continued to receive the GFP regimen with irinotecan 80 mg/m^2 inserted on day 1 following gemcitabine, the G-FLIP regimen (gemcitabine, 5-fluorouracil, leucovorin, irinotecan, and cisplatin). Measured from G-FLIP initiation, the TTP for the 31 patients treated sequentially was 10 weeks, and for the 14 patients attaining SD or PR the TTP was 25 weeks. The median overall survival measured from GFP initiation was 11.8 months. The response rate, non-cross resistance, TTP, OS, and tolerability warrant prospective development of this novel combination. This experience also demonstrates that adding a single new drug such as irinotecan to the same first-line chemotherapy combination upon disease progression may be an important alternative for the treatment of relapsed/resistant cancer.

Key Words: Gemcitabine; 5-Fluorouracil; Cisplatin; Pancreatic cancer; Metastatic.

INTRODUCTION

Approximately 30,000 cases of adenocarcinoma of the exocrine pancreas are diagnosed in the United States each year. The majority of these tumors are unresectable at the time of diagnosis and almost all patients develop metastatic disease. The response rate to single-agent chemotherapy in the metastatic setting is less than 10%, with a median survival of less than 6 months. Gemcitabine produces clinical benefit response and improves survival in patients with advanced and metastatic carcinoma of the exocrine pancreas. In a phase III clinical trial, clinical benefit response (CBR) derived from a composite of pain control, performance status, and weight stabilization/gain was obtained by 24% of patients treated with gemcitabine. The median survival was 5.65 months and 1-year survival was 18%.[1]

The effectiveness of gemcitabine may be improved by altering the standard infusion schedule to a fixed dose rate. A phase II trial randomized patients to either receive gemcitabine 2200 mg/m^2 over a standard 30-minute infusion or gemcitabine 1500 mg/m^2 at a fixed rate of 10 mg/m^2/min weekly × 3 every 4 weeks. The fixed-rate infusion was associated with a higher response rate of 16.6% vs. 2.7%, longer median survival of 6.1 vs. 4.7 months, and a higher 1-year survival rate, 23% vs. 0%.[2]

Gemcitabine's unique mechanism of action and favorable toxicity profile have prompted development of numerous combinations. Preclinical as well as clinical data suggest that an additive or synergistic effect is attained by combining cisplatin and gemcitabine. Heinemann et al. administered gemcitabine 1000 mg/m^2 weekly × 4 in combination with cisplatin 50 mg/m^2 on days 1 and 15 to 41 patients. Therapy was well tolerated without major compromises in quality of life. Grade 3 and 4 neutropenia was the major toxicity (29% and 6%, respectively). An overall response rate of 11.5%, median survival of 8.3 months, and a 1-year survival of 28% was demonstrated in 35 patients evaluable for response.[3] A phase II trial randomized patients with unresectable or metastatic pancreatic cancer to standard infusion of gemcitabine 1000 mg/m^2 weekly × 3 every 4 weeks with or without cisplatin 25 mg/m^2. The cisplatin arm was associated with a response rate of 31% compared to a 10% response rate associated with gemcitabine alone.[4]

The addition of 5-fluorouracil (5-FU) administered as a prolonged intravenous infusion to standard infusional gemcitabine or cisplatin has demonstrated good patient tolerability as well as improved response rates and clinical benefit compared to the reported activity of these drugs as single agents. Gemcitabine with 5-FU as a 5-day continuous infusion was associated with a clinical benefit response in 7 of 11 patients and maintained for 26.5 weeks.[5] Fifty-seven percent of patients attained a clinical benefit response and 19% had objective responses in a trial of gemcitabine and 5-FU 3 gr/m^2 over 48 hours. The median follow-up was 16 weeks and median progression-free survival was 12 weeks.[6] Twenty-six patients were given 5-FU as a continuous infusion 4.5 gr over 72 hours in combination with cisplatin as a 1-hour infusion every 3 weeks. A partial or minor response was seen in 10 of the 20 patients evaluable for response. The median time to disease progression (TTP) was 4 months and the median survival was 11 months.[7]

Preclinical studies have evaluated combinations of gemcitabine, cisplatin, 5-fluorouracil, mitomycin C, and irinotecan in ex vivo unreated gastrointestinal tumors using an ATP inhibition assay. Favorable drug interactions were demonstrated when gemcitabine was

coupled with either cisplatin, irinotecan, or fluorouracil.[8] The GFP regimen was designed to approximate sequence-dependent additive or synergistic interactions while attempting to minimize sequence-dependent toxic effects among these three drugs. The dosage, schedule, and sequence were based on preclinical data as well as phase I and II trials of the components as doublets.[2–8] Based on the reported tolerability and interaction among all of these drugs given as doublets, we hypothesized that a three-drug combination of gemcitabine, 5-FU, and cisplatin (GFP) would be an effective therapy for patients with metastatic adenocarcinoma of the exocrine pancreas.

METHODS

Patients

This retrospective study analyzed the outcome of 49 consecutive patients treated with GFP. All patients had histologically confirmed metastatic adenocarcinoma of the pancreas. Characteristics of the patients are outlined in Table 1. Patients were treated between July 1998 and September 2000. All patients had measurable disease with at least one lesion measurable by computed tomography (CT). Upon disease progression, 31 patients continued to receive the GFP regimen with irinotecan 80 mg/m^2 inserted on day 1 following gemcitabine, the G-FLIP regimen (gemcitabine, 5-fluorouracil, leucovorin, irinotecan, and cisplatin). Institutional review board exemption was granted for this case series analysis, which used existing data without associated patient identifiers.

Table 1. Patients characteristics on study entry.

Characteristics	No.	% Patients
Total patients	49	100
Sex		
Male	36	74
Female	13	26
Median age	61.5	
Stage IV	49	100
Site of metastases		
Liver	29	60
Lung	8	16
Peritoneum	6	12
Other sites	4	8
Two or more sites	6	12

Response Criteria and Toxicity

History and physical exam were obtained prior to each biweekly chemotherapy course. Complete blood counts, liver function profiles, serum electrolytes, and serum creatinine were planned weekly. Toxicity was graded according to the common toxicity criteria of the National Cancer Institute.[9]

CT scans of the chest, abdomen, and pelvis as well as tumor markers (CA 19-9 and CEA levels) were obtained at baseline and after every third or fourth chemotherapy course or sooner if disease progression was clinically suspected. Elevation of tumor markers was correlated with CT scans to evaluate for tumor progression. RECIST criteria were retrospectively applied to grade the responses. In order to apply the RECIST criteria, a measurable target lesion of at least 10-mm in one dimension must have been identified by spiral CT.

The RECIST criteria, which take into account the measurement of only the longest diameter of each target lesion, define a complete response as the disappearance of all target and nontarget lesions, no new lesions, and normalization of all tumor markers. Partial response is defined as at least a 30% decrease in the sum of the longest diameters of the target lesion from baseline, nonprogressive disease in nontarget lesions, and no new lesions. Tumor markers may remain above normal. Progressive disease (PD) is defined as at least a 20% increase in the sum of the longest diameters of the target lesions, taking as a reference the smallest sum of long diameters since treatment started or the appearance of new lesions. Stable disease is defined as insufficient shrinkage to qualify for either partial response or increase in size insufficient to qualify for progressive disease. Responses were confirmed by an independent radiologist.

TREATMENT

The GFP treatment consisted of a 2-day therapy repeated every 2 weeks. Day 1 treatment consisted of sequentially administered gemcitabine 500 mg/m^2 via fixed dose rate infusion 10 mg/m^2/min, leucovorin 300 mg bolus, 5-FU 400 mg/m^2 bolus, followed by infusional 5-FU 600 mg/m^2 over 8 hours. Day 2 consisted of leucovorin 300 mg bolus, 5-FU 400 mg/m^2 bolus, followed by cisplatin 50–75 mg/m^2 and then infusional 5-FU 600 mg/m^2 infusion over 8 hours (Table 2). Previously treated patients who had developed NCI grade 3 or worse thrombocytopenia with prior therapy

Table 2. GFP treatment schema.

Day 1	Day 2
Gemcitabine 500 mg/m^2 IV 10 mg/m^2/min	Leucovorin 300 mg IV over 30 minutes
Leucovorin 300 mg IV over 30 minutes	5-FU bolus 400 mg/m^2 IV over 10 minutes
5-FU bolus 400 mg/m^2 IV over 10 minutes	Cisplatin 50–75 mg/m^2 IV over 30 minutes
5-FU 600 mg/m^2 IV over 8 hours	5-FU 600 mg/m^2 IV over 8 hours

were assigned to receive cisplatin 50 mg/m^2. Anti-emetic prophylaxis was administered 30 minutes prior to chemotherapy on days 1 and 2 and consisted of granisetron 2 mg orally and decadron 10 mg IV. Intravenous normal saline at 200 cc/hr with lasix 10 mg IV was given to ensure urine output of at least 100 cc/hr prior to cisplatin administration. Normal saline hydration was continued for 6 hours at 125 cc/hr after completion of cisplatin infusion. Dose modifications and/or deletions to address specific toxicities were made at the discretion of the treating physician. In particular, renal toxicity, neurotoxicity, and vomiting prompted cisplatin dose reduction/deletion. Mucositis required modification of 5-Fu dosages. Filgrastim and erythropoietin were used at the discretion of the treating physician to promote dose intensity. Patients with disease progression continued to receive the GFP regimen with irinotecan 80 mg/m^2 inserted on day 1 following gemcitabine, the so-called G-FLIP regimen (gemcitabine, 5-fluorouracil, leucovorin, irinotecan, and cisplatin).

STATISTICS

Survival time (OS) and TTP were calculated from the first day of therapy until death, disease progression, or last follow-up. The probability of survival was calculated using the Kaplan-Meier method.

RESULTS

The outcomes of 49 consecutive patients treated between July 1998 and September 2000 were retrospectively analyzed. The median patient age was 61.5 years, and 36 were men. All patients had metastatic adenocarcinoma of the exocrine pancreas, 29 patients had liver metastasis, 8 lung metastases, 6 peritoneal metastases, and 6 had two or more sites of disease (Table 1). Twenty patients received prior therapies; 11 patients had disease progression upon gemcitabine-based therapy (Table 3).

A total of 214 cycles of GFP were administered. The median number of cycles administered was 4.2 (range 2–18). The median dose intensity for each drug, expressed as mg/m^2/2 weeks, and percentage of intended dose (%) were as follows: gemcitabine 461 (92%), 5-FU bolus 343 (85%), 5-FU infusion 600 (100%), and cisplatin 50 (66%) (Table 4). Full-intensity chemotherapy was most often decreased to allow recovery from cytopenias. Less frequently, specific drug doses were modified at the discretion of the treating physician to address specific toxicities.

The GFP regimen was in general well tolerated. Grade 3–4 toxic effects were mainly hematological, manageable with growth factor and blood product support, and rarely were associated with significant clinical events. These toxicities consisted of grade 3–4 neutropenia in 15/49 patients (30%), thrombocytopenia in 7/49 patients (14%), anemia in 4/49 patients (8%), and neutropenic fever in 1/49 patients (2%). Grade 3–4 nonhematological toxic side effects were rare. Per-patient grade 3–4 neuropathy occurred in 2% of patients, nausea 2%, and vomiting 6%. Grade 1–2 nonhematological toxicities per patient consisted of neuropathy 14%, ototoxicity 8%, nephrotoxicity 6%, nausea/vomiting 14%, and mucositis 10% (Table 5).

Response and survival outcomes are summarized in Table 6. Eight patients attained partial response (16%) and 14 (28%) had stable disease. Two patients with partial response and two with stable disease had disease progression with prior gemcitabine-based therapy. Nine previously treated with non-gemcitabine based regimens

Table 3. Prior therapies.

Treatment	No.	% Patients
Gemcitabine	7	14
Gemcitabine/5-FU	1	2
Gemcitabine/CPPD	3	6
Others regimens	9	18
Total	20	40

Table 4. Dose intensity.

Median number of cycles	4.2
Range	2–18
Median dose intensity	mg/m^2/2 weeks (% intended dose)
Gemcitabine	461 (92%)
5-FU bolus	342.9 (85%)
5-FU infusion	600 (100%)
Cisplatin	50 (66%)

had progression upon treatment with the GFP regimen. Median TTP from GFP start was 9 weeks and 20 weeks for the 22 patients with partial or stable disease, respectively. The median overall survival from GFP start was 10.6 months (95% confidence interval: 6.04 to 15.16 months). The 12-month survival was 46%, and 24-month survival was 30%. Upon disease progression, 31 patients were able to continue chemotherapy with the G-FLIP regimen. The response rates and survival outcomes for this sequentially treated group are outlined in Table 7. The TTP was 10 weeks for all 31 patients and 25 weeks for the patients attaining SD or PR. For this sequentially treated group, the median survival was 11.8 months from initiation of GFP regimen. The 1-year survival was 47% and the 2-year survival was 24% [Fig. 1].

CONCLUSION

Attempts to develop effective systemic therapies for patients with metastatic pancreatic cancer disease have achieved definite but modest success. The most extensively studied single agent has been 5-FU using a variety of doses and schedules, but the response rate rarely exceeds 20%, and no consistent effect on disease-related symptoms or survival has been demonstrated.[10] Gemcitabine, a nucleoside analog with broad spectrum of antitumor activity, has showed a response rate up to 11%, better survival response, and improvements in disease-related symptoms compared with bolus 5-fluorouracil.[14]

The initial response rates reported for several multiagent regimens, such as the Mallinson regimen (5-FU, methotrexate, vincristine, and cyclophosphamide induction followed by maintenance 5-FU and mytomycin)[11]; the 5-FU, doxorubicin, and mitomycin (FAM) regimen[12]; and the streptozotocin, mitomycin, and 5-FU (SMF) regimen[13] appeared to herald advances in the treatment of patients with advanced pancreas cancer. Unfortunately, subsequent randomized phase III trials

Table 5. Toxic side effects (percent of patients).

	Grade 3–4	Grade 1–2
Hematological		
Neutropenia	30	55
Thrombocytopenia	14	47
Anemia	8	70
Neutropenic fever	2	0
Nonhematological		
Neuropathy	2	14
Ototoxicity	0	8
Nephrotoxicity	0	6
Nausea	2	14
Vomiting	6	8
Mucositis	0	10

Table 6. GFP outcomes.

	No.	% Patients
All patients	49	100
Partial response (PR)	8	16
Stable disease (SD)	14	28
Median TTP		9 weeks
Median TTP in patients with PR or SD		22 weeks
Median overall survival		10.6 months
12-Month survival		46%
24-Month survival		30%
Subsequent therapies		33
G-FLIP		31 patients
Other regimens		2 patients

Table 7. G-FLIP outcomes: patients treated sequentially with GFP and G-FLIP.[a]

	No.	% Patients
All patients	31	100
Partial response (PR)	7	23
Stable disease (SD)	7	23
Progressive disease	17	54
TTP (all patients)		10 weeks
TTP pts w/SD or PR		25 weeks
Median survival measured from initiation of GFP		11.8 months
1-year survival		47%
2-year survival		24%

[a] G-FLIP, irinotecan 80 mg/m^2 inserted on day 1 of GFP regimen.

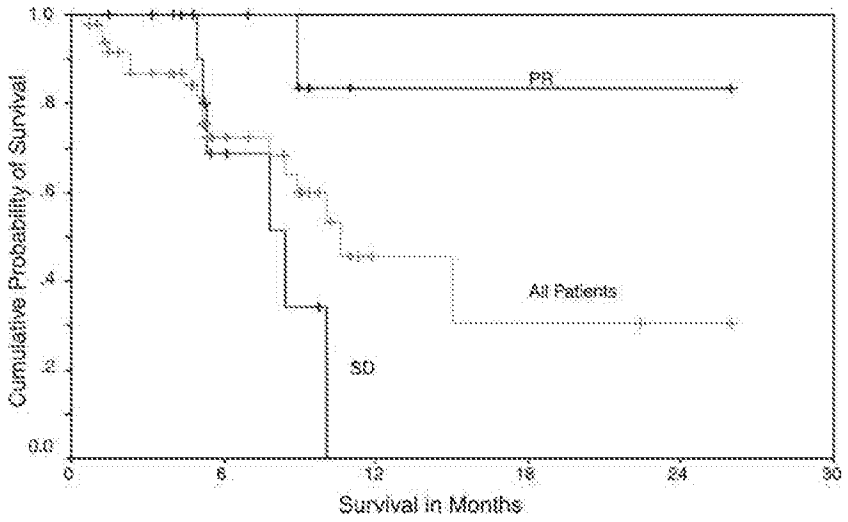

Figure 1. Patient survival curves.

failed to confirm the initial survival outcomes observed in these trials.

Attempts at developing two-, three-, and four-drug gemcitabine-based regimens deserve attention. Several phases II studies have demonstrated good patient tolerability and high response rates when gemcitabine is combined with cisplatin.[13] A phase II trial was done to evaluate the efficacy and toxicity of cisplatin, epirubicin, 5-fluorouracil continuous infusion and gemcitabine (PEF-G) in patients with stage IV pancreatic cancer. Thirty-nine consecutive patients were treated, the response rate was 58% (25 PR), and the median overall survival was 9.4 months. The clinical benefit response was 78% and 1-year survival was 48%.[15]

GFP is a regimen based on laboratory evidence of disease-specific chemotherapy interaction and was designed to approximate the known sequence-dependent synergistic activities and minimize sequence-dependent toxic effects among the three drugs.[8] Pharmacokinetic studies have not demonstrated a difference between sequences of gemcitabine and cisplatin when the two drugs are given 4 hours apart. However, when gemcitabine and cisplatin administration are separated by 24 hours, cisplatin administration before gemcitabine leads to the highest gemcitabine-triphosphate levels in white blood cells, which is associated with significantly more leukopenia. Although gemcitabine given 24 hours prior to cisplatin, as in the GFP regimen, is associated with a 2.1-fold lower plasma AUC of cisplatin, there is a tendency for this sequence to be associated with an increase in 24-hour retention of platinum-DNA adducts.[16]

In vitro studies support the sequence-dependent synergistic relationship between 5-Fu and cisplatin. Using a HST-1 human squamous carcinoma cell line, 5-Fu followed by cisplatin was more active than the reverse sequence. Synergistic activity is maximal when the interval between 5-Fu and cisplatin is at least 24 hours. A significant reduction of DNA interstrand cross-link removal occurred in cells exposed to 5-Fu prior to cisplatin with a drug-free interval of 48 hours compared to cells exposed to cisplatin alone or immediately preceded by 5-FU. This finding suggests that 5-FU modulates the repair of platinum-DNA adducts, thereby potentiating antitumor activity.[17]

There have been no published analyses comparing sequences of 5-Fu and gemcitabine. As a potential inhibitor of ribonucleotide reductase, gemcitabine may inhibit the formation of dUMP, thereby enhancing the activity of 5-Fu and leucovorin. Based on these preclinical and clinical data, the dosage, schedule, and sequence of GFP was developed.[2–8]

The GFP regimen was well tolerated. While quality-of-life assessments were not done, nonhematological toxicity was mild with a low incidence of grade 3–4 nauseas, vomiting, neuropathy, nephrotoxicity, and mucositis. Grade 3–4 hematological toxicities were easily managed and rarely associated with clinically significant events. Blood product and growth factor

supports were used at the discretion of the treating physician.

The median overall survival and response rate observed with the use of the GFP regimen in this retrospective, exploratory analysis compares favorably with single-agent therapy. Despite a 16% partial response obtained with this regimen, the improved survival may be associated with an objectively measured stable disease rate of 28%.

Sequential treatment in over half of our patients may have contributed to survival outcomes with the GFP regimen. Upon disease progression, 31 patients were able to continue subsequent systemic therapy with G-FLIP. The median time to progression was 10 weeks for all patients, 25 weeks for patients with SD or PR, and the median overall survival from GFP start was 11.8 months. These results demonstrate that modifying an upfront chemotherapy regimen by inserting an additional drug (irinotecan) may overcome resistance to the GFP regimen.[18]

The significant rate of clinical benefit, favorable toxicity profile, and unique mechanism of action gemcitabine warrant its integration in chemotherapy combinations. The response rate, tolerability, and overall survival observed with the GFP regimen warrant prospective disease-specific study of this regimen in pancreatic cancer and biliary malignancies.[19]

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A phase I study of nanoliposomal irinotecan and 5-fluorouracil/folinic acid in combination with interleukin-1-alpha antagonist for advanced pancreatic cancer patients with cachexia (OnFX)

Katelyn M. Atkins[1], Jun Gong[1], Mourad Tighiouart[2], Samuel J. Klempner[3], Richard Tuli[3], Veronica Placencio-Hickok[1], Andrew E. Hendifar[1]
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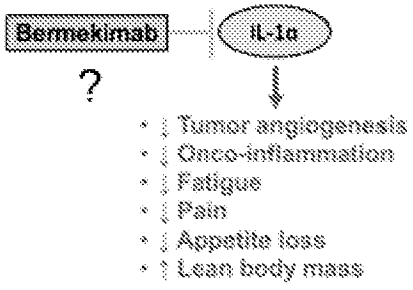
BACKGROUND

- Patients with pancreatic cancer have the highest rate of weight loss among all advanced cancers. Of which, the majority develop **cachexia**, characterized by progressive and involuntary loss of weight and skeletal muscle mass.
- In *preclinical studies*, **interleukin-1-alpha (IL-1α) antagonism** has been found to neutralize tumor angiogenesis and onco-inflammation.
- *Early phase single-agent studies* in cancer cachexia have demonstrated **increased lean body mass and decreased fatigue, pain, and appetite loss**.

IL-1α antagonism:



OBJECTIVES

- Establish the **safety** of an IL-1α antagonist (**Bermekimab**) in combination with nanoliposomal irinotecan (**Nal-Iri**) and 5-fluorouracil (**5FU**)/folinic acid (**FA**) in patients with **advanced pancreatic adenocarcinoma and cachexia** who have *failed gemcitabine-based chemotherapy*.

Bermekimab ◈ **Nal-Iri** ◈ **5FU/FA**

- **Primary objective**:
  - Assess the MTD of Bermekimab in combination with Nal-Iri and 5FU/FA.
- **Secondary objectives**:
  - Assess weight, lean body mass, inflammatory cytokines, OS, PFS, patient QOL, and functional status.

METHODS

- **Single arm, single center, phase I study.**
- MTD = probability of dose-limiting toxicities at MTD is θ = 0.33.
- The first cohort (up to 3 patients) will receive:
  - **7.5 mg/kg Bermekimab**
  - **50 mg/m2 Nal-Iri**
  - **2000 mg/m2 5FU/400 mg/m2 FA**

METHODS, CONT'D

- Subsequent doses will be determined by the EWOC algorithm.
- Treatment is administered on days 1 and 15 of each 28-day cycle.

- **Key inclusion criteria**:
  - Advanced or locally advanced pancreatic adenocarcinoma that has progressed through or intolerant of gemcitabine-based chemotherapy
  - Cachexia (defined as > 5% unexplained weight loss 6 months prior to screening) or as documented by physician
  - ECOG PS 0-2 or KPS ≥ 60%
  - Normal organ and marrow function.
- Since January 2019, 23 patients have been screened and 21 enrolled.

Cedars Sinai

FUNDING

XBiotech IPSEN

Clinical trial information: NCT03207724

PANCREATIC CANCER

A phase I study of nanoliposomal irinotecan and 5-fluorouracil/folinic acid in combination with interleukin-1-alpha antagonist for advanced pancreatic cancer patients with cachexia (OnFX).

Katelyn Mae Atkins, Jun Gong, Mourad Tighiouart, Samuel J. Klempner, Richard Tuli, Veronica Placencio-Hickok, Andrew Eugene Hendifar

Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; Cedars-Sinai Medical Center, Los Angeles, CA; Massachusetts General Hospital, Boston, MA; Memorial Sloan Kettering Cancer Center, New York City, NY

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Abstract Disclosures

Abstract

TPS780

Background: Patients with pancreatic cancer have the highest rate of weight loss among all advanced cancers. Of which, the majority develop cachexia, characterized by progressive and involuntary loss of weight and skeletal muscle mass. In preclinical studies, interleukin-1-alpha (IL-1α) antagonism has been found to neutralize tumor angiogenesis and onco-inflammation. Early phase single-agent studies in cancer cachexia have demonstrated increased lean body mass and decreased fatigue, pain, and appetite loss. The present study aims to establish the safety of an IL-1α antagonist (Bermekimab) in combination with nanoliposomal irinotecan (Nal-Iri) and 5-fluorouracil (5FU)/folinic acid (FA) in patients with advanced pancreatic adenocarcinoma and cachexia who have failed gemcitabine-based chemotherapy. **Methods:** This is a single arm, single center, phase I study. The primary objective is to assess the maximum tolerated dose (MTD) of Bermekimab in combination with Nal-Iri and 5FU/FA. MTD is defined as the dose such that the probability of dose-limiting toxicities at MTD is $\theta = 0.33$. The first cohort of up to 3 patients will receive 7.5 mg/kg Bermekimab, 50 mg/m2 nanoliposomal irinotecan, 2000 mg/m2 5FU, and 400 mg/m2 FA and the subsequent doses will be determined by the escalation with overdose control (EWOC) algorithm. Treatment is administered on days 1 and 15 of each 28-day cycle. Key inclusion criteria include: advanced or locally advanced pancreatic adenocarcinoma that has

progressed through or intolerant of gemcitabine-based chemotherapy, cachexia defined as > 5% unexplained weight loss 6 months prior to screening or as documented by physician, ECOG PS 0-2 or KPS ≥ 60%, and normal organ and marrow function. Secondary objectives are to assess weight, lean body mass, inflammatory cytokines, overall survival, progression free survival, patient quality of life, and functional status. Since January 2019, 23 patients have been screened and 21 enrolled. Clinical trial information: NCT03207724.

Research Sponsor:

Ipsen and XBiotech, Inc

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Differentiation of liposomal irinotecan from dose-dense non-liposomal irinotecan in patient-derived pancreatic cancer xenograft tumor models.

Sandrine Barbier, Stephane Lezmi, Benjamin Beaufils, Adreanne Lortie, Marc Hillairet de Boisferon, Sophie Chaumeron, Anne Espirito, Stephan G Klinz, Arunthathi Thiagalingam, Florence Meyer-Losic

Ipsen Innovation, Les Ulis, France; Oncodesign, Dijon Cedex, France; Ipsen Bioscience, Cambridge, MA

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Abstract Disclosures

Abstract

e16724

Background: Liposomal irinotecan (ONIVYDE) is approved with 5-fluorouracil/leucovorin for metastatic pancreatic ductal adenocarcinoma (PDAC) post progression on gemcitabine-based therapy. The liposomal formulation prolongs payload residence time in the circulation and tumor lesions, where local conversion to the active metabolite SN-38 is thought to occur. The effect of the liposomal formulation on therapeutic index (TI) was assessed in patient-derived xenograft PDAC models (IM-PAN-001 [untreated tumor] and SA-PAN-077) in severe combined immunodeficiency mice. **Methods:** Liposomal (2.5, 10 or 50 mg/kg, intravenous [IV] 1 x weekly) and non-liposomal irinotecan (2, 5 or 10 mg/kg, IV 5 x weekly) were administered for 3 weeks (n = 8/group). Maximum tolerated dose (MTD) and clinically-relevant weekly doses (10 mg/kg, liposomal; 33 mg/kg, non-liposomal) of irinotecan were evaluated. TI was the ratio of MTD/lowest dose with anti-tumoral activity; time to reach tumor volume of 600 mm^3 (TTV600) was a proxy for overall survival. Tumor, plasma, gut and bone marrow were sampled for pharmacokinetics and safety assessment; DNA damage was evaluated via pH2AX and 53BP1 IHC. **Results:** The Table reports results of the more sensitive IM-PAN-001 model: TI of weekly liposomal irinotecan was 4-fold higher than for 5 x weekly non-liposomal irinotecan (TI was narrower for SA-PAN-077). For liposomal vs non-liposomal irinotecan in IM-PAN-001, TTV600 was longer at both MTD and clinically equivalent doses, and tumoral irinotecan levels were higher at MTD. High levels of DNA damage were present in most cancer cells in IM-PAN-001 compared to SA-PAN-077 one week after the last liposomal treatment cycle. **Conclusions:** In both PDAC models, TI was higher for weekly liposomal vs 5 x weekly non-liposomal irinotecan, suggesting potential benefits of the liposomal formulation in a clinical setting.

	Liposomal irinotecan	Non-liposomal irinotecan
IM-PAN-001 model		

IM-PAN-001 model		Liposomal irinotecan (SD)			Non-liposomal irinotecan (SD)		
		Dose (# x mg/kg/week)	TTVdoc, median (days)	Mean tumor level (nmol/g)[a,b]	Dose (# x mg/kg/week)	TTVdoc, median (days)	Mean tumor level (nmol/g)[a,c]
MTD	*CPT-11*	1 x 50	90.5	43.6 ± 26.3	5 x 10	60.6	6.11 ± 0.78
	SN-38			0.074 ± 0.039			0.092 ± 0.018
Lowest dose with anti-tumoral activity	*CPT-11*	1 x 2.5	26.4	0.31 ± 0.10	5 x 2	28.6	0.60 ± 0.06
	SN-38			0.013 ± 0.018			0.038± 0.014
Therapeutic index		20			5		
Clinical equivalent, dose		1 x 10	50.5	NA	1 x 33	28.1	NA

N = 8 mice/group; [a]N = 4 mice. Collected [b]24 and [c]25 hours post-injection of third treatment cycle. CPT-11, irinotecan; NA, not available.

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Differentiation of liposomal irinotecan from dose-dense non-liposomal irinotecan in patient-derived pancreatic cancer xenograft tumor models.

Sandrine Barbier, Stephane Lezmi, Benjamin Beaufils, Adreanne Lortie, Marc Hillairet de Boisferon, Sophie Chaumeron, ...

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Abstract Disclosures

Abstract

e16724

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Published online May 25, 2020.

WE RECOMMEND

Phase I evaluation of SF1126, a vascular targeted PI3K inhibitor, administered twice

lesions, where local conversion to the active metabolite SN-38 is thought to occur. The effect of the liposomal formulation on therapeutic index (TI) was assessed in patient-derived xenograft PDAC models (IM-PAN-001 [untreated tumor] and SA-PAN-077) in severe combined immunodeficiency mice. **Methods:** Liposomal (2.5, 10 or 50 mg/kg, intravenous [IV] 1 x weekly) and non-liposomal irinotecan (2, 5 or 10 mg/kg, IV 5 x weekly) were administered for 3 weeks (n = 8/group). Maximum tolerated dose (MTD) and clinically-relevant weekly doses (10 mg/kg, liposomal; 33 mg/kg, non-liposomal) of irinotecan were evaluated. TI was the ratio of MTD/lowest dose with anti-tumoral activity; time to reach tumor volume of 600 mm^3 (TTV600) was a proxy for overall survival. Tumor, plasma, gut and bone marrow were sampled for pharmacokinetics and safety assessment; DNA damage was evaluated via pH2AX and 53BP1 IHC. **Results:** The Table reports results of the more sensitive IM-PAN-001 model: TI of weekly liposomal irinotecan was 4-fold higher than for 5 x weekly non-liposomal irinotecan (TI was narrower for SA-PAN-077). For liposomal vs non-liposomal irinotecan in IM-PAN-001, TTV600 was longer at both MTD and clinically equivalent doses, and tumoral irinotecan levels were higher at MTD. High levels of DNA damage were present in most cancer cells in IM-PAN-001 compared to SA-PAN-077 one week after the last liposomal treatment cycle. **Conclusions:** In both PDAC models, TI was higher for weekly liposomal vs 5 x weekly non-liposomal irinotecan, suggesting potential benefits of the liposomal formulation in a clinical setting.

IM-PAN-001 model		Liposomal irinotecan			Non-liposomal irinotecan		
		Dose (IV x mg/kg/week)	TTV600, median (days)	Mean (±D) tumor level (nmol/g)[a,b]	Dose (IV x mg/kg/week)	TTV600, median (days)	Mean (±D) tumor level (nmol/g)[a,c]
MTD	*CPT-11*	1 x 50	90.5	43.6 ± 26.3	5 x 10	60.6	6.11 ± 0.
	SN-38			0.074 ± 0.039			0.092 ± 0.018
Lowest dose with anti-tumoral activity	*CPT-11*	1 x 2.5	26.4	0.31 ± 0.10	5 x 2	28.6	0.60 ± 0.
	SN-38			0.013 ± 0.018			0.038 ± 0.014
Therapeutic index		20			5		
Clinical equivalent, dose		1 x 10	50.5	NA	1 x 33	28.1	NA

N = 8 mice/group; [a]N = 4 mice. Collected [b]24 and [c]25 hours post-injection of third treatment cycle. CPT-11, irinotecan; NA, not available.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Real world outcomes of metastatic pancreatic cancer (mPC) patients (pts) treated with liposomal irinotecan (nal-IRI) in the US.

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Abstract Disclosures

Abstract

e16229

Background: The NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in overall survival (OS), progression-free survival (PFS), and objective response rate with nal-IRI + folinic acid/ leucovorin (5-FU/LV) vs. 5-FU/LV. In this analysis, we describe real world characteristics and outcomes of mPDAC pts treated with nal-IRI in the US. **Methods:** This retrospective observational study utilized data from Flatiron Health's longitudinal database derived from electronic health records data from over 265 diverse cancer clinics. Patient characteristics, OS, time-to-treatment failure (TTF), and adverse events (AEs) abstracted from structured lab data were assessed in adult pts diagnosed with mPDAC who received nal-IRI treatment between November 18, 2015 and August 31, 2017. **Results:** Of the 257 mPDAC pts treated with nal-IRI, 51% were male, 28% had a pancreatectomy, and median age was 67 (IQR: 61-74). Among pts with an ECOG score recorded at nal-IRI initiation (n=189), 20% had an ECOG of 2 or greater. Following diagnosis of metastatic or recurrent disease, 57% of pts received nal-IRI in the first or second line, and 43% in third line or later. Median OS was 5.59 months [95% CI 4.83,7.33] for pts receiving nal-IRI as the first or second treatment (n=145) and 4.11 months [95% CI 3.38, 4.9] for those receiving it in third or later lines (n=112), respectively. TTF was 2.33 [1.64, 3.02] for those treated in first or second line, and 1.64 [1.38, 1.87] for those in third line or later. Among pts for

whom reasons for discontinuation were available(n=186), disease progression (57%), disease-related symptoms (17%), and treatment toxicity (14%) were reported most often. Structured AEs were generally consistent with those reported in NAPOLI-1. **Conclusions:** In this real world US population with older median age and poorer performance status, median OS, TTF, and structured AEs were similar to those reported in NAPOLI-1. As would be expected, pts receiving nal-IRI treatment in earlier lines had a higher median OS.

Multivariate Analysis of Health Related Quality of Life (HR QoL) in Metastatic Health-HR-Pancreatic Cancer Treated with 5-Fluorouracil and Leucovorin (5-FU/LV), with and without Liposomal Irinotecan (nal-IRI)

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Background

- Irinotecan Liposome (nal-IRI) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. non-liposomal irinotecan. [1-3]
- NAPOLI-1, a global, phase 3 study, demonstrated, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy, that nal-IRI in combination with 5-FU/LV significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio = 0.67; *P* = 0.012) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified hazard ratio = 0.56; *P* = 0.0001) compared with 5-FU/LV alone. [4]
- Quality of life was not compromised in patients treated wtih nal-IRI + 5-FU/LV as demonstrated by proportions of patients with improved, stable, or worsening EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer quality-of-life core questionnaire) symptom, global health status - quality of life (GHS-QL) and functional scale scores (secondary end-point).[4]
- The most frequent Grade ≥ 3 treatment-emergent adverse events (TEAEs) in patients treated with nal-IRI+5-FU/LV were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%). [4]

Objective

We conducted a post hoc analysis of EORTC QLQ-C30 measures from NAPOLI-1 and compared overall HR-QoL change following treatment initiation with 5-FU/LV, with or without nal-IRI.

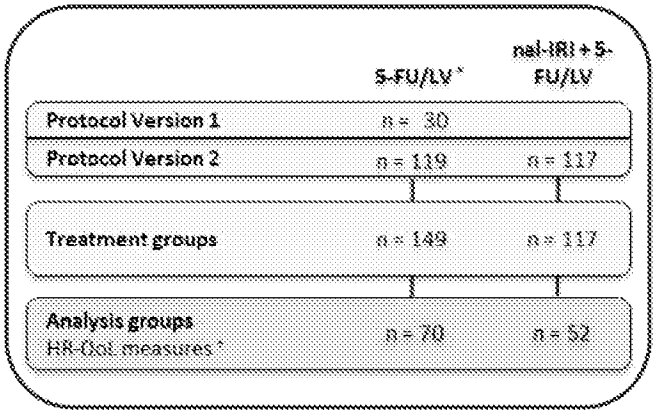
Methods

- In NAPOLI-1, patients were initially randomized to nal-IRI monotherapy or 5-FU/LV (protocol version 1). Once safety data for the combination treatment became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a nal-IRI + 5-FU/LV arm (protocol version 2). This trial is registered at ClinicalTrials.gov, number NCT01494506.
- Patients randomized to 5-FU/LV alone or to nal-IRI + 5-FU/LV (protocol version 1, or 2), and who had EORTC QLQ-C30 scale measurements at baseline and week-6 were included in the analysis.
- Mean week-6 increments from baseline in EORTC QLQ-C30 scale scores were compared between treatment groups.
- Spearman correlations between week-6 increments in GHS-QL score and other EORTC QLQ-C30 scale scores (along with 95% confidence intervals and *P*-values for departure from zero) were examined.
- A principal component (PC) analysis was performed on week-6 changes from baseline in EORTC QLQ-C30 scale scores, retaining PC explaining about 60% of the variance.
- *P*-values for between-group differences in scores or score increments were obtained using univariate and multivariate parametric tests.

Results

- A total of 266 patients were assigned to 5-FU/LV; 117 to 5-FU/LV + nal-IRI and 149, including 30 patients randomized prior to protocol amendment, assigned to 5-FU/LV alone. Among these, respectively 52 (44.4%) and 70 (47.0%) had both baseline and week-6 EORTC QLQ-C30 scale measures, and were included in the analysis. (Figure 1)

Figure 1. Study analysis flow chart



* The study was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination became available; 30 patients had already been assigned to 5-FU/LV alone at the time of amendment (protocol version 1). † Patients who had both baseline and week-6 EORTC QLQ-C30 scale measures. nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; HR-QoL, health-related quality of life.

- Treatment groups were comparable at baseline with similar age, gender, body mass index and Karnofsky performance status score. (Table 1)

Table 1. Baseline characteristics in patient treated with nal-IRI + 5-FU/LV or 5-FU/LV

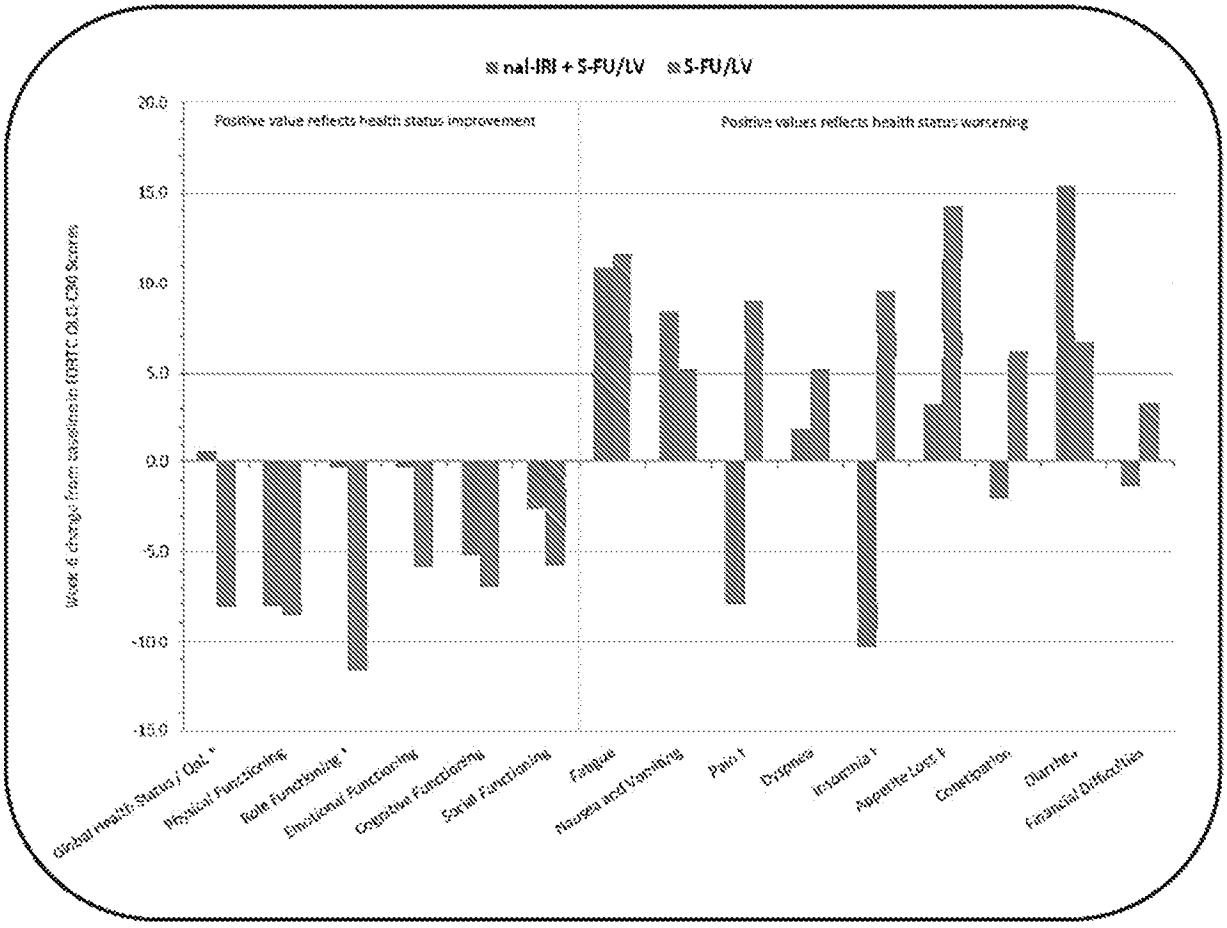
Baseline characteristics	Anticancer therapy	
	nal-IRI + 5-FU/LV (n = 52)	5-FU/LV (n = 70)
Age, mean (SD)	62.7 (9.3)	63.3 (10.4)
Female, % (n)	46.2 (24)	44.3 (31)
BMI, mean (SD)	24.1 (4.7)	23.5 (4.7)
KPS score, % (n)		
100	15.4 (8)	15.7 (11)
90	40.4 (21)	44.3 (31)
80	36.5 (19)	32.9 (23)
70	5.8 (3)	7.1 (5)
60	1.9 (1)	0.0 (0)

nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin ; BMI, Body Mass Index ; KPS, Karnofsky performance status

- Figure 2 compares EORTC QLQ-C30 scale score changes, 6 weeks following treatment initiation. Comparison of increments in the following EORTC QLQ-C30 scales were in favor of patients receiving nal-IRI + 5-FU/LV vs. 5-FU/LV alone: pain (–8.0 vs +9.0; P = 0.0060), insomnia (–10.3 vs +9.5; P = 0.0023), role functioning (–0.3 vs –11.7; P = 0.0346), global health status / quality of life (+0.6 vs –8.2; P = 0.0318)

- None of the differences in EORTC QLQ-C30 scale increments favored patients receiving 5-FU/LV alone ($P \geq 0.1039$), although diarrhea scores were numerically lower in this group compared to patient receiving nal-IRI (+15.4 vs +6.7; P = 0.1039). (Figure 2)

Figure 2. Change from baseline at week-6 in EORTC QLQ-C30 scale scores among patients treated with 5-FU/LV + nal-IRI or 5-FU/LV alone



† $P < 0.01$; * $P < 0.05$; ‡ $P < 0.1$

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; QoL, quality of life;

- Table 2 presents correlations between GHS-QL and other EORTC QLQ-C30 scale scores increments:
  - Changes in GHS/QL were not correlated with increments in the following symptoms: diarrhea (–0.02), nausea/vomiting (–0.08), constipation (–0.09), dyspnea (–0.09)
  - Changes in GHS/QL were however correlated with increments in pain (–0.47), fatigue (–0.37), insomnia (–0.33), appetite loss (–0.33)
  - Role functioning change was found to have the strongest positive correlation with GHS/QL increment (+0.39).
  - As expected, increments in physical, emotional, cognitive and social functioning were also all positively correlated with those in GHS/QL (+0.23 ≤ Rho ≤ +0.29).

- The first 4 PCs explained about 60% of the variance. With positive weights on functioning and GHS/QL scales, and negative weights on symptoms and financial difficulties scales, the first PC (explained variance: 34%) was found to reflect general HR-QoL. (Table 2)
- Comparisons of these PCs founds treatment groups to differ regarding post treatment EORTC QLQ-C30 scale score increments (P = 0.0051, Table 3).
- Compared to patient receiving 5-FU/LV alone, nal-IRI-treated patients had a higher first PC score (-0.34 vs. 0.45, P = 0.0478), revealing better post-treatment HR-QoL increments. (Table 3)

Table 2. Change from baseline at week-6 in EORTC QLQ-C30 scale scores: Principal components and Spearman correlation with GHS-QL increments

EORTC QLQ-C30 Scale	Principal Components				Spearman correlation with GHS-QL		
	1st	2nd	3rd	4th	Rho	[95% CI]	*P*-value *
GHS-QL	0.28	-0.29	0.11	-0.13	1.00	---	---
Physical Functioning	0.32	0.09	-0.37	-0.16	0.28	[0.11 ; 0.43]	0.0020
Role Functioning	0.33	0.09	0.08	-0.02	0.39	[0.23 ; 0.53]	< 0.0001
Emotional Functioning	0.31	0.19	-0.05	-0.33	0.23	[0.06 ; 0.39]	0.0101
Cognitive Functioning	0.26	0.09	-0.18	-0.27	0.24	[0.07 ; 0.40]	0.0070
Social Functioning	0.31	0.19	-0.08	-0.09	0.29	[0.12 ; 0.44]	0.0013
Fatigue	-0.33	-0.01	0.24	0.01	-0.37	[-0.51 ; -0.21]	0.0001
Nausea and Vomiting	-0.19	-0.28	-0.29	-0.55	-0.08	[-0.25 ; 0.10]	0.3787
Pain	-0.29	0.40	-0.22	-0.03	-0.47	[-0.60 ; -0.32]	< 0.0001
Dyspnea	-0.18	-0.05	0.29	-0.48	-0.09	[-0.26 ; 0.09]	0.3253
Insomnia	-0.19	0.39	-0.47	0.21	-0.33	[-0.48 ; -0.16]	0.0002
Appetite Loss	-0.31	-0.08	-0.16	-0.29	-0.33	[-0.48 ; -0.16]	0.0002
Constipation	-0.21	0.33	0.21	-0.26	-0.09	[-0.26 ; 0.09]	0.3255
Diarrhoea	-0.06	-0.55	-0.34	0.19	-0.02	[-0.19 ; 0.16]	0.8487
Financial Difficulties	-0.13	-0.08	-0.35	-0.07	-0.15	[-0.32 ; 0.03]	0.1041
Cumulative variation explained, %	33.6	43.3	51.8	59.3			

* *P*-value for rho being different from 0.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire ; GHS-QL, Global Health Status / Quality of life

Table 3. Between group comparisons of principal components scores for week-6 changes from baseline in EORCT QLQ-C30 scales

PC	nal-IRI + 5-FU/LV		5-FU/LV		Difference between groups	P-value for difference between groups	
	mean	(SD)	mean	(SD)	Mean [95% CI]	Univariate	Multivariate
1st	0.45	(1.97)	-0.34	(2.38)	0.79 [0.01 ; 1.57]	0.0478	0.0051
2nd	-0.38	(1.18)	0.28	(1.17)	-0.66 [-1.08 ; -0.23]	0.0028	
3rd	0.16	(1.13)	-0.12	(1.12)	0.27 [-0.14 ; 0.68]	0.1874	
4th	-0.02	(1.18)	0.02	(0.97)	-0.04 [-0.44 ; 0.36]	0.8421	

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; PC, principal component; nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin

Conclusion

- NAPOLI-1 previously showed nal-IRI + 5-FU/LV to be an effective treatment option that improves OS and PFS without compromising quality of life. [4]
- Although a limited number of patients had EORTC QLQ-C30 change from baseline measurements, results of this post hoc analysis suggest that post treatment HR-QoL may be improved with nal-IRI + 5-FU/LV compared to 5-FU/LV alone. More specifically, nal-IRI administered with 5-FU/LV was associated with better global health status / quality of life scores, less pain, reduced insomnia and improved role functioning.
- Results also indicate that certain chemotherapy adverse effects are not associated with HR-QoL detriments.

References

[1] Roy AC, et al. Ann Oncol. 2013;24(6):1567-1573. ; [2] Kalra AV, et al. Cancer Res. 2014;74(23):7003-7013. ;[3] Ramanathan RK, et al. Annual Meeting AACR; April 5-9, 2014; San Diego, CA. abstract CT224 (and poster). ; [4] Wang-Gillam A, et al. Lancet. 2016;387:545-557.

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Multivariate Analysis of Health-Related Quality of Life (HR-QoL) in Metastatic Pancreatic Cancer Treated with 5-Fluorouracil and Leucovorin (5-FU/LV), with and without Liposomal Irinotecan (nal-IRI)

PCN 182

Pierre Bonnet, Alain Gueret, Jean-Luc Raoul, Antoine Hollebecque, Jean-Frédéric Blanc, Jean-Louis Legoux, Thierry Conroy, Jean-Luc Van Laethem

Background

- Irinotecan Liposome (nal-IRI) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. non-liposomal irinotecan. [1,2]
- NAPOLI-1, a global, phase 3 study, demonstrated, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy, that nal-IRI in combination with 5-FU/LV significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio = 0.67; $P = 0.012$) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified hazard ratio = 0.56; $P < 0.0001$) compared with 5-FU/LV alone. [3]
- Quality of life was not compromised in patients treated with nal-IRI + 5-FU/LV as demonstrated by proportions of patients with improved, stable, or worsening EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer quality-of-life core questionnaire) symptom, global health status / quality of life (GHS QL) and functional scale scores (secondary end-point). [3]
- The most frequent Grade ≥ 3 treatment-emergent adverse events (TEAEs) in patients treated with nal-IRI+5-FU/LV were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (11%). [3]

Objective

We conducted a post hoc analysis of EORTC QLQ-C30 measures from NAPOLI-1 and compared overall HR-QoL change following treatment initiation with 5-FU/LV, with or without nal-IRI.

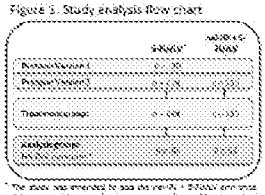
Methods

- In NAPOLI-1, patients were initially randomized to nal-IRI monotherapy or 5-FU/LV (protocol version 1). Once safety data for the combination treatment became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a nal-IRI + 5-FU/LV arm (protocol version 2). This trial is registered at ClinicalTrials.gov, number NCT01494506.
- Patients randomized to 5-FU/LV alone or to nal-IRI + 5-FU/LV (protocol version 1, or 2), and who had EORTC QLQ-C30 scale measurements at baseline and week-6 were included in the analysis.
- Mean week-6 increments from baseline in EORTC QLQ-C30 scale scores were compared between treatment groups.
- Spearman correlations between week-6 increments in GHS-QL score and other EORTC QLQ-C30 scale scores (along with 95% confidence intervals and *P*-values for departure from zero) were examined.
- A principal component (PC) analysis was performed on week-6 changes from baseline in EORTC QLQ-C30 scale scores, retaining PC explaining about 60% of the variance.
- *P*-values for between-group differences in scores or score increments were obtained using univariate and multivariate parametric tests.

Results

- A total of 266 patients were assigned to 5-FU/LV, 117 to 5-FU/LV + nal-IRI and 149, including 30 patients randomized prior to protocol amendment, assigned vs. 5-FU/LV alone. Among these, respectively 52 (44.4%) and 78 (47.0%) had both baseline and week-6 EORTC QLQ-C30 scale measures, and were included in the analysis. (Figure 1)

Figure 1. Study analysis flow chart



* The study was amended to add nal-IRI. † 5-FU/LV arm since safety data on the combination became available. ‡ Patient has evaluable week-6 EORTC QLQ-C30 score at the time of assessment (protocol version 1). § Patient who had both baseline and week-6 EORTC QLQ-C30 scale measures, and were included in the analysis. 5-FU/LV, fluorouracil and leucovorin; HR-QoL, health-related quality of life.

- Treatment groups were comparable at baseline with similar age, gender, body mass index and Karnofsky performance status score. (Table 1)

Table 1. Baseline characteristics in patients treated with nal-IRI + 5-FU/LV or 5-FU/LV

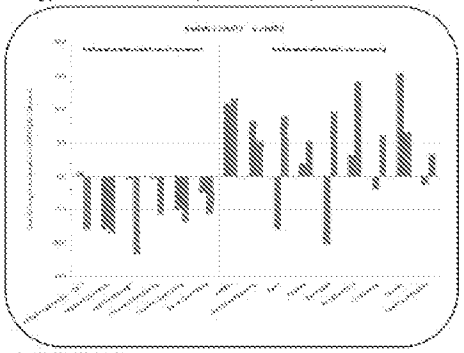
	nal-IRI + 5-FU/LV		5-FU/LV	
	N = 52		N = 78	
Age, mean (SD)	62.7	(9.2)	63.5	(10.6)
Female, N (%)	40.0	(77)	44.9	(35)
BMI, mean (SD)	24.0	(3.7)	23.0	(3.7)
KPS score, N (%)				
100	15.4	(8)	10.7	(8)
90	40.4	(21)	44.0	(33)
80	36.5	(19)	32.0	(24)
70	7.7	(4)	13.3	(10)
60	0.0	(0)	1.3	(1)

KPS, Karnofsky performance; 5-FU/LV, fluorouracil and leucovorin; BMI, Body Mass Index = kg/m²; SD, standard deviation; mass.

- Figure 2 compares EORTC QLQ-C30 scale score changes, 6 weeks following treatment initiation. Comparison of increments in the following EORTC QLQ-C30 scales were in favor of patients receiving nal-IRI + 5-FU/LV vs. 5-FU/LV alone: pain (−8.0 vs +6.0; $P = 0.0060$), insomnia (−10.3 vs +9.5; $P = 0.0023$), role functioning (−8.3 vs −11.7; $P = 0.0346$), global health status / quality of life (+0.6 vs −6.2; $P = 0.0818$)
- None of the differences in EORTC QLQ-C30 scale increments favored patients receiving 5-FU/LV alone ($P \geq 0.1035$), although diarrhea scores were numerically lower in this group compared to patient receiving nal-IRI (+15.4 vs +6.2; $P = 0.1059$). (Figure 2)

Results (cont'd)

Figure 2. Change from baseline at week-6 in EORTC QLQ-C30 scale scores among patients treated with 5-FU/LV + nal-IRI or 5-FU/LV alone



EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; GHS, Global Health Status / Quality of Life; PF, Physical Functioning; RF, Role Functioning; EF, Emotional Functioning; CF, Cognitive Functioning; SF, Social Functioning; FA, Fatigue; NV, Nausea and Vomiting; PA, Pain; DY, Dyspnea; SL, Insomnia; AP, Appetite Loss; CO, Constipation; DI, Diarrhea; FI, Financial Difficulties.

- Table 2 presents correlations between GHS-QL and other EORTC QLQ-C30 scale scores increments:
  - Changes in GHS/QL were not correlated with increments in the following symptoms: diarrhea (−0.02), nausea/vomiting (−0.08), constipation (−0.09), dyspnea (−0.09)
  - Changes in GHS/QL were however correlated with increments in pain (−0.47), fatigue (−0.27), insomnia (−0.33), appetite loss (−0.33)
  - Role functioning change was found to have the strongest positive correlation with GHS/QL increment (+0.39).
  - As expected, increments in physical, emotional, cognitive and social functioning were also all positively correlated with those in GHS/QL (+0.22 ≤ Rho ≤ +0.29)
- The first 4 PCs explained about 60% of the variance. With positive weights on functioning and GHS/QL scales, and negative weights on symptoms and financial difficulties scales, the first PC (explained variance: 34%) was found to reflect general HR-QoL (Table 2)
- Comparisons of these PCs found treatment groups to differ regarding post treatment EORTC QLQ-C30 scale score increments ($P = 0.0051$, Table 3).
- Compared to patient receiving 5-FU/LV alone, nal-IRI-treated patients had a higher first PC score (−0.34 vs. −0.45, $P = 0.0478$), revealing better post-treatment HR-QoL increments. (Table 3)

Table 2. Change from baseline at week-6 in EORTC QLQ-C30 scale scores: Principal components and Spearman correlation with GHS-QL increments

EORTC QLQ-C30 Scale	Principal Components				Spearman Correlation with GHS-QL		
	PC1	PC2	PC3	PC4	Rho	95% CI	P-value
GHS-QL	0.00	0.00	0.00	0.00	1.00	--	--
Physical Functioning	0.32	0.01	0.27	0.05	0.28	(0.05 ; 0.47)	0.0020
Role Functioning	0.37	0.19	0.06	0.02	0.39	(0.23 ; 0.55)	<0.0001
Emotional Functioning	0.21	0.38	-0.05	-0.33	0.23	(0.06 ; 0.39)	0.0028
Cognitive Functioning	0.26	0.09	0.49	-0.07	0.24	(0.07 ; 0.40)	0.0029
Social Functioning	0.31	0.21	-0.08	0.09	0.29	(0.12 ; 0.46)	0.0003
Fatigue	-0.39	0.01	0.24	0.16	-0.27	(-0.51 ; -0.11)	0.0008
Nausea and Vomiting	-0.10	-0.38	-0.20	0.58	-0.08	(-0.25 ; 0.10)	0.3730
Pain	-0.38	-0.40	-0.22	0.01	-0.47	(-0.61 ; -0.30)	<0.0001
Dyspnea	-0.18	-0.05	-0.35	-0.48	-0.09	(-0.26 ; 0.08)	0.2850
Insomnia	-0.35	-0.29	-0.47	0.21	-0.33	(-0.49 ; -0.16)	0.0002
Appetite Loss	-0.33	-0.33	-0.31	-0.39	-0.33	(-0.49 ; -0.16)	0.0002
Constipation	-0.21	-0.35	0.22	0.20	-0.09	(-0.26 ; 0.08)	0.3055
Diarrhoea	-0.08	-0.05	-0.34	0.39	-0.02	(-0.19 ; 0.15)	0.8427
Financial Difficulties	-0.35	-0.08	-0.05	0.07	-0.25	(-0.42 ; -0.07)	0.0069
Cumulative explained variance, %	33.6	53.6	59.8	65.2			

Principal components obtained from PC1 to PC4 explain about 60% of the variance.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire ; GHS-QL, Global Health Status / Quality of Life

Table 3. Between group comparisons of principal components scores for week-6 changes from baseline in EORTC QLQ-C30 scales:

PC	5-FU/LV	nal-IRI + 5-FU/LV	Univariate Analysis		Multivariate Analysis (adjusted for baseline PC scores)	
	Mean (SD)	Mean (SD)	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value
1st	-0.45 (1.57)	-0.34 (2.08)	0.10 (-0.52 ; 0.72)	0.7371	0.0933	0.0051
2nd	-0.08 (1.68)	0.18 (1.47)	0.26 (-0.38 ; 0.90)	0.4201	0.0033	
3rd	0.08 (1.50)	-0.12 (1.43)	-0.20 (-0.83 ; 0.43)	0.5374		
4th	0.02 (1.48)	0.02 (1.69)	0.00 (-0.63 ; 0.63)	0.9933		

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life core questionnaire; PC, principal component; 5-FU/LV, fluorouracil and leucovorin

Conclusion

- NAPOLI-1 previously showed nal-IRI + 5-FU/LV to be an effective treatment option that improves OS and PFS without compromising quality of life. [3]
- Although a limited number of patients had EORTC QLQ-C30 change from baseline measurements, results of this post hoc analysis suggest that post treatment HR-QoL may be improved with nal-IRI + 5-FU/LV compared to 5-FU/LV alone. More specifically, nal-IRI administered with 5-FU/LV was associated with better global health status / quality of life scores, less pain, reduced insomnia and improved role functioning.
- Results also indicate that certain chemotherapy adverse effects are not associated with HR-QoL detriments.

References

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progression health state. Differences between health states were statistically significant ($p<0.0001$) and clinically relevant. Adjusting for the presence of AEs had minimal impact. Parameter estimates of dis-utilities associated with experiencing ≥ 1 grade 3-4 AE based on US (UK) value sets were –0.02191 (–0.02439). Dis-utilities for treatment-related AEs of any grade were smaller (–0.00532 and –0.01028 for US and UK value sets). **CONCLUSIONS:** In patients with metastatic MCC, non-progression during treatment with avelumab contributed to gains in health utility scores. The dis-utility impact of AEs during treatment with avelumab was minimal, suggesting a manageable safety profile from a patient perspective.

PCN181

ASSOCIATION OF PATIENT-PHYSICIAN COMMUNICATION WITH FINANCIAL BURDEN AND QUALITY OF LIFE OF CANCER PATIENTS

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OBJECTIVES: Cancer is one of the most prevalent diseases in the United States. Approximately 39% of men and women are diagnosed with cancer based on 2011-2013 data. The objective of our study is to compare the quality of life (QOL) and financial burden of cancer patients who had good patient-physician communication to patients who had poor/no communication. **METHODS:** This was a retrospective study using 2011 Medical Expenditure Panel Survey (MEPS) data. The full year consolidated file was used. The sample consisted of all individuals who experienced cancer after the age of 18. The QOL and financial burden of cancer patients who reported having detailed discussions with their physician were compared with those with brief/no discussions. Chi-square tests were used for all comparisons. **RESULTS:** The sample consisted of 1592 cancer patients. Of these, 58.86% were females, 54.71% were married, 49.75% were in the 65-85 years' age group, with a typical cancer patient having a median total income of $21334 (interquartile range = 31681). Of those patients with higher QOL, a higher percentage (65.20% vs. 8.77%) reported good patient-physician communication as compared to those who had no communication. A larger percentage (66.84% vs. 8.05%) of patients with no financial burden had good patient-physician communication as compared to those with no communication. All results were statistically significant at $p<0.05$. **CONCLUSIONS:** Patients with good communication with their doctors were more likely to have lower financial burden and a better quality of life.

PCN182

MULTIVARIATE ANALYSIS OF HEALTH-RELATED QUALITY OF LIFE (HR-QOL) IN METASTATIC PANCREATIC CANCER (MPC) TREATED WITH 5- FLUOROURACIL AND LEUCOVORIN, WITH AND WITHOUT LIPOSOMAL IRINOTECAN (NAL-IRI)

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OBJECTIVES: The survival benefits of nal-IRI+5-fluorouracil/leucovorin vs 5-fluorouracil/leucovorin in mPC patients who progressed after prior gemcitabine-based therapy were demonstrated in a phase 3 study (NAPOLI-1); preplanned analyses of QoL demonstrated no differences between treatment groups. While chemotherapy causes toxicities that impair HR-QoL, its clinical benefits may improve HR-QoL. We conducted a post hoc analysis of NAPOLI-1 EORTC-QLQ-C30 questionnaire measures to compare overall HR-QoL change. **METHODS:** A principal component (PC) analysis was performed on the EORTC-QLQ-C30 scales week-6 changes. PC scores were compared between groups, and correlations between EORTC-QLQ-C30 scale increments examined. **RESULTS:** Of 266 randomized patients, 122 had baseline and week-6 EORTC-QLQ-C30 scale measures and were included in the analysis. EORTC-QLQ-C30 increments in pain (–8.0 vs +9.0; P=0.0060), insomnia (–10.3 vs +9.5; P=0.0023), role functioning (–0.3 vs –11.7; P=0.0046), and Global Health Status/Quality of Life (GHS/QL; +0.6 vs –8.2; P=0.0318) favored patients receiving nal-IRI+5-fluorouracil/leucovorin vs 5-fluorouracil/leucovorin alone. No differences favored patients receiving 5-fluorouracil/leucovorin (P-values ≥0.1033), although diarrhea scores were numerically lower (+15.4 vs +6.7). GHS/QL increments were not correlated with diarrhea (P=0.8487), nausea/vomiting (P=0.3787), constipation (P=0.3255), or dyspnea (P=0.3253); pain (P<0.0001), fatigue (P<0.0001), insomnia (P<0.0002), and appetite loss (P<0.0002) were. Role functioning change had the strongest positive correlation with GHS/QL increment (+0.39, P<0.0001). Multivariate comparison of the first 4 EORTC-QLQ-C30 scales changes PCs (variance explained: 59%) found treatment groups to be different (P=0.0051). With positive weights on functioning and GHS/QL scales, and negative weights on symptoms and financial difficulties scales, the first PC (explained variance: 34%) reflected general HR-QoL. nal-IRI+5-fluorouracil/leucovorin patients (vs. 5-fluorouracil/leucovorin) had higher first PC score (P=0.0478). **CONCLUSIONS:** Results of this post hoc analysis suggest that nal-IRI+5-fluorouracil/leucovorin improves HR-QoL vs 5-fluorouracil/leucovorin alone, and that certain chemotherapy adverse effects are not associated with HR-QoL detriments.

PCN183

QUALITATIVE INTERVIEWS TO UNDERSTAND THE PATIENT EXPERIENCE OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK AND EXPLORE THE CONTENT OF PATIENT REPORTED OUTCOME MEASURES

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OBJECTIVES: To understand the patient experience of squamous cell carcinoma of the head and neck (SCCHN) and guide selection of relevant measurement concepts for clinical trials. Patient reported outcome (PRO) instruments (EORTC QLQ-C30 and H&N-35) were also assessed for their suitability in this population. **METHODS:** A literature review and clinician interviews were conducted to inform in-depth semi-structured telephone interviews with patients who had received treatment in the past 12 months for metastatic and/or recurrent SCCHN. Interview transcripts were analysed thematically in ATLAS.ti v7; patient quotes were coded to identify concepts and themes to develop a conceptual model of SCCHN experience. **RESULTS:** Thirteen patients were interviewed (77% male, aged 35-84), the majority diagnosed for >1 year. Patients reported few symptoms pre-diagnosis; commonly a neck lump/swelling (n=7) and/or difficulty swallowing (n=3). Treatment generally comprised of surgery and chemotherapy and/or radiotherapy. Key side effects included pain (n=8), fatigue (n=8), and weight loss (n=8). These impaired health-related quality of life (HRQoL) including work (n=6), socializing (n=7), and emotional wellbeing (n=11). Tumour location, surgery and radiation particularly affected difficulty speaking (n=7) and difficulty eating/drinking (n=9). This was most severe in patients who had a feeding tube in-situ. Patients generally found the QLQ-C30 and H&N-35 content to be understandable and conceptually relevant; some additions were suggested including excessive mucous production and neuropathic symptoms. Patient data generally corroborated with the clinician interview and the literature review findings. **CONCLUSIONS:** SCCHN diagnosis, symptoms, and treatment impacts patients' physical functioning, emotional wellbeing, and overall HRQoL. PRO instruments included in clinical trials should assess the effect of novel therapies on fatigue, pain and oral problems including swallowing. The QLQ-C30 and H&N-35 appeared generally relevant and suitable to capture symptoms and impacts associated with SCCHN. However, some items could be amended/added to ensure conceptual comprehensiveness.

PCN184

EVALUATING CLINICALLY MEANINGFUL CHANGE OF THE EORTC QLQ-C30 IN PATIENTS WITH NSCLC

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OBJECTIVES: The EORTC QLQ-C30 has been extensively validated in cancer patients, but its responsiveness to individual changes in clinical outcomes in anaplastic lymphoma kinase (ALK+) non-small cell lung cancer (NSCLC) was not previously evaluated. The ALK in Lung Cancer Trial of brigatinib (ALTA trial; NCT02094573), an open-label, Phase 2, randomized, multicenter, international study, evaluated the efficacy and safety of brigatinib (Arm A: 90 mg qd and Arm B: 180 mg qd with a 7-day lead-in at 90 mg) in patients (pts) with locally advanced or metastatic ALK+ NSCLC whose disease had progressed on prior therapy with crizotinib. To interpret meaningful change in patient-reported outcomes (PROs), the responder definition (RD) threshold for the minimum individual pt change representing treatment benefit was established. **METHODS:** PRO data collection included the EORTC QLQ-C30 at baseline and first day of each cycle. The RD of the Global Health Status (GHS)/QOL scale of the QLQ-C30 was examined with anchor and distribution-based methods. Anchors included time point response per RECIST v 1.1 criteria and ECOG performance status. **RESULTS:** Of 222 randomized pts, 208 (94%) completed PRO data at baseline and at least one subsequent on treatment visit. The ANCOVA adjusted (sex and age) mean group difference between pts with stable disease (n=76) vs. complete or partial response (n=99) in change from baseline to cycle 3 in GHS/QOL was 9.8. Distribution-based estimates of the RD were 5.04, 12.6 and 17.6 (0.2 SD, 0.5, SD, and 1.0 SEM). A change of 8.33 (1 point on the raw scale, the minimum change possible) was selected as the RD threshold for GHS/QOL based on corresponding changes in response at cycle 3. **CONCLUSIONS:** A change of 8.33 points from baseline to cycle 3 can be interpreted as a meaningful score change in GHS/QOL indicative of treatment benefit for an individual patient with ALK+ NSCLC.

PCN185

PATIENT REPORTED HRQOL IN PATIENTS WITH STAGE IV SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

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OBJECTIVES: To evaluate the quality of life (QoL) reported by stage IV SCCHN patients. **METHODS:** Real world data was gathered using Adelphi's Disease-Specific Programme (DSP) - a cross-sectional survey administered to physicians and patients in the USA, France, Germany and the UK (April - September 2016). 182 physicians (54 US, 128 EU) provided data on consulting SCCHN patients regarding treatment patterns and staging. 373 current stage IV SCCHN patients (60 US, 313 EU) completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), SCCHN-specific module (QLQ-HN35) and EQ-5D. Summary statistics were reported and differences between sub-groups assessed using pairwise t-tests. **RESULTS:** Patient global QoL, indicated by the EORTC QLQ-C30 global health scale, was poor with a (mean) score of 46.9. Some difference was observed between stage IVA/B and IVC patients (48.6 vs. 45.0 (p=0.0997)), most notably in physical function scores (59.4 vs. 63.8 (p=0.0150)). The most commonly reported symptoms were weight loss (61.3), less sexuality (54.9) and trouble with social eating (42.9). EORTC QLQ-C30 global QoL scores based on primary tumour site showed differentiation (mean) - floor of mouth (38.9), larynx (42.4), lip/tongue/gum (47.3), hypopharynx (49.4) and oropharynx (52.4). This was seen again in social function scores - floor of mouth (50.6), larynx (54.2), lip/tongue/gum (53.0), hypopharynx (61.0) and oropharynx (61.9). The reported EQ-5D score (mean) also showed low QoL (0.57), with no difference between stage IVC (0.57) and stage IVA/B patients (0.57). Some differences were seen based on primary tumour site (mean) – floor of mouth (0.46), larynx (0.51), lip/tongue/gum (0.58), hypopharynx (0.60) and oropharynx (0.64). **CONCLUSIONS:** Overall QoL for stage IV SCCHN patients is low, although not significantly lower for stage IVC vs. IVA/B patients.

CANCER - Cost Studies

PCN53
ECONOMIC EVALUATION OF DRUG WASTAGE IMPACT ON HEALTHCARE EXPENDITURES IN FRENCH HOSPITALS
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OBJECTIVES: Most intravenous expensive oncology drugs have dosing schedules that are based on patients' weight or surface area. After drug reconstitution, leftovers can remain and due to short stability, products can be discarded if no other patient is treated within the next 24 hours. The aim of the study is to provide an estimation of the vial-sharing benefits in terms of savings from the hospital perspective. **METHODS:** To estimate the vial-sharing benefits, we developed a budget impact model to compare three scenarios: 1) no vial sharing is carried out and the leftover of each vial used is lost; 2) the leftover is administered to the next patient (if one comes within the 24h after vial opening), 3) the leftover is always administered to the next patient, there is no product loss. Data were collected focussing on nivolumab, pembrolizumab and trastuzumab-emtansine in two French centres for cancer research (Gustave Roussy in Villejuif and Eugene Marquis in Rennes), covering a one month period prescription. Data on patients' weight or surface area, treatment and drug indication as well as the total number of vials used were analysed to model the savings generated by an optimal management of leftovers. We considered the public French price of 1,798.40€ for the 100mg trastuzumab-emtansine vial and 2,876.86€ for the 160mg vial, and the recommended posology of 3.6mg/kg in order to estimate drug wastage, while the price of nivolumab and pembrolizumab will shortly be available. **RESULTS:** The data of about 200 patients/month were collected at the Gustave Roussy Institute for both nivolumab and pembrolizumab. Data showed that the leftover was avoided in most of the cases and showed that hospitals achieved good levels of vial sharing. **CONCLUSIONS:** Overall, vial sharing generates significative savings for hospital.

PCN54
CHOOSING FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER BASED ON BIOMARKER RAS STATUS: A BUDGET IMPACT ANALYSIS FROM BRAZILIAN HEALTH INSURANCE SYSTEM PERSPECTIVE
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OBJECTIVES: To compare budget requirements for 1st line treatment of metastatic Colorectal Cancer (mCRC) patients with cetuximab or bevacizumab plus FOLFIRI/FOLFOX (CT) or CT alone. **METHODS:** A budget impact model was developed from private payer perspective in a 5-year time horizon (2017-2021). mCRC incidence data from National Cancer Institute was adjusted based on median population growth. Drug acquisition costs were considered and prices, in Brazilian Real (BRL), were derived from official drug list price. Base scenario considered no RAS testing and all patients receiving bevacizumab+CT. Alternative scenario considered RAS testing in which RAS wild-type (wt) patients are treated with cetuximab+CT and RAS mutated (mut) receive CT alone. **RESULTS:** RAS screening is mandatory for HMOs since January 2016 in Brazil. Before that, normally 1st line treatment would be bevacizumab+CT as cetuximab+CT is registered to treat only mCRC RASwt patients. In 5 years, approximately 9,000 patients will be diagnosed with mCRC in Brazil. If bevacizumab+CT is given to all patients regardless of their RAS status, more than 2,06 billion BRL will be spent in 5 years (412 million BRL per year, approximately). If patients are tested and combination treatment of cetuximab+CT is given only to RASwt subset of patients, approximately 1,60 billion BRL will be spent in 5 years (321 million BRL per year, on average). RASmt mCRC patients could receive CT alone in 1stline to further rational resource utilization as bevacizumab+CT failed to show superiority to CT alone in many clinical trials. **CONCLUSIONS:** Biomarker selection of RASwt subgroup, which actually have the greatest potential to benefit from cetuximab+CT, allows rational resource utilization, generating savings of 454.7 million BRL to HMOs in 5-year time. Cetuximab has State tax exemption in Brazil, but even if bevacizumab is granted with such incentive there is still a saving favoring cetuximab.

PCN55
ECONOMIC IMPACT OF OLAPARIB IN PATIENTS WITH PLATINUM SENSITIVE RELAPSED BRCA MUTATED EPITHELIAL OVARIAN CANCER IN SPAIN
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OBJECTIVES: Ovarian cancer (OC) is a rare disease but an important cause of cancer mortality in women in Spain (4.8%). 90% are epithelial OC and 70% are high-grade serous OC (HGSOC). Approximately 20% of HGSOC are BRCA1/2 mutated (BRCAm). Despite advances in treatment, 70%-80% of epithelial OC patients relapse after surgery and first-line platinum-based chemotherapy requiring further treatment. Olaparib is the first PARP inhibitor approved and the only oral maintenance therapy for platinum-sensitive relapsed (PSR) BRCAm HGSOC patients. Olaparib has shown to delay progression and thus the need for subsequent chemotherapies. The aim of this study is to estimate the economic impact of olaparib in those patients in Spain. **METHODS:** From an initial number of patients, based on Spanish published OC epidemiology data (prevalence for year 1 and incidence for years 1 to 5), a patient flow is used to get the target population of olaparib. Target patients are distributed through a decision tree model within four lines of treatment during a 5-year time horizon. We use clinical trials Kaplan Meier survivals curves to model treatment durations. The model considered direct costs as chemotherapy and maintenance drugs, genetic test and administration costs (€2015). **RESULTS:** Olaparib uptake is associated with a potential patient increase in second line due to olaparib longer PFS. The budget impact on the National Health System (NHS) ranging from €1.6M to €5.6M (1-5 years). The total NHS oncology drugs expenditure was €2,944M in 2015, therefore, olaparib introduction would represent 0.05% of expenditure in the first year and 0.19% five years later. **CONCLUSIONS:** The introduction of olaparib as maintenance treatment in the PSR BRCAm HGSOC patients has a manageable budget impact in Spain and suggest that it it could increase PFS and delay subsequent chemotherapy.

PCN56
A BUDGET IMPACT ANALYSIS OF ALTERNATIVE TREATMENT OPTIONS FOR COLORECTAL CANCER IN GREECE
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OBJECTIVES: Colorectal cancer (CRC) is a major burden of disease and a key contributor to healthcare costs internationally. Available treatment options, especially for the metastatic phase of the disease, are numerous and are accompanied by varying degrees of efficacy and costs. Bearing in mind the quest for efficiency, the purpose of this analysis was to estimate the budget impact of the most frequently used treatment options for CRC in Greece. **METHODS:** The analysis is based on a budget impact model that estimates the costs of alternative treatment approaches in patients with metastatic CRC, depending on the presence of RAS mutations. Data on the clinical effectiveness of the interventions under review were obtained from published literature, whereas the most frequently used treatment algorithms (treatment strategies) in Greece were developed by an expert panel of 11 oncologists. The analysis follows a third party payer perspective and costs are in year 2015 Euros. **RESULTS:** For patients without RAS mutations, the average cost/patient for the strategy of FOLFOX/CapeOX plus bevacizumab (1st line), FOLFIRI plus anti-EGFR (2nd line) and chemotherapy alone (3rd line) was estimated at €35,186, while for a strategy of FOLFOX/CapeOX plus anti-EGFR (1st line), FOLFIRI plus aflibercept (2nd line) and chemotherapy alone (3rd line) the average cost per patient was €49,225. For patients with RAS mutations, the corresponding cost per treatment strategy was €29,542 (FOLFOX/CapeOX plus bevacizumab -FOLFIRI plus aflibercept – chemotherapy alone) and €31,161 (FOLFOX/CapeOX - FOLFIRI plus aflibercept – chemotherapy alone). **CONCLUSIONS:** Based on the available epidemiological data for Greece, there are currently 2,054 metastatic CRC patients under treatment. According to the results of the present study (and not withstanding its limitations), bevacizumab-based strategies could lead to an average reduction of €8,312/patient under treatment or at an excess 524 patients that could receive treatment, under the current pharmaceutical expenditure levels for CRC.

PCN57
BUDGET IMPACT ANALYSIS OF SUNITINIB VERSUS BEST SUPPORTIVE CARE FOR THE TREATMENT OF METASTATIC RENAL CELL CARCINOMA IN CHILE
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OBJECTIVES: Assess the budget impact of Sunitinib (SU) versus Pazopanib (PA) and Best Supportive Care (BSC) for the treatment of metastatic renal cell carcinoma (MRCC) from the perspective of the Chilean public healthcare system. **METHODS:** A cohort of patients with MRCC was estimated using local prevalence and incidence data for kidney cancer. The proportion of renal cell carcinoma and metastatic state was obtained from international literature, in accordance with ISPOR good practice. Two scenarios were compared, one representing the current practice in Chile were all patients are treated with BSC and the other scenario were all patients are treated with SU. Expected costs were measured in Chilean pesos (1 USD = 654.07 CLP$). The analysis was made from the perspective of Chilean public health system assuming a 100% reimbursement. We considered pharmacological, adverse event and follow up costs. Annual costs were estimated considering a time horizon of five years. **RESULTS:** The budget impact was presented for two possible prices of SU. When considering current full monthly price of US$2,974, an additional of US$3,961,373 relative to BSC are needed in the first year, and US$5,886,952 for the second year. A price reduction of 25% reduced the incremental cost to US$2,859,193 relative to BSC in the first year, and US$4,249,082 in the second year. **CONCLUSIONS:** For the range of the prices assessed, the impact of the implementation of SU for the treatment of MRCC on the Chilean health system's budget varies from 0,034% to 0,027% on the first year and increases to 0.05% and 0.04% respectively from the second year.

PCN58
BUDGET IMPACT ANALYSIS OF NANOLIPOSOMAL IRINOTECAN FOR TREATMENT OF PANCREATIC CANCER FOLLOWING PROGRESSION ON GEMCITABINE - A US PAYER PERSPECTIVE
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OBJECTIVES: Pancreatic cancer is predicted to be the second highest cause of cancer-related death by 2030 in the US. Based on significant improvement in overall survival, the FDA approved irinotecan liposome injection (nal-IRI, ONIVYDE®), in combination with fluorouracil and leucovorin (5-FU/LV), to treat patients with metastatic pancreatic cancer (mPC) previously treated with gemcitabine-based chemotherapy. The objective of this research was to estimate the budget impact (BI) of adopting nal-IRI for a U.S. commercial payer. **METHODS:** Epidemiologic data, including SEER incidence rates, were used to estimate the total number of patients with pancreatic cancer in a hypothetical 1,000,000 member U.S. health plan. The fraction of these who have the metastatic form of pancreatic cancer, have been exposed to gemcitabine, are still seeking treatment, and receive nal-IRI was estimated based on a claims analysis and expert input. Eligible patients were assumed to be treated with one of the following: gemcitabine only, gemcitabine plus nab-paclitaxel, other gemcitabine-based regimen, FOLFIRINOX, FOLFOX, capecitabine, or nal-IRI plus 5-FU/LV. Cost of medicines were obtained from CMS ASP pricing files; administration and monitoring from the CMS physician fee schedule; adverse events from the claims analysis, except for nal-IRI where it was estimated. The incremental aggregate BI and per-member-per-month (PMPM) impacts were calculated. Given the high mortality of pancreatic cancer, later lines of therapy were not considered. **RESULTS:** A

million-member commercial plan with average demographics, but no seniors, was estimated to have 52 members/year with pancreatic cancer of which 15 would be eligible for nal-IRI, and of which 3 would get the drug. Total incremental annual cost was estimated to be $74,629 or $0.006 PMPM. **CONCLUSIONS:** The survival benefits of nal-IRI plus 5-FU/LV as a treatment option for patients with pancreatic cancer is associated with a PMPM of $0.006, a modest increment due to cost offsets.

PCN59
NEW APPROACH TO BUDGET IMPACT ANALYSIS - IBRUTINIB IN TREATMENT OF RELAPSED/REFRACTORY CLL PATIENTS IN THE CZECH REPUBLIC
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OBJECTIVES: Chronic lymphocytic leukemia (CLL) is a severe disease. Ibrutinib is an oral, first-in class Bruton's tyrosine kinase inhibitor approved for treatment of relapsed/refractory (R/R) CLL. The aim of this paper was to estimate the 5 year budget impact of ibrutinib in the treatment of R/R CLL in the Czech Republic from a payer's perspective and to show ibrutinib's benefits. **METHODS:** A patient-flow model was developed based on real-world data from the University Hospital Brno. The model works with yearly probabilities of relapse and death calculated from real-world data. These were calibrated so that the model keeps a stable structure of patient population corresponding with the real-world data. Number of patients was extrapolated to reflect the whole Czech Republic (524 patients start any treatment through all lines). Drug acquisition costs, hospital admission costs, administration costs, follow-up care and Best Supportive Care (BSC) costs were considered. **RESULTS:** Net budget impact of ibrutinib in R/R CLL in 1st year was estimated at EUR 3.116 mil. which represents 0.009 % of the national health care expenditure budget and 0.118 % of the oncology budget. Cumulative budget impact during five years was estimated at EUR 23.786 mil. which is 0.034 % of the national health care expenditure budget and 0.368 % of the oncology budget. Over a 5 year period, 222 patients will be treated with ibrutinib. Of these, 149 patients (67%) would remain alive after 5 years. Without ibrutinib, only 75 patients (34%) would remain alive after 5 years. **CONCLUSIONS:** Ibrutinib treatment is associated with significantly prolonged survival and higher total costs largely due to ibrutinib continuous administration and longer PFS. As CLL is an orphan indication, the budget impact is negligible compared to total healthcare or oncology expenditures.

PCN60
INVISIBLE LEVER FOR ACCESS TO INNOVATIVE THERAPIES IN BULGARIA
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OBJECTIVES: Expenses for companion diagnostics (CD) for innovative therapies are not covered by the sole payer of health care services in Bulgaria. They are paid for out of pocket or the cost is borne by external treatment access program. Patients and health administrators are advocating for extending coverage for CD. This study uses the payer's perspective and aims to estimate the budget impact of extending reimbursement to CD for innovative therapies in solid tumor treatment. **METHODS:** Incidence and prevalence of solid tumors and the respective genetic markers, was obtained from the cancer registry and scientific literature. Medication DDD prices, dose regimens and the average length of treatment were calculated based on the official EMA product specification. The reimbursement sums for innovative therapies, requiring CD, were collected from the National Health Insurance Fund (NHIF). CD test prices were acquired from leading commercial companies in country. The cost of diagnosing one mutation was calculated by allocating the cost for exhaustive investigation of all cancer patients, who present at clinic, to the ones with mutation status and eligible for the respective innovative product. In order to estimate the BI, percentage growth in the cost of single patient treatment course was calculated first, followed by estimating the total reimbursement sum increase for treating newly diagnosed patients. **RESULTS:** In 2015, EUR 38.3 million were paid by NHIF, covering 12 innovative medications in four cancer types. The projected additional expenditure for covering CD for 8 248 eligible cancer patients can reach EUR 3.1 million per year. Consequently the percentage increase in the cost of single patient treatment course ranges from 0.68% to 24%. **CONCLUSIONS:** Extending CD testing coverage for innovative medications for solid tumors would not only load the NHIF's bill but also double the yearly expense for treatment of eligible patients with certain types of cancer.

PCN61
A BUDGET IMPACT ANALYSIS TO ESTIMATE THE COST SAVINGS FROM ALECTINIB ON PATIENTS WITH ANAPLASTIC LYMPHOMA KINASE (ALK) POSITIVE LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PREVIOUSLY TREATED WITH CRIZOTINIB
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OBJECTIVES: To assess the economic impact of alectinib for patients with ALK+ locally advanced or metastatic NSCLC previously treated with crizotinib, focusing on the efficacy of alectinib in both systemic disease and CNS metastasis related symptoms. **METHODS:** A 3-year budget impact model was developed for Italy for the period 2017–2019. Docetaxel and ceritinib were considered as representative comparators of alectinib in Italy. Clinical inputs (e.g. dosing regimens, treatment duration, progression free survival (PFS), CNS complete response and duration of CNS response) were obtained from the literature and the pooled analysis of two phase II clinical studies for comparative treatments and alectinib respectively. Market shares forecasting and epidemiological data on NSCLC prevalence, ALK test rates and rates of patients who discontinued crizotinib were provided by Roche Italy. Costs and resource use were derived from the literature. The cost savings from response to CNS metastasis were deducted from the total cost for each treatment in order to estimate the overall budget impact. **RESULTS:** The population with ALK+ NSCLC was determined to be approximately 350 patients per year for Italy, which shows the low budget impact of this indication for the National Healthcare System. Estimating the incremental budget impact with and without alectinib and taking into account the potential cost savings from delay and prevention of appearance of CNS metastasis, the analysis showed that when alectinib is introduced in the market, cost savings between 5% and 18% of the total budget impact can be achieved over the three years period, compared to the scenario when alectinib is not a treatment option. **CONCLUSIONS:** The analysis showed that introducing alectinib in the market is a beneficiary option for the healthcare system and the patients since it is likely to reduce the healthcare budget while providing longer control of systemic disease and related CNS metastasis.

PCN62
BUDGET IMPACT ANALYSIS OF USING PAZOPANIB-EVEROLIMUS IN FIRST AND SECOND LINE OF TREATMENT, IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA
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OBJECTIVES: To develop a budget impact analysis from the perspective of the Colombian state, related to pazopanib-Everolimus use in first and second line of treatment, respectively, compared with pazopanib-Axitinib, sunitinib-everolimus and sunitinib-axitinib in patients with metastatic renal cell carcinoma. **METHODS:** A three years analysis was designed, with the shares of the possible combinations of technologies in first-line (pazopanib and sunitinib) with second-line (everolimus and axitinib), which were consulted clinical experts to evaluate the combinations in the current scenario of the four treatment options. The shares in the new scenario, starting in the first year with increasing share of the main combination of analysis (Pazopanib-everolimus), which comes from 21.95% to 30% in the first year, with progressive increases up to 40 % in the third year, and the other 60% spread among the other three combinations of technologies. The costs are showed in United States dollars, using current exchange rate to Colombian pesos. **RESULTS:** According to the base case analyzed in terms of total cumulative impact in Colombian pesos and impact on Capitation payment unit, the use of pazopanib-everolimus in first and second line of treatment respectively generates savings of US $0.1016 at third year, representing a -0.0503% impact on capitation payment unit of 2016. **CONCLUSIONS:** The use of pazopanib-Everolimus is an option that turns out to be thrifty from the first year for the third payer, as well as an impact with a negative sign on the capitation payment unit from the first to the third year as a result of the comparison of the impact between current and new scenario

PCN63
RELIABILITY OF MANUFACTURERS' BUDGET IMPACT ESTIMATES FOR MELANOMA DRUGS IN POLAND
Iwanczuk T, Tatara T, Zaremba A, Misiak J, Krakowian P, Czeczot J
Agency for Health Technology Assessment and Tariff System in Poland (AOTMiT), Warsaw, Poland
OBJECTIVES: To compare the total value of payer's expenditures on vemurafenib and ipilimumab in patients with advanced melanoma estimated in the manufacturers' Budget Impact Analyses (BIAs) submitted with the reimbursement applications to AOTMiT and actual expenditures of the National Health Fund (NHF). **METHODS:** Annual public payer's expenditures estimated in manufacturers' BIAs for vemurafenib and ipilimumab and actual expenditures reported by the NHF were compared. RSSs were not taken into account. Analysed drugs were chosen on the basis of the same indication and financing through the therapeutic programmes in Poland. Actual expenditures were taken from the financial reports of the NHF for the first and second year (actual data on 9 months for expenditures were extrapolated to one year) of reimbursement for each drug. **RESULTS:** For vemurafenib and ipilimumab in patients with advanced melanoma, the sum of total expenditures estimated in BIAs submitted with the reimbursement applications was 123,4 million PLN in the first year and 146,7 million PLN in the second year, and they were higher (96,9 million PLN) and lower (153,8 million PLN) respectively in the first and in the second year than the actual expenditures reported by the NHF. The expenditures estimated in BIAs were overestimated by 27,4% in the first year of reimbursement and were underestimated by 4,7% in the second year of reimbursement. **CONCLUSIONS:** In the case of drugs chosen for this analysis, total payer's expenditures estimated in BIAs submitted with the reimbursement applications were overestimated in comparison to the real life expenditures of the NHF in Poland.

PCN64
BUDGET IMPACT ANALYSIS OF REGORAFENIB FOR THE TREATMENT IN THIRD AND FOURTH LINES OF METASTASIC COLORECTAL CANCER IN SPAIN
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OBJECTIVES: Regorafenib has been recently approved and funded in Spain for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. The aim of this analysis was to analyze the budget impact of regorafenib for the treatment of mCRC in third and fourth lines in patients with an ECOG 0-1 and over a 3 years' time horizon. **METHODS:** A study on prescription pattern for mCRC treatment from Hospital Parc Taulí was considered as the basis to be extended and updated by an expert panel. The economic analysis compared a scenario with regorafenib in front of a baseline scenario based on the treatment patterns resulting from the expert panel, in a patient cohort determined by epidemiological parameters. Only pharmacological costs were included

Subgroup analysis by prior non-liposomal irinotecan therapy in NAPOLI-1: a phase 3 study of nal-IRI±5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is an innovative liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. non-liposomal irinotecan.[1–3]
- NAPOLI-1, a global, phase 3 study, demonstrated that nal-IRI (80 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 irinotecan free base; Q2W) in combination with 5-fluorouracil and leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67; p = 0.0122) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56; *P* = 0.0001) compared with 5-FU/LV alone in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy.[4]
  - The nal-IRI monotherapy arm (120 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m^2 irinotecan free base; Q3W) demonstrated clinical activity (tumor response and reduction in CA19-9 levels), but no significant improvement in OS or PFS vs. the control 5-FU/LV arm.
  - The most frequent grade ≥3 treatment-emergent adverse events (TEAEs) in patients treated with nal-IRI+5-FU/LV were neutropenia (27%; broad definition, including e.g., pancytopenia), diarrhea (13%), vomiting (11%), and fatigue (14%).
- nal-IRI is approved in combination with 5-FU and LV for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy by the US Food and Drug Administration (FDA), the Taiwan FDA, the European Medicines Agency and Australian Therapeutic Goods Administration.
  - NCCN guidelines recommend nal-IRI+5-FU/LV as a second-line option for patients with locally advanced and mPDAC previously treated with gemcitabine-based therapy (category 1), or fluoropyrimidine-based therapy (if no prior irinotecan; category 2A).[5]

- A 2017 eUpdate of the ESMO 2015 Clinical Practice Guidelines states that second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. For fit patients, nal-IRI+5-FU/LV may constitute an active and tolerable second-line treatment option.[6]

- Here, we present results from a *post hoc* subgroup analysis by prior non-liposomal irinotecan-containing therapy from the NAPOLI-1 study.

METHODS

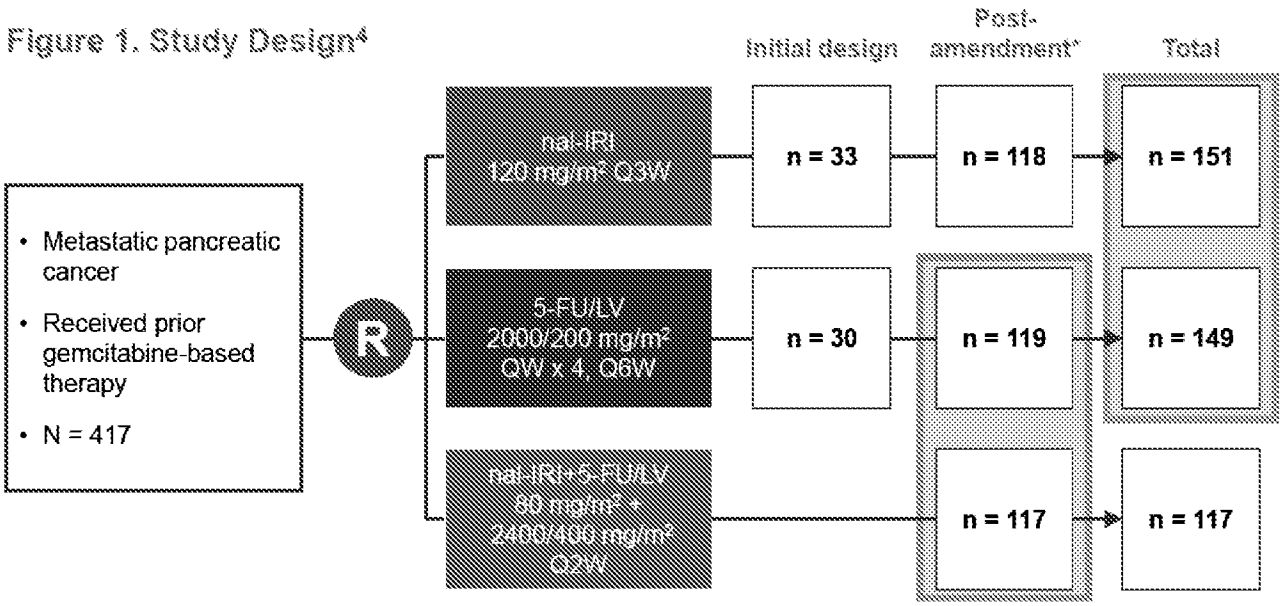
Objectives and Subgroup Analysis

- This *post hoc* subgroup analysis aimed to assess the efficacy and safety of patients receiving nal-IRI+5-FU/LV Q2W (n = 117) vs. 5-FU/LV 4Q6W (n = 119), within subgroups of patients who had or had not received prior non-liposomal irinotecan-based therapy.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study Design[4]



*The study 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. (Trial registered at ClinicalTrials.gov, number NCT01494506).
QW, weekly; Q2W, once every two weeks; Q3W, once every three weeks, Q6W, once every six weeks

Key Inclusion Criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented measurable or non-measurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, 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.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5 × 10^9 cells per L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key Exclusion Criteria

- Active central nervous system metastasis.
- Clinically significant gastrointestinal disorders.
- Severe arterial thromboembolic events <6 months before inclusion.

RESULTS

Patient Characteristics

- In the nal-IRI+5-FU/LV arm, 10% had received prior irinotecan-based therapy; in the 5-FU/LV control arm, 14% of patients had received prior irinotecan-based therapy (Table 1).
- Patient demographics and baseline characteristics were generally similar between treatment arms and within subgroups (Table 1); numerical differences are difficult to interpret due to small patient numbers in the prior-irinotecan subgroup.

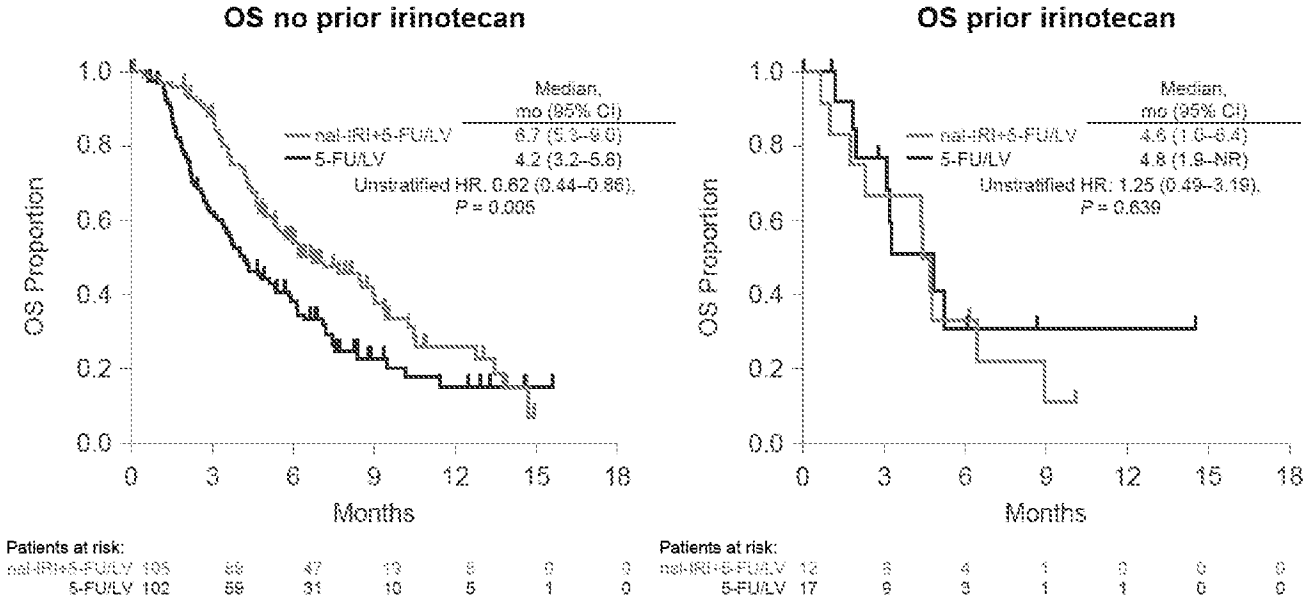
Table 1. Patient demographics and baseline characteristics (ITT population)

	Overall population		No prior irinotecan		Prior irinotecan	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 105 [90%])	5-FU/LV (n = 102 [86%])	nal-IRI+ 5-FU/LV (n = 12 [10%])	5-FU/LV (n = 17 [14%])
Sex, n (%)						
Female	48 (41)	52 (44)	44 (42)	44 (43)	4 (33)	8 (47)
Male	69 (59)	67 (56)	61 (58)	58 (57)	8 (67)	9 (53)
Median age, years (IQR) (Full range)	63 (57–70) (41–81)	62 (55–69) (34–80)	64 (57–70) (41–81)	62 (55–69) (34–80)	58 (50–65) (45–70)	62 (50–66) (41–72)
KPS score, n (%)						
90–100	69 (59)	57 (48)	63 (60)	48 (47)	6 (50)	9 (53)
70–80	45 (38)	61 (51)	39 (37)	54 (53)	6 (50)	7 (41)
50–60	3 (3)	0	3 (3)	0	0	0
Missing	0	1 (1)	0	0	0	1 (6)
Pancreatic tumor location, n (%)						
Head	76 (65)	69 (58)	68 (65)	60 (59)	8 (67)	9 (53)
Other	41 (35)	50 (42)	37 (35)	42 (41)	4 (33)	8 (47)
Mean CA19-9, U/mL (SD)	19884 (66258)	32457 (102301)	21688 (69819)	32912 (10624)	4554 (7348)	29205 (70643)
Liver metastases, n (%)	75 (64)	83 (70)	68 (65)	68 (67)	7 (58)	15 (88)
Previous therapies or procedures, n (%)						
Radiotherapy	24 (21)	27 (23)	22 (21)	24 (24)	2 (17)	3 (18)
Whipple procedure	30 (26)	33 (28)	27 (26)	31 (30)	3 (25)	2 (12)
Biliary stent	15 (13)	8 (7)	14 (13)	7 (7)	1 (8)	1 (6)
Previous anticancer therapy, n (%)						
Gemcitabine alone	53 (45)	55 (46)	49 (47)	47 (46)	4 (33)	8 (47)
Gemcitabine combination	64 (55)	64 (54)	56 (53)	55 (54)	8 (67)	9 (53)
Previous lines of metastatic therapy, n (%)						
0	15 (13)	15 (13)	14 (13)	15 (15)	1 (8)	0
1	62 (53)	67 (56)	61 (58)	66 (65)	1 (8)	1 (6)
≥2	40 (34)	37 (31)	30 (29)	21 (21)	10 (83)	16 (94)

IQR, interquartile range; ITT, intent to treat; KPS, Karnofsky Performance Status; SD, standard deviation.

Overall Survival

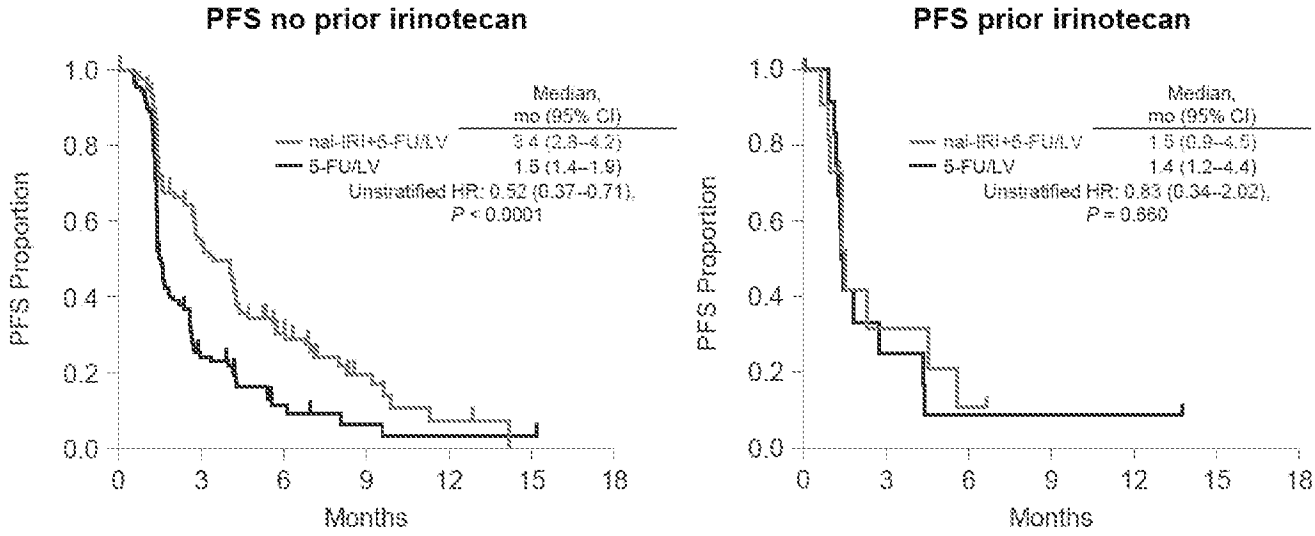
- In patients **without** prior irinotecan-containing therapy, median OS for nal-IRI+5-FU/LV vs. 5-FU/LV was 6.7 months vs. 4.2 months (unstratified HR = 0.62 [95% CI 0.44–0.86]; *P* = 0.005) (Table 2; Figure 2).
- In patients **with** prior irinotecan-containing therapy, median OS for nal-IRI+5-FU/LV vs. 5-FU/LV was 4.6 months vs. 4.8 months (unstratified HR = 1.25 [95% CI 0.49–3.19]; *P* = 0.639) (Table 2; Figure 2).



CI, confidence interval; HR, hazard ratio; mo, month; NR, not reported

Progression-free Survival

- In patients **without** prior irinotecan-containing therapy, median PFS for nal-RI+5-FU/LV vs. 5-FU/LV was 3.4 months vs. 1.5 months (unstratified HR = 0.52 [95% CI 0.37–0.71; *P* < 0.0001) (Table 2; Figure 3).
- In patients **with** prior irinotecan-containing therapy, median PFS for nal-IRI+5-FU/LV vs. 5-FU/LV was 1.5 months vs. 1.4 months (unstratified HR = 0.83 [95% CI 0.34–2.02]; *P* = 0.660) (Table 2; Figure 3).



Patients at risk:							
nal-IRI+5-FU/LV	105	47	21	7	2	0	0
5-FU/LV	102	20	5	2	1	1	0

Patients at risk:							
nal-IRI+5-FU/LV	12	3	1	0	0	0	0
5-FU/LV	17	3	1	1	1	0	0

CI, confidence interval; HR, hazard ratio; mo, month

Tumor Response

- Patients **without** prior irinotecan-based therapy had a significantly higher objective response rate (ORR; 19 [18%] vs. 1 [1%]; $P < 0.0001$) and CA 19 9 response rate (28 [32%] vs. 7 [10%]; $P < 0.0009$) when treated with nal-IRI+5-FU/LV compared with those receiving 5-FU/LV alone (Table 2).

- In patients **with** prior irinotecan-containing therapy, the ORR was 0 for nal-IRI+5-FU/LV and for 5-FU/LV alone. The CA 19-9 response rate was also 0 in both treatment groups (Table 2).

Table 2. Summary of efficacy in patients with and without prior irinotecan-containing therapy (primary analysis data cut-off)

	All patients			No prior irinotecan			Prior irinotecan		
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	Unstratified HR (95% CI) log-rank *P*-value	nal-IRI+ 5-FU/LV (n = 105 [90%])	5-FU/LV (n = 102 [86%])	Unstratified HR (95% CI) log-rank *P*-value	nal-IRI+ 5-FU/LV (n = 12 [10%])	5-FU/LV (n = 17 [14%])	Unstratified HR (95% CI) log-rank *P*-value
Median OS, months (95% CI)	6.1 (4.8–8.9)	4.2 (3.3–5.3)	0.67 (0.5–0.9) $P = 0.012$	6.7 (5.3–9.0)	4.2 (3.2–5.8)	0.62 (0.44–0.86) $P = 0.005$	4.6 (1.0–6.4)	4.8 (1.9–NR)	1.25 (0.49–3.19) $P = 0.639$
Median PFS, months (95% CI)	3.1 (2.7–4.2)	1.5 (1.4–1.8)	0.56 (0.4–0.8) $P = 0.0001$	3.4 (2.8–4.2)	1.5 (1.4–1.9)	0.52 (0.37–0.71) $P < 0.0001$	1.5 (0.9–4.5)	1.4 (1.2–4.4)	0.83 (0.34–2.02) $P = 0.660$
Median TTF, months (95% CI)	2.3 (1.6–2.8)	1.4 (1.3–1.4)	0.60 (0.5–0.8) $P = 0.0002$	2.4 (1.6–2.9)	1.4 (1.3–1.4)	0.57 (0.43–0.76) $P = 0.0002$	1.5 (0.9–4.5)	1.3 (0.6–1.5)	0.73 (0.34–1.56) $P = 0.407$
Best overall response, n (%)									
ORR, n (%)	19 (16)	1 (1)	$P < 0.0001$†	19 (18)	1 (1)	$P < 0.0001$†	0	0	N/A
PR, n (%)	19 (16)	1 (1)		19 (18)	1 (1)		0	0	
SD, n (%)	39 (33)	26 (22)		37 (35)	22 (22)		2 (17)	4 (24)	
Non-CR / non-PD, n (%)	3 (3)	2 (2)		2 (2)	2 (2)		1 (8)	0	
PD, n (%)	34 (29)	56 (47)		30 (29)	50 (49)		4 (33)	6 (35)	
Not evaluable, n (%)	22 (19)	34 (29)		17 (16)	27 (27)		5 (42)	7 (41)	
CBR, n (%)	58 (50)	27 (23)		56 (53)	23 (23)		2 (17)	4 (24)	
CA19-9 response rate,* n/N (%)	28/97 (29)	7/81 (9)	$P = 0.0006$†	28/87 (32)	7/71 (10)	$P = 0.0009$†	0/10 (0)	0/10 (0)	N/A

*Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post baseline CA19-9 measurement; †Two-sided p values from pairwise Fisher's exact test. CI, confidence intervals; CBR, clinical benefit rate (CR + PR + SD); CR, complete response; N/A, not applicable; NR, not reported; ORR, objective response rate; PD, progression of disease; PR, partial response; SD, stable disease; TTF, time to treatment failure

Safety, Dose Modifications and Treatment Exposure

- The safety profile was similar between subgroups in the nal-IRI+5-FU/LV arm (grade ≥3 drug-related AEs: 57 [54%] **without** prior irinotecan and 6 [50%] **with** prior irinotecan).
- Numerical differences between subgroups were observed for alopecia, diarrhea, nausea, fatigue, asthenia and hematologic AEs. However, these are difficult to evaluate due to small patient numbers in the prior irinotecan subgroup (Table 3).

Table 3. Adverse events in patients with and without prior irinotecan-based therapy (safety population)

	No prior irinotecan		Prior irinotecan	
	nal-IRI+5-FU/LV (n = 105)	5-FU/LV (n = 120)	nal-IRI+5-FU/LV (n = 12)	5-FU/LV (n = 14)
Alopecia,* n (%)	15 (14)	6 (5)	0	0
Grade 3/4 non-hematologic AEs in >5% of the overall safety population, n (%)				
Diarrhea, late onset**	15 (14)	5 (4)	0	1 (7)
Vomiting	11 (11)	4 (3)	2 (17)	0
Nausea	8 (8)	4 (3)	1 (8)	0
Fatigue	14 (13)	4 (3)	2 (17)	1 (7)
Febrile neutropenia	2 (2)	0	0	0
Asthenia	8 (8)	8 (7)	1 (8)	1 (7)
Abdominal pain	7 (7)	8 (7)	1 (8)	0
Grade 3/4 hematologic AEs based on laboratory values, n (%)				
Neutrophil count decreased	21 (20)	4 (3)	2 (17)	0
Hemoglobin decreased	7 (7)	7 (6)	1 (8)	0
Platelet count decreased	2 (2)	1 (1)	0	0
Drug-related AE of CTCAE Grade ≥3, n (%)	57 (54)	22 (18)	6 (50)	2 (14)

*According to the CTCAE, version 4, alopecia can only be grade 1 or 2; **>24 h after starting nal-IRI. No grade 3/4 early onset diarrhea reported (≤24 h after starting nal-IRI).
AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

- Dose modifications for TEAEs were needed in 73% of patients in the nal-IRI+5-FU/LV arm **without** prior irinotecan-containing therapy (35%, 64% and 12%, for dose reductions, delays and discontinuations, respectively) vs. 37% of patients in the 5-FU/LV arm (4%, 33%, and 8%, respectively) (Table 4).
- Dose modifications for TEAEs were needed in 50% of patients in the nal-IRI+5-FU/LV arm **with** prior irinotecan containing therapy (17%, 42% and 0%, for dose reductions, delays and discontinuations, respectively) vs. 29% of patients in the 5-FU/LV arm who had received prior irinotecan-containing therapy (0%, 21% and 7%, respectively) (Table 4).

Table 4. Dose modifications and treatment exposure in patients with and without prior irinotecan-containing therapy (safety population)

	No prior irinotecan		Prior irinotecan	
	nal-IRI+ 5-FU/LV (n = 105)	5-FU/LV (n = 120)	nal-IRI+ 5-FU/LV (n = 12)	5-FU/LV (n = 14)
TEAE leading to any dose modification, n (%)	77 (73)	44 (37)	6 (50)	4 (29)
Dose reduction, n (%)	37 (35)	5 (4)	2 (17)	0
Dose delays, n (%)	67 (64)	40 (33)	5 (42)	3 (21)
Treatment discontinuation, n (%)	13 (12)	9 (8)	0	1 (7)
Dose modifications, n (%)	77 (73)	44 (37)	6 (50)	4 (29)
Average relative dose intensity, % nal-IRI 5-FU	 82.4 83.1	 95.5	 90.1 92.1	 96.0
Average duration of treatment exposure, weeks*	15.5	10.5	10.1	10.1

*Duration of exposure is the time from the date of the last administration of study drug + projected days to next dose of study drug administration - date of first study drug administration
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV has demonstrated clinical activity and predictable and manageable toxicity in adult patients with mPDAC previously treated with gemcitabine-based therapy.[4]
- This *post hoc* subgroup analysis from the NAPOLI-1 study shows significant clinical benefit with nal-IRI+5-FU/LV treatment compared with 5-FU/LV in patients who had not received prior non-liposomal irinotecan-based therapy, with a 2.5 month improvement in median OS (6.7 months vs. 4.2 months, unstratified HR 0.62 [95% CI, 0.44–0.86]), and improved median PFS, ORR and CA19-9 response
- This effect does not seem to be observed in patients who had received prior irinotecan and were treated with nal-IRI+5-FU/LV. However, due to the low patient numbers, wide confidence intervals, and variation in baseline characteristics between arms and subgroups, it is difficult to draw any firm conclusions.
- nal-IRI+5-FU/LV demonstrated a similar safety profile in patients with or without prior irinotecan-containing therapy.
- These data strongly support the use of nal-IRI+5-FU/LV in patients without prior irinotecan-containing therapy.
  - Due to the low patient numbers and wide confidence intervals in the prior irinotecan subgroup, additional data are required to confirm the benefit of this combination in patients who have received prior non-liposomal irinotecan.

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Acknowledgments

- This study (ClinicalTrials.gov identifier: NCT01494506) was sponsored by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; rights for nal-IRI now reside with Ipsen in the US (April 2017); PharmaEngine, Inc. holds the rights in Taiwan; Shire holds rights in the rest of the world through a licensing agreement with Ipsen.
- Parul Bhargava (former Shire employee, currently Sunovion Pharmaceuticals Inc, Marlborough, MA, USA) was responsible for statistical analyses for the abstract on which this poster is based.
- This is an encore poster that was originally presented at ESMO-GI 2017 (poster number PD-018)
- Editorial assistance for this poster was provided by Physicians World Europe GmbH, Mannheim, Germany, with financial support from Shire, Zug, Switzerland.

Presented at the European Society for Medical Oncology Asia 2017 Congress, Singapore, 17–19 November 2017.

Disclosures: J-FB: Honoraria received from Bayer Sp, Merrimack; Consultant/Advisor for Bristol-Myers Squibb, Novartis, Lilly Oncology; Travel/Accommodation/Expenses received from Bayer Sp.RAH: Consultant/Advisor for Celgene, BTG, Baxalta (now part of Shire); Speakers' Bureau for Abbott, Ipsen; Travel/Accommodation/Expenses received from Celgene. AW-G: Consultant/Advisor for Merrimack, Pfizer, Newlink Genetics; Research funding from Newlink Genetics, AstraZeneca, BioMed Valley Discoveries, Lilly, AbbVie, Verastem, Precision Biologics. GB: Honoraria received from Servier, Roche, Bayer, Pfizer, Janssen, Novartis, Lilly; Advisory boards for Bayer, Roche, Pfizer, Janssen, Novartis, Lilly, Taiho, Nordic. AD: Honoraria received from Specialised Therapeutics Australia; Consultant/Advisor for Baxalta (now part of Shire), Celgene. GJ: Honoria received from Celgene; Speakers' Bureau for Celgene. DC: Research funding from Amgen, AstraZeneca, Bayer, Celgene, Merrimack, Medimmune, Merck Serono, Sanofi. FSB (relevant to this publication): Consultant fees received from Ipsen and Merrimack; Honoraria from Ipsen: Travel/Accommodation fees from Ipsen and Merrimack; Speaker's Bureau for Ipsen and Merrimack. DDVH (relevant to this publication): Research funding from Merrimack; Consultant for Alphamed Consulting and Baxalta (now part of Shire). L-TC:Consultant/Advisor for ONO, Eli Lilly, MSD, PharmaEngine, Merrimack, TTY Biopharm, SynCore Biotechnology, Five Prime Therapeutics, Novartis; Research funding from Novartis, GSK, Merck Serono, TTY Biopharm, Polaris; Patents/Royalties/Intellectual property with HuniLife Biotechnology. KKM: Former Merrimack employee; Ipsen employee; Merrimack and Blueprint Medicines stockholder. FAdJ: Shire employee and stockholder. JTS: Consultant/Advisor for Merrimack. Other authors have nothing to disclose.

Subgroup analysis by prior nanoliposomal irinotecan therapy in NAPOLI-1: a phase 3 study of nal-IRI5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

228P **Subgroup analysis by prior non-liposomal irinotecan therapy in NAPOLI-1: a phase 3 study of nal-IRI ± 5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy**

J.F. Blanc[1], R. Hubner[2], C-P. Li[3], A. Wang-Gillam[4], G. Bodoky[5], A. Dean[6], Y-S. Shan[7], G. Jameson[8], T. Macarulla Mercade[9], K-H. Lee[10], D. Cunningham[11], C-F. Chiu[12], G. Schwartsmann[13], F. Braiteh[14], D. von Hoff[15], L-T. Chen[16], K. Marrouk[17], F. de Jong[18], J. Sivek[19]

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Background: In the global, randomized phase 3 NAPOLI-1 study, liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) significantly increased median OS vs. 5-FU/LV by 45% (6.1 vs. 4.2 mo; unstratified HR = 0.67 [0.49–0.92]; P = 0.012) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy. Here, we present a subgroup analysis by prior non-liposomal irinotecan (NLI)

Methods: Study methodology has been published (Wang-Gillam; Lancet 2016). Robustness of overall treatment effect was assessed by prospectively-defined subgroups, including prior NLI, based on primary survival analysis data (cut-off February 2014) of the ITT population.

Results: OS, PFS and CA19-9 response rates in patients with (n = 29) and without (n = 207) prior NLI are shown (see Table). In patients without prior NLI, nal-IRI+5-FU/LV (n = 105) improved median OS vs. 5-FU/LV (n = 102) by 2.5 mo to 6.7 mo (HR = 0.62; P < 0.01). Most frequent TEAEs were GI disorders (diarrhea, vomiting, nausea), regardless of prior NLI. ≥Grade 3 TEAEs and TEAEs leading to dose modification were similar in patients with (9 [75%], 6 [50%]) and without (81 [77%]; 77 [73%]) prior NLI in the nal-IRI+5-FU/LV arm.

Conclusions: This post-hoc subgroup analysis shows significant increases for nal-IRI+5-FU/LV vs. 5-FU/LV in OS, PFS and CA19-9 response rates in patients without prior NLI. Outcomes were similar in both arms in patients with prior NLI. The low number of patients with prior NLI preclude firm conclusions from being drawn and further research is needed to explore the impact of prior NLI.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: This study was sponsored by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; rights for nal-IRI now reside with Ipsen in the US (April 2017); PharmaEngine, Inc. holds the rights in Taiwan; Shire holds rights in the rest of the world through a licensing agreement with Ipsen.

Table: 228P

	Prior NLI		
	nal-IRI+5-FU/LV (n = 12 [10.3%])	5-FU/LV (n = 17 [14.3%])	Unstratified HR (95%CI); p-value
Median OS, mo (95%CI)	4.57 (0.99–6.44)	4.83 (1.94–NR)	1.25 (0.49–3.19); *P*=0.64
Median PFS, mo (95%CI)	1.51 (0.92–4.53)	1.43 (1.18–4.40)	0.83 (0.34–2.02); *P*=0.66
CA19-9 response rates, n/N (%)	0/10 (0)	0/10 (0)	N/A
	No prior NLI		
	nal-IRI+5-FU/LV (n = 105 [89.7%])	**5-FU/LV (n = 102 [85.7%])**	
Median OS, mo (95%CI)	6.67 (5.26–8.97)	4.17 (3.15–5.82)	0.62 (0.44–0.86); *P*<0.01
Median PFS, mo (95%CI)	3.45 (2.76–4.24)	1.48 (1.41–1.87)	0.52 (0.37–0.71); *P*<0.0001
CA19-9 response rates, n/N (%)	28/87 (32.2)	7/71 (9.9)	*P*<0.001

Funding: This study by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; editorial assistance was funded by Shire (previously Baxalta), Zug, Switzerland.

Disclosure: J.F. Blanc: Honoraria received from Bayer Sp, Merrimack: Consultant/Advisor for Bristol-Myers Squibb, Novartis, Lilly Oncology; Travel/Accommodation/Expenses received from Bayer Sp. R. Hubner: Consultant/Advisor for Celgene, BTG, Baxalta (now part of Shire); Speakers' Bureau for Abbott, Ipsen; Travel/Accommodation/Expenses received from Celgene. A. Wang-Gillam: Consultant/Advisor for Merrimack, Pfizer, Newlink Genetics; Research funding from Newlink Genetics, AstraZeneca, BioMed Valley Discoveries, Lilly, AbbVie, Verastem, Precision Biologics. G. Bodoky: Honoraria received from Servier, Roche, Bayer, Pfizer, Janssen, Novartis, Lilly; Advisory boards for Bayer, Roche, Pfizer, Janssen, Novartis, Lilly, Taiho, Nordic. A. Dean: Honoraria received from Specialised Therapeutics Australia: Consultant/Advisor for Baxalta (now part of Shire), Celgene. G. Jameson: Honoria received from Celgene; Speakers' Bureau for Celgene. D. Cunningham: Research funding from Amgen, AstraZeneca, Bayer, Celgene, Merrimack, Medimmune, Merck Serono, Sanofi. F. Braiteh. Relevant to this publication: Consultant fees received from Ipsen and Merrimack; Honoraria from Ipsen: Travel/Accommodation fees from Ipsen and Merrimack; Speaker's Bureau for Ipsen and Merrimack. D. von Hoff: Relevant to this publication: Research funding from Merrimack; Consultant for Alphamed Consulting and Baxalta (now part of Shire). L-T. Chen: Consultant/Advisor for ONO, Eli Lilly, MSD, PharmaEngine, Merrimack, TTY Biopharm, SynCore Biotechnology, Five Prime Therapeutics, Novartis; Research funding from Novartis, GSK, Merck Serono, TTY Biopharm, Polaris; Patents/Royalties/Intellectual property with HuniLife Biotechnology. K. Mamluk: Employment – Ipsen: former Merrimack employee Stock and Other Ownership Interests – Blueprint Medicines, Merrimack, F. de Jong: Shire employee and stockholder. J. Siveke: Consultant/advisor: Celgene, Merrimack, Baxalta, Boehringer-Ingelheim, Lilly; Honoraria: Celgene, Merrimack, Baxalta, Lilly; Research funding: Novartis, Boehringer-Ingelheim, Celgene, BMS.

All other authors have declared no conflicts of interest.

PD – 018

Subgroup analysis by prior non-liposomal irinotecan therapy in NAPOLI-1: A phase 3 study of nal-IRI ± 5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

Blanc Jean-Frédéric[1], Hubner Richard[2], Li Chung-Pin[3], Wang-Gillam Andrea[4], Bodoky Gyorgy[5], Dean Andrew[6], Shan Yan-Shen[7], Jameson Gayle[8], Macarulla Teresa[9], Lee Kyung-Hun[10], Cunningham David[11], Chiu Chang-Fang[12], Schwartsmann Gilberto[13], Braiteh Fadi[14], Von Hoff Daniel[15], Chen Li-Tzong[16], Mamluk Khalid[17], Bhargava Parul[18], de Jong Floris[19], Sivek e Jens[20]

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Introduction: In the global, randomized phase 3 NAPOLI-1 study, liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) significantly increased median OS vs. 5-FU/LV by 45% (6.1 vs. 4.2 mo; unstratified HR = 0.67 [0.49–0.92], p=.012) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy. Here, we present a subgroup analysis by prior non-liposomal irinotecan (NLI).

Methods: Study methodology has been published (Wang-Gillam: Lancet 2016). Robustness of overall treatment effect was assessed by prospectively-defined subgroups, including prior NLI, based on primary survival analysis data (cut-off February 2014) of the ITT population.

Results: OS, PFS and CA19-9 response rates in pts with (n = 29) and without (n = 267) prior NLI are shown (see Table). In pts without prior NLI, nal-IRI+5-FU/LV (n = 165) improved median OS vs. 5-FU/LV (n = 102) by 2.5 mo to 6.7 mo (HR = 0.62; p<.01). Most frequent TEAEs were GI disorders (diarrhea, vomiting, nausea), regardless of prior NLI. ≥Grade 3 TEAEs and TEAEs leading to dose modification were similar in pts with (9 [75%]; 6 [50%]) and without (81 [77%]; 77 [73%]) prior NLI in the nal-IRI+5-FU/LV arm.

Conclusion: This post-hoc subgroup analysis shows significant increases for nal-IRI+5-FU/LV vs. 5-FU/LV in OS, PFS and CA19-9 response rates in pts without prior NLI. Outcomes were similar in both arms in pts with prior NLI. The low number of pts with prior NLI preclude firm conclusions from being drawn and further research is needed to explore the impact of prior NLI.

	Prior NLI		
	nal-IRI+5-FU/LV (n = 12 [10.3%])	5-FU/LV (n = 17 [14.5%])	Unstratified HR (95%CI); p-value
Median OS, mo (95%CI)	4.57 (0.89–8.64)	4.93 (1.84–NR)	1.25 (0.48–3.19); p = .64
Median PFS, mo (95%CI)	1.91 (0.92–4.83)	1.48 (1.18–4.40)	0.83 (0.34–2.02); p = .66
CA19-9 response rates, n/N (%)	1/10 (10)	0/10 (0)	NA
	No prior NLI		
	nal-IRI+5-FU/LV (n = 165 [59.7%])	5-FU/LV (n = 102 [65.7%])	
Median OS, mo (95%CI)	6.57 (5.26–8.97)	4.17 (3.15–5.82)	0.62 (0.44–0.86); p < .01
Median PFS, mo (95%CI)	3.45 (2.76–4.24)	1.68 (1.41–1.87)	0.32 (0.23–0.43); p < .0001
CA19-9 response rates, n/N (%)	28/87 (32.2)	7/71 (9.9)	p < .0001

PD-018 Figure 1

Corporate Medical Policy

Bevacizumab in Advanced Adenocarcinoma of the Pancreas

File Name:	bevacizumab_in_advanced_adenocarcinoma_of_the_pancreas
Origination:	3/2010
Last CAP Review:	11/2018
Next CAP Review:	11/2019
Last Review:	2/2019

Description of Procedure or Service

Bevacizumab (Avastin®, Genentech BioOncology) is a humanized monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A). Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis. This policy examines the available evidence for the off-label use of bevacizumab in patients with advanced adenocarcinoma of the pancreas.

In the U.S., pancreatic adenocarcinoma is the tenth most common cancer in men and the fourth leading cause of cancer deaths in men and women. Only 7% of cases are detected at an early stage, and more than 90% of patients develop metastases. The 1-year survival rate is 25%; the 5-year survival rate is 6% overall, and 22% for those diagnosed early with only local disease. For patients with advanced, unresectable disease, the standard of care is gemcitabine. Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) as single-agent first-line treatment for patients with locally advanced (stage II or stage III when surgery is not an option) or metastatic (stage IV) adenocarcinoma of the pancreas, including patients previously treated with 5-fluorouracil. Gemcitabine is sometimes given as part of combination therapy with erlotinib (Tarceva®) which is approved by the FDA for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis, the growth of new vasculature. Without angiogenesis, nutrients, oxygen and other essential molecules reach malignant cells only by passive diffusion from pre-existing blood vessels, which would limit most tumors to diameters of several millimeters. Certain normal physiologic processes (e.g., embryonic development, menstruation, wound healing) require angiogenesis, and some non-cancer pathologic processes are linked to angiogenesis (e.g., macular degeneration, atherosclerosis, psoriasis).

Approximately 89% to 93% of pancreatic cancer patients have a VEGF mutation, which is associated with early recurrence after surgery, liver metastases, and poor prognosis. A VEGF mutation in tumors also correlates with tumor size. Bevacizumab, a vascular endothelial growth factor-specific angiogenesis inhibitor, is used in the treatment of a variety of cancers. Because vascular endothelial growth factor (VEGF) appears to play a role in pancreatic cancer, bevacizumab was considered a promising therapy. The results of 2 phase 2 trials seemed to indicate potential benefit.

Regulatory Status

Bevacizumab for the treatment of advanced pancreatic adenocarcinoma is not a U.S. Food and Drug Administration (FDA)-labeled indication.

Bevacizumab in Advanced Adenocarcinoma of the Pancreas

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Bevacizumab in advanced adenocarcinoma of the pancreas is considered investigational for all applications.

BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Bevacizumab in Advanced Adenocarcinoma of the Pancreas is covered

Not applicable.

Use of bevacizumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

When Bevacizumab in Advanced Adenocarcinoma of the Pancreas is not covered

Bevacizumab is considered **investigational** for treatment of advanced adenocarcinoma of the pancreas.

BCBSNC does not provide coverage for investigational services or procedures.

Bevacizumab is considered investigational when criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Bevacizumab in Advanced Adenocarcinoma of the Pancreas is covered."

Policy Guidelines

Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not a U.S. Food and Drug Administration (FDA) approved indication.

For individuals who have advanced pancreatic cancer and who receive bevacizumab, the evidence includes phase 2, and 3 randomized controlled trials (RCTs) and a BCBSA TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, quality of

life, and treatment-related morbidity. Studies have failed to demonstrate that bevacizumab, either alone or in combination with another therapy, improves overall survival; data for progression free survival have not been consistent. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *C9257, J9035, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual – 5.01.18, 10/6/2009

Senior Medical Director - 2/2010

Specialty Matched Consultant Advisory Panel – 11/2010

BCBSA Medical Policy Reference Manual – 5.01.18, 11/10/2011

Specialty Matched Consultant Advisory Panel 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 9/13/2012

Specialty Matched Consultant Advisory Panel – 12/2012

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 10/15/2013

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 10/9/2014

Specialty Matched Consultant Advisory Panel – 11/2014

Medical Director review 3/2015

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 10/15/2015

Specialty Matched Consultant Advisory Panel – 11/2015

Medical Director review 8/2016

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 10/13/2016

Specialty Matched Consultant Advisory Panel – 11/2016

Specialty Matched Consultant Advisory Panel – 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 11/9/2017

BCBSA Medical Policy Reference Manual [Electronic Version]– 5.01.18, 10/10/2018

Specialty Matched Consultant Advisory Panel – 11/2018

Policy Implementation/Update Information

3/2/10 New Evidence Based Guideline implemented. "Bevacizumab for patients with advanced adenocarcinoma of the pancreas is not recommended." Senior Medical Director review 2/1/2010. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

12/21/10 Specialty Matched Consultant Advisory Panel review 11/29/2010. No changes to the intent of the guideline. (btw)

2/7/12 Added 6th bullet to Description section to indicate; "November 2011: FDA approval withdrawn for breast cancer." Specialty Matched Consultant Advisory Panel review 11/30/2011. Reference added. (btw)

1/15/13 Specialty Matched Consultant Advisory Panel review 12/4/12. No change to policy intent. Reference added. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/13. No change to policy. Reference added. (btw)

1/28/14 Description section updated. (btw)

12/9/14 Reference added. Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)

7/28/15 Evidence based guideline converted to corporate medical policy. Medical Director review. Notification given 7/28/15 for effective date 10/1/15. (lpr)

12/30/15 Updated Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)

12/30/16 Updated Description and Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 11/30/2016. Medical Director review 11/2016. Added HCPCS codes S0353 and S0354 to Billing/Coding section. No change to policy statement. Notification given 12/30/16 for effective date 4/1/17. (lpr)

12/8/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. Reference added. (lpr)

1/15/19 Minor changes made to Description section for clarity. Added code C9257 to Billing/Coding section. References added. Specialty Matched Consultant Advisory Panel review 11/28/2018. (krc)

2/12/19 Added the following statement to "When Covered" section: "Use of bevacizumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached." Under "When Not Covered" section, added the statement "Bevacizumab is considered investigational when criteria are not met regarding FDA labeling **OR** strong endorsement/ support by nationally recognized compendia, as stated under "When Bevacizumab in Advanced Adenocarcinoma of the Pancreas is covered." Added the following statements under "Policy Guidelines" section: "1) Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services. 2) Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia." (krc)

Second-Line Therapy in Gemcitabine-Pretreated Patients With Advanced Pancreatic Cancer

TO THE EDITOR: We read with great interest the article by Kulke et al[1] on second-line therapy with capecitabine and erlotinib in advanced pancreatic cancer. While we congratulate the authors to the results of their well-designed trial, we think that it is about time to reappraise the clinical position and relevance of second-line therapy in advanced pancreatic cancer. During the last years, only few clinical trials (mainly phase II) have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine or a gemcitabine-based combination regimen. However, final results from a randomized study confirming a survival advantage for second-line treatment (compared to best supportive care [BSC] only) are still lacking. A small randomized trial (n = 46) comparing BSC alone versus fluorouracil, folinic acid, and oxaliplatin plus BSC had to be terminated prematurely due to low accrual. Preliminary results from this trial indicated that chemotherapy may prolong median survival by about 2.6 months (2.3 *v* 4.9 months).[2] Based on phase II data, a median survival of about 4 to 6 months (after the initiation of second-line treatment) may be achieved with salvage chemotherapy in selected patients.[1,3] Thus, the use of second-line therapy may also have a possible impact on the survival results of first-line phase III trials. In this context, it may be a general request that results on second-line therapy should be reported in phase III trials evaluating first-line treatment of advanced pancreatic cancer (Table 1). This request becomes specifically important in those trials which set out to define new treatment standards.[4]

To better understand the clinical relevance of second-line therapy, we need to ask how many patients actually received second-line therapy. Only about half of the currently published randomized phase III studies of first-line therapy have reported data on second-line treatment in their study populations (Table 1). The percentage of patients receiving salvage chemotherapy in these randomized studies ranged widely from 16% to 57%.[5,6] To the greatest part, it remains unclear why second-line therapy was not applied. In many patients with progressive disease, second-line therapy is precluded due to a rapid deterioration of performance status. Other patients may not receive salvage therapy since there is no recommended standard of treatment to date. This is of interest since outside of clinical trials—second-line therapy implies off-label use of anticancer agents in most countries.

Randomized clinical trials of second-line therapy are urgently needed in pancreatic cancer to provide evidence-based guidelines of treatment. The increased awareness of pancreatic cancer and improved imaging techniques are factors responsible for earlier diagnosis of advanced disease. As a consequence, an increasing proportion of patients are still in a good performance status when progression on gemcitabine-based therapy is diagnosed. Preliminary data from a clinical trial randomly comparing fluorouracil/folinic acid versus fluorouracil/folinic acid plus oxaliplatin provide first evidence for a possible survival benefit with the use of oxaliplatin in the second-line setting after gemcitabine failure.[7]

Table 1. Selected First-Line, Two-Arm, Phase III Trials Comparing Single-Agent Gemcitabine Versus Gemcitabine Plus a Second Drug in Patients With Advanced Pancreatic Cancer: Data on Overall Survival and Second-Line Therapy

Phase III study	Author	Overall Survival (months)		% Patients Receiving Second-Line Chemotherapy	
		(Gem arm)	(Gem+x arm)	(Gem arm)	(Gem+x arm)
Gem + 5-FU (bolus)	Berlin JD	5.4	6.7	NA	NA
Gem + 5-FU/FA (infusional)*	Riess H	6.2	5.85	36	36
Gem + Capecitabine	Herrmann R	7.2	8.4	57	56
Gem + Capecitabine*	Cunningham D	6.0	7.4	NA	NA
Gem + Cisplatin	Heinemann V	6.0	7.5	17	18
Gem + Oxaliplatin	Louvet C	7.1	9.0	55	55
Gem + Irinotecan	Rocha Lima CM	6.6	6.3	46	39
Gem + Exatecan	Abou-Alfa GK	6.2	6.7	NA	NA
Gem + Pemetrexed	Oettle H	6.3	6.2	43	34
Gem + Marimastat	Bramhall SR	5.5	5.5	19	18
Gem + Tipifarnib	van Cutsem E	6.1	6.4	NA	NA
Gem + Erlotinib	Moore MJ	5.9	6.2	NA	NA
Gem + Cetuximab*	Philip PA	5.9	6.4	NA	NA
Gem + Bevacizumab*	Kindler HL	6.1	5.8	NA	NA

Abbreviations: Gem, gemcitabine; 5-FU, fluorouracil; FA, folinic acid; NA, data not available.
*(abstract publication).

A further aspect is the investigation of new agents. In pancreatic cancer, new treatment strategies have predominantly been explored in the setting of first-line therapy. This is explained by the rather short survival of patients with metastatic pancreatic cancer. The trial by Kulke et al now indicates that capecitabine plus erlotinib is active in gemcitabine-pretreated patients.[1] These results suggest that this all-oral regimen may also be effective in first-line treatment of chemotherapy-naive patients. Currently, an ongoing German multicenter phase III study (ClinicalTrials.gov Identifier: NCT00440167) of the "Arbeitsgemeinschaft Internistische Onkologie" is randomly assigning patients with treatment-naive pancreatic cancer between a capecitabine + erlotinib arm (using the same regimen like Kulke et al) and a gemcitabine + erlotinib arm.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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IN REPLY: We appreciate the comments of Drs Boeck and Heinemann regarding our study of capecitabine and erlotinib in patients with gemcitabine-refractory advanced pancreatic cancer.[1] We concur that the role of second-line treatment has been understudied in this disease. The results of our study, taken together with the data from the other studies they describe, suggest that the administration of second-line therapy has the potential to positively influence overall survival. Larger studies formally investigating the role of second-line therapy in advanced pancreatic cancer are warranted.

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HIGHLIGHT ARTICLE

Second Line Therapy for Advanced Pancreatic Adenocarcinoma: Where Are We and Where Are We Going?

Highlights from the "2010 ASCO Annual Meeting", Chicago, IL, USA, *June 4-8, 2010*

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Summary

Most patients with adenocarcinoma of the pancreas present with locally advanced or metastatic disease. Although single agent gemcitabine is widely accepted as first-line therapy, there is no current standard of care for gemcitabine-refractory patients. Common second-line chemotherapy regimens included oxaliplatin and 5-FU/leucovorin (OFF), gemcitabine and oxaliplatin (GEMOX), oxaliplatin and capecitabine (XELOX), and irinotecan-oxaliplatin. At the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, several new second-line chemotherapy regimens were presented, including gemcitabine and oxaliplatin with imatinib, single agent nab-paclitaxel, and the combination of high-dose capecitabine with oxaliplatin and sorafenib. These abstracts provide exciting new directions for the treatment of gemcitabine-refractory advanced pancreatic cancer.

Introduction

In 2009, 42,470 patients were diagnosed with pancreatic cancer in the United States, and pancreatic cancer remains the fourth leading cause of cancer related death among both men and women [1]. Although surgical resection remains the only potentially curative treatment for adenocarcinoma of the pancreas, only 15-20% of patients present with early-stage disease amenable to surgical resection. For patients with locally advanced or metastatic disease, first-line treatment with single agent gemcitabine has been shown to have a clinical benefit and a modest survival advantage over treatment with bolus 5-fluorouracil (5-FU) [2]. Very few patients who experience progression of disease with first-line gemcitabine chemotherapy have an adequate performance status to warrant the use of second line chemotherapy. As a result, there are very few randomized trials for gemcitabine-refractory patients, and there is no widely accepted standard of care.

What We Knew Prior to ASCO 2010

The use of second-line chemotherapy versus best supportive care was established with the preliminary report of the CONKO-003 trial, in which patients were assigned to best supportive care with or without OFF chemotherapy (oxaliplatin, 5-FU, leucovorin) [3]. Patients receiving chemotherapy were found to have a longer median overall survival. The addition of oxaliplatin to infusional 5-FU and leucovorin has also been shown to result in an improved overall survival of 26 weeks *vs.* 13 weeks when compared with 5-FU and leucovorin alone [4]. The combination of gemcitabine and oxaliplatin has demonstrated efficacy as a second-line therapy in gemcitabine-refractory patients [5, 6]. A clinical benefit has also been seen with the use of irinotecan and oxaliplatin in patients previously treated with gemcitabine [7, 8]. XELOX, the combination of capecitabine and oxaliplatin, has also been used as second line therapy after gemcitabine failure [9]. Single agent paclitaxel has also shown to be an effective second-line chemotherapy agent with a low toxicity profile [10].

Key words 130-nm albumin-bound paclitaxel; capecitabine; gemcitabine-oxaliplatin regimen; Pancreatic Neoplasms

Abbreviations ASCO: American Society of Clinical Oncology; SPARC: secreted protein, acidic and rich in cysteine

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What We Learned at ASCO 2010

Three important abstracts were presented focusing on the use of gemcitabine and oxaliplatin plus imatinib, single agent nab-paclitaxel, and high dose capecitabine, oxaliplatin and sorafenib (Table 1).

Oxaliplatin-Based Regimens

Starling *et al.* presented a dose escalation study of gemcitabine plus oxaliplatin in combination with imatinib in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma [11]. As discussed above, the combination of gemcitabine and oxaliplatin has activity in the first and second line treatment of advanced pancreatic adenocarcinoma. As

Table 1. Summary of 2010 ASCO Annual Meeting abstracts for second-line advanced pancreatic adenocarcinoma

Abstract	Study design	Drugs	Overall survival (median)	Progression free survival (median)
#4155 Starling, *et al.* [11]	Dose escalation	Gemcitabine and oxaliplatin plus imatinib	5.7 months	4.6 months
#4120 Hosein, *et al.* [15]	Phase II	Nab-paclitaxel (abraxane)	7.3 months	1.6 months
#4143 Lubner, *et al.* [12]	Phase II	High-dose capecitabine, oxaliplatin, and sorafenib	Not reported	5.98 months

many pancreatic adenocarcinomas overexpress platelet-derived growth factor receptors (PDGFRs), the combination of imatinib with gemcitabine and oxaliplatin was thought to possibly enhance anti-tumor activity or chemotherapy delivery. Twenty-six patients with gemcitabine refractory locally advanced or metastatic pancreatic cancer were enrolled in the study. Doses of gemcitabine at 1,000 mg/m^2 (day 1) and oxaliplatin 85 mg/m^2 (day 2) with intermittently administered imatinib (400 mg) for 7 days were safely tolerated. The median number of cycles given was 4. Two patients showed a partial response, and eleven patients demonstrated stable disease. The median progression free survival and overall survival were 4.6 months (95% CI: 2.3-6.9 months) and 5.7 months (95% CI: 4.6 to 6.7 months), respectively.

Lubner *et al.* presented the results of the phase II portion of an open label phase Ib/II trial involving high dose capecitabine with oxaliplatin, and sorafenib [12]. As described above, the combination of capecitabine and oxaliplatin (XELOX) has demonstrated activity in second line therapy of patients with advanced pancreatic adenocarcinoma. In this study, 24 patients received sorafenib 200 mg *bid* with oxaliplatin 85 mg/m^2 i.v. on days 1 and 15, followed by high-dose capecitabine (2,250 mg/m^2 *po* every eight hours for six doses) also on days 1 and 15, every 28 days. Only one patient experienced grade 3 hand-foot syndrome. Two patients demonstrated a partial response, and thirteen patients demonstrated stable disease. Progression free survival was 5.98 months, and the median overall survival endpoint has not yet been reached, although the 6-month overall survival was 62%. Although further study is needed, this combination may prove efficacious in patients who cannot tolerate other forms of chemotherapy.

Novel Taxane Regimens

Secreted protein, acidic and rich in cysteine (SPARC) is a protein frequently expressed by stromal fibroblasts adjacent to pancreatic adenocarcinomas [13]. Previous research has demonstrated that a series of patients whose pancreatic cancer stromal fibroblasts expressed SPARC had a worse prognosis than patients whose tumor stroma did not express SPARC [13]. Nab-paclitaxel, a nanoparticle albumin-bound form of paclitaxel, is thought to increase tumor accumulation of paclitaxel through binding of albumin to SPARC [14]. A phase I/II study presented at the 2009 American Society of Clinical Oncology (ASCO) Annual Meeting demonstrated the safety and efficacy of the combination gemcitabine and nab-paclitaxel; SPARC positive status by immunohistochemistry was associated with a higher response rate and longer progression free survival [14].

At 2010 ASCO Annual Meeting, Hosein *et al.* presented a phase II study evaluating the effectiveness of nab-paclitaxel monotherapy in patients with advanced pancreatic cancer who progressed on previous gemcitabine-based therapy [15]. Nineteen patients received nab-paclitaxel 100 mg/m^2 weekly for three weeks every 28 days. One patient demonstrated a partial response and six demonstrated stable disease. The median progression free survival and overall survival were 1.6 months (95% CI: 1.5-3.4 months) and 7.3 months (95% CI: 2.8-13.3 months), respectively. Five patients were alive at a median follow-up of 12.7 months. Immunohistochemical analysis of tissue samples is ongoing to determine the predictive value of SPARC expression in these patients.

Commentary

For patients with locally advanced or metastatic pancreatic adenocarcinoma refractory to gemcitabine monotherapy, options remain limited. For patients with adequate performance status, the CONKO-003 trial helped to establish the superiority of second line chemotherapy versus best supportive care [3]. The CONKO-003 trial also demonstrated an overall survival benefit with the addition of oxaliplatin to infusional 5-FU and leucovorin (OFF regimen) [4]. At the 2010 ASCO Annual Meeting, the combination of high-dose capecitabine with oxaliplatin and sorafenib was shown to be beneficial in selected patients [12]. Previous studies have also demonstrated the effectiveness of gemcitabine and oxaliplatin therapy in patients with gemcitabine refractory advanced pancreatic adenocarcinoma [5, 6]. At the 2010 ASCO Annual Meeting, a dose escalation study was presented involving the combination of gemcitabine and oxaliplatin with imatinib [11]. Small series have demonstrated a worse prognosis in patients whose pancreatic cancer stromal fibroblasts expressed SPARC [13]. These patients may respond to nab-paclitaxel, a nanoparticle albumin-bound form of paclitaxel which is thought to increase tumor accumulation of paclitaxel through binding of albumin to SPARC [14]. The efficacy of single-agent nab-paclitaxel was demonstrated at the ASCO 2010 Annual Meeting [15]. Although further phase III studies and longer follow-up data are needed, these abstracts build upon previous research and provide exciting new directions for the treatment of gemcitabine-refractory advanced pancreatic cancer.

Conflict of interest The authors have no potential conflicts of interest

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New Therapeutic Directions for Advanced Pancreatic Cancer: Targeting the Epidermal Growth Factor and Vascular Endothelial Growth Factor Pathways

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate the existing chemotherapeutic options for advanced pancreatic cancer.
2. Interpret data from trials of HER-1/EGFR- and VEGFR-targeted agents in advanced pancreatic cancer.
3. Take advantage of the potential of biomarkers in selecting optimal molecular-targeted therapies for advanced pancreatic cancer.

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ABSTRACT

In advanced pancreatic cancer, single-agent gemcitabine became the standard therapy approximately 10 years ago. Subsequently, combinations of gemcitabine with fluorouracil, cisplatin, irinotecan, oxaliplatin, or pemetrexed produced no clear survival benefit. Among the newer approaches, targeting human epidermal growth factor receptor (HER-1/EGFR) shows promise. The U.S. Food and Drug Administration recently approved erlotinib (a HER-1/EGFR tyrosine kinase inhibitor) combined with gemcitabine for the first-line treatment of advanced pancreatic cancer. This combination showed a statistically significant survival benefit over gemcitabine alone in locally advanced or metastatic disease (the median overall survival time was 6.24 months versus 5.91 months; hazard ratio, 0.82; $p = .038$); however, the clinical significance of this survival difference has been questioned. Additionally, a large phase III trial where the addition of cetuximab (an anti–HER-1/EGFR monoclonal antibody [mAb]) to gemcitabine failed to result in a longer overall survival time than with gemcitabine alone has been reported. Targeting vascular endothelial growth factor (VEGF) with bevacizumab (a recombinant, humanized IgG_1 mAb that binds to VEGF) in combination with gemcitabine was investigated in a phase II trial, with promising outcomes that were unfortunately not supported by a subsequent phase III study. While the future treatment of pancreatic cancer may be influenced by the potential of certain biomarkers to predict better response to

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molecular-targeted therapies, allowing individualization of patient therapy, there are currently no clear candidates, and this remains an interesting area for further investigation. *The Oncologist* 2008;13:289–298

Introduction

Pancreatic cancer is the thirteenth most common cancer and the eighth leading cause of cancer death worldwide [1]. In the U.S. it is the fourth leading cause of cancer-related deaths in males and females [2]. The prognosis for pancreatic cancer is extremely poor, with 98% of patients expected to die from the disease [3]. Progress in the management and early detection of pancreatic cancer has been slow. Because of inherent difficulties in early detection and a high risk for metastases, few patients with pancreatic cancer (15%–20%) present with resectable disease, where surgery offers a chance of a cure [4].

In locally advanced, unresectable disease, patients typically receive 5-fluorouracil (5-FU)-based chemoradiation or chemotherapy alone [4]. The benefits of chemoradiation over chemotherapy alone in locally advanced disease have not been well established [5]. For patients with advanced, metastatic pancreatic cancer, the median survival time is just 4–6 months [6, 7]. The common symptoms of progressive disease are severe pain, nausea, weight loss, and weakness, and treatment is generally palliative at best. Since single-agent gemcitabine became the standard treatment for advanced pancreatic cancer approximately 10 years ago [8], most strategies to improve the management of this disease have been unsuccessful, and it is only recently that some progress has been made.

Our understanding of the underlying genetic and molecular abnormalities that drive the development of pancreatic cancer has expanded significantly over the last decade. Alterations to oncogenes and tumor suppressor genes, such as *K-Ras*, *TP53*, and $p16^{INK4}$ are thought to play a critical role in the development of pancreatic cancer, as are changes in the expression of a range of proteins involved in the control of the cell cycle, proliferation, apoptosis, and invasiveness, such as Bcl-2, and the human epidermal growth factor receptor (HER-1/EGFR) [9, 10]. In addition, a number of growth factors, such as vascular endothelial growth factor (VEGF), transforming growth factor β, fibroblast growth factors, and nerve growth factor, are known to be expressed at higher levels in chronic pancreatitis and pancreatic cancer [9]. These observations have allowed for the rational development of targeted therapies for this hard-to-treat disease.

Gemcitabine Combinations for Advanced Disease

Between 1997 and 2005, gemcitabine was combined with several agents in investigational clinical studies (Table 1). Trials were undertaken with gemcitabine plus either 5-FU, cisplatin, irinotecan, oxaliplatin, pemetrexed, or exatecan [11–17]. Disappointingly, while tumor response and time to cancer progression were greater with some of these regimens, no clear survival benefit has been reported. Higher rates of grade 3 or 4 toxicities were also observed with chemotherapeutic additions.

One exception might have been the addition of capecitabine to gemcitabine. In 2005, preliminary survival data from a phase III study were reported for gemcitabine plus capecitabine, an oral fluoropyrimidine that is metabolized to 5-FU in tumor cells. The hazard ratio (HR) for overall survival (OS) was 0.80 ($p = .026$). The median survival time was 6 weeks longer in the combination arm [17]. The final results of that trial are awaited; however, it should be noted that the addition of 5-FU to gemcitabine [11, 18] failed to produce longer survival than with gemcitabine alone in previous randomized trials.

An alternative strategy to improve the efficacy of gemcitabine was to prolong its infusion time. Fixed dose rate (FDR) infusion gemcitabine (10 mg/m^2 per minute) is based on the observation that the triphosphate form of gemcitabine, one of gemcitabine's active metabolites, was greater in leukemia cell lines with a longer incubation time [19]. The clinical benefit of this approach has been postulated but not clearly proved [20]. Higher 1-year and 2-year survival rates were reported with FDR versus standard delivery in a small randomized phase II trial, supporting further evaluation [21]. In a subsequent phase II study, combining FDR gemcitabine with cisplatin for metastatic pancreatic cancer was well tolerated but did not appear to be superior to other gemcitabine/platinum-based regimens [22]. A recently reported phase III trial compared standard gemcitabine by 30-minute infusion (1,000 mg/m^2) with FDR gemcitabine (1,500 mg/m^2 over 150 minutes) and with FDR gemcitabine (1,000 mg/m^2 over 100 minutes) plus oxaliplatin (100 mg/m^2) (GEMOX) [23]. The complete/partial tumor response rates were 5% with gemcitabine 1,000 mg/m^2 over 30 minutes, 10% with FDR gemcitabine, and 9% with GEMOX. The median survival times for patients in these arms were 4.9, 6.0, and 5.9 months, respectively, with 1-year survival rates of 17%, 21%, and 21%, respectively. However, neither the HR nor p-value targets for significance ($\geq$0.75; $p = .025$) were met with FDR or GEMOX versus standard gemcitabine. Grade 3 or 4 toxicity (myelosuppression) was highest in the FDR arm, and GEMOX was associated with treatment-related

Table 1. Key phase III trials of cytotoxic agents in advanced pancreatic cancer

Regimen	Results versus gemcitabine monotherapy
5-Fluorouracil + gemcitabine [11]	OS, 6.7 versus 5.4 months (p = .09) PFS, 3.4 versus 2.2 months (p = .022) RR, 9.9% versus 5.6%
Irinotecan + gemcitabine [12]	OS, 6.3 versus 6.6 months (p = .789) 1-year survival, 21% versus 22% TTP, 3.5 versus 3 months (p =.352) RR, 16.1% versus 4.4% (p < .001)
Cisplatin + gemcitabine [13]	PFS, 5.3 versus 3.1 months (p = .053) OS, 7.5 versus 6.0 months (p = .15) RR, 10.2% versus 8.2%
Oxaliplatin + gemcitabine [14]	OS, 9 versus 7.1 months (p = .13) PFS, 5.8 versus 3.7 months (p = .04) RR, 26.8% versus 17.3% (p = .04)
Pemetrexed + gemcitabine [15]	OS, 6.2 versus 6.3 months (p = .848) 1-year survival, 21.4% versus 20.1% (p = .718) PFS, 3.9 versus 3.3 months (p = .11) TTF, 3 versus 2.2 months (p = .368) RR, 14.8% versus 7.1% (p = .004)
Exatecan + gemcitabine [16]	OS, 6.7 versus 6.2 months (p = .52) TTP, 3.7 versus 3.8 months (p = .22) RR, 6.9% versus 5.2%
Capecitabine + gemcitabine [17]	OS, 7.4 versus 6 months (HR, 0.8; p = .026)[a] RR, 14% versus 7% (p = .008)[a]

[a]Preliminary data.
Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, response rate; TTF, time to treatment failure; TTP, time to progression.

neuropathy. The investigators concluded that there was no significant benefit of either experimental regimen over gemcitabine by 30-minute infusion.

Advances in Molecular-Targeted Therapies

Initial experiences of combining gemcitabine with molecular-targeted agents were also disappointing (Table 2). Adding the matrix metalloproteinase inhibitor marimastat to gemcitabine failed to result in greater efficacy, and talomastat was associated with a worse outcome than with gemcitabine alone [24–27]. Other molecular-targeted therapies include tipifarnib, a farnesyl-transferase inhibitor (which is implicated in K-Ras regulation), G17 DT (a novel immunoconjugate that targets gastrointestinal-tumor growth factor G17 gastrin), and HER-1/EGFR and VEGF inhibitors, all of which failed to produce longer survival times [28–32].

Despite such setbacks, new approaches to pancreatic cancer treatment are emerging, driven by increased knowledge of the underlying molecular biology of this disease. HER-1/EGFR has a role in carcinogenesis across many types of cancer, and greater coexpression of HER-1/EGFR and its ligand is common in pancreatic tumors [33–38]. This coexpression has been shown to stimulate tumor cell proliferation, and elevated HER-1/EGFR levels are linked to poor disease outcomes and lower sensitivity to chemotherapy [39, 40]. Blocking HER-1/EGFR should therefore help to stabilize tumor growth and improve prognosis via the inhibition of multiple HER-1/EGFR downstream signaling pathways [33, 40].

Erlotinib

Erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA), a small-molecule HER-1/EGFR tyrosine kinase inhibitor (TKI), acts on the intracellular domain of this receptor, preventing receptor activation and inhibiting downstream signal transduction and cell proliferation [41]. Erlotinib received U.S. Food and Drug Administration approval when combined with gemcitabine as first-line ther-

Table 2. Key phase III trials of molecular-targeted agents in advanced pancreatic cancer

Agent class	Regimen	Results versus gemcitabine monotherapy
MMP inhibitor	Marimastat [24]	OS, 105–125 versus 167 days (p = .19) 1-year survival, 14%–20% versus 19% PFS, 56–59 versus 115 days (p = .0001) TTP, 59–64 versus 84 days (p = .80) RR, 3% versus 26%
MMP inhibitor	Gemcitabine + marimastat [25]	OS, 165.5 versus 164 days (p = .95) 1-year survival, 18% versus 17% PFS, 92.5 versus 96 days (p = .68) TTP, 107 versus 89 days (p = .70) RR, 11% versus 16%
MMP inhibitor	Talomastat [26]	OS, 3.74 versus 6.59 months (p < .001) 1-year survival, 10% versus 25% PFS, 1.68 versus 3.5 months (p < .001) RR, <1% versus 5%
Ras-farnesyl-transferase inhibitor	Gemcitabine + tipifarnib [28]	OS, 193 versus 182 days (p = .75) 1-year survival, 27% versus 24% PFS, 112 versus 109 days RR, 6% versus 8%
HER-1/EGFR inhibitor	Erlotinib + gemcitabine [29]	OS, 6.4 versus 6 months (HR, 0.81; p = .028) PFS, 3.8 versus 3.5 months (HR, 0.76; p = .006) RR, 8.6% versus 7.9%
HER-1/EGFR inhibitor	Cetuximab [30]	OS, 6.5 versus 6 months (p = .14) PFS, 3.5 versus 3 months (p = .058) RR, 7% versus 7%
VEGF inhibitor	Bevacizumab [31]	OS, 5.8 versus 6.1 months (p = .78) PFS, 4.7 versus 4.9 months (p = .99) RR, 11% versus 10%

Abbreviations: HER-1/EGFR, human epidermal growth factor receptor; HR, hazard ratio; MMP, matrix metalloproteinase; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression; VEGF, vascular endothelial growth factor.

apy in locally advanced or metastatic pancreatic cancer based on a statistically significant survival benefit over gemcitabine alone [29, 42]. In the pivotal phase III trial (National Cancer Institute of Canada PA.3), patients receiving erlotinib (100 mg/day) plus gemcitabine (1,000 mg/m^2 weekly) had a median survival time of 6.24 months, compared with 5.91 months in the gemcitabine plus placebo arm. The HR for risk of death was 0.82 in favor of the gemcitabine plus erlotinib arm, representing an 18% relatively longer OS time (p = .038) [29]. Secondary endpoint results from the PA.3 trial showed a 1-year survival rate of 23% in the erlotinib plus gemcitabine arm, versus 17% with gemcitabine monotherapy (p = .023). The progression-free survival (PFS) duration was also significantly longer with the combination regimen (3.75 versus 3.55 months; HR, 0.77; p = .004).

The clinical significance of these efficacy results has been questioned by several investigators and treating physicians. The benefit derived from the addition of erlotinib to gemcitabine cannot be predicted based on patient characteristics as assessed by the standard processes performed in advanced and metastatic pancreatic cancer. The treatment of pancreatic cancer may be influenced by the potential of certain biomarkers to predict better response to molecular-targeted therapies (as seen in non-small cell lung cancer [NSCLC] with erlotinib and another HER-1/EGFR TKI gefitinib; also in colorectal cancer with cetuximab) [43–51]. The advantage of individualizing therapy to patients could be possible if we could better understand which factors predict response to treatment. Research into predictive markers in pancreatic cancer is in its infancy. The investigation of HER-1/EGFR expression in tumor samples from

patients in PA.3 did not find a correlation with response. However, this remains an interesting area for further research, as any biomarker would help simplify drug choice, should the portfolio of options for advanced pancreatic cancer continue to widen.

The combination of gemcitabine and erlotinib was well tolerated; grade 3 or 4 toxicities were similar, except for diarrhea and cutaneous rash, which were more frequent with the two-drug combination (6% each). Patients with advanced pancreatic cancer who experienced grade 2 rash or higher ($n = 102$) had a reported median survival time of 10.5 months and a 1-year survival rate of 43%. A similar observation has been reported in patients with NSCLC treated with erlotinib or gefitinib (Iressa®; AstraZeneca Pharmaceuticals, LP, Macclesfield, UK) and in colon cancer patients treated with cetuximab (Erbitux®; ImClone Systems, Inc., New York) [52–54]. This cannot be explained by patients who stay on treatment longer being at greater risk for rash, but may be an indication of interpatient variability in drug absorption or metabolism, or the strength of the immune system [29]. This observation can only be validated and confirmed by a well-designed randomized clinical trial in which the efficacy of a HER-1/EGFR inhibitor "dosed to rash" (i.e., dose increased until rash is experienced) is compared with the same HER-1/EGFR inhibitor at standard doses. However, regardless of the cause, it may be advantageous to continue treatment of pancreatic cancer patients exhibiting HER-1/EGFR inhibitor–related rash, and provide the appropriate management for the rash based on its severity [55].

The possibility of building on the efficacy provided by erlotinib and gemcitabine has been evaluated. A phase I study of erlotinib plus gemcitabine and paclitaxel plus radiation, followed by maintenance with erlotinib, for locally advanced pancreatic cancer resulted in a partial response rate of 46% and median survival time of 14 months [56]. These results are supported by a second phase I trial of erlotinib plus gemcitabine and radiation for patients with locally advanced, unresectable pancreatic cancer [57].

Erlotinib has been investigated as second-line therapy in pancreatic cancer patients previously treated with gemcitabine. Disappointing results were reported in a retrospective analysis of 13 patients treated with single-agent erlotinib. No responses and a median time to progression (TTP) of only 1 month were observed [58]. A phase II study of erlotinib combined with capecitabine for gemcitabine-refractory pancreatic cancer demonstrated a median survival time of 5.7 months. Erlotinib plus capecitabine combination therapy had a reasonable safety profile, with the most common grade 3 or 4 toxicities including diarrhea (14%), rash (14%), hand–foot syndrome (11%), stomatitis (7%), and thrombosis (7%) [59]. The clinical application of this two-drug combination awaits a prospective comparative trial.

Cetuximab

Cetuximab, an anti–HER-1/EGFR monoclonal antibody (mAb), has also been evaluated as a treatment for pancreatic carcinoma. This agent blocks the extracellular domain of HER-1/EGFR to prevent receptor activation (either ligand dependent or independent) and signaling [60, 61]. Cetuximab given alone or combined with radiation was recently approved in the U.S. and the European Union for head and neck squamous cell carcinoma in patients expressing HER-1/EGFR. Cetuximab was previously approved for HER-1/EGFR-positive metastatic colorectal cancer (either as a single agent or in combination with irinotecan, in patients who can tolerate this chemotherapy).

Adding gemcitabine to cetuximab in pancreatic xenograft models increased the inhibition of tumor regression, growth, or metastasis [62]. Phase I studies suggested that cetuximab alone and in combination with chemotherapy was tolerable, with HER-1/EGFR inhibitor–related rash as the most frequent side effect [40]. In a phase II study, patients screening positively for HER-1/EGFR were treated with cetuximab at an initial dose of 400 mg/m^2 followed by 250 mg/m^2 weekly for 7 weeks. Gemcitabine was administered at 1,000 mg/m^2 for 7 weeks, followed by 1 week of rest; in subsequent cycles, cetuximab was administered weekly, and gemcitabine was administered weekly for 3 weeks at 4-week intervals [63]. The median OS time for patients treated with this regimen was 7.1 months, the median TTP was 3.8 months, and the 1-year PFS and OS rates were 12% and 31.7%, respectively. Twelve percent of patients achieved a partial response, and 63.4% had stable disease. The most frequently reported grade 3 or 4 adverse events were neutropenia (39%), asthenia (22%), abdominal pain (22%), and thrombocytopenia (17%) [63].

An open-label, randomized phase III trial of gemcitabine monotherapy or gemcitabine plus cetuximab first line for patients with locally advanced, unresectable or metastatic pancreatic cancer was subsequently initiated (Southwest Oncology Group S0205) [64]. More than 700 patients were enrolled in centers throughout the U.S. and Canada. Unfortunately, preliminary reports indicate that this trial failed to meet its primary study endpoint of a statistically longer OS time [30]. The median OS time for gemcitabine plus cetuximab was 6.5 months versus 6 months for gemcitabine alone (HR, 1.09; $p = .14$). The median PFS time was 3.5 months for gemcitabine plus cetuximab versus 3.0 months for gemcitabine alone (HR, 1.13; $p = .58$). The

Table 3. Ongoing clinical trials with HER-1/EGFR- and VEGF(R)-targeted agents in patients with advanced pancreatic cancer [64]

Regimen	Phase	Indication
Capecitabine + gemcitabine + erlotinib	I	Advanced disease
Valatinib + gemcitabine	I/II	Advanced disease
Erlotinib + gemcitabine + bevacizumab + capecitabine	I/II	Advanced disease
Lapatinib + gemcitabine	II	Metastatic disease
Gemcitabine + bevacizumab + erlotinib	II	Locally advanced or metastatic disease
Genistein + gemcitabine + erlotinib	II	Advanced or metastatic disease
Gemcitabine + capecitabine + bevacizumab	II	Metastatic or unresectable disease
Bevacizumab + gemcitabine + 5-fluorouracil	II	Advanced disease
Bevacizumab + gemcitabine + oxaliplatin	II	Metastatic disease
Gemcitabine + cisplatin + bevacizumab	II	Metastatic disease
Cetuximab + gemcitabine + oxaliplatin	II	Advanced or metastatic disease
Ixabepilone + cetuximab	II	Metastatic disease
Sunitinib	II	Metastatic disease
Cetuximab + bevacizumab ± gemcitabine (FDR)	II (randomized)	Advanced or metastatic disease
Bevacizumab + gemcitabine + cetuximab/erlotinib	II (randomized)	Advanced disease
Irinotecan + docetaxel ± cetuximab	II (randomized)	Metastatic disease
Erlotinib + gemcitabine + bevacizumab versus erlotinib + gemcitabine	III	Metastatic disease
Erlotinib + capecitabine followed by gemcitabine versus erlotinib + gemcitabine followed by capecitabine	III	Metastatic disease

Abbreviations: FDR, fixed dose rate; HER-1/EGFR, human epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

therapeutic value of cetuximab for treating advanced pancreatic cancer remains unclear.

Data have recently been reported for a randomized phase II trial of the nongemcitabine combination of irinotecan plus docetaxel with or without cetuximab, as first-line therapy in patients with advanced pancreatic cancer. In total, 47 patients received chemotherapy alone, 45 received chemotherapy plus cetuximab. The efficacy results (including the response rate and PFS and OS times) were slightly better for the cetuximab arm (7% versus 2.3%, 4.5 months versus 2.8 months, and 7.4 months versus 6.5 months, respectively) but not historically different from what has been observed with gemcitabine. However, high toxicity was observed with both regimens, with high rates of grade 3 or 4 neutropenia and diarrhea observed in the cetuximab arm [65].

Bevacizumab

As the overexpression of VEGF and its receptors VEGFR-1, VEGFR-2, and VEGFR-3 promote tumor growth via paracrine angiogenic and autocrine mitogenic pathways [66], targeting the VEGF pathway holds promise for the treatment of advanced pancreatic cancer. Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a recombinant, humanized IgG_1 mAb that binds to VEGF, disrupting its interactions with VEGFR-1 and VEGFR-2. It is approved in combination with i.v. 5-FU–based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer, and in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous NSCLC [67]. Bevacizumab was investigated in combination with gemcitabine in a phase II trial of patients with advanced pancreatic tumors [68]. Fifty-two patients were enrolled and received gemcitabine (1,000 mg/m^2 i.v. over 30 minutes) on days 1, 8, and 15 every 28 days. Bevacizumab (10 mg/kg) was administered after gemcitabine on days 1 and 15. Eleven patients (21%) had confirmed partial responses, and 24 (46%) had stable disease. The median survival time was 8.8 months, the median PFS time was 5.4 months, and the 6-month survival rate was 77% [68]. These results supported the initiation of a phase III study (Cancer and Leukemia Group B 8030) [64]. However, an interim analysis on 64% of the acquired information for OS led to early termination of the trial [31]. Analysis of the acquired data showed no significant differ-

Table 4. Ongoing phase I and II clinical trials of other molecular-targeted agents for advanced or metastatic pancreatic cancer [64]

Agent	Target	Regimen	Phase	Indication
KU-0059436	PARP	+ Gemcitabine	I	Advanced disease
AZD0530	Src/Abl	+ Gemcitabine	I/II	Locally advanced disease or metastatic disease
MGCD0103	HDAC	+ Gemcitabine	I/II	Locally advanced disease or metastatic disease
Imatinib	Abl	+ Gemcitabine	II	Locally advanced disease or metastatic disease
ISIS-2503	Ha-*Ras*	+ Gemcitabine	II	Advanced disease or metastatic disease
Triapine (3-AP)	Ribonucleotide reductase	+ Gemcitabine	II	Locally advanced disease
WX-671	UPA	± Gemcitabine	II (randomized)	Locally advanced disease
Dasatinib	Src/Abl	Monotherapy	II	Metastatic disease
Everolimus	mTOR	Monotherapy (second-line)	II	Metastatic disease

Abbreviations: HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; PARP, poly ADP-ribose polymerase; UPA, urokinase plasminogen activator.

ences between the OS times (HR, 1.03; $p = .78$) or PFS times (HR, 1.0; $p = .99$) for the gemcitabine (OS, 6.1 months; PFS, 4.9 months) or gemcitabine plus bevacizumab (OS, 5.8 months; PFS, 4.7 months) arms [31]. The discrepancies in the results of the phase II and III trials are probably related to patient selection in the phase II trial. Other VEGF inhibitors are being studied in this disease and may help to better understand the value of targeting this pathway in this disease.

Other HER-1/EGFR- and VEGF(R)-Targeted Agents in Clinical Development for Advanced Pancreatic Cancer

Sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT) is a multikinase inhibitor targeting VEGFR, platelet-derived growth factor receptor (PDGFR), Kit, and Flt-3 that is indicated for the treatment of patients with advanced renal cell carcinoma [69]. A recent phase II trial enrolled 17 patients with unresectable pancreatic cancer who had received no prior chemotherapy. All patients had good organ function and a performance status score of 0–1. Patients received gemcitabine (1,000 mg/m^2) i.v. over 30 minutes on days 1, 8, and 15 of a 28-day cycle plus sorafenib (400 mg orally twice a day on days 1–28). No responses were observed; three patients (23%) had stable disease and the median survival time was only 4 months. The authors concluded that sorafenib plus gemcitabine was well tolerated but inactive in patients with advanced pancreatic cancer [70]. Despite these negative results, a phase II randomized trial of sorafenib with gemcitabine is under way in patients with pancreatic cancer [64].

Another VEGFR-targeted agent, the small-molecule TKI axitinib (Pfizer Inc., New York), is also being studied in patients with advance pancreatic cancer. Data from a randomized phase II trial have recently been reported for this agent in combination with gemcitabine [71]. In total, 103 patients were enrolled and 69 received axitinib plus gemcitabine. The response rate was 7% in the experimental arm, compared with 0% in the gemcitabine control arm. In addition, the combination regimen demonstrated good tolerability and reduced the likelihood of death by 26% (HR, 0.74) compared with gemcitabine alone. A randomized, controlled, phase III trial of axitinib plus gemcitabine for locally advanced and metastatic pancreatic cancer is planned.

Other agents that target HER-1/EGFR or VEGFR are in clinical development. Phase II trials are under way for sunitinib (Sutent®; Pfizer Inc., New York), a VEGFR- and PDGFR-targeted small-molecule TKI, valatinib (Pfizer Inc., New York), a VEGFR-targeted small-molecule TKI, and lapatinib (Tykerb®; GlaxoSmithKline plc., London, UK), a HER-1/EGFR- and HER-2–targeted small-molecule TKI [64].

Considerations for Selecting Molecular-Targeted Agents

As a result of pioneering clinical trial research and advances in molecular biology, it appears that treatment options for pancreatic cancer are finally beginning to expand. Agents

that target the HER-1/EGFR or VEGF pathway are at the forefront of development, and a significant number of ongoing trials continue to explore the potential of these therapies for this disease (Table 3 [64]). In addition, a wide range of other targeted agents is also in clinical development for advanced pancreatic cancer; their targets include Src/Abl, histone deacetylase, and mammalian target of rapamycin (Table 4).

The key to taking the management of pancreatic cancer to the next level resides in identifying the pathway or pathways that drive this challenging cancer. Clinical research into molecular-targeted agents, alongside the routine acquisition of tumor samples and surrogate tissues for correlative studies, may soon unveil better ways to treat this devastating disease.

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Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

In Europe, cancer of the pancreas is the 10th most frequent cancer, accounting for some 2.6% of cancer in both sexes, and the eighth leading cause of cancer-related death with ~65 000 deaths each year. In men, the annual incidence rates range between 8.7 (East) and 7.3 (North and West) per 100 000, and in women between 5.7 (North) and 4.5 (East). Men have approximately a half greater age-adjusted incidence rate than women. Incidence increases steeply with age from 1.5 per 100 000/year in patients 15–44 years of age to 55 per 100 000/year in patients >65 year of age. Pancreatic cancer is one of the most highly fatal cancers, with >95% of those affected dying of their disease. The high mortality rate is due to the high incidence of metastatic disease at diagnosis. No survival increases have been observed in the last years.

diagnosis

There are three histological types of pancreatic cancer. Infiltrating ductal adenocarcinomas account for 90% of pancreatic neoplasms, the remaining 10% being represented by acinar cell carcinoma, accounting for <1% of pancreatic cancers (in this type overproduction of lipase may lead to metastatic fat necrosis syndrome, which includes peripheral fat necrosis, eosinophilia and polyarthralgias) and pancreatoblastoma (a tumour occurring mainly in children). More than 90% of pancreatic cancers carry mutations in the K-ras oncogene, a fact that negatively affects therapeutic use of EGFR blocking agents.

Early detection of pancreatic cancer is unfortunately an infrequent situation at the present time. Consequently, there are no current screening programmes that can be recommended in the general population. However, some patients are at greater risk of developing a pancreatic cancer. The risk of pancreatic cancer is increased significantly (18-fold) in families with an affected first-degree relative. Pancreatic cancer is associated with several genetic syndromes including hereditary pancreatitis syndrome, hereditary non-polyposis colorectal cancer, hereditary atypical multiple mole melanoma syndrome, hereditary BRCA2-related breast and ovarian cancer and Peutz–Jeghers syndrome. For these patients specific programmes have been established in order to recognize pre-cancerous lesions.

Clinical presentation is generally characterized by weight loss, pain and jaundice. Jaundice predominates in patients with cancer in the head of the pancreas, and pain in patients with tail and body tumours. In up to 10% of patients new onset of diabetes may be the first clinical feature. Pancreatitis may also be the first signal of a pancreatic neoplasia, especially in the elderly when there is no obvious cause such as gallstones or alcohol abuse. Another important feature of pancreatic cancer is weight loss.

Currently CT scan is the preferred imaging modality used for the diagnosis and staging of pancreatic cancer. In addition to the assessment of the primary tumour localization and size, CT is used to evaluate major vessels adjacent to the pancreas for neoplastic invasion or thrombosis, as well as to evaluate hepatic or distant metastases, enlargement of peripancreatic regional lymph nodes, invasion of retroperitoneal structures and intraperitoneal dissemination. Selected cases may benefit from MRI and laparoscopy. The actual role of ERCP is only therapeutic. At the present time, the rote of PET scanning in the management of patients with pancreatic cancer is under development.

For small tumours endoscopic ultrasound (EUS) has been reported to be superior to CT. Because of this, it may be useful in family screening protocols. An additional aspect of the application of endoscopic technology includes the ability to combine EUS with fine needle aspiration cytological examination.

Tumour markers such as CA19.9 are of limited diagnostic value (it is not specific for pancreas cancer and persons lacking the Lewis antigen are unable to synthesize CA19.9), although they are often taken as a baseline in order to guide treatment and follow-up.

Pathological proof of malignancy is mandatory in unresectable cases or when preoperative treatment is planned. For patients expected to undergo surgery with radical intent, a previous biopsy is not necessary, and even preoperative percutaneous

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sampling should be avoided. In the presence of metastatic lesions they can be biopsied under ultrasound or CT guidance.

staging and risk assessment

The most widely used staging system for pancreatic cancer is the one developed by the TNM committee of the AJCC-UICC, and is presented in Table 1. Stage grouping of pancreatic cancer is presented in Table 2. A simpler staging system is often used, based on whether or not it is likely that the cancer can be removed surgically (Table 3).

CT scan is the preferred and more diffuse imaging modality for staging. MRCP may add additional information about both the biliary and pancreatic ducts and the presence or absence of vascular invasion. Moreover it is able to distinguish better than CT a solid from a cystic mass and is indicated in the case of sever liver and renal failures. PET scanning is in development and it should not routinely be recommended at the present time as a staging procedure. EUS may provide useful information about vascular and nodal involvement. Moreover it represents a useful tool in any case in which pathological material is requested. While chest X-ray is usually recommended in the evaluation of patients, bone scan is not useful since only a few pancreatic patients present with bone involvement at diagnosis. Laparoscopy may detect small peritoneal and liver metastases changing the therapeutic strategy in <15% of patients. It can be suggested before resection in left-sided large tumours and/or with high CA19.9 levels or if neoadjuvant treatment is planned. However, from a practical standpoint, the extent of cancer spread in cancer of the pancreas can often be determined accurately only during surgery. Specific recommendations for the assessment of margins in surgical specimens, especially the superior mesenteric artery margin have also been published by the AJCC-UICC (sixth edition) and are present in the guidelines of the College of American Pathologists.

The prognosis of patients who have undergone radical resection for pancreatic adenocarcinoma depends mainly on presence of negative resection margins. Tumour size, nodal involvement and histological grade are strong prognostic factors. Recently the prognostic role of post-resection CA19.9 has been confirmed. Less well-defined prognostic factors are the biological features of the tumour such as tumour DNA content. An important consideration is the previous experience of the hospital team and the skill of the surgeon.

treatment plan

The treatment of pancreatic cancer is undertaken with two different aims. The first is radical surgery for patients with early stage of disease, mainly stage I and some stage II. In all other cases, the aim of treatment is the palliation of the several distressing symptoms related to this cancer. It is possible to define some treatment strategies according to the tumour stage.

stage I

For this stage disease, the standard treatment option is radical pancreatic resection. For patients with pancreatic head tumours a pylorus-preserving pancreaticoduodenectomy is the procedure of choice which is a modified Whipple procedure preserving distal stomach and pylorus. The most common surgical approach for tumours of the pancreatic body and tail is a distal pancreatectomy which also routinely includes splenectomy.

Postoperatively, six cycles of 5-fluorouracil (5-FU) or gemcitabine (GEM) chemotherapy may be suggested on the basis of two randomized trials. Recently, it was reported that there was no substantial differences in terms of disease-free survival or overall survival in a formal comparison between 5-FU and GEM as adjuvant therapy in pancreatic adenocarcinoma. The role of adjuvant chemoradiation (CT-RT) is controversial as reported in a few randomized Phase III trials. 5-FU-based chemoradiation following GEM chemotherapy as described in the RTOG 97-04 protocol may be an option for individual clinical use, especially in patients with tumours of the pancreatic head, large tumour diameter (>3 cm) and in patients with R1 resection as reported in a meta-analysis of adjuvant randomized trials.

stage II A

Most patients with stage II pancreatic cancer who have tumours that are technically unresectable may benefit from palliative bypass of intestinal obstruction followed by chemotherapy or chemoradiation as described for stages IIB and III. Nevertheless, when feasible, pancreatectomy can be considered a standard approach. Patients should be encouraged to participate in clinical trials for neoadjuvant treatment as recently published results from Phase II studies conducted on preoperative GEM-based chemoradiation seemed to indicate that the neoadjuvant approach can identify a subgroup of patients unlikely to benefit from surgical resection, without compromising survival in patients who ultimately undergo surgery.

Recently the role of intraoperative radiotherapy (IORT) has been addressed in a joint analysis of European centres. The association of preoperative radiotherapy with IORT was associated with improved local control and overall survival, especially in patients with a lower trend to systemic disease spread. Nevertheless, at this time we cannot recommend it as a routine treatment in clinical practice.

Indications for adjuvant chemotherapy or in combination with radiation therapy is similar to stage I.

stage IIB and III

The majority of patients with stage IIB and III have tumours that encase blood vessels. Patients who present borderline resectable disease may benefit from preoperative therapy (chemoradiation or induction chemotherapy followed by chemoradiation) in order to increase the rate of R0 resections.

In patients with unresectable disease 5-FU chemoradiation can be considered. However, two recent trials which compared chemoradiation with chemotherapy alone reported contradictory results. A relevant suggestion for the treatment of patients with locally advanced pancreatic cancer arose from a retrospective analysis of patients enrolled in the GERCOR studies and from a systematic review of trials of chemoradiation

in locally advanced pancreatic cancer. In fact, patients treated with GEM and not progressing after 3 months of treatment and with a good performance status achieved an improvement in survival with the addition of chemoradiation.

stage IV

While treatment with GEM may be a reasonable choice, the use of a combination of GEM and other cytotoxic agents, such as 5-FU, irinotecan, cisplatin and oxaliplatin, is not supported by an advantage in survival apart from capecitabine. However, this combination showed a survival advantage in a trial although it was not confirmed in another one. A meta-analysis of randomized trials with a combination of GEM and platinum analogues seemed to suggest a role for this combination for young patients with good performance status. Nevertheless, the results of a large randomized trial comparing GEM alone with GEM plus cisplatin, presented at the last ASCO meeting, failed to show any benefit for the combination. Another therapeutic possibility is a combination of GEM and erlotinib, recently approved by the FDA and EMEA on the basis of a randomized trial from the NCI of Canada. However, the very modest survival gain (~2 weeks) and the high economic costs of the treatment question the role of this combination in metastatic pancreatic cancer. At the moment there is no evidence supporting the use of either cetuximab or bevacizumab in the overall setting of pancreatic cancer.

There is no standard chemotherapy for patients who have progressed in first-line treatment. The CONKO 003 study has shown a benefit in the second line setting therefore 5-FU/oxaliplatin should be considered as standard. Since the treatment results even in first line are still disappointing the enrolment in clinical trials should be considered not only for second line therapy but for all lines.

palliative therapy

Jaundice is common (70%–80%) in cancers involving the pancreatic head. For unresectable patients, endoscopic stent placement is the preferred procedure since it is associated with lower frequency of complications than percutaneous insertion and it is as successful as the surgical procedure but has a shorter hospital stay. Metal prostheses should be preferred for patients with a life expectancy of >3 months since they present fewer complications (occlusion) than plastic endoprostheses.

Fewer than 5% of patients with pancreatic cancer present with duodenal obstruction, while gastric outlet obstruction may be more common during the course of disease.

Neither chemotherapy nor radiotherapy provided palliation in this setting. In some cases, proximal obstruction may be overcome by the use of an expandable metalc stent. The role of prophylactic gastroenterostomy remains controversial. In fact, only 13%–15% of patients will require gastroenterostomy during the course of disease; it should not be performed as standard procedure but can be a reasonable choice for individual patients. Patients who present with severe pain must receive opioids. Morphine is generally the drug of choice. Usually, the oral route is preferred in routine practice. Parenteral routes of administration should be considered for patients who have impaired swallowing or gastrointestinal obstruction. Also hypofractionated radiotherapy may be delivered to these patients in order to improve pain control and reduce analgesic consumption.

Percutaneous celiacoplexus blockade can be considered, especially for patients who experience poor tolerance of opiate analgesics. Analgesic response rates as high as 50%–90% are reported with 1 month to 1 year duration of effect.

response evaluation and follow-up

Patients should be followed at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 2 months. Clinical benefit and CA19.9 may be useful tools to assess the course of disease in the metastatic setting. Imaging procedures such as CT scan may be indicated mainly in locally advanced disease in order to rule out the presence of metastases and to add radiotherapy to the treatment plan.

There is no possibility of cure, even for recurrences diagnosed early, so a follow-up schedule should be discussed with the patient and designed to avoid emotional stress and economic burden for the patient. In the case of elevated preoperative serum CA19.9 levels the assessment of this marker could be performed every 3 months for 2 years and an abdominal CT scan every 6 months.

However, it is important to bear in mind that there is no advantage in an earlier detection of recurrences.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Identifying continuing educational needs among oncologists in managing patients with pancreatic cancer.

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Show Less

CE Outcomes, LLC., Birmingham, AL; CE Outcomes, LLC, Birimingham, AL; Ipsen Bioscience, Inc., Cambridge, MA; Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ; Baylor College of Medicine, Houston, TX

Abstract Disclosures

Abstract

e16233

Background: Most patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed with advanced disease and are ineligible for potentially curative surgical resection. Oncologists are faced with considering all treatment options, including experimental agents in clinical trials. The goal of this study was to identify the current practice of US-practicing medical oncologists in the management of patients with advanced PDAC in order to ascertain future continuing medical educational (CME) needs. **Methods:** Oncologist practice was assessed using a case-vignette survey with multiple-choice and Likert-type questions designed to elicit clinical management decisions, determine familiarity with new and emerging therapy, and assess challenges to managing patients with PDAC. The survey featured two vignettes: 1) a 55 year-old male with a pancreatic tail mass and numerous liver metastases 2) a 77 year-old male with a pancreatic head mass, biliary obstruction, and metastases to the liver and peritoneal cavity. **Results:** Responses were collected from 150 medical oncologists using a quota method; 69% practiced in a community setting and 31% were academicians. Results demonstrated a lack of consensus in management selections, notably when sequencing therapy. Further, few (< 10%) recommended a clinical trial in either vignette. Academic oncologists reported a higher percentage of patients with stage IV PDAC enrolled in clinical trials compared to community oncologists (30% vs 14%, $P < .001$). However, 36% of all oncologists rated 'lack of access to clinical trials' as a significant barrier to patient care. Variation was also noted in familiarity with pathophysiology and knowledge of therapies to treat PDAC, with academic oncologists reporting significantly higher

familiarity compared to community oncologists. **Conclusions:** By assessing the practice patterns of oncologists managing patients with advanced PDAC, this study identified variation in management decisions and demonstrated continuing educational needs. Future CME that is centered on identified educational needs will help oncologists continue to translate the latest evidence into practice and provide optimal care of patients with PDAC.

Expanded Analyses of NAPOLI-1: Phase 3 Study of MM-398 (nal-IRI), with or without 5-Fluorouracil and Leucovorin, versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer (mPAC) Previously Treated with Gemcitabine-based Therapy

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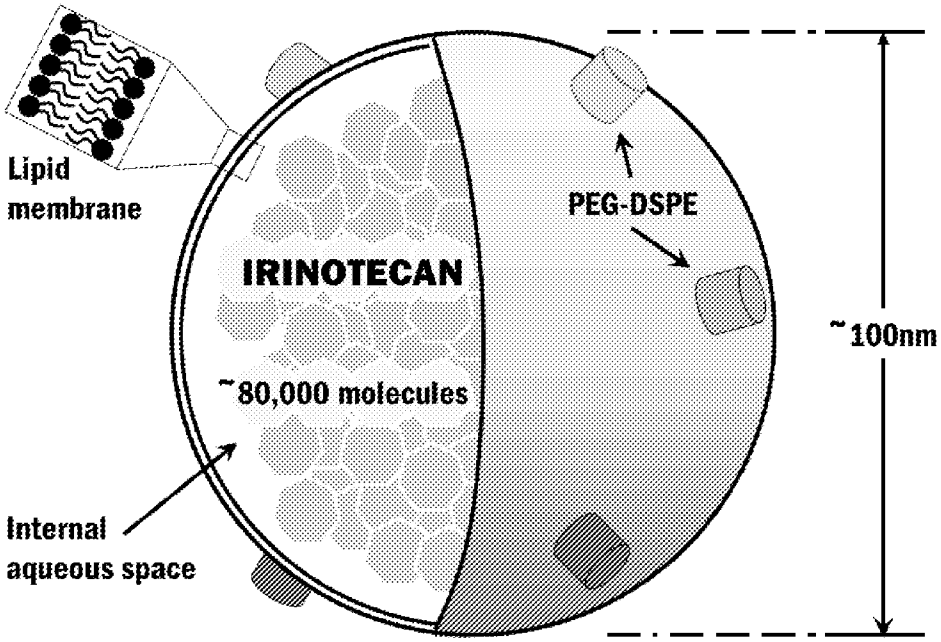
MM-398, Nanoliposomal Irinotecan (nal-IRI)*



~80,000 irinotecan molecules/liposome

- MM-398, liposome irinotecan injection, (120 mg/m^2) has extended circulation
  - AUC of total irinotecan in blood is 1652 *vs.* 24 hr·μg/ml of conventional irinotecan (300 mg/m^2)[1]
- 72 hours after MM-398 dosing, SN-38 (active metabolite) level was 9.6 ng/g in tumor tissue and 1.7 ng/ml in blood[2]

Median OS of 5.2 months for MM-398 in single arm Phase 2 study of gemcitabine-refractory metastatic pancreatic cancer[3]

*Also known as PEP02, PharmaEngine, Inc., Taiwan.

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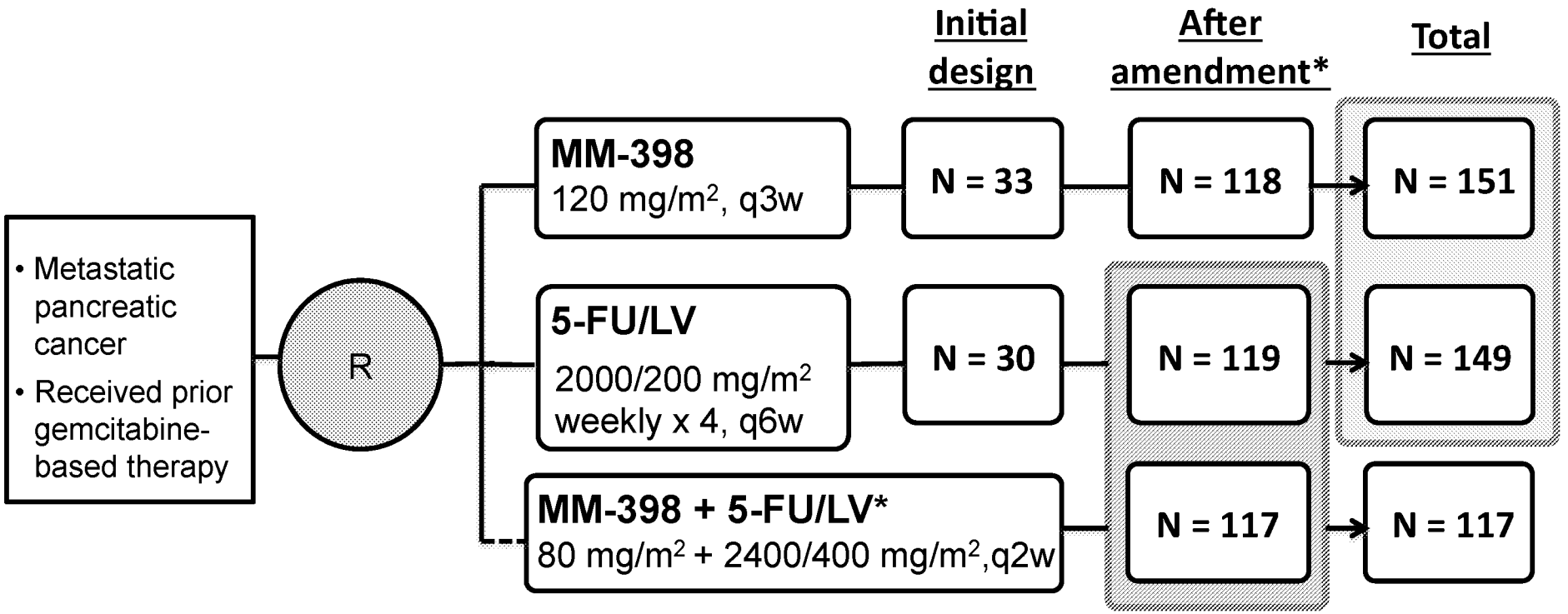
NAPOLI-1 Study Design



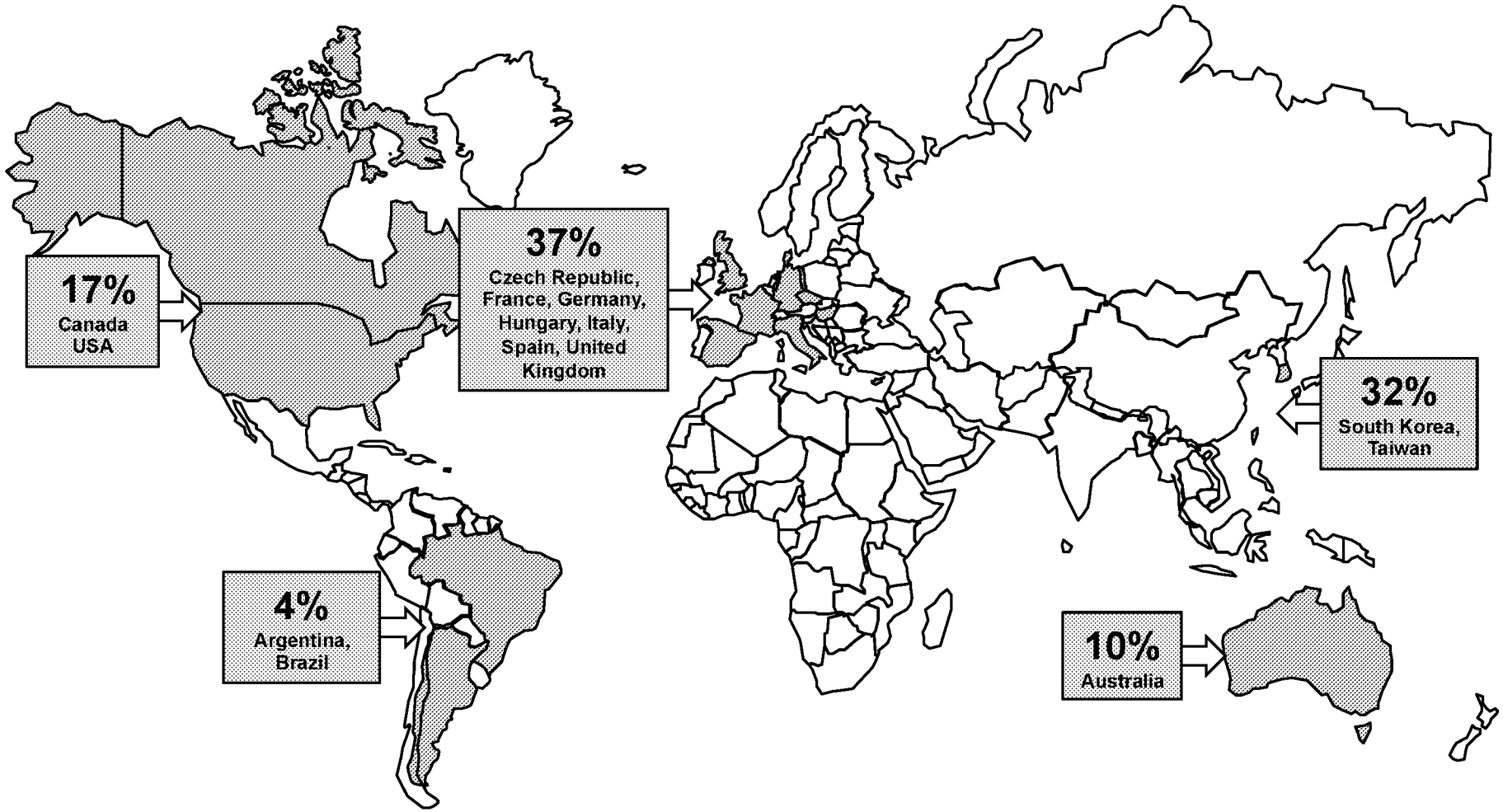
Stratification factors: Albumin, KPS and ethnicity

Primary endpoint: Overall survival

Key secondary endpoints: PFS, ORR, CA19-9 response and safety

* Study was amended to add the MM-398 + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5FU/LV arm after the amendment (N=119), were used as the control for the combination arm.

NAPOLI-1 Enrollment



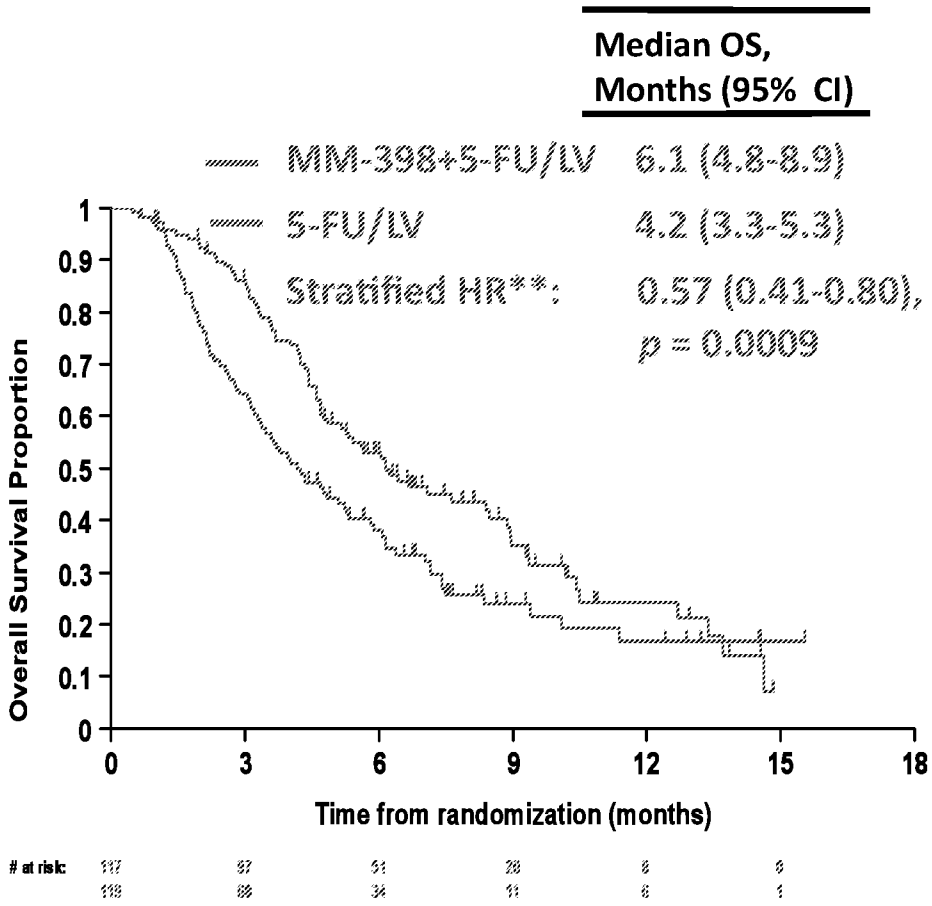
A total of 76 sites, of the 105 sites initiated, enrolled 417 patients between Jan 2012 and Sep 2013

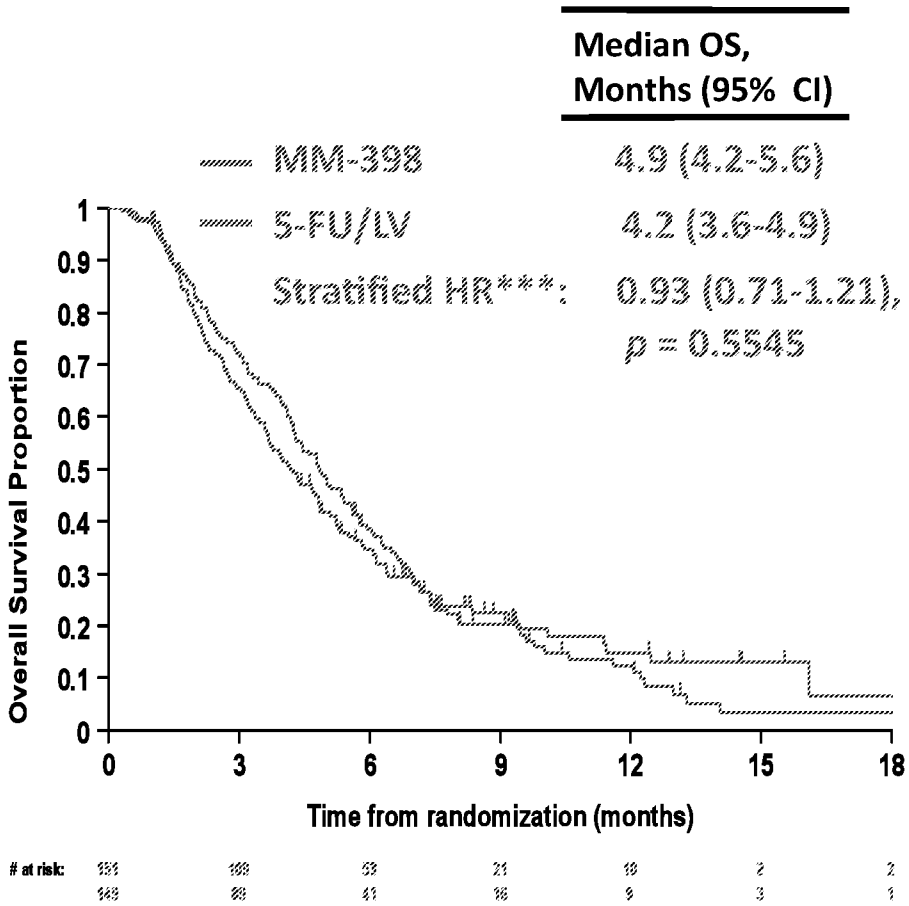
Baseline Characteristics of ITT Population

		MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)	MM-398 (N=151)	5-FU/LV (N=149)
Age	Median years (min, max)	63 (41, 81)	62 (34, 80)	65 (31, 87)	63 (34, 83)
Sex	Male, %	59	56	58	54
	Female, %	41	44	42	46
KPS	90-100, %	56	56	56	56
	70-80, %	44	44	44	44
Race	Caucasian, %	64	63	60	60
	East Asian, %	29	30	35	34
	Other, %	7	7	5	6
Pancreatic primary location	Head, %	64	58	65	54
	Other, %	36	42	35	46
CA19-9*	> 30 U/mL, %	84	81	86	81

* CA19-9 at baseline was unknown in 3% of patients

Overall Survival: Intent to Treat Population (ITT)*





* Protocol-defined primary analysis data cut (14Feb2014, after 305 events). Survival follow-up is ongoing and the final results will be reported once all patients are off treatment and at least 90% events have taken place. Primary analysis for the study was by un-stratified log-rank test.

** Un-stratified HR: 0.67 (0.49-0.92), $p = 0.0122$

*** Un-stratified HR: 0.99 (0.77-1.28), $p = 0.9416$

Tumor Response and Control[1]

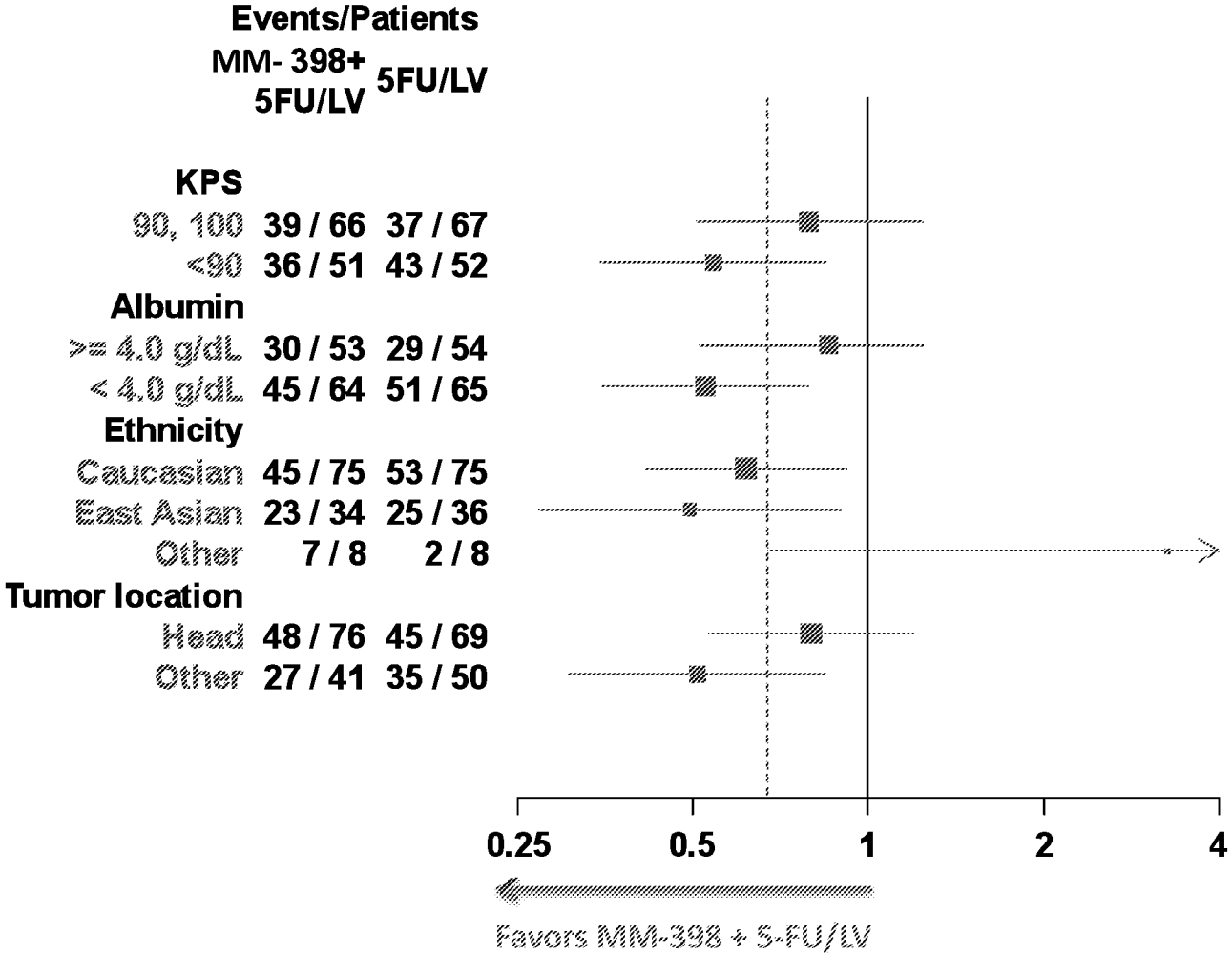
	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)
Median PFS, months (95% CI)	**3.1 (2.7 – 4.2)**	**1.5 (1.4 – 1.8)**
	p=0.0001 (Log-rank test)	
PFS rate at 12 weeks, % (95% CI)	**57 (47 - 66)**	**26 (18 - 35)**
Overall Response Rate, %[2] (95% CI)	**16 (9.6 - 22.9)**	**1 (0.0 - 2.5)**
	p<0.001 (Fisher's exact test)	
CA19-9 reduction, %[3] (responders/evaluable, n)	**36 (27 / 76)**	**12 (8 / 69)**
	p=0.0009 (Fisher's exact test)	

[1] Protocol-defined primary analysis data cut (14Feb2014)

[2] Per RECIST version 1.1

[3] Response defined as ≥ 50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post-baseline CA19-9 measurement

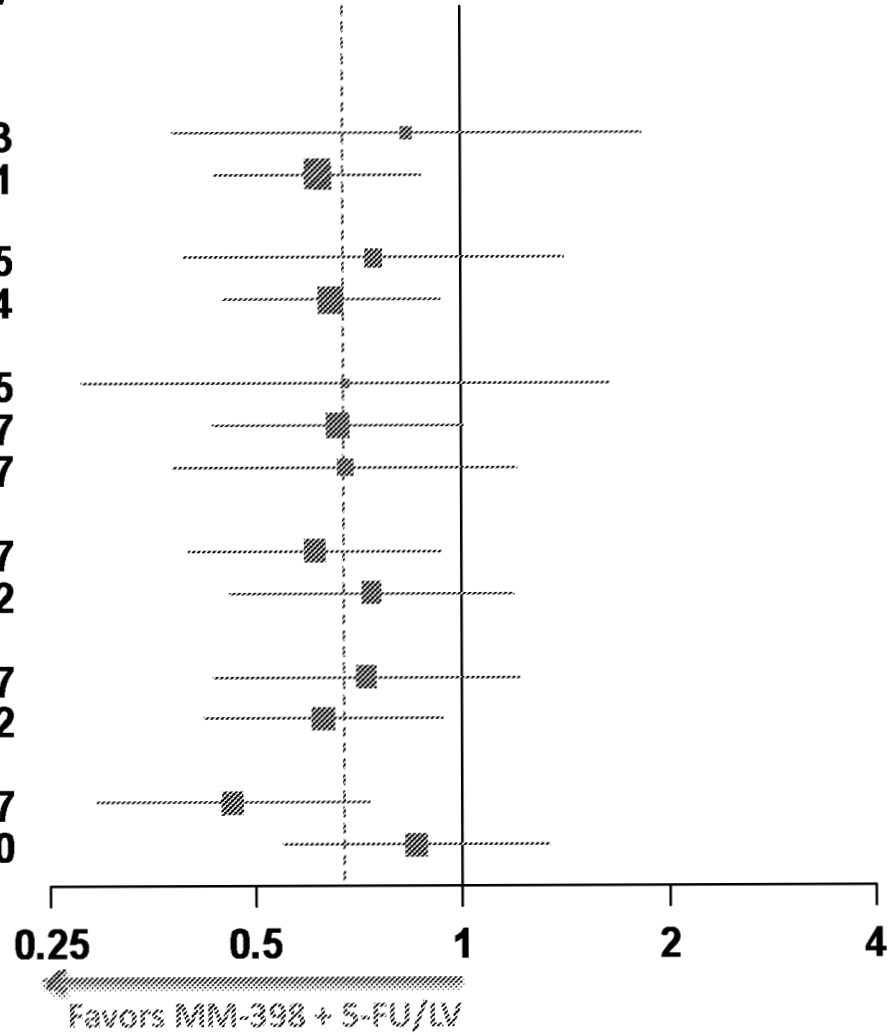
Forest Plot (OS): MM-398+5FU/LV *vs.* 5-FU/LV*



* Protocol-defined primary analysis by un-stratified log-rank test, data cut (14Feb2014)

Forest Plot (OS): MM-398+5FU/LV *vs.* 5-FU/LV*

	Events/Patients MM-398+ 5FU/LV	5FU/LV
CA 19-9		
<40 U/mL	12 / 22	13 / 23
>=40 U/mL	63 / 92	66 / 91
Liver mets**		
No	21 / 42	18 / 35
Yes	54 / 75	62 / 84
Line of therapy		
1st line metastatic	10 / 15	10 / 15
2nd line metatstatic	40 / 62	47 / 67
Post-2nd line metastatic	25 / 40	23 / 37
Time since last therapy		
<= 1.3 months	41 / 55	46 / 67
>1.3 months	34 / 62	34 / 52
Stage at diagnosis		
Not Stage IV	29 / 56	29 / 57
Stage IV	46 / 61	51 / 62
Time since diagnosis		
<=10.1 months	37 / 55	42 / 57
> 10.1 months	38 / 62	38 / 60

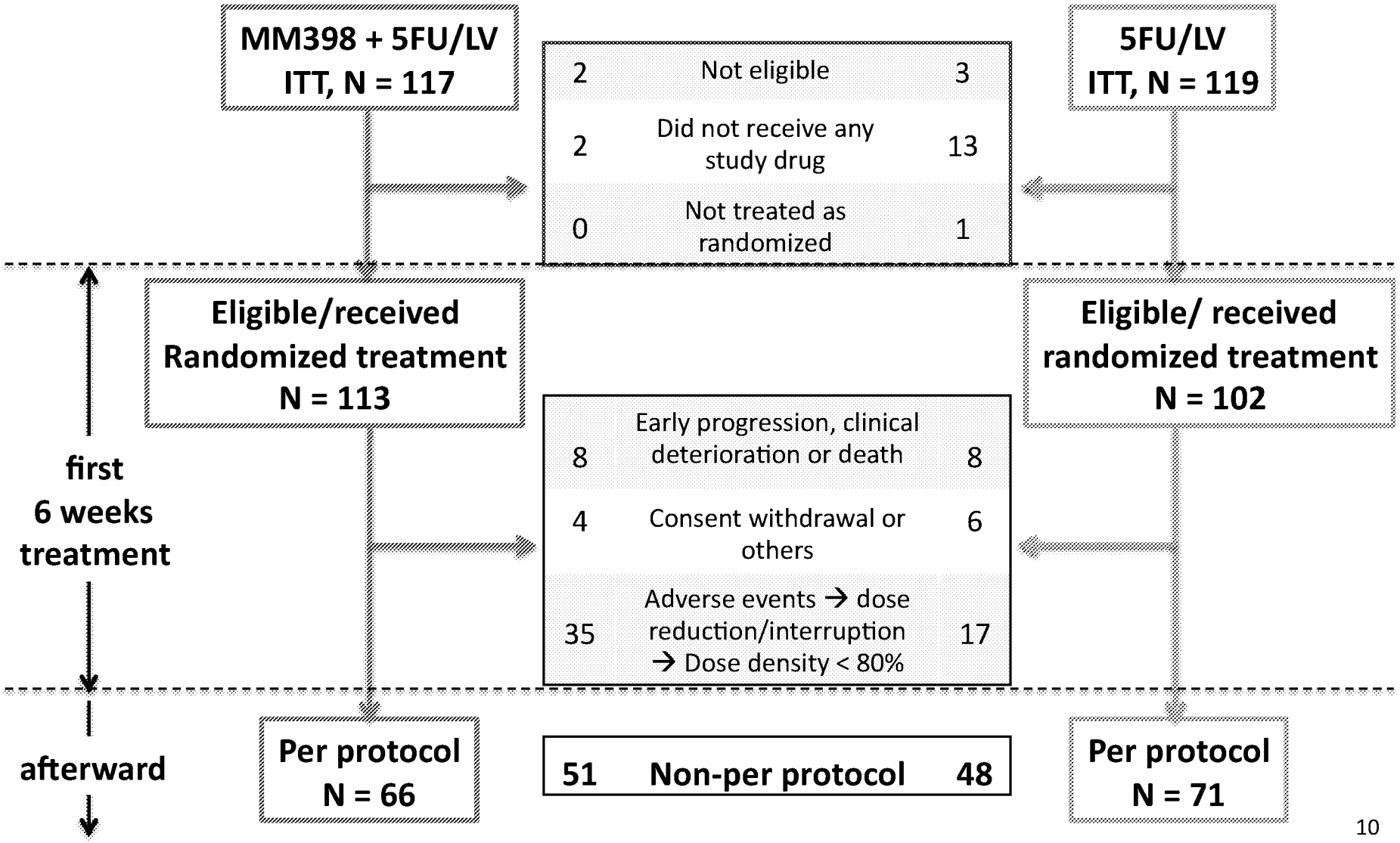


* Protocol-defined primary analysis by un-stratified log-rank test, data cut (14Feb2014)

** As reported by investigators

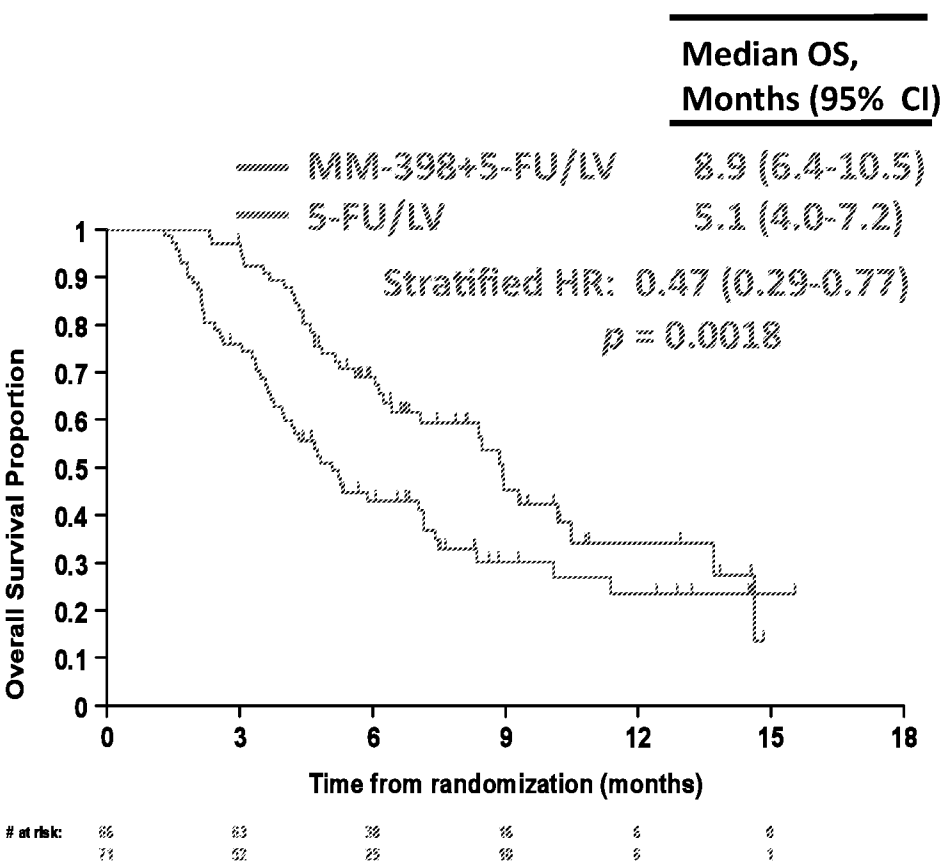
Explanation of ITT and PP Populations

Per Protocol (PP) population: Eligible patients who received ≥ 80% dose density of the protocol defined treatment during the first 6 weeks of treatment

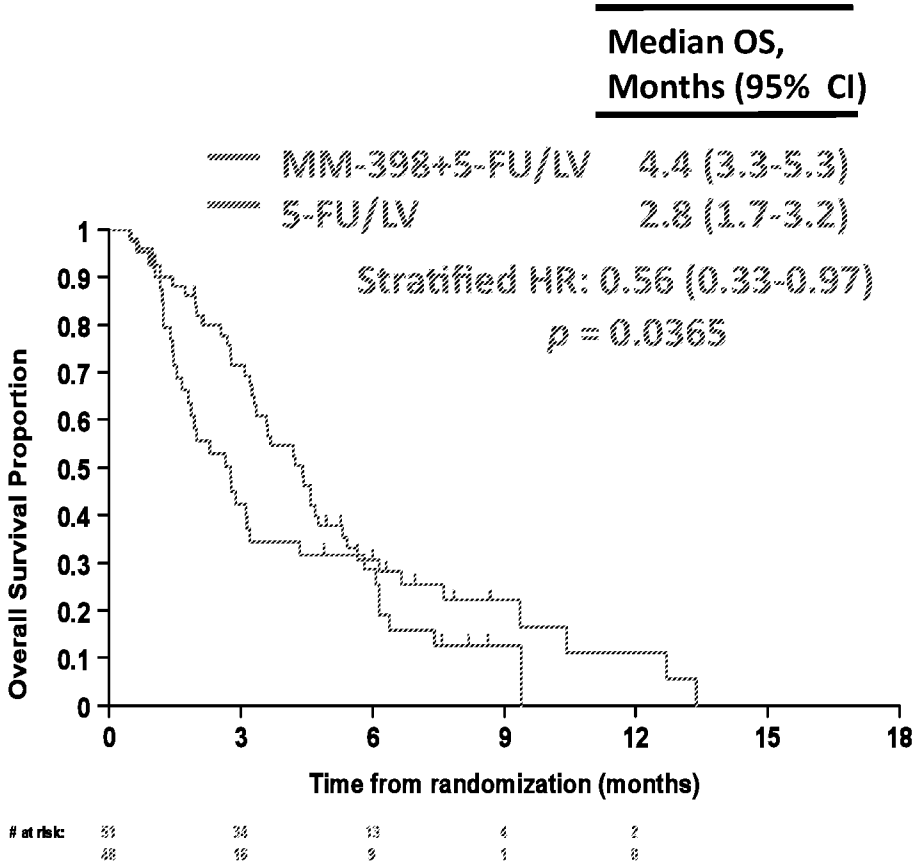


Overall Survival: PP* *vs.* Non-PP

Per Protocol Population



Non-Per Protocol Population



* Protocol-defined primary analysis data cut (14Feb2014). Per protocol population was defined as patients who received at least 80% of the protocol defined treatment during the first 6 weeks of treatment and did not have protocol deviations related to inclusion/exclusion criteria, receiving prohibited therapies or not receiving treatment as randomized.

Demographic Characteristics: PP *vs.* Non-PP

Parameter	MM398 + 5FU/LV		5-FU/LV	
	PP (N=66)	Non-PP (N=51)	PP (N=71)	Non-PP (N=48)
KPS 90 and 100, %	62	49	61	50
Albumin ≥ 4.0 g/dL, %	48	41	48	42
Race, (%)				
Caucasian	71	55	63	63
East Asian	21	39	31	29
CA 19-9 ≥ 40, %*	82	79	76	86
Pancreatic head tumor, %	61	71	68**	44**
Liver Metastasis, %	64	65	75	65
Line of Treatment, %				
First line	14	12	13	13
Second line	53	53	59	52
Post-second line	33	35	28	35
Time since last therapy, months***	1.4 (0.9 , 2.1)	1.4 (1.0, 2.8)	1.2 (1.0, 2.3)	1.2 (1.0, 2.1)
Time since diagnosis, months***	10.3 (5.2, 15.8)	10.8 (6.6, 19.1)	10.3 (6.5, 15.1)	10.5 (5.6, 16.2)
Stage 4 at diagnosis, %	53	51	51	54

* Includes only patients who had a measured CA 19-9 prior to treatment; ** Showed a statistically significant difference (*p* value: 0.01)

*** Median (1st quartile, 3rd quartile)

Dose Modifications and Treatment Exposure

	Safety Population		PP	
	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=134)	MM-398 + 5-FU/LV (N=66)	5-FU/LV (N=71)
Number of patients with Treatment Emergent Adverse Events resulting in, n (%)				
Dose Reduction	39 (33)	5 (4)	22 (33)	2 (3)
Dose Delays	72 (62)	43 (32)	40 (61)	15 (21)
Treatment Discontinuation	13 (11)	10 (8)	3 (5)	2 (3)
Average relative dose intensity (%)				
MM-398	83.2	-	85.4	-
5-FU	83.9	95.6	86.4	97.9
Average duration of exposure (weeks)*	15	10	21	13

* Duration of exposure is the time from {the date of the last administration of study drug + projected days to next dose of study drug administration - date of first study drug administration}/7

Safety

	Safety Population[1]		PP	
	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=134)	MM-398 + 5-FU/LV (N=66)	5-FU/LV (N=71)
Grade ≥ 3 nonhematologic AEs in > 5% patients, %[2]				
Fatigue	14	4	14	6
Diarrhea	13	5	12	7
Vomiting	11	3	8	3
Nausea	8	3	9	1
Asthenia	8	7	5	6
Abdominal pain	7	6	5	3
Grade ≥ 3 hematologic AEs based on laboratory values, %[2, 3]				
Neutrophil count decreased	20	2	15	3
Hemoglobin decreased	6	5	6	4
Platelet count decreased	2	0	2	0
Patients with at least 1 AE leading to death (all causes), %	2	7	0	6

[1] Patients receiving at least one dose of study drug; [2] Per CTCAE Version 4; [3] Includes only patients who had at least one post-baseline assessment

Summary

- **ITT analysis demonstrated statistically significant increase in overall survival (OS) of MM-398 + 5-FU/LV (MM-398 80 mg/m^2 q2w regimen) over 5-FU/LV**
  - **Significant increase also observed in PFS, ORR and CA19-9 response**
  - **MM-398 single agent, 120 mg/m^2 q3w regimen, did not show a significant difference in OS**
- **Forest plot sensitivity analyses favored MM-398 + 5-FU/LV over 5-FU/LV across prognostic subgroups, tumor characteristics and previous treatment**
- **In the PP population, the MM-398 + 5-FU/LV combination regimen achieved a median OS of 8.9 months (stratified HR: 0.47, *p* = 0.0018)**
- **Safety profile was manageable, with most frequent Grade ≥ 3 AEs including neutropenia, fatigue and GI effects (diarrhea and vomiting)**

Acknowledgements

We would like to thank the patients, their families, caregivers, investigators, and research staff for their participation

Additional details presented in
General Poster Session B (Board A5) on Friday, 16 JAN 2015
from noon – 2:00 pm and 5:30 – 7:00 pm.

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PD-023

Safety Across Subgroups in NAPOLI-1: a Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin Versus 5-Fluorouracil and Leucovorin in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy

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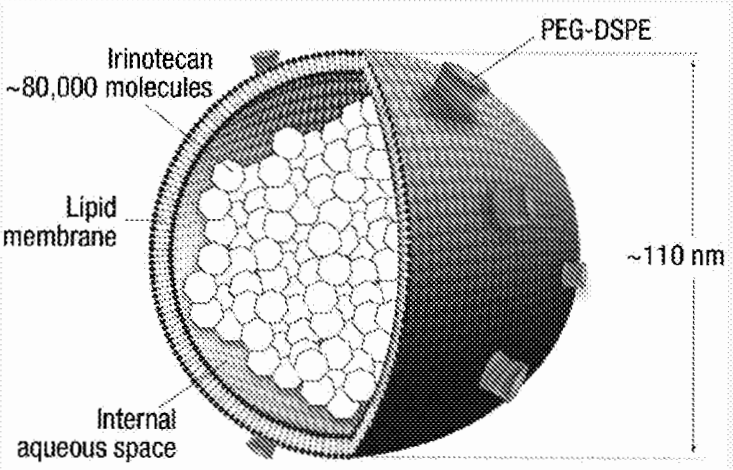
BACKGROUND

- Pancreatic cancer is the fourth leading cause of cancer-related deaths in Europe and the seventh leading cause worldwide[1,2]
- Metastatic pancreatic ductal adenocarcinoma (mPDAC) represents a significant unmet need, with approximately 80% of patients dying within 12 months[3]
- nal-IRI (MM-398) is a novel liposomal formulation of irinotecan that exhibits extended circulation and facilitates intratumoral drug deposition when compared with nonliposomal (ie, conventional) irinotecan (**Figure 1**)[4,5]
- nal-IRI is approved by the US Food and Drug Administration, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), for use following disease progression in patients with mPDAC previously treated with gemcitabine-based therapy[6]

Figure 1. nal-IRI design.



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

- NAPOLI-1 was a phase 3 trial evaluating the efficacy and safety of nal-IRI, as monotherapy and in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with mPDAC previously treated with gemcitabine-based therapy[7]
- As of the data cutoff of February 14, 2014, 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]; $P = 0.012$), but did not differ significantly between nal-IRI monotherapy and 5-FU/LV (4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77-1.28]; $P = 0.94$)[7]
- The most common treatment-emergent adverse events (TEAEs) of all grades in patients whose treatment included nal-IRI were diarrhea, nausea, and vomiting (**Table 1**)[7]
  - Adverse events that resulted in a dose reduction occurred in 39 (33%) patients in the nal-IRI + 5-FU/LV arm, 46 (31%) patients in the nal-IRI monotherapy arm, and 5 (4%) patients in the 5-FU/LV arm
  - Adverse events leading to treatment discontinuation occurred in 13 (11%) patients in the nal-IRI + 5-FU/LV arm, 17 (12%) patients in the nal-IRI monotherapy arm, and 10 (7%) patients in the 5-FU/LV arm

Table 1. Treatment-Emergent Adverse Events From the Primary Analysis of the NAPOLI-1 Trial[7]

	nal-IRI + 5-FU/LV n = 117		5-FU/LV n = 134	
	Any Grade	Grades 3/4	Any Grade	Grades 3/4
Diarrhea	69 (59)	15 (13)	35 (26)	6 (4)
Vomiting	61 (52)	13 (11)	35 (26)	4 (3)
Nausea	60 (51)	9 (8)	46 (34)	4 (3)
Decreased appetite	52 (44)	5 (4)	43 (32)	3 (2)
Fatigue	47 (40)	16 (14)	37 (28)	5 (4)
Neutropenia[a]	46 (39)	32 (27)	7 (5)	2 (1)
Anemia	44 (38)	11 (9)	31 (23)	9 (7)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
Data are number of patients (%). The table shows grade 3 and 4 adverse events reported in ≥5% of patients with ≥2% incidence versus 5-FU/LV.
[a]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

OBJECTIVES

- To evaluate the safety of nal-IRI + 5-FU/LV and 5-FU/LV in the following subgroups:
  - Age (≥65 years vs <65 years)
  - Ethnicity (white vs east Asian)
  - *UGT1A1*28* allele (TA7/TA7 genotype; yes vs no)
  - Albumin level (≥4.0 g/dL vs <4.0 g/dL)
  - Karnofsky performance status (KPS) score (≥90 vs <90)

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial
  - Patients were initially randomized to nal-IRI monotherapy (120 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 100 mg/m^2 irinotecan free base every 3 weeks) or 5-FU/LV (200 mg/m^2 LV and 2000 mg/m^2 5-FU, every week for the first 4 weeks of each 6-week cycle)

- Once safety data for the combination regimen became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a third arm, nal-IRI + 5-FU/LV (80 mg/m^2 irinotecan hydrochloride trihydrate salt [equivalent to 70 mg/m^2 irinotecan free base], 400 mg/m^2 LV, and 2400 mg/m^2 5-FU over 46 hours, every 2 weeks)
  - The initial nal-IRI dose in the nal-IRI + 5-FU/LV arm was 60 mg/m^2 for patients homozygous for the *UGT1A1*28* allele (TA7/TA7 genotype) and could be increased to the standard dose (80 mg/m^2) in the absence of drug-related toxic effects
- Randomization was stratified by baseline albumin levels (≥4.0 g/dL vs <4.0 g/dL), KPS (70 and 80 vs ≥90), and ethnicity (white vs east Asian vs all others)
- TEAEs were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and coded by Medical Dictionary for Regulatory Activities, version 14.1
- All TEAEs were followed until resolution or patient discontinuation
- The safety analysis population included all patients who received ≥1 dose of study drug
- The presence of the *UGT1A1*28* allele was determined by genotype testing, and homozygous patients were identified (TA7/TA7 genotype)
  - The *UGT1A1* gene codes an enzyme responsible for glucuronidation of the active metabolite of irinotecan, SN-38
  - Patients homozygous for the *UGT1A1*28* allele may be at increased risk for neutropenia, diarrhea, and other SN-38 exposure related side-effects during irinotecan treatment because of reduced glucuronidation of SN-38
- Data from the nal-IRI + 5-FU/LV arm (nal-IRI combination arm) and the 5-FU/LV arm (control arm) are presented herein (data cutoff of February 14, 2014)

Eligibility Criteria

Key Inclusion Criteria

- Adults ≥18 years of age
- Histologically or cytologically confirmed PDAC
- Documented measurable or nonmeasurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, 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 score ≥70
- Adequate hematologic (including absolute neutrophil count >1.5 × 10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function

Key Exclusion Criteria

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

RESULTS

Patient Characteristics

- Of the 417 patients included in the intention-to-treat population, 398 (95%) received ≥1 dose of any study drug (safety analysis population)
- Patient demographics and baseline characteristics were well balanced between the nal-IRI combination and control arms (**Table 2**)

Table 2. Demographics and Baseline Characteristics (Safety Population)

Parameter	nal-IRI + 5-FU/LV n = 117	5-FU/LV n = 134
Sex, n (%)		
Male	67 (57.3)	73 (54.5)
Female	50 (42.7)	61 (45.5)
Age, median (range), years	63 (41-81)	63 (39-83)
Ethnicity, n (%)		
White	73 (62.4)	85 (63.4)
East Asian	33 (28.2)	44 (32.8)
Other	11 (9.4)	5 (3.7)
KPS score, n (%)		
100	19 (16.2)	16 (11.9)
90	50 (42.7)	50 (37.3)
80	39 (33.3)	57 (42.5)
70	7 (6.0)	11 (8.2)
60	2 (1.7)	0
Previous lines of metastatic therapy, n (%)		
0[a]	15 (12.8)	18 (13.4)
1	63 (53.8)	79 (59.0)
≥2	39 (33.3)	37 (27.6)
Previous anticancer therapy,[b] n (%)		
Gemcitabine alone	54 (46.2)	61 (45.5)
Gemcitabine combination	63 (53.8)	73 (54.5)
Fluorouracil	50 (42.7)	53 (39.6)
Irinotecan	12 (10.3)	14 (10.4)
Platinum	37 (31.6)	38 (28.4)

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease.
[b]Columns add to >100% because some patients received more than 1 line of therapy, and regimens may include multiple drug classes.

Treatment Exposure

- Median duration of exposure to nal-IRI in the nal-IRI combination arm was 8.7 weeks (interquartile range [IQR], 5.4-22.0 weeks); mean dose intensity of nal-IRI over 6 weeks was 167.5 mg/m^2 (standard deviation [SD], 52.05 mg/m^2)
- Median duration of exposure to 5-FU was 8.7 weeks (IQR, 5.4-22.0 weeks) in the nal-IRI combination arm and 6.0 weeks (IQR, 5.9-12.1 weeks) in the control arm; mean dose intensities of 5-FU over 6 weeks were 5065.0 mg/m^2 (SD, 1539.1 mg/m^2) and 6718.0 mg/m^2 (SD, 1770.18 mg/m^2), respectively

Safety Subgroup Analysis

Age

- Incidence of any-grade and grade ≥3 TEAEs was similar between patients aged <65 years and those aged ≥65 years in each treatment arm (**Table 3**)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of vomiting (14.3% vs 7.4%) was higher in patients <65 years; incidence of nausea (11.1% vs 4.8%) was higher in patients ≥65 years

Table 3. TEAEs by Age

	nal-IRI + 5-FU/LV				5-FU/LV			
	<65 Years n = 63		≥65 Years n = 54		<65 Years n = 78		≥65 Years n = 56	
Any TEAE	63 (100)		53 (98.1)		77 (98.7)		55 (98.2)	
Any TEAE, grade ≥3	53 (84.1)		37 (68.5)		44 (56.4)		31 (55.4)	
Any TEAE resulting in dose modification[a]	46 (73.0)		37 (68.5)		25 (32.1)		23 (41.1)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Vomiting	41 (65.1)	9 (14.3)	20 (37.0)	4 (7.4)	22 (28.2)	2 (2.6)	13 (23.2)	2 (3.6)
Diarrhea	39 (61.9)	9 (14.3)	30 (55.6)	6 (11.1)	22 (28.2)	5 (6.4)	13 (23.2)	1 (1.8)
Nausea	38 (60.3)	3 (4.8)	22 (40.7)	6 (11.1)	29 (37.2)	1 (1.3)	17 (30.4)	3 (5.4)
Decreased appetite	30 (47.6)	2 (3.2)	22 (40.7)	3 (5.6)	22 (28.2)	3 (3.8)	21 (37.5)	0
Neutropenia[b]	24 (38.1)	17 (27.0)	22 (40.7)	15 (27.8)	4 (5.1)	2 (2.6)	3 (5.4)	0
Fatigue	23 (36.5)	8 (12.7)	24 (44.4)	8 (14.8)	21 (26.9)	3 (3.8)	16 (28.6)	2 (3.6)
Anemia	19 (30.2)	5 (7.9)	25 (46.3)	6 (11.1)	13 (16.7)	5 (6.4)	18 (32.1)	4 (7.1)
Abdominal pain	17 (27.0)	5 (7.9)	10 (18.5)	3 (5.6)	23 (29.5)	6 (7.7)	19 (33.9)	2 (3.6)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Ethnicity

- Incidence of any-grade TEAEs was similar between white and east Asian patients in each treatment arm, with the exception of diarrhea, which occurred less frequently in east Asians (**Table 4**)
- Incidence of grade ≥3 TEAEs in the control arm was similar between white and east Asian patients (56.5% vs 54.5%), whereas the incidence of grade ≥3 TEAEs in the nal-IRI combination arm was higher for east Asians compared with whites (87.9% vs 69.9%)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of diarrhea (19.2% vs 3.0%), fatigue (19.2% vs 0%), and vomiting (13.7% vs 6.1%) was higher in white patients; incidence of anemia (21.2% vs 5.5%), neutropenia (54.5% vs 17.8%), and white blood cell decrease (21.2% vs 2.7%) was higher in east Asian patients
  - In the control arm, incidence of abdominal pain (8.2% vs 2.3%) was higher in white patients; incidence of anemia (13.6% vs 3.5%) was higher in east Asian patients

Table 4. TEAEs by Ethnicity

	nal-IRI + 5-FU/LV				5-FU/LV			
	White n = 73		East Asian n = 33		White n = 85		East Asian n = 44	
Any TEAE	72 (98.6)		33 (100)		84 (98.8)		43 (97.7)	
Any TEAE, grade ≥3	51 (69.9)		29 (87.9)		48 (56.5)		24 (54.5)	
Any TEAE resulting in dose modification[a]	48 (65.8)		28 (84.8)		33 (38.8)		13 (29.5)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	45 (61.6)	14 (19.2)	16 (48.5)	1 (3.0)	24 (28.2)	4 (4.7)	11 (25.0)	2 (4.5)
Nausea	37 (50.7)	6 (8.2)	18 (54.5)	2 (6.1)	28 (32.9)	3 (3.5)	16 (36.4)	1 (2.3)
Fatigue	35 (47.9)	14 (19.2)	8 (24.2)	0	25 (29.4)	3 (3.5)	10 (22.7)	2 (4.5)
Vomiting	34 (46.6)	10 (13.7)	22 (66.7)	2 (6.1)	23 (27.1)	4 (4.7)	12 (27.3)	0
Anemia	29 (39.7)	4 (5.5)	13 (39.4)	7 (21.2)	16 (18.8)	3 (3.5)	15 (34.1)	6 (13.6)
Decreased appetite	24 (32.9)	2 (2.7)	22 (66.7)	2 (6.1)	24 (28.2)	1 (1.2)	18 (40.9)	2 (4.5)
Neutropenia[b]	21 (28.8)	13 (17.8)	22 (66.7)	18 (54.5)	4 (4.7)	0	2 (4.5)	1 (2.3)
Abdominal pain	20 (27.4)	6 (8.2)	6 (18.2)	2 (6.1)	30 (35.3)	7 (8.2)	11 (25.0)	1 (2.3)
White blood cell count decreased	4 (5.5)	2 (2.7)	12 (36.4)	7 (21.2)	1 (1.2)	0	0	0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

*UGT1A1*28* Allele (TA7/TA7 Genotype)

- Although the low number of patients with the TA7/TA7 genotype makes comparison difficult, the incidence of any-grade and grade ≥3 TEAEs appeared to be similar between patients with or without the TA7/TA7 genotype (**Table 5**)
- In the nal-IRI combination arm, 3 of the 7 patients with the TA7/TA7 genotype were able to escalate the nal-IRI dose to 80 mg/m^2 without needing dose reduction
  - 1 patient escalated but required dose reduction back to 60 mg/m^2
  - 2 patients maintained the initial dose
  - 1 patient required dose reduction to 40 mg/m^2
- 1 additional patient in the nal-IRI combination arm with the TA7/TA7 genotype discontinued treatment (without dose reduction) because of grade 3 vomiting

Table 5. TEAEs by *UGT1A1*28* Allele (TA7/TA7 Genotype)

	nal-IRI + 5-FU/LV				5-FU/LV			
	TA7/TA7 Genotype n = 7		No TA7/TA7 Genotype n = 110		TA7/TA7 Genotype n = 13		No TA7/TA7 Genotype n = 121	
Any TEAE	7 (100)		109 (99.1)		13 (100)		119 (98.3)	
Any TEAE, grade ≥3	5 (71.4)		85 (77.3)		8 (61.5)		67 (55.4)	
Any TEAE resulting in dose modification[a]	4 (57.1)		79 (71.8)		5 (38.5)		43 (35.5)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	5 (71.4)	0	39 (35.5)	11 (10.0)	1 (7.7)	0	30 (24.8)	9 (7.4)
Nausea	3 (42.9)	0	57 (51.8)	9 (8.2)	8 (61.5)	1 (7.7)	38 (31.4)	3 (2.5)
Vomiting	3 (42.9)	1 (14.3)	58 (52.7)	12 (10.9)	7 (53.8)	1 (7.7)	28 (23.1)	3 (2.5)
Abdominal pain	2 (28.6)	0	25 (22.7)	8 (7.3)	6 (46.2)	1 (7.7)	36 (29.8)	7 (5.8)
Decreased appetite	2 (28.6)	0	50 (45.5)	5 (4.5)	7 (53.8)	0	36 (29.8)	3 (2.5)
Diarrhea	2 (28.6)	1 (14.3)	67 (60.9)	14 (12.7)	4 (30.8)	1 (7.7)	31 (25.6)	5 (4.1)
Neutropenia[b]	2 (28.6)	2 (28.6)	44 (40.0)	30 (27.3)	0	0	7 (5.8)	2 (1.7)
Constipation	1 (14.3)	0	25 (22.7)	0	4 (30.8)	1 (7.7)	28 (23.1)	1 (0.8)
Fatigue	1 (14.3)	0	46 (41.8)	16 (14.5)	4 (30.8)	1 (7.7)	33 (27.3)	4 (3.3)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Albumin

- Incidence of any-grade and grade ≥3 TEAEs was similar between patients with albumin levels ≥4.0 g/dL or <4.0 g/dL (**Table 6**)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of diarrhea (17.6% vs 6.4%) and fatigue (16.2% vs 10.6%) was higher in patients with albumin levels ≥4.0 g/dL
  - In the control arm, incidence of diarrhea (8.1% vs 1.4%) was higher in patients with albumin levels <4.0 g/dL

Table 6. TEAEs by Albumin Level

	nal-IRI + 5-FU/LV				5-FU/LV			
	Albumin ≥4.0 g/dL n = 68		Albumin <4.0 g/dL n = 47		Albumin ≥4.0 g/dL n = 70		Albumin <4.0 g/dL n = 62	
Any TEAE	68 (100)		46 (97.9)		70 (100)		60 (96.8)	
Any TEAE, grade ≥3	55 (80.9)		33 (70.2)		32 (45.7)		42 (67.7)	
Any TEAE resulting in dose modification[a]	48 (70.6)		33 (70.2)		21 (30.0)		26 (41.9)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	41 (60.3)	12 (17.6)	27 (57.4)	3 (6.4)	12 (17.1)	1 (1.4)	23 (37.1)	5 (8.1)
Nausea	38 (55.9)	4 (5.9)	20 (42.6)	4 (8.5)	24 (34.3)	3 (4.3)	21 (33.9)	1 (1.6)
Vomiting	38 (55.9)	8 (11.8)	23 (48.9)	5 (10.6)	17 (24.3)	2 (2.9)	17 (27.4)	2 (3.2)
Decreased appetite	33 (48.5)	2 (2.9)	19 (40.4)	3 (6.4)	22 (31.4)	1 (1.4)	20 (32.3)	2 (3.2)
Fatigue	31 (45.6)	11 (16.2)	16 (34.0)	5 (10.6)	21 (30.0)	3 (4.3)	15 (24.2)	2 (3.2)
Neutropenia[b]	29 (42.6)	20 (29.4)	17 (36.2)	12 (25.5)	4 (5.7)	1 (1.4)	3 (4.8)	1 (1.6)
Anemia	24 (35.3)	6 (8.8)	20 (42.6)	5 (10.6)	14 (20.0)	4 (5.7)	16 (25.8)	5 (8.1)
Abdominal pain	19 (27.9)	6 (8.8)	7 (14.9)	2 (4.3)	24 (34.3)	4 (5.7)	17 (27.4)	4 (6.5)
Constipation	16 (23.5)	0	9 (19.1)	0	22 (31.4)	2 (2.9)	10 (16.1)	0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Karnofsky Performance Status

- Incidence of any-grade TEAEs was similar between patients with KPS score of ≥90 or <90 (**Table 7**)
- Incidence of grade ≥3 TEAEs was similar between patients with KPS score of ≥90 or <90 in the nal-IRI combination arm; incidence of grade ≥3 TEAEs was lower in patients with KPS score of ≥90 vs patients with KPS score of <90 in the control arm (40.9% vs 70.6%)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of decreased appetite (8.3% vs 1.4%) and abdominal pain (10.4% vs 4.3%) was higher in patients with KPS score <90
  - In the control arm, incidence of abdominal pain (8.8% vs 3.0%) was higher in patients with KPS score <90

Table 7. TEAEs by KPS Score

	nal-IRI + 5-FU/LV				5-FU/LV			
	KPS Score ≥90 n = 69		KPS Score <90 n = 48		KPS Score ≥90 n = 66		KPS Score <90 n = 68	
Any TEAE	69 (100)		47 (97.9)		65 (98.5)		67 (98.5)	
Any TEAE, grade ≥3	52 (75.4)		38 (79.2)		27 (40.9)		48 (70.6)	
Any TEAE resulting in dose modification[a]	48 (69.6)		35 (72.9)		19 (28.8)		29 (42.6)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	40 (58.0)	8 (11.6)	29 (60.4)	7 (14.6)	22 (33.3)	3 (4.5)	13 (19.1)	3 (4.4)
Nausea	37 (53.6)	4 (5.8)	23 (47.9)	5 (10.4)	19 (28.8)	1 (1.5)	27 (39.7)	3 (4.4)
Vomiting	36 (52.2)	8 (11.6)	25 (52.1)	5 (10.4)	16 (24.2)	2 (3.0)	19 (27.9)	2 (2.9)
Fatigue	29 (42.0)	8 (11.6)	18 (37.5)	8 (16.7)	18 (27.3)	1 (1.5)	19 (27.9)	4 (5.9)
Neutropenia[b]	29 (42.0)	20 (29.0)	17 (35.4)	12 (25.0)	4 (6.1)	1 (1.5)	3 (4.4)	1 (1.5)
Decreased appetite	28 (40.6)	1 (1.4)	24 (50.0)	4 (8.3)	21 (31.8)	0	22 (32.4)	3 (4.4)
Anemia	25 (36.2)	6 (8.7)	19 (39.6)	5 (10.4)	18 (27.3)	4 (6.1)	13 (19.1)	5 (7.4)
Abdominal pain	16 (23.2)	3 (4.3)	11 (22.9)	5 (10.4)	18 (27.3)	2 (3.0)	24 (35.3)	6 (8.8)
Constipation	11 (15.9)	0	15 (31.3)	0	12 (18.2)	0	20 (29.4)	2 (2.9)

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

CONCLUSIONS

- **The safety profiles for nal-IRI + 5-FU/LV and 5-FU/LV were generally similar across patient subgroups; diarrhea, vomiting, and nausea were the most commonly occurring TEAEs**
- **The incidence of grade ≥3 TEAEs within the subgroups was in line with the safety profile of the overall population**
- **Study limitations included small patient numbers in some of the subgroups and lack of statistical analysis, which preclude definitive conclusions from being drawn**
- **The results of this subgroup analysis further support that nal-IRI + 5-FU/LV has a manageable safety profile in patients with mPDAC previously treated with gemcitabine-based therapy**

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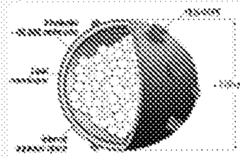
Safety Across Subgroups in NAPOLI-1: a Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin Versus 5-Fluorouracil and Leucovorin in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy



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Safety across subgroups in NAPOLI-1: a phase 3 study of nal-IRI (MM-398) ± 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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Introduction: NAPOLI-1 was a randomized phase 3 study evaluating nal-IRI, a nanoliposomal formulation of irinotecan, with or without 5-FU/LV versus 5-FU/LV in patients with mPAC previously treated with gemcitabine-based therapy. Nal-IRI + 5-FU/LV significantly improved overall survival compared with 5-FU/LV (6.1 vs 4.2 months; $P = 0.012$) and was generally well tolerated (Wang-Gillam et al, *Lancet*. 2016). The most common grade ≥3 treatment-emergent adverse events (TEAEs) in the nal-IRI + 5-FU/LV arm were neutropenia, fatigue, diarrhea, and vomiting. Based on NAPOLI-1, the nal-IRI + 5-FU/LV regimen received regulatory approval from the US. Food and Drug Administration for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Here, we present results of a prespecified safety analysis by patient subgroup from NAPOLI-1.

Methods: TEAEs were graded by NCI CTCAE v4.0 and coded by MedDRA v14.1 for the following prespecified subgroups: sex, age (<65 vs ≥65 years), ethnicity (white vs Asian), *UGT1A1*28* status, prior conventional irinotecan therapy (yes vs no), and prior 5-FU therapy (yes vs no). All TEAEs were followed until resolution or patient discontinuation. Analyses were performed on the safety population (ie, those who received ≥1 dose of study medication). Results herein are for the nal-IRI + 5-FU/LV arm unless otherwise noted.

Results: Overall, the incidence and severity of TEAEs were similar between men (n = 67) and women (n = 50). Patients aged ≥65 years (n = 54) generally had a higher incidence of TEAEs than those <65 years (n = 63) (eg, stomatitis: 20.4% vs 7.9%; anemia: 46.3% vs 30.2%), although the most common types of TEAEs were similar regardless of age. Overall, Asian (n = 33) patients had a higher incidence of grade ≥3 TEAEs than white (n = 73) patients (87.9% vs 69.9%), primarily because of an increased incidence of neutropenia (24.2% vs 12.3%) and decreased neutrophil counts (33.3% vs 1.4%); febrile neutropenia was reported in 3.0% of Asian patients and 0 white patients. Gastrointestinal disorders also occurred slightly more frequently in Asian patients than white patients (any grade: 100% vs 87.7%), although diarrhea was less frequent and less severe among Asian patients (any grade: 48.5% vs 61.6%; grade ≥3: 3.0% vs 19.2%). The *UGT1A1* gene encodes an enzyme responsible for glucuronidation of the active metabolite of irinotecan, SN-38. Patients homozygous for the *UGT1A1*28* allele (*UGT1A1* 7/7 genotype) may be at increased risk for neutropenia during irinotecan treatment due to reduced glucuronidation of SN-38. However, in this analysis, there were no differences in incidence, type, and severity of TEAEs between patients homozygous (n = 7) for the *UGT1A1*28* allele and those who were not (n = 110). There were also no notable differences in the incidence or severity of TEAEs between patients with (n = 12) and without (n = 105) prior conventional irinotecan therapy, or between patients with (n = 50) or without (n = 67) prior 5-FU therapy.

Conclusion: Overall, the safety profile of nal-IRI + 5-FU/LV was generally similar across patient subgroups, apart from an increased risk of grade ≥3 neutropenia/reduced neutrophil counts in Asian patients. The results of this prespecified subgroup analysis further support the tolerability profile of nal-IRI + 5-FU/LV in patients with mPAC previously treated with gemcitabine-based therapy.

CA19-9 decrease and overall survival (OS) in the NAPOLI-1 trial of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

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Introduction

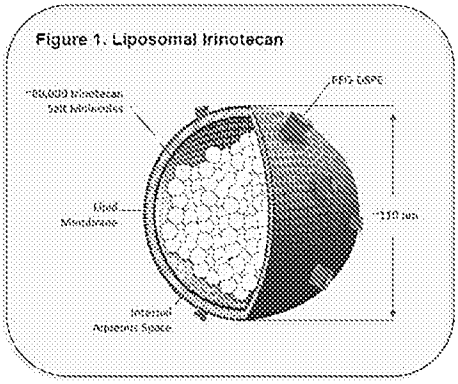
CA19-9

- Carbohydrate antigen sialyl Lewis a, more commonly known as cancer antigen 19-9 or CA19-9, is a biomarker used in the management of pancreatic ductal adenocarcinoma (PDAC)[1]
- CA19-9 levels have been shown to correlate positively with clinical stage and inversely with response to chemotherapy and survival in mPDAC patients[2-5]
- Decreases in CA19-9 from baseline have been shown to be associated with improved outcomes in clinical trials of patients with mPDAC[6,7]
- A previous post-hoc analysis[8] of NAPOLI-1[9] data showed that
  - OS and PFS in patients who received nal-IRI+5-FU/LV were greatest among patients with the highest baseline CA 19-9 levels.
  - ORR was greater with nal-IRI+5-FU/LV relative to 5-FU/LV control in the overall population, but there was no clear trend in impact on ORR relative to baseline CA19-9

Liposomal Irinotecan

- Liposomal irinotecan (nal-IRI, MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (Figure 1)[10]
- nal-IRI is approved 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 metastatic pancreatic ductal adenocarcinoma (mPDAC) after disease progression following gemcitabine-based therapy
- Liposomal irinotecan demonstrated longer half-lives and higher total, average, and maximal concentrations of irinotecan, while maintaining lower maximal concentrations of SN-38 (the active metabolite of irinotecan) in a study evaluating plasma pharmacokinetics of nal-IRI (120 mg/m^2) and conventional irinotecan hydrochloride trihydrate salt (300 mg/m^2) in gastric cancer patients[11,12]
  - 95% of irinotecan remains liposome encapsulated in circulation for up to 169.5 hours following administration
- Intratumoral drug deposition via the enhanced permeability and retention effect was demonstrated in a mouse xenograft model of human colon carcinoma[13]

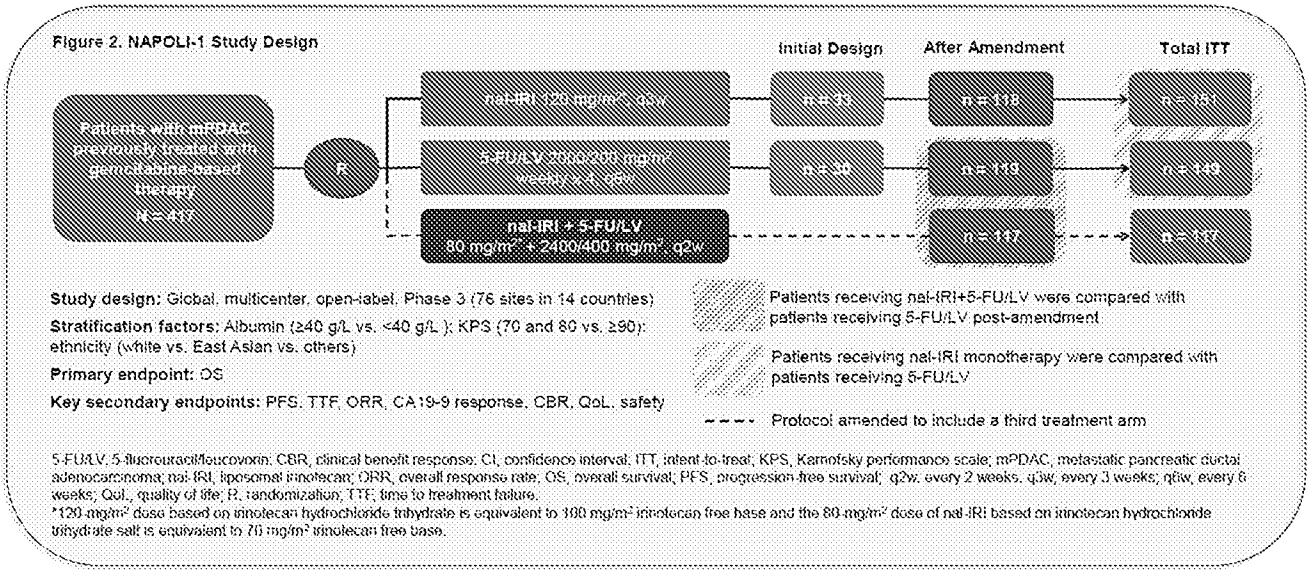
Figure 1. Liposomal Irinotecan



Methods

NAPOLI-1

- NAPOLI-1 was a large (N = 417; NCT01494506), phase 3 trial that evaluated liposomal irinotecan alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, for patients with mPDAC previously treated with gemcitabine-based therapy (Figure 2)[9]



5-FU/LV, 5-fluorouracil/leucovorin; CBR, clinical benefit response; CI, confidence interval; ITT, intent-to-treat; KPS, Karnofsky performance scale; mPDAC, metastatic pancreatic ductal adenocarcinoma; nal-IRI, liposomal irinotecan; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks, q3w, every 3 weeks; qtiw, every 6 weeks; QoL, quality of life; R, randomization; TTF, time to treatment failure.
*120 mg/m² dose based on irinotecan hydrochloride trihydrate is equivalent to 100 mg/m² irinotecan free base and the 80 mg/m² dose of nal-IRI based on irinotecan hydrochloride trihydrate salt is equivalent to 70 mg/m² irinotecan free base.

Exploratory Post Hoc Objective

* This was an exploratory post hoc analysis using CA19-9 data collected prospectively in NAPOLI-1 to evaluate the relationship between changes in CA19-9 and OS (data cutoff, November 16, 2015; 382 OS events)

Methods

* Blood samples for CA19-9 measurement were obtained at baseline and every 6 weeks thereafter until disease progression, initiation of a new antineoplastic treatment, or withdrawal of consent by a central laboratory

Analysis

* Data from patients who received study drug, had a baseline CA19-9 assessment, and ≥1 postbaseline CA19-9 measurement up to the week 12 assessment patients in the trial were pooled across treatment arms to assess the association between CA19-9 decrease and OS
* Patients were grouped by CA19-9 response from baseline within the first 12 weeks from treatment initiation: no decrease, any decrease, ≥20% decrease, or ≥50% decrease
* OS was calculated by the Kaplan-Meier method
* Hazard ratios (HRs) for OS comparisons based on different thresholds for change in CA19-9 were estimated by Cox regression analysis and Fisher's exact test was for comparisons; P-values were descriptive

Results

Patient Characteristics

* A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013
* 398 received study drug in the 3 study arms; 283 (71%) of these had CA19-9 data at baseline and at any time post-baseline up to week 12 (Table 1)

Table 1. Patient Characteristics in Post-hoc Analysis

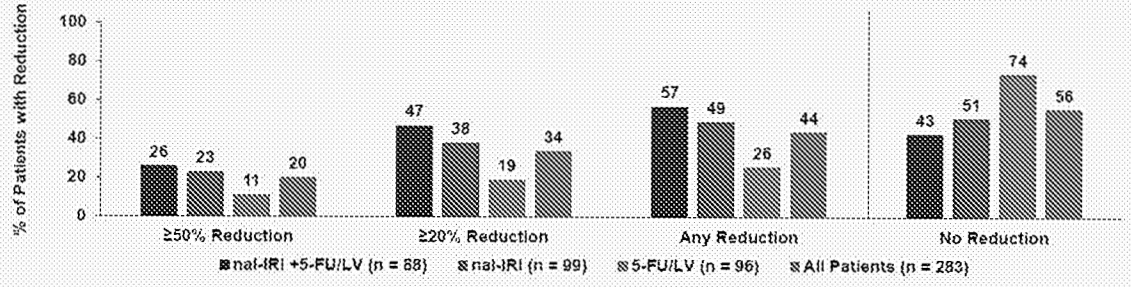
Characteristic	nal-IRI+5-FU/LV n = 88	nal-IRI n = 99	5-FU/LV n = 96	Overall N = 283
Age, mean (range), y	63.3 (41-81)	63.2 (31-87)	61.5 (39-83)	62.7 (31-87)
Men, %	60	61	52	58
Race, %				
Caucasian	63	52	60	58
Asian	28	43	36	36
Other	9	5	3	6
Albumin, %				
<4 g/dL	39	40	45	41
≥4 g/dL	61	60	55	59
KPS, %				
<90	42	37	46	42
≥90	58	63	54	58
Prior lines of metastatic therapy, %				
0	15	11	17	14
1	56	56	55	55
2 or more	30	33	28	30
Mean (SD) CA19-9, U/L	24161.1 (74757.8)	34195.9 (137543.4)	14556.4 (47184.8)	24413.4(95474.1)
Baseline level				
>40 U/L, %	82	88	74	81
>110 U/L, %	80	79	65	74
>1100 U/L, %	56	58	38	50
>11000 U/L, %	26	24	15	22

5-FU/LV, 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan; SD, standard deviation; y, years

CA19-9 Reductions

- A greater proportion of patients receiving nal-IRI+5-FU/LV had decreases in CA19-9 from baseline (Figure 3).

Figure 3. Percent of Patients with ≥50%, ≥20%, Any, or No Reduction in CA19-9 from Baseline



[a]Patients with data at baseline and at any time postbaseline up to week 12.
[b]Reduction categories are not mutually exclusive; patients in greater reduction categories are included in the lower reduction categories.

Association of CA19-9 Response with Efficacy

- Any reduction in CA19-9 from baseline within first 12 weeks was associated with a prolonged overall survival (Figure 4) and response (Figure 5)
- Patients who achieved a ≥20% decrease in CA19-9 by week 12 (n = 97) had an estimated median OS of 8.4 mo (95% CI, 7.1-10.5 mo) vs 5.1 mo (95% CI, 4.7-5.9 mo) for those patients (n = 186) who did not achieve this decrease (HR, 0.58; 95% CI, 0.45-0.76; *P*<0.0001)
- Patients who achieved a ≥50% decrease in CA19-9 by week 12 (n=57) had an estimated median OS of 9.5 mo (95% CI, 7.5-11.7 mo) vs 5.5 mo (95% CI, 4.9-6.1 mo) for those patients (n = 226) who did not achieve this decrease (HR, 0.60; 95% CI, 0.44-0.81; *P*=0.0009)

Figure 4. Association of CA19-9 Response with Efficacy

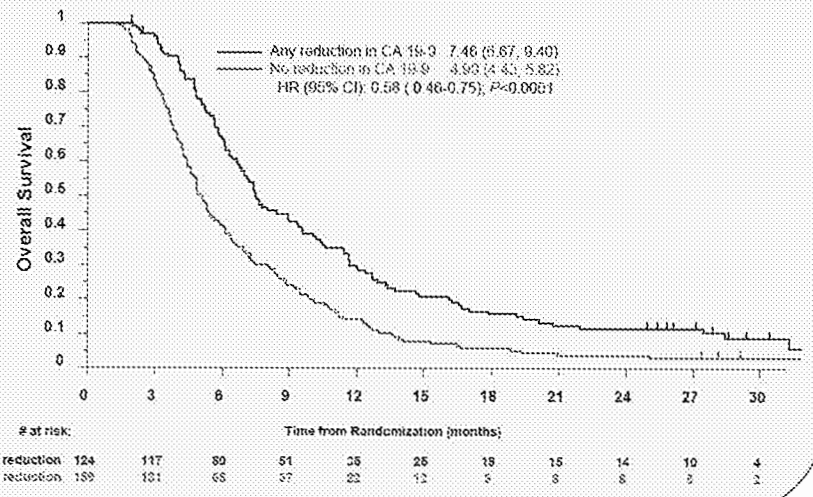
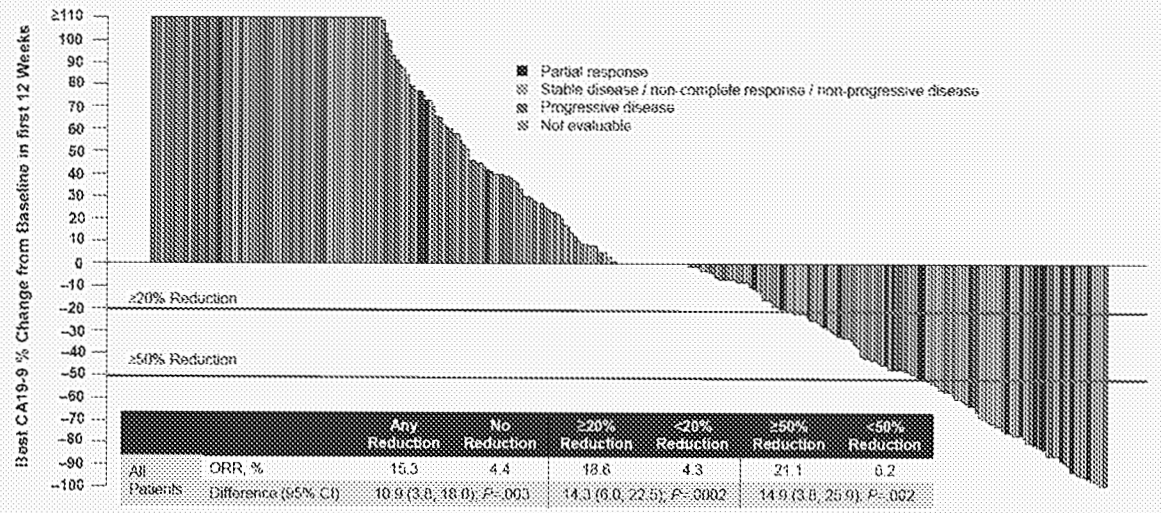


Figure 5. Association of Change in CA19-9 with Objective Response Rate



		Any Reduction	No Reduction	≥20% Reduction	<20% Reduction	≥50% Reduction	<50% Reduction
All Patients	ORR, %	15.3	4.4	18.6	4.3	21.1	6.2
	Difference (95% CI)	10.9 (3.8, 18.0); *P*=.003		14.3 (6.0, 22.5); *P*=.0002		14.9 (3.8, 25.9); *P*=.002	

Safety

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

Table 2. Grade 3/4 Adverse Events Reported ≥10% in Any Group in Post hoc Analysis Population[a]

AE by Preferred Term[b], n (%)	nal-IRI+5-FU/LV n=98	nal-IRI n=99	5-FU/LV n=96	Overall N=293
Anemia	9 (10.2)	14 (14.1)	7 (7.3)	30 (10.6)
Neutropenia	15 (17)	5 (5.1)	1 (1.0)	21 (7.4)
Vomiting	9 (10.2)	16 (16.2)	5 (5.2)	30 (10.6)
Fatigue	13 (14.8)	9 (9.1)	3 (3.1)	25 (8.8)
Decreased neutrophil count	12 (13.6)	10 (10.1)	1 (1.0)	23 (8.1)
Decreased White Blood Cell Count	9 (10.2)	4 (4.0)	0	13 (14.6)
Hypokalemia	3 (3.4)	14 (14.1)	3 (3.1)	20 (7.1)

[a]Patients included received study drug, had a baseline CA19-9 assessment, and ≥1 postbaseline CA19-9 measurement up to the week 12 assessment.
[b]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
5-FU/LV, 5-fluorouracil/leucovorin; AEs, adverse events; nal-IRI, liposomal irinotecan.

Conclusions

- nal-IRI+5-FU/LV significantly improved OS, PFS, and ORR compared with 5-FU/LV control in the NAPOLI-1 trial of patients with mPDAC following gemcitabine-based therapy.[4]
- In NAPOLI-1[4] and this analysis, reductions in CA19-9 were more commonly observed in patients who received nal-IRI+5-FU/LV
- In this post hoc analysis, patients who achieved any CA19-9 decrease from baseline, ≥20% decrease, or ≥50% decrease by week 12 had significantly longer OS than patients who did not achieve these decreases
- The observed OS was greater among patients with greater decreases from baseline CA 19-9 levels
- Adverse events in this population were consistent with the overall population
- Results of this exploratory post hoc analysis are consistent with data from prior reports[6,7] demonstrating that decreases from baseline in CA19-9 are associated with improved outcomes
- These analyses may be limited by the small sample size of post hoc analysis subgroups

Acknowledgements

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Poster presented at the 19th World Congress on Gastrointestinal Cancer, Barcelona, Spain, June 28–July 1, 2017.

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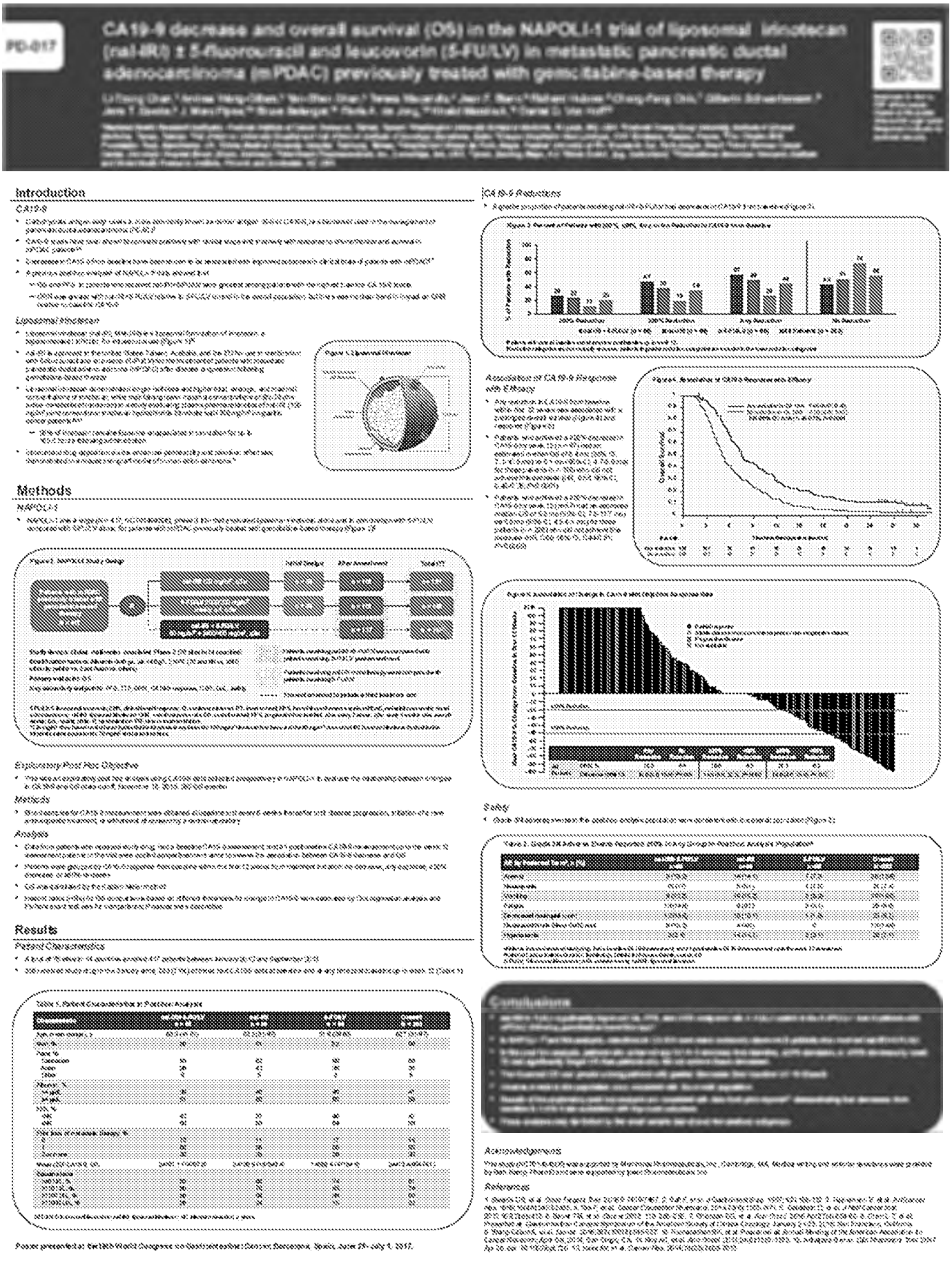

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227P

CA19-9 decrease and overall survival in the NAPOLI-1 trial of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

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INTRODUCTION

CA19-9

- Carbohydrate antigen sialyl Lewis a, more commonly known as cancer antigen 19-9 or CA19-9, is a biomarker used in the management of pancreatic ductal adenocarcinoma (PDAC).[1]
- CA19-9 levels have been shown to correlate positively with clinical stage and inversely with response to chemotherapy and survival in metastatic (m) PDAC.[2–5]
- Decreases in CA19-9 from baseline have been shown to be associated with improved outcomes in clinical trials of patients with mPDAC.[6,7]
- A previous *post hoc* analysis[8] of NAPOLI-1[9] data showed that
  - Overall survival (OS) and progression free survival (PFS) in patients who received nal-IRI+5-FU/LV were greatest among patients with the highest baseline CA 19-9 levels.
  - Overall response rate (ORR) was greater with nal-IRI+5-FU/LV relative to 5-FU/LV control in the overall population, but there was no clear trend in impact on ORR relative to baseline CA19-9.

Liposomal Irinotecan

- Liposomal irinotecan (nal-IRI, MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (Figure 1).[10]
- nal-IRI is approved in the United States, Taiwan, South Korea, Australia, Canada, Switzerland 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.
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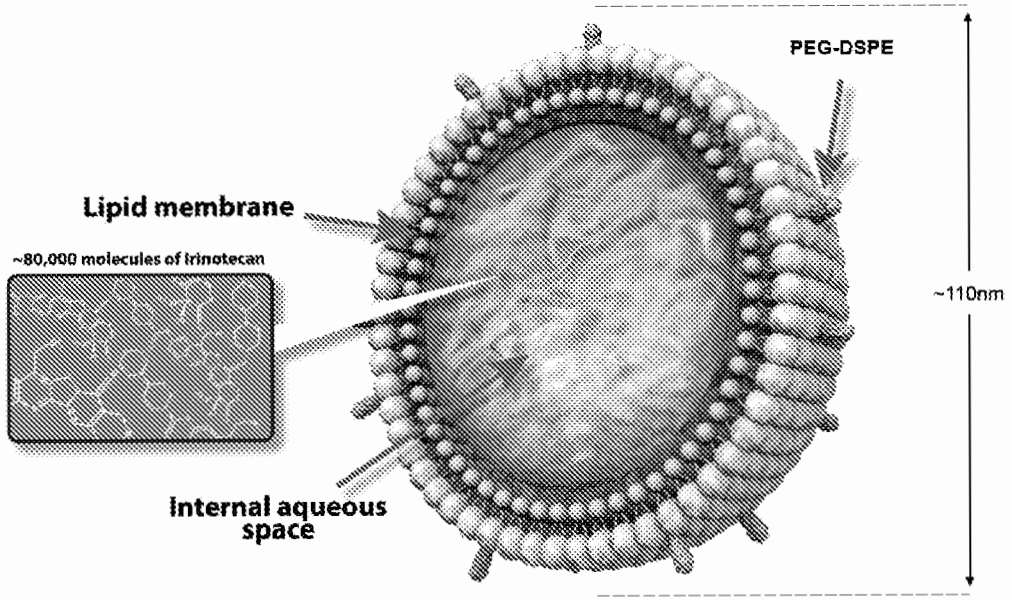
  - 95% of irinotecan remains liposome encapsulated in circulation for up to 169.5 hours following administration.
- Intratumoral drug deposition via the enhanced permeability and retention effect was demonstrated in a mouse xenograft model of human colon carcinoma.[13]

Figure 1. nal-IRI Design[16]



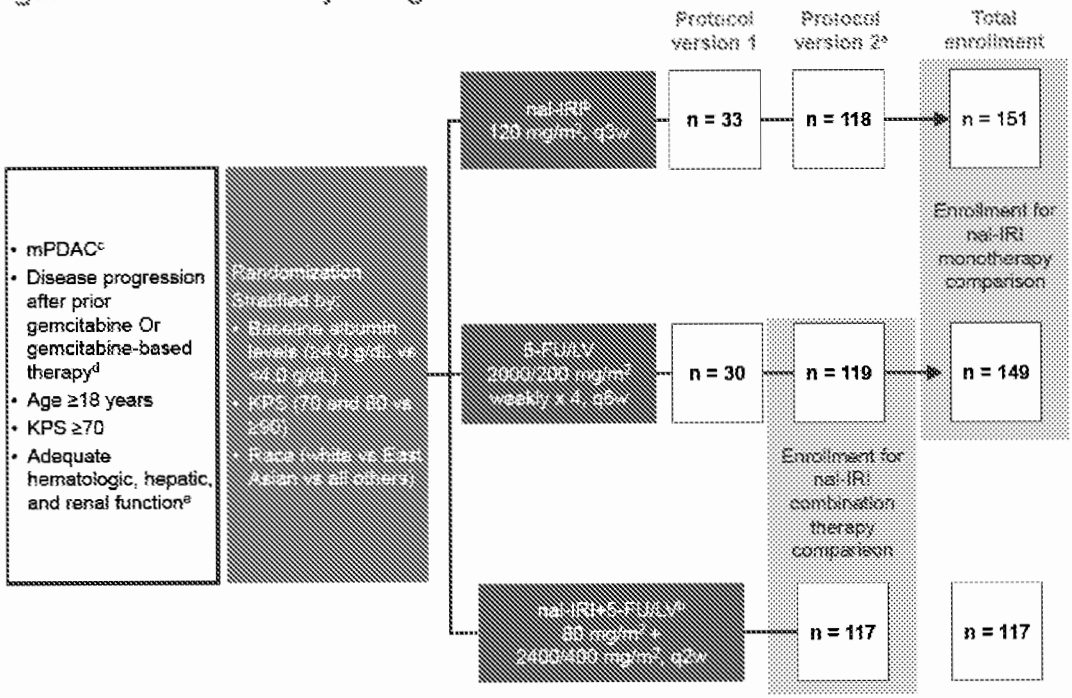
nal-IRI, liposomal irinotecan; PEG-DSPE, poly(ethylene glycol)-distearoylphosphatidylethanolamine

METHODS

NAPOLI-1

- NAPOLI-1 was a large (N = 417; NCT01494506), phase 3 trial that evaluated liposomal irinotecan alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, for patients with mPDAC previously treated with gemcitabine-based therapy (Figure 2).[9]

Figure 2. NAPOLI-1 Study Design



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/m^2 approximate to 100 and 70 mg/m^2 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.

Exploratory *Post Hoc* Objective

- This was an exploratory, *post hoc* analysis using CA19-9 data collected prospectively in NAPOLI-1 to evaluate the relationship between changes in CA19-9 and OS (data cutoff, November 16, 2015; 382 OS events).

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- Blood samples for CA19-9 measurement were obtained at baseline and every 6 weeks thereafter until disease progression, initiation of a new antineoplastic treatment, or withdrawal of consent by a central laboratory.

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- OS was calculated by the Kaplan-Meier method.
- Hazard ratios (HRs) for OS comparisons based on different thresholds for change in CA19-9 were estimated by Cox regression analysis and Fisher's exact test was for comparisons; P-values were descriptive.

RESULTS

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- 398 received study drug in the 3 study arms; 283 (71%) of these had CA19-9 data at baseline and at any time post-baseline up to week 12 (Table 1).

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Characteristics	nal-IRI+5-FU/LV n = 88	nal-IRI n = 99	5-FU/LV n = 96	Overall n = 283
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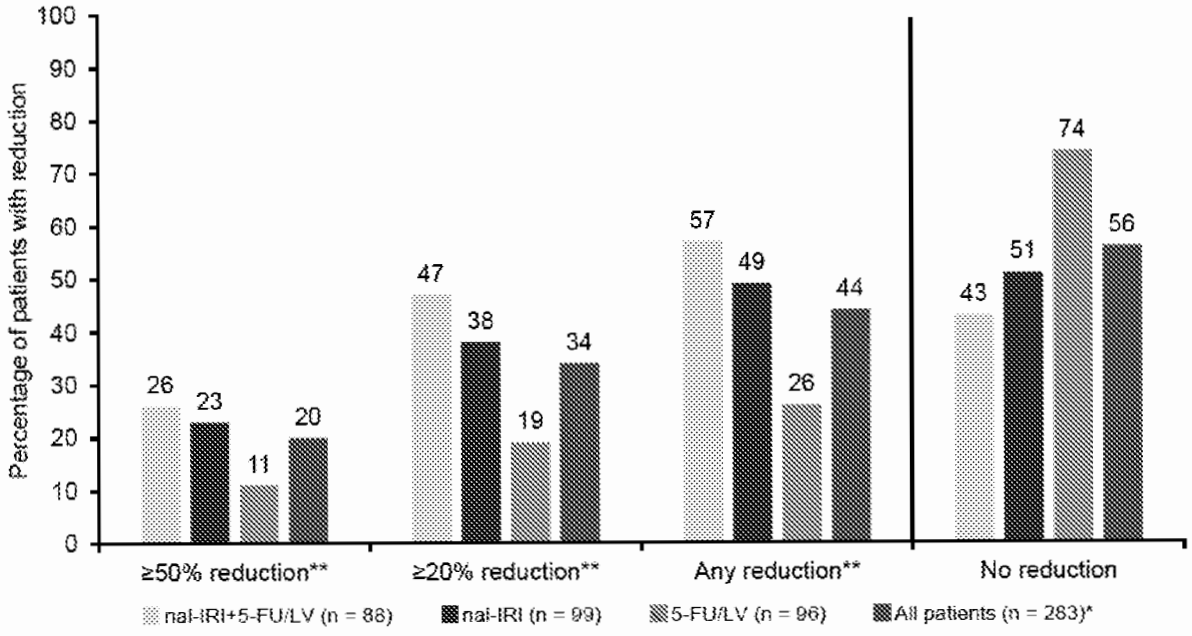
5-FU/LV, 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan; SD, standard deviation; y, years.

CA19-9 Reductions

- A greater proportion of patients receiving nal-IRI+5-FU/LV had decreases in CA19-9 from baseline (Figure 3).

Figure 3. Percentage of patients with ≥50%, ≥20%, any or no reduction in CA19-9 levels from baseline



5-FU/LV, 5-fluorouracil/leucovorin; nal-IRI, liposomal irinotecan
*Patients with data at baseline and any time post-baseline up to week 12
**Reduction categories are not mutually exclusive; patients in greater reduction categories are also included in lower reduction categories

Association of CA19-9 Response with Efficacy

- Any reduction in CA19-9 from baseline within the first 12 weeks was associated with a prolonged OS (Figure 4) and response (Figure 5).
- Patients who achieved a ≥20% decrease in CA19-9 by week 12 (n = 97) had an estimated median OS of 8.4 mo (95% CI, 7.1–10.5 mo) vs 5.1 mo (95% CI, 4.7–5.9 mo) for those patients (n = 186) who did not achieve this decrease (HR, 0.58; 95% CI, 0.45–0.76; P<0.0001).
- Patients who achieved a ≥50% decrease in CA19-9 by week 12 (n=57) had an estimated median OS of 9.5 mo (95% CI, 7.5–11.7 mo) vs 5.5 mo (95% CI, 4.9–6.1 mo) for those patients (n = 226) who did not achieve this decrease (HR, 0.60; 95% CI, 0.44-0.81; P=0.0009).

Figure 4. Association of CA19-9 response with OS

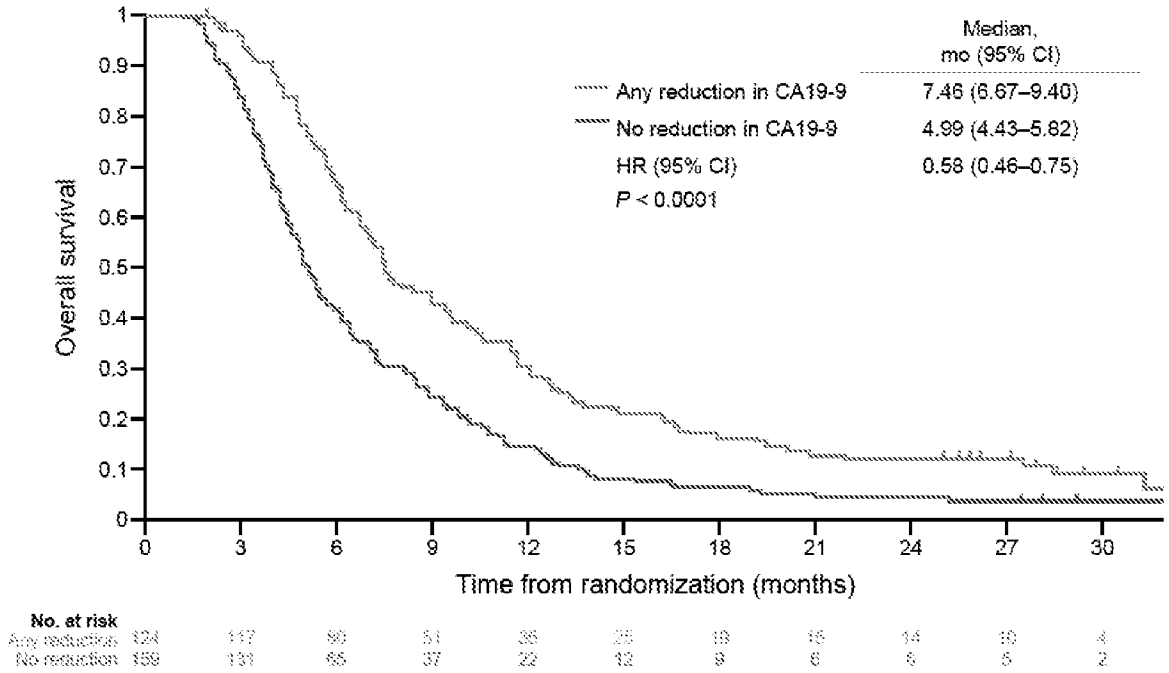
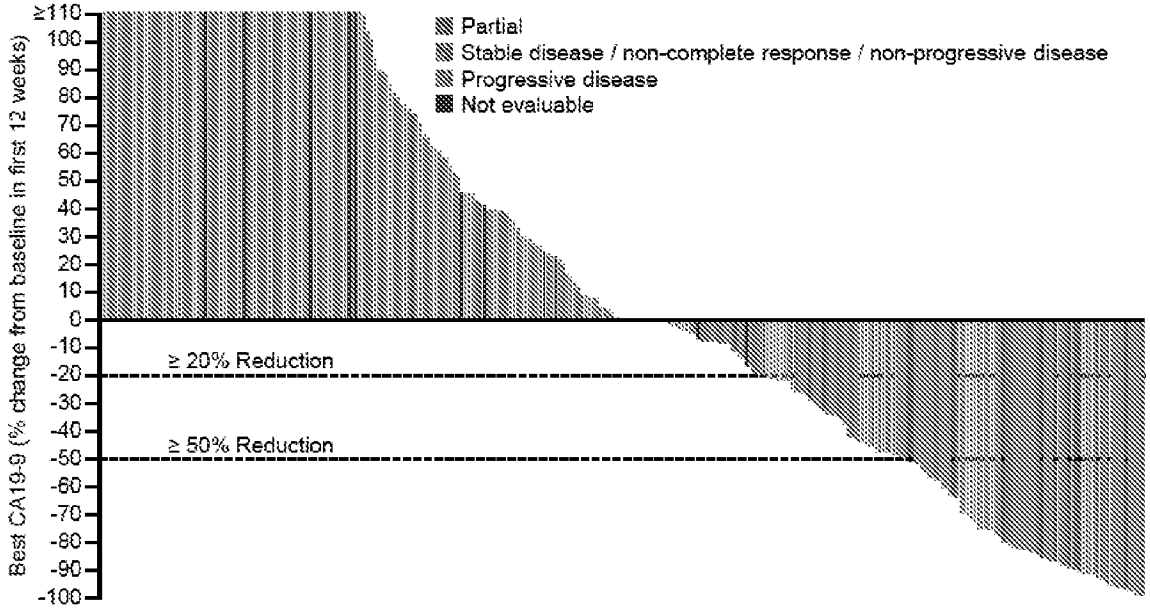


Figure 5. Association of change in CA19-9 with ORR



		Any Reductions	No Reduction	≥20% Reduction	<20% Reduction	≥50% Reduction	<50% Reduction
All Patients	ORR, %	15.3	4.4	18.6	4.3	21.1	6.2
	Difference (95% CI)	10.9 (3.8–18.0); $P = 0.003$		14.3 (6.0–22.5); $P = 0.0002$		14.9 (3.8–25.9); $P = 0.002$	

Safety

- Grade 3–4 adverse events in this *post hoc* analysis population were consistent with the overall population (Figure 3).

Table 2. Grade 3–4 adverse events reported ≥10% in any group in the *post hoc* analysis population[a]

AE by preferred term[b], n (%)	nal-IRI+5-FU/LV n = 88	nal-IRI n = 99	5-FU/LV n = 96	Overall n = 283
Anemia	9 (10.2)	14 (14.1)	7 (7.3)	30 (10.6)
Neutropenia	15 (17.0)	5 (5.1)	1 (1.0)	21 (7.4)
Vomiting	9 (10.2)	16 (16.2)	5 (5.2)	30 (10.2)
Fatigue	13 (14.8)	9 (9.1)	3 (3.1)	25 (8.8)
Decreased neutrophil count	12 (13.6)	10 (10.1)	1 (1.0)	23 (8.1)
Decreased White Blood Cell Count	9 (10.2)	4 (4.0)	0	13 (14.6)
Hypokalemia	3 (3.4)	14 (14.1)	3 (3.1)	20 (7.1)

[a]Patients who received study drug, had a baseline CA19-9 assessment, and ≥1 post-baseline CA19-9 measurement up to the week 12 assessment.
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5-FU/LV, 5-fluorouracil/leucovorin; AEs, adverse events; nal-IRI, liposomal irinotecan.

CONCLUSIONS

- nal-IRI+5-FU/LV significantly improved OS, PFS, and ORR compared with 5-FU/LV control in the NAPOLI-1 trial of patients with mPDAC following gemcitabine-based therapy.[9]
- In NAPOLI-1[9] and this analysis, reductions in CA19-9 were more commonly observed in patients who received nal-IRI+5-FU/LV.
- In this *post hoc* analysis, patients who achieved any CA19-9 decrease from baseline, ≥20% decrease, or ≥50% decrease by week 12 had significantly longer OS than patients who did not achieve these decreases.
- The observed OS was greater among patients with greater decreases from baseline CA19-9 levels.
- Adverse events in this population were consistent with the overall population.
- Results of this exploratory *post hoc* analysis are consistent with data from prior reports[6,7] demonstrating that decreases from baseline in CA19-9 are associated with improved outcomes.
- These analyses may be limited by the small sample size of *post hoc* analysis subgroups.

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Original Article

Early dose reduction/delay and the efficacy of liposomal irinotecan with fluorouracil and leucovorin in metastatic pancreatic ductal adenocarcinoma (mPDAC): A post hoc analysis of NAPOLI-1

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ABSTRACT

Background: Chemotherapy dose modification to manage adverse events is commonplace in clinical practice. This exploratory analysis evaluates the impact of liposomal irinotecan dose modification on overall survival (OS) and progression-free survival (PFS) in the NAPOLI-1 clinical trial (NCT01494506).
Methods: Analysis includes only patients enrolled under protocol version 2 who received at least the first 2 scheduled doses of study drug. Within the liposomal irinotecan +5 fluorouracil/leucovorin (5 FU/LV) arm, patients were grouped according to whether or not they had a dose modification within the first 6 weeks. *Dose reduction* was defined as any decrease from initial dose; *dose delay* was any dosing delay >3 days from target date. OS and PFS (Kaplan-Meier estimates) were compared within the liposomal irinotecan+5-FU/LV arm and between treatment arms. Unstratified hazard ratios (HRs) were calculated using Cox regression analysis.
Results: Of the 93 patients from the liposomal irinotecan+5 FU/LV arm included in the analysis, 53 experienced a dose modification (both delay and reduction, n = 30; delay only, n = 19; reduction only, n = 4). No apparent difference in median OS or PFS was observed between patients who did versus patients who did not have a dose modification (OS: 8.4 vs 6.7 months; HR, 0.89; PFS: 4.2 vs 3.1 months; HR, 0.74).
Conclusion: An early dose reduction or delay of liposomal irinotecan+5-FU/LV in the first 6 weeks does not significantly impact OS or PFS compared to patients without dose modifications. This finding suggests that tolerability-guided dose modification of liposomal irinotecan does not adversely affect efficacy outcomes.

Introduction

Pancreatic cancer is one of the most common causes of cancer-related deaths in the United States and Europe. In contrast with a steady decline in death rates for many cancer types, the death rate for pancreatic cancer has remained largely unchanged over the last 10 years [1,2]. The 5-year survival rate in individuals diagnosed with pancreatic cancer is about 5–8% [2,3]. Surgical resection is considered the only potentially curative therapy; however, 70–80% of patients present with unresectable disease, and more than 50% of patients present with metastatic disease at initial diagnosis. Only

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about 10% of patients are diagnosed with localized disease, for which the 5-year survival rate is 29.3% [4]. Thus far, systemic chemotherapy is the primary therapeutic option for the treatment of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). Targeted therapies and immunotherapies have to date shown only limited success [5,6]. Combination chemotherapy can provide improved efficacy over monotherapy; however, increased toxicity means that successful, continuous treatment may require dose modifications in some patients [5,7,8]. Frontline therapy is built upon two therapeutic backbones: gemcitabine-based regimens [9,10] and fluorouracil-based regimens [11]. There have been limited therapeutic options following progression during first-line chemotherapy.

Results from the NAPOLI-1 study (NCT01494506) demonstrated a survival benefit of liposomal irinotecan (ONIVYDE®, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM-398 or PEP02) plus 5-fluorouracil and leucovorin (5-FU/LV) in patients with mPDAC previously treated with gemcitabine-based therapy [12]. In patients randomized to liposomal irinotecan+5-FU/LV in the NAPOLI-1 study, median overall survival (OS) was 6.1 months, compared with 4.2 months in those randomized to 5-FU/LV (hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.49–0.92; $P = 0.012$) [12]. Median progression-free survival (PFS) was 3.1 months in patients assigned to liposomal irinotecan+5-FU/LV, compared with 1.5 months in those assigned to 5-FU/LV (HR: 0.56; 95% CI: 0.41–0.75; $P = 0.0001$) [12]. Treatment with liposomal irinotecan+5-FU/LV demonstrated a manageable safety and tolerability profile. The most commonly occurring grade 3 or 4 treatment-emergent adverse events (TEAEs) included neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%) [12]. In the final analysis of OS of long-term survivors (survival of ≥1 year) in NAPOLI-1, the overall survival advantage for liposomal irinotecan+5-FU/LV was maintained with the estimated 1-year OS rates were 26% with liposomal irinotecan+5-FU/LV and 16% with 5-FU/LV. No new safety concerns were detected [13].

Based on the NAPOLI-1 results, the National Comprehensive Cancer Network guidelines list second-line therapy with liposomal irinotecan+5-FU/LV as a category 1 recommendation for mPDAC previously treated with gemcitabine-based therapy [5]. In 2017, the European Society for Medical Oncology (ESMO) published an online update of its 2015 guidelines stating that, for suitable patients, liposomal irinotecan+5-FU/LV may constitute an active and tolerable second-line treatment option [14]. In addition, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines recommend offering liposomal irinotecan+5-FU/LV to patients as second-line therapy following treatment with gemcitabine plus nanoparticle albumin-bound paclitaxel, an Eastern Cooperative Oncology Group performance status of 0–1, and a favorable comorbidity profile [15].

Dose modifications, including dose reductions or delays, can be utilized to manage toxicity-related TEAEs among patients with cancer [7,8,16]. Dose modification is intended to improve tolerability and increase the likelihood that a patient can remain on treatment for a longer period to maximize chemotherapeutic benefit and delay disease progression. The fluorouracil-based regimen FOLFIRINOX (consisting of 5-FU, LV, irinotecan, and oxaliplatin) is associated with improved OS and PFS [11]. Upon initiation with the full-dose FOLFIRINOX regimen, dosing may be reduced to decrease the frequency of side effects. One study demonstrated that dose reductions did not significantly influence survival times for patients compared with those receiving full-dose FOLFIRINOX [7]. Dose reduction and/or delay were used to manage toxicities associated with nab-paclitaxel plus gemcitabine treatment in the MPACT trial, with slight improvement in efficacy for patients who underwent dose modifications compared to those who did not [8]; while *ad hoc* modification of starting dose could be considered for toxicity management in patients deemed only borderline fit for treatment [5,7].

In NAPOLI-1, patients could have up to two dose reductions for liposomal irinotecan and 5-FU and a dose delay of up to 3 weeks to allow for recovery from TEAEs [12]. This analysis was conducted to examine if early dose modification of liposomal irinotecan + 5FU/LV may have any impact on clinical outcomes.

Methods

NAPOLI-1 was an international, multicenter, phase 3 study conducted at 76 sites in 14 countries between January 11, 2012, and September 11, 2013 [12]. Prior to patient enrollment, this study was registered with ClinicalTrials.gov (NCT01494506) in December 2011. All versions of the study protocol were approved by the institutional review board or ethics committees for every site [12]. NAPOLI-1 was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonisation, and the requirements of the US Food and Drug Administration and local regulatory authorities regarding the conduct of human clinical trials. All patients provided written informed consent [12].

The NAPOLI-1 study methods have been previously described [12]. Briefly, patients aged 18 years or older with confirmed pancreatic adenocarcinoma with documented distant metastatic disease and disease progression after previous gemcitabine-based therapy were included. The source population for this post hoc analysis comprised NAPOLI-1 patients who were treated with either the 5-FU/LV or liposomal irinotecan+5-FU/LV under protocol version 2 and received at least 1 dose of study drug (safety population). Of note, all patients were required to have determination of *UGT1A1*28* prior to enrollment in the study. Patients who were homozygous for the *UGT1A1*28* allele were treated at a lower initial dose.

Patients in the 5-FU/LV arm were administered an intravenous infusion of LV at a dose of 200 mg/m^2 followed by 5-FU at a dose of 2000 mg/m^2 weekly for 4 weeks of each 6-week cycle. Patients in the liposomal irinotecan+5-FU/LV arm received liposomal irinotecan at a dose of 80 mg/m^2 (salt; equivalent to 70 mg/m^2 free base) followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 every 2 weeks. Patients known to be homozygous for the *UGT1A1*28* allele (n = 7) received a liposomal irinotecan starting dose of 60 mg/m^2 (salt; equivalent to 50 mg/m^2 free base) and received liposomal irinotecan at a dose of 80 mg/m^2 as tolerated in subsequent cycles.

TEAEs were reported at each patient visit and graded according to severity. The treatment-emergent period for TEAEs started at the time of first administration of the study drug and ended 30 days after administration of the last dose of study drug. Treatment was continued until disease progression or unacceptable toxicity occurred [12]. Infusion reactions were defined according to the definition of an allergic reaction/anaphylaxis and infusion reaction in the National Cancer Institute CTCAE (Version 4.0) [17].

Dose-modification protocol

The NAPOLI-1 study protocol allowed for up to two dose reductions for liposomal irinotecan and 5-FU and for a dosing delay of up to 3 weeks to allow for recovery from toxicity-related TEAEs. In general, for patients not homozygous for the *UGT1A1*28* allele, dose reductions were not required for TEAEs grade ≤2. For grade 3/4 TEAEs in patients not homozygous for the *UGT1A1*28* allele, patients in the liposomal irinotecan+5-FU/LV arm received a liposomal irinotecan dose of 60 mg/m^2 (salt; equivalent to 50 mg/m^2 free base) for the first occurrence and 50 mg/m^2 (salt, equivalent to

43 mg/m^2 free base) for the second occurrence.

Dosing could be held (delayed) for up to 3 weeks to allow for recovery from TEAEs. If the time required for recovery from toxicity exceeded 3 weeks, study treatment was generally discontinued. If dosing of liposomal irinotecan or 5-FU needed to be delayed, then the other drugs in the combination were also not administered.

Post hoc analysis

Within the liposomal irinotecan+5-FU/LV arm, patients were divided into two groups: those with a liposomal irinotecan dose modification (comprising liposomal irinotecan dose reduction and/or liposomal irinotecan+5-FU/LV dose delay) and those without. Dose reduction was defined as any reduction in the scheduled dose of liposomal irinotecan from the initial administered dose occurring in the first 6 weeks of the study. A dose delay was defined as any delay in dosing at least 3 days from the targeted dosing date (up to 3 weeks) occurring in the first 6 weeks of the study.

Within the dose dose-modified cohort, all patients received at least 2 doses of liposomal irinotecan +5 FU/LV (ie, a patient had to receive more than 1 dose to qualify as dose modified; patients who received only 1 dose were excluded by definition). Consequently, patients with only 2 study drug administrations and dose modification on the second dose are included in the dose-modified cohort. To balance the cohort of patients without dose modification, we included only patients who received at least the first 2 scheduled doses of liposomal irinotecan+5-FU/LV within the first 6 weeks, thereby excluding patients with disease progression, treatment discontinuation or death after 1 dose treatment. Patients known to be homozygous for the dose-modified*UGT1A1*28* allele who initiated liposomal irinotecan treatment at a reduced dose (60 mg/m^2) and then received the 80-mg/m^2 dose in subsequent cycles were not included in the dose-modified population because the starting dose reduction was not administered in response to TEAEs. Because few patients in the 5-FU/LV arm had a dose modification, between-arm comparisons were made using all 5-FU/LV patients who received at least 4 doses of 5-FU/LV in the first 6 weeks with no other major protocol violations. It shoud be noted that, per protocol, once a patient's dose was reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to the earlier dose was not permitted.

Statistical analysis

The primary efficacy endpoint was OS, and the secondary endpoint was PFS. Comparisons of OS and PFS were made between

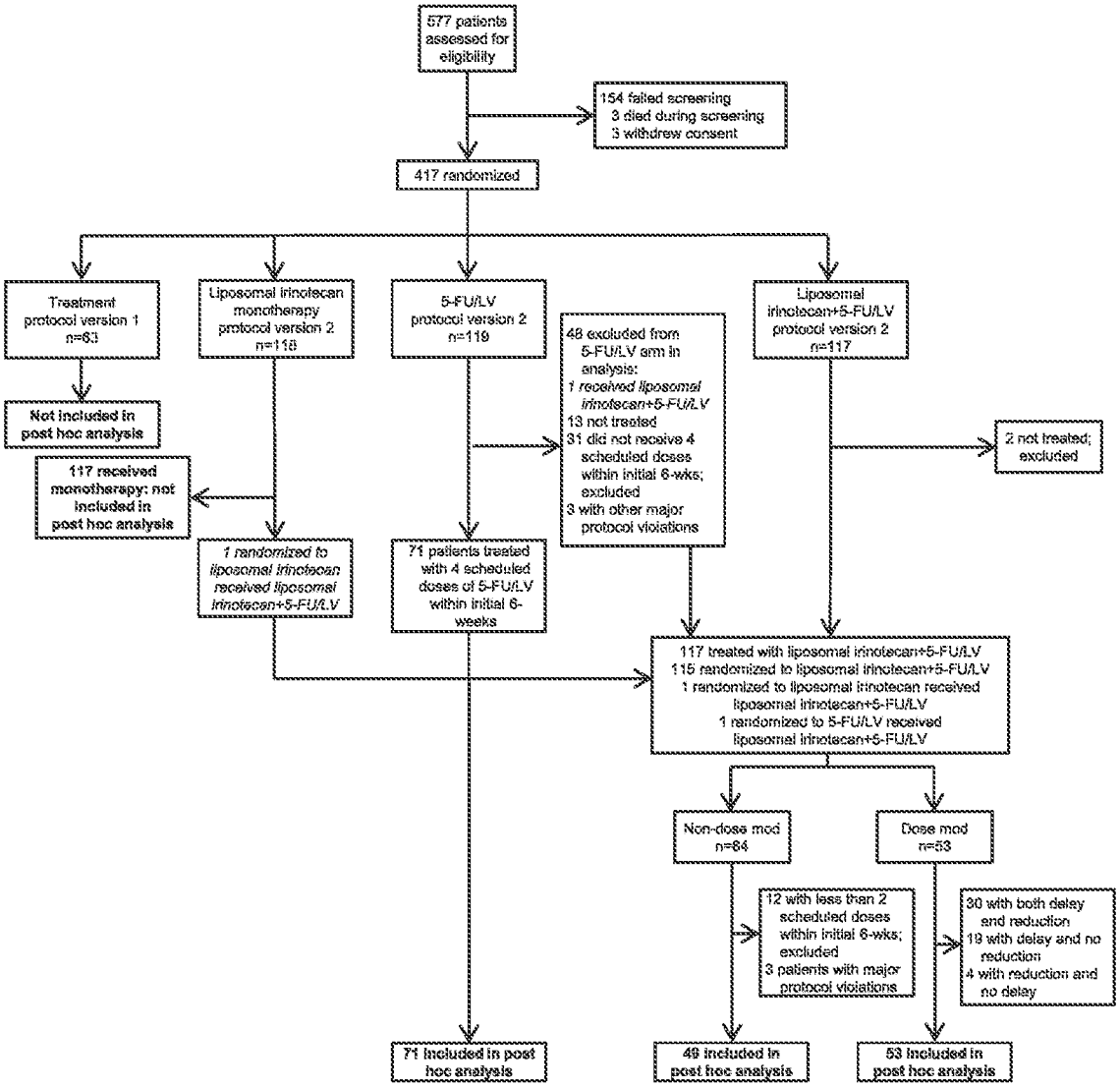

Fig. 1. NAPOLI-1 and exploratory post hoc analysis: patient disposition flow diagram.

patients within the liposomal irinotecan+5-FU/LV arm who had a liposomal irinotecan dose modification and those without dose modification. Additional comparisons of OS and PFS were made between patients in the liposomal irinotecan+5-FU/LV arm with dose modifications and the population in the 5-FU/LV arm.

Kaplan-Meier analysis was used to estimate median OS and PFS. Hazard ratios and 95% CIs were estimated using Cox regression analysis. Fisher's exact test was used for comparisons. All calculated *P* values were descriptive in nature.

Results

Patients

This post hoc analysis included 102 patients treated with liposomal irinotecan+5-FU/LV and 71 patients treated with 5-FU/LV alone (Fig. 1). A total of 14 patients were homozygous for *UGT1A1*28* allele, with 7 patients randomized to the liposomal irinotecan+5-FU/LV arm and 7 patients randomized to the liposomal irinotecan-only arm. Doses for these pateints was adjusted per protocol. Among the patients treated with liposomal irinotecan+5-FU/LV during the first 6 weeks of treatment, 53 patients underwent dose modification(s) and 49 did not. Dose delay occurred in 49 and dose reduction in 34 patients; 30 patients had both delay and reduction; 19 patients had delay only and 4 patients had reduction only. Adverse events led to dose reduction and/or delay are provided in Supplemental Table 1. The most common grade 3/4 TEAEs ($n \geq 5$) in patients who required a dose delay were white blood cell decrease (n = 11), neutrophil count decrease (n = 9), neutropenia (n = 8), diarrhea (n = 6), and platelet count decrease (n = 5). In patients requiring a dose reduction, the most common grade 3/4 TEAEs were neutrophil count decrease (n = 7), neutropenia (n = 5), and white blood cell decrease (n = 5). Table 1 shows baseline disease characteristics of patients in the liposomal irinotecan+5-FU/LV arm separately for patients who had a dose modification and those who did not have a dose modification, as well as patients in the 5-FU/LV population. The three groups were generally well balanced. A higher proportion of patients in the liposomal irinotecan+5-FU/LV arm who did not have a dose modification had a Karnofsky performance status score of 90 or 100 and a higher level of cancer antigen 19-9 compared with patients in the liposomal irinotecan+5-FU/LV arm who had a dose modification. Those in the liposomal irinotecan+5-FU/LV arm who had dose modifications had a higher proportion of men and more patients of Asian ethnicity.

Impact of dose modification on survival

Within the liposomal irinotecan+5-FU/LV arm, survival outcomes were similar between patients with and patients without a dose modification (OS: 8.4 vs 6.7 months; HR, 0.89, p-value: 0.5948. Fig. 2A; PFS: 4.2 vs 3.1 months; HR, 0.74, p-value: 0.1647. Fig. 2B). Median OS in patients who had a dose reduction (n = 34) was 9.36 months (95% CI, 6.14–13.90), whereas the median OS in patients who did not have a dose reduction (n = 68) was 6.44 months (95% CI, 4.70–8.74), with an HR of 0.73, p-value: 0.1546 (95% CI, 0.47–1.22) (Supplemental Fig. 1A). The median OS in patients who had a dose delay (n = 49) was 8.44 months (95% CI, 5.26–11.04) compared with 6.67 months (95% CI, 4.77–8.87) for patients who did not have a dose delay (n = 53; HR, 0.97, p-value: 0.8907 [95% CI, 0.64–1.47]) (Supplemental Fig. 1B). In the liposomal irinotecan+5-FU/LV arm, the median PFS in patients with versus without a dose

Table 1
Baseline characteristics of the liposomal irinotecan+5-FU/LV arm (separately by whether or not patients had a dose modification) and the 5-FU/LV arm.

Characteristic	Liposomal irinotecan +5-FU/LV		5-FU/LV
	Dose modification (n = 53)[a]	No dose modification (n = 49)	(n = 71)
Sex, n (%)			
Men	33 (62.3)	27 (55.1)	37 (52.1)
Women	20 (37.7)	22 (44.9)	34 (47.9)
Age (y), mean (SD)	62.2 (9.5)	63.4 (8.3)	60.6 (9.85)
Weight (kg), mean (SD)	63.0 (13.7)	67.8 (15.0)	65.2 (16.0)
BMI (kg/m^2), mean (SD)	22.7 (4.2)	23.9 (4.0)	23.66 (4.7)
Ethnicity, n (%)			
Caucasian	26 (49.1)	36 (73.5)	47 (66.2)
Asian	22 (41.5)	8 (16.3)	22 (31.0)
Black or African American	1 (1.9)	3 (6.1)	1 (1.4)
Other	4 (7.5)	2 (4.1)	1 (1.4)
Region, n (%)			
Europe	17 (32.1)	25 (51.0)	34 (47.9)
Asia	22 (41.5)	8 (16.3)	21 (29.6)
North America	5 (9.4)	11 (22.4)	9 (12.7)
Other	9 (17.0)	5 (12.5)	7 (9.9)
KPS score, n (%)			
100	6 (11.3)	12 (24.5)	9 (12.7)
90	20 (37.7)	23 (46.9)	28 (39.4)
80	22 (41.5)	11 (22.4)	28 (39.4)
70	5 (9.4)	2 (4.1)	6 (8.5)
60	0	1 (2.0)	0
Serum albumin (g/dL), mean (SD)	4.03 (0.43)	4.01 (0.42)	4.02 (0.49)
Serum CA 19-9 (U/mL), mean (SD)	14 482 (31 689)	19 641 (66 740)	15 991 (43 090)
Previous anticancer therapy, n (%)			
Gemcitabine monotherapy	23 (43.4)	23 (46.9)	35 (49.3)
Gemcitabine combination	30 (56.6)	26 (53.1)	36 (50.7)
Fluorouracil-based	22 (41.5)	21 (42.9)	26 (36.6)
Irinotecan-based	4 (7.5)	7 (14.3)	10 (14.1)
Platinum-based	18 (34.0)	15 (30.6)	20 (28.2)

[a] Of the 53 patients with dose modification, 30 patients had both a dose delay and a dose reduction, 19 patients had only a dose delay, and 4 patients had only a dose reduction. 5-FU/LV, 5-fluorouracil/leucovorin; BMI, body mass index; CA 19-9, cancer antigen 19-9; KPS, Karnofsky performance status; SD, standard deviation.

reduction was 4.21 months (95% CI, 2.79–6.97) versus 3.09 months (n = 34, 95% CI, 1.58–4.34), respectively, with an HR of 0.78, p-value: 0.2864 (95% CI, 0.49–1.23) (Supplemental Fig. 2A). Median PFS in patients who had a dose delay (n = 49) was 4.17 months (95% CI, 2.76–5.65) compared with 3.09 months (95% CI, 1.51–5.56) for patients who did not have a dose delay (n = 49), with an HR of 0.91, p-value: 0.6539 (95% CI, 0.59–1.40) (Supplemental Fig. 2B).

Between treatment arms, survival outcomes were greater for patients in the liposomal irinotecan+5-FU/LV arm regardless of dose reduction or delay when compared to patients in the 5-FU/LV arm (ie, those who received 4 doses of 5-FU/LV in the first 6 weeks). Median OS for patients in the liposomal irinotecan+5-FU/LV arm who had dose reduction and delay was 9.36 months (95% CI, 6.14–13.90; HR 0.70, p-value: 0.1149 [95% CI, 0.45–1.09]) and 8.44 months (95% CI, 5.26–11.04; HR 0.81, p-value: 0.2731 [95% CI, 0.55–1.18]), respectively, compared to 5.09 months (95% CI, 3.98–7.16) in the 5-FU/LV arm (Fig. 3). Median PFS in the liposomal irinotecan+5-FU/LV arm who had dose reduction and delay was 4.21 months (95% CI, 2.79–6.97; HR 0.50, p-value: 0.003 [95% CI, 0.32–0.79]) and 4.17 months (95% CI, 2.76–5.65; HR, 0.55, p-value: 0.0035 [95% CI, 0.37–0.82]), respectively, compared to 1.61 months (95% CI, 1.41–2.60) in the 5-FU/LV arm (Fig. 4).

For the 7 patients who were homozygous for *UGT1A1*28* allele and were treated with liposomal irinotecan+5-FU/LV, 3 out of the 7 patients were able to have liposomal irinotecan dose escalation to 80 mg/m^2 without the need for further dose reduction. One patient dose escalated but required dose reduction back to 60 mg/m, while in 2 patients the initial dose was not changed; and in 1 patient, the dose was reduced to 40 mg/m2. For these 7 patients, 1 patient discontinued treatment due to an adverse event and one due to

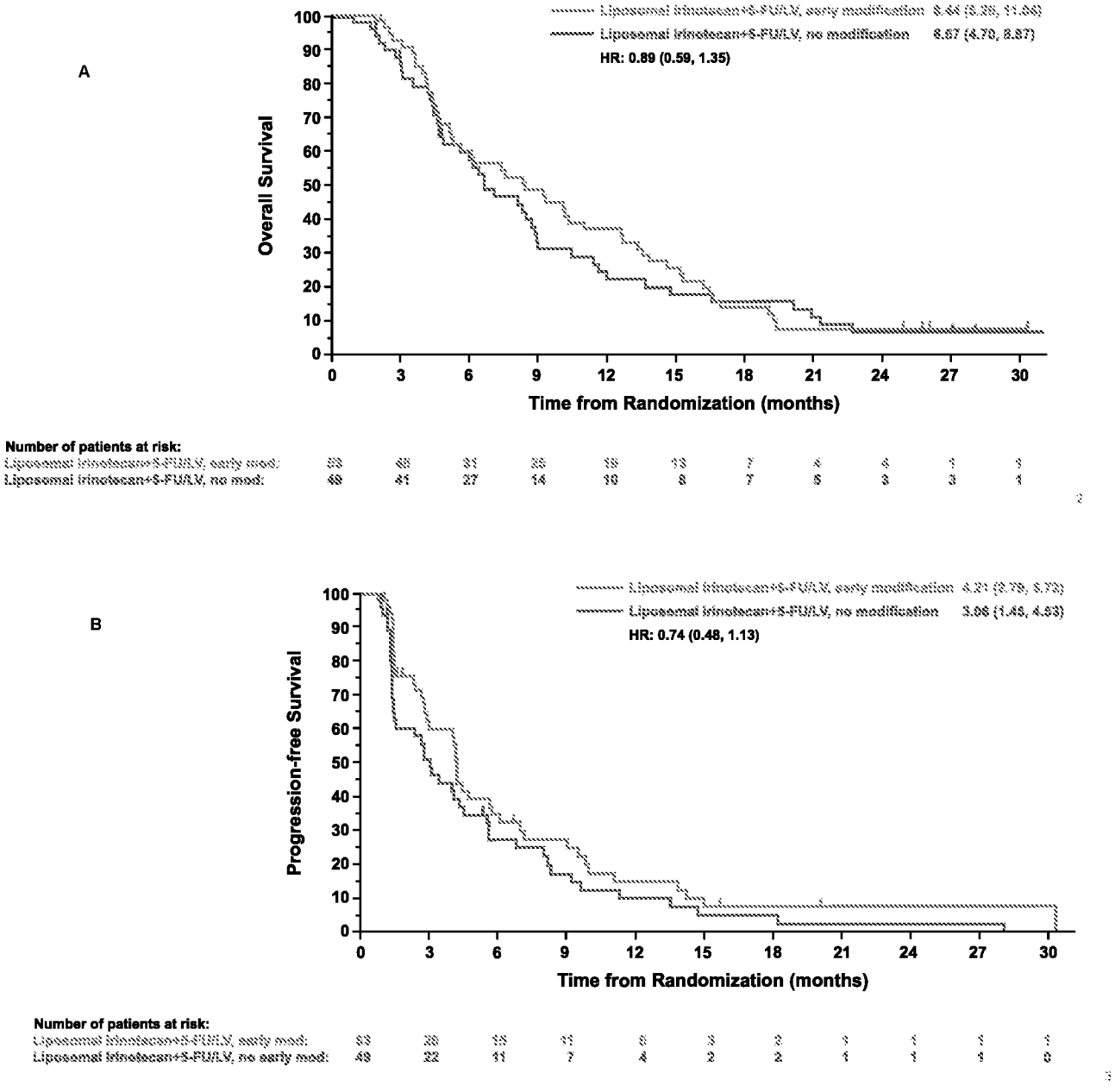

Fig. 2. Kaplan-Meier curves for (A) overall survival in the liposomal irinotecan+5-FU/LV arm for patients who had any dose modification (dose delay, reduction in dosage, or both delay and dose reduction) versus those who did not have a dose modification and (B) progression-free survival in the liposomal irinotecan+5-FU/LV arm for patients who had any dose modification versus those who did not have a dose modification.

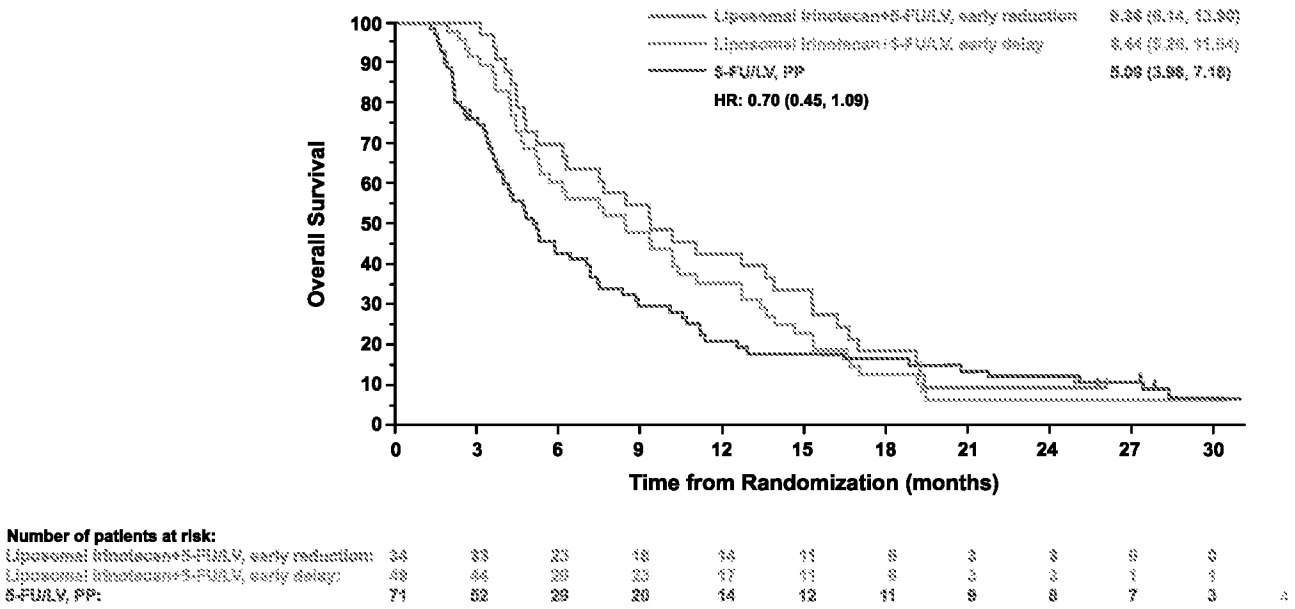

Fig. 3. Kaplan-Meier curves for overall survival in the liposomal irinotecan+5-FU/LV arm in patients who had a dose reduction or dose delay versus overall survival in the 5-FU/LV arm.

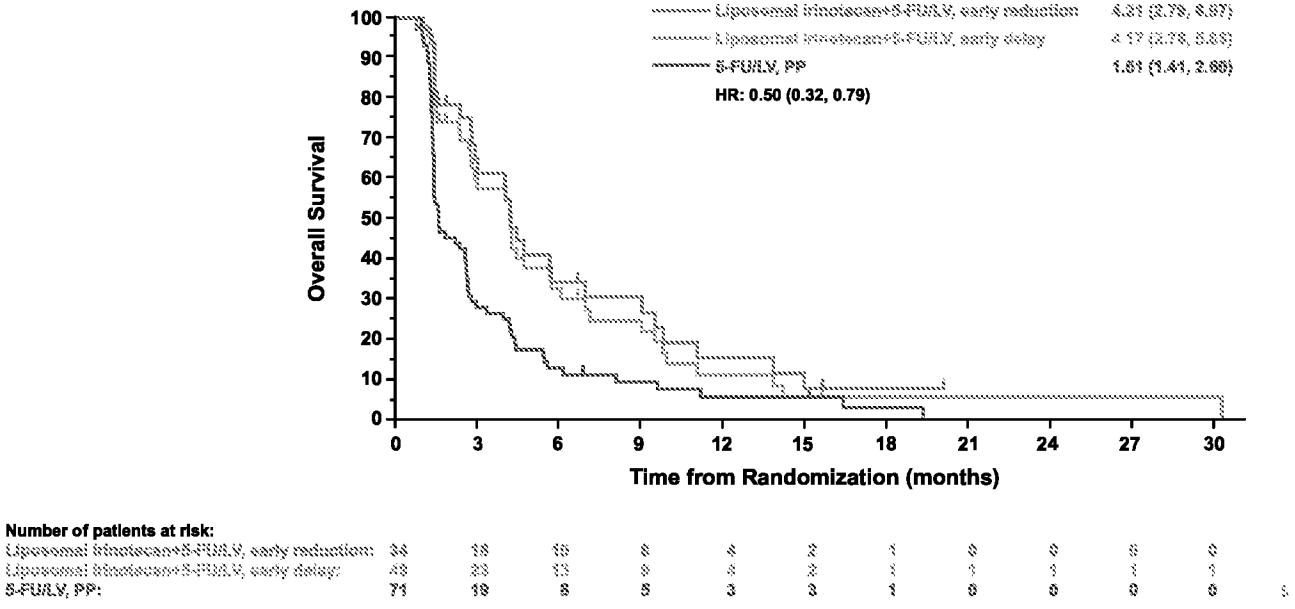

Fig. 4. Kaplan-Meier curves for progression-free survival in the liposomal irinotecan+5-FU/LV arm in patients who had a dose reduction or dose delay versus progression-free survival in the 5-FU/LV arm.

patient's decision. The other patients discontinued due to progressive disease (3 patients) or were still on treatment at the time of data cutoff (2 patients). No efficacy comparisons were possible.

Discussion

The findings of the NAPOLI-1 clinical trial demonstrated that liposomal irinotecan+5-FU/LV is an effective therapy for patients with mPDAC previously treated with gemcitabine-based therapy. Treatment with liposomal irinotecan+5-FU/LV significantly improved OS and PFS compared with 5-FU/LV in the NAPOLI-1 study, and demonstrated a manageable safety and tolerability profile [12]. The current post hoc analysis of data from the NAPOLI-1 study evaluated the impact of early dose modifications of liposomal irinotecan+5-FU/LV therapy on OS and PFS of patients who received assigned treatment in the first 6 weeks of the study. The results of the current analysis demonstrated that OS and PFS outcomes were similar between liposomal irinotecan+5-FU/LV patients with early dose modifications (delay and/or reduction) when compared to those without. Dose reduction was associated with numerically better survival outcome than dose delay. Overall, the survival analysis of patients with any dose modification closely resembled the outcome of patients with a dose delay. This finding is likely because the most common treatment modification utilized to manage toxicity-related adverse events from chemotherapy was liposomal irinotecan+5-FU/LV dose delay (either alone or in conjunction with a dose reduction).

For patients treated with liposomal irinotecan+5-FU/LV, the

incidence of toxicity-related TEAEs (such as neutropenia, diarrhea, nausea, and vomiting) was generally highest in the first 6 weeks of treatment, with fewer incident events as time progressed [18]. Dose modifications, including dose reductions or dose delays, during the first 6 weeks of treatment were used to manage TEAEs and prevent treatment discontinuation, thereby allowing patients to remain on treatment longer and achieve clinical benefit.

To minimize the impact of rapid disease progression, treatment discontinuation, or death on survival outcomes in the cohort of patients who did not have a dose modification in the first 6 weeks, this analysis only included patients who received at least the first 2 scheduled doses of liposomal irinotecan+5-FU/LV without any qualifying dose delay or reduction. If patients with early disease progression, death, or treatment discontinuation were to be included in the cohort of patients without dose modification (ie, these patients may have received only 1 dose prior to progression/death – and would therefore be characterized as "without dose modification"), the clinical outcomes analyses would become skewed, creating the appearance of an improvement in survival with dose modification. The exclusion of these patients may also explain the apparent "increase" in survival outcomes when compared to the overall results of NAPOLI-1 (OS rates: 6.1 months (Total Population) vs. 8.4 months (Without Dose Modification Population); PFS rates: 3.1 months (Total Population) vs. 4.1 months (Without Dose Modification Population)).

Survival outcomes of the patients in this post hoc analysis are similar to the outcomes reported from a prespecified, expanded analysis of outcomes in the NAPOLI-1 per-protocol (PP) population comprising patients who received ≥80% of planned treatment during the first 6 weeks, with no major protocol violations [19] (OS rates: 8.9 months (PP Population) vs. 8.4 months (Without Dose Modification Population); PFS rates: 4.3 months (PP Population) vs. 4.1 months (Without Dose Modification Population)). However, the objective of this analysis was to explore the impact of liposomal irinotecan+5-FU/LV dose modifications on survival outcomes, whereas the PP analysis provided a sensitivity analysis of the survival advantage with the liposomal irinotecan+5-FU/LV versus 5-FU/LV alone originally reported for the intent-to-treat population.

Limitations of the current analysis include its post hoc nature and the small number of patients in each of the liposomal irinotecan dose-modification groups, and descriptive nature of the statistical analysis. Only liposomal irinotecan tolerability-guided dose modifications occurring during the first 6 weeks of the study were included in the analysis.

Conclusion

This post hoc analysis suggests that implementing an early dose reduction or delay strategy to manage toxicities associated with liposomal irinotecan+5-FU/LV therapy may not adversely affect clinical outcomes. There was no apparent impact on survival outcomes within the liposomal irinotecan+5-FU/LV arm between patients who required tolerability-guided dose modifications and those who did not. Consistent with the reported results in NAPOLI-1, OS and PFS were greater in patients who received liposomal irinotecan+5-FU/LV and required an early dose modification (dose reduction or delay) compared with those who received 5-FU/LV. Patients who receive liposomal irinotecan+5-FU/LV therapy and their caregivers should be aware of strategies for managing toxicity-related TEAEs, including dose modifications.

Declaration of competing interest

Li-Tzong Chen: Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, Merrimack, MSD, Novartis, Ono Pharmaceutical, PharmaEngine, Syncope, Taiwan, TTY Biopharm (C/A); GlaxoSmithKline, Merck Serono, Novartis, Polaris (Inst); TTY Biopharm (Inst, RF); Anti-alpha-enolase (ENO-1) monoclonal antibody to HuniLife Technology, Taiwan (I/P). **Teresa Macarulla:** Nothing to disclose. **Jean-Frédéric Blanc:** Baxalta/Shire, Bayer Schering Pharma, Gilead Sciences (H); Baxalta/Shire, Bristol-Myers Squibb, Novartis, Onxeo (C/A); Bayer Schering Pharma (ET. **Beloo Mirakhur:** Ipsen (E); Bristol-Myers Squibb (OI). **Floris A. de Jong:** Servier (E); Shire (OI). **Bruce Belanger:** Ipsen, Merrimack (E). **Tanios Bekaii-Saab:** Amgen, Bayer, Boehringer Ingelheim, Celgene, Genentech/Roche, Glenmark, Lilly, Merrimack, NCCN, Pfizer, Research to Practice, Sirtex Medical, Taiho Pharmaceutical (C/A); Exelixis, Merck, Polaris (Other Relationship). **Jens T. Siveke:** Baxalta, Celgene, Lilly, Shire (C/A); 4SC, Bristol-Myers Squibb, Celgene (RF); Celgene; Roche; Shire (T/Exp).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.10.029.

Data sharing

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

B.B., T.B.-S., J.-F.B., L.-T.C., F.A.deJ., T.M., B.M., and J.T.S. developed concept and design. T.B.-S., J.-F.B., L.-T.C., T.M., and J.T.S. provided study materials or patients. B.B., T.B.-S., J.-F., L.-T.C., F.A.deJ., T.M., B.M., J.T.S. collected and/or assembled data. B.B., T.B.-S., J.-F.B., L.-T.C., F.A.deJ., T.M., B.M., and J.T.S. analyzed and interpreted data. B.B., T.B.-S., J.-F.B., L.-T.C., F.A.deJ., T.M., B.M., and J.T.S. approved the final manuscript.

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Poster #303

Efficacy and Safety of Liposomal Irinotecan (nal-IRI) + 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Who Previously Received Gemcitabine-Based Therapy: Post Hoc Analysis of the NAPOLI-1 Trial

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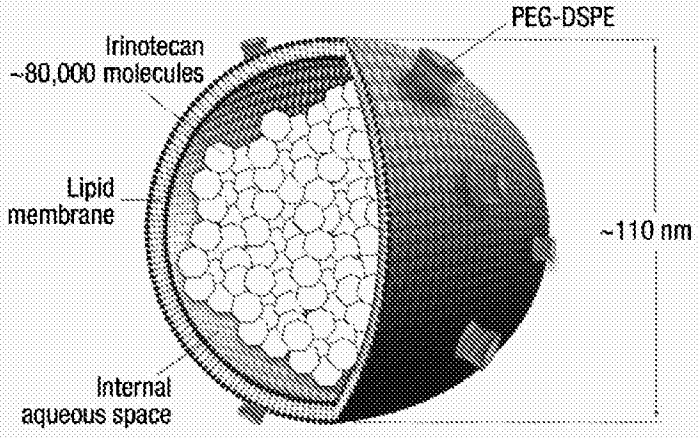
BACKGROUND

- 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 worldwide[1,2]
- Treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) represents a significant unmet need; studies have shown approximately 20% to 50% survival at 1 year 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]

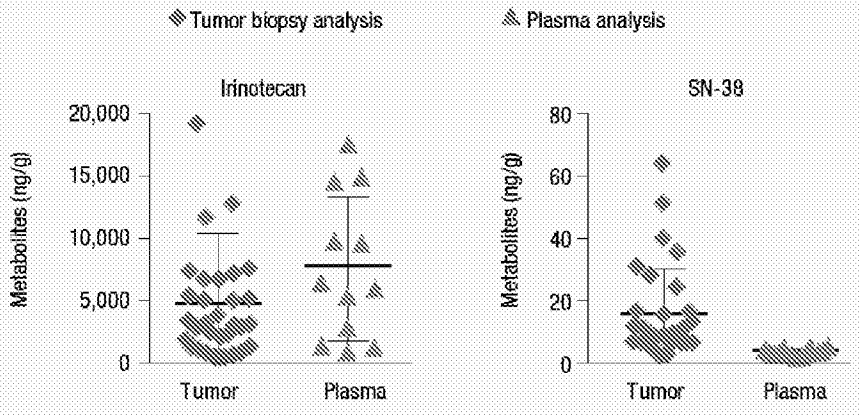
Figure 1. nal-IRI Design[6]



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

- In a study evaluating plasma pharmacokinetics of nal-IRI (120 mg/m^2) and conventional irinotecan hydrochloride trihydrate salt (300 mg/m^2) in gastric cancer patients, nal-IRI resulted in longer half-lives and higher total, average, and maximal concentrations of irinotecan, while maintaining lower maximal concentrations of SN-38 (the active metabolite of irinotecan)[7,8]
- A mouse xenograft model of human colon carcinoma demonstrated that the liposomal encapsulation facilitates intratumoral drug deposition through the enhanced permeability and retention effect[9]
- Preliminary data from a pilot study in different cancer types showed higher levels of SN-38 in tumor biopsies compared with plasma at 72 hours, suggesting local metabolic conversion (and thus activation) of irinotecan to SN-38 (**Figure 2**)[6]

Figure 2. 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 800 pg/mL for SN-38.

- nal-IRI is approved 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, based on results from the primary analysis of the large (N = 417), phase 3 NAPOLI-1 trial (NCT01494506)[10]
  - nal-IRI+5-FU/LV significantly improved median overall survival (OS; the primary endpoint) vs 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio [HR] = 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$)
  - nal-IRI+5-FU/LV significantly improved median progression-free survival (PFS) vs 5-FU/LV (3.1 vs 1.5 months; unstratified HR = 0.56 [95% CI, 0.41-0.75]; $P = 0.0001$)
  - nal-IRI+5-FU/LV significantly improved objective response rate (ORR) vs 5-FU/LV (16% vs 1%; $P < 0.0001$)
  - The most common grade ≥3 treatment-emergent adverse events (TEAEs) 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, regardless of treatment; quality of life was maintained in patients treated with nal-IRI+5-FU/LV, even with the addition of another chemotherapy[11]
- FOLFIRINOX (a combination of folinic acid, 5-FU, irinotecan, and oxaliplatin) and gemcitabine+nab-paclitaxel are the main frontline treatments currently recommended for patients with mPDAC and good performance status, based on the ACCORD 11/PRODIGE 4[3] and MPACT[4] trials, respectively, and gemcitabine alone remains an option for patients with worse performance status[12-14]; however, no second-line treatment has yet become standard
  - The CONKO-003 trial,[15] which evaluated the OFF (oxaliplatin, folinic acid, and 5-FU) regimen, included patients previously treated with gemcitabine monotherapy only, and 12% of patients in the experimental arm had locally advanced disease
  - The PANCREOX trial,[16] which evaluated a modified FOLFOX6 (folinic acid, 5-FU, and oxaliplatin) regimen, mainly included patients previously treated with gemcitabine monotherapy vs gemcitabine combination therapy (74% vs 26% in modified FOLFOX6 arm; 78% vs 22% in control arm), and 7% of patients in the experimental arm had locally advanced disease
  - The NAPOLI-1 trial,[10] which evaluated nal-IRI in combination with 5-FU/LV, mostly included patients previously treated with gemcitabine combination therapy vs gemcitabine monotherapy (55% vs 45% in nal-IRI+5-FU/LV arm; 54% vs 46% in combination control arm), and all patients had metastatic disease
- Patients were enrolled in the NAPOLI-1 trial between January 2012 and September 2013,[10] when gemcitabine+nab-paclitaxel was not yet an approved regimen for frontline treatment of mPDAC; therefore, patients in NAPOLI-1 received various gemcitabine-based regimens

OBJECTIVES

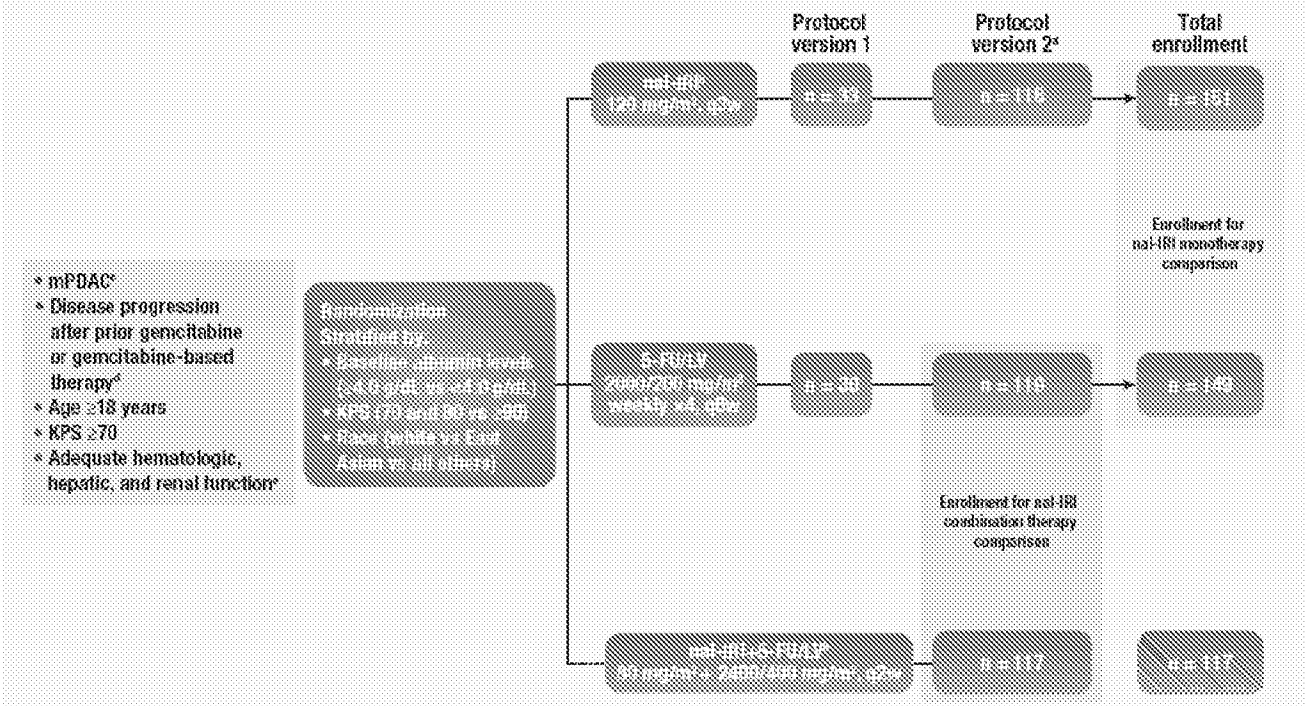
- This was a post hoc analysis of the NAPOLI-1 trial to evaluate the efficacy and safety of nal-IRI+5-FU/LV in the following subgroups defined by prior gemcitabine regimen:
  - Gemcitabine monotherapy
  - Gemcitabine combination therapy

METHODS

Study Design

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

Figure 3. NAPOLI-1 Study Design[19]



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.

Subgroup Analysis

- This post hoc analysis (data cutoff, November 16, 2015) focuses on the 236 patients assigned (under protocol version 2) to nal-IRI+5-FU/LV every 2 weeks (n = 117) or 5-FU/LV weekly for weeks 1-4 of 6-week cycles (n = 119)
- 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
- HRs and 95% CIs are reported based on post hoc analyses of subgroups and are for descriptive purposes only; these analyses were not powered to detect statistically significant differences

RESULTS

Patient Characteristics

- Of the 117 patients in the nal-IRI+5-FU/LV arm:
  - 53 (45%) previously received gemcitabine monotherapy
  - 64 (55%) previously received a gemcitabine combination, including gemcitabine with erlotinib (n = 9) or nab-paclitaxel (n = 20)
- Of the 119 patients in the 5-FU/LV arm:
  - 55 (46%) previously received gemcitabine monotherapy
  - 64 (54%) previously received a gemcitabine combination, including gemcitabine with erlotinib (n = 17) or nab-paclitaxel (n = 11)
- Patient demographics and baseline characteristics were well balanced between the nal-IRI combination and control arms for each subgroup (**Table 1**)

Table 1. Patient Demographics and Baseline Clinical Characteristics

	Gemcitabine Monotherapy		Gemcitabine Combination[a]	
	nal-IRI+5-FU/LV (n = 53)	5-FU/LV (n = 55)	nal-IRI+5-FU/LV (n = 64)	5-FU/LV (n = 64)
Age, years, median (IQR)	65 (59-72)	62 (55-67)	63 (55-68)	61 (54-69)
Race, %				
White	62	71	61	58
East Asian	25	24	33	36
Black	4	4	3	2
Other	9	2	3	5
KPS, %				
≥90	55	56	58	56
<90	45	44	42	44
Albumin, %				
≥40 g/L	42	45	48	45
<40 g/L	58	55	52	55
CA19-9, n/N (%)[b]				
≥40 U/mL	43/52 (83)	42/53 (79)	49/62 (79)	49/61 (80)
<40 U/mL	9/52 (17)	11/53 (21)	13/62 (21)	12/61 (20)
Pancreatic head tumor, %	68	62	63	55
Prior therapy, %				
5-FU	26	27	56	58
Platinum	17	20	45	47
Irinotecan	8	15	13	14
Prior lines of metastatic therapy, %				
0[c]	17	18	9	8
1	64	60	44	53
>1	19	22	47	39

5-FU, 5-fluorouracil; CA19-9, carbohydrate antigen 19-9; IQR, interquartile range; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Gemcitabine combinations included nab-paclitaxel, erlotinib (with and without 5-FU), oxaliplatin (with and without 5-FU), cisplatin (with and without 5-FU), 5-FU, cisplatin+irinotecan, dasatinib, and various investigational therapies.
[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

- In the gemcitabine monotherapy subgroup, mean duration of treatment (time from first to last study drug administration) was 15 weeks (median, 8 weeks; range, 0.4-65 weeks) in the nal-IRI+5-FU/LV arm and 10 weeks (median, 4 weeks; range, 1-67 weeks) in the 5-FU/LV arm
- In the gemcitabine combination subgroup, mean duration of treatment was 19 weeks (median, 6 weeks; range, 0.4-126 weeks) in the nal-IRI+5-FU/LV arm and 8 weeks (median, 3 weeks; range, 0.3-59 weeks) in the 5-FU/LV arm
- In the gemcitabine monotherapy subgroup, the mean (median) relative dose intensity of nal-IRI was 81% (84%), and the mean (median) relative dose intensities of 5-FU were 82% (92%) and 96% (100%) in the nal-IRI+5-FU/LV and 5-FU/LV arms, respectively; in the gemcitabine combination subgroup, the mean (median) relative dose intensity of nal-IRI was 84% (87%), and the mean (median) relative dose intensities of 5-FU were 84% (88%) and 95% (100%) in the nal-IRI+5-FU/LV and 5-FU/LV arms, respectively

Efficacy

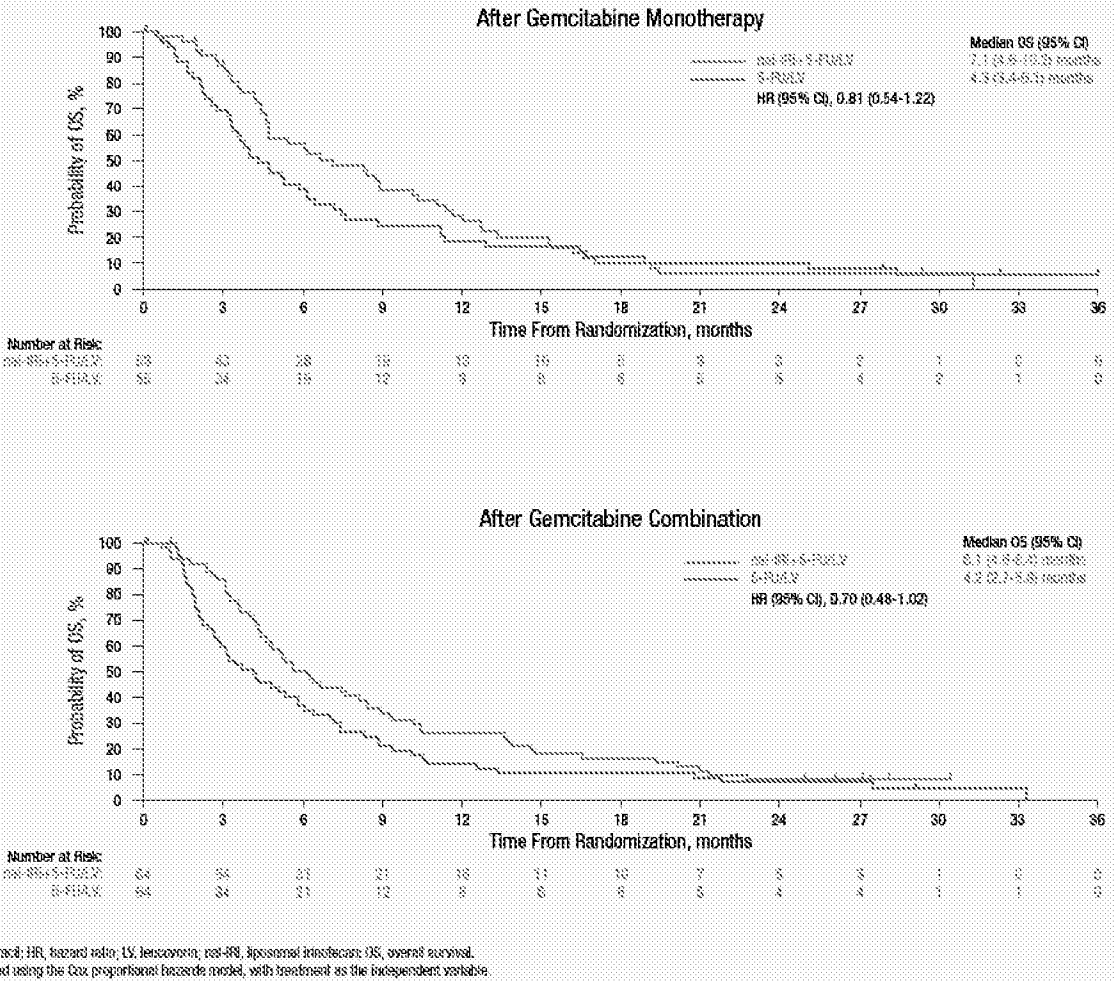
- Median OS (Kaplan-Meier estimate) was numerically longer with nal-IRI+5-FU/LV vs 5-FU/LV in patients pretreated with gemcitabine monotherapy (7.1 vs 4.3 months; HR = 0.81 [95% CI, 0.54-1.22]) or a gemcitabine combination (6.1 vs 4.2 months; HR = 0.70 [95% CI, 0.48-1.02]) (**Table 2** and **Figure 4**)
  - Median OS results were similar to those observed in the overall study population (nal-IRI+5-FU/LV vs 5-FU/LV: 6.1 vs 4.2 months; unstratified HR = 0.67 [95% CI, 0.49-0.92]; $P = 0.012$)[10]
- Median PFS was numerically longer with nal-IRI+5-FU/LV vs 5-FU/LV in patients pretreated with gemcitabine monotherapy (4.1 vs 2.2 months; HR = 0.63 [95% CI, 0.41-0.95]) or a gemcitabine combination (3.1 vs 1.4 months; HR = 0.54 [95% CI, 0.36-0.81]) (**Table 2** and **Figure 5**)
- In both subgroups, the observed ORRs (from partial responses) and disease control rates (DCRs) were higher with nal-IRI+5-FU/LV vs 5-FU/LV (**Table 2**)

Table 2. Summary of Efficacy by Prior Gemcitabine-Based Regimen

Endpoint	Gemcitabine Monotherapy			Gemcitabine Combination		
	nal-IRI+5-FU/LV (n = 53)	5-FU/LV (n = 55)	HR[a] (95% CI)	nal-IRI+5-FU/LV (n = 64)	5-FU/LV (n = 64)	HR[a] (95% CI)
OS, months, median (95% CI)[b]	7.1 (4.6-10.2)	4.3 (3.4-6.1)	0.81 (0.54-1.22)	6.1 (4.6-8.4)	4.2 (2.7-5.6)	0.70 (0.48-1.02)
12-month OS, % (95% CI)[b]	26 (15-39)	16 (9-30)	----	26 (16-37)	14 (7-24)	----
PFS, months, median (95% CI)[b]	4.1 (2.7-5.6)	2.2 (1.4-2.7)	0.63 (0.41-0.95)	3.1 (1.5-4.2)	1.4 (1.3-1.6)	0.54 (0.36-0.81)
TTF, months, median (95% CI)[b]	2.7 (1.6-3.1)	1.4 (1.3-2.4)	0.72 (0.49-1.05)	1.9 (1.4-2.9)	1.3 (1.1-1.4)	0.51 (0.36-0.74)
ORR, % (95% CI)[c]	15 (5-25)	2 (0-5)	----	19 (9-28)	0 (0-0)	----
Best overall response, n (%)						
PR[c]	8 (15)	1 (2)	----	12 (19)	0	----
SD[d]	21 (40)	14 (25)	----	17 (27)	12 (19)	----
Non-CR/non-PD[d]	2 (4)	0	----	1 (2)	2 (3)	----
PD	15 (28)	24 (44)	----	19 (30)	32 (50)	----
Not evaluable	7 (13)	16 (29)	----	15 (23)	18 (28)	----
DCR (CR + PR + SD + non CR/non-PD), % (95% CI)[c,d]	58 (45-72)	27 (16-39)	----	47 (35-59)	22 (12-32)	----

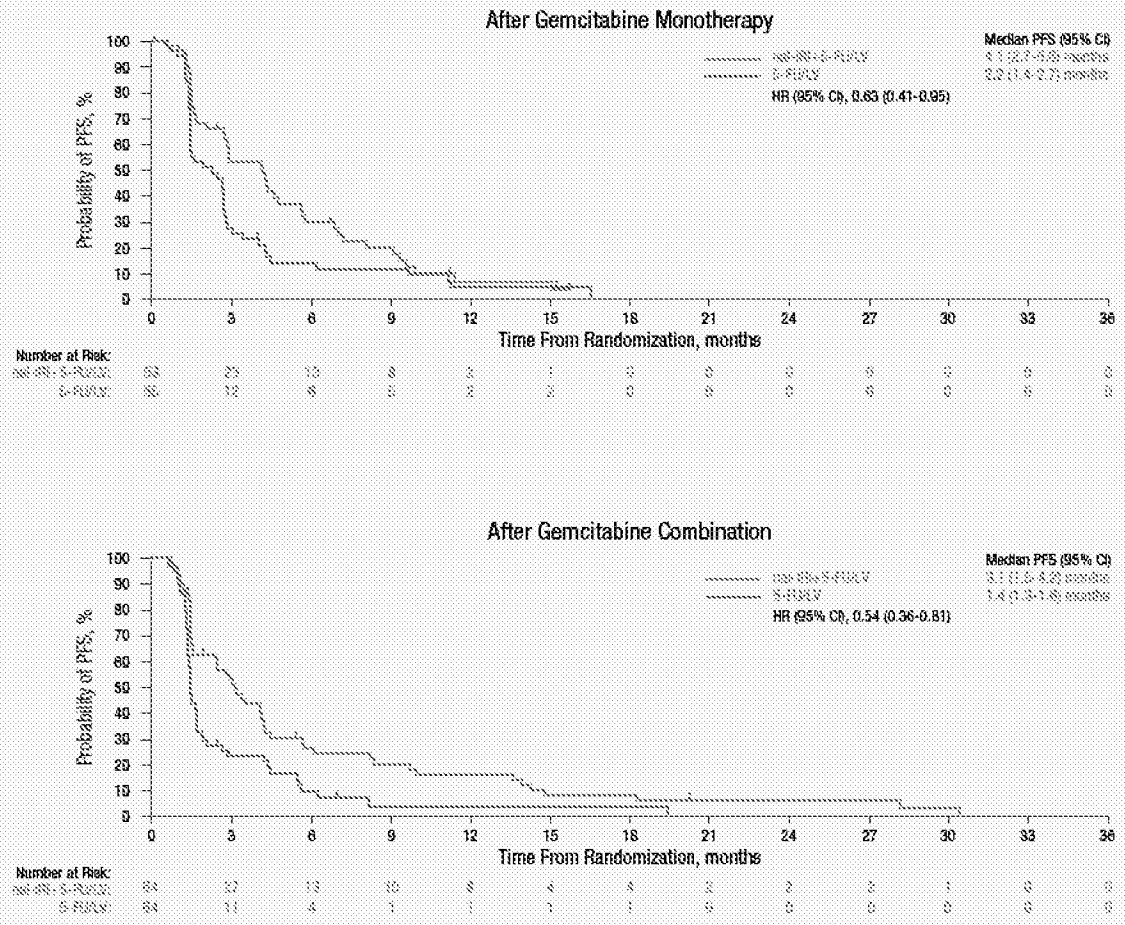
5-FU, 5-fluorouracil; CI, confidence interval; CR, complete response; DCR, disease control rate; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; TTF, time to treatment failure.
[a]Derived using the Cox proportional hazards model, with treatment as the independent variable.
[b]Kaplan-Meier estimate.
[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 8 weeks after starting treatment.

Figure 4. Overall Survival



5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; OS, overall survival.
HRs were derived using the Cox proportional hazards model, with treatment as the independent variable.

Figure 6. Progression-Free Survival



5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; PFS, progression-free survival.
HRs were derived using the Cox proportional hazards model, with treatment as the independent variable.

Safety/Tolerability

- The most common grade ≥3 TEAEs in the nal-IRI+5-FU/LV arm (reported in >10% of patients in either subgroup and shown in **Table 3**) were neutropenia (28%, after gemcitabine monotherapy; 29%, after gemcitabine combination therapy), fatigue (13%; 15%), diarrhea (13%; 13%), vomiting (11%; 13%), anemia (4%; 15%), and asthenia (11%; 5%)

Table 2. Treatment-Emergent Adverse Events (Based on Grade ≥3 Events Reported for ≥5% of Patients in Any Subgroup of the Safety Population)

	Gemcitabine Monotherapy				Gemcitabine Combination			
	nal-IRI+5-FU/LV (n = 54)		5-FU/LV (n = 50)		nal-IRI+5-FU/LV (n = 62)		5-FU/LV (n = 55)	
TEAE, %	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	98	74	96	54	100	84	100	60
Neutropenia[a]	39	26	12	4	40	29	7	4
Fatigue	37	13	26	4	44	15	25	4
Diarrhea	69	13	30	4	52	13	22	7
Vomiting	54	11	26	4	55	13	25	4
Anemia	46	4	22	4	32	15	22	5
Asthenia	22	11	20	8	21	5	15	4
Decreased WBC count	7	6	2	0	21	10	2	0
Nausea	56	9	30	2	53	6	38	2
Abdominal pain	26	7	36	2	23	6	29	11
Decreased appetite	44	7	34	4	45	3	24	0
Sepsis	9	6	4	2	2	2	0	0

5-FU, 5-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 (with gemcitabine monotherapy and gemcitabine combination subgroups combined).
[a]Neutropenia includes agranulocytosis (2%, 0%, 0%, and 0%, any grade, in the subgroups shown, left to right), febrile neutropenia (2%, 0%, 3%, 2%), granulocytopenia (2%, 0%, 0%, 0%), neutropenia (22%, 6%, 24%, 2%), neutropenic sepsis (2%, 0%, 0%, 0%), decreased neutrophil count (11%, 4%, 18%, 4%), and pancytopenia (2%, 0%, 2%, 0%)

- In the gemcitabine monotherapy subgroup, TEAEs led to dose modification (dose delay, reduction, and/or discontinuation) in 69% of patients receiving nal-IRI+5-FU/LV (59%, 31%, and 13%, respectively) and 38% receiving 5-FU/LV (28%, 8%, and 12%, respectively)
  - Corresponding rates in the gemcitabine combination subgroup were 76% for nal-IRI+5-FU/LV (66%, 37%, and 13%, respectively) and 35% for 5-FU/LV (35%, 2%, and 4%, respectively)
- The most common TEAE requiring dose modification of nal-IRI+5-FU/LV was neutropenia in both subgroups (33% and 35% in the gemcitabine monotherapy and gemcitabine combination subgroups, respectively), followed by:
  - Diarrhea and vomiting in the gemcitabine monotherapy subgroup (17% and 11%, respectively)
  - Decreased white blood cell count, anemia, and diarrhea in the gemcitabine combination subgroup (16%, 10%, and 10%, respectively)

CONCLUSIONS

- **In this post hoc analysis of the NAPOLI-1 trial, nal-IRI+5-FU/LV improved OS, PFS, TTF, and both the ORR and DCR relative to 5-FU/LV, regardless of prior gemcitabine-based therapy**
  - Numerical differences favoring nal-IRI+5-FU/LV vs 5-FU/LV were observed for all efficacy outcomes; therefore, this sensitivity analysis supports the benefit of nal-IRI+5-FU/LV in patients who previously received gemcitabine monotherapy or gemcitabine combination therapy
  - Of note, patients who received gemcitabine combination therapy vs gemcitabine monotherapy had a greater number of prior lines of metastatic therapy, which could have influenced outcomes
  - Gemcitabine+nab-paclitaxel is one of the new standards of care for mPDAC and the current data could help shed light on the applicability of NAPOLI-1 to patients who had disease progression following gemcitabine+nab-paclitaxel therapy
  - These analyses may be limited by the small sample size of post hoc analysis subgroups
- **The safety profiles observed in the individual subgroups were similar to those in the parent patient populations[8] and did not appear to be influenced by prior treatment**
- **These results show consistent benefit of nal-IRI+5-FU/LV treatment across subgroups of patients who had previously received gemcitabine-based therapy**

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POSTER PRESENTED AT THE GASTROINTESTINAL CANCERS SYMPOSIUM OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO GI); JANUARY 19–21, 2017; SAN FRANCISCO, CALIFORNIA

Efficacy and Safety of Liposomal Irinotecan (nal-IRI) + 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer Administered With Previously Received Oxaliplatin Based Therapy: Post Hoc Analysis of the NAPOLI-1 Trial

POSTER PRESENTED AT THE GASTROINTESTINAL CANCERS SYMPOSIUM OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO GI), JANUARY 19–21, 2017, SAN FRANCISCO, CALIFORNIA

Final Results of NAPOLI-1: A Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy

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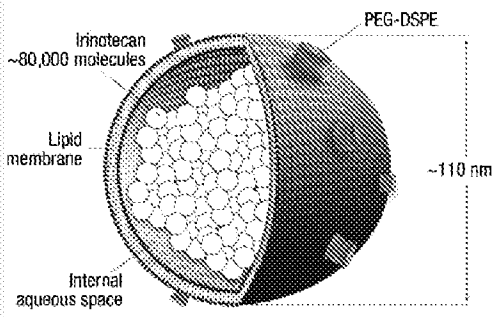
BACKGROUND

- Pancreatic cancer is the fifth leading cause of cancer-related death in Europe, and the seventh leading cause of cancer-related death worldwide[1]
- Treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC) represents a significant unmet need, with approximately 80% of patients with mPDAC succumbing to disease within 12 months[2]
- nal-IRI (liposomal irinotecan; MM-398) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use (**Figure 1**)[3]
  - Pharmacokinetic analyses in patients with gastric cancer showed extended circulation of irinotecan within the liposome[4,5]
  - 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[6]

Figure 1. nal-IRI design.[7]



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

- 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)[3,7]
  - 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]; $P = 0.012$)[7]
  - 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]; $P = 0.94$)[7]

OBJECTIVES

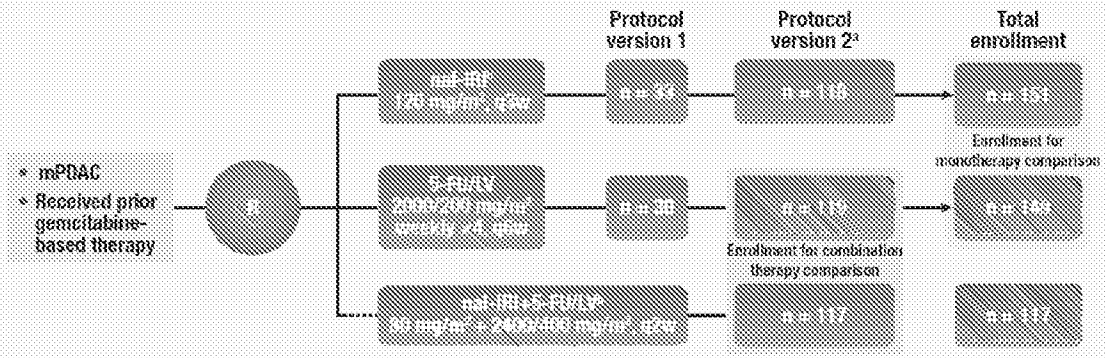
- The objectives of the current descriptive analysis of the NAPOLI-1 trial are to
  - Evaluate the robustness of the previously observed OS treatment effect for nal-IRI+5-FU/LV versus 5-FU/LV control using data from longer follow-up
  - Assess the long-term safety and tolerability of nal-IRI in combination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

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (**Figure 2**)
  - Patients were initially randomized to nal-IRI monotherapy (120 mg/m^2 irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m^2 irinotecan free base every 3 weeks) or 5-FU/LV (2000 mg/m^2 5-FU and 200 mg/m^2 LV, 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 (80 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 70 mg/m^2 irinotecan free base every 2 weeks; 2400 mg/m^2 5-FU and 400 mg/m^2 LV every 2 weeks) once safety data of the combination became available from a concurrent study in metastatic colorectal cancer. Sixty-three 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 2. 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.
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/m^2 approximate to 100 and 70 mg/m^2 irinotecan free base.

Statistical Analysis

- 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
- Results presented in this poster are based on an updated analysis of the long-term survival of patients in the NAPOLI-1 trial after 382 OS events had occurred in the intention-to-treat (ITT) population (data cutoff, November 16, 2015)
- Descriptive statistical summaries of the scores for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) were performed
  - Patients were categorized as "improved," if the patients had scores ≥10% relative to baseline and remained above the baseline value for ≥6 weeks; "stable," if the patients did not meet criteria for improved or worsened; or "worsened," if the patients did not meet improvement criteria and died or had scores that decreased by 10%
  - Pairwise treatment group comparisons were performed using Cochran-Mantel-Haenszel testing adjusted for multiplicity with a Benjamini-Hochberg correction to control false discovery rate at the 0.05 level for the 15 comparisons

Key Inclusion Criteria

- Adults aged ≥18 years
- Histologically or cytologically confirmed mPDAC
- Documented measurable or nonmeasurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1])
- Disease progression after previous gemcitabine or gemcitabine-based 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 >1.5 × 10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function

Key Exclusion Criteria

- Active central nervous system metastasis
- Clinically significant gastrointestinal disorders
- Severe arterial thromboembolic event <6 months before inclusion

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	64
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 before 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 382 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 3**)
  - With OS events in nearly all patients, the Kaplan-Meier OS curves converged at approximately 20 months, with 23 (9.8%) patients surviving beyond 20 months
- Median PFS was 3.1 months for nal-IRI+5-FU/LV versus 1.5 months for the 5-FU/LV combination control (**Table 2** and **Figure 4**)
- Objective response rate (ORR) was higher for nal-IRI+5-FU/LV (difference of 16.3% [95% CI, 9.2%-23.3%], **Table 2**) compared with the 5-FU/LV combination control
- The disease control rate was higher for nal-IRI+5-FU/LV (52%) compared with the 5-FU/LV (24%) combination control

Table 2. Summary of Updated Efficacy

End Point	nal-IRI+5-FU/LV (n = 117)	5-FU/LV Combination Control (n = 119)	Treatment Effect[a]	nal-IRI Monotherapy (n = 151)	5-FU/LV Monotherapy Control (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* = 0.039	4.9 (4.2-5.6)	4.2 (3.6-4.9)	HR, 1.07 *P* = 0.568
OS rate at 6 months, % (95% CI)	53 (44-62)	38 (29-47)	--	39 (31-46)	35 (27-43)	--
OS rate at 12 months, % (95% CI)	26 (18-35)	16 (10-24)	--	11 (6-16)	15 (9-21)	--
PFS, months, median (95% CI)	3.1 (2.7-4.2)	1.5 (1.4-1.8)	HR, 0.57 *P* = 0.0001	2.7 (2.1-2.9)	1.6 (1.4-1.8)	HR, 0.81 *P* = 0.105
ORR, % (95% CI)[b]	17 (10-24)	1 (0-2)	*P* < 0.0001	6 (2-10)	1 (0-2)	*P* = 0.020
Disease control rate (CR + PR + SD), % (95% CI)	52 (43-61)	24 (16-32)	--	44 (36-52)	26 (19-33)	--
Best overall response, n (%)[b]						
Partial response	20 (17)	1 (1)	--	9 (6)	1 (1)	--
Stable disease[c]	38 (32)	26 (22)	--	54 (36)	35 (23)	--
Progressive disease	34 (29)	56 (47)	--	51 (34)	71 (48)	--
Other[d]	3 (3)	2 (2)	--	3 (2)	2 (1)	--
Not evaluable	22 (19)	34 (29)	--	34 (23)	40 (27)	--

5-FU, 5-fluorouracil; CI, confidence interval; CR, complete response; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

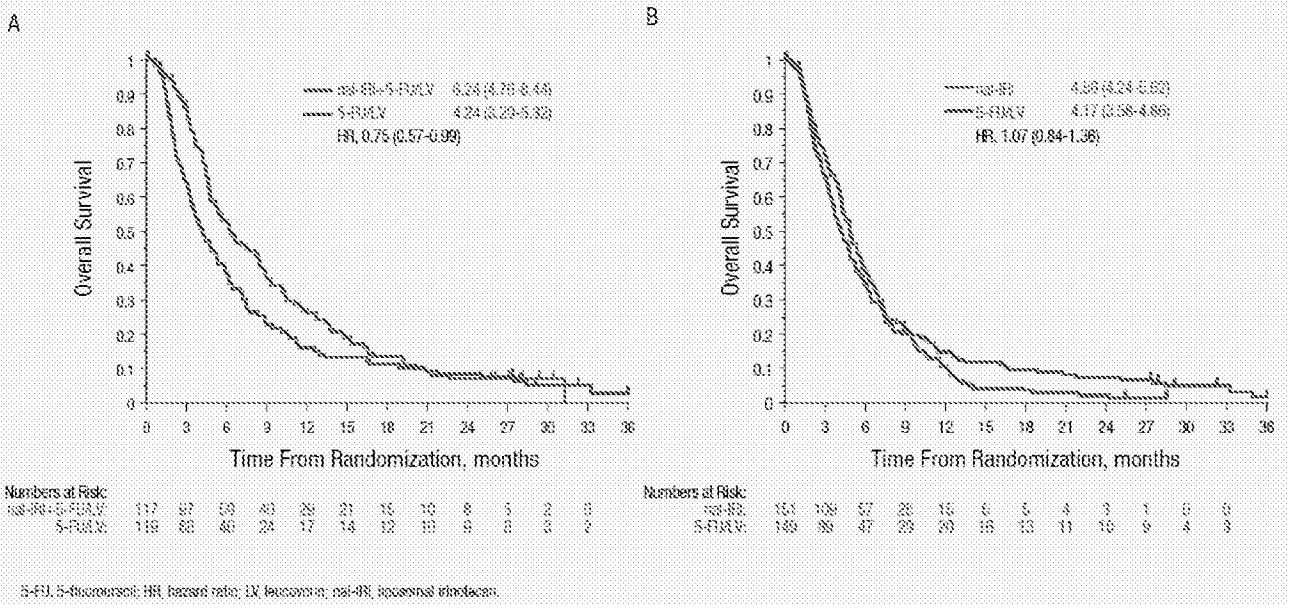
[a]HRs and the associated *P* values were derived using the Cox proportional hazards model, with treatment as the independent variable.

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

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

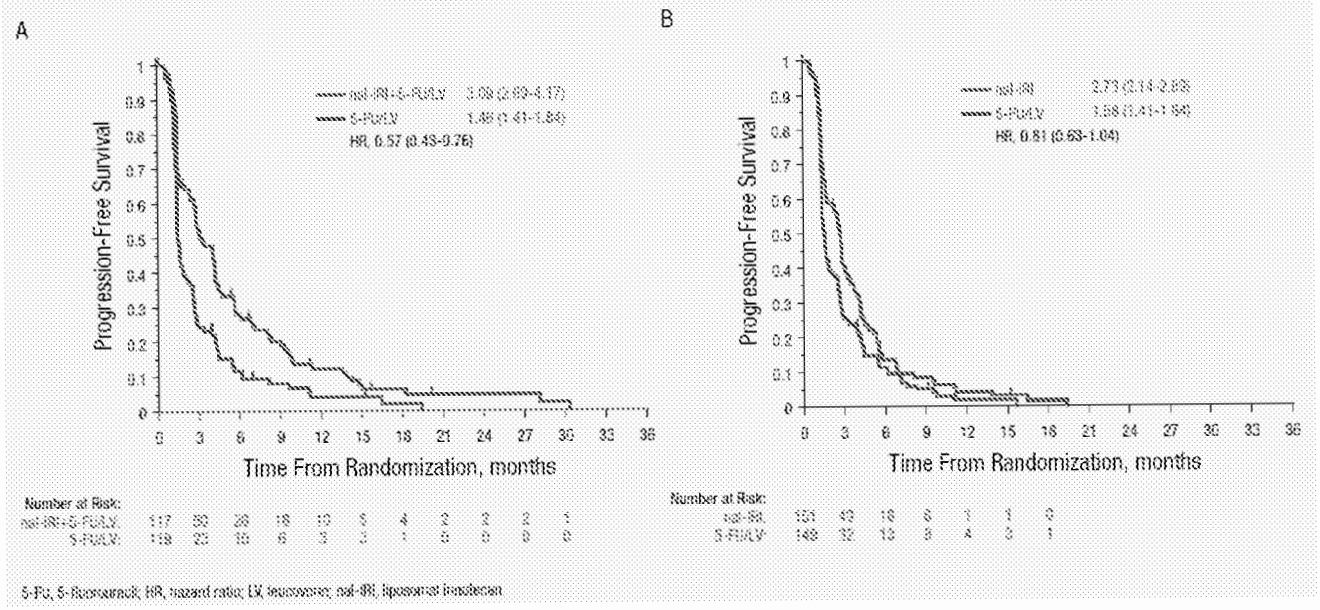
[d]Patients without measurable (target) disease at baseline may have a best overall response of non-complete response/non-partial response.

Figure 3. Comparison of overall survival in patients receiving nal-IRI+5-FU/LV versus 5-FU/LV combination control arm (A) and for nal-IRI monotherapy versus 5-FU/LV monotherapy control arm (B). Hazard ratios were derived using the Cox proportional hazards model, with treatment as the independent variable.



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

Figure 4. Comparison of progression-free survival in patients receiving nal-IRI+5-FU/LV versus 5-FU/LV combination control arm (A) and for nal-IRI monotherapy versus 5-FU/LV monotherapy control arm (B). Hazard ratios were derived using the Cox proportional hazards model, with treatment as the independent variable.



5-Fu, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan

Treatment Exposure

- The mean duration of treatment exposure was 18.6 weeks (median, 8.7 weeks; range, 2-127 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

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[3]
- The most frequently reported grade ≥3 TEAEs in the nal-IRI–containing arms were neutropenia, diarrhea, vomiting, and fatigue (**Table 3**)
- Grade ≥3 febrile neutropenia occurred in 2 (2%) patients receiving nal-IRI+5-FU/LV and 6 (4%) patients receiving nal-IRI monotherapy
  - No patients in the control arm experienced grade ≥3 febrile neutropenia

Table 3. Grade ≥3 TEAEs Reported for ≥5% of Patient in Any Treatment Arm (safety population)

Grade ≥3 TEAE, %	nal-IRI+5-FU/LV (n = 117)	nal-IRI Monotherapy (n = 147)	5-FU/LV (n = 134)
Any TEAE	80	76	56
Neutropenia[a]	28	15	1
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.
[a]Neutropenia includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

- 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 (**Table 4**)

Table 4. Treatment-Emergent Adverse Events Resulting in Dose Delay or Dose Reduction (in ≥5% of patients in any treatment arm) or Treatment Discontinuation (in ≥2 patients in any treatment arm)

	nal-IRI+5-FU/LV (n = 117)	nal-IRI monotherapy (n = 147)	5-FU/LV (n = 134)
Dose delay			
Leukopenia	8 (6.8)	1 (0.7)	1 (0.7)
Neutropenia	18 (15.4)	6 (4.1)	3 (2.2)
Diarrhea	11 (9.4)	9 (6.1)	4 (3.0)
Fatigue	8 (6.8)	3 (2.0)	1 (0.7)
Platelet count decreased	6 (5.1)	1 (0.7)	1 (0.7)
White blood cell count decreased	14 (12.0)	1 (0.7)	1 (0.7)
Dose reduction			
Neutropenia	10 (8.5)	3 (2.0)	0
Diarrhea	7 (6.0)	17 (11.6)	0
Vomiting	2 (1.7)	9 (6.1)	0
Neutrophil count decreased	8 (6.8)	7 (4.8)	0
Treatment discontinuation			
Neutropenia	2 (1.7)	1 (0.7)	0
Ascites	2 (1.7)	0	0
Diarrhea	2 (1.7)	3 (2.0)	0
Vomiting	2 (1.7)	3 (2.0)	1 (0.7)
Jaundice	0	0	2 (1.5)
Sepsis	2 (1.7)	1 (0.7)	1 (0.7)
White blood cell count decreased	2 (1.7)	0	0

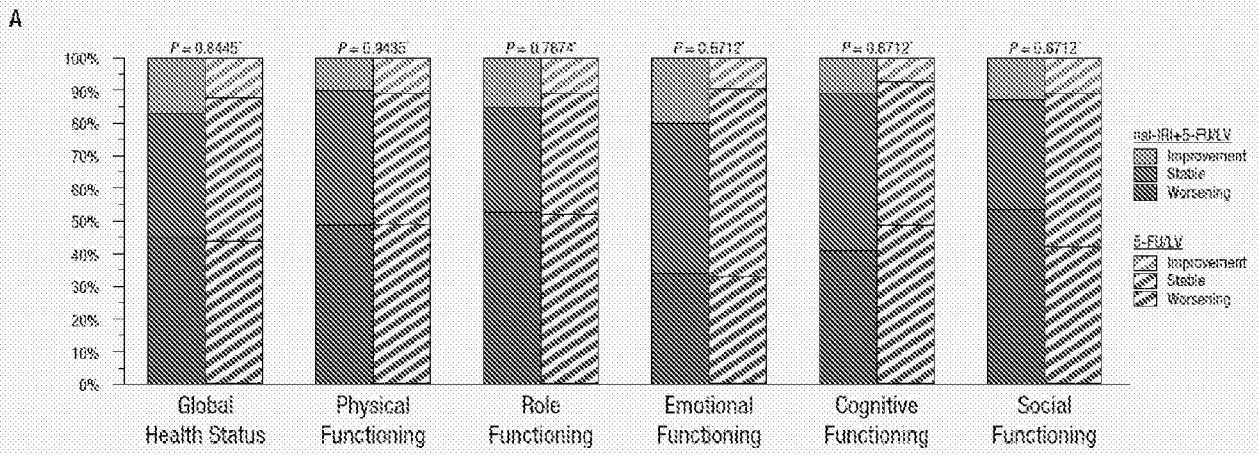
5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.

- Overall, TEAEs leading to death occurred in 2 (2%) patients receiving nal-IRI+5-FU/LV, 16 (11%) patients receiving nal-IRI monotherapy, and 10 (7%) patients receiving 5-FU/LV

Quality of Life

- Quality of life (QoL) was assessed at baseline, every 6 weeks, and at the 30-day post–follow-up visit, using the EORTC-QLQ-C30 questionnaire, in all patients in the ITT population who provided baseline and ≥1 subsequent QoL assessment
- No substantial differences were identified in the proportion of patients exhibiting improved, stable, or worsening QoL in the domains of global health status or functional scale scores between the nal-IRI+5-FU/LV and 5-FU/LV arms (**Figure 5A**)
- No substantial differences were identified in the proportion of patients exhibiting improved, stable, or worsening QoL in symptom scale scores between the nal-IRI+5-FU/LV and 5-FU/LV arms (**Figure 5B**)
- As previously reported, there were no appreciable changes from baseline in global health status, functional scale, and symptom scale scores between the nal-IRI+5-FU/LV and 5-FU/LV arms

Figure 5. Proportion of patients demonstrating improvement, stability, or worsening in (A) global health status and functional scale scores or (B) symptom scale scores (nal-IRI+5-FU/LV, n = 71; 5-FU/LV, n = 57). *Benjamini-Hochberg–adjusted *P* values. The adjustment was conducted across the 15 domains of the QoL questionnaire to control the overall false discovery rate.



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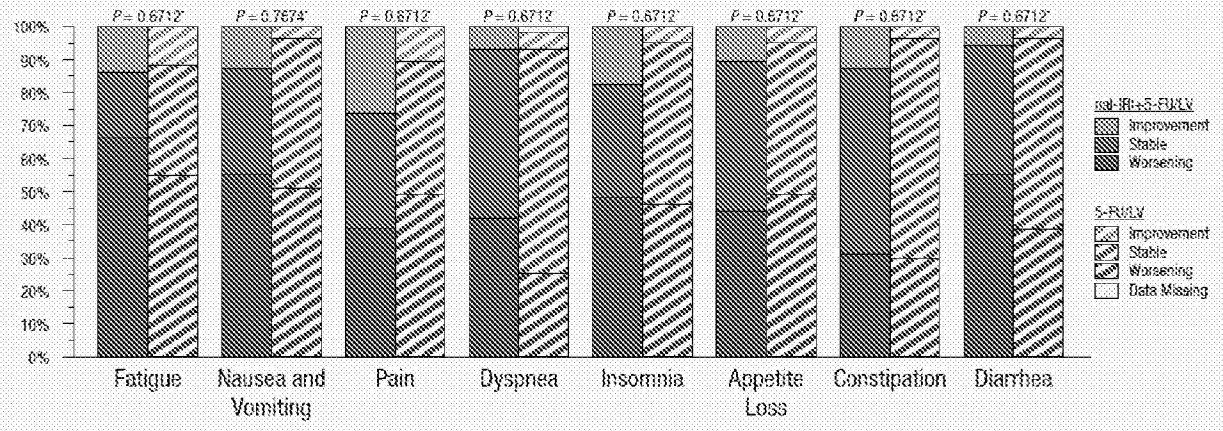

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.

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**
  - The extended data cutoff following 382 survival events confirmed the OS survival advantage in favor of nal-IRI+5-FU/LV vs 5-FU/LV for OS (6.2 vs 4.2 months; HR, 0.75; 95% CI, 0.57-0.99; $P = 0.039$)
  - Convergence of the OS curves at 20 months (with 23 [9.8%] patients surviving beyond 20 months) is likely a reason for the observed attenuation of the OS HR estimate and unstratified log-rank P value.
  - Probability of survival at 1 year was 26% in the nal-IRI+5-FU/LV arm and 16% in the 5-FU/LV arm
  - The difference in ORR with nal-IRI+5-FU/LV vs 5-FU/LV was 16% (17 vs 1 %; $P < 0.0001$)
  - Treatment with nal-IRI+5-FU/LV provided a 2-fold improvement in disease control rate compared with 5-FU/LV (52% vs 24%, respectively)
- **No new safety concerns were detected with nal-IRI as monotherapy or in combination with 5-FU/LV, and the overall safety profile was manageable, with the most common grade ≥3 AEs being neutropenia, diarrhea, fatigue, and vomiting**
- **Overall, patients treated with nal-IRI+5-FU/LV had no deterioration in QoL over 12 weeks, despite the addition of a second chemotherapeutic agent**
- **nal-IRI+5-FU/LV may represent a new standard of care for patients with mPDAC following treatment with gemcitabine-based therapy**

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Final Results of NAPOLI-1: A Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy
POSTER PRESENTED AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) ANNUAL CONGRESS; OCTOBER 7-11, 2016; COPENHAGEN, DENMARK.

734P

Impact of dose reduction or dose delay on the efficacy of liposomal irinotecan (nal-IRI)+5-fluorouracil/leucovorin (5-FU/LV): survival analysis from NAPOLI-1

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BACKGROUND

- According to estimates available in the GLOBOCAN 2018 report, pancreatic cancer is the 7th most frequent cause of cancer-related mortality worldwide.[1] Regional mortality rates due to pancreatic cancer are higher in the United States (3rd) and Europe (4th), with Asia (7th) reporting similar rates to global estimates.[2,3] Despite surgery, locoregional therapy, chemotherapy, and molecular therapies, the 5-year survival rate is only 5% to 8%.[1–4]
- In the United States, Europe, and Asia, chemotherapeutic approaches to the management of patients with advanced/metastatic pancreatic cancer vary among clinical practice guidelines based on patient performance status, with the majority recommending gemcitabine monotherapy or in combination with nab-paclitaxel or 5-fluorouracil-oxaliplatin-irinotecan (FOLFIRINOX) as first-line therapy.[4–7]
- Liposomal irinotecan (nal-IRI) is approved in the United States, Europe, and other countries in combination with 5-fluorouracil/leucovorin (5-FU/LV) for treatment of adult patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy.[4–7]
- NAPOLI-1 (NCT01494506) was a randomised phase 3 study of nal-IRI in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, in combination with 5-FU/LV.[8]
- Dose modifications, including dose reductions or delays, can be utilised to manage toxicity-related treatment-emergent adverse events (TEAEs) among patients with pancreatic cancer. Dose modification is intended to improve tolerability and increase the likelihood that a patient can remain on treatment for a longer period to maximise chemotherapeutic benefit and delay disease progression.[9,10]
- 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 AEs.[8]

OBJECTIVE

- This exploratory analysis of NAPOLI-1 examined the impact of nal-IRI dose modifications during the first 6 weeks of treatment when used to manage TEAEs on overall survival (OS) and progression-free survival (PFS).

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]
- Dosing
  - Patients randomised to the 5-FU/LV arm were administered an intravenous infusion of LV at a dose of 200 mg/m^2 followed by 5-FU at a dose of 2,000 mg/m^2 weekly for 4 weeks of each 6-week cycle.
  - Patients in the nal-IRI+5-FU/LV arm received nal-IRI at a dose of 80 mg/m^2 (salt; equivalent to 70 mg/m^2 free base) followed by LV 400 mg/m^2 and then 5-FU 2,400 mg/m^2 every 2 weeks. Treatment was continued until disease progression or unacceptable toxicity.
    - Patients known to be homozygous for the *UGT1A1*28* allele received a nal-IRI starting dose of 60 mg/m^2 (salt; equivalent to 50 mg/m^2 free base) and received nal-IRI at a dose of 80 mg/m^2 as tolerated in subsequent cycles.
- The primary endpoint was OS, with key secondary endpoints including PFS, objective response rate, quality of life, and safety.[3]

Post hoc analysis

- This exploratory post hoc analysis included patients in NAPOLI-1 who were randomised to either the 5-FU/LV arm or the nal-IRI+5-FU/LV arm under protocol version 2, and received at least 1 dose of the study drug (safety population).
  - A dose reduction was defined as any reduction in the scheduled dose from the initial administered dose.
    - The study protocol allowed for up to 2 dose reductions for nal-IRI and 5-FU.
    - Patients known to be homozygous for the *UGT1A1*28* allele who initiated nal-IRI treatment at a reduced dose and then received nal-IRI at a dose of 80 mg/m^2 in subsequent cycles were not included in the dose-modified population because the starting dose reduction was not administered in response to TEAEs.
  - A dose delay was defined as any delay in dosing greater than 3 days from the targeted dosing date.
    - The study protocol permitted a dosing delay of up to 3 weeks to allow for recovery from toxicity-related TEAEs.
    - If dosing of nal-IRI or 5-FU needed to be delayed, then the other drugs in the combination were also not administered.
- Within the nal-IRI+5-FU/LV arm, patients were divided into 2 groups: those with a nal-IRI dose modification and those without.
  - To account for patients with disease progression or treatment discontinuation within the first 6 weeks, the cohort of patients without dose modification included only those who received the first 3 scheduled doses of nal-IRI+5-FU/LV without qualifying delay/reduction.
  - Because few patients in the 5-FU/LV arm had a dose modification, between-arm comparisons were made using all 5-FU/LV patients who received 4 doses of 5-FU/LV in the first 6 weeks.
- Comparisons of OS and PFS were made between patients within the nal-IRI+5-FU/LV arm who had a nal-IRI dose modification and those without dose modification.
- Additional comparisons of OS and PFS were made between patients in the nal-IRI+5-FU/LV arm with dose modifications and the population in the 5-FU/LV arm.
- OS and PFS were calculated using the Kaplan-Meier method.

- Hazard ratios (HRs) were calculated to assess the impact of dose modifications on OS and PFS in the individual and pooled treatment arms.
  - HRs and 95% confidence intervals (CIs) 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

- This post hoc analysis included 93 patients randomised to nal-IRI+5-FU/LV and 71 patients randomised to 5-FU/LV alone.
- Among the patients randomised to nal-IRI+5-FU/LV, 40 patients did not have a dose modification and 53 patients received a dose modification during the first 6 weeks of treatment.
  - Patients requiring dose delay: n=49
  - Patients requiring dose reduction: n=34
  - Patients with both a dose delay and a dose reduction: n=30
- 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 characteristics of the nal-IRI+5-FU/LV arm (separately by whether or not patients had a dose modification) and the 5-FU/LV arm

Characteristic	nal-IRI+5-FU/LV		5-FU/LV
	Dose Modification (n=53)	No Dose Modification (n=40)	(n=71)
Sex, n (%)			
Men	33 (62.3)	22 (55.0)	37 (52.1)
Women	20 (37.7)	18 (45.0)	34 (47.9)
Age (y), mean (SD)	62.2 (9.5)	63.0 (9.2)	60.6 (8.65)
Weight (kg), mean (SD)	68.0 (13.7)	68.6 (16.0)	65.2 (15.99)
BMI (kg/m²), mean (SD)	23.7 (4.2)	24.4 (4.1)	23.66 (4.653)
Ethnicity, n (%)			
Caucasian	26 (49.1)	29 (72.5)	47 (66.2)
Asian	22 (41.5)	7 (17.5)	22 (31.0)
Black or African American	1 (1.9)	2 (5.0)	1 (1.4)
Other	4 (7.5)	2 (5.0)	1 (1.4)
Region, n (%)			
Europe	17 (32.1)	20 (50.0)	34 (47.9)
Asia	22 (41.5)	7 (17.5)	21 (29.6)
North America	5 (9.4)	8 (20.0)	9 (12.7)
Other	9 (17.0)	5 (12.5)	7 (9.9)
KPS score, n (%)			
100	6 (11.3)	11 (27.5)	8 (11.3)
90	20 (37.7)	19 (47.5)	28 (39.4)
80	22 (41.5)	8 (20.0)	28 (39.4)
70	5 (9.4)	1 (2.5)	6 (8.5)
60	0	1 (2.5)	0
Serum albumin (g/dL), mean (SD)	4.03 (0.43)	4.02 (0.40)	4.02 (0.488)
Serum CA19-9 (U/mL), mean (SD)	16 481 (31 588)	21 554 (72 394)	15 921 (62 095)
Previous anticancer therapy, n (%)			
Gemcitabine monotherapy	23 (43.4)	18 (45.0)	30 (40.3)
Gemcitabine combination	33 (62.3)	22 (55.0)	38 (50.7)
Fluorouracil-based	22 (41.5)	16 (40.0)	28 (39.4)
Irinotecan-based	4 (7.5)	4 (10.0)	10 (14.1)
Platinum-based	18 (34.0)	11 (27.5)	20 (28.2)

5-FU/LV, 5-fluorouracil/leucovorin; BMI, body mass index; CA19-9, cancer antigen 19-9; KPS, Karnofsky performance status; nal-IRI, liposomal irinotecan; SD, standard deviation.

- 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), neutropaenia (n=8), diarrhoea (n=6), platelet count decrease (n=5)
  - Patients requiring dose reduction: neutrophil count decrease (n=7), neutropaenia (n=5), white blood cell decrease (n=5)

Impact of dose modification in the first 6 weeks of treatment on survival

- Within the nal-IRI+5-FU/LV arm, median OS and PFS in patients with dose modifications were similar to the median OS and PFS in patients without dose modifications (Table 2).

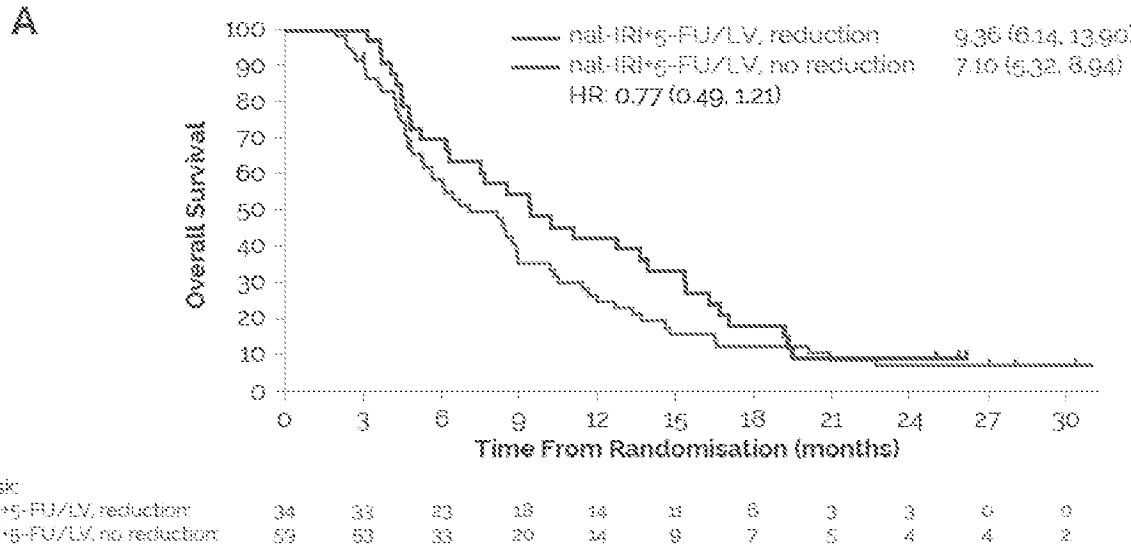
Table 2. Within-group analysis of the impact of dose modification during the first 6 weeks of treatment on Survival

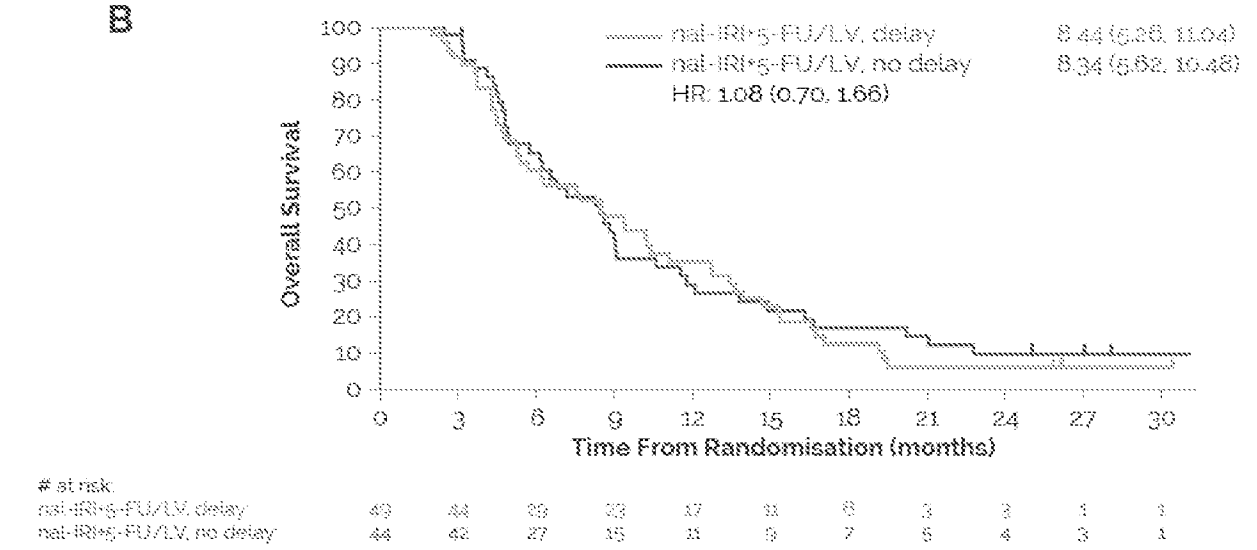
	Pts (n)	Median Overall Survival		Median Progression-Free Survival	
		Months	HR (95% CI)	Months	HR (95% CI)
nal-IRI+5-FU/LV reduction	34	9.36	0.77	4.21	0.85
nal-IRI+5-FU/LV no reduction	59	7.10	(0.49, 1.21)	4.11	(0.53, 1.38)
nal-IRI+5-FU/LV dose delay	49	8.44	1.08	4.17	1.03
nal-IRI+5-FU/LV no delay	44	8.34	(0.70, 1.66)	4.04	(0.66, 1.61)

5-FU/LV, 5-fluorouracil/leucovorin; CI, confidence interval; HR, hazard ratio; nal-IRI, liposomal irinotecan; pts, patients.

- Within the nal-IRI+5-FU/LV arm, median OS in patients who had a dose reduction was 9.36 months (95% CI, 6.14, 13.90), whereas the median OS in patients who did not have a dose reduction was 7.10 months (95% CI, 5.32, 8.94); HR = 0.77 (95% CI, 0.49, 1.21) (Figure 1A).
- The median OS in patients who had a dose delay was 8.44 months (95% CI, 5.26, 11.04) compared with 8.34 months (95% CI, 5.62, 10.48) for patients who did not have a dose delay; HR = 1.08 (95% CI, 0.70, 1.66) (Figure 1B).

Figure 1. Kaplan-Meier curves for overall survival in the nal-IRI+5-FU/LV arm for (A) patients who had a dose reduction and (B) patients who had a dose delay



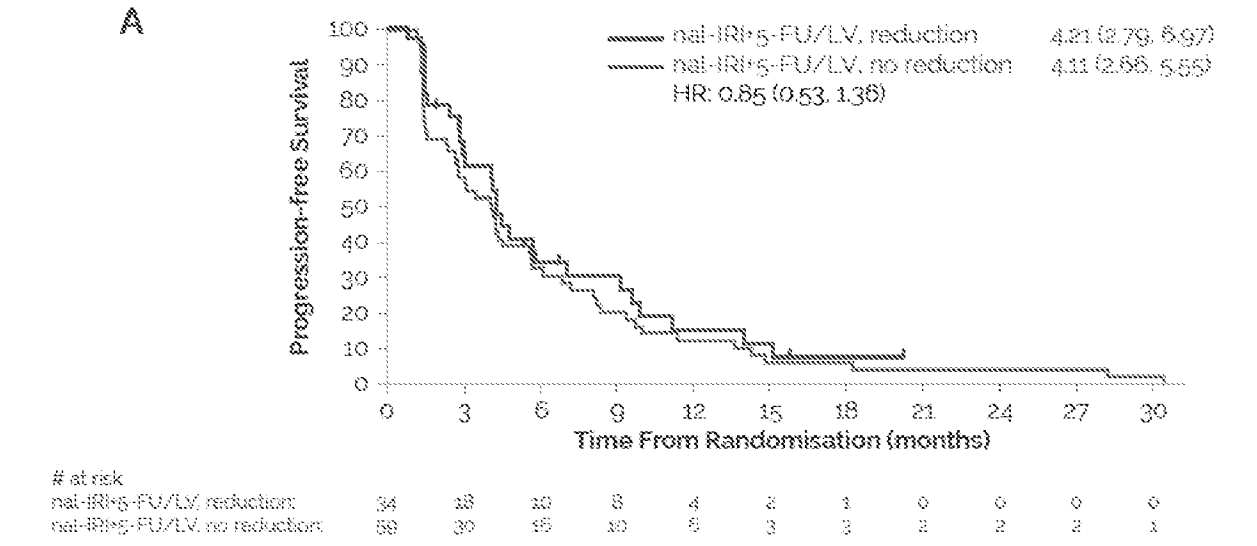


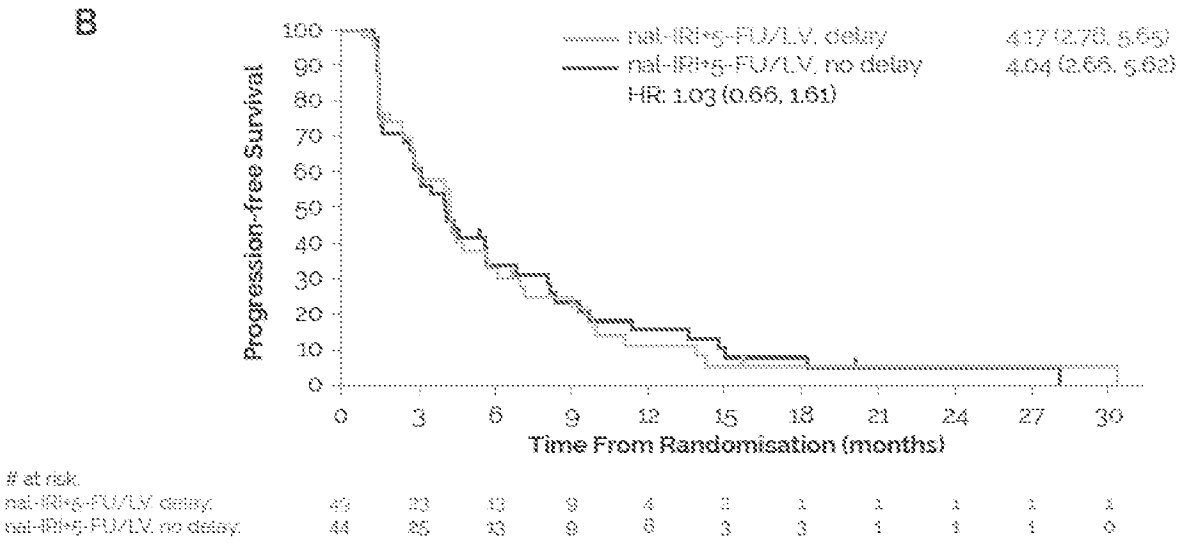
5-FU/LV, 5-fluorouracil/leucovorin; HR, hazard ratio; nal-IRI, liposomal irinotecan.

– Dose reduction was numerically greater in terms of survival outcome than dose delay

- The median PFS in patients with versus without a dose reduction was 4.21 months (95% CI, 2.79, 6.97) versus 4.11 months (95% CI, 2.66, 5.55), respectively; HR = 0.85 (95% CI, 0.53, 1.36) (Figure 2A).
- Median PFS in patients who had a dose delay (n=49) was 4.17 months (95% CI, 2.76, 5.65) compared with 4.04 months (95% CI, 2.66, 5.62) for patients who did not have a dose delay; HR = 1.03 (95% CI, 0.66, 1.61) (Figure 2B).

Figure 2. Kaplan-Meier curves for progression-free survival in the nal-IRI+5-FU/LV arm for (A) patients who had a dose reduction and (B) patients who had a dose delay





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

- Between treatment arms, survival outcomes were greater for patients in the nal-IRI+5-FU/LV arm regardless of dose reduction or delay when compared to the 5-FU/LV arm (Table 3).

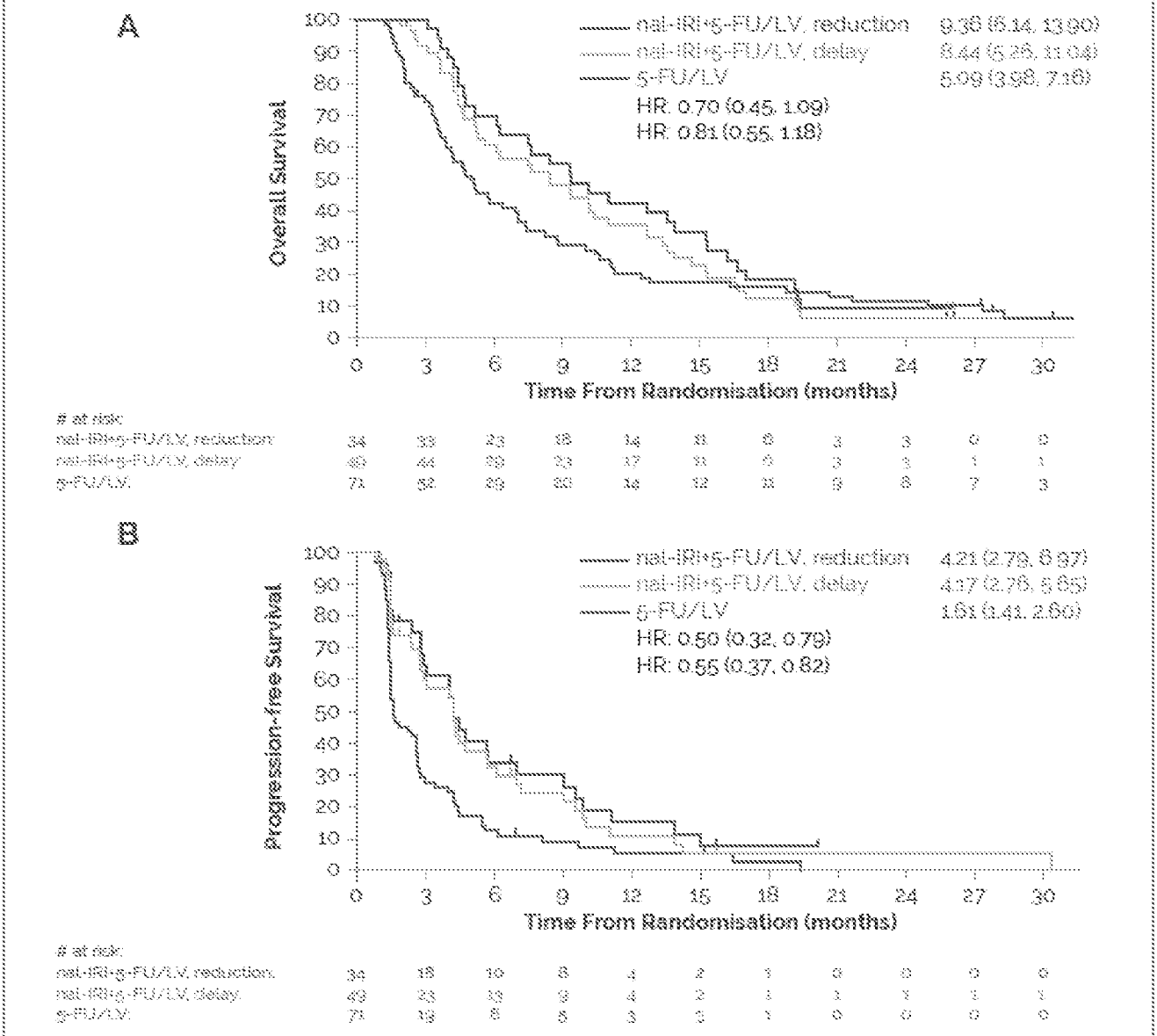
Table 3. Between group analysis of the impact of dose modification during the first 6 weeks of treatment on survival outcomes

	Pts (n)	Median Overall Survival		Median Progression-Free Survival	
		Months	HR (95% CI)	Months	HR (95% CI)
nal-IRI+5-FU/LV reduction	34	9.36	0.70 (0.45, 1.09)	4.21	0.50 (0.32, 0.79)
5-FU/LV	71	5.09		1.61	
nal-IRI+5-FU/LV dose delay	49	8.44	0.81 (0.55, 1.18)	4.17	0.55 (0.37, 0.82)
5-FU/LV	71	5.09		1.61	

5-FU/LV, 5-fluorouracil/leucovorin; CI, confidence interval; HR, hazard ratio; nal-IRI, liposomal irinotecan; pts, patients.

- Median OS for patients in the nal-IRI+5-FU/LV arm who had dose reduction or delay, respectively, was 9.36 months (95% CI, 6.14, 13.90) and 8.44 months (95% CI, 5.26, 11.04) compared to 5.09 months (95% CI, 3.98, 7.16) in the 5-FU/LV arm (Figure 3A).
- Median PFS in the nal-IRI+5-FU/LV arm who had dose reduction or delay, respectively, was 4.21 months (95% CI, 2.79, 6.97) and 4.17 months (95% CI, 2.76, 5.65) compared to 1.61 months (95% CI, 1.41, 2.60) in the 5-FU/LV arm (Figure 3B).

Figure 3. Kaplan-Meier curves for overall survival (A) and progression-free survival (B) for patients in the nal-IRI+5-FU/LV arm in patients who had a dose reduction or dose delay versus patients in the 5-FU/LV arm



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

LIMITATIONS

- These post-hoc analyses are limited due to the relatively small number of patients.
- When taking the results of NAPOLI-1 into account (6.1 and 3.1 months median OS & PFS), the median OS & PFS of the nal-IRI+5FU/LV groups (both modified and non-modified) appear to have increased. This is due to the analysis excluding patients with disease progression or treatment discontinuation within the first 6 weeks (see: Methods).

CONCLUSIONS

- This post hoc analysis suggests that implementing dose modification strategies (reduction and/or delay) to manage toxicities associated with nal-IRI+5-FU/LV therapy may not adversely affect clinical outcomes.
- There was no apparent impact on survival outcomes within the nal-IRI+5-FU/LV arm between patients who required tolerability-guided dose modifications and those who did not.
- Consistent with the reported results in NAPOLI-1,[8] OS and PFS were greater in patients who received nal-IRI+5-FU/LV and required a dose modification compared with those who received 5-FU/LV.

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734P

749P

The prognostic value of the modified Glasgow prognostic score (mGPS) in predicting overall survival (OS) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving liposomal irinotecan (nal-IRI)+5-fluorouracil and leucovorin (5-FU/LV)

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INTRODUCTION

- Adenocarcinoma of the pancreas has a poor prognosis, and is the 7th leading cause of cancer-related deaths worldwide. By region, pancreatic cancer is the 3rd leading cause of cancer-related deaths in the United States, 4th leading cause in Europe, and 7th leading cause in Asia.[1-3]
- Globally, it is estimated that over 458,000 new cases of pancreatic cancer are diagnosed every year, with approximately the same number of deaths occuring on an annual basis.[3-5]
- Although the usefulness of various prognostic factors has been reported in the past, most reports of prognostic factors for patients with pancreatic cancer have focused on cases of resectable disease.[6-8]
- Inflammation and inflammatory conditions have been associated with pancreatic cancer risk and progression in a number of clinical, epidemiological, and animal model studies.[9] In particular, the ratio of C-reactive protein to albumin ratio has been demonstrated to predict long-term outcomes in patients with pancreatic cancer after pancreatic resection.[10]
- The modified Glasgow Prognostic Score (mGPS), an inflammation-based prognostic score, was proposed by McMillan and colleagues as a prognostic factor for patients with solid tumours,[11] primarily due to its overall clinical utility and simplicity. Specifically, the modified GPS does not assign value for low albumin as a singular finding, which is different from the original GPS. Elevated c-reactive protein value must also be present for points to be assigned.
- Although the mGPS has become accepted as a useful prognostic factor for a variety of gastrointestinal tumours, including colorectal[12-14] and gastric cancers,[15-18] the initial utility in patients with pancreatic cancer was primarily based on patients with surgical resection of early-stage cancers.
- Imaoka and colleagues recently established the prognostic value of the mGPS for overall survival (OS) in patients with pancreatic cancer,[19] identifying that the mGPS score is an independent prognostic factor of survival, especially for those with more advanced disease.

OBJECTIVE

- To evaluate the association between mGPS and OS in a post hoc analysis of the NAPOLI-1 study,[20] which demonstrated improved survival for nal-IRI+5-FU/LV vs. 5-FU/LV in the treatment of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy.

Clinical trial identification: NCT01494506

METHODS

- All patients treated in the NAPOLI-1 study (NCT01494506) with available baseline plasma C-reactive protein (CRP) and albumin data (data cutoff: February 14, 2014) were included in this post hoc analysis.
  - Baseline demographic criteria of the NAPOLI-1 study have been previously published.[18]
- Eligible patients were stratified according to the following criteria, which were based on baseline serum CRP and albumin levels:
  - mGPS-0: CRP ≤10 mg/L regardless of albumin level
  - mGPS-1: CRP >10 mg/L, albumin ≥35 g/L
  - mGPS-2: CRP >10 mg/L, albumin <35 g/L
- OS was assessed in individual and pooled treatment arms.
- A stepwise Cox regression model of OS was used to evaluate the prognostic significance of mGPS, utilising the following parameters at a 0.05 level:
  - Baseline Karnofsky score, baseline albumin, neutrophil/lymphocyte ratio, sum of longest diameter of target lesions, presence of liver metastases, baseline CA19-9, stage 4 disease at diagnosis, primary tumour location, prior biliary stent, prior Whipple procedure, prior radiotherapy, line of therapy, prior exposure to 5-FU, prior exposure to irinotecan, prior exposure to platinum-based therapy, age, body mass index, race, sex, weight, mGPS, and treatment

RESULTS

- Baseline plasma CRP and albumin data were available for n=184 of the N=411 patients who enrolled in the NAPOLI-1 study.
  - mGPS-0, n=79
  - mGPS-1, n=88
  - mGPS-2, n=17
- Baseline characteristics of the n=184 patients included in this analysis are included in Table 1. Demographics for this post hoc analysis differed slightly from the NAPOLI-1 population due to changes in study protocol and individual site variances in the collection of both plasma CRP and albumin.

Table 1. Demographics of patients in NAPOLI-1 with both plasma C-reactive protein and albumin available at baseline

Characteristic Category/Statistic	All Eligible Patients (N=184)	nal-IRI+5-FU/LV (n=58)	nal-IRI Monotherapy (n=65)	5-FU/LV (n=61)
Gender, n (%)				
Female	74 (40.2)	20 (34.5)	26 (40.0)	28 (45.9)
Age (yrs)				
Median	64	63.5	66	63

Race, n(%)				
White	150 (81.5)	46 (79.3)	52 (80.0)	52 (86.2)
Black or African American	7 (3.8)	3 (5.2)	2 (3.1)	2 (3.3)
American Indian or Alaska Native	1 (0.5)	0	1 (1.5)	0
Asian	12 (6.5)	2 (3.4)	4 (6.2)	6 (9.8)
Other	14 (7.6)	7 (12.1)	6 (9.2)	1 (1.6)
Weight (kg)				
Median	67.5	69.7	67.0	65.3
BMI (kg/m)				
Median	23.55	22.99	23.87	23.44
BSA (m)				
Median	1.78	1.84	1.76	1.74
Baseline albumin (g/dL)				
Median	4.00	4.10	4.00	4.00
Baseline CA19-9 (U/mL)				
Median	2018.0	2452.0	4182.0	701.5
Baseline KPS level, n (%)				
60	2 (1.1)	2 (3.4)	0	0
70	20 (10.9)	6 (10.3)	7 (10.8)	7 (11.5)
80	69 (37.5)	18 (31.0)	23 (35.4)	28 (45.9)
90	65 (35.3)	22 (37.9)	24 (36.9)	19 (31.1)
100	28 (15.2)	10 (17.2)	11 (16.9)	7 (11.5)
Pancreatic tumour location, n (%)				
Head (and other locations)	120 (65.2)	37 (63.8)	46 (69.2)	38 (62.3)
Other (Not including Head)	54 (29.3)	15 (25.9)	19 (29.2)	20 (32.8)
Unknown	10 (5.4)	6 (10.3)	1 (1.5)	3 (4.9)
Stage at diagnosis, n (%)				
IA	1 (0.5)	0	1 (1.5)	0
IB	1 (0.5)	0	1 (1.5)	0
IIA	16 (8.7)	4 (6.9)	7 (10.8)	5 (8.2)
IIB	38 (20.7)	13 (22.4)	12 (18.5)	13 (21.3)
III	32 (17.4)	9 (15.5)	13 (20.0)	10 (16.4)
IV	95 (51.6)	32 (55.2)	30 (46.2)	33 (54.1)
Unknown	1 (0.5)	0	1 (1.5)	0
Prior radiotherapy, n (%)	41 (22.3)	10 (17.2)	18 (27.7)	13 (21.3)
Prior Whipple, n (%)	51 (27.7)	12 (20.7)	21 (32.3)	18 (29.5)
Prior stent, n (%)	17 (9.2)	8 (13.8)	6 (9.2)	3 (4.9)
Anatomical location of lesions at baseline, n (%)				
Distant lymph node	62 (33.7)	20 (34.5)	24 (36.9)	18 (29.5)
Liver	119 (64.7)	38 (65.5)	43 (66.2)	38 (62.3)
Lung	69 (37.5)	22 (37.9)	22 (33.8)	25 (41.0)
Pancreas	116 (63.0)	34 (58.6)	41 (63.1)	41 (67.2)
Peritoneal	42 (22.8)	9 (15.5)	21 (32.3)	12 (19.7)
Regional lymph node	23 (12.5)	7 (12.1)	7 (10.8)	9 (14.8)
Other	47 (25.5)	10 (17.2)	16 (24.6)	21 (34.4)

Number of measureable metastatic lesions at baseline, (n, %)				
1	38 (20.7)	7 (12.1)	16 (24.6)	15 (24.6)
2	81 (44.0)	25 (43.1)	27 (41.5)	29 (47.5)
3	26 (14.1)	13 (22.4)	8 (12.3)	5 (8.2)
>3	12 (6.5)	3 (5.2)	6 (9.2)	3 (4.9)
Prior gemcitabine monotherapy, n (%)	95 (51.6)	28 (48.3)	35 (53.8)	32 (52.5)
Prior gemcitabine in combination, n (%)	89 (48.4)	30 (51.7)	30 (46.2)	29 (47.5)
Prior 5-FU, n (%)	81 (44.0)	30 (51.7)	28 (43.1)	23 (37.7)
Prior irinotecan, n (%)	25 (13.6)	8 (13.8)	10 (15.4)	7 (11.5)
Prior platinum, n (%)	55 (29.9)	21 (36.2)	21 (32.3)	13 (21.3)

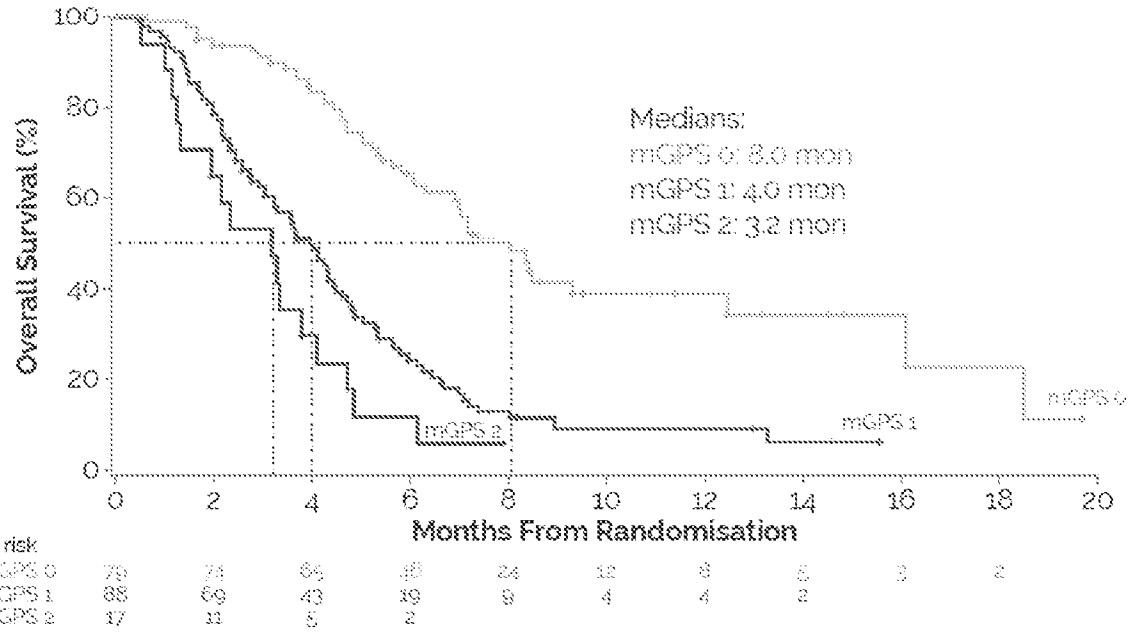
*Only patients with baseline plasma c-reactive protein and albumin data are included.

- For patients in pooled treatment arms, median OS was worse for the mGPS-1 and mGPS-2 groups than for the mGPS-0 group (4.0, 3.2 vs. 8.0 months, respectively), but was comparable between the mGPS-2 and mGPS-1 groups (3.2 vs. 4.0 months, respectively) (Table 2, Figure 1).

Table 2. Overall survival by modified Glasgow Prognostic Score (mGPS) in pooled treatment arms of NAPOLI-1

mGPS Level	Number of Patients	Median Follow-up (months)	Number of Deaths	Median Survival (95% CI, months)
0	79	9.3	44 (56%)	8.0 (6.3, 12.5)
1	88	12.9	78 (89%)	4.0 (3.0, 4.5)
2	17	7.9	16 (94%)	3.2 (1.3, 4.1)

Figure 1. Kaplan-Meier curve of overall survival by modified Glasgow Prognostic Score (mGPS) in pooled treatment arms of NAPOLI-1



mGPS, modified Glasgow Prognostic Score.

- Multivariate analysis revealed both mGPS-1 and mGPS-2 were independent predictive factors of death.
  - mGPS-1: HR, 3.34; 95% CI, 2.25–4.95, $p<0.0001$
  - mGPS-2: HR, 5.89; 95% CI, 3.21–10.80, $p<0.001$

Table 3. Cox regression analysis of overall survival in the NAPOLI-1 study for the 181 patients with baseline modified Glasgow Prognostic Score (mGPS)

Parameter	N	Univariate Analysis			Multivariate (Adjusted) Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
mGPS							
0	78	1.00			1.00		
1	86	2.92	(1.99, 4.27)	<0.0001	3.34	(2.25, 4.95)	<0.0001
2	17	5.01	(2.78, 9.03)	<0.0001	5.89	(3.21, 10.80)	<0.0001
KPS (%)							
≥90	91	1.00			1.00		
60–80*	90	1.89	(1.34, 2.67)	0.0003	2.04	(1.42, 2.93)	0.0001
CA19-9 (U/mL)							
≤1.542	86	1.00			1.00		
>1.542	95	1.71	(1.21, 2.42)	0.0023	1.77	(1.24, 2.54)	0.0017
Age (yrs)							
<65	95	1.00			1.00		
≥65	86	1.29	(0.92, 1.81)	0.15	1.65	(1.15, 2.36)	0.0059
Treatment							
nal-IRI+5-FU/LV	58	1.00			1.00		
nal-IRI or 5-FU/LV	122	1.41	(0.97, 2.06)	0.072	1.52	(1.04, 2.22)	0.031

*Only 4 patients report a KPS of 60.
5-FU/LV, 5-fluorouracil/leucovorin; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; mGPS, modified Glasgow Prognostic Score; nal-IRI, liposomal irinotecan.

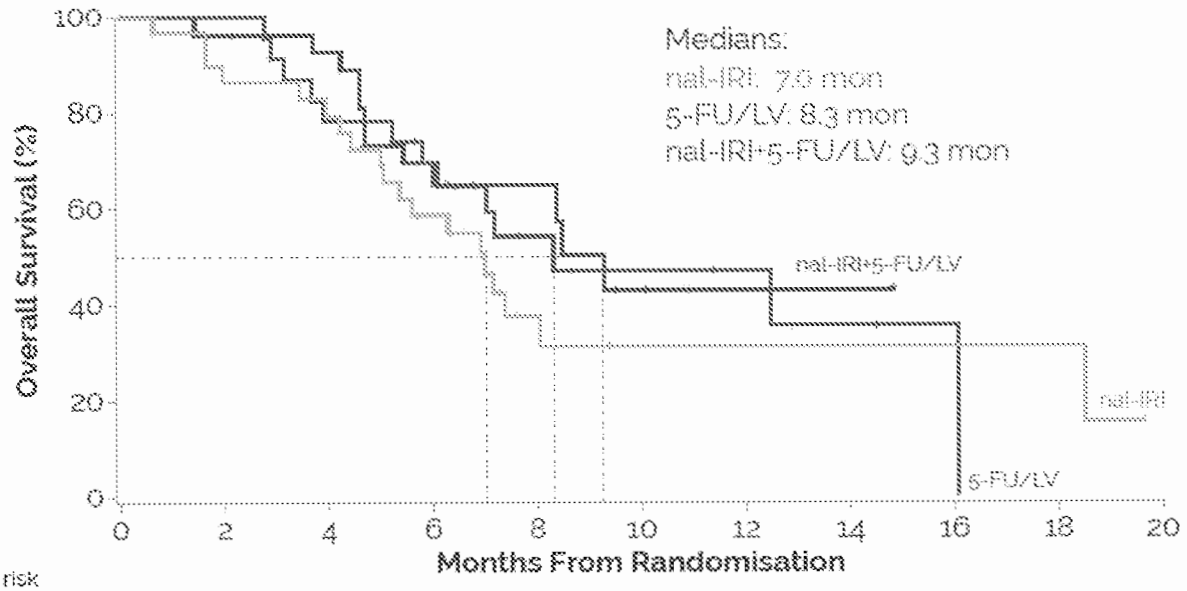
- In the analysis of OS by individual treatment arm according to mGPS criteria, a similar effect was noted. Patients treated with nal-IRI+5-FU/LV demonstrated lower OS in the mGPS-1 (n=26) and mGPS-2 (n=5) groups than in the mGPS-0 (n=27) group (4.6, 3.3 vs. 9.3 months, respectively).

Table 4. Overall survival by modified Glasgow Prognostic Score (mGPS) according to individual treatment arms

mGPS Level	Treatment Arm	Number of Patients	Median Follow-up (months)	Number of Deaths	Median Survival (months)
0	nal-IRI	29	8.4	19 (66%)	7.0
	5-FU/LV	23	9.3	13 (57%)	8.3
	nal-IRI+5-FU/LV	27	9.5	12 (44%)	9.3
1	nal-IRI	32	*	32 (100%)	3.0
	5-FU/LV	30	8.9	24 (80%)	3.4
	nal-IRI+5-FU/LV	26	12.9	22 (85%)	4.6
2	nal-IRI	4	*	4 (100%)	1.3
	5-FU/LV	8	*	8 (100%)	3.9
	nal-IRI+5-FU/LV	5	7.9	4 (80%)	3.3

5-FU/LV, 5-fluorouracil/leucovorin; mGPS, modified Glasgow Prognostic Score; nal-IRI, liposomal irinotecan.
*Not applicable because all eligible patients within this cohort died.

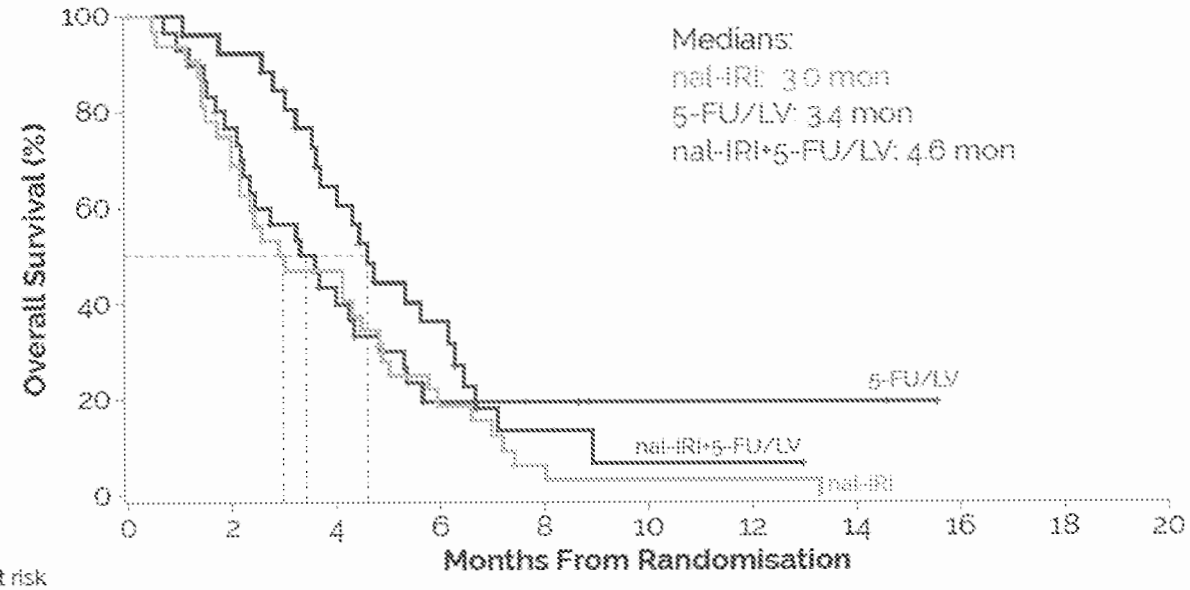
Figure 2. Kaplan-Meier curve of overall survival by modified Glasgow Prognostic Score = 0 in individual treatment arms of NAPOLI-1



At risk										
nal-IRI	59	26	23	16	6	3	3	2	1	2
5-FU/LV	33	23	18	15	9	5	4	2	1	
nal-IRI+ 5-FU/LV	27	26	24	15	9	4	1	1		

5-FU/LV, 5-fluorouracil/leucovorin; mGPS, modified Glasgow Prognostic Score; nal-IRI, liposomal irinotecan.

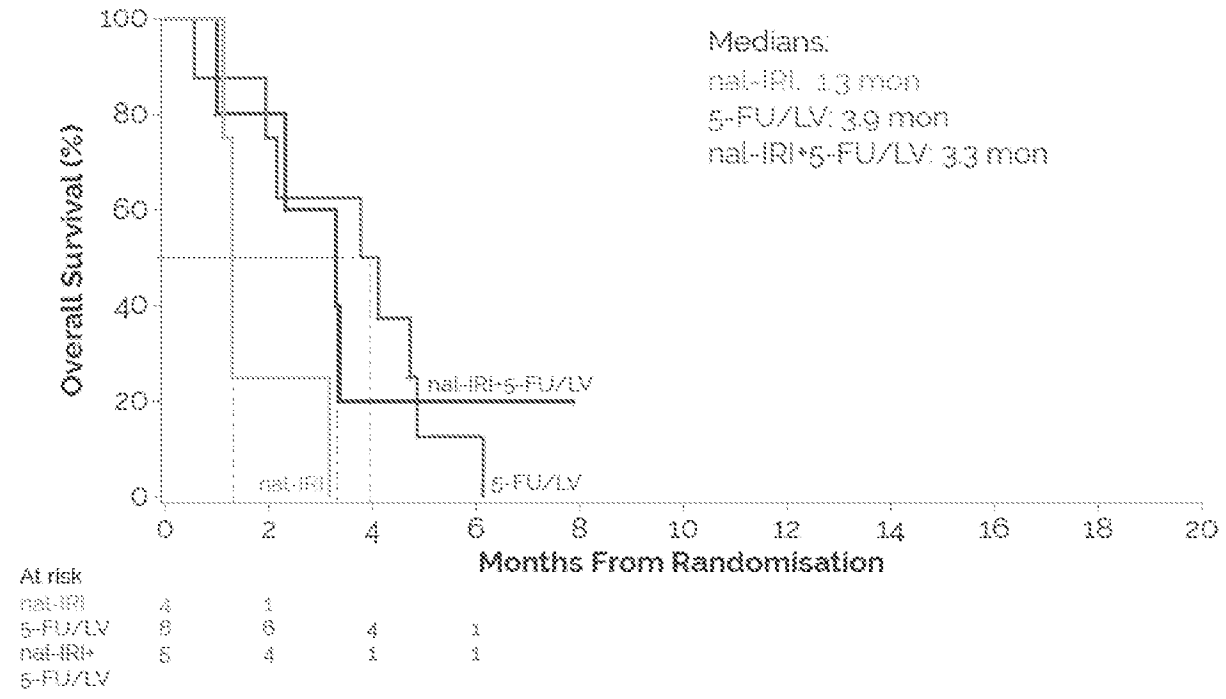
Figure 3. Kaplan-Meier curve of overall survival by modified Glasgow Prognostic Score = 1 in individual treatment arms of NAPOLI-1



At risk								
nal-IRI	32	22	15	6	2	1	1	
5-FU/LV	39	23	12	5	4	2	2	2
nal-IRI+ 5-FU/LV	26	24	16	8	3	1	1	

5-FU/LV, 5-fluorouracil/leucovorin; mGPS, modified Glasgow Prognostic Score; nal-IRI, liposomal irinotecan.

Figure 4. Kaplan-Meier curve of overall survival by modified Glasgow Prognostic Score = 2 in individual treatment arms of NAPOLI-1



5-FU/LV, 5-fluorouracil/leucovorin; mGPS, modified Glasgow Prognostic Score; nal-IRI, liposomal irinotecan.

LIMITATIONS

- This analysis is limited by the small number of patients in the NAPOLI-1 study who had baseline serum laboratory values for both CRP and albumin.
- The results of this analysis are potentially not generalisable to the overall population due to differences in demographics between this post hoc population and the overall NAPOLI-1 study population.

CONCLUSIONS

- Data from this post hoc analysis of mGPS in patients from the NAPOLI-1 study who had mPDAC that was previously treated with gemcitabine-based therapy are consistent with the reports of the prognostic value of the mGPS in estimating OS.
- Median OS was significantly improved in patients with an mGPS-0 versus mGPS-1 or mGPS-2, including in the treatment group of patients receiving nal-IRI+5-FU/LV.

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2200 **Claudin 18.2 – a novel treatment target in the multicenter, randomized, phase II FAST study, a trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without the anti-CLDN18.2 antibody IMAB362 as 1st line therapy in advanced gastric and gastroesophageal junction (GEJ) cancer**

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Background: Claudin(CLDN)18.2 is a stomach specific tight junction protein. The chimeric monoclonal anti-CLDN18.2 antibody IMAB362 potently activates complement and antibody dependent cellular cytotoxicity. FAST investigated CLDN18.2 tumor expression and therapy with IMAB362 in combination with first line chemotherapy in pts with advanced gastric and GEJ cancer.

Methods: Pts with advanced gastric and GEJ cancer were centrally evaluated for CLDN18.2 by immunohistochemistry (CLAUDETECT18.2® Kit). CLDN18.2 expression of ≥ 2+ in ≥ 40% tumor cells was defined positive. Eligible pts required CLDN18.2+ tumors, an ECOG PS of 0–1, and no medical need for trastuzumab treatment. Pts were randomized 1:1 to first line EOX (epirubicin 50 mg/m^2, oxaliplatin 130 mg/m^2 d1, and capecitabine 625 mg/m^2 bid, d1–21; qd22) with or without IMAB362 (loading dose 800 mg/m^2, then 600 mg/m^2 d1, qd21). An exploratory 3rd arm was added after arms 1 and 2 had enrolled ~80% of pts to test a higher dose of IMAB362 (1000 mg/m^2) plus EOX. The primary study endpoint was PFS (arm1 v 2, 70% power, HR 0.72, 1-sided p = 0.1).

Results: 686 pts were assessed for CLDN18.2, 334 tumors (48%) were positive per protocol criteria, most with homogenous expression. 161 pts (44% diffuse, 33% intestinal) were randomized into arms 1 and 2, 116 pts had 2+/3+ CLDN18.2 staining in ≥ 70% of tumor cells. IMAB362 plus EOX consistently improved PFS (median 4.8 v 7.9 mon; HR 0.47; 95% CI 0.31–0.70, p = 0.0001), OS (8.4 v 13.2 mon; HR 0.51, 95% CI 0.36–0.73, p = 0.0001) and ORR (28% vs 43%) compared to EOX. Pts with high CLDN18.2 showed stronger effects (PFS HR 0.36; p < 0.0005; OS HR 0.45, p = <0.0005). The exploratory arm 3 also met the primary endpoint (PFS HR 0.59, p = 0.0026). IMAB362-related adverse events included vomiting, neutropenia, and anemia, mostly of NCI-CTC grade 1 or 2. Grade 3/4 events were not significantly increased by IMAB362.

Conclusions: CLDN18.2 is a promising novel treatment target for IMAB362 combined with first line chemotherapy in pts with advanced gastric and GEJ cancer.

Clinical trial identification: NCT01630083

Legal entity responsible for the study: Ganymed Pharmaceuticals AG

Funding: Ganymed Pharmaceuticals AG

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2210PD **Efficacy and safety of nanoliposomal irinotecan (nal-IRI, MM-398, PEP02, SAR-2368) in patients with metastatic pancreatic cancer in Asia: A subgroup analysis of the phase 3 NAPOLI-1 Study**

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Background: The global Phase 3 trial, NAPOLI-1, demonstrated that nal-IRI + 5-fluorouracil and leucovorin (5-FU/LV) significantly improved overall (OS), progression-free survival (PFS) and objective response rate (ORR) vs 5-FU/LV in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPAC) previously treated with gemcitabine-based therapy. Herein, we present a post hoc subgroup analysis of the Asia cohort in the NAPOLI-1 study.

Methods: Pts were randomly assigned (1:1:1) to receive nal-IRI (80 mg/m^2, equivalent to 70 mg/m^2 of irinotecan base) + 5-FU/LV (2400/400 mg/m^2) q2w, nal-IRI (120 mg/m^2, equivalent to 100 mg/m^2 of irinotecan base) q3w, or 5-FU/LV (2000/200 mg/m^2 weekly for weeks 1–4 q6w). The primary endpoint was OS.

Results: Of 132 pts randomized in Asian centers, 34 were assigned to treatment with nal-IRI+5-FU/LV, 50 with nal-IRI, and 48 with 5-FU/LV. In the Asia cohort, nal-IRI+5-FU/LV significantly improved median OS versus 5-FU/LV (8.9 vs 3.7 months, P = 0.0281) (Table). Improvements in PFS and ORR were also observed. There were no significant differences in outcomes between 5-FU/LV and nal-IRI monotherapy. Grade ≥3 treatment-emergent adverse events in ≥ 15% of pts in either nal-IRI arm were neutropenia (55%, 34%, and 2% in the nal-IRI+5-FU/LV, nal-IRI, and 5-FU/LV arms, respectively), white blood cell count decreased (21%, 8%, 0%), diarrhea (3%, 16%, 5%), and anemia (18%, 24%, 14%). There were no cases of Grade ≥3 peripheral neuropathy.

Conclusions: This subgroup analysis confirmed that nal-IRI+5-FU/LV is an efficacious treatment option with a manageable safety profile in patients with mPAC treated in Asia. Nal-IRI+5-FU/LV may represent a new standard of care for patients with mPAC previously treated with gemcitabine-based therapy.

Clinical trial identification: NCT01494506.

Legal entity responsible for the study: Merrimack.

Funding: Merrimack

Disclosure: L-T. Chen: Received data monitoring board, statistician, and support of medical writer from Merrimack, and honorarium from PharmaEngine, Inc. F. de Jong: Employee of and hold stock in Shire. M. Pipas: Employee of and hold stock in Merrimack. B. Belanger: Employee of, hold stock in, and have received reimbursement for travel/accommodations/expenses from Merrimack. E. Wang: Employee of

Table 2. (cont.)

Summary of Treatment Efficacy

End Point	Nal-IRI + 5-FU/LV (N = 34)	5-FU/LV Combo Control (N = 35)	HR (95% CI)*	P value†	Nal-IRI (N = 50)	5-FU/LV Mono Control (N = 48)	HR (95% CI)*	P value†
OS, months, median (95% CI)	8.9 (4.4, 10.4)	3.7 (2.7, 6.4)	0.5087 (0.28, 0.93)	0.0281	5.7 (4.8, 7.4)	4.3 (3.1, 5.7)	0.8339 (0.53, 1.3)	0.4263
PFS, months, median (95% CI)	4.0 (1.5, 5.7)	1.4 (1.2, 2.0)	0.4818 (0.27, 0.85)	0.0116	2.8 (1.5, 4.1)	1.4 (1.3, 1.9)	0.6874 (0.44, 1.1)	0.0950
ORR, %	8.8%	0%	8.8 (-0.1, 18.4)	0.1142	10.0%	0%	10.0 (1.7, 18.3)	0.0564

*Values reported for ORR represent a difference in proportions rather than a HR, and the CI limits for the difference in ORR are based on normal approximation.

†P value is based on Fisher exact test. P values are 2-sided.

PharmaEngine, Inc. The company has the licensing partnership with Merrimack Pharmaceuticals for the product. Y-J. Bang: Consultant for Merrimack. All other authors have declared no conflicts of interest.

222PD **Efficacy of consolidation chemotherapy for clinical responder to concurrent chemoradiation in stage II-III squamous cancer of the esophagus**

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Background: Concurrent chemoradiotherapy (CCRT) has become the standard of care in esophageal cancer patients who are not surgical candidates, but the benefit of consolidation chemotherapy is unknown. The aim of this study was to assess whether consolidation chemotherapy improves the outcome in responders after CCRT in patients with stage II-III squamous cancer of the esophagus.

Methods: The characteristics of patients treated with CCRT from September 2005 to September 2013 were reviewed, and those who achieved clinical complete response (CR) and partial response (PR) following CCRT were included in this study. Patients who received CCRT alone (observation group) were compared with patients who underwent CCRT followed by consolidation chemotherapy (consolidation group) with regard to overall survival, treatment failure and toxicity. Baseline characteristics were matched using the propensity score matching method.

Results: Of 666 patients recruited (234 observation, 432 consolidation), 249 (37.4%) had clinical stage II disease and 417 (62.6%) had stage III disease. Comparisons of the observation and consolidation groups in the matched population (234 patients in each group) showed median recurrence-free survival rates of 33.8 and 28.6 months (hazard ratio [HR], 1.08; 95%CI [confidence interval], 0.84 to 1.37; P = .549), and median overall survival rates of 44.5 and 41.8 months (HR, 1.03; 95%CI, 0.81 to 1.33; P = .788), respectively. For the patients with stage III disease, median OS did not differ between the observation and consolidation groups, the median OS was 35.6 and 33.7 months, respectively, P = .294. Of those with positive lymph nodes, the median OS was 31.2 months in the observation group and 34.9 months in the consolidation group, P = .638. More mild gastrointestinal reactions were noted in patients receiving consolidation chemotherapy. There was no significant difference in local/regional failure (49.1% vs. 45.3%) and distant failure (21.4% vs. 25.2%) between groups.

Conclusions: Consolidation chemotherapy did not increase survival or disease control for patients with stage II-III squamous cancer of the esophagus who respond to CCRT. The role of consolidation chemotherapy remains to be defined.

Legal entity responsible for the study: Zhengzhou University

Funding: Zhengzhou University

Disclosure: All authors have declared no conflicts of interest.

223PD **Neoadjuvant nimotuzumab plus chemoradiotherapy compared to neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy for locally advanced esophageal cancer**

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Background: We present the study in which combining neoadjuvant treatment of nimotuzumab with chemoradiotherapy (Bio-nCRT) is compared with neoadjuvant chemoradiotherapy (nCRT) and neoadjuvant chemotherapy (nCT) for patients with potentially resectable locally advanced esophageal cancer

Methods: The data of patients with stage II-III squamous cell carcinoma of the thoracic esophagus who underwent neoadjuvant therapy and esophagectomy was reviewed. Patients who underwent nCT were treated with two cycles of paclitaxel 175 mg/m^2 day 1 and cisplatin 25 mg/m^2 days 1-3 of a 3-week cycle. Concomitant radiotherapy (40Gy in 20 fractions, 5 days/week) was added in the nCRT group. Participants in Bio-nCRT group were treated with the same nCRT regimen and the administration of nimotuzumab at a flat dose of 200 mg weekly on week 1-5. Esophagectomy was performed 4-6 weeks after the end of neoadjuvant therapy.

Results: In total, 195 patients received neoadjuvant therapy and 172 (88.2%) completed the entire trimodal therapy. Surgical resection was performed in 94.4% after Bio-nCRT, versus 92.5% after nCRT and 83.5% after nCT (P = 0.026). The R0 resection rate was 100% after Bio-nCRT, 95.9% after nCRT and 92.6% after nCT (P = 0.030). Pathological complete response (pCR) was achieved in 41.2% after Bio-nCRT, versus 32.4% after nCRT and 14.8% after nCT (P = 0.000). Lymph-node metastases were observed in 29.4% in the Bio-nCRT group, versus 21.6% in the nCRT group and 34.6% in the nCT group (P = 0.126; nCRT vs. nCT, P = 0.042).

Conclusions: Comparing to neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy results in higher surgical resection rate, pCR rate and a lower frequency of lymph node metastases. Adding nimotuzumab to neoadjuvant chemoradiotherapy is safe and appears to facilitate complete resection and increase the pCR rate.

Legal entity responsible for the study: Zhengzhou University

Funding: Zhengzhou University

Disclosure: All authors have declared no conflicts of interest

224PD **Predictors for recurrence after initial clinical complete response to definitive chemoradiotherapy in esophageal squamous cell carcinoma patients**

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Background: Definitive chemoradiotherapy(dCRT) is a curative treatment option for esophageal cancer and could be an alternative to esophagectomy. However, due to lack of effective diagnostic methods for the response evaluation, some patients who actually harbor residual disease after dCRT were falsely diagnosed as clinical complete response(cCR) and eventually exhibit relapse. The purpose of this study was to

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ABSTRACT BOOK

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227P **CA19-9 decrease and overall survival (OS) in the NAPOLI-1 trial of liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy**

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Background: nal-IRI+5-FU/LV showed efficacy in a randomized phase 3 trial in mPDAC (NAPOLI-1). CA19-9 decreases were more common with nal-IRI+5-FU/LV vs 5-FU/LV, and a greater improvement in OS (primary endpoint) with nal-IRI+5-FU/LV vs 5-FU/LV was observed in patients (pts) with higher baseline CA19-9. We present an exploratory post hoc analysis of the association of CA19-9 decrease with OS in the final dataset.

Methods: 417 pts with mPDAC were randomly assigned to treatment with nal-IRI+5-FU/LV, nal-IRI monotherapy, or 5-FU/LV. Data from all pts were pooled to assess the association of CA19-9 decrease with OS. CA19-9 was evaluated at baseline and every 6 weeks (wks).

Results: 283 pts (71%) of 398 pts who received ≥1 dose of study drug had CA19-9 data at baseline and at any time postbaseline up to wk 12. Median OS for pts with any CA19-9 decrease (n = 124) vs no decrease (n = 159) was 7.5 vs 5.0 mo (HR = 0.58, 95% CI = 0.46–0.75; P < 0.0001). Similar trends were observed with ≥20% and ≥50% decreases by wk 12. Pts with a ≥ 20% decrease by wk 12 (n = 97) had a median OS of 8.4 vs 5.1 mo for pts (n = 186) without this decrease (HR = 0.58; 95% CI = 0.45–0.76; P < 0.0001). Pts with a ≥ 50% decrease by wk 12 (n = 57) had a median OS of 9.3 vs 5.5 mo for pts (n = 226) without this decrease (HR = 0.60, 95% CI = 0.44–0.81; P = 0.0009). Decreases in CA19-9 from baseline by wk 12 were more frequently observed in pts receiving nal-IRI+5-FU/LV or nal-IRI monotherapy than 5-FU/LV (Table).

Table: 2279

Change in CA19-9 From Baseline up to Week 12, n (%)	nal-IRI+ 5-FU/LV n = 88	nal-IRI Monotherapy n = 99	5-FU/LV n = 96	All Evaluable Patients n = 283
No decrease	38 (43)	50 (51)	71 (74)	159 (56)
Any decrease	50 (57)	49 (49)	25 (26)	124 (44)
≥20% decrease	41 (47)	38 (38)	18 (19)	97 (34)
≥50% decrease	23 (26)	23 (23)	11 (11)	57 (20)

Conclusions: Pts with any CA19-9 decrease from baseline up to wk 12, ≥20% decrease by wk 12, or ≥ 50% decrease by wk 12 had significantly longer OS than pts without these decreases. These findings in the post-gemcitabine setting seem consistent with previous reports in the front-line setting. Higher proportions of pts treated with nal-IRI+5-FU/LV vs 5-FU/LV had CA19-9 decreases.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: This study was sponsored by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; rights for nal-IRI now reside with Ipsen in the US (April 2017); PharmaEngine, Inc. holds the rights in Taiwan; Shire holds rights in the rest of the world through a licensing agreement with Ipsen.

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CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Efficacy and safety of liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) who previously received gemcitabine (gem)-based therapy: Post-hoc analysis of the NAPOLI-1 trial.

Li-Tzong Chen, Andrea Wang-Gillam, Shan Yanshen, Teresa Macarulla, Jean-Frédéric Blanc, Richard Hubner, ...

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Abstract Disclosures

Abstract

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Background: nal-IRI+5-FU/LV is approved in the United States and Taiwan for pts with mPDAC previously treated with gem-based therapy based on the NAPOLI-1 study which showed that nal-IRI+5-FU/LV improved overall survival (OS) vs 5-FU/LV (6.1 vs 4.2 mo; HR, 0.67; 95% CI, 0.49-0.92; *P*= 0.012; Wang-Gillam et al, *Lancet*. 2016). This post hoc analysis evaluated the efficacy and safety of nal-IRI+5-FU/LV in subgroups of pts defined by prior gem regimen including gem monotherapy and gem combinations (combo). **Methods:** This analysis (data cutoff, Nov 2015) focuses on the 236 pts assigned to nal-IRI+5-FU/LV q2w (n = 117) or 5-FU/LV qw for weeks 1-4 q6w cycle (n = 119). Pts previously received gem-based therapy in a neoadjuvant, adjuvant, locally advanced, or metastatic setting. **Results:** Of 117 pts in the nal-IRI+5-FU/LV arm, 53 (45%) previously received gem monotherapy and 64 (55%) previously received gem combo including erlotinib (n = 9) or nab-paclitaxel (n = 20). Of the 119 pts in the 5-FU/LV arm, 55 (46%) previously received gem monotherapy and 64 (54%) previously received gem combo including erlotinib (n = 17) or nab-paclitaxel (n = 11). Nal-IRI+5-FU/LV improved median OS, median PFS, and ORR vs 5-FU/LV, regardless of prior therapy (Table). Grade ≥3 treatment-emergent adverse events were not influenced by prior treatment. Clinical trial information: NCT01494506.**Conclusions:** These resultsshow consistent benefit of nal-IRI+5-FU/LV treatment across subgroups of pts who previously received gem therapy and support the ASCO guidelines recommending nal-IRI+5-

FU/LV for this pt population. These analyses may be limited by the small sample size of treatment arms.

Efficacy by prior gem-based regimen

	Gem Mono				Gem Combo			
	Nal-IRI+ 5-FU/LV n = 53	5-FU/LV n = 55	P	HR (95% CI)	Nal-IRI+ 5-FU/LV n = 64	5-FU/LV n = 64	P	HR (95% CI)
OS, months, median (95% CI)	7.1 (4.6-10.2)	4.3 (3.4-6.1)	0.31	0.81 (0.54-1.22)	6.1 (4.6-8.4)	4.2 (2.7-5.8)	0.06	0.7 (0.49-1.02)
PFS, months, median (95% CI)	4.1 (2.7-5.6)	2.2 (1.4-2.7)	0.03	0.63 (0.41-0.96)	3.1 (1.5-4.2)	1.4 (1.3-1.6)	<0.01	0.54 (0.36-0.81)
ORR	15%	2%	0.01		19%	0%	<0.01	

FINAL RESULTS OF NAPOLI-1: A PHASE 3 STUDY OF NAL-IRI (MM-398) ± 5-FLUOROURACIL AND LEUCOVORIN (5-FU/LV) VS 5-FU/LV IN METASTATIC PANCREATIC CANCER (MPAC) PREVIOUSLY TREATED WITH GEMCITABINE-BASED THERAPY

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Resources

Abstract 3707

Background

nal-IRI, a liposomal formulation of irinotecan, plus 5-FU/LV is approved in the US for patients (pts) with mPAC previously treated with gemcitabine-based therapy. Primary analysis (data cutoff, Feb 14, 2014) of the NAPOLI-1 trial (NCT01494506) showed that, after 313 events, nal-IRI + 5-FU/LV significantly improved median overall survival (OS) vs 5-FU/LV (6.1 vs 4.2 mo; HR 0.67; 95% CI 0.49-0.92; P = 0.012; Wang-Gillam et al, Lancet, 2016). Here we report the final analysis of NAPOLI-1 (data cutoff, Nov 16, 2015).

Methods

417 pts were randomly assigned to nal-IRI 70 mg/m^2 (equivalent to 80 mg/m^2 irinotecan HCl trihydrate salt) + 5-FU/LV 2400/400 mg/m^2 q2w (n = 117), nal-IRI 100 mg/m^2 (equivalent to 120 mg/m^2 irinotecan HCl trihydrate salt) q3w (n = 151), or 5-FU/LV 2000/200 mg/m^2 weekly for weeks 1-4 q6w (n = 149). Log-rank P values are 2-sided.

Results

After 382 events, median OS was improved with nal-IRI + 5-FU/LV vs 5-FU/LV (6.2 vs 4.2 mo, HR 0.75; 95% CI 0.57-0.99, P = 0.038), but not for nal-IRI vs 5-FU/LV (4.9 vs 4.2 mo; HR 1.07; 95% CI 0.84-1.36; P = 0.567). Kaplan-Meier estimates of OS for nal-IRI + 5-FU/LV and 5-FU/LV, respectively, were 53% and 38% at 6 mo, and 26% and 16% at 12 mo. Median progression-free survival was longer for nal-IRI + 5-FU/LV vs 5-FU/LV (3.1 vs 1.5 mo; HR 0.57; 95% CI 0.43-0.76; P

Conclusions

Final results from NAPOLI-1 continue to show OS benefit for nal-IRI + 5-FU/LV vs 5-FU/LV. No new safety concerns were identified. nal-IRI + 5-FU/LV provides a new treatment option for pts with mPAC previously treated with gemcitabine-based therapy.

Clinical trial identification

NCT01494506

Legal entity responsible for the study

Merrimack Pharmaceuticals, Inc.

Disclosure

L-T. Chen: Merrimack/ NAPOLI-1 study Steering Committee Member, uncompensated. Advisory Meeting, honorarium: Baxalta. Consultant, honorarium: PharmaEngine. A. Wang-Gillam: Advisory Board: Merrimack, Pfizer. A. Dean: Investigator meeting, travel grant: Merrimack. D. Cunningham: Research funding to institution: Amgen, AstraZeneca, Bayer, Celgene, Medimmune, Merck Serono, Merrimack, Sanofi. J-F. Blanc: Honoraria: Baxalta. F. Braiteh: Research funding: Merrimack. B. Belanger: Employee of Merrimack. E. Bayever: Former employee, stock options: Merrimack. F. de Jong: Employee and stock options: Baxalta. D.D. von Hoff: Clinical trial: Merrimack. J.T. Sivets: Advisory Board, Honoraria: Baxalta. All other authors have declared no conflicts of interest.

Resources from the same session

08 Oct 2016

Randomized, open-label, phase III study comparing irinotecan plus S-1 with S-1 alone in patients with advanced esophageal squamous cell carcinoma after failure of prior platinum- or taxane-based chemotherapy: Results of an interim analysis

Presenter: Jing Huang Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

08 Oct 2016

Randomized phase II study of S-1 and concurrent radiotherapy with versus without induction chemotherapy of gemcitabine for locally advanced pancreatic cancer (LAPC): Final analysis of JCOG1106

Presenter: Tetsuya Ieka Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

08 Oct 2016

Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Prognosis, efficacy, and safety by liver disease etiology

Presenter: Takuji Okusaka Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

08 Oct 2016

Prognostic factors in curative treatment of gallbladder cancer - Data of 950 cases of "The German- Registry"

Presenter: Thorsten Goetze Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

1/cisplatin in gastric cancer patients with peritoneal metastasis: PHOENIX-GC trial

Presenter: Yoshiyuki Fujiwara Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

08 Oct 2015

Molecular characteristics of hepatocellular carcinomas (HCC) from different age groups

Presenter: Celina Ang Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

08 Oct 2015

Invited discussant abstracts LBA26, LBA27 and 616PD

Presenter: Eric Van Cutsem Session: Gastrointestinal tumours, non-colorectal

Resources

Presentation

08 Oct 2015

Invited discussant abstracts 620PD, 621PD and 622PD

Presenter: Eduardo Diaz Rubio Session: Gastrointestinal tumours, non-colorectal

Resources

Presentation

08 Oct 2015

Invited discussant abstracts 617PD, 618PD, 619PD and LBA28

Presenter: Florian Lordick Session: Gastrointestinal tumours, non-colorectal

Resources

Presentation

08 Oct 2015

Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial

Presenter: Jordi Bruix Session: Gastrointestinal tumours, non-colorectal

Resources

Abstract

734P Impact of dose reduction or dose delay on the efficacy of liposomal irinotecan (nal-IRI)+5-fluorouracil/leucovorin (5-FU/LV): Survival analysis from NAPOLI-1

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Background: Chemotherapy dose modifications to manage adverse events (AEs) is common in clinical practice. 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). The study protocol permitted dose modifications (reduction or delay) to address toxicity. In this exploratory post-hoc analysis, we evaluated the impact of nalIRI dose modifications on overall survival (OS) and progression-free survival (PFS).

Methods: All pts enrolled under protocol v2 who received nal-IRI+5-FU/LV during the first 6 wks were included in the analysis. Pts were grouped according to those with dose modification or those without dose modification. Dose reduction was defined as any decrease from initial dose, delay as any dosing delay > 3 days from target date. Pts without dose modification received the first 3 scheduled doses of nal-IRI+5-FU/LV without qualifying delay/reduction. OS and PFS (KaplanMeier estimates) were compared within the nal-IRI+5-FU/LV arm. Unstratified hazard ratios (HRs) were calculated using Cox regression.

Results: Among pts in the nal-IRI+5-FU/LV arm (n = 93), 40 pts had no dose modification and 53 had a dose modification (delay, n = 49; reduction, n = 34). Within the nal-IRI+5-FU/LV arm, there was no significant difference in median OS or PFS between pts with vs without dose modification (Table).

Conclusions: Dose modification of nal-IRI+5-FU/LV in the first 6 wks does not significantly impact OS or PFS compared to patients without dose modifications. This suggests that tolerability-guided dose modification of nal-IRI does not adversely affect efficacy outcomes.

Table: 734P

	Median OS			Median PFS		
	Pts (n)	Months	HR (95% CI)	Pts (n)	Months	HR (95% CI)
nal-IRI+5-FU/LV Delay	40	8.4	1.10 (0.71, 1.70)	40	4.2	1.03 (0.66, 1.61)
nal-IRI+5-FU/LV No delay	43	8.3		43	4.0	
nal-IRI+5-FU/LV Reduction	34	9.4	0.87 (0.54, 1.39)	34	4.2	0.91 (0.56, 1.48)
nal-IRI+5-FU/LV No reduction	46	8.4		46	4.1	

Clinical trial identification: NCT01494506.

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Legal entity responsible for the study: Ipsen Biopharmaceuticals, Inc.

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Disclosure: L-T. Chen: Consulting, Advisory role: Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, Merrimack, MSD, Novartis, Ono Pharmaceutical, PharmaEngine, Syncope, Taiwan, TTY Biopharm Research funding (Inst): GlaxoSmithKline, Merck Serono, Novartis, Polaris, TTY Biopharm, Patents, Royalties, Other intellectual property: Anti-alpha-enolase (ENO-1) monoclonal antibody to HuniLife Technology, Taiwan. J. Blanc: Honoraria: Baxalta/Shire, Bayer Schering Pharma, Gilead Sciences; Consulting, Advisory role: Baxalta/Shire, Bristol-Myers Squibb, Novartis, Onxeo, Travel, accommodations, expenses: Bayer Schering Pharma. B. Mirakhur, B. Belanger: Employee, Stock and other ownership interests: Ipsen Biopharmaceuticals, Inc. F.A. de Jong: Employee: Shire; Stock and other ownership interests: Amgen, Shire. T. Bekaii-Saab: Consulting, Advisory role: Amgen, Bayer, Boehringer Ingelheim, Celgene, Genentech/Roche, Glenmark, Lilly, Merrimack, NCCN, Pfizer, Research to practice, Sirtex Medical, Taiho Pharmaceutical, Other relationship: Exelixis, Merck, Polaris. J. Siveke: Consulting, advisory role: Baxalta, Celgene, Lilly, Merrimack Research funding:

ASC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Novartis, Travel, accommodations, expenses: Celgene, Roche. All other authors have declared no conflicts of interest.

749P **The prognostic value of the modified glasgow prognostic score (mGPS) in predicting overall survival (OS) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV)**

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Background: mGPS has been identified as a prognostic factor of OS in patients with pancreatic cancer. Here we report the association between mGPS and OS in a post-hoc analysis of the NAPOLI-1 study (NCT01494506), which demonstrated improved

survival for nal-IRI+5-FU/LV vs 5-FU/LV in the treatment of patients with mPDAC previously treated with gemcitabine-based therapy.

Methods: All patients treated in the NAPOLI-1 study with available baseline plasma C-reactive protein (CRP) and albumin data (data cutoff: Nov 16, 2015) were included in this post-hoc analysis. Eligible patients were stratified by mGPS (mGPS-0: CRP ≤10 mg/L regardless of albumin level; mGPS-1: CRP >10 mg/L, albumin ≥35 g/L; and mGPS-2: CRP >10 mg/L, albumin <35 g/L). OS was assessed in individual and pooled treatment arms. A stepwise Cox regression model of OS was used to evaluate the prognostic significance of mGPS.

Results: Baseline plasma C-reactive protein and albumin data was available for N = 184 patients: mGPS-0, n = 79; mGPS-1, n = 88; mGPS-2, n = 17. For patients in pooled treatment arms, median OS was worse for the mGPS-1 group than for the mGPS-0 group (4.0 vs 8.0 months, respectively), but was comparable between the mGPS-2 and mGPS-1 groups (3.2 vs 4.0 months, respectively). Multivariate analysis revealed both mGPS-1 and mGPS-2 were independent predictive factors of death (mGPS-1: HR, 3.54; 95% CI, 2.25–4.95, P < 0.0001; mGPS-2: HR, 5.89, 95% CI, 3.21–10.80, P < 0.001). Similarly, analysis by treatment arm showed OS of patients treated with nal-IRI+5-FU/LV was significantly worse in the mGPS-1 (N = 26) and mGPS-2 (N = 5) groups than in the mGPS-0 (N = 27) group (4.6, 3.3 vs 9.3 months, respectively)

Conclusions: Data from this post-hoc analyses of mGPS in patients with mPDAC previously treated with gemcitabine-based are consistent with the reports of the prognostic value of the mGPS in estimating OS. Median OS was significantly improved in pts with a mGPS-0 vs mGPS-1 or mGPS-2, including the treatment group of patients receiving nal-IRI+5-FU/LV.

Clinical trial identification: NCT01494506.

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PD – 017 CA19-9 decrease and overall survival (OS) in the NAPOLI-1 trial of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV) in metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

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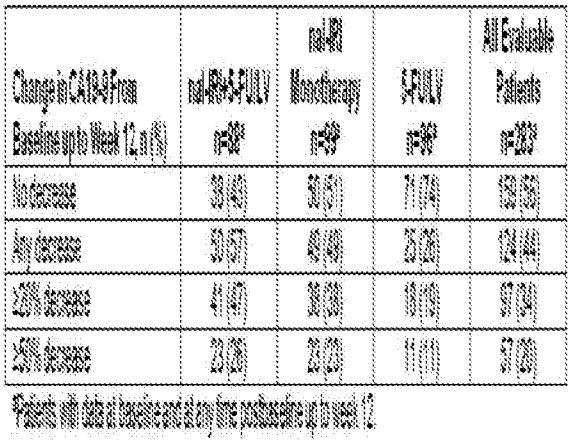
Introduction: nal-IRI+5-FU/LV showed efficacy in a randomized phase 3 trial in mPDAC (NAPOLI-1). Decreases in CA19-9 were more common with nal-IRI+5-FU/LV vs 5-FU/LV, and a greater improvement in OS (primary endpoint) with nal-IRI+5-FU/LV vs 5-FU/LV was observed in patients with higher baseline CA19-9 levels. nal-IRI+5-FU/LV also significantly improved progression-free survival and objective response rate, with a manageable safety profile. Here, we present an exploratory post hoc analysis of the association of CA19-9 decrease with OS in the final NAPOLI-1 dataset (data cutoff, November 16, 2015).

Methods: In NAPOLI-1, patients with mPDAC received nal-IRI+5-FU/LV, nal-IRI monotherapy, or 5-FU/LV. Data from all patients in the trial were pooled to assess the association of CA19-9 decrease with OS. CA19-9 was evaluated at baseline and every 6 weeks. OS was calculated by the Kaplan-Meier method. Hazard ratios (HRs) for OS comparisons based on different thresholds for change in CA19-9 were estimated by Cox regression analysis. Of 417 patients randomly assigned to treatment in NAPOLI-1, 398 received ≥1 dose of study drug.

Results: Of the 398 patients treated in the NAPOLI-1 trial, 283 (71%) had CA19-9 data at baseline and at any time postbaseline up to week 12. Among these 283 patients, the estimated median OS for patients with any reduction in CA19-9 (n = 124) vs no reduction (n = 159) was 7.5 mo (95% CI, 6.7-9.4 mo) vs 5.0 mo (95% CI, 4.4-5.8 mo), with an HR of 0.58 (95% CI, 0.46-0.75; $P<0.0001$). Similar trends were observed when ≥20% and ≥50% decreases by week 12 were considered in this exploratory analysis. Patients who achieved a ≥ 20% decrease in CA19-9 by week 12 (n = 97) had an estimated median OS of 8.4 mo (95% CI, 7.1-10.5 mo) vs 5.1 mo (95% CI, 4.7-5.9 mo) for those patients (n = 186) who did not achieve this decrease (HR, 0.58; 95% CI, 0.45-0.76; $P<0.0001$). Patients who achieved a ≥ 50% decrease in CA19-9 by week 12 (n = 57) had an estimated median OS of 9.5 mo (95% CI, 7.5-11.7 mo) vs 5.5 mo (95% CI, 4.9-6.1 mo) for those patients (n = 226) who did not achieve this decrease (HR, 0.60; 95% CI, 0.44-0.81; $P=0.0009$). Decreases in CA19-9 levels from baseline (any decrease, ≥20% decrease, or ≥ 50% decrease) by week 12 were more frequently observed in patients treated with nal-IRI+5-FU/LV or with nal-IRI monotherapy than with 5-FU/LV (Table).

Conclusion: Patients who achieved any CA19-9 decrease from baseline up to week 12, ≥20% decrease by week 12, or ≥ 50% decrease by week 12 had significantly longer OS than patients who did not achieve these decreases. These findings in the post-gemcitabine setting seem consistent with previous reports in the front-line setting. Higher proportions of patients treated with nal-IRI+5-FU/LV vs 5-FU/LV were observed to have CA19-9 decreases.



PD-017 Figure 1