CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

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

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Abstract

459

Background: Results from NAPOLI-1 (NCT01494506), a phase 3 study in pts with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in OS (primary endpoint), progression-free survival, and objective response rate with nal-IRI+5-FU/LV vs 5-FU/LV. The MPACT study reported a nomogram to predict OS using baseline pt variables in previously untreated mPDAC. We conducted an exploratory post hoc analysis of NAPOLI-1 variables to develop a nomogram to predict OS in the post-gemcitabine setting. **Methods:** In NAPOLI-1, pts were randomized to receive nal-IRI 80 mg/m2 q2w + 5-FU/LV, nal-IRI 100 mg/m2 q3w, or 5-FU/LV. Univariate and multivariate analyses determined factors significantly predictive of OS. A multivariable Cox model was created using these factors to develop a nomogram that assigned points equal to the weighted sum of relative significance of each variable. Predictive accuracy of the nomogram as measured by the concordance index (c-index) was evaluated by internal bootstrap validation. **Results:** Data from the 417-pt univariate analysis and 399-pt multivariate analysis (18 pts excluded for missing baseline data) were used. Eight of 21 variables were retained in the multivariate analysis ($p < 0.01$ except BMI [$p=0.08$]). **Conclusions:** In NAPOLI-1, predictors of OS were nal-IRI+5-FU/LV treatment, KPS, NLR, albumin level, baseline

CA19-9, stage 4 at diagnosis, BMI, and presence of liver metastasis. The nomogram, which will distinguish between risk groups and may aid in clinical decision making, will be presented in the poster. Clinical trial information: NCT01494506.

Multivariate Cox Model for OS[a]	HR	95% CI
Karnofsky Performance Status (KPS) ≥ 90	0.58	0.45, 0.73
Albumin ≥ 4 g/dL	0.70	0.55, 0.89
Neutrophil-to-lymphocyte ratio (NLR) > 5	0.61	0.47, 0.78
Presence of liver metastases	1.72	1.33, 2.24
CA19-9 > median (1542 U/mL)	1.59	1.26, 2.01
Stage 4 at diagnosis	1.61	1.27, 2.04
Received nal-IRI + 5-FU/LV	0.60	0.46, 0.78
Body mass index (BMI)	0.98	0.95, 1.00

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

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Article Tools

GASTROINTESTINAL (NONCOLORECTAL) CANCER

The prognostic value of baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for predicting clinical outcome in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan (nal-IRI; MM-398) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV.

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Abstract

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Background: Increased NLR and PLR have been associated with poor survival in several malignancies. Here we report the association of NLR and PLR with overall survival (OS) and progression-free survival (PFS) in the NAPOLI-1 trial (NCT01494506), which evaluated nal-IRI+5-FU/LV for the treatment of mPDAC patients (pts) after disease progression following gemcitabine-based therapy. **Methods:** Pts missing baseline NLR/PLR data were excluded. Medians reflect Kaplan-Meier estimates; hazard ratios (HRs) reflect Cox regression analysis. *P* values in this exploratory analysis are descriptive. **Results:** Of 116 evaluable pts in the nal-IRI+5-FU/LV arm, 82 (71%) had NLR ≤5 and 44 (38%) had PLR ≤150 (data cutoff: Nov 16, 2015). Of 105 evaluable pts in the 5-FU/LV control arm, 73 (70%) had NLR ≤5 and 36 (34%) had PLR ≤150. In pts with

baseline NLR ≤5 or PLR ≤150, median OS and PFS were significantly longer in the nal-IRI+5-FU/LV treatment arm vs the 5-FU/LV control arm (Table). In pts with baseline NLR >5 or PLR >150, median OS and PFS were numerically longer in the treatment vs control arm, but differences were less compelling (95% CIs for HRs included 1). **Conclusions:** Median OS and PFS were improved with nal-IRI+5-FU/LV vs 5-FU/LV in pts with baseline NLR ≤5 or PLR ≤150. This exploratory analysis extends the prognostic significance of NLR and PLR to the post-gemcitabine setting. Clinical trial information: NCT01494506.

Median OS, mo 95% CI n (12-mo OS)	nal-IRI+5-FU/LV	5-FU/LV	HR 95% CI *P*
NLR ≤5	8.4	4.8	0.62
	6.1-10.2	3.6-6.1	0.44-0.86
	82	73	0.005
	(30%)	(14%)	
NLR >5	4.3	3.1	>0.99
	3.4-4.7	1.9-4.2	0.59-1.68
	34	32	0.99
	(12%)	(16%)	
PLR ≤150	8.4	4.7	0.52
	4.7-14.6	2.6-5.9	0.32-0.84
	44	36	0.008
	(36%)	(11%)	
PLR >150	5.4	3.7	0.91
	4.4-7.1	3.1-5.8	0.64-1.29
	72	69	0.60
	(18%)	(16%)	
Median PFS, mo 95% CI			
NLR ≤5	4.2	1.5	0.41
	3.1-5.6	1.4-2.6	0.29-0.59
			<0.0001

Median OS, mo 95% CI n (12-mo OS)	nal-IRI+5-FU/LV	5-FU/LV	HR 95% CI *P*
NLR >5	1.4	1.4	1.01
	1.4-2.8	1.3-1.9	0.60-1.71
			0.96
PLR ≤150	4.2	1.5	0.33
	2.7-6.1	1.4-2.6	0.19-0.56
			<0.0001
PLR >150	2.8	1.4	0.72
	1.4-4.1	1.4-1.9	0.50-1.03
			0.07

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

A survival prediction nomogram for liposomal irinotecan (nal-IRI)+5-fluorouracil/leucovorin (5-FU/LV) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy.

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Abstract Disclosures

Abstract

e16204

Background: NAPOLI-1 (NCT01494506) was a global phase 3 study in pts with mPDAC previously treated with gemcitabine-based therapy that showed a significant improvement in overall survival (OS) in pts treated with nal-IRI+5-FU/LV vs 5-FU/LV alone. A nomogram assists in predicting individualized risk for prespecified events, such as OS, death, or adverse events. A post hoc analysis of NAPOLI-1 was conducted to develop a nomogram to predict OS for nal-IRI+5-FU/LV in the post-gemcitabine setting. **Methods:**In NAPOLI-1, pts received nal-IRI+5-FU/LV, nal-IRI, or 5-FU/LV. Univariate and multivariate analyses identified baseline factors that were significantly predictive of OS. A multivariable Cox regression model was created to develop a nomogram that assigned points equal to the weighted sum of relative significance of each variable. The predictive accuracy of the nomogram, as measured by the concordance index (c-index), was evaluated by internal bootstrap validation. **Results:** Data from pts in the univariate analysis (n = 417) and multivariate analysis (n = 399; n = 18 pts excluded for missing data) were used. Eight of 21 variables were retained in the multivariate analysis and re-tested through stratification (all factors significant at the $P < 0.01$ level, except BMI [$P = 0.08$]). **Conclusions:** Key predictors of OS in NAPOLI-1 were nal-IRI+5-FU/LV treatment, KPS, NLR, albumin level,

baseline CA19-9, stage 4 at diagnosis, BMI, and presence of liver metastasis. Clinical trial information: NCT01494506.

Stratified Multivariate Cox Regression of OS (N = 399)[a]	Wald P-value	HR	95% CI
Karnofsky Performance Status (KPS) ≥ 90 vs 60–80	< 0.0001	0.58	0.46, 0.74
Albumin ≥4 g/dL vs < 4 g/dL	0.0013	0.68	0.54, 0.86
Neutrophil-to-lymphocyte ratio (NLR) > 5 vs ≤5	0.0001	0.61	0.47, 0.79
No liver metastasis vs Presence of liver metastases	< 0.0001	0.59	0.45, 0.76
CA19-9 > median ≤ 1542 U/mL) vs > 1542 U/ml	< 0.0001	0.63	0.50, 0.79
Stage < 4 vs Stage 4 at diagnosis	< 0.0001	0.62	0.49, 0.78
Body mass index (BMI) > 25 vs ≤25 kg/m^2	0.030	0.75	0.58, 0.97
nal-IRI+5-FU/LV vs 5-FU/LV or nal-IRI	0.0001	0.59	0.45, 0.77

[a]Model excluded pts with missing values.

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Nanoliposomal Irinotecan in the Clinical Practice Guideline for Metastatic Pancreatic Cancer: Applicability to Clinical Situations

TO THE EDITOR: In their recent article in *Journal of Clinical Oncology*, Sohal et al[1] undertook a systematic review of the literature published between April 2004 and June 2015 in the development of the ASCO Clinical Practice Guideline for patients with metastatic pancreatic cancer. These guidelines include results from NAPOLI-1,[2] presumably because the study was a randomized phase III trial that demonstrated a survival benefit with nanoliposomal irinotecan (nal-IRI) in combination with fluorouracil and leucovorin (FU + LV; published electronically in November 2015). That trial subsequently led to approvals by the US Food and Drug Administration and the Taiwan Food and Drug Administration and a positive Committee for Medicinal Products for Human Use opinion of this combination in this patient population with limited options.

The panel recommended, by informal consensus, that nal-IRI, in combination with fluorouracil, was a second-line therapy option for patients who progressed after first-line treatment with gemcitabine/nab-paclitaxel, Eastern Cooperative Oncology Group performance status 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and chemotherapy port and infusion pump management. The authors incorrectly stated that the NAPOLI-1 trial had evaluated patients with metastatic pancreatic cancer who had progressed on first-line gemcitabine only. Furthermore, the authors rated the quality of evidence as low, stating that the results do not apply to most clinical situations because most patients now receive multiagent regimens instead of gemcitabine in the first-line setting. They state that "no good data exist for the second-line (or greater) treatment of patients with metastatic pancreatic cancer that has progressed on contemporary first-line regimens."[1]

NAPOLI-1 was a prospective, international, multicenter, randomized phase III study that evaluated nal-IRI alone or in combination with FU + LV versus a common control (FU + LV) in patients treated previously with gemcitabine-based therapies (ie, not restricted to gemcitabine monotherapy). Analysis of the NAPOLI-1 patient population shows that 55% of the patients in the nal-IRI plus FU + LV arm received previous gemcitabine in combination with another therapy (Table 1). Similar percentages were observed in the nal-IRI monotherapy and control arms (Table 1). In particular, of the 236 patients randomly assigned to nal-IRI plus FU + LV (n = 117) or to FU + LV (n = 119), 13% received gemcitabine in combination with nab-paclitaxel as a prior regimen.[3] Furthermore, 33% of the overall patient population had received two or more lines of prior therapy.[2] In contrast, the CONKO-003[4] trial examined second-line therapy in patients with locally advanced or metastatic pancreatic cancer after progression on first-line gemcitabine monotherapy only.

Although Sohal et al[1] endorsed the NAPOLI-1 regimen in the second-line setting, it is important to provide clarification on the study design and results so that practicing oncologists use this regimen in appropriate patients. The results of the NAPOLI-1 trial showed a survival advantage for the combination of nal-IRI with FU + LV for a group of patients treated with a diverse array of prior therapies.[2] The trial results provide evidence for broad applicability of this combination for the management of patients with advanced pancreatic cancer whose disease has failed therapy with a gemcitabine-containing regimen, including the combination of gemcitabine and nab-paclitaxel.

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ACKNOWLEDGMENT
Written on behalf of the NAPOLI-1 Study Group

Table 1. Previous Anticancer Therapy in NAPOLI-1

Previous Therapy	nal-IRI Plus FU + LV (n = 117)	FU + LV Combination Therapy Control (n = 119)	nal-IRI Monotherapy (n = 151)	FU + LV Monotherapy Control (n = 149)
Gemcitabine alone	53 (45)	55 (46)	67 (44)	66 (44)
Gemcitabine combination	64 (55)	64 (54)	84 (56)	83 (56)

NOTE. Data are presented as No. (%). Reprinted with permission from Wang-Gillam et al.[2]
Abbreviations: FU + LV, fluorouracil and leucovorin; nal-IRI, nanoliposomal irinotecan.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DOI: 10.1200/JCO.2016.70.1607; published online ahead of print at www.jco.org on December 5, 2016.

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Nanoliposomal Irinotecan in the Clinical Practice Guideline for Metastatic Pancreatic Cancer: Applicability to Clinical Situations

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Research Funding: Eli Lilly (Inst), Genentech (Inst), Celgene (Inst), Agios (Inst), Incyte (Inst), Merrimack (Inst), Plexxikon (Inst), Minneamrita Therapeutics (Inst), 3-V Biosciences (Inst), Abbvie (Inst), Aduro Biotech (Inst), ArQule (Inst), Baxalta (Inst), Cleave Biosciences (Inst), CytRx Corporation (Inst), Daiichi Sankyo (Inst), Deciphera (Inst), Endocyte (Inst), Exelixis (Inst), ESSA (Inst), Five Prime Therapeutics (Inst), Gilead Sciences (Inst), Merck (Inst), miRNA Therapeutics (Inst), Pfizer (Inst), Pharmacyclics (Inst), Phoenix Biotech (Inst), Proderm IQ (Inst), Samumed (Inst), Strategia (Inst), Trovagene (Inst), Verastem (Inst), Halozyme Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Intramedullary Catheter, Methods of Human Prostate Cancer, Use of 5,6-Dihydro-5-Azacytidine in the Treatment of Prostate Cancer, Targeting Site-2 Protease (S2P) for the Treatment of Pancreatic Cancer (pending), Targeting Ecto-5-Nucleotidase (Cd73) for the Treatment of Pancreatic Cancer, Targeting a Protein Tyrosine Phosphotase-PRL-1 for the Treatment of Pancreatic Cancer (pending), Targeting a Protein PRC1 for the Treatment of Pancreatic Cancer (pending), Targeting Ecto-5-Nucleotidase (CD73) for the Treatment of Pancreatic Cancer (pending), Protein Kinase Inhibitors (pending), Methods, Compounds and Compositions with Genotype Selective Anticancer Activity (pending), Methods and Kits to Predict Therapeutic Outcome of BTK Inhibitors (pending), Muscle Fatigue Substance Cytokines and Methods of Inhibiting Tumor Growth Therewith (pending), 2-aryl-pyridylazoles for the Treatment of Solid Tumors such as Pancreatic Cancer (pending)

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Phase 2 Trial of Oxaliplatin Plus Capecitabine (XELOX) as Second-line Therapy for Patients With Advanced Pancreatic Cancer

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BACKGROUND. To the authors' knowledge, there is no established second-line chemotherapy for patients with pancreatic cancer who have received gemcitabine-based therapy. A phase 2 trial was conducted to explore the efficacy of capecitabine and oxaliplatin (XELOX) in patients with advanced pancreatic cancer previously who were treated with gemcitabine.

METHODS. Patients aged ≤65 years who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 received oxaliplatin at a dose of 130 mg/m^2 given on Day 1 and capecitabine at a dose of 1000 mg/m^2 twice daily for 14 days. For patients aged >65 years or with an ECOG PS of 2, the oxaliplatin dose was 110 mg/m^2 on Day 1 and the capecitabine dose was 750 mg/m^2 twice daily for 14 days. The treatment was repeated every 3 weeks. Tumor measurements were performed every 9 weeks and the primary study objective was 6-month overall survival.

RESULTS. The study enrolled 41 patients. Of the 39 evaluable patients, 1 patient had a partial response and 10 patients demonstrated stable disease. The Kaplan-Meier estimate of the overall median survival was 23 weeks (95% confidence interval [95% CI], 17.0-31.0 weeks). Progression-free survival was 9.9 weeks (95% CI, 9.6-14.5 weeks). The 6-month and 1-year survival rates were 44% (95% CI, 31%-62%) and 21% (95% CI, 11%-38%), respectively. The most common grade 3-4 nonhematologic toxicity was fatigue (toxicity was graded using the National Cancer Institute Common Toxicity Criteria [version 2.0]).

CONCLUSIONS. The combination of capecitabine and oxaliplatin is active in gemcitabine-pretreated patients with advanced pancreatic cancer, especially in patients with a good PS and those who have responded to first-line chemotherapy. *Cancer* 2008;113:2046–52. © *2008 American Cancer Society.*

KEYWORDS: Xelox, pancreatic cancer, performance status, capecitabine, oxaliplatin.

In 1997, gemcitabine became the standard of care as first-line therapy for advanced pancreatic cancer based on a pivotal randomized phase 3 trial that compared gemcitabine against bolus 5-fluorouracil (5-FU) for clinical benefit response, objective tumor response, and survival.[1] In that study, gemcitabine produced a better clinical benefit response rate (23.8% vs 4.8%; $P = .0022$) and a better median survival (5.7 months vs 4.4 months; $P = .0025$). These results led the US Food and Drug Administration to recommend it as front-line therapy for advanced pancreatic cancer. Since that time, several large randomized trials have been conducted in an attempt to improve gemcitabine's efficacy as front-line therapy by combining it with other cytotoxic agents or molecular targeted agents.[2–5] In general, neither statistically significant nor clinically

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Received March 14, 2008; revision received May 12, 2008; accepted May 23, 2008.

© 2008 American Cancer Society
DOI 10.1002/cncr.23810
Published online 28 August 2008 in Wiley InterScience (www.interscience.wiley.com).

Printed by [American Cancer Society Journals - 024.177.117.113 - /doi/epdf/10.1002/cncr.23810] at [18/11/2009]

significant improvements in overall survival have been observed with any gemcitabine doublet except for gemcitabine and erlotinib.[6] Unfortunately, the observed incremental survival advantage conferred with the addition of erlotinib has been very small (6.24 months vs 5.91 months; $P = .025$). Although efforts to improve on gemcitabine as front-line therapy have been going on for years, studies for those patients whose tumors are initially resistant to gemcitabine, or become refractory after initial response to gemcitabine-based therapy, have not taken priority. This is clinically important because high-quality cross-sectional imaging is able to identify patients with relatively low volume metastatic disease, many of whom will present with well-preserved performance status (PS). There is an increasing proportion of patients who will quickly fail gemcitabine and yet maintain sufficient PS to receive second-line therapy, which to our knowledge has not been defined to date.

In previous studies, both capecitabine and oxaliplatin have been used as components of front-line therapy for advanced pancreatic cancer. Capecitabine is an oral fluoropyrimidine carbamate designed to generate 5-FU preferentially in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase.[7] A phase 3 trial of capecitabine for patients with advanced pancreatic cancer reported that 10 (24%) of 42 patients experienced a clinical benefit response (95% confidence interval [95% CI], 12.1%-39.5%) as evidenced by improvement in pain intensity, analgesic consumption, and/or Karnofsky PS. Three of the 41 patients with measurable disease had an objective partial response (7.3%), and for the entire cohort the median overall survival was 6.1 months.[8] Two subsequent phase 3 trials compared gemcitabine plus capecitabine (GemCap) versus gemcitabine alone.[9,10] The Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group study demonstrated that GemCap does not improve the overall survival duration compared with gemcitabine alone. However, subgroup analysis suggested that patients with good PS (Karnofsky score of 90%-100%) had a significant improvement of median overall survival when treated with the combination compared with the good PS patients receiving gemcitabine. A similarly designed trial was conducted in 533 untreated patients in the UK.[10] Preliminary results have demonstrated a statistically significant improvement in overall survival duration (7.4 months vs 6 months; $P = .014$) in patients who received GemCap compared with those who received gemcitabine alone and the final analysis had not been reported at the time of last follow-up. Taken together, these trials demonstrate that when capecitabine is given alone or in combination with gemcitabine it has antitumor activity in pancreatic cancer, especially when delivered to patients with a good PS.

Oxaliplatin is a diaminocyclohexane (DACH)-platinum compound that is active in several solid tumor types and synergistic effects have been observed when it is combined with gemcitabine, 5-FU, or capecitabine.[11–13] Oxaliplatin has been studied in combination with gemcitabine (GemOx) in 2 large randomized trials and, although neither demonstrated a statistically significant survival advantage compared with gemcitabine alone, both showed that GemOx improved progression-free survival.[4,14]

Importantly, the combination of oxaliplatin and capecitabine has been an effective and well-tolerated regimen for metastatic colorectal cancer and there is limited preclinical and clinical experience with these agents that also suggest activity in pancreatic cancer. For example, in a randomized phase 2 trial in untreated patients with advanced pancreatic cancer comparing oxaliplatin alone, 5-FU alone, and 5-FU combined with oxaliplatin, no responses were observed in the single-agent arms but there was a response rate of 11% and a median survival duration of 8.5 months for patients randomized to the combined arm. Second-line treatment with the OXFU regimen was then offered to patients progressing after single-agent treatment. Eighteen of 32 patients treated in the single-agent arms received the OXFU combination in second-line treatment. There was no objective response and 3 patients (17%) had disease stabilization.[15]

These previous results were sufficiently compelling to lead us to conduct a phase 2 study to evaluate the efficacy of oxaliplatin in combination with capecitabine (XELOX) in gemcitabine-pretreated patients with advanced pancreatic cancer.

MATERIALS AND METHODS

Patient Eligibility Criteria

Patients with histologically confirmed locally advanced or metastatic pancreatic cancer (adenocarcinoma or carcinoma) who had received only 1 prior chemotherapy regimen (gemcitabine, gemcitabine-containing regimens, or investigational regimen) were enrolled in the study. Chemotherapy used as a radiation sensitizer or given in an adjuvant or neoadjuvant setting was permitted if it was administered >6 months before study entry. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2 and adequate hepatic, renal, and

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bone marrow function (leukocyte count ≥3000/μL, an absolute neutrophil count 1500/uL, platelet count ≥ 100,000/μL, total bilirubin ≥1.5 times the institutional upper limits of normal [ULN], aspartate/alanine aminotransferase levels ≤2.5 times the institutional ULN, and creatinine ≥1.5 mg/dL). Patients were not eligible for the study if they had previously received oxaliplatin or capecitabine, had gastrointestinal dysfunction that caused moderate to severe (≥grade 2) diarrhea, or were unable to take oral medications. Patients with uncontrolled concurrent illnesses, known brain metastasis, known dihydropyrimidine dehydrogenase (DPD) deficiency, extensive lung fibrosis, peripheral neuropathy (≥grade 1), or receiving therapeutic doses of warfarin for anticoagulation were excluded. The Institutional Review Board approved this study protocol and all patients were required to provide written informed consent.

Treatment and Dose Modifications

Oxaliplatin (Sanofi-Aventis, Collegeville, Penn) was given intravenously on Day 1 as a 120-minute infusion and capecitabine (Roche, Nutley, NJ) was administered orally twice daily for 14 days to patients with previously treated locally advanced or metastatic pancreatic cancer. A cycle of therapy was defined as 21 days. Tumor restaging was performed every 9 weeks. In patients aged <65 years and with an ECOG PS <2, the oxaliplatin dose was 130 mg/m^2 and the capecitabine dose was 1000 mg/m^2 twice daily (total daily dose of 2000 mg/m^2). In patients aged >65 years, or with PS of 2, or having significant comorbidities as determined by the treating physician, the initial oxaliplatin dose was 110 mg/m^2 and the capecitabine starting dose was 750 mg/m^2 twice daily (total daily dose 1500 mg/m^2). These dose adjustments were mandated for safety reasons because patients with progressive disease on frontline therapy may have declining PS or face multiple symptoms, potentially increasing the risk of toxicity with full-dose cytotoxic therapy. Treatment was continued until occurrence of disease progression, unacceptable toxicity, or the patient elected to discontinue study participation.

Dose modifications and treatment delays were based on observed drug-related toxicity. At the start of subsequent cycles of therapy, the oxaliplatin dose was reduced by 25% for neutropenic fever, grade 3-4 hematologic and nonhematologic toxicity, and for grade 2 neurotoxicity. During a cycle of therapy and for subsequent cycles of therapy, the capecitabine dose was reduced by 25% for febrile neutropenia, for grade 3 nonhematologic toxicity, and grade 2 hand–foot syndrome. If a patient experienced laryngopharyngeal dysesthesias, subsequent doses of oxaliplatin were to be administered as 6-hour infusions (instead of the normal 2-hour infusion). For grade 3 or 4 acute hypersensitivity reactions secondary to oxaliplatin, treatment was discontinued. The capecitabine dose was reduced by 50% for grade 4 nonhematologic toxicity or grade 3 hand/foot syndrome. Two dose reductions were allowed for each drug. If a third reduction was required, continuation of treatment was at the discretion of the investigator if it was considered to be in the best interest of the patient.

Evaluation During Study and Response Assessment

Evaluations before and during treatment consisted of a complete medical history and physical examination; assessment of ECOG PS; laboratory studies, including hematologic and biochemical profiles; computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis or other body areas with disease involvement; and chest X-ray. Tumor measurement (CT or MRI) was performed every 3 cycles (9 weeks). Response Evaluation Criteria in Solid Tumors (RECIST) criteria were applied for tumor measurement in patients with measurable disease, although the presence of measurable disease was not an entry criterion. Patients' toxicities were evaluated at each clinic visit before a new cycle of treatment. In addition, patients were asked to document toxicities and concurrent medications in a diary and a research nurse or designee contacted patients at least once a week for assessment of toxicity. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2). Survival duration was measured from the initiation of therapy to death or to the last follow-up assessment.

Statistical Analysis

The primary endpoint of this trial was to determine the overall survival at 6 months. Because at the intiation of the study there was no established survival data for patients who have failed 1 treatment for pancreatic cancer, survival data from a published phase 2 study in a similar clinical setting was used. Based on prior phase 2 trials, patients who failed prior chemotherapy had a 6-month survival rate of 0.3% and a median survival of 3.4 months. This trial was sized to be able to discriminate between a 6-month survival rate of 0.3% and 0.5% and the appropriate sample size was estimated to be 40 patients.

The method of Thall and Simon[16] was used to perform continuous interim monitoring for efficacy. Accrual was not to be suspended for this monitoring; data were analyzed as they accrued. We used the his-

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TABLE 1
Patient Demographics (N=39) (%)

Median age (range), y	62 (45-76)
Sex	
Male	22
Female	17
ECOG PS	
0	4 (14.3)
1	16 (57.1)
2	8 (28.6)
Metastatic pancreatic cancer	37 (95)
Prior pancreaticoduodenectomy or pancreatectomy	16 (41)

ECOG PS indicates Eastern Cooperative Oncology Group performance status.

TABLE 2
Clinically Relevant Nonhematologic Toxicities (N=39)

	Grade, (%)†	
Toxicity*	Grade 2	Grade 3
Abdominal pain	3 (7.7)	1 (2.6)
Anorexia	6 (15)	0
Diarrhea	5 (13)	2 (5)
Fatigue	14 (36)	5 (13)
Nausea	9 (23)	0
Vomiting	7 (18)	1 (2.6)
Hand-foot syndrome	1 (2.6)	1 (2.6)
Sensory neuropathy	1 (2.6)	0

*Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (version 2.0).
†There were no grade 4 events noted.

torical 6-month survival rate of 0.3 as a reference for computing the stopping rule. In this way, we would avoid a high probability of stopping if the true success rate was 0.2. The rule suggested that we will stop the study if at any time during the study we determine there is <1% chance that the surviving proportion with the new treatment is greater than the historical rate. We assumed a uniform prior distribution (ie, beta[1]) for the surviving proportion for the new treatment and this distribution was updated as data accrued. Using this rule, we would stop the study if the surviving proportion ({number surviving}/{number evaluated}) was not greater than 0 of 10, 1 of 17, 2 of 23, 3 of 28, 4 of 33, or 5 of 38. Computer simulations were run to determine the operating characteristics of this rule. The probability of early stopping was 99% for a true surviving proportion of 0.05, 88% for 0.1, 31% for 0.2, and 6% for 0.3.

The principal investigator reviewed survival data each month to determine whether the above parameters for stopping the study had been met. After the first 6 months the patients were followed every 3 months for survival.

RESULTS

Patient Characteristics

A total of 41 patients were enrolled in the study from January 9, 2004 to December 6, 2005. Two patients dropped out before therapy (1 patient was unable to take pills and 1 required warfarin anticoagulation). Among the 39 patients who received treatment and were evaluable for toxicity and survival, 17 were women, 20 patients had an ECOG PS of 0 to 1 (71.4%), and the median age was 62 years (range, 45-76 years). Eighteen of 39 patients initiated chemotherapy at a reduced dose because of age >65 years or PS of 2. Time from the original diagnosis to enrollment in the current study was 36.7 weeks (8.6 months). Sixteen patients had undergone prior pancreaticoduodenectomy or pancreatectomy with recurrence of disease and 3 patients had undergone palliative bypass surgeries. The characteristics of the 39 evaluable patients are presented in Table 1.

Treatment Compliance and Toxicities

A total of 108 cycles were delivered with a median of 3 cycles per patient (range, 1-8 cycles). Twenty-one patients completed 3 cycles of treatment. The most common reason for discontinuation was disease progression (21 patients; 54%) followed by drug-related toxicity (8 patients; 21%). Dose reductions were required in 6 of 39 (15%) patients because of nonhematologic toxicities. Table 2 lists the common nonhematologic treatment-related toxicities.

Efficacy

One of 39 patients (2.6%) had a partial response at initial tumor assessment and 10 patients (26%) had stable disease. Progression-free survival was 9.9 weeks (95% CI, 9.6-14.5 weeks). The median overall survival was 23 weeks (95% CI, 17.0-31.0 weeks) (Fig. 1). The 6-month overall survival was 44% (95% CI, 31%-62%) and the 1-year overall survival was 21% (95% CI, 11%-38%).

Baseline CA 19-9 data were available for all 39 evaluable patients and the median CA 19-9 U/mL level was 727.5 (range, 4-19,012). Univariate regression analysis was performed and there was no correlation noted between baseline CA 19-9 and progression-free survival.

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DISCUSSION

In the majority of patients, pancreatic cancer remains a chemoresistant cancer and doublet combination regimens have produced, at best, marginal results over single-agent gemcitabine. The median survival with best supportive care in patients who have failed gemcitabine therapy is approximately 2 months.[17,18] Approximately half of the patients with gemcitabine-pretreated disease may be candidates for further treatment. Several clinical trials have evaluated the efficacy of salvage chemotherapeutic regimens in gemcitabine-pretreated patients and the survival duration is in the range of 3 to 8 months (Table 3).[19–30]

The present study evaluated the combination of oxaliplatin with capecitabine in patients with advanced pancreatic cancer who had progressed on first-line gemcitabine-based therapy. Treatment was well tolerated and resulted in a median overall survival of 23 weeks with a 6-month survival rate of 44%. A higher-than-usual number of patients (41%) enrolled in this trial had presented initially with localized disease and underwent surgical resection, subsequently developing metastases. Of the 11 patients with a partial response or stable disease, 9 had a PS of 0 to 1, 7 patients had responded to prior gemcitabine, 5 patients had locally advanced pancreatic cancer, 6 patients had prior cisplatin exposure, and 5 patients had undergone a pancreaticoduodenectomy or distal pancreatectomy followed by recurrence of their cancer.

In a recent report, patients from a Cancer and Leukemia Group B (CALGB) trial were followed for their natural history and therapies after gemcitabine failure in advanced pancreatic cancer.[31] Older patients and those with a poorer ECOG PS were less likely to receive postprogression therapy. However, even when considered in total, 28% of the patients died within 4 weeks of developing disease progression on first-line therapy, suggesting that any meaningful improvement in survival with a second-line therapy is important. The study also noted that only 1.4% of the patients received further experimental treatment. This may be a reflection of nihilism among clinicians, but also suggests that there is a need to encourage previously treated patients to enroll in second-line trials.

The clinical factors that may help select patients with advanced pancreatic cancer who will benefit most from second-line therapy are good PS, previous response to first-line therapy (suggesting a chemoresponsiveness trait), and recurrence after their pancreatectomy, especially those with a long disease-free interval (suggesting a better tumor biology).

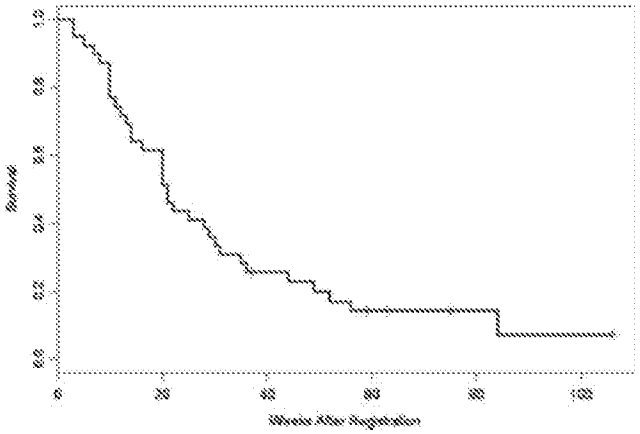


FIGURE 1. Survival curve for all 39 patients evaluable on protocol.

TABLE 3
Selected Trials in Patients With Advanced Pancreatic Cancer Who Were Pretreated With Gemcitabine

Reference	Treatment	Patient No.	PFS, Months	OS, Months
Ulrich-Pur 2003[19]	Irinotecan versus irinotecan plus raltitrexed*	38	4.0	6.5
Milella 2004[20]	5-FU plus celecoxib	17	1.9	3.5
Cantore 2004[21]	Irinotecan plus oxaliplatin	30	4.1	5.9
Jacobs 2004[22]	Rubitecan versus best supportive care	198	1.9	3.6
Androulakis 2005[23]	Oxaliplatin	18	NA	3.9
Tsavaris 2005[24]	5-FU plus leucovorin plus oxaliplatin	30	5.1	5.8
Demols 2006[25]	Gemcitabine plus oxaliplatin	33	4.2	6.0
Reni 2006[26]	Raltitrexed plus oxaliplatin	41	1.8	5.2
Ignatiadis 2006[27]	Docetaxel plus gefitinib	26	2.1	2.9
Boeck 2007[28]	Pemetrexed	52	1.7	4.7
Kulke 2007[29]	Capecitabine plus erlotinib	30	3.4	6.5

PFS indicates progression-free survival; OS, overall survival; 5-FU, 5-fluorouracil; NA, not available.
*The PFS and OS were reported for 19 patients in the combination arm.

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We believe that given the manageable toxicity, XELOX has a role in selected good PS patients with gemcitabine-pretreated advanced pancreatic cancer. We recognize that only with randomized phase 2 and 3 trials stratified for prognostic factors (PS, time to disease progression on first-line therapy, and history of previous surgery) can we define the benefit of second-line chemotherapy. Furthermore, better understanding of validated prediction markers will provide new opportunities to optimize the management of patients with advanced pancreatic cancer.

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Printed by [American Cancer Society Journals - 024.177.117.113 - /doi/pdf/10.1002/cncr.23810] at [18/11/2020]

Hospitalizations and Real-world Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-based Regimen among Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review

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BACKGROUND AND STUDY OBJECTIVE

- Pancreatic cancer is an aggressive and difficult to treat form of cancer. Although pancreatic cancer represents only 3% of new cancer cases, it is projected to be the second leading cause of cancer death by 2030[1]
- The NAPOLI-1 trial showed that, compared to treatment with fluorouracil (5-FU)/leucovorin (LV) alone, treatment with liposomal irinotecan in combination with 5-FU/LV significantly increased median overall survival (OS) and progression-free survival of patients with pancreatic cancer who previously received gemcitabine-based therapy[2]
- Liposomal irinotecan is currently approved in combination with 5-FU/LV for the treatment of patients with mPDAC who have progressed after treatment with gemcitabine
- There is limited real-world data on economic and clinical outcomes associated with liposomal irinotecan
- This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving doublet liposomal irinotecan in a NAPOLI1-based regimen for the management of mPDAC

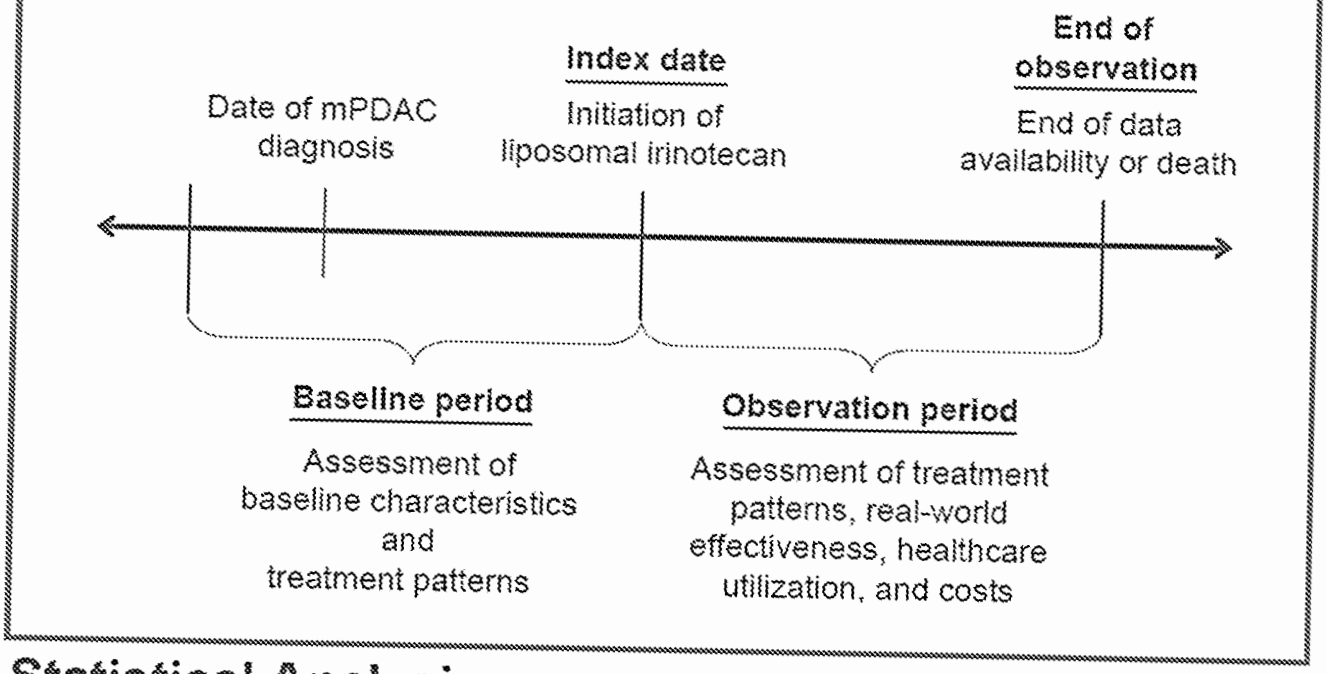
METHODS

Study Design and Population

- This was a non-interventional, retrospective, multi-center chart review study among patients with mPDAC treated with liposomal irinotecan at six academic cancer centers in the US
- Eligible patients were treated with liposomal irinotecan from 2015–2020 and diagnosed with mPDAC

CSPC Exhibit 1100
Page 18 of 333

Figure 1. Study Design Scheme



Statistical Analysis

- Summary statistics were reported using means, standard deviations (SDs), and medians for continuous variables; frequencies and proportions were used for categorical variables
- Duration of liposomal irinotecan treatment and OS were all measured from initiation of liposomal irinotecan and assessed using Kaplan-Meier (KM) analysis
  - These were also stratified by the line of therapy in the metastatic setting that patients received liposomal irinotecan (i.e., first-line [1L], second-line [2L], or third-line or later [3L+])
- Associations between baseline characteristics and OS were assessed using a multivariate Cox proportional hazards model. Covariates were included based on clinical and statistical significance. Hazard ratios (HRs), 95% CIs, and p-values were reported
- Hospitalizations and granulocyte colony stimulating factor (GCSF) administrations during liposomal irinotecan treatment were described using event rates. Hospitalization costs from a payer perspective were imputed by applying unit cost inputs from the literature to the frequency of hospitalization encounters, then dividing by duration of liposomal irinotecan treatment. A similar approach was used to estimate GCSF costs

RESULTS

Baseline Characteristics

- 325 patients met the study eligibility criteria. Overall, mean age at index date was 68 years, 51% were female, and the majority were White (70%) (Table 1)
- 9% had ECOG of 0, 57% had ECOG of 1, and 23% had ECOG 2 or greater (Table 1)

Table 1. Baseline Demographic and Clinical Characteristics

	N = 325
Age (years) at index date, mean ± SD [median]	67.7 ± 9.6 [68.5]
Female, n (%)	167 (51.4)
Race/Ethnicity, n (%)	
White	228 (70.2)
Black/African-American	43 (13.2)
Asian/Pacific Islander	23 (7.1)
Hispanic/Latino	13 (4.0)
Native American/American Indian	1 (0.3)
Unknown	17 (5.2)
Index date, n (%)	
2015	1 (0.3)
2016	57 (17.5)
2017	75 (23.1)
2018	107 (32.9)
2019	81 (24.9)
2020	4 (1.2)
Cancer stage at initial diagnosis of pancreatic adenocarcinoma, n (%)	
I A	4 (1.2)
I B	6 (1.8)
II A	18 (5.5)
II B	46 (14.2)
III	61 (18.8)
IV	162 (49.8)
Unknown	28 (8.6)
ECOG performance score, n (%)	
0	30 (9.2)
1	184 (56.6)
2	65 (20.0)
3	8 (2.5)
4	2 (0.6)
Unknown	36 (11.1)

[1] Sum of proportions may exceed 100% as multiple responses were allowed.

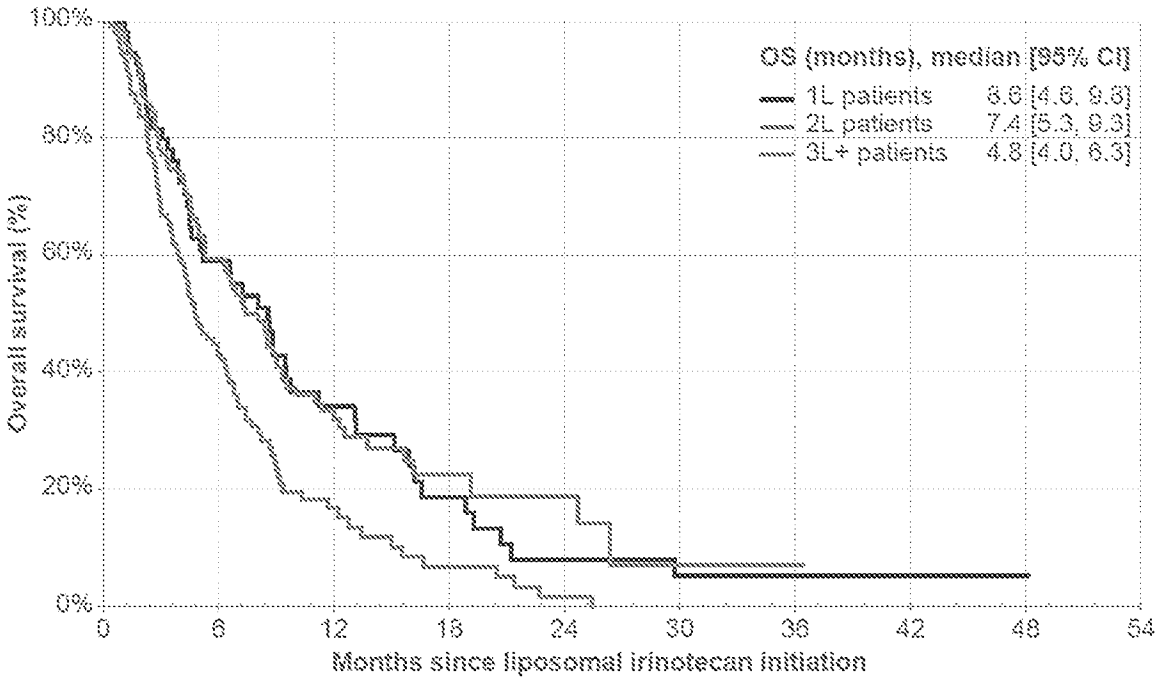
Liposomal Irinotecan Treatment Characteristics

- All patients received liposomal irinotecan with 5-FU, and 75% also received LV
- Patients were treated with liposomal irinotecan in 1L (17%), 2L (43%), or 3L+ (40%) in the metastatic setting (Table 2)
- Median duration of liposomal irinotecan treatment was 3.4, 2.1, and 1.4 months for 1L, 2L, and 3L+ patients, respectively (Table 2)

Table 2. Liposomal Irinotecan Treatment

	N = 325
Liposomal irinotecan line of therapy, n (%)	
1L	56 (17.2)
2L	138 (42.5)
3L+	131 (40.3)
Duration of liposomal irinotecan treatment (months), median [95% CI]	
All patients	1.7 [1.5, 2.1]
1L	3.4 [1.4, 6.1]
2L	2.1 [1.6, 2.8]
3L+	1.4 [1.3, 1.7]

Figure 2: Kaplan-Meier Analysis of Overall Survival by Line of Therapy



Associations between Baseline Characteristics and OS

- Patients treated with liposomal irinotecan in 2L versus 3L+ had significantly lower risk of death (Table 3)
- Patients with liver or brain metastatic sites or congestive heart failure had significantly higher risk of death (Table 3)

Table 3. Associations between Baseline Characteristics and OS

	OS N = 325		
	HR	95% CI	p-value[1]
Age at index date	1.00	(0.98, 1.01)	0.864
Male (ref: female)	1.15	(0.87, 1.51)	0.331
Time from mPDAC diagnosis to liposomal irinotecan initiation (months)	0.98	(0.96, 1.00)	0.033*
Race/Ethnicity (ref: white)			
Black/African-American	1.27	(0.76, 2.13)	0.360
Hispanic/Latino	0.98	(0.48, 2.03)	0.962
Other	0.75	(0.42, 1.34)	0.330
Unknown	0.77	(0.43, 1.40)	0.399
Geographic Location (ref: northeast)			
Midwest	0.77	(0.45, 1.32)	0.344
South	0.58	(0.36, 0.93)	0.025*
West	0.48	(0.30, 0.76)	0.002*
Cancer stage at first diagnosis of pancreatic adenocarcinoma (ref: metastatic)			
Non-metastatic	0.83	(0.59, 1.17)	0.278
Unknown	0.72	(0.39, 1.34)	0.297
Line of therapy for liposomal irinotecan (ref: 2)			
1	0.88	(0.54, 1.43)	0.599
3+	1.84	(1.31, 2.60)	<0.001*
Metastatic sites			
Liver	1.65	(1.21, 2.25)	0.002*
Brain	6.24	(1.71, 22.73)	0.005*
Number of metastatic sites (ref: 1)			
2	1.13	(0.75, 1.70)	0.555
3+	1.08	(0.64, 1.84)	0.771

ECOG performance score (ref: < 2)			
≥ 2	1.06	(0.75, 1.49)	0.747
Unknown	1.21	(0.79, 1.85)	0.378
Selected comorbidities			
Congestive heart failure	3.47	(1.66, 7.26)	<0.001*

[1] P-values less than 0.05 were marked with *.

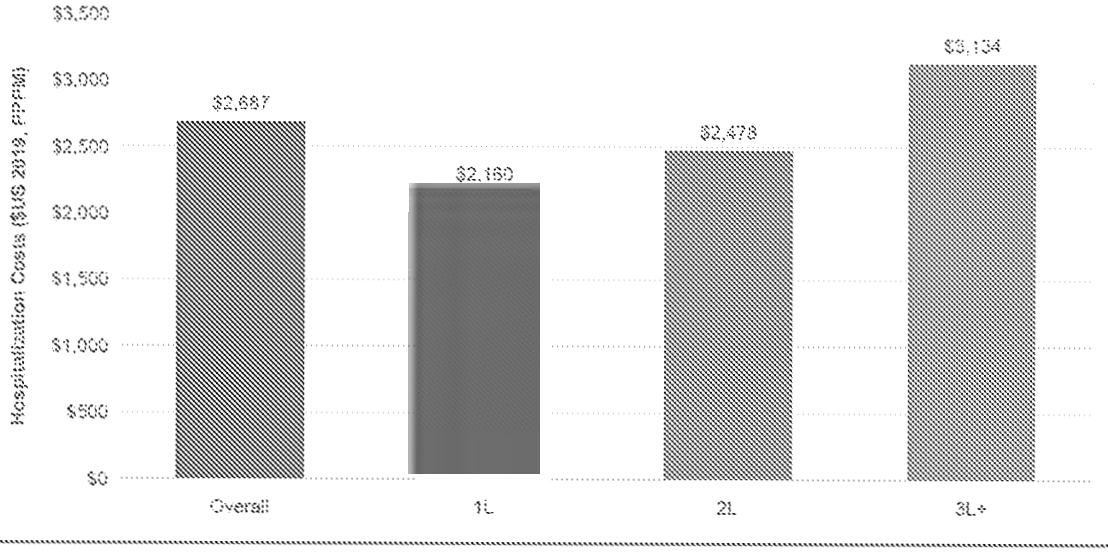
Hospitalizations and GCSF administrations

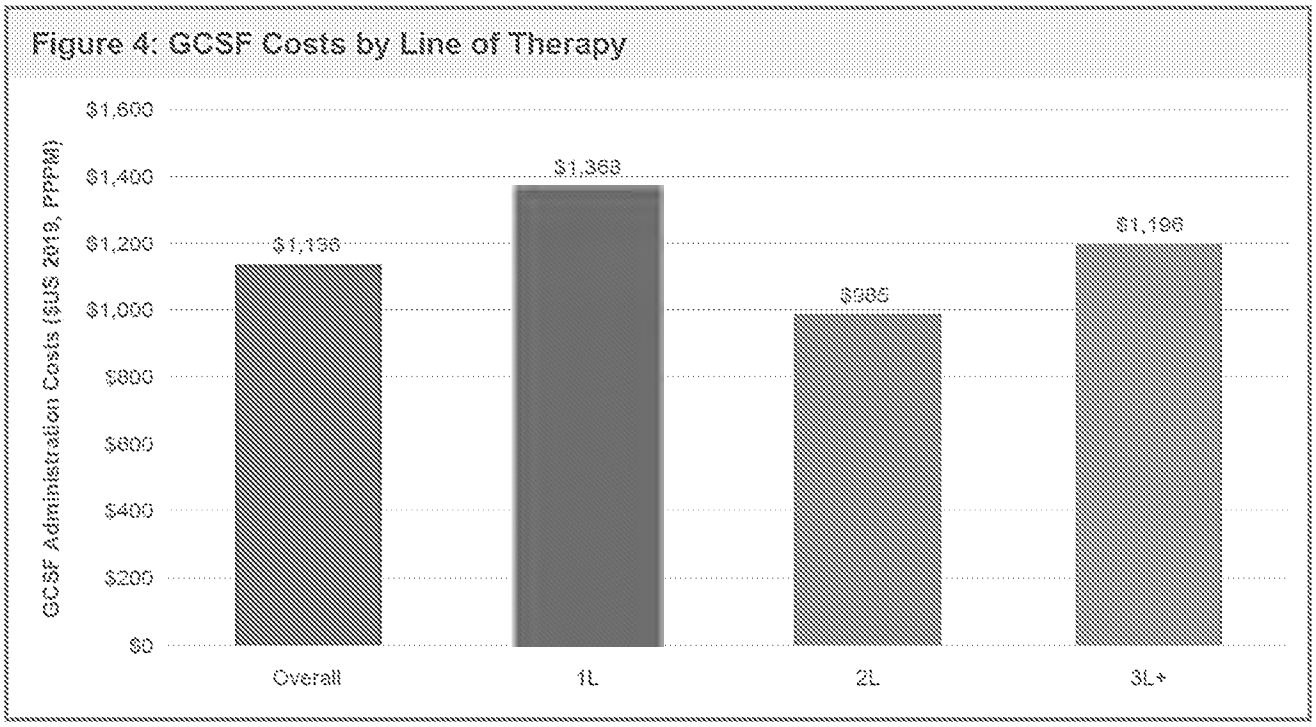
- Mean hospitalizations (corresponding costs) per-patient-per-month (PPPM) were 0.2 ($2,160), 0.2 ($2,478), and 0.2 ($3,134), for 1L, 2L, and 3L+, respectively

Table 4: Hospitalizations, GCSF administrations, and Costs by Line of Therapy

	1L N = 56	2L N = 139	3L+ N = 131
Hospitalizations			
Patients with at least one visit, n (%)	18 (32.1)	32 (23.2)	30 (22.9)
Visits, PPPM, mean ± SD [median]	0.2 ± 0.7 [0.0]	0.2 ± 0.4 [0.0]	0.2 ± 0.5 [0.0]
Length of stay (days), per visit	5.4 ± 4.3 [4.0]	5.9 ± 4.9 [4.0]	5.9 ± 4.6 [5.0]
GCSF administrations			
Patients with at least one administration, n (%)	14 (25.0)	29 (21.0)	28 (21.4)
Administrations, PPPM, mean ± SD [median]	0.4 ± 1.0 [0.0]	0.2 ± 0.4 [0.0]	0.2 ± 0.5 [0.0]
Pegfilgrastim	0.2 ± 0.5 [0.0]	0.2 ± 0.4 [0.0]	0.2 ± 0.5 [0.0]
Filgrastim	0.1 ± 0.5 [0.0]	0.0 ± 0.1 [0.0]	0.0 ± 0.0 [0.0]
Filgrastim-sndz	0.0 ± 0.0 [0.0]	0.0 ± 0.0 [0.0]	0.0 ± 0.0 [0.0]
Tbo-filgrastim	0.1 ± 0.6 [0.0]	0.0 ± 0.1 [0.0]	0.0 ± 0.1 [0.0]
Healthcare costs, mean ± SD [median]			
Hospitalizations, $US 2019, PPPM	$2,160 ± 4,628 [$0]	$2,478 ± 7,014 [$0]	$3,134 ± 11,112 [$0]
GCSF administration costs, $US 2019, PPPM	$1,368 ± 3,383 [$0]	$985 ± 2,574 [$0]	$1,196 ± 3,148 [$0]

Figure 3: Hospitalization Costs by Line of Therapy





Limitations

- Results reported in this study are based on data collected at academic cancer centers and may not be generalizable to patients with mPDAC treated in other settings
- Patients may have healthcare encounters at other institutions, so data collected from the sites in this study may not be entirely complete. Missing data may bias study results if the missing-ness is not completely random
- Due to the non-randomized, retrospective nature of the study, residual confounding may impact the associations and conclusions identified
- Hospitalizations costs were estimated based on the number of hospitalizations that occurred during liposomal irinotecan treatment multiplied by the unit cost of a hospitalization for an mPDAC patient, and did not take into account any treatment-related costs that may have been incurred during the hospitalizations

Conclusions

- This real-world study suggests patients treated with liposomal irinotecan were older and had a higher proportion with ECOG ≥2 as well as lines of therapy ≥2 compared to the pivotal trial
- Additionally, patients were treated with liposomal irinotecan in 3L+, a setting with no currently approved options, and demonstrated reasonable benefit
- In descriptive and adjusted analyses, patients treated with liposomal irinotecan in earlier versus later lines of therapy had increased OS benefit
- Hospitalization costs were slightly higher among patients treated with liposomal irinotecan in 3L+ compared to earlier lines

References

1. Rahib L et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Research.* 2014;74(11):2913–21. doi: 10.1158/0008-5472.
2. Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet.* 2016;387(10018):545–57. doi: 10.1016/s0140-6736(15)00986-1.

Disclosures

PC is an employee of Ipsen Biopharmaceuticals, Inc. (Ipsen), the sponsor of this study. RB, MD, CN, and MSD are employees of Analysis Group, Inc., a consulting company that has received funding for this and other studies from Ipsen. KHY, AH, OBA, AD, MA, EB, GK, and NB are employees of institutions that have received research funding from Ipsen.

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Presented at the AMCP Nexus 2020 Virtual Congress | Oct 19–23, 2020
This study was sponsored by Ipsen

Hospitalizations and Real-world Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-based Regimen among Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review

BACKGROUND AND STUDY OBJECTIVE

METHODS

RESULTS

LIMITATIONS

CONCLUSIONS

were described including the line of therapy, treatment duration, and sequencing. Kaplan-Meier estimates were used to evaluate real world overall survival (RW OS) and time to next treatment (TTNT).

RESULTS: 726 patients met the inclusion criteria and were included in this analysis. Mean age was 66 years, 74% were white, and 76% were male. Mean follow-up time from LOT1 was 9.6 months (SD=9 mo). The median time from locoregional treatment to LOT1 initiation was 5.5 months, and the median TTNT from LOT1 initiation was 5.8 months for the overall population. The most common LOT1 regimens were nivolumab (18.7%), pembrolizumab (16.8%), carboplatin+paclitaxel (12.8%), and cetuximab (10.2%). 41% of patients advanced to LOT2, and the most common regimens were pembrolizumab (29.9%) and nivolumab (28. 5%). 23.2% of patients had LOT3 regimens documented in iKM. The unadjusted median RW OS from start of LOT1 was 13.0 months (95% CI: 11.1-15.1 mo).

CONCLUSIONS: This study provides information on the evolving therapy landscape in R/M HNSCC. Pembrolizumab-based regimens were approved in the U.S. and Europe for use in the first-line setting in 2019, and there are multiple ongoing clinical trials assessing novel regimens as there remains an unmet need for this indication. Further planned analyses will establish the real world clinical and safety outcomes associated with current treatment regimens and explore the clinical burden for this population.

SPONSORSHIP: GSK study 207139.

C3 Hospitalizations and real-world clinical outcomes of liposomal irinotecan in a NAPOLI1-based regimen among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): a multi-center chart review

Yu K[1], Hendifar A[2], Alese O[3], Draper A[3], Abdelrahim M[4], Burns E[4], Khan G[5], Cockrum P[6], Bhak R[7], Nguyen C[7], DerSarkissian M[7], Duh M[7], Bahary N[8]; yuk1@mskcc.org

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BACKGROUND: The NAPOLI1 trial demonstrated that liposomal irinotecan in combination with fluorouracil (5-FU) and leucovorin (LV) prolonged survival with a manageable safety profile in patients with mPDAC previously treated with gemcitabine-based therapy. There is limited real-world (rw) data on economic and clinical outcomes associated with liposomal irinotecan in NAPOLI1-based regimens.

OBJECTIVE: This retrospective multi-center chart review study evaluated rate of hospitalizations and related costs along with clinical outcomes in mPDAC patients in the United States who received NAPOLI1-based regimens.

METHODS: Eligible patients had mPDAC treated with liposomal irinotecan in a NAPOLI1-based doublet regimen (treatment initiation defined index date) at six academic cancer centers. Hospitalizations were assessed per-patient-per-month (PPPM) during liposomal irinotecan treatment (i.e., within line of therapy during which liposomal irinotecan was received), based on data available at the centers. Hospitalization costs from a payer perspective were imputed by applying unit cost inputs from literature to the frequency of hospitalization encounters. Kaplan-Meier methodology was used to assess median rw overall survival (rwOS). Initial results are presented here.

RESULTS: Of the 325 patients included in this analysis, median age was 68 years, 51% were female, ECOG status 0 (9%), 1 (54%) and ≥2 (22%). Patients received liposomal irinotecan in first-line (1L; 17%), 2L (43%), and 3L+ (40%), in a NAPOLI1-based regimen with 5-FU, with 75% also receiving LV. Median treatment duration was 3.4, 2.1, and 1.4 months, for 1L, 2L, and 3L+, respectively. Mean±standard deviation (SD) hospitalizations (corresponding costs) PPPM during line of liposomal irinotecan treatment were 0.2±0.7 ($2,160±4,628), 0.2±0.4 ($2,478±7,014), and 0.2±0.5 ($3,134±11,112), for 1L, 2L, and 3L+, respectively. Median (95% confidence interval [CI:]) rwOS in months was 8.6 (4.6, 9.8), 7.4 (5.3, 9.3), and 4.8 (4.0, 6.3), for 1L, 2L, and 3L+, respectively.

CONCLUSIONS: Patients treated with NAPOLI1-based liposomal irinotecan doublet regimens in academic centers are older with poorer prognosis based on ECOG scores compared to participants in the trial, though rw effectiveness was comparable. Liposomal irinotecan was also used in 3L+ settings, providing benefit in rw where no treatment has been approved. Hospitalization costs were slightly higher among patients treated with liposomal irinotecan in 3L+ compared to earlier lines.

SPONSORSHIP: Ipsen Biopharmaceuticals.

C4 Comorbidities and economic burden of patients diagnosed with hepatocellular carcinoma treated with systemic therapy in the United States

Aly A[1], Lingohr-Smith M[2], Lin J[2], Seal B[1]; abdalla.aly@astrazeneca.com

[1]AstraZeneca Pharmaceuticals; [2]Novosys Health

BACKGROUND: Many patients with hepatocellular carcinoma (HCC) have advanced disease either at diagnosis or following progression from earlier stages.

OBJECTIVE: The objectives of this study were to examine patient comorbidities and healthcare costs of patients with HCC who initiated first line of systemic therapy (LOT1).

METHODS: Adult patients with HCC who initiated systemic therapy (index date) were identified from the MarketScan Commercial and Medicare Supplemental databases (July 1, 2013-May 31, 2018). Patients were required to have ≥6 months of continuous insurance enrollment before the index date (baseline) and ≥1 month after the index date (follow-up). Patient comorbidities and prior transarterial procedures (including, embolization [TAE], chemoembolization [TACE] and radioembolization [TARE]) were examined. Additionally, all-cause and HCC-related healthcare costs (total and patient out-of-pocket [OOP] payments per patient per month [PPPM]) during the follow-up period were estimated.

RESULTS: Of the 744 HCC patients who initiated systemic therapy (median age: 63 years, male: 78%), 92% received sorafenib in LOT1, 5% bevacizumab, and 3% immune checkpoint inhibitors (ICI). Among the study population, the most prevalent hepatic comorbidities were cirrhosis (62%), chronic HCV infection (40%), and portal hypertension (24%). Prevalent non-hepatic comorbidities included those which were cardiovascular (hypertension: 64% and congestive heart failure: 8%) and diabetes (38%). Additionally, 22% had esophageal varices

CSPC Exhibit 1100
Page 27 of 333

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Supplement ◇ Volume 26 ◇ Number 10-a ◇ October 2020

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CSPC Exhibit 1100
Page 28 of 333

A US Multicenter Chart Review Study Of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan After Gemcitabine-based Therapy

Kenneth H. Yu, MD[1]; Andrew Hendifar, MD[2]; Olatunji B. Alese, MD[3]; Amber Draper, PharmD[3]; Maen Abdelrahim, MD[4]; Ethan Burns, MD[4]; Gazala Khan, MD[5]; Paul Cockrum, PharmD, RPh[6]; Rachel Bhak, MS[7]; Maral DerSarkissian, PhD[8]; Catherine Nguyen, MPH[7]; Mei Sheng Duh, MPH, ScD[7]; Nathan Bahary, MD, PhD[8]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Emory Winship Cancer Institute, Atlanta, GA; [4]Houston Methodist Cancer Center, Houston, TX; [5]Henry Ford Cancer Institute, Detroit, MI; [6]Ipsen Biopharmaceuticals, Inc., Cambridge, MA; [7]Analysis Group, Inc., Boston, MA; [8]University of Pittsburgh Medical Center, Pittsburgh, PA

BACKGROUND AND STUDY OBJECTIVE

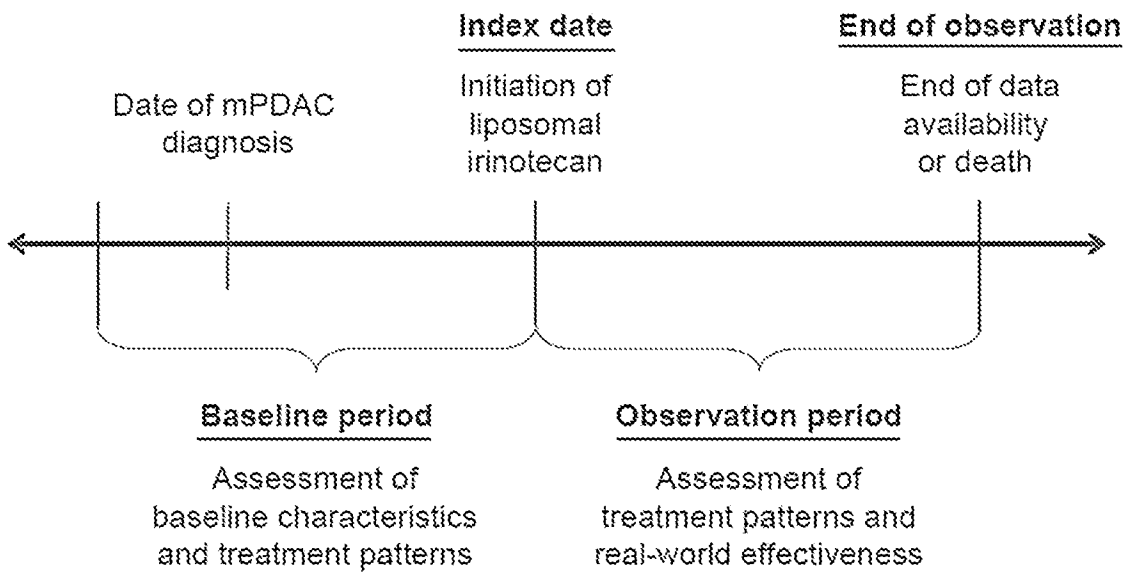
- Pancreatic cancer is an aggressive and difficult to treat form of cancer. Although pancreatic cancer represents only 3% of new cancer cases, it is projected to be the second leading cause of cancer death by 2030[1]
- The NAPOLI-1 trial showed that, compared to treatment with fluorouracil (5-FU)/leucovorin (LV) alone, treatment with liposomal irinotecan in combination with 5-FU/LV significantly increased median overall survival (OS) and median progression-free survival of patients with pancreatic cancer[2] Liposomal irinotecan is currently approved in combination with 5-FU/LV for the treatment of patients with mPDAC who have progressed after treatment with gemcitabine
- Real-world data allows healthcare decision-makers to assess and manage therapeutic and economic options for patients, including those who would and would not have met eligibility criteria for randomized control trials (RCT) and are instead managed under usual care
- This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving doublet liposomal irinotecan in a NAPOLI1-based regimen for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC)

CSPC Exhibit 1100
Page 29 of 333

Study Design and Population

- This was a non-interventional, retrospective, multi-center chart review study among patients with mPDAC treated with liposomal irinotecan at six academic cancer centers in the US
- Eligible patients were treated with liposomal irinotecan from 2015–2020 and diagnosed with mPDAC

Figure 1. Study Design Scheme



Statistical Analysis

- Summary statistics were reported using means, standard deviations (SDs), and medians for continuous variables; frequencies and proportions were used for categorical variables
- Duration of liposomal irinotecan treatment and OS were both measured from initiation of liposomal irinotecan and assessed using Kaplan-Meier (KM) analysis
  - These were also stratified by the line of therapy in the metastatic setting that patients received liposomal irinotecan (i.e., first-line [1L], second-line [2L], or third-line or later [3L+])

- Associations between baseline characteristics and OS were assessed using a multivariate Cox proportional hazards model. Covariates were included based on clinical and statistical significance. Hazard ratios (HRs), 95% CIs, and p-values were reported

RESULTS

Baseline Characteristics

- 325 patients met the study eligibility criteria. Overall, mean age at index date was 68 years, 51% were female, and the majority were White (70%) (Table 1)
- 9% had ECOG of 0, 57% had ECOG of 1, and 23% had ECOG 2 or greater (Table 1)
- Among 230 patients with genetic mutation information available, common genetic mutations included *KRAS* (26%), *TP53* (20%), and *CDKN2A* (9%)

Table 1. Baseline Demographic and Clinical Characteristics

	N = 325
Age (years) at index date, mean ± SD [median]	67.7 ± 9.6 [68.5]
Female, n (%)	167 (51.4)
Race/Ethnicity, n (%)	
White	228 (70.2)
Black/African-American	43 (13.2)
Asian/Pacific Islander	23 (7.1)
Hispanic/Latino	13 (4.0)
Native American/American Indian	1 (0.3)
Unknown	17 (5.2)
Year of Index, n (%)	
2015	1 (0.3)
2016	57 (17.5)
2017	75 (23.1)
2018	107 (32.9)
2019	81 (24.9)
2020	4 (1.2)

Cancer stage at first diagnosis of pancreatic adenocarcinoma: n (%)	
I A	4 (1.2)
I B	6 (1.8)
II A	18 (5.5)
II B	46 (14.2)
III	61 (18.8)
IV	162 (49.8)
Unknown	28 (8.6)
ECOG performance score, n (%)	
0	30 (9.2)
1	184 (56.6)
2	65 (20.0)
3	8 (2.5)
4	2 (0.6)
Unknown	36 (11.1)

[1] Sum of proportions may exceed 100% as multiple responses were allowed.

Treatment Patterns Prior to Liposomal Irinotecan

- Non-metastatic treatment
  - Among 159 patients that had non-metastatic disease at first diagnosis of pancreatic adenocarcinoma, 30% received neoadjuvant therapy, 58% had surgery (e.g., Whipple procedure, stent placement), and 32% received adjuvant therapy in the non-metastatic setting
- Metastatic treatments prior to index liposomal irinotecan
  - 78% patients had a treatment regimen including gemcitabine, and 30% had a treatment regimen including 5-FU
  - Common treatments received for metastatic disease included gemcitabine + nab-paclitaxel (59%) and 5-FU/LV + irinotecan + oxaliplatin [FOLFIRINOX] (15%)
  - Prior to liposomal irinotecan, 22% of patients were treated with any irinotecan

Liposomal Irinotecan Treatment Characteristics

- All patients received liposomal irinotecan with 5-FU, and 75% also received LV
- Patients were treated with liposomal irinotecan in 1L (17%), 2L (43%), or 3L+ (40%) in the metastatic setting (Table 2)

- Median duration of liposomal irinotecan treatment was 3.4, 2.1, and 1.4 months for 1L, 2L, and 3L+ patients, respectively (Table 2)
- 50% of patients had a starting liposomal irinotecan dose of 70 mg/m^2

Table 2. Liposomal Irinotecan Treatment

	N = 325
Liposomal irinotecan line of therapy, n (%)	
1L	56 (17.2)
2L	138 (42.5)
3L+	131 (40.3)
Duration of liposomal irinotecan treatment (months), median [95% CI]	
All patients	1.7 [1.5, 2.1]
1L	3.4 [1.4, 6.1]
2L	2.1 [1.6, 2.8]
3L+	1.4 [1.3, 1.7]

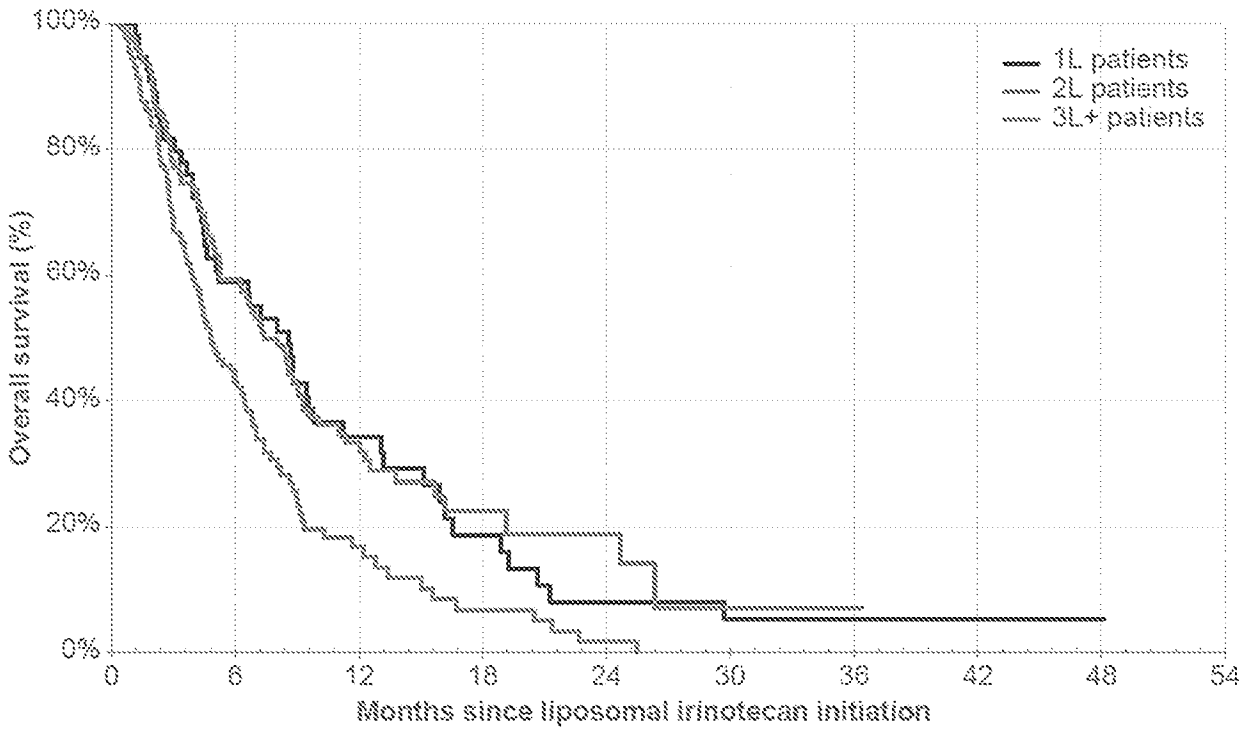
Real-World Effectiveness of Liposomal Irinotecan

- Median OS was 8.6, 7.4, and 4.8 months for 1L, 2L, 3L+ patients, respectively (Table 3 & Figure 2)
- Results presented here are based on updated analyses as compared to the abstract

Table 3. Real-World Effectiveness of Liposomal Irinotecan

	N = 325
OS	
Deaths, n (%)	228 (70.2)
OS (months), median [95% CI]	
1L	8.6 [4.6, 9.8]
2L	7.4 [5.3, 9.3]
3L+	4.8 [4.0, 6.3]

Figure 2: Kaplan-Meier Analysis of Overall Survival by Line of Therapy



Associations between Baseline Characteristics and OS

- Patients treated with liposomal irinotecan in 3L+ versus 2L had significantly higher HR for OS (Table 4)
- Patients with liver or brain metastatic sites or congestive heart failure had significantly higher HR for OS (Table 4)

Table 4. Associations between Baseline Characteristics and OS

	OS N = 328		
	HR	95% CI	p-value[1]
Age at index date	1.00	(0.98, 1.01)	0.864
Male (ref: female)	1.15	(0.87, 1.51)	0.331
Time from mPDAC diagnosis to liposomal irinotecan initiation (months)	0.98	(0.96, 1.00)	0.033*
Race/ethnicity (ref: White)			
Black/African-American	1.27	(0.76, 2.13)	0.360
Hispanic/Latino	0.98	(0.48, 2.03)	0.962
Other[5]	0.75	(0.42, 1.34)	0.330
Unknown	0.77	(0.43, 1.40)	0.399
Geographic region (ref: Northeast)			
Midwest	0.77	(0.45, 1.32)	0.344
South	0.58	(0.36, 0.93)	0.025*
West	0.48	(0.30, 0.76)	0.002*
Stage at initial diagnosis of metastatic disease (ref: metastatic)			
Non-metastatic	0.83	(0.59, 1.17)	0.278
Unknown	0.72	(0.39, 1.34)	0.297

Line of therapy at time of metastatic diagnosis (ref: 1)			
1	0.88	(0.54, 1.43)	0.599
3+	1.84	(1.31, 2.60)	<0.001*
Metastatic sites			
Liver	1.65	(1.21, 2.25)	0.002*
Brain	6.24	(1.71, 22.73)	0.005*
Number of metastatic sites (ref: 1)			
2	1.13	(0.75, 1.70)	0.555
3+	1.08	(0.64, 1.84)	0.771
ECOG performance status (ref: 0,1)			
≥ 2	1.06	(0.75, 1.49)	0.747
Unknown	1.21	(0.79, 1.85)	0.378
Select baseline comorbidities			
Congestive heart failure	3.47	(1.66, 7.26)	<0.001*

[1] P-values less than 0.05 were marked with *.

LIMITATIONS

- Results reported in this study are based on data collected at academic cancer centers and may not be generalizable to patients with mPDAC treated in other settings
- Patients may have healthcare encounters at other institutions, so data collected from the sites in this study may not be entirely complete. Missing data may bias study results if the missingness is not completely random
- Due to the non-randomized, retrospective nature of the study, residual confounding may impact the associations and conclusions identified

CONCLUSIONS

- Real-world data from this study suggest patients were older and had a higher proportion with ECOG, as well as lines of therapy, ≥2 compared to the pivotal trial
- Patients were treated with liposomal irinotecan in 3L+, a setting with no currently approved options, and demonstrated reasonable benefit
- In descriptive and adjusted analyses, patients treated with liposomal irinotecan in earlier versus later lines of therapy had increased survival benefit

References

1. Rahib L et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Research*. 2014;74(11):2913-21. doi: 10.1158/0008-5472.
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Presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) All Access | 16–17 September 2020

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A US Multicenter Chart Review Study Of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan After Gemcitabine-based Therapy

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BACKGROUND AND STUDY OBJECTIVE

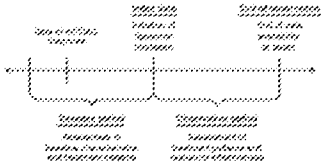
- Pancreatic cancer is an aggressive and difficult-to-treat form of cancer. Although pancreatic cancer represents only 3% of new cancer cases, it is projected to be the second leading cause of cancer-related death by 2030[1]
- The NAPOLI-1 trial showed that, compared to treatment with fluorouracil (5-FU)+leucovorin (LV) alone, treatment with liposomal irinotecan in combination with 5-FU/LV significantly increased median overall survival (OS) and median progression-free survival in patients with pancreatic cancer. Liposomal irinotecan is currently approved in combination with 5-FU/LV for the treatment of patients with mPDAC whose progressed after treatment with gemcitabine[2]
- Real-world data sheds light on how doctors make decisions in assess and manage therapeutic and economic options for patients, including those who would and would not have met eligibility criteria for randomized control trials (RCT) and are treated most typical under usual care
- This retrospective multi-academic center chart review study describes outcomes, characteristics and outcomes of US patients receiving second-line liposomal irinotecan in a NAPOLI-1-based regimen for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC)

METHODS

Study Design and Population

- This was a non-interventional, retrospective, multi-center chart review study among patients with mPDAC treated with liposomal irinotecan at six academic cancer centers in the US
- Eligible patients were treated with liposomal irinotecan from 2015–2020 and diagnosed with mPDAC

Figure 1. Study Design Schema



Statistical Analysis

- Summary statistics were reported using means, standard deviations (SDs), and medians for continuous variables; frequencies and proportions were used for categorical variables
- Factors of liposomal irinotecan treatment and OS were both measured from initiation of liposomal irinotecan and assessed using Kaplan-Meier (KM) analysis
  - These were also stratified by the line of therapy in the metastatic setting that patients received liposomal irinotecan (i.e., first-line [1L], second-line [2L], or third-line or later [3L+])
- Associations between baseline characteristics and OS were assessed using a multivariable Cox proportional hazards model. Covariates were included based on clinical and statistical significance. Hazard ratios (HRs), 95% CIs, and p-values were reported

RESULTS

Baseline Characteristics

- 108 patients met the study eligibility criteria. Overall, mean age at index date was 62 years. 51% were female, and the majority were White (72%) (Table 1)
- 9% had ECOG of 0, 57% had ECOG of 1, and 33% had ECOG 2+ or greater (Table 1)
- Among 330 patients with genetic mutation information available, common genetic mutations included KRAS (94%), TP53 (59%), and CDKN2A (9%)

Table 1. Baseline Demographic and Clinical Characteristics

	Overall
Age (years) at index date, mean ± SD [median]	62.3 ± 9.4 [62.0]
Female, n (%)	58 (53.7)
White	78 (72.2)
Black/African American	15 (13.9)
Asian/Pacific Islander	10 (9.3)
Hispanic/Latino	1 (0.9)
Native American/Alaskan Native	1 (0.9)
Unknown	3 (2.8)
2015	1 (0.9)
2016	6 (5.6)
2017	15 (13.9)
2018	32 (29.6)
2019	41 (38.0)
2020	13 (12.0)
1L	4 (3.7)
2L	6 (5.6)
3L	39 (36.1)
4L	45 (41.7)
5L	11 (10.2)
6L+	3 (2.8)
Unknown	1 (0.9)
0	10 (9.3)
1	62 (57.4)
2	18 (16.7)
3	7 (6.5)
4	2 (1.9)
Unknown	9 (8.3)

1L = first-line; 2L = second-line; 3L = third-line; 4L = fourth-line; 5L = fifth-line; 6L+ = sixth-line or later; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation.

Treatment Patterns Prior to Liposomal Irinotecan

- Non-metastatic setting:
  - Among 108 patients who had non-metastatic disease at the diagnosis of pancreatic adenocarcinoma, 30% received neoadjuvant therapy, 58% had surgery (e.g., Whipple procedure, distal pancreatectomy), and 22% received adjuvant therapy in the non-metastatic setting
- Metastatic treatments prior to initial liposomal irinotecan:
  - 79% patients had a treatment regimen including gemcitabine, and 63% had a treatment regimen including 5-FU
  - Common treatments received for metastatic disease included gemcitabine + nab-paclitaxel (34%) and 5-FU/LV + irinotecan + oxaliplatin (FOLFIRINOX) (24%)
  - Prior to liposomal irinotecan, 63% of patients were treated with any combination

Liposomal Irinotecan Treatment Characteristics

- All patients received liposomal irinotecan with 5-FU, and 75% also received LV
- Patients were treated with liposomal irinotecan in 1L (27%), 2L (53%), or 3L+ (20%) in the metastatic setting (Table 2)
- Median duration of liposomal irinotecan treatment was 3.4, 2.1, and 1.3 months for 1L, 2L, and 3L+ patients, respectively (Table 2)
- 90% of patients had a starting liposomal irinotecan dose of 70 mg/m²

Table 2. Liposomal Irinotecan Treatment

	Overall
1L	29 (27%)
2L	58 (53%)
3L+	22 (20%)
70 mg/m²	97 (90%)
1L	29 (100%)
2L	52 (90%)
3L+	16 (73%)

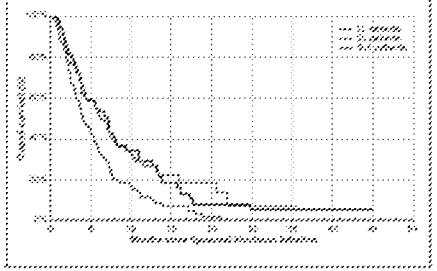
Real-World Effectiveness of Liposomal Irinotecan

- Median OS was 9.9, 7.4, and 4.2 months for 1L, 2L, 3L+ patients, respectively (Table 3 & Figure 2)
- Results presented here are based on updated analysis as compared to the abstract

Table 3. Real-World Effectiveness of Liposomal Irinotecan

	Overall
Deaths, n (%)	108 (100%)
OS (months), median (95% CI)	
1L	9.9 (6.4, NR)
2L	7.4 (5.3, 9.9)
3L+	4.2 (3.0, 5.6)

Figure 2. Kaplan-Meier Analysis of Overall Survival by Line of Therapy



Associations between Baseline Characteristics and OS

- Patients treated with liposomal irinotecan in 1L+ versus 2L had significantly higher HR for OS (Table 4)
- Patients who had a dose reduction, dose interruption had significantly higher HR for OS (Table 4)

Table 4. Associations between Baseline Characteristics and OS

	HR	95% CI	p-value
Age at index date	1.00	0.98, 1.03	0.844
Male (ref: female)	1.15	0.82, 1.60	0.424
Time from initial diagnosis to liposomal irinotecan initiation (months)	0.99	0.96, 1.02	0.527
Race (ref: White)			
Black/African American	1.07	0.70, 1.63	0.760
Asian/Pacific Islander	0.68	0.33, 1.40	0.293
Other	1.15	0.45, 2.94	0.769
Unknown	0.77	0.40, 1.48	0.428
Ethnicity			
Hispanic	0.77	0.45, 1.33	0.349
Other	0.92	0.58, 1.46	0.727
Unknown	0.82	0.54, 1.25	0.358
Smoking status			
Former/Current	1.42	0.99, 2.03	0.059
Unknown	0.72	0.49, 1.04	0.080
1	0.46	0.34, 0.63	<0.001
2+	1.00	0.72, 1.39	0.997
ECOG			
1	1.06	0.75, 1.50	0.742
2+	1.64	1.03, 2.61	0.037
Dose reduction			
Yes	2.04	1.31, 3.18	0.002
Dose interruption			
Yes	1.73	1.20, 2.49	0.003
Dose delay			
Yes	1.29	0.91, 1.84	0.154
Liposomal irinotecan			
1L+	0.47	0.29, 0.76	0.002

1L+ = first-line or later; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ref = reference.

LIMITATIONS

- Results reported in this study are based on data collected in academic cancer centers and may not be generalizable to patients with mPDAC treated in other settings
- Patients may have had other treatments at other institutions, so data collected from the sites in this study may not be entirely complete. Missing data may bias study results if the missingness is not completely random
- Due to the non-randomized, retrospective nature of the study, residual confounding may impact the associations and conclusions reported

CONCLUSIONS

- Real-world data from this study suggest patients were older and had a higher proportion with ECOG 2+ and up to one of the key 42 comorbid in the prior trial
- Patients were treated with liposomal irinotecan in 3L+ a setting with no currently approved options, and demonstrated meaningful benefit
- In addition and advanced analyses, patients treated with liposomal irinotecan in earlier versus later lines of therapy had increased survival benefit

References

1. Rahib L, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Research. 2014;74(11):2913-21. doi: 10.1158/0008-5472.
2. Wang-Gillam A, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545-57. doi: 10.1016/S0140-6736(15)00986-1.

This study was sponsored by Ipsen.

Presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE); 48 Annual | 16-17 September 2023

CSPC Exhibit 1100
Page 36 of 333

1555P

Real-world Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-based Regimen among Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review

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BACKGROUND AND STUDY OBJECTIVE

- Pancreatic cancer is aggressive and difficult to treat, and although it represents only 3% of new cancer cases, it is projected to be the second leading cause of cancer death by 2030[1]
- The NAPOLI-1 trial showed that, compared to treatment with fluorouracil (5-FU)/leucovorin (LV) alone, treatment with liposomal irinotecan in combination with 5-FU/LV significantly increased median overall survival (OS) and median progression-free survival (PFS) of patients with pancreatic cancer who previously received gemcitabine-based therapy[2]
- There is limited data on the efficacy and use of liposomal irinotecan in routine clinical practice
- This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving doublet liposomal irinotecan in a NAPOLI1-based regimen for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC)

METHODS

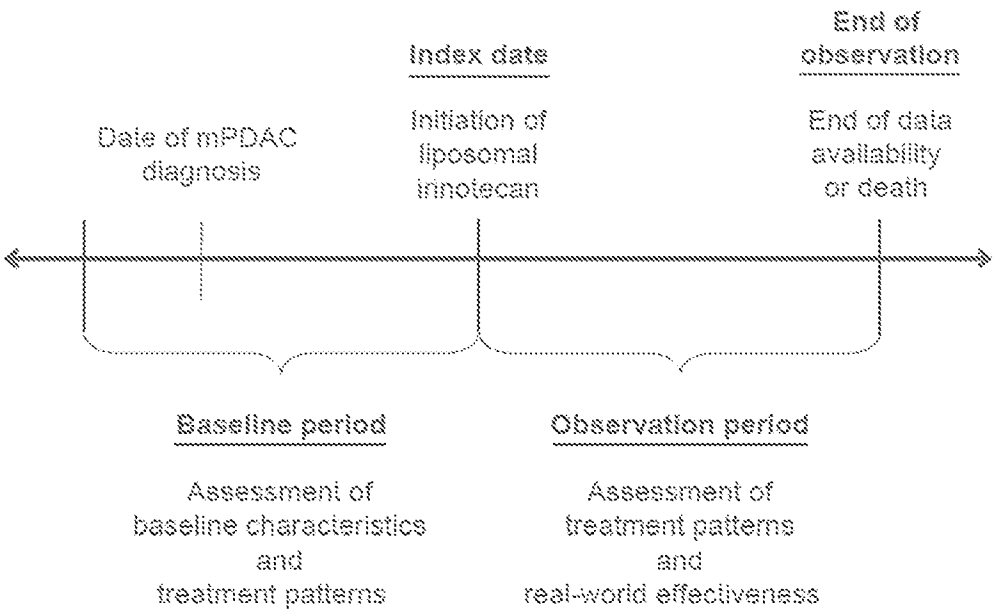
Study Design and Population

- This was a non-interventional, retrospective, multi-center chart review study among patients with mPDAC treated with liposomal irinotecan at six academic cancer centers in the US

CSPC Exhibit 1100
Page 37 of 333

- Eligible patients were treated with liposomal irinotecan from 2015-2020 and diagnosed with mPDAC

Figure 1. Study Design Scheme



Statistical Analysis

- Summary statistics were reported using means, standard deviations (SDs), and medians for continuous variables; frequencies and proportions were used for categorical variables
- Duration of liposomal irinotecan treatment, OS, and PFS were all measured from initiation of liposomal irinotecan and assessed using Kaplan-Meier (KM) analysis
  - These were also stratified by the line of therapy in the metastatic setting that patients received liposomal irinotecan (i.e., first-line [1L], second-line [2L], or third-line or later [3L+])
- Associations between baseline characteristics and OS and PFS were assessed using a multivariate Cox proportional hazards model. Covariates were included based on clinical and statistical significance. Hazard ratios (HRs), 95% CIs, and p-values were reported

RESULTS

Baseline Characteristics

- 325 patients met the study eligibility criteria. Overall, mean age at index date was 68 years, 51% were female, and the majority were White (70%) (Table 1)
- 9% had ECOG of 0, 57% had ECOG of 1, and 23% had ECOG 2 or greater (Table 1)
- Among 230 patients with genetic mutation information available, common genetic mutations included *KRAS* (26%), *TP53* (20%), and *CDKN2A* (9%)

Table 1. Baseline Demographic and Clinical Characteristics

	N = 325
Age (years) at index date, mean ± SD [median]	67.7 ± 9.6 [68.5]
Female, n (%)	167 (51.4)
Race/Ethnicity, n (%)	
White	228 (70.2)
Black/African-American	43 (13.2)
Asian/Pacific Islander	23 (7.1)
Hispanic/Latino	13 (4.0)
Native American/American Indian	1 (0.3)
Unknown	17 (5.2)
Year of Index, n (%)	
2015	1 (0.3)
2016	57 (17.5)
2017	75 (23.1)
2018	107 (32.9)
2019	81 (24.9)
2020	4 (1.2)
Cancer stage at first diagnosis of pancreatic cancer, n (%)	
I A	4 (1.2)
I B	6 (1.8)
II A	18 (5.5)
II B	46 (14.2)
III	61 (18.8)
IV	162 (49.8)
Unknown	28 (8.6)
ECOG performance score, n (%)	
0	30 (9.2)
1	184 (56.6)
2	65 (20.0)
3	8 (2.5)
4	2 (0.6)
Unknown	36 (11.1)

[1] Sum of proportions may exceed 100% as multiple responses were allowed

Liposomal Irinotecan Treatment Characteristics

- All patients received liposomal irinotecan with 5-FU, and 75% also received LV
- Patients were treated with liposomal irinotecan in 1L (17%), 2L (43%), or 3L+ (40%) in the metastatic setting (Table 2)
- Median duration of liposomal irinotecan treatment was 3.4, 2.1, and 1.4 months for 1L, 2L, and 3L+ patients, respectively (Table 2)
- 50% of patients had a starting liposomal irinotecan dose of 70 mg/m^2

Table 2. Liposomal Irinotecan Treatment

	N = 325
Liposomal irinotecan line of therapy, n (%)	
1L	56 (17.2)
2L	138 (42.5)
3L+	131 (40.3)
Duration of liposomal irinotecan treatment (months), median [95% CI]	
All patients	1.7 [1.5, 2.1]
1L	3.4 [1.4, 6.1]
2L	2.1 [1.6, 2.8]
3L+	1.4 [1.3, 1.7]

Real-World Effectiveness of Liposomal Irinotecan

- Median OS was 8.6, 7.4, and 4.8 months for 1L, 2L, 3L+ patients, respectively (Table 3 & Figure 2)
- Median PFS was 4.2, 3.0, and 2.0 months for 1L, 2L, 3L+ patients, respectively (Table 3 & Figure 3)
- Results presented here are based on updated analyses as compared to the abstract

Table 3. Real-World Effectiveness of Liposomal Irinotecan

	N = 325
OS	
Deaths, n (%)	228 (70.2)
OS (months), median [95% CI]	
1L	8.6 [4.6, 9.8]
2L	7.4 [5.3, 9.3]
3L+	4.8 [4.0, 6.3]
PFS	
Patients with progression, n (%)	287 (88.3)
PFS (months), median [95% CI]	
1L	4.2 [2.1, 5.7]
2L	3.0 [2.5, 3.7]
3L+	2.0 [1.7, 2.3]

Figure 2: Kaplan-Meier Analysis of Overall Survival by Line of Therapy

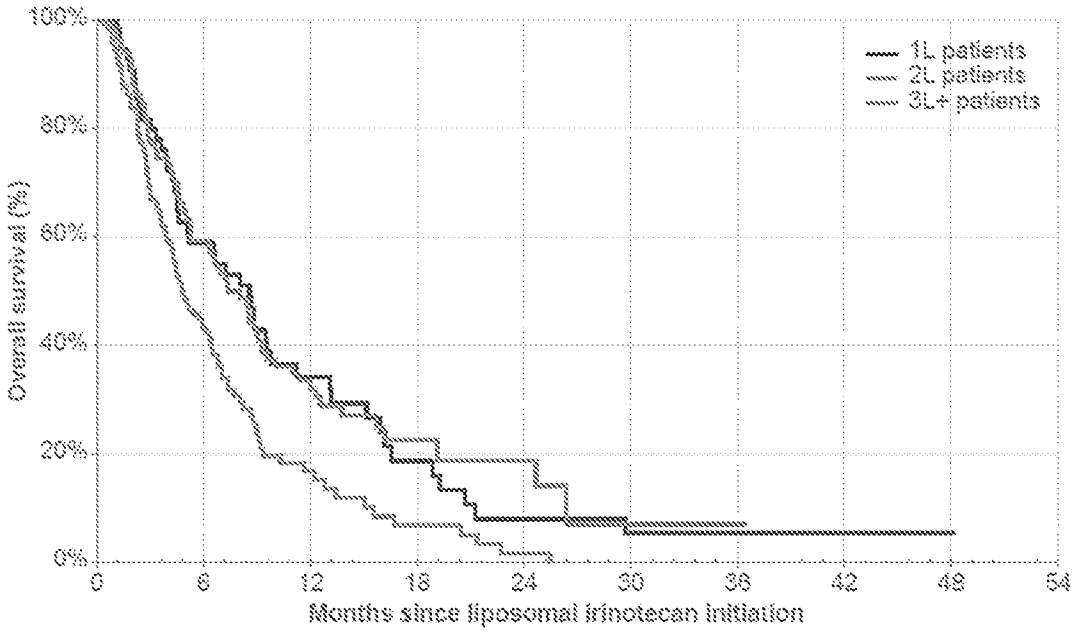
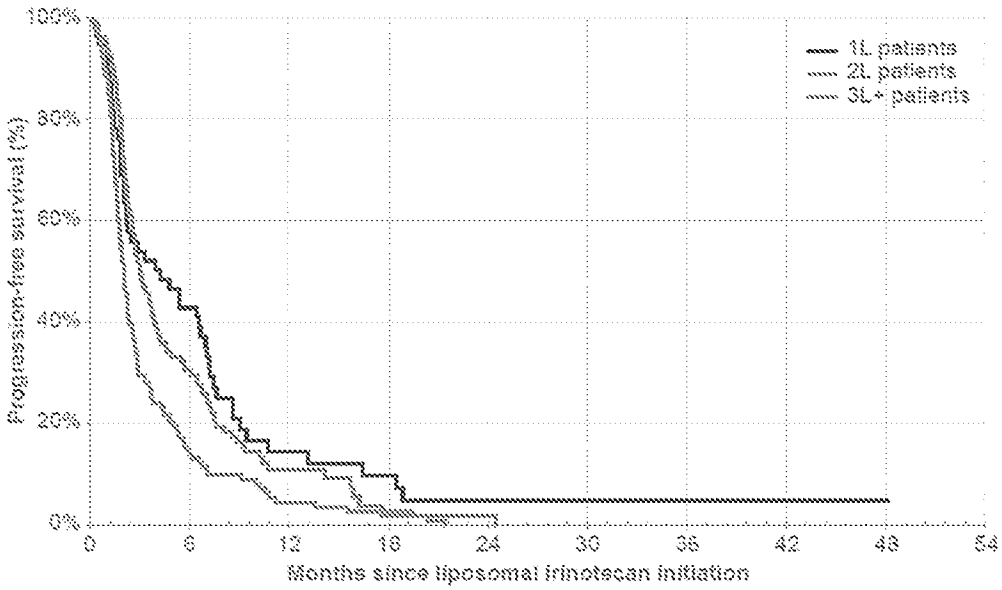


Figure 3: Kaplan-Meier Analysis of Progression-Free Survival by Line of Therapy



Associations between Baseline Characteristics and OS/PFS

- Patients treated with liposomal irinotecan in 3L+ versus 2L had significantly higher HR for OS and PFS (Table 4)
- Patients with liver metastatic sites or congestive heart failure had significantly higher HR for OS and PFS (Table 4)

Table 4. Associations between Baseline Characteristics and OS/PFS

	OS N = 325			PFS N = 325		
	HR	95% CI	p-value[1]	HR	95% CI	p-value[1]
Age at index date	1.00	(0.98, 1.01)	0.664	0.99	(0.98, 1.00)	0.180
Male (ref: female)	1.15	(0.87, 1.51)	0.331	1.04	(0.82, 1.33)	0.737
Time from mPDAC diagnosis to liposomal irinotecan initiation (months)	0.98	(0.96, 1.00)	0.033*	0.98	(0.96, 0.99)	0.006*
[illegible]						
Black/African-American	1.27	(0.76, 2.13)	0.360	1.02	(0.66, 1.58)	0.935
Hispanic/Latino	0.98	(0.48, 2.03)	0.962	1.12	(0.56, 2.26)	0.742
Other[2]	0.75	(0.42, 1.34)	0.330	0.78	(0.48, 1.27)	0.309
Unknown	0.77	(0.43, 1.40)	0.399	0.65	(0.37, 1.14)	0.134
[illegible]						
Midwest	0.77	(0.45, 1.32)	0.344	1.00	(0.63, 1.61)	0.990
South	0.58	(0.36, 0.93)	0.025*	0.94	(0.63, 1.39)	0.743
West	0.48	(0.30, 0.76)	0.002*	0.68	(0.46, 1.00)	0.052
[illegible]						
Non-metastatic	0.83	(0.59, 1.17)	0.278	0.91	(0.67, 1.23)	0.534
Unknown	0.72	(0.39, 1.34)	0.297	0.69	(0.42, 1.13)	0.138
[illegible]						
1	0.88	(0.54, 1.43)	0.598	0.80	(0.52, 1.24)	0.324
3+	1.84	(1.31, 2.60)	<0.001*	1.78	(1.32, 2.41)	<0.001*
[illegible]						
Liver	1.65	(1.21, 2.25)	0.002*	1.64	(1.24, 2.17)	<0.001*
Brain	6.24	(1.71, 22.73)	0.005*	2.33	(0.66, 8.25)	0.192
[illegible]						
2	1.13	(0.75, 1.70)	0.565	1.29	(0.91, 1.81)	0.160
3+	1.08	(0.64, 1.84)	0.771	0.97	(0.61, 1.52)	0.886
[illegible]						
≥ 2	1.06	(0.75, 1.49)	0.747	0.90	(0.67, 1.22)	0.498
Unknown	1.21	(0.79, 1.85)	0.378	1.02	(0.71, 1.46)	0.909
[illegible]						
Congestive heart failure	3.47	(1.66, 7.26)	<0.001*	3.05	(1.55, 6.00)	0.001*

(1) P-values less than 0.05 were marked with *.

LIMITATIONS

- Results reported in this study are based on data collected at academic cancer centers and may not be generalizable to patients with mPDAC treated in other settings
- Patients may have healthcare encounters at other institutions, so data collected from the sites in this study may not be entirely complete. Missing data may bias study results if the missingness is not completely random
- Due to the non-randomized, retrospective nature of the study, residual confounding may impact the associations and conclusions identified

CSPC Exhibit 1100
Page 43 of 333

CONCLUSIONS

- This real-world study suggests patients treated with liposomal irinotecan were older and had a higher proportion with ECOG, as well as lines of therapy, ≥2 compared to the pivotal trial
- Additionally, patients were treated with liposomal irinotecan in 3L+, a setting with no currently approved options, and demonstrated reasonable benefit
- In descriptive and adjusted analyses, patients treated with liposomal irinotecan in earlier versus later lines of therapy had increased OS and PFS benefit

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1. Rahib L et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Research*. 2014;74(11):2913–21. doi: 10.1158/0008-5472.
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Disclosures PC is an employee of Ipsen Biopharmaceuticals, Inc. (Ipsen), the sponsor of this study. RB, MD, CN, and MSD are employees of Analysis Group, Inc., a consulting company that has received funding for this and other studies from Ipsen. KHY, AH, OBA, AD, MA, EB, GK, and NB are employees of institutions that have received research funding from Ipsen.

Presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020 | virtual format | 19–21 September 2020

This study was sponsored by Ipsen

Real-world Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-based Regimen among Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review

BACKGROUND AND STUDY OBJECTIVE

METHODS

RESULTS

CONCLUSIONS

LIMITATIONS

Legal entity responsible for the study: The authors.

Funding: Has not received any funding

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2035

1553P Incidence of and risk factors for venous thromboembolism in patients with pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is among the most common malignancies associated with venous thromboembolism (VTE). However, despite recommendations basing on Khorana score commonly known to predict the risk of VTE, thromboprophylaxis has not been prescribed routinely in clinical practice, especially in patients with advanced PDAC.

Methods: Medical charts of patients consecutively treated for advanced PDAC from 2010 to 2019 without thromboprophylaxis were retrospectively reviewed. The cumulative incidence of VTE was estimated using Kaplan-Meier method. Factors associated with VTE were identified using a multivariate Cox's proportional hazard model with stepwise selection process. Similar analyses were performed for survivals. Early VTE was defined as VTE occurring within the third months from PDAC diagnosis.

Results: A total of 155 patients were included (median age: 68 years; males: 56.1%; performance status 0-1: 85.8%) with metastatic (70.3%) or locally advanced disease (29.7%). At baseline, Khorana score was high (≥3) for the vast majority of cases (94.3%). The cumulative incidences of VTE were 12.2% (95% CI: 6.7-17.3) at 3 months, 20.5% (95%CI: 13.5 - 26.9) at 6 months and 30.1% (95% CI: 21.2-37.9) at 12 months. Independent factors associated with VTE occurrence were age ≥80 years (HR=2.67; 95%CI: 1.06-6.71; P=0.04), body mass index (BMI)>30kg/m^2 (HR=2.45; 95%CI: 1.02-5.86; P=0.04), and CRP>150mg/L (HR=8.63; 95%CI: 2.45-30.40; P<0.001). Khorana score≥4 trended to be associated with VTE risk (HR=1.86; 95%CI: 0.91-3.80; P=0.09). Early VTE was associated with shorter progression-free survival (3.5 months vs. 7.1 months; HR=2.35; 95%CI: 1.38-4; P=0.001) and shorter overall survival (5.1 months vs. 15.3 months; HR=2.92; 95%CI: 1.63-5.23; P<0.001) compared to the remnant patients, independently of PS, presence of metastases and chemotherapy regimen. The median time-to-death from the date of VTE was 5.8 months (95%CI: 2.9-8.4 months).

Conclusions: this study confirmed the high incidence of VTE in patients with PDAC and its strong prognostic value. Age≥80 years, BMI>30kg/m^2 and CRP>150mg/L should be taken into account additionally to the Khorana score.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding

Disclosure: N. Willet: Advisory/Consultancy: Servier; Advisory/Consultancy: Sanofi. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2035

1554P Can thromboprophylaxis impact PFS in patients with advanced pancreatic cancer? Intermediate results of PaCT study

M.V. Karamouzis[1], I. Athanasiadis[2], G.F. Samelis[3], C. Vallilas[4], A. Bokas[5], A. Nikolaidi[6], A. Dimitriadou[7], Z. Kakosaiou[1], N.F. Pistamaltzian[8], D. Schizas[9], A. Papalampros[9], E. Felekouras[9], D. Dimitroulis[7], E. Antoniou[7], G. Sotiropoulos[7], P. Papakotoulas[8]

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Background: PaC is one of the most fatal cancers and cancer associated thrombosis (CAT) is a leading cause of death in these pts. 5-year survival rate for PaC is estimated around 8%. PaC induces a prothrombotic and hypercoagulable state. LMWHs are attributed to various non anticoagulant effects and could enhance the anti-tumor effect of therapy.

Methods: PaCT (Pancreatic Cancer & Tinzaparin) is a retrospective observational study aiming to collect data regarding progression free survival (PFS) in active advanced PaC pts who received thromboprophylaxis with tinzaparin, as suggested by SCC ISTH guidance, during chemotherapy. Primary end point is the impact of LMWHs in PFS compared to PFS with chemotherapy only; secondary are efficacy and safety of anticoagulation.

Results: We report intermediate results. 127 PaC pts, 87% with advanced or metastatic disease, treated with highly thrombogenic agents and receiving thromboprophylaxis were enrolled. 54% males, median age 66.1±9.9 years, BMI 25.3±4.0 Kg/m2. A sub-cohort of 68 pts, all with advanced or metastatic disease at 1st line treatment with nab-paclitaxel + gemcitabine who received tinzaparin [10,348±1,418 Anti-Xa IU, OD, median duration 7.8, IQR: 5.4-11.8mo] had median PFS 7.8 months (mo) (IQR: 5.4-11.8mo). PFS in 2 studies in pts with same characteristics, apart use of thromboprophylaxis, was [patients/median PFS]: 431/5.5mo, 75/5.2 and in a recent meta-analysis of 21 studies median PFS was 5.4 mo. Comparing[FC1] in our sub-cohort, PFS of pts receiving tinzaparin was 44% higher than in patients without such protection (p<0.05). During follow up period of 16.7±9.9 mo of 68 pts, no thrombotic events were recorded while 2 clinically relevant non major bleeding events occurred.

Conclusions: PFS in advanced PaC pts undergoing chemotherapy seems to positively impacted by anticoagulation. Thromboprophylaxis with tinzaparin in treatment doses is an efficient and safe approach.

Legal entity responsible for the study: Karamouzis Michalis.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2037

1555P Real-world treatment patterns and effectiveness of liposomal irinotecan in a NAPOLI1-based regimen among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): A multi-academic center chart review

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Background: Liposomal irinotecan in combination with fluorouracil (5-FU) and leucovorin (LV) extended survival with a manageable safety profile in patients with mPDAC who previously received gemcitabine-based therapy in the NAPOLI1 trial. Limited data are available on the efficacy and use of liposomal irinotecan for mPDAC in routine clinical practice. This retrospective multi-center chart review assessed real-world (rw) characteristics and outcomes of patients in the US who received NAPOLI1 trial-based regimens.

Methods: Patients with mPDAC treated with liposomal irinotecan were eligible. Liposomal irinotecan initiation defined index date, with duration of therapy, clinical characteristics, and treatment patterns reported. Rw overall survival (rwOS) and progression-free survival (rwPFS) were assessed with Kaplan-Meier methods. Six large cancer centers were included.

Results: 216 patients were initially assessed; median age was 68 years and 54% were female. 13% of patients had ECOG of 0, 53% had ECOG 1, and 20% had ECOG ≥2. Liposomal irinotecan was received in a doublet with 5-FU in a NAPOLI1-based regimen, with 70% receiving LV. Patients received liposomal irinotecan in first-line (1L; 17%), 2L (43%), and 3L+ (40%). Prior regimens were gemcitabine-based (80%) or contained 5-FU (27%). Median duration of therapy was 1.8, 1.7, and 1.4 months for 1L, 2L, and 3L+, respectively. Starting dose was commonly 70 mg/m^2 (47%), and 30% had dose modification. Median rwOS and rwPFS are shown in the table.

Table: 1555P rwOS and rwPFS among Patients Treated with Liposomal Irinotecan in a NAPOLI1-based regimen

rwOS	N	Median (95% CI), months
1L	37	8.8 (4.4, 13.2)
2L	93	7.4 (5.3, 9.0)
3L+	86	4.9 (3.2, 6.6)
rwPFS		
1L	37	2.7 (2.3, 3.0)
2L	93	3.0 (2.6, 3.9)
3L+	86	2.2 (1.8, 2.8)

Conclusions: Patients treated with a doublet liposomal irinotecan in a NAPOLI1-based regimen in academic centers are older with poorer prognosis based on ECOG compared to the trial; however, rw effectiveness is comparable. In addition, liposomal irinotecan is frequently used in 3L+ where no treatment has been approved, providing reasonable benefit.

CSPC Exhibit 1100
Page 46 of 333

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.

Disclosure: K.H. Yu: Advisory/Consultancy: Ipsen; Research grant/Funding (self): Ipsen, Bristol-Myers Squibb, Halozyme. A. Hendifar: Advisory/Consultancy: Novartis, Ipsen, Perthera, Celgene, Abbvie, Travel/Accommodation/Expenses: Halozyme; Research grant/Funding (self): Ipsen. O. Alese: Advisory/Consultancy: Exelixis, AstraZeneca, Conjupro Biotherapeutics, Ipsen; Travel/Accommodation/Expenses: Exelixis; Research grant/Funding (institution): Bristol-Myers Squibb, Five Prime Therapeutics, Acetylon Pharmaceuticals, Tesaro, Ipsen, Taiho Pharmaceutical. A. Draper: Advisory/Consultancy: Array Biopharma; Honoraria (self): Wellstat Therapeutics. M. Abdelrahim: Advisory/Consultancy: Ipsen; Speaker Bureau/Expert testimony: Ipsen. G. Khan: Honoraria (self), Travel/Accommodation/Expenses: Bayer, Eisai; Advisory/Consultancy: Bayer, Celgene, Eisai. P. Cockrum: Travel/Accommodation/Expenses, Shareholder/Stockholder/Stock options, Full/Part-time employment: Ipsen. R. Bhat: Research grant/Funding (institution): Janssen Scientific Affairs, Novartis, GSK, Takeda, Pfizer, Bayer, Seattle Genetics, Ipsen, Mallinckrodt. C. Nguyen: Research grant/Funding (institution): GSK, Ipsen, Sanofi Pasteur, Celgene, Taiho Oncology, Takeda, Shire, Vertex, Janssen, Merck, Kiniksa, Intercept, AstraZeneca, Novo Nordisk, Novartis, Pfizer. M. DerSarkissian: Research grant/Funding (institution): AstraZeneca, Novartis, Pfizer, GSK, Takeda, Novo Nordisk, Ipsen, Sanofi/Regeneron, Janssen, Kiniksa, LivaNova, Merck, Medtronic, Mallinckrodt, Seattle Genetics, VIV. M.S. Duh: Advisory/Consultancy: Seattle Genetics, Sanofi, Taris, Alexion; Research grant/Funding (institution): Ipsen, Taiho, Merck, Novartis, Pfizer. N. Bahary: Advisory/Consultancy: Celgene, Bristol-Myers Squibb, AstraZeneca, Exelixis, Thermo Fisher Scientific. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2038

1556P **Extended pancreatectomy in patients with pancreatic cancer**

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Background: Extended pancreatectomy (EP) is the only potential cure for patients with borderline resectable and locally advanced pancreatic cancer

Methods: In the period 2011-2018, 618 resections were performed in patients with pancreatic adenocarcinoma. Standard resections were performed in 476 (77%) patients. EP was performed in 142 (23%) patients. Extended pancreaticoduodenectomy was performed in 79 (55.6%), extended distal resections in 52 (36.6%), extended total pancreatectomy in 11 (7.8%). EP with arterial resections was performed in 14 (2.3%) patients, with venous resections in 91 (14.7%) patients.

Results: One or more postoperative complications occurred in 182 patients (38.2%) in the standard resection group and in 63 (44.3%) in the EP group. Mortality was 13.2% (15 patients): 6 (4.2%) patients died after EP and 9 (1.9%) after standard pancreatectomy. Median survival and 5-year overall survival rates were reduced in patients having EP compared with those undergoing a standard resection (15 months, 18% and 25 months, 33%, respectively; c^2= 2.83, P= 0.09, c^2 = 0.16, P=0.69).

Conclusions: These results suggest that morbidity and mortality after EP are comparable with standard pancreatectomy. However, long term results of EP are worse compared with standard pancreatectomy. Extended resections are possible and can increase the number of radically operated patients.

Legal entity responsible for the study: Liudmyla Pererva.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2035

1557P **Clinical and epidemiological characteristics of pancreatic acinar cell carcinoma: A study from the United States**

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Background: Acinar cell carcinomas are rare tumors, which constitute about 4% of the whole pancreatic tumors. Consequently, little data, about their clinical and survival characteristics are available. In this study, we demonstrate the clinico- epidemiological properties of patients with pancreatic acinar cell carcinoma in the united states between 1990 and 2015.

Methods: The study was conducted through SEER* Stat version 8.3.6. Data about pancreatic acinar cell carcinoma were obtained from SEER Reg Nov 2018, then these data were statistically analyzed using SPSS version 22.

Results: A total number of 447 patients with pancreatic acinar cell carcinoma were diagnosed at the period from 1990 till 2015. The incidence rate of pancreatic acinar cell Carcinoma was 0.25 per 1,000,000. Male patients represented 63.3% of patients, with the mean age at diagnosis 64.5 years. The majority of the tumors occupied the head of pancreas (n=193, 43.25%). 44%of patients had metastatic disease at presentation and only 49% of patients underwent primary pancreatic surgery. The tumor was the only primary malignancy diagnosed in the vast majority of cases (n= 362,81.5%). The median survival was 13 months.

Conclusions: Pancreatic acinar cell carcinoma is, quiet, uncommon tumor, with the incidence rate is estimated to be of 0.25 per 1,000,000. Most of the tumors were metastatic at presentaion, with a short median survival (13 months).

Legal entity responsible for the study: Belal Abousaida.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2040

1558P **Pancreatic cancer (PC) in patients (pts) younger than 50 years: Clinical outcomes and actionable genomic/genetic alterations**

A. Garcia-Alvarez[1], H. Verdaguer[1,2], M. Guardiola[3], D.A. Acosta Eyzaguirre[3,4], E. Buxò[3,4], E. Sardo[1], N. Saoudi[1], D.H. Marmolejo Castaneda[1], J. Hernando[1,2], M. Diez Garcia[1,2], I. Baraibar Argota[1,2], F.J. Ros Montañá[1,2], A. Sierra[1], C. Molero[5], J.M. Miquel[5], A. Vivancos[1], R. Dienstmann[6], T. Macarulla Mercadé[1,2]

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Background: Limited data has been reported about PC in young pts. Here we describe the epidemiologic, pathologic, and molecular characteristics of the disease in pts ≤ 50 years.

Methods: VHIO institutional database was queried for medical and treatment history, tumor comprehensive genomics profiling, and germline genetic findings for those pts younger than 50 years old diagnosed with PC between January 2010 and April 2020. Neuroendocrine cancers were excluded. Overall survival (OS) from date of PC diagnosis was estimated using Kaplan-Meier methods. Fisher exact test was used for molecular alterations statistics.

Results: In total, 102 pts ≤ 50 years old were identified. Median age at diagnosis was 45 years (55% males). Most pts (54%) were metastatic (M), 19% were locally-advanced (LA) and 27% resectable at diagnosis. First-line treatment (ttm) of choice was FOLFIRINOX in 35 pts (n=14 at LA and n=21 at M stetting) followed by gemcitabine + nab-paclitaxel for 20 pts (n=1 at LA and n=19 at M stetting). Median OS was 19 months (CI95%14-24) in the entire cohort and 42 pts (41%) were included (at least once) in clinical trials. N = 64 underwent successful molecular testing with next generation sequencing and 13/64 (20%) tumors were KRAS wild-type (WT). Young PC pts with KRAS WT PC did not have improved OS as compared to KRAS mutant (mt) population (29.9 vs 20.7 months; p=0.6). Actionable mutations were found in 28% of pts (n=18) with DNA damage repair (DDR) gene mutations accounting for 50% (n=9). Overall, actionable alterations were enriched in KRAS WT as compared to KRAS mt (Odds ratio 6.32; p=0.005), but this association was not significant for germline events (Odds ratio 1.66; p=0.62). In KRAS WT actionable alterations included NRG1 fusions (n=1) and DDR genes mutations in BRCA2 (n=2, both germline), BRCA1 (n=1), PALB2 (n=1) and ATM (n=1). Actionability in KRAS mutant (mt) pts was mostly germline events in DDR genes BRCA2 (n=3, 1 germline), MSH2 (n=1, germline), BRCA1 (n=1, germline).

Conclusions: Young PC pts have higher than expected prevalence of KRAS WT tumors (20%) compared to general PC population. KRAS WT PC pts are enriched for somatic actionable alterations compared to KRAS mt population. We advocate for molecular profiling in young-onset PC pts.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: H. Verdaguer: Advisory/Consultancy: Ipsen. J. Hernando: Speaker Bureau/Expert testimony: EISAI, Ipsen, Roche, Novartis, AAA, Angelini. I. Baraibar Argota: Honoraria (self): Sanofi; Travel/Accommodation/Expenses: Amgen. R. Dienstmann: Advisory/Consultancy: Roche, Boehringer Ingelheim; Speaker Bureau/Expert testimony: Roche, Ipsen, Amgen, Servier, Sanofi, Merck Sharp & Dohme; Research grant/Funding (self), Research grant/Funding (institution): Merck and Pierre Fabre. T. Macarulla Mercadé: Advisory/Consultancy: Advance Medical HCMS, Bayer, BioLineRX Ltd, Celgene SLU, Eisai, Genzyme, Incyte, IPSEN Pharma Lab, Menarini, Lab. Servier, Lilly, QED Therapeutics, Merck, Sharp and Dhome, Prime Oncology EU, QED Therapeutics Inc, Sanofi-Avenris; Research grant/Funding (self): Agios, Aslan, AstraZecena, Bayer, Celgene, Genentech, Hallozyme, Immunomedics, Lilly, Merimarck, Millenim, Novartis, Pfizer, Pharmacyclics and Roche. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.2041

CSPC Exhibit 1100
Page 47 of 333

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

A multicenter chart review study of patients with metastatic pancreatic ductal adenocarcinoma receiving liposomal irinotecan after gemcitabine-based therapy.

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Kenneth H. Yu, Andrew Eugene Hendifar, Olatunji B. Alese, Amber Draper, Maen Abdelrahim, Ethan Burns, Gazala Naaz Khan, Paul Cockrum, Rachel Bhak, Maral DerSarkissian, Catherine Nguyen, Mei Sheng Duh, Nathan Bahary

Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY; Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA; Winship Cancer Institute, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA; Houston Methodist, Houston, TX; Houston Methodist Hospital, Houston, TX; Henry Ford Health System, Detroit, MI; Ipsen Biopharmaceuticals, Cambridge, MA; Analysis Group, Inc., Boston, MA; Analysis Group, Inc. and UCLA Fielding School

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DOI: 10.1200/JCO.2020.38.15_suppl.e16733
Journal of Clinical Oncology 38, no. 15_suppl

Published online May 25, 2020.

WE RECOMMEND

FDA Approves Liposomal Irinotecan for Advanced Pancreatic Cancer

of Public Health, Los Angeles, CA; Analysis Group, Inc. and Harvard T. H. Chan School of Public Health, Boston, MA; UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA

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Abstract Disclosures

Abstract

e16733

Background: Real-world data allows healthcare decision-makers to assess and manage therapeutic and economic options for patients, including those who would and would not have met eligibility criteria for randomized control trials (RCT) and are instead managed under usual care. This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving liposomal irinotecan for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC). **Methods:** Patients with mPDAC treated with liposomal irinotecan were eligible. Initiation of liposomal irinotecan defined index date; covariates assessed included clinical characteristics and treatment patterns; real-world overall survival (rwOS) was assessed via Kaplan-Meier methodology. The target enrollment is 300 patients. The study centers included were Memorial Sloan Kettering Cancer Center, Cedars-Sinai Medical Center, Emory Winship Cancer Institute, Houston Methodist Cancer Center, Henry Ford Cancer Institute, and University of Pittsburgh Medical Center. **Results:** Data on 26 patients were available for initial analyses. Mean age was 68 years; 58% were female and 65% Caucasian. 54% of patients had stage IV disease at first diagnosis, and 17%, 65%, and 17% had index ECOG score of 0, 1, and 2, respectively. Common genetic mutations include KRAS (40%) and TP53 (40%). Prior to liposomal irinotecan, treatments received for metastatic disease include gemcitabine+nab-paclitaxel (77%) and fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (19%). Patients had

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received 0 (12%), 1 (23%), and ≥2 (65%) lines of therapy in the metastatic setting prior to liposomal irinotecan. Mean duration of liposomal irinotecan use was 3.0 months; liposomal irinotecan was mostly received with 5-FU (23%) or 5-FU/LV (69%). Median rwOS was 4.9 months (95% CI: 3.0, 6.3). **Conclusions:** Real-world data of the first 26 patients in this study show patients treated with liposomal irinotecan are older, sicker, and have had more lines of therapy than previously reported in RCT data.

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Track: Disease Epidemiology/Clinical Course -> Cancer

(PO-3727) A Us Multicenter Chart Review Study Of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan After Gemcitabine-based Therapy

Monday, September 14, 2020

Kenneth H Yu, Andrew Hendifar, Olatunji Alese, Amber Draper, Maen Abdelrahim, Ethan Burns, Gazala Khan, Paul Cockrum, Rachel Bhak, Maral DerSarkissian, Catherine Nguyen, Mei S Duh and Nathan Bahary

Background: Real-world data allows healthcare decision-makers to assess and manage therapeutic and economic options for patients, including those who would and would not have met eligibility criteria for randomized control trials (RCT) and are instead managed under usual care.

Objectives: This retrospective multi-academic center chart review study describes real-world characteristics and outcomes of US patients receiving liposomal irinotecan for the management of metastatic pancreatic ductal adenocarcinoma (mPDAC).

Methods: Patients with mPDAC treated with liposomal irinotecan were eligible. Initiation of liposomal irinotecan defined index date; covariates assessed included clinical characteristics and treatment patterns; real-world overall survival (rwOS) was assessed via Kaplan-Meier methodology. The target enrollment is 300 patients. The study centers included were Memorial Sloan Kettering Cancer Center, Cedars-Sinai Medical Center, Emory Winship Cancer Institute, Houston Methodist Cancer Center, Henry Ford Cancer Institute, and University of Pittsburgh Medical Center.

Results: Data on 26 patients were available for initial analyses. Mean age was 68 years; 58% were female and 65% Caucasian. 54% of patients had stage IV disease at first diagnosis, and 17%, 65%, and 17% had index ECOG score of 0, 1, and 2, respectively. Common genetic mutations include KRAS (40%) and TP53 (40%). Prior to liposomal irinotecan, treatments received for metastatic disease include gemcitabine+nab-paclitaxel (77%) and fluorouracil (5-FU)/leucovorin (LV)+irinotecan+oxaliplatin (19%). Patients had received 0 (12%), 1 (23%), and ≥2 (65%) lines of therapy in the metastatic setting prior to liposomal irinotecan. Mean duration of liposomal irinotecan use was 3.0 months; liposomal irinotecan was mostly received with 5-FU (23%) or 5-FU/LV (69%). Median rwOS was 4.9 months (95% CI: 3.0, 6.3).

Conclusions: Real-world data of the first 26 patients in this study show patients treated with liposomal irinotecan are older, sicker, and have had more lines of therapy than previously reported in RCT data.

NIH Public Access
Author Manuscript
Biochim Biophys Acta. Author manuscript; available in PMC 2011 January 1.

Published in final edited form as:
Biochim Biophys Acta. 2010 January ; 1805(1): 97. doi:10.1016/j.bbcan.2009.10.001.

Targeted Drug Delivery in Pancreatic Cancer

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Abstract

Effective drug delivery in pancreatic cancer treatment remains a major challenge. Because of the high resistance to chemo and radiation therapy, the overall survival rate for pancreatic cancer is extremely low. Recent advances in drug delivery systems hold great promise for improving cancer therapy. Using liposomes, nanoparticles, and carbon nanotubes to deliver cancer drugs and other therapeutic agents such as siRNA, suicide gene, oncolytic virus, small molecule inhibitor and antibody has been a success in recent pre-clinical trials. However, how to improve the specificity and stability of the delivered drug using ligand or antibody directed delivery represent a major problem. Therefore, developing novel, specific, tumor-targeted drug delivery systems is urgently needed for this terrible disease. This review summarizes the current progress on targeted drug delivery in pancreatic cancer, and provides important information on potential therapeutic targets for pancreatic cancer treatment.

Keywords

targeted drug delivery; pancreatic cancer

Introduction

Pancreatic cancer has the worst mortality rate and the lowest overall survival (OS) in all cancers. The incidence of pancreatic cancer is gradually increased with 42,470 predicated new cases in the United States in 2009, in which 35,240 will die. Only about 10% of patients are presented with resectable disease and are suitable for potentially curative surgery [1]. Even for patients who are qualified for surgery, aggressive metastasis often occurs after the operation, which is highly resistant to conventional chemotherapy and radiation therapy. Therefore, prognosis of pancreatic cancer is very poor, and the incidence almost equals with the mortality rate, with 5-year survival less than 5%.Patients with locally advanced disease have 6--10 months of median survival, and patients with metastatic disease only have 3-6 months of median survival [2,3]. Novel strategies to treat this deadly disease are urgently needed.

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Chemotherapy is still the only option in metastatic pancreatic cancer treatment although at most of the times chemotherapy is purely palliative with minimal impact on survival [4]. Gemcitabine (2′-2′-difluorodeoxycytidine) represents the standard chemotherapy for all stages of pancreatic adenocarcinoma in the last decade [5]. However, neither gemcitabine alone nor gemcitabine-based combinational chemotherapy achieve a favorable outcome in advanced disease. New adjuvant therapy targeting at specific markers in pancreatic cancer using molecular approach may represent a promising strategy in the diagnosis and treatment of pancreatic cancer. Those molecular approaches have been rapidly developed in recent years, which include antisense oligonucleotides, RNA interference (RNAi), gene restoration, suicide gene therapy, small molecule inhibitors, antiangiogenic and matrix metalloproteinase inhibitors, oncolytic viral therapy, immunotherapy, and antibody therapy. Currently many of those approaches have not been tested in clinical applications, and most of the treatments are combined with standard chemotherapy or radiotherapy for maximum benefits [6]. In order to achieve ideal efficiency of chemotherapy or adjuvant therapies, effective delivery is a key issue in pancreatic cancer treatment. This review summarized the current progress on targeted drug delivery in pancreatic cancer including the therapeutic agents, vehicles, delivery routes, and targets for specific delivery to pancreas, and provides important information on new strategies for pancreatic cancer treatment.

Therapeutic Agents

In addition to the conventional chemotherapy drugs such as gemcitabine, fluorouracil (5-FU), and platinum agents (oxaliplatin, cisplatin, carboplatin), new therapeutic agents have been developed recently which target at cell surface receptors, ligands, transcriptional factors, mutant genes, or the immune system in pancreatic cancer. Those agents include small interfering RNAs (siRNAs), antisense nucleotides, suicide genes, toxins, oncolytic viruses, small molecule inhibitors, and antibodies through non-toxic, controlled released vectors such as liposomes, nanoparticles, and carbon nanotubes (Table 1) [7-13]. These therapeutic agents will provide a new perspective on pancreatic cancer treatment using molecular approaches.

siRNA

RNA interference (RNAi) is a new technology and has become a powerful tool in silencing gene expression in most cells. siRNA or short hairpin RNA (shRNA) based therapy have shown great promise in many cancers. Targets for siRNA therapy are usually oncogenes, or genes that are important in tumor growth and metastasis such as key molecules in angiogenesis, survival, anti-apoptosis, and resistance to chemotherapy. A few examples using siRNA therapy to treat pancreatic cancer are listed below. In BxPC-3 cells, siRNA against matrix metalloproteinase-2 (MMP-2) suppressed the tumor cell adhesion and invasion [14]. Under hypoxic conditions, siRNA targeting HIF-1α decreased pancreatic cancer cell proliferation and induced cell apoptosis [15]. A recent study showed that blocking the sphingosine kinase-1 activity using siRNA can sensitize the pancreatic cancer cells to gemcitabine treatment, indicating that development of a combinational therapy of siRNA with gemcitabine may represent a promising approach in pancreatic cancer treatment [16]. Our study also found that silencing of a zinc transporter ZIP4 by shRNA inhibits pancreatic cancer growth and significantly increases the survival of nude mice with pancreatic cancer xenografts [17]. A common limitation often seen in siRNA therapy is the unanticipated off-target effects that occur by siRNA recognition of other mRNA with partial homology, and non-specific silencing of genes in the normal tissues other than the target organ. Therefore, effective targeted delivery system is warranted in siRNA therapy [8].

CSPC Exhibit 1100
Page 54 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Gene therapy

Gene therapy by expressing, restoring or inhibiting a particular gene of interest is expected to prevent or reverse the growth of cancer cells. In pancreatic cancer, transfection of the tumor suppressor gene p53 was found to suppress the growth of multiple human pancreatic cancer cell lines. Adenovirus mediated wild-type p53 gene therapy induced cancer cell apoptosis and suppressed tumor growth in a nude mouse subcutaneous model [18]. Moreover, reintroduction of p53 to pancreatic cancer cells which were previously treated with gemcitabine increased the cytotoxicity both *in vitro* and *in vivo* [19]. Xu el al has shown that efficient restoration of wild type p53 function in squamous cell carcinoma of the head and neck (SCCHN) cells through liposome delivery resulted in a significant increase in radiation-induced apoptosis which was proportional to the level of exogenous wild type p53 in the tumor cells. Intravenous administration of liposome-p53 sensitized established SCCHN nude mouse xenograft tumors to radiotherapy. The combination of systemic liposome-p53 gene therapy and radiation caused complete tumor regression and inhibition of their recurrence even 6 months after the end of the treatment [9]. Restoration of other tumor suppressor, somatostatin receptors (SSTRs), also inhibits pancreatic cancer growth. Our previous studies have shown that transfection of SSTR-1 induces cell cycle arrest and inhibits tumor growth in pancreatic cancer, and cotransfection of SSTR-1 and SSTR-2 further inhibits pancreatic cancer cell proliferation and renders pancreatic cancer cells responsive to somatostatin analogue treatment [20,21]. Other tumor suppressor genes used in gene therapy include Rb, p21, and p16 which regulate the G1 to S phase checkpoint during the cell cycle. Reestablishing the expression of those genes could restrain cancer cell proliferation [22].

Suicide gene therapy

Suicide gene therapy, also called prodrug system, is a two-step gene therapy, in which a suicide gene is delivered to the tumor first which will lead to the expression of an active enzyme. And a prodrug is subsequently administered which is cleaved and activated selectively by the suicide gene encoded enzyme [23]. Cytosine deaminase (CD) is a bacteria derived enzyme that converts the nontoxic agent 5-fluorocytosine (5-FC) to the active chemotherapeutic agent 5-fluorouracil (5-FU). Transfection of the CD gene into BxPC-3 cells in combination with 5-FC treatment inhibited tumor growth *in vivo* [24]. Similarly, administration of microencapsulated genetically modified allogeneic cells, which expressed cytochrome P450, an enzyme that activates the chemotherapeutic agent ifosfamide to its cytotoxic form, led to local activation of systemically administered ifosfamide, and tumor reduction in a phase I/II trial in 14 pancreatic cancer patients. The median survival was doubled in the treatment group compared with the control, and 1-year survival was three times better [25]. The herpes simplex virus (HSV) thymidine kinase gene (HSV-TK) is the most widely studied gene for suicide gene therapy. HSVTK gene metabolizes the nontoxic prodrug, Gancyclovir (GCV), and turns it into a GCV triphosphate, the active form. This metabolite can incorporate into the DNA helix and inhibit both DNA synthesis and cell cycle progression, leading to apoptosis and cell death. HSV-TK gene delivery followed by GCV, was found to be effective on inhibiting tumor growth and metastasis of pancreatic cancer [26,27]. Tissue specific promoters are preferred in the suicide gene therapy in order to achieve maximal efficacy and minimal toxicity.

Oncolytic virus therapy

Replication-deficient oncolytic viruses are engineered to replicate only in tumor cells, which makes it an ideal therapeutic agent for cancer treatment. Those viruses kill tumor cells by a variety of mechanisms including direct cell lysis, cell-cell fusion, toxic proteins, and induction of antitumor immune responses [6,13]. Commonly used oncolytic viruses include adenovirus, herpes simplex virus, and reovirus. ONYX-015 is an E1B-deleted replication-selective adenovirus that preferentially replicates in malignant cells. A phase II clinical trial using

CSPC Exhibit 1100
Page 55 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

ONYX-015 oncolytic adenovirus in patients with pancreatic cancer achieved favorable outcome (tumor reduction or stabilization) in about half of the patients [28]. Most oncolytic herpes simplex viruses (HSVs) are from type 1 HSV. Recently a novel oncolytic virus (FusOn-H2) from the type 2 HSV has been developed. The FusOn-H2 virus hosts a deletion of the PK domain in the ICP10 gene, and only replicates in Ras activated cells such as pancreatic cancer cells. Delivery of FusOn-H2 through intraperitoneal route completely eradicated established orthotopic tumors in 75% of the animals and prevented local metastases [13]. Reovirus can also be used as an oncolytic agent targeting the activated Ras signaling pathway. In an immunocompetent animal model, reovirus treatment could inhibit the peritoneal dissemination of pancreatic cancer cells and decrease the liver metastasis. Immunohistochemical analysis revealed that reovirus replication was only seen within the tumor cells but not in the surrounding normal tissues [29-31].

Small molecule inhibitors

The first effective biological drug approved for the treatment of advanced pancreatic cancer was erlotinib (Tarceva™), a small molecule Tyrosine Kinase Inhibitor, which was licensed by FDA in 2006 [32]. Erlotinib targets the intracellular domain of the epidermal growth factor receptor (EGFR), and has been shown to improve survival when used in combination with gemcitabine to treat metastatic pancreatic cancers [7,33]. Antiangiogenic agents have also been used in the treatment of pancreatic cancer due to the fact that they could overcome some drug resistance caused by insufficient penetration of cytotoxic chemotherapy in solid tumors. Other small molecule inhibitors include farnesyl transferase inhibitors, matrix metalloproteinase inhibitors, and COX 2 inhibitors [34].

Antibody therapy

More and more evidence suggest that the immune system plays an important role in the control of tumor progression. Immunotherapies especially antibody therapy have shown great promise in pancreatic cancer treatment. Many studies suggest that EGF and vascular endothelial growth factor (VEGF) pathways are activated in a large amount of human pancreatic cancers. EGFR and VEGF expression are associated with the prognosis of pancreatic cancer. It has been shown that anti-EGFR monoclonal antibodies including Cetuximab and Matuzumab inhibit the tumor growth and angiogenesis. Combination of anti-EGFR antibodies with gemcitabine or radiotherapy led to significant growth inhibition of pancreatic cancer cells compared with the single or double therapy [35]. In a recent case report, a patient with stage IV pancreatic cancer showed response to chemotherapy with the addition of bevacizumab, a recombinant humanized monoclonal antibody targeting VEGF, while initially was unresponsive to gemcitabine, 5-FU, irinotecan and cisplatin treatment [36]. This study demonstrated the benefit of bevacizumab used in combination with previously failed chemotherapy for pancreatic cancer. Anti-MUC1 antibody, (90)Y-DOTA-cPAM4, in combination with gemcitabine showed a significant inhibition of tumor growth and prolonged survival of the mice [37]. The *in vitro* study showed that another anti-MUC1 antibody (213)Bi-C595 was specifically cytotoxic to MUC1-expressing pancreatic cancer cells compared with the controls [38]. Mesothelin (MSLN) is a tumor differentiation antigen that is highly expressed in human malignant tumors including pancreatic cancer [39,40]. Anti-MSLN antibody MORAb-009 kills MSLN expressing cell lines via antibody dependent cellular cytoxicity (ADCC). In addition, another anti-MSLN antibody SS1P in combination with chemotherapy drugs also play a critical role in anti-cancer therapy [41,42].

Drug Delivery Methods

The most commonly used carriers for drug delivery in pancreatic cancer treatment include liposomes, nanoparticles, and carbon nanotubes. Those carriers can protect the drugs from

CSPC Exhibit 1100
Page 56 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

degradation and will effectively deliver them to the target organs. The advantages of the carrier encapsulation of the drugs include increased drug solubility, prolonged drug exposure time, selective drug delivery to the target, improved therapeutic outcome, decreased toxic effects and low drug resistance.

Liposomes

Liposomes have been successfully used as pharmaceutical carriers for anti-cancer drugs. The liposomes contain lipid-based formulations to enhance the solubility of poorly soluble antitumor drugs, and vector-conjugated liposomal carriers can be used for specific targeted delivery to the designated tumor tissues [43]. Liposomes have been used to increase the concentrations of lipophilic drugs in aqueous media as well as preventing the encapsulated drugs from enzymatic degradation. The liposomal formulation of anti-cancer drugs such as Doxorubicin or 5-FU are usually stable for several months to several years [44,45]. In a phase I clinical study, a new liposomal cisplatin formulation, lipoplatin, showed an improved effect and reduced toxicity in advanced malignant tumors [46]. Administration of gemcitabine loaded pegylated liposome in human pancreatic cancer cell lines showed a significant reduction of cell viability compared with the gemcitabine alone [47]. In a SCID mouse model which bears BxPC-3 or PSN-1 xenografts, animals treated with gemcitabine loaded pegylated liposomes showed a survival advantage, enhanced systemic bioavailability and increased inhibition of tumor growth than gemcitabine alone, without obviously increased toxicity [47].

Traditionally, liposomes have also been used as a vector-conjugated carrier for gene transfection *in vitro*. DNA can be incorporated with cationic lipids and then transported into cancer cells for gene therapy. KAI1 gene, a metastasis suppressor gene, was transfected into pancreatic cancer cell line MIA PaCa-2 by liposome, which showed an inhibition of cancer metastasis [48]. Furthermore, liposome can also deliver siRNAs or shRNAs to silence oncogenes in pancreatic cancer. A liposome delivered siRNA targeting protein kinase N3 significantly inhibits tumor growth and lymph node metastasis in an orthotopic mouse model for pancreatic cancers [49]. Our previous study indicates that liposome wrapped shRNA targeting pancreatic and duodenal homeobox 1 (PDX-1) inhibited pancreatic cancer growth in immunodeficiency mice [50]. We also found that liposome/human ZIP4 shRNA treatment reduced the expression of ZIP4 in established xenografts, and inhibited pancreatic cancer growth in an immunodeficient mouse model (unpublished data). In summary, more and more basic research and clinical applications have indicated the great potential of liposome as pharmaceutical or genetic carrier in cancer treatment. Further investigations are needed to optimize this promising carrier to become more effective, nontoxic and highly selective for drug delivery and gene targeting strategy in pancreatic cancer therapy.

Nanoparticle

The nanotechnology in cancer research has been developed rapidly which significantly advances the diagnosis and treatment of pancreatic cancer. The novel applications of nanotechnology in cancer treatment include drug delivery, new diagnostic imaging system, development of advanced biocompatible materials, and nano-nutriment. Engineered nanoparticles have become an important carrier for the above applications due to its unique structure and characteristics such as a bigger surface to mass ratio compared with other particles, the quantum properties, and the ability to bind, absorb and carry other compounds such as drugs, nucleotides, and proteins. Particles within 1 to 100 nanometers appear to be the optimal size for drug delivery [51,52]. A number of nanoparticle-drug combined formulations (oral or intravenous) are at different stages of clinical trials. Oral nano-delivery systems are developing quickly for its distinct merits in cancer therapy and the ease of administration. Using bioavailable polymeric nanoparticle encapsulated rapamycin as a prototype for oral nano-drug delivery has generated favorable pharmacokinetics and therapeutic effects as shown in a

CSPC Exhibit 1100
Page 57 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

xenograft model of human pancreatic cancer. Oral nanoparticle/rapamycin administration results in significant growth inhibition in cancer cells [53].

Nanoparticle can also be used to deliver imaging agents in cancer diagnosis. Semiconductor quantum dots are popular luminescence probes for many biomedical applications because of the particle size (approximately 10 nm in diameter), high photostability, tunable optical properties, and multimodality. These composite nanomaterials have shown promising efficiency in cancer diagnosis [54]. Manganese-doped quantum dots (Mnd-QDs) with lysine are stably dispersed in aqueous media, which made it easy to combine with targeting molecules. Receptor-mediated delivery of these quantum dots into pancreatic cancer cells has indicated that the multimodal Mnd-QDs could be diagnostic probes for early pancreatic cancer imaging and detection [55]. These studies suggest that quantum dots have a great potential to be a novel safe and efficient optical imaging agent in diagnostic imaging for early cancer detection [56].

One of the major obstacles in cancer therapy is the toxicity and poor bioavailability of the chemotherapy drugs. Nano-materials can reduce the systemic toxicity of the anti-cancer drugs through targeted delivery. A gold nanoparticle delivered gemcitabine (directed by EGFR inhibitor cetuximab) showed significant growth inhibition of pancreatic cancer cell both *in vitro* and *in vivo* with minimal toxicity [57]. A PLGA-poloxamer nanoparticle was used as a carrier to transfect a MBD1-siRNA plasmid into BxPC-3 cells and inhibited cell growth and induced apoptosis [58]. A liposomal nanoparticle containing Raf-1 antisense oligonucleotides also showed a therapeutic benefit against human pancreatic tumors in an athymic mouse model [59]. Further studies on the safety, specificity, and delivery efficiency of nanoparticles are warranted in order to extend the application of nanoparticles in cancer treatment [54].

Carbon nanotubes

Carbon nanotubes (CNTs) hold great promise in drug delivery, imaging, cancer targeting and therapies. It has been proved to be a versatile carrier for a wide variety of agents, including chemotherapy drugs. CNTs are chemically and mechanically stable with easy incorporation and slow release of the delivered drugs. The outside walls of CNTs can be chemically modified to achieve any desired targeting effect. CNTs also have a large surface area, which makes it capable to absorb and incorporate larger amount of drugs. There have not been any major concerns on the cytotoxicity of CNTs, making them a potentially applicable drug delivery vehicle [11,60].

The ability of carbon nanotubes to deliver drugs into tumor cells has generated huge enthusiasm in the potential cancer treatment. Paclitaxol conjugated single-walled carbon nanotubes (SWNT-PTX) led to higher efficacy in suppressing tumor growth than the clinical Taxol treatment in a breast cancer animal model. Prolonged blood circulation and elevated PTX uptake were observed suggesting that SWNT delivery provides enhanced permeability and better drug retention. The incorporated drugs or other molecules are first uptaken by the cancer cells and then slowly released from the SWNTs before excreting via biliary tract without systemic toxicity. When combined with monoclonal antibodies to target specific receptors on cancer cells, the carbon nanotubes complex could be used as targeted agents with better efficiency and less toxicity [61]. A recent study using EGF-directed carbon nanotube delivered cisplatin has shown selective killing of the human head and neck squamous carcinoma cells (HNSCC) which overexpress EGF receptors [62].

The carbon nanotube complexes could also be used for imaging as a biosensor. Single-walled carbon nanotubes conjugated with cyclic Arg-Gly-Asp (RGD) peptides was used as a contrast agent for photoacoustic imaging of xenograft tumors which showed strong photoacoustic signals in the tumors. This may contribute to the non-invasive tumor imaging and monitoring of nanotherapies in living subjects [63]. Moreover, the presence of carbon nanotubes with

CSPC Exhibit 1100
Page 58 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

associated metal impurities can be detected *in vivo* by noninvasive magnetic resonance imaging (MRI) techniques. Gadolinium-based carbon nanotubes have shown 100 times better efficacy than the currently used clinical contrast agents, which will have a significant impact on MRI technology in cancer treatment as an improved contrast agent.

There is growing body of literature recently on carbon nanotube delivered therapy in cancer treatment. CNT-mediated heat release of the drug could produce thermal cytotoxicity to tumor cells in cancer hyperthermia therapy [64,65]. Carbon nanotubes have also been used to form stable complexes with small molecules such as siRNAs for delivery into cancer cells [66]. In a lymph node metastasis animal model of pancreatic cancer, we have used modified magnetic multi-walled carbon nanotubes (mMWNTs) to investigate the feasibility of targeting mMWNTs to the lymph nodes through subcutaneous administration, and we found that the degree of positive staining of lymph nodes correlates with the concentration of mMWNTs. Aggregation of magnetic particles was found around the metastatic foci within the lymph nodes, and no particle agglomerates were found in other major organs. Therefore, mMWNTs appear to be a novel lymph node tracer which enables the small lymph nodes to be easily recognized during a surgical resection to remove positive lymph nodes. This finding suggests that subcutaneous administration of mMWNTs may be useful for diagnostic and therapeutic purpose in regional lymph nodes [67].

Potential Targets for Specific Delivery

Any therapeutic agents and delivery vehicles have side effects at varying degrees when administered systemically. Identification of specific surface receptors or ligands in pancreatic cancer that enables targeted delivery of chemotherapy drugs or other therapeutic agents to pancreatic cancer cells will significantly reduce the toxicity and increase the efficacy of cancer treatment. Several candidate genes have been indicated as potential targets for the specific delivery in pancreatic cancer including EGFR, urokinase plasminogen activator receptor (uPAR), transferrin, ERBB2, CA125, and stem cell markers such as epithelial cell adhesion molecule (EpCAM), CD44, and CD133 (Table 2).

EGFR

EGFR is overexpressed in majority of human pancreatic cancers. Activation of EGFR could trigger key downstream signaling cascades in cancer cell proliferation, apoptosis, migration, sensitivity to chemo-radiation therapy, and tumor angiogenesis. Moreover, conjugating EGF in a delivery vector carrying anti-cancer drugs or imaging agents can facilitate the specific delivery into cancer cells overexpressing EGFR such as pancreatic cancer cells [62,68]. In a recent study, cisplatin and EGF were attached to single-wall carbon nanotubes (SWNTs) to target squamous cancer cells HNSCC which overexpress EGFR. Through Qdot luminescence and confocal microscopy, it was shown that SWNT-Qdot-EGF bioconjugates was rapidly internalized into the cancer cells, and HNSCC cells were selectively killed *in vitro*, while tumor growth was regressed *in vivo* [62]. EGF target delivery system has also been used in cancer molecular imaging diagnosis. An EGF and dye conjugate were delivered into oral tumor cells and tissues, and the presence of oral neoplasia could be easily visualized by an increase in fluorescence contrast compared with normal mucosa [69]. In a colorectal cancer nude mice model, optical imaging probes targeting EGFR (NIR800-EGF) were synthesized and used to evaluate the therapeutic efficacy of cetuximab, an EGFR inhibitor. The NIR800-EGF accumulation in tumors correlated with relative EGFR expression and EGFR occupancy by cetuximab. The imaging approaches could benefit the noninvasive monitoring of the biological effects of EGFR targeted cancer therapy [70].

CSPC Exhibit 1100
Page 59 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

uPAR

Urokinase plasminogen activator receptor (uPAR) is highly expressed on most of pancreatic cancer cells, and can be used as an optimal surface molecule for receptor-targeted therapy in pancreatic cancer. An uPAR-targeted drug or toxin delivery system could selectively kill the uPAR-expressing tumor cells [71,72]. In an orthotopic xenograft model for pancreatic cancer, uPAR-targeted nanoparticles conjugated with a near-infrared dye-labeled fragment bind and accumulated in uPAR highly expressing pancreatic cancer cells. Optical and MRI were used to monitor the uPAR-elevated pancreatic cancer lesions. This novel receptor-targeted nanoparticle is a potential molecular imaging agent for the detection of primary and metastatic pancreatic cancer lesions [72].

Transferrin receptor

Transferrin receptor (TfR) is overexpressed in many types of cancer cells including breast cancer, prostate cancer, and squamous cell carcinomas, and correlate with the aggressiveness or proliferation of the tumor cells. Addition of the transferrin (Tf) ligand to a cationic liposome complex resulted in significantly increased *in vitro* and *in vivo* transfection efficiency in squamous cell carcinoma of the head and neck (SCCHN, 70-80% transfection rate compared with only 5--20% by liposome alone). Both p53 gene and siRNAs have been successfully delivered to the target organs using TfR conjugated liposomes or nanoparticles in treating many types of cancers including pancreatic cancer [9,73-76].

ERBB2

ERBB2 is a member of the EGFR family of receptor tyrosine kinases, also known as HER-2 or HER-2/neu. HER-2/neu is reported to be overexpressed on the surface of a panel of human pancreatic cancer cell lines and can be used as a therapeutic target. Lyu *et al* used a single chain Fv antibody (scFv23) targeting HER-2/neu to deliver tumor necrosis factor (TNF) to TNF-resistant pancreatic cancer cells, and compared the cell responses to TNF alone, scFv23/TNF, Herceptin, and combinations of scFv23/TNF with various chemotherapeutic agents including 5-FU, cisplatin, doxorubicin, gemcitabine and etoposide. Their results indicated that delivery of TNF to HER-2/neu expressing pancreatic cancer cells using HER-2/neu as a targeting molecule may be an effective therapy for pancreatic cancer especially when utilized in combination with 5-FU [77]. In another study, a nanosized immunoliposome-based delivery complex (scL) has been developed to deliver anti-HER-2 siRNA preferentially to tumor cells, and sensitize human tumor cells to chemotherapeutics by silencing the target gene and affecting its downstream pathways. This delivery method has been shown to significantly inhibit tumor growth in a pancreatic cancer model [78]. The advantage of using HER-2/neu as a target molecule is that it not only benefits pancreatic cancer treatment, but also can apply to other cancer with HER-2/neu overexpression.

CA125

CA125 is a cell surface associated glycosylated mucin protein, also known as MUC16. CA125 has been used for early detection of ovarian cancer in the past decades, and is also a valuable serum marker in gastrointestinal cancers, including pancreatic cancer. Duska *et al* have used a photosensitizer chlorin e_6 to conjugate to the F(ab')2 fragment of the CA125 antibody, which serves as a targeting molecule, in combination with cisplatin to treat cisplatin-resistant cells. This treatment showed a synergistic effect on human ovarian cancer cells [79]. Recent studies indicate that CA125 can bind to mesothelin, which is also overexpressed in pancreatic cancer. Targeted therapy using CA125 and maybe in combination with mesothelin could be a promising strategy for drug delivery in pancreatic cancer.

CSPC Exhibit 1100
Page 60 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Stem cell markers

Tumors contain a few embryonic-like cells, known as cancer stem cells or cancer-initiating cells (CIC), which count for primary and metastatic tumor growth. Therefore, targeting those cells is particularly important to eliminate tumors and prevent from tumor relapse. Gene profiling of cancer stem cells in many tumors have identified several unique markers such as CD24, CD44, CD133, CD166, EpCAM, and integrins. Their functions in cancer stem cell maintenance and activity is largely unknown [80,81]. EpCAM is a carcinoma-associated antigen and is overexpressed on most pancreatic tumor cells but not on normal cells. Salnikov *et al* have shown that targeting of EpCAM by bispecific antibody EpCAMxCD3 inhibits pancreatic cancer growth by using a BxPC-3 pancreatic carcinoma xenografts model [82]. Adjuvant treatment with monoclonal antibody of EpCAM reduced the 5-year mortality rate among colorectal cancer patients with minimal residual disease [83]. Hong *et al* found that CD44-positive cells are responsible for gemcitabine resistance in pancreatic cancer cells. After high-dose gemcitabine treatment to eliminate most of the cells, CD44-positive cells proliferated and reconstituted the resistant population of HPAC and CFPAC-1 cells. These data indicate that in therapeutic applications, targeted therapy against CD44 may overcome drug resistance in the treatment of pancreatic cancer [84]. CD133 is a pentaspan transmembrane glycoprotein overexpressed in many solid tumors and has also been indicated as a potential marker for cancer stem cell in gastrointestinal tract [85]. CD133 was found to be highly expressed in more than 50% of pancreatic cancer, gastric cancer and intrahepatic cholangiocarcinomas, and CD133 expression was shown to be correlated with lymph node metastasis and vascular endothelial growth factor-C expression in pancreatic cancer [86,87]. Recently CD133 has been used as a potential target for antibody-drug conjugates in hepatocellular and gastric cancers. A murine anti-human CD133 antibody conjugated to a potent cytotoxic drug, monomethyl auristatin F, effectively inhibited the growth of Hep3B hepatocellular and KATO III gastric cancer cells [88]. Further studies are warranted for using the stem cell markers as targeting molecules to treat pancreatic cancer.

Current Clinical Trials using Targeted Delivery

Targeted therapy against specific markers in pancreatic cancer, or targeted drug delivery which use specific markers in pancreatic cancer to deliver chemotherapy or other drugs may significantly improve the current therapies for pancreatic cancer treatment. There are preclinical data that indicate synergistic effects using gemcitabine, erlotinib and capecitabine to treat pancreatic cancer, and several inhibitors against cell surface receptors or cellular factors have also been used for targeted therapy in pancreatic cancer including IGFR inhibitors, antiangiogenic agents (axitinib, sorafenib), other EGFR inhibitors (gefitinib, lapatinib), anti-NFκB agents (curcumin), anti-mesothelin antibody, and anti-integrin antibody (volociximab), etc. [35,36,41,42,89-92]. However, there are very few clinical trials using targeted drug delivery to treat pancreatic cancer. A phase I trial evaluating the safety of Rexin-G gene transfer for advanced pancreatic cancer was initiated in 2005, in which a tumor targeted gene therapy against cyclin G1 was delivered using a modified virus vector to treat pancreatic cancer. Another phase I study used transferrin as a targeting agent to deliver nanocomplex with siRNA against the M2 subunit of ribonucleotide reductase (CALAA-01) in adults with solid tumors refractory to standard-of-care therapies. Thirty six patients are estimated to enroll from 2008 to 2010. In a recent phase I/II study, a chemotherapy drug Doxorubicin (DOX) is adsorbed to magnetic beads (MTCs), and the MTC-DOX is directed to the area of a tumor. The iron component of the particle makes it possible to direct MTC-DOX to specific tumor sites by placing a magnet on the body surface. It is hoped that MTC-DOX used with the magnet may target the drug directly to liver tumors and provide a treatment to patients with cancers that have spread to the liver. In the future, more specific targeting markers need to be identified to

CSPC Exhibit 1100
Page 61 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

help deliver the chemotherapy and other drugs for pancreatic cancer treatment. And the safety and efficacy of those targeted delivery should be tested as well.

Summary

Pancreatic cancer is a malignant disease with poor prognosis. For almost 20 years, there are no major breakthroughs in early detection and effective treatment for this terrible disease. Biological approaches that target pancreatic cancer at a molecular level are rapidly evolving and represent promising strategies in the diagnosis and treatment of pancreatic cancer. Using a highly efficient, non-toxic, control released delivery system to carry anti-cancer drugs or imaging agents to cancer cells through specific receptors expressed on cancer cell surfaces has been proved to be a novel and effective approach in pancreatic cancer therapy and diagnosis. The safety and specificity of the vectors such as liposomes, nanoparticles, and carbon nanotubes should be further studied.

Acknowledgments

This work is partially supported by the National Institutes of Health (NIH) Grant R21CA133604 (Li M), and the Dan L. Duncan Cancer Center Cancer Biology Program Pilot Grant (Li M).

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Page 62 of 333

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Page 63 of 333

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CSPC Exhibit 1100
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CSPC Exhibit 1100
Page 65 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

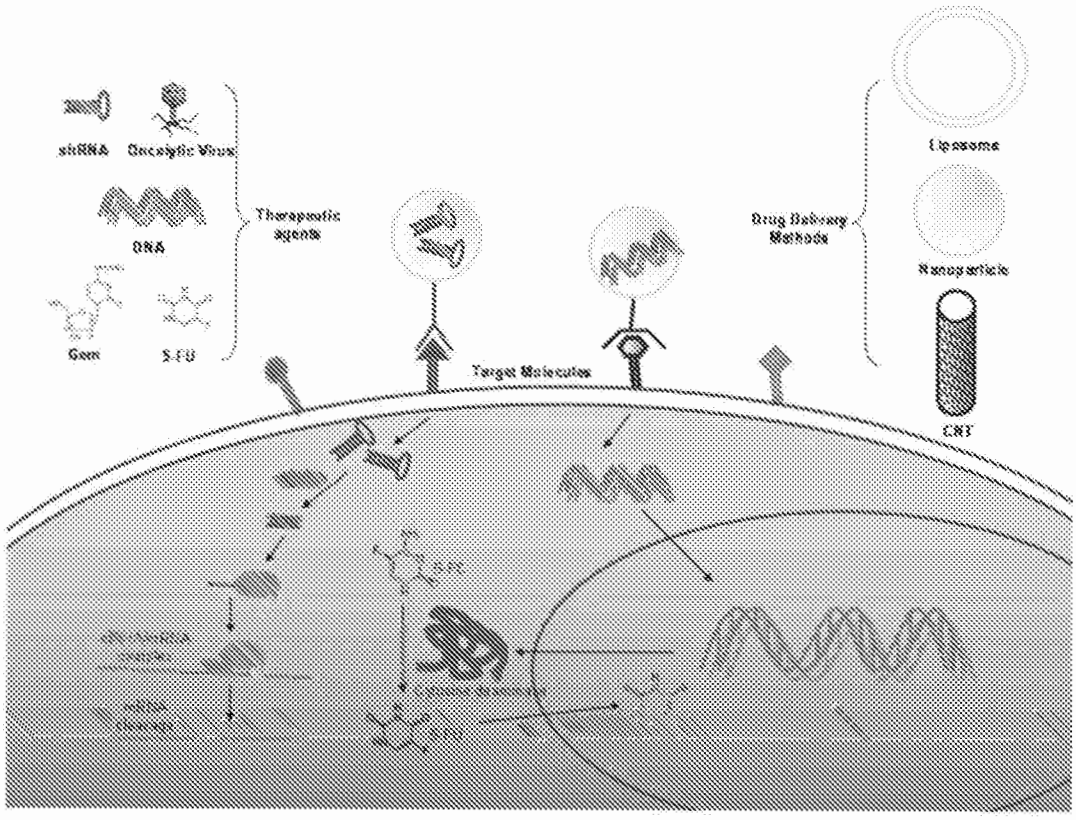


Figure 1. Targeted drug delivery models in pancreatic cancer

Liposomes, nanoparticles, and carbon nanotubes are most commonly used vectors to deliver cancer chemotherapy drugs and other therapeutic agents such as shRNA, tumor suppressor gene, suicide gene, oncolytic virus, small molecule inhibitor and antibody for pancreatic cancer treatment. Specific surface receptors or ligands in pancreatic cancer can be used to enable targeted delivery of the therapeutic agents to reduce the toxicity and increase the efficacy of therapy. A few examples of target molecules include EGFR, uPAR, transferrin, ERBB2, CA125, and stem cell markers such as EpCAM, CD44, and CD133. A representative delivery model in which nanoparticles carrying shRNA or suicide gene conjugated with target molecules, and the corresponding pathways inside the cells are shown.

CSPC Exhibit 1100
Page 66 of 333

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 1

Therapeutic Agents for Pancreatic Cancer Treatment.

Therapeutic Agents	Examples	References
siRNAs and shRNAs	MMP-2, HIF-1α, PDX-1, ZIP4, etc	14,15,16,17,50
Gene therapy/Suicide genes	p53, SSTR, CD, TK	9,18,19,20,21,24,25,26,27
Oncolytic viruses	Adenovirus, HSV, reovirus	13,28,29,30,31
Small molecule inhibitors	EGFR inhibitor	7,32,33
Antibodies	EGFR, VEGFR, MUC1, MSLN Abs	35,36,37,38,39,40,41,42

CSPC Exhibit 1100
Page 67 of 333

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Table 2

Potential Targets for Specific Delivery.

Delivery Targets	Therapeutic Agents and Organ Systems	References
EGFR	Chemotherapy drugs and imaging agents, Pancreas, colorectal cancer, and SCCHN	62,68,70
uPAR	Chemotherapy drugs and imaging agents, Pancreatic cancer	71,72
TfR	Gene therapy and shRNA therapy, Breast, prostate cancer, and SCCHN	9,73,76
ERBB2	Cytokine and chemotherapy, pancreatic cancer	77,78
CA125	Chemotherapy drug, ovarian caner	79
EpCAM	Antibody, pancreatic cancer	80,83
CD133	Cytotoxic drug, hepatocellular and gastric cancers	85,88

CSPC Exhibit 1100
Page 68 of 333

Electronic Acknowledgement Receipt

EFS ID:	42019178
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:	20:30:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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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

	1	MACARULLA MERCADÉ T, et al., Abstract 379. "Subgroup Analysis by Baseline Pain Intensity (BPI) and Analgesic Use (BAU) in NAPOLI-1: A phase III Study of Liposomal Irinotecan (nal IRI)±5-Fluorouracil/ Leucovorin (5-FU/LV) in Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy," J Clin Oncol. 36(4_Suppl):379 DOI: 10.1200/JCO.2018.36.4_suppl.379 (2018), 4 printed pages.
	2	MACARULLA MERCADÉ T, et al., Abstract 410. "Subgroup Analysis by Baseline (BL) Weight-Associated Parameters: A phase III Study of Liposomal Irinotecan (nal-IRI)±5-Fluorouracil/Leucovorin (5-FU/LV) in Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based (Gem) Therapy," J Clin Oncol. 36(4_Suppl):410 DOI: 10.1200/JCO.2018.36.4_suppl.410 (2018), 6 printed pages.
	3	MACARULLA MERCADÉ T, et al., Abstract 733P. "NAPOLI-1 Phase III Trial Outcomes by Prior Surgery, and Disease Stage, in Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Ann Oncol. 29(Supp_8)viii249-viii250 doi:10.1093/annonc/mdy282 (2018).
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	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-02-25
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Abstract

379

Background: We report an exploratory, *post hoc* subgroup analysis in pts with BPI and BAU data receiving nal-IRI+5-FU/LV, nal-IRI or 5-FU/LV in NAPOLI-1 (NCT01494506). In this pivotal trial, nal-IRI+5-FU/LV improved median OS (mOS) vs. 5-FU/LV (6.1 vs. 4.2 mo [HR=0.67; p=0.012]). **Methods:** BPI/BAU included an average of 3-7 days pt-recorded data before randomisation. Greater values indicated greater pain for BPI using a 100 mm visual analogue scale. BAU was converted to morphine equivalent mg/day. **Results:** Of 417 ITT pts, 295 had BPI and 299 had BAU data. Mean and median BPI were 28.6 and 25.0, respectively, and BAU were 33.3 and 8.1 mg/day, respectively. The percentage of pts with KPS ≥ 80 was higher in ≤ mean/≤ median (n=159/148) BPI groups vs. > mean/> median (n=136/147) BPI groups (96-97 vs. 83%) and in ≤mean/≤median (n=207/150) BAU groups vs. > mean/> median (n=92/149) BAU groups (95-97 vs. 82-85%). mOS and median PFS (mPFS) were higher for nal-IRI+5-FU/LV vs 5-FU/LV in all groups, with ≤ mean/≤ median BPI or BAU showing better outcomes vs. > mean/> median BPI or BAU (Table). **Conclusions:** BPI and BAU appear to have a prognostic effect on outcomes in mPDAC pts in the NAPOLI-1 study. No predictive effect was observed, with nal-IRI+5-FU/LV showing higher mOS vs. 5-FU/LV in all groups. Clinical trial information: NCT01494506.

	ITT population (N = 417)																					
	Mean BPI = 28.6						Median BPI = 25.0						Mean BAU = 33.3 mg/day						Median B			
	≤			>			≤			>			≤			>			≤			
	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI+ 5-FU/LV	5-FU/LV	HR; p-val
n	48	38		40	38		45	35		43	41		56	56		33	21		46	37	
mOS, mo	8.9	5.1	0.73; ns	4.8	2.8	0.52; 0.01	8.9	5.9	0.77; ns	4.7	2.8	0.50; <0.01	8.5	4.8	0.68; ns	4.9	2.6	0.40; <0.01	8.9	6.1	0.8; ns
mPFS, mo	4.1	1.6	0.66; ns	2.8	1.4	0.44; <0.01	4.2	1.6	0.66; ns	2.7	1.4	0.45; <0.01	4.1	1.4	0.60; <0.05	3.0	1.4	0.34; <0.01	4.3	2.2	0.6; ns

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Abstract

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Background: We report an exploratory, *post hoc* subgroup analysis in pts with BPI and BAU data receiving nal-IRI+5-FU/LV, nal-IRI or 5-FU/LV in NAPOLI-1 (NCT01494506). In this pivotal trial, nal-IRI+5-FU/LV improved median OS (mOS) vs. 5-FU/LV (6.1 vs. 4.2 mo [HR=0.67; p=0.012]). **Methods:** BPI/BAU included an average of 3-7 days pt-recorded data before randomisation. Greater values indicated greater pain for BPI using a 100 mm visual analogue scale. BAU was converted to morphine equivalent mg/day. **Results:** Of 417 ITT pts, 295 had BPI and 299 had BAU data. Mean and median BPI were 28.6 and 25.0, respectively,

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and BAU were 33.3 and 8.1 mg/day, respectively. The percentage of pts with KPS ≥ 80 was higher in ≤ mean/≤ median (n=159/148) BPI groups vs. > mean/> median (n=136/147) BPI groups (96-97 vs. 83%) and in ≤mean/≤median (n=207/150) BAU groups vs. > mean/> median (n=92/149) BAU groups (95-97 vs. 82-85%). mOS and median PFS (mPFS) were higher for nal-IRI+5-FU/LV vs 5-FU/LV in all groups, with ≤ mean/≤ median BPI or BAU showing better outcomes vs. > mean/> median BPI or BAU (Table). **Conclusions:** BPI and BAU appear to have a prognostic effect on outcomes in mPDAC pts in the NAPOLI-1 study. No predictive effect was observed, with nal-IRI+5-FU/LV showing higher mOS vs. 5-FU/LV in all groups. Clinical trial information: NCT01494506.

	Median BPI = 2.5						Median BPI = 2.5					
	≤			>			≤			>		
	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value
n	48	38		40	38		45	35		43	33	21
mOS, mo	8.9	5.1	0.73; ns	4.8	2.8	0.52; 0.01	8.9	5.9	0.77; ns	4.7	4.9	2.6
mPFS, mo	4.1	1.6	0.66; ns	2.8	1.4	0.44; <0.01	4.2	1.6	0.66; ns	2.7	3.0	1.4

	Median BAU = 8.1 mg/day						Median BAU = 8.1 mg/day					
	≤			>			≤			>		
	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value	nal-IRI + 5-FU/LV	5-FU/LV	HR; p-value
n	46	37		43	40							
mOS, mo	8.9	6.1	0.82; ns	4.8	3.1	0.47; <0.01						
mPFS, mo	4.3	2.2	0.67; ns	3.0	1.4	0.37; <0.001						

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CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Subgroup analysis by baseline (BL) weight-associated parameters: A phase III study of liposomal irinotecan (nal-IRI)±5-fluorouracil/leucovorin (5-FU/LV) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based (gem) therapy.

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Teresa Mercade Macarulla, Richard Hubner, Jean-Frédéric Blanc, Andrea Wang-Gillam, Chung-Pin Li, Gyorgy Bodoky, Andrew Peter Dean, Shan Yanshen, Gayle S. Jameson, Kyung-Hun Lee, Chang-Fang Chiu, Gilberto Schwartsmann, Fadi S. Braiteh, David Cunningham, Li-Tzong Chen, Daniel D. Von Hoff, Khalid Kevin Mamiouk, Floris A de Jong, Jens T. Siveke

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Abstract

410

Background: We report prognostic evaluation of BL weight-associated parameters (body-mass index [BMI], body surface area [BSA] and weight) in pts with mPDAC after progression following gem-based therapy (NAPOLI-1 trial; NCT01494506). Pts received nal-IRI+5-FU/LV, nal-IRI monotherapy or 5-FU/LV in NAPOLI-1, an international, randomised, phase 3 trial; nal-IRI+5-FU/LV treatment resulted in a 45% increased median OS vs. 5-FU/LV (unstratified HR = 0.67; p = 0.012). **Methods:** This exploratory subgroup analysis compares outcomes by BL BMI, BSA and weight, using primary survival analysis data from the ITT population for all treatment arms combined (n = 417) and the nal-IRI+5-FU/LV arm on its own (n = 117). **Results:** OS and PFS were not significantly different between BL BMI, BSA and weight median subgroups in the entire NAPOLI-1 ITT population (HR range 1.06–1.15; log-rank p-value range 0.21–0.60; Table) and in the nal-IRI+5-FU/LV arm (HR range 0.94–1.19; log-rank p-value range 0.43–1.00). **Conclusions:** This *post-hoc* subgroup analysis did not detect any prognostic impact on treatment outcome by BL BMI, BSA and weight for mPDAC pts progressed following gem-based therapy. This observation rules out a treatment-independent effect. No evidence of a predictive effect on nal-IRI+5-FU/LV efficacy was found. Clinical trial information: NCT01494506.

At BL: All NAPOLI-1 pts. randomised to nal-IRI+5-FU/LV, nal-IRI monotherapy or 5-FU/LV (n = 417)

At BL: NAPOLI-1 = modified nal-IRI + 5-FU/LV; nal-IRI = nanoliposomal irinotecan; BL = baseline; BMI = body mass index; kg/m² = kilograms per square meter; mo = months; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; cm = centimeters; kg = kilograms.

	Median BL BMI = median kg/m² (n = 209)	Median BL BMI = median kg/m² (n = 208)	HR (95% CI) log-rank p-value (2-sided)	Median BL albumin = median g/dL (n = 208)	Median BL albumin = median g/dL (n = 209)	HR (95% CI) log-rank p-value (2-sided)	Median BL weight = median kg (n = 207)	Median BL weight = median kg (n = 210)	HR (95% CI) log-rank p-value (2-sided)
	< median	≥ median		< median	≥ median		< median	≥ median	
Median OS, mo (95%CI)	4.8 (4.2–5.5)	5.2 (4.5–6.1)	1.15 (0.92–1.44) p = 0.21	4.8 (4.2–5.6)	4.9 (4.5–5.8)	1.06 (0.85–1.32) p = 0.60	4.8 (4.2–5.4)	5.2 (4.5–5.9)	1.13 (0.91–1.42) p = 0.27
Median PFS, mo (95%CI)	2.3 (1.6–2.8)	2.6 (1.7–2.8)	1.07 (0.86–1.33) p = 0.53	2.4 (1.6–2.8)	2.6 (1.6–2.8)	1.09 (0.88–1.36) p = 0.42	2.4 (1.6–2.8)	2.6 (1.7–2.8)	1.12 (0.90–1.39) p = 0.32

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CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Subgroup analysis by baseline (BL) weight-associated parameters: A phase III study of liposomal irinotecan (nal-IRI)±5-fluorouracil/leucovorin (5-FU/LV) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based (gem) therapy.

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Teresa Mercade Macarulla, Richard Hubner, Jean-Frédéric Blanc, Andrea Wang-Gillam, Chiang-Pin Li, Gyorgy Bodoky, Andrew Peter Dean, Shan Yanshen, Gayle S. Jameson, Kyung-Hun Lee, Chang-Fang Chiu, Gilberto Schwartsmann, Fadi S. Braiteh, David Cunningham, Li-Tzong Chen, Daniel D. Von Hoff, Khalid Kevin Mamlouk, Floris A de Jong, Jens T. Siveke

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Abstract

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Background: We report prognostic evaluation of BL weight-associated parameters (body-mass index [BMI], body surface area [BSA] and weight) in pts with mPDAC after progression following gem-based therapy (NAPOLI-1 trial; NCT01494506). Pts received nal-IRI+5-FU/LV, nal-IRI monotherapy or 5-FU/LV in NAPOLI-1, an international, randomised, phase 3 trial; nal-IRI+5-FU/LV treatment resulted in a 45% increased median OS vs. 5-FU/LV (unstratified HR = 0.67; p = 0.012). **Methods:** This exploratory subgroup analysis compares outcomes by BL BMI, BSA and weight, using primary survival analysis data from the ITT population for all treatment arms combined (n = 417) and the nal-IRI+5-FU/LV arm on its own (n = 117). **Results:** OS and PFS were not significantly different between BL BMI, BSA and weight median subgroups in the entire NAPOLI-1 ITT population (HR range 1.06–1.15; log-rank p-value range 0.21–0.60; Table) and in the nal-IRI+5-FU/LV arm (HR range 0.94–1.19; log-rank p-value range 0.43–1.00). **Conclusions:** This *post-hoc* subgroup analysis did not detect any prognostic impact on treatment outcome by BL BMI, BSA and weight for mPDAC pts progressed following gem-based therapy. This observation rules out a treatment-independent effect. No evidence of a predictive effect on nal-IRI+5-FU/LV efficacy was found. Clinical trial information: NCT01494506.

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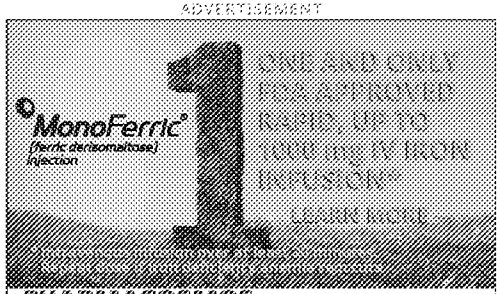
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At BL	All NAPOLI-1 pts randomised to nal-IRI+5-FU/LV, nal-IRI monotherapy or 5-FU/LV (n = 417)							
	Median BL BMI = 22.95 kg/m²			Median BL BSA = 1.71 m²			Median BL weight	
	< median (n = 209)	≥ median (n = 208)	HR (95%CI) log-rank p-value	< median (n = 208)	≥ median (n = 209)	HR (95%CI) log-rank p-value	< median (n = 207)	≥ median (n = 210)
Median OS, mo (95%CI)	4.8 (4.2–5.5)	5.2 (4.6–6.1)	1.15 (0.92–1.44) p = 0.21	4.8 (4.2–5.6)	4.9 (4.5–5.8)	1.06 (0.85–1.32) p = 0.60	4.8 (4.2–5.4)	5.2 (4.5–5.9)
Median PFS, mo (95%CI)	2.3 (1.6–2.8)	2.6 (1.7–2.8)	1.07 (0.86–1.33) p = 0.53	2.4 (1.6–2.8)	2.6 (1.6–2.8)	1.09 (0.88–1.36) p = 0.42	2.4 (1.6–2.8)	2.6 (1.7–2.8)

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733P NAPOLI-1 phase III trial outcomes by prior surgery, and disease stage, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

T. Macarulla Mercade[1], G. Bodoky[2], J. Siveke[3], K-H. Lee[4], J. Chen[5], B. Mirakhur[6], A. Dean[7], L-T. Chen[8], F. de Jong[9]

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Background: The NAPOLI-1 phase 3 trial (NCT01494506) reported significantly increased median OS with nal-IRI+5-FU/LV vs 5-FU/LV (6.1 mo vs 4.2 mo; HR = 0.67; p = 0.012) in mPDAC patients who progressed after gemcitabine-based therapy. We report subgroup analysis outcomes in NAPOLI-1 patients who had undergone prior surgery and by disease stage at diagnosis.

Methods: This post-hoc analysis investigated outcomes with or without prior surgery, and by disease stage at diagnosis (stage IIA, IIB, or III, vs IV). *P* values are descriptive.

Results: In the NAPOLI-1 trial, OS and PFS were increased in ITT patients who had undergone prior surgery compared to those who did not (Table). In patients with prior surgery receiving nal-IRI+5-FU/LV (n = 40), OS and PFS were increased vs 5-FU/LV (n = 43) (HR = 0.84 and 0.72). Patients without prior surgery had significantly increased OS and PFS with nal-IRI+5-FU/LV (*n* = 77) vs 5-FU/LV (n = 76) (HR = 0.56, *p* = 0.003 and HR = 0.47, p < 0.001). OS was significantly increased in ITT patients with disease stages IIA (n = 36, HR = 0.59, p = 0.613), IIB (n = 77, 0.54, < 0.001), and III (n = 75, 0.57, <0.001) vs stage IV (n = 213). A consistent OS increase was also seen in patients treated with nal-IRI+5-FU/LV: stage IIA (HR = 0.63, ns) stage IIB (HR = 0.50, p = 0.024) and stage III (HR = 0.43, p = 0.021) vs stage IV.

Conclusions: OS and PFS were increased in ITT patients who had undergone surgery prior to trial inclusion. Patients treated with nal-IRI+5-FU/LV showed a consistent increase in OS and PFS vs 5-FU/LV. ITT patients with stages IIA, IIB, and III had significantly improved OS vs those with stage IV disease. Treatment with nal-IRI+5-FU/LV showed a survival benefit across disease stages IIA, IIB, and III, vs stage IV. Limited patient numbers should be taken into consideration when interpreting these findings.

Clinical trial identification: NCT01494506.

Editorial acknowledgement: Medical writing support for the preparation of this abstract was provided by Physicians World Europe GmbH, Mannheim, Germany, with financial support from Shire (previously Baxalta), Zug, Switzerland.

Legal entity responsible for the study: Merrimack Pharmaceuticals.

Funding: The analysis was funded by Shire, the study was funded by Merrimack Pharmaceuticals.

Disclosure: G. Bodoky: Consulting, Advisory role: Bayer, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche; Support for travel, accommodation and expenses: Janssen, Lilly, Novartis, Pfizer, Roche. J. Siveke: Consulting, Advisory role: Merrimack Pharmaceuticals, Baxalta (now part of Shire), Celgene, Lilly; Research funding: Celgene, Bristol-Myers Squibb, sSC, Novartis, Boehringer Ingelheim; Travel, accommodation, expenses: Roche, Celgene, Shire. J. Chen, F. de Jong: Employee, Stockholder: Shire. B. Mirakhur: Employee: Ipsen, Stockholder: Ipsen, GlaxoSmithKline. A. Dean: Honoraria: Specialised Therapeutics Australia; Consultant/Advisor: Baxalta (now part of Shire), Celgene. L-T. Chen: Honoraria, Consultant, Advisor: Bristol-Myers Squibb, Ono Pharmaceutical, Lilly, MSD, Pharmaengine, Merrimack Pharmaceuticals, TTY Biopharm, SynCoreBio, Five Prime, Novartis; Patent: Humilife Technology; Research funding: Novartis, GlaxoSmithKline, Merck Serono, TTY Biopharm, Polaris, SyncoreBio, Pfizer, Celgene. All other authors have declared no conflicts of interest.

CSPC Exhibit 1100
Page 91 of 333

Table 73P

Prior surgery

	All ITT		Yes*		No*	
	Yes n=142	No n=275	nal-IRI+5-FU/LV n=40	5-FU/LV n=43	nal-IRI+5-FU/LV n=77	5-FU/LV n=76
mOS	6.8	4.4	8.4	6.1	5.3	3.4
HR	0.62		0.81		0.56	
P value	<0.001		0.547		0.005	
mPFS	2.6	2.2	2.8	2.6	3.3	1.4
HR	0.84		0.72		0.47	
P value	0.129		0.217		<0.001	
Disease stage at diagnosis						
	Stage IIA			Stage IIB		
	All ITT	nal-IRI+5-FU/LV	5-FU/LV	All ITT	nal-IRI+5-FU/LV	5-FU/LV
	n = 36	n = 8	n = 9	n = 77	n = 26	n = 22
mOS	6.4	8.6	6.1	6.1	10.2	5.6
HR†	0.59	0.63	0.42	0.54	0.50	0.43
P value	0.013	0.390	0.070	<0.001	0.024	0.012
	Stage III			Stage IV		
	All ITT	nal-IRI+5-FU/LV	5-FU/LV	All ITT	nal-IRI+5-FU/LV	5-FU/LV
	n = 75	n = 21	n = 19	n = 213	n = 61	n = 62
mOS	6.3	9.0	7.0	4.2	4.7	3.1
HR†	0.57	0.43	0.49			
P value	<0.001	0.021	0.039			

*Comparing treatments;
†vs Stage IV

CSPC Exhibit 1100
Page 92 of 333

O – 008 **Selected subgroup analyses of liposomal irinotecan (nal-IRI) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the global NAPOLI-1 phase III trial**

I Macarulla Mercadé[1], K Lee[2], G Lakatos[3], A Wang-Gillam[4], L Chen[5], B Mirakhur[6], F De Jong[7]

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Introduction: NAPOLI-1 (NCT01494506; Wang-Gillam et al., Lancet 2016;387:545-57) was a global phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy. In patients receiving nalIRI+5FU/LV, median overall survival (mOS) was significantly higher (6.1 months) compared with 5FU/LV (4.2 months; unstratified HR = 0.67; P = 0.012). Here, we summarise four separate NAPOLI-1 subgroup analyses investigating the effect of selected baseline parameters.

Methods: These post-hoc analyses explored outcomes in patients with or without metabolism and nutrition disorders (including hypercholesterolemia and decreased appetite, comprising anorexia, poor appetite, lack of appetite and loss of appetite; abstract_#327), by primary tumour location (pancreatic head only, body only, tail only, and multiple locations including or excluding the head; abstract_#335), with or without a biliary stent (abstract_#338), and by best response to prior therapy (complete response/partial response [CR/PR] vs not-CR/PR, and CR/PR/stable disease [CR/PR/SD] vs not-CR/PR/SD; abstract_#339).

Results: For ITT patients in the metabolism and nutrition disorders analysis (abstract_#327), survival was significantly reduced in those patients (n = 77) with baseline decreased appetite compared with patients (n = 348) without decreased appetite (mOS: 3.6 vs 5.3 months; HR = 1.65, P < 0.001). A trend for lower survival was observed in patients with hypercholesterolemia.

In the analysis investigating the effect of primary tumour location on outcomes (abstract_#335), survival was comparable across primary tumour location subgroups (HRs=0.87–1.06). However, patients receiving nal-IRI+5-FU/LV showed an increased survival across primary tumour location subgroups compared with 5-FU/LV (HRs=0.59–0.88 for groups n > 10 per arm).

In ITT patients with a biliary stent at baseline (n = 37), survival was comparable to those without a stent (mOS: 5.3 vs 4.8 months; HR = 0.97) (abstract_#338). In patients with a stent and receiving nal-IRI+5-FU/LV (n = 15), we observed a trend for increased survival compared with patients receiving 5-FU/LV (mOS: 6.2 vs 5.2 months; HR = 0.44; n = 8). In patients without a stent, a similar survival benefit was seen for nal-IRI+5-FU/LV (n = 102) versus 5-FU/LV (n = 111) (mOS: 6.1 vs 4.2 months; HR = 0.68).

For subgroups stratified by response to prior therapy (abstract_#339), there was a trend for increased survival in patients with CR/PR compared with not-CR/PR (mOS: 5.6 vs 4.8 months; HR = 0.73). In patients with CR/PR/SD survival was similar compared with not-CR/PR/SD (mOS both 4.9 months, HR = 0.95). A trend for increased survival was also shown in patients receiving nal-IRI+5-FU/LV with CR/PR (n = 11) compared with not-CR/PR (n = 106) (mOS: 9.3 vs 6.1 months; HR = 0.64). Survival was comparable in patients with CR/PR/SD (n = 58) vs not-CR/PR/SD (n = 59) (mOS: 6.2 vs 6.1 months; HR = 1.04).

Drug related AEs and dose modifications/discontinuations in the different subgroups were generally comparable to the NAPOLI-1 study.

Conclusion: In the NAPOLI-1 study, decreased appetite at baseline was shown to be prognostic for survival in patients with mPDAC who progressed after gemcitabine-based therapy. These results indicate that appropriate management is essential in patients with decreased appetite. We did not identify a significant prognostic effect of primary tumour location, biliary stent, or best response to prior therapy in either the NAPOLI-1 ITT population or the nal-IRI+5-FU/LV treatment arm on survival after trial inclusion. Nonetheless, a consistent treatment benefit was observed in patients treated with nal-IRI+5-FU/LV vs 5-FU/LV alone across subgroups.

P – 150 **Prognostic effect of primary tumor location in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)**

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Introduction: In NAPOLI-1 (NCT01494506), treatment with liposomal irinotecan + 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) significantly increased median overall survival (mOS) 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) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who had progressed following gemcitabine-based therapy. A potential prognostic impact of primary tumor location on metastatic pancreatic cancer outcomes has been reported. We investigated the effect of primary tumor location on survival following inclusion in the NAPOLI-1 study.

Methods: This post-hoc analysis explored outcomes in patients with primary tumor locations of the pancreatic head only (H only), body only (B only), tail only (T only), and multiple locations including (H_incl) and excluding (H_excl) the head.

Results: Of 417 patients, 239 (57%) had a primary tumor location of H only, 54 (13%) B only, 62 (15%) T only, 17 (4%) H_incl and 30 (7%) H_excl. Karnofsky performance status was lower in patients with a primary tumor location of T only versus the intent-to-treat population. The mOS (HRs: 0.87–1.06) and median progression-free survival (mPFS) (HRs: 0.82–0.98) were similar across primary tumor location subgroups and no clear prognostic signal for OS was detected. The mOS and mPFS in patients with a primary tumor location of H only were 5.0 and 2.7 months, respectively, versus 5.4 and 2.8 months, respectively, for those with B only (mOS: HR = 1.06, 95%CI:0.75–1.50, P = 0.737; mPFS: HR = 0.98, 95%CI:0.70–1.37, P = 0.925). For patients with T only, mOS and mPFS were 4.3 and 1.7 months respectively (mOS H only vs. T only: HR = 0.89, 95%CI:0.64–1.23, P = 0.469; mPFS H only vs. T only HR = 0.89, 95%CI:0.66–1.22, P = 0.471). For patients with H_incl, mOS and mPFS were 5.7 and 2.3 months respectively, while for H_excl patients they were 4.6 and 1.4 months, respectively. For the comparison of mOS between the H only and B only+T only+H_excl subgroup (mOS=4.6, mPFS=1.7 months), HR = 0.88 (95%CI:0.69–1.11, P = 0.285) while for mPFS HR = 0.83 (95%CI:0.66–1.05, P = 0.116). For the comparison of mOS between the H only and B only+T only+H_excl+H_incl subgroup (mOS=4.6, mPFS=1.7 months), HR = 0.91 (95%CI:0.72–1.15, P = 0.421), while for mPFS HR = 0.87 (95%CI:0.70–1.09, P = 0.233). For the comparison of mOS between the H only+H_incl and B only+T only+H_excl subgroup HR = 0.87 (95%CI:0.69–1.10, P = 0.240), while for mPFS HR = 0.82 (95%CI:0.65–1.03, P = 0.084). Both mOS and mPFS were higher in patients treated with nal-IRI+5-FU/LV vs. 5-FU/LV across primary tumor location subgroups (mOS: HRs: 0.39–0.88; two groups with n < 10 per arm were discounted). Safety, drug related AEs and dose modifications/discontinuations in the PTL subgroups were broadly similar to the overall NAPOLI-1 study arms.

Conclusion: In NAPOLI-1, 61% of patients had a primary tumor location including the pancreatic head. This analysis did not detect a clear prognostic effect of primary

tumor location on survival for mPDAC patients progressing after gemcitabine-based treatment. Patients with primary tumors in the head only or including head had similar mOS and mPFS to other patients. A consistent treatment benefit was shown with nal-IRI+5-FU/LV vs. 5-FU/LV regardless of primary tumor location.

P – 152 **The effect of best response to prior anticancer therapy on efficacy outcomes in the NAPOLI-1 trial of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy**

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Introduction: In the NAPOLI-1 phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy (NCT01494506), nal-IRI+5-FU/LV significantly increased median overall survival (mOS) vs 5-FU/LV control (6.1 vs 4.2 months; unstratified hazard ratio [HR] 0.67 [0.49–0.92]; P = 0.012). Best response to prior therapy may influence treatment outcomes, prognosis and subsequent therapy choices.

Methods: This post-hoc analysis explored outcomes in NAPOLI-1 patients based on best response to prior anticancer therapy. Treatment response groups were: complete response/partial response as prior best response (CR/PR) vs not CR/PR, and complete response/partial response/stable disease as prior best response (CR/PR/SD) vs not CR/PR/SD.

Results: Prior to study entry, 55/417 patients (13%) had CR/PR on prior anticancer therapy, and 211 (51%) had CR/PR/SD. In the overall intent-to-treat (ITT) population, trends towards improved outcomes were observed in CR/PR vs not CR/PR patients (mOS 5.6 vs 4.8 months, HR = 0.73, P = 0.08; median progression-free survival [mPFS] 3.8 vs 2.4 months, HR = 0.73, P = 0.06; objective response rate [ORR] 13% vs 6%, P = 0.085). mOS, mPFS and ORR were similar in CR/PR/SD vs not CR/PR/SD patients (mOS 4.9 vs 4.9 months, HR = 0.95, P = 0.68, mPFS 2.5 vs 2.6 months, HR = 1.00, P = 0.95; ORR 7% vs 7%, P = 1.00). In the nal-IRI + 5-FU/LV arm, a trend towards improved mOS, mPFS and ORR was observed in patients with CR/PR (n = 11) vs not CR/PR (n = 106) (mOS 9.3 vs 6.1 months, HR = 0.64, P = 0.34, mPFS 4.2 vs 3.0 months, HR = 0.53, P = 0.13; ORR 27% vs 15%). mOS, mPFS and ORR were similar in patients with CR/PR/SD (n = 58) vs not CR/PR/SD (n = 59) (mOS 6.2 vs 6.1 months, HR = 1.04, P = 0.88; mPFS 4.0 vs 3.3 months, HR = 1.18, P = 0.45, ORR 14% vs 19%, P = 0.62). Patients with CR/PR numerically benefited from treatment with nal IRI+5 FU/LV (n = 11) vs 5 FU/LV (n = 21) (mOS 9.3 vs 5.1 months, HR = 0.46, P = 0.14; mPFS 4.2 vs 1.4 months, HR = 0.33, P = 0.03; ORR 27% vs 0, P = 0.03). Patients with not CR/PR also benefited from treatment with nal IRI+5-FU/LV (n = 106) vs 5-FU/LV (n = 98) (mOS 6.1 vs 4.6 months, HR = 0.69, P = 0.03; mPFS 3.0 vs 1.5 months, HR = 0.58, P < 0.01; ORR 15% vs 1%, P < 0.01). Similar trends towards improved outcomes were also observed in patients with CR/PR/SD when treated with nal-IRI+5-FU/LV (n = 58) vs 5-FU/LV (n = 61) (mOS 6.2 vs 4.8 months, HR = 0.68, P = 0.09; mPFS 4.0 vs 1.4 months, HR = 0.53, P < 0.01; ORR 14% vs 2%, P < 0.05). A treatment benefit was observed for patients with not CR/PR/SD when treated with nal IRI+5-FU/LV (n = 59) vs 5-FU/LV (n = 58) (mOS 6.1 vs 3.6 months, HR = 0.63, P = 0.04; mPFS 3.3 vs 1.6 months, HR = 0.56, P < 0.01; ORR 19% vs 0%, P < 0.01).

Conclusion: In both the overall ITT NAPOLI-1 population and the nal-IRI+5-FU/LV arms, there was a trend towards improved efficacy outcomes in patients with CR/PR vs not CR/PR, however this trend was not observed in CR/PR/SD vs not CR/PR/SD patients. Patients in all treatment response subgroups benefited from treatment with nal-IRI+5-FU/LV vs 5-FU/LV, regardless of best response to prior therapy.

CSPC Exhibit 1100
Page 96 of 333

691P

Integrated population pharmacokinetic modelling of liposomal irinotecan in patients with various tumour types, including untreated metastatic pancreatic cancer (mPC)

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BACKGROUND

- Liposomal irinotecan (nal-IRI) is a liposomal encapsulation of the topoisomerase 1 inhibitor irinotecan to allow prolonged circulation of irinotecan and its active metabolite SN-38.[1]
- nal-IRI+5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA for the treatment of metastatic pancreatic cancer (mPC) after disease progression following gemcitabine-based therapy,[2] based on findings from the NAPOLI-1 trial.[3]
  - In the NAPOLI-1 trial, the combination of nal-IRI+5-FU/LV significantly prolonged overall survival compared with 5-FU/LV treatment alone in patients with mPC.[3]
- The combination of nal-IRI+5-FU/LV and oxaliplatin (NAPOX) is being investigated as first-line treatment for patients with mPC in a phase 1/2 dose-exploration and dose-expansion study (NCT02551991) to determine the most appropriate dose for phase 3 studies.

OBJECTIVE

- This analysis describes the population pharmacokinetics (PK) of nal-IRI in patients with various tumour types, including untreated mPC.

METHODS

Study population

- PK data from overall 440 patients with various tumour types (mPC, n = 316) were derived from seven studies (Table 1).

Population PK analyses

- PK parameters for total irinotecan (tIRI) and SN-38 following nal-IRI administration were estimated with non-linear mixed effects modelling.
  - The adequacy of the model was assessed based on the uncertainty of parameter estimates and on advanced evaluation methods such as a visual predictive check.
- Potential covariates, such as patient demographics and variants of the uridine diphosphate glucuronosyltransferase (UGT; encoded by *UGT1A1*28*) were investigated to examine interindividual variability.
  - Certain genetic polymorphisms of *UGT1A1*28* can alter the PK, the pharmacodynamics and the risk of toxicities of UGT substrates such as irinotecan.[4]

CSPC Exhibit 1100
Page 97 of 333

RESULTS

Study population

- Overall, 35% (n/N = 154/440) of patients were Asian and 51% (n/N = 226/440) were male.
- Among patients with the known *UGT1A1*28* status, 17% (n/N = 27/155) had a *UGT1A1*28 *7/*7* homozygous genotype.

Table 1. Studies used in this analysis

Study	Phase	Patients[a]	N[a]	nal-IRI dose regimen, mg/m²[b]	Co-administration
NCT02551991	1/2	mPC	56	60, 65, 80 q2w	5-FU/LV + oxaliplatin
PEP0201	1	Various tumour types	11	60, 120, 180 q3w	None
PEP0203 (NCT02884128)	1	Various tumour types	16	60, 80, 100, 120 q3w	5-FU/LV
PEP0206 (NCT00813072)	2	Various tumour types	37	120 q3W	None
PIST-CRC-01 (NCT00940758)	1	Metastatic colorectal cancer	18	80, 90, 100 q2w	None
CITS (NCT02551991)	1	Various tumour types	42	40, 60, 80 q2w	None
NAPOLI-1 (NCT01494506)	3	mPC	260	80 q2w, 120 q3w	None or 5-FU/LV

[a]Patients included in this analysis. [b]Expressed as salt base equivalent.
5-FU, 5-fluorouracil; LV, leucovorin; mPC, metastatic pancreatic cancer; nal-IRI, liposomal irinotecan; PK, pharmacokinetics; q2w, every 2 weeks; q3w, every 3 weeks.

Population PK modelling of nal-IRI

- Observed concentration–time profiles of irinotecan and its metabolite SN-38 in each study are shown in Figure 1.
- The PK of tIRI is described by a two-compartment model with first-order elimination.
- SN-38 is formed directly by a first-order constant from the central compartment of nal-IRI (9%) or after using a transit compartment (main part, 35%) (Figure 2).
- Model evaluation was satisfactory for both tIRI and SN-38 (Figure 3).

PK parameters after nal-IRI administration

- Population PK parameters of the pooled population are shown in Table 2.
  - Clearance was 17 L/week and 118 L/h for tIRI and SN-38, respectively.
  - Central and peripheral volumes of distributions for tIRI were 4 L and 0.4 L, respectively.

Figure 1. Observed concentrations of (A) irinotecan and (B) SN-38 over time by study

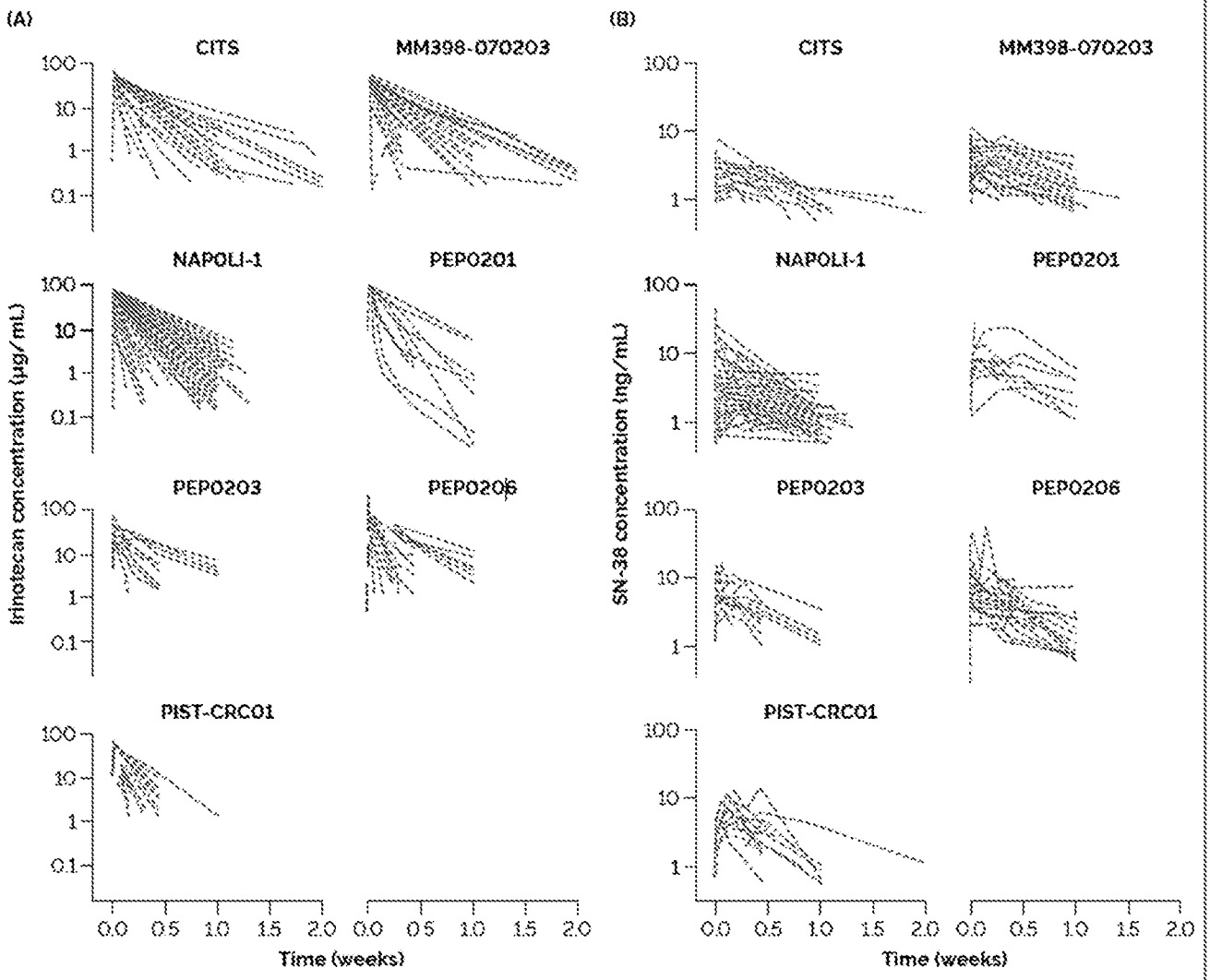
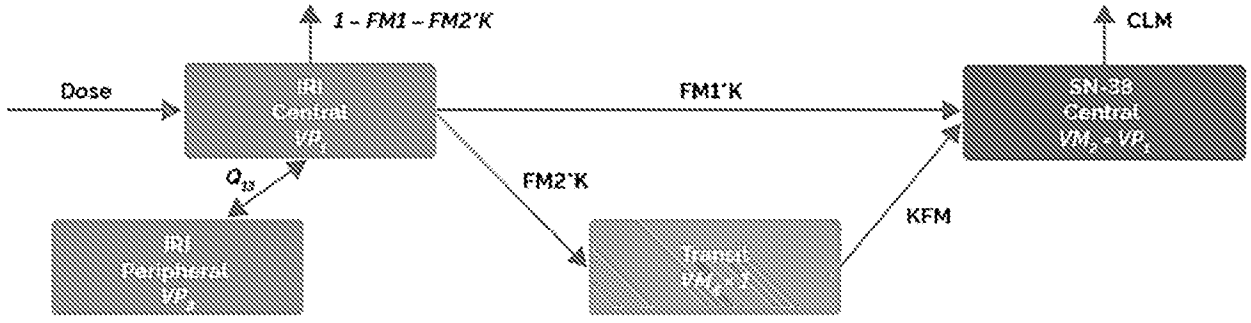


Figure 2. Population PK model representation



IRI, irinotecan
K, irinotecan total clearance/irinotecan central volume
Q_{12}, intercompartmental clearance
VP_1, irinotecan central volume
VP_2, irinotecan peripheral volume
FM1, fraction of parent metabolized via first-order process
FM2, fraction of parent metabolized via transit
FM1'K, fraction of total clearance to SN-38 (first-order)
FM2'K, fraction of total clearance to SN-38 (transit)
(1 – FM1 – FM2')K, fraction of total clearance not transformed to SN-38
VM_3, SN-38 central volume (fixed to VP_1)
VM_4, transit compartment
KFM, rate of transformation after delay
CLM, SN-38 clearance
PK, pharmacokinetics

- tIRI clearance was 20% higher in patients of Asian ethnicity than in patients of other ethnicities.
- Increasing bilirubin levels were associated with lower SN-38 clearance.
- tIRI and SN-38 clearances were 20% lower in women than in men.
- Although no PK interaction is expected between irinotecan and oxaliplatin, co-administration of oxaliplatin seems to be associated with an increase in tIRI clearance and a decrease in SN-38 clearance (each by 30%).
- Distribution of the tIRI volume increases with greater body surface area.

Impact of *UGT1A1*28* genotype on nal-IRI PK parameters

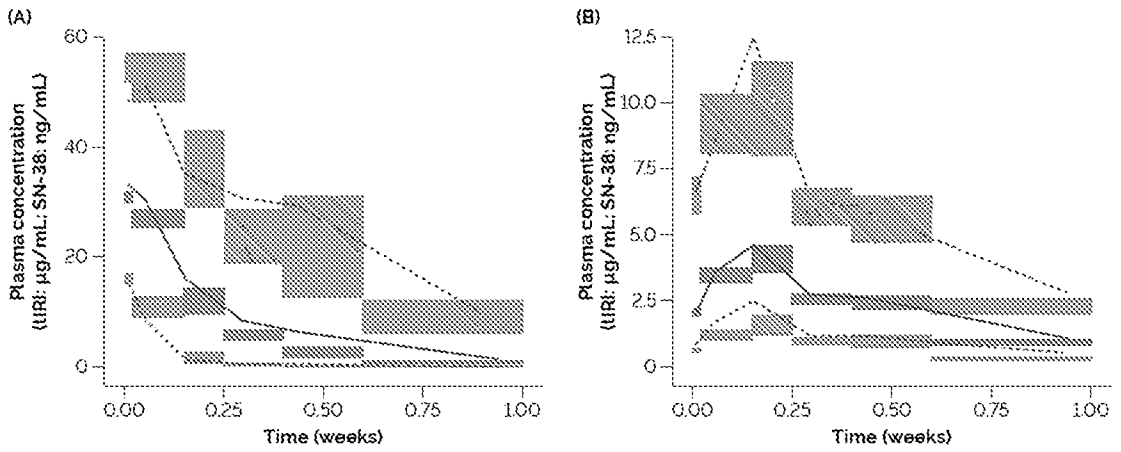
- The association between SN-38 clearance and *UGT1A1*28* genotype is shown in Figure 4.
- SN-38 clearance was not significantly different in patients with a *UGT1A1*28* *7/*7 homozygous genotype compared with those without.

Table 2. Population PK parameters of the pooled population (N = 440)

Parameter	Point estimate	RSE, %	Median	95% CI[a]
Irinotecan total clearance, L/week	17.9	5.14	17.8	16.3
Asian race	× 1.204[a]	44.6	0.192	0.0423
Manufacturing site	× 1.515[a]	27.9	0.547	0.275
Sex	× 0.796[a]	23.5	−0.159	−0.282
Oxaliplatin administration	× 1.339[a]	28.1	0.345	0.166
Irinotecan central volume, L	4.09	2.23	4.07	3.92
BSA	× (BSA/1.73)$^{0.653}$	17.9	0.587	0.383
Manufacturing site	× 0.872[a]	29.4	−0.117	−0.19
Sex	× 0.898[a]	22.9	−0.116	−0.167
Fraction of delayed irinotecan total rate of elimination	0.629	23.4	0.625	0.399
Manufacturing site	× 1.376[a]	41	0.379	0.124
Fraction of direct irinotecan total rate of elimination	0.152	22.4	0.15	0.095
Irinotecan intercompartmental clearance, L/week	1.35	28.6	1.28	0.681
Irinotecan peripheral volume, L	0.421	22.6	0.405	0.177
SN-38 total clearance, L/week	19.800	12.8	19.700	15.000
BIL	× (BIL/0.41)$^{-0.208}$	17.5	−0.234	−0.329
CRCL	× (CRCL/85.04)$^{0.438}$	28.7	0.235	0.0821
Sex	× 0.802[a]	20.3	−0.158	−0.278
Oxaliplatin administration	× 0.858[a]	14.1	−0.348	−0.432
Rate of transformation after delay, /week	2	5.1	2.01	1.81
Between-individual variability				
Irinotecan total clearance	0.545 (CV = 66.2%)	11	0.532	0.428
Irinotecan central volume	0.066 (CV = 25.1%)	27.5	0.0577	0.035
Fraction of delayed irinotecan total rate of elimination	0.183 (CV = 45.4%)	26.4	0.18	0.09
Fraction of direct irinotecan total rate of elimination	0.928 (CV = 124%)	10.9	0.916	0.737
SN-38 total clearance	0.126 (CV = 36.6%)	13.6	0.123	0.0892
Rate of transformation after delay	0.135 (CV = 38%)	29.1	0.133	0.0576
Correlation between irinotecan total clearance and fraction of direct transformation	−0.588 (corr = −0.785)	12	−0.55	−0.681
Correlation between irinotecan total clearance and central volume	0.117 (corr = 0.617)	17.8	0.109	0.0768
Correlation between irinotecan central volume and fraction of direct transformation	−0.103 (corr = −0.410)	24.4	−0.0952	−0.147
Residual error				
Proportional error on irinotecan	0.243 (CV = 29.3%)	6.26	0.24	0.215
Proportional error on SN-38	0.231 (CV = 29.1%)	5.23	0.229	0.26
Correlation between irinotecan and SN-38 errors	0.323	20.4	0.279	0.149

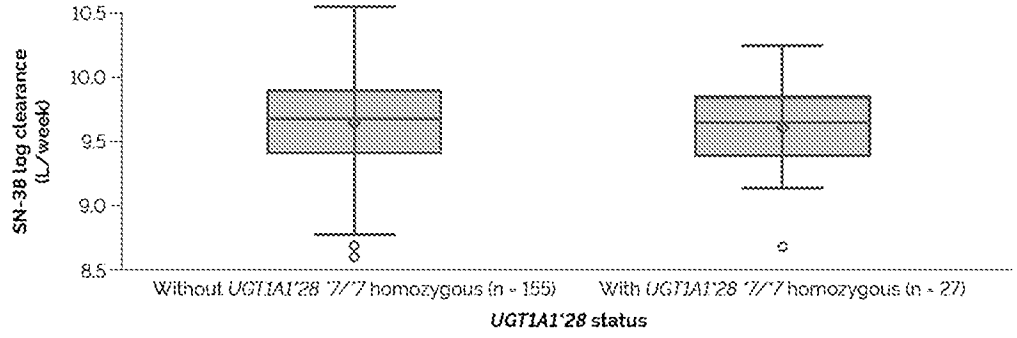
[a]Values obtained as (1 + x) where x is the point estimate.
[b]CIs calculated using bootstrapping; number of successful runs for bootstrap = 721.
BIL, bilirubin; BSA, body surface area; CI, confidence interval; corr, correlation; CL, clearance; CRCL, creatinine clearance; CV, coefficient of variation; PK, pharmacokinetic; RSE, relative standard error.

Figure 3. Model evaluation: visual predictive checks of the final population PK model for (A) tIRI and (b) SN-38



Solid lines represent the observed median concentrations.
Dashed lines represent the 90th percentiles of the observation.
Pink areas represent the CIs of the prediction intervals.
Green areas represent the CIs of the 5th and 95th prediction intervals.
CI, confidence interval; PK, pharmacokinetics; tIRI, total irinotecan.

Figure 4. Box plots of SN-38 log clearances by *UGT1A1*28* status



CONCLUSIONS

- This study characterized PK parameters of nal-IRI using data from > 400 patients with various tumour types, including mPC.
- The PK of nal-IRI and SN-38 in patients with mPC are well described by the population model.
- The *UGT1A1*28* status had no significant impact on the PK of nal-IRI.

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Medical writing support

The authors thank Oxford PharmaGenesis, Oxford, UK, for providing medical writing support/editorial support, which was sponsored by Ipsen, Abingdon, UK, in accordance with Good Publication Practice guidelines.

Acknowledgements

The authors thank all patients involved in the study, as well as their caregivers, care team, investigators and research staff in participating institutions.

Conflicts of interest

TM: consultation for Bayotte, Baxter, Bayer, Celgene, Genzyme, Incyte, QED Therapeutics, Sanofi, Shire Pharmaceuticals, Roche and Tesaro; travel and accommodation support from Bayer, H3 Biomedicine, Merck and Sanofi.
KB, BZ, BB, YM, AP-D and FM: employees of Ipsen.
CHL: nothing to disclose.
ZAW: consultation for Bayer, Bristol-Myers Squibb, Eli Lilly, Ipsen, Merck and Novartis.
FD: consultation for Array, Eisai and Genentech; speaker's bureau for Amgen, Eisai, Ipsen, Genetech and Sirtex.
AD: non-paid consultation for Shire and Specialised Therapeutics Australia; travel and accommodation support from Amgen.

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Presented at the European Society for Medical Oncology (ESMO) Congress 2019, 27 September-1 October 2019, Barcelona, Spain
This analysis was sponsored by Ipsen

691P

Integrated population pharmacokinetic modelling of liposomal irinotecan in patients with various tumour types including untreated metastatic pancreatic cancer (mPC)

BACKGROUND

OBJECTIVE

METHODS

RESULTS

CONCLUSIONS

Subgroup analysis by prior lines of metastatic therapy in NAPOLI-1, a global, randomized, phase 3 study of liposomal irinotecan ±5-fluorouracil and leucovorin, vs. 5-fluorouracil and leucovorinin patients with metastatic pancreatic ductal adenocarcinoma who have progressed following 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 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 = 0.012) 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 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%).
- Currently, nal-IRI is approved in combination with 5-FU/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 an option for mPDAC patients previously treated with gemcitabine-based therapy (category 1), or fluoropyrimidine-based therapy (if no prior irinotecan; category 2A).[5]
  - ESMO 2015 Clinical Practice Guidelines state that nal-IRI "when available in all countries may be the best option for 2nd-line treatment" for patients with advanced gemcitabine-refractory pancreatic cancer.[6]
- Here, we present results from a *post-hoc* subgroup analysis by prior lines of metastatic therapy from the NAPOLI-1 study.

CSPC Exhibit 1100
Page 103 of 333

METHODS

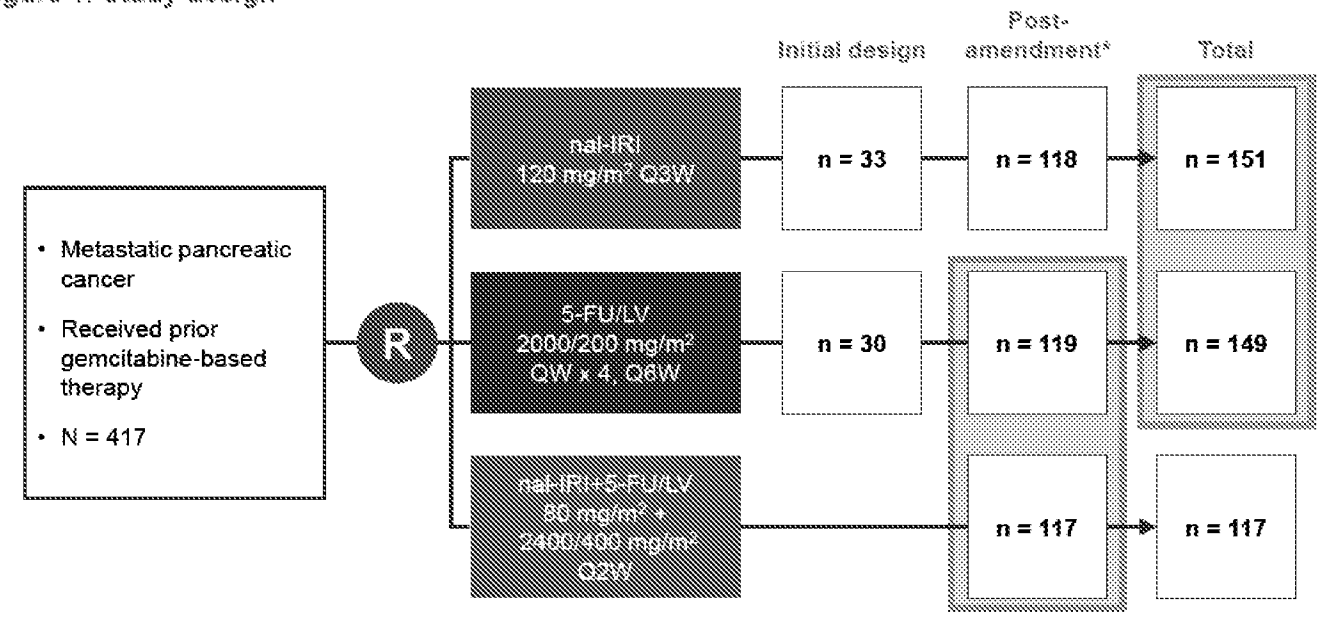
Objectives and subgroup analysis

- 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 4WQ6W (n = 119), within the following subgroups:
  - Patients who had received 0–1 prior lines of metastatic therapy, i.e., receiving treatment in the NAPOLI-1 study as 1st- or 2nd-line for metastatic disease.
    - Patients may have received previous gemcitabine-based therapy in, for example, the adjuvant setting.
  - Patients who had received ≥2 prior lines of metastatic therapy (mtx), i.e., receiving treatment in the NAPOLI-1 study as ≥3rd-line for metastatic disease.

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)

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).

Key inclusion criteria (continued)

- 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 >1.5x10^9 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.

CSPC Exhibit 1100
Page 104 of 333

RESULTS

Patient characteristics

- In the nal-IRI+5-FU/LV arm, 66% and 34% of patients had received 0–1 and ≥2 prior mtx lines, respectively; 69% and 31% of patients in the 5-FU/LV control arm had received 0–1 and ≥2 prior mtx lines, respectively (Table 1).
- Patient demographics and baseline characteristics were generally similar between treatment arms and within subgroups; evaluation of any differences is limited by small patient numbers in this *post-hoc* analysis (Table 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

	Overall population		0–1 prior mtx lines		≥2 prior mtx lines	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 77 [66%])	5-FU/LV (n = 82 [69%])	nal-IRI+ 5-FU/LV (n = 40 [34%])	5-FU/LV (n = 37 [31%])
Sex, n (%)						
Female	48 (41)	52 (44)	33 (43)	37 (45)	15 (38)	15 (41)
Male	69 (59)	67 (56)	44 (57)	45 (55)	25 (63)	22 (60)
Median age, years	63	62	63	63	64	61
(IQR)	(57–70)	(55–69)	(57–70)	(56–69)	(57–69)	(50–66)
(Full range)	(41–81)	(34–80)	(41–81)	(34–77)	(40–80)	(41–80)
KPS score, n (%)						
90–100	69 (59)	57 (48)	46 (60)	39 (48)	23 (58)	18 (49)
70–80	45 (38)	61 (51)	28 (36)	43 (52)	17 (42)	18 (49)
50–60	3 (3)	0	3 (4)	0	0	0
Missing	0	1 (1)	0	0	0	1 (3)
Pancreatic tumor location, n (%)						
Head	76 (65)	69 (58)	49 (64)	50 (61)	27 (68)	19 (51)
Other	41 (35)	50 (42)	28 (36)	32 (39)	13 (32)	18 (49)
Mean CA19-9, U/mL (SD)	19884.1 (66258.4)	32456.6 (102301.4)	18126.2 (67443.5)	33406.6 (113190.6)	23542.6 (64476.6)	30221.4 (71818.5)
Liver metastases, n (%)	75 (64)	83 (70)	48 (62)	58 (71)	27 (68)	25 (68)
Previous therapies or procedures, n (%)						
Radiotherapy	24 (21)	27 (23)	11 (14)	17 (21)	13 (33)	10 (27)
Whipple procedure	30 (26)	33 (28)	24 (31)	30 (37)	6 (15)	3 (8)
Biliary stent	15 (13)	8 (7)	8 (10)	4 (5)	7 (18)	4 (11)
Previous anticancer therapy, n (%)						
Gemcitabine alone	53 (45)	55 (46)	43 (56)	43 (52)	10 (25)	12 (32)
Gemcitabine combination	64 (55)	64 (54)	34 (44)	39 (48)	30 (75)	25 (68)
Irinotecan based	12 (10)	17 (14)	2 (3)	1 (1)	10 (25)	16 (43)

IQR, interquartile range; ITT, intent-to-treat; KPS, Karnofsky Performance Status; mtx, metastatic therapy; SD, standard deviation.

Tumor response

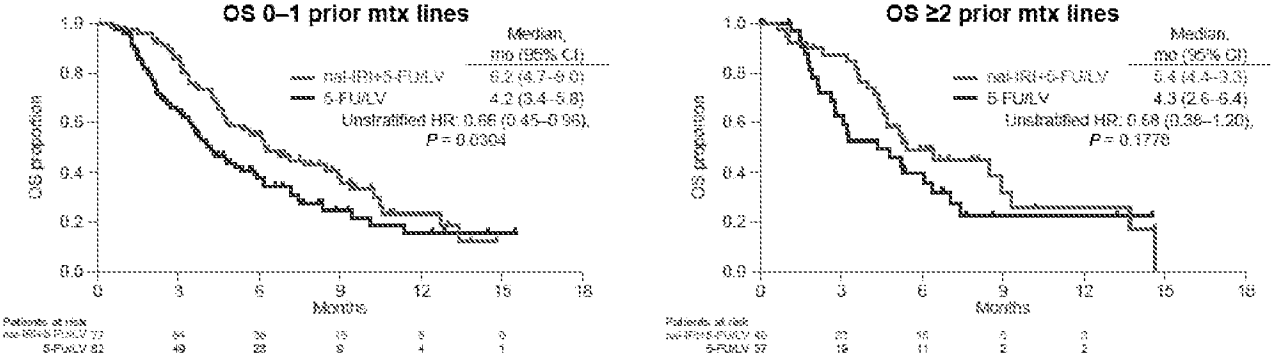
- Patients who had 0–1 prior lines of mtx had a significantly higher objective response rate (ORR; 14 [18%] vs. 1 [1%]; $P < 0.001$) and CA19-9 response rate (21 [31%] vs. 6 [11%]; $P < 0.01$), and a doubled clinical benefit rate (CBR; 39 [51%] vs. 19 [23%]) when treated with nal-IRI+5-FU/LV compared with those receiving 5-FU/LV alone (Table 2).
- In patients following ≥2 prior lines of mtx, nal-IRI+5-FU/LV vs. 5-FU/LV treatment also showed increases in ORR (5 [13%] vs. 0; $P = 0.0554$) and CA19-9 response rate (7 [24%] vs. 1 [4%]; $P = 0.06$), and a doubled CBR (19 [48%] vs. 8 [22%]) (Table 2).

CSPC Exhibit 1100
Page 105 of 333

Overall survival

- In patients with 0–1 prior mtx lines, median OS for nal-IRI+5-FU/LV vs. 5-FU/LV improved by 2.0 months to 6.2 months (unstratified HR = 0.66; *P* = 0.03) (Table 2; Figure 2).
- In patients with ≥2 prior mtx lines, median OS for nal-IRI+5-FU/LV vs. 5-FU/LV improved by 1.1 months to 5.4 months (unstratified HR = 0.68; *P* = 0.18) (Table 2; Figure 2).

Figure 2. Overall survival of patients receiving 0–1 or ≥2 prior metastatic therapy lines (ITT population; primary data cut-off)

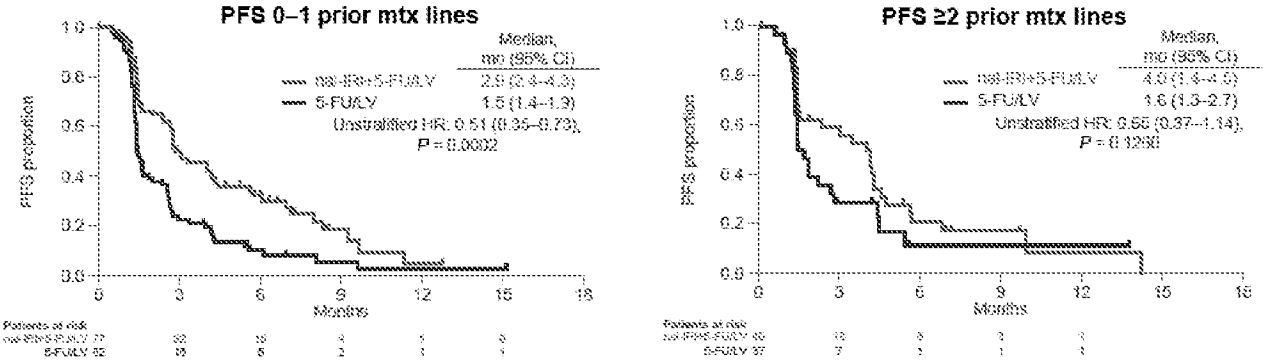


CI, confidence interval; HR, hazard ratio; ITT, intent to treat; mo, month; mtx, metastatic therapy.

Progression-free survival

- In patients with 0–1 prior mtx lines, median PFS for nal-IRI+5-FU/LV vs. 5-FU/LV improved by 1.4 months to 2.9 months (unstratified HR = 0.51; *P* = 0.0002) (Table 2; Figure 3).
- In patients with ≥2 prior mtx lines, median PFS for nal-IRI+5-FU/LV vs. 5-FU/LV improved by 2.4 months to 4.0 months (unstratified HR = 0.65; *P* = 0.1260) (Table 2; Figure 3).

Figure 3. Progression-free survival of patients receiving 0–1 or ≥2 prior metastatic therapy lines (ITT population; primary data cut-off)



CI, confidence interval; HR, hazard ratio; ITT, intent to treat; mo, month; mtx, metastatic therapy.

Table 2. Summary of efficacy in patients with 0–1 or ≥2 prior mtx lines (primary analysis data cut-off)

	All patients			0–1 prior mtx lines			≥2 prior mtx lines		
	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 = 77 [66%])	5-FU/LV (n = 82 [69%])	Unstratified HR (95% CI) log-rank p-value	nal-IRI+ 5-FU/LV (n = 40 [34%])	5-FU/LV (n = 37 [31%])	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	6.2 (4.7–9.0)	4.2 (3.4–5.8)	0.66 (0.5–1.0) *P* = 0.03	5.4 (4.4–9.3)	4.3 (2.6–6.4)	0.68 (0.38–1.20) *P* = 0.18
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	2.9 (2.4–4.3)	1.5 (1.4–1.9)	0.51 (0.4–0.7) *P* = 0.0002	4.0 (1.4–4.5)	1.6 (1.4–2.7)	0.65 (0.4–1.1) *P* = 0.13
Median TTF, months (95% CI)	2.3 (1.6–2.8)	1.4 (1.3–1.4)	0.66 (0.5–0.8) *P* = 0.0002	2.4 (1.6–2.8)	1.4 (1.3–1.5)	0.58 (0.4–0.8) *P* = 0.0011	1.9 (1.4–3.0)	1.3 (1.0–1.4)	0.82 (0.4–1.6) *P* = 0.0469

Best overall response, n (%)									
ORR, n (%)	19 (16)	1 (1)	$P < 0.0001$†	14 (18)	1 (1)	$P = 0.0002$†	5 (13)	0	$P = 0.0554$†
PR, n (%)	19 (16)	1 (1)		14 (18)	1 (1)		5 (13)	0	
SD, n (%)	39 (33)	26 (22)		25 (33)	18 (22)		14 (35)	8 (22)	
Non-CR/non-PD, n (%)	3 (3)	2 (2)		2 (3)	1 (1)		1 (3)	1 (3)	
PD, n (%)	34 (29)	56 (47)		24 (31)	42 (51)		10 (25)	14 (38)	
Not evaluable, n (%)	22 (19)	34 (29)		12 (16)	20 (24)		10 (25)	14 (38)	
CBR, n (%)	58 (50)	27 (23)		39 (51)	19 (23)		19 (48)	8 (22)	
CA19-9 response rate,* n/N (%)	26/97 (29)	7/81 (9)	$P = 0.0006$†	21/68 (31)	6/56 (11)	$P < 0.01$†	7/29 (24)	1/25 (4)	$P = 0.06$†

*Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >38 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; mtx, metastatic therapy; ORR, objective response rate (CR + PR); PD, disease progression; PR, partial response; SD, stable disease; TTF, time to treatment failure.

Safety, dose modifications and treatment exposure

- The incidence of adverse events (AEs) was similar between subgroups in the nal-IRI+5-FU/LV arm (grade ≥3 drug-related AEs: 43 [55%] with 0–1 and 20 [51%] with ≥2 prior mtx lines) (Table 3).

Table 3. Adverse events in patients with 0–1 or ≥2 prior lines of metastatic therapy (safety population)

	0–1 prior mtx lines		≥2 prior mtx lines	
	nal-IRI+ 5-FU/LV (n = 78)	5-FU/LV (n = 97)	nal-IRI+ 5-FU/LV (n = 39)	5-FU/LV (n = 37)
Alopecia*	10 (13)	4 (4)	5 (13)	2 (5)
Grade 3/4 non-hematologic AEs in >5% of the overall safety population, n (%)**				
Diarrhea, late onset†	13 (17)	4 (4)	2 (5)	2 (5)
Vomiting	10 (13)	4 (4)	3 (8)	0
Nausea	7 (9)	3 (3)	2 (5)	1 (3)
Fatigue	11 (14)	4 (4)	5 (13)	1 (3)
Febrile neutropenia	1 (1)	0	1 (3)	0
Asthenia	5 (6)	6 (6)	4 (10)	3 (8)
Abdominal pain	5 (6)	5 (5)	3 (8)	3 (8)
Grade 3/4 hematologic AEs based on laboratory values, n (%)				
Neutrophil count decreased	13 (17)	3 (3)	10 (26)	1 (3)
Hemoglobin decreased	5 (6)	6 (6)	3 (8)	1 (3)
Platelet count decreased	1 (1)	0	1 (3)	1 (3)
Drug-related AE of CTCAE grade ≥3, n (%)	43 (55)	18 (19)	20 (51)	6 (16)

*According to the CTCAE, version 4, alopecia can only be grade 1 or 2. **All non-hematologic AEs presented were grade 3, with the exception of grade 4 asthenia in 1 patient with ≥2 prior mtx lines receiving nal-IRI+5-FU/LV; †>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; mtx, metastatic therapy.

- Dose modifications for TEAEs were needed in 71% of patients in the nal-IRI+5-FU/LV arm with 0–1 prior mtx lines (35%, 63% and 13%, for dose reductions, delays and discontinuations, respectively) vs. 37% of patients in the 5-FU/LV arm (5%, 33% and 7%, respectively) (Table 4).
- Dose modifications for TEAEs were needed in 72% of patients in the nal-IRI+5 FU/LV arm with ≥2 prior mtx lines (31%, 59% and 8%, for dose reductions, delays and discontinuations, respectively) vs. 32% of patients in the 5-FU/LV arm (0%, 30%, and 8%, respectively) (Table 4).

CSPC Exhibit 1100
Page 107 of 333

Table 4. Dose modifications and treatment exposure in patients with 0–1 or ≥2 prior lines of metastatic therapy (safety population)

	0–1 prior mtx lines		≥2 prior mtx lines	
	nal-IRI+ 5-FU/LV (n = 78)	5-FU/LV (n = 97)	nal-IRI+ 5-FU/LV (n = 39)	5-FU/LV (n = 37)
TEAE leading to any dose modification, n (%)	55 (71)	36 (37)	28 (72)	12 (32)
Dose reduction, n (%)	27 (35)	5 (5)	12 (31)	0
Dose delays, n (%)	49 (63)	32 (33)	23 (59)	11 (30)
Treatment discontinuation, n (%)	10 (13)	7 (7)	3 (8)	3 (8)
Dose modifications, n (%)	55 (71)	36 (37)	28 (72)	12 (32)
Average relative dose intensity, (%)				
nal-IRI	83.2	–	83.2	–
5-FU	83.7	95.0	84.3	97.0
Average duration of treatment exposure, weeks*	15.2	10.2	14.5	11.0

*Duration of exposure is the time from (the date of the last administration of study drug - date of first study drug administration)/7.
mtx, metastatic therapy; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV has demonstrated overall survival benefit, predictable and manageable toxicity, while maintaining quality of life vs. 5-FU/LV alone in adult patients with mPDAC previously treated with gemcitabine-based therapy.[4]
- This *post-hoc* subgroup analysis from the NAPOLI-1 study shows significant increases for nal-IRI+5-FU/LV over 5-FU/LV in median OS, median PFS, ORR and CA19-9 response in patients treated for mPDAC in the 1st- and 2nd-line.
- A survival and response benefit was observed, but was less prominent, in patients with mPDAC treated with nal-IRI+5-FU/LV as ≥3rd-line therapy, however, this conclusion is restricted by limited patient numbers.
- nal-IRI+5-FU/LV demonstrated a similar safety profile when given as 1st and 2nd metastatic line, and ≥3rd metastatic line for PDAC after previous gemcitabine-based therapy.
- These data further support the timely use of nal-IRI in mPDAC patients who progress on gemcitabine-based therapy.

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Acknowledgments

- This study (ClinicalTrials.gov identifier: NCT01494506) was supported by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; rights for nal-IRI now reside with Ipsen (April 2017); PharmaEngine, Inc. holds rights in US; Shire holds rights outside the US through a licensing agreement with Ipsen.
- Editorial assistance for the creation of this poster was provided by Physicians World Europe GmbH, Mannheim, Germany, with financial support from Shire (previously Baxalta), Zug, Switzerland.

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Presented at the American Society for Clinical Oncology 2017 Congress, Chicago, IL, USA, June 2–6 2017

GASTROINTESTINAL (NONCOLORECTAL) CANCER

Subgroup analysis by prior lines of metastatic therapy (mtx) in NAPOLI-1: A global, randomized phase 3 study of liposomal irinotecan (nal-IRI) ± 5-fluorouracil and leucovorin (5-FU/LV), vs. 5-FU/LV in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy.

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Show Less

Abstract Disclosures

Abstract

4127

Background: In the NAPOLI-1 study, nal-IRI+5-FU/LV significantly increased median OS vs. 5-FU/LV control (6.1 vs. 4.2 mo; unstratified HR = 0.67 [0.49–0.92]; p = .012). This is a subgroup analysis by prior lines of mtx. **Methods:** Study methodology has been published (Wang-Gillam; Lancet 2016). This exploratory subgroup analysis compares outcomes in pts with 0–1 vs. ≥2 prior mtx lines, 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 0–1 (65.8% of pts) or ≥2 (34.2%) prior mtx lines are shown (see Table). Median OS for nal-IRI+5-FU/LV improved vs. 5-

FU/LV by 2.1 mo to 6.2 mo (HR = 0.66; p = .03) in pts with 0–1 prior mtx lines and by 1.1 mo to 5.4 mo (HR = 0.68; p = .18) in pts with ≥2 prior mtx lines. The safety profile was similar between subgroups with nal-IRI+5-FU/LV (≥grade 3 drug-related AEs: 43 [55%] with 0–1 and 20 [51%] with ≥2 prior mtx lines). **Conclusions:** This post-hoc subgroup analysis shows significant increases for nal-IRI+5-FU/LV over 5-FU/LV in OS, PFS and CA19-9 response in pts with 0–1 prior mtx lines. Median OS benefit was less prominent in later lines, but conclusions are restricted by limited pt numbers. Clinical trial information: NCT01494506.

	0–1 prior mtx lines		
	nal-IRI+5-FU/LV (n = 77 [65.8%])	5-FU/LV (n = 82 [68.9%])	Unstratified HR (95%CI); p-value
Median OS, mo (95%CI)	6.24 (4.70–8.97)	4.17 (3.35–5.82)	0.66 (0.45–0.96); p = .03
Median PFS, mo (95%CI)	2.89 (2.40–4.34)	1.46 (1.38–1.87)	0.51 (0.35–0.73); p < .001
CA19-9 response rates, n/N (%)	21/68 (30.9)	6/56 (10.7)	p < .01
	≥2 prior mtx lines		
	nal-IRI+5-FU/LV (n = 40 [34.2%])	**5-FU/LV (n = 37 [31.1%])**	
Median OS, mo (95%CI)	5.42 (4.44–9.30)	4.34 (2.63–6.37)	0.68 (0.38–1.20); p = .18
Median PFS, mo (95%CI)	4.01 (1.41–4.53)	1.56 (1.35–2.66)	0.65 (0.37–1.14); p = .13
CA19-9 response rates, n/N (%)	7/29 (24.1)	1/25 (4.0)	p = .06

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691P **Integrated population pharmacokinetic modelling of liposomal irinotecan in patients with various tumour types, including untreated metastatic pancreatic cancer (mPC)**

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Background: Liposomal irinotecan (nal-IRI) is a liposomal formulation of irinotecan which prolongs circulation of irinotecan and its active metabolite SN-38. This analysis describes the population pharmacokinetics (PK) of nal-IRI in patients with various tumour types, including untreated mPC.

Methods: Plasma concentration data for total irinotecan (tIRI) and SN-38 from an open-label, phase 2 study of nal-IRI plus 5-fluorouracil/leucovorin and oxaliplatin in patients with untreated mPC (NCT02551991; N = 48) were pooled with data from six other nal-IRI studies (five phase 1/2, one phase 3) in various tumour types. Data from overall 440 patients were used in the population PK model for tIRI and SN-38 after nal-IRI administration. PK parameters were estimated with non-linear mixed effects modelling. The adequacy of the model was assessed based on the uncertainty of parameter estimates, and on advanced evaluation methods such as visual predictive check. Potential covariates such as patient demographics and genotype were investigated to examine inter-individual variability.

Results: tIRI is described by a two-compartment model with first-order elimination. SN-38 is formed directly by a first-order constant from the central compartment of nal-IRI or after using a transit compartment. In the pooled population ($N = 440$), clearance was 0.1 L/h and 150 L/h for tIRI and SN-38, respectively. Central and peripheral volumes of distributions for tIRI were 4 L and 0.4 L, respectively. Consistent with previous data, tIRI clearance was 30% higher in patients of Asian ethnicity (n = 154/440) than other populations. Increasing bilirubin levels were associated with lower SN-38 clearance, and tIRI and SN-38 clearance were 20% lower in females than males. The UGT1A128 7/7 homozygous genotype (6% of the study population) had no statistically significant impact on SN-38 clearance. Model evaluation was satisfactory for both tIRI and SN-38.

Conclusions: The PK of nal-IRI and SN-38 in patients with mPC is well described by the population model. The results suggest that UGT status has no impact on the PK of nal-IRI.

Editorial acknowledgement: Oxford PharmaGenesis, Oxford, UK for providing editorial support, which was sponsored by Ipsen, Abingdon, UK.

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.

Disclosure: T. Macarulla: Honoraria (institution): Shire Pharmaceuticals; Honoraria (institution): Roche; Honoraria (institution): Tesaro; Honoraria (institution): Baxter; Honoraria (institution), Travel / Accommodation / Expenses: Sanofi; Honoraria (institution): Celgene; Honoraria (institution): QED Therapeutics; Honoraria (institution): Genzyme Europe; Honoraria (institution): Bexalta; Honoraria (institution), Travel / Accommodation / Expenses: Bayer; Honoraria (institution): Incyte; Honoraria (institution): Genzyme; Travel / Accommodation / Expenses: Merck; Travel / Accommodation / Expenses: H3 Biomedicine. K. Brendel: Full / Part-time employment: Ipsen. Z.A. Wainberg: Advisory / Consultancy: Lilly; Advisory / Consultancy: Merck; Advisory / Consultancy: BMS; Advisory / Consultancy: Bayer; Advisory / Consultancy: Novartis; Advisory / Consultancy: Ipsen. F. Dayyani: Advisory / Consultancy: Array; Advisory / Consultancy, Speaker Bureau / Expert testimony: Eisai; Advisory / Consultancy, Speaker Bureau / Expert testimony: Genentech; Speaker Bureau / Expert testimony: Ipsen; Speaker Bureau / Expert testimony: Amgen; Speaker Bureau / Expert testimony: Sirtex. B. Zhang: Full / Part-time employment: Ipsen. B. Belanger: Full / Part-time employment: Ipsen. Y. Moore: Full / Part-time employment: Ipsen. A. Pedret-Dunn: Full / Part-time employment: Ipsen. F. Maxwell: Full / Part-time employment: Ipsen. A. Dean: Advisory / Consultancy, Non-paid: Shire; Advisory / Consultancy, Non-paid: Specialised Therapeutics Australia; Travel / Accommodation / Expenses, Grant: Amgen. All other authors have declared no conflicts of interest.

CSPC Exhibit 1100
Page 112 of 333

British Journal of Cancer (2003) 89, 1860–1864
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A phase II irinotecan–cisplatin combination in advanced pancreatic cancer

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We report a cisplatin and irinotecan combination in patients with biopsy-proven advanced pancreatic adenocarcinoma. Patients were selected from a specialist centre and required good performance status (KPS > 70%), measurable disease on CT scan, and biochemical and haematological parameters within normal limits. Based on a two-stage phase II design, we aimed to treat 22 patients initially. The study was stopped because of the death of the 19th patient during the first treatment cycle, with neutropenic sepsis and multiorgan failure. A total of 89 treatments were administered to 17 patients. Serious grade 3/4 toxicities were haematological (neutropenia) 6%, diarrhoea 6%, nausea 7% and vomiting 6%. Using the clinical benefit response (CBR) criteria, no patients had an overall CBR. For responses confirmed by CT examination, there was one partial response (5%), three stable diseases lasting greater than 6 weeks (16%), with an overall 22% with disease control (PR + SD). The median progression-free and overall survival was 3.1 months (95% CI: 1.3–3.7) and 5.0 (95% CI: 3.9–10.1) months, respectively. Although this synergistic combination has improved the response rates and survival of other solid tumours, we recommend caution when using this combination in the palliation of advanced pancreatic cancer, because of unexpected toxicity.

British Journal of Cancer (2003) **89,** 1860 – 1864. doi:10.1038/sj.bjc.6601377 www.bjcancer.com
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Keywords: pancreatic cancer; irinotecan; cisplatin; palliative chemotherapy; patient selection

Once diagnosed, patients with pancreatic adenocarcinoma have an average life expectancy of 16–20 weeks. Clinical management has an emphasis on palliative support because of the poor prognosis and the rapidly deteriorating quality of life due to the syndrome of fatigue, weight loss, pain and jaundice (Wigmore *et al*, 1997; Andreyev *et al*, 1998). Standard selection criteria, as used for most other solid tumours, can often exclude a significant proportion of pancreatic cancer patients, with trials reporting results in selected patients with good performance status. Toxic treatments that follow can lead to early withdrawal from studies, may worsen otherwise the good quality of life and, in some instances, shorten the duration of life. The use of low-toxicity agents, such as gemcitabine and metalloproteinase inhibition, have had notable success in terms of trial recruitment, patient compliance and treatment tolerance (Carmichael *et al*, 1996; Burris *et al*, 1997; Bramhall *et al*, 2001).

The 5-year survival rate for pancreatic cancer remains at 2% (Bramhall *et al*, 1995). Single-agent chemotherapy, such as 5-flurouracil, paclitaxel and gemcitabine, all result in radiological response rates between 5 and 15% (Burris *et al*, 1997; Whitehead *et al*, 1997). Combination chemotherapy, including drugs such as cisplatin, 5-FU, adriamycin and gemcitabine, have generally improved the response rates slightly, at the expense of increasing toxicity in some combinations (Cascinu *et al*, 1996; Evans *et al*, 1996; Hidalgo *et al*, 1999). Aside from the differences in patient selection, one problem with the interpretation of these studies is the reliability of radiological response, mainly because of the dense fibrotic reaction that often occurs within pancreatic tumours (Ahlgren, 1996). As a result, survival data are often quoted in combination with surrogate factors, for example, the clinical benefit response (CBR). The latter incorporates a scoring system for positive and negative changes in pain, performance status and weight, and has been an important tool in establishing gemcitabine efficacy (Rothenberg *et al*, 1996a).

Here we report the activity and toxicity of the drug combination, irinotecan and cisplatin, in previously untreated patients with advanced pancreatic cancer. This combination has been shown to generate significant short-term radiological response rates and improvement in survival in solid tumours, most notably in small-cell lung cancer (Noda *et al*, 2002, Ilson *et al*, 2003; Souid *et al*, 2003).

Irinotecan is a camptothecin analogue and topoisomerase I inhibitor with a highly active metabolite (Sn38). This agent has demonstrated improved survival in metastatic 5-FU refractory colorectal cancer (Cunningham and Glimelius, 1999; Rothenberg *et al*, 1999). Laboratory studies show high response rates of pancreatic tumour cells in culture and in xenograft studies (Takeda *et al*, 1992; Bissery *et al*, 1996). Single-agent phase II

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Received 17 March 2003; revised 20 August 2003; accepted 11 September 2003

studies of irinotecan in pancreatic carcinoma (dose intensity 100 mg m^{-2} week^{-1}) have shown typical response rates of around 10%, again similar to other single agents (Wagener *et al*, 1995; Armand *et al*, 1996). There are now data showing significant synergy between cisplatin and irinotecan in lung cancer cell lines *in vitro* (Kanzawa *et al*, 2001). However, there are no published data concerning cisplatin and irinotecan alone in advanced pancreatic cancer, although other agents have been successfully combined with irinotecan in this disease, for example, gemcitabine (de Jonge *et al*, 2000; Kozuch *et al*, 2001; Rocha Lima *et al*, 2002; Slater *et al*, 2002).

MATERIAL AND METHODS

Patient selection and study design

Eligible patients were chemotherapy naïve (>18 years), and had pancreatic adenocarcinoma diagnosed by histology with measurable disease on CT scan. Karnofsky performance status (KPS) >70%, either stent insertion or hepato-jejunostomy for biliary drainage, bilirubin <1.5× upper limit of the normal (<35 μmol l^{-1}), AST <5× upper limit of the normal, GFR >60 ml min^{-1} based on Cockcroft formula and confirmed by creatinine clearance in borderline cases, neutrophils >1.5 × 10^9 l^{-1} and normal blood count profile with no clinical history of inflammatory bowel disease or previous malignancy (except non-melanoma skin cancer and *in situ* cervical carcinoma). The study was approved by the South Birmingham Local Ethics Committee and all patients gave written informed consent. All patients were requested to complete a pain inventory of all analgesic medication, and pain was assessed using the Wisconsin brief pain questionnaire and visual analogue scale (assessed every evening at the same time).

The end points of this study were the radiological response rate (CR + PR), disease control (CR + PR + SD), overall survival (defined as the time from entry into the trial to the date of death or censor), progression-free survival (PFS) at 3 months (defined as the time from entry into the trial to the first objective documentation of progression), CBR and toxicity. Clinical benefit response was assessed as recommended by Rothenberg *et al* (1996b). In summary, primary measures were defined as >20% increase in performance status lasting greater than 4 weeks from a baseline score of <70%, >50% reduction in morphine-equivalent analgesic consumption for 4 weeks from a baseline of >10 mg morphine equivalent per day, >50% improvement in pain scores from baseline >20 mm (visual analogue scale), with a secondary measure of >7% increase in weight sustained for >4 weeks. No CBR was assumed for patients who progressed within 4 weeks.

The aim was to recruit an initial 22 patients into the first stage of a two-stage Gehan design (based on 90% power and estimated 10% response rate), with the number of further patients recruited to stage two based on patient response in stage one. The trial was terminated at 19 patients following a presumed toxic death.

Treatment

Irinotecan (a gift from Aventis) with atropine sulphate (300 μg) prophylaxis (Gandia *et al*, 1993) was administered over 90 min following hydration (500 ml N/saline + 20 mmol KCl + magnemagnesium) over 30 min and cisplatin (25 mg m^{-2}) administered over 30 min, on days 1 and 8 of a 21-day cycle. (The calculated dose intensity for irinotecan is approximately 50% of that utilised in single-agent Phase I studies, 46 mg m^{-2} week^{-1}.) A maximum of five cycles could be administered (15 weeks), with weekly patient visits for clinical examination, toxicity evaluation, FBC, biochemistry, weight (prior to hydration), pain inventory and performance status assessment (worser of two scores determined independently by two observers). Loperamide and ciprofloxacin were provided for prophylaxis against irinotecan-induced delayed diarrhoea, as advised by the manufacturer. Chemotherapy was administered only if KPS ≥70%, neutrophils >1.5 × 10^9/l and all other haematological and liver functions tests remained within normal limits. If either grade 3–4 diarrhoea or grade 4 neutropenia, or grade 3 neutropenia and infection occurred, then irinotecan dose was reduced to 35 mg m^{-2} (diarrhoea and neutropenia) and cisplatin reduced to 20 mg m^{-2} (neutropenia only) in all subsequent cycles. All other toxicities were recorded weekly, and any greater than grade 2 were treated with supportive care and a maximum delay in chemotherapy of 2 weeks. Continuous treatment with steroids was discouraged unless the patient had been on a constant maintenance dose for 2 weeks prior to trial entry, or there was persistent and severe loss of appetite following chemotherapy, severe liver capsular pain or there was chemotherapy-related delayed nausea and vomiting.

Response and toxicity

Staging abdominal CT scans with contrast enhancement were performed within 2 weeks of the start and end of chemotherapy following a minimum of two cycles of treatment, and every 4–6 weeks thereafter, unless there was obvious clinical evidence of progression. The response evaluation criteria in solid tumours (RECIST) criteria were employed to immediately assess CT scans and to guide subsequent management, and all CT scans were again reviewed independently by one radiologist after closure of the study (Therasse *et al*, 2000). Toxicity was assessed after each treatment and graded using the National Cancer Institute of Canada Clinical Trials group (NCIC-CTG) expanded common toxicity criteria (CTC version 1).

RESULTS

A total of 19 out of the 22 patients planned were recruited into this study from a single institution and analysed by intention to treat. One patient was excluded from response and toxicity analysis from the outset due to a rapid deterioration of a concurrent clinical condition that precluded consent to chemotherapy. Patient characteristics for the 18 remaining patients are shown in Table 1. In summary, the majority of patients had a KPS >90% at study entry (78%), metastatic disease (67%, stage IVB) from a pancreatic head primary (83%), and had not received previous chemotherapy or radiotherapy (one patient had previous immunisation against gastrin, which completed 6 weeks prior to study entry). One patient was taking steroids at entry, five patients had previous bypass gastro-jejunostomy and nine patients had concurrent medical conditions: ankylosing spondylitis + diabetes (1), bilateral deep venous thrombosis (1), diabetes (2), epilepsy (1), hypertension (3), controlled chronic schizophrenia (1). Delay between histological diagnosis and entry into the trial was approximately 4 weeks, but had a wide range. The first treatment was usually on the day of entry to the trial for 15 (83%) patients (two patients starting 4 and 7 days after entry and one consented patient did not receive treatment due to deterioration of performance status on the day of treatment). In all, 17 patients received a total of 89 treatments of combination chemotherapy between March 2000 and June 2001. Altogether, 75 (84%) of treatments were full dose (70 mg m^{-2} irinotecan, 25 mg m^{-2} cisplatin). In 14 cases, doses were reduced (14 doses to 35 mg m^{-2} irinotecan, 20 mg m^{-2} cisplatin) and six patients missed a total of 10 treatments because of toxicity. The actual mean dose intensity per patient of chemotherapy was 37.0 (range 17.5–46.7, median 40.8, protocol 46.7) mg m^{-2} week^{-1} for irinotecan and 13.7 (range 7.5–16.7, median 14.6, protocol 16.7) mg m^{-2} week^{-1} for cisplatin.

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CSPC Exhibit 1100
Page 114 of 333

Table 1 Patient characteristics at trial entry

	N	(%)
Sex		
Male	8	(44)
Female	10	(56)
Karnofsky performance status		
100	2	(11)
90	12	(67)
80	4	(22)
Site of disease		
Pancreatic head	15	(83)
Body and tail	3	(17)
Stage of disease		
IVA	6	(33)
IVB	12	(67)
Differentiation		
Well	2	(14)
Moderate	7	(50)
Poor	5	(36)
Age		
Median	61 years	
Range	38–74	
Weight		
Median	67.5 kg	
Range	42–93	
Body mass index		
Median	24.5	
Range	16.3–34.6	
Diagnosis to entry		
Median	26.5 days	
Range	9–258	
Analgesic consumption (mg day^{-1} morphine equivalent)		
Median	32.1 mg	
Range	0–120	

Survival

In all, 15 of the 18 patients had died at the time of analysis. The three alive patients were censored in the survival analysis at 6, 6.5 and 16 months. The median overall survival was 5.0 (95% CI: 3.9, 10.1) months and median PFS was 3.1 (95% CI: 1.3, 3.7) months. All patients, but one, had stable disease or had progressed either radiologically or clinically within the 15 weeks study duration.

Radiological response

Seven (39%) patients did not undergo post-treatment scans because of clinical evidence of progression (one patient with intrahepatic cholestasis from metastasis confirmed on ultrasound examination, four patients with a combination of rapid loss of weight, increased pain and rapid deterioration of performance status, one pulmonary embolism and one death). The remaining 11 patients had pre- and post-treatment CT scans with repeat post-treatment scans after at least 6 weeks. Using RECIST criteria, there were no complete responders, one partial response of low volume disease in pancreatic body and liver (PR = 5%), three with stable disease, who were stage IVA ($n = 2$) and IVB ($n = 1$) (SD = 17%, PR + SD = 22%), and seven (39%) with progressive disease.

Clinical benefit response (CBR)

Only one patient had a positive response to pain intensity (negative to analgesia), five patients had a positive/stable response to analgesia (all nonassessable for pain intensity), five patients were negative for both pain scores. The majority of patients were not eligible for KPS assessment, as their baseline performance status was above 70%, and were stable for weight, meaning that no CBR were detected using the strictly applied criteria of Rothenberg.

Toxicity

Almost all grade 3 and 4 toxicity occurred within the first 4 weeks of treatment (Table 2). Of the 89 doses administered, five (6%) were associated with grade 3/4 diarrhoea, five (6%) with grade 3/4 haematological toxicity (neutropenia), six (7%) with grade 3/4 nausea and 5 (6%) with grade 3/4 vomiting.

The trial was stopped because of a serious adverse event classified as a toxic death, even though *postmortem* was refused: concurrent grade 4 diarrhoea, nausea, vomiting, pain and haematological toxicity, resulting in multiorgan failure and death. The patient had liver metastasis and a large head of pancreas primary encasing superior mesenteric vessels. Obstructive jaundice was slow to clear following biliary stent insertion prior to trial entry, although within normal limits on the day of chemotherapy administration. Emergency admission occurred after week 2 as a result of acute abdominal pain, hypotension and neutropenic fever. Neither the pain nor the fever responded to antibiotics, and the patient died of a presumed intra-abdominal catastrophic event, multiorgan failure and neutropenic sepsis.

Three additional serious adverse events were reported and all disease related (pulmonary embolus, deep venous thrombosis and gastrointestinal bleed after 1, 2 and 10 weeks (1, 2 and 7 doses) of treatment, respectively). Grade 3 and 4 neutropenia occurred during weeks 2–4 of treatment and were often associated with nausea and vomiting. In two patients, this correlated with slightly

Table 2 Treatment related toxicity

Reported toxicity episodes CTC Grade	No. of patients (max 18) N (%)	No. of doses (max 88) N (%)
Diarrhoea		
1/2	10 (56%)	17 (19%)
3	2 (11%)	1 (1%)
4	2 (11%)	4 (5%)
Haematological		
1/2	10 (56%)	28 (32%)
3	3 (17%)	3 (3%)
4	2 (11%)	2 (2%)
Nausea		
1/2	11 (61%)	23 (26%)
3	4 (22%)	4 (5%)
4	2 (11%)	2 (2%)
Vomiting		
1/2	7 (39%)	14 (16%)
3	2 (11%)	2 (2%)
4	3 (17%)	3 (3%)
Other		
1/2	11 (61%)	39 (44%)
3	1 (6%)	1 (1%)
4	1 (6%)	1 (1%)
Nontoxic SAE	3 (17%)	3 (3%)

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CSPC Exhibit 1100
Page 115 of 333

higher bilirubin levels in the normal range at entry into the study (not shown). This suggested that either intrahepatic cholestasis from metastasis or slow recovery from obstructive jaundice may have increased the half-life of Irinotecan metabolites (Sn38) and resulted in increased susceptibility to toxicity. 'Other' toxicities reported were 21, Grade 1 and 18, Grade 2 events: pain (5), alopecia (9), constipation (8), tiredness (4), appetite (1), oral (6), skin (1), pulmonary embolus and atrial fibrillation (1), transient raised creatinine (1), steatorrhoea (2), and upper respiratory tract infection (1).

DISCUSSION

Our results show that the majority of patients with advanced pancreatic adenocarcinoma and good performance status can tolerate an irinotecan and cisplatin combination at modest doses, but that this combination appears not all that active, with response rates that are in line with other chemotherapy combinations in this disease. However, the disadvantage of this combination may be the severe toxicity in patients with advanced pancreatic cancer, as others have reported (Slater *et al*, 2002), which may be the result of either interindividual variability in drug metabolism or decreased biliary drainage from the liver following obstructive jaundice. Despite the small size of this study, we urge caution in the adoption of this combination in pancreatic cancer, even though some patients appeared to respond to treatment. Furthermore, recent reports also highlight the unpredictable toxicity that can occur with irinotecan using dosing based on body weight, which suggests that the use of a fixed dosing of this agent may be preferential (Mathijssen *et al*, 2002). If this combination were used again in advanced pancreatic cancer, we would dose irinotecan at a low level for at least the first cycle and judge dose escalation by nadir blood counts. We would also wish to obtain more information about the appropriate selection of patients prior to treatment (see below). Aside from unpredictable toxicity, we note that the haematological toxicity from this combination appears no different from single-agent irinotecan or combinations of irinotecan and gemcitabine (Wagener *et al*, 1995; Armand *et al*, 1996; Rocha Lima *et al*, 2002).

Radiological response rates and survival in this study are compatible with other single agent and combination treatments. Clinical benefit response criteria remain subjective and may be difficult to compare across studies depending on modified criteria, so we chose to follow the original criteria (Cascinu *et al*, 1996; Burris *et al*, 1997; Rocha Lima *et al*, 2002). With the modest trial selection parameters chosen here, almost all patients who tolerated full-course treatment had preserved weight and performance status, and controlled pain over the study period (not shown). While these patients are better at tolerating a 15-week chemotherapy course, they tended not to contribute to a CBR analysis, as strictly judged by the original published criteria of Rothenberg *et al* (1996b). The main reason for a lack of detectable benefit was the magnitude and duration of improvement from the baseline level at trial entry. Furthermore, the selection criteria for most trials lead to bias, as enrollment of patients with good performance status, with little pain and weight loss, are selected. Any change in CBR may be unrepresentative of the total population of patients presenting with advanced pancreatic cancer. A further selection bias may be related to the extent of disease, as patients with locoregional disease tend to have a prolonged survival (Bramhall *et al*, 2001). Thus, because we have adopted a Phase II approach with small numbers of patients, we cannot exclude a role for this combination in the treatment of a subgroup of patients that might tolerate treatment with minimal toxicity even at higher doses, and which may also have a higher response rate. One approach that might avoid continued reporting of negative Phase II studies such as this might be to attempt to optimise current combination therapy to clinical subgroups of patients with advanced pancreatic adenocarcinoma. For example, good performance status patients with locoregional disease may tolerate high-dose combination treatments and gain most palliative benefit from their use. The assessment of palliative benefit *vs* toxicity for new combinations of chemotherapy and biological therapy in pancreatic cancer may require the stratification of patients in future phase II trials.

ACKNOWLEDGEMENTS

We thank the staff of the Liver Unit, Pharmacy and Cancer Centre of the Queen Elizabeth Hospital, the referring medical and surgical teams, and the families who have been involved in the care of these patients. We thank the Eveson charity (CEM), Cancer Research UK (DDS, ABH) for support. Primary treatment and management was directed by two of the investigators (CEM and ABH). Data management was directed by DDS and CEM, analysis performed by DDS and the manuscript written by ABH, DDS and CEM. There were, and remain, no conflict of interests in reporting this study.

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CSPC Exhibit 1100
Page 116 of 333

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CSPC Exhibit 1100
Page 117 of 333

The Past, Present, and Future of Pancreatic Cancer Clinical Trials

Lynn M. Matrisian, PhD, MBA, and Jordan D. Berlin, MD

OVERVIEW

Upper gastrointestinal malignancies comprise half of the deadliest cancers as defined by those with a 5-year survival rate less than 50%. Using pancreatic adenocarcinoma (PAC) as an example, we retrospectively evaluated the success of phase III clinical trials, examined the current landscape of clinical trials, and identified emerging areas that foretell the future for this disease. Pancreatic and liver cancers are on the rise and will be the second and third leading causes of cancer deaths in 2030. A total of 35 different agents or combinations have been tested in randomized phase III clinical trials for patients with advanced PAC over the past 25 years, but only 11% have been incorporated into clinical practice. There has been a 37% increase in the number of PAC trials open in the United States between 2011 to 2012 and 2014 to 2015. Enrollment has also increased slightly, from 3.85% of the newly diagnosed cases in 2011 to 4.15% in 2014. However, the demand for patients far exceeds the number of patients available for these trials. On the horizon is the realization that stratification of patients with PAC using biomarkers that predict a high probability of a response could reallocate patients to faster, smaller trials with a greater chance of a survival benefit. The current landscape of PAC clinical trials and the launch of the Pancreatic Cancer Action Network's Know Your Tumor initiative indicate this shift is starting to occur, with particular emphasis on targeted therapies, immunotherapies, and agents that disrupt the stroma.

Historically, the big four cancers in the United States have been considered lung, colorectal, breast, and prostate because of their high incidence and mortality rates. However, trends are changing dramatically, and cancers that have not been "top of mind" are becoming increasing threats to public health in the United States. Eight major cancers are considered the deadliest, characterized by 5-year survival rates below 50%.[1,2] These eight cancers will account for half of the cancer deaths in the United States this year, and four of the eight cancers are diseases of the upper gastrointestinal tract (i.e., pancreas, liver, esophagus, and stomach).[3] This article focuses on PAC, representing 95% of pancreatic cancer diagnoses and defines the problem from the perspective of a patient with PAC through the lens of an advocacy organization and a medical oncologist working in this field for many years. We outline some of the historical challenges to successful clinical trial design and execution, describe efforts currently underway, and highlight future directions that may bring urgently needed progress to this deadly disease. These insights provide lessons learned relevant to deadly upper gastrointestinal malignancies in general.

Although overall incidence and death rates for cancer in the United States are declining, pancreatic cancer is on the rise. It is the only major cancer with a 5-year relative survival in the single digits. Despite pancreatic cancer being the 11th most commonly diagnosed cancer in men and 9th in women, deaths from it surpassed breast cancer and moved to the third leading cause of cancer-related death in the United States this year. An estimated 53,070 Americans will be diagnosed with pancreatic cancer in 2016 and 41,780 are expected to lose their lives to the disease.[3]

The threat of pancreatic cancer is only expected to increase in the coming years. A 2014 study predicted that pancreatic cancer deaths would surpass breast cancer and further projects that pancreatic cancer deaths will exceed those caused by colorectal cancer around 2020, positioning pancreatic cancer as the second leading cause of cancer-related deaths in the United States before 2030 (Fig. 1).[4] Moreover, deaths from liver cancer have surpassed prostate cancer this year, placing it among the top-five cancer killers in the United States. Projections show that liver cancer deaths will continue to rise quickly, leading to it becoming the third leading cause of cancer-related death in the United States by 2030.[4]

The clinical advances required to slow the alarming trajectory of pancreatic cancer deaths will be made as a result of clinical research. National Comprehensive Cancer Network

From the Pancreatic Cancer Action Network, Manhattan Beach, CA; Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN.

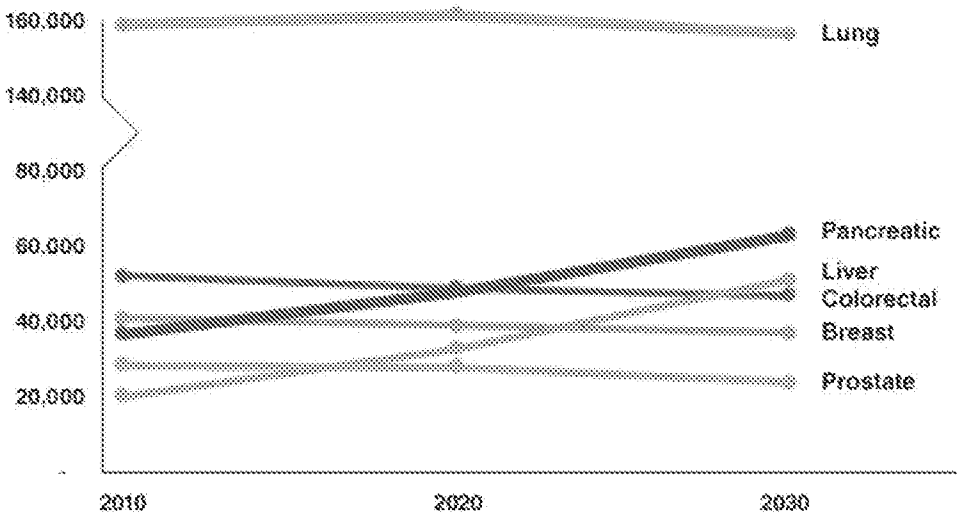
Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

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CSPC Exhibit 1100
Page 118 of 333

FIGURE 1. Projected Number of Cancer Deaths, 2010 to 2030



guidelines indicate that a clinical trial is the preferred course of treatment at all stages of PAC.[5] The Pancreatic Cancer Action Network encourages all patients who call its Patient Central call center to consider clinical trials when making treatment decisions. But enrollment rates remain low, and clinical trials do not always match patients' needs, leading to slow progress and continued poor outcomes for patients. The following sections evaluate the past, present, and future of pancreatic cancer clinical trials.

KEY POINTS

- Deaths from pancreatic cancer are rising, making the disease the third leading cause of cancer deaths in the United States in 2016.
- Randomized phase III trials over the past 25 years have resulted in a new standard of care for PAC 11% of the time.
- The number of clinical trials for PAC open in the United States has increased by 37% over the past 5 years. Although there has been a slight increase in the number of patients who enroll in PAC trials from 3.85% in 2011 to 4.15% in 2014, the demand for patients to enroll in trials far exceed the number of patients available, and it will take, on average, more than 6 years to accrue those trials open in 2014.
- The landscape of current PAC clinical trials is changing, with an increase in the number of neoadjuvant trials, particularly focusing on radiation therapy and an increase in the number of trials for previously treated patients, such as for targeted therapies.
- The Pancreatic Cancer Action Network's Know Your Tumor initiative has offered molecular profiling opportunities to more than 500 individuals from 38 states; 40% of them demonstrate an actionable alteration that suggests a therapeutic option that would not otherwise be identified for these patients.

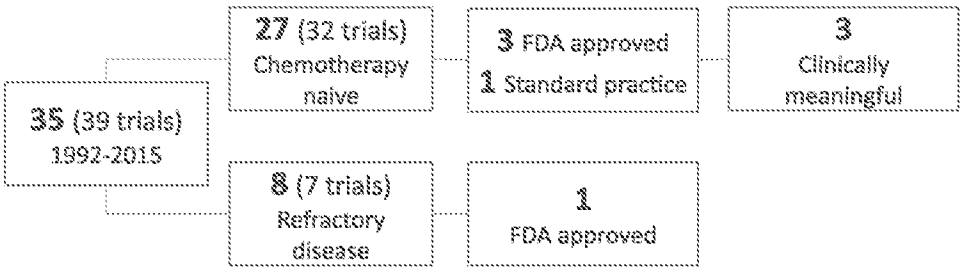
THE PAST

Progress in advanced PAC can be measured by treatment options considered clinically meaningful enough to be available as standard of care to patients: gemcitabine (approved by the U.S. Food and Drug Administration [FDA] in 1996), FOLFIRINOX (positive phase III data published in 2011),[6] gemcitabine with nab-paclitaxel (FDA approved in 2013) for first-line treatment, and the recent FDA approval of irinotecan liposome injection (2015) for patients previously treated with gemcitabine. To achieve this degree of success, a total of 35 different agents or combinations were tested in 39 phase III clinical trials in advanced-stage PAC between 1997 and 2015 (Fig. 2, unpublished data, LR, PhD 2016). Twenty-seven of these were tested in patients with treatment-naive disease, and eight of the 35 agents or combinations were tested in patients with previously treated disease. Although the FDA approved the combination of gemcitabine and erlotinib in 2005 based on a hazard ratio (HR) of 0.82 for overall survival, the modest improvement in median survival of 6.2 months compared with 5.9 months with gemcitabine alone[7] is generally viewed as being insufficient to warrant the additional toxicity and expense of erlotinib. Thus, the overall success rate of PAC phase III trials is a dismal 11%, despite a prior phase II trial in the majority of cases.

In the purest sense of trial design, the phase II trial is written with the ultimate goal that (1) if the primary endpoint is positive, it will lead to a phase III trial, and (2) if negative, the drug or regimen will not go further in that setting. However, in 85% of the cases where we could identify a prior phase II trial, a phase III trial was pursued irrespective of the phase II not meeting its primary endpoint (Rahib et al, unpublished data, 2016). The decision to

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CSPC Exhibit 1100
Page 119 of 333

FIGURE 2. Agents/Combinations in Phase III Clinical Trials for Pancreatic Adenocarcinoma, 1992 to 2015



Abbreviation: FDA, U.S. Food and Drug Administration.
Adapted from Rahib et al (unpublished data, 2016).

proceed was based on encouraging secondary endpoints, subset analyses results, or a second phase II trial conducted elsewhere that showed promise. Factors that are not mentioned but contribute to corporate go/no-go decisions involve economic and logistic considerations by the trial sponsors that are influenced by whether the trial is the first indication for a new drug and by the size of the company.[8] If the past is prelude to the future, there is considerable concern that the trend of negative phase III trials will continue and thwart the chance for any major advancement in PAC survival.

THE PRESENT

The Pancreatic Cancer Action Network maintains a database of pancreatic cancer clinical trials in the United States that is constantly updated to be able to give those who contact the Patient Central call center accurate, up-to-date information on clinical trials that match the patients' stage of disease and that are open within a distance they are willing to travel. We analyzed the portfolio of pancreatic cancer clinical trials in 2011 and 2012 by type, phase, disease stage, and treatment approaches.[9] We extended this study to include the years 2013 to 2015 and report the results in this article. We are encouraged to find that the number of PAC-specific clinical trials open in the United States has steadily increased between 2011 and 2015 (Fig. 3A). This trend is observed for all phases of clinical trials, with the most dramatic growth observed in phase I trials (Fig. 3B).

During 2011 to 2012, the majority of PAC clinical trials were designed for patients with treatment-naive, metastatic disease (51% of total PAC trials for these 2 years; Fig. 4). Since then, there has been a dramatic shift toward a greater number of trials to accommodate patients who have already been treated. In fact, the majority of the trials during 2014 to 2015 focused on patients with refractory and previously treated disease (38%), whereas the percentage of first-line metastatic trials during 2014 to 2015 (22%) decreased by more than two fold compared with 2011 to 2012. This shift from metastatic/treatment-naive trials to trials for patients with previously treated disease is viewed very positively from a patient perspective. In 2011, we observed that two-thirds of the patients that call the Pancreatic Cancer Action Network's Patient Central were ineligible for 90% of the clinical trials that were open because they had already started treatment.[9] The increase in clinical trials that include patients with previously treated disease opens up more options and encourages a multistep treatment plan that provides several opportunities for interventions that may improve survival. In this respect, the study of patients with more refractory disease in later line is encouraging, but we acknowledge that due to the severity of this illness risks missing potentially active agents if had they been studied in an earlier line of therapy.

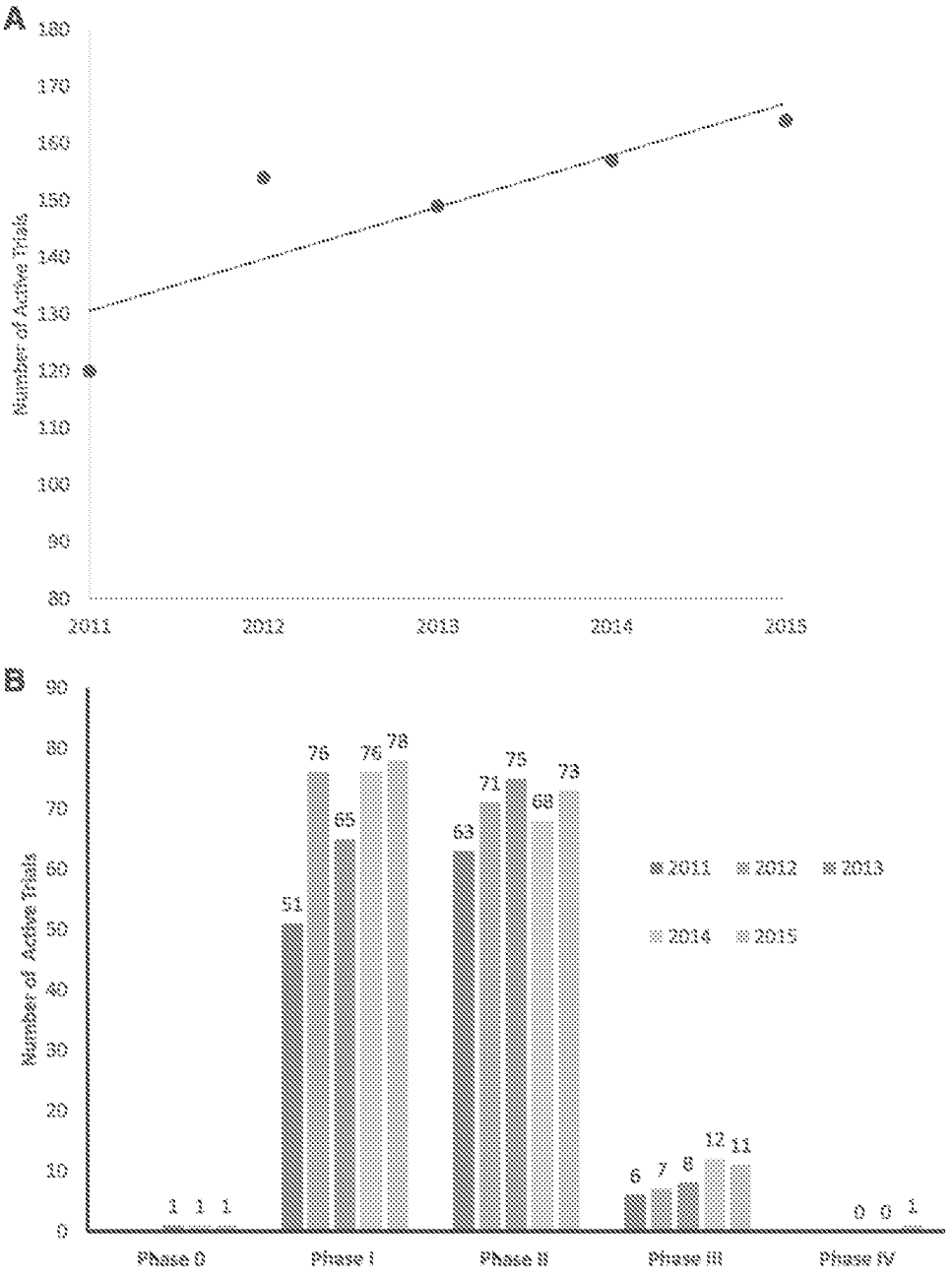
For patients with early-stage resectable disease, 13% of trials were active for neoadjuvant treatment and 10% for adjuvant treatment from 2011 to 2012. From 2014 to 2015, there was an approximately two fold increase in trials for neoadjuvant treatment (24% of active trials) and a slight decrease to 7% of the trials requiring patients for adjuvant studies (Fig. 4). The increase in neoadjuvant trials may be attributed to the recognition that even patients with resectable PAC have dismal outcomes because of the rapid development of metastatic disease—a clinical observation that was supported with preclinical evidence in 2012.[10] In addition, the eligibility criteria for neoadjuvant trials have shown an expansion to patients with borderline resectable disease with the hope that neoadjuvant treatment shrinks the tumor and permits a negative margin resection.

The landscape of PAC clinical trials was also examined by treatment type (Fig. 5A). Trials that focused on therapies targeted to specific molecular pathways increased markedly between 2011 and 2015, comprising 29% of the PAC landscape from 2011 to 2012 and 40% from 2014 to 2015. The majority of these targeted trials are for patients with refractory disease and those who received previous treatments (Fig. 5B) and include targets for PARP, JAK, WEE1, mTOR, and several others.

In addition, trials focused on radiation therapy increased from 13% of total PAC trials during 2011 to 2012 to 18% during 2014 to 2015 (Fig. 5A). The majority of these trials were in the neoadjuvant setting, which comprised 58% of the total radiation trials from 2014 to 2015 (Fig. 5B). Many of these neoadjuvant trials (> 50%) used intensity-modulated radiotherapy or stereotactic body radiotherapy in combination with chemotherapy.

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Page 120 of 333

FIGURE 3. Pancreatic Adenocarcinoma Trials Open in the United States from 2011 to 2015



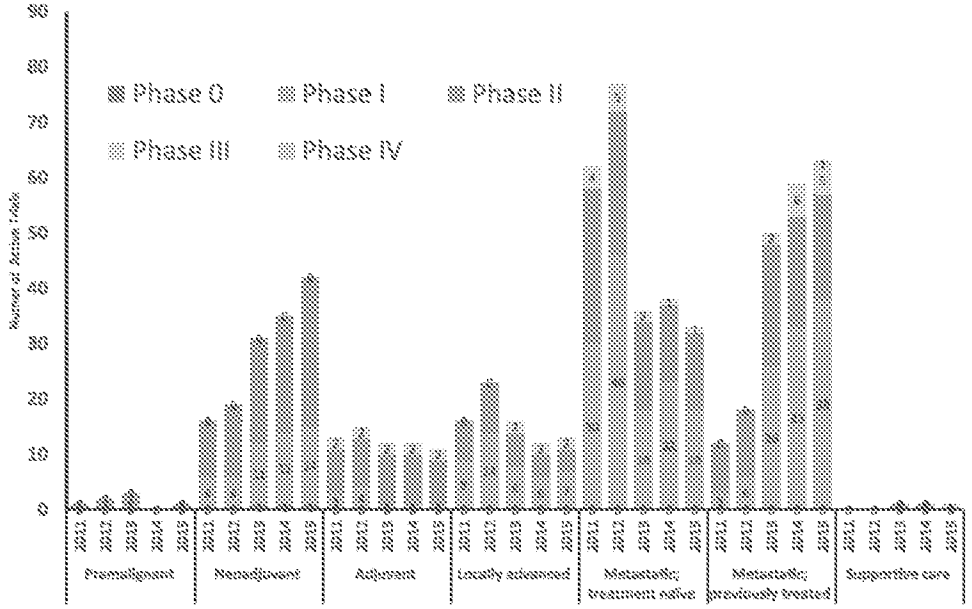
(A) Trials open (2011-2015) (B) Trials open by phase.

Trials focused on an immunotherapeutic approach were relatively steady, with an average of 14 trials per year over the past 5 years (Fig. 5A). There has been a change, however, in the stage of disease of treatment. From 2011 to 2012, the majority of trials were for patients with metastatic disease (52%), whereas from 2014 to 2015 the majority of immunotherapy trials were for patients with refractory disease and those who received previous treatments (62%; Fig. 5B). Approximately 60% of these trials involved a vaccine treatment, 20% included T-cell–modified therapy, and 7% included checkpoint blockade therapy.

As a result of regularly updating clinical trial information stored in the organization's comprehensive database, the Pancreatic Cancer Action Network has established strong relationships with trial sponsors. These relationships allowed the accumulation of data to estimate the number of patients with pancreatic cancer in the United States who were accrued to clinical trials in 2011,[9] and this analysis was repeated for 2014 clinical trials. Considering only those patients with a PAC diagnosis who enrolled in trials (in contrast to the previous analysis, which considered all pancreatic cancer diagnoses), 1,612 patients with PAC enrolled in clinical trials in 2011 (93% of trials reporting), and

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FIGURE 4. Pancreatic Adenocarcinoma Clinical Trials Open in the United States from 2011 to 2015 by Disease Stage



1,835 patients with PAC enrolled in clinical trials in 2014 (94% of trials reporting). As a percentage of the estimated number of new cases of PAC in that year (95% of the estimated total pancreatic cancer incidence),[3] we calculate that 3.85% of patients with PAC went on a clinical trial in 2011, and 4.16% went on a trial in 2014.

Although the slight increase is encouraging, the time it will take to enroll patients with PAC in clinical trials based on this accrual rate is unacceptably slow. For example, the number of newly diagnosed patients with resectable disease who could be eligible for clinical trials for neoadjuvant or adjuvant treatment approaches in 2014 is estimated to be 4,178 (Table 1). However, the 47 trials that were open in these categories required 3,437 patients, indicating that 82% of the eligible patients in the United States would need to go on one of these clinical trials to complete enrollment during that year. The actual percentage of enrollment for these trials for 2014 was 10%, indicating that it would take 9.7 years to complete enrollment of the neoadjuvant/adjuvant trials open in 2014. On the other hand, it is encouraging that the time necessary to complete enrollment of trials for patients with locally advanced and previously treated metastatic disease has decreased, from 9.0 years to 3.8 years and 7.1 years to 6.0 years, respectively (Table 1). Nevertheless, for a disease with a 71% 1-year mortality, it is clear we must identify a new paradigm for clinical advancement to accelerate progress.

THE FUTURE

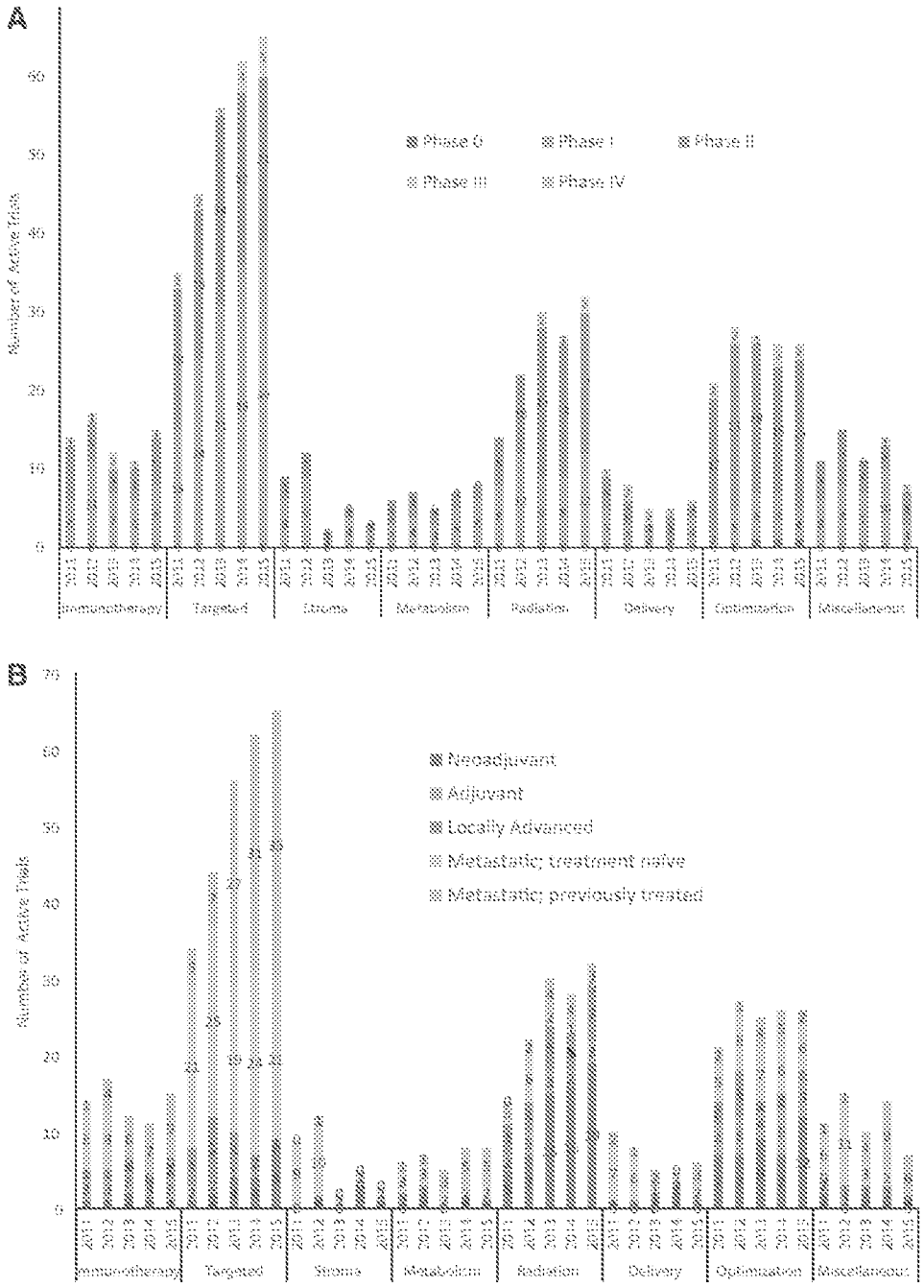
There has been a palpable shift away from the nihilistic attitude toward PAC that bodes well for the future for these patients. In October 2015, the FDA approved irinotecan liposomal injection for patients with metastatic PAC who had received prior chemotherapy. Irinotecan liposome injection was shown to improve overall survival by nearly 2 months when administered in combination with fluorouracil and leucovorin. This approval was a historic achievement, as it was the first drug combination approved with an indication specific to this patient population.[11] As described above, in the past few years, the amount of clinical trials focused on patients with previously treated disease has increased. As oncologists and patients are often eager to begin chemotherapy treatments as soon as possible upon diagnosis, providing expanded options for patients with treatment-refractory PAC fills a critical gap and has the potential to positively affect patient outcomes.

Clinical research provides the evidence for treatments that prolong survival. The randomized phase III trial is the gold standard for FDA approval of new treatments and acceptance as standard of care. However, progress in pancreatic cancer using this paradigm has been agonizingly slow. A transformative shift in approach is emerging as a result of the incorporation of molecular profiling as a basis of identifying subsets of patients with cancer with a high probability of responding to a specific treatment. For example, the care of patients with breast cancer is routinely stratified by their estrogen receptor and HER2 status, and the genotyping of non–small cell lung cancer for ALK translocations as an indicator of specific chemotherapeutic treatments is becoming routine.

The ability to identify those patients whose disease has a high probability of responding strongly to a specific treatment has enormous implications for clinical trial design. For example, a treatment with a true HR of 0.4 requires only 70 patients if all the patients enrolled in the trial have the drug target.[12] However, if the trial occurs in an unselected

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Page 122 of 333

FIGURE 5. Pancreatic Adenocarcinoma Clinical Trials Open in the United States from 2011 to 2015 by Treatment Type



(A) Trials open by treatment type and phase (B) Trials open by treatment type and disease stage

patient population, the number of patients needed is proportional to the prevalence of the target. Further, the observed HR decreases with proportion of patients. The same treatment above requiring 70 selected patients, if evaluated in an unselected population containing 20% of patients with the target, requires 1,750 patients, and the HR observed is only 0.84. A trial requires 29,620 patients if the marker is present in only 5% of the unselected population. Past trials, in large numbers of unselected patients with pancreatic cancer, have resulted in relatively small observed HR and improvement in survival. Given that pancreatic cancer is heterogeneous, it seems possible that a missing component is identification of patients who are most likely to respond to specific treatments. Continuing with the paradigm of treating all patients with the same chemotherapeutic agents will continue to reap low rewards and squander the precious resource of patients willing and eligible to enroll in clinical trials.

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TABLE 1. Anticipated Total and Actual Accrual in the United States in 2011 and 2014

Stage at Diagnosis	Year	Distribution (%)	Est. No. Patients*	No. of Trials	Potential Enrollment	Enrollment Capacity (%)**	Enrolled† (%)	Years to Completion‡
Localized ([Neo] Adjuvant)	2011	9	3,963	29	2,874	73	15	6.9
	2014	9	4,178	47	3,437	82	10	9.7
Regional (Locally Advanced)	2011	28	12,328	16	756	6	13	9.0
	2014	28	12,998	12	800	6	27	3.8
Distant (Metastatic)	2011	53	23,336	62	6,394	27	18	6.2
	2014	53	24,603	38	3,535	14	15	6.6
Metastatic; Previously Treated	2011	27	11,668	12	524	4	14	7.1
	2014	27	12,301	59	4,364	35	17	6.0

The distribution by disease stage was determined using the Surveillance, Epidemiology, and End Results (SEER) 18 2005-2011 Registry, All Races, both Sexes by SEER Summary Stage 2000 for localized, locally advanced, and metastatic. The number of estimated patients diagnosed with pancreatic cancer for each year was multiplied by 95% to account for pancreatic adenocarcinomas only. The distribution of previously treated metastatic disease was determined by multiplying the percentage of patients with metastatic disease by 50%, as it is reported that about 50% of patients with pancreatic cancer are eligible for second-line therapy.[36-38]

*The number of new patient cases of pancreatic cancer was estimated to be 44,030 for 2011 and 46,420 for 2014.

**Enrollment capacity is total potential enrollment for open trials divided by the estimated number of available patients for 2011 and 2014.

†Percentage enrolled is the number of patients enrolled divided by the potential enrollment for trials within that subgroup for which accrual numbers were available for 2011 and 2014.

‡Years to completion is the number of potential enrollment divided by the accrual numbers (for each subgroup) for which accrual numbers were available for 2011 and 2014.

Is molecular stratification feasible in pancreatic cancer? Recent genomics analyses have revealed high numbers of genetic changes that contribute to the initiation and progression of PAC. Although we know that oncogenic *KRAS* drives 95% of PAC cases, more recent studies have shown greater genetic diversity than previously expected. Efforts remain underway to devise methods to directly attack KRAS, which would certainly be game-changing for the treatment of PAC.[13] In the meantime, identifying genetic changes and signatures that could predict patient response to targeted or more traditional therapies could have immediate and major effect on patient care.

Results from the Australian Pancreatic Cancer Genome Initiative within the International Cancer Genome Consortium defined four subtypes of PAC: stable, locally rearranged, scattered, and unstable. Of particular interest is the unstable phenotype, which was observed in 14% of the 100 patient samples analyzed. Unstable genomes were found to contain more than 200 structural variation events, which often suggests damage to the DNA repair pathways.[14] This group and others have shown that patients with PAC who have DNA damage repair alterations may be particularly sensitive to platinum-containing chemotherapeutics and/or PARP inhibitors.[15-17] A recent paper further refines the molecular subtypes of pancreatic cancer based on genomic analysis.[18]

An additional targeted therapeutic approach involves assessing patients' levels of hyaluronan (HA), which is a glycosaminoglycan present in the microenvironment surrounding PAC tumors. Hyaluronan contributes to elevated interstitial pressure, and its inhibition with an agent called PEGPH20 leads to the expansion of tumor-associated blood vessels, allowing delivery of other drugs to the tumor.[18,19] Interim analyses of a phase II randomized study of patients with previously untreated metastatic PAC treated with PEGPH20, nab-paclitaxel, and gemcitabine (PAG) or nab-paclitaxel plus gemcitabine (AG) were presented at the 2015 American Society of Clinical Oncology Annual Meeting. Among patients with high HA levels treated with PAG, median progression-free survival was 9.2 months, which was more than double that observed with AG alone (4.3 months).[20] This ongoing trial represents an example of customizing treatment to a patient's tumor characteristics and provides promising preliminary evidence in favor of this approach.

Finally, multiple studies are underway to investigate immunotherapy for the treatment of PAC. Pancreatic adenocarcinoma is known to be a highly immunosuppressive disease, rendering immunotherapeutic approaches that have shown success in other cancer types ineffective as single agents in PAC. To combat this immunosuppression and recruit T cells to the PAC microenvironment, immune checkpoint inhibitors such as anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies are being tested. Preliminary results suggest that these tactics can be successful in combating the immunosuppression but do not lead to cancer cell death. Therefore, focus has shifted to combination of checkpoint inhibitors with a therapeutic vaccine strategy or other agents such as chemotherapy or radiation (e.g., NCT02303990).[21-25]

Correlative studies are revealing stratification approaches that indicate patients most likely to respond to immunotherapeutic approaches, including anti–CTLA-4 and anti–PD-1 therapy. A study published in 2015 showed that the overall mutational load, neoantigen load, and expression of cytolytic markers in the immune microenvironment of patients with metastatic melanoma were significantly associated with clinical benefit to ipilimumab.[26] Another study, also published in 2015 that included patients with non–small cell lung cancer, melanoma, and renal cell cancer, showed

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CSPC Exhibit 1100
Page 124 of 333

that nine out of 25 patients with PD-L1–positive tumors had an objective response to anti–PD-1 therapy, while all 17 patients with PD-L1–negative tumors had no response.[27,28] Standardized testing of PD-L1 on tumor cells for the prediction and evaluation of treatment efficacy is needed. In addition, mismatch repair–deficient tumors may be sensitive to immune checkpoint blockade. Currently, multiple trials are underway testing the sensitivity of anti–PD-1 therapy in this subset of patients in several gastrointestinal cancers, including a phase II trial in patients with previously treated advanced colorectal cancer,[29] a phase III first-line randomized trial comparing anti–PD-1 therapy to standard chemotherapy in patients with metastatic colorectal cancer,[30] and a phase II trial for patients with previously treated colorectal and other gastrointestinal cancers. This phase II trial reported promising response to anti–PD-1 therapy in noncolorectal gastrointestinal cancers with mismatch repair deficiency, including ampullary, pancreas, biliary small bowel, and gastric cancers.[31]

As we gather more genomic, proteomic, and immune cell information about PAC and accumulate evidence from this and other cancer types about molecularly targeted treatment approaches, efforts such as the Pancreatic Cancer Action Network's Know Your Tumor precision medicine initiative will play an important role in providing patients access to personalized treatment approaches so that hypotheses on the predictive value of these markers can be tested. Patients with pancreatic cancer across the United States are able to access Know Your Tumor for multi-omic molecular profiling information on their tumor by contacting the Pancreatic Cancer Action Network's Patient Central. A highly trained Patient Central associate determines the eligibility and interest of the patient in enrolling in the program and transfers suitable patients to a partnering organization, Personalized Cancer Therapy, Inc. (doing business as [d.b.a] Perthera). Perthera obtains patient consent, talks to the treating physician, facilitates obtaining suitable biopsy tissue according to standard operating procedures, and sends the sample to appropriate diagnostic laboratories. Multi-omic testing is performed, including genomic, protein, and phosphoprotein analysis. The results are returned to Perthera for data analysis and integration, and an expert medical review is conducted that combines this information with current literature and knowledge of pancreatic cancer clinical trial results and the patient's history. The medical review team includes a medical oncologist with considerable experience and expertise in treating pancreatic cancer. Treatment options are ranked and include clinical trials with up-to-date information on availability from the Pancreatic Cancer Action Network database, solid tumor phase I trials, off-label treatments, and standard of care options. The report is sent to the treating physician, the patient, and the Pancreatic Cancer Action Network, and outcomes data are collected from both the patient and the treating physician. All patients using Know Your Tumor are encouraged to participate in the Pancreatic Cancer Action Network's patient-reported outcomes registry to obtain more detailed information on their experience and the outcome of treatment. Since its inception in June 2014 to December 2015, Know Your Tumor has enrolled 496 patients with pancreatic cancer from 38 different states.[32]

There were 175 molecular profiles from Know Your Tumor participants evaluated as of December 31, 2015. Of the 175 patients with completed reports, 58% were treated at an academic institution or high-volume center, while 42% were treated at a community center (Fig. 6). The distribution of pathologic genomic alterations as determined by analysis with the Foundation One panel of 343 genes is shown in Fig. 7.[32] Forty percent of patients had at least one actionable alteration as defined based on a high response rate in patients with an identified molecular abnormality in any cancer type, or based on a mechanism/pathway-defined implication of response to treatment.[33] For example, 18% of patients' tumors had alterations in genes involved in DNA damage repair, including *BRCA2*, *PALB2*, *ATM*, and others indicated in Fig. 7. These alterations suggest treatment with a DNA-damaging agent such as platinum and/or a PARP inhibitor. Based on patient follow-up as of December 31, 2015, 34 patients received their next line of treatment consistent with the Perthera report, eight of whom enrolled in a clinical trial and three of whom used an off-label treatment. In addition, six patients received therapy that was not indicated by the report. Although the numbers are small, preliminary analysis suggests an improved outcome for patients who followed options based on the Perthera report compared with those who received treatment not listed on the report (median overall survival 45 vs. 32 weeks).[33]

Clinical trials for pancreatic cancer are incorporating biomarkers for patient selection. In January 2016, an analysis of the Pancreatic Cancer Action Network's clinical trial database revealed 21 of 174 (12%) clinical trials required a molecular indicator for enrollment. It is anticipated that this percentage will increase over time as more knowledge is gained and a targeted approach is applied to the deadliest cancers.

OTHER UPPER GASTROINTESTINAL CANCERS

Similar to pancreatic cancer, other upper gastrointestinal cancers have also had limited successes. Biliary tract cancer and hepatocellular cancers each have only one standard regimen. After initial success with sorafenib as first-line therapy for hepatocellular carcinoma, multiple other vascular endothelial growth factor receptor (VEGFR) inhibitors were unsuccessfully tested in phase III trials.[34] Although it is not surprising that other VEGFR inhibitors were tested, it is remarkable that the sheer number of trials were conducted and no other targets were evaluated in a substantive manner. Similarly, based on almost no preclinical evidence—simply overexpression of the protein—EGFR inhibitors were tested in multiple randomized studies in gastroesophageal cancer, all of which were negative.

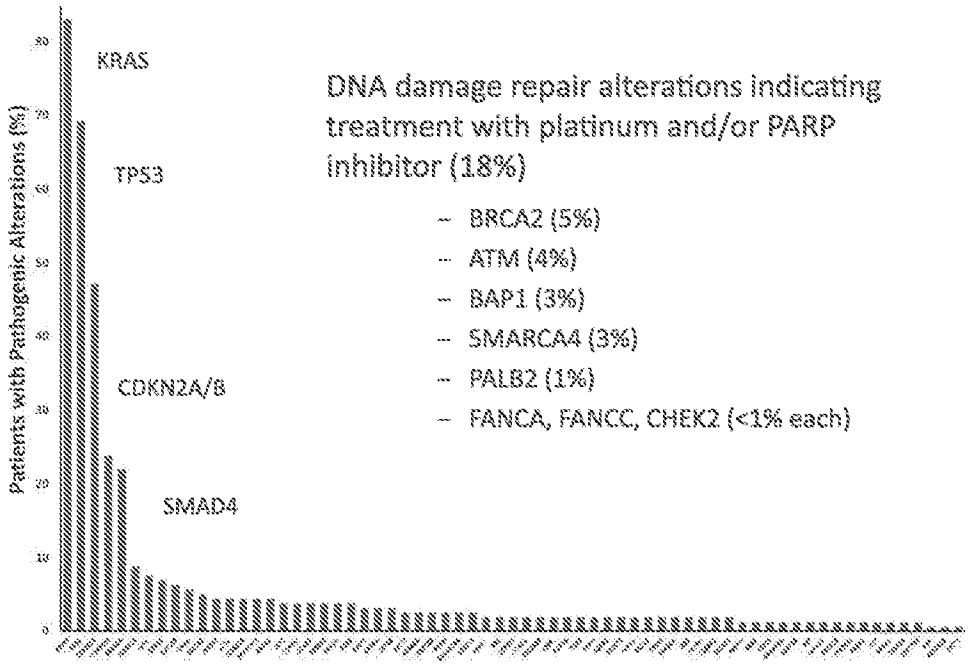
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CSPC Exhibit 1100
Page 125 of 333

FIGURE 6. Know Your Tumor Recruitment Across the United States and Community and Academic/High-Volume Sites



The question for the future of all upper gastrointestinal cancers—and all cancers in general—is whether we can start conducting smarter trials. In 2009, the State of the Science meeting results for pancreatic cancer were published.[35] The meeting emphasized having preclinical data guide the development of the clinical trials, rather than becoming an afterthought used as rationalization for a planned study. As noted above, designing clinical trials in the era of personalized medicine may allow for smaller trials with greater effect. Others have recommended "n of 1" studies, testing different agents or combinations for an individual patient, but how this can be done without simply being an anecdote

FIGURE 7. Pathogenic Alterations Observed by Next-Generation Sequencing in Know Your Tumor Participants



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has yet to be defined. Smarter trials can be smaller, but it unlikely that one patient can define the utility of a drug.

CONCLUSION

The lessons we have learned from pancreatic cancer reflect the potential that exists in upper gastrointestinal malignancies in general. Although we celebrate the few successes, it is essential that we learn from the failures. Clinical trials must be smarter in their design to conserve the precious resource of patients willing to enroll in clinical trials. Applying biomarkers that identify patients with a high probability of response is one way to leverage remarkable advances in cancer research with the practical outcome of reducing the number of patients needed to identify a clinically meaningful result. Initiatives such as the Pancreatic Cancer Action Network's Know Your Tumor provide a mechanism to disseminate the practice of interrogating the molecular characteristics of the tumor from patients across the United States and learn from them. This will set the stage for vast improvements in the current approach and rapid advances toward improving the survival of those with the deadliest cancers.

ACKNOWLEDGMENT

Pancreatic Cancer Action Network staff and associates that contributed to this work include Lynn Matrisian, PhD, MBA (concepts, writing, oral presentation); Lola Rahib, PhD (data analysis, writing, figure preparation); Porsha James, MPH, and Kyia Holmes (data collection for clinical trial landscape and accrual); Allison Rosenzweig, PhD (writing); William Hoos, MBA (concepts); and our partners from Personalized Cancer Therapy, Inc. (Perthera) and the Know Your Tumor initiative. We thank all trial sponsors that provided accrual information.

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Page 127 of 333

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CSPC Exhibit 1100
Page 128 of 333

Annals of Oncology 27 (Supplement 4): iv17–iv28, 2016
doi:10.1093/annonc/mdw333.4

gastrointestinal (non-colorectal) cancers

B04 **Effects of nanoliposomal irinotecan (nal-IRI; MM-398) + 5-fluorouracil and leucavorin (5-FU/LV) on quality of life (QoL) in patients (pts) with metastatic pancreatic adenocarcinoma (mPAC) previously treated with gemcitabine-based therapy: results from the phase 3 NAPOLI-1 study**

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Background: Here we report QoL results from the randomized, phase 3 NAPOLI-1 study of nal-IRI + 5-FU/LV vs 5-FU/LV alone in pts with mPDAC previously treated with gemcitabine-based therapy.

Methods: QoL was assessed using the EORTC-QLQ-C30, which includes Functional, Symptom, and Global Health and QoL scales. Pts completed the questionnaire at treatment start, every 6 weeks (wks) and 30 days post-follow-up. Pts who were assessed at baseline and at ≥1 subsequent visit were included. Scores were reported in a 0–100 range after linear transformations were applied to raw scores. For each subscale, pt response was classified as improved (≥10% increase in scale of breadth at a post-baseline time point and remained above baseline for ≥6 wks), worsened (did not meet improvement criteria and died, or had ≥10% decrease from baseline in scale of breadth at a post-baseline time point), or stable (did not meet criteria for improvement or worsening). Pairwise comparisons of response classification between groups were performed for each subscale and adjusted for multiplicity to control false discovery rate at 0.05 level for the 15 comparisons.

Results: 154 pts were included in the analysis. Evaluable data at 12 wks was available for 69% (49/71) in the nal-IRI + 5-FU/LV group and 53% (44/83) in the 5-FU/LV group. At baseline, values were similar between groups: median Global Health Status scores were near the midpoint of the scoring range, median Functional Scale scores were high, and Symptom Scale scores were low. For both treatment groups, the observed median change in score at 12 wks was 0 for Global Health Status and the following subscale scores: role functioning, emotional functioning, cognitive functioning, social functioning, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. For subscale scores where the median change was not 0 (nal-IRI + 5-FU/LV: physical functioning and fatigue), the differences between the treatment groups were not substantial. There were no significant differences in the proportion of pts classified as improved, worsened, or stable between the treatment groups (adjusted P values >0.05 across subscales).

Conclusions: While this analysis was limited by pt numbers, pts treated with nal-IRI + 5-FU/LV tended to maintain baseline QoL over 12 wks. When compared with pts treated with 5-FU/LV, there were no significant differences in QoL response despite the addition of a second cytotoxic agent.

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VOLUME 25 · NUMBER 15 · MAY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

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Submitted June 26, 2006; accepted November 8, 2006; published online ahead of print at www.jco.org on April 23, 2007.

Supported in part by OSI Pharmaceuticals, Melville, NY.

Presented in part at the American Society of Clinical Oncology Gastrointestinal Symposium, Hollywood, FL, January 27-29 2005; and the 41st Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 13-17, 2005.

A list of participating investigators can be found in the online-only Acknowledgment.

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

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0732-183X/07/2515-1960/$20.00

DOI: 10.1200/JCO.2006.07.9525

ABSTRACT

Purpose

Patients with advanced pancreatic cancer have a poor prognosis and there have been no improvements in survival since the introduction of gemcitabine in 1996. Pancreatic tumors often overexpress human epidermal growth factor receptor type 1 (HER1/EGFR) and this is associated with a worse prognosis. We studied the effects of adding the HER1/EGFR-targeted agent erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer.

Patients and Methods

Patients were randomly assigned 1:1 to receive standard gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo in a double-blind, international phase III trial. The primary end point was overall survival.

Results

A total of 569 patients were randomly assigned. Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/gemcitabine arm with a hazard ratio (HR) of 0.82 (95% CI, 0.69 to 0.99; $P = .038$, adjusted for stratification factors; median 6.24 months *v* 5.91 months). One-year survival was also greater with erlotinib plus gemcitabine (23% *v* 17%; $P = .023$). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; $P = .004$). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization. There was a higher incidence of some adverse events with erlotinib plus gemcitabine, but most were grade 1 or 2.

Conclusion

To our knowledge, this randomized phase III trial is the first to demonstrate statistically significantly improved survival in advanced pancreatic cancer by adding any agent to gemcitabine. The recommended dose of erlotinib with gemcitabine for this indication is 100 mg/d.

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death with approximately 35,000 new cases and the same number of deaths estimated in North America in 2005.[1] Gemcitabine became the standard treatment for advanced disease 10 years ago after showing superiority over fluorouracil.[2] Since then, eight phase III trials of newer cytotoxic[3-8] or biologic agents[9-11] combined with gemcitabine have not shown any survival improvement compared with gemcitabine alone.

Human epidermal growth factor receptor type 1 (HER1/EGFR) is overexpressed in many pancreatic tumors[12,13] and is associated with poor prognosis and disease progression.[14,15] Blocking HER1/EGFR tyrosine kinase signaling decreases the growth and metastasis of human pancreatic tumor xenografts[16] and improves the anticancer effects of gemcitabine.[17] Erlotinib is an oral HER1/EGFR tyrosine kinase inhibitor currently approved for patients with non–small-cell lung cancer.[18] The present trial was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in cooperation with Australasian Gastrointestinal Tumor

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CSPC Exhibit 1100
Page 130 of 333

Group (AGITG) and investigators in 15 other countries to investigate the effect of erlotinib in combination with gemcitabine on survival in patients with advanced pancreatic cancer. The trial was cosponsored by OSI Pharmaceuticals (Melville, NY).

PATIENTS AND METHODS

Study Design and Treatment

NCIC CTG PA.3 was a double-blind, placebo-controlled, international, phase III trial of erlotinib (Tarceva; OSI Pharmaceuticals) plus gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma. Patients were stratified by center, performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 *v* 2), and stage (locally advanced *v* metastatic) and randomly assigned in a 1:1 ratio to receive gemcitabine plus either erlotinib or a matched placebo. Gemcitabine 1,000 mg/m^2 was given by 30-minute intravenous infusion on days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest in cycle one (8 weeks), and on days 1, 8 and 15 in all subsequent 4-week cycles. Erlotinib plus placebo was taken orally at 100 or 150 mg/d until disease progression or unmanageable toxicity. During an initial safety evaluation phase, the tolerability of erlotinib 100 mg/d with gemcitabine was established in selected centers in Canada before general enrollment using this dose. The erlotinib dose was increased to 150 mg/d in a subsequent Canadian cohort to assess the tolerability of this higher dose. Doses of erlotinib or gemcitabine could be reduced or delayed (no more than 20 days) to allow recovery from toxicity.

The primary end point was overall survival. Secondary end points included progression-free survival, response rate, response duration, toxicity, quality of life, and correlation of baseline tissue HER1/EGFR level with outcome. The ethics boards of all institutions approved the protocol and all patients provided written, informed consent. Data were collected, managed, and analyzed at the NCIC CTG central office, and the database was locked from additional changes on September 17, 2004. Follow-up information was updated in June 2005.

Eligibility Criteria

Patients had histologic or cytologic evidence of locally advanced or metastatic adenocarcinoma of the pancreas with measurable or assessable disease; ECOG performance status 0, 1, or 2; and adequate hematologic, renal, and hepatic function. Prior radiotherapy for local disease was allowed provided disease progression had been documented, and treatment completed at least 4 weeks before random assignment. Prior chemotherapy was not permitted, except for fluorouracil or gemcitabine given concurrently as a radiosensitizer.

Assessments

Responses and progression were evaluated using Response Evaluation Criteria in Solid Tumors every 8 weeks.[19] Toxicity was assessed at every visit using the National Cancer Institute Common Toxicity Criteria version 2.0. Quality of life was measured using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 questionnaire (sites in Canada and United States) every 4 weeks until documentation of progressive disease. HER1/EGFR analysis was conducted on archival tissue by immunohistochemistry using DAKO EGFR Pharm Dx kits (DAKO, Carpinteria, CA). A positive test was defined as ≥ 10% of tumor cells demonstrating membranous staining.

Statistical Analysis

Survival analyses were performed on all randomly assigned patients as per the intent-to-treat principle. The trial was powered to detect a hazard ratio (HR) of 0.75 between patients randomly assigned to gemcitabine plus erlotinib or gemcitabine plus placebo. In order to detect the postulated difference with 80% power using a two-sided 5% level test, a minimum of 381 events (deaths) were required for the final analysis. The trial had an initial planned sample size of 800, which would allow an analysis shortly after study closure to accrual. A reduction in sample size to 450 occurred just after the study opened for resource related reasons. This change did not alter the power but necessitated a longer follow-up (estimated to be 18 months after study closure) to achieve the predetermined event rate of 381. Time-to-event variables were estimated using the Kaplan-Meier method, and 95% CIs for median duration by the Brookmeyer and Crowley method.[20] Treatment arms were compared using log-rank tests stratified by performance status, extent of disease, and pain score at baseline. The adjusted HR with 95% CI was used as the primary estimate of the difference between the arms. The effects of potential prognostic factors were assessed using Cox regression. Schoenfeld residual plots were used to check the model assumption for the Cox regression.

A Cochran-Mantel-Haenszel test was used to compare response rates, adjusting for stratification factors at baseline. Fisher's exact tests were used to compare the toxicities between treatment groups, when appropriate. Patients' quality of life response distributions were categorized based on change scores from their own baseline, and were analyzed between treatment groups using χ^2 tests followed by Mantel-Haenszel χ^2 tests for trend. A change in score of 10 points was defined as clinically relevant.

The association between epidermal growth factor receptor (EGFR) status and treatment outcome was evaluated using a univariate, unadjusted analysis. A Cox regression model with a time-dependent covariate[21] was used to correlate skin rash to time-to-event outcomes, while a logistic regression model was used to correlate tumor response to skin rash and other baseline factors.

RESULTS

Patient Characteristics

Between October 2001 and January 2003, 569 patients were randomly assigned (285 erlotinib and gemcitabine and 284 placebo and gemcitabine) at 176 centers in 17 countries. Baseline characteristics were well-balanced between the arms (Table 1), except for more females in the erlotinib and gemcitabine arm (52.3% *v* 43.0%; $P = .03$). Three patients on the erlotinib and gemcitabine arm and four on the placebo and gemcitabine arm received no treatment. Nineteen patients (10 erlotinib and gemcitabine and nine placebo and gemcitabine) were ineligible because of elevated liver function tests (n = 7), other primary malignancy (n = 5), or other miscellaneous reasons (n = 7). Determination of ineligibility was done before unblinding. All 569 randomly assigned patients were included in an intent-to-treat analyses.

An interim safety analysis of the first 50 patients treated with gemcitabine plus erlotinib 100 mg/d showed no major increase in toxicity. As planned, accrual at 150 mg/d was then opened at selected Canadian centers. The accrual worldwide (at 100 mg) occurred more rapidly than had been anticipated and by the time an evaluation of the safety of the 150-mg cohort was completed, 80% of the planned sample size of 450 had been accrued. Because too few patients would be accrued to the 150-mg cohort to draw definitive conclusions, a decision was made toward the end of the study, before unblinding, to accrue a sufficient number of patients to have 80% power to detect the prespecified HR within the 100-mg cohort.

A data field cutoff date was established when the 381st death was documented in the NCIC CTG database. When all case report forms had been submitted centrally, an additional 63 deaths within the 100-mg cohort were documented before the data field cutoff date, bringing the total to 444 deaths The results presented are for both dose cohorts combined, except when indicated.

Survival and Response

The final analysis was conducted after 486 deaths (239 on erlotinib and gemcitabine and 247 on placebo and gemcitabine). Overall survival was significantly longer in the erlotinib and gemcitabine arm

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CSPC Exhibit 1100
Page 131 of 333

Table 1. Baseline Characteristics

Characteristic	Erlotinib and Gemcitabine (n = 285)		Placebo and Gemcitabine (n = 284)		Total (n = 569)	
	No.	%	No.	%	No.	%
Sex						
Female	149	52.3	122	43.0	271	47.6
Male	136	47.7	162	57.0	298	52.4
Age, years						
Median	63.7		64.0		63.9	
Range	37.9-84.4		36.1-92.4		36.1-92.4	
ECOG performance status						
0	85	29.8	85	29.9	170	29.9
1	146	50.9	147	51.8	292	51.3
2	54	18.9	52	18.3	106	18.6
Pain intensity (scale 0-100)*						
Median	21.3		23.4		22.2	
Range	0-100		0-100		0-100	
≤ 20	131	46.0	127	44.7	258	45.3
> 20	145	50.9	151	53.2	296	52.0
Extent of disease						
Locally advanced	67	23.5	71	25.0	138	24.3
Distant metastases	218	76.5	213	75.0	431	75.7
At least one target lesion	268	94.0	262	92.3	530	93.1
Prior therapy						
Radiotherapy†	22	7.7	25	8.8	47	8.3
Chemotherapy†	20	7.0	25	8.8	45	7.9
Prior surgical resection of primary tumor	19	6.7	29	10.2	48	8.4

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Pain intensity data were available for 554 patients (276 erlotinib and gemcitabine, 278 placebo and gemcitabine).
†Used as a radiosensitizer only.

with an estimated HR of 0.82 (95% CI, 0.69 to 0.99; $P = .038$; log-rank test stratified for performance status, extent of disease, and pain score at baseline; Fig 1A). Median survival times were 6.24 months versus 5.91 months for the erlotinib and gemcitabine versus placebo and gemcitabine groups with 1-year survival rates of 23% (95% CI, 18% to 28%) and 17% (95% CI, 12% to 21%), respectively ($P = .023$). A multivariate Cox regression analysis showed that erlotinib treatment (HR, 0.82; 95% CI, 0.69 to 0.99; $P = .04$) and female sex ($P = .03$) were significantly associated with longer overall survival. While there was an imbalance in male:female ratio between the arms, the treatment effect remains significant when adjusted for sex.

Results of subgroup analyses of survival by baseline stratification factors and other factors such as sex, race, pain intensity score, and age are displayed in Figure 2.

Progression-free survival was significantly longer in the erlotinib and gemcitabine arm than the placebo and gemcitabine arm with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; $P = .004$; log-rank test stratified for performance status, extent of disease, and pain score at baseline; median, 3.75 months *v* 3.55 months; Fig 1B).

Five hundred thirty patients had at least one measurable lesion and were assessable for response. The complete plus partial response rate was 8.6% with erlotinib and gemcitabine and 8.0% with placebo and gemcitabine, and the median duration of response was 163 days in both arms. The incidence of stable disease was 48.9% with erlotinib and gemcitabine and 41.2% with placebo and gemcitabine. The overall disease control rate (complete response plus partial response plus stable disease) was 57.5% on erlotinib and gemcitabine and 49.2% on placebo and gemcitabine ($P = .07$).

Toxicity and Dosage Modifications

Two hundred eighty-two patients on the erlotinib and gemcitabine arm and 280 on the placebo and gemcitabine arm received at least one dose of study medication and were available for assessment of toxicity. Adverse events are summarized in Table 2. Treatment was generally well-tolerated in both arms. Patients receiving erlotinib and gemcitabine experienced higher frequencies of rash, diarrhea, infection, and stomatitis, but these were generally grade 1 or 2. The incidence of other adverse events was similar in both arms.

There were six protocol-related deaths, all in the erlotinib and gemcitabine arm. Two were attributed to treatment complications (interstitial pneumonitis and sepsis) and four were attributed to a combination of cancer and protocol treatment complications (interstitial pneumonitis, sepsis, cerebrovascular accident, and neutropenic sepsis).

A total of eight patients had an interstitial lung disease (ILD)-like syndrome possibly related to therapy, seven receiving erlotinib and gemcitabine and one receiving placebo and gemcitabine.

Hematologic toxicity was balanced between the arms with grade 3/4 neutropenia and thrombocytopenia seen in 24% and 10% of erlotinib and gemcitabine and 27% and 11% of placebo and gemcitabine patients, respectively. Grade 3 or greater elevations of

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Page 132 of 333

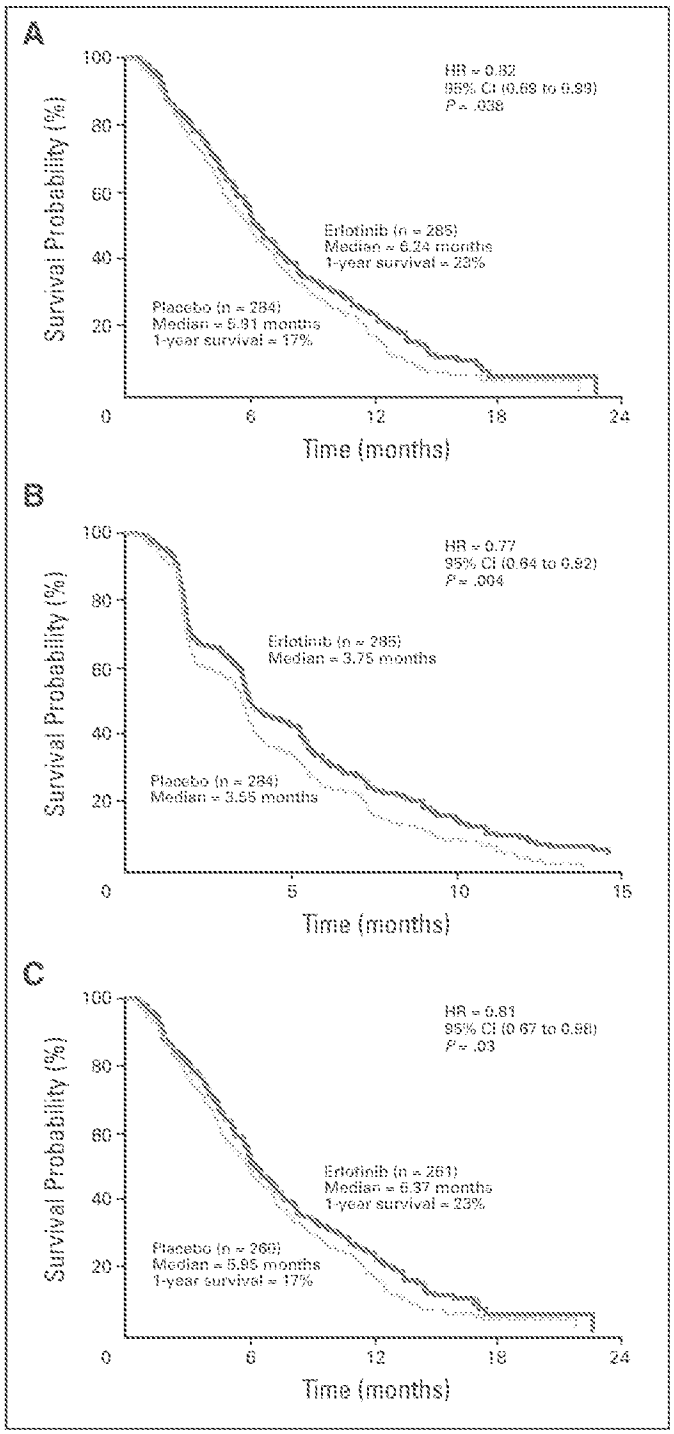


Fig 1. Kaplan-Meier curves for (A) overall survival; (B) progression-free survival; and (C) overall survival in the 100-mg cohort. HR, hazard ratio.

AST were seen in 11% and 8% of patients receiving erlotinib and placebo, respectively.

In total, 44 (16%) of 282 patients receiving erlotinib and gemcitabine and 13 (5%) of 280 receiving placebo and gemcitabine had at least one dose reduction of their oral agent. A higher incidence of patients had a dose reduction in the 150-mg/d cohort on the erlotinib and gemcitabine arm than on the placebo and gemcitabine arm (48% *v* 8%) compared with the 100-mg/d cohort (13% *v* 4%). The dose intensity of gemcitabine was similar in both arms.

Quality of Life

Quality of life analysis was conducted in 376 assessable patients. Questionnaire compliance was similar by treatment group and higher than 64% for each cycle before disease progression. There was no significant difference between the arms in global quality of life or in the individual domains with the exception of worse diarrhea change scores in the erlotinib plus gemcitabine arm ($P < .001$).

EGFR Analysis

Tumor samples for EGFR analysis were collected from 184 patients of whom 162 had sufficient tumor in the specimen to allow for immunohistochemical analysis. Eighty-six (53%) were classified as EGFR positive and 76 (47%) were EGFR negative. EGFR status was not associated with response or disease stability. In both groups, the HR favored the erlotinib and gemcitabine arm (EGFR positive, n = 86; HR, 0.80; 95% CI, 0.50 to 1.26; for EGFR negative, n = 76; HR, 0.83; 95% CI 0.51 to 1.34). The overall HR for erlotinib and gemcitabine patients in the 162 patients who had an EGFR analysis done was 0.82 (95% CI, 0.59 to 1.14) and for the 407 who had an unknown EGFR status it was 0.85 (95% CI, 0.69 to 1.05).

Skin Rash and Erlotinib

Of the 282 patients who received erlotinib, 79 had no rash, 102 had grade 1 rash, and 101 had a grade 2 or higher skin rash. Patients younger than 65 ($P = .01$) and those with a good performance status ($P = .03$) had a higher likelihood of developing rash. The presence of a rash was associated with a higher likelihood of achieving disease control ($P = .05$) after controlling other prognostic factors. Cox regression analysis showed that patients survived significantly longer after they developed skin rash ($P = .037$; HR, 0.74; 95% CI, 0.56 to 0.98). The median survival rates for patients with grade 0, 1, and 2+ rash were 5.3, 5.8, and 10.5 months, respectively; and the 1-year survival rates were 16%, 9%, and 43% ($P < .001$; Fig 3).

DISCUSSION

We found that overall survival in patients with advanced pancreatic cancer was significantly improved with erlotinib and gemcitabine compared with placebo plus gemcitabine; the HR of 0.82 represents a 18% reduction in the risk of death, or alternately, an overall 22% improvement in survival. HR is the most appropriate measure of overall and progression-free survival in rapidly progressive diseases such as pancreatic cancer because it encompasses the whole observation period and not just a single point estimate, such as the median. The improvement in median overall survival with erlotinib and gemcitabine is modest (6.24 *v* 5.91 months) while the 1-year survival rate with erlotinib and gemcitabine is 23% versus 17% with placebo and gemcitabine. The improvement in progression-free survival with a HR of 0.77 supports the beneficial effects of erlotinib. This benefit was achieved without a difference in response rate between the arms. The disease control rate, complete response, partial response, and stable disease combined, was significantly higher with erlotinib plus gemcitabine than placebo plus gemcitabine in the 100-mg cohort (59% *v* 49.4%; $P = .036$), but not in the overall study population (57.5% *v* 49.2%; $P = .058$).

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CSPC Exhibit 1100
Page 133 of 333

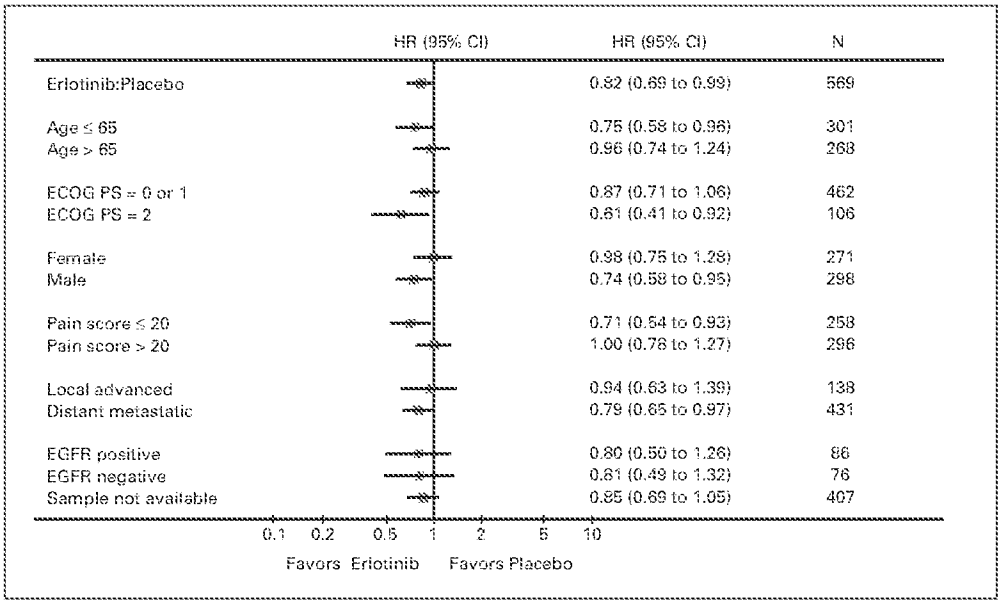


Fig 2. Hazard ratio of survival by pretreatment characteristics. HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

Most adverse events associated with erlotinib plus gemcitabine treatment in this study were mild-to-moderate, and consistent with previous experience with both agents.[2,22,23] Rash was more frequent with erlotinib plus gemcitabine than placebo plus gemcitabine and we did observe an association between rash and a better outcome that has also been seen in other studies of EGFR inhibitors.[24-26] This is not explained by patients who stay on treatment longer being at greater risk for rash; analysis was adjusted for this potential bias and the rash related to EGFR tyrosine kinase inhibitors tends to occur early. Potential reasons for this observation could include variability in drug absorption or metabolism; the ability to generate a rash predicting for a more immunocompetent individual; or a pharmacogenetic basis that is seen in both germline and tumor cells. There were more deaths and ILD-like syndromes seen in the gemcitabine plus erlotinib arm. Gemcitabine and EGFR tyrosine kinase inhibitors are both known to cause an ILD-like syndrome in approximately 0.5% to 1.0% of patients, and there is the possibility that there could be a more than additive effect when these agents are combined.[27] The incidence seen is this study (2.4%) is higher than in other trials where gemcitabine and erlotinib have been combined. The incidence of ILD in the Tarceva Lung Cancer Evaluation (TALENT) trial which compared gemcitabine and

Table 2. Adverse Events and Dosage Modifications

Variable	%			
	Erlotinib and Gemcitabine (n = 282)		Placebo and Gemcitabine (n = 280)	
	All	Grade 3/4	All	Grade 3/4
Any toxicity				
All patients	100	62	98	57
100 mg/d erlotinib and placebo	100	61		
150 mg/d erlotinib and placebo	100	78		
Specific toxicity				
Diarrhea	56	6	41	2
Fatigue	89	15	86	15
ILD-like syndrome*	2.1		0.4	
Infection (any)	43	17	34	16
Rash	72	6	29	1
Stomatitis	23	< 1	14	0
Dose reduction				
Erlotinib and placebo (n = 562)		16		5
100 mg (n = 515)		13		6
150 mg (n = 47)		45		4
Treatment discontinuation				
Progressive disease		47		58
Symptomatic progression		15		14
Toxicity		10		6
Death		9		8
Intercurrent illness		4		4
Refused treatment		8		6
Other		2		3
Still on therapy		4		1

Abbreviation: ILD, interstitial lung disease.
*Pneumonitis, pulmonary infiltrate.

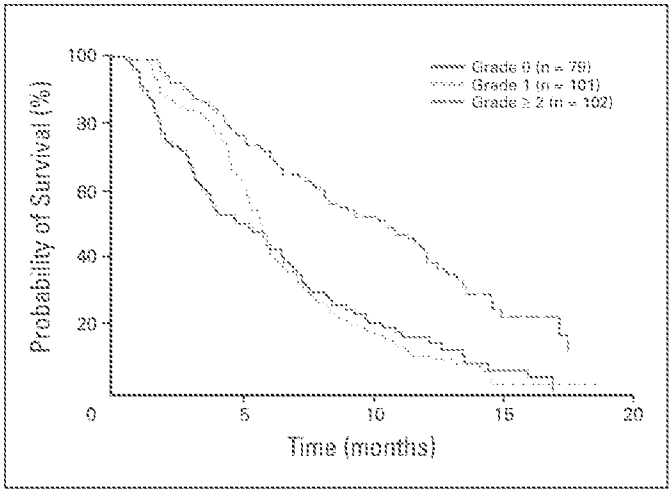


Fig 3. Overall survival by grade of rash in erlotinib-treated patients.

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CSPC Exhibit 1100
Page 134 of 333

cisplatin with or without erlotinib in 1,059 patients with advanced lung cancer was less than 1% and no difference was seen between the treatment arms.[28]

There is interest in the use of EGFR status of tumors as a predictive factor. In this study using an immunohistochemical analysis on a subset of patients, an obvious impact of EGFR expression on outcome was not seen. The overall rate of EGFR expression observed was 57%, which is lower than has been reported in previous studies.[29,30] More recent analyses in lung cancer have suggested that the presence of EGFR mutations or EGFR amplification measured by fluorescence in situ hybridization may be more useful.[31,32] However, studies of more than 200 pancreatic tumors did not identify any EGFR mutations. These analyses are also more complex in a combination study where the outcome will be a function of both the chemotherapy and EGFR inhibitor.

The dose of erlotinib as a single agent and in combination studies in non–small-cell lung cancer is 150 mg per day. In this study, we found the dose of 100 mg to be well-tolerated and efficacious in combination with gemcitabine (Fig 1C). There were 23 patients treated at a starting dose of 150 mg of erlotinib of whom 11 required protocol-prescribed dose reductions for toxicity, suggesting that this may be too high a starting dose. The pharmacokinetics of erlotinib has shown significant variability in previous studies with clearance rates and area under the curve varying up to seven-fold.[33,34] It is possible that escalation of the dose of erlotinib beyond 100 mg in patients not experiencing toxicity may be useful.

The failure of combination chemotherapy to improve outcomes in pancreatic cancer means we need to look at alternate systemic approaches to this disease. Combinations of gemcitabine with the anti-EGFR monoclonal antibody, cetuximab, and with the anti- vascular endothelial growth factor antibody, bevacizumab, do show promise in phase II studies.[29,35] Both approaches are currently in phase III testing versus single-agent gemcitabine in the North American cooperative groups. The recent announcement that the gemcitabine plus bevacizumab trial did not meet its primary end point of improved survival is a reminder of the difficulties of improving outcomes in pancreatic cancer. Other phase II studies are exploring other targeted agents in combination with gemcitabine, or multiple targeted agents in combination with chemotherapy. The recent demonstration of benefit from chemotherapy in the adjuvant setting suggests that studies of erlotinib after surgery for localized disease may also be warranted.[36,37]

This trial provides proof of principle of targeting HER1/EGFR in pancreatic cancer and shows erlotinib can improve survival when used concurrently with chemotherapy; it also offers a basis for further investigation of targeted agents in this setting. NCIC CTG PA.3 is the first evidence of a survival benefit with an EGFR tyrosine kinase inhibitor in combination with chemotherapy in any form of cancer. It is also the first phase III trial to demonstrate a significant improvement in survival beyond that seen with gemcitabine alone in pancreatic cancer and is a new treatment option for these patients.

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.

Employment: Gary Clark, OSI Pharmaceuticals; Mieke Ptasynski, OSI Pharmaceuticals **Leadership:** N/A **Consultant:** Malcolm J. Moore, OSI Pharmaceuticals; Joel R. Hecht, OSI Pharmaceuticals; Heather J. Au, OSI Pharmaceuticals **Stock:** N/A **Honoraria:** Malcolm J. Moore, OSI Pharmaceuticals; Joel R. Hecht, OSI Pharmaceuticals; Heather J. Au, OSI Pharmaceuticals; Robert A. Wolff, OSI Pharmaceuticals **Research Funds:** N/A **Testimony:** Malcolm J. Moore, OSI Pharmaceuticals; Joel R. Hecht, OSI Pharmaceuticals; Wendy Paruleker, OSI Pharmaceuticals **Other:** N/A

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Page 135 of 333

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Acknowledgment

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

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CSPC Exhibit 1100
Page 136 of 333

PCN302: Comparing service utilization and costs for Medicare FFS patients with metastatic pancreatic cancer by chemotherapy regimen and line of therapy

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OBJECTIVE

- To analyze treatment patterns, costs and survival rates for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer (m-PANC) by:
  - Line of therapy (LOT), and
  - Chemotherapy regimen

DATA SOURSES

100% Medicare Limited Data Set (LDS) Claims Files

- Contain Medicare-paid fee-for-service Part A and B claims for all beneficiaries in the U.S. for all services except professional and DME claims
- 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

Oncology Care Model (OCM) documentation: Initiating cancer therapies and codes, Performance and Baseline period lists

- Used as comprehensive lists of all chemotherapies to identify beneficiaries in the “Other Therapy” group

METHODS

- First LOT is defined as the first episode of an eligible therapy given after or in the 14 days preceding the beneficiary’s index date
- LOTs include other eligible drugs given within 28 days of the beginning of an episode for eligible therapy, and the “regimen” is the combination of eligible therapies given during that LOT
- End of the most recent LOT is 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)

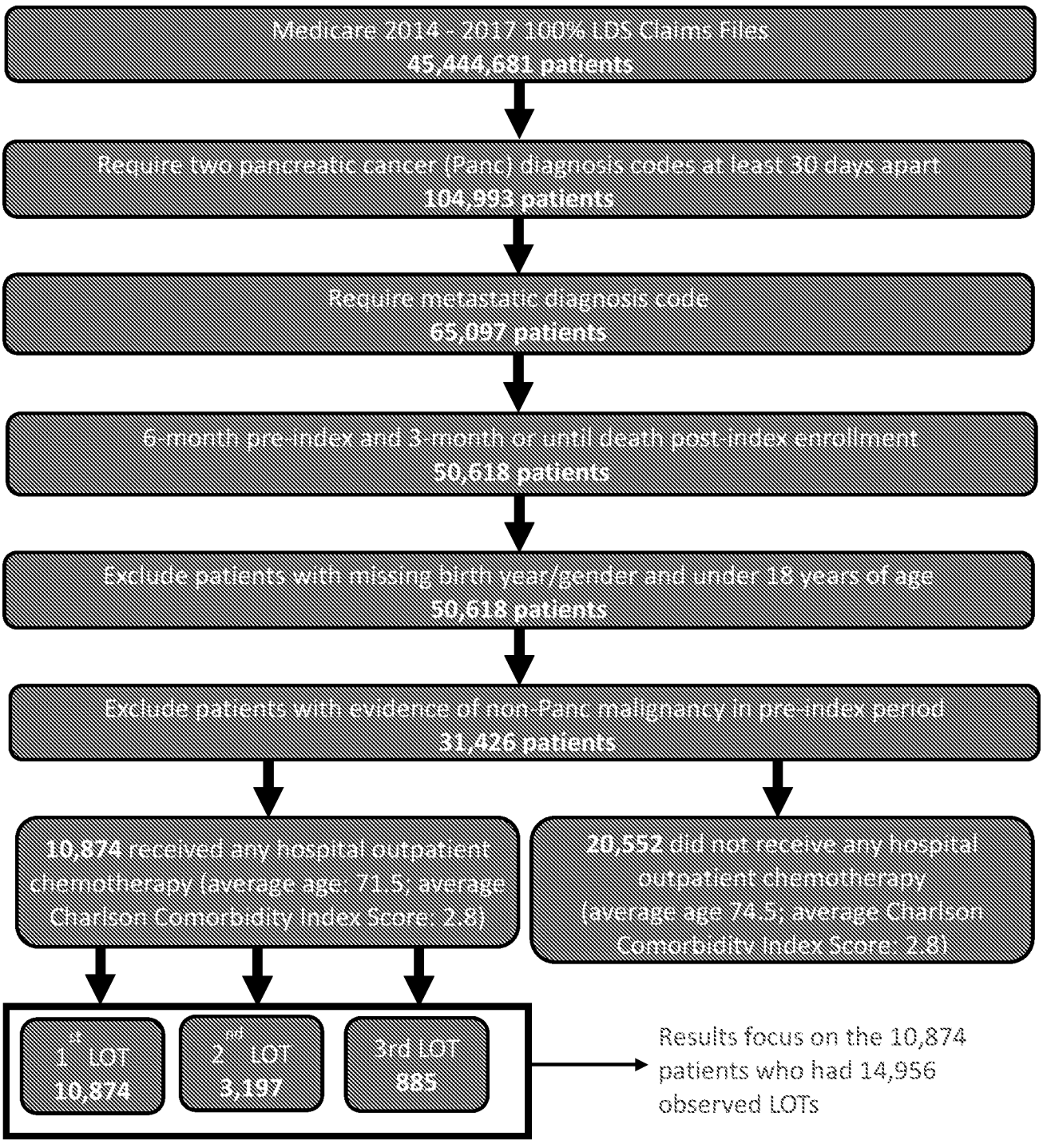
  - The date of death, if applicable
- Other LOT end dates are defined as the day before the start date of the next LOT (which begins when a beneficiary switches regiments
- If a beneficiary does not receive or stops receiving hospital outpatient chemotherapy, then we follow the beneficiary for 90 days (or until death) from the index date (for beneficiaries not receiving any chemotherapy) or the end of the previous LOT (for beneficiaries stopping chemotherapy)
- We identified 31,426 target patients with m-PANC and 14,956 LOTs **(Figure 1)**.

CSPC Exhibit 1100
Page 137 of 333

RESULTS

- Across LOTs, common regimens included gemcitabine/nab-paclitaxel (38% of patients), gemcitabine monotherapy (21%), FOLFIRINOX (11%), FOLFOX (6%), and liposomal irinotecan (3%) (Figure 2).
- Average LOT cost varied by regimen from under $15,000 to more than $30,000 (Figure 3).
- The 90-day survival rate decreased from 79% in 1L to 73% in 3L (Figure 4).
- Average LOT duration decreased from 150 days in 1L to 108 days in 3L (Figure 5).

Figure 1. Patient identification cascade chart



Figures 2-5 show common regimens, costs by regimen, LOT 90-day survival rate, and LOT duration

Figure 2. Common regimens across all LOTs

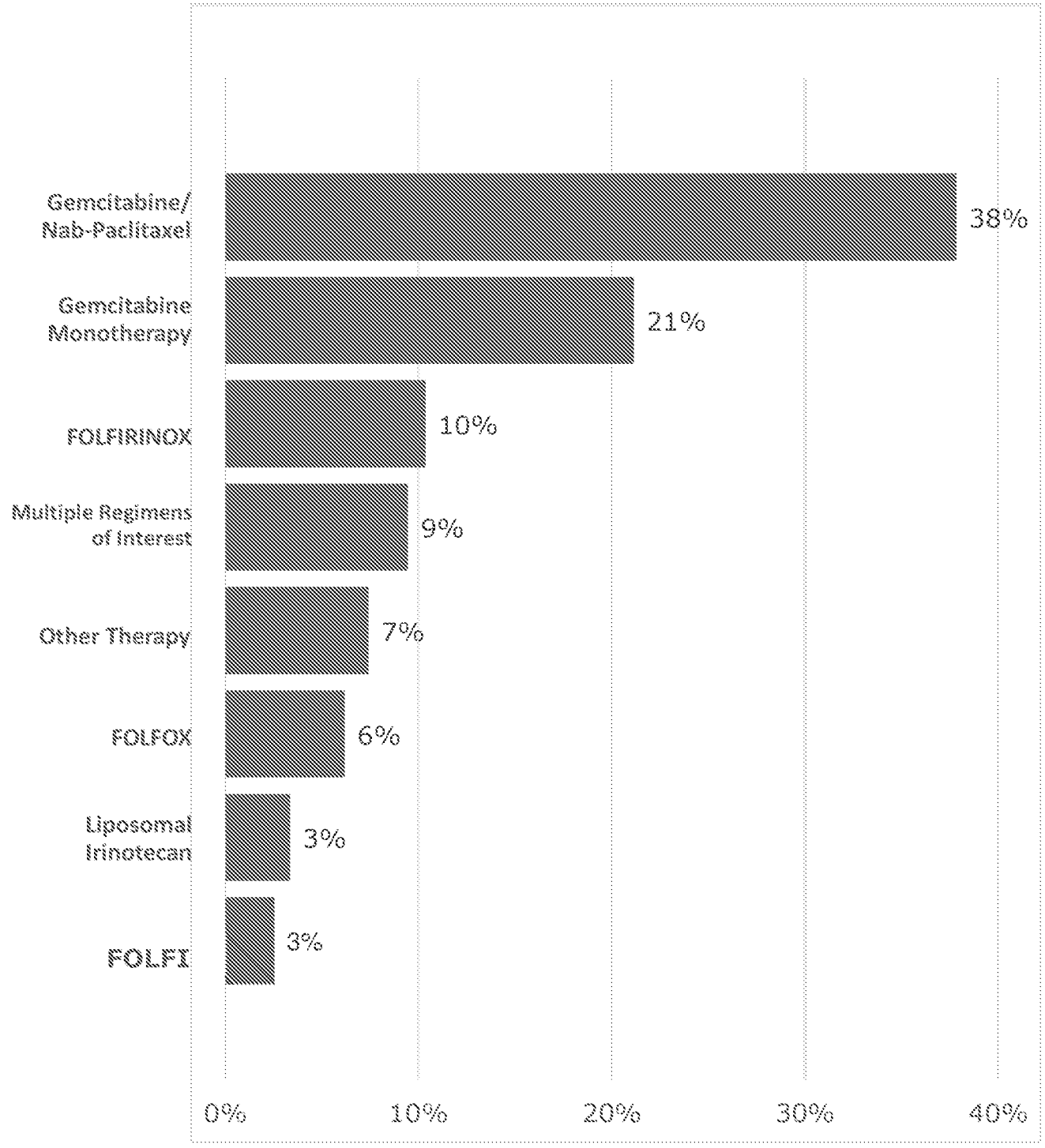


Figure 3. Average LOT cost by regimen

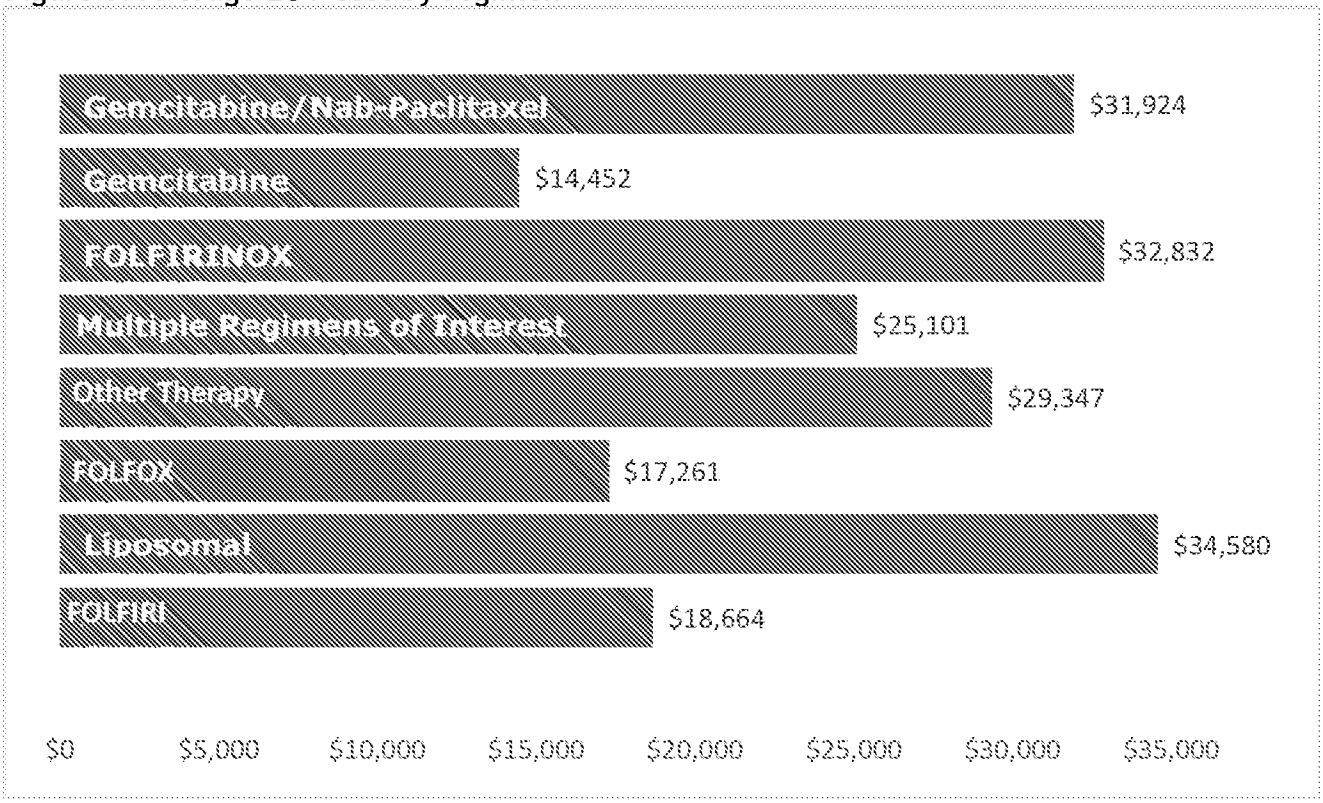


Figure 4. 90-day survival rate by LOT

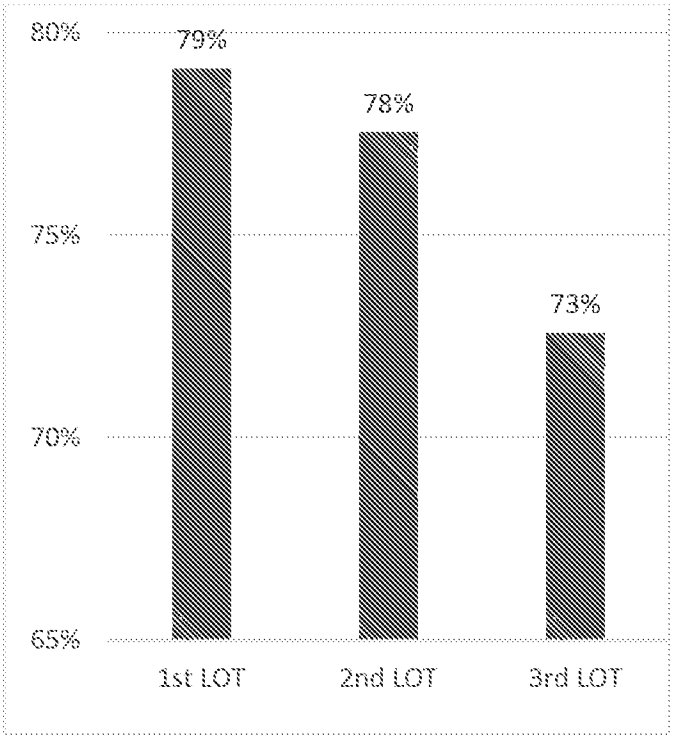
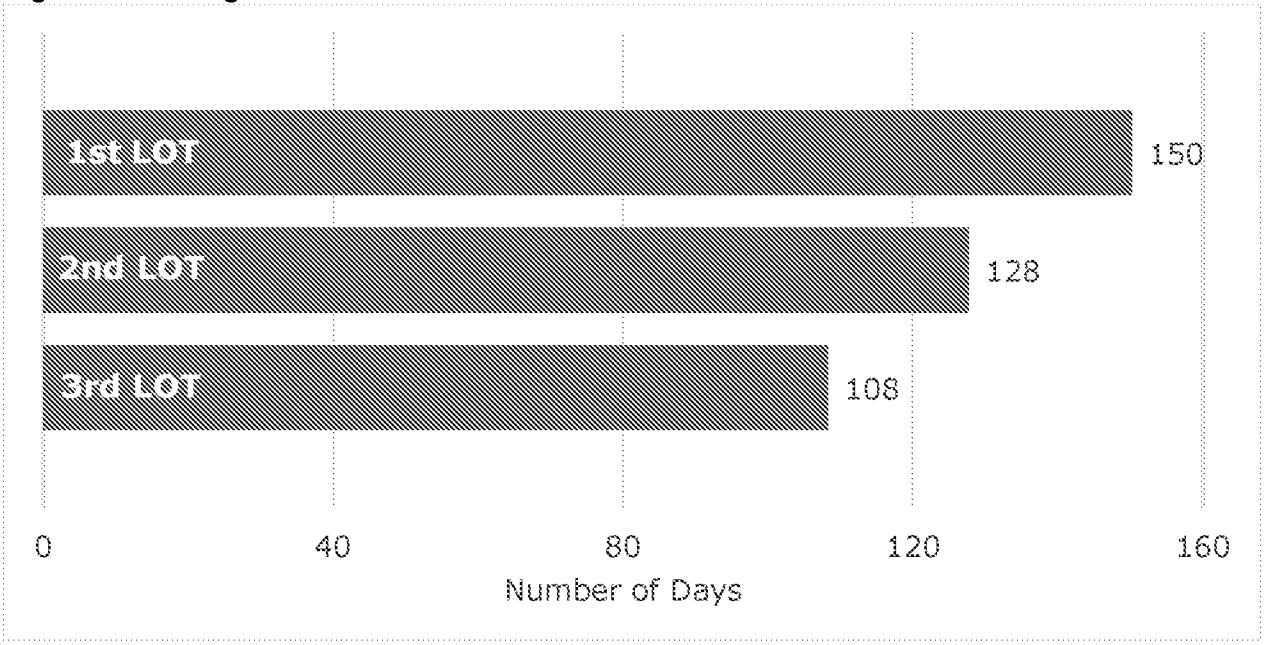


Figure 5. Average LOT duration



LIMITATIONS

- Certain Part B (Professional and DME) and all Part D chemotherapy services are not captured because the 100% Medicare LDS claims files do not include these data. This data limitation likely causes our analysis to understate the portion of m-Panc patients receiving chemotherapy.
- The data analyzed covers the Medicare FFS population from 2014 - 2017. Analysis of different populations or time periods will yield different results.

CONCLUSIONS

- 35% of the Medicare FFS m-PANC patients identified received chemotherapy in the hospital outpatient setting, of which the majority received gemcitabine-based therapy.
- Average LOT costs varied substantially by regimen.
- Therapy duration and 90-day survival rate decreased by LOT.

Acknowledgements

The authors thank Umang Gupta and Shachi Mistry at Milliman, Inc. for research assistance.

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Presented at ISPOR 2019 | New Orleans, LA | May 2019
This study was sponsored by Ipsen

PCN302: Comparing service utilization and costs for Medicare FFS patients with metastatic pancreatic cancer by chemotherapy regimen and line of therapy

Muldoon LD[1], Hirsch J[1], Dieguez G[1], Valderrama A[1], Cockrum P[1]

OBJECTIVE

- To analyze treatment patterns, costs and survival rates for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer (m-PANC) by:
  - Line of therapy (LOT), and
  - Chemotherapy regimen

DATA SOURCES

100% Medicare Limited Data Set (LDS) Claims Files

- Contain Medicare paid fee-for-service Part A and B claims for all beneficiaries in the U.S. for all services except professional and DME claims
- 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

Oncology Care Model (OCM) documentation: Defining cancer therapies and codes; Performance and Baseline period lists

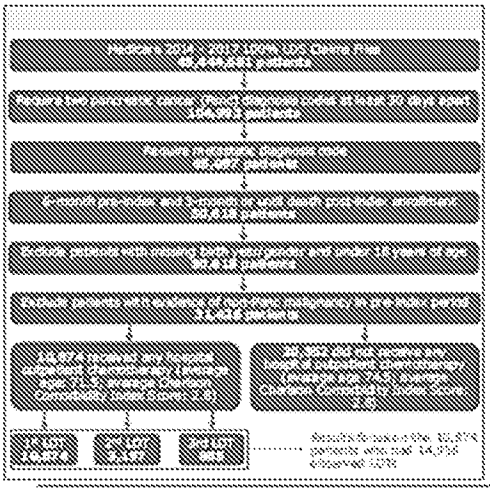
- Used as comprehensive lists of all chemotherapies to identify beneficiaries in the "Other Therapy" group

METHODS

- First LOT is defined as the first episode of an eligible therapy given after or in the 14 days preceding the beneficiary's index date
- LOTs include other eligible drugs given within 28 days of the beginning of an episode for eligible therapy, and the "regimen" is the combination of eligible therapies given during that LOT
- End of the most recent LOT is 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)
- If a beneficiary does not receive or stops receiving hospital outpatient chemotherapy, then we follow the beneficiary for 90 days (or until death) from the index date (for beneficiaries not receiving any chemotherapy) or the end of the previous LOT (for beneficiaries receiving chemotherapy)
- We identified 21,405 Target patients with m-PANC and 14,936 LDS (Figure 1)

RESULTS

- Across LOTs, common regimens included gemcitabine/nab-paclitaxel (39% of patients), gemcitabine monotherapy (21%), FOLFIRINOX (11%), FOLFOX (7%), and liposomal irinotecan (3%) (Figure 2).
- Average LOT cost varied by regimen from under $15,000 to more than $30,000 (Figure 3).
- The 90-day survival rate increased from 79% in 1L to 93% in 3L (Figure 4).
- Average LOT duration decreased from 150 days in 1L to 108 days in 3L (Figure 5).



Figures 2-5 show common regimens, costs by regimen, LOT 90-day survival rate, and LOT duration

Figure 2. Common regimens across all LOTs

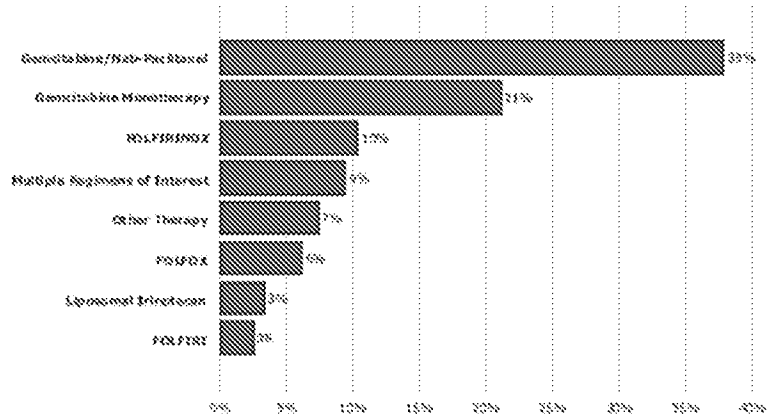


Figure 3. Average LOT cost by regimen

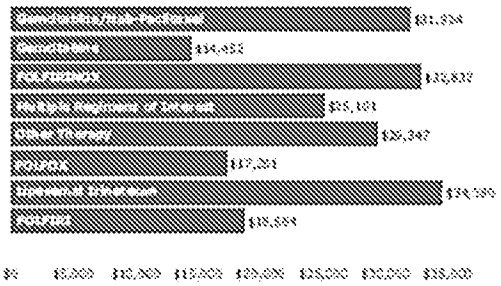


Figure 4. 90-day survival rate by LOT

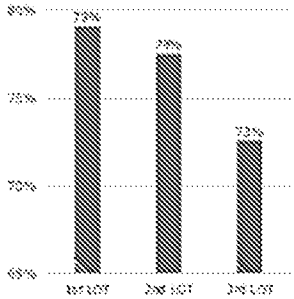
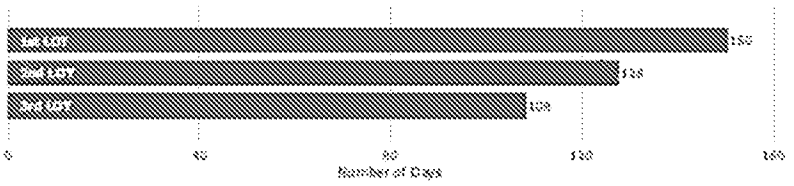


Figure 5. Average LOT duration



LIMITATIONS

- Claims Part B (Professional and DME) and all Part D pharmacy services are not captured because the 100% Medicare LDS claims files do not include these data. This data limitation may cause our analysis to underestimate the portion of the beneficiaries receiving chemotherapy.
- The data analyzed covers the Medicare FFS population from 2014 - 2017. Analysis of different populations or time periods will yield different results.

CONCLUSIONS

- 35% of the Medicare FFS m-PANC patients identified received chemotherapy in the hospital outpatient setting, of which the majority received gemcitabine-based therapy.
- Average LOT costs varied substantially by regimen.
- Time on duration and 90-day survival rate decreased by LOT.

Acknowledgements

The authors thank Wendy Fujita and Joseph Kelly at Milliman, Inc. for research assistance.

Presented at ISPOR 2018 | New Orleans, LA | May 2018

This study was sponsored by Ipsen

Article Tools

HEALTH SERVICES RESEARCH, CLINICAL INFORMATICS, AND QUALITY OF CARE

Treatment patterns, survival rate, and Parts A and B costs by line of therapy for FDA-approved/NCCN Category 1 treatments for patients with metastatic pancreatic cancer.

Check for updates

L. Daniel Muldoon, Jared Hirsch, Gabriela Dieguez, Paul Cockrum

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Milliman, Inc., New York, NY; Ipsen Inc, Ft Worth, TX

Abstract Disclosures

Abstract

e18357

Background: There is currently limited real-world evidence regarding metastatic pancreatic cancer (m-PANC) FDA-approved/NCCN Category 1 treatment patterns, resource utilization, and survival rate. We analyzed these outcomes 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 paid FFS claims, except professional services, for 45 million Medicare FFS beneficiaries. We studied mean costs and survival rate by regimen and LOT. Patients in our study had 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. We defined index date as the earliest metastasis diagnosis date. We excluded patients with pre-index non-PANC malignancies and those without six months pre-index and three months (or until death, if earlier) post-index Medicare FFS enrollment. LOTs were assigned based on therapies used. LOTs ended the day before a new chemotherapy began, 28 days after the last chemotherapy (if no new chemotherapy), or upon death. **Results:** Gemcitabine monotherapy, gemcitabine/nab-paclitaxel, and FOLFIRINOX were most commonly used as first line (1L) therapy (91%, 80%, and 80%, respectively). Mean total Parts A and B (excluding professional) cost for 1L gemcitabine monotherapy was lower than gemcitabine/nab-paclitaxel or FOLFIRINOX ($14,601, $32,447, and $33,628, respectively), but FOLFIRINOX had a higher 90-day survival rate (86%) than gemcitabine-based regimens (76-79%). Liposomal irinotecan was most commonly used in

second and third lines (2L, 3L) (54% and 28%, respectively); 97% of these patients previously received gemcitabine, consistent with approved labeling. Despite disease progression, 2L and 3L liposomal irinotecan had similar costs ($36,350 and $35,010, respectively) to 1L gemcitabine/nab-paclitaxel and FOLFIRINOX. As expected, 2L and 3L liposomal irinotecan 90-day survival rates were lower (68% and 73%, respectively). **Conclusions:**Mean total Parts A and B (excluding professional) costs for common 1L-3L regimens varied from less than $15,000 to greater than $30,000. 90-day survival rates for common regimens varied between 1L (86%) to 3L (68%).

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interpretation are the most detailed, and include examples to facilitate application. **Conclusions:** The guidelines provide detailed recommendations for use of the IL, from the early stage of item selection to the analysis and reporting of results, thereby responding directly to the needs of commercial and academic users while promoting scientific rigor.

Cancer – Real World Data & Information Systems

PCN298
AUTOMATED CLINICAL DATA PREPROCESSING ACCELERATES ELECTRONIC CASE REPORT FORM COMPLETION

Labrador M,[1] Seshatri A,[1] Garofalo D,[1] Webster J,[1] Gopalkrishna M,[2] Guffar S,[2] Singaraju M,[2] Pai N,[1] Gross H,[1] Singleton N,[1] Malik A,[1] Scott J,[1] Gierman H[1]
[1]*Integra Connect, LLC, West Palm Beach, FL, USA,* [2]*Omega Healthcare Management Services Pvt Ltd., Bengaluru, India*

Objectives: Real-World Evidence (RWE) data is increasingly used to evaluate clinical outcomes. Incomplete documentation is a primary reason why manual abstraction, while time-consuming, is necessary. For this study, we created an electronic Case Report Form (eCRF) that automatically extracts known data elements from Electronic Medical Record, Practice Management and other systems, to prepopulate the eCRF software and reduce chart abstraction time. ***Methods:*** We created a Real-Time Data Preprocessing (RTDP) eCRF portal using MS PowerApps hosted in a secure and HIPAA audited Azure environment with 2-factor authentication, which prepopulated the software with data from Integra Connects' Data Transformation and Exchange (DTX) Database. 1,200 cancer patient records were abstracted by a team of trained abstractors who collected tumor stage, date of diagnosis, response and genetic testing status, including mutations. 22 patient records were randomly assigned for a second abstraction by different team members using a standard eCRF form without RTDP and blank values. We electronically measured time spent (in seconds) on each patient's chart and compared the results of both methods using a Wilcoxon Rank Sum test. ***Results:*** Median abstraction time per patient record was reduced from 35 minutes to 16 minutes by implementing the RTDP-eCRF process ($P = 8.4\text{-}e05$). In the manual eCRF, 858 fields were filled out manually across the 22 patients, of which 60% were prepopulated by the RDTP-eCRF. 8 fields (1%) had manual entry errors, which were all prevented in the RTDP-eCRF. Since then, we have implemented our RDTP-eCRF software across 8 projects in Lung Cancer, Ovarian Cancer, Prostate Cancer, Leukemia, Multiple Myeloma, Beta-thalassemia, lymphoma, and Myelodysplastic syndrome, abstracting over 7,000 patients ***Conclusions:*** Using our RDTP-eCRF software reduced abstraction time by 54% and prevented manual entry errors.

PCN299
COST TREND ANALYSIS OF BREAST CANCER DRUGS IN LEBANON USING A PRIVATE PAYER DATA SET

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Objectives: Lebanon has the sixth highest rate of breast cancer globally. Cancer cost analyses are increasingly based on insurance claims. The aim of the study was to identify the breast cancer drugs incurring the highest cost in Lebanon and track the changes in their market share. ***Methods:*** The analysis was based on a dataset from GlobeMed gathered retrospectively over a 4-year period (2015- mid 2018). Annual drug specific costs and usages as well as overall costs and usages were calculated for 462 patients. There were 112 inpatient and outpatient breast cancer drugs in the studied dataset ranked according to their marketed annual costs. ***Results:*** Total breast cancer drug costs were $1,467,300, $1,639,511, $1,776,859 and $823,392 for the years 2015, 2016, 2017, 2018 respectively. The top 5 highest incurring cost drugs varied across the studied period and constituted 80%, 83%, 82%, 78% of total drugs costs (value share) for years 2015, 2016, 2017, 2018 respectively. They also represented 26%, 26%, 23%, 19% of total drug uses (volume share) for the same years. Trastuzumab was found to be the most expensive drug each year across the study period. This result matches the findings of the Lebanese Ministry of Public Health. Trastuzumab volume share ranged from 12% in 2015 with 38 drug uses to 8% in 2018 with 26 drug uses. Ado-trastuzumab emtansine, Pertuzumab, and Palbociclib which are newly approved immunotherapy drugs were listed among the 5 highest incurring cost drugs in 2015, 2016, 2017 respectively. The percentage use of these drugs is slightly increasing, for example Ado-trastuzumab emtansine use grew from 1% in 2015 to 3% in 2018. ***Conclusions:*** This study confirms that new immunotherapy drugs introduced in 2015 constitute the majority of the top 5 highest incurring cost drugs. Additionally, the market share of these new drugs is progressively increasing.

PCN300
EVALUATION OF OVERALL SURVIVAL ASSOCIATED WITH CHANGE IN DOSING OF BORTEZOMIB, MELPHALAN, AND PREDNISONE REGIMEN IN TRANSPLANT INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: A REAL-WORLD STUDY

Mehra M,[1] Potluri R,[2] Lam A,[1] Slavcev M[1]
[1]*Janssen, Raritan, NJ, USA,* [2]*SmartAnalyst Inc , New York, NY, USA*

Objectives: Combination of bortezomib, melphalan, and prednisone (VMP) is a standard of care for patients with newly diagnosed multiple myeloma, ineligible for stem-cell transplantation (NDMM-TI). While various bortezomib doses have been studied in clinical trials involving VMP, assessment in the real-world (RW) population remains unexplored. Our study aims to evaluate association between change in VMP dosing and overall survival (OS) in NDMM-TI patients identified in RW data sources. ***Methods:*** NDMM-TI patients were identified from SEER-Medicare (January 2007 – December 2014), OPTUM™ Commercial Claims (January 2000 – March 2017), and OPTUM™ Integrated (January 2007 – March 2016) databases, and were included in the analysis cohort if they had 1) an MM index diagnosis on or after 1 January 2007, 2) medical + prescription coverage at diagnosis, 3) a 1-year look-back period, 4) no prior primary cancers, 5) received ≥1 line-of-treatment and 6) no evidence of stem cell transplantation. VMP exposed patients were categorized into recipients of (i) VISTA dose, if bortezomib was administered twice weekly for ≥2 cycles, and (ii) less intensive modified dose, if bortezomib was administered twice weekly in cycle 1 only, or, once weekly in all cycles. Baseline patient characteristics, comorbidities and OS were compared between the VISTA and modified cohorts. ***Results:*** A total of 7,724 NDMM-TI patients were evaluated. About 1% (N=79) of this cohort received VMP as first line therapy. A majority of the patients received modified dose (78.5%) compared to VISTA dose (21.5%). The modified cohort was significantly younger than the VISTA cohort (mean age 72.3 vs. 76.2 years; $P=0.0308$). Comorbidity burden was statistically similar in both cohorts. Comparison of modified vs. VISTA cohorts showed similar OS when adjusted for age, renal impairment and CCI-Score (adjusted-HR=1.074 (0.455 - 2.531)). ***Conclusions:*** Reduced dosing of bortezomib did not change OS among NDMM-TI patients treated with VMP.

PCN301
DEVELOPMENT OF PLAYBOOK FOR CHART REVIEW IN REAL WORLD DATA

Robert NJ,[1] Espirito J,[1] Haydon W,[2] Jenson K,[1] Montelonge N,[1] Spark S[1]
[1]*McKesson Specialty Health, The Woodlands, TX, USA,* [2]*McKesson Specialty Health, Spring, TX, USA*

Objectives: Electronic health records are a common source of real world data. The objective of creating a playbook was to facilitate chart abstraction in a complex medical field and to harmonize abstracted terms by developing a standard source as a reference across multiple retrospective chart review studies in oncology. ***Methods:*** Key terms with variability or challenges in interpretation during studies, such as date of metastatic disease, line of therapy and treatment end dates for example, were identified during planning sessions. Weekly meetings were established to discuss terms and create rules for data abstraction. Team members who participated came from multi-disciplinary backgrounds, e.g. pharmacy, nursing, physician, computer technologist. Educational slides with definitions and examples were created. Chart reviewers were instructed to utilize educational slides as a reference across all studies. We then measured the application of these rules. ***Results:*** Several terms have been standardized. We evaluated 18 studies that applied playbook rules, which included approximately 4000 charts. Quality control was performed on approximately 20% of the charts. We assessed quality metrics on three select variables. The average accuracy rate for these variables ranged from 78 to 91 percent. The line of therapy averaged 91%, date of metastasis averaged 78%, and response assessments averaged 86 percent. ***Conclusions:*** In real world data, variability exists in clinical terms. The playbook has been a tool to improve quality control in chart review. Medical histories are also presented in different linguistic terms. These challenges reinforce the need to have established playbook rules. The playbook is dynamic and will continue to evolve as additional areas benefitting from standardization are identified. Overall, quality is good and there remains opportunity for improvement in education and operational definitions.

PCN302
COMPARING SERVICE UTILIZATION AND COSTS FOR MEDICARE FFS PATIENTS WITH METASTATIC PANCREATIC CANCER BY CHEMOTHERAPY REGIMEN AND LINE OF THERAPY

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[1]*Milliman, Inc, New York, NY, USA,* [2]*Formerly of Ipsen Biopharmaceuticals Inc, Cambridge, MA, USA,* [3]*Ipsen Biopharmaceuticals Inc., Cambridge, MA, USA*

Objectives: To analyze treatment patterns, costs, and survival rate for patients with metastatic pancreatic cancer (m-PANC) by 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 paid fee-for-service (FFS) claims, except professional services, for 45 million Medicare FFS beneficiaries. We studied treatment patterns, costs, and survival rate by LOT. Patients in our study had 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. We defined index date as the earliest metastasis diagnosis date. We excluded patients with pre-index non-PANC malignancies and those without six months pre-index and three months post-index (or until death) Medicare FFS enrollment. LOTs were assigned based on therapies

used. LOTs ended the day before a new chemotherapy began, 28 days after the last chemotherapy (if no new chemotherapy), or upon death. **Results:** We identified 31,426 m-PANC patients (average age at index: 73.5 years; average Charlson comorbidity index score: 2.8); 10,874 patients (35%) received first line (1L) chemotherapy, 3,197 (10%) received a second line (2L), and 885 (3%) received a third line (3L). Across LOTs, common regimens included gemcitabine/nab-paclitaxel (38% of patients), gemcitabine monotherapy (21%), FOLFIRINOX (11%), FOLFOX (6%), and liposomal irinotecan (3%). Average LOT duration decreased from 150 days in 1L to 108 days in 3L. Average LOT cost varied by regimen from under $15,000 to more than $30,000. The 90-day survival rate decreased from 79% in 1L to 73% in 3L. **Conclusions:** 35% of Medicare FFS m-PANC patients received chemotherapy, of which the majority received gemcitabine-based therapy. Average LOT costs varied by regimen. LOT duration and 90-day survival rate decreased by LOT.

PCN303
COMPARATIVE ANALYSIS OF PROFILES OF 65+ YEAR OLD STAGE IV PROSTATE CANCER PATIENTS BY TIME FROM DIAGNOSIS TO FIRST TREATMENT IN THE UNITED STATES

Spindel J, DaSilva C, Moseley A
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Objectives: This research compares profiles of 65+ year old men diagnosed with Stage IV prostate cancer, segmented by time from diagnosis to treatment. **Methods:** Data from real-world patient record database (Global Oncology Monitor©), from 10/2017 to 9/2018 on eligible patients in the US (n=1,328) was included. Physicians randomly selected patients diagnosed with metastatic disease currently on an anti-cancer regimen and extracted data on demographics, disease and treatment patterns. Patients were segmented based on time from diagnosis to first treatment: immediate treatment (≤ 1 month from diagnosis), n=325 and delayed treatment (> 3 months from diagnosis), n=523. Comparisons were made using inferential statistics. **Results:** Immediately treated patients were younger than delayed treatment patients with a mean age of 75.7 (vs 77.0; $p<0.05$). These patients were more likely to have an ECOG performance score of 0-1 (83% vs 76%; $p<0.05$), a low-risk Gleason assessment score (11% vs 4%; $p<0.01$) and less likely to suffer from ≥ 2 comorbidities (49% vs 60%; $p<0.01$). While in better overall health, immediately treated patients were more likely to present ≥ 2 sites of metastases (23% vs 16%; $p<0.05$), particularly bone metastases (91% vs 83%, $p<0.01$). In the 1st line, they were more likely treated with combination therapy (52% vs 25%; $p<0.01$) in university/teaching hospitals (19% vs 10%; $p<0.01$) and with greater patient involvement in the treatment decision ($p<0.05$). Physician reason for selecting initial treatment was based more on new clinical data (18% vs 5%; $p<0.01$) and reported a higher level of satisfaction. **Conclusions:** Immediately treated patients were younger, in better overall health, and treated in a university/teaching hospital. Compared to delayed treatment patients, their disease has metastasized more and they are more likely to be on a combination therapy in which they had greater involvement in the treatment decision and a higher physician satisfaction with the current regimen.

PCN304
CARDIAC MONITORING AMONG CHEMOTHERAPY,TARGETED THERAPY AND RADIATION THERAPY TREATED BREAST CANCER PATIENTS

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Objectives: ASCO advisory group recommends cardiac monitoring before initiation of cancer therapy and during therapy. This study examined the rates of cardiac monitoring among newly diagnosed breast cancer patients. **Methods:** Retrospective cohort study was conducted using nationally representative administrative claims data (2007 – 2014). Female breast cancer patients older than 18 years of age with at least 4 months of continuous enrollment before therapy initiation and 12 months after were included. Patients treated with anthracyclines, taxanes, trastuzumab or radiation therapy were identified. Cardiac monitoring procedures including echocardiogram, multiple gates acquisition scan (MUGA) and cardiac magnetic resonance were determined within 4 months before ("baseline monitoring") and within 12 months after initiation of cancer treatment ("followup monitoring"). Bi-variate descriptive statistics were used to compare demographic characteristics between patients who received baseline monitoring to those who did not and one-year follow up monitoring to those who did not receive. t-test for continuous variable and chi-square for categorical variables were used. All statistical analysis was conducted in SAS version 9.4, Cary N.C. **Results:** Final data set included 6130 patients, 15.7% of whom received baseline cardiac monitoring and 13.2% received followup cardiac monitoring within one year of initiating cancer treatment therapy. 391 patients (6.3%) received cardiac monitoring at both time points. Patients who received baseline cardiac monitoring were younger (mean: 55 vs. 56, $p=0.04$) as compared to patients who did not receive baseline cardiac monitoring. In the one-year follow up period patients receiving followup monitoring were older at 58 years vs. 56 years ($p = 0.01$). People who did not receive any cardiac monitoring were higher in any of the regions studied ($p = 0.53$). **Conclusions:** Less than two in ten newly diagnosed breast cancer patients received baseline or followup monitoring. More patients received baseline cardiac monitoring than followup monitoring within one year after initiation of treatment.

PCN306
REAL-WORLD STUDY OF HEALTHCARE UTILIZATION AND LONG-TERM PRODUCTIVITY LOSS IN CHRONIC GRAFT VERSUS HOST DISEASE IN SWEDEN

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Objectives: To address the paucity of data concerning the real-world loss of work productivity and healthcare utilization associated with chronic graft versus host disease (cGVHD). **Methods:** Longitudinal population-based Swedish registers were used to identify individuals with cGVHD after undergoing hematopoietic stem cell transplantation (HSCT) from 2006 to 2015. Individuals 18-75 years of age who survived 6 months post-HSCT were classified as having mild cGVHD based on steroid or immunosuppressive treatment or as moderate-severe cGVHD based on extracorporeal photopheresis, immunosuppressive, or steroid treatment. Sickness absence days were defined as the total number of days an individual was unable to work due to sickness; multivariate negative binomial regression was used to determine incidence rate ratios (IRRs) for sickness absence (individuals 18-65 years) and inpatient/outpatient healthcare utilization. **Results:** Of 1246 individuals classified 6 months post-HSCT, 28.1% were classified as non-cGVHD and 71.9% as cGVHD (27.7% mild cGVHD, 44.2% moderate-severe cGVHD). After a 5-year follow-up (n=364), 31.5% of moderate-severe cGVHD individuals were unable to work due to sickness, versus 7.7% for non-cGVHD and 17.7% for mild cGVHD. During the overall study period, compared with moderate-severe cGVHD individuals, sickness absence rate ratios (IRR [95% CI]) were 0.54 (0.46-0.62) for non-cGVHD and 0.63 (0.54-0.73) for mild cGVHD. Compared with moderate-severe cGVHD individuals, non-cGVHD and mild cGVHD individuals spent less time in inpatient (IRR [95% CI]: non-GVHD, 0.41 [0.33-0.51]; mild cGVHD, 0.69 [0.56-0.85]) or outpatient healthcare (IRR [95% CI]: non-GVHD, 0.46 [0.43-0.50]; mild cGVHD, 0.64 [0.59-0.69]). Individuals aged 40-65 years had a higher risk of sickness absence than individuals aged 18-39 years; age did not affect inpatient/outpatient care rates. **Conclusions:** This is the first study to describe productivity loss in cGVHD. Our novel analysis, using real-world data, revealed that moderate-severe cGVHD individuals had significantly greater sickness absence rates and healthcare utilization than non- and mild cGVHD individuals.

PCN307
IMPACT OF EHR TECHNOLOGY UPDATES ON PATIENTS' ACCESS TO ONCOLOGY DRUGS

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Objectives: The amount of time that lapses between a new drug approval in oncology and the drug's availability in the electronic health records system for physicians to order has a direct impact on patients' lives. This assessment will evaluate the iKnowMed (iKM) Electronic Health Records(EHR) system to assess the timeliness of the system updates. **Methods:** The iKM system is web-based electronic health record (EHR) developed in collaboration with community oncologists from the US Oncology Network. iKM utilizes an integrated a regimen support tool called Clear Value Plus which is based on evidence-based treatment options based on NCCN and provides clinical and reimbursement information at the point-of-care. Together these tools were designed to support quality and efficiency of cancer care delivery with an emphasis improve clinical outcomes. The system is updated routinely to reflect new drug approvals based on NCCN guidelines. Thus, to evaluate the impact of the potential time lapse between drug approval and the iKM EHR system update an assessment of 40 new oncology drug approvals/label updates from January 2018 – June 2018 was completed. The duration of time between the NCCN guideline update date and the iKM/CVP update was calculated. **Results:** On average the iKM/CVP system was updated within 15 days of the NCCN guideline publication date for new oncology therapies. Of the 40 therapies reviewed, 37.5% (15) were available for the physicians to order within 7 days or less from the NCCN guideline update. Alternatively, roughly 25% (11) were available after 30 days. **Conclusions:** The time from drug approvals being incorporated in NCCN guidelines and being available for physicians to access in the EHR for the majority of drugs was less than 30 days. This provides the opportunity for new treatments to impact on patient outcomes and quality of care.

British Journal of Cancer (2010) 103, 1644–1648
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www.bjcancer.com

Inhibition of renin–angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine

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BACKGROUND: The renin–angiotensin system (RAS) is thought to have a role in carcinogenesis, and RAS inhibition may prevent tumour growth.

METHODS: We retrospectively investigated the impact of angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) in 155 patients with pancreatic cancer receiving gemcitabine monotherapy. Patients were divided into three groups: the ACEI/ARB group (27 patients receiving an ACEI or ARB for hypertension (HT)), the non-ACEI/ARB with HT group (25 patients receiving antihypertensive drugs other than ACEIs or ARBs), and the non-HT group (103 patients receiving no antihypertensive drugs).

RESULTS: Patient characteristics were not different, except for age and HT medications. Progression-free survival (PFS) was 8.7 months in the ACEI/ARB group, 4.5 months in the non-ACEI/ARB with HT group, and 3.6 months in the non-HT group. Overall survival (OS) was 15.1 months in the ACEI/ARB group, 8.9 months in the non-ACEI/ARB with HT group, and 9.5 months in the non-HT group. The use of ACEIs/ARBs was a significant prognostic factor for both PFS ($P = 0.032$) and OS ($P = 0.014$) in the multivariate analysis.

CONCLUSIONS: The ACEIs/ARBs in combination with gemcitabine might improve clinical outcomes in patients with advanced pancreatic cancer. Prospective trials are needed to test this hypothesis.

British Journal of Cancer (2010) **103,** 1644–1648. doi:10.1038/sj.bjc.6605955 www.bjcancer.com
Published online 26 October 2010
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Keywords: angiotensin I-converting enzyme inhibitors; angiotensin II type-1 receptor blockers; chemotherapy; gemcitabine; pancreatic cancer; renin–angiotensin system

Systemic administration of gemcitabine has been the standard chemotherapy for advanced pancreatic cancer since Burris *et al* (1997) demonstrated the superiority of gemcitabine over 5-flurouracil. Combination therapies of gemcitabine with other cytotoxic drugs (Berlin *et al*, 2002; Louvet *et al*, 2005; Herrmann *et al*, 2007; Cunningham *et al*, 2009; Nakai *et al*, 2009, 2010) have been thoroughly investigated, but only two randomised control trials have shown significant improvements in the survival so far (Reni *et al*, 2005; Conroy *et al*, 2010). Many molecular target drugs have been recently investigated in clinical trials (Van Cutsem *et al*, 2009; Kindler *et al*, 2010; Philip *et al*, 2010). Erlotinib in combination with gemcitabine was the only drug that showed prolonged survival in advanced pancreatic cancer (Moore *et al*, 2007) but the survival benefit was modest, with only a 2-week improvement in survival, and was accompanied by high costs and greater toxicity than gemcitabine alone. Thus, more effective and safe drugs are awaited.

The systemic renin–angiotensin system (RAS) is associated with cardiovascular regulation and angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1 receptor blockers (ARBs) are some of the most widely used antihypertensive drugs. Since Lever *et al* (1998) reported that the use of ACEI was associated with a decreased incidence of cancer in a large cohort study, the potential role of the local RAS in carcinogenesis has attracted substantial attention. The local RAS reportedly promotes angiogenesis and proliferation via vascular endothelial growth factor (VEGF) expression or epidermal growth factor receptor (EGFR) expression (Ager *et al*, 2008; Khakoo *et al*, 2008). Synergistic inhibition of tumour growth in a murine pancreatic cancer has been demonstrated with combined gemcitabine and losartan treatment via VEGF suppression (Noguchi *et al*, 2009). In addition, the inhibition of RAS is also reported to induce apoptosis in pancreatic cancer cells (Amaya *et al*, 2004; Gong *et al*, 2010). Thus, the use of ACEIs or ARBs may inhibit tumour growth in patients with pancreatic cancer. In this study, we retrospectively analysed clinical outcomes in patients with pancreatic cancer receiving gemcitabine monotherapy to clarify the impact of ACEIs and ARBs.

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Received 1 September 2010; revised 17 September 2010; accepted 22 September 2010; published online 26 October 2010

PATIENTS AND METHODS

Patients

All patients with locally advanced and metastatic pancreatic cancer who received first-line chemotherapy with gemcitabine monotherapy without previous treatment, including surgical resection

and radiotherapy at the University of Tokyo Hospital between April 2001 and August 2009 were retrospectively studied. The use of hypertension (HT) medications including ACEIs or ARBs was retrospectively retrieved from the medical records, and patients were divided into three groups: the ACEI/ARB group (patients who received ACEIs or ARBs for HT), the non-ACEI/ARB with HT group (patients who received antihypertensive drugs other than ACEIs or ARBs), and the non-HT group (patients who did not receive antihypertensive drugs). This study was approved by The University of Tokyo Hospital ethics committee.

Treatment and tumour response

Gemcitabine was administered at a dose of 1000 mg m^{-2} in a 30-min intravenous infusion on days 1, 8, and 15 in 4-week cycles. The relative dose intensity (RDI) for gemcitabine was defined as the ratio of the actual dose intensity to the standard dose intensity. Tumour response was assessed via computed tomography using the Response Evaluation Criteria in Solid Tumours version 1.0 (Therasse *et al*, 2000). The evaluation was repeated every two courses, or more frequently in patients with clinically suspected progression.

Statistical methods

Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared using the log-rank test. The χ^2-test or Fisher's exact test was used to compare categorical variables. The independent *t*-test, Mann–Whitney *U*-test, or Kruskal–Wallis test was used to compare continuous variables as appropriate. All reported *P*-values were the result of two-sided tests, with $P<0.05$ considered statistically significant.

To exclude possible confounding factors, the Cox proportional hazards model was used to estimate hazard ratios of the use of ACEIs/ARBs adjusted for significant prognostic factors. Prognostic factors included age (<65 or ⩾65 years old), gender (male or female), performance status (PS; 0–1 or ⩾2), distant metastasis (yes or no), pretreatment carbohydrate antigen 19-9 level, and treatment group (the ACEI/ARB group, the non-ACEI/ARB with HT group, or the non-HT group). Prognostic factors with $P<0.05$ in the univariate analysis were included in the multivariate analysis.

RESULTS

Patients' characteristics

In total, 155 patients received first-line gemcitabine monotherapy between April 2001 and August 2009 at The University of Tokyo Hospital, with a median follow-up time of 9.5 months. In all, 52 patients received medication for HT (Table 1) and of these, 27 patients took an ACEI ($n=6$) or ARB ($n=21$). Other antihypertensive drugs included calcium-channel blockers ($n=22$) and β-blockers ($n=3$). The most commonly administered drug was candesartan ($n=12$). The doses of ACEIs and ARBs were as follows: enalapril 5 mg in three patients and 2.5 mg in one patient, lisinopril 10 mg in one patient, temocapril 4 mg in one patient, candesartan 4 mg in eight patients and 8 mg in four patients, losartan 25 mg in four patients, olmesartan 10 mg in three patients and valsartan 40 mg in two patients. Except one patient in the ACEI/ARB group, all the patients with HT continued to receive their antihypertensive drugs at least during their chemotherapy. One patient in the ACEI/ARB group stopped taking valsartan 1 month after starting chemotherapy because of the decrease in blood pressure. Patient characteristics of the ACEI/ARB group ($n=27$), the non-ACEI/ARB with HT group ($n=25$), and the non-HT group ($n=103$) are shown in Table 2.

Table 1 Number of patients receiving antihypertensive drugs

Drugs	Number of patients
ACEI	6
Enalapril	4
Lisinopril	1
Temocapril	1
ARB	21
Candesartan	12
Losartan	4
Olmesartan	3
Valsartan	2
Calcium-channel blockers	22
Amlodipine	8
Nifedipine	6
Manidipine	4
Diltiazem	4
β-Blockers	3
Atenolol	2
Betaxolol	1

Abbreviations: ACEI = angiotensin I-converting enzyme inhibitor; ARB = angiotensin II type-1 receptor blocker.

Table 2 Patient characteristics

Characteristics	ACEI/ARB ($n=27$)	Non-ACEI/ARB with HT ($n=25$)	Non-HT ($n=103$)	*P*-value
Median age, years (range)	71 (53–87)	73 (56–88)	63 (41–89)	<0.001
Gender (male/female)	15/12	11/14	58/45	0.538
PS				0.621
0	14	11	40	
1	9	13	47	
2	4	1	14	
3	0	0	2	
Location				0.355
Head	12	16	53	
Body/tail	15	9	50	
Stage				0.668
Locally advanced	12	10	40	
Metastatic	15	15	63	
Site of metastasis, n (%)				
Liver	10 (37.0%)	12 (48.0%)	46 (44.7%)	0.942
Lung	1 (3.7%)	3 (12.0%)	13 (12.6%)	0.473
Lymph node	13 (48.2%)	12 (48.0%)	50 (48.5%)	1.000
Peritoneum	3 (11.1%)	1 (4.0%)	15 (14.6%)	0.412
Median CEA, ng ml^{-1} (range)	4.0 (0.8–120.2)	6.1 (2.4–2964.3)	5.7 (1–2756.9)	0.201
Median CA19-9, U ml^{-1} (range)	490 (1–145600)	421 (1–102100)	324 (1–182600)	0.788
Hypertension	27	25	0	<0.001

Abbreviations: ACEI = angiotensin I-converting enzyme inhibitor; ARB = angiotensin II type-1 receptor blocker; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; HT = hypertension; PS = performance status.

Baseline characteristics did not differ significantly among groups, apart from age and HT medications. The mean RDI of gemcitabine was 67.3% in the ACEI/ARB group, 64.6% in the non-ACEI/ARB with HT group, and 66.4% in the non-HT group ($P=0.914$). At the time of analysis, five patients in the ACEI/ARB group and two patients each in the non-ACEI/ARB with HT and non-HT groups continued to receive gemcitabine without disease progression, with a median follow-up time of 7.9 months (range, 5.2–17.3 months). Among 146 patients who showed disease progression during

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CSPC Exhibit 1100
Page 148 of 333

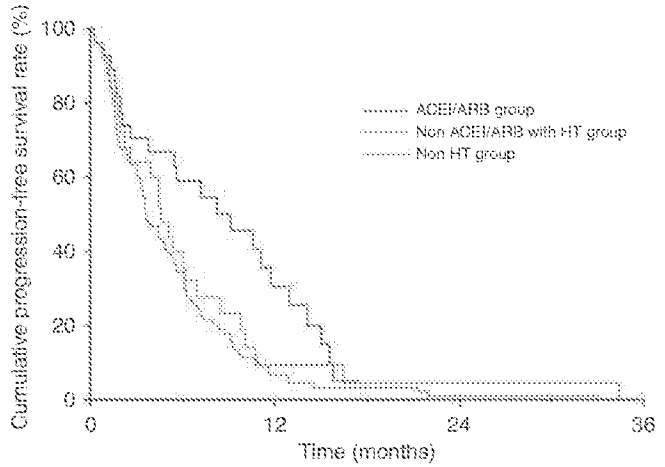


Figure 1 Kaplan–Meier curves for progression-free survival by treatment groups. The median progression-free survival was 8.7 months in the ACEI/ARB group, 4.5 months in the non-ACEI/ARB with HT group, and 3.6 months in the non-HT group.

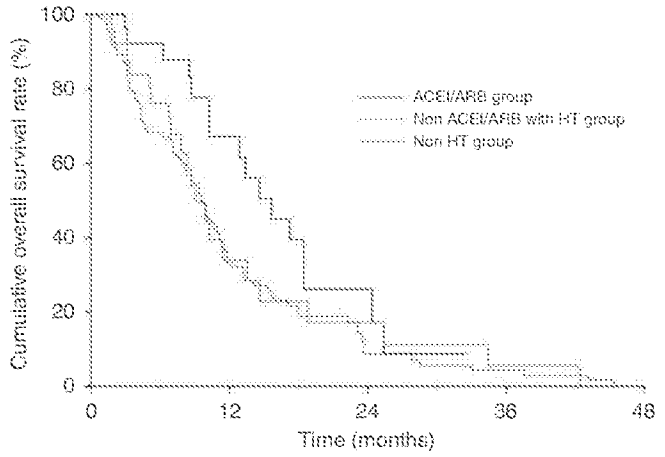


Figure 2 Kaplan–Meier curves for overall survival by treatment groups. The median overall survival was 15.1 months in the ACEI/ARB group, 8.9 months in the non-ACEI/ARB with HT group, and 9.5 months in the non-HT group.

gemcitabine treatment, second-line chemotherapy was administered in 23.8% of the ACEI/ARB group, 52.2% of the non-ACEI/ARB with HT group, and 33.7% of the non-HT group ($P = 0.134$). Four patients (2.6%) were lost to follow after disease progression; one patient in the ACEI/ARB group, one patient in the non-ACEI/ARB with HT group, and two patients in the non-HT Group. The median follow-up period of these four patients was of 7.7 months.

Impact of ACEIs/ARBs on clinical outcomes

Response rates were comparable among the three groups; 3.7% in the ACEI/ARB group, 4.0% in the non-ACEI/ARB with HT group, and 2.9% in the non-HT group ($P = 0.485$), whereas the disease control rate was 63.0% in the ACEI/ARB group compared with 36.0% in the non-ACEI/ARB with HT group and 44.7% in the non-HT group ($P = 0.131$). The median PFS (Figure 1) was 8.7 months (95% confidence interval (CI), 2.6–11.1) in the ACEI/ARB group, 4.5 months (95% CI, 2.2–6.1) in the non-ACEI/ARB with HT group, and 3.6 months (95% CI, 3.1–4.8) in the non-HT group ($P = 0.015$ by log-rank test). The median OS (Figure 2) was 15.1 months (95% CI, 10.2–18.5) in the ACEI/ARB group, 8.9 months (95% CI, 6.7–11.4) in the non-ACEI/ARB with HT group, and 9.5 months (95% CI, 7.8–11.2) in the non-HT group ($P = 0.140$ by log-rank test). There were no significant differences between patients taking ACEIs and ARBs. The median PFS was 10.6 months (95% CI, 1.5–15.1) in patients taking ACEIs and 8.2 months (95% CI, 2.0–12.9) in patients taking ARBs ($P = 0.756$ by log-rank test). The median OS was 13.3 months (95% CI, 3.0–24.6) in patients taking ACEIs and 15.6 months (95% CI, 8.7–25.4) in patients taking ARBs ($P = 0.794$ by log-rank test).

Table 3 Univariate and multivariate analyses for progression-free survival

	Univariate analysis		Multivariate analysis	
Factor	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age, years				
<65	1	0.032	1	0.605
⩾65	0.69 (0.50–0.97)		0.90 (0.61–1.33)	
Gender				
Male	1	0.387		
Female	0.87 (0.62–1.20)			
PS				
0–1	1	<0.001	1	0.026
⩾2	2.69 (1.64–4.21)		2.04 (1.09–3.58)	
Stage				
Locally advanced	1	0.002	1	0.031
Metastatic	1.70 (1.21–2.40)		1.47 (1.04–2.10)	
CA19-9				
Per 1000 increase	1.01 (1.00–1.01)	0.023	1.00 (0.99–1.01)	0.559
Group				
Non-HT	1		1	
Non-ACEI/ARB with HT	0.79 (0.49–1.22)	0.294	0.97 (0.58–1.56)	0.890
ACEI/ARB	0.51 (0.31–0.80)	0.003	0.58 (0.34–0.95)	0.032

Abbreviations: ACEI = angiotensin I-converting enzyme inhibitor; ARB = angiotensin II type-I receptor blocker; CA19-9 = carbohydrate antigen 19-9; CI = confidence interval; HR = hazard ratio; HT = hypertension; PS = performance status.

Although patient characteristics of the three groups were similar among groups except for age and HT medications, we performed Cox proportional hazard analyses to exclude the possible influence of confounding prognostic factors. The Cox univariate and multivariate analyses for PFS and OS are shown in Tables 3 and 4, respectively. The use of ACEIs/ARBs remained significant as a prognostic factor for both PFS and OS, in addition to the previously reported prognostic factors, PS and disease stage. The hazard ratios for the ACEI/ARB group against the non-HT group were 0.58 ($P = 0.032$) for PFS and 0.52 ($P = 0.014$) for OS. Those for the non-ACEI/ARB group were 0.97($P = 0.890$) for PFS and 1.23 ($P = 0.430$) for OS.

DISCUSSION

This retrospective study is the first report to clarify the clinical impact of the use of ACEIs or ARBs in pancreatic cancer. The use of ACEIs or ARBs was associated with longer PFS and OS in patients with advanced pancreatic cancer receiving gemcitabine monotherapy. These data suggest that inhibition of the RAS in human pancreatic cancer may inhibit tumour growth and improve survival, in accordance with previous *in vitro* studies and *in vivo* animal studies.

ACEIs and ARBs are widely used as antihypertensive drugs, and the reports of organ protective effects (Grandi and Maresca, 2006) by ACEIs are increasing, including inhibition of cardiac hypertrophy, diabetic nephropathy, and diabetic retinopathy. With respect to anticancer effects, Lever *et al* (1998) reported that the long-term use of ACEIs reduced the incidence of cancer in a

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Page 149 of 333

Table 4 Univariate and multivariate analyses for overall survival

	Univariate analysis		Multivariate analysis	
Factor	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age, years				
<65	1	0.142		
⩾65	0.76 (0.53–1.10)			
Gender				
Male	1	0.041	1	0.006
Female	0.69 (0.48–0.98)		0.59 (0.40–0.86)	
PS				
0–1	1	<0.001	1	<0.001
⩾2	4.14 (2.42–6.76)		4.08 (2.22–7.05)	
Stage				
Locally advanced	1	0.007	1	0.030
Metastatic	1.65 (1.14–2.41)		1.69 (1.16–2.47)	
CA19-9				
Per 1000 increase	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.01)	0.058
Group				
Non-HT	1		1	
Non-ACEI/ARB with HT	0.92 (0.55–1.45)	0.718	1.23 (0.73–1.98)	0.430
ACEI/ARB	0.59 (0.33–0.97)	0.038	0.52 (0.29–0.88)	0.014

Abbreviations: ACEI = angiotensin I-converting enzyme inhibitor; ARB = angiotensin II type-1 receptor blocker; CA19-9 = carbohydrate antigen 19-9; CI = confidence interval; HR = hazard ratio; HT = hypertension; PS = performance status.

prospective cohort study, though they did not explore the underlying mechanisms. Since then, in addition to cardiovascular homostasis by the systemic RAS, increasing evidence indicates a role of the local RAS in various aspects of carcinogenesis, including angiogenesis, cell proliferation, apoptosis, and inflammation (Ager *et al*, 2008; Khakoo *et al*, 2008). On the other hand, a meta-analysis denied the reduced cancer incidence with ACEIs (Coleman *et al*, 2008) and the increased risk of cancer incidence was also reported with ARBs (Sipahi *et al*, 2010). Both the clinical impact of inhibition of RAS on cancer incidence and its underlying mechanism remains unclear.

The existence of the local RAS was first reported in the canine pancreas in 1991 (Chappell *et al*, 1991) and in the human pancreas in 1999 (Tahmasebi *et al*, 1999). The local pancreatic RAS has been implicated in various physiological conditions including pancreatitis, fibrosis, and diabetes mellitus (Leung, 2007). The involvement of the local RAS in pancreatic cancer was suggested because of the expression of angiotensin II (Ohta *et al*, 2003) and the angiotensin II type-1 receptor (Fujimoto *et al*, 2001) in human pancreatic cancer. The ACEIs and ARBs inhibit pancreatic cancer cell proliferation *in vitro* (Arafat *et al*, 2007) and also slow murine pancreatic cancer progression *in vivo* via down-regulation of VEGF expression (Noguchi *et al*, 2009; Fendrich *et al*, 2010). Inhibition of RAS is also reported to induce apoptosis in pancreatic cancer cells (Amaya *et al*, 2004; Gong *et al*, 2010). Accordingly, these drugs were suggested to be potential treatments for pancreatic cancer or for the prevention of pancreatic cancer. However, the clinical impact of ACEIs and ARBs in pancreatic cancer treatment has not been fully clarified. With respect to other cancer types, a pilot study reported that ARBs had cytostatic activity in hormone-refractory prostate cancer, as indicated by decreased prostate-specific antigen levels (Uemura *et al*, 2005), and the addition of ACEIs/ARBs to platinum-based chemotherapy was associated with prolonged survival in patients with advanced non-small cell lung cancer in a retrospective study (Wilop *et al*, 2009). ACEIs in combination with vitamin K were also reported to suppress the recurrence of hepatocellular carcinoma in a prospective study (Yoshiji *et al*, 2009).

It is possible that ACEIs and ARBs have different influences on cancer because ACEIs block both angiotensin II type-1 and type-2 receptors, whereas ARBs block only type-1 receptor. The role of angiotensin II type-2 receptor is less investigated than angiotensin II type-1 receptor, which is shown to induce angiogenesis, proliferation, and inflammation. Angiotensin II type-2 receptor is reported to be both anti- and pro-angiogenetic (Ager *et al*, 2008). In this study, there were no significant differences in survival between patients taking ACEIs and ARBs. Our study population was too small to analyze the differences between these two types of drugs.

The disappointing results of combination therapy with gemcitabine and cytotoxic drugs have led to intense investigation of molecular target drugs for pancreatic cancer (Burris and Rocha-Lima, 2008). Inhibition of VEGF or EGFR failed to demonstrate significant survival prolongation except one trial with erlotinib (Moore *et al*, 2007). The inhibition of RAS by ACEI or ARB reportedly influences multiple pathways including angiogenesis, proliferation, and apoptosis, and can be a safe and inexpensive strategy against pancreatic cancer, but a prospective study is warranted to evaluate antitumour effects by the inhibition of RAS.

This study had some limitations. As this was a retrospective study in a single institution and the sample size of the ACEI/ARB group was small, unknown sources of bias may exist in the findings. However, other than age and HT medications, no significant differences were detected in patient characteristics among groups, and the multivariate analysis revealed that ACEI/ARB use remained a significant prognostic factor for both PFS and OS, though we cannot fully correct the bias that patients with HT were much older than patients without HT. Gemcitabine dose intensity and the induction rate of second-line chemotherapy were also similar in the three groups. The results of the non-ACEI/ARB with HT group also excluded the possibility that patients who did not receive antihypertensive drugs had a poorer prognosis. However, a prospective study with a larger population is warranted to confirm our hypothesis.

In conclusion, our retrospective analysis suggests that ACEIs or ARBs in combination with gemcitabine may improve clinical outcomes in patients with advanced pancreatic cancer. We have started a phase I trial of candesartan in combination with gemcitabine, which is currently ongoing (UMIN registration number 000002152).

Conflict of interest

The authors declare no conflict of interest.

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CSPC Exhibit 1100
Page 150 of 333

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CSPC Exhibit 1100
Page 151 of 333

Stromal biology and therapy in pancreatic cancer

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Published Online First 21 October 2010

ABSTRACT

Pancreatic ductal adenocarcinoma (PDA) is an almost uniformly lethal disease. One explanation for the devastating prognosis is the failure of many chemotherapies, including the current standard of care therapy gemcitabine. Although our knowledge of the molecular events underlying multistep carcinogenesis in PDA has steadily increased, translation into more effective therapeutic approaches has been inefficient over the last several decades. Evidence for this innate resistance to systemic therapies was recently provided in an accurate mouse model of PDA by the demonstration that chemotherapies are poorly delivered to PDA tissues because of a deficient vasculature. This vascular deficiency correlated with the presence of a dense stromal matrix that is a prominent histological hallmark of PDA tumours. Therapeutic targeting of stromal cells decreased the stroma from pancreatic tumours, resulting in increased intratumoral perfusion and therapeutic delivery of gemcitabine. Stromal cells contained within the PDA tumour microenvironment therefore represent an additional constituent to neoplastic cells that should be critically evaluated for optimal therapeutic development in preclinical models and early clinical trials.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is one of the most lethal human malignancies.[1] The rapid clinical decline commonly observed in patients with pancreatic cancer has been ascribed to both the aggressive biological nature of PDA and to the ineffectiveness of systemic therapies available for patients with advanced disease.[2 3] Indeed, even among patients with pancreatic cancer who undergo surgery and adjuvant chemotherapy, the median survival rate for those with clean microscopic surgical margins (R0 resection) is approximately 2 years, with a 5-year survival of 15–20%.[4–6] One explanation for the poor response of patients to systemic therapies was recently provided in an accurate mouse model of PDA by the demonstration that chemotherapies are poorly delivered to PDA tissues because of a deficient vasculature.[7] This vascular deficiency correlated with the presence of the dense stromal matrix that makes up the bulk mass of PDA tumours, and chemical inhibition of stromal cells decreased the matrix and increased intratumoral perfusion and therapeutic delivery. Stromal cells contained within the PDA tumour microenvironment therefore represent an additional constituent to neoplastic cells that should be critically evaluated for optimal therapeutic development.

Pancreatic carcinogenesis is currently understood as a multistage process characterised by the accumulation of genetic alterations accompanied by typical morphological and histological changes in pancreatic ductal cells. Activating mutations in the K-*ras* gene occur early during malignant transformation, followed by subsequent somatic mutations involving the tumour suppressor genes *p16*, *p53* and *DPC4*.[8 9] In addition, approximately 10% of all patients have an inherited predisposition to the development of PDA, and this has been partially ascribed to several germline mutations including BRCA2, STK11/LKB1, p16/CDKN2A and PRSS1.[10] On the basis of these histopathological and molecular studies, a model similar to that of the adenoma-carcinoma sequence in the development of colon cancer[11] was proposed to describe the progression from normal pancreas via preneoplastic lesions to invasive cancer.[9] According to their stepwise accumulation of histopathological and molecular alterations, the preneoplastic lesions have been classified as pancreatic intraepithelial neoplasms (PanINs) 1a/b, 2 and 3.

The knowledge of high-grade PanIN lesions that are known to be a risk for developing PDA has led to early pancreatectomy; however, the impact of survival on such patients is currently unknown,[12] and the extension of this concept to the general population has not been feasible. In addition, there have yet to be any effective molecular therapies reported based upon our knowledge of the PanIN progression scheme.

After decades of intensive efforts in genomic research focusing on molecular alterations in tumour cells,[13] attention has increasingly expanded to include the tumour microenvironment, in particular the stromal cells. Many epithelial tumours including breast, prostate and ovarian cancers exhibit a prominent desmoplastic reaction with accumulation of stromal cells. Among them, pancreatic cancer displays the most extensive stromal reaction accounting for up to 90% of the tumour volume. Several notable studies have provided evidence that the microenvironment co-evolves with transformed epithelial cells in different carcinomas.[14–20] However, the pathophysiological mechanisms of tumour stromal signalling and its contribution to tumour progression and therapeutic

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resistance are still poorly understood in pancreatic cancer and other solid carcinomas.[21–23] Here we discuss recent preclinical models that hold great promise as they allow new concepts for improving the efficacy of chemotherapeutics to be tested rapidly and with high fidelity.

STROMAL MICROENVIRONMENT IN PDA

One of the most prominent histological features of PDA is the presence of an abundant tumour stroma (figure 1).[24] The stromal microenvironment is a complex structure composed of an extracellular matrix (ECM), activated fibroblasts and myofibroblasts, inflammatory cells and blood and lymphatic vessels that distort the normal architecture of pancreatic tissue. Interactions between the neoplastic and non-neoplastic cells and acellular matrix have been proposed to stimulate the extensive desmoplastic reaction. At the molecular level, stroma production is promoted by the activation of multiple cancer cell-derived signalling pathways such as transforming growth factor β (TGFβ), hepatocyte growth factor (HGF/Met), fibroblast growth factors (FGFs), insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF) via autocrine and paracrine mechanisms.[25 26] These receptor-mediated signalling cascades lead to secretion of structural matrix components including proteoglycans, collagens and fibronectin as well as catalytically active enzymes such as proteinases.

The exact composition of the ECM is regulated by a multitude of different mechanisms. For instance, matrix metalloproteinases (MMPs) are a large family of zinc-containing proteolytic enzymes involved in the degradation, dynamic remodelling and turnover of ECM proteins in physiological and pathological conditions.[27] In particular, MMP-2 and MMP-9 are commonly overexpressed in pancreatic cancer and play an important role in tumour cell migration and invasion by degrading the surrounding ECM.[28 29] Recent evidence suggests that the interplay of extracellular proteinases and their inhibitors in invasion and metastasis is much more complex than previously anticipated. In particular, the biological functions of proteinase inhibitors extend far beyond their roles as inactivators of their target proteinases. For example, tissue inhibitors of metalloproteinases (TIMPs), in particular TIMP-1 and TIMP-2, are frequently overexpressed in pancreatic cancer and various other malignancies, along with their target proteinases.[30 31] Another example is the serine protease inhibitor SERPINE2 (protease nexin I), which is overexpressed in various gastrointestinal malignancies and promotes ECM production and local invasion of pancreatic tumours in vivo.[32] In addition, a multitude of proteins has evolved which modulate the composition of the ECM. Among them, the ECM metalloproteinase inducer (EMMPRIN) stimulates MMP-1 expression in fibroblasts and is frequently overexpressed in various solid tumours correlating with tumour size, stage and prognosis in primary breast and ovarian cancer.[33] In pancreatic cancer, EMMPRIN is expressed on the cell surface and supernatant of EMMPRIN-positive pancreatic cancer cell lines such as MiaPaCa and Panc1 induces MMP-2 synthesis in cultured pancreatic stellate cells (PSCs).[34]

The complex interplay between tumour cells and stroma also leads to distinct changes in the transcriptional programme of the cellular components within the stroma, such as activated fibroblasts, stellate cells and inflammatory cells, which in turn promotes cancer cell motility, resistance to hypoxia and stromal neovascularisation. These effects in stromal cells include altered integrin expression patterns, increased expression levels of cyclooxygenase 2, vascular endothelial factor A (VEGF-A), collagen I and hypoxia-inducible factor-1α.[35–40]

Recently, activation of the developmental sonic hedgehog (SHH) pathway has been identified as another mediator that promotes stromal desmoplasia.[20 41] Binding of SHH ligands to the patched1 receptor relieves repression of the 12-transmembrane domain protein Smoothened (SMO), resulting in activation of the Gli family of transcription factors. SHH is overexpressed in neoplastic cells of human pancreatic tumours[42] while downstream signalling is confined to the stromal compartment, forming a paracrine signalling axis from neoplastic to stromal cells.[43 44]

Interestingly, PSCs have emerged as pancreas-specific mesenchymal cells and important regulators of desmoplasia in pancreatic cancer.[36 45] PSCs share many morphological and functional characteristics with hepatic stellate cells (HSCs) whose central role in liver fibrosis is well established. However, distinct differences in expression patterns were observed between HSCs and PSCs, reflecting organ-specific variations of the common stellate cell-specific phenotype.[46] Isolation and in vitro culture of PSCs was first achieved in 1998 and provides a useful platform to investigate the mechanisms mediating epithelial–stromal interactions in pancreatic cancer.[47 48] PSCs are normally located in the space between the acini and endothelial cells and store vitamin A as retinyl palmitate

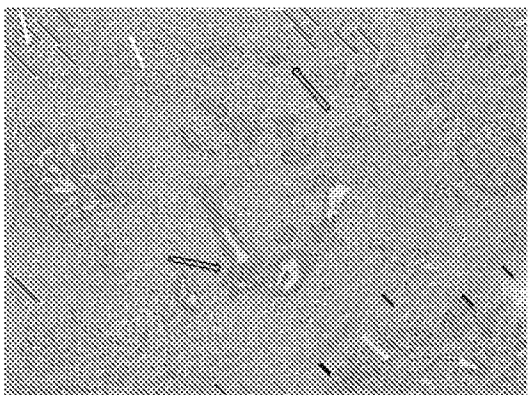


Figure 1 H&E stain of human pancreatic ductal adenocarcinoma showing a prominent desmoplastic reaction (black arrows), neoplastic ductal cells (arrows) and inflammatory cells (white arrows).

Gut 2011;60:861–868. doi:10.1136/gut.2010.226092

CSPC Exhibit 1100
Page 153 of 333

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in lipid droplets.[49] Two different functional stages can be clearly defined in PSCs—the quiescent state and the activated state (or 'myofibroblastic' state). In quiescence, PSCs store vitamin A droplets and are characterised by the presence of desmin and glial fibrillar acidic protein. Upon activation by growth factors, cytokines or oxidant stress, PSCs transform into a myofibroblast-like phenotype and secrete excessive amounts of collagen I, III, fibronectin and matrix degrading enzymes such as MMPs.[48] Figure 2 shows immunofluorescence stains of cultured primary human PSCs. Notably, several studies suggest that activated PSCs rather than cancer cells are the main source of MMPs and TIMPs.[50 51] Although proangiogenic molecules such as periostin and VEGF are secreted by PSCs, sustained PSC activation promotes fibrogenesis and ultimately may create a highly desmoplastic, hypovascular and hypoxic tumour microenvironment.[52–54] Interestingly, pancreatic cancer cells induce PSC activation in vitro by growth factors such as TGF-β1, platelet-derived growth factor (PDGF) and VEGF.[45 55] In vivo, co-injection of PSCs and cancer cells results in increased tumour growth accompanied by a pronounced desmoplastic reaction.[55 56] A recent study using an orthotopic tumour model with co-cultured PSCs and pancreatic cancer cells showed increased migratory potential in both cell types but inhibition of apoptosis in cancer cells only, suggesting a pro-survival and pro-growth mutual interaction.[57] Strikingly, stellate cells were also detected in metastatic foci in the liver of nude mice, suggesting co-migration of PSCs with cancer cells to establish a potentially tumour-favourable microenvironment at distant sites.[57] Figure 3A schematically depicts the various critical pathways involved in the interaction between stromal cells and cancer cells.

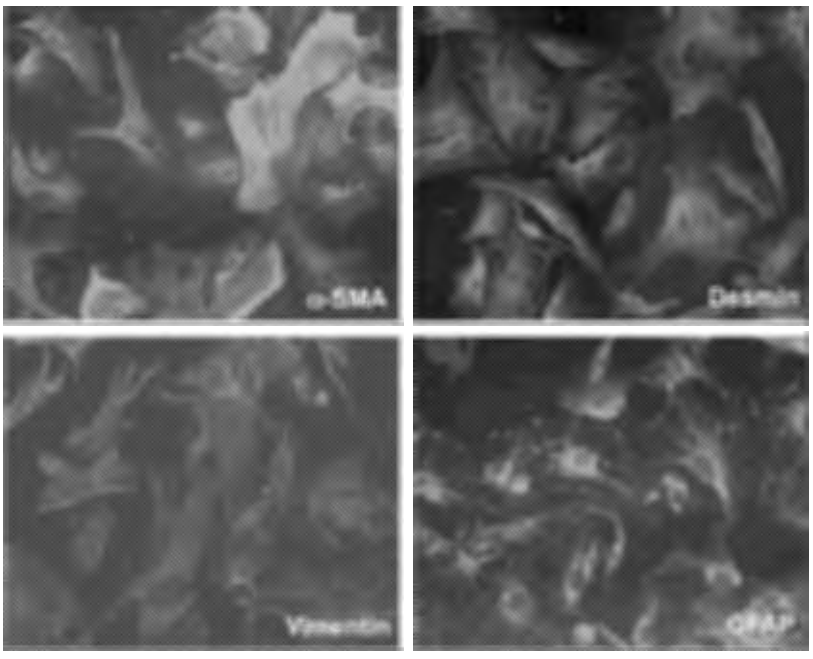


Figure 2 Immunofluorescence stain of cultured primary human pancreatic stellate cells.

The relevance of these findings is underscored by the histological evaluation of clinical specimens indicating that the prognosis and outcome of patients with pancreatic cancer heavily depends on the stromal activity and the ECM composition within the tumours. High activity of myofibroblasts as evidenced by immunohistochemistry against α-smooth muscle actin or secretion of distinct proteins such as secreted protein acidic and rich in cysteine (SPARC) were associated with a worse prognosis in patients with PDA, highlighting the impact of the stromal microenvironment on disease progression and patient survival.[58–60]

Taken together, the previously held notion that the tumour stroma of PDA is a defensive reaction of the host protecting against invasive growth and formation of metastases has been abandoned. In contrast, a highly dynamic tumour microenvironment is now being proposed that promotes tumour growth and invasion, protects from apoptosis and potentially creates barriers to the delivery of therapeutic compounds.[35 36 61 62]

IN VIVO MODELLING OF TUMOUR MICROENVIRONMENT: GENETICALLY ENGINEERED MICE IN PDA

Various mouse models of pancreatic cancer have been developed in the past few years, providing a crucial platform for the investigation of basic biological principles of cancer development and tumour biology.[63] More recently, mouse models of cancer have been increasingly employed to investigate and discover novel preclinical and clinical anticancer agents.

Historically, the most commonly used animal models for PDA were xenograft tumours in immunodeficient mice generated by subcutaneous injection or orthotopic transplantation of tumour cell lines. These models are relatively simple to establish and human cancer cells can be assessed in the murine in vivo environment. Recently, primary patient-derived tumour xenografts have been described as a platform to develop personalised drug screening.[64–66] However, major drawbacks of xenograft models include the impaired immune response owing to the need to use immunocompromised mice as hosts, the inability to perpetuate the human tumour microenvironment and the profound differences in tumour structure and vasculature compared with endogenous human PDAs.[67] Accordingly, results obtained from a number of xenograft studies have not translated well into the clinic. For instance, PDA xenografts often respond well to anti-angiogenic agents,[68] but these same agents often fail to show any clinical benefit in the cognate human tumour.[69]

An important milestone in PDA research was therefore the development of genetically engineered mouse models (GEMM).[63] Of special interest are mutant mice that have been engineered to lose the expression of tumour suppressor genes (TSGs) or express oncogenes or dominant negative TSGs from

CSPC Exhibit 1100
Page 154 of 333

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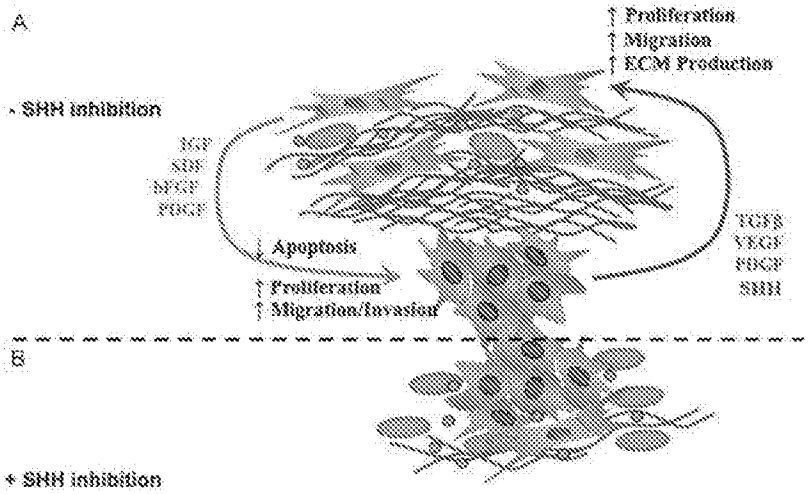


Figure 3 (A) Schematic depiction of various pathways and growth factors (green dots) interacting between stromal cells (yellow) and cancer cells (blue). (B) Sonic hedgehog (SHH) inhibition decreases desmoplasia (fibrous reddish bundles) and increases the density of tumour vessels (red) around cancer cells (blue). ECM, extracellular matrix; FGF, fibroblast growth factor; IGF, insulin-like growth factor 1; PDGF, platelet-derived growth factor; SDF, stromal cell-derived factor; TGFβ, transforming growth factor β; VEGF, vascular endothelial growth factor.

their native promoters by using knock-out or knock-in technologies. To control and direct the spatiotemporal expression of the mutant alleles, site-specific recombinases such as Cre are used. Two GEMMs were recently developed that bear striking resemblance to human PDA. The first is based on mutation of the endogenous murine *Kras* gene specifically in pancreatic progenitor cells by crossing mice with a conditionally activated *Kras* allele (LSL-$Kras^{G12D}$) to transgenic strains that express Cre recombinase in pancreatic lineages (FdxCre or p48Cre). These 'KC' mice develop murine PanIN lesions with 100% penetrance, but only a small subset of these animals progress to PDA at an advanced age, suggesting that additional genetic alterations are necessary for tumour formation.[70] To accelerate the process of tumorigenesis, FdxCre-expressing compound mutant mice were generated with conditional mutations in both *Kras* and *Trp53* in analogy to the genetic alterations in human PDA. These 'KPC' mice develop advanced PDA with 100% penetrance at an early age, thus recapitulating human PDA including histopathological similarities in neoplastic cells, desmoplasia, occurrence and site of metastasis and comorbidities such as cachexia, activation of biochemical pathways and evidence for genomic instability.[71] Further important work was done by the Barbacid group providing striking evidence that temporal expression of endogenous *Kras* in acinar cells of adult mice results in PanINs and invasive PDA only in the context of caerulein-induced pancreatitis.[72] Thus, GEMMs (in contrast to xenograft models) are particularly suited to elucidate the role of the tumour-microenvironment interactions in the disease initiation and progression of pancreatic cancer. Furthermore, preclinical studies can be established that examine the effects of drugs on the tumour microenvironment and specifically target tumour-associated stromal cells.

STROMA-TARGETED THERAPIES IN PANCREATIC CANCER

Over the last decade, major efforts have been undertaken to enhance the effect of the current standard of care chemotherapy, gemcitabine, by the combination with a second cytotoxic drug.[73] To this end, large randomised phase III trials were performed to evaluate additional effects of cisplatin,[74 75] oxaliplatin,[76 77] 5-FU,[78] irinotecan,[79 80] exatecan[81] and pemetrexed,[82] but there was no significant overall survival benefit. For the combination capecitabine and gemcitabine versus gemcitabine alone, initial data suggest no significant advantage for overall survival.[83] Notably, a recent phase III trial revealed a trend towards improved overall survival, and a meta-analysis involving 935 patients showed a significant survival benefit for the combination of capecitabine and gemcitabine.[84] Until recently, the mechanism for the extremely poor responsiveness to therapeutic agents has been mainly ascribed to the heterogeneity of transformed cells rather than to the tumour microenvironment.

The improved knowledge of the genetic and molecular alterations not only occurring in tumour cells but also in the surrounding stromal cells has recently led to the development of novel therapeutic approaches specifically targeting profibrotic pathways, cytokines and growth factors involved in tumour desmoplasia and angiogenesis to control tumour growth, prevent formation of metastases and increase the cytotoxic effect of chemotherapeutics.

Following promising results from preclinical studies, marimastat, a broad-spectrum synthetic MMP inhibitor, was the first compound tested in a large randomised phase III trial in 414 patients with advanced pancreatic cancer. Initially fuelled with great enthusiasm, the results were rather disappointing as neither marimastat alone nor the combination of marimastat and gemcitabine showed any improvement in overall survival or tumour control compared with gemcitabine alone.[85 86] One year later in 2003, Moore *et al* reported the results of a phase III trial with BAY-12-9566, a specific inhibitor of MMP-2, MMP-3, MMP-9 and MMP-13. Patients with locally advanced or metastatic pancreatic cancer were treated with BAY-12-9566 or standard intravenous gemcitabine; however, the study was discontinued after completion of the second interim analysis showed that the new substance was significantly inferior to gemcitabine (median overall survival 3.74 months vs 6.59 months).[87] As pointed out earlier, the role of proteases in cancer biology, in particular MMPs, is highly complex and the failure of broad-spectrum anti-MMP therapies might at least partly be explained by the fact that MMPs have pro-tumorigenic as well as tumour suppressive functions.

As cardinal mediators of tumour neoangiogenesis, overexpression of VEGF and its receptors

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Gut 2011;60:861–868. doi:10.1136/gut.2010.226092
CSPC Exhibit 1100
Page 155 of 333

(VEGFR-1, VEGFR-2 and VEGFR-3) has been associated with poor prognosis and increased metastatic potential in pancreatic cancer.[88] Bevacizumab, a recombinant humanised anti-VEGF monoclonal antibody approved for the treatment of colon cancer, has also been investigated in PDA. Despite promising results from a previous phase II trial,[89] the combination of bevacizumab and gemcitabine failed to significantly prolong survival in a large phase III trial with 602 patients with pancreatic cancer.[89] Similar discouraging results were obtained with a clinical phase II trial in 103 patients with pancreatic cancer using gemcitabine and axitinib, an oral inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3.[90]

The only targeted agent which demonstrated a statistically significant effect on overall survival is erlotinib, a small molecule inhibitor of the EGFR tyrosine kinase. EGFR is frequently overexpressed in pancreatic cancer and correlates with poor prognosis and disease progression.[91] EGFR signalling has also been shown to impact pancreatic stromal reaction by activating PSCs.[92] The combination of gemcitabine and erlotinib conferred a marginal but significant improvement in survival over gemcitabine alone in a large phase III randomised trial (median survival 6.24 months vs 5.91 months).[93]

Taken together, numerous clinical trials have failed to substantially improve the prognosis of patients with advanced pancreatic cancer during the last decade. The general resistance of human PDA to systemic therapies in vivo is unusual compared with other solid carcinomas, casting doubt on the transferability of preclinical results to the clinical situation in PDA.[94] It can be assumed that the lack of survival benefit shown by conventional and targeted agents in patients with pancreatic cancer might at least partly evolve from the predominant desmoplastic stroma reaction and the pronounced hypovascularity.

Indeed, experimental evidence was provided very recently demonstrating that the hypovascular tumour stroma affects delivery of chemotherapeutics in a GEMM of PDA. We showed that the active intracellular metabolite of gemcitabine, 2′,2′-difluorodeoxycytidine triphosphate (dFdCTP), was detectable in transplanted xenograft tumours but undetectable in tumours of KPC mice which are characterised by a pronounced desmoplastic reaction highly resembling the human PDA phenotype. Subsequent inhibition of the SHH signalling pathway by IPI-926, a semisynthetic derivative of cyclopamine, resulted in a dramatic depletion of stromal components paralleled by an increase in intratumoral vascular density. Although stroma depletion alone had no immediate antitumour effect in this experimental setting, co-administration of gemcitabine and IPI-926 resulted in a significantly enhanced intratumoral concentration of dFdCTP, transient disease stabilisation and a statistically significant prolongation of survival.[7] However, the pronounced stromal reaction ultimately returned in the KPC model, suggesting that the tumours can adapt to chronic SHH inhibition.[7] The effects of SHH inhibition on the stromal and vascular architecture are schematically displayed in figure 3B.

This study therefore provides a proof of principle that disruption of the desmoplastic stroma facilitates the delivery and enhances the efficacy of gemcitabine in PDA. Poor perfusion and a deficient non-angiogenic vasculature limits drug delivery and may also help to explain the recent failures of anti-VEGF strategies in pancreatic cancer.

Three months after we published these murine data, exciting clinical results on non-invasive quantification of blood flow and metabolic activity of pancreatic tumours using oxygen-15-labelled water [^{15}O]-H_2O and [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging were presented by a Finnish group.[95] In this small study, pancreatic tumours were characterised by reduced blood flow and high metabolic activity compared with normal pancreatic tissue.[95] Furthermore, a high ratio of glucose uptake to blood flow was a predictor of poor prognosis, further supporting the novel concept that a highly dynamic but hypovascular tumour microenvironment contributes to chemoresistance and poor therapeutic outcome in patients with pancreatic cancer by creating barriers for drug delivery.[95]

CONCLUSIONS

The desmoplastic hypovascular tumour microenvironment consisting of large amounts of ECM proteins, activated fibroblasts, stellate cells and inflammatory cells is now recognised to represent the cardinal histological hallmark feature of PDA. Recent preclinical and clinical data suggest that this stromal microenvironment creates a 'fortress-like' hypovascular barrier that impairs the delivery of chemotherapeutics and promotes aggressive neoplastic cell behaviour. The extremely poor prognosis and resistance to systemic therapies might therefore be partly explained by inefficient drug delivery to the tumour cells rather than drug resistance of the tumour cells. Breaching this 'stroma fortress' represents a promising strategy to improve the delivery and efficacy of systemic chemotherapeutics and might open new therapeutic avenues for patients with PDA. One challenge in translating these findings to the clinical care of patients is the need to develop means to accurately measure drug levels in PDA tumours with non-invasive techniques or small biopsies. However, clinical trial design is often hampered by the fact that PDA most commonly occurs in elderly people and is associated with severe cachexia and other age-related conditions. GEMMs of PDA are particularly suited to study the biology and treatment of this disease and may also be useful for developing novel pharmacokinetic approaches. GEMMs should also help define the role of PSCs in stimulating the desmoplastic stroma, and determine whether these are the target cells of hedgehog inhibitors. Additional pathways known to be involved in the activation of PSCs such as EGF,

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CSPC Exhibit 1100
Page 156 of 333

Key points 1: Basic science

- A pronounced desmoplastic and hypovascular microenvironment is a hallmark feature in pancreatic cancer.
- The stromal microevironment contributes to disease progression, promoting tumour growth and invasion.
- Pancreatic stellate cells have emerged as pancreas-specific mesenchymal cells and key regulators of desmoplasia in pancreatic cancer.
- The cellular and molecular mechanisms underlying the regulation and perpetuation of desmoplasia in pancreatic cancer are still poorly understood.

Key points 2: Clinical science

- The devastating prognosis for patients with pancreatic cancer has remained virtually unchanged over the last three decades.
- Targeting the stromal microenvironment is a novel and promising concept for tailored therapies in pancreatic cancer.
- Genetically engineered mice are particularly suited to study the tumour microenvironment and test novel therapeutic regimens targeting the tumour stroma (eg, sonic hedgehog inhibition).
- The extremely poor prognosis and the resistance to systemic chemotherapies are at least partly explained by low drug delivery caused by stromal barriers rather than epithelial tumour cell resistance itself.
- The development of effective means to measure intratumoral levels of chemotherapy (eg, dFdCTP) with either non-invasive imaging or using reliable microscopic biopsies is an important challenge for the field of pancreatic cancer.

PDGF or IGF-1 should also be interrogated as potential therapeutic targets in the GEMM.[51 96] Furthermore, efforts aimed at inducing PSC trans-differentiation from an activated to a quescent state via administration of vitamin A analogues could also be an attractive modality as reported in culture-activated rat PSCs.[96]

However, as observed in the mouse PDA model, tumours adapt to chronic inhibition of profibrotic signalling and ultimately resume stromal desmoplasia and hypovascularity. We therefore anticipate that multiple approaches that target the PDA stroma will probably be necessary in order to circumvent this adaptive response and maximise therapeutic benefits for patients.

Competing interests None

Provenance and peer review Not commissioned; externally peer reviewed.

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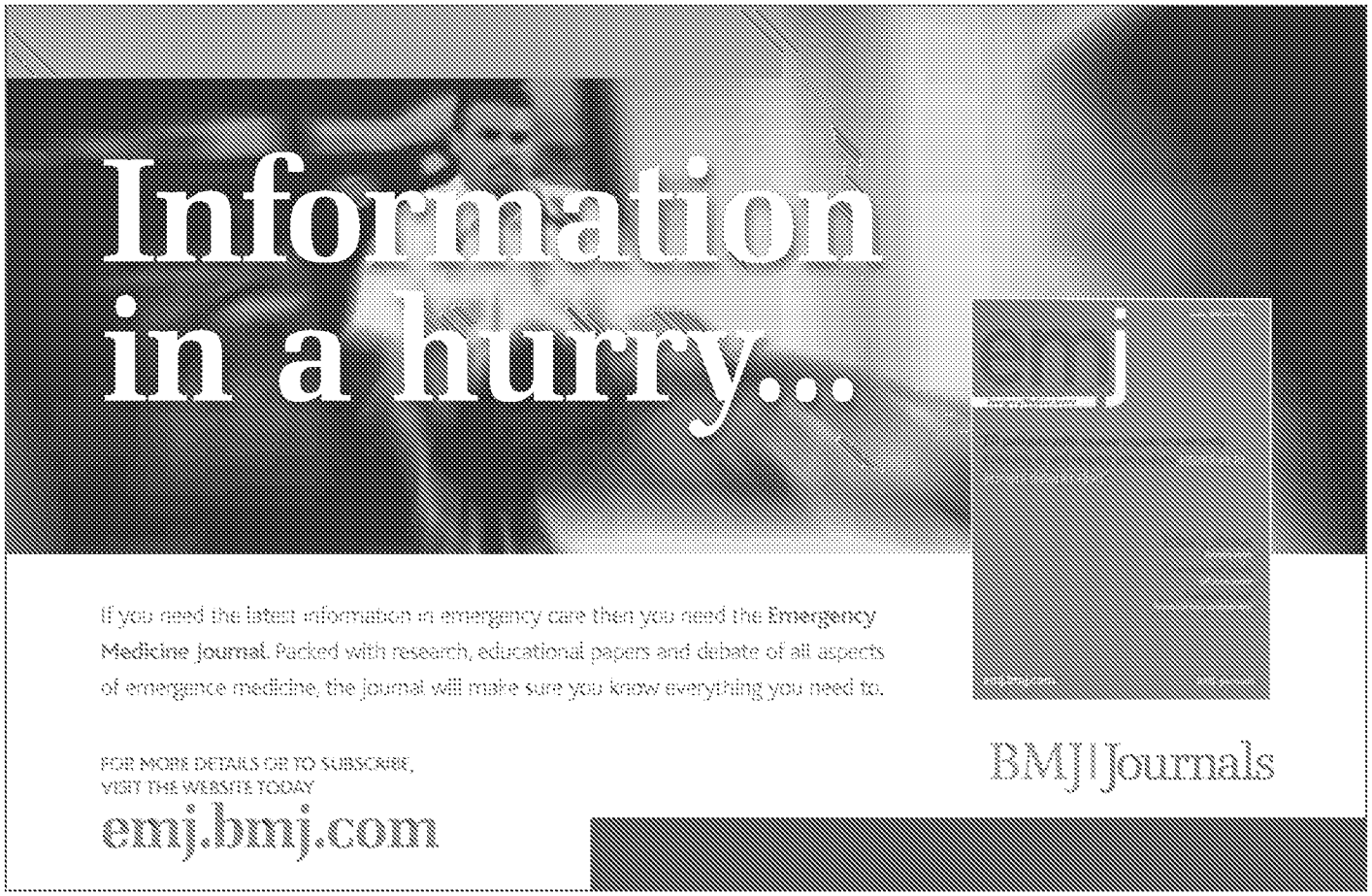
CSPC Exhibit 1100
Page 157 of 333

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CSPC Exhibit 1100
Page 159 of 333

Liposomal Irinotecan Boosts Survival in Pancreatic Cancer

Roxanne Nelson

January 21, 2015

SAN FRANCISCO — An expanded analysis of the phase 3 NAPOLI-1 trial supports the benefit of adding MM-398 (irinotecan liposome injection) to 5-fluorouracil (5-FU) plus leucovorin (LV) in patients with metastatic pancreatic cancer previously treated with gemcitabine. The new data were presented here at the 2015 Gastrointestinal Cancers Symposium.

Median overall survival was better with MM-398 plus 5-FU/LV than with 5-FU/LV alone (8.9 vs 5.1 months; hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.29 - 0.77; *P* = .0018).

The updated analysis evaluated MM-398 in the per protocol population, which involved patients who received at least 80% of the target dose in the first 6 weeks.

These findings confirm previous results from the primary intent to treat (ITT) analysis, said study author Li-Tzong Chen, MD, PhD, from the National Institute of Cancer Research in Tainan City, Taiwan. "The data are continuing to mature and these analyses reinforce our conclusions about the potential for MM-398 in patients with metastatic pancreatic cancer who have previously received gemcitabine," he said.

MM-398, currently under development by Merrimack, is an investigational nanotherapeutic that consists of 80,000 molecules of the chemotherapeutic irinotecan stably encapsulated in a 100 mm liposome sphere.

The level of SN-38, the active metabolite of MM-398, was 9.6 ng/g in the tumor and was 1.7 ng/mL in blood at 72 hours.

In a phase 2 trial, median survival was 5.2 months for patients with refractory metastatic pancreatic cancer treated with MM-398 (*Br J Cancer*. 2013;109:920-925).

Consistent Benefit Seen

In the NAPOLI-1 study, an international multicenter trial conducted at more than 100 sites, 417 patients with metastatic pancreatic cancer previously treated with gemcitabine were randomized to one of three treatments. The primary end point was overall survival.

One-third of the patients received single-agent MM-398 120 mg/m² every 3 weeks; one-third received 5-FU 2000 mg/m² over 24 hours and racemic LV 200 mg/m² over 30 minutes for 4 weeks followed by 2 weeks off (the control group); and one-third received MM-398 80 mg/m² every 3 weeks followed by 5-FU 2400 mg/m² over 46 hours and racemic LV 400 mg/m² over 30 minutes.

Primary results from NAPOLI-1 were presented last year at the European Society for Medical Oncology meeting. At that time, researchers reported that overall survival was better with the combination of MM-398 plus 5-FU/LV than with 5-FU/LV alone (6.1 vs 4.2 months; HR, 0.67; *P* = .012).

In the per protocol analysis, overall survival was significantly longer with the combination therapy, Dr Chen reported. "It also significantly improved overall survival in the non-per protocol population, compared with the control arm" (4.4 vs 2.8 months; HR, 0.56; 95% CI, 0.33 - 0.97; *P* = .0365).

"We looked to see if there were any demographic characteristics that were more likely to be included in the per protocol population, but they were similar and there were no real differences in the population," Dr Chen said.

Significant differences were also observed between the combination of MM-398 plus 5-FU/LV and 5-FU/LV alone for overall progression-free survival (3.1 vs 1.5 months; log-rank test *P* = .0001), median progression-free survival at 12 weeks (57% vs 26%), overall response rate (16% vs 1%; Fisher's exact test *P* = .001), and CA19-9 response (36% vs 12%; Fisher's exact test *P* = .0009).

No benefit was observed with single-agent MM-398; however, in the ITT analysis, median overall survival was better with single-agent MM-398 than with 5-FU/LV (4.9 vs 4.2 months; *P* = .5545).

A sensitivity analysis favored the combination therapy over 5FU/LV alone across prognostic subgroups, tumor characteristics, and previous treatments, Dr Chen explained.

The safety profile for the combination was manageable and consistent with previously reported safety results, the researchers report. The most frequent adverse events were neutropenia (20% in the combination group vs 2% in the control group), fatigue

(14% vs 4%), and gastrointestinal effects such as diarrhea (13% vs 5%) and vomiting (11% vs 3%).

In a discussion of the study, Laura Goff, MD, assistant professor of medicine at Vanderbilt University Medical Center in Nashville, Tennessee, noted that MM-398 resulted in an increase in overall survival, and that a partial response rate of 16% in a second-line population is "provocative."

"MM-398 appears to have activity in combination with 5-FU/leucovorin in previously treated pancreas cancer, and it has received fast-track status from the FDA," Dr Goff said.

The study was funded by Merrimack Pharmaceuticals Inc.

2015 Gastrointestinal Cancers Symposium (GICS): Abstract 234. Presented January 16, 2015.

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Cite this: Liposomal Irinotecan Boosts Survival in Pancreatic Cancer - *Medscape* - Jan 21, 2015.

The Oncologist®
Gastrointestinal Cancer

Metastatic Pancreatic Cancer 2008: Is the Glass Less Empty?

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Key Words. Metastatic pancreatic cancer • Gemcitabine • Oxaliplatin • Pancreatic enzyme replacement therapy • Erlotinib

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

Editor's Note

This article is not available for CME.

ABSTRACT

Pancreatic cancer is the fourth most common cause of adult cancer death in the U.S. The high mortality rate from pancreatic cancer is a result of the high incidence of metastatic disease at the time of diagnosis, an often fulminant clinical course, and the lack of adequate systemic therapies. Unfortunately, only 5%–25% of patients present with tumors amenable to resection. The median disease-free survival interval following resection for operable pancreatic cancer is 13.4 months for patients treated with adjuvant gemcitabine and 6.9 months for untreated patients. A much higher percentage of patients present with metastatic disease (40%–45%) or locally advanced disease (40%), and have median survival times of 3–6 months or 8–12 months, respectively. The frustrating lack of significant clinical advancements in the treatment of metastatic pancreatic cancer remains one of medical oncology's biggest disappointments. The past decade-long frustration has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Two of the more important examples of this include the approval of gemcitabine plus erlotinib and the use of a progression-free survival advantage to defend the use of gemcitabine plus oxaliplatin. Given the marginal benefit of systemic antineoplastics, a scholarly review inclusive of other palliative strategies will help oncologists optimize the care of pancreatic cancer patients. This article examines the existing evidence in support of a role for palliative therapy in metastatic pancreatic cancer, describes recent developments with newer chemotherapeutic and molecular-targeted agents, and explores future study designs. *The Oncologist* 2008;13:562–576

INTRODUCTION

Pancreatic cancer is the fourth most common cause of adult cancer death in the U.S.. In 2007, 37,170 people were expected to develop pancreatic cancer, with 33,370 anticipated deaths resulting from this disease [1]. The high mortality rate from pancreatic cancer is a result of the high

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incidence of metastatic disease at the time of diagnosis, an often fulminant clinical course, and the lack of adequate systemic therapies. Unfortunately, only 5%–25% of patients present with tumors amenable to resection. Following resection for operable pancreatic cancer, the median disease-free survival interval is 13.4 months for patients treated with adjuvant gemcitabine and 6.9 months for untreated patients. Although the longer median disease-free survival time associated with adjuvant gemcitabine has not translated into a median overall survival (OS) advantage (22.1 versus 20.2 months), a trend toward a higher survival rate at 3 years (34% versus 20.5%) and 5 years (22.5% versus 11.5%; $p = .06$) has been observed [2]. A much higher percentage of patients present with metastatic disease (40%–45%) or locally advanced disease (40%), and have median survival times of 3–6 months or 8–12 months, respectively [3].

The frustrating lack of significant clinical advancements in the treatment of metastatic pancreatic cancer remains one of medical oncology's biggest disappointments. The past decade-long frustration has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Two of the more important examples of this include the approval of gemcitabine plus erlotinib and the use of a progression-free survival (PFS) advantage to defend the use of gemcitabine plus oxaliplatin. Given the marginal benefit of systemic antineoplastics, a scholarly review inclusive of other palliative strategies will help oncologists optimize the care of pancreatic cancer patients. This article examines the existing evidence in support of a role for palliative therapy in metastatic pancreatic cancer, describes recent developments with newer chemotherapeutic and molecular-targeted agents, and explores future study designs.

Treatment of Metastatic Pancreatic Cancer

Effective symptom palliation requires an integrated management strategy to improve both survival and quality of life (Table 1). Because patients often struggle with several weeks to months of progressive pain, weight loss, and a declining Karnofsky performance status (KPS) score prior to diagnosis, the initial oncology consultation should be accommodated as soon as possible. Patients' pain and nutritional needs should be addressed at this first encounter along with a discussion of palliative chemotherapy options.

Pain Control

The treatment of pancreatic cancer pain includes pharmacotherapy, chemotherapy and/or radiotherapy, psychosocial support, celiac/splanchnic neurolytic blocks, and epidural or intrathecal infusion of medications [4]. Typically, the initial approach to characteristic pancreatic cancer–associated pain (constant midepigastric pain radiating through to the back or circumferentially and/or right upper quadrant pain resulting from hepatic metastases) is the initiation of long-acting narcotics such as extended-release oral morphine, oxycodone preparations, or transdermal fentanyl coupled with their immediate-acting counterparts to address breakthrough pain. Intermittent, postprandial epigastric discomfort, suggesting pancreatic enzyme insufficiency, may be successfully palliated with the initiation of pancreatic enzyme replacement therapy (PERT) alone. Lastly, reassuring the patient and his family that pain will be promptly and satisfactorily controlled helps soothe the fear and distress that this symptom causes.

Neurolytic celiac plexus block (NCPB) is typically reserved for tumor-associated pain that fails to respond adequately to systemic narcotic analgesics. NCPB is likely to have prompt and long-lasting analgesic efficacy for pancreatic cancer. A meta-analysis, composed mainly of retrospective studies, suggests that NCPB has durable (at least 3 months) partial or complete pain relief in approximately 90% of patients with pancreatic and other intra-abdominal cancers [5]. While the administration of NCPB is typically reserved for patients with ongoing significant pain despite optimized opioid therapy (maximum analgesia achievable without intolerable opioid-related adverse effects), a randomized, double-blind, controlled trial evaluated the implementation of NCPB while opioid therapy was being initiated or increased [6]. That study demonstrated that pain intensity was significantly less at 1 and 6 weeks following NCPB compared with sham injection. However, additional opioid consumption, the frequency of opioid-related adverse events, and quality of life were not different between interventions. Another study, which accrued patients from 1987 until 1991, demonstrated that a durable (up to 6 months) improvement in pain intensity could be achieved with intraoperatively placed alcohol NCPB compared with saline placebo [7]. In that trial, notably, both patients with and without pre-existing pain (preoperative pain) experienced a durable benefit from intraoperative alcohol NCPB.

PERT

Patients with pancreatic cancer are vulnerable to pancreatic enzyme deficiency and the associated malabsorption resulting from tumor-associated pancreatic duct obstruction as well as the tumor- or surgery-associated loss of normal pancreatic parenchyma (up to 25% of patients who have under-

CSPC Exhibit 1100
Page 163 of 333

Table 1. Treatment algorithm for patients with metastatic pancreatic cancer

Initial visit
Initial visit should be accommodated as soon as possible.
Symptom-directed palliation should be initiated:
• Pain control
• Pancreatic exocrine replacement therapy
• Referral for endoscopic biliary tree decompression, common bile duct stenting if not already accomplished
• First-line palliative chemotherapy should be planned
First-line palliative chemotherapy options
Weekly gemcitabine by standard infusion rate, 1,000 mg/m^2[a]
Gemcitabine by standard infusion schedule plus erlotinib, 100 mg orally daily
Gemcitabine plus capecitabine (dose/schedule per Cunningham et al. [35])
Participation in a clinical trial
Second-line palliative chemotherapy
Oxaliplatin plus 5-fluorouracil (5-FU), OFF regimen as developed by Oettle et al. [62]: oxaliplatin (85 mg/m^2) on days 8 and 22 plus 5-FU (2 g/m^2) over 24 hours with leucovorin (200 mg/m^2) over 30 minutes on days 1, 8, 15, and 22, repeated every 42 days

[a]For the rare patient fortunate enough to attain disease control for ≥4 months, a chemotherapy holiday can be offered, with same treatment rechallenge or transition to noncrossresistant therapy to be based on duration of the unmaintained progression-free interval. This recommendation is not evidence based but is a reasonable extrapolation from data in other solid tumors such as breast cancer, colon cancer, and non-small cell lung cancer.

gone a Whipple resection have pancreatic exocrine insufficiency) [8]. Furthermore, gastric and duodenal resection/bypass may be associated with decreased endogenous stimulation of pancreatic enzymes as well as a decreased mixture of chyme and pancreatic enzymes. Symptoms of exocrine insufficiency may include abdominal discomfort and/or distension, pain, excessive flatus, belching, diarrhea, steatorrhea, and weight loss. Standardly, restoration of normal digestion in pancreatic exocrine insufficiency can be achieved with 25–40,000 IU of lipase for a standard meal. Commonly prescribed preparations such as Pancrease® (Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ), Lipram® (Global Pharmaceutical Corporation, Philadelphia), Protilase® (Rugby, Inc., Rockville Centre, NY), Cotazym® (Organon, Inc., Roseland, NJ), Zymase® (Organon, Inc.), Ultrase® (Axcan Scandipharm, Inc., Birmingham, AL), Viokase® (Axcan Scandipharm, Inc.), and Creon® (Solvay Pharmaceuticals, Inc., Marietta, GA) contain porcine pancreatin protected within acid-resistant microspheres. The dosage may be increased if steatorrhea or other evidence of malabsorption persists. Another important strategy demonstrated to optimize the efficacy of enteric-coated pancreatic enzyme extracts is the additional use of potent inhibition of gastric acid secretion by a proton pump inhibitor. Up to 50% of patients with pancreatic exocrine insufficiency are thought to also suffer with either inadequate secretion of pancreatic bicarbonate or increased gastric acid secretion, with either mechanism leading to an intestinal pH sufficiently low enough to inactivate PERT [9]. If a patient continues to have malabsorption symptomatology despite titration of PERT dosing and the use of concurrent proton pump inhibition then evaluation and empiric treatment of bacterial overgrowth, particularly in patients with prior gastric or intestinal resection, may be beneficial. Powder preparations should be considered in patients prone to accelerated gastric emptying, particularly patients with prior gastroenterostomies. While bovine-derived pancreatin preparations have inferior lipase content and may be difficult to obtain, they may represent an important option for patients who refuse ingestion of pork-based products based on a religious or other ethical basis.

Endoscopic Stenting of Biliary and Pancreatic Obstruction

Biliary tract obstruction may lead to jaundice, pruritus, abdominal discomfort, nausea, malabsorption, and hepatic dysfunction. In unresectable patients, obstructive jaundice is routinely managed by endoscopic placement of plastic or metal biliary stents [10]. In addition to the relief of jaundice and pruritus, biliary decompression has been shown to improve quality of life by increasing appetite and reducing indigestion [11, 12].

Expandable metal stents are typically chosen over plastic stents because of their superior patency. Typically, expandable metal stents remain patent for a median of 8 months, compared with 4 months of patency for plastic

stents. As well, given a reduction in the need for recurrent endoscopic intervention, initial placement of metal stents has been shown to be cost-effective [13].

Pancreatic stenting may restore pancreaticoduodenal flow impaired by strictures. The main indication for pancreatic ductal stenting is "obstructive" pain related to meals in patients with a dilated main pancreatic duct beyond a stricture. However, this procedure is rarely used and the literature suggests that at most 15% of patients will have symptoms that may benefit from this intervention [14].

Chemotherapy for Metastatic Pancreatic Cancer

The goal of systemic therapy for metastatic pancreatic cancer is to minimize disease-related symptoms and prolong survival. The superior survival outcomes achieved with 5-fluorouracil (5-FU)-based combinations compared with best supportive care (BSC) alone provided an initial validation of chemotherapy benefit for advanced pancreatic cancer patients. The median survival times associated with 5-FU were consistently in the 6-month range, as summarized in Table 2 [15–17]. However, in a meta-analysis, 5-FU combinations did not demonstrate a survival benefit when compared with 5-FU alone [17].

Table 2. 5-FU–based chemotherapy regimens versus BSC

Regimen	*n* of patients	MS (months)	*p*-value
Meta-analysis [17]			
5-FU	262	6.38	<.0001
BSC	434	3.87	
RCT [15]			
FAM	43	33 wks	<.002
BSC		15 wks	
RCT [16]			
Mallinson regimen	40	LA/Met, 48/33 wks	LA/Met, .048/.001
BSC		LA/Met, 12/7 wks	
Meta-analysis [17]			
5-FU alone	428	5.23	.1
5-FU combinations	414	4.98	

Abbreviations: 5-FU, 5-fluorouracil; BSC, best supportive care; FAM, 5-FU, doxorubicin, and mitomycin-c; LA, locally advanced; Met, metastatic, stage 4 disease; MS, median survival; ORR, objective response rate; RCT, randomized controlled trial.

Gemcitabine

Because of its favorable toxicity profile and modest ability to palliate typical pancreatic cancer symptoms, single-agent gemcitabine has been the global reference regimen for this disease since its approval in 1996. Gemcitabine (2′-deoxy-2′,2′-difluorocytidine monohydrochloride [beta-isomer]) is a deoxycytidine analogue structurally related to cytarabine (cytosine arabinoside) originally investigated for its antiviral effects [18, 19]. It is a prodrug that requires cellular uptake and intracellular phosphorylation to gemcitabine di- and triphosphate, the active metabolites. Gemcitabine triphosphate competitively inhibits DNA chain elongation, leading to DNA fragmentation and cell death [18].

In the pivotal trial that helped gemcitabine gain regulatory approval in the U.S., 126 patients were randomized to receive either weekly gemcitabine (1,000 mg/ m^2 over 30 minutes) or weekly bolus 5-FU. The primary efficacy measure was clinical benefit response (CBR), a composite measurement of pain (analgesic consumption and pain intensity), KPS score, and weight. Clinical benefit required improvement for at least 4 weeks in one or more parameters without a worsening of the other parameters. CBR was observed in 23.8% of the gemcitabine-treated patients, compared with 4.8% of the 5-FU–treated patients ($p = .0022$). The median survival times for gemcitabine and 5-FU patients were 5.65 and 4.41 months, respectively ($p = .0025$). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients [20].

Myelosuppression is the main toxicity associated with gemcitabine. However, postmarketing surveillance has documented rare occurrences of acute lung, liver, and kidney injury. Therefore, gemcitabine-induced acute lung injury should be considered if new symptoms such as cough or dyspnea develop, and consistent monitoring of renal and hepatic function should be included in the follow-up of patients treated with gemcitabine.

Gemcitabine is a renally cleared drug. One phase I evaluation study in patients with hepatic or renal dysfunction showed that patients with baseline hyperbilirubinemia were at risk for liver function deterioration with gemcitabine. However, that study indicated that gemcitabine may be safely given to patients with elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (patients in the trial had baseline AST levels up to 530 U/l). Also observed in that trial was the fact that patients with impaired renal function were at risk for significant gemcitabine toxicity, including skin toxicity [21]. The authors of the paper conceded that the heterogeneity of the studied patients and

CSPC Exhibit 1100
Page 165 of 333

the small sample size (15 patients) did not permit specific dosing recommendations for patients with renal dysfunction. Indeed, a subsequent phase I trial of weekly gemcitabine in 18 patients showed no evidence of greater toxicity in patients with impaired creatinine clearance [22]. The currently available data suggest that gemcitabine may reasonably be offered to chemotherapy-naïve patients with compromised renal function, although initiating treatment at a lower weekly dose (800 mg/m^2) with incremental increases to 1,000 mg/m^2, depending on patient tolerance, is a reasonable consideration.

Striving to Optimize Gemcitabine Efficacy

While the optimal dose and schedule of gemcitabine have not been identified, studies have shown that dosing intervals <1 week or infusion times ≥60 minutes are associated with substantially greater toxicity without clinical benefit. A phase I study evaluating the maximum-tolerated dose (MTD) of gemcitabine on a daily for 5 days schedule showed that patients developed intolerable, dose-related hypotension and severe flu-like symptoms at doses >10 mg/m^2 per day [23]. Phase I studies using a twice-weekly schedule reached MTDs of only 65 mg/m^2 (30-minute infusion) and 150 mg/m^2 (5-minute bolus). Thrombocytopenia and flu-like symptoms, particularly asthenia, were dose-limiting toxicities [24]. Lastly, a phase I study to assess the maximum-tolerated infusion time of gemcitabine identified ≥270 minutes for weekly doses of 300 mg/m^2 as the maximum-tolerated infusion duration [25].

Phase II and III trials evaluating fixed-dose rate (FDR) gemcitabine infusions of 10 mg/m^2 per minute were based on the fact that phosphorylation of gemcitabine by deoxycytidine kinase is the rate-limiting step in the accumulation of active diphosphate and triphosphate gemcitabine metabolites. Early phase I studies demonstrated that a gemcitabine plasma concentration of 20 μmol/l was associated with a maximized rate of gemcitabine triphosphate formation (in mononuclear cells). This plasma concentration and gemcitabine triphosphate accumulation were best achieved using dose rates approximating 10 mg/m^2 per minute [26, 27]. Also, preclinical data with cell lines, including pancreatic carcinoma, suggested a possible dose–response relationship [28, 29]. Therefore, a randomized phase II trial was designed to compare weekly high-dose (2,200 mg/m^2) gemcitabine administered using a standard 30-minute infusion with weekly FDR gemcitabine (10 mg/m^2 per minute; 1,500 mg/m^2 over 150 minutes). Ninety-two patients were enrolled in this study; 91% had metastatic disease. Time to treatment failure, the primary endpoint, was comparable in the two treatment groups. The median survival times were 5.0 months in the standard arm and 8.0 months in the FDR arm (p = .013). For patients with metastases, the median survival times were 4.9 months in the standard arm and 7.3 months in FDR arm (p = .094). The 1-year survival rate was 28.8% versus 9% (p = .014) and the 2-year survival rate was 18.3% versus 2.2% (p = .007), favoring FDR [30]. However, in a confirmatory randomized phase III trial, the same FDR dose/schedule failed to show a statistically significant difference in the median OS time compared with the standard infusion schedule of gemcitabine at 1,000 mg/m^2 over 30 minutes weekly [31].

Phase III Combination Chemotherapy Trials

Because of its unique mechanism of action and favorable nonhematogical toxicity profile, investigators have undertaken intense efforts to develop gemcitabine-based combinations that offer at least additive benefit for pancreatic cancer patients. Table 3 summarizes 13 randomized phase III trials that attempted to improve upon the survival outcomes achieved with gemcitabine alone, typically by adding a second cytotoxic agent [20, 31–42]. With the exception of the gemcitabine plus capecitabine experimental arm reported by Cunningham et al. [35] in abstract form only as of this review, these efforts have failed to identify a gemcitabine-based *chemotherapy* doublet that has produced significantly better median or 1-year survival outcomes.

One caveat in applying these data to clinical practice and research is to not dismiss a particular agent or class of drugs as inactive in pancreatic cancer simply because combining it with gemcitabine failed to produce superior clinical outcomes. The most relevant example of this is the role of oxaliplatin and 5-FU in patients with gemcitabine-refractory metastatic pancreatic cancer, detailed later in this manuscript.

Gemcitabine plus a Platinum Analogue: A Closer Look

Gemcitabine (1,000 mg /m^2 over 100 minutes on day 1) followed by oxaliplatin (100 mg/m^2 as a 2-hour infusion on day 2), the GemOx regimen, was administered every other week to 157 patients (experimental arm) in a phase III trial that accrued 313 patients [37]. GemOx was superior to gemcitabine in terms of response rate (26.8% versus 17.3%, respectively; p = .04), PFS time (5.8 versus 3.7 months, respectively; p = .04), and CBR (38.2% versus 26.9%, respectively; p = .03). The median OS times for GemOx and gemcitabine were 9.0 and 7.1 months, respectively (p = .13). GemOx was well tolerated, albeit with higher grade 3–4 per patient thrombocytopenia (14.0% versus 3.2%), vomiting (8.9% versus 3.2%), and neurosensory symptoms (19.1% versus 0%).

CSPC Exhibit 1006
Page 166 of 333

Table 3. Phase III gemcitabine-based combination chemotherapy trials

	n of patients	ORR	Disease control (CR + PR + SD)	TTP/PFS (mos)	OS (mos)	1-Yr survival
Gemcitabine versus 5-FU [30]	126	23.8% versus 4.8%; $p = .0022$	44.4 % versus 19%	2.33 versus 0.92; $p = .0002$ (TTP)	5.65 versus 4.41; $p = .0025$	18% versus 2%
Gemcitabine versus FDR gemcitabine versus gemcitabine + oxaliplatin [31]	833				4.96 versus 6.01 versus 6.47 p = NS	
Gemcitabine versus gemcitabine + bolus 5-FU [32]	327	5.6% versus 6.9%		2.2 versus 3.4; $p = .022$ (PFS)	5.4 versus 6.7; $p = .09$	18% versus 2%
Gemcitabine versus gemcitabine + 5-FU/ folinic acid [33]	466				6.2 versus 5.85; $p = .68$	22% versus 21%; $p = .68$
Gemcitabine versus gemcitabine + capecitabine [34]	319	7.9% versus 10.1%		4.0 versus 4.8 (TTP)	7.3 versus 8.4; $p = .314$	
Gemcitabine versus gemcitabine + capecitabine [35]	533	7% versus 14%; $p = .008$			6.0 versus 7.4; HR, 0.8; $p = .026$	19% versus 26%
Gemcitabine versus gemcitabine + cisplatin [36]	190	8.2% versus 10.2%	48.5% versus 70.4%; $p < .001$	3.1 versus 5.3; $p = .053$ (PFS)	6.0 versus 7.5; $p = .15$	
Gemcitabine versus gemcitabine + oxaliplatin [37]	313	17.3% versus 26.8%; $p = .04$		3.7 versus 5.8; $p = .04$ (PFS)	7.1 versus 9.0; $p = .13$	27.8% versus 34.7%; $p = .22$
Gemcitabine versus gemcitabine + irinotecan [38]	342	4.4% versus 16.1%; $p < .001$		3.0 versus 3.5; $p = .352$ (TTP)	6.6 versus 6.3; $p = .789$	
Gemcitabine versus gemcitabine + irinotecan [39]	130	10% versus 15%; $p = .387$	28.6% versus 41.7%; $p = .800$	2.9 versus 2.8; $p = .795$ (TTP)	6.5 versus 6.4; $p = .970$	21.8% versus 24.3%; $p = .666$
Gemcitabine versus gemcitabine + exatecan [40]	349			3.8 versus 3.7; $p = .22$ (TTP)	6.2 versus 6.7; $p = .52$	21% versus 23%; $p = .5205$
Gemcitabine versus PEFG [41]	104	8.5% versus 38.5%	34% versus 67.3%	3.3 versus 5.4; $p = .0033$ (PFS)		21.3% versus 38.5%; $p = .1119$; 2-yr, 2.1% versus 11.5%; $p = .033$
Gemcitabine versus gemcitabine + pemetrexed [42]	565	7.1% versus 14.8%; $p = .004$		3.3 versus 3.9; $p = .1109$ (PFS)	6.3 versus 6.2; $p = .8477$	20.1% versus 21.4%

Abbreviations: CR, complete response; FDR, fixed dose rate; HR, hazard ratio; NS, nonsignificant; ORR, objective response rate; OS, overall survival; PEFG, cisplatin, epirubicin, gemcitabine, and 5-FU; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.

Notably, second-line therapy may have muted a possible survival advantage of GemOx in that trial. While second-line chemotherapy was administered to 55% of the gemcitabine patients and to 55.4% of the GemOx patients, the majority of gemcitabine patients (74.0%) received a true crossover regimen containing oxaliplatin or a crossover-like regimen (with a platinum), whereas 31.1% of GemOx patients received a cisplatin-based regimen as second-line therapy [37].

A pooled analysis of individual patient data collected from two randomized trials comparing gemcitabine with either gemcitabine plus oxaliplatin or gemcitabine plus cisplatin suggests that pancreatic cancer patients with an excellent performance status may benefit from more intensive combination therapy [43]. Survival was better in patients treated with the combination (median, 8.3 versus 6.7 months; $p = .031$; hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.02–1.49). Patients with an Eastern Cooperative Oncology Group (ECOG) PS score of 0 (40% of patients) may have had a greater benefit from combination therapy (HR, 1.38; 95% CI, 0.99–1.93; $p = .063$).

Capecitabine

Capecitabine has demonstrated activity similar to that of gemcitabine, as reported in a phase II trial in chemotherapy-

CSPC Exhibit 1100
Page 167 of 333

Table 4. Phase III trials evaluating molecularly targeted therapies

	n of patients	ORR	Disease control (CR + PR + SD)	TTP/PFS (mos)	OS (mos)	1 Yr survival
Gemcitabine + placebo versus gemcitabine + tipifarnib [45]	673	8% versus 6%	60% versus 59%	3.6 versus 3.7; $p = .72$ (PFS)	6.0 versus 6.4; $p = .75$	24% versus 27%
Gemcitabine versus BAY12–9566 [46]	277	5% versus 0.92%	58.9% versus 29.62%	3.5 versus 1.68; $p = .001$ (PFS)	6.59 versus 3.74; $p = .001$	25% versus 10%
Gemcitabine + placebo versus gemcitabine + marimastat [47]	239	16% versus 11%			5.4 versus 5.5; $p = .95$	17% versus 18%
Gemcitabine + placebo versus gemcitabine + erlotinib [48]	569	8.0% versus 8.6%	49% versus 57%; $p = .07$	3.55 versus 3.75; $p = .004$ (PFS)	5.91 versus 6.24; $p = .038$	17% versus 24%; $p = .023$
Gemcitabine versus gemcitabine + bevacizumab [49]	602	11.3% versus 13.1%	47% versus 54%	4.3 versus 4.8	6.0 versus 5.7	
Gemcitabine + cetuximab versus gemcitabine [50]	735	7% versus 7%		3.5 versus 3; $p = .058$ (PFS)	6.5 versus 6; $p = .14$	
G17DT + gemcitabine versus placebo + gemcitabine [51]	383	11% versus 13%;[a] $p = .46$		3.9 versus 3.9; $p = 0.09$ (TTP)	5.9 versus 6.7; $p = .10$	

[a]Confirmed.
Abbreviations: CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.

naïve patients with either locally advanced or metastatic pancreatic cancer. Forty-two patients were treated with oral capecitabine (1,250 mg/m^2) administered twice daily for 14 days followed by a 1-week treatment holiday. While the number of patients with metastatic disease was not detailed in that small study, the 24% CBR and median OS duration of 6 months are comparable with outcomes with gemcitabine [44].

However, two phase III trials attempting to demonstrate at least additive activity between gemcitabine and capecitabine have produced conflicting results. One multicenter trial involving 319 patients, 79% with metastatic disease, randomized patients to either gemcitabine (1,000 mg/m^2 on days 1 and 8) plus capecitabine (650 mg/m^2 twice daily on days 1–14) with cycles repeated every 3 weeks or standard weekly gemcitabine. The median OS time was 8.4 months for the gemcitabine plus capecitabine patients and 7.3 months for the gemcitabine only patients ($p = .314$). A post hoc analysis showed that patients with a KPS score ≥90 attained a statistically significant longer median OS time of 10.1 versus 7.4 months ($p = .014$) [34]. A second randomized phase III trial involving 533 patients, reported in abstract form only as of this writing, evaluated gemcitabine plus capecitabine (GEMCAP) versus gemcitabine alone. GEMCAP was shown to produce a statistically significant longer median OS time, 7.4 months, versus 6.0 months (HR, 0.77; $p = .014$). One possible reason why the experimental arm in that trial attained better outcomes may be the fact that capecitabine was given on a more prolonged schedule: 1,660 mg/ m^2 daily for 21 days repeated every 4 weeks [35].

Targeted Therapies

Gemcitabine plus Erlotinib: Statistical Significance Versus Clinical Relevance

Molecularly targeted agents have a solid preclinical rationale as treatment for advanced pancreatic cancer. However, as summarized in Table 4, with the exception of erlotinib, the completed phase III trials have not confirmed an important clinical benefit [45–51].

Because of its observed overexpression in a high percentage of pancreatic cancers and its association with poor prognosis, the human epidermal growth factor receptor 1 (HER-1/EGFR) signaling cascade has been targeted for anticancer drug development. Erlotinib, an orally available molecule, interrupts HER-1/EGFR signaling by inhibiting the tyrosine kinase integrated in the intracellular receptor domain.

Based on a phase III randomized, placebo-controlled trial, erlotinib in combination with gemcitabine received U.S. Food and Drug Administration approval as treatment for chemotherapy-naïve locally advanced and metastatic pancreatic cancer in 2005 [48]. In total, 569 patients were randomly assigned in a 1:1 ratio to receive standard gemcitabine plus erlotinib (100 or 150 mg/day orally) or gem-

citabine plus placebo in a double-blind, international phase III trial. The primary endpoint of a longer OS time was achieved statistically with an HR of 0.82 (95% CI, 0.69–0.99; $p = .038$) and a median survival duration of 6.24 versus 5.91 months. A 1-year survival advantage was also attained with erlotinib plus gemcitabine (23% versus 17%; $p = .023$). The PFS time was significantly longer with erlotinib plus gemcitabine, with an estimated HR of 0.77 (95% CI, 0.64–0.92; $p = .004$) and with a median PFS interval of 3.75 versus 3.55 months. Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization.

When the statistically positive results of this trial were initially presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2005, two U.S. Cooperative Group trials in patients with advanced pancreatic cancer were approximately halfway through patient accrual. Both studies used standard gemcitabine as the control arm. The Cancer and Leukemia Group B (CALGB) 80303 trial compared gemcitabine plus placebo with gemcitabine plus bevacizumab and the Southwest Oncology Group (SWOG) S0205 trial compared gemcitabine alone with gemcitabine plus cetuximab. The fact that both of these trials continued brisk accrual after the announcement of the results of the National Cancer Institute of Canada Clinical Trials Group PA.3 trial can be interpreted as early evidence of hesitancy on the part of treating clinicians, clinical investigators, and patients to accept gemcitabine plus erlotinib as a reference regimen.

A review of toxicities may further discourage the use of gemcitabine plus erlotinib. Patients receiving erlotinib and gemcitabine experienced higher frequencies of rash (72%), diarrhea (56%), infection (43%), and stomatitis (23%), generally grade 1 or 2. The six protocol-related deaths were all in the erlotinib–gemcitabine arm. Two were attributed to treatment complications (interstitial pneumonitis and sepsis) and four were attributed to a combination of cancer and protocol treatment complications (interstitial pneumonitis, sepsis, cerebrovascular accident, and neutropenic sepsis). Interstitial lung disease was observed in seven patients receiving erlotinib plus gemcitabine and in one patient receiving placebo plus gemcitabine.

An unplanned analysis showed an association between the severity of rash and survival. Grade 0 rash (79 patients) and grade 1 rash (108 patients) were associated with median survival times of 5.29 and 5.75 months, respectively. Grade 2 rash was observed in 103 patients and was associated with a median survival time of 10.51 months. The concept of exploiting a possible erlotinib dose–related rash for therapeutic benefit in patients with metastatic pancreatic cancer has not been validated. Erlotinib as a single agent for the treatment of chemotherapy-resistant pancreatic cancer is just beginning to be evaluated [52].

Finally, a pharmacoeconomic analysis for years of life gained (YLG) using the January 2006 Centers for Medicare and Medicaid Services Drug Payment Table and Physician Fee Schedule does not support the addition of erlotinib to gemcitabine as cost-effective [53]. The addition of erlotinib increases the costs of treating advanced pancreatic cancer by $12,156 wholesale or $16,613 retail per patient. Factoring in 0.4-month longer median survival time compared with gemcitabine alone, the addition of erlotinib costs $364,680 per YLG wholesale and $498,379 per YLG retail. In order to be cost-effective, even at the $100,000/YLG level, 6 months of erlotinib would have to be reduced to 20% of the current retail cost (i.e., to $18.52 per tablet). The minimal additional clinical benefit, side effects, and financial impact have discouraged patients and clinicians when deciding on the inclusion of erlotinib in combination with gemcitabine as palliative treatment for metastatic pancreatic cancer.

Gemcitabine plus Bevacizumab

Vascular endothelial growth factor (VEGF) plays a key role in the growth and metastasis of many tumors, including pancreatic cancer [54]. Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a recombinant humanized anti-VEGF monoclonal antibody with clinical benefit in metastatic colon, breast, and non-small cell lung cancer. Kindler and colleagues reported the results of a phase II trial of bevacizumab plus gemcitabine in 52 patients with metastatic pancreatic cancer. Partial responses were observed in 21% of patients, the median survival time was 8.8 months, and the 1-year survival rate was 29% [55]. These data prompted the CALGB to conduct a double-blind, placebo-controlled randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in 590 advanced pancreatic cancer patients [49]. That trial was designed to detect, with 90% power, a difference in the median OS of 6 versus 8.1 months. Gemcitabine was given in the standard fashion and bevacizumab was given at a dose of 10 mg/kg on days 1 and 15 of each 28-day cycle. The median OS times were 5.7 months and 6.0 months for gemcitabine plus bevacizumab and gemcitabine plus placebo, respectively.

The CALGB 80303 trial included a higher percentage of poorer performance status patients (36%/53% with an ECOG PS score of 0/1) than the phase II gemcitabine–bevacizumab trial (60%/38% with an ECOG PS score of 0/1). While this fact almost certainly contributed to the inferior survival outcomes in the gemcitabine–bevacizumab arm in the CALGB 80303 trial, the arms in that trial were

CSPC Exhibit 1100
Page 169 of 333

well balanced with regard to patient and disease characteristics. Not surprisingly, an ECOG PS score of 0 was associated with a statistically significant longer median survival time of 8 months, compared with 4.8 months for patients with an ECOG PS score of 1. Pharmacogenetics as possible predictors of outcome were collected and will be reported as a separate study.

Further disappointment in the development of bevacizumab as treatment for pancreatic cancer occurred in AVITA [Study of Avastin (bevacizumab) added to a chemotherapeutic regimen in patients with metastatic pancreatic cancer), a Roche-sponsored randomized, double-blind, placebo-controlled trial comparing gemcitabine plus erlotinib with or without bevacizumab, which did not meet the primary endpoint for survival. Reports of a further analysis to define benefit regarding other endpoints and patient subsets is awaited.

Another antiangiogenic therapy that has not been shown to have activity in metastatic pancreatic cancer, when combined with gemcitabine at least, is sorafenib, an inhibitor of Raf-1 kinase and VEGF receptor 2. Among 17 evaluable patients in a phase II trial of standard-schedule gemcitabine plus sorafenib (400 mg orally twice daily), no responses were seen, the median survival time was 4 months, and the 6-month survival rate was 23% [56].

Antiangiogenesis will continue to be evaluated in pancreatic cancer in a randomized trial comparing gemcitabine with VEGF Trap (aflibercept; Regeneron Pharmaceuticals, Inc., Rensselaer, NY) with gemcitabine. Aflibercept is a fusion protein made of human VEGF receptor extracellular domains fused to the Fc portion of human IgG_1, designed to bind and inactivate circulating VEGF. Also, another oral tyrosine kinase inhibitor of the VEGF receptor as well as the platelet-derived growth factor receptor, sunitinib, is being evaluated as a second-line treatment option by the CALGB in a phase II study (CALGB 80603).

Gemcitabine With or Without Cetuximab—SWOG S0205

The SWOG and Clinical Trial Support Unit enrolled 766 patients (735 were eligible) with a median age of 64 years (range, 30–91) into this phase III trial between January 2004 and April 2006 [50]. Eligibility included locally advanced unresectable (21.5%) or metastatic pancreatic cancer and a PS score ≥2 (13% of patients had a PS score = 2), no prior EGFR therapy, and no prior palliative chemotherapy. The study was designed to detect a median improvement in survival to 8 months (HR, 1.33) with 90% power for the experimental arm. Patients were randomized to standard weekly gemcitabine alone or with cetuximab given as a loading dose of 400 mg/m^2 on week 1 and then 250 mg/m^2 weekly. The median survival times were 6 months in the control arm and 6.5 months in the cetuximab arm, for an overall HR of 1.09 (95% CI, 0.93–1.27; $p = .14$). The corresponding PFS times were 3 months and 3.5 months, for the control and cetuximab arms, respectively (HR, 1.13; 95% CI, 0.97–1.3; $p = .058$). The confirmed response rate was 7% in each arm.

Immunotherapy: Gemcitabine plus Gastrin Vaccine

Immunotherapy, defined in the context of clinical oncology, involves the stimulation of a patient's immune system to achieve antitumor activity. Nonspecific strategies include the use of exogenous immunostimulants or cytokines, the transfer of nonspecific immune effector cells, and the inhibition of immunosuppressive pathways. Alternatively, specific immunotherapeutic strategies strive to enhance the response to defined tumor antigens or induce antitumor antibody activity, often via vaccination.

Gastrin was shown to demonstrate the necessary criteria for a potential immunotherapy target against pancreatic cancer. Gastrin receptors and precursor gastrin forms were shown to be broadly expressed, demonstrated in up to 90% of pancreatic cancer resection tissues. Also, gastrin demonstrated a possible pathogenic role, because in vivo gastrin had a proliferative effect on pancreatic cancer cells, and antigastrin antibodies raised against G17DT, an immunoconjugate of gastrin-17, inhibited the proliferation of pancreatic cancer cells [57]. Early human studies of G17DT in patients with other forms of cancer demonstrated that G17DT was safe and well tolerated [58]. In a phase II study of G17DT in advanced pancreatic cancer, 67% of 30 patients produced an antibody response [59]. The 250-μg dose resulted in a significantly greater antibody response rate of 82%, compared with 46% for the 100-μg group ($p = .018$). The most significant side effects, seen in three patients, were local abscess and/or fever. The median survival time for the whole group measured from first immunization was 187 days; the median survival times were 217 days for the antibody responders and 121 days for the antibody nonresponders ($p = .0023$).

However, a randomized, double-blind study of gemcitabine plus placebo versus gemcitabine plus G17DT in 383 chemotherapy-naïve advanced and metastatic pancreatic cancer patients did not demonstrate a survival advantage [51]. The median OS time for the group receiving G17 DT was 178 days; the median OS time for patients receiving placebo was 201 days ($p = .1$). The time to disease progression (TTP) was the same in both arms, 118 days ($p = .09$). Interestingly, titer responses in women were substantially weaker. Also, higher anti-G17 titer levels were associated

with longer survival both overall and in gender-specific analyses. Similar antibody–survival correlations have been seen in other studies of G17DT.

Future strategies to validate the efficacy of immunotherapy in the treatment of pancreatic cancer may include better selection of patients able to mount an antibody response or development of superior immunogens. One candidate immunogen is telomerase, expressed in 85%–90% of pancreatic cancers. Immunogenic telomerase peptides have been characterized and a phase I–I/I study investigating the safety, tolerability, and immunogenicity of a telomerase peptide vaccination, GV1001, in combination with GM-CSF enrolled 48 patients with unresectable pancreatic cancer [60]. GV1001 was well tolerated and immune responses were observed in 24 of 38 evaluable patients. The median and 1-year survival outcomes among 27 evaluable patients were 8.6 months and 25%, respectively. The TeloVac trial in the United Kingdom is a phase III evaluation comparing GV1001 given either concurrently or sequentially with gemcitabine and capecitabine with the same chemotherapy given alone. This three-arm trial is expected to accrue 1,100 patients through 2012. A second, 520-patient phase III multinational trial including U.S. sites will evaluate GV1001 plus GM-CSF followed by gemcitabine upon disease progression against gemcitabine monotherapy.

Investigators at Johns Hopkins have pioneered the development of lethally irradiated allogeneic pancreatic tumor cells transfected with the *GM-CSF* gene as immunotherapy for pancreatic cancer. This vaccine was first developed in their single-institution, phase II study of 60 patients with resected pancreatic adenocarcinoma. The first vaccine was administered 8–10 weeks following resection and patients were subsequently treated with 5-FU chemoradiation. Patients who remained disease free received up to four additional vaccines. With a median follow-up duration of 36 months, the median survival time is approximately 26 months, which compares favorably with recent phase III outcomes of adjuvant gemcitabine [61].

Johns Hopkins investigators are now developing this vaccine in combination with immune-modulating doses of cyclophosphamide and additional cetuximab in patients with advanced disease. Currently 47 of the planned 60 patients have been enrolled. The preclinical rationale supporting this combination is that monoclonal antibody therapy of epidermal growth factor (EGF) proteins will lead to better presentation of EGF proteins to the immune system (Laheru D, personal communication).

Planned development of immunotherapy at Johns Hopkins includes a trial of the allogeneic vaccine plus anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody. The hope is that anti–CTLA-4 antibody suppression of host immune suppression factors will optimize the efficacy of allogeneic pancreatic tumor cell vaccine therapy. Another trial that Johns Hopkins investigators hope to activate in 2008 involves the development of attenuated *Listeria* carrying mesothelin peptide. In two adjuvant and one palliative trials, the Johns Hopkins group has observed that responding patients were largely able to recognize mesothelin as opposed to nonresponders. *Listeria* is a very efficient bacterium in generating an immune response and is therefore hypothesized to be a very useful vector (Laheru D, personal communication).

Second-Line Therapy

A significant advance in the care of metastatic pancreatic cancer patients is the recently reported Charite Onkologie (CONKO) 003 trial that has identified a much needed option for patients with disease progression during or shortly after first-line palliative therapy with standard gemcitabine [62]. Patients with advanced pancreatic cancer and confirmed disease progression with first-line gemcitabine were randomized to BSC with or without oxaliplatin (85 mg/m^2 on days 8 and 22) plus 5-FU (2 g/m^2 over 24 hours) with folinic acid (leucovorin; 200 mg/m^2 over 30 minutes on days 1–8 and 15–22), repeated every 42 days (the OFF regimen). After 46 of 165 planned patients were enrolled, the BSC alone arm was closed because an early efficacy analysis showed a significant survival benefit with OFF. The two arms of this trial were balanced with regard to age, tumor stage, gender, PS score, and median duration of first-line therapy gemcitabine (19.9 versus 20.7 weeks). The median survival time measured from the initiation of second-line therapy was 21 weeks versus 10 weeks (p = .0077), favoring treatment with OFF. The OS times measured from the initiation of gemcitabine were 39.6 weeks for OFF and 34.4 weeks for BSC (p = .0312). Given the fact that second-line OFF was shown to be feasible and effective, CONKO 003 was modified into a comparison of OFF with FF (same 5-FU/leucovorin program as in OFF). As of the ASCO 2007 Annual Meeting update, 76 and 89 patients were randomized to OFF and FF, respectively. The median TTP (12.3 versus 8 weeks) and OS time (45 versus 35.6 weeks, measured from the initiation of first-line gemcitabine) both favored the OFF regimen [63].

Multidrug Regimens

Given the frustrating outcomes from phase III trials of gemcitabine-based chemotherapy doublets, investigators began investigating three- and four-drug regimens. Only one of these regimens, PEFG, has been evaluated in a randomized phase III trial [41]. PEFG consists of cisplatin (40 mg/ m^2), epirubicin (40 mg/ m^2 i.v. on day 1), gemcitabine (600

CSPC Exhibit 1100
Page 171 of 333

mg/m^2 given over 1 hour on days 1 and 8), and 5-FU (200 mg/m^2) daily for the duration of chemotherapy. Cycles are repeated every 28 days. One hundred four patients were randomized to PEFG or standard gemcitabine. The treatment groups were balanced in terms of age, gender, PS score, and proportion of patients with metastatic disease (57% versus 56%). This study met its primary endpoint by demonstrating a greater 4-month PFS rate in PEFG-treated patients (60% versus 28%; $p = .001$). OS outcomes also favored PEFG, with an HR for death of 0.65 ($p = .047$). Grade 3–4 neutropenia and thrombocytopenia favored the gemcitabine group; one patient treated with PEFG required hospitalization for febrile neutropenia. The 1- and 2-year survival rates for the PEFG group were 38.5% and 11.5%, respectively. Salvage therapy was received by 49% of PEFG-treated patients and by 60% of gemcitabine-treated patients (with 70% receiving true crossover therapy with PEFG).

Additional multiagent chemotherapy programs are summarized in Table 5 [41, 64–68]. Notable among these are two nongemcitabine regimens. The single-arm, phase II experience of FOLFIRINOX (5-FU/leucovorin, irinotecan, and oxaliplatin) included 35 patients with chemotherapy-naïve metastatic disease. The confirmed response rate was 26%, TTP was 8.2 months, and median OS time was 9.5 months [66]. These encouraging results prompted a randomized phase II–III study, the so called ACCORD (Actions Concertées sur les cancers COlo-Rectaux et Digestifs) 11 trial, which compared FOLFIRINOX with standard gemcitabine as initial therapy for metastatic pancreatic cancer. Forty-three patients treated with FOLFIRINOX were evaluable for toxicity and efficacy outcomes. The febrile neutropenia rate was 2%, grade 3–4 vomiting occurred in 23% of patients, and grade 3–4 neuropathy occurred in 23% of patients. The response rate and disease control rate were 31.8% and 59%, respectively [69]. This trial will transition into a phase III study. The ECOG characterized the toxicity and efficacy of weekly irinotecan plus docetaxel with or without cetuximab in a randomized phase II trial. That study was limited to patients with chemotherapy-naïve metastatic pancreatic cancer. Grade 3–4 toxicities were significant in both treatment arms: febrile neutropenia, 6% and 9%; diarrhea, 30% and 44%; both worse in the cetuximab arm. The cetuximab arm had a 4.4% death rate, compared with a 2.2% death rate in the noncetuximab arm. The median survival time was shorter in the cetuximab-containing arm, 5.3 months versus 6.5 months [67]. While this small dataset did produce survival outcomes similar to those seen with gemcitabine, the current iteration of this protocol appears prohibitively toxic. Lastly, capecitabine (750 mg/ m^2 orally, twice daily on days 1–14), gemcitabine (750 mg/ m^2 over 75 minutes), and docetaxel (30 mg/ m^2 on days 4 and 11) repeated every 21 days has demonstrated an encouraging median OS time of 11.2 months and a 20% survival rate at 2 years [64]. However, these results come from a small retrospective analysis of 35 patients.

Chemotherapy plus Low Molecular Weight Heparin: A Prospective, Randomized Trial of Simultaneous Pancreatic Cancer Treatment with Enoxaparin and Chemotherapy

Approximately 20% of patients diagnosed with pancreatic adenocarcinoma develop venous thromboembolism, contributing to the poor prognosis of this disease. A small phase II trial suggested longer survival with the addition of low molecular weight heparin (LMWH) to chemotherapy [70]. In that study, 69 patients received standard gemcitabine with or without LMWH (nadroparine calcium, 2,850 IU/day until disease progression). Ten of 35 patients in the LMWH group and 10 of 34 patients in the chemotherapy-alone group had primary inoperable locally advanced disease and the rest of the patients had metastatic disease. The response rate (58.8% with an 11.7% complete response [CR] rate versus 12% with no CRs), TTP (7.3 months versus 4.0 months; $p = .0001$), and median OS time (13.0 versus 5.5 months; $p = .0001$) all favored the LMWH arm.

These encouraging outcomes prompted European investigators to evaluate primary venous thromboembolic prophylaxis with enoxaparin in a phase III trial, PROSPECT (Prospective, Randomized trial Of Simultaneous Pancreatic cancer treatment with Enoxaparin and Chemo-Therapy)-CONKO 004 [71]. In that trial, patients receive gemcitabine (1 g/m^2 over 30 minutes), cisplatin (30 mg/m^2 over 90 minutes), 5-FU (750 mg/m^2 over 24 hours), and leucovorin (200 mg/m^2 on days 1 and 8) every 3 weeks with or without enoxaparin (1 mg/kg daily s.c.). Patients with a KPS score <80% and an elevated creatinine plasma level (>1.3 mg/dl) will be assigned to treatment with gemcitabine alone (1 g/m^2 over 30 minutes on days 1, 8, and 15) every 28 days with or without enoxaparin (1 mg/kg per day s.c.). After 12 weeks of initial chemotherapy, all patients who have not progressed will continue treatment with single-agent gemcitabine weekly with or without enoxaparin (40 mg daily). Accrual to this trial is ongoing.

Future Drug Development

Unfortunately, broad, empiric clinical testing of novel gemcitabine-based combinations has been disappointing. One strategy to improve the productivity of the phase III mechanism is to increase the rigor by which phase II trials are designed and interpreted. Future phase II results should be interpretable with specific regard to survival outcomes for

Table 5. Multiagent and nongemcitabine chemotherapy for metastatic pancreatic cancer

	n of patients	ORR	Disease control (CR + PR + SD)	TTP/PFS (mos)	OS (mos)	1-Yr survival
Gemcitabine versus PEFG [41]	104	8.5% versus 38.5%	34% versus 67.3%	3.3 versus 5.4; $p = .0033$	HR for death, 0.65 for PEGF versus gemcitabine; $p = 0.047$	21.3% versus 38.5%; $p = .1119$; 2-yr, 11.5% versus 2.1%; $p = .033$
GTX[a] [64]	35	29%	60%		11.2	43%; 2-yr, 20%
5-FU versus 5-FU + cisplatin [65]	207	0% versus 10%		1.96 versus 2.43	3.6 versus 4	8.7% versus 17.3%; $p = 0.07$
FOLFIRINOX [66]	47 (35 with metastatic disease)	26%	65%	8.2	9.5, metastatic patients; 15.7, locally advanced patients	43%
Irinotecan + docetaxel versus irinotecan + docetaxel + cetuximab [67]	43 versus 43	2.3% versus 7%	41.8% versus 44.2%	2.8 versus 4.5	6.5 versus 5.3	
G-FLIP [68]	33	27%	68%	6.1	8.1	33%; 18-mo, 21%

[a]Retrospective analysis.
5-FU: bolus 5-FU, 500 mg/m^2 per day via rapid infusion, <1 hour, for five consecutive days with courses repeated every 4 weeks.
5-FU and cisplatin: 5-FU, 1,000 mg/m^2 per 24 hours for five consecutive days; cisplatin on day 1 or 2 over 2–3 hours, 100 mg/m^2; cycles repeated every 4 weeks.
GTX: capecitabine, 750 mg/m^2 orally twice daily on days 1–14; gemcitabine, 750 mg/m^2 over 75 minutes; docetaxel, 30 mg/m^2 on days 4 and 11; cycles repeated every 21 days.
PEFG: cisplatin, 40 mg/m^2; epirubicin, 40 mg/m^2, both given on day 1; gemcitabine, 600 mg/m^2 given i.v. over 1 hour on days 1 and 8; 5-FU, 200 mg/m^2 per day given by continuous infusion on days 1–28 of a 4-week cycle.
FOLFIRINOX: sequential oxaliplatin (85 mg/m^2), irinotecan (180 mg/m^2), and leucovorin (400 mg/m^2) followed by bolus 5-FU (400 mg/m^2) followed by 5-FU at a dose of 2,400 mg/m^2 as a 46-hour continuous infusion; cycles repeated every 2 weeks.
Irinotecan plus docetaxel: docetaxel (35 mg/m^2) over 1 hour followed by irinotecan (50 mg/m^2) over 30 minutes weekly for four cycles, repeated every 6 weeks; patients assigned to arm B received the same docetaxel plus irinotecan program plus cetuximab (loading dose, 400 mg/m^2 on week 1 followed by weekly 250 mg/m^2 doses).
G-FLIP: biweekly (once every 14 days) cycles of sequential gemcitabine (500 mg/m^2), irinotecan (120 mg/m^2) (phase II dose), bolus 5-FU (400 mg/m^2), and leucovorin (300 mg) on day 1 followed by a 24-hour 5-FU infusion (1,500 mg/m^2) followed by cisplatin (35 mg/m^2) on day 2.
Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to disease progression.

patients with measurable metastatic disease, because inclusion of patients with locally advanced, nonmetastatic disease proportionately improves survival outcomes by virtue of disease biology rather than treatment effect. Also, increasingly, the use of second-line palliative treatment data should be captured and used to interpret phase II results, especially if these data will be used to select regimens for phase III testing.

Identification of new pathogenic targets hopefully will have a clinical impact as well. One such candidate target, S100P, has recently been found to be overexpressed in pancreatic, breast, and lung cancer. Overexpressed S100P may increase tumor growth and metastasis and decrease patient survival. Pancreatic cancer cells with high endogenous levels of S100P have shown resistance to cytotoxic drugs in vitro and gemcitabine in vivo. Most recent studies have shown that the antiallergy drug cromolyn inhibits the interaction between S100P and the receptor for advanced glycation end products (RAGE). Cromolyn binds S100P, prevents activation of RAGE, inhibits tumor growth, and increases the effectiveness of gemcitabine in experimental models. However, further studies are necessary to determine the anticancer activity of cromolyn and cromolyn analogues [72, 73].

Beyond the broad testing of novel agents intended to have efficacy against most patients' pancreatic cancer, advances in the treatment of pancreatic cancer may be achieved by identifying strategies to match an individual's cancer with the most effective available drug. For example, preclinical testing has demonstrated that pancreatic cancers that develop in patients with a *BRCA-2* germline mutation

CSPC Exhibit 1100
Page 173 of 333

are close to 1,000 times more sensitive to mitomycin-C than cancers from patients without this mutation. Approximately 7% of pancreatic cancers in the U.S. are associated with *BRCA-2* mutations. At Johns Hopkins, pancreatic cancer patients with *BRCA-2* mutations are being treated with mitomycin-C in a phase II trial with the 6-month survival rate as the primary endpoint. Another approach to effective drug selection would be prospective development and validation of in vitro chemotherapy sensitivity and/or resistance assays, of which details have been expertly discussed by others [74, 75]. A potential predictor of gemcitabine efficacy is human equilibrative nucleoside transporter 1 (hENT)-1, a gemcitabine transporter in human pancreatic adenocarcinoma cells. Studies have shown that overexpression of hENT-1 correlates with a longer OS time in patients who have been treated with gemcitabine [76].

Conclusions

With nearly 20 randomized phase III trials that have failed to produce a relevant improvement in survival outcomes since 1996, metastatic pancreatic cancer has confirmed its status as one of the most frustrating malignancies to investigate and treat. Given the modest palliative benefits associated with either gemcitabine or gemcitabine plus erlotinib and second-line 5-FU plus oxaliplatin therapy, oncologists should emphasize supportive care strategies in helping patients cope with this disease. For the majority of patients with metastatic disease, the current data support opting for sequential gemcitabine followed by 5-FU plus oxaliplatin as second-line treatment. First-line doublet therapy, fox example, gemcitabine plus a platinum or GEMCAP, or entry into protocols evaluating three- or four-drug chemotherapy combinations may be appropriately reserved for select patients with both tumor volume–associated symptomatology and an ECOG/World Health Organization PS score of 0 or KPS score ≥90. Hopefully ongoing or planned trials will identify advancements relevant to our practice and research efforts. Ideally, however, technologies will emerge that will allow physicians to detect pancreatic cancer at a much earlier, more treatable stage.

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CSPC Exhibit 1100
Page 175 of 333

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ERRATUM

Metastatic Pancreatic Cancer 2008: Is the Glass Less Empty?

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The Oncologist 2008;13:562–576; doi: 10.1634/theoncologist.2007-0181

The continuing medical education (CME) statement that appeared with this article in the May issue was incorrect. This article has never been available for CME credit. Therefore, the CME credit statement and learning objectives have been removed.

Oxaliplatin, 5-Fluorouracil, and Leucovorin as Second-Line Treatment for Advanced Pancreatic Cancer

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Objective: A phase II study was performed to assess the activity of oxaliplatin plus 5-fluorouracil (5-FU) modulated by leucovorin, as second-line treatment in locally advanced or metastatic pancreas adenocarcinoma pretreated with gemcitabine-containing schedule.

Methods: Patients received weekly intravenous infusions of oxaliplatin 40 mg/m^2, 5-FU 500 mg/m^2, and leucovorin 250 mg/m^2 (3 weeks on, 1 week off).

Results: Twenty-three patients affected with metastatic (16) or locally advanced (7) pancreas adenocarcinoma were involved in this study. A total of 148 weeks of chemotherapy was delivered (median 2 courses each patient). Among 17 assessable patients, no objective response was registered and 4 patients had stable disease, whereas 13 had tumor progression. Median duration of stable disease was 14 weeks. Median time to progression of disease (TTP) was 11.6 weeks [95% confidence interval (CI), 7.6–5.6]. Kaplan-Meier estimated median overall survival (OS) was 17.1 week (95% CI, 4.0–30.1) and 3 months survival rate was 69.6%. Seven patients experienced grade 3 to 4 toxicity. The regimen was associated with 36% clinical benefit.

Conclusions: The median TTP and median OS in this population with poor prognosis suggests some activity, however, only further investigations will be able to establish the clinical value of this combination.

Key Words: pancreatic cancer, oxaliplatin, 5-fluorouracil

(*Am J Clin Oncol* 2009;32: 44–48)

Pancreatic adenocarcinoma has a very poor prognosis, with a 5-year survival of 4%. Most patients have locally advanced or metastatic tumor at the time of diagnosis. Gemcitabine chemotherapy is the standard therapy to control disease-related symptoms and prolong survival in patients with metastatic disease. In phase III clinical trials, gemcitabine monotherapy resulted in 5.4 to 7.2 months median survival.[1–6] Several studies have attempted to develop more efficacious chemotherapy regimens through the combination of gemcitabine with a second drug. So far all single trials but one[5] have failed to meet the primary end point of significantly prolonged survival in the combination arm. Nevertheless, a recent meta-analysis[7] on 53 randomized studies involving 9970 patients, showed significant survival benefit for chemotherapy over best supportive care, and for gemcitabine combinations over gemcitabine alone.

Before approval of gemcitabine, 5-FU was the most widely used agent in the treatment of pancreatic cancer. Activity for bolus and continuous infusion (0%–20%) of 5-FU have been reported. Two phase III studies suggested an improvement in overall survival without impairing quality of life with 5-FU-based regimens.[8–9] Single-agent 5-FU therapy in randomized studies showed a response rate of 0% to 7% and median survival of less than 5 months.[1] However, a gemcitabine and 5-FU combination in a randomized trial[2] failed to improve overall survival compared with gemcitabine alone (6.7 vs. 5.4 months), showing only a significant advantage in term of progression free survival (3.4 vs. 2.2 months).

5-FU continuous infusion monotherapy has shown small but consistent activity, with a 8.5% objective response rate (ORR) in the control arm of a multicenter randomized trial.[10] Improvement in response rate, median TTP, but not in OS has been reported in a controlled trial with a combination of cisplatin and infusional 5-FU compared with bolus 5-FU,[11] confirming the lack of activity of 5-FU as single agent against pancreatic cancer, but demonstrating the potential synergistic activity with other anticancer drugs.

Oxaliplatin has activity in several gastrointestinal tumors,[12–14] but like 5-FU failed to show effectiveness as a single agent against pancreatic cancer.[15] The combination of oxaliplatin and infusional 5-FU in untreated patients with advanced pancreas adenocarcinoma was associated with a 10% response rate, 9 months median overall survival, and an encouraging safety profile in a randomized phase II study,[15] suggesting better activity than infusional 5-FU alone. Louvet et al[4] reported activity of the combination of gemcitabine and oxaliplatin (GEMOX) as first-line therapy against advanced and metastatic pancreatic cancer.[16,17] Overall GEMOX was well tolerated and has been shown to be superior to gemcitabine alone in terms of clinical benefit, response rate, progression free survival, and a better trend in survival of almost 2 months. It was postulated that the lack of a statistically significant advantage in survival compared with gemcitabine could be the result of a confounding effect of second-line therapy, administered to 55% of patients.

An increasing number of patients maintain good clinical conditions after optimized first-line chemotherapy and supportive care, and it is unclear if they could take advantage from second-line chemotherapy. Preclinical data[18] suggested that the 5-FU plus oxaliplatin combination is more cytotoxic when 5-FU is given as a short exposure. This suggests the potential interest of such a schedule in the clinical setting. We conducted a single-center study with the primary aim of evaluating the efficacy and safety of a combination of weekly oxaliplatin, bolus 5-FU, and leucovorin as second-line treatment in patients with progression of pancreatic cancer after gemcitabine-based therapy.

PATIENTS AND METHODS

Patient Selection

Patients with histologically proven locally advanced or metastatic pancreatic adenocarcinoma, with at least 1 measurable lesion according to modified response evaluation criteria in solid tumors (RECIST)[19] [longest diameter at least 20 mm using the conventional technique or at least 10 mm with spiral computed tomography (CT) scan] and tumor progression during or after first-line gemcitabine

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ISSN: 0277-3732/09/3201-0044

DOI: 10.1097/COC.0b013e31817be5a9

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CSPC Exhibit 1100

Page 178 of 333

therapy were eligible for this study. Additional requirements included Eastern Cooperative Oncology Group (ECOG) performance status equal or less than 2; expected survival longer than 12 weeks; biliary obstruction controlled before the start of the study; no other serious concomitant illness; no prior malignancy; no brain metastases; no prior treatment with either of the study drugs. Patients had adequate hematologic (leukocytes $\geq$3000/mm^3; neutrophil count $\geq$1500 mm^3; platelet count $\geq$100,000 mm^3), hepatic (bilirubin $\leq$1.5 mg/dL), and renal (creatinine $\leq$1.5 mg/dL) function. All participating patients were required to give written informed consent before the start of the whole procedure, according to the Helsinki Declaration.

Treatment Plan

Treatment included a 2-hour intravenous infusion of oxaliplatin 40 mg/m^2, followed by bolus leucovorin 250 mg/m^2, and bolus 5-FU 500 mg/m^2. Each course consisted of weekly administrations for 3 consecutive weeks followed by a week of rest. Therapy continued until disease progression, unacceptable toxicity, patient's refusal, or a maximum of 6 courses. All patients received intravenous dexamethasone 8 mg, metoclopramide 10 mg as antiemetic prophylaxis. Therapy was withheld in case of a platelet count of less than 100,000/mm^3 or a neutrophil count of less than 1500/mm^3 or for bilirubin greater than 1.5 times the upper reference level (URL) or transaminases greater than 3 times the URL. During the entire study period, patients received full supportive care to control pain or other symptoms, with careful recording of the treatment.

Evaluation and Statistical Methods

Complete blood counts, serum biochemistry, physical examination, and assessment of adverse events were examined before every infusion. Adverse events were graded according to National Cancer Institute criteria version 2.0. CT scans were repeated every 12 weeks or earlier, if clinically indicated. Measurable disease response was assessed by RECIST criteria. According to RECIST recommendations,[19] patients occurring in early death for malignant disease, toxicity or other cause, or patients not assessable were considered as subject to disease progression (as failing to respond to treatment). Clinical benefit was evaluated according to a definition modified by Andersen[20]: patients with less pain (at least 50% improvement from baseline on visual analog scale) and/or at least 50% decreased analgesic consumption from baseline and/or improved Zubrod performance status compared with baseline, lasting at least 4 consecutive weeks, without degradation of any of these parameters, were considered to have a clinical benefit.

The TTP was calculated from the first treatment infusion to the first objective evidence of disease progression assessed by CT scan measurements or early death or date of clinical deterioration and patient not assessable for response. The OS was measured from initial treatment until death. Performance status, pain and disease-related symptoms, analgesic consumption, and weight were recorded at study entry and reassessed weekly. All patients with at least 1 chemotherapy administration were assessed for toxicity. Efficacy assessments were performed on patients who received at least 1 course of therapy. TTP and OS since the start of treatment were estimated on an intent-to-treat basis and analyzed according to the Kaplan-Meier method.

The required number of patients for this phase II study was determined according to a Simon phase II optimal design[21] for a goal of 25% true response rate, with an α and β error probability of 0.05 and 0.20, respectively, an accrual of 17 patients assessable for response was planned. If 2 or more responses were observed, the conclusion would be that the regimen is promising.

TABLE 1. Patients Characteristics

Characteristics	No. Patients (23)
Age	
Median	61
Range	43–71
Zubrod performance status	
0	6
1	11
2	6
Disease at presentation	
Metastatic	16
Locally advanced	7
Site of Metastases	
Liver	12
Lung	1
Abdominal lymphnodes	7
Extra-abdominal lymphnodes	1
Peritoneum	8
Other	2
Previous Chemotherapy	
Gemcitabine	13
Gemcitabine, 5-fluorouracile, cisplatin	5
Gemcitabine, 5-fluorouracile	4
Gemcitabine, oxaliplatin	1
Previous surgery	
None	8
Palliative	2
Radical resection	13
Patients with pain at presentation	11 (48%)

RESULTS

Patients Characteristics

Between February 2003 and May 2006, 23 patients were enrolled in this study. The demographic and clinical characteristics of the patients are outlined in Table 1. Fifteen of the patients were men and 8 were women, with a median age of 61 years (range 43–71). Seventy percent of patients had metastatic disease. Sixty-five percent of patients had previously undergone surgery. One patient underwent prior radiation therapy. All the patients received prior chemotherapy with a gemcitabine-based regimen stopped a median of 4.9 weeks before. The majority of patients had an ECOG performance status of 0 or 1 (74%).

Toxicity

A total of 148 weekly doses of chemotherapy was administered (median 6 weeks, range 1–17). Six patients started the therapy but did not complete the first course as a result of accelerated clinical worsening and performance status deterioration and did not have their disease reassessed. The reasons for discontinuation of treatment were completion of 6 courses in 2 cases, patient's refusal in 2 cases, and disease progression in the others. All patients were included in the safety analysis.

Overall, side effects were moderate and manageable (Table 2). Neither neutropenia exceeding grade 2, nor febrile neutropenia were observed. Grade 3 anemia and thrombocytopenia were recorded in 1 patient each. Most nonhematological side effects were less than grade 3. One case of vomiting was the only grade 4 adverse event reported. Grade 3 adverse events included diarrhea (2 pa-

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CSPC Exhibit 1100
Page 179 of 333

TABLE 2. Toxicity Data (N = 23)

Characteristics	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Neutropenia	2 (9)	1 (4)	—	—
Anemia	4 (17)	1 (4)	1 (4)	—
Thrombocytopenia	4 (17)	—	1 (4)	—
Nausea	7 (30)	6 (26)	1 (4)	
Vomiting	4 (17)	1 (4)	—	1 (4)
Diarrhea	4 (17)	—	2 (9)	—
Constipation	3 (13)	1 (4)	—	—
Stomatitis	4 (17)	—	—	—
Transaminases	1 (4)	—	—	—
Fatigue	2 (9)	7 (30)	1 (4)	—
Neuropathy sensory	5 (22)	—	—	—
Rash	—	1 (4)	—	—
Fever	3 (13)	—	—	—

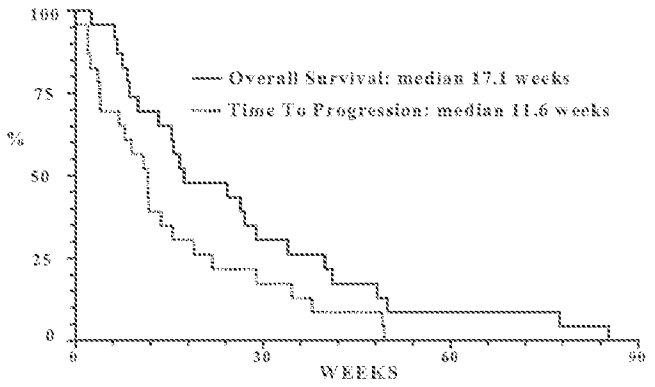


FIGURE 1. Intent-to-treat Kaplan-Meier curves of overall survival and time to progression since start of study treatment.

tients), nausea (1 patient), and fatigue (1 patient). Neither deep-vein thrombosis nor toxic death were observed in this study.

Efficacy

No objective response was registered among the first assessable 17 patients. Four patients (23.5%) had stable disease, with a median duration of 14 weeks (range 8–20). Median TTP (Fig. 1) of the whole population was 11.6 weeks (95% CI, 7.6–15.6). Median survival time of second-line therapy (Fig. 1) was 17.1 week (95% CI, 4.0–30.1), and the 3 months survival rate was 69.6% (95% CI, 50.8–88.4). Median survival from start of first line therapy was 44.1 week (95% CI, 38.6–49.7). Four out of 11 patients with pain at presentation (36%; 95% CI, 11–69) had clinical benefit.

DISCUSSION

Advanced pancreatic cancer remains a rapidly lethal cancer, with a median survival of 6 months with currently approved therapies.[1] Combination of gemcitabine with other chemotherapeutic agents have failed to show improvement in survival in single randomized clinical trials, but a meta-analysis found a survival benefit against gemcitabine alone.[7] It is unclear whether a second-line treatment could be useful in a disease with such a short life expectancy.

This phase II study was initiated to assess efficacy and safety of a weekly combination of oxaliplatin plus bolus 5-fluorouracil modulated by leucovorin as second-line treatment in locally advanced or metastatic pancreas adenocarcinoma. According to the design of the study, at least 2 objective responses should be observed in the 17 assessable patients, to qualify this regimen for further evaluation. This criterion was not met in this study and only 23.5% stable disease was observed.

Even when considering other outcomes registered, such as median TTP of 11.6 weeks or OS of 17.1 week, and the moderate and easily manageable toxicity, the results of our study hardly support the hypothesis that this treatment confers a clinically significant advantage in patients with pancreas adenocarcinoma pretreated with gemcitabine. Nevertheless, despite disappointing results in terms of response rate, overall survival data obtained in our study population match those reported in other studies suggesting a conceivable advantage from second-line therapy. For patients with such short survival expectancy, all efforts of amelioration are justified, if not detrimental to the quality of life.

A number of studies explored the role of oxaliplatin-based salvage therapy in gemcitabine pretreated pancreatic cancer patients.

A phase III trial after failure of first-line gemcitabine, compared BSC plus with biweekly oxaliplatin combined with weekly 5-FU as 24 hours infusion plus leucovorin, versus BSC alone.[22] After the first 46 patients out of 165 planned, the BSC arm had to be closed because BSC alone was no longer accepted by participating centers, with a possible survival benefit for second-line chemotherapy: 21 weeks (95% CI; 18.7; 23.3) versus 10 weeks (95% CI, 7.7; 12.3).

A second-line weekly combination of oxaliplatin, leucovorin, and bolus 5-fluorouracil in a phase II study on 30 patients mainly (75%) with locally advanced pancreas cancer obtained 23.3% partial responses, 30.0% stable disease with a 25 weeks median overall survival, but 27% neutropenic fever.[23] A phase II study on 18 patients treated with second line oxaliplatin combined with 5-FU continuous infusion every 3 weeks gave no response, 17% disease stabilization, and a median survival of 1.9 months.[24] A multicenter retrospective survey on 42 patients treated with FOLFOX IV as salvage therapy registered 14% partial responses, 4 months median TTP, and 6.7 months median OS.[25] Another 2 studies on gemcitabine-resistant metastatic pancreatic cancer patients combining, respectively, bi-weekly and tri-weekly oxaliplatin with raltitrexed[26] and gemcitabine,[27] obtained a 24% and 22.6% response rate with a median survival of 5.2 and 6 months. In a phase II study with pemetrexed[28] after gemcitabine failure, a 3-month survival rate, considered more clinically relevant than response rate in advanced pancreatic cancer, was chosen as the primary end point, and the results, 75% in the 3-month survival rate and 20 weeks in median survival, despite a 3.8% response rate, were comparable to those obtained in an oxaliplatin-based combination regimen as second-line therapy. Comparison of survival in the phase II study is difficult as a result of a nonhomogeneous population in terms of many characteristics including performance status, extension of disease, and previous treatments, but we wonder if such a wide range of response rates obtained in small phase II studies, often even greater than response rates in first line large phase III studies on gemcitabine alone or gemcitabine based regimen, could really be an effective surrogate end point of survival and not suffer from a selection bias. Moreover, the evaluation of response in pancreatic cancer might be difficult, even with newer imaging techniques, because of confounding desmoplastic reaction.

In a randomized study of patients refractory or resistant to prior therapy, median survival time reported with rubitecan versus "physicians' best choice of care" (BC) showed a significant survival advantage for those among the 211 BC treated patients who crossed over to raltitrexed versus "BC treated patients nonrescue."[29] Irino-

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CSPC Exhibit 1100
Page 180 of 333

tecan plus raltitrexed versus raltitrexed alone in another randomized phase II study appeared to be an effective salvage regimen in patients with gemcitabine-pretreated pancreatic cancer.[30]

Meta-analyses results[7] showed significantly better survival for chemotherapy versus best supportive care (HR 0.64; 95% CI, 0.42–0.98) and for gemcitabine-based combination versus gemcitabine alone (HR 0.91; 95% CI, 0.85–0.97), but not for gemcitabine versus 5-FU(HR 0.75; 95% CI, 0.42–1.31) or for 5-FU alone versus 5-FU-based combination (HR 0.94; 95% CI, 0.82–1.08). However, for the heterogeneity of the study, the upper limits of the CI are close to 1 even for better arms of treatment. Since 1996, clinical practice shifted from 5-FU to gemcitabine for the results of the trial of Burris[1] for the marginal survival advantage and the improvement in clinical benefit response, whereas only 1 phase III randomized study on gemcitabine-based combination with erlotinib showed a slight but significant increase in median survival to 6.4 months.[5]

A multicenter phase II trial investigating the combination of oxaliplatin and high-dose 5-FU with gemcitabine as first line therapy for advanced pancreatic cancer obtained median OS 7.5 months and TTP 5.7 months, probably better than single agent gemcitabine but not better than a two-agent regimen, at the expense of a high rate of cardiovascular events.[31] After gemcitabine progression, we chose to assess this weekly oxaliplatin, 5-FU, and leucovorin regimen based on its activity and tolerability profile, reported with first-line use.[15] In an extension of this latter study, a subgroup of patients who had initially received monotherapy and subsequently experienced disease progression received second-line treatment with a combination of oxaliplatin and infusional 5-FU.[24] No objective response was reported, but there was evidence of a modest value of the combination in this setting, with disease stabilization achieved in 3 patients (17%). This level of activity appears to be inferior to that observed in a similar study investigating a second-line combination of oxaliplatin (50 mg/m^2 weekly) with leucovorin and and bolus 5-FU in a group of 30 patients[23] with reported 23% partial responses and 30% stable disease. In comparison to the present study in the study of Tsavaris et al,[23] the majority of patients (96%) had locally advanced disease and there were dissimilarities regarding totally delivered chemotherapy doses (148 weeks in the present study, whereas 380 weeks in the latter study), regimens (3 weeks on, 1 week off in the present study, whereas consecutive weekly in the latter), and the different oxaliplatin dose (40 mg per square meter in the present study, whereas 50 mg per square meter in the latter). Both slightly better prognosis population and a more dose-intense regimen could explain the better response rate in the latter study.

Results of our study confirm acceptable toxicity and some clinical benefit in a population where palliation is a primary target. We found only 23.5% disease stabilization and no objective response, but advanced pancreatic cancer is a poor chemotherapy-responsive disease, with 5.4% partial responses after first line standard treatment with gemcitabine.[1] The percentage of metastatic patients in our trial is among the highest reported and prognosis and treatment outcome in this population could be different than in locally advanced disease. Characteristics of the patient population and of the regimen adopted, such as dose intensity, drug interactions also in terms of the modality, and timing of administration[18,32] could influence the outcome of the treatment. Many issues regarding the management of pancreatic cancer remain unanswered. The determination of prognostic and predictive factors and also the potential characteristics of the subgroup with extremely poor prognosis are essential to address optimal management for each patient. The emergence of biologic therapies will require this kind of prospective selection of patients based on these factors.[33]

The combination of oxaliplatin, leucovorin, and 5-FU was tolerated with manageable toxicity in the current study, offering an encouraging option for second-line treatment of patients with advanced or metastatic pancreatic adenocarcinoma, previously treated with gemcitabine.

Further studies investigating the efficacy and tolerability of this regimen in gemcitabine-relapsed pancreatic cancer patients are warranted, considering that outside of a well conducted randomized phase III trial a confounding effect because of selection bias cannot be excluded.

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CSPC Exhibit 1100
Page 181 of 333

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CSPC Exhibit 1100
Page 182 of 333

Pancreatic cancer: why is it so hard to treat?

Ther Adv Gastroenterol
(2013) 6(4) 321–337
DOI: 10.1177/1756283X13478680

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Abstract: No common malignancy is as rapidly and inevitably fatal as pancreatic ductal adenocarcinoma (PDA). This grim fact has driven substantial research efforts into this disease in recent decades. Unfortunately, the investment has yet to result in a meaningful increase in 5-year survival. This has prompted many pancreatic cancer researchers and advocates to redouble their efforts, but also requires one to step back and ask why the previous efforts were lacking and to consider why pancreatic cancer is so difficult to treat. The difficulties are legion. PDA is characterized by an insidious clinical syndrome, but is rarely diagnosed at a time when surgical resection is feasible. We lack markers of early detection and screening programs remain unproven even in high risk populations. The location of the tumor in the retroperitoneum, the advanced age of patients, and the systemic effects of disease limit the options for local therapy. Chemotherapy may provide a small benefit, but most efforts to improve on the current regimens consistently and stubbornly fail in advanced clinical trials. The molecular and cellular features of ductal pancreatic tumors are aggressive and underlay multiple levels of therapeutic resistance. Non-cell-autonomous features including stromal proliferation, reduced vascular density and immune suppression also contribute to therapeutic resistance. Growing awareness of these the fundamental features of PDA has begun to guide ongoing research efforts. Clinical trials are now specifically targeting these tumor properties and actively focusing on the therapeutic implications of tumor stroma. As reviewed here, reflecting on the fundamental question of why pancreatic cancer is so difficult to treat is a necessary and informative exercise that will aid our efforts to improve patient outcomes. These efforts will lead to improvements in clinical trial design, expand our focus to include the molecular and histologic implications of novel treatment paradigms, and ultimately change the lives of our patients.

Keywords: pancreatic cancer, chemotherapy resistance, tumor desmoplasia

Introduction

In the modern era of cancer research, pancreatic ductal adenocarcinoma (PDA) has proven to be among the most unyielding of adversaries. The oncology community has expended its entire arsenal at this disease with little effect: the 5-year survival rate has ticked up to 6% over the past 40 years, but nearly all diagnosed patients ultimately succumb to the disease. An estimated 37,390 people will die of pancreatic cancer in the US in 2012 [Siegel *et al.* 2012] with a similar pattern in the rest of the developed world [Jemal *et al.* 2011]. Over 80% of them will be found to have unresectable tumors at diagnosis [Stathis and Moore, 2010], giving them an expected overall survival of just 6 months. There are few therapeutic options for these patients and the most efficacious are also the most burdensome. Those who do undergo surgery improve their overall survival compared with patients of a similar stage by about 10 months [Bilimoria *et al.* 2007], but must tolerate significant morbidity and face almost inevitable recurrence. Given the slow progress against this disease, one must ask the question 'why is pancreatic cancer so hard to treat?'.

The particular problem of pancreatic cancer is multifactorial in its nature. The patient population in PDA is predominantly elderly and in poor overall health. There is no simple early detection method for pancreatic cancer and the earliest indications of disease are nonspecific. The tumor

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CSPC Exhibit 1100
Page 183 of 333

itself has its own peculiarities. For example, it has become apparent that PDA metastasizes microscopically early in the disease course, limiting the effectiveness of local therapies such as surgery and radiation. At the cellular level, the actual neoplastic epithelial cells at the heart of the disease harbor some of the most profoundly oncogenic alterations known to biology, and these are found at unusually high frequencies in PDA. In addition to driving growth and promoting cell survival, these alterations alter the metabolism of pancreatic cancer to one that can better support the manufacture of new cellular components. Layered on top of these high penetrance mutations is a host of rare alterations that are found in effectively unique combinations in each patient. The extent of genetic alterations in pancreatic tumors bears witness to a genomic instability phenotype that appears to play a significant role in the biology of PDA and implies an ability to rapidly develop acquired resistance to therapies that do manage to provoke an initial response. In addition to features of the tumor epithelium, PDA harbors a dense, desmoplastic stroma that can serve to limit the delivery of agents to tumors and foreshadows an incredibly complex interplay of intercellular signals that confound our ability to study the disease *in vitro*. Certain cell types within this stroma construct an immune-suppressed microenvironment that prevents the local immune system from clearing the tumor. Finally, PDA manifests as a syndrome, not just a mass, with systemic comorbidities that have a profoundly negative impact on quality of life.

Together, these raw observations paint a grim picture of the battle against pancreatic cancer that has at times led to a sense of nihilism. In reality, there are many signs that the research efforts of the past few decades have altered the momentum of this battle. Each of the challenges listed above has, in recent years, been the subject of intense research, leading to new ideas that are now being developed in the lab and in the clinic. For example, an understanding of the dynamics of drug delivery in PDA has led to a focus on targeted agents with desirable pharmacological properties. Another approach is to target the tumor stroma directly in order to facilitate the delivery of genotoxic agents or relieve local immune suppression. Other agents take advantage of the hypoxic microenvironment conferred by the desmoplastic stroma, or specific metabolic dependencies. Furthermore, decades of failed trials have led to improvements in clinical trial design and in the diagnostic and interventional techniques used in patients. By addressing the manifold difficulties that underpin the challenge of pancreatic cancer, a new sense of optimism is apparent. These barriers are surmountable and the nascent efforts to address them will ultimately be reflected in improved patient outcomes.

Patient population and diagnosis

Pancreatic ductal adenocarcinoma is largely a disease of old age, with an average age of diagnosis of 71 years. Yet the presenting symptoms are nonspecific such as weight loss and abdominal pain [Bakkevold *et al.* 1992]. This population of patients (and their general practitioners) is accustomed to aches and pains, and so in most cases, the earliest signs of malignancy go unnoticed; a high level of perception is required to avoid delays in diagnostic workup. Furthermore, in contrast to breast, prostate, melanoma and testicular cancers, there are no simple examinations that can elevate the level of suspicion: the pancreas is too deep to palpate and there is no specific blood test available for PDA. Other symptoms at diagnosis can include new onset of diabetes [Chari *et al.* 2005], unexplained jaundice [Porta *et al.* 2005] and unprovoked thrombosis [Khorana and Fine, 2004]; the most specific of these is unexplained painless jaundice, but many other explanations are possible. Thus, by the time that a patient seeks medical advice and their GP successfully navigates the diagnostic maze, often many months have passed and the patient's condition has further deteriorated.

PDA is associated with a syndrome of comorbidities that affect patients' overall health and in some cases can be life threatening. Symptoms related to pain [Porta *et al.* 2005] and depression [Kelsen *et al.* 1995] are components of this syndrome and are often present at the time of diagnosis, but become more severe with progression of the disease. PDA is intrinsically associated with biliary obstruction, infection, jaundice, ascites and pancreatic insufficiency, but beyond these factors PDA patients frequently experience the hypercatabolic state of cachexia and muscle wasting [Pausch *et al.* 2012]. In addition, PDA is classically associated with hypercoagulability and development of thromboembolic disease (Trousseau's syndrome) [Khorana and Fine, 2004]. Combined with the host of unrelated ailments typical of patients in their seventh, eighth and ninth decades of life, the average condition of PDA patients is poor, and many in this population may never be eligible or receive therapy.

CSPC Exhibit 1100
Page 184 of 333

From an epidemiological standpoint, efforts to change the long-term outcome of PDA patients through modification of risk factors have also been disappointing. Few behaviors reliably predict an increased risk for PDA [Raimondi *et al.* 2009]. Of those factors, cigarette use [Iodice *et al.* 2008; Heinen *et al.* 2010] should be discouraged but others, such as dietary habits, are less definitive [Thiebaut *et al.* 2009] and there is not sufficient evidence to recommend dietary changes to reduce the risk of PDA. The most promising chemopreventative agent is low-dose aspirin, which has been shown to significantly reduce the risk of pancreatic cancer in a dose-dependent manner [Tan *et al.* 2011]. There are familial clusters of PDA [Hruban *et al.* 1999; Bartsch *et al.* 2004; Shi *et al.* 2009] and first-degree relatives of affected patients are at increased risk [Klein *et al.* 2004; Hruban *et al.* 2010]. However, these comprise a minority of the overall population of PDA patients (5–10%) [Bartsch *et al.* 2012].

Furthermore, this knowledge is of limited benefit due to the lack of validated screening tests for early diagnosis of PDA. Due to its location in the retroperitoneum, the pancreas is difficult to access and sample with traditional endoscopic techniques. Endoscopic ultrasound techniques provide for higher yields but the morbidity associated with this procedure makes it unsuitable as a screening tool in an unselected population. Studies are ongoing in targeted populations of patients at high risk [Langer *et al.* 2009; Verna *et al.* 2010; Canto *et al.* 2012]. Cross-sectional imaging has the potential to identify small and even asymptomatic pancreatic lesions while they are still amenable to surgical resection [Canto *et al.* 2012]. However, due to poor innate contrast between PDA and the surrounding pancreas, specialized imaging protocols are required to optimally image pancreatic cancer by computerized tomography (CT) and magnetic resonance imaging (MRI) [Erkan *et al.* 2012]. As discussed later, PDA is characterized by hypovascularity and reduced perfusion compared with normal pancreatic tissue and this property may be utilized to obtain greater resolution in the detection of early lesions using techniques such as diffusion-weighted MRI [Holzapfel *et al.* 2011].

Serum sampling has not yet identified a suitable screening test for early detection of PDA. Many pancreatic lesions secrete CA19-9 (carbohydrate antigen 19-9) and this serum assay has a role in some patients in monitoring disease activity and response to therapy [Steinberg, 1990]. However CA19-9 has little use alone as a screening test due to high rates of false positivity in patients with non-malignant hepatobiliary disease [Frebourg *et al.* 1988]. There are ongoing efforts to identify molecular markers for early diagnosis of PDA [Goggins, 2005] but so far there are no validated agents and, as a consequence, diagnosis is often delayed.

The limited effect of local therapies

Currently, complete surgical resection provides the only potential for long-term cure of PDA but only a minority of patients have tumors that are amenable to surgery [Shaib *et al.* 2006]. This is due to the fact that, upon diagnosis, tumors have generally spread to involve critical abdominal vessels as well as adjacent organs. Significant advances have been made in the technical aspects of surgical resection with decreases in short-term morbidity and mortality at major centers [Winter *et al.* 2012]. Yet even in the most experienced centers, long-term survival after surgery is poor [Farnell *et al.* 2005; Ferrone *et al.* 2012], with tumors recurring in virtually all patients [Allison *et al.* 1998]. Due to the high rate of recurrence, local targeted therapy with radiation has been suggested following surgery. However, controlled studies of the long-term impact of adjuvant radiation therapy have proved inconclusive to date [Neoptolemos *et al.* 2004]. The cytotoxic effect of radiation therapy relies in part on the presence of oxygen [Harrison *et al.* 2002]. However, intraoperative oxygen measurements on human patients have found that these tumors are extremely hypoxic [Koong *et al.* 2000], which may contribute to the limited impact of this modality.

The limited long-term efficacy of surgery and adjuvant radiation therapy has led many to conclude that residual tumor tissue remains even in the case of complete surgical resection with no evidence of residual tumor. One possible explanation is that of 'field effect' mutations that may affect otherwise normal appearing cells present in the residual pancreatic tissue. Alternatively, PDA may simply metastasize at a microscopic level at a very early stage. Indeed, provocative data in a genetically engineered mouse model of PDA suggest that mutant cells may delaminate from the pancreatic epithelium and enter circulation in the very early stages of tumorigenesis even prior to the development of an overt carcinoma [Rhim *et al.* 2012]. If this is true, then PDA should be considered an inherently metastatic disease for which local therapy is simply a delaying action. This also highlights

CSPC Exhibit 1100
Page 185 of 333

the importance of identifying chemotherapeutic agents that effectively target microscopic metastases. It is notable that mutation evolution analysis based on deep sequencing of human pancreatic tumor samples has suggested a long latency period for PDA, estimating that it may take an average of 17 years for a tumor to evolve from a single common progenitor [Yachida *et al.* 2010]. However, a computational modeling study is consistent with the notion that PDA metastasizes early in disease [Haeno *et al.* 2012].

Clinical data of therapeutic efforts following resection of PDA are summarized in Table 1. These trials are consistent in demonstrating a small benefit when assessing recurrence but limited impact on long-term survival regardless of the intervention [Neoptolemos *et al.* 2004, 2010; Stocken *et al.* 2005; Oettle *et al.* 2007]. The modest achievements of adjuvant therapy compare poorly with the experience in other common cancers. Unfortunately PDA cells display broad and intractable resistance to chemotherapy, the subject of the remainder of this review.

Chemotherapy resistance in PDA

The track record of the clinical trials in advanced and metastatic pancreatic cancer is dismal (summarized in Table 2). Gemcitabine and erlotinib (Tarceva) remain the only two agents approved for use in advanced disease despite their modest benefits. Gemcitabine was approved on the basis of a study [Burris *et al.* 1997] showing that it was superior to 5-FU (5-fluorouracil) in providing a clinical benefit among advanced PDA patients with pain symptoms (clinical benefit rate = 23.8% *versus* 4.8%; $p = 0.0022$) and modestly prolonged median survival from 4.4 to 5.6 months ($p = 0.0025$). The incremental median survival benefit seen with the addition of erlotinib to gemcitabine is even smaller (5.9 to 6.2 months, $p = 0.038$), albeit statistically significant [Moore *et al.* 2007].

As summarized in Table 2, over 20 phase III trials have been conducted to improve on the modest efficacy of gemcitabine and these have been overwhelmingly disappointing. These trials covered traditional chemotherapeutic agents and combinations, targeted therapies such as the anti- vascular endothelial growth factor (anti-VEGF) monoclonal antibody, bevacizumab [Kindler *et al.* 2010] and the anti-epidermal growth factor receptor (anti-EGFR) antibody, cetuximab [Philip *et al.* 2010], as well as experimental targeted therapies including farnesyltransferase inhibitors [van Cutsem *et al.* 2004]. It is difficult to overstate the physical, financial and psychological costs of these unsuccessful attempts.

Two notable exceptions to this tale have been reported in the past 2 years. In 2011, a robust clinical benefit was found in a phase III randomized trial of FOLFIRINOX (a four-drug combination of 5-FU, leucovorin, oxaliplatin and irinotecan) compared with gemcitabine in metastatic PDA (median overall survival [OS] of 11.1 *versus* 6.8 months; $p \leq 0.001$) [Conroy *et al.* 2011]. However, this advantage comes at the cost of significant toxicity, making the regimen appropriate only for those patients with good performance status. As recently as November 2012, after exciting phase II results [von Hoff *et al.* 2011], a phase III trial of *nab*-paclitaxel (Abraxane) plus gemcitabine was reported to have met its primary overall survival endpoint. We look forward to learning the magnitude of this effect in the coming months and are excited at the prospect of having a range of chemotherapeutic tools to treat patients in different states of health.

This collective history has delivered a consistent overarching message: the response of PDA to chemotherapy is poor. Using standard criteria that define radiographic response as a decrease of 30% (or 50% in older studies) in tumor size, very few patients treated with chemotherapy experience an objective response (noted in Table 2). Thus, the initial resistance of these tumors is primary (innate), rather than the secondary (acquired) resistance that is classically observed in most cancers. This is an important clue to understanding the recalcitrant nature of pancreatic cancer.

Cell-autonomous mechanisms of resistance to chemotherapy

It is informative to think of the resistance of PDA to chemotherapy as occurring due to cell-autonomous and non-cell-autonomous pathways. Although ductal pancreatic tumors display clinical and pathologic heterogeneity, a striking characteristic of PDA is the consistent pattern of high penetrance genetic alterations that occur in four genetic loci: K-ras, p53, cdkn2a and smad4/DPC4. Over 90% of pancreatic tumors harbor activating mutations in K-ras, one of the most potent of all human oncogenes, far exceeding the rate of any other cancer [Almoguera *et al.* 1988; Pellegata *et al.* 1994; Hezel *et al.* 2006; Maitra and Hruban, 2008]. Mutant K-ras initiates a signal

CSPC Exhibit 1100
Page 186 of 333

Table 1. Phase III trials of adjuvant therapy following resection of PDA and comparison with other common tumors.

Study	Study period	Study population	Treatment arm(s)	Survival		
				Median OS (months)	*p* value	5-year survival %
EORTC 40891 [Klinkenbijl *et al.* 1999]	1987–1995	Stage I–II resected PDA (others excluded from this analysis)	Observation	12.6	NS	10
			Chemoradiotherapy (5-FU based)	17.1		20
ESPAC-1 [Neoptolemos *et al.* 2004]	1994–2000	Stage I–II resected PDA	Observation	16.9	0.009 (for chemo versus no chemo)	11
			Chemotherapy alone (5-FU)	21.6		29
			Chemoradiotherapy	13.9		7
			Chemoradiotherapy + chemotherapy	19.9		13
CONKO-001 [Oettle *et al.* 2007]	1998–2004	Stage I–II, resected PDA	Observation	20.7	NS	11.5
			Chemo (gemcitabine)	22.1		22.8
RTOG 9704 [Regine *et al.* 2008, 2011]	1998–2002	Stage I–II, resected PDA in head of pancreas	5-FU + chemoradiotherapy	16.9	NS	22
			Gemcitabine + chemoradiotherapy	20.5		18
ESPAC-3 [Neoptolemos *et al.* 2010]	2000–2007	Stage I–II, resected PDA	5-FU	23.0	NS	NR
			Gemcitabine	23.6		NR
Lung cancer				mOS		5 year survival
ANITA [Douillard *et al.* 2006]		Stage IB–IIIA resected, NSCLCa	Observation	43.7	0.017	43
			Chemotherapy	65.7		51
Colon cancer						6 year survival
MOSAIC [Andre *et al.* 2004, 2009]	1998–2001	Stage II–III, resected colon cancer	Chemotherapy (FOLFOX)	NR		78.5
Breast cancer						5 year survival
[Sparano *et al.* 2008]	1999–2002	Stage II–III breast cancer	Chemotherapy (most effective group)	NR		89.7

5-FU: 5-fluorouracil; chemo: chemotherapy; NR: not reported; NS: not significant ($p > 0.05$); NSCLCa: non-small cell lung cancer; OS: overall survival; PDA: pancreatic ductal adenocarcinoma.

transduction cascade that provides a strong pro-growth signal, increases cell motility and invasion, and profoundly rearranges cell metabolism to a growth-promoting state. In pancreatic cancer, Ras mutation initiates paracrine signals that promote and maintain stromal desmoplasia, a key mediator of non-cell-autonomous resistance (see below). Unfortunately, K-ras is an extremely challenging therapeutic target for which no effective targeted inhibitors have been identified to date.

Overlaid on this oncogenic scaffold are mutations in four extremely potent tumor suppressor genes. The cdkn2a locus encodes two tumor suppressor genes, $p16^{Ink4a}$ and $p15^{ARF}$. These genes are inactivated through a variety of mechanisms in >90% of human pancreatic tumors [Caldas *et al.* 1994; Schutte *et al.* 1997]. The p53 tumor suppressor gene is another major tumor suppressor and is altered in 75–90% of pancreatic tumors [Pellegata *et al.* 1994; Redston *et al.* 1994], resulting in impaired DNA damage responses, impaired apoptosis, loss of cell cycle control, and promotion of genomic instability. p53 is typically altered through 'gain of function' missense mutations that may further promote cancer beyond the loss of classical p53 tumor suppressor functions [Olive *et al.* 2004; Morton *et al.* 2010]. Alterations in DPC4 [Hahn *et al.* 1996a, 1996b] are observed in more than half of cases and confer a prometastatic phenotype. The combined effect of these mutations

CSPC Exhibit 1100
Page 187 of 333

Table 2. Phase III randomized trials with gemcitabine comparison in advanced PDA.

Study*	Accrual period	Number of patients	Treatment groups	Median OS		Response rate	
				Months	*p*	%	*p*
[Burris *et al.* 1997]	1992–1994	126	5-FU	4.4	0.0025	0	NS
			Gemcitabine	5.6		5.4	
[Bramhall *et al.* 2001]	1997–1998	239	Gem	5.5	NS	11	NS
			G + marimistat	5.5		16	
[Moore *et al.* 2003]	1997–1999	277	Gem	6.6	<0.001	NR	
			G + BAY 12-9566 (MMP inhibitor)	3.7		NR	
[Heinemann *et al.* 2006]	1997–2002	195	Gem	6.0	NS	8.2	NS
			G + cisplatin	7.5		10.2	
[Berlin *et al.* 2002]	1998–1999	322	Gem	5.4	NS	5.6	NS
			G + 5-FU	6.7		6.9	
[Van Cutsem *et al.* 2004]	1999–2001	688	Gem	6.1	NS	8	NS
			G + tipifarnib	6.4		6	
[Rocha Lima *et al.* 2004]	2000–2001	360	Gem	6.6	NS	4.1	<0.001
			G + irinotecan	6.3		16.1	
[Louvet *et al.* 2005]	2001–2003	313	Gem	7.1	NS	17.3	0.044
			G + oxaliplatin	9.0		26.8	
[Herrmann *et al.* 2007]	2001–2004	319	Gem	7.2	NS	7.8	NS
			G + capecitabine	8.4		10	
[Abou-Alfa *et al.* 2006]	2001–2003	349	Gem	6.2	NS	5.2	NS
			G+ exatecan	6.7		6.8	
[Moore *et al.* 2007]	2001–2003	569	Gem	5.9	0.038	8.0	NS
			G + erlotinib	6.2		8.6	
[Oettle *et al.* 2005]	2001–2003	565	Gem	6.3	NS	7.1	0.004
			G + pemetrexed	6.2		14.8	
[Colucci *et al.* 2010]	2002–2007	400	Gem	8.3	NS	10.1	NS
			G + cisplatin	7.2		12.9	
[Cunningham *et al.* 2009]	2002–2005	532	Gem	6.2	NS	12.4	0.034
			G + capecitabine	7.1		19.1	
[Poplin *et al.* 2009]	2003–2005	832	Gem (standard rate)	4.9	NS	6	NS
			Gem-FDR	6.2		10	
			Gem-FDR + oxaliplatin	5.7		9	
[Philip *et al.* 2010]	2004–2006	745	Gem	5.9	NS	7	NS
			G + cetuximab	6.3		8	
[Kindler *et al.* 2010]	2004–2006	602	Gem	5.9	NS	10	NS
			G + bevacizumab	5.8		13	
[Van Cutsem *et al.* 2009]	2005–2006	607	Gem + erlotinib	6.0	NS	8.6	NS
			Gem + erlotinib + bevacizumab	7.1		13.5	
[Conroy *et al.* 2011]	2005–2009	342	Gem	6.8	<0.001	9.4	<0.001
			FOLFIRINOX	11.1		31.6	
[Heinemann *et al.* 2012]	2006–2008	281	Gem + erlotinib (capecitabine for second line)	6.2	NS	16	NR
			Capecitabine + erlotinib (gem for second line)	6.9		5	

(Continued)

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CSPC Exhibit 1100
Page 188 of 333

Table 2. (Continued)

Study*	Accrual period	Number of patients	Treatment groups	Median OS		Response rate	
				Months	*p*	%	*p*
[Goncalves *et al.* 2012]	2006–2009	104	Gem G + sorafenib	9.2 8	NS	19 22	NS
[Kindler *et al.* 2011]	2007–2008	632	Gem G + axitinib	8.3 8.5	NS	2 5	0.018

5-FU: fluorouracil; FDR: fixed dose rate 5 and Gem: gemcitabine; NR: not reported; NS: not statistically significant ($p > 0.05$).
In addition to these trials, several phase III trials have been completed or terminated and remain unpublished. These include fluorouracil plus triacetyluridine [Clinical Trials.gov identifier: NCT00244270], aflibercept [Clinical Trials.gov identifier: NCT00376766], TS-1 [Clinical Trials.gov identifier: NCT00922259], GV1001 vaccine [ClinicalTrials.gov identifier: NCT00360568], or erlotinib [ClinicalTrials.gov identifier: NCT00027222] and AMG 479 – gemtuzumab [ClinicalTrials.gov identifier: NCT01231347].

is formidable and likely explains a large portion of the difficulty in treating this disease. Indeed, patients with three or four of these alterations in their tumors have a much worse prognosis than those with one or two (median survival of 9 *versus* 23 months) [Yachida *et al.* 2012].

Besides these well-established 'driver' variations, many other genetic changes occur at lower frequencies [Hansel *et al.* 2003; Jones *et al.* 2008; Biankin *et al.* 2012; Perez-Mancera *et al.* 2012]. An effort to sequence the entire exome of 24 PDA samples revealed that the average PDA contains more than 60 genomic changes [Jones *et al.* 2008]. Some of these may contribute to the specific resistance to chemotherapy in as yet unidentified ways. This high degree of genomic changes seen in PDA is suggestive of significant genomic instability and may limit the effectiveness of therapy, especially targeted agents, by contributing to secondary or acquired chemoresistance.

Despite the survival benefits observed in clinical studies, only 5–10% of pancreatic tumors exhibit a radiographic response to gemcitabine therapy. Pharmacological investigations into the mechanisms of gemcitabine activity have led to some of the best characterized determinants of patient prognosis. Gemcitabine [2′,2′-difluorodeoxycytidine (dFdC)] is a nucleoside analog of cytidine that must be actively transported into cells and then sequentially phosphorylated to the active triphosphate [2′,2′-difluorodeoxycytidine triphosphate (dFdCTP)] [Heinemann *et al.* 1988, Mini *et al.* 2006]. Transport across the cell membrane is primarily mediated by human equilibrative nucleoside transporter (hENT1), though other transporters play a minor role [Mackey *et al.* 1998, Mini *et al.* 2006]. Cell lines that are resistant to gemcitabine are often hENT1 deficient [Achiwa *et al.* 2004] and hENT1 expression in human tissues can predict response to gemcitabine [Oguri *et al.* 2007]. In pancreatic cancer, patients with elevated hENT1 have improved survival when treated with gemcitabine but not among untreated patients [Marechal *et al.* 2012]. In a large clinical trial [Farrell *et al.* 2009], patients treated with gemcitabine who had no hENT1 staining had poorer survival than those with positive hENT1 staining (hazard ratio for survival = 0.51, 95% confidence interval [CI] = 0.29–0.91; $p = 0.02$).

Enzymes associated with the metabolic activation and inactivation of gemcitabine may also impact tumor sensitivity. The monophosphorylation of gemcitabine is a rate-limiting step in its activation and is mediated by deoxycytidine kinase (dCK). Reduced levels of dCK are associated with gemcitabine resistance in some tumor cell lines [Achiwa *et al.* 2004], while elevated dCK expression is associated with improved survival among those receiving adjuvant gemcitabine in PDA [Marechal *et al.* 2012]. Conversely, gemcitabine can be deaminated to its inactive metabolite [2′,2′-difluorodeoxyuridine (dFdU)] in a process catalyzed by the enzyme cytidine deaminase (CDA) [Eliopoulos *et al.* 1998], levels of which are a key determinant of gemcitabine activity. One frequent polymorphism 79A>C (Lys27Gln) is associated with decreased enzymatic activity, improved clinical outcomes, and increased toxicity in combination therapy with gemcitabine in lung cancer [Tibaldi *et al.* 2008]. In pancreatic cancer, the data are conflicting; one group failed to find an effect of this polymorphism on gemcitabine activity [Sugiyama *et al.* 2007], while another group saw increased toxicity but no change in

CSPC Exhibit 1100
Page 189 of 333

outcomes in patients with intact CDA treated with gemcitabine [Farrell *et al.* 2012]. Other polymorphisms have also been identified [Sugiyama *et al.* 2007; Tanaka *et al.* 2010] and may be clinically relevant. Other studies suggest that the most relevant measure of CDA is functional testing which can predict rate of severe toxicity to gemcitabine [Ciccolini *et al.* 2010], though the clinical implications of these findings await validation in prospective trials [Giovannetti *et al.* 2010]. It is the high levels of CDA in human plasma that leads to the short (~15 minute) half-life of gemcitabine. This short half-life is compounded by non-cell-autonomous features of pancreatic tumors that limit the delivery of drugs to pancreatic tissues.

Non-cell-autonomous barriers to drug efficacy

A defining characteristic of PDA is the presence of a dense fibrotic proliferation surrounding the epithelial cells that may form the majority of the tumor mass [Chu *et al.* 2007; Neesse *et al.* 2011]. This 'desmoplastic reaction' is composed of various leukocytes, fibroblasts, endothelial cells and neuronal cells, as well as extracellular matrix components such as collagen and hyaluronan. The desmoplastic reaction is driven by paracrine signals originating in the epithelial compartment. These signals are driven by the oncogenic signals such as those initiated by mutant K-ras. A pair of studies in genetically engineered mouse models that utilized 'switchable' alleles of mutant K-ras found that the loss of mutant K-ras expression led to rapid quiescence and involution of the stroma over the course of just a few days [Collins *et al.* 2012; Ying *et al.* 2012]. In recent years, significant effort has been invested in identifying the signals that mediate the relationships between the different cell types in pancreatic tumors. For example, early in pancreatic tumor development, the neoplastic epithelial cells begin to overexpress Sonic Hedgehog (SHH), a secreted ligand that normally plays a role during organ development [Berman *et al.* 2003]. This upregulation has no effect on hedgehog pathway activity in the epithelial compartment [Nolan-Stevaux *et al.* 2009]. Rather, SHH activates the pathway in nearby stromal fibroblasts, promoting their activation and proliferation [Bailey *et al.* 2008; Tian *et al.* 2009]. This pathway has served as a paradigm for how tumor cells influence the behavior of their neighboring stromal cells.

The desmoplastic stroma of pancreatic cancer has physiological effects on the tumor that have a direct impact on drug efficacy. In contrast to many tumors that are dependent on neo-angiogenesis, ductal pancreatic tumors are very poorly vascularized relative to normal tissues and consequently poorly perfused [Olive *et al.* 2009]. Indirect evidence suggests that this is mediated by an anti-angiogenic effect of the tumor stroma, though the precise mechanism is an area of active research. Regardless, the poor perfusion of pancreatic tumors has the unfortunate consequence of limiting the delivery of therapeutic agents into the tumor parenchyma. Indeed, studies in a genetically engineered mouse model found that the delivery of two different chemotherapeutic agents, gemcitabine and doxorubicin, was approximately one third that of surrounding normal tissues [Olive *et al.* 2009]. Furthermore, poor perfusion in pancreatic tumors has been correlated with poor prognosis in patients [Komar *et al.* 2009]. The drug delivery effect is visualized every time a contrast agent is used to image a patient with pancreatic cancer: the finding of a 'hypoenhancing mass' in the pancreas is diagnostic for pancreatic ductal adenocarcinoma, particularly compared with endocrine carcinomas of the pancreas, which are hyperperfused [Fusaroli *et al.* 2010; Matsubara *et al.* 2011; Saftoiu *et al.* 2012]. Another consequence of poor perfusion is a hypoxic microenvironment, which can have important effects on radiosensitivity, cell metabolism and cell invasion. Direct measurements of oxygen partial pressure in human pancreatic tumors found that pancreatic tumors are profoundly hypoxic [Koong *et al.* 2000].

Tumor stroma is also the site of interaction between cancer and the immune system. Pancreatic tumors establish a profoundly immunosuppressed microenvironment that is nearly devoid of T lymphocytes. Several stromal cell types harbor immunosuppressive properties, including tumor associated macrophages (TAMs), cancer associated fibroblasts (CAFs), regulatory T cells (T_{reg}) and myeloid derived suppressor cells. Recently, two groups identified a K-ras dependent signal that promotes immunosuppression. Following activation, the principle upregulated cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF), which was found to promote the recruitment and activation of immature myeloid progenitor cells to become myeloid derived suppressor cells [Bayne *et al.* 2012; Pylayeva-Gupta *et al.* 2012]. Undoubtedly, other such signals exist and should be explored in the coming years.

CSPC Exhibit 1100
Page 190 of 333

Future therapeutic options

The many complexities of pancreatic tumors have, to date, overwhelmed our best clinical efforts. However, the investments of the past 30 years in establishing a fundamental understanding of the disease uncovered a number of important and promising leads for new therapeutic approaches. At the most basic level, improved patient management and the advent of multidisciplinary centers specializing in the care of pancreatic cancer patients is improving the quality of life of our patients. High volume centers clearly have improved surgical outcomes [Lieberman *et al.* 1995; Birkmeyer *et al.* 2002] and similar expertise in the endoscopy suite is likely to also improve patient care. Indeed, a recent report described the diagnostic and financial advantages of direct histological processing of fine needle aspiration (FNA) samples rather than use of cytology [Brais *et al.* 2012]. The recent introduction of endoscopic core biopsy needles has also improved the ability to acquire samples for both diagnostic and experimental purposes.

Several promising techniques are under development that may improve diagnostic imaging. Advanced MRI sequences such as diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI capitalize on the altered perfusion of pancreatic tumor to provide functional contrast relative to normal or inflamed pancreatic tissue [Fattahi *et al.* 2009; Bali *et al.* 2011; Hur *et al.* 2012; Wiggermann *et al.* 2012; Yao *et al.* 2012]. Advanced endoscopic ultrasound techniques such as contrast ultrasound (which measure tissue perfusion) and ultrasound elastrography (which measures tissue stiffness) have shown initial promise as diagnostic and prognostic indicators [Sofuni *et al.* 2005; Sakamoto *et al.* 2008; D'Onofrio *et al.* 2009]. A number of efforts are under way to identify targered contrast agents that discriminate early cancer or late-stage premalignancies. Among the most promising is a peptide that recognizes extracellular expression of Plectin-1, which was identified initially through a phage-display screen in genetically engineered mouse models of pancreatic cancer [Kelly *et al.* 2008; Bausch *et al.* 2009]. This probe appears to be upregulated in carcinomas *in situ* (PanIN 3) and is being developed for clinical trials as a single photon emission computed tomography (SPECT) probe.

For patients with advanced or metastatic PDA, a number of new therapeutic avenues are being explored. A variety of approaches have been taken to target components of the pancreatic tumor stroma. PEGPH20, a modified enzyme that breaks down hyaluronan crosslinks in the extracellular matrix, has been shown by two groups to facilitate the delivery of drugs to pancreatic tumors in genetically engineered mice and increase their overall survival [Jacobetz *et al.* 2013; Provenzano *et al.* 2012] A phase Ib/II clinical trial of PEGPH20 in combination with gemcitabine is now active at multiple sites. Two agents are in clinical trials that take advantage of the paucity of vasculature in pancreatic cancer. The gamma secretase inhibitor RO4929097 (Hoffman La Roche) is being evaluated in previously treared metastatic pancreatic cancer patients in a phase II study. Gamma-secretase is required for activation of Notch pathway signaling, which plays a role in pancreatic rumor angiogenesis. In a genetically engineered mouse model, inhibition of γ-secretase reduced vascularity to critically low levels within the tumor, resulting in cavitating necrosis and increased overall survival when combined with gemcitabine [Cook *et al.* 2012]. A second approach utilizes the presence of hypoxia to activate a chemotherapeutic prodrug. TH-302 is a potent DNA alkylator that is selectively activated in regions of hypoxia and is now undergoing clinical evaluation in combination with gemcitabine. Unfortunately, inhibition of the Hedgehog pathway, one of the earliest stroma targeting strategies, has so far failed to meet expectations. Two different targeted inhibitors of the Smoothened protein, IPI-926 (Saridegib, Infinity Pharmaceuticals) and GDC-0449 (Vismodegib, Genentech) were evaluated in phase II clinical trials, with negative results reported for IPI-926. Investigations are ongoing to understand this disconnect between preclinical and clinical results for these agents. On a positive note, a phase III study of gemcitabine plus Abraxane, a nanoparticle reformulation of taxol, was recently found to have met the primary endpoint, after an encouraging phase II study in which metastatic patients lived an average of 12.2 months [von Hoff *et al.* 2011]. One proposed mechanism of action is the targeting of SPARC, an extracellular matrix protein that is upregulated in the stroma of pancreatic tumors [Desai *et al.* 2009]. However, a recent analysis in genetically engineered mice found that Abraxane alters the sensitivity of pancreatic tumors to gemcitabine through downregulation of cytidine deaminase, leading to higher concentrations of dFdCTP in tumors [Frese *et al.* 2012]. In either case, with a toxicity profile that may be more reasonable than FOLFIRINOX, the regimen may prove to be a welcome new tool for the treatment of pancreatic cancer patients.

CSPC Exhibit 1100
Page 191 of 333

Finally, two novel immunotherapy approaches are under development in pancreatic cancer. The observation that GM-CSF promotes a paracrine circuit that helps maintain an immunosuppressive microenvironment has led to the proposal that anti-GM-CSF targeted antibodies may be useful in treating patients with pancreatic cancer [Bayne *et al.* 2012; Pylayeva-Gupta *et al.* 2012]. Another approach was reported in a phase I trial of a CD40 agonist in combination with gemcitabine in metastatic PDA patients. CD40 is an immunostimulant, and the combination therapy resulted in partial responses in 19% of patients and stable disease in 52% of patients. Contrary to initial expectations, the regimen relied on a macrophage-based mechanism of action, as revealed in a genetically engineered mouse model [Beatty *et al.* 2011].

Lessons learned

It is important to heed the hard-won lessons of a generation of clinical researchers [Tabernero and Macarulla, 2009]. As our molecular understanding of cancer in general and PDA specifically increases, it will become increasingly useful to obtain more information about the tumors we are treating. Currently many patients are diagnosed with PDA on the basis of imaging characteristics and a fine needle aspiration, which demonstrates adenocarcinoma but provides little additional tissue for further analysis. In many advanced clinical trials, the reason for failure of encouraging agents is never determined and this limits further directions in PDA research. Where therapies are developed and justified on the basis of tumor biology, it is critical to include pretreatment biopsies and, whenever feasible, to obtain additional post-treatment tumor samples to monitor the effect of targeting interventions on tumor histology and biology. Although this can increase trial costs and is an additional burden to patients, many patients believe in the importance of research efforts and are willing to undergo these procedures as a meaningful contribution to this effort. Moreover, in successful trials, correlative studies can provide valuable guidance for future development efforts. Treatment-related biopsies also facilitate the ability to prospectively test biomarkers, an important tool in identifying appropriate agents for advanced clinical trials [Philip *et al.* 2009].

It is also useful to bear in mind the many missed signals: situations where single arm phase I or II trials led to great hope, only to be disappointed by randomized phase III trials. In some cases this relates to the marked heterogeneity in outcomes among patients with advanced PDA based on other clinical characteristics such as age, pain status, function status and other comorbidities. These factors are complex and difficult to control. One way to address this limitation is to incorporate a control group in phase II trials to provide context to the reported results. Although this will require more patients and will still necessitate large phase III trials of positive agents [Rubinstein *et al.* 2011], it may reduce the number of agents that progress to expensive, large-scale, but ultimately futile phase III studies [Sharma *et al.* 2011].

Consideration must also be given to the caution necessary when utilizing surrogate markers in clinical trials. Particularly in pancreatic cancer, response rate and progression-free survival have often failed to correlate with increased overall survival. Although additional surrogate markers may prove to be beneficial, ultimately well-designed randomized trials with survival or clinical benefit outcomes will remain the gold standard of therapeutic effect.

In addition, it is important to remember that the majority of patients with PDA are elderly and many have poor functional status related to their tumors. These patients may ultimately benefit from different therapies than a younger, fitter population, and they should be represented in clinical trials. We therefore advocate for dedicated trials of less toxic regimens in the setting of performance status 2 patients. Perhaps most importantly, numerous advanced clinical trials have been terminated early and the data from many of these experiences are not publicly available. An effort must be made to make these data available to researchers in a timely fashion to inform future clinical trial design.

In conclusion, while the clinical outcomes for PDA have not improved sufficiently in the last decades, a large wealth of knowledge has been developed and is now being translated towards the ultimate goal of improving treatment outcomes for patients with PDA. We are filled with optimism that these efforts will be successful.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

CSPC Exhibit 1100
Page 192 of 333

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CSPC Exhibit 1100
Page 193 of 333

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CSPC Exhibit 1100
Page 194 of 333

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CSPC Exhibit 1100
Page 196 of 333

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CSPC Exhibit 1100
Page 197 of 333

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CSPC Exhibit 1100
Page 198 of 333

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CSPC Exhibit 1100
Page 199 of 333

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Published Online
November 22, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01035-1

See Articles page 545

In *The Lancet*, Andrea Wang-Gillam and colleagues[1] report on a randomised phase 3 trial (NAPOLI-1) in 417 patients with metastatic gemcitabine-resistant pancreatic cancer. The primary endpoint of overall survival was improved significantly with the combination of nanoliposomal irinotecan plus fluorouracil and folinic acid when compared with a control of fluorouracil and folinic acid (6·1 months [95% CI 4·8–8·9] *vs* 4·2 months [3·3–5·3]; hazard ratio [HR] 0·67, 95% CI 0·49–0·92). Subgroup analyses consistently favoured the combination treatment, further supporting a robust treatment effect on overall survival. NAPOLI-1 is one of two phase 3 trials to be done in the second-line gemcitabine-resistant setting, the other study being CONKO-003.[2] In that trial, second-line oxaliplatin plus fluorouracil and folinic acid was assessed with fluorouracil and folinic acid alone, and the primary endpoint of overall survival was also met.

Metastatic pancreatic cancer has a dismal prognosis, with median survival of 4–6 months, and is associated with substantial morbidity.[3,4] Because of its particular biology, pancreatic cancer is notoriously resistant to many types of chemotherapy. As a result, few treatment options currently exist for patients who have progressed on first-line gemcitabine-based therapy and are willing and able to undergo further chemotherapy. Hence, a confirmed survival benefit in this population of patients with an unmet clinical need is especially exciting.

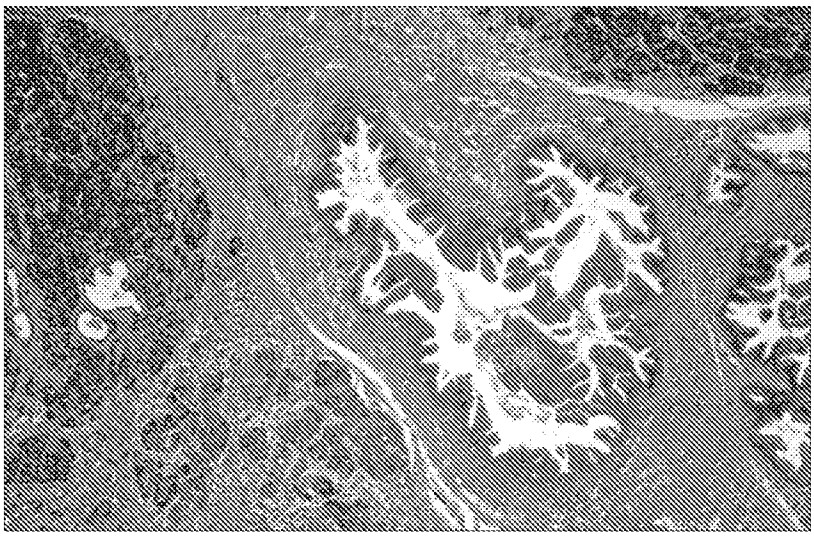
Expanded analyses of NAPOLI-1 in the per-protocol population have further confirmed the favourable effects of nanoliposomal irinotecan plus fluorouracil and folinic acid on overall survival, compared with fluorouracil and folinic acid.[5] In patients who received an 80% or higher dose intensity of assigned treatment within the first 6 weeks of the study, median overall survival was 8·9 months in those receiving the combination treatment versus 5·1 months in controls (HR 0·57, 95% CI 0·37–0·88), and this finding was similar across various subgroups. Of note, nanoliposomal irinotecan plus fluorouracil and folinic acid also improved overall survival in the non-per-protocol population compared with controls (median 4·4 months vs 2·8 months; HR 0·56, 95% CI 0·33–0·97).[5]

Several secondary endpoints also recorded gains with nanoliposomal irinotecan plus fluorouracil and folinic acid compared with control, including progression-free survival (HR 0·56, 95% CI 0·41–0·75) and time to treatment failure (0·6, 0·45–0·78). A partial response or better was achieved by 19 (16%) of 117 patients assigned nanoliposomal irinotecan plus fluorouracil and folinic acid, which is especially noteworthy in view of the second-line setting.[1]

Findings of phase 3 studies assessing use of standard irinotecan for treatment of pancreatic cancer have been disappointing. In an earlier study,[6] addition of irinotecan to first-line gemcitabine did not improve the primary endpoint of median survival compared with gemcitabine alone. Similar outcomes were seen in another trial,[7] in which first-line irinotecan plus gemcitabine was also compared with gemcitabine alone.

Similar to albumin-bound paclitaxel for pancreatic cancer,[8] reformulation of an existing drug can produce very interesting results. A key feature of nanoliposomal irinotecan administration is the resulting high intratumour concentration of its active metabolite SN-38 after administration, up to 5·6-fold higher than concentrations seen with the standard formulation irinotecan.[9] High intratumour concentrations of a chemotherapeutic agent confer important benefits, with respect to both efficacy and toxic effects.

In NAPOLI-1,[1] nanoliposomal irinotecan plus fluorouracil and folinic acid had a fairly favourable safety profile, including little neurotoxicity and a low incidence of alopecia. Because of the low frequency



Section from pancreatic adenocarcinoma

of neurotoxicity, nanoliposomal irinotecan plus fluorouracil and folinic acid would be more suitable to be administered after first-line albumin-bound paclitaxel plus gemcitabine, a regimen associated with substantial neurotoxicity, than would another neurotoxic regimen such as oxaliplatin plus fluorouracil and folinic acid.[2,3] This schedule would give the patient a break from this debilitating and cumulative adverse event, and pave the way for possible third-line administration of oxaliplatin plus fluorouracil and folinic acid. The low incidence of alopecia is also an important feature of nanoliposomal irinotecan plus fluorouracil and folinic acid in NAPOLI-1,[1] because this adverse event can have profoundly negative effects on a cancer patient's body image and self-esteem.

In addition to toxic effects, it is important to consider possible resistance to previous treatments when administering a second-line or later regimen. Along with albumin-bound paclitaxel plus gemcitabine, FOLFIRINOX—a regimen of folinic acid, fluorouracil, irinotecan, and oxaliplatin—has been designated for first-line treatment of metastatic pancreatic cancer.[10] Because FOLFIRINOX contains irinotecan, there is the potential for increased resistance to nanoliposomal irinotecan. Indeed, this effect is hinted at in a subgroup analysis of patients who had received previous irinotecan in NAPOLI-1, whereby ten of 12 individuals assigned to nanoliposomal irinotecan plus fluorouracil and folinic acid and eight of 17 people allocated to control died (HR 1·25, 95% CI 0·49–3·19). But, as Wang-Gillam and colleagues state,[1] there were very few patients in this particular subgroup and this idea remains a suggestion. As more patients are given front-line FOLFIRINOX, data for this potential effect should become clearer.

Administration of nanoliposomal irinotecan within new chemotherapy combinations and sequences and alongside new drugs (eg, programmed death-ligand 1 inhibitors)[11] could provide even better disease control in the future. Better disease control might create a situation similar to that seen with metastatic colorectal cancer, whereby resection of single liver metastases is worth doing, with the possibility of some patients being cured. Moreover, as well as reducing cumulative toxic effects, the sequence of first-line albumin-bound paclitaxel plus gemcitabine, second-line nanoliposomal irinotecan plus fluorouracil and folinic acid, then third-line oxaliplatin, fluorouracil, and folinic acid could also represent an overall therapeutic strategy, thereby providing patients with ongoing effective options.

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We declare no competing interests.

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Interpregnancy weight gain—a modifiable cause of stillbirth?

Published Online December 2, 2015 http://dx.doi.org/10.1016/S0140-6736(15)01089-2
See Articles page 558

In *The Lancet*, Sven Cnattingius and Eduardo Villamor[1] capitalise once more on the extraordinary resource of the Swedish Medical Birth Register to identify risk factors for stillbirth and infant death. In a population-based cohort study of 456 711 women with data on height and early gestational weight, the authors investigated the association between change in body-mass index (BMI) between first and second pregnancies and risks

CSPC Exhibit 1100
Page 201 of 333

J Gastrointest Cancer (2013) 44:182–189
DOI 10.1007/s12029-012-9466-2

ORIGINAL RESEARCH

Phase I Study of Oxaliplatin in Combination with Gemcitabine, Irinotecan, and 5-Fluorouracil/Leucovorin (G-FLIE) in Patients with Metastatic Solid Tumors Including Adenocarcinoma of the Pancreas

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Published online: 4 December 2012
© Springer Science+Business Media New York 2012

Abstract
Purpose The aims of this study were to establish the maximum tolerated dose (MTD) of oxaliplatin in combination with fixed doses of gemcitabine, irinotecan, and 5-fluorouracil/leucovorin (G-FLIE) in solid tumors, including advanced pancreatic cancer, and to evaluate the toxicity of the regimen.
Methods Patients with metastatic solid tumors were treated with a regimen consisting of gemcitabine (500 mg/m^2 by fixed-dose-rate infusion), irinotecan (120 mg/m^2), leucovorin 300 mg, bolus/infusion 5-fluorouracil (400 and 1,500 mg/m2, respectively), and oxaliplatin at doses from 50 to 85 mg/m^2 according to the escalation schema. Treatment was repeated every 14 days.
Results The study enrolled 25 patients with a median age of 64 years and median Karnofsky performance score of 80. Patients had metastatic adenocarcinomas of pancreas (n=9), as well as gastroesointestinal, hepatobiliary, or unknown primary tumors. With only one dose limiting toxicity (neutropenia and constipation), the MTD of oxaliplatin was not reached up to the pre-specified maximum level of 85 mg/m^2. Other toxicities predictably included cytopenias, fatigue, sensory neuropathy, nausea/vomiting, diarrhea, and constipation. Four partial responses and ten disease stabilizations were observed. The overall median time to disease progression was 17 weeks (2–110 weeks) with median overall survival of 31.5 weeks (7–139 weeks).
Conclusions G-FLIE is a tolerable multi-agent chemotherapy regimen with the oxaliplatin dose up to 85 mg/m^2. The combination of full-dose oxaliplatin with gemcitabine, irinotecan, and 5-fluorouracil is feasible with attenuated doses of the drugs, but further optimization is necessary before assessment of efficacy.

Keywords Phase I · Pancreatic cancer · Oxaliplatin · Gemcitabine · 5-Fluorouracil · Irinotecan

Introduction

Multi-agent chemotherapy regimens play a central role in treatment of gastrointestinal malignancies, such as gastroesophageal and colon cancer. In contrast, in advanced pancreatic cancer, single-agent gemcitabine remained the standard palliative chemotherapy, since no single study has been able to demonstrate meaningful impact of gemcitabine combinations on overall survival [1, 2]. Doublet regimens of gemcitabine with oxaliplatin, capecitabine, or irinotecan appeared to improve response rates but could not produce significantly improved survival in randomized studies [3–5]. A combination of gemcitabine with the targeted agent erlotinib led to a marginal survival advantage when applied in the unselected population [6]. The recent report of survival improvement associated with the regimen of oxaliplatin, irinotecan, and 5-fluorouracil (FOLFIRINOX) reignited the interest in coadministration of these active agents with gemcitabine [7].

Study results, in part, are previously presented at the Proceedings of the 2006 ASCO Gastrointestinal Cancers Symposium, 26–28 January 2006, San Francisco, CA.

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CSPC Exhibit 1100
Page 202 of 333

The exploration of gemcitabine-based combination chemotherapy underscored the conflict between treatment intensity and limits imposed by the disease-related nutritional and constitutional impairments. Safe incorporation of gemcitabine into three- and four-drug regimens can only be done in the context of careful phase I studies. Our group previously investigated one combination of gemcitabine with 5-fluorouracil (5-FU), irinotecan, and cisplatin (G-FLIP). The schedule and dosing of the drugs were designed based on sequence-dependent antitumor synergy derived from preclinical data with a defined maximal tolerated dose of irinotecan. The phase I–II trial in metastatic cancer of the pancreas resulted in an encouraging 22 % radiographic response rate and an acceptable adverse effect profile, with most grade 3–4 toxicities consisting of hematological events [8].

Motivated by the clinical results of oxaliplatin in gastrointestinal malignancies, we subsequently designed a study of a novel four-drug combination based on the above experience. Oxaliplatin appears to have a different spectrum of activity than cisplatin and may induce cell death more efficiently in cisplatin-resistant colorectal and pancreatic cancer cell lines [9–12]. In vitro and in vivo studies indicated synergistic effect with 5-FU, gemcitabine, and irinotecan [13–15]. Lower rates of gastrointestinal toxicity make oxaliplatin particularly suited for therapy of pancreatobiliary cancers. Although randomized phase III trials of gemcitabine/oxaliplatin doublets showed no significant survival advantage, the combination of oxaliplatin at the dose of 85 mg/m^2 with infusional 5-FU indicated benefit in patients with gemcitabine-resistant metastatic pancreatic cancer [16, 17].

Patients and Methods

Objectives

We conducted an open-label phase I dose-finding study of oxaliplatin in combination with fixed doses of gemcitabine, 5-FU, leucovorin, and irinotecan. The study was conducted at St. Luke's–Roosevelt Hospital Center and Beth Israel Medical Center in New York, NY in accordance with the Declaration of Helsinki and guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The protocol was approved and monitored by the local institutional review board. A signed informed consent was obtained from all patients before study entry. The trial was registered at clinicaltrials.gov with the identifier NCT00220649.

The primary objective of the study was to determine the maximum tolerated dose (MTD) of oxaliplatin and the toxicities of the experimental regimen. Secondary objectives included assessment of antitumor activity with objective response rate and survival outcomes for enrolled patients with carcinoma of the pancreas.

Patient Eligibility

Inclusion criteria required all patients to have a pathologically confirmed diagnosis of a solid tumor, either metastatic or advanced inoperable stage that was refractory to conventional treatment or for which no standard therapy existed. Patients were 18 years or older with a life expectancy of at least 12 weeks and a Karnofsky performance score (KPS) of ≥60, absolute granulocyte count ≥1,500/mm^3, platelet count ≥100,000/mm^3, bilirubin ≤2.0 mg/dL, and creatinine of ≤1.5 mg/dL. In addition, all patients had measurable or evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) and did not receive any chemotherapy, immunotherapy, or radiotherapy for at least 4 weeks prior to study entry (6 weeks for nitrosoureas or mitomycin C). No additional concurrent chemotherapy, radiotherapy, immunotherapy, or other investigational drugs were permitted while participating in this study.

Important exclusion criteria included brain metastases or leptomeningeal disease; progressive sensory neuropathy or hearing loss; tinnitus; pregnancy or lactation; uncontrolled medical conditions such as diabetes, hypertension, arrhythmias, congestive heart failure, angina pectoris, and myocardial infarction within 1 year of entry; active infections; and history of prior invasive malignancies within 5 years of entry with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix.

Study Design and Treatment

The study regimen comprised sequentially administered fixed-dose-rate gemcitabine, irinotecan, leucovorin, and 5-FU as bolus and 24 h infusion on day 1. The doses and schedules of each drug are listed in Table 1 and were determined based on previously established maximally tolerated doses in our experience with the G-FLIP regimen. Oxaliplatin was administered on day 2 at a dose based on the traditional 3 + 3 escalation design with pre-specified dose increments [18]. Treatment cycles were repeated every 14 days. All chemotherapy was administered intravenously in the ambulatory setting. Standard prophylactic antiemetics including serotonin antagonists and steroids were routinely administered. Prophylactic anticoagulation with warfarin to maintain the international normalized ratio of 2.0–3.0 was recommended for prevention of catheter-related thrombosis. During the first two cycles of therapy, the use of hematopoietic colony-stimulating factors was restricted to indications set forth by the American Society of Clinical Oncology [19], and during subsequent cycles, it was at the discretion of the treating physician.

CSPC Exhibit 1100
Page 203 of 333

Table 1 G-FLIE regimen–doses and schedules

Drug	Dose	Administration
Day 1		
Gemcitabine	500 mg/m^2	In 100 mL of 0.9 % sodium chloride over 30 min
Irinotecan	120 mg/m^2	In 500 mL of 5 % dextrose over 90 min
Leucovorin	300 mg	In 50 mL of 0.9 % sodium chloride over 10 min
5-Fluorouracil	400 mg/m^2	In 50 mL of 0.9 % sodium chloride over 10 min
5-Fluorouracil	1,500 mg/m^2	Via ambulatory infusion pump over 24 h
Day 2		
Oxaliplatin	50–85 mg/m^2	In 250 mL of 5 % dextrose over 120 min

All adverse events were defined by the National Cancer Institute Common Toxicity Criteria version 2.0. A serious adverse event occurring during the first two cycles (28 days) of chemotherapy constituted a dose limiting toxicity (DLT). Hematological DLTs were defined as grade 4 neutropenia lasting 5 or more days, neutropenic fever (≥38.5 °C), or grade 4 thrombocytopenia. Other criteria for DLT included any grade 3 or 4 non-hematological toxicity (excluding nausea/vomiting rapidly controlled with aggressive antiemetic support) or inability to receive at least 75 % of the planned chemotherapy dose during the treatment period. All adverse events not meeting the criteria for DLT were also recorded.

The first three patients were assigned to receive the oxaliplatin dose of 50 mg/m^2. Subjects were studied for a minimum of 28 days (two treatment cycles) at each dose level before opening a cohort at the next escalated dose and, at each level, the initial patient was observed for one course prior to the entry of subsequent participants. The cohorts were expanded to six patients if a DLT was noted in one of the initial three subjects. The dose of oxaliplatin was escalated by increments of 10 mg/m^2 up to 80 mg/m^2 and then up to the pre-specified ceiling of 85 mg/m^2. This ceiling dose reflected apparent MTD in the oxaliplatin three-drug combinations as well as the relative dose intensity achieved in prior gemcitabine–oxaliplatin studies [16, 20, 21]. The MTD was defined as the highest dose level that did not cause a DLT in more than one of three (or two of six) patients treated at that level. If the MTD of oxaliplatin was defined, up to ten additional patients were to be treated at this level for further assessment of toxicity and efficacy before recommending the regimen for further phase II testing.

The chemotherapy was discontinued in case of progressive disease, development of toxicity precluding further therapy, poor compliance with protocol requirements, development of intercurrent illness, or withdrawal of consent.

Safety and Efficacy Assessments

All patients were evaluated with pretreatment CT scans, chest X-rays, and CA 19-9 (when applicable) within 14 days prior to treatment initiation. History, physical examination, and toxicity assessment were performed every 2 weeks. Complete blood count with differential, basic metabolic panel, and liver function tests were performed weekly during the initial two cycles and then biweekly. Tumor assessment with CT scans was performed every 8 weeks. Patients who received at least two cycles were evaluated for response and patients who received any treatment were evaluated for toxicity assessment.

A granulocyte count of ≥1,000/mm^3 and platelets ≥100,000/mm^3 as well as resolution of all side effects to less than grade 2 were required prior to administration of each treatment cycle, otherwise chemotherapy was delayed. Patients were removed from the trial if treatment was held beyond day 28. No intra-patient dose escalation was allowed. Dose reductions in individual patients were pre-specified and based on hematologic and drug-specific toxicities. For example, 5-FU bolus was decreased by 50 % in the event of absolute neutrophil count (ANC) <1,000/mm^3 on or before day 7 and it was eliminated if ANC was <500/mm^3 on or before day 7. Infusional 5-FU dose was reduced by 25 % for any grade 3–4 stomatitis and for grade 2 or higher hand–foot syndrome. Any grade 3–4 diarrhea, despite atropine and loperamide use, required dose reduction of irinotecan by 25 %. Oxaliplatin dose was decreased by 25 % for grade 2 sensory neuropathy or if the platelet count was ≤100,000/mm^3 on day 14 or nadir was ≤50,000/mm^3. Oxaliplatin was discontinued for grade 3 sensory neuropathy.

Response Assessment

The RECIST criteria were used to determine tumor response. Target lesions were defined as at least 10 mm in one dimension by spiral CT scan or 20 mm with conventional technique. Complete response (CR) was defined as the disappearance of all target and non-target lesions without appearance of any new lesions. Partial response (PR) was defined as at least 30 % decrease in the sum of the longest diameters of the target lesions from baseline without appearance of any new lesions lasting at least 4 weeks. Progressive disease (PD) was established with at least 20 % increase in the sum of the longest diameters of the target lesions or the appearance of any new lesions. Stable disease (SD) was defined as a change in tumor size that did not qualify for response or progression. Patients who achieved a CR would continue to receive therapy for up to 6 months beyond the documentation of CR. Patients with a PR or SD could continue treatment until disease progression.

CSPC Exhibit 1100
Page 204 of 333

Results

Patient Characteristics

Twenty-five patients were enrolled between March 2004 and March 2008. Patients' clinical characteristics are summarized in Table 2. Median KPS was 80 (range 60–100). Half of the participants had pancreatobiliary adenocarcinomas, while others had other gastrointestinal or unknown primaries. All patients had metastatic disease with the most common sites in liver (56 %), regional lymph nodes (40 %), peritoneum (24 %), lung (12 %), and bone (8 %). Patients had received a median of 1 prior chemotherapy regimen (range 0–2). Twenty-three patients were evaluable for radiographic response, but two patients died of progressive disease prior to scheduled imaging. All were included in the toxicity assessment.

Treatment Administration and Toxicity

In total, 200 cycles of chemotherapy were administered, with a median of six cycles per patient (range 1–22 cycles). The first three patients received oxaliplatin at the starting dose level of 50 mg/m^2 and there was one DLT in this cohort with grade 4 neutropenia and constipation. According to the protocol, three additional patients were treated at that dose level without any further DLT. Consequently, dose escalation was performed in the remaining patients unhindered up to dose level 85 mg/m^2 without any further DLTs. Per protocol, oxaliplatin dosing was capped at 85 mg/m^2 and additional seven patients with pancreatic cancer were enrolled at this level to further assess regimen activity. Therefore, the MTD of oxaliplatin was not established in this population. All enrolled patients discontinued the treatment at the time of disease progression.

The frequencies of non-dose limiting (i.e., lesser grade or beyond the first two cycles) toxicities are summarized in Table 3. There were no episodes of febrile neutropenia or thrombosis. One subject developed grade 3 sensory neuropathy after eight cycles, at oxaliplatin dose level 85 mg/m^2.

There were four instances of non-DLT-related, protocol-mandated dose reductions of oxaliplatin: due to grade 2 thrombocytopenia during cycle 3 (dose level 70 mg/m^2), grade 3 diarrhea during cycle 4 (dose level 80 mg/m^2), grade 2 dysgeusia during cycle 2 (dose level 85 mg/m^2), and grade 2 fatigue and stomatitis with treatment delay at cycle 2 (dose level 85 mg/m^2, also with reduction of irinotecan dose to 100 mg/m^2). No further dose reductions were required after resolution of the above adverse effects.

Table 2 Patient characteristics

Characteristic	Number of patients	% of total
Total patients enrolled	25	100
Sex		
Male	11	44
Female	14	56
Age (years)		
Median	64	
Range	44–77	
Performance score (KPS)		
60–70	4	16
71–80	10	40
81–90	9	36
91–100	2	8
Number of prior chemotherapy regimens		
0	11	44
1	12	48
2	2	8
Primary cancer site		
Pancreas	9	36
Gastroesophageal	7	28
Hepatobiliary	2	8
Gallbladder	1	4
Duodenum	1	4
Oropharynx	1	4
Unknown primary	4	16

Response and Survival Assessment

Response and survival outcomes were evaluated as a secondary outcome. There were no complete responses. Four patients (16 %, including three with gastric cancer and one with adenocarcinoma of unknown primary) achieved a partial response while ten (40 %) had stable disease and nine (36 %) progressed while on therapy. The median time to progression was 17 weeks (range, 2–110) and the median overall survival was 31.5 weeks (range, 7–139).

Among subjects with pancreatic cancer (nine patients with median age of 68 years and median KPS of 85, range 65–90), there were no RECIST-defined radiographic responses. Four patients demonstrated stable disease and five progressed at first assessment with a median time to progression of 9 weeks (range 2–63 weeks) and a median overall survival of 28 weeks (7 months) (range 7–76 weeks).

Discussion

We report the first evaluation of a novel multi-agent chemotherapy incorporating gemcitabine, oxaliplatin, irinotecan, and 5-FU/leucovorin. In previous phase II and III studies, gemcitabine appeared to have synergism in combination with each of these agents as indicated by improved response rates, although doublet regimens have not significantly

CSPC Exhibit 1100
Page 205 of 333

Table 3 Non-dose limiting toxicities in all cycles by dose level

Oxaliplatin dose	50 mg/m^2		60 mg/m^2		70 mg/m^2		80 mg/m^2		85 mg/m^2		All patients (*N*, %)			
N	6		3		3		3		10		25			
Toxicity grade	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4		1–2	
Hematological														
Neutropenia	2	–	–	1	1	–	1	1	1	–	5	20 %	2	8 %
Lymphopenia	1	–	–	1	1	–	–	–	–	–	2	8 %	1	4 %
Leukopenia	2	1	–	2	1	1	–	3	–	1	3	12 %	8	32 %
Anemia	–	1	–	2	–	3	–	3	–	3	–	–	12	48 %
Thrombocytopenia	–	1	–	–	–	1	–	–	–	2	–	–	4	16 %
Neutropenic fever	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Thromboembolism	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hemorrhage	–	1	–	–	–	–	–	–	–	–	–	–	1	4 %
Non-hematological														
Anorexia	1	3	–	2	–		–	1	–	2	1	4 %	8	32 %
Fatigue/asthenia	–	4	–	3	–	3	1	2	–	4	1	4 %	16	64 %
Nausea/vomiting	1	3	–	2	–	2	–	2	–	4	1	4 %	13	52 %
Constipation	1	2	–		–	1	–	–	–		1	4 %	3	12 %
Diarrhea	–	–	–	2	–	3	1	–	–	5	1	4 %	10	40 %
Sensory neuropathy	–	1	–	2	–	2	–	2	1	3	1	4 %	10	40 %
Taste alteration	–	2	–	–	–	–	–	–	–	1	–	–	3	12 %
Edema	–	1	–	–	–	–	–	–	–	–	–	–	1	4 %
Dyspnea	–	1	–	–	–	–	–	–	–	–	–	–	1	4 %
Dehydration	1	–	–	–	–	–	1	–	–	–	2	8 %	–	–
Stomatitis	1	1	–	–	–	–	–	–	–	1	1	4 %	2	8 %
Pain, headache	1	2	–	1	–	1	–	1	–	–	1	4 %	5	20 %
Fever or rigors	–	2	–	–	–	1	–	–	–	1	–	–	4	16 %
Infection	1	–	–	–	–	1	–	–	–	–	1	4 %	1	4 %
Rash	–	1	–	1	–	–	–	–	–	–	–	–	2	8 %

The following grade 1 toxicities occurred in single cases: vision or hearing disturbance, flatulence, xerosis, urinary frequency, insomnia, dyspnea, and weight gain; in two patients: alopecia, abdominal cramping, hiccups, and hyperpigmentation

improved outcomes in pancreatic cancer [5, 16, 22–24]. Synergistic multi-drug combinations offer a potential to overcome the high chemotherapy resistance in pancreatic cancer. One Italian group developed a gemcitabine combination with cisplatin, epirubicin, and 5-FU via continuous infusion [25]. In a phase III study of 92 patients with locally advanced and metastatic pancreatic cancer, an improved progression-free survival (3.3 versus 5.4 months, $P=0.0033$) and a borderline overall survival advantage ($P=0.047$) was noted. The toxicity was predominantly hematologic, though with occurrences of febrile neutropenia and higher rates of grade 3–4 toxicity than in the present study (neutropenia 43 %, anemia 7 %, thrombocytopenia 30 %, and stomatitis 7 %). Our previous G-FLIP phase II study was similarly promising with 22 % response rate and 33 % 12-month survival and comparable toxicity [8]. Other drugs with different mechanisms of action, such as nab-paclitaxel, docetaxel, and pemetrexed are also being studied in combination with gemcitabine [26–29]. The success of FOLFIRINOX might encourage further development of multi-agent regimens for the treatment of pancreatic cancer.

This phase I study confirmed the feasibility of administering oxaliplatin at the dose of 85 mg/m^2 every 2 weeks in combination with irinotecan, 5-FU, and gemcitabine. We designed our study with the maximum 85 mg/m^2 oxaliplatin dose level, an efficacious dose in combination with 5-FU in pancreatic cancer [30]. Gemcitabine, irinotecan, and 5-FU were given at levels derived from our previously studied four-drug combination with cisplatin [31]. However, considering different toxicity profiles of cisplatin and oxaliplatin, the doses of these drugs may have been unnecessarily lower than in oxaliplatin combinations, such as the phase I FOLFIRINOX trial [20]. The median age in our cohort (64 versus 56 years in the referenced trial) was closer to the realistic age of pancreatic cancer population (median 71 years) and our eligibility criteria with regard to functional status were

CSPC Exhibit 1100
Page 206 of 333

also less stringent. The fact that 36 % of patients in the present trial experienced grade 3 or 4 adverse events during therapy indicates that attempts to escalate the doses of gemcitabine, irinotecan, or 5FU may not be straightforward. The intended dose intensity of FOLFIRINOX was associated with substantial hematologic and constitutional toxicities in the phase III trial requiring significant attenuation, so that the relative dose intensities (RDI) of 5-FU, irinotecan, and oxaliplatin were 82, 81, and 78 %, respectively. The toxicity concerns in patients who are elderly or with impaired liver function limit the utility of the combination and its acceptance in the general oncology community [32]. By contrast, 100 % oxaliplatin RDI, 67 % irinotecan RDI, 68 % 5-fluorouracil RDI, but only 33 % gemcitabine RDI was administered in the G-FLIE regimen, as compared to the typical single-agent doses of these drugs: oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, and 5-FU 400 mg/m^2 bolus with 2,400 mg/m^2 over 46 h every 2 weeks and gemcitabine 1,000 mg/m^2 on days 1-8-15 every 28 days. While the dose–response curve for these agents in combination has not been defined, reductions to less than 75 % RDI could certainly impair efficacy.

Our study has several weaknesses. Oxaliplatin is usually administered 24 h after gemcitabine due to sequence-dependent synergy demonstrated in vitro, although this dependence has not been evaluated in vivo [14, 33]. On the other hand, oxaliplatin exhibits significant synergy when administered with 5-FU [13]. This may occur by virtue of reducing clearance of the fluoropyrimidine or through suppression of deoxyuridine triphosphate nucleotidohydrolase, an enzyme conferring 5-FU resistance [34, 35]. In vitro data show similar synergy regardless of the sequence of the two drugs, although oxaliplatin may be optimally timed in the vicinity of 5-FU bolus and is usually given in this fashion [36]. While the most favorable sequence of these three agents remains undetermined, recent studies deliver oxaliplatin on the same day as gemcitabine in regimens incorporating 5-FU or capecitabine [37]. Since we did not observe any radiographic responses in pancreatic cancer in our study, we cannot rule out the possibility that the particular drug sequence we utilized was suboptimal with regard to antitumor efficacy. Moreover, we used the fixed-dose-rate mode of delivery of gemcitabine at a reduced dose based on the suggestion from early clinical studies that the intracellular drug accumulation with fixed-dose-rate infusion was approximately twice the amount generated by the standard 30-min infusion [38]. This was however subsequently shown to have no clinical benefit over the standard infusion rate [4]. The data in colorectal cancer suggest that the efficacy of 5-fluorouracil is highly dose-dependent [39]. The feasibility of the full infusion dose of 2,400 mg/m^2 as well as the relative contribution of 5-FU bolus can be further explored. The 4 years needed to enroll an adequate cohort in this phase I study bespeaks the challenge of studying potentially toxic therapy in patients with poor baseline prognosis and symptomatic malignancy. While we employed the traditional "3 + 3" dose escalation design with pre-specified dose increments, alternative model-based designs such as the continual reassessment method offer theoretical advantages in a more rapid dose escalation and use of composite information from all treated patients [40]. These could be utilized to further optimize the four-drug combination by escalating the dose of gemcitabine or infusional 5-FU.

In designing the present trial, it was our hope to develop a tolerable, active regimen to move to a phase II clinical study in patients with pancreatic cancer. Achieving this goal would require further dose optimization for the other agents. The future treatment success in advanced pancreatic cancer is dependent upon better understanding of the molecular mechanisms involved in carcinogenesis and chemotherapy resistance. Reliable predictors of response or resistance to oxaliplatin, irinotecan, or 5-fluorouracil are still lacking. Their efficacy and toxicity may greatly depend on constitutional genetic polymorphisms affecting activation and metabolism (such as uridine diphosphate-glucuronosyltransferase 1A1 for irinotecan or cytidine deaminase for gemcitabine), so pharmacogenomic optimization needs to be accounted for in the design of future dose-finding trials. The goal of defining promising cellular targets remains so far elusive despite accumulating research on the EGFR, K-Ras, and other pathways [41]. The presence of secreted protein acidic and rich in cysteine in the microenvironment of the pancreatic cancer appears to have prognostic value and this mechanism may be targeted by nab-paclitaxel, perhaps the most promising cytotoxic agent recently studied with gemcitabine [28, 42]. Ultimately, a combination of traditional chemotherapy with rationally selected targeted agents can hopefully lead to better outcomes. American and European research committees recommend increasing emphasis on biomarker development, use of functional imaging for response assessment, and limitation of phase III trials to therapies demonstrating strong efficacy in earlier phase trials [43, 44].

Acknowledgments This study was supported by Sanofi US. SM received honoraria as a consultant for Sanofi US. PSK received research funding from Sanofi US.

Conflict of interest The other authors have no conflict of interest to declare.

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CSPC Exhibit 1100
Page 207 of 333

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CSPC Exhibit 1100
Page 208 of 333

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CSPC Exhibit 1100
Page 209 of 333

Impact of prior irinotecan exposure on outcomes of metastatic pancreatic cancer patients

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BACKGROUND

- In the USA, pancreatic cancer is the third leading cause of cancer-related death (with an estimated 45,750 deaths in 2019), and 53% of cases are metastatic at diagnosis.[1]
- Irinotecan is a topoisomerase 1 inhibitor that is used in combination therapies, but its half-life is short[2] and adverse events can be dose limiting.[3]
- Liposomal irinotecan is an intravenous liposomal formulation that encapsulates irinotecan in a lipid-bilayer vesicle, leading to prolonged circulation.[4]
- Liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy.[5]
- Findings from a small US study (n = 56) have suggested that patients with mPDAC who had disease progression with prior irinotecan exposure may have poorer overall survival (OS) when receiving subsequent liposomal irinotecan + 5-FU/LV than those who did not have, or did not progress with, prior irinotecan exposure;[6] however, real-world evidence in larger populations is lacking.

OBJECTIVE

- The aim of this study was to evaluate OS in adults with mPDAC who were receiving second- or later-line regimens (including liposomal irinotecan + 5-FU/LV), stratified by prior irinotecan exposure, using data from a large US electronic-health-record (EHR) database.

METHODS

Data source

- The Flatiron Health database contains EHRs from over 280 cancer clinics (approximately 800 sites of care), representing more than 2.2 million patients with cancer.
- Deidentified data were extracted for the period January 1, 2014, to June 30, 2019.

Treatment regimens

- Treatment regimens were derived from structured medication orders and administration records.
- All drugs given within 28 days of an initial therapy were considered to be part of the same treatment regimen.
- The addition of a new therapy after 28 days was considered to be the start of a subsequent treatment regimen.

Study population

- Patients included in the study were considered to have mPDAC based on the following criteria.
  - Pancreatic cancer documented using diagnostic codes 157 and C25 from the International Classification of Diseases and Related Health Problems, 9th and 10th revisions, Clinical Modification.
  - Pathology consistent with PDAC.
  - Evidence of stage IV or progressive/recurrent disease on or after January 1, 2014.
- Included patients had received:
  - first-line treatment, defined as the first regimen initiated after, or up to 14 days before, a diagnosis of metastatic disease

CSPC Exhibit 1100
Page 210 of 333

- second- or later-line treatment with one or more of the following study regimens.
  - Gemcitabine + nab-paclitaxel (gem/nab).
  - Liposomal irinotecan + 5-FU/LV.
  - Folinic acid + 5-FU + oxaliplatin (FOLFOX).
  - Folinic acid + 5-FU + irinotecan (FOLFIRI).
  - Folinic acid + 5-FU + irinotecan + oxaliplatin (FOLFIRINOX).
- Patients were also required to:
  - be 18 years of age or older at the diagnosis of metastatic disease
  - have at least two documented clinical visits on or after January 1, 2014
  - have a documented activity (clinic visit or documented order) on, or in the first 90 days after, the diagnosis of metastatic disease.

Treatment groups and subgroups

- Treatment groups were based on receipt of a study regimen in the second- and later-line settings. Individual patients receiving more than one study regimen could, therefore, be included in the analysis more than once.
- Prior irinotecan subgroups were based on exposure to generic non-liposomal irinotecan prior to the study regimen, from first-line treatment in the metastatic setting onwards.

Overall survival

- OS from initiation of study regimen was estimated using Kaplan–Meier methods.
- Mortality hazard ratios in patients with or without prior irinotecan exposure were analyzed using Cox proportional hazard models.
- Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Population characteristics

- In total, data were retrieved for 1,634 patients who had collectively received 1,978 distinct lines of therapy.
  - Of these 1,978 lines of therapy, 747 (37.77%) were received by patients with prior irinotecan exposure, and 1,231 (62.23%) by patients without prior irinotecan exposure (**Table 1**).
- Proportions of patients with prior irinotecan exposure varied among treatment groups (1.61–74.17%) (**Table 1**).

Overall survival

- In patients receiving gem/nab or liposomal irinotecan + 5-FU/LV, OS was not significantly different between those with prior irinotecan exposure and those without (**Figures 1A** and **1B**).
- In patients receiving FOLFOX, those with prior irinotecan exposure had significantly poorer OS than those without (**Figure 2**).
- Analyses for patients receiving FOLFIRI or FOLFIRINOX were not meaningful owing to small numbers in the subgroups with prior irinotecan exposure (**Figures 3A** and **3B**).

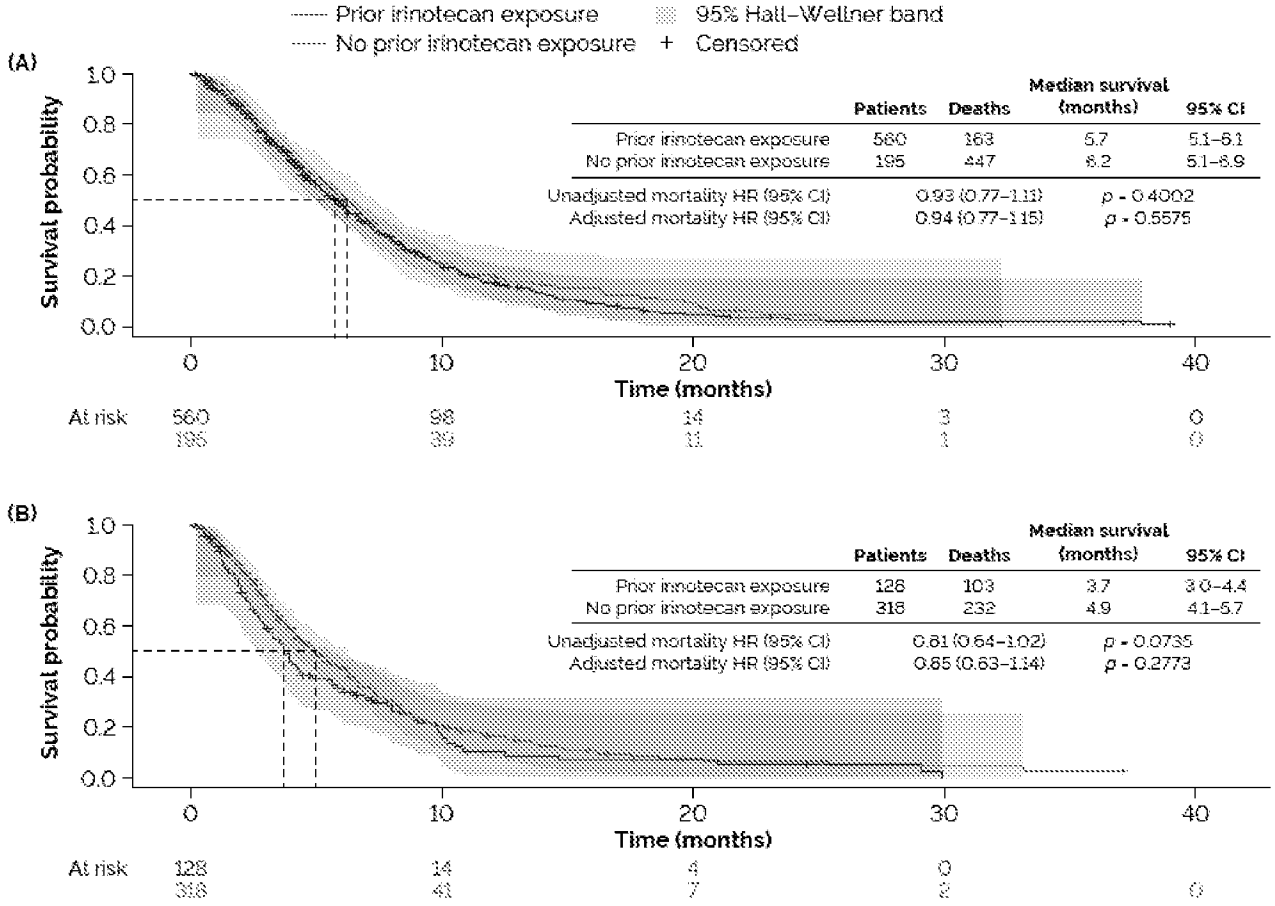
Table 1. Patient demographic and disease characteristics at the start of the study regimen (second- or later-line therapy)

	Gem/nab (n = 755)	Liposomal irinotecan + 5-FU/LV (n = 446)	FOLFOX (n = 353)	FOLFIRI (n = 113)	FOLFIRINOX (n = 311)
Age, years					
Mean (SD)	64.0 (9.3)	67.8 (8.8)	68.9 (9.1)	68.3 (8.6)	65.7 (9.0)
Median (IQR)	64.0 (58.0–70.0)	69.0 (62.0–74.0)	69.0 (63.0–76.0)	69.0 (63.0–75.0)	66.0 (60.0–72.0)
Sex, n (%)					
Male	411 (54.44)	241 (54.04)	186 (47.03)	49 (43.36)	163 (52.41)

Practice type, n (%)					
Academic	131 (17.35)	38 (8.07)	77 (21.61)	36 (31.86)	36 (11.58)
Community	624 (82.65)	410 (91.93)	276 (78.19)	77 (68.14)	275 (88.42)
Prior irinotecan exposure, n (%)					
Yes	560 (74.17)	128 (28.70)	46 (13.03)	8 (7.08)	5 (1.61)
Stage at initial diagnosis of pancreatic cancer, n (%)					
IV	546 (72.32)	280 (62.78)	245 (69.41)	79 (69.91)	211 (67.85)
Other	209 (27.68)	166 (37.22)	108 (30.59)	34 (30.09)	100 (32.15)
ECOG score, n (%)					
0	132 (17.49)	73 (16.37)	44 (12.46)	13 (11.50)	62 (19.94)
1	259 (34.30)	177 (39.69)	124 (35.13)	34 (30.09)	110 (35.37)
≥ 2	102 (13.51)	74 (16.59)	58 (16.43)	20 (17.70)	30 (9.65)
Missing	262 (34.70)	122 (27.35)	127 (35.98)	46 (40.71)	109 (35.05)
Number of previous lines, n (%)					
1	680 (90.07)	240 (53.81)	247 (69.97)	61 (53.98)	258 (82.96)
2	68 (9.01)	159 (35.65)	84 (23.80)	44 (38.94)	47 (15.11)
3	6 (0.79)	38 (8.52)	15 (4.25)	8 (7.08)	6 (1.93)
≥ 4	1 (0.13)	9 (2.02)	7 (1.98)	0 (0.00)	0 (0.00)

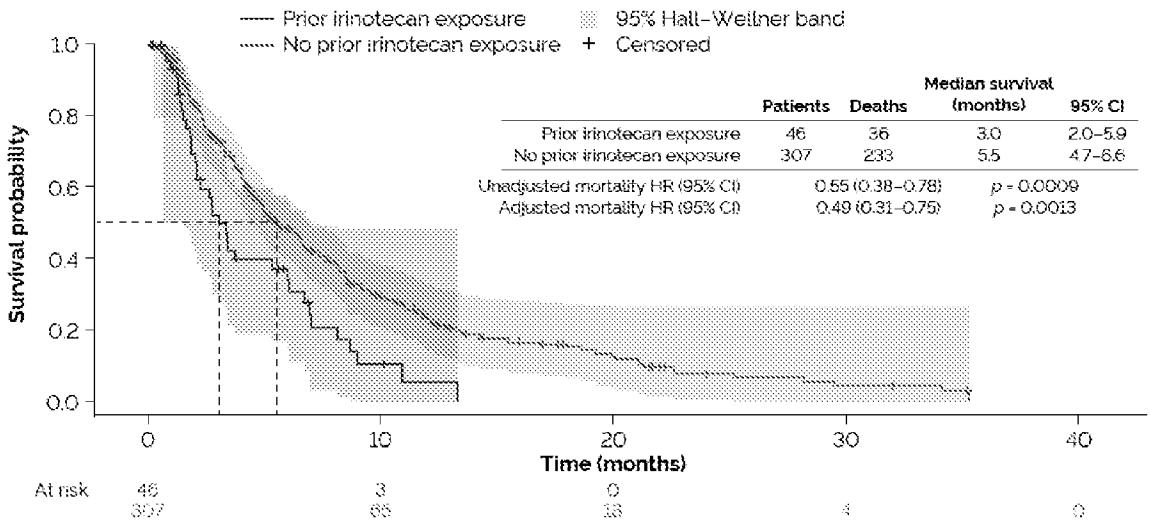
5-FU/LV, 5-fluorouracil/leucovorin; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid + 5-FU + irinotecan; FOLFIRINOX, folinic acid + 5-FU + irinotecan + oxaliplatin; FOLFOX, folinic acid + 5-FU + oxaliplatin; gem/nab, gemcitabine + nab-paclitaxel; IQR, interquartile range; SD, standard deviation.

Figure 1. Overall survival from the start of second or later lines of therapy with (A) gem/nab and (B) liposomal irinotecan + 5-FU/LV



Data are for patients with or without prior exposure to irinotecan (from first-line treatment onwards). Death dates were imputed to the 15th day of the month. Adjusted HRs and p values are from a Cox proportional hazards model adjusted for index year, age at index year, race, smoking status, ECOG score, tumor stage, tumor site, baseline serum albumin level, number of previous lines of therapy, duration of previous line of therapy and practice type. HRs less than 1 represent worse survival for patients with prior irinotecan exposure than for those without.
5-FU/LV, 5-fluorouracil/leucovorin; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; gem/nab, gemcitabine + nab-paclitaxel; HR, hazard ratio.

Figure 2. Overall survival from the start of second or later lines of therapy with FOLFOX

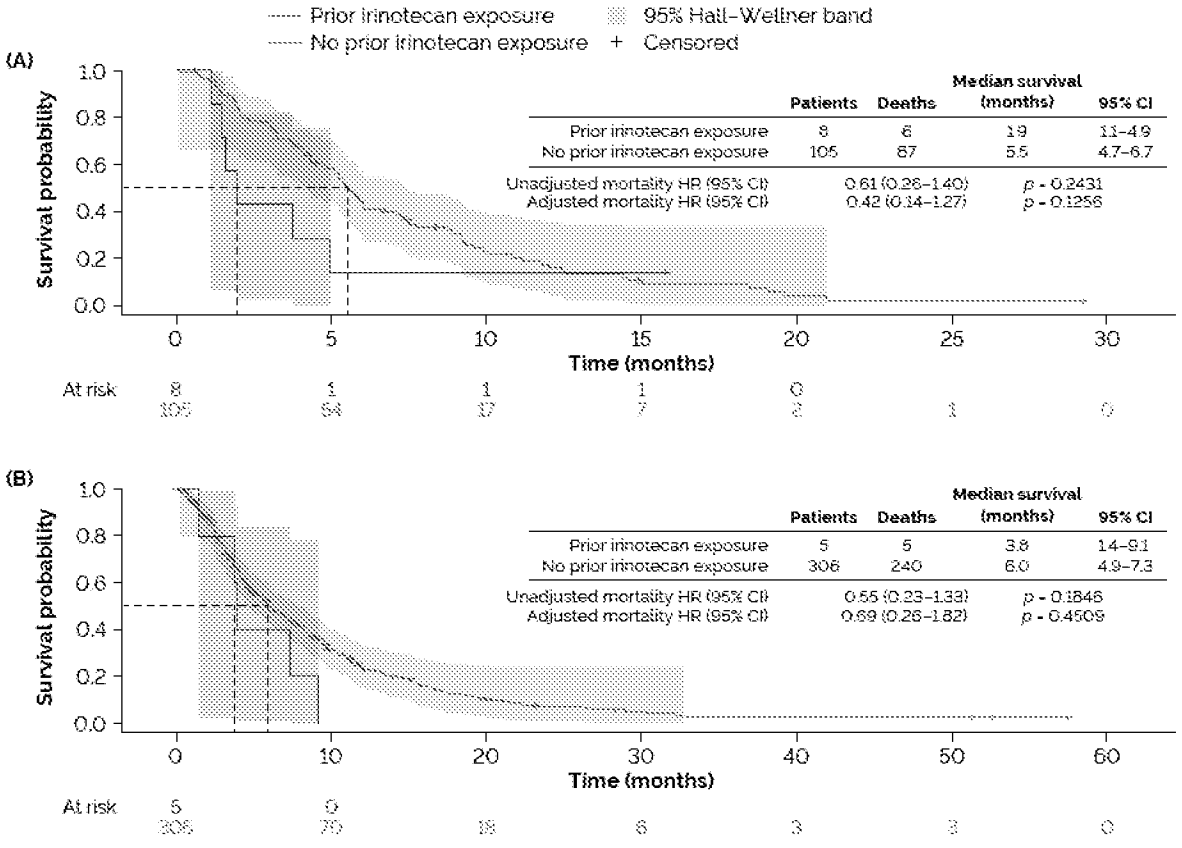


	Patients	Deaths	Median survival (months)	95% CI
Prior irinotecan exposure	46	36	3.0	2.0–5.9
No prior irinotecan exposure	307	233	5.5	4.7–6.6

Unadjusted mortality HR (95% CI)	0.55 (0.38–0.78)	$p = 0.0009$
Adjusted mortality HR (95% CI)	0.49 (0.31–0.75)	$p = 0.0013$

Data are for patients with or without prior exposure to irinotecan from first-line treatment onwards. Death dates were imputed to the 15th day of the month. Adjusted HRs and p values are from a Cox proportional hazards model adjusted for index year, age at index year, race, smoking status, ECOG score, tumor stage, tumor site, baseline serum albumin level, number of previous lines of therapy, duration of previous line of therapy and practice type. HRs less than 1 represent worse survival for patients with prior irinotecan exposure than for those without.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid + 5-fluorouracil + oxaliplatin; HR, hazard ratio.

Figure 3. Overall survival from the start of second or later lines of therapy with (A) FOLFIRI[a] and (B) FOLFIRINOX[a]



(A)

	Patients	Deaths	Median survival (months)	95% CI
Prior irinotecan exposure	8	6	1.9	1.1–4.9
No prior irinotecan exposure	105	87	5.5	4.7–6.7

Unadjusted mortality HR (95% CI)	0.61 (0.26–1.40)	$p = 0.2431$
Adjusted mortality HR (95% CI)	0.42 (0.14–1.27)	$p = 0.1256$

(B)

	Patients	Deaths	Median survival (months)	95% CI
Prior irinotecan exposure	5	5	3.8	1.4–9.1
No prior irinotecan exposure	306	240	6.0	4.9–7.3

Unadjusted mortality HR (95% CI)	0.55 (0.23–1.33)	$p = 0.1846$
Adjusted mortality HR (95% CI)	0.69 (0.26–1.82)	$p = 0.4509$

Data are for patients with or without prior exposure to irinotecan from first-line treatment onwards. Death dates were imputed to the 15th day of the month. Adjusted HRs and p values are from a Cox proportional hazards model adjusted for index year, age at index year, race, smoking status, ECOG score, tumor stage, tumor site, baseline serum albumin level, number of previous lines of therapy, duration of previous line of therapy and practice type. HRs less than 1 represent worse survival for patients with prior irinotecan exposure than for those without.
[a]Results were not meaningful owing to small numbers in the group with prior exposure to irinotecan.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid + 5-fluorouracil + irinotecan; FOLFIRINOX, folinic acid + 5-fluorouracil + irinotecan + oxaliplatin; HR, hazard ratio.

CONCLUSIONS

- Data from this large, retrospective analysis of the second and later lines of therapy received by patients with mPDAC suggest that prior irinotecan exposure may not preclude benefit from later treatment with gem/nab or liposomal irinotecan + 5-FU/LV.
- Further investigation is required to understand why, in patients who were receiving FOLFOX as a second or later line of therapy, poorer OS was observed in those with prior irinotecan exposure than in those without prior exposure.
- These findings are hypothesis generating and should be considered in the context of wide confidence intervals and the inherent limitations of the retrospective study design.

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Medical writing support

The authors thank Maria Theodoridou, PhD, of Oxford PharmaGenesis, Oxford, UK, for providing medical writing support, which was sponsored by Ipsen Biopharmaceuticals, Inc., in accordance with Good Publication Practice guidelines.

Acknowledgments

The study was supported by Ipsen Biopharmaceuticals, Inc.

Conflicts of interest

EMO'R's institution has received research funding from Acta Biologica, AstraZeneca, Bristol-Myers Squibb, Genentech, Matrix Therapeutics, Roche and Silenseed, and she has received compensation for consulting and advisory services from Bayer, BioLineRx, Bristol-Myers Squibb, OncoMX Therapeutics, Ipsen, Lead Oncology, Merck, Polaris and Targovax. AS and AD are employees of Genesis Research LLC, which received consulting funding from Ipsen Biopharmaceuticals, Inc.
PC is an employee of Ipsen Biopharmaceuticals, Inc., and holds stock or stock options.
KHY has received research funding from Bristol-Myers Squibb and Ratiopharm and compensation for advisory services from Ipsen.

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Presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) 2020, January 23–25, 2020, San Francisco, CA, USA

This study was sponsored by Ipsen

Impact of prior irinotecan exposure on outcomes of metastatic pancreatic cancer patients
H2O
BACKGROUND
OBJECTIVE
METHODS
RESULTS
CONCLUSIONS

Real-world patterns of care among patients with metastatic pancreatic cancer

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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]
  - The estimated number of deaths from pancreatic cancer is predicted to increase by 57.2% between 2018 (50,745 deaths) and 2040 (79,756 deaths).[2]
- Of pancreatic cancer cases in the USA between 2009 and 2015, 53.0% were metastatic at diagnosis.[3]
  - The 5-year survival rate of metastatic pancreatic cancer was 2.9%,[3] highlighting the need to understand the impact of available treatments and to determine optimal treatment sequencing.
- Metastatic pancreatic ductal adenocarcinoma (mPDAC) accounts for the majority of this cancer type.[4]
- Currently, real-world evidence on the impact of treatment sequence on outcomes in patients with metastatic pancreatic cancer is limited.

OBJECTIVE

- The aims of this study were to examine treatment regimens and sequencing received by patients with mPDAC in the real-world setting, and to compare overall survival (OS) in patients who received treatment and in those who did not.

METHODS

Data source

- The Flatiron Health database contains electronic health records from over 280 cancer clinics (approximately 800 sites of care), representing more than 2.2 million patients with cancer.
- Deidentified data were extracted from the database for the period January 1, 2014, to June 30, 2019.

Study population

- Patients included in the study were considered to have mPDAC based on the following criteria.
  - Pancreatic cancer documented using diagnostic codes 157 and C25 from the International Classification of Diseases, 9th and 10th revisions, Clinical Modification.
  - Pathology consistent with PDAC.
  - Evidence of stage IV or progressive/recurrent disease on or after January 1, 2014.
- Patients had to be 18 years of age or older on the date they were diagnosed with metastatic disease.
- Patients were also required to have at least two documented clinical visits on or after January 1, 2014, and to have a documented activity (clinic visit or documented order) on, or in the first 90 days after, the diagnosis of metastatic disease.

Treatment

- Treatments were derived from structured medication orders and administration records. Those received by patients after, or up to 14 days before, the date of diagnosis of metastatic disease were included in the analysis.
- All drugs given within 28 days of an initial therapy were considered to be part of the same treatment regimen.
- The addition of a new therapy after 28 days was considered to be the start of a subsequent treatment regimen.

Overall survival

- OS from the date of diagnosis of metastatic disease was estimated using the Kaplan–Meier method.

Statistical analyses

- Differences between patients who received treatment for metastatic disease and those who did not were analyzed using a Pearson chi-squared test (categorical variables), T-test (continuous variables) or log-rank test (OS).
- All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Patient characteristics at the date of diagnosis of metastatic disease

	Treated (n = 5,687)	Untreated (n = 1,979)	*p* value[a]	Overall (N = 7,666)
Age category, years, n (%)				
18–44	97 (1.71)	22 (1.11)	< 0.0001	119 (1.55)
45–64	1,967 (34.59)	493 (24.91)		2,460 (32.09)
65–74	2,124 (37.35)	737 (37.24)		2,861 (37.32)
≥ 75	1,499 (26.36)	727 (36.74)		2,226 (29.04)
≤ 65	2,255 (39.65)	590 (29.81)	< 0.0001	2,845 (37.11)
≥ 66	3,432 (60.35)	1,389 (70.19)		4,821 (62.89)
Age, years				
Mean (SD)	67.4 (9.7)	70.1 (9.5)	< 0.0001	68.1 (9.7)
Median	68.0	71.0		69.0
Interquartile range (Q1–Q3)	61.0–75.0	64.0–78.0		62.0–76.0
Range (min–max)	22.0–85.0	25.0–85.0		22.0–85.0
Sex, n (%)				
Male	3,082 (54.19)	1,024 (51.74)	0.060	4,106 (53.56)
Female	2,605 (45.81)	955 (48.26)		3,560 (46.44)

Stage, n (%)				
IV	3,910 (68.75)	1,212 (61.24)	< 0.0001	5,122 (66.81)
Other	1,777 (31.25)	767 (38.76)		2,544 (33.19)
ECOG score, n (%)				
0	502 (8.83)	126 (6.37)	< 0.0001	628 (8.19)
1	617 (10.85)	210 (10.61)		827 (10.79)
≥ 2	179 (3.15)	124 (6.27)		303 (3.95)
Missing	4,389 (77.18)	1,519 (76.76)	–	5,908 (77.07)

[a]Based on a Pearson chi-squared test.
ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; Q, quarter; SD, standard deviation.

RESULTS

Patient characteristics

- Of 7,666 patients with mPDAC identified from the database, 5,687 (74.2%) had received treatment after the diagnosis of metastatic disease.
- Patients who had received treatment were significantly younger than those who had not received treatment and a significantly larger proportion had disease at a stage other than IV (**Table 1**).

Treatment sequence

- The most common first- and second-line therapy was gemcitabine + nab-paclitaxel; the most common third-line treatment regimen was liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) (**Table 2**).
- Use of first-line gemcitabine monotherapy decreased from 12.9% in 2014 to 7.3% in 2018.
- Use of second-line liposomal-irinotecan-based regimens increased from 6.0% in 2015 to 17.6% in 2018.

Overall survival

- Median OS was approximately 5 months longer among treated patients (8.1 months) than among untreated patients (2.8 months); hazard ratio, 0.44, $p < 0.0001$ (**Figure 1**).

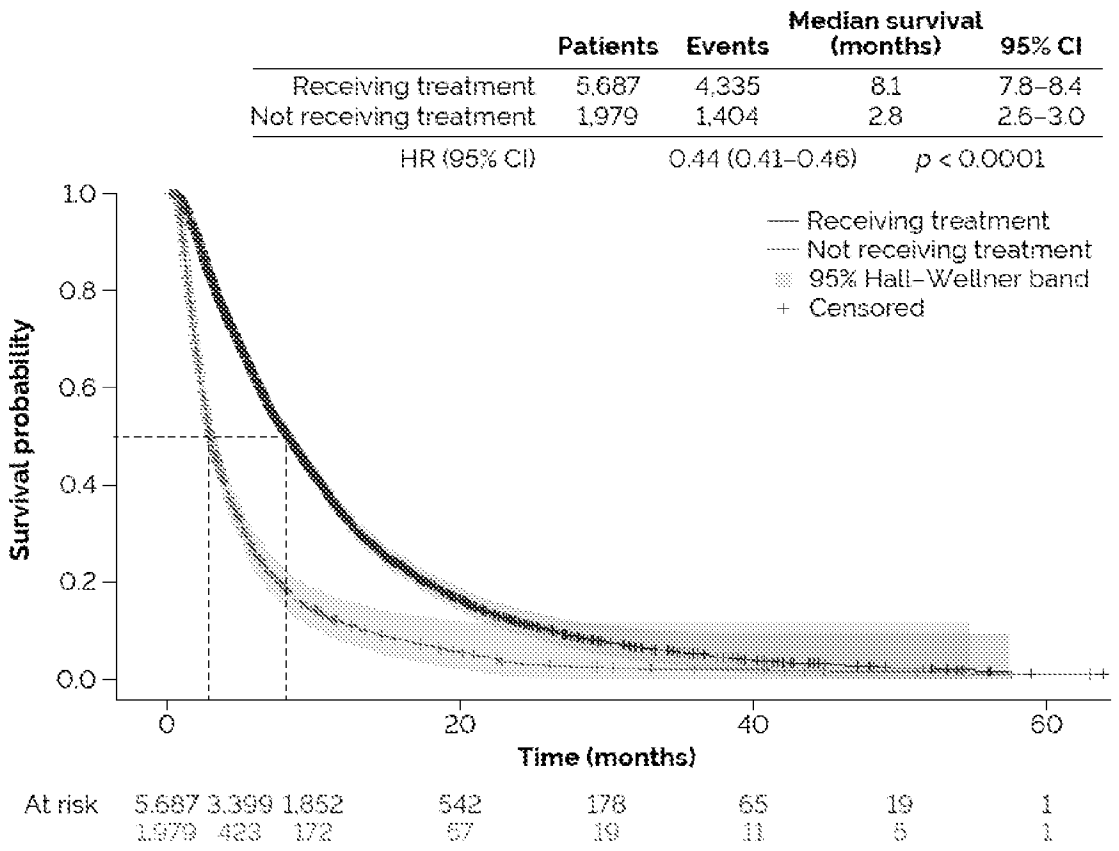
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Page 218 of 333

Table 2. Four most common treatment regimens per line of therapy

First-line therapy (N = 5,687)		Second-line therapy (N = 2,374)		Third-line therapy (N = 745)	
Regimen	Patients, n (%)	Regimen	Patients, n (%)	Regimen	Patients, n (%)
Gem/nab	2,662 (46.8)	Gem/nab	663 (31.4)	Liposomal irinotecan + 5-FU/LV	144 (19.3)
FOLFIRINOX	1,368 (24.1)	FOLFIRINOX	267 (12.3)	Gem/nab	90 (12.1)
Gemcitabine monotherapy	531 (9.3)	FOLFOX	248 (11.4)	FOLFOX	85 (11.4)
FOLFOX	217 (3.8)	Liposomal irinotecan + 5-FU/LV	221 (10.2)	FOLFIRINOX	68 (9.1)

5-FU/LV, 5-fluorouracil/leucovorin; FOLFIRINOX, folinic acid + 5-FU + irinotecan + oxaliplatin; FOLFOX, folinic acid + 5-FU + oxaliplatin; gem/nab, gemcitabine + nab-paclitaxel.

Figure 1. Overall survival from the date of diagnosis of metastatic disease



Data are for patients who did or did not receive treatment for metastatic disease. Death dates were imputed to the 15th of the month. HR and *p* value are from a log-rank test.
CI, confidence interval; HR, hazard ratio.

CONCLUSIONS

- In these analyses of real-world data, OS was significantly longer among patients with PDAC who received treatment after a diagnosis of metastatic disease than among those who did not receive treatment.
- Gemcitabine + nab-paclitaxel was the most commonly used first- and second-line treatment regimen, and liposomal irinotecan + 5-FU/LV was the most common third-line therapy.
- Further studies are needed to advance understanding of treatment patterns and outcomes in patients with mPDAC

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Medical writing support

The authors thank Maria Theodosiou, PhD, of Oxford PharmaGenesis, Oxford, UK, for providing medical writing support, which was sponsored by Ipsen Biopharmaceuticals, Inc., in accordance with Good Publication Practice guidelines.

Acknowledgments

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AS and ZW are employees of Genesis Research LLC which received consulting funding from Ipsen Biopharmaceuticals, Inc.

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Real-world patterns of care among patients with metastatic pancreatic cancer
BACKGROUND
OBJECTIVES
METHODS
RESULTS
CONCLUSIONS

PANCREATIC CANCER

Real-world patterns of care among patients with metastatic pancreatic cancer (mPC).

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Eileen Mary O'Reilly, Andy Surinach, Zheng Wu, Paul Cockrum

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Memorial Sloan Kettering Cancer Center, New York, NY; Genesis Research, Hoboken, NJ; Ipsen Biopharmaceuticals, Cambridge, MA

Abstract Disclosures

Abstract

666

Background: Pancreatic cancer is the third deadliest cancer in the US and mPC has a 2.9% 5-year survival. The analyses herein describe treatment patterns, trends in usage, and overall survival (OS) in mPC. **Methods:** Using the Flatiron Health EHR-derived database, data were extracted and analyzed for patients with mPC (pts) between Jan 1, 2014 and Jun 30, 2019. The database includes de-identified data from over 280 cancer clinics (~800 sites of care) representing more than 2.2 million U.S. cancer patients available for analysis, with 80% of pts from community centers and 20% from academic centers. Lines of therapy in the metastatic setting are derived from structured medication records. OS from metastatic diagnosis was reported using the Kaplan-Meier method. **Results:** 7,666 pts with mPC were identified. 5,687 (74.2%) received therapy in the metastatic setting. Pts who didn't receive therapy in the metastatic setting were more likely to be older ($p < 0.0001$) and less likely to have been diagnosed initially with stage IV disease ($p < 0.0001$) than pts who were treated. The frequency of (1L) regimens were gemcitabine plus nab-paclitaxel (GnP) 46.8%, FOLFIRINOX (FFX) 24.1%, gemcitabine monotherapy 9.3%, and FOLFOX 3.8%. Gemcitabine monotherapy use was 12.9% in 2014 and 7.3% in 2018. GnP (31.4%), FFX (12.3%), FOLFOX (11.4%), and liposomal irinotecan (nal-IRI) + 5-FU/LV (10.2%) were the most frequent second line (2L) regimens. Between 2015 and 2018 nal-IRI based regimens increased from 6% to 17.6% in 2L. In the third line (3L) setting nal-IRI + 5FU/LV (19.3%), GnP (12.1%), FOLFOX (11.4%), and FFX (9.1%) were the most common treatments. Aggregate median OS (mOS) for treated pts was 8.1 mos (95% CI

7.8 – 8.4), and mOS for untreated pts was 2.8 mos (2.6 – 3.0), p < 0.0001. **Conclusions:** Survival for mPC is improving and practice patterns are changing. GnP is the most commonly used 1L regimen, followed increasingly by nal-IRI + 5-FU/LV in 2L and 3L. Further studies are necessary to understand the treatment gaps for pts with mPC.

Line Number	Regimen	N	% (of line)
1	GnP	2662	46.8
1	FFX	1368	24.1
1	Gemcitabine	531	9.3
1	FOLFOX	217	3.8
2	GnP	683	31.4
2	FFX	267	12.3
2	FOLFOX	248	11.4
2	nal-IRI + 5-FU/LV	221	10.2
3	nal-IRI + 5-FU/LV	144	19.3
3	GnP	90	12.1
3	FOLFOX	85	11.4
3	FFX	68	9.1

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PANCREATIC CANCER

Impact of prior irinotecan exposure on outcomes of metastatic pancreatic cancer (mPC) patients.

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Eileen Mary O'Reilly, Andy Surinach, Allison Dillon, Paul Cockrum, Kenneth H. Yu

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Abstract Disclosures

Abstract

667

Background: Published data suggests prior exposure to irinotecan infers a lower likelihood of benefit to liposomal irinotecan. This analysis seeks to expand this hypothesis by evaluating U.S. patterns of care to understand how prior irinotecan therapy impacts outcomes in mPC. **Methods:** Using the Flatiron Health database, data were extracted and analyzed for treated mPC patients (pts) in the 2L+ setting between Jan 1, 2014 and Jun 30,2019. Therapies of interest included: gemcitabine/ nab-paclitaxel (GnP), FOLFOX, FOLFIRI, FOLFIRINOX (FFX), and liposomal irinotecan/5-FU/LV (nal-IRI). The reference date for each treatment group was the date of treatment initiation. Prior irinotecan was defined as any irinotecan given in a prior regimen in mPC diagnosis. Cox proportional hazard (PH) methods were used to calculate mortality hazard ratios (HRs). HRs were adjusted to account for demographics and relevant covariates. Pts with prior exposure to irinotecan were used as the reference population for the Cox PH model (an HR < 1 represents worse survival for exposed pts relative to the unexposed). **Results:** N = 1,978 were included in this analysis. The median age at treatment initiation, and the proportion of pts previously treated with irinotecan are reported in table. Crude mortality was: GnP pts, HR 0.93 [95% CI: 0.77 – 1.11, adjusted HR, 0.94, 0.76 – 1.15]; nal-IRI pts, HR 0.81 [0.64 – 1.02, adjusted HR: 0.89, 0.67 – 1.19]; HR for FOLFOX was 0.55 [0.38 – 0.78, adjusted HR: 0.51, 0.33 – 0.79]. HRs are not reported for FFX and FOLFIRI due to the small numbers with prior irinotecan exposure. **Conclusions:** In mPC, prior irinotecan treatment may not preclude benefit from later treatment with nal-IRI or GnP as can be seen from the adjusted and unadjusted HRs. These findings are hypothesis-generating and need to be considered in the context of wide CI's,

retrospective nature and the limitations of such data. Further study is required to understand the less-favorable signal observed with FOLFOX and prior irinotecan.

Therapy	N	Age at treatment initiation, years, median (IQR)	Prior irinotecan, N(%)
GnP	755	64 (58 – 70)	560 (74.2%)
Nal-IRI	446	67 (62 – 74)	128 (28.7%)
FOLFOX	353	69 (63 – 76)	46 (13%)
FOLFIRI	113	69 (63 – 75)	8 (7.1%)
FFX	311	66 (60 – 72)	5 (1.6%)

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A Cancer and Leukemia Group B Phase II Study of Sunitinib Malate in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma (CALGB 80603)

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Key Words. Sunitinib • Phase II • Refractory • Pancreas adenocarcinoma • CALGB 80603

Disclosures: Eileen M. O'Reilly: None; **Donna Niedzwiecki:** None; **Margaret Hall:** None; **Donna Hollis:** None; **Tanios Bekaii-Saab:** *Research funding/contracted research:* Pfizer; **Timothy Pluard:** None; **Kathe Douglas:** None; **Ghassan K. Abou-Alfa:** None; **Hedy L. Kindler:** *Research funding/contracted research:* Pfizer; **Richard L. Schilsky:** None; **Richard M. Goldberg:** *Research funding/contracted research:* Pfizer.

Sunitinib malate is not an approved drug for the treatment of pancreas adenocarcinoma.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

Abstract

Background. **The Cancer and Leukemia Group B (CALGB) conducted a phase II study evaluating sunitinib in patients with progressive metastatic pancreas adenocarcinoma following prior gemcitabine-based therapy (trial CALGB 80603; ClinicalTrials.gov identifier, NCT00397787). The primary endpoint was to determine the disease control rate (DCR) as measured by the Response Evaluation Criteria in Solid Tumors (complete response, partial response [PR], and stable disease) at 6 weeks.**

Patients and Methods. **Patients aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 and with progressive pancreas adenocarcinoma following treatment with gemcitabine were eligible. Sunitinib was dosed at 50 mg orally days 1–28, every 42 days (1 cycle). The statistical plan called for a three-stage design. A DCR ≥15% was considered worthy of further study.**

Results. **In total, 77 patients were enrolled. Forty-two (54.6%) enrollees were male. The median age was 65 years. The ECOG performance status score distribution was: 0, 39%; 1, 50%; 2, 11%. The DCR was 21.6%; one patient (1.4%) had a PR and 15 patients (20.3%) had stable disease as their best response. The progres-**

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CSPC Exhibit 1100
Page 226 of 333

sion-free survival time was 1.31 months (95% confidence interval [CI] 1.25–1.38 months) and overall survival time was 3.68 months (95% CI, 3.06–4.24 months).

Conclusions. **The study met its primary endpoint; however sunitinib had minimal activity and moderate toxicity in a population of gemcitabine-refractory pancreas adenocarcinoma patients. For future studies, limiting enrollment to patients with an ECOG performance status score of 0–1 is recommended.** *The Oncologist* 2010;15:1310–1319

Introduction

Pancreas adenocarcinoma is a very challenging malignancy because of its refractoriness to available treatments. About 42,000 people were estimated to have been diagnosed with this disease in the U.S. in 2009, the substantial majority of whom would have either locally advanced or metastatic pancreas adenocarcinoma. These patients received either gemcitabine or a gemcitabine-based combination as initial therapy for locally advanced or metastatic disease [1, 2]. Most patients derive modest benefit from frontline therapy, with a median time to progression of 2–4 months. About half of all patients who receive frontline therapy are well enough and eligible for second-line therapy [3, 4]. There is not a standard second-line therapy for pancreas adenocarcinoma, nor a set of well-defined prognostic factors for second-line therapy, and there is a relative dearth of trials conducted in this disease setting [5]. Data from the randomized Charité Onkologie (CONKO)-003 trial and single-institution data have suggested that a fluoropyrimidine combined with oxaliplatin may represent a reasonable second-line option [6–8]. Also, recent observations have demonstrated that only a tiny fraction, approximately 2%, of patients with pancreas adenocarcinoma who are potentially eligible for a second-line therapy actually receive such therapy in the context of a clinical trial [9]. This latter observation may be related to the limited availability of second-line trials in this disease setting.

Sunitinib malate (SU11248, NSC #736511) is an orally bioavailable, multitargeted small molecule inhibitor of several receptor tyrosine kinases that are involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor, and stem cell factor receptor (KIT) [10, 11]. VEGF and its receptors are over expressed in pancreas adenocarcinoma and have been associated with the development of metastases and a poor prognosis [12]. In part, the rationale for assessing sunitinib in pancreas adenocarcinoma in this study relates to the contribution of multiple signaling pathways to the pathogenesis of this disease and the potential to impact these pathways with a relatively broad-spectrum targeted therapy along with, at the time, promising data from other anti-VEGF inhibitors in this disease [13]. There is a precedent for the development of novel targeted agents in pancreatic cancer [14]. Treatment with erlotinib combined with gemcitabine has been shown to result in a longer time to tumor progression and higher median and 1-year survival rates than with gemcitabine alone in advanced pancreas cancer [15]. Pancreatic adenocarcinoma is also characterized by a profound desmoplastic and stromal reaction that has rarely been considered as a potential therapeutic target [16, 17]. Sunitinib, via its broad inhibition of receptor tyrosine kinases, offers the potential to target both the tumor directly and the stromal matrix. This paper reports a trial performed by a National Cancer Institute (NCI)-funded cooperative group evaluating the antitumor efficacy and safety of sunitinib malate in patients with previously treated pancreas adenocarcinoma.

Patients and Methods

Patients

This phase II study was conducted by the Cancer and Leukemia Group B (CALGB). Men and women aged ≥18 years with pancreas adenocarcinoma with histologic or cytologic proof of malignancy and with evidence of disease progression on a gemcitabine-containing frontline regimen were eligible. Patients had to fall into one of the following groups: (a) only one prior regimen of gemcitabine or a gemcitabine-containing combination was to have been administered; (b) one prior combined chemoradiotherapy regimen containing gemcitabine for inoperable locally advanced pancreas adenocarcinoma was permitted, as long as the patient had subsequently progressed with measurable disease outside the radiation port; (c) one prior adjuvant gemcitabine-containing regimen or combined chemoradiotherapy regimen containing gemcitabine could have been administered, if the patient subsequently experienced progression of disease within 3 months of completion of adjuvant therapy. Prior erlotinib was allowed. Measurable, metastatic disease was required (≥20 mm by conventional computerized tomography [CT] or ≥10 mm by spiral CT); locally advanced pancreatic cancer with the primary tumor as the sole site of disease was not allowed. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 was required. Required initial laboratory cri-

CSPC Exhibit 1100
Page 227 of 333

teria included the following: absolute neutrophil count ≥1,500/ul, platelet count ≥100,000/μl, bilirubin <1.5 mg/dl, prothrombin time and partial thromboplastin time <1.5× the upper limit of normal (ULN), serum creatinine ≤1.5 mg/dl, and aspartate aminotransferase ≤2.5× ULN if no liver metastases r ≤5× ULN if liver metastases were present. Written informed consent was required and the protocol was reviewed and approved by the local institutional review board at each participating site.

Exclusion criteria included the following. No prior therapy with any other antiangiogenic agent (e.g., bevacizumab, sorafenib, etc.) was permitted. No significant cardiac disease was permitted; specifically, the QTc interval had to be ≤500 msec. No prior myocardial infarction, cardiac arrhythmia, active angina, active congestive cardiac failure (New York Heart Association class III or class IV), or coronary artery bypass grafting or stenting in the previous 12 months prior to registration was allowed. No history of a cerebrovascular accident or transient ischemic attack within 12 months or pulmonary emboli within 6 months prior to registration was allowed. Patients with a nonhealing wound, ulcer, or bone fracture were not enrolled. No history of significant bleeding (within 6 months), abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess was permitted. Patients with duodenal invasion by tumor on CT were not enrolled. Inhibitors and inducers of cytochrome P450 3A4 had to be discontinued prior to and during treatment with sunitinib. Also, drugs with proarrhythmic potential were not allowed during the study. Use of warfarin anticoagulants was not allowed. No "currently active" second malignancy, other than nonmelanoma skin cancer, was permissible. Patients were not considered to have a "currently active" malignancy if they had completed therapy and were considered by their physician to have a <30% risk for relapse. Brain metastases excluded patients from enrollment.

Study Procedures

Prior to registration, patients underwent a history and physical examination including notation of height, weight, ECOG performance status score, vital signs (blood pressure, temperature, pulse, respiration), and a pregnancy test for all females of child-bearing potential. A baseline CT or magnetic resonance imaging scan documenting all sites of metastatic disease was required within 4 weeks of study enrollment. A baseline electrocardiogram and either echocardiogram (ECHO) or multigated acquisition (MUGA) scan were performed prior to the initiation of therapy. Patients were evaluated weekly for toxicity and blood pressure monitoring during the first cycle. Tumor restaging was performed every cycle (every 6 weeks) for each of the first four cycles and then every other cycle thereafter. A follow up ECHO or MUGA scan was performed after the second cycle of therapy (every 12 weeks). Treatment was continued indefinitely until either disease progression or unacceptable toxicity occurred.

As part of the quality assurance program of the CALGB, members of the audit committee visit all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 11 patients (14%) of the 77 patients under this study.

Treatment and Dose Adjustments

Sunitinib malate was provided by the Division of Cancer Treatment and Diagnosis (DCTD), NCI, under a collaborative agreement between Pfizer and the DCTD. The starting dose of sunitinib was 50 mg. Sunitinib was dosed at 50 mg orally daily irrespective of timing of food, for days 1–28 followed by 14 days of rest, constituting one treatment cycle (42 days, 6 weeks). Dose level −1 of sunitinib was 37.5 mg and level −2 was 25 mg. No dose re-escalation was permitted following dose adjustment for toxicity. Patients requiring dose reduction beyond the −2 level were to discontinue protocol therapy. A treatment break of up to 4 weeks was permitted for toxicity or other disease-related complications. Protocol-specific dose modifications were prescribed for grade 3 or 4 hematologic toxicity (neutropenia, thrombocytopenia), grade 3 or 4 fatigue, hypertension, QTc prolongation, decreases in left ventricular ejection fraction, and grade 3 or 4 skin toxicity or grade 3 or 4 bleeding. For all other grade 3 toxicities, sunitinib was held until toxicity improved to grade ≤2. For other grade 4 toxicities, protocol therapy was permanently discontinued.

Statistical Plan and Analysis

The study was designed as a single-arm, nonrandomized, multicenter cooperative group (CALGB) phase II trial of single-agent sunitinib for previously treated pancreas adenocarcinoma in patients with measurable metastatic disease. The primary endpoint of the study was disease the control rate (DCR), specified as either a complete response (CR), partial response (PR), or stable disease (SD) as measured by the Response Evaluation Criteria in Solid Tumors (RECIST) 6 weeks following the initiation of protocol therapy [18, 19]. The null hypothesis that the DCR according to the RECIST was ≤5%, versus the alternative that the DCR was ≥15%, was tested using a three-stage design. If the

DCR was ≥15%, then single-agent sunitinib was to be considered worthy of further study in gemcitabine-refractory pancreas adenocarcinoma. Nineteen patients were to be entered in stage 1. If a DCR of 0% was observed during the first 19 patients studied, the trial was to be closed because of a lack of efficacy. If a DCR >5% was observed among the first 19 patients studied, 20 additional patients were to be enrolled in stage 2. If a DCR ≤2% was observed among the first 39 patients studied, the trial was to close at stage 2 because of a lack of efficacy. If two or more cases of a CR, PR, or SD (DCR >5%) were observed among the first 39 patients studied, 21 additional patients were to be enrolled in stage 3. Sunitinib was to be considered worthy of further investigation at stage 3 if six cases of CR, PR, or SD (DCR of 10%) were observed among 60 eligible patients treated. The simulated power and significance level under this design (10,000 simulations) are 0.9 and 0.08, respectively. The sample size was increased to 64 to allow for replacement of patients who did not initiate protocol therapy. All patients who met the eligibility criteria and received at least one dose of protocol therapy were included in the analysis of the primary endpoint.

The secondary endpoints of the study were: response duration, progression-free survival (PFS), toxicity, and overall survival. Duration of response was determined for the subset of patients who achieved a confirmed response (CR or PR). Duration of an objective response was defined as the time from the first tumor assessment indicating response to the time of disease progression or death from any cause. PFS and overall survival times were assessed using the Kaplan–Meier method. Toxicity data were graded using the NCI Common Toxicity Criteria for Adverse Events, version 3.0. Particular attention was paid to hypertension, cardiac events, bleeding, and thrombotic events. All adverse events were reported to the CALGB. All patients who received at least one dose of sunitinib were evaluable for toxicity.

Results

Patient Characteristics

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson (E.O.'R.). Statistical analyses were performed by CALGB statisticians.

In total, 77 patients were enrolled from November 2006 through November 2007. The study met the criteria for proceeding to the third stage. Enrollment to the study was very brisk in the last several weeks and hence, in view of commitment to multiple study sites, the study recruitment exceeded the goal of 64 patients. Forty-two patients (54.5%) were male. The median age was 65 years (range, 42–87 years). The ECOG performance status score was 0 in 30 patients (38.9%), 1 in 38 patients (49.4%), and 2 in nine patients (11.7%). Eight-four percent of patients had liver metastases on entry to the study. Thirty-six percent of patients had had stable disease to prior gemcitabine and 10.4% had experienced a response to gemcitabine therapy. A detailed summary of patient characteristics is provided in Table 1.

Primary Endpoint

Seventy-four patients were eligible for analysis of the primary study endpoint. Three of the 77 patients enrolled never received treatment. The median follow-up time was 22.1 months. The median number of cycles delivered was one. The (CR, PR, or SD by the RECIST at 6 weeks) was 21.6%, with one patient (1.4%) with a PR and 15 patients (20.3%) with SD. Forty patients (54%) had progressive disease as their best response. Eighteen patients (24.3%) did not have a follow-up scan and were not evaluable for the primary endpoint. Those patients ended treatment prior to completing one cycle of therapy as a result of progressive disease ($n = 3$), death resulting from progressive disease ($n = 9$), and withdrawal of consent prior to receiving any treatment ($n = 3$). Only one of those patients was reported to have gone on to receive further treatment. For the patient with an observed PR, this was maintained for 16 weeks. For the 15 patients who had SD as their best response, the median SD duration was 11.3 weeks (range, 5.7–55 weeks). Response data are summarized in Table 2.

Secondary Endpoints

Seventy-four patients were eligible for the survival analysis. The median duration of protocol therapy was 28 days (range, 2–126 days). The median PFS interval for all 74 patients was 1.31 months (95% confidence interval [CI], 1.25–1.38 months) (Fig. 1). Seventy-three patients had died and one was alive at the time of the final study analysis. The overall median survival duration was 3.68 months (95% CI, 3.06–4.24 months) (Fig. 2).

Toxicity

All 74 patients who received any dose of study drug were eligible for toxicity assessment. Twenty-one (27.1%) patients required a dose modification during cycle 1. The principal grade 3–5 toxicities observed were hematologic ($n = 16$, 21.7%, and nonhematologic ($n = 32$, 43.2%). Specifically, relevant grade 3 toxicities included: hypertension in three patients (4%), fatigue in 13 patients (17.6%), bleeding

CSPC Exhibit 1100
Page 229 of 333

Table 1. Patient characteristics ($n = 77$)

Characteristic	n (%)
Gender	
Male	42 (54.6%)
Female	35 (45.4%)
Race	
White	66 (85.7%)
Black	9 (11.7%)
Asian	1 (1.3%)
Multiracial	1 (1.3%)
Median age (range), yrs	65 (42–87)
ECOG performance status score	
0	30 (39%)
1	38 (49.4%)
2	9 (11.7%)
Disease site	
Pancreas/primary bed	50 (64.9%)
Liver	65 (84.4%)
Lung	23 (29.9%)
Intra-abdominal (other)[a]	15 (19.5%)
Bone	1 (1.3%)
Prior surgery[b]	
No	40 (51.9%)
Yes	37 (48.1%)
Prior therapy	
Gemcitabine	47 (61%)
Gemcitabine-based cytotoxic combination	29 (38%)
Gemcitabine + tyrosine kinase inhibitor (erlotinib)	12 (15.6%)
(Chemo)radiation therapy	19 (24.7%)
Experimental therapy with or without gemcitabine	4 (5.2%)
Best response to prior gemcitabine therapy[c]	
Complete response	2 (2.6%)
Partial response	6 (7.8%)
Stable disease	28 (36.4%)
Progression of disease	38 (49.4%)
Unknown response	3 (3.9%)
Prior therapy context	
Adjuvant therapy	5 (6.5%)
Locally advanced disease	5 (6.5%)
Metastatic disease	67 (87%)
Months from initial diagnosis to start of protocol therapy, median (range)	8 (2.8–80)
Weeks from prior therapy to start of protocol therapy, median (range)	5 (2.9–31) wks

[a]Other sites include lymph nodes, ascites, retroperitoneum, spleen.
[b]Prior surgery included prior definitive resection, exploratory laparotomy, and surgical bypass.
[c]As reported by investigator.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Response data ($n = 74$)

Characteristic	n (%)
Primary endpoint: disease control rate at 6 wks (CR, PR, SD)	16 (21.6%)
Response 6 wks after starting therapy	
PR	1 (1.4%)
SD[a]	15 (20.3%)
Progressive disease	40 (54%)
Insufficient evaluation	18 (24.3%)

[a]One patient had an insufficient response evaluation at 6 weeks, but the best overall response was SD and the patient subsequently progressed after 1 year on study.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

in five patients (6.8%), thrombotic microangiopathy/renal failure in two patients (2.7%), and thrombosis in two patients (2.7%). There were two (2.7%) grade 5 events on study, a gastrointestinal perforation and respiratory distress. Both of these grade 5 toxicities were attributed to the study drug and related to progression of underlying pancreas adenocarcinoma. The commonest reasons for study discontinuation were progression of disease (POD) during therapy (61%), adverse event (9.1%), death during treatment/POD (14.3%), or declining further treatment (9.1%). Toxicity information is summarized in Table 3.

Discussion

Progressive metastatic pancreas adenocarcinoma following frontline gemcitabine-based therapy represents a very poor prognostic disease setting with median survival times measured in the several month range [20, 21]. However, this patient group represents a significant patient number in that about 40%–60% of patients who receive frontline therapy are well enough and eligible to receive further therapy [4]. New therapies are desperately needed for this patient population. This study assessed the single-agent utility of sunitinib, a broad-spectrum receptor tyrosine kinase inhibitor, in this patient population in the context of a large, cooperative group, single-arm, phase II clinical trial. Sunitinib represents an attractive drug to assess given its inhibition of multiple targets and the importance of the VEGF pathway in pancreas adenocarcinoma [12, 22] and, notwithstanding, potential activity against the desmoplastic stromal matrix, which appears to be fundamental to the development and maintenance of the pancreatic neoplastic phenotype [23]. This study technically met its primary endpoint of disease control in that 21.7% of patients had a CR, PR, or SD at 6 weeks (mostly SD). However, the very short time on study of less than one treatment cycle, reflected in

CSPC Exhibit 1009
Page 230 of 333

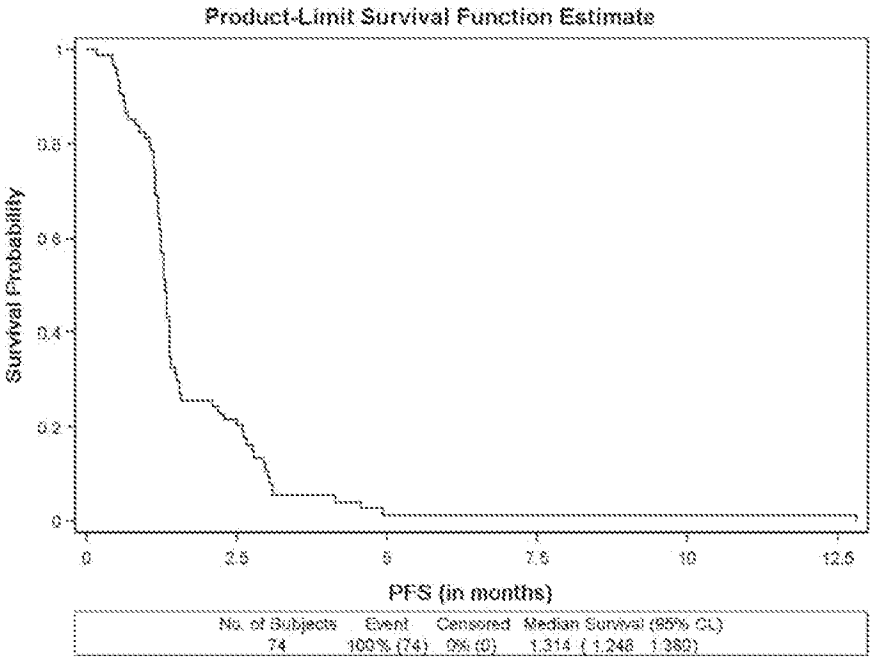


Figure 1. PFS in patients treated with sunitinib in the setting of prior gemcitabine treatment for metastatic pancreas adenocarcinoma.

Abbreviations: CI, confidence interval; PFS, progression-free survival.

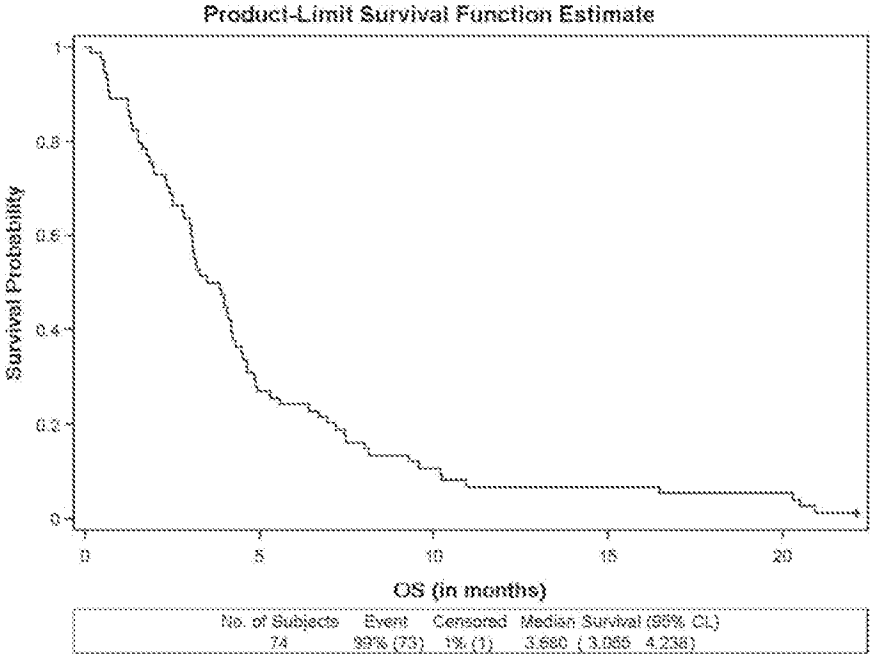


Figure 2. OS in patients treated with sunitinib in the setting of prior gemcitabine treatment for metastatic pancreas adenocarcinoma.

Abbreviations: CI, confidence interval; OS, overall survival.

the short PFS time of 1.31 months, the moderate toxicity, and the limited survival argue against any usefulness of sunitinib in this patient population. The experience and results observed in this study have been mirrored by other trials conducted with other targeted agents in a similar treatment population [20, 24–27]. One positive note was the interest in this trial evident in its very brisk recruitment, suggesting that a cooperative group can provide a good forum for conducting second-line clinical trials with novel agents in patients with previously treated pancreas adenocarcinoma.

Since the time of study conception, notwithstanding the

CSPC Exhibit 1100
Page 231 of 333

Table 3. Toxicity data ($n = 74$)

Adverse event	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
Hematologic			
Hemoglobin	4 (5.4%)	–	–
Neutrophils	5 (6.8%)	–	–
Platelets	6 (8.1%)	1 (1.4%)	–
Cardiovascular			
Hypertension	3 (4%)	–	–
Constitutional			
Fatigue	13 (17.6%)	1 (1/4%)	–
GI			
Anorexia	1 (1.4%)	–	–
Dehydration	5 (6.8%)	–	–
Diarrhea	2 (2.7%)	–	–
Constipation	2 (2.7%)	–	–
Bloating	2 (2.7%)		
Stomatitis	1 (1.4%)	–	–
Nausea	7 (9.5%)	–	–
Vomiting	5 (6.8%)	–	–
GI obstruction	1 (1.4%)	–	–
GI perforation	–	–	1 (1.4%)
GI stricture	1 (1.4%)	–	–
Hemorrhage			
Respiratory	1 (1.4%)	–	–
GI	4 (5.4%)	–	–
Infection			
Febrile neutropenia	2 (2.7%)	–	–
Fever and grade 1–2 ANC	4 (5.4%)	–	–
Other	3(4.1 %)	–	–
Metabolic/laboratory			
AST/ALT	5 (6.8%)	–	–
Bilirubin	3 (4.1%)	1 (1.4%)	
Hypercalcemia	1 (1.4%)		
Hypocalcemia	2 (2.7%)	–	–
Hypoglycemia	1 (1.4%)	–	–
Hypokalemia	2 (2.7%)	–	–
Hyponatremia	3 (4.1%)	1 (1.4%)	–
Hypernatremia	1 (1.4%)	–	–
Prolonged PT	2 (2.7%)	–	–
Neurologic			
Confusion	2 (2.7%)	–	–
Dizziness	1 (1.4%	–	–
Muscle weakness	2 (2.7%)	–	–
Pain	9 (12.2%)	1 (1.4%)	–
Pulmonary			
Dyspnea	3 (4.1%)	–	1 (1.4%)
Renal			
Thrombotic microangiopathy	1 (1.4)	–	–
Renal failure	1 (1.4)	–	–
GU stricture	1 (1.4%)	–	–
Vascular			
Thrombosis/embolism	2 (2.7%)	1 (1.4%)	–

Toxicity information pertains to all causes.
Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; GI, gastrointestinal; GU, genitourinary; PT, prothrombin time.

CSPC Exhibit 1006
Page 232 of 333

Table 4. Selected phase II trials of second-line therapy for pancreas adenocarincoma using targeted agents

Therapy	*n*	RR	Median survival	Study
Bevacizumab + erlotinib	36	2.7%	102 days (3.4 mos)	Ko et al. [20]
Capecitabine + erlotinib	30	11%	6.7 mos	Kalke et al. [36]
Erlotinib	18	NR	3.1 mos	Iyer et al. [25]
Saracatinib	19	NR	2.5 mos	Messersmith et al. [24]
5-Fluorouracil + celecoxib	17	11.7%	15 weeks (3.5 mos)	Milella et al. [39]
Capecitabine + celecoxib[a]	35	9%	19 weeks (4.4 mos)	Pino et al. [40]
Nab-paclitaxel	20	5%	7.3 mos	Hosein et al. [41]
Gemcitabine + oxaliplatin + imatinib (phase I)	26	7.7%	5.7 mos	Starling et al. [42]
Everolimus (RAD001)	33	0%	4.5 mos	Wolpin et al. [26]
Sunitinib	77	1.4%	3.68 mos	O'Reilly et al. [present study]

[a]Included patients with pancreas and biliary malignancies.
Abbreviations: NR, not reported; RR, response rate.

strong preclinical rationale for antivascular therapy in pancreas adenocarcinoma [12, 22, 28], the accumulating clinical data speak against the utility of targeting VEGFR pathways as being a useful clinical approach. In the treatment of frontline advanced pancreas adenocarcinoma, there are now two fully reported randomized trials that have failed to meet a primary survival endpoint of demonstrating superiority for the addition of the antivascular agent [29–34], and two other studies evaluating the addition of axitinib to gemcitabine and the addition of aflibercept (VEGF-Trap) to gemcitabine have been preliminarily reported as not meeting a survival endpoint. The reasons for the failure of antivascular therapy remain relatively poorly understood and may relate to the hypoxic microenvironment of pancreas adenocarcinoma, along with drug delivery and distribution challenges [17, 35].

Targeted agents have been extensively assessed in both the first- and second-line setting in pancreas adenocarcinoma. Using single or combination targeted agents in a second-line setting has yielded rare responses, short PFS and overall survival times, and limited value to this strategy (Table 4). Drugs assessed include erlotinib [25], saracatinib [24], everolimus [26], bevacizumab plus erlotinib [20], and sunitinib. Somewhat more activity has been observed for combining a targeted agent with cytotoxic therapy in the refractory disease setting [36], although here the benefit may relate to the cytotoxic backbone alone because no randomized trials have evaluated the addition of a targeted agent in the second-line setting when combined with cytotoxic therapy.

Where do we go from here in the second-line treatment of pancreas adenocarcinoma? Treating patients with advanced pancreas cancer refractory to frontline therapy remains very challenging. Of fundamental importance is the patient's functional status at the time of second-line treatment initiation [5, 30]. Arguably, performance status may be one of the key predictors of outcome in the second-line setting of treatment for pancreas adenocarcinoma, along with whether or not patients responded to initial gemcitabine-based therapy. The latter characteristic was not formally assessed as part of this particular study, but was provided by the investigator. In the trial reported herein, response to prior therapy did not appear to correlate with outcome; however, other cytotoxic-based trials have stratified for response to frontline therapy [21]. In another retrospective analysis, the first-line PFS interval was identified to be the main prognostic factor for benefit from second-line therapy [3]. The current study permitted patients with an ECOG performance status score of 2. In reality, these patients probably never really had a chance to benefit from second-line therapy because their disease-related complications/comorbidities were always likely to overwhelm the potential benefit of the therapeutic agent under study. Restricting enrollment in this second-line setting to patients with an ECOG performance status score of 0–1 is recommended going forward, particularly in studies accrued from a broad base spanning academic centers through community practice settings.

Regardless, the fundamental challenge for making progress in the treatment of pancreas adenocarcinoma, irrespective of disease setting, does not relate to patient selection. It relates to the dearth of truly active drugs with meaningful impacts on pathways that are important for maintenance and progression of the malignant metastatic state and the natural history of the disease. In these authors' opinions, cytotoxic therapy remains entrenched as part of

CSPC Exhibit 1100
Page 233 of 333

the treatment of pancreas cancer either first- or second-line. Conroy et al. [37] recently reported preliminary results from the Partenariat de Recherche Oncologie Digestive (PRODIGE) 4/ACCORD 11 trial demonstrating clear superiority for 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (the FOLFIRINOX regimen) over gemcitabine in patients with untreated metastatic pancreas cancer. This signal deserves further evaluation, and indeed, variants of it (infusional 5-fluorouracil and oxaliplatin [6, 21, 38]) are already established as a second-line treatment. For now, the role of targeted agents in previously treated pancreas cancer patients appears to be with integration with cytotoxic therapy. Olive and colleagues elegantly demonstrated that inhibition of Hedgehog signaling in a pancreas cancer mouse model refractory to gemcitabine may enhance drug delivery and effect short-term disease stabilization in the presence of IPI-926, a hedgehog signaling inhibitor [35]. If the proof of principle of this strategy holds, the implications could be significant for the treatment of pancreas adenocarcinoma.

Acknowledgments

The research for CALGB 80603 trial was supported, in part, by grants from the NCI (CA31946) to the CALGB (Richard L. Schilsky, M.D., Chairman) and to the CALGB Statistical Center (Stephen George, Ph.D., CA33601). This trial was also supported by the Cancer Treatment Evaluation Program and Pfizer. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NCI.

The following institutions participated in the study: Christiana Care Health Services, Inc. CCOP, Wilmington, DE—Stephen Grubbs, M.D., supported by CA45418; Dana-Farber Cancer Institute, Boston, MA—Harold J Burstein, M.D., Ph.D., supported by CA32291; Dartmouth Medical School–Norris Cotton Cancer Center, Lebanon, NH—Konstantin Dragnev, M.D., supported by CA04326; Duke University Medical Center, Durham, NC—Jeffrey Crawford, M.D., supported by CA47577; Georgetown University Medical Center, Washington, DC—Minetta C. Liu, M.D., supported by CA77597; Hematology-Oncology Associates of Central New York CCOP, Syracuse, NY—Jeffrey Kirshner, M.D., supported by CA45389; Illinois Oncology Research Association, Peoria, IL—John W. Kugler, M.D., supported by CA35113; Long Island Jewish Medical Center, Lake Success, NY—Kanti R. Rai, M.D., supported by CA35279; Memorial Sloan-Kettering Cancer Center, New York, NY—Clifford A. Hudis, M.D., supported by CA77651; Missouri Valley Consortium-Ccop, Omaha, NE—Gamini S. Soori, M.D.; New Hampshire Oncology-Hematology PA. Concord, NH—Douglas J. Weckstein; Northern Indiana Cancer Research Consortium CCOP, South Bend, IN—Rafat Ansari, M.D., supported by CA86726; Rhode Island Hospital, Providence, RI—William Sikov, M.D., supported by CA08025; Southeast Cancer Control Consortium Inc. CCOP, Goldsboro, NC—James N. Atkins, M.D., supported by CA45808; The Ohio State University Medical Center, Columbus, OH—Clara D. Bloomfield, M.D., supported by CA77658; University of California at San Diego, San Diego, CA—Barbara A. Parker, M.D., supported by CA11789; University of Chicago, Chicago, IL—Hedy L. Kindler, M.D., supported by CA41287; University of Iowa, Iowa City, IA—Daniel A. Vaena, M.D., supported by CA47642; University of Nebraska Medical Center, Omaha, NE—Anne Kessinger, M.D., supported by CA77298; University of Vermont, Burlington, VT—Steven M. Grunberg, M.D., supported by CA77406; Washington University School of Medicine, St. Louis, MO—Nancy Bartlett, M.D., supported by CA77440.

This work was presented previously in part at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, 2008.

Author Contributions

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CSPC Exhibit 1100
Page 235 of 333

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Irinotecan Liposome (Onivyde) Submitted Reimbursement Request: For the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treated with gemcitabine-based therapy	
Submitted By: Shire Canada	Manufactured By: Shire Canada
NOC Date: August 9, 2017	Submission Date: April 27, 2017
Initial Recommendation: November 2, 2017	Final Recommendation: January 5, 2018

Drug Costs	
Approximate per Patient Drug Costs, per Month (28 days) Submitted list price of $1,000.00 per 43 mg vial/10 mL * Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7m².	Irinotecan liposome in combination with 5-FU and LV costs: • $6,819.94 per 28-day course

pERC RECOMMENDATION

pERC recommends the reimbursement of irinotecan liposome in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients with locally advanced, unresectable or metastatic adenocarcinoma of the pancreas who have progressed on gemcitabine-based therapy conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for patients with good performance status. Treatment should continue until disease progression or unacceptable toxicity.

The Committee made this Recommendation because it was satisfied that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone based on a modest improvement in overall survival and progression-free survival. pERC noted that the combination therapy is associated with increased, but manageable, toxicities.

pERC agreed that irinotecan liposome in combination with 5-FU/LV aligns with patient values, as there is a need for effective treatment options that prolong survival.

The Committee concluded that, at the submitted price, irinotecan liposome in combination with 5-FU/LV could not be considered cost-effective compared with 5-FU/LV alone.

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POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV in patients who have progressed on gemcitabine-based therapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve cost-effectiveness to an acceptable level. **Insufficient Evidence to Support the Use of Irinotecan Liposome in Patients Who Progress After Treatment with Irinotecan-Containing Regimens** There is currently insufficient evidence to support the use of irinotecan liposome in combination with 5-FU/LV in patients who progress after being previously treated with irinotecan-containing regimens (ex. FOLFIRINOX). pERC also noted that there is insufficient evidence to support the substitution of irinotecan liposome in other irinotecan-containing combination therapies. **Time-Limited Need for Irinotecan Liposome for Patients in Third-Line Treatment and Beyond** At the time of implementing a reimbursement recommendation for irinotecan liposome in combination with 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy, jurisdictions may consider addressing the short-term, time-limited need for patients who are currently receiving gemcitabine-based therapy for second-line therapy, based on the clinical discretion of the treating physician. **Clear Labelling of Dose and Packaging to Minimize the Potential for Confusion and Error With Irinotecan Free Base** pERC noted that the Health Canada product monograph indicates that the dose of irinotecan liposome is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI-1 trial indicates that the dose of irinotecan liposome is 80 mg/m^2, which is equivalent to 70 mg/m^2 of irinotecan free base. pERC noted that upon implementation of irinotecan liposome, the dose must be clearly labelled, and packaging should clearly differentiate it from irinotecan free base in order to minimize confusion between the two products.

SUMMARY OF pERC DELIBERATIONS

Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016. However, it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. Patients often experience a rapid decline in health and die soon after diagnosis. The majority of patients present with either metastatic or locally advanced, unresectable disease. The mainstay of treatment for such patients is palliative chemotherapy. Although the palliative treatment of advanced pancreatic cancer has significantly improved in the past several years, with median survival exceeding eight months, long-term survival is not common for most advanced pancreatic cancer patients, with fewer than 20% remaining alive at 18 months. In the first-line setting, for patients fit enough to receive systemic therapy, treatment options include FOLFIRINOX, gemcitabine with nab-paclitaxel, and gemcitabine alone. The Clinical Guidance Panel (CGP) noted that progress in second-line therapy for advanced pancreatic cancer has been modest, with few randomized controlled trials (RCTs). In the second-line setting, treatment options include oxaliplatin with 5-FU (OFF), 5-FU alone, or capecitabine. Registered clinicians noted that there are no high-level data to support the usage of any one regimen over another; however, the choice of second-line therapy is affected by the first-line treatment regimen. Registered clinicians and the CGP indicated an unmet need for second-line treatment options for patients with metastatic pancreatic cancer who have progressed on first-line gemcitabine-based chemotherapy, as there is currently no standard of care for that group of patients. Therefore, pERC agreed that there is a need for more effective and tolerable therapies in the post-progression setting, for which there are limited therapeutic options to prolong survival.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one RCT, NAPOLI-1, that compared irinotecan liposome monotherapy with 5-FU/LV or irinotecan liposome plus 5-FU/LV with 5-FU/LV alone. The Committee primarily focused its deliberations on the comparison between the combination of irinotecan liposome and 5-FU/LV compared with 5-FU/LV alone. pERC noted that the NAPOLI-1 trial demonstrated a statistically significant improvement in overall survival (OS) in favour of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone. pERC considered that in a patient population that experiences a rapid decline in health post-progression, and for whom few treatment options are available, a modest OS improvement of 1.9 months was considered to be clinically meaningful. The Committee also noted that there was a similar trend favouring the combination therapy in all key secondary outcomes including progression-free survival (PFS).

pERC discussed whether the results of the NAPOLI-1 trial in patients with metastatic adenocarcinoma of the pancreas could be generalized to the locally advanced disease population. pERC noted that in clinical practice, both patient populations receive similar systemic therapies, and that transition from locally advanced unresectable disease to metastatic disease often occurs rapidly. Therefore, pERC agreed with the CGP that treatment availability should be extended to patients with locally advanced unresectable disease. pERC also discussed the fact that the majority of patients enrolled in the NAPOLI-1 trial had a good performance status, and that in clinical practice, pancreatic cancer patients are more likely to have a worse performance status at this stage of their disease. Registered clinicians also noted that patients often have poor performance status in the post-progression setting, and that many would not be well enough to receive second-line therapy. Therefore, pERC agreed that the use of irinotecan liposome in combination with 5-FU/LV in the post-progression setting should be restricted to patients with good performance status based on the discretion of the treating oncologist.

pERC deliberated on the toxicity profile of the combination of irinotecan liposome and 5-FU/LV, and noted there were more frequent grade 3 or higher treatment-emergent adverse events (TEAEs) compared with 5-FU/LV alone. The most common adverse events (AEs) reported among patients receiving the combination therapy included diarrhea, vomiting, nausea, decreased appetite, and fatigue. pERC noted that febrile neutropenia was more frequent among patients treated with irinotecan liposome combination therapy. Furthermore, the Committee noted that patients could be treated with growth factor support in the NAPOLI-1 trial. pERC discussed the fact that the use of growth factor support is typically low in the

palliative setting, and that growth factor support was used in 17% of patients in the NAPOLI trial, which the Committee noted is much higher than what is used in the Canadian setting. pERC also discussed that the rates of neutropenia and febrile neutropenia may be much higher in clinical practice if growth factor support is not used during treatment with combination therapy. pERC also considered that registered clinicians providing input noted that irinotecan liposome is a new delivery method for an old drug, so clinicians have experience with managing the side effects associated with irinotecan free base. Overall, pERC agreed that the toxicities with the combination therapy are expected and manageable in the context of the disease and drug.

pERC discussed the available quality-of-life (QoL) data from the NAPOLI-1 trial and noted that no significant improvement or deterioration was observed between the irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. However, pERC noted that the QoL data should be interpreted with caution, as there was a low compliance rate and a high amount of missing data due to the discontinuation of treatment because of disease progression, AEs, or death. Overall, pERC concluded that the impact of the combination therapy on QoL is uncertain.

pERC considered the comparison with 5-FU/LV in the NAPOLI-1 trial to be reasonable in this setting, but also considered the results of a network meta-analysis (NMA) provided by the submitter that compared irinotecan liposome in combination with 5-FU/LV with other relevant comparators in Canada, including 5-FU/LV, OFF, mFOLFOX, mFOLFIRI, and best supportive care. pERC discussed the critical appraisal of the NMA and noted that, in agreement with the Methods Team and CGP, the substantial heterogeneity between the included studies made the results highly unreliable and uncertain. Therefore, the comparative efficacy of irinotecan liposome plus 5-FU/LV with other anticancer agents is unknown. pERC also noted that there was no comparison between irinotecan liposome and irinotecan free base; therefore, the comparative efficacy is unknown.

Upon reconsideration of the pERC Initial Recommendation, pERC noted feedback from the Provincial Advisory Group (PAG) stating that it is unknown whether the benefit seen with the irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. PAG noted that jurisdictions have made generic oxaliplatin and irinotecan free base in combination with 5-FU/LV, capecitabine, and fluoropyrimidine available as treatment options, recognizing that there is a lack of high-level evidence for a standard of care in patients previously treated with gemcitabine-based therapies. pERC reiterated that despite available treatment options in the second-line setting, there is no standard of care or high-level data to support the usage of any one regimen over another. The Committee also reiterated the fact that 5-FU/LV was considered to be a reasonable comparator in this setting by the CGP and registered clinicians. pERC reiterated its conclusion that irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone in patients who have progressed on gemcitabine-based therapies demonstrated a statistically significant and clinically meaningful improvement in outcomes important to decision-making, including OS and PFS. The Committee also noted that the use of irinotecan liposome in combination with 5-FU/LV will be limited to a small group of patients with an acceptable performance status who can receive second-line therapy in the post-progression setting.

In addition, although pERC recognized and discussed the concerns raised by PAG, they also reflected on the impact this kind of feedback may have had on patients' timely access to treatments. The Committee noted that there were no data available to inform the comparison of irinotecan free base to irinotecan liposome at the time of deliberations on the pERC Initial Recommendation. pERC acknowledged the importance of balancing the obligation of providing due process for substantive concerns raised by stakeholders with the goal of providing timely access to treatment for patients.

Overall, pERC concluded that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone based on the modest improvement in OS and PFS as well as the need for more effective treatments options for patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy.

pERC deliberated on joint input from two patient advocacy groups. Patient input indicated that patients value new effective treatment options that improve QoL and prolong survival. The Committee noted that patients strongly valued a modest improvement in OS for this patient population with rapid decline in health post-progression, for which few treatment options are available. pERC also noted that patient input indicated that patients strongly valued the option of trying new therapies but also valued balancing the benefits and risks of a drug therapy with the overall impact on QoL. pERC noted that patients indicated they would be willing to try new therapies; however, the Committee also acknowledged

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comments that patients and their families want to have honest discussions with their oncologists to assess the risks and benefits associated with treatment so that they can make informed and personalized decisions about treatment. pERC noted that, although the results from the NAPOLI trial did not demonstrate an improvement in QoL, it appeared that no appreciable detriment in QoL was observed. However, the Committee noted that there was low compliance and a large amount of missing data, which increases the uncertainty in the results. pERC also noted that the toxicity profile of irinotecan liposome in combination with 5-FU/LV was considered manageable by most patients. Overall, pERC concluded that the therapeutic intent of irinotecan liposome as an effective treatment option that prolongs survival aligns with patient values. However, the Committee was limited by the available QoL data from the NAPOLI trial and was uncertain on how treatment with irinotecan liposome in combination with 5-FU/LV truly impacts QoL.

pERC deliberated on the cost-effectiveness of irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. The Committee noted that the pCODR Economic Guidance Panel's (EGP's) estimates were higher than the manufacturer's estimates. This was primarily due to differences in the estimate of drug wastage, the source of drug costs, the use of time-to-treatment failure as a proxy for treatment duration, and utility values derived from the literature. pERC considered that the use of time-to-treatment failure as a proxy for treatment duration does not account for patients who may have discontinued treatment with irinotecan liposome plus 5-FU/LV prior to progression due to AEs, then re-initiated therapy prior to progressing. Furthermore, since the intent of treatment with irinotecan liposome plus 5-FU/LV is to continue until progression, pERC agreed that the use of PFS as a proxy for treatment duration was more reasonable. The Committee also discussed the fact that the cost of the use of growth factor support that may be required to treat toxicities such as febrile neutropenia while on the combination therapy was not accounted for in the model; therefore, pERC agreed that the costs of managing such toxicities are likely underestimated in the pharmacoeconomic model. Furthermore, pERC noted that the cost of irinotecan liposome is four times that of irinotecan free base; therefore the Committee agreed that a substantial reduction in the drug price of irinotecan liposome would be required. pERC concluded that at the submitted price, the combination therapy could not be considered cost-effective. pERC also agreed with the EGP's assessment regarding the considerable uncertainty in the efficacy estimates from the provided NMA between relevant comparators, including mFOLFOX and OFF and irinotecan liposome plus 5-FU/LV.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted input from PAG that it is unknown whether the benefit observed with irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. In the absence of a comparison with irinotecan free base, the true cost-effectiveness and value of funding irinotecan liposome is difficult to determine. pERC reiterated that there are currently no available data on the comparison between irinotecan liposome and irinotecan free base, and, therefore, the Committee noted that the comparative effectiveness and the relative cost-effectiveness are unknown.

pERC discussed the feasibility of implementing a reimbursement recommendation for irinotecan liposome plus 5-FU/LV. pERC noted that irinotecan liposome is provided in a single 50 mg vial. In most instances, vial sharing will not be feasible, given the small number of patients with pancreatic cancer receiving second-line treatment; therefore, the Committee agreed that there will be significant wastage. As an additional systemic therapy to chemotherapy, pERC noted the PAG's concern that there will be increased chair time for treatment administration to patients. Furthermore, pERC discussed PAG's concern regarding the different dosing in the Health Canada product monograph compared with the NAPOLI-1 trial publication. pERC noted that the product monograph dose is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI-1 trial indicates that irinotecan liposome 80 mg/m^2 is equivalent to 70 mg/m^2 of irinotecan free base. pERC cautioned that the dose must be clearly labelled, and the packaging should clearly differentiate it from irinotecan free base to minimize confusion between the two products.

pERC also discussed the place of irinotecan liposome plus 5-FU/LV in therapy and noted that there is limited evidence evaluating the effectiveness of irinotecan liposome in combination with 5-FU/LV in patients who have progressed after being previously treated with irinotecan-containing regimens (e.g., FOLFIRINOX). pERC noted that both the CGP and registered clinicians indicated that they do not support the use of irinotecan liposome after previous treatment with irinotecan-containing regimens like FOLFIRINOX. Therefore, pERC concluded that irinotecan liposome plus 5-FU/LV should not be considered for patients who have progressed after previous irinotecan-based therapy. Additionally, pERC noted the potential need for the short-term, time-limited need for the combination therapy for patients who are

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currently receiving gemcitabine-based therapy as second-line therapy, based on the clinical discretion of the treating physician.

Finally, pERC discussed the budget impact and noted that the factor that most influenced the budget-impact analysis (BIA) is the cost of oxaliplatin in the comparator regimen (e.g., mFOLFOX, OFF). pERC noted that using the generic price of oxaliplatin (approximately $0.70 per mg) in the comparator regimen instead of the brand name price of oxaliplatin increases the budget impact substantially as a lower price of the comparator increases the incremental difference. Other factors that influence the BIA include market share assumptions, time on treatment, and dose intensity. pERC noted that wastage was not considered in the BIA, but that the inclusion of wastage would increase the budget-impact estimate substantially.

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EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget-impact analysis (BIA)
- guidance from pCODR clinical and economic review panels
- input from a joint submission from Pancreatic Cancer Canada (PCC) and the Canadian Organization for Rare Disorders (CORD)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one registered clinician group
- the PAG.

The pERC Initial Recommendation was to recommend reimbursement of irinotecan liposome (Onivyde) for the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treated with gemcitabine-based therapy. Feedback on the pERC Initial Recommendation indicated that the registered clinicians agreed with the Initial Recommendation and PAG disagreed with the Initial Recommendation. The submitter and the patient advocacy group did not provide feedback on the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of irinotecan liposome (Onivyde) for the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-FU/LV in adult patients who have been previously treated with gemcitabine-based therapy.

Studies included: One randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial (RCT), NAPOLI-1. The NAPOLI-1 trial publication refers to irinotecan liposome as nanoliposomal irinotecan. Patients were initially randomized (1:1) to receive either irinotecan liposome monotherapy (120 mg/m^2 every three weeks) or 5-FU/LV (2,000 mg/m^2 and 200 mg/m^2 every week for the first four weeks of a six-week cycle) (Protocol version 1). However, after a protocol amendment, a third arm was added to the trial: irinotecan liposome (80 mg/m^2) plus 5-FU/LV (2,400 mg/m^2 and 400 mg/m^2) every two weeks (Protocol version 2). Henceforth, patients were randomized on a 1:1:1 ratio to receive irinotecan liposome monotherapy (n = 151), 5-FU/LV (n = 119), or irinotecan liposome plus 5-FU/LV (n = 117), which was stratified by baseline albumin, Karnofsky performance status (KPS), and ethnic origin. The focus of pERC's deliberations was on irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. Patients continued to be treated until disease progression (radiological or clinical deterioration), intolerable toxic effects, or other withdrawal criteria.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis (NMA) of irinotecan liposome versus other comparators, such as 5-FU/LV plus oxaliplatin, a modified FOLFIRI regimen, 5-FU/LV plus non-liposomal irinotecan, and best supportive care. pERC noted that there was no comparison made between irinotecan free base and irinotecan liposome.

Patient populations: Karnofsky performance status of greater than 70; majority of patients had received one previous line of metastatic treatment

Baseline characteristics were generally well balanced between the treatment arms. Patients were eligible to participate in the NAPOLI-1 trial if they had histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas; metastatic disease; documented disease progression after prior gemcitabine-based therapy; KPS ≥ 70; and adequate bone marrow, hepatic, and renal function. Previous treatment with irinotecan was allowed.

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Overall, the median age of all patients was 63 years (range: 31 to 87); the majority of patients were male (56.8%), white (60.7%), and had a KPS score of 90 (40.5%) or 80 (35.7%). In addition, patients were more likely to have a tumour in the head of the pancreas (57.3%) and have two measurable metastatic sites (44.1%). Additionally, 44.6% of patients had previously received gemcitabine alone and 55.4% had received gemcitabine in combination with another anticancer therapy. 56% of patients had received one previous line of metastatic treatment and 32% had previously received two or more lines of metastatic treatment. Twelve per cent of patients had received gemcitabine-based therapy in the adjuvant, neoadjuvant, or locally advanced setting, but had not had previous treatment for metastatic disease.

pERC discussed whether the results of the NAPOLI-1 trial in patients with metastatic adenocarcinoma of the pancreas could be generalized to the locally advanced unresectable disease population. pERC noted that in clinical practice, both patient populations receive similar systemic therapies, and that the transition from locally advanced unresectable disease to metastatic disease often occurs rapidly. Therefore, pERC agreed with the Clinical Guidance Panel (CGP) that treatment availability should be extended to include patients with locally advanced unresectable disease. pERC also discussed the fact that the majority of enrolled patients had a KPS of 80 or higher, and that in clinical practice, pancreatic cancer patients are more likely to have a worse performance status at this stage of their disease. Therefore, pERC agreed that the use of liposomal irinotecan liposome should be limited to patients with good performance status.

Key efficacy results: Statistically significant difference in overall survival and progression-free survival in favour of Irinotecan liposome plus 5-FU/LV compared with 5-FU/LV

pERC deliberated on overall survival (OS), the primary outcome, as well as progression-free survival (PFS), a key secondary outcome. pERC noted that there was a statistically significant improvement in OS in favour of the irinotecan liposome combination arm (6.1 months [95% CI, 4.76 to 8.87]) compared with 5-FU/LV (4.2 months [95% CI, 3.3 to 5.3]). Irinotecan liposome plus 5-FU/LV therapy was associated with a significantly prolonged OS compared with 5-FU/LV therapy (HR 0.67; 95% CI, 0.49 to 0.92; $P = 0.012$). pERC discussed the magnitude of clinical benefit and noted that it was clinically meaningful in patients who experience rapid decline following progression on gemcitabine-based therapy.

The median PFS for the combination group was 3.1 months (95% CI, 2.7 to 4.2) and 1.5 months (95% CI, 1.4 to 1.8) in the 5-FU/LV group. The combination therapy was associated with a prolonged PFS compared with the 5-FU/LV (HR 0.56; 95% CI, 0.41 to 0.75; $P = 0.0001$). At the final analysis of the NAPOLI trial conducted on November 16, 2015, PFS was prolonged with irinotecan liposome combination therapy compared with 5-FU/LV therapy (3.09 months [95% CI, 2.69 to 4.17] versus 1.46 months [95% CI, 1.41 to 1.84]; HR 0.57; 95% CI, 0.43 to 0.76; $P < 0.001$). pERC agreed with the CGP that, in a patient population with limited treatment options who otherwise face a rapid decline following progression, the consistency of the observed effects across major primary and secondary end points represented clinically meaningful outcomes for patients.

pERC noted that mFOLFOX and oxaliplatin with 5-FU (OFF) were considered relevant comparators in Canada in a NMA provided by the submitter. pERC discussed the critical appraisal of the NMA and noted that, in agreement with the Methods Team and CGP, the substantial heterogeneity between the included trials made the results highly unreliable and uncertain.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from PAG stating that it is unknown whether the benefit seen with the irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. PAG noted that jurisdictions have made generic oxaliplatin and irinotecan in combination with 5-FU/LV, capecitabine, and fluoropyrimidine therapy available as treatment options, recognizing that there is a lack of high-level evidence for a standard of care in patients previously treated with gemcitabine-based therapies. pERC reiterated that despite available treatment options in the second-line setting, there is no standard of care or high-level data to support the usage of any one regimen over another. While oxaliplatin may be available in some jurisdictions, there is evidence from a phase III RCT that demonstrated no survival benefit with the addition of oxaliplatin. The Committee reiterated the fact that 5-FU/LV was considered to be a reasonable comparator in this setting by the CGP and registered clinicians. pERC also noted that while irinotecan free base may be available in some jurisdictions, there is currently no evidence to support the use of irinotecan free base in combination with 5-FU/LV in the post-progression setting. Furthermore, irinotecan free base was not considered a comparator in this setting by the CGP and registered clinicians. pERC reiterated its conclusion that irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone in patients who have progressed on gemcitabine-based therapies demonstrated a statistically

significant and clinically meaningful improvement in outcomes important to decision-making, including OS and PFS.

Quality of life: Low compliance rates, high attrition rates; no appreciable improvements or deterioration between the irinotecan liposome plus 5-FU/LV arm compared with the 5-FU/LV arm

Patient-reported quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Patient-related outcomes were measured at baseline and then every six weeks until disease discontinuation. At week 6 and week 12, there were no appreciable changes in the proportion of patients who demonstrated improvements or deterioration between the irinotecan liposome plus 5-FU/LV arm and the 5-FU/LV arm. pERC noted that this is most likely due to a high degree of missing data, due in turn to high attrition rates.

Safety: Increased toxicity with irinotecan liposome plus 5-FU/LV compared with 5-FU/LV

pERC discussed the toxicity profile of irinotecan liposome in combination with 5-FU/LV. Patients who received treatment with irinotecan liposome, regardless of arm, had more grade 3 or higher treatment-emergent adverse events (TEAEs) than those treated with 5-FU/LV. pERC noted that 92% of patients in the combination therapy group and 87% in the monotherapy group had an adverse event (AE) related to the study drug compared with 69% in the 5-FU/LV group. The most common TEAEs for patients were diarrhea (combination: 59%; control: 26%); nausea (combination: 51%; control: 34%); and vomiting (combination: 52%; control: 26%). Febrile neutropenia was reported in 3% and 4% of patients in the irinotecan liposome combination and monotherapy arms respectively. Furthermore, 17% and 12% in the irinotecan liposome combination and monotherapy arms, respectively, received growth factor support, a practice not common with palliative chemotherapy treatments in Canada.

More patients in the combination arm (70.9%) had an AE that required at least one dose modification as compared with the control groups (35.8%). This was similar for patients who had at least one TEAE that resulted in a dose delay (combination: 61.5%; control: 32.1%).

Sixteen deaths resulted from an AE, five of which were treatment-related, based on the opinion of the investigator. One treatment-related grade 5 AE death occurred in the combination arm (septic shock [N = 1]).

Registered clinician input: Unmet need post-progression on gemcitabine-based therapy

pERC noted that the clinicians providing input indicated that there is no standard of care in second-line treatments of metastatic pancreatic cancer for patients previously treated with gemcitabine-based therapies; therefore, there is an unmet need for this patient population. The clinicians noted that in some provinces, oxaliplatin with 5-FU, 5-FU alone, or capecitabine are options, but that there are no high-level data to support the usage. However, they also noted that patients often have poor performance status in this setting, and many do not have a sufficient performance status to receive second-line therapy. Clinicians reported that approximately one-quarter to one-third of all patients who received gemcitabine (with or without nab-paclitaxel) would be fit enough for treatment with irinotecan liposome plus 5-FU/LV. The clinicians providing input identified that irinotecan liposome should be used according to the NAPOLI trial: second-line with 5-FU/LV (dose as described in trial) after first-line gemcitabine (with or without nab-paclitaxel) in patients with good performance status.

Input from clinicians in Ontario noted that more patients may be treated with gemcitabine/nab-paclitaxel in first-line therapy if irinotecan liposome with 5-FU/LV is approved for second-line therapy. As the sequence of first-line LV, 5FU, irinotecan and oxaliplatin in combination (FOLFIRINOX) followed by gemcitabine plus nab-paclitaxel second-line therapy is not funded in Ontario, there is already a high rate of first-line gemcitabine/nab-paclitaxel usage. Over time, second-line irinotecan liposome will have little impact on first-line gemcitabine/nab-paclitaxel usage.

Need: More effective treatment options required that improve survival and offer more favourable toxicity profiles

Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016 and an equal distribution between men and women. However, it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. The majority of patients present with either metastatic or locally advanced, unresectable disease. The mainstay of treatment for such patients is palliative chemotherapy. Although

the palliative treatment of advanced pancreatic cancer has significantly improved in the past several years, with median survival now exceeding eight months, long-term survival remains elusive for most pancreatic cancer patients, with fewer than 20% being alive at 18 months. Clinicians now have a choice between FOLFIRINOX, gemcitabine with nab-paclitaxel, and gemcitabine alone for the first-line treatment of locally advanced and metastatic pancreatic cancer patients who are well enough for systemic therapy. To date, no drug or drug combination has been approved for previously treated patients post-progression, and there is currently no standard-of-care therapy in this setting. pERC noted that this post-progression setting represents an unmet need in the management of advanced pancreatic cancer.

PATIENT-BASED VALUES

Experiences of patients with adenocarcinoma of the pancreas: High symptom burden and poor quality of life

Patient input noted that pancreatic cancer is a rare type of cancer with a very low prevalence. However, pERC noted that it is not considered a rare disease, as it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. Patient input noted that patients are often diagnosed at a very late stage; thus, their disease may not be amenable to treatment. Respondents reported a high degree of distress due to cancer symptoms, including nausea, vomiting, and pain. The majority of respondents indicated that a diagnosis of pancreatic cancer was devastating and has significantly impacted their QoL.

PCC and CORD indicated that treatment options are limited for metastatic pancreatic patients, and that the current drug therapies for managing cancer symptoms and progression are ineffective. Side effects related to all types of therapies were considered manageable, and side effects were tolerable by patients.

Patient values regarding treatment: Improved quality of life, more effective options, and better balance between the benefits and risks of drug therapy

PCC and CORD indicated that the majority of respondents were not aware of the new therapy, irinotecan liposome. Both patients and caregivers agreed that patients should be given the option to try the new therapy for the potential to prolong life. Patient input indicated that patients value new effective treatment options that improve QoL and prolong survival. The Committee noted that patients strongly valued a modest improvement in OS for this patient population with rapid decline in health post-progression, for which few treatment options are available. pERC also noted that patient input indicated that patients strongly valued the option of trying new therapies but also valued balancing the benefits and risks of a drug therapy with the overall impact on QoL pERC noted that patients indicated they would be willing to try new therapies; however, the Committee also noted comments that patients and their families want to have an honest discussion with their oncologists to assess the risks and benefits associated with treatment so they can make informed and personalized decisions about treatment. pERC noted that the results from the NAPOLI trial did not demonstrate an improvement in QoL; however, it appeared that no appreciable detriment was observed. This may be attributable to low compliance and a large amount of missing data, which increases the uncertainty in these QoL results.

Eight respondents who had direct experience with irinotecan liposome provided input. All noted that irinotecan liposome had positive effects for reducing pain and fatigue. Most respondents felt that the side effects were manageable. Overall, pERC concluded that the therapeutic intent of irinotecan liposome as an effective treatment option that prolongs survival aligns with patient values. However, the Committee was limited by the QoL data from the NAPOLI trial, and was uncertain about how treatment with irinotecan liposome in combination with 5-FU/LV impacts QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed the submitter's cost-effectiveness and cost-utility analysis of irinotecan liposome in combination with 5-FU/LV for patients with metastatic pancreatic cancer who have been previously treated with gemcitabine-based therapy as compared with 5-FU/LV alone (NAPOLI-1, direct comparison), or mFOLFOX or OFF (NMA, indirect treatment comparison).

CSPC Exhibit 1100
Page 245 of 333

Basis of the economic model: No extrapolation of efficacy outcomes

The pharmacoeconomic model was comprised of four health states: pre-progression on treatment, pre-progression off treatment, post-progression, and death. The pre-progression off treatment state is meant to account for patients who discontinue treatment for reasons other than progression.

Costs considered in the analysis included treatment costs, administration costs, and AE costs.

The clinical effect considered in the analysis was based on OS, PFS, time-to-treatment failure, the incidence of AEs, and utilities. No extrapolation of outcomes was needed, as these estimates were based entirely on full data from the trial. By the end of three years of total follow-up, all trial patients were dead.

Drug costs: High cost of irinotecan liposome

The list price of irinotecan liposome is $1,000.00 per 43 mg 10 mL vial. The cost of the combination of irinotecan liposome plus 5-FU/LV is $243.57 per day, or $6,819.94 per 28-day course, assuming an average body weight of 70 kg.

The costs of relevant comparators, assuming an average body weight of 70 kg, are as follows:

- The cost of the FOLFIRI regimen is $89.68 per day, or $2,511.18 per 28-day course.
- The cost of the OFF regimen is $40.92 per day, or $1,145.99 per 28-day course.
- The cost of the mFOLFOX6 regimen is $53.47 per day, or $1,497.29 per 28-day course.
- The cost of the 5-FU/LV regimen is $35.87 per day, or $1,004.49 per 28-day course.

Cost-effectiveness estimates: Not cost-effective at the submitted price

pERC deliberated upon the cost-effectiveness of irinotecan liposome in combination with 5-FU/LV with other possible therapies. pERC noted that the pCODR EGP's best estimates (lower bound: $326,774 per quality-adjusted life-year [QALY] to upper bound: $335,528 per QALY) were much higher than the submitter's estimate ($182,719 per QALY). pERC noted that this was primarily due to differences in the estimate of drug wastage, the source of drug costs, the use of time-to-treatment failure as a proxy for treatment duration, and utility values derived from the literature. The EGP conducted reanalyses to adjust for these limitations in the submitted model, including:

- Using PFS as a proxy for treatment duration, as the intent of treatment is to treat until progression; no vial sharing of irinotecan liposome to account for wastage
- Including disutilities, as patients on the combination therapy are likely to experience AEs due to increased toxicity
- Using Canadian utilities to reflect Canadian utility values
- Removing post-progression treatment, as the CGP identified that currently in Ontario, no subsequent treatments are funded for another line of therapy, and it is likely that patients who progress further would not be eligible to receive any further treatment
- Sourcing drug costs from Quintile IMS for standard pricing
- Discounting both costs and effects by 1.5% to align with current CADTH guidelines.

The Committee discussed that the cost of growth factor support, which may be required to treat toxicities such as febrile neutropenia while on the combination therapy, was not included in the submitted model. Therefore, the costs of managing such toxicities are likely underestimated in the submitted economic model. Furthermore, pERC noted that the cost of irinotecan liposome is four times greater than that of irinotecan free base; the Committee agreed that a substantial reduction in the drug price of irinotecan liposome would be required to improve the cost-effectiveness to an acceptable level. Therefore, pERC noted that at the submitted price, the combination therapy could not be considered cost-effective. pERC also agreed with the EGP's assessment regarding the uncertainty of estimates provided using the NMA between relevant comparators, including mFOLFOX, OFF, and irinotecan liposome plus 5-FU/LV.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted input from PAG that it is unknown whether the benefit observed with irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. In the absence of a comparison with irinotecan free base, the true cost-effectiveness and value of funding irinotecan liposome is difficult to determine. pERC reiterated the

CSPC Exhibit 1100
Page 246 of 333

fact that there are currently no available data on the comparison between irinotecan liposome and irinotecan free base, and, therefore, the Committee noted that the comparative effectiveness and the cost-effectiveness are unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Second-line therapy post-progression on gemcitabine therapy; no use for patients who have progressed on irinotecan-containing regimens

pERC discussed the feasibility of implementing a reimbursement recommendation for irinotecan liposome in combination with 5-FU/LV. pERC noted that irinotecan liposome is provided in a single 50 mg vial. In most instances, vial sharing will not be feasible given the small number of patients with pancreatic cancer receiving second-line treatment; therefore, there will be significant wastage. As an additional systematic therapy to chemotherapy, pERC noted PAG's concern that there will be increased chair time for treatment administration to patients. Furthermore, pERC discussed PAG's concern regarding the different dosing in the Health Canada product monograph compared with the NAPOLI-1 trial publication. pERC noted that the product monograph dose is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI trial indicates that irinotecan liposome 80 mg/m^2 is equivalent to 70 mg/m^2 of irinotecan free base. pERC cautioned that the dose must be clearly labelled, and the packaging should clearly differentiate it from irinotecan free base to minimize confusion between the two products.

pERC also discussed the place of irinotecan liposome plus 5-FU/LV in therapy, and noted that there is limited evidence evaluating the effectiveness of irinotecan liposome in combination with 5-FU/LV in patients who have progressed after being previously treated with irinotecan-containing regimens (e.g., FOLFIRNOX). pERC noted that both the CGP and registered clinicians indicated that they do not support the use of irinotecan liposome after previous treatment with irinotecan-containing regimens like FOLFIRINOX. Therefore, pERC concluded that irinotecan liposome plus 5-FU/LV should not be considered for patients who have progressed after previous irinotecan-based therapy. Additionally, pERC discussed the potential for the short-term, time-limited need for the combination therapy for patients currently receiving gemcitabine-based therapy as second-line therapy, based on the clinical discretion of the treating physician.

Finally, pERC discussed the budget impact, and noted that the factor that most influences the BIA is the cost of oxaliplatin in the comparator regimens (ex. mFOLFOX, OFF). Using the generic price of oxaliplatin (approximately $0.70 per mg) instead of the brand name price of oxaliplatin increases the budget impact substantially, as a lower price of the comparator regimen increases the incremental difference. Other factors that influence the BIA include market share assumptions, time on treatment, and dose intensity. The key limitations of the BIA model include the lack of consideration of wastage (vial sharing) of irinotecan liposome. The EGP was not able to modify or explore these parameters, but the inclusion of wastage would increase the BIA.

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DRUG AND CONDITION INFORMATION

Drug Information	• Irinotecan liposome (Onivyde) is administered by intravenous infusion 70 mg/m^2 over 90 minutes, followed by leucovorin (LV) 400 mg/m^2 IV over 30 minutes, followed by 5-fluorouracil (5-FU) 2,400 mg/m^2 IV over 46 hours, every two weeks. • One vial contains 43 mg of irinotecan free base, which is equivalent to 50 mg irinotecan liposome.
Cancer Treated	• Locally advanced unresectable or metastatic adenocarcinoma of the pancreas with previous treatment with gemcitabine-based therapy.
Burden of Illness	• Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016 and equal distribution among men and women. • It is fourth-leading cause of cancer death, with 4,700 deaths in 2016.
Current Standard Treatment	• FOLFIRI • OFF • mFOLFOX • 5-FU/LV
Limitations of Current Therapy	• No standard of care in this patient population • Current available treatments do not have high-level data to support usage.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan and Lauren Flay Charbonneau, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a Patient Member Alternate.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Avram Denburg and Dr. Craig Earle, who were not present for the meeting
- Lauren Flay Charbonneau, who did not vote due to a conflict of interest
- Cameron Lane, who did not vote due to his role as a patient member alternate.

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Avoidance of conflicts of interest

All members of the pCODR pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of irinotecan liposome for metastatic pancreatic cancer, through their declarations, no members had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting. For the Final Recommendation, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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EXPERT REVIEWS

FOLFIRINOX – a new paradigm in the treatment of pancreatic cancer

Expert Rev. Anticancer Ther. 14(10), 1115–1125 (2014)

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Treatment of metastatic and locally advanced pancreatic cancer has made slow progress during the last decade. Single agent gemcitabine or in combination with capecitabine or erlotinib remained the preferred systemic treatment options until 2010 when the ACCORD study demonstrated significantly improved outcomes achieved with FOFIRINOX compared with gemcitabine monotherapy. Since 2010, use of FOLFIRINOX has increased both in metastatic and locally advanced cancer. Despite its gaining popularity among oncologists, unanswered questions remain. Do the often necessary dose modifications affect its efficacy? Are the toxicities manageable and how applicable are the results of the ACCORD study in the general population of patients with newly diagnosed pancreatic cancer? In the present manuscript, we review the published literature regarding the use of FOLFIRINOX, the challenges associated with its use and how it will be optimally incorporated into the management of patients with different stages of pancreatic cancer and ultimately, in a more biomarker-driven pathway algorithm.

Keywords: chemoradiotherapy • chemotherapy • clinical trials • genomics • pancreas cancer

Overview of the market

Pancreatic carcinoma (PC) is the fourth leading cause of cancer-related death in men and women, with a 5-year survival rate of approximately 6% [1]. Incidence of pancreatic cancer has remained stable in Europe since mid-1990s; however, there is a possible trend of increased incidence in females [2]. Only a small proportion of patients will have localized disease at diagnosis (10–20%), where surgery and adjuvant chemotherapy can be used with a curative intent, whereas the majority of patients will present with either unresectable disease or metastatic spread and in this case palliative treatment with chemotherapy is the preferred option [3]. 5-Fluorouracil (5-FU) was the systemic therapy of choice for advanced pancreatic cancer until the Phase III, randomized trial by Burris *et al.* demonstrated the superiority of single agent gemcitabine over 5-FU [4]. More specifically, there was a statistically significant 5-week overall survival (OS) benefit (5.6 vs 4.4 months; p = 0.025) and an improvement in the 1-year survival rate (18 vs 2%) in favor of the experimental arm, but more importantly gemcitabine was better in controlling disease-related symptoms. Gemcitabine was thus established as the standard of care for advanced disease and was subsequently exhaustively evaluated in combination with other cytotoxic and molecularly targeted drugs. The addition of 5-FU or capecitabine to gemcitabine yielded modest benefits with an increased cost in toxicities [5,6]. Despite the inconclusive results of individual studies, the combination of capecitabine and gemcitabine demonstrated an improvement in OS in a meta-analysis that included three trials and is, therefore, considered to be a reasonable alternative treatment option to single agent gemcitabine. On the other hand, oxaliplatin or cisplatin demonstrated only a marginal increment in survival when added to gemcitabine, despite the 25% (p = 0.003) reduction of risk to progression compared with monotherapy [7].

Following the identification of several mutations and other genetic alterations that were thought to contribute to the development and progression of pancreatic cancer, new agents targeting these mutations were used in an effort to improve outcomes [8]. Despite the

 10.1586/14737140.2014.957188 © 2014 Informa UK Ltd ISSN 1473-7140

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Page 250 of 333

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fact that EGFR is overexpressed in pancreatic cancer, the addition of erlotinib, a tyrosine kinase inhibitor of EGFR, to gemcitabine has shown only a small (6.2 vs 5.9 months) but statistically significant improvement in OS in unselected patients with pancreatic cancer [9]. Similar to erlotinib, cetuximab, a chimeric monoclonal antibody against EGFR, did not have a clinically meaningful effect when added to gemcitabine [10]. Other EGFR-targeting strategies have shown no significant benefit in the treatment of PC [11]. Activating mutations of *KRAS* are frequently found (70–90%) in tumors of patients with PC but compounds that interfere with the function of *KRAS*, such as tipifarnib, a farnesyl transferase inhibitor, have been studied in patients with PC with no success to date [12]. Angiogenesis has been recognized as a hallmark of cancer and overexpression of the VEGF is associated with a poor prognosis in patients with PC [13]. A randomized Phase III trial of gemcitabine with or without bevacizumab, a monoclonal antibody against circulating VEGF, did not meet its primary end point of improving OS [14]. Similar negative results were produced in clinical trials of orally bioavailable tyrosine kinase inhibitors (sorafenib, axitinib) that interfere with the function of molecules involved in neoangiogenesis [15,16].

Since the pivotal study by Burris *et al.* that established the efficacy of gemcitabine monotherapy over 15 years ago, only the recent trial evaluating the addition of nab-paclitaxel to gemcitabine has produced a clinically meaningful survival benefit. In the study by Von Hoff *et al.*, 861 patients were randomly assigned in a 1:1 ratio to receive nab-paclitaxel plus gemcitabine or gemcitabine. The median OS was 8.5 months in the combination arm compared with 6.7 months in the gemcitabine arm (hazard ratio [HR] for death: 0.72; 95% CI: 0.62–0.83; $p < 0.001$). The median progression-free survival was prolonged by 1.8 months (5.5 vs 3.7 months) in favor of the nab-paclitaxel-gemcitabine group and the response rate was 23 versus 7% in the two groups ($p < 0.001$) [17]. The first Phase III trial to report a median OS of over 11 months in advanced PC was the study conducted by Conroy *et al.*, who compared gemcitabine with FOLFIRINOX (leucovorin 400 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusional over 48 h 2400 mg/m^2, irinotecan 180 mg/m^2 and oxaliplatin 85 mg/m^2) [18]. In the present manuscript, we describe the published literature regarding the use of this regimen, discuss the challenges associated with its use and give our suggestions in order to derive the maximum benefits for this difficult-to-treat patient population.

Introduction to the drug

Clinical efficacy in metastatic disease

FOLFIRINOX was compared with gemcitabine in a Phase III randomized controlled trial that demonstrated the superior efficacy of the combination treatment [18]. The primary end point was median OS, which was reported to be 11.1 and 6.8 months for the FOLFIRINOX and gemcitabine arms, respectively (HR for death: 0.57; 95% CI: 0.45–0.73; $p < 0.001$). Other efficacy end points such as median progression-free survival (6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group [HR for disease progression: 0.47; 95% CI: 0.37–0.59; $p < 0.001$]) and the objective response rate (31.6% in the FOLFIRINOX group vs 9.4% in the gemcitabine group; $p < 0.001$) clearly favored the investigational arm. Despite the increased toxicity of FOLFIRINOX, quality of life was not negatively affected at 6 months, with 31% of the patients in the FOLFIRINOX group reporting a definitive degradation of the quality of life versus 66% in the gemcitabine group (HR: 0.47; 95% CI: 0.30–0.70; $p < 0.001$). This highlighted the fact that benefit of disease control with FOLFIRINOX outweighed treatment-related toxicities.

Following the results demonstrating the superiority of FOLFIRINOX over gemcitabine, many other groups have replicated the impressive efficacy of FOLFIRINOX in patients with metastatic PC (Table 1) [18–26], with median OS ranging from 7.2 to 13.3 months in these retrospective studies. However, it must be noted that in some studies FOLFIRINOX was given as second-line therapy and in the study of Goncalves *et al.*, a small number of patients with performance status (PS) >1 were included in the analysis [23].

Safety & tolerability: challenges associated with the use of FOLFIRINOX

FOLFIRINOX is now considered a first-line treatment option for selected patients with advanced PC, with the pivotal trial by Conroy *et al.* demonstrating impressive improvements in outcomes compared with single agent gemcitabine; however, there are significant challenges associated with the use of this regimen.

Concerns have been raised as to whether or not the results of the trial by Conroy *et al.* would be applicable to the general population of patients with newly diagnosed PC, since the patients recruited in the study had to have an Eastern Cooperative Oncology Group PS 0-1. In addition, the majority of the tumors were located in areas other than the head of the pancreas, which is the most frequent site of pancreatic cancer. Although this does not necessarily alter the biology of the disease, patients with tumors in the body or tail of the pancreas have an anatomical advantage over those with tumors in the head of the pancreas as they are less susceptible to biliary obstruction and, therefore, less likely to require interventions that could increase their risk of infection, especially when on treatment with chemotherapy. To address the concern of patient selection, Gill *et al.* performed a retrospective study of 100 patients diagnosed with PC in the pre-FOLFIRINOX era and demonstrated that only 26 patients would fulfill the eligibility criteria of the ACCORD study, highlighting the highly selected population of patients enrolled in the trial [27]. The most common reasons that patients would be excluded is poor PS (n = 64), raised bilirubin (n = 22) and age >76 years (n = 22). Patients with PS >1 have been excluded from trials, and because of this, data regarding the use of FOLFIRINOX in these patient population are scarce. Nevertheless, it would be interesting to assess the activity of this regimen in patients with PS of 2 secondary to cancer-associated symptoms, given the

CSPC Exhibit 1100
Page 251 of 333

Table 1. FOLFIRINOX in metastatic pancreatic cancer.

Study (year)	Design	Patients (treatment line)	N	Response rate	Median OS (months)	Median PFS (months)	Ref
Conroy *et al.* (2011)	Phase III	First line[1]	342	31.6% (95% CI: 24.7–39.1%)	11.1	5.4	[18]
Gunturu *et al.* (2013)	Retrospective	Both first and second line	17	8/17 (47%)	11.2	9.5	[23]
Fans *et al.* (2013)	Retrospective	Both first and second line	26	7 (33%)	Not reached	Not reached	[20]
Peddi *et al.* (2012)	Registry	Both first and second line	38	4/22(18%)	10.5	6	[19]
Lowery *et al.* (2012)	Retrospective	First line	61	4/19 (21%)	12.5	Not stated	[24]
Goncalves *et al.* (2012)	Retrospective	First line	54	39%	7.2	3.8	[21]
Assaf *et al.* (2011)	Retrospective	Second line	27	5/22 (13%)	8.5	5.4 (TTP)	[25]
Breysacher *et al.* (2010)	Retrospective	Second line	13	0%	13.3	Not stated	[26]
Mahaseth *et al.* (2013)	Retrospective	First line	36	30%	8.5	9	[22]

Response rate = partial and complete response.
[1]First-line setting vs gemcitabine.
OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression.

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superior symptom control and quality of life reported for the combination treatment compared with gemcitabine. It is possible that, in this context, aggressive chemotherapy with FOLFIRINOX will lead to a quicker response and better control of the disease-related symptoms.

FOLFIRINOX-proven efficacy as first-line treatment in PC comes with a significant cost in toxicities as described in the ACCORD trial. More specifically, patients in the combination arm had more grade 3 or 4 toxicities compared to gemcitabine, including neutropenia (45.7 vs 21%; $p < 0.001$), febrile neutropenia (5.4 vs 1.2%; $p = 0.03$), thrombocytopenia (9.1 vs 3.6%; $p = 0.04$) and diarrhea (12.7 vs 1.8%; $p < 0.001$). Although granulocyte colony stimulating factor was not recommended by the study protocol, 42.5% of patients in the FOLFIRINOX arm received it either as primary or secondary prophylaxis. It must be noted that there were two treatment-related deaths in the experimental arm. The authors conclude that the side effects of FOLFIRINOX are manageable in this selected patient population. Data from other studies are inconsistent, and while the use of FOLFIRINOX is generally deemed to be safe and widely used in major centers, it is not clear if it is suitable for treatment in hospitals with more limited supportive care back up [19-21]. For example, Peddi *et al.* reported that 34.4% (n = 21) of the patients required hospitalization for treatment related adverse events [19]. To overcome the significant toxicity of FOLFIRINOX, different modifications to the original regimen have been evaluated. In a single arm study, Mahaseth *et al.* omitted the bolus 5-FU from the regimen [22]. The modified FOLFIRINOX regimen had improved tolerability (grade 4 neutropenia 3%, grade 3 or 4 diarrhea 13% and fatigue 13%) and maintained efficacy as the OS in patients with locally advanced and metastatic disease was 17.8 months (95% CI: 9.9 months to not estimable) and 9.0 months (95% CI: 7.1 months to not estimable), respectively. Gunturu *et al.* reported a cohort of 35 patients treated with FOLFIRINOX with the doses used in the ACCORD study [23]. Only six (17%) patients received full doses for the duration of their treatment. The remaining 29 patients had dose modifications from the first cycle, which were at the discretion of the treating physician. Irinotecan was reduced in 27 patients, oxaliplatin in 10 and bolus 5-FU reduced or omitted in 16 patients. Efficacy end points were comparable to those reported by Conroy *et al.*, whereas grade 3 or 4 toxicities were significantly less frequent. Although attenuated/modified FOLFIRINOX regimens are expected to be better tolerated, it is not known if efficacy will remain the same and efficacy data cannot safely be extrapolated from small or retrospective studies.

FOLFIRINOX in locally advanced/ non-metastatic pancreatic cancer

Approximately 10–20% of patients diagnosed with PC present with surgically resectable disease, and for this cohort, 5-year OS rate is 15–20% [1]. However, nearly 30% of patients will have locally advanced PC [1]. The optimal treatment strategy for the latter group of patients, which is further subdivided into patients with borderline resectable and unresectable disease, has yet to be fully defined [28]. The use of gemcitabine-based chemoradiation (CRT) has been proposed as an effective treatment approach following the results from the study

CSPC Exhibit 1100
Page 252 of 333

Table 2. Efficacy of FOLFIRINOX in borderline resectable pancreatic cancer.

Study (year)	Treatment	n	Borderline (BRPC)	Resection	R0 resection*	Ref.
Peddi *et al.* (2012)	FOLFIRINOX	61	4	4/4	Unknown	[19]
Hosein *et al.* (2012)	FOLFIRINOX, then chemoradiotherapy (9 patients)	18	4	3/4	3	[37]
Boone *et al.* (2013)	FOLFIRINOX + SBRT (two patients)	25	12	5/12	4	[38]
Kharofa *et al.* (2012)	FOLFIRINOX (4 cycles), then chemoradiotherapy with gemcitabine	12	12	7/12	7	[39]
Tinchon *et al.* (2013)	FOLFIRINOX	12	12†	10/12	Unknown	[40]

*R0 resection indicates microscopically (≥1 mm) margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed.
†Two patients reported to have minimal liver metastases.
SBRT: Stereotactic body radiotherapy.

published by Chauffert *et al.*, who demonstrated an improved OS favoring the arm treated with CRT [29]. Loehrer *et al.* confirmed the superior outcomes of CRT, but with a significant increase in the cost of toxicities [30]. Downstaging has also been observed in some patients with initially unresectable disease, rendering surgical excision possible [31]. However, the exact role of CRT remains uncertain. The recently reported multicenter Phase III LAP07 study demonstrated that while CRT was well tolerated, OS in the CRT arm demonstrated no significant difference in OS compared with chemotherapy alone [32]. Management of patients with borderline resectable PC remains controversial, with some centers advocating a trial of chemotherapy to provide a trial of disease biology as well as potentially reducing the risk of distant relapse prior to surgery.

Clinicopathologic features of pancreatic cancer are insufficient to predict the metastatic potential of locally advanced non-metastatic pancreatic cancer (LAPC). Recent evidence suggests that pancreatic cancer appears to be a systemic disease at the time of diagnosis. By the time most pancreatic cancers are diagnosed, the primary tumor already contains clonal populations of cells that are capable of giving rise to distant metastases [33]. Preclinical models have demonstrated that circulating pancreatic cells are present even in animals with premalignant pancreatic lesions, suggesting that pancreatic cancer is systemically disseminated even in its early stages [34]. *DPC4 (Smad4)* is a tumor suppressor gene that has been linked with a high risk for metastatic spread of LAPC when absent. In contrast, pancreatic tumors that overexpress it tend to have a potential for local expansion and indeed patients tend to die from complications of locoregional spread [35,36]. *DPC4* could potentially be used as a biomarker of the metastatic potential of LAPC and aid in selecting patients more likely to benefit from aggressive locoregional treatment (when overexpressed) or those who would benefit from systemic treatment (when absent). Although promising, this approach needs to be validated in appropriately designed randomized clinical trials.

Given the high response rates reported in advanced disease, the potential role of FOLFIRINOX in both LAPC and borderline resectable PC as neoadjuvant treatment is undergoing evaluation in several trials (Table 2) [19,37–40]. Hosein *et al.* performed a single-arm study assessing FOLFIRINOX in 18 patients with initially unresectable LAPC [37]. Seven (39%) patients underwent surgical excision and five were found to have clear margins (R0) post-resection. Three out of the 11 patients who remained unresectable post-FOLFIRINOX, received CRT and subsequently underwent surgery. Overall, the authors conclude that the high conversion rates observed with the use of FOLFIRINOX and CRT merit further evaluation in randomized trials. Similarly, Peddi *et al.* reported that four patients with borderline resectable disease underwent resection following FOLFIRINOX, while another four (21%) with locally advanced disease had radiotherapy and subsequently surgery [19]. The OS for patients with non-metastatic disease (irrespective of whether they had surgery or not) was 13.5 months. Boone *et al.* also reported a high resectability rate of patients with non-metastatic PC following treatment with FOLFIRINOX with or without the use of stereotactic radiotherapy [38].

The paradigm of patients with unresectable, non-metastatic PC potentially undergoing radical resection after significant response to systemic and/or locoregional treatment is therefore becoming increasingly accepted (Table 3) [19,20,22–24,37,38,41–44]. Retrospective data suggest that chemotherapy followed by CRT has the theoretical advantage of eradicating micrometastatic disease early on, and also helps to identify patients who progress early on during initial chemotherapy (an estimated 25–30%) to avoid the morbidities associated with radiotherapy [39]. A report from the Massachusetts General Hospital describes the use of neoadjuvant FOLFIRINOX, followed by intensity-modulated radiation therapy (50.4 Gy) along with infusional 5-FU or capecitabine as a radiosensitizer [41]. In 22 patients with LAPC, the authors reported a response rate of 27.3% and 5 patients underwent a R0 resection [41]. Nevertheless, it must be noted

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CSPC Exhibit 1100
Page 253 of 333

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Table 3. Efficacy of FOLFIRINOX in locally advanced pancreatic cancer.

Study group	Regimen	n	Response rate	No. of patients with resection	Median OS (months)	Median PFS (months)	Ref.
Conroy *et al.* (2005)	FOLFIRINOX	11	3/11 (27%)	0	15.7	Unknown	[43]
Vasile *et al.* (2012)	FOLFIRINOX, then chemoradiotherapy (3 patients)	15	6/15 (40%)	5/6	30.1	24.5	[44]
Lowery *et al.* (2012)	FOLFIRINOX (80% dose)	19	4/19 (21%)	Not stated	13.7	Not stated	[24]
Marthey *et al.* (2012)	FOLFIRINOX (62% of patients)	77	22/77 (28.6%)	28 (36%)	Not reached	Not reached	[42]
Faris *et al.* (2012)	FOLFIRINOX (80% dose)	12	5/12 (42%)	2 (R0 = 2)	Not reached	Not reached	[41]
Faris *et al.* (2013)	FOLFIRINOX + chemoradiation	22	6/22 (27.3%)	12/22 (R0 = 5)	Not reached	11.7	[20]
Gunturu *et al.* (2013)	FOLFIRINOX	16	8/16 (50%)	2/16 (R0 = 0)	Not reached	Not reached	[23]
Peddi *et al.* (2012)	FOLFIRINOX	19	6/18 (33%)	4/19 (21%)	13.5[1]	7.5[1]	[19]
Hosein *et al.* (2012)	FOLFIRINOX, then chemoradiotherapy (9 patients)	14	Not stated	4[2] (R0 = 2)	1-year OS 100% (interim)	83% 1-year PFS (overall)	[37]
Boone *et al.* (2013)	FOLFIRINOX + SBRT (two patients)	13	Not stated	2/13 (1 R0)	Not reached	Not reached	[38]
Mahaseth *et al.* (2013)[3]	FOLFIRINOX (omitting 5-FU bolus), then chemoradiotherapy	28	6/28	Not stated	Not reached	Not reached	[22]

Response rate = partial and complete response.
[1]Median OS and PFS for the whole population, including metastatic and locally advanced disease.
[2]Four resectable after chemotherapy, but three after chemoradiotherapy (R0 was 2, 3, respectively).
[3]Note this study included a mixture of both metastatic and locally advanced disease.
5-FU: 5-Fluorouracil; OS: Overall survival; PFS: Progression-free survival; SBRT: Stereotactic body radiotherapy.

that three out of five patients who had a successful operation experienced a relapse within 5 months. Another report on the role of conventional FOLFIRINOX in unresectable PC was a prospective database analysis by Marthey *et al.* [42]. Preliminary data from the first 53 enrolled patients showed a response rate of 30% with a corresponding disease control rate of 83%. Sequential chemoradiotherapy was applied in 62% of patients and 32% underwent subsequent tumor resection.

Incorporation of FOLFIRINOX into personalized therapy pathways

The stroma of PC is rich in extracellular matrix that is designed not only to provide adequate mechanical support, but also to facilitate tumor growth [45]. Molecules that facilitate the interaction of the stroma and the tumor cells are therefore a rational therapeutic target in PC. Initial approaches evaluating the use of the orally administered matrix metalloproteinase inhibitor marimastat failed to demonstrate benefit either as a single agent or in combination with gemcitabine [46,47]. The role of anti-neoangiogenesis drugs such as bevacizumab and small molecules kinase inhibitors has been described in a previous section and results have been unconvincing of significant activity. Tivantinib (c-MET inhibitor), masitinib (PDGFR and c-KIT inhibitor), rigosertib (PI3K inhibitor) are all in development and results of clinical trials in PC are awaited with interest. Modified FOLFIRINOX has been assessed in combination with saridegib, a hedgehog pathway inhibitor, in a Phase Ib trial showing early signs of activity in terms of response rates [48]. Interestingly, toxicities were manageable suggesting that FOLFIRINOX can be combined with novel agents when doses of the chemotherapy drugs are carefully adjusted.

Interest in utilizing immune-based therapies for the treatment of malignant diseases has rejuvenated following the licensing of ipilimumab for the treatment of patients with metastatic melanoma [49]. The addition of immunotherapies to conventional cytotoxics has been assessed in patients with resected pancreatic cancer. Hardacre *et al.* reported a Phase II trial of algenpantucel-L, a vaccine comprising irradiated allogeneic pancreatic cancer cells transfected to express murine α-1,3-galactosyltransferase with potential antitumor activity, in combination

CSPC Exhibit 1100
Page 254 of 333

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Table 4. Grade 3 and 4 toxicities in trials of FOLFIRINOX.

Regimen	Neutropenia	Febrile neutropenia	Anemia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Neuropathy	Ref.
FOLFIRINOX *Conroy et al. (2011)*	75/164	9/166	13/166	15/165	24/166	21/165	15/166	12/165	39/165	[18]
FOLFIRINOX *Gunturu et al. (2013)*	4/35	1/35	0/35	1/35	1/35	0/35	–	–	2/35	[23]
FOLFIRINOX + ChemoXRT *Faris et al. (2013)*	4/22	0/22	0/22	1/22	–	–	–	2/22	–	[28]
FOLFIRINOX *Pedel et al. (2012)*	12/61	3/61	–	2/61	–	2/61	–	–	3/61	[19]
FOLFIRINOX (bolus omitted in 15%) *Gonsalves et al. (2012)*	9/54	2/54	4/54	2/54	10/54	5/54	4/54	–	9/54	[21]
FOLFIRINOX *Assaf et al. (2011)*	15/24	1/27	1/27	4/27	–	5/27	3/27	1/27	–	[35]
mFOLFIRINOX + ChemoRT *Mahaseth et al. (2013)*	2/60	–	–	3/60	–	5/60	8/60	3/60	8/60	[32]
FOLFIRINOX *Conroy et al. (2005)*	24/46	2/46	8/46	3/46	17/46	8/46	7/46	–	–	[43]
FOLFIRINOX *Marthey et al. (2012)*	9/77	–	1/77	–	7/77	5/77	–	–	5/77	[42]
FOLFIRINOX *Hosein et al. (2012)*	4/18	3/18	2/18	3/18	0	2/18	0	–	2/18	[37]
FOLFIRINOX *Boone et al. (2013)*	4/25	0	0	3/25	0	1/25	1/25	–	0	[38]

mFOLFIRINOX: Modified FOLFIRINOX.

with 5-FU chemoradiotherapy in individuals who had a R0 or R1 resection. One-year OS was 86% and there were no safety concerns, therefore, a Phase III trial is underway [50]. Lutz *et al.* tested the safety and efficacy of a GM-CSF-based immunotherapy administered in patients with resected pancreatic adenocarcinoma [51]. Sixty patients were enrolled and treated post-resection initially with the vaccine followed by chemoradiotherapy. The median disease-free survival was 17.3 months (95% CI: 14.6–22.8) with median survival of 24.8 months (95% CI: 21.2–31.6). Given the efficacy and safety of this single-arm trial, further studies are planned. Other immunotherapies include peptide vaccines that recognize KRAS point mutations (exclusive in cancer cells in PC) [52], telomerase-based vaccines (exploiting the fact that this enzyme is expressed in 80–95% of cancer but not in healthy cells) [53] and carcinoembyonic antigen-directed vaccines [54]. A comprehensive update on the progress of immune-directed therapies in PC is provided in the review by Gunturu *et al.* [55]. The promising efficacy and, more importantly, the safety profile of immunotherapies suggest that they can be added to FOLFIRINOX and to that end many trials are underway. For example, the combination of ipilimumab, FOLFIRINOX and an allogenic GM-CSF transfected pancreatic tumor vaccine is being assessed in a Phase II study [56].

The identification of molecules that can predict toxicity is of particular interest in multichemotherapy regimens such as FOLFIRINOX. Irinotecan is a prodrug that is converted to its active form, SN-38, by carboxylesterases CES1 and CES2 and subsequently inactivated by glucuronidation via members of the uridine diphosphate-glucuronosyltransferase family [57]. The most

CSPC Exhibit 1100
Page 255 of 333

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Table 3. Ongoing trial with chemoradiotherapy.

Regimen	Control	Setting	Phase	Status	Resectability	Primary endpoint	Estimated enrollment	Identifier	Ref.
Modified FOLFIRINOX + SBRT	Modified FOLFIRINOX	Stanford University	Unresectable	II	Recruit	LA	PFS	172	NCT01926197	[64]
FOLFIRINOX + Accelerated Short Course Radiation Therapy With Proton Beam	Single arm	Massachusetts General Hospital	Neoadjuvant	II	Recruit	BR	Resection rate	50	NCT01591733	[62]
Modified FOLFIRINOX followed by external beam radiation therapy	Single arm	MD Anderson Cancer Center	Neoadjuvant	II	Recruit	Resectable/BR	Resection rate	65	NCT01560949	[63]
FOLFIRINOX with losartan before proton beam radiation therapy	FOLFIRINOX alone	Massachusetts General Hospital	Neoadjuvant	II	Recruiting	LA	Feasibility, defined as proportion free of radiographic progression at the time of restaging and consideration of proton therapy after induction chemotherapy	32	NCT01821729	[64]
FOLFIRINOX + SBRT	Single arm	University of Maryland	Neoadjuvant	Pilot study	Not yet recruit	BR	Resectability	20	NCT01932705	[65]
FOLFIRINOX and FDR-Gemcitabine With Concurrent IMRT	Single arm	University of Michigan Cancer Center	Neoadjuvant	II	Recruit	BR	R0 resection rate	31	NCT01661088	[66]
FOLFIRINOX chemotherapy and SBRT	Single arm	Emory University	Neoadjuvant	I	Recruit	Resectable/BR	MTD	24	NCT01448486	[67]
Neoadjuvant FOLFIRINOX Chemotherapy Followed by Capecitabine with Concurrent Limited Field Radiation Therapy	Single arm	Medical University of South Carolina	Neoadjuvant	II	Recruit	Localized pancreatic head adenocarcinoma	Resection rate	30	NCT01677988	[68]
Oxaliplatin, irinotecan, leucovorin and fluorouracil and CCRT	Gemcitabine, oxaliplatin, leucovorin and fluorouracil + CCRT	National Health Research Institutes, Taiwan	Neoadjuvant	II	Enrolling by invite only	LA	Response rate, disease control rate, overall survival and patients' quality of life	96	NCT01867892	[69]

BR: Borderline resectable; CCRT: Concurrent chemoradiotherapy; LA: Locally advanced; MTD: Maximum tolerated dose; SBRT: Stereotactic body radiotherapy.

CSPC Exhibit 1100
Page 256 of 333

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studied gene linked to toxicity with irinotecan is *UGT1A1*. Patients bearing the *UGT1A1*28* allele have reduced expression of the UGT1A1 enzyme and subsequently are less efficient in metabolizing SN-38 leading to its accumulation and to a high risk for diarrhea, neutropenia and other irinotecan-associated side effects. It has been estimated that it is found in 28–36 and 45% of the Caucasian and African population, respectively [58]. Given its relative high frequency, screening prior to the use of FOLFIRINOX could substantially reduce the likelihood of toxicities, and a genotype-guided dosing study of modified FOLFIRINOX [59] will evaluate this potential approach further.

Regulatory affairs

FOLFIRINOX comprises generic drugs, so it is routinely used off-label for treatment of advanced pancreatic cancer. No formal approval process of FOLFIRINOX through the US FDA or UK NICE has ever been sought as the regimen is routinely available through standard local funding arrangements for cytotoxics.

Conclusion

Clinical trials in pancreatic cancer during the last couple of decades have almost uniformly yielded disappointing results. A wide range of agents have been evaluated in combination with the long-term reference standard gemcitabine, resulting in low response rate and short survival times in the range of 6 months [5,7,9]. The results of the ACCORD trial, first presented by Conroy *et al.* in ASCO 2010, enhanced the interest in systemic chemotherapy for PC. In this randomized Phase II/III trial, FOLFIRINOX was shown to be superior to single-agent gemcitabine in response, progression-free survival and OS. It is the only regimen to show a median OS beyond 10 months in locally advanced or metastatic pancreatic cancer [18]. However, the cost in grade 3 and 4 toxicities is significant and has limited the use of FOLFIRINOX to highly selected patients and many investigators attempt to modify the original dosing regimen (Table 4) [18–23,25,37,38,42]. Despite the higher rate of adverse events, patients in the FOLFIRINOX arm reported a higher quality of life compared to those in the gemcitabine arm.

Expert commentary

The role of FOLFIRINOX as the new standard of care has been met with some concerns and a number of questions are yet to be answered. First, the patient population recruited in the ACCORD trial was highly selected with an Eastern Cooperative Oncology Group PS of 0-1 and a median age of 58 years. Furthermore, approximately 60% of participants in this study had non-head of pancreatic tumors, which is the reverse of what is seen in routine clinical practice. The impressive objective response rate seen in the metastatic cohort has led to preliminary interest in exploring the efficacy of FOLFIRINOX in patients with earlier stages of disease. In particular, neoadjuvant treatment seems an attractive option in downstaging inoperable LAPC. The role of combination CRT neoadjuvant regimens in LAPC remains controversial and has not yet translated into meaningful survival benefit in Phase III clinical trials (e.g., LAP07) [52]. Nevertheless, this approach remains of significant interest and many trials have incorporated FOLFIRINOX into combination chemo/CRT regimens with different schedules (Table 5). A small number of retrospective studies have emerged providing real-world data on the use of FOLFINOX in LAPC, with similar response rates as those seen in metastatic disease. However, we need greater experience to define the optimal timing and duration of FOLFIRINOX chemotherapy and to determine this translate into a meaningful survival advantage in this cohort. Adequately powered and well-designed prospective studies are needed to answer these important questions.

The recent approval of gemcitabine in combination with nab-paclitaxel for first-line metastatic pancreatic cancer has led to some uncertainty about the relative roles of both regimens in routine practice and which patients might be better suited to either individual regimen. Data from a small retrospective study suggest that patients whose tumors overexpress secreted protein acidic and rich in cysteine (SPARC), an extracellular matrix glycoprotein that plays a vital role in cell–matrix interactions, collagen binding and promotion of cell attachment and spreading, have an improved clinical outcome compared with those who had low expression of SPARC when treated with nab-paclitaxel [60]. It is therefore possible to hypothesize that if SPARC is validated as a predictive biomarker of response to nab-paclitaxel in future trials, patients with low expression of SPARC would be more suitable to receive FOLFIRINOX compared with the combination of nab-paclitaxel and gemcitabine.

Five-year view

Although FOLFIRINOX has a high objective response rate and improves outcomes in this difficult-to-treat patient population, there remains significant room for improvement. Advancing our understanding of the molecular and genetic basis of the disease and incorporating new molecularly targeted agents in the treatment of PC is of outmost importance. FOLFIRINOX could serve as a 'backbone' chemotherapy to which targeted agents could be added; however, care is required to overcome the potential toxicities associated with these combinations. Future advances in PC are likely to be based on more biomarker-driven personalized therapy regimens, and FOLFIRINOX is likely to be incorporated into treatment paradigms for patients with locally advanced, borderline resectable and metastatic PC for the foreseeable future.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

CSPC Exhibit 1100
Page 257 of 333

Key issues

- FOLFIRINOX is the first regimen to demonstrate a median overall survival of over 11 months in patients with metastatic pancreatic cancer.
- Despite the increased toxicity of FOLFIRINOX, quality of life is not negatively affected as the benefit of disease control outweighs treatment-related toxicities.
- FOLFIRINOX is currently being assessed as neoadjuvant treatment in patients with both borderline resectable and locally advanced pancreatic cancer. Results from small cohorts are encouraging.
- FOLFIRINOX can potentially serve as a chemotherapy backbone and could be assessed in combination with novel molecularly targeted agents; however, there are concerns as to the tolerability of these regimens and how pharmacodynamically relevant doses of targeted therapy can be administered.
- Identification of biomarkers of response and increasing our understanding on the pharmacogenomics of FOLFIRINOX will aid in selecting patients more likely to benefit from aggressive upfront therapy.

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CSPC Exhibit 1100
Page 259 of 333

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CSPC Exhibit 1100
Page 260 of 333

A Phase II, Open-label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination with 5-FU and Oxaliplatin in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI Study)

Hiral D. Parekh[1], Jessica L. Cioffi[2], Kathryn Hitchcock[3], Ji-Hyun Lee[4], Z. Hugh Fan[4], Carmen Joseph Allegra[1], Steven J. Hughes[5], Jose Gilberto Trevino[5], David L. DeRemer[2], Thomas J. George[1]
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BACKGROUND

- Neoadjuvant treatment for borderline resectable pancreatic cancer (PCa) is increasing in acceptability, but an optimal regimen has yet to be established.
- Multiple studies have demonstrated feasibility and effectiveness of FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) in the perioperative setting.
- However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly.
- Irinotecan liposomal injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PCa.
- The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen and demonstrate safe and effective neoadjuvant delivery.

METHODS

- Phase 2, open-label, single-arm study for newly diagnosed patients with borderline resectable or resectable PCa without overt metastatic disease.
- Other key eligibility criteria include age ≥18 years, measurable disease by RECIST v1.1, adequate cardiac, renal, hepatic function and ECOG PS of 0 or 1.
- Patients receive FOLFNal-IRINOX regimen as per **Table 1** every 2 weeks for four months followed by reassessment.
- Patients who remain surgical candidates will undergo resection within 4 to 8 weeks following last dose of therapy.
- Radiotherapy is allowed pre or post-operatively if surgical margins are believed to be compromised.

Table 1. FOLFNal-IRINOX treatment regimen

Agent	Dose	Infusion Duration
Nal-IRI	50 mg/m^2	90 min
Oxaliplatin	60 mg/m^2	120 min
Leucovorin	400 mg/m^2	120 min
5-fluorouracil	2400 mg/m^2	Continuous infusion for 46 hours
Each agent is given by IV infusion every 14 days		

CSPC Exhibit 1100
Page 261 of 333

Table 2. Study objectives

Primary Objective
Assess safety and feasibility of regimen in perioperative setting
Secondary Objectives
R0 resection rate
Clinical, biochemical and radiological response rates
Patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale.
Exploratory Objectives
Collect tissues and blood for post-hoc exploratory biomarker, CTC, ctDNA, microbiome, pharmacogenomic, tumor mutational profile assessments as well as potential PDX development.

CONTACTS

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STATISTICAL PLAN

- Evaluable patients are defined as those who complete surgery.
- A total of 28 evaluable patients will be needed to achieve the primary endpoint (**Table 2**).
- This is based on the assumption of a 66% reduction (HR 0.34) in the 30-day post-operative complication rate from 30% (historical data) to 10% (expected). (alpha = 0.05; beta = 0.20), using a one-sided exact test of binomial proportion.
- This pilot phase II study and this sample size, while not definitive, will allow determination of safety, feasibility, compliance, toxicity, and generation of robust clinicopathologic outcome assessment to serve as a benchmark control for subsequent comparative studies.

TRIAL STATUS

- Active enrollment continues.
- Additional sites are being recruited.
- No unexpected toxicities have thus far been identified.
- NCT03483038

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Funding for trial provided by
Ipsen Pharmaceuticals and University of Florida Health Cancer Center

CSPC Exhibit 1100
Page 262 of 333

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CSPC Exhibit 1100
Page 263 of 333

Article Tools

PANCREATIC CANCER

A phase II, open-label pilot study evaluating the safety and activity of Nal-IRI in combination with 5-FU and oxaliplatin in preoperative treatment of pancreatic adenocarcinoma (NEO-Nal-IRI Study) (NCT03483038).

Check for updates

Hiral D. Parekh, Jessica L. Cioffi, Kathryn Hitchcock, Ji-Hyun Lee, Z. Hugh Fan, Carmen Joseph Allegra, Steven J. Hughes, Jose Gilberto Trevino, David L. DeRemer, Thomas J. George

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Abstract

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Background: Neoadjuvant treatment for borderline resectable pancreatic cancer (PCa) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly. Irinotecan liposomal injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PCa. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with borderline resectable PCa without metastatic disease. Other key eligibility criteria include age ≥18 years, resectability confirmed by multiD GI tumor board, adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive FOLFNal-IRINOX regimen as per Table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in perioperative setting. Secondary endpoints include R0

resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30 day postoperative complication rate. Clinical trial information: NCT03483038.

FOLFNal-IRINOX Regimen components given every 14 days.

Agent	Dose	Route/Duration
Nal-IRI	50 mg/m^2	IV over 90 minutes
Oxaliplatin	60 mg/m^2	IV over 120 minutes
Leucovorin	400 mg/m^2	IV over 120 minutes
5-fluorouracil infusion	2400 mg/m^2	IV continuous infusion for 46 hours

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Research Sponsor:

IPSEN

Korean J Gastroenterol Vol. 57, No. 4, 207-212
DOI: 10.4166/kjg.2011.57.4.207

REVIEW ARTICLE

췌장암의 2차 항암치료

박정엽

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Second Line Chemotherapy for Pancreatic Cancer

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Pancreatic cancer is a very lethal cancer. It is the 5th most common cause for cancer related mortality in Korea. Most of patients have unresectable pancreatic cancer, and systemic chemotherapy remains the only treatment option for them. Gemcitabine has been adopted as the standard first-line agent for advanced pancreatic cancer, but the progression free survival with gemcitabine is short. Many of patients need further treatment. We reviewed the clinical trials of second line chemotherapy for gemcitabine refractory pancreatic cancer and tried to show currently available treatment options. **(Korean J Gastroenterol 2011;57:207-212)**

Key Words: Pancreatic Cancer; Chemotherapy

서 론

2009년도 우리나라 암통계에 따르면 췌장암은 암 발생률로는 9번째로 흔하고 암연관 사망의 원인으로는 5번째를 차지하며 전체 암 사망률 중 5.8%를 가지한다. 암발생 숫자와 암사망 숫자가 거의 똑같은 매우 치명적인 암이다. 다른 암들처럼 조기에 발견되는 경우 수술적 치료가 가능하지만 대부분의 경우는 수술이 불가능한 국소 진행되었거나 원격전이가 이미 있는 상태로 진단된다. 수술이 불가능한 환자들은 항암약물치료를 받게 되는데 이 경우 중앙 생존 기간은 약 6개월이며 5년 생존율은 거의 기대할 수 없다.[1,2]

1997년에 gemcitabine이 5-fluorouracil (5-FU)에 비하여 우월성을 입증한 이래 지금까지 계속해서 췌장암의 1차 치료의 역할을 수행했다. Burris 등[3]은 gemcitabine으로 치료한 군에서 중앙 생존기간이 5.65개월로 5-FU의 4.41개월보다 길어 gemcitabine 치료의 효과를 입증한 바 있다. 그리고 그 이후 여러 가지 약제들이 gemcitabine과 병용되어 gemcitabine 단독 치료와 비교되었지만 임상시험에서 우월성을 입증한 것은 아직까지 거의 없다. Erlotinib의 경우 gemcitabine과 조합으로 gemcitabine 단독 치료에 비하여 우월성을 증명하기는 하였으나 생존율의 증가가 미미하고 비용 대비 효과 면에서 다소 불리한 결과를 보였다.[4] 최근에는 gemcitabine이 아닌 다른 약제를 이용한 임상시험들이 시도되고 있으나 아직까지는 gemcitabine을 기반으로 하는 항암제가 췌장암의 1차 치료로 선호되고 있다.

비록 더 나은 결과들을 얻지는 못했지만 어느 정도 정립이 되어 있는 췌장암의 1차 항암 치료에 비해서 아직까지 2차 치료에 대하여는 정립된 바가 없으며 심지어는 2차 치료가 췌장암 환자에서 도움이 되는지 조차 잘 알려져 있지 않다.[5] 최근 연구 결과에 따르면 gemcitabine으로 치료받은 환자들 중 약 55-60%의 환자들이 비교적 양호한 신체활력도를 보여 2차 항암 치료를 필요로 한다는 것이 알려졌으며 이렇게 상당히 많은 환자들에서 어떤 2차 항암치료가 적절한지 고려해야 하는 상황이 발생한다.[6] 또한 우리나라에서는 항암제의 보험

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Financial support: None. Conflicts of interest: None

CSPC Exhibit 1100
Page 266 of 333

적용 여부가 어떤 항암제를 사용할지 결정하는데 중요한 사항이기 때문에 결정이 더 어려운 경향이 있다. 이번 논고에서는 gemcitabine 치료에 실패한 췌장암 환자에서 2차 항암약물 치료로 어떤 치료가 있는지 지금까지 있었던 임상시험들과 문헌들을 바탕으로 논하고자 한다.

2차 항암치료가 도움이 되는가?

최근까지 2차 항암치료의 효과에 대하여는 확실히 정립된 바가 없었다. 이유는 gemcitabine을 바탕으로 하는 1차 치료에 반응을 보이지 않는 환자들의 상태가 2차 치료를 받지 못할 정도로 악화되는 경우가 많아 2차 치료의 유용성을 평가하기 위한 대규모 연구가 힘들기 때문이다. 최근까지의 여러 소규모 임상 시험의 결과들을 바탕으로 간접적으로 2차 항암치료의 유용성을 예상할 수는 있다.[5]

2상 연구들 결과에 따르면 gemcitabine에 반응하지 않는 췌장암 환자에서 시도한 2차 항암 치료들은 대략적으로 0-29%의 치료 반응률을 보였으며 중앙 생존 기간을 길게는 9개월까지 보고하였고 또한 생존기간의 연장효과뿐만 아니라 삶의 질 향상도 역시 보고한 바 있다.[5] 이러한 연구 결과들은 2차 항암치료의 가능성을 보여주기는 하지만 대부분 연구 규모가 30명을 넘는 경우가 없어 췌장암의 항암치료 결과가 신체활력도의 영향을 많이 받는다는 점을 고려할 때 2상 연구의 결과만 바탕으로는 이들 치료를 실제 임상에 적용했을 때 효과도 비슷할 것이라고 예측하기는 쉽지 않다.

2005년도에 보고된 oxaliplatin과 5-FU의 조합이 보존적 치료에 비하여 생존기간을 증가시킨다는 연구 (CONKO 003)를 통해 그 동안 가능성만 보였던 2차 항암치료의 효과에 대한 객관적인 자료가 비로소 제시되었다. 이 연구에서 2차 항암치료를 받은 환자군의 중앙생존기간이 4.9개월로 나타나 보존적 치료만 한 환자군의 2.3개월보다 의미있게 증가되었음이 나타났다.[7] 그 후 oxaliplatin과 5-FU 조합의 치료는 5-FU와 엽산 치료보다 생존률이 더 증가됨을 다시 증명하여 췌장암에서도 2차 항암치료가 유용할 수 있음을 보여주었다.[8] 이 연구들을 통해서 2차 항암치료가 실질적으로 도움이 될 수 있음이 증명되어 그 후 다른 약제들을 이용한 2상 연구결과들이 따라서 수행되었거나 수행되고 있으며 미국종합암네트워크(National Comprehensive Cancer Network, NCCN)에서는 췌장암 치료 가이드라인에 2차 항암치료에 대한 내용을 포함시키고 있다.

비록 2차 항암치료가 생존기간의 연장 등의 좋은 결과를 가지고 올 수 있다는 가능성은 증명되었으나 1차 항암치료를 끝낸 환자들의 상태는 1차 치료를 받기 시작할 때보다 더 좋지 않으며 이는 임상시험이 어떤 상태의 환자들을 포함시키는지에 따라서 약물치료의 효과가 다르게 나타날 수도 있다는 것을 의미한다. 또한 몇몇 연구에서는 신체활력도 이외에도 알부민이나 1차 치료에 대한 반응 등의 추가 변수들이 2차 항암치료의 효과에 영향을 미친다고 보고하고 있다.[9] 따라서, 2차 항암치료의 효과를 입증하는 연구와 어떠한 약이 효과가 좋은 지를 검증하는 연구와 함께 2차 항암치료로 도움을 받을 수 있는 환자를 예측할 수 있는 연구의 결과도 주목할 필요가 있다.

어떤 치료가 있는가?

1. Oxaliplatin-Fluoropyrimidine 조합

Oxaliplatin과 5-FU를 이용한 약제들은 2상 연구에서 좋은 결과들을 보였으며 이러한 결과들을 바탕으로 3상 연구가 진행되어 2005년 미국임상종양학회에서 5-FU와 oxaliplatin 그리고 엽산을 조합으로 하는 oxaliplatin, folinic acid, 5-fluorouracil (OFF) 약제 조합(oxaliplatin 85 mg/m^2 8일과 22일, 엽산 200 mg/m^2, 5-FU 2,000 mg/m^2 24시간 주입 1일, 8일, 15일, 22일)이 보존적 치료에 비하여 생존기간의 연장을 가지고 왔음이 보고되었다. OFF 조합의 중앙생존기간은 22주였으며 보존적 치료는 10주의 중앙생존기간을 보여 유의한 생존기간의 차이를 보였다.[7] 보존적 치료와의 차이가 너무 압도적인 관계로 5-FU과 엽산의 조합과 OFF 조합으로 총 165명의 환자을 대상으로 하는 무작위 비교 임상 3상 연구가 다시 진행되었다. 그 결과는 2008년에 발표되었으며 이 연구에서도 OFF 조합은 무진행생존기간 13주 중앙생존기간 26주를 보여 대조군의 9주, 13주와 비교하여 더 우월한 결과를 보여주었다(Table 1).[8]

Table 1. Randomised III Trials in Gemcitabine-resistant Pancreatic Cancer

Regimen	No of patients	Treatment response (%)	Median progression free survival (months)	Median overall survival (months)
OFF vs.	46	n/a	n/a	4.9*
Best support	(total)			2.3
OFF vs.	76	n/a	3.0*	6.0*
FF	84		2.1	3.0
Irinotecan, raltitrexed vs.	19	16	4.0	6.5
Raltitrexed	19	0	2.5	4.3
Rubitecan vs.	198	11*	1.9*	3.5
Best support	211	1	1.6	3.1
Bevacizumab vs.	15	0	1.4	5.9
Bevacizumab, docetaxel	15	7	1.5	4.0

OFF, oxaliplatin, folinic acid, 5-fluorouracil; FF, folinic acid, 5-fluorouracil; n/a, not associated.
*$p < 0.05$

CSPC Exhibit 1100
Page 267 of 333

그 후로도 더 다양한 방법의 oxaliplatin과 5-FU 조합의 결과가 보고되었다. 대장암에서 사용하는 것과 같은 FOLFOX4 조합(oxaliplatin 85 mg/m^2 1일, levo-folinic acid 100 mg/m^2 2시간 이상 동안 투여, 5-FU 400 mg/m^2 iv bolus 후 600 mg/m^2 22 시간 동안 투여 1일과 2일, 매 2주 투여)을 투여한 결과에 따르면 42명의 환자 중 14명에서 부분 관해를 보였으며 질병진행까지 4개월이 걸렸고 중앙생존기간은 6.7개월이었다.[10] 이와 비슷한 결과들이 소규모 2상 연구들을 통해서 발표된 바 있으며 이들 결과 역시 oxliaplatin과 5-FU의 조합의 치료 효과를 입증하는 것이라고 할 수 있다.[11,12]

Capecitabine과 oxaliplatin 조합의 치료 결과도 보고된 바 있다. Xiong 등[13]이 시행한 XELOX (oxaliplatin 130 mg/m^2, capecitabine 1,000 mg/m^2 po bid 1-14일, 매 3주 투여)를 이용한 2상 연구에서 41명의 환자 중 1명의 환자가 부분 관해를 보였고 질병 진행까지 걸린 시간은 10주 그리고 중앙생존기간은 23주였다. 비록 2상 연구였지만 그 후에도 몇 개의 2상 연구에서 XELOX 조합은 비슷한 결과를 보여 5-FU와 oxaliplatin의 조합과 마찬가지로 2차 항암치료제로 좋은 치료 효과가 기대되며 3상 연구를 통해서 조금 더 객관적인 결과가 나오기를 바란다.

아직까지 oxaliplatin과 5-FU 조합은 gemcitabine에 반응하지 않는 췌장암 환자에서 2차 항암치료로 효과를 3상 비교연구를 통해 인정받은 유일한 약제들이다. XELOX 조합은 경구 투여가 가능하다는 장점이 있으며 2상 연구지만 정맥 투여되는 약제와 비슷한 치료 효과를 보였다. 이러한 가능성을 바탕으로 미국종합암네트워크는 capecitabine과 oxaliplatin 조합 또한 정맥 투여제제로 이루어진 5-FU와 oxaliplatin 조합을 gemcitabine 치료에 실패한 췌장암의 2가 항암치료로 추천하고 있다(Fig. 1).

2. 다른 Oxaliplatin 기반 조합

5-FU가 아닌 다른 약제와 oxaliplatin 조합 또는 oxaliplatin 단독 치료의 임상 연구 결과들이 있다. Demols 등[14]은 gemcitabine에 반응하지 않는 33명의 환자들을 대상으로 gemcitabine과 oxaliplatin 조합(GEMOX, gemcitabine 1,000 mg/m^2 over 100 min 1일, oxaliplatin 100 mg/m^2 2일, 매 2주 투여) 치료를 시도하였다. 이 조합은 독성이 상당해서 3도 이상의 독성을 보인 환자가 46%에 달했다. 7명(21%)의 환자에서 부분관해를 보였으며 중앙 생존기간은 6개월이었다. 또 다른 2상 연구에서도 치료 효과는 좋았으나 독성도 여전히 높게 나타났다.[15] GEMOX는 1차 췌장암 치료로도 3상 연구(E6201)가 진행된 바 있다.[16] 이 3상 연구에서는 gemcitabine 단독치료와 비교하여 독성이 더 많기는 않았으나 더 나은 생존기간 연장이나 삶의 질 향상을 보여주지 못해 결과적으로는 GEMOX는 1가 또는 2차 치료로 사용하기 힘들 것으로 판단된다.

Oxaliplatin과 irinotecan의 조합인 IROX도 연구된 바 있다. IROX 연구에는 30명의 환자가 포함되었으며 1일과 15일에 oxaliplatin 60 mg/m^2 그리고 1일, 8일, 15일에는 irinotecan 60 mg/m^{2}으로 4주마다 반복해서 치료했다. 비교적 독성은 적은 편이었으며 무진행생존기간은 4.1개월 그리고 중앙생존기간은 5.9개월이었다.[17] Oxaliplatin과 pemetrexed의 조합(ox-

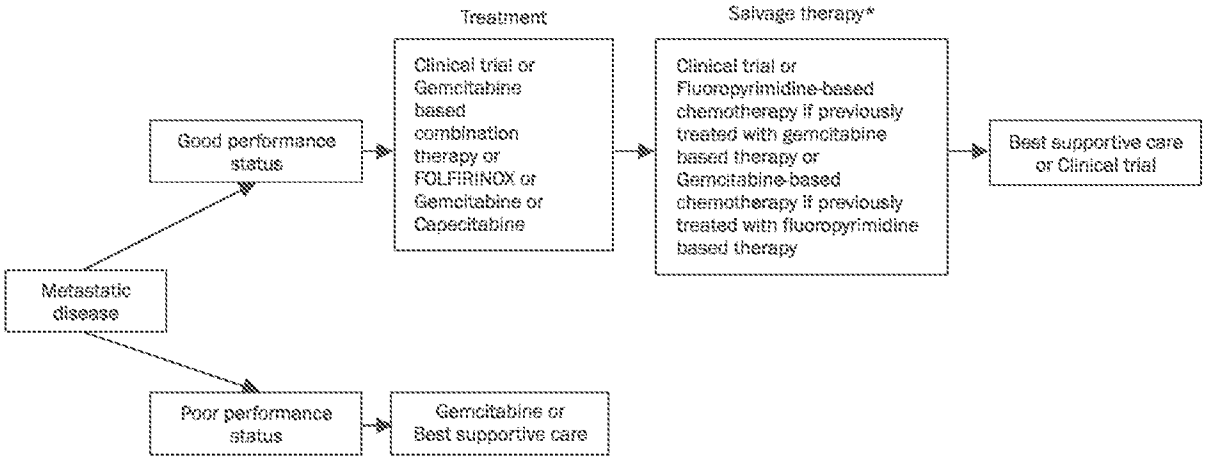


Fig. 1. NCCN guideline for the treatment of metastatic pancreatic cancer (modified from NCCN guidelines™ version 1.2011). *Second-line therapy may consist of gemcitabine for those patients not previously treated with the drug. Other options include capecitabine (1,000 mg/m^2 PO twice days 1-14 days every 21 days) or 5-FU/leucovorin/oxaliplatin or CapeOx. Results of the CONKO003 trial demonstrated a significant improvement in overall survival with addition of oxaliplatin to 5-FU/leucovorin.

CSPC Exhibit 1100
Page 268 of 333

aliplatin 120 mg/m^{2}과 pemetrezed 500 mg/m^2 매 3주마다 투여)도 소수의 환자들을 대상으로 하는 연구였지만 질병진행기간 14주로 좋은 결과를 보였다.[18]

3. Fluoropyrimidines 단독 치료

여러 암에서 5-FU 제제를 경구용 제제로 교체하여 효과를 본 것처럼 췌장암에서도 경구용 제제를 이용하여 효과를 확인하려는 임상연구들이 있었다. S-1은 플로우로유라실의 전구체인 ftorafur와 dihydropyrimidine dehydrogenase 억제제인 chloro-dihydroxypyridine과 orotate phosphoribosyltransferase 억제제를 조합해서 만든 약이다. 일본에서 진행된 40명의 환자를 대상으로 한 2상 연구에서 S-1은 매일 40 mg/m^{2}을 4주 동안 복용 후 2주 휴식하는 방법으로 투여하여 17%의 환자에서 부분관해를 유도했으며 질병진행기간 2개월 중앙생존기간 4.5개월의 결과를 보여주었다.[19] 비록 후향적 연구결과들이지만 이와 비슷한 결과를 보여주는 데이터를 Nakai 등[20]도 발표한 바 있으며 여기서는 중앙 생존기간을 7.8개월로 보고하였다.

또 다른 경구용 5-FU 제제인 capecitabine의 경우 3주마다 2주 동안 경구 투여한 결과 비록 종양의 감소는 가지고 오지 못했지만 중앙생존기간을 7.6개월까지 늘려 가능성을 보여준 바 있다.[21] 경구용 투여가 가능하다는 장점과 함께 좋은 생존기간의 연장 효과를 바탕으로 미국종합암네트워크에서는 capecitabine 단독 치료(3주마다 2주 동안 1,000 mg/m^2 bid)를 췌장암의 2차 항암치료로 추천하고 있다(Fig. 1).

4. Fluoropyrimidine 조합

경구용 5-FU들이 나름 좋은 결과를 보여주는 것에 비하여 cisplatin과 5-FU의 조합 결과들은 좋은 결과를 보인 경우가 적고 또한 논란의 여지가 있어 왔다. 일본에서 발표된 S-1과 cisplatin의 조합의 결과는 중앙생존기간을 9개월로 보고하였으나 대상 환자들이 수술 후 gemcitabine을 adjuvant로 투여하다 재발환자들만 대상으로 했다는 점에서 이의를 제기할 수 있다.[22] cisplatin과 5-FU 외에도 epirubicin과 gemcitabine을 추가로 하는 4제 요법과 gemcitabine과 irinotecan, 엽산, 그리고 5-FU의 조합과 같이 여러 약제를 복합한 치료 요법도 시도된 바 있으며 이들 조합들은 대부분 혈액학적 부작용이 심한 것으로 나타났다.[23,24] Cisplatin의 경우 오심 구토가 oxliapaltin보다 심하고 치료 결과도 더 좋지 못한 것으로 나와 5-FU와의 조합으로 oxaliplatin이 더 우월한 것으로 판단된다.[6]

한국에서 시행된 임상연구에서는 5-FU와 paclitaxel과의 조합이 시도된 바 있다. 5-FU는 1일에서 3일까지 1,000 mg/m^{2}이 투여되었으며 paclitaxel은 175 mg/m^{2}이 투여되었다. 이 연구에서 부분관해가 28명 중 2명에서 있었으며 질병진행기간은 2.8개월 그리고 중앙생존기간은 7.6개월이었다.[25] 또 다른 한국에서 진행된 2상 임상연구에서 5-FU, doxorubicin과 mitomycin-C의 조합으로 췌장암과 담도암이 혼합된 환자군을 대상으로 치료하여 6.7개월의 중앙생존기간을 보였다.[26] 그 이외에도 5-FU는 celecoxib과 같은 COX2 억제제나 한약제와의 병용으로 연구된 바 있다.[27,28] 5-FU의 경우 cisplatin 이외의 조합이 현재로는 더 가능성이 있을 것으로 판단된다.

5. Camptothecins

Irinotecan은 앞서 언급한 IROX외에도 단독 요법으로도 2차 항암치료제로 연구된 바 있다. Yi 등[29]의 연구결과에 따르면 irinotecan 단독 치료로 중앙 무진행생존기간 2개월 그리고 생존기간 6.6개월의 결과를 얻을 수 있었다. 하지만 docetaxel과의 조합은 부작용이 너무 심해서 임상시험이 중단되는 결과를 가지고 왔다.[30] Irinotecan과 raltitrexed의 조합의 경우 비록 소수의 환자들을 대상으로 했지만 무진행생존기간 4개월 중앙생존기간 6.8개월의 결과를 보이고 비교적 독성도 적어 가능성을 보인바 있다(Table 1).[31]

Rubitecan은 경구 투여되는 camptothecin 제제로 gemcitabine에 저항성을 가지는 췌장암에서 시행된 2차 항암치료제에 대한 3상 연구 중 가장 규모가 큰 연구에서 사용되었다. Rubitecan은 1주일 중 5일 동안 경구로 1.5 mg/m^2 용량으로 투여되었으며 상당히 많은 환자에서 용량감소가 필요하였다. 409명의 환자를 대상으로 하는 3상 연구에서 rubitecan은 대조군으로 주치의가 선택한 항암제 또는 보존적 치료와 비교되었으며 치료반응과 무진행생존기간에서는 11%과 1% 그리고 1.9개월과 1.6개월로 차이를 보였으나 생존기간에서는 3.5개월과 3.1개월로 차이를 보이지 못했다(Table 1).[32] 현재 rubitecan은 생산 중단된 상태이다.

Camptothecins 계열의 약들은 가능성은 나름대로 보여주었다고 판단되나 임상시험 결과들이 상대적으로 적어 현재로는 더 많은 데이터가 필요하다.

6. Taxanes

5-FU와 조합 그리고 irinotecan과의 조합은 이미 언급된 바 있으며 전체적으로 Taxol을 이용한 조합들의 결과는 그다지 좋지 않다. Docetaxel 단독 치료의 경우 무진행생존기간 2.5개월 그리고 생존기간 4개월로 그렇게 좋은 결과를 보이지 못했다.[33] Paclitaxel을 매주 90 mg/m^2 단독 투여하는 방법은 중앙 생존기간 17.5주의 결과를 보였다.[34] Taxane 계열의 조합은 췌장암에서는 단독 또는 다른 약과의 조합 모두 효과가 불투명하다.

CSPC Exhibit 1100
Page 269 of 333

7. Biological Agents

최근 각광받기 시작하는 각종 biological agents들의 경우 그렇게 많은 임상시험들이 진행되거는 않았지만 아직까지는 gemcitabine 치료가 실패한 췌장암에서 좋은 결과는 보여주지 못하고 있다. Erlotinib의 경우 1차 항암 치료제로 gemcitabine과 조합이 치료 효과를 인정받은 바 있고 capecitabine과의 조합이 2차 항암 치료제로도 연구된 바 있다. 이 연구 결과에 따르면 중앙 무진행 생존기간은 3.4개월 그리고 생존기간은 6.5개월로 비교적 좋았으나 설사와 피부 독성이 상당히 심해 상당히 많은 환자들에서 용량의 감소나 치료 주기의 변동이 필요했다.[35] mTOR 억제제인 everolimus 그리고 vascular endothelial growth factor (VEGF)에 대한 단클론 항체인 bevacizumab과 같은 다른 약제와의 조합도 그다지 좋은 결과를 보이지 못했다.[36,37] 또 다른 epidermal growth factor receptor를 타깃으로 하는 약제인 gefitinib의 경우 doxetacel과의 조합에서 생존기간 2.9개월을 보고하였으며 심한 부작용마저 초래하였다(Table 1).[38]

VEGF와 platelet-derived growth factor 수용체를 타겟으로 하는 경구용 제제인 vatalinib의 경우 65명의 환자가 포함된 2상 연구에서 14%와 31%의 6개월 무진행 생존율과 생존율을 보여 추가 임상 연구결과가 기대된다.[39] 하지만 같은 수용체들을 타겟으로 하는 sunitinib의 경우 그렇게 좋은 결과를 가지고 오지 못했다.[40] mTOR 억제제인 temsirolimus, sirolimus, 그리고 everolimus의 경우 단독으로 사용해서는 좋은 결과를 가지고 오지 못했다.[35,41,42]

결 론

현재 췌장암에서 gemcitabine 치료가 실패한 경우 2차 항암치료로 가장 좋은 효과를 기대할 수 있는 치료는 oxaliplatin과 fluoropyrimidine의 조합 또는 capecitabine 단독 치료이다. 하지만 모든 췌장암 환자보다는 신체활력도가 좋은 일부 환자에서 더 좋은 치료결과를 예상할 수 있다. 신약과 더 다양한 조합의 항암치료가 연구되어 췌장암의 2차 항암치료가 정립되기를 기대한다. 또한 대규모 3상 연구가 힘든 2차 항암치료에 대하여는 국내 보험인정기준이 유연하게 적용되어 비록 조그마한 혜택이라도 많은 환자들에게 골고루 돌아가기를 바란다.

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CSPC Exhibit 1100
Page 270 of 333

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CSPC Exhibit 1100
Page 271 of 333

660

Observational retrospective evaluation of treatment with liposomal irinotecan plus fluorouracil/leucovorin for metastatic pancreatic cancer patients: An Italian large real-world analysis

Antonio Pellino[1], Chiara Manai[1], Valeria Merz[2], Mario Scartozzi[3], Michele Milella[4], Ferdinando De Vita[5], Lorenzo Antonuzzo[6], Clizia Zichi[7], Maria Antonietta Satolli[8], Michele Panebianco[9], Silvia Noventa[10], Guido Giordano[11], Floriana Nappo[1], Camilla Zecchetto[2], Marco Puzzoni[3], Vanja Vaccaro[4], Annalisa Pappalardo[5], Elisa Giommoni [6], Davide Melisi[12], Sara Lonardi[1]

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Background

Historically, multiple phase II studies in the 2nd line setting failed to improve survival in patients (pts) with metastatic Pancreatic Cancer (MPC).

In the NAPOLI I phase III trial, Nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) showed better outcome compared to 5FU/LV in pts with MPC progressed to 1st line gemcitabine-based therapy. However, efficacy and safety of 5FU/LV-nal-IRI in a "real-life" clinical context still need to be verified.

Patients and Methods

- This is a retrospective multicenter analysis including pts with MPC who received 5FU/LV-nal-IRI after failure of a gemcitabine-based therapy.
- A total of 296 pts from 11 Italian institutions treated with 5FU/LV-nal-IRI by a nominal use program between June 2016 and November 2018 have been included in the study.
- The clinical, biomolecular and pathological features for each patient have been collected in a real life database.

CSPC Exhibit 1100
Page 272 of 333

- Aim of this study is to explore the real-world efficacy and safety of 5FU/LV-nal-IRI and to identify potential prognostic factors that could affect survival in this setting.

- Survival analyses were carried out by the Kaplan-Meier method. The association of baseline characteristics, biomolecular and pathological features and OS was firstly assessed in univariate analyses by means of log-rank test, and significantly prognostic variables ($p<0.10$) were included in a multivariable Cox proportional hazard model.

Results

Baseline characteristics at 5FU/LV-nal-IRI beginning	n = 296 (%)
Sex (M / F)	51% / 49%
Median age (range)	69 (30-82)
ECOG PS (0/1-2/NA)	44% / 55% / 1%
Ductal adenocarcinoma histology	97%
CA 19.9 (normal/ > ULN / NA)	19% / 77% / 4%
CEA (normal/ > ULN / NA)	35% / 51% / 13%
Number of metastatic sites (1 / >1)	42% / 58%
BMI (< 18.5 / > 18.5)	20% / 80%

5FU/LV-nal-IRI administration characteristics

- 34% of pts were previously resected on their primary tumor.

- 76% of pts received gemcitabine-nab-paclitaxel as first line treatment.

- 5FU/LV-nal-IRI was administered as second line in 72% of pts, while in 23% and 2% of cases as third line and fourth line respectively.

- The median time on treatment was 3.91 months (range 0.5-26.5); The median number of cycles administered was 5 (range 1-48); 39% and 18% of pts received more than 6 and 12 cycles respectively. A subgroup of pts (8%) was treated for more than 12 months.

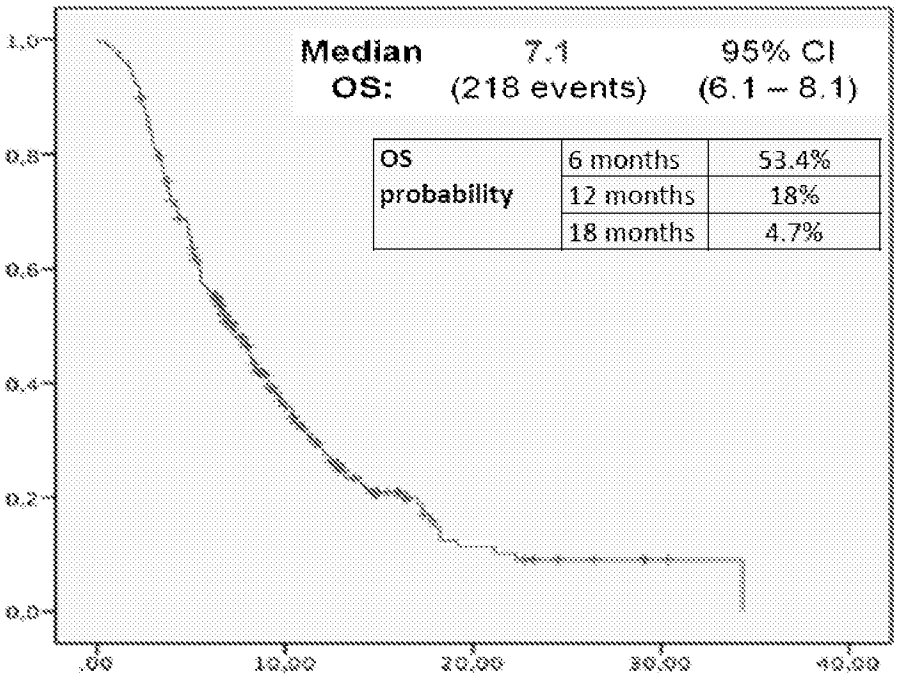
CSPC Exhibit 1100
Page 273 of 333

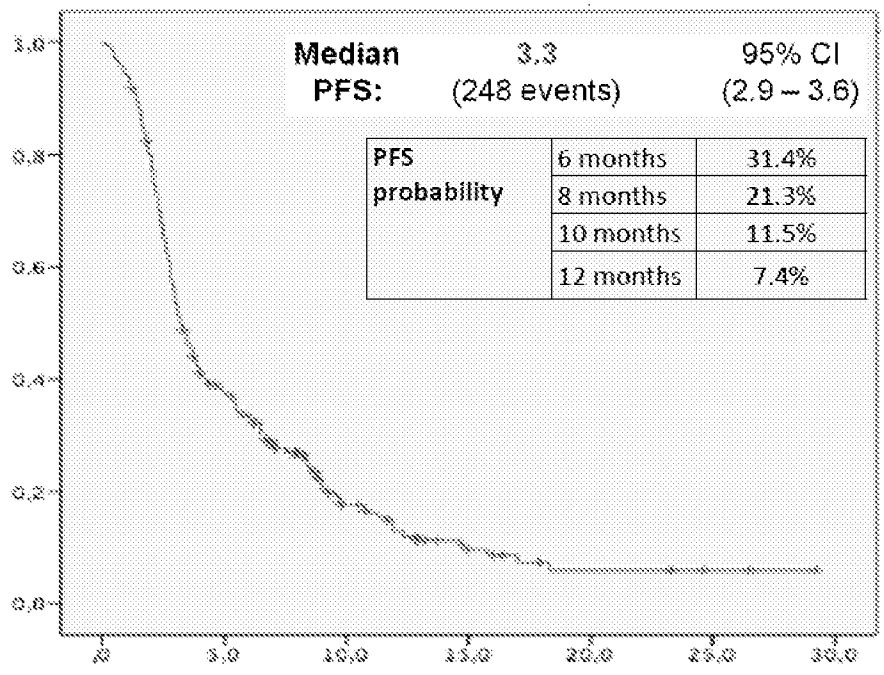
➢ Dose reductions of 5FU/LV-nal-IRI were performed in 50 % of pts.

Clinical outcomes	n = 296 (%)
CR	1%
PR	11%
SD	28%
PD	60%
ORR	12%
DCR	40%

Toxicity (G3–4)*	n = 296 (%)
Neutropenia	14%
Diarrhea	11%
Other	14%

* Toxicities observed in ≥ 5 % of pts are reported





Multivariate analysis			
Characteristics	Overall Survival		
	HR	95% CI	p
Baseline ECOG PS ≥1	1.01	0.71 – 1.45	0.934
CA 19.9 > ULN (37 ng/mL)	1.14	0.74 – 1.75	0.553
Number of metastatic sites > 1	1.23	0.88 – 1.71	0.220
Neutrophil-to-lymphocyte ratio >5	2.25	1.50-3.39	0.0001
Haemoglobin ≥11 g/dl	0.92	0.64-1.33	0.683
Albumin ≥4 g/dL	0.59	0.38 – 0.91	0.017

Discussion

- The 2nd line treatment for MPC following a gemcitabine-based therapy is ill-defined. The treatment choice in this setting is largely guided by patient performance status, patient age and physician preference.

- Compared to NAPOLI-1 study, our population was less favorably selected including **older pts** (range of age 30-81 vs 57-70) with worse PS (**ECOG PS ≥ 1**: 55% vs 41%).

- Our survival outcomes were similar to those of NAPOLI-1 study (**mPFS:** 3.3 months vs 3.1 months; **mOS:** 7.1 months vs 6.1 months). No major differences in toxicities have been reported.

Conclusions

These real-world data confirm the efficacy and safety of 5FULV-nal-IRI in pts with MPC progressed to a gemcitabine-based therapy. In this cohort, well known prognostic markers have been confirmed, as expected.

Observational retrospective evaluation of treatment with liposomal irinotecan plus fluorouracil/leucovorin for metastatic pancreatic cancer patients: An Italian large real-world analysis
Background
Patients and Methods
Results
Discussion
Conclusion

PANCREATIC CANCER

Observational retrospective evaluation of treatment with liposomal irinotecan plus fluorouracil/leucovorin for metastatic pancreatic cancer patients: An Italian large real-world analysis.

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Antonio Pellino, Chiara Manai, Valeria Merz, Mario Scartozzi, Michele Milella, Ferdinando De Vita, Lorenzo Antonuzzo, Clizia Zichi, Maria Antonietta Satolli, Michele Panebianco, Silvia Noventa, Guido Giordano, Floriana Nappo, Camilla Zecchetto, Marco Puzzoni, Vanja Vaccaro, Annalisa Pappalardo, Elisa Giommoni, Davide Melisi, Sara Lonardi

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Abstract Disclosures

Abstract

660

Background: In the NAPOLI I phase III trial, Nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) showed better outcome compared to 5FU/LV in patients with metastatic Pancreatic Cancer (MPC) progressed to 1st- line gemcitabine-based therapy. Aim of this study is to explore the real-world efficacy and safety of 5FU/LV-nal-IRI by a compassionate use programme and to identify potential prognostic factors that could affect survival in this setting. **Methods:** This is a retrospective multi-center analysis including patients with MPC who received 5FU/LV-nal-IRI after failure of a gemcitabine-based therapy. Survival analyses were carried out by the Kaplan-Meier method. Univariate and multivariate analyses were performed by using the log-rank test and the Cox regression. **Results:** A total of 296 pts (median age, 69 years,

range 30-82; 50% male; ECOG PS 0, 44%) were treated at 11 Italian institutions from June 2016 and November 2018. 34% of the pts have been previously resected on their primary tumor, and 76% received gemcitabine-nabpaclitaxel as 1st - line treatment. 5FU/LV-nal-IRI has been administered as 2nd - line in 72% of the pts, while in 23% of the cases as 3rd - line or more. The median OS was 7.1 months [95% confidence interval (CI) 6.1 - 8.1] and the median PFS was 3.3 months (95% CI 2.9 - 3.6). At six months, OS and PFS rate were 53.4% and 31.4% respectively. ORR was 12% and DCR was 40%. 52% of pts received more than 4 cycle with dose reduction in 148 pts (50%). Most common grade 3 toxicities were neutropenia (14%), diarrhea (11%), anemia (3%), nausea (3%), fatigue (3%), mucositis (2%) and vomiting (1%). Baseline characteristics associated with better OS were ECOG PS 0, normal CEA, neutrophil-to-lymphocyte ratio ≤5 and haemoglobin ≥11 g/dL. **Conclusions:** These real-world data confirm the efficacy and safety of 5FU/LV-nal-IRI in patients with MPC progressed to a gemcitabine-based therapy, with outcome comparable to NAPOLI-1 even in a less selected population and with more active 1st - line combination therapy. In this cohort, well known prognostic markers has been confirmed, as expected.

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Research Sponsor:

None

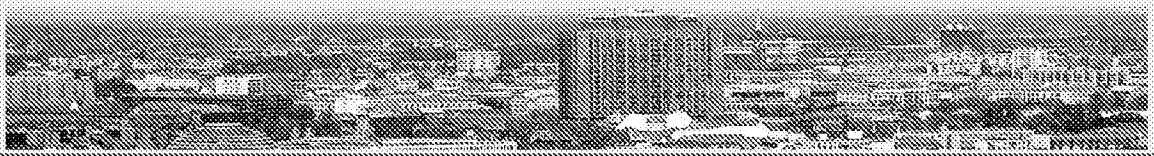
A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO-003 study.

- CONKO*-003 -

U. Pelzer

Kubica K[1], Stieler J[1], Schwaner I[2], Heil G[3]; Görner M[4], Mölle M[5]; Hilbig A[1], Dörken B[1], Riess H[1], Oettle H[1]

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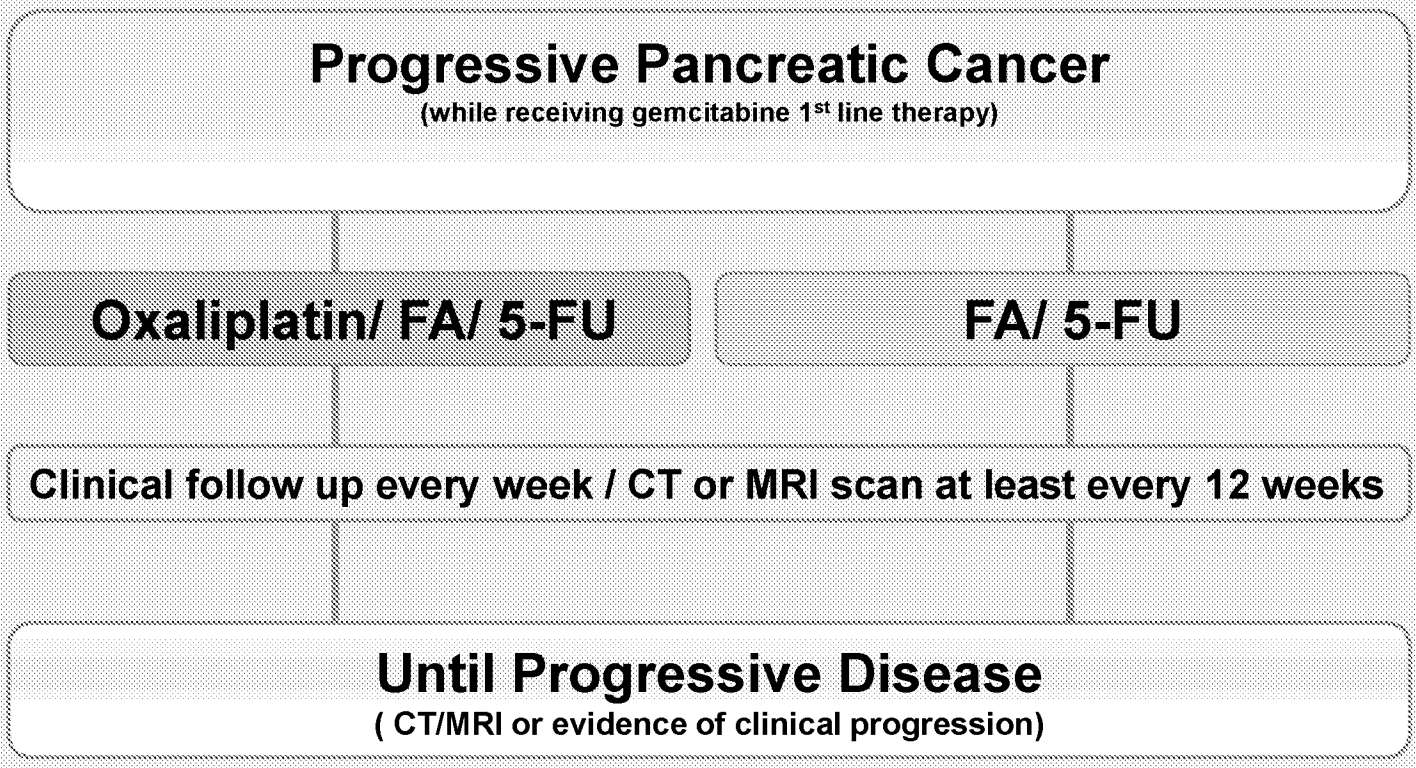
ASCO Disclosure Form

I have no relevant relationships to disclose.

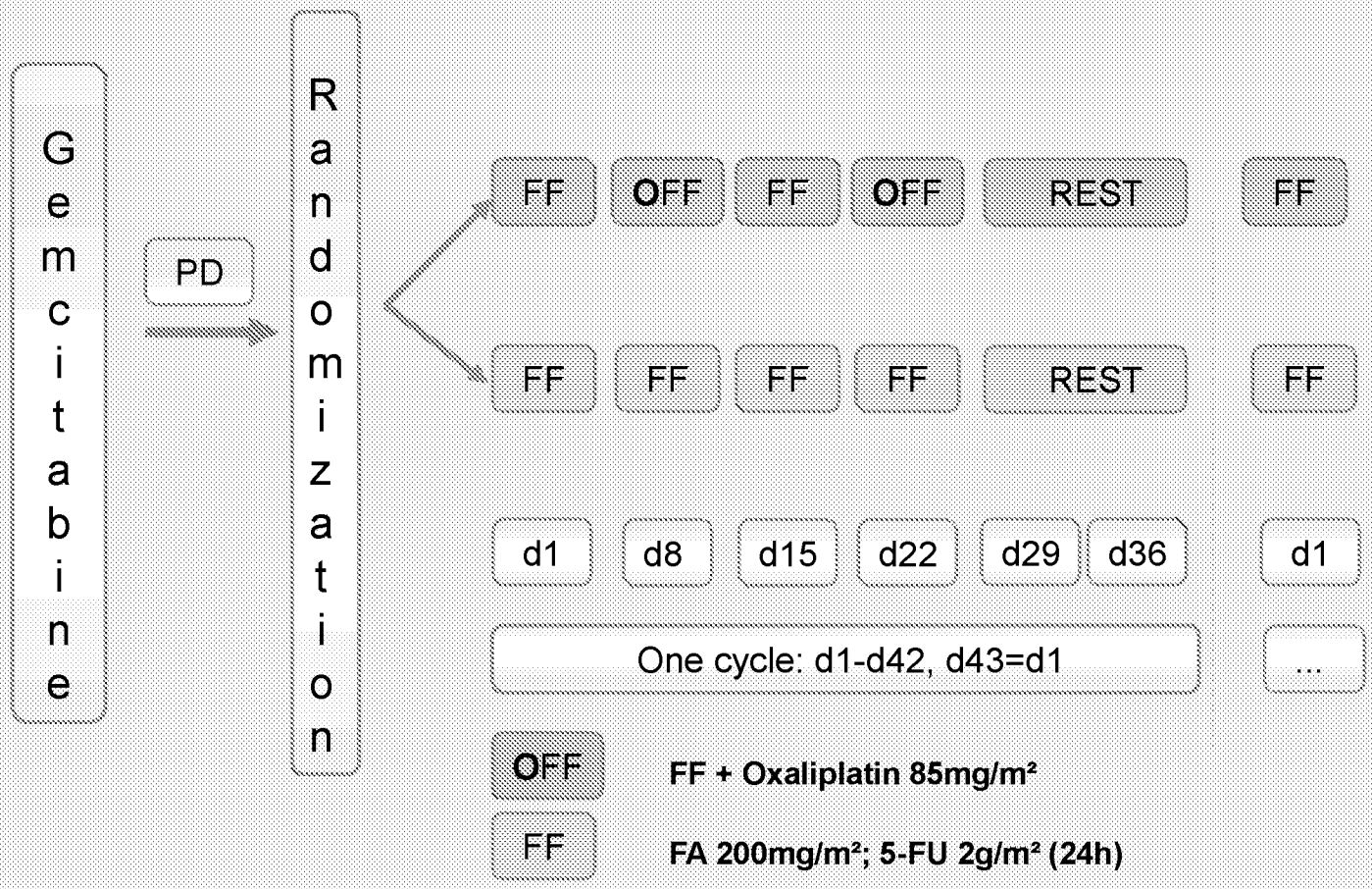
CONKO-003 Rationale

- there is no established 2nd line treatment for APC
- 30%-50% of pts. receive any 2nd line therapy
- OFF as effective regimen in phase II trial
  (Pelzer et al. ASCO 2002)
- OFF vs. BSC as phase III trial
- BSC was not accepted by the patients

CONKO-003 Study Design



CONKO-003 Regimen



CONKO-003 Entry Criteria

- Histologically proven pancreatic carcinoma
- Confirmed PD during GEM 1st line therapy (CT/ MRI)
- Karnofsky performance status ≥ 70%
- Adequate hematologic, renal and hepatic function
- Start with 2nd line within 3 weeks after 1st line PD
- Signed informed consent

CONKO-003 Endpoints

- **Primary Endpoint**
  - Overall survival (OS)
- **Secondary Endpoints**
  - Disease free survival (DFS)
  - Toxicity

CONKO-003 Statistics

- **Hypothesis:**
  - Significant increase in overall survival (OS) after randomization of at least 2 months due to chemotherapy with OFF
- **Statistics:**
  - Kaplan-Meier estimates and two-tailed log-rank test with significance level of 0.05 and a power of 90%
- **Sample size:**
  - 165 pts (1:1 ratio), including drop out rate up to15%
- **Strata:**
  - KPS (70-80%/ 90-100%), time on 1st line (< 3 months/ 3-6 months/ > 6 months), stage (M0/ M1)

CONKO-003 Recruitment and Analysis

Time of recruitment:	02/04 - 06/07
Recruited patients:	168
Drop out rate:	4.7%

Date of Analysis:	March 2008
Observation since LPI:	296 days

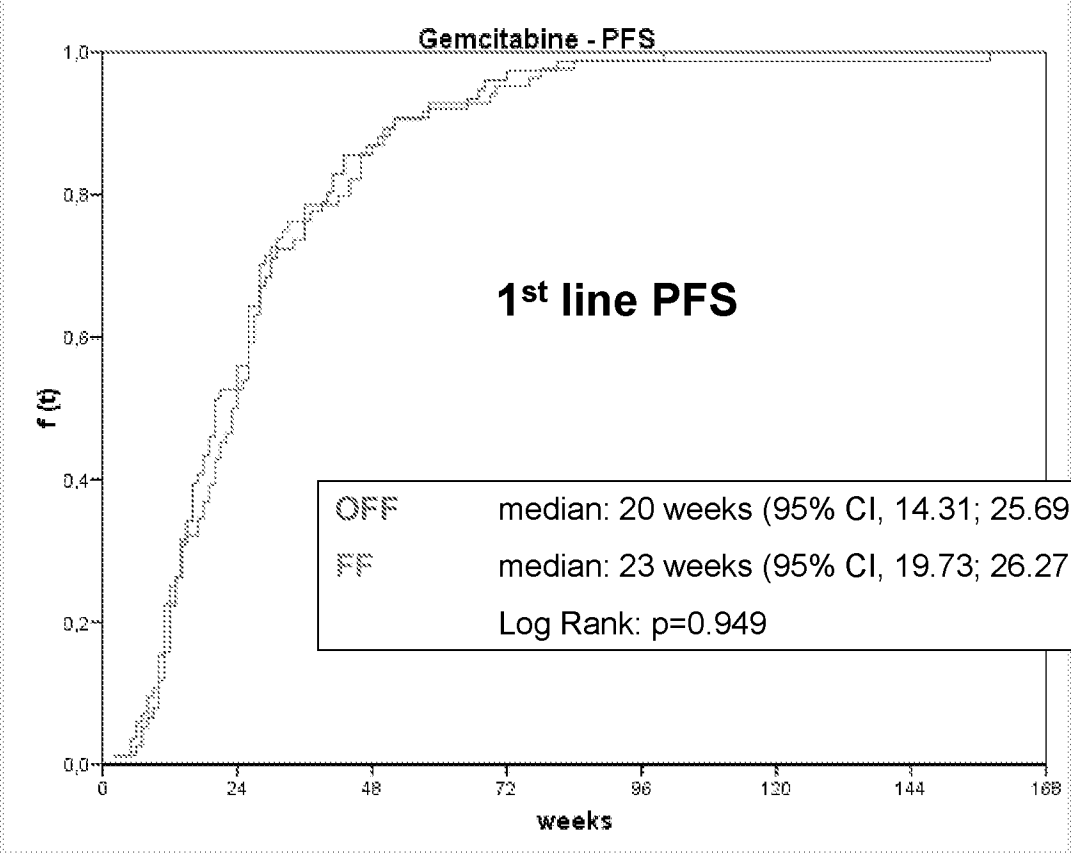
CONKO-003 Patient Characteristics

Characteristic	OFF (N=76)	FF (N=84)
Weeks to randomisation after GEM		
Median [range]	2 [0 – 6]	2 [0 – 6]
Age – years		
Median [range]	61 [36 – 76]	60 [42 – 77]
Gender – no. (%)		
Female	36 (47%)	36 (43%)
Male	40 (53%)	48 (57%)

CONKO-003 Patient Characteristics - Strata

Characteristic	OFF (N=76)	FF (N=84)
Stage IV a (M 0)	11	9
Stage IV b (M 1)	65	75
KPS 90-100%	41	42
KPS 70-80%	35	42
GEM < 3 months	21	21
GEM 3-6 months	24	30
GEM > 6 months	31	33

CONKO-003 Patient Characteristics



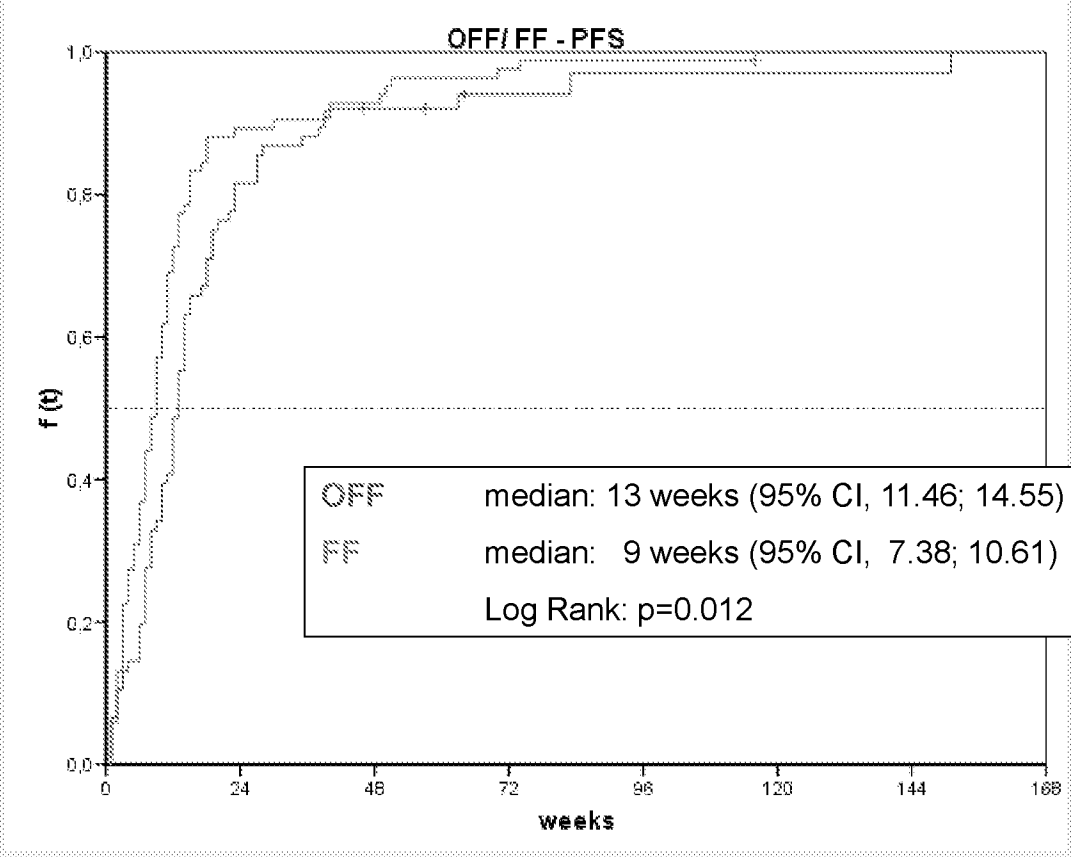
CONKO-003 Results - Toxicities

	OFF 232 [0;25] cycles				FF 187 [0;19] cycles			
NCI - Grading	**I°**	**II°**	**III°**	**IV°**	**I°**	**II°**	**III°**	**IV**
Leucopenia	16	3	0	0	5	1	0	0
Anemia	26	17	3	0	35	17	2	0
Thrombocytopenia	12	5	1	0	14	4	0	0

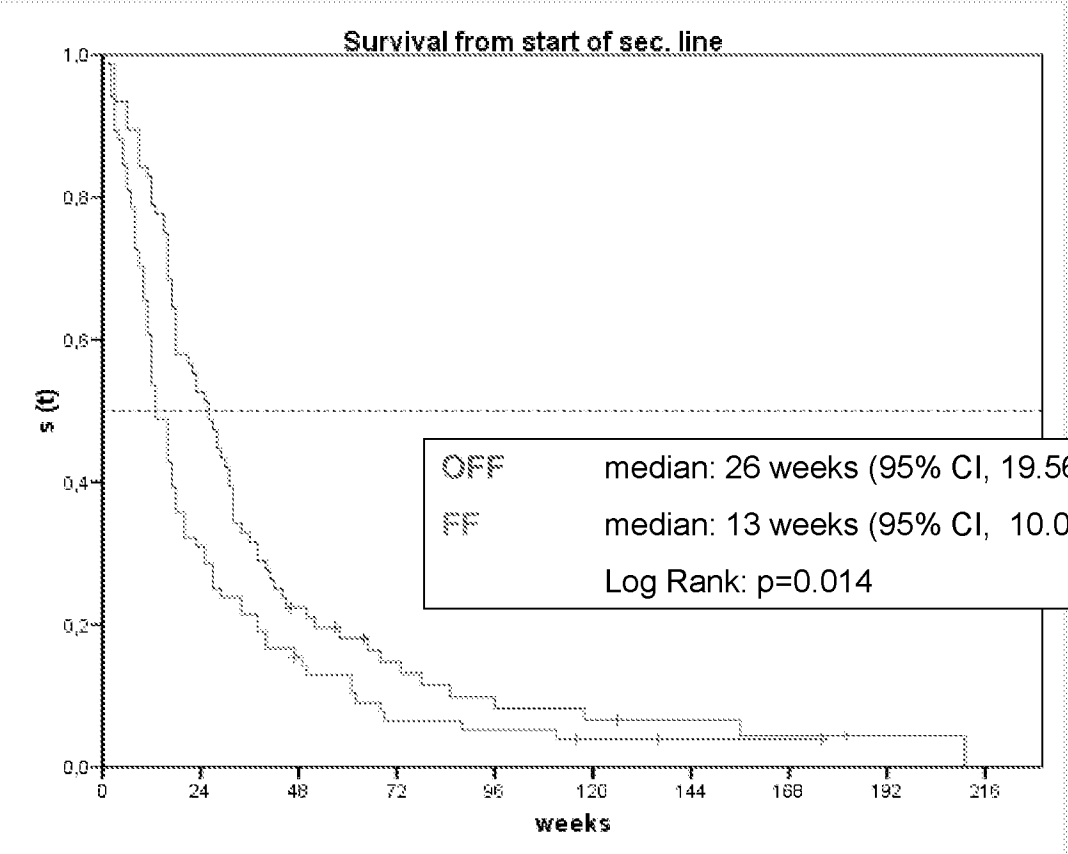
CONKO-003 Results - Toxicities

	OFF 232 [0;25] cycles				FF 187 [0;19] cycles			
NCI - Grading	**I°**	**II°**	**III°**	**IV°**	**I°**	**II°**	**III°**	**IV°**
Neurologic	19	10	3	0	3	3	0	0
Diarrhea	9	6	1	0	15	4	0	0
Pain	16	19	24	0	10	24	32	2
Nausea/ Emesis	26	18	1	0	25	11	3	0

CONKO-003 Results - 2nd line PFS



CONKO-003 Results - 2nd line OS



CONKO-003 Results – 2nd line PFS - Strata

Characteristics	OFF median (weeks)	FF median (weeks	p value
Stage IV a (M 0)	13	13	0.311
Stage IV b (M 1)	13	8	
KPS 90 - 100%	14	10	0.012
KPS 70 - 80%%	11	7	
GEM < 3 months	13	5	0.001
GEM 3-6 months	12	8	
GEM > 6 months	14	10	

CONKO-003 Data Summary

- Both regimen are feasible
- Toxicities are tolerable
- Treatment with OFF results in a significant improvement in PFS and 2nd line OS
- OFF is an effective 2nd line regimen and can be safely administered in pts with gemcitabine refractory APC

EUROPEAN JOURNAL OF CANCER 47 (2011) 1676–1681

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Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: A phase III-study from the German CONKO-study group

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ARTICLE INFO

Article history:
Available online 10 May 2011

Keywords:
Pancreatic cancer
Gemcitabine
Best supportive care
Second-line

ABSTRACT

Background: Gemcitabine usually given until progressive disease (PD) is the main first-line treatment option for patients with inoperable advanced pancreatic cancer (APC). Currently there is no accepted active regimen for second-line chemotherapy. Previous phase II studies suggest clinical relevant activity of oxaliplatin, folinic acid and 5-FU (OFF). We initiated a phase III multicentre study comparing OFF versus best supportive care (BSC) in patients with APC progressing while on gemcitabine therapy.

Methods: In this open randomized study, patients with CT and/or MRI confirmed progressive disease while on gemcitabine therapy were randomized 1:1 to OFF or BSC. Stratification included duration of first-line therapy (<3, 3 to 6 and >6 months), performance status (KPS 70–80%; 90–100%) and tumour stage (M1/M0). OFF consisted of folinic acid 200 mg/m^2 followed by 5-fluorouracil 2 g/m^2 (24 h) on d1, d8, d15, d22 and oxaliplatin 85 mg/m^2 on days 8 and 22. After a rest of 3 weeks the next cycle was started on d43. A total of 165 patients were calculated to demonstrate a doubling of survival time after progression on first-line therapy.

Results: After inclusion of forty six patients the trial was terminated according to predefined protocol regulations due to insufficient accrual (lack of acceptance of BSC by patients and physicians). Patient characteristics were well balanced between both study arms. The OFF regimen was well tolerated with more patients with grade I/II paraesthesia and grade II/III nausea/emesis and diarrhoea. Median second-line survival was 4.82 [95% Confidence Interval; 4.29–5.35] months for OFF treatment and 2.30 [95% CI; 1.76–2.83] months with BSC alone (0.45 [95% CI: 0.24–0.83], $p = 0.008$). Median overall survival for the sequence GEM-OFF was 9.09 [95% CI: 6.97–11.21] and 7.90 [95% CI: 4.95–10.84] months for GEM-BSC (0.50 [95% CI: 0.27–0.95], $p = 0.031$) respectively.

Interpretation: Although stopped prematurely, this randomized trial provides at first time evidence for the benefit of second-line chemotherapy as compared to BSC alone for

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0959-8049/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2011.04.011

patients with APC. OFF significantly prolonged survival time compared to BSC alone after failure of first-line therapy with gemcitabine.

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1. Introduction

Adenocarcinoma of the pancreas is a highly aggressive cancer, characterized by extensive local invasion, early regional and rapid systemic spread and a high degree of chemo-resistance. In spite of intensive research in the last decade, the 5 years survival rate in patients with advanced pancreatic cancer (APC) is still less than 5%.[1] At present, pancreatic cancer is the fourth most frequent cause of death from solid tumours in the western world.[2] In parallel with disease progression, patients with APC suffer from several symptoms such as abdominal pain, taste abnormalities, nausea and emesis, leading to inadequate nutrition intake, weight loss and fatigue. These symptoms contribute substantially to the deterioration in performance status and quality of life. Gemcitabine (GEM), the standard first-line chemotherapy for pancreatic cancer during the last decade, can lead to improvements of tumour-related symptoms and has shown modest survival advantage.[3] Many multi-agent therapies have been tested but most of them failed to prove superiority over single-agent gemcitabine.[4–6] At the time this trial was planned, best supportive care (BSC) was standard care for patients who progressed on first-line chemotherapy. However, patients with good performance status despite disease progression on gemcitabine therapy generally ask for further anti-cancer therapies. Indeed, several phase-II studies suggested second-line anticancer activity but there are no phase-III studies confirming the benefit of further chemotherapies after progression while on gemcitabine. [7–9] First-line therapy studies report the use of second-line chemotherapies in nearly 30% of patients.[5,6] This clearly underlines the clinical need for evidence based recommendations for patients progressing while on first-line therapy. Based on our phase-II results with the second-line regimen of oxaliplatin, 5-fluorouracil (24 h) and folinic acid (OFF),[10] we initiated the CONKO-003 (CharitéONKOlogie) randomized phase-III trial aimed to investigate the role of OFF + BSC versus BSC alone in patients with APC following disease progression during gemcitabine treatment.

2. Patients and methods

2.1. Eligibility criteria

Patients with histologically confirmed APC who had progressed during first-line gemcitabine therapy were eligible for this open randomized multicentre study. Other major inclusion criteria were: age ⩾ 18 years; Karnofsky performance status (KPS) > 60%; measurable reference lesion, adequate laboratory values for haematology (white blood cell [WBC] count $>3.5 \times 10^9$/L, platelet count $>100 \times 10^9$/L), renal (creatinine clearance >30 ml/min) and hepatic function (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] < 2.5 × upper normal limit [UNL]; in case of liver metastasis <5 × UNL). Patients were excluded from the study if they had any severe concurrent medical condition interfering with the planned therapy, serious cardiac disease (e.g.: myocardial infarction within the last 4 weeks, unstable coronary heart disease), sensory/motor neuropathy >grade 2, uncontrolled pain, or had previous or active malignancies of other origin. Pregnant or breastfeeding women were excluded. Prior radiotherapy with or without chemosensitization was not allowed. Patients who developed recurrence while receiving adjuvant gemcitabine post curative surgery were not recruited. All patients provided written informed consent. The trial was approved by the Scientific and Research Ethics Committee of the participating institutions. The United States National Health Institute registry number is NCT00786058.

2.2. Treatment

Patients were stratified according to duration of first-line therapy (<3, 3 to <6 and >6 months), KPS (70–80%; 90–100%) and stage (M0/M1) and were randomized to either OFF + BSC or BSC alone. The OFF regimen consisted of a 6 weeks cycle of folinic acid (FA) (0.2 g/m^2, 0.5h, iv.) followed by 5-FU (2 g/m^2,

Table 1 – Patient characteristics.

Treatment	Oxaliplatin, folinic acid and 5-fluorouracil (OFF)	BSC alone
Total number of patients	23	23
Sex		
Male	14 pts	15 pts
Female	9 pts	8 pts
Age		
Median (range)/years	60 [38–76]	61 [34–80]
Median Karnofsky performance status/%	80 (70–100)	80 (70–100)
Stratification		
KPS 70–80%	12 pts	11 pts
KPS 90–100%	11 pts	12 pts
PFS GEM <3 months	6 pts	5 pts
PFS GEM 3–6 months	10 pts	11 pts
PFS GEM >6 months	7 pts	7 pts
M0	6 pts	7 pts
M1	17 pts	16 pts
Pts. with gemcitabine first line therapy	23 pts	23 pts
Progression free survival in 1st line therapy median (months)	4.75	4.57

24-h, iv.) administered on days 1, 8, 15 and 22. Oxaliplatin (0.85 g/m^2, 2–4 h, iv.) was administered prior to FA/5-FU on days 8 and 22. Patients received antiemetic prophylaxis with alizapride and dexamethasone. After a 3 weeks rest (d23 to 42) the next cycle was started (d43 = d1 of next cycle). BSC was provided to all patients according to current palliative care guidelines. BSC included in particular adequate pain management, therapy of infection, biliary-stent intervention if needed, social supply and on demand psychooncologically intervention and nutrition consultation/intervention. Patients in the BSC arm regularly were seen in the outpatient department at least every 14 d. They were visited not so often like patients in the treatment group, but if needed the visit number was equal or even higher. Both groups do not receive additional specific anticancer therapy.

2.3. Response and toxicity assessments

Pre-treatment evaluation included a complete medical history and physical examination, blood cell count, standard biochemical profile and a computed tomography scan (CT) or magnet resonance tomography (MRT) confirming disease progression while on gemcitabine. Prior to each treatment cycle a medical history was taken and a physical examination performed. During treatment complete blood cell counts were carried out weekly. Biochemical tests were done at least prior to each cycle and more often in cases of toxicities. A CT- or MRT-scan took place when clinical or laboratory signs suggestive of cancer progression became evident or at least every two treatment cycles.

2.4. Statistical methods

The primary study end-point was survival measured from treatment randomization until death or last contact. Secondary end-points were overall survival (OS) from the start of first-line gemcitabine and treatment toxicity.

The sample size calculation was based on the null hypothesis that median patient survival would be 2 months from first-line treatment failure to death ($\mu 1$). The alternative hypothesis was that second-line treatment would lead to an OS of at least 4 months ($\mu 2$) after randomization.

According to these assumptions ($\mu 2$–$\mu 1$, difference $\delta = 2$ months, standard deviation $\sigma = 15$, two-sided test, level of significance $\alpha = 5\%$, power 90%) 165 patients were calculated for the trial, including a drop-out rate of 10%. Data were analysed by SPSS version 13.0 on an intent to treat basis. The probability of survival was estimated by the method of Kaplan

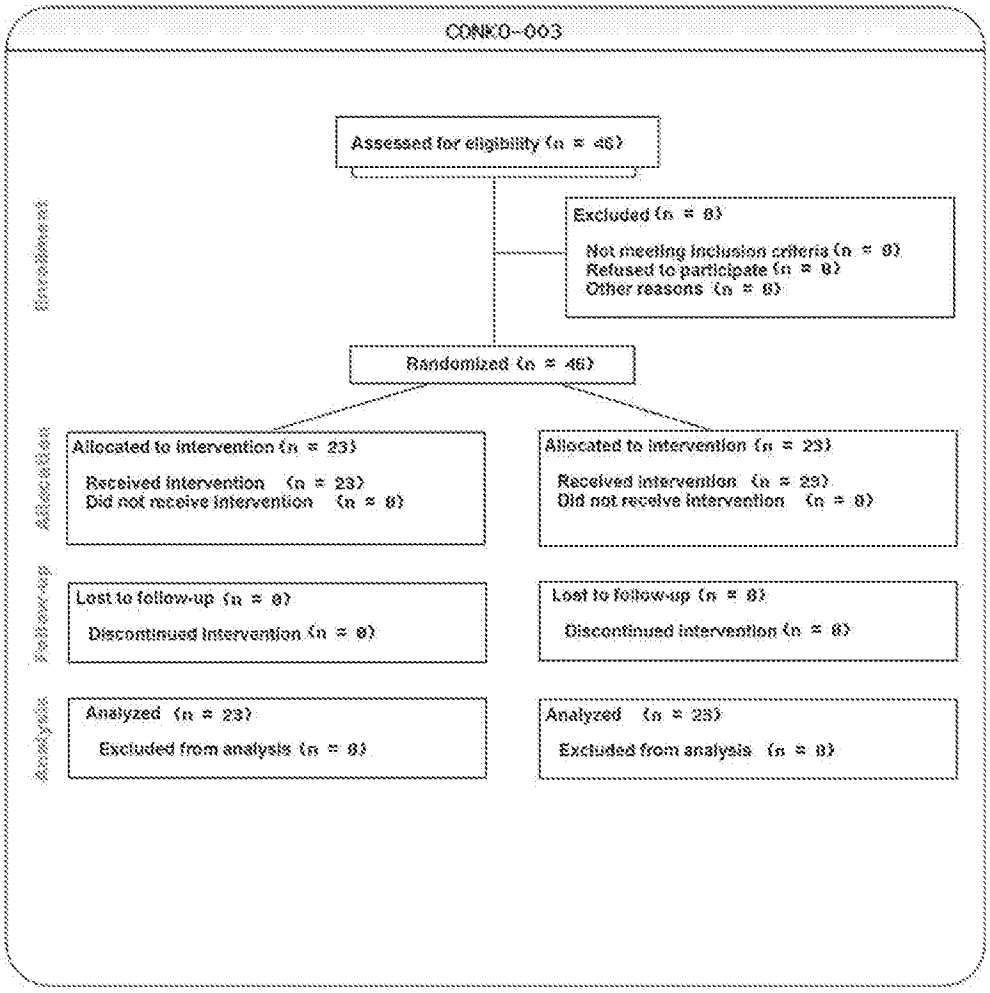


Fig. 1 – Consort diagram.

and Meier, the comparison between the two arms was done using the log-rank test.

3. Results

Recruitment started in December 2002. It was stopped in December 2003 by the protocol committee according to predefined protocol regulations (low recruitment). At that time 46 (OFF + BSC 23 pts/BSC 23 pts) patients from 12 study centres (average pt. recruitment 3) had been included. The major reason for low accrual was due to the diminishing acceptance of BSC alone by oncologists and patients after publishing the phase-II results of the OFF-regimen. Patient characteristics are well balanced between both groups (Table 1, Fig. 1). Patients had been treated with gemcitabine in first-line therapy until progression for a median of 4.57 months (BSC) and 4.75 months (OFF) (HR 0.88 [95% Confidence Interval: 0.49–1.59]; $p = 0.67$).

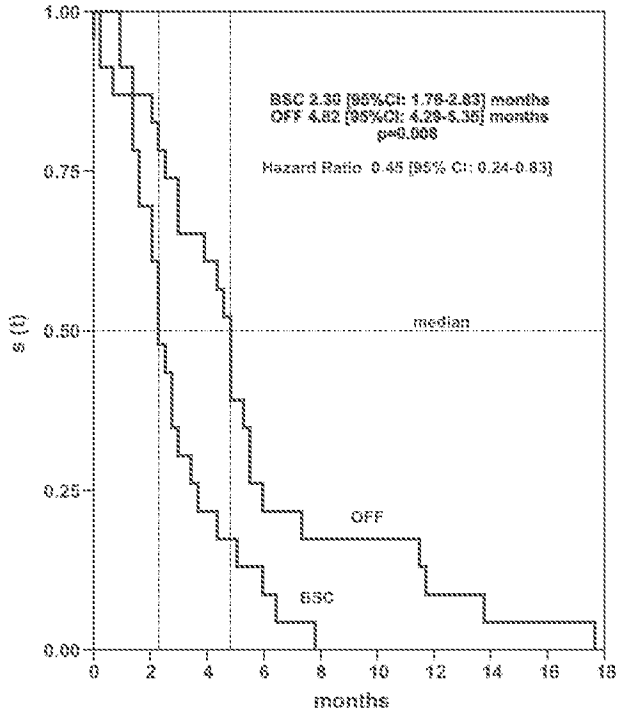


Fig. 2 – Kaplan–Meier plot – second-line survival.

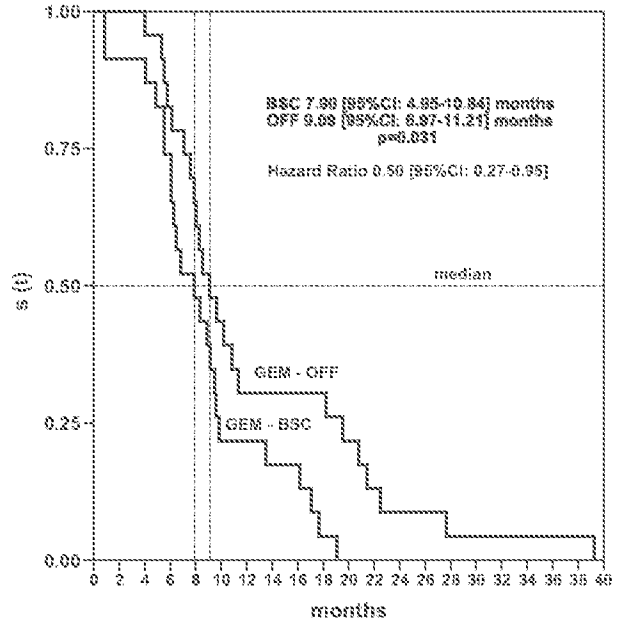


Fig. 3 – Kaplan–Meier plot – overall survival.

Table 2 – Toxicities (NCI-CTC 2.0).

	No. of pts. with toxicity							
	OFF				BSC alone			
	I	II	III	IV	I	II	III	IV
Haemoglobin	5	11	0	0	5	2	1	0
Leucopenia	4	0	0	0	0	0	0	0
Thrombocytopenia	2	2	0	0	0	0	1	0
Diarrhoea	5	1	2	0	1	1	0	0
Nausea/emesis	6	4	1	0	1	1	0	0
Paraesthesia	10	1	0	0	1	0	1	0

3.1. Efficacy

Despite the low enrolment numbers, second-line chemotherapy significantly prolonged the survival after first-line progression (Fig. 2). OFF treatment resulted in a median survival of 4.82 [95% CI: 4.29–5.35] months whereas patients in the BSC arm survived for 2.30 [95% CI: 1.76–2.83] months (HR 0.45 [95% CI: 0.24–0.83], $p = 0.008$). No confirmed response better than stable disease was observed. Overall survival was significantly longer in the GEM-OFF sequence with 9.09 [95% CI: 6.97–11.21] months as compared to the GEM–BSC alone sequence with 7.90 [95% CI: 4.95–10.84] months (HR 0.50 [95% CI: 0.27–0.95], $p = 0.031$) (Fig. 3).

The mean administered cumulative dose for oxaliplatin was 281 [0–850] mg for folinic acid 1591 [200–3000] mg and for 5-FU 15630 [2000–20000] mg.

3.2. Safety

Side-effects in both groups were given as worst toxicity of all causalities per patient. Moderate haematologic toxicities (NCI-CTC grade 1–2) were reported in 24 patients of the OFF group and in 7 of the BSC group. No grade 3 or 4 haematologic toxicities were reported in the OFF treatment group, one patient in the BSC group experienced a grade 3 thrombocytopenia with non-fatal gastrointestinal bleeding and consequent anaemia grade 3. The most common non-haematologic toxicities were sensory neuropathy, diarrhoea and nausea/emesis. There were no reports of grade 4 non-haematologic toxicities. NCI-CTC grade 1–2 reversible neurotoxicity was seen in 11 (48%) patients in the OFF treatment group. Sensory neurotoxicity was also reported in the BSC group with one pt grade 1 and one pt grade 3 (most likely of paraneoplasic origin) (Table 2).

4. Discussion

Adenocarcinoma of the pancreas remains a malignancy with dismal prognosis. In addition to intensive ongoing research for more effective first-line protocols there is still an unmet

need for evidence-based treatment options other than best supportive care for patients progressing while on gemcitabine therapy. Study results on second-line treatment in this disease are rare. We focused our attention on the combination of oxaliplatin, folinic acid and 5 fluorouracil (OFF) and demonstrated a median overall survival time of 5.05 [0.92–74.82+] months in a phase II study.[10] Another small trial reported a similar survival time (median 5.74 months) but more severe toxicities with these drugs using increased dose intensities,[11] with 57% of the patients requiring granulocyte colony stimulating factor support. Other treatments options had been tested for patients progressing on gemcitabine first-line therapy, too. A combination study of irinotecan and docetaxel was considered too toxic and was therefore stopped prematurely.[12] Weekly docetaxel monotherapy resulted in acceptable toxicity and an overall second-line survival of 3.67 months in 10 patients.[13] Single agent raltrexed resulted in a remarkable median overall survival of 4.59 months,[14] and for the combination of raltrexed plus oxaliplatin a similar median survival of 4.82 months and tolerable side-effects were reported.[15] Paclitaxel showed a moderate median survival time of 4.02 months.[8] S-1 resulted in a survival of 4.13 months in 40 patients with acceptable side-effects.[16] Arsenic trioxide in a 13-patient cohort resulted in a survival of 3.44 months.[17] More recently, regimens using combinations of cytotoxic drugs and targeted therapies were investigated in patients after progression during gemcitabine containing first-line therapy. Whereas capecitabine plus erlotinib showed a promising median overall survival of 5.97 months,[9] for the combination of docetaxel plus gefitinib a median survival of 2.52 months was reported.[18]

Second-line treatment options with documented survival times of at least 4–5 months are reported so far only in small phase-II studies. We are not aware of any completed second-line phase-III study in this indication when we initiated our randomized trial of OFF + BSC versus BSC alone.[10] Due to declining acceptance of BSC alone by patients as well as participating oncologists recruitment progressively decreased below 3 pts per months (initial calculation was 3 pts per week) and the study had to be stopped pre term according to protocol.

Both patient groups, although being small, are well balanced with regard to baseline characteristics. The duration of time to progression in first-line treatment with gemcitabine was similar to results of large phase-III first-line trials, ranging from 2.0 to 5.1 months.[19]

Treatment was well tolerated. No grade 4 toxicities were observed. No patient stopped chemotherapy due to side-effects. Despite the small patient cohort we demonstrated a statistically, and clinically as well, significant survival advantage for the chemotherapy cohort, with more than doubling of the median overall survival.

In conclusion, the OFF-regimen represents a feasible and effective approach with acceptable toxicity for second-line outpatient treatment of advanced adenocarcinoma of the pancreas after progression on first-line gemcitabine.

Contributors

UP, IS, JSt, MA, JS, HR and HO contributed to patient enrolment, to the collection and assembly of the data. HR, HO and BD provided capacities for the trial. UP and HR drafted the article. HO, HR and UP were responsible for the study idea, study design, data analysis and interpretation. All authors provided final approval.

Previous presentation of preliminary data

H. Oettle, U. Pelzer et al. Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement): A4031.

Conflict of interest statement

None declared.

Acknowledgements

This study was supported by 'Charité-Forschungsförderung', 'Arbeitsgemeinschaft internistischer Onkologie – AIO', 'Deutsche Krebsgesellschaft e.V.' and Sanofi-Aventis GmbH (Frankfurt, Germany), medac GmbH (Wedel, Germany) who provided oxaliplatin, folinic acid and 5-fluorouracil free of charge.

We thank all patients for the participation and the study nurses and physicians for the support in this trial.

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P865

Quality-adjusted time without symptoms or toxicity (Q-TWiST) of nanoliposomal irinotecan (nal-IRI;MM-398) plus 5-fluorouracil and leucavorin (5-FU/LV) vs 5-FU/LV alone in patients with metastatic pancreatic adenocarcinoma (mPAC) previously treated with gemcitabine-based therapy

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Introduction: In the primary analysis of the phase 3 NAPOLI-1 trial, nal-IRI+5-FU/LV significantly improved median overall survival (OS; 6.1 vs 4.2 months; hazard ratio [HR]=0.67, P = 0.012) and progression-free survival (PFS; 3.1 vs 1.5 months; HR = 0.56; P = 0.0001) vs 5-FU/LV alone in mPAC patients previously treated with gemcitabine-based therapy. Here we report between-treatment differences in quality-adjusted survival using the Q-TWiST methodology, commonly used in oncology.

Methods: The total 12-month survival in NAPOLI-1 intent-to-treat cohort was partitioned into time before disease progression without toxicity grade ≥3 (TWiST), time with adverse event grade ≥3 (TOX), and time of disease progression (REL). Mean Q-TWiST was calculated by multiplying mean time spent in each health state by its respective utility. In the base case, the utility for TWiST (uTWiST), toxicity (uTOX), and post-progression (uREL) were set to 1.0, 0.5, and 0.5, respectively. The relative gain in Q-TWiST in nal-IRI+5-FU/LV over 5-FU/LV was calculated as the difference in Q-TWiST divided by the OS of the 5-FU/LV group. Non-parametric bootstrapped 95% confidence intervals (CIs) were derived around estimates. Threshold analyses varied uTOX and uREL between 0.0 and 1.0. An additional scenario analysis was conducted using the per protocol (PP) population.

Results: Compared with patients receiving 5-FU/LV (n = 119), those receiving nal-IRI+5-FU/LV (n = 117) spent significantly more time in TWiST (mean 3.4 vs 2.4 months) and TOX (1.0 vs 0.3 months), but similar time in REL (2.5 vs 2.7 months). After weighing time spent in TWiST, TOX, and REL with their respective base-case utilities, nal-IRI+5-FU/LV resulted in 1.3 months (95% CI: 0.4-2.1; 5.1 vs 3.9) greater Q-TWiST, with relative Q-TWiST gain of 24%. In the threshold analyses varying uTOX and uREL, the Q-TWiST ranged from 0.9 to 1.7 months, and the relative Q-TWiST gain ranged from 17% to 31%. In the PP population, Q-TWiST was also significantly superior in patients recieving nal-IRI+5-FU/LV (Q-TWiST gain = 1.8 months; 95% CI: 0.7-3.0).

Conclusion: In NAPOLI-1, nal-IRI+5-FU/LV resulted in statistically significantly and clinically important gains in quality-adjusted survival vs 5-FU/LV alone. This confirms the clinical outcome benefit of nal-IRI+5-FU/LV in patients with mPAC.

Disclosure: Uwe Pelzer: Advisory Role: Baxalta advisory boards
Richard Hubner: Advisory Role: Baxalta Advisory boards

CSPC Exhibit 1100
Page 303 of 333

What Else in Gemcitabine-Pretreated Advanced Pancreatic Cancer? An Update of Second Line Therapies

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Abstract: Advanced pancreatic cancer is usually treated with first-line gemcitabine (GEM) (alone or in combination). More recently, GEM has become an established part of an adjuvant therapy based on two recently-reported randomized trials. There remains unresolved the problem of second-line therapy in patients relapsed during or after adjuvant or first-line GEM-based treatment.

As of today, platinum analogues in combination with fluoropyrimidine or with GEM represent the most common schedule in clinical practice with data from single-centre or multicentric phase II studies. In 2008, for the first time, a randomized phase III trial conducted on good performance status GEM-refractory patients (CONKO 003) confirmed their benefit in progression-free and overall survival by adding oxaliplatin to a bolus 5-FU/folinic acid schedule.

Other agents (irinotecan, taxanes, antifolates, biological) have been tested, although only dismal results have been achieved, as they turned out to be too toxic in combination and to have too low activity when used as single agents.

Which is the optimal candidate for second-line therapies, is debatable. Good performance status and discrete progression-free survival since the beginning of the GEM therapy (more than 6 months?) are likely to be the best indicators of subsequent line benefit.

The benefit of biological agents is unknown, also given the poor results achieved in the first-line treatment.

In summary, as of today, there is one randomized study that confirms the benefit of second-line chemotherapy for the treatment of GEM-relapsed pancreatic cancer. Current data indicate 5-FU plus a platinum agent (oxaliplatin) as the standard of care for PS 0-1 patients.

Ongoing clinical trials will clarify whether there is obviously a place for improvement and for other agents. At present, even though no data on benefits in unfit patients (Karnofsky < 70) are available, a fluopyrimidine agent still remains a reasonable treatment option.

Keywords: Pancreatic cancer, second line, chemotherapy, gemcitabine.

Presently, only gemcitabine (GEM) has been approved by the FDA for the treatment of metastatic pancreatic cancer (PC), based on relatively dramatic improvement in clinical benefit response (24 *versus* 5%), compared with 5-fluorouracil (5-FU) [1]. The median overall survival (OS) was only modestly improved from 4.4 to 5.6 months, and the 1-year survival favored the GEM arm (18 *versus* 2%). Multiple phase III trials using platinum doublets did not lead to any improvement in the OS, although platinum doublets (GEM plus oxaliplatin and GEM plus cisplatin regimens) showed a significant improvement in terms of response rate (RR), progression-free survival (PFS) and clinical benefit [2]. The RR of platinum doublets is higher than any other combination. In contrast with Phase III data, a pooled analysis of two randomized studies [3] and 5 meta-analyses [4-8] suggested a survival benefit from the use of a GEM/platinum combination in the treatment of PC. The pooled-data analysis of 2 studies [3] concluded that the combination of GEM with a platinum analogue such as oxaliplatin or cisplatin improves the PFS and the OS significantly more than a single-agent GEM in the treatment of advanced PC. This benefit was most pronounced in patients with performance status (PS) ECOG 0. These data are similar to those reported by Herrmann's study on GEM plus capecitabine (significant prolongation of median OS time in the GEM plus capecitabine arm compared with the GEM arm: 10.1 *vs.* 7.4 months respectively in PS 0 patients; P = .014) [9]. More recently, GEM has become an established part of adjuvant therapies too, based on two recently reported randomized trials (Charité Onkologie [CONKO]-001, Radiation Therapy Oncology Group [RTOG] 97-04) [10,11].

Once it has been established that the majority of patients is now treated with a first-line GEM-based therapy during the adjuvant phase (if the disease was radically resected) or in case of advanced disease (in the palliative setting), the treatment of metastatic disease in patients who experienced a relapse after or during GEM–therapy is still an unsolved problem.

Also, there is no agreement yet on how long the relapse-free interval should be, after which the disease can still be considered GEM-sensitive (6 months? 12 months?), and a re-treatment with GEM can be taken into consideration. Generally, relapses after or during a GEM-based treatment are normally approached with other potentially active drugs in

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1574-8871/10 $55.00+.00 © 2010 Bentham Science Publishers Ltd.

CSPC Exhibit 1100
Page 304 of 333

second-line treatments, given the fact that potential adjuvant GEM-chemotherapy is considered as the first-line of treatment (in most cases, PC is formally considered micrometastatic at the moment of the diagnosis).

Now, the question is: what is the optimal systemic treatment of GEM-refractory or relapsed PC? And also, do these patients achieve any benefit from a second-line therapy?

In this review, we have updated the results of studies that investigate the role of a second-line therapy performed exclusively after GEM-failure (so enrolling patients relapsed during or after this first-line treatment) in metastatic or advanced PC.

GEM RE-CHALLENGE AS SECOND-LINE THERAPY (SEE TABLE 1)

There are no formal data from randomized trials that either exclude or confirm the value of re-treatment with GEM as second-line therapy after a previous administration of GEM.

Table 1. Gemcitabine Rechallenge

Ref.	Author	Schedule	Phase of Study	N° of pts	Features of pts and Toxicities	RR	TTP/PFS Median	OS Median
[12]	Fortune BE	GEMOX: Gemcitabine 1000 mg/m2 over 100 min on day 1 and Oxaliplatin 100 mg/m2 over 2h on day 2 every 2 weeks	II	17	All failure after GEM standard dose rate (30 min). Median age 62 years. No unexpected toxicities.	PR 24% SD 29% PD 47%	mPFS 2,6 m	6,4 m
[13]	Demois A	GEMOX: Gemcitabine 1000 mg/m2 over 100 min on day 1 and Oxaliplatin 100 mg/m2 over 2h on day 2 every 2 weeks	II	33	Median age 57 years. Progressio during or after GEM therapy. Grade III/IV non-neurologic toxicities occurred in 12/33 patients (36.3%), and grade I, II, and III neuropathy in 17(51%), 3(9%), and 4(12%) patients, respectively.	PR 22,6% SD 38,7% PD 38,7%	PFS 4,5 m TTP 4,2 m	6 m
[14]	Reni M	Classic PEFG (Cisplatin and Epirubicin 40 mg/m2 day 1, Gemcitabine 600 mg/m2 day 1 and 8, FU 200 mg/m2/d continuous infusion day 1-28) or dose-intense PEFG (Cisplatin and Epirubicin 30 mg/m2, Gemcitabine 800 mg/m2 every 14 days; FU 200 mg/m2/d continuous infusion day 1-28)	II	46	Main grade >2 toxicity consisted of neutropenia in 26 patients (56%), thrombocytopenia in 10 (22%), anemia in 11 (24%), fatigue and stomatitis in 4 (9%), vomiting, diarrhea and hand-foot syndrome in 2 (4%).	PR 24%	PFS 5 m	8,3 m
[15]	Reni M	All schedules	retrospective	183	Median age 62 years; median PS 1; 63 submitted to prior curative surgery, 32 to prior radiotherapy.		PFS 3 m	6,2 m
[16]	Boxberger F	Oxaliplatin (L-OHP), Gemcitabine and high-dose 5-Fluorouracil (5-FU) as a 24-h infusion	II	4	Thrombocytopenia grade 4 was observed in 1 patien.	PR 25% SD 75%		13,2 m
[17]	Kozuch P	G-FLIP (Day 1: Gemcitabine 500 mg/m2, Irinotecan 80 mg/m2, Leucovorin 300 mg, 5-fluorouracil 400 mg/m2 bolus followed by infusional 5-FU 600 mg/m2 over 8 h. Day 2: Leucovorin 300 mg and 5-FU 400 mg/m2 bolus, followed by Cisplatin 50 to 75 mg/m2, infusional 5-FU 600 mg/m2 over 8 h) repeated every 2 weeks	II	34	Grade 3-4 hematological toxicities included anemia (23%), thrombocytopenia (53%), and neutropenia (38%). There were no grade 3-4 neutropenic fevers, treatment-related mortalities, or withdrawals. Non-hematological grade 3-4 toxicities were rare: nausea/vomiting (3%), neurotoxicity (3%), nephrotoxicity (6%), and diarrhea (3%).	PR 24% SD 21%	TTP 3,9 m	10,3 m
[18]	Stathopoulos GP	Gemcitabine 1000 mg/m2 and Lipoplatin (liposomal cisplatin) dose escalated from 25 mg/m2 to 125 mg/m2	I-II	24	PS 2 50%. Previous GEM 46%, previous GEM + irinotecan 54%. At MTD for lipoplatin maximum toxicity neutropoenia (grade 2-3). Alopecia and fatigue more frequent grade 1 non haematological toxicities (58 and 33%)	PR 8,3% SD 58,3%	Not reported	4 m

RR: response rate; CR: complete response; PR: partial response; PD: progression of disease; SD: stable disease; PFS: progression free survival; TTP: time to progression; OS: overall survival; N°: number; MTD: maximum tolerated dose; PS: performance status; pts: patients; m: months; w: weeks.

In a retrospective review of a single-centre experience with GEM-fixed dose rate (over a time of 100 minutes) plus oxaliplatin, namely GEMOX, 17 patients who had been treated at the Ohio State University with GEMOX following a standard-dose GEM failure between November 2003 and January 2008 were analyzed [12]. Twenty-four percent of all patients had a partial response (PR), 29% had stable disease (SD) and 47% had progressive disease (PD). The median PFS was 2.6 months and the median OS was 6.4 months. No unexpected toxicities occurred.

Following a similar schedule, Demols and colleagues [13] treated 33 patients who had progressed during or following GEM therapy. The response in 31 evaluable patients was as follows: PR: 22.6%, SD $\geq$ 8 weeks: 35.5%, SD < 8 weeks: 3.2%, PD: 38.7%. The average duration of the response and the TTP was respectively 4.5 and 4.2 months. The median OS was 6 months (range 0.5-21). A clinical benefit response was observed in 54.8% of patients.

Patients with progressive or recurrent PC after GEM-containing chemotherapy were treated with either classic PEFG (until April 2004) or dose-intense PEFG (since May 2004) until progressive disease or a maximum of 6 cycles of 28 days [14]. A partial response was observed in 11 patients (24%) (5 classic PEFG 28% plus 6 dose-intense PEFG 21%). The median and 1-year survival was 8.3 months (8.0 *vs.* 9.0 months) and 26% (17% *vs.* 32%). The median and 6-months PFS was 5.0 months (4.5 *vs.* 5.0 months) and 34% (33% *vs.* 38%). The PEFG regimen in GEM-refractory PC had an acceptable toxicity profile and an interesting activity, and may represent a good treatment option in this setting. The same authors reviewed their experience with institutional second-line therapies in patients with prior GEM-including therapy [15]. The median and 6-month PFS after initiation of salvage therapy was 3.0 months and 20%. The median 1- and 2-year OS after initiation of salvage therapy was 6.2 months, respectively 17 and 4%. Previous PFS, CA19.9 levels and age predicted the OS independently. They concluded that re-challenge with GEM and 5-FU administration may be effective in selected patients.

Four patients in a German institution were treated with a palliative second-line therapy with Oxaliplatin, GEM and high-dose 5-FU after a first-line therapy with GEM and weekly high-dose 5-FU [16]. As a result of second-line therapy, SD with a significant decrease in CA 19.9 levels was achieved in 3 patients and PR in 1 patient. After a palliative first- and second-line treatment, the survival time of patients was 9, 9, 15 and 20 months.

The G-FLIP schedule was administered to 34 patients with histologically confirmed metastatic PC [17] over a time of 48 hours and repeated every 2 weeks. Based on RECIST criteria, a PR was attained in 8 patients (24%) and 7 patients had SD. Seven and 6 patients who attained respectively a PR or SD experienced disease progression with prior GEM-based therapy. The median time to progression (TTP) for all 34 patients was 3.9 months and 5.9 months for the 8 patients who attained a PR. The median overall survival for all 34 patients was 10.3 months.

A phase I-II study with escalating doses of lipoplatin combined with GEM at standard dose has been published [18]. The treatment was administered to advanced pre-treated PC patients who were refractory to previous chemotherapy which included GEM. Lipoplatin at 125 mg/m2 was defined as dose limiting toxicity (DLT) and 100 mg/m2 as the maximum tolerated dose (MTD) in combination with 1000 mg/m2 of GEM. Preliminary overall response rate (ORR) data showed a PR in 2/24 patients (8.3%), disease stability in 14 patients (58.3%) for an average duration of 3 months (range 2-7 months), and clinical benefit in 8 patients (33.3%). Liposomal cisplatin is a non-toxic alternative agent of cisplatin. In combination with GEM, it has an MTD of 100 mg/m2 and shows promising efficacy in the treatment of refractory PC.

PLATINUM ANALOGUES-BASED COMBINATIONS AS SECOND-LINE THERAPY (SEE TABLE 2)

Historically, before the advent of the GEM era, 5-FU as a single-agent or 5-FU–based regimens were typically employed as treatment of advanced pancreas cancer. In most studies on pancreatic cancer, cisplatin has been administered in combination with GEM, although a small study conducted by Wils *et al.* showed that cisplatin used as a single-agent had a response rate of 21% and a median duration of response of 5 months [19]. Oxaliplatin used as a single agent has a very minimal efficacy in the treatment of pancreatic cancer, but there are preclinical data suggesting that it provides synergistic activity **in particular in combination with GEM**. Thus, platinum agents are expected to be combined with fluoropyrimidines (agents with activity in PC other than GEM) as a second-line therapy in GEM pre-treated patients.

The CONKO-003 (Charité Onkologie) showed the benefit of an oxaliplatin-based regimen in the second-line treatment of PC [20]. The study indicated that the alternation of OFF/FF and continuous FF are feasible and tolerable regimens as second-line treatments of advanced PC performed after GEM failure. OFF/FF results in significantly longer PFS (P=0.012) and OS (P=0.014) *vs.* FF, and also in a substantially greater clinical benefit in patients with poor prognostic features. The authors suggested that OFF/FF should be considered as the standard second-line treatment in patients who progress on GEM.

In a randomized, phase III trial, Ychou and colleagues [21] from France evaluated the sequential therapy of either leucovorin plus 5-FU (LV5FU2)/cisplatin followed by second-line GEM therapy or the reverse sequence in patients with metastatic PC. Sequential regimens were compared to determine which chemotherapy sequence offered the most clinical benefit. This trial randomized 202 patients to either standard GEM (n = 100) and then cross-over to the LV5FU2/cisplatin combination upon progression or unacceptable toxicity, or to receive the agents in reverse sequence (n = 102). The median follow-up was 44 months. The therapy performed with administration of LV5FU2/cisplatin followed by GEM resulted in an overall median survival of 6.6 months. This is only slightly longer than the OS of patients who received GEM followed by no additional therapy. By contrast, the treatment performed with administration of GEM first and then LV5FU2/cisplatin led to a longer median survival of 8 months, although these differences were not

Table 2. Platinum Analogues-Based Combinations

Ref.	Author	Schedule	Phase of Study	N° of pts	Features of pts and Toxicities	RR	TTP/PFS Median	OS Median
[20]	Pelzer U	ARM 1 (FF). 5-Fluorouracil 2 g/m2 c.i. 24 h – Folinic acid 200 mg/m2 day 1,8,15,22 ARM 2 (OFF): FF + Oxaliplatin 85 mg/m2 day 8,22	III	160	Anaemia and neurotoxicity grade 3 n=3/76 pts.	Not reported	9 *vs* 13 w (p=0,012)	13 *vs* 20 w (p=0,014)
[21]	Ychou M	ARM 1: Leucovorin +5FU/CDDP → Gemcitabine ARM 2: Gemcitabine → Leucovorin+ 5FU/CDDP	III crossover	202	There did appear to be more hematologic toxicities when gemcitabine was administered as second-line therapy *vs* first-line therapy (60% *vs* 43.2%, respectively, *P* = .018).	ORR ARM1: 18% ORR ARM2: 22%	ARM 1 -2: PFS 3,5 m	ARM1: 6,6 m ARM2: 8 m
[22]	Pelzer U	OFF: Fluorouracil 2 g/m2 c.i. 24 h – Folinic acid 200 mg/m2 day 1,8,15,22 + Oxaliplatin 85 mg/m2 day 8,22	II	37	A total of 12 patients had grade 3 nonhematologic toxicities: nausea and vomiting (4 patients), reversible neurotoxicity (5 patients), and diarrhea (3 patients). No grade 4 toxicities were observed.	CR 3% PR 3% SD 43%	TTP 12 w	22 w
[23]	Novarino A	Weekly oxaliplatin 40 mg/m2, 5-FU 500 mg/m2, and Leucovorin 250 mg/m2 (3 weeks on, 1 week off)	II	23 (17 assessable)	Seven patients experienced grade 3 to 4 toxicity	PR 0% SD 17% PD 83%	TTP 11,6 w	17,1 w
[24]	Xiong HQ	Oxaliplatin 130 mg/m2 on Day 1 + Capecitabine 1000 mg/m2 twice daily for 14 days	II	41 (39 evaluable)	PS 2 28,6%. Fatigue grade 3 13%, diarrhoea grade 3 5%.	PR 2,6% SD 25,6%	PFS 9,9 w	23 w
[25]	Gebbia V	FOLFOX-4	retrospective	42	PS 2 38%. Grade 3 anemia was recorded in 14% of patients, grade 3–4 neutropenia occurred in 17% of patients (two cases of febrile neutropenia). Most of the non-hematological symptoms were mild being less than grade 3.	PR 14% SD 38%	TTP 4 m	6,7 m
[26]	Tsavaris N	Oxaliplatin 50 mg/m2 2 h + Leucovorin 50 mg/m2 bolus + 5-FU 500 mg/m2 1 h, weekly	II	30	PS ≥ 50 100%. 93% locally advanced. Grade 3/4 toxicity expressed per chemotherapy dose included leukopenia 16%, anemia 3.2%, thrombocytopenia 3.2%, diarrhea 14.2%, fatigue 16.1% and neurotoxicity 4.2%.	PR 23,3% SD 30% PD 46,7%	TTP 22 w	25 w
[27]	Androulakis N	Oxaliplatin 130 mg/m2 Day 1 every 21 days	II	18	Toxicity was mild.	OR 0% SD 16,7%	TTP 4, 8 and 12 m for 3 pts with SD	3,5 m
[28]	Reni M	Raltitrexed 3 mg/m2 + Oxaliplatin 130 mg/m2 every 3 weeks	II	41	PS 0-1 100%. 15% pts > 1 line previous chemotherapy. Main grade >2 toxicity was: neutropenia in five patients (12%), thrombocytopenia, liver and vomiting in three (7%), fatigue in two (5%).	PR 10% SD 26,8%	PFS at 6m: 14,6%	5,2 m
[29]	Togawa A	S-1 80 mg/m2 daily for 21 days + CDDP 40 mg/m2 day 8; every 5 weeks	II	17	Major adverse reactions in the 15 patients included gastrointestinal toxicities of grade 1 or 2. Only one patient (5.9%) developed grade 3 leucopenia.	PR 29,4% SD 11,8%	Not reported	10 m
[30]	Rougier P	5-FU 1000 mgm2 c.i. daily from day 1 to day 5 + CDDP 100 mgm2 on day 2		40 (38 evaluable)	65 % of pts PS 2 or 3. Leukopenia was the most important toxicity; 11 pts (27%) had a grade 4 leukopenia and 3 had neutropenic fever.	CR 2,6% PR 23,7% ORR 26,5%	TTP 10 m	7 m

RR: response rate; CR: complete response; PR: partial response; PD: progression of disease; SD: stable disease; PFS: progression free survival; TTP: time to progression; OS: overall survival; N°: number; PS: performance status; pts: patients; m: months; w: weeks.

statistically significant. The median PFS in both arms was approximately 3.5 months. Patients' quality of life also did not differ significantly. The overall response rates were 18% to 22%, therefore the difference between the groups wasn't statistically significant either.

The same authors published also a phase II study conducted according to the OFF schedule. The median TTP was 12 (1-125) weeks. Survival in the second-line setting was 22 (4-326+) weeks. The overall disease control rate was 49% (CR = 3%; PR = 3%; SD > 12 weeks = 43%) [22].

Some Italian authors reported the activity of an oxaliplatin/5-FU/folinic acid weekly schedule in 23 GEM pretreated patients [23]. Among 17 assessable patients, no objective response was registered and 4 patients had SD, whereas 13 had tumour progression. The median duration of SD was 14 weeks. The median TTP was 11.6 weeks [95% confidence interval (CI), 7.6-5.6]. Kaplan-Meier estimated that the median OS was 17.1 week (95% CI, 4.0-30.1) and the 3-month survival rate was 69.6%.

Xiong *et al.* [24] published phase II data on the administration of capecitabine and oxaliplatin in patients previously exposed to GEM. Out of the 39 evaluable patients, one had a PR and 10 patients showed SD. Kaplan-Meier's estimate of the median OS was 23 weeks (95% confidence interval [95% CI], 17.0-31.0 weeks). Progression-free survival was 9.9 weeks (95% CI, 9.6-14.5 weeks). The 6-month and 1-year survival rates were 44% (95% CI, 31%-62%) and 21% (95% CI, 11%-38%), respectively.

A retrospective Italian survey was carried out involving 42 patients [25]. Patients received classical FOLFOX4 regimen biweekly until progression or unacceptable toxicity. Six PR (14%) and 16 SD (38%) were reported and the tumour growth control rate was 57%. The median TTP was 4 months (range 1-7 months), and the median OS was 6.7 months (range 2-9 months). A stabilization PS and a subjective improvement of cancer-related symptoms were recorded in 27 patients. This data support the use of FOLFOX4 regimen in the second-line treatment for patients with pancreas adenocarcinoma.

A study on a bolus weekly 5-FU/folinic acid schedule combined with weekly oxaliplatin 50 mg/m2 was published by some Greek authors [26]. Patients (n=30) with advanced PC previously treated with GEM were included in the study. Partial responses were observed in 7 patients (23.3%), SD in 9 (30.0%), while 14 patients progressed (PD 46.7%). Improved PS was observed in 18 (42.8%) patients. Patients that had responded to the first-line GEM treatment turned out to be more likely to respond or stabilize their disease with a second-line treatment. The median duration of the response was 22 weeks, and the median OS was 25 weeks. This combination was tolerated with manageable toxicity, and showed an encouraging activity as second-line treatment for patients with advanced or metastatic PC previously treated with GEM.

In another Greek phase II study [27], 18 patients with advanced PC previously treated with GEM-based chemotherapy received oxaliplatin 130 mg/m2 every 21 days. No objective response was observed among the 18 treated patients. Three (16.7%) had SD for more than 2 months. A clinical benefit response was observed in five patients (27.7%). The toxicity was mild, but oxaliplatin administrated as single agent seems to be ineffective as monotherapy.

Other patients received a combination of raltitrexed and oxaliplatin every 3 weeks until progression, toxicity, or a maximum of six cycles [28]. In total, 10 patients (24%) yielded a PR, 11 a SD. Progression-free survival at 6 months was 14.6%. The median OS was 5.2 months. Survival was significantly longer in patients with previous PFS > 6 months and in patients without pancreatic localization. A clinically relevant improvement of the quality of life was observed in numerous domains. Raltitrexed-oxaliplatin regimen may represent a good treatment opportunity in GEM-resistant metastatic pancreatic cancer.

S1 and cisplatin were tested in 17 patients with histologically diagnosed invasive ductal PC [29]. Five (29.4%) patients achieved a PR and 2 (11.8%) had SD. In 5 out of 15 patients (33.3%) who had high serum CA 19-9 levels at the beginning of the treatment, CA19-9 levels were reduced by more than 50%. The median survival time was 10 months (range, 20 months), with 63.7% and 31.9% of patients alive at 6 and 12 months respectively.

Finally, cisplatin plus c.i. 5-FU was tested in 40 eligible patients [30]. One out of 38 evaluable patients had a CR and 9 achieved a PR; the ORR was 26.5% (95% CI: 12% to 40%). The median duration of responses was 10 months (range 4-18). A palliative effect was observed in 45% of patients (17/38). The median survival was 7 months and 29% of patients were alive at 1 year.

FLUOROPYRIMIDINE-BASED COMBINATIONS WITHOUT PLATINUM AGENTS AS SECOND-LINE THERAPY (SEE TABLE 3)

The fluoropyrimidine agent alone or in combination without platinum agents is another viable option for GEM pre-treated patients.

A report on a combination of c.i. (continuous infusion) 5-FU/adriamycin/Mytomicin C has been recently published. A total of 31 patients received 95 cycles of chemotherapy. Four (12.9%) patients showed a PR, and eight patients (25.8%) had SD. The median TTP and OS times were 2.3 (95% CI: 1.0-3.6) months and 6.7 (95% CI: 4.4-9.0) months respectively [31].

Capecitabine and celecoxib were associated with an ORR of 9% and a median survival duration of 19 weeks in 35 patients with documented PD after administration of a GEM-containing agent. Sixty percent of patients were free from progression 3 months after the start of the treatment. Multivariate analyses identified a positive clinical benefit response and a decline in CA 19.9 serum levels higher than 25% compared with baseline levels as independent predictors of prolonged survival [32]. In 2004, the same authors had published a similar pilot experience with c.i. 5-FU plus celecoxib in 17 patients who failed GEM-based chemotherapy [33]. Two of them had a PR (the duration was respectively 23 weeks and 68 weeks) and 2 patients with SD (the duration was respectively 10 weeks and 13 weeks) were observed for an ORR of 12% (95% confidence interval, 0-27%) within the

Table 3. Fluoropyrimidine-Based Combinations Without Platinum Agents

Ref.	Author	Schedule	Phase of Study	N° of pts	Features of pts and Toxicities	RR	TTP/PFS Median	OS Median
[31]	Lee S	5-Fluorouracil 800 mg/m2 on days 1 to 5 over 10 h + Mitomycin-C 8 mg/m2 on day 1 +Doxorubicin 30 mg/m2 on day 1 every 4 weeks.	II	31 (15/31 pancreatic cancer)	Major hematologic toxicities included grade 1 to 2 anemia (64.2%), neutropenia (32.6%), thrombocytopenia (20%), and grade 3 to 4 neutropenia (10.5%). The most frequently detected nonhematological toxicities were grade 2 and 3 nausea/vomiting (35.5%). One patient was diagnosed with hemolytic uremic syndrome after 8 cycles of treatment.	PR 12,9% SD 25,8%	TTP 2,3 m	6,7 m
[32]	Pino MS	Capecitabine 1000 mg/m2 b.i.d. for 2 consecutive weeks followed by 1 week of rest; Celecoxib continuously at 200 mg b.i.d.	II	35	The treatment protocol was well tolerated with negligible hematological toxicity. The most common grade 3 non-hematological toxicities were hypertransaminasemia, diarrhea and asthema.	ORR 9%	66% of pts free of progression at 3 months	19 w
[33]	Milella M	Celecoxib 400 mg twice daily + i.v. 5-fluorouracil 200 mg/m2 daily, both given continuously for a maximum of 9 months	II (pilot)	17	PS 2 1/17 pts. Asymptomatic transaminase elevation was the most common toxicity and reached Grade 3-4 in 4 of 133 treatment weeks. No other hematologic or nonhematologic toxicity > Grade 2 was observed. Four patients discontinued celecoxib due to upper gastrointestinal tract toxicity.	PR 11,8 % SD 11,8%	TTP 8 w	15 w
[34]	Kulke MH	Capecitabine 1000 mg/m2 twice daily for 2 weeks, followed by a 1-week break + Erlotinib 150 mg daily	II	30	PS 0/1- 23 and 77%. In five cases (17%), diarrhea was severe (grade 3). Rash developed in 67%; in four (13%), rash was graded as severe (grade 3). Other common toxicities included fatigue, hand-foot syndrome, and stomatitis. Hand-foot syndrome and stomatitis were severe (grade 3) in four (13%) and three (10%) cases, respectively. Hematologic toxicity was uncommon and generally mild, with only two (7%) cases of grade 3 neutropenia observed; thrombocytopenia was not observed as a treatment-related adverse event.	ORR 10% Marker response 17%	PFS 3,4 m	6,5 m
[35]	Boeck S	Capecitabine 1250 mg/m2 twice daily for 14 days followed by 7 days of rest	II	39 (27 evaluable)	Predominant grade 2 and 3 toxicities (per patient analysis) were hand-foot syndrome 28% (13% grade 3); anemia 23%; leg edema 15%; diarrhea 13%; nausea/vomiting 10%; and leukocytopenia 10%.	PR 0% SD 39% Marker response 15%	TTP 2,3 m	7,6 m
[36]	Morizane C	S-1 orally 40 mg/m2 twice daily for 28 days with a rest period of 14 days	II	40	PS 80-100 all pts. The most common adverse reactions were fatigue and anorexia, although most of those adverse reactions were tolerable and reversible. One patient developed grade 3 pneumonitis without neutropenia and recovered with appropriate antibiotic treatment.	PR 15% SD 43% PD 38%	PFS 2 m	4,5 m
[57]	Yoo C	mFOLFIRI3 *vs* mFOLFOX (mFOLFIRI3: irinotecan (70 mg m(-2); days 1 and 3); leucovorin (400 mg m(-2); day 1), and 5-FU (2000 mg m(-2); days 1 and 2) every 2 weeks mFOLFOX: oxaliplatin (85 mg m(-2); day 1), leucovorin (400 mg m(-2); day 1), and 5-FU (2000 mg m(-2); days 1 and 2) every 2 weeks)	II randomised	61	The number of patients with at least one grade 3/4 toxicity was identical (11 patients, 38%) in both groups: neutropenia (7 patients under mFOLFIRI.3 regimen *vs* 6 patients under mFOLFOX regimen), asthaenia (1 *vs* 4), vomiting (3 in both), diarrhoea (2 *vs* 0), and mucositis (1 *vs* 2).	Disease control rate 23 *vs* 17%		16,6 *vs* 14,9 m

RR: response rate; CR: complete response, PR: partial response; PD: progression of disease; SD: stable disease; PFS: progression free survival; TTP: time to progression; OS: overall survival; N°: number; m: months; w: weeks.

intent-to-treat population. A significant decrease (≥ 50%) in serum CA 19.9 levels was observed in 3 out of 9 evaluable patients. The median TTP was 8 weeks, and the median OS was 15 weeks.

A study on a combination of capecitabine and erlotinib was published in the Journal of Clinical Oncology in 2008 [34]. The treatment with capecitabine and erlotinib in GEM-refractory patients was associated with an overall objective

radiological response rate of 10% and a median OS duration of 6.5 months. In addition, 17% of treated patients experienced decreases in tumour marker (CA 19-9) levels by more than 50% from baseline. However, capecitabine as single agent does not show any activity in pre-treated PC. In a German study, an average of 3 capecitabine cycles (range 1-36) were performed on 39 patients [35]. After a median follow-up of 6.6 months, 27 patients were evaluable for response: no CR or PR was observed, but 15 patients (39%) had SD. A CA19-9 level reduction by more than 20% after 2 cycles of capecitabine was documented in 6 patients (15%). The median TTP was 2.3 months (range 0.5-45.1) and the median OS (since the beginning of the Cap treatment) was 7.6 months (range 0.7-45.1).

S1 alone was tested in PC patients who had PD during GEM-based therapy. Although no CR was seen, a PR was achieved in six patients (15, 95% confidence interval, 3.9-26%). Stable disease was observed in 17 patients (43%), and PD in 15 patients (38%). A clinical benefit response was observed in four (21%) out of 19 evaluable patients. The median PFS was 2.0 months, and the median survival time was 4.5 months with a 1-year survival rate of 14.1%. S1 showed minimal activity, but this study raises once more the issue of different responses to drugs in Far-Eastern patients [36].

OTHER CHEMOTHERAPIES AND BIOLOGICAL AGENTS AS SECOND-LINE THERAPY (SEE TABLE 4)

Irinotecan monotherapy is a marginally effective and well tolerated regimen for GEM pre-treated patients with advanced PC. In an intent-to-treat analysis, three patients (9%) had a PR and 13 patients with SD were observed, for a disease control rate of 48%. Median progression-free and overall survivals were respectively 2.0 months (95% CI, 0.7-3.3) and 6.6 months (95% CI, 5.8-7.4) in 33 patients [37].

Table 4. Other Chemotherapies and Biological Agents

Ref.	Author	Schedule	Phase of Study	N° of pts	Features of pts and Toxicities	RR	TTP/PFS Median	OS Median
[37]	Yi SY	Irinotecan 150 mg/m2 every 2 weeks	II	33	PS 2 2/33 pts. Toxic effects were mainly gastrointestinal (nausea in 64% of patients, diarrhea in 36%),	PR 9% SD 39,4%	PFS 2 m	6,6 m
[38]	Ko AH	Docetaxel 65 mg/m2 + Irinotecan 160 mg/m2 every 21 days	II	14 (study closet for excess toxicity)	The most common grade 3/4 toxicities included neutropenia/leukopenia, nausea and vomiting, and diarrhea.	SD 21,4%	TTP 36 days	134 days
[39]	Reni M	Mitomycin 6 mgm2 day 1, docetaxel and irinotecan on days 2 and 8 with escalating doses, every 4 weeks. (Dose levels were level 1:30 and 70 mg/m2; level 2:30 and 100 mg/m2; level 3:30 and 85 mg/m2; and level 4:35 and 85 mg/m2)	I-II	15 (13 evaluable)	Toxicity consisted of grade 3 to 4 neutropenia in 23% of cycles, fatigue, diarrhea, and vomiting in 10% of cycles, and one toxic death.	SD 23%	TTP 1,7 m	6,1 m
[40]	Brell JM	Docetaxel 75 mg/m2 then reduced to 60 mg/m2 on day 1 every 21 days + Gefitinib, 250 mg/day continuously	II	41	Febrile neutropenia was seen in 11 patients (27%), with most events occurring at the docetaxel dose of 75 mg/m(2) (8 of 18 patients). Common treatment-related grade 3/4 toxicities were: fatigue (7%), nausea (7%), diarrhea (5%) and vomiting (2%).	PR 2,4% SD 46,3 %	TTP 1,8 m	4,5 m
[41]	Ignatiadis M	Docetaxel 75 mg/m2 every 3 weeks for a maximum of 6 cycles and gefitinib 250 mg/day, p.o. continuously	II	26	Grade 3/4 neutropenia was recorded in 9 (34.6%) patients, although only 1 (3.8%) developed grade 2 febrile neutropenia. One (3.8%) patient experienced grade 3 fatigue and 2 (7.7%) grade 3 diarrhea. Grade 1/2 rash was observed in 13 (50%) patients.	SD 19,2%	TTP 2,1 m	2,9 m
[42]	Cereda S	Weekly docetaxel 30 mg/m2	II	10	PS > 50. No grade >2 toxicity was observed.	ORR 0%	PFS 1,5 m	4 m
[43]	Oettle H	Weekly paclitaxel	II	18	Only one patient each presented with anemia and leukocytopenia of WHO grade III. Hepatotoxicity with a temporary increase in aminotransferase of WHO grade II occurred in three patients. Higher-grade symptomatic toxicity was rare, except alopecia.	CR 5,5% SD 27,8%		17,5 w

Table 4. contd....

Ref.	Author	Schedule	Phase of Study	N° of pts	Features of pts and Toxicities	RR	TTP/PFS Median	OS Median
[44]	Boeck S	Pemetrexed 500 mg/m2 every 3 weeks	II	52	PS 2 5,8%. Overall, hematological toxic effects of any grade included neutropenia (11 patients, 21.2%), thrombocytopenia (11 patients, 21.2%) and anemia (10 patients, 19.2%). The most frequent grade 3/4 hematological toxic effects were neutropenia (17.3%), thrombocytopenia (5.8%) and anemia (3.8%). Febrile neutropenia occurred in two patients (3.8%). The most frequent non-hematological toxic effects (any grade) were diarrhea, nausea and stomatitis/pharyngitis (23.1% each). Three patients (5.8%) had a grade 3 infection and two patients (3.8%) each had grade 3 diarrhea or abdominal pain. No grade 4 non-hematological toxicity and no treatment-related death occurred.	PR 3,8% SD 19,2%	TTP 7 w	20 w
[45]	Ulrich-Pur H	ARM A: Raltitrexed 3 mg/m2 on day 1 ARM B: Irinotecan 200 mg/m2 on day 1 plus Raltitrexed 3 mg/m2 on day 2 3-weekly courses	II	38	PS 2 26 and 32%. Gastrointestinal symptoms (42 *vs* 68%), partial alopecia (0 *vs* 42%), and cholinergic syndrome (0 *vs* 21%) were more commonly noted in arm B; however, grade 3 adverse events occurred in only three patients in both treatment groups.	ARM A: ORR 0% ARM B: PR 16%	ARM A: PFS 2,5 m ARM B: PFS 4 m	ARM A: 4,3 m ARM B: 6,5 m
[46]	Carvajal RD	Docetaxel 35 mg/m2 followed by Flavopiridol 80 mg/m2 on days 1, 8, 15 of a 28-day cycle	II	10 (9 evaluable)	Adverse events were significant, with 7 patients (78%) requiring >or= 1 dose reduction for transaminitis (11%), grade 4 neutropenia (33%), grade 3 fatigue (44%), and grade 3 diarrhea (22%).	OR 0% SD 33%	Time to treatment failure 8 weeks	4,2 m
[47]	Kindler HL	Arsenic trioxide 0.3 mg/kg i.v daily for 5 consecutive days every 28 days	II	13	There were no grade 3/4 hematologic toxicities; grade 1/2 anemia and leukopenia occurred in 50% and 25% of patients, respectively. Grade 3 toxicities included fatigue and thrombosis in 17% of patients. Only 1 patient developed a prolongation of the QTc interval.	OR 0%	PFS 1,6 m	3,8 m
[48]	Burris HA 3rd	Rubitecan 1.5 mg/m2 on five consecutive days per week, for 8 weeks	II	58 (43 evaluable)	PS 50-100. The most commonly reported nonhematologic adverse events were asthenia, alopecia, diarrhea, anorexia, abdominal pain, and nausea and vomiting (Table 4). Over half the patients experienced nausea and/or vomiting, although in most cases, these events were of grade 1 or 2 severity. The rates of grade 3 nausea and vomiting were 12% and 14%, respectively, and no patient had a grade 4 event. Diarrhea was reported in 40% of patients and was severe (grade 3) in 9% of patients. Hematologic toxicities were also frequently reported; however, many of these patients had grade 1–2 hematologic toxicities at baseline. Fifteen patients (26%) developed grade 3 or 4 leukopenia, 12 (21%) had grade 3 or 4 neutropenia, six (10%) had grade 3 or 4 thrombocytopenia, and seven (12%) had grade 3 anemia during the study.	PR 7% SD 16%	TTP 59 days	3 m (10 m in responders)

RR: response rate, CR: complete response; PR: partial response; PD: progression of disease; SD: stable disease, PFS: progression free survival; TTP: time to progression; OS. overall survival; N°. number. pts.patients, m: months, w: weeks.

The combination of Docetaxel plus irinotecan was investigated as well [38]. Fourteen patients were enrolled before the study was closed due to excessive toxicity. No objective responses were observed, although 3 patients had stable disease for at least 6 cycles.

The triple combination of mitomycin C plus docetaxel plus irinotecan has been studied as salvage therapy in 15 patients (phase I-II study) [39]. The MTD was mitomycin 6 mg/m2 on day one, and docetaxel 30 and irinotecan 85 mg/m2 on days 2 and 8. This regimen was inactive in metastatic PC.

Docetaxel was combined with gefitinib in 2 phase II studies (an oral EGFR inhibitor) with no evidence of activity [40, 41]. At the same manner, weekly administration of single-agent docetaxel does not seem to produce any activity in the treatment of GEM-resistant metastatic PC [42]. Weekly administration of paclitaxel is another potentially active agent tested in GEM pre-treated patients. One patient in a group of 18 treated people achieved CR within 37 weeks. At this time, he has survived for more than 56 weeks after confirmed progression under first-line therapy. In conclusion, this schedule demonstrates that weekly therapy with pacli-

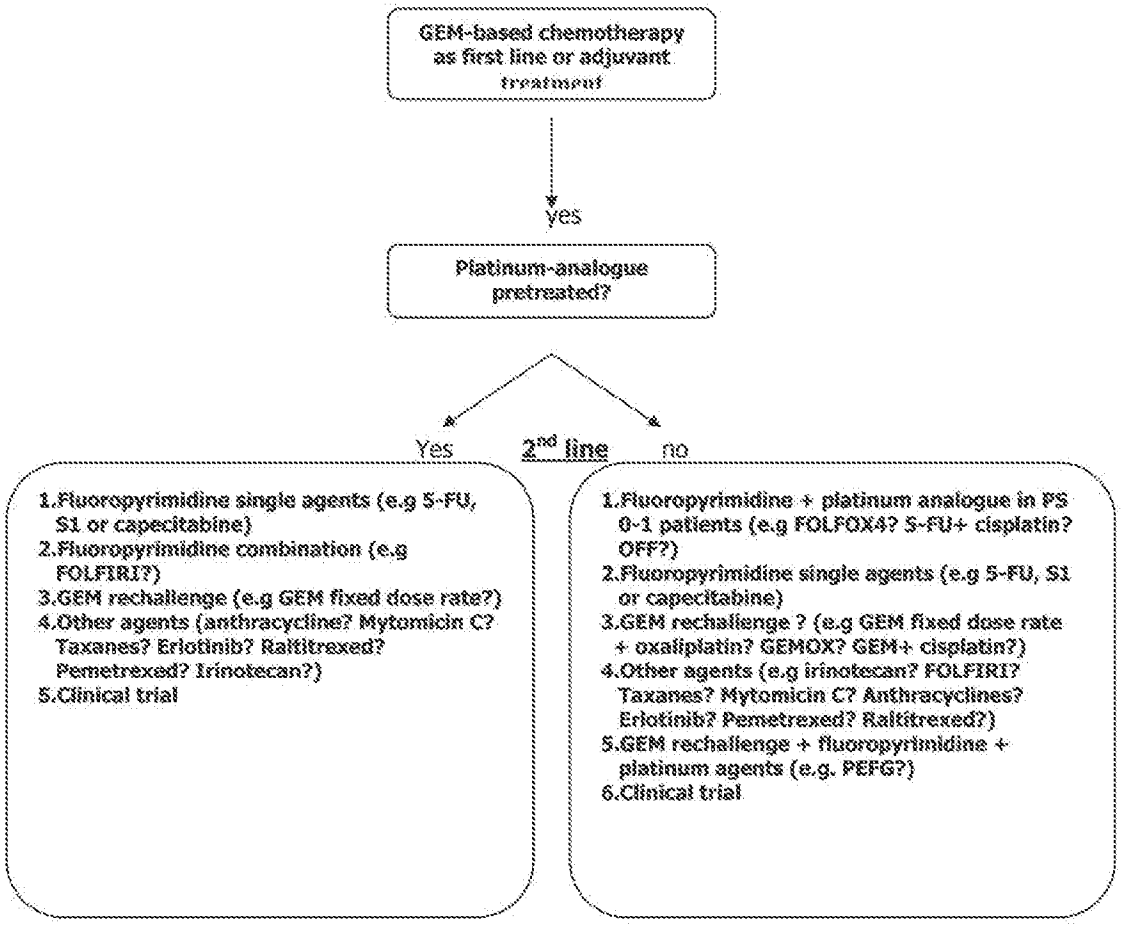


Fig. (1). Flux diagram for the choice of second line of therapy after GEM failure in patients fit for an active treatment.

taxel after pre-treatment can be effective with a low toxicity profile [43].

The anti-folate agent pemetrexed has been studied in GEM pre-treated patients as monotherapy [44]. Pemetrexed is a safe treatment option with moderate activity (PR 3,8%) in patients with advanced PC after GEM failure. The addition of irinotecan to raltitrexed, at the same manner, seems to be an effective salvage regimen in patients with GEM pre-treated PC [45]. The superior response activity, PFS and OS (when compared to raltitrexed alone), as well as tolerability and ease of administration guarantee future trials with this combination.

Other agents whose data have been published are flavopiridol (a pan-cyclin-dependent kinase inhibitor), associated with docetaxel (minimal activity and significant toxicity), the antiproliferative and proapoptotic agent arsenic trioxide (but with no activity in this setting) and rubitecan (an oral active camptothecine derivative), that produced 7% of responses and was well tolerated by heavily pre-treated patients with refractory PC. The overall risk-benefit profile of oral rubitecan appears to be promising, supporting further evaluation in phase III trials in patients with refractory and chemotherapy-naive PC [46-48].

An emerging combination that will be used in a phase II study by the Gruppo Italiano Studio Malattie Apparato Digerente (GISCAD), is the FOLFIRI combination [49]. A similar schedule called FOLFIRI3 has been used as first-line therapy in 40 naive patients yielding a RR of 37,5%. An ongoing trial will compare FOLFOX and FOLFIRI3 in GEM-refractory advanced PC [50].

These data show that the therapeutic arsenal available to oncologists beyond conventional agents is very poor. Usually, cytotoxic agents are either largely ineffective or have a minimal activity and a large amount of toxic effects. New agents and new combinations are now awaited with hope (see tables 1-5 for further details of the studies).

CONCLUSIONS

The choice of a second-line chemotherapy after GEM failure in patients fit for an active treatment is summarized in Fig. (1).

The studies presented here suggest that the administration of a second-line chemotherapy produces minimal although significant activity and outcome benefit. What the gold standard is, is still unknown, even though the only randomized study available suggests that the oxaliplatin/5-FU combination is the best at the moment, offering a 7-week advantage in survival. It seems to be reasonable to offer fit patients platinum analogue agents plus a fluoropyrimidine (5-FU or capecitabine) combination as a second-line treatment. Conversely, a fluopyrimidine single agent represents a reasonable option in unfit (for aggressive therapy) patients or in case of request for an active treatment. The natural choice of

Table 5. Other Ongoing Clinical Trials Investigating Second Line Agents in PC Only

	pts	Stage		
A Phase II Study of PEP02 as a Second Line Therapy for Patients With Metastatic Pancreatic Cancer	39	Metastatic	Survival at 3 months	PEP02 (experimental liposome irinotecan 120 mg/m2, IV infusion for 90 minutes on day 1 of each 21 days as a treatment cycle.
A Pilot Study of Pioglitazone as Second Line Therapy for Patients With Previously Treated Metastatic Adenocarcinoma of the Pancreas With Disease Progression After Gemcitabine Based Chemotherapy	20	Metastatic	- changes in markers of insulin resistance - changes in weight of patients - changes in ECOG performance status in these patients - changes in symptoms and quality of life of these patients using the validated FACT-Hep scale version 4 questionnaire	Patients receive oral pioglitazone hydrochloride once daily on days 1-28. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.
A Phase II Trial to Assess the Efficacy of Efavirenz as Second-line Monotherapy for the Treatment of Advanced Pancreatic Adenocarcinomas	72	Metastatic	Evaluate the efficacy of efavirenz as second-line monotherapy, in terms of non-morphological progression at 2 months, in patients with metastatic adenocarcinoma of the pancreas.	Patients receive oral efavirenz once daily in the absence of disease progression or unacceptable toxicity.
Phase II Study of Paclitaxel, Oxaliplatin, Leucovorin and 5-Fluorouracil (POLF) in Gemcitabine-Refractory Advanced Pancreatic Cancer	80	Advanced (non candidate to surgery or RT)	Pain control and other aspects of quality of life Reduction of the tumor size or stabilization of tumor growth Progression free survival Overall survival	Paclitaxel 60mg/m2 IV weekly; Oxaliplatin 50mg/m2 IV weekly; Leucovorin 20 mg/m2 IV weekly, minimum of 40 mg; 5FU 425mg/m2 IV weekly; Weekly for 12 weeks; Calcium and magnesium 1gram each IV prior to and after Oxaliplatin therapy; Glutathione 1500mg/m2 prior to Oxaliplatin.
Phase II Study: Docetaxel Plus Oxaliplatin as Second-Line Therapy in Patients With Advanced Metastatic Pancreatic Cancer	44	Metastatic or locally advanced	Tumour respose	Docetaxel 75 mg/m2 IV on day 1 of each 22 day cycle Oxaliplatin 80 mg/m2 IV on day 2 of each 22 day cycle
A Phase II Trial of Sorafenib and Erlotinib in Unresectable Pancreatic Cancer	47	Unresectable	efficacy	Patients receive oral sorafenib tosylate twice daily and oral erlotinib hydrochloride once daily on days 1-28.
Phase II Trial of Abraxane® in the Treatment of Patients With Pancreatic Cancer Who Have Failed First-Line Treatment With Gemcitabine-Based Therapy	20	Unresectable or metastatic	To establish preliminary evidence of efficacy of paclitaxel albumin-stabilized nanoparticle formulation in patients with locally advanced (unresectable) or metastatic pancreatic cancer that failed first-line therapy with a gemcitabine hydrochloride-containing regimen.	Patients receive paclitaxel albumin-stabilized nanoparticle formulation IV over 30 minutes on days 1, 8, and 15.
A Phase II Trial of AZD0530 in Previously Treated Metastatic Pancreas Cancer	36	Metastatic	To determine the 6-month survival of patients with previously treated metastatic pancreatic cancer receiving AZD0530. To determine the adverse events of this drug in these patients.	Patients receive oral AZD0530 once daily on days 1-28.

Table 5. contd...

Phase I-II Study Evaluating Combined Treatment of Cetuximab and Trastuzumab in Metastatic Pancreatic Cancer Patients Progressing After Gemcitabine Based Chemotherapy.	67	Metastatic	Recommended dose of trastuzumab to be combined con cetuximab. Response rate	Patients receive cetuximab IV over 1-2 hours and trastuzumab IV over 30-90 minutes on day 1.
Phase Ib Trial Evaluating the Safety and Feasibility of Ipilimumab (BMS-734016) Alone or in Combination With Allogeneic Pancreatic Tumor Cells Transfected With a GM-CSF Gene for the Treatment of Locally Advanced, Unresectable or Metastatic Pancreatic Adenocarcinoma	30	Unresectable or metastatic	Safety	Ipilimumab 10mg/kg will be administered at weeks 1, 4, 7 and 10. Subjects will also be offered maintenance phase dosing every 12 weeks or the same schedule + PANC 10.05 pcDNA-1/GM-Neo and PANC 6.03 pcDNA-1 neo vaccine.
A Phase I Open-Label Dose Escalation Study to Assess the Safety and Tolerability of the BikDD Nanoparticle in Patients With Advanced Pancreatic Cancer	30	Unresectable or metastatic	MTD and DLT	BikDD Nanoparticle 0.04 mg/kg once weekly by IV over 10 minutes.
Mitomycin and Ifosfamide (MI) as Salvage Therapy for Metastatic Pancreatic Adenocarcinoma: a Phase II Study	34	Stage IV/metastatic	PFS at 6 months	Patients receive mitomycin C IV on day 1 and ifosfamide IV on days 1-3.
Capecitabine and Oxaliplatin in Patients With Advanced or Metastatic Pancreatic Adenocarcinoma	37	Advance or metastatic	RR	Participants will receive capecitabine orally twice daily for 14 days, from the evening of Day 1 to the morning of Day 15 of the study, and oxaliplatin on Day 1 of each cycle (one cycle is 3 weeks long) until their cancer worsens or they experience any serious side effects.
Phase Ib Trial Evaluating the Safety and Feasibility of Ipilimumab (BMS-734016) Alone or in Combination With Allogeneic Pancreatic Tumor Cells Transfected With a GM-CSF Gene for the Treatment of Locally Advanced, Unresectable or Metastatic Pancreatic Adenocarcinoma	30	Unresectable or metastatic	Safety	Ipilimumab 10mg/kg will be administered at weeks 1, 4, 7 and 10. Subjects will also be offered maintenance phase dosing every 12 weeks or the same schedule + PANC 10.05 pcDNA-1/GM-Neo and PANC 6.03 pcDNA-1 neo vaccine
A Phase I Open-Label Dose Escalation Study to Assess the Safety and Tolerability of the BikDD Nanoparticle in Patients With Advanced Pancreatic Cancer	30	Unresectable or metastatic	MTD and DLT	BikDD Nanoparticle 0.04 mg/kg once weekly by IV over 10 minutes.
Mitomycin and Ifosfamide (MI) as Salvage Therapy for Metastatic Pancreatic Adenocarcinoma: a Phase II Study	34	Stage IV/metastatic	PFS at 6 months	Patients receive mitomycin C IV on day 1 and ifosfamide IV on days 1-3.
Capecitabine and Oxaliplatin in Patients With Advanced or Metastatic Pancreatic Adenocarcinoma	37	Advance or metastatic	RR	Participants will receive capecitabine orally twice daily for 14 days, from the evening of Day 1 to the morning of Day 15 of the study, and oxaliplatin on Day 1 of each cycle (one cycle is 3 weeks long) until their cancer worsens or they experience any serious side effects.

a second-line therapy remains however at minimum 5-FU or analogues (e.g. capecitabine or S1) plus or minus a platinum agent (in fit patients) for several reasons:

1. Historically, 5-FU is the only drug compared with the best supportive care (combinations compared with no chemotherapy or the best supportive care provided a survival advantage of 33 weeks for the treated group compared with 15 weeks for the untreated group9 ($p < 0.002$))
2. a recent meta-analysis of 29 trials of chemotherapy involving 3,458 patients, including nine containing 5-FU–based combinations, compared to supportive care, demonstrated a survival advantage of chemotherapy, with a median survival of 6.4 months *versus* 3.9 months
3. the drug is normally well tolerated even in unfit patients, at least as single agent

4. a platinum analogue offers a benefit in response and survival both in first- and second-line therapy (in randomized trials), and represents therefore an active drug in PC (although, unfortunately, it is unknown whether offering all active drugs in PC patients is beneficial for the natural history of the disease, as colorectal cancer literature teaches) [51-54].

Of concern the potential toxicities to which we expose the patients, given the palliative aim second-line treatment. It seems that classical platinum-based combinations (platinum agents + Gem or fluoropyrimidines) don't put the patient at risk of serious (grade 3-4) toxicities. For example in phase III trial (OFF *vs* FF) severe events in oxaliplatin arm were rare and appear comparable to standard first line treatment. Risk of serious toxicity increases as regimen sums the effects of more than 2 agents or of cytotxics with overlapping toxicities (see docetaxel + irinotecan study closed for excess of adverse events). Overall we consider appropriate to treat with polychemotherapy (2 or more agents) only very young patients, with good PS, normal nutritional status and optimal hepatorenal /haemotological reserve. Possibly the treatment can be supported with growth factors in this case. In frail/elderly patients, or in presence of poor clinical conditions a single agent is probably a more reasonable choice.

PITFALLS AND FUTURE PERSPECTIVES

The current sequence of drugs administered in first- and second-line treatments is unfortunately unknown. So do have we to start with GEM and then choose other agents after the relapse, or the opposite? An ongoing randomized cross-over phase III trial is being performed on advanced and metastatic PC not previously exposed to chemotherapy [55]. The study compares a standard arm treated with GEM plus erlotinib with an experimental arm treated with capecitabine plus erlotinib. It is the first trial of its kind to incorporate a second-line treatment into the study design. Patients who achieve no results with first-line therapy are switched to the comparator chemotherapy without erlotinib. Therefore, not only the trial compares two different regimens of first-line treatment, but it also compares two sequential treatment strategies.

Moreover, what is the benefit of second-line therapy in patients with poor prognostic features (unfit, truly GEM-refractory, poor PFS)? Data from the CONKO 003 study confirm the benefit of Oxaliplatin/5-FU/folinic acid combination in PS 1 patients as well as in PS 0 ones. **What is still unknown** is the benefit provided to poor PS patients, but this was an exclusion criteria of the above-mentioned study. Good prognostic indicators in GEM-refractory patients obtaining potential benefit from second-line treatments appear to be PFS, C reactive protein level, PS, albumin level, **weight loss**, AST level and the presence of peritoneal carcinomatosis.

The benefit of other classes of agents is at the moment unknown, even though irinotecan-based regimens are promising. Other combinations or single agents either are too toxic or have poor activity.

The role of target therapies in second-line setting is still completely unexplored. The poor benefit of biologicals in first-line treatments make them not so appealing in refractory/resistant settings in a disease where not only one, but rather countless signal transduction pathways seem to be working and co-operating, practically making the disease unresponsive to treatments.

An industry-sponsored trial study has the aim to find out whether the drugs, capecitabine and Lapatinib (a dual EGFR and HER2-neu inhibitor), prolong survival and improve the quality of life of patients who have failed first-line GEM-based therapy [56].

In summary, as of now, one randomized study confirms the benefit of second-line chemotherapy on GEM-relapsed PC. Current data indicate 5-FU plus a platinum agent (oxaliplatin) to be the standard of care in PS 0-1 patients. Ongoing clinical trials will clarify whether there is room for improvement and for other agents (see Table 5). At present, even though no data on benefits in unfit patients (Karnofsky < 70) are available, a fluopyrimidine agent still remains a reasonable treatment option.

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Received: November 15, 2009 Revised: January 22, 2010 Accepted: January 25, 2010

VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment

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See accompanying editorial on page 5487 and articles on pages 5499, 5506, and 5513

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Submitted January 21, 2009; accepted April 15, 2009; published online ahead of print at www.jco.org on October 26, 2009.

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

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

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0732-183X/09/2733-5660/$20.00

DOI: 10.1200/JCO.2009.21.9027

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality, despite significant improvements in diagnostic imaging and operative mortality rates. The 5-year survival rate remains less than 5% because of microscopic or gross metastatic disease at time of diagnosis. The Clinical Trials Planning Meeting in pancreatic cancer was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee to discuss the integration of basic and clinical knowledge in the design of clinical trials in PDAC. Major emphasis was placed on the enhancement of research to identify and validate the relevant targets and molecular pathways in PDAC, cancer stem cells, and the microenvironment. Emphasis was also placed on developing rational combinations of targeted agents and the development of predictive biomarkers to assist selection of patient subsets. The development of preclinical tumor models that are better predictive of human PDAC must be supported with wider availability to the research community. Phase III clinical trials should be implemented only if there is a meaningful clinical signal of efficacy and safety in the phase II setting. The emphasis must therefore be on performing well-designed phase II studies with uniform sets of basic entry and evaluation criteria with survival as a primary endpoint. Patients with either metastatic or locally advanced PDAC must be studied separately.

J Clin Oncol 27:5660-5669. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death among both men and women in the United States.[1] Despite significant improvements in diagnostic imaging and operative mortality rates during the past two decades, the 5-year survival rate remains lower than 5%. Most patients present with either locally advanced or clinically evident metastatic disease due in part to a lack of screening tests to detect early stage PDAC. The median survival for optimally staged patients who undergo a pathologically margin negative (R0) resection is approximately 2 years with a 5-year survival of approximately 15% to 20%, and for those with metastatic disease is shorter than 6 months. The median survival of patients with localized but unresectable disease is 8 to 10 months.

The poor survival of patients with resected PDAC is due to the fact that nearly all patients have metastatic disease at the time of initial diagnosis. Gemcitabine has been the most commonly used drug therapy over the past decade. Its very modest benefit over fluorouracil (FU) was first demonstrated in advanced disease.[2,3] Unfortunately, numerous phase III trials testing gemcitabine combined with other cytotoxic drugs have failed to reveal any additional benefit compared with gemcitabine alone.[4] Several targeted agents have been tested in combination with gemcitabine and have similarly failed to confer any added benefit, with the notable exception of erlotinib, a small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, which conferred a very modest improvement in survival over gemcitabine alone.[5]

While our knowledge of the genetic events that underpin multistep carcinogenesis in PDAC has increased dramatically, and despite a steady identification of new targets and new drugs for clinical testing, researchers still continue to work with an incomplete understanding of how the complex molecular biology contributes to the aggressive behavior of this disease. For example, our understanding of how key signaling pathways interact and the role of the microenvironment (stroma) in initiating and maintaining PDAC remains severely limited. The

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complex molecular biology of pancreatic cancer makes it unlikely that we will define new drugs with substantial single-agent activity. However, research aimed at developing therapies that benefit subsets of patients and use of multitargeted approaches should be encouraged. Selected targeted agents now available provide an opportunity to test new strategies that could ultimately improve the treatment of this disease.

The Clinical Trials Planning Meeting in pancreatic cancer was convened by the National Cancer Institute (NCI) Gastrointestinal Cancer Steering Committee (GISC) to discuss the integration of basic and clinical knowledge in the design of clinical trials in PDAC. Participants of this 2-day meeting included clinical, translational, and basic science investigators in pancreas cancer, and representatives from the patient advocacy community, pharmaceutical industry, and government agencies. This meeting was the first substantial follow-up gathering of major stakeholders in pancreas cancer treatment since the Pancreatic Cancer Progress Review Group was held in 2000. The following report summarizes major topics discussed and key recommendations for future research in PDAC.

OBJECTIVES

Major objectives of the meeting were to address critical questions and unmet needs in treatment and translational research in PDAC; to facilitate innovation and collaboration among clinical and basic investigators; to develop key strategic priorities for future clinical trials; and to address how to disseminate these priorities to the relevant oncology communities. The major focus of the meeting was to define the direction for clinical trial investigation for treatment of this disease over the next 3 to 5 years.

POTENTIAL TARGETS FOR INVESTIGATION AND VALIDATION

Potential Targets

A major challenge to the development of targeted therapies is the molecular heterogeneity of pancreatic cancer, both genetic alterations and epigenetic changes. Frequently occurring mutations, such as those of the *K-ras* oncogene are of high interest. Additional targets of interest include EGFR, PI3 kinase, insulin-like growth factor-1 receptor, vascular endothelial growth factor (VEGF)/ VEGF receptor (VEGFR), c-Met, and the Hedgehog pathways (Table 1). Special emphasis was placed on studying the following targets.

K-ras. Activating K-ras mutations occur in more than 90% of PDAC.[6,7] These mutations are among the earliest detectable genetic changes in PDAC.[8,9] Chemically induced[10] and genetically engineered[11,12] animal models suggest that oncogenic K-ras mutations initiate preinvasive disease. Although preclinical work supports K-ras as a valid target for drug development, its relevance as a therapeutic strategy is not fully established. Specifically, whether pancreas cancers continue to depend on mutant ras activity to maintain their malignant phenotype remains to be determined.

No direct ras inhibitors currently exist. Early anti-ras strategies that were focused on a post-translational modification (farnesylation) necessary for localization of the ras protein to the cell membrane were unsuccessful.[13-15] However, this was likely because these agents did not inhibit alternate prenylation pathways (geranylgeranylation) that preserved ras-mediated signal transduction. A major challenge to targeting ras itself is the intracellular location of the GTPase, which poses difficulties for the development of new drugs against this target.

Table 1. Molecular Targets of Interest in Preclinical and Clinical Target Validation in Pancreas Cancer

Parameter	Target
Tumor cell signaling	K-Ras
	Raf
	MEK
	PI3-K
	EGFR
	IGF-1R
	VEGF/VEGFR
	HIF-1alpha
	TGF-beta
	c-Met
Stem cell signaling	Hedgehog
	CXCR4
	Bmi-1
	Notch
Microenvironment	Stellate cells signaling pathways
	VEGF/VEGFR and other vascular targets
	CTLA-4
	OX-40
	PD-1 and VEGF
	B7-H1/B7-H4
	Tregs
	MDSC
	COX-2
	STATs

Abbreviations: Raf, rapid abundant factor; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase; PI3-K, phosphoinositide 3-kinase; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; HIF-1 alpha, hypoxia-inducible factor-1 alpha; TGF-beta, transforming growth factor-beta; c-MET; mesenchymal-epithelial transition factor; CXCR4, C-X-C chemokine receptor type 4; Bmi-1, BMI1 polycomb ring finger oncogene; CTLA-4, cytotoxic T lymphocyte–associated protein 4; OX-40, a tumor necrosis factor receptor superfamily member; PD-1, prephenate dehydratase; B7-H1, Cd274; B7-H4, V-set domain containing T cell activation inhibitor 1; Tregs, regulatory T cells; MDSC, myeloid-derived suppressor cell; COX-2, cyclooxygenase-2; STATs, signal transducers and activators of transcription.

Another approach to target K-ras–mediated signaling is to inhibit downstream effector molecule(s). These may include Raf and MEK, for which drugs are available (eg, sorafenib and PD0325901, respectively). Other molecules that may be targeted in relation to the K-ras pathway include proteins such as Rac,[17] Aurora,[18] and GGTase I.[19,20] However, the complexity of signaling pathways mediated by K-ras present substantial challenges to effective blockade of ras signaling and therefore the therapeutic index of anti-ras agents as single-agent interventions remains uncertain. Despite these challenges, there was general agreement that developing methods to target K-ras was a high priority that should be pursued at both preclinical and clinical levels. Targeting ras as part of an approach to inhibit multiple signaling pathways to assess whether this improves the efficacy of other signaling inhibitors is also an important strategy to be tested. More preclinical work is also needed to demonstrate reversal of the malignant phenotype by switching off ras-signaling in preclinical models.

Cancer stem cell signaling. Emerging data suggest that malignant tumors are heterogeneous, and that tumors are composed of a small set of cells, termed cancer stem cells (CSCs) that are responsible for tumor initiation and propagation, and a much larger set of more differentiated cells that have limited proliferative potential.[21] These

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CSPC Exhibit 1100
Page 319 of 333

CSCs are like their normal stem cell counterparts because they possess the ability to self-renew and produce differentiated progeny. Identification of human PDAC stem cells was recently reported[22] and was defined by expression of the cell surface markers CD44+CD24+ESA+ (0.2% to 0.8% of all pancreatic cancer cells). These cells were highly tumorigenic and possessed the ability to both self-renew and produce differentiated progeny, which reflected the heterogeneity of the patient's primary tumor. Upregulation of developmental signaling pathways, including Hedgehog and Bmi-1 signaling was observed in the CSC population.

From a clinical standpoint, the identification of CSCs within human PDAC may have important implications for treatment. In several types of cancer, CSCs have been shown to be resistant to conventional chemotherapy and radiation therapy and these cells are thought to produce metastases and recurrence after clinical remission. Recently published data suggests that pancreatic CSC may also be resistant to chemotherapy and radiation.[23] Hermann and colleagues[24] found that CD133+ populations in pancreatic cancer cells were enriched after exposure to gemcitabine. More detailed studies are needed to understand the biologic properties of CSCs in PDAC. Targeting aberrant signaling pathways regulating self-renewal in pancreatic CSCs may offer improved novel therapies for this disease.

Stromal signaling and angiogenesis. Despite the long-standing recognition of a characteristic fibroinflammatory reaction in primary PDAC,[25-28] the pathophysiologic mechanisms of tumor-stromal signaling and contribution to disease pathogenesis and disease progression are not well characterized. Moreover, the contribution of each component of the host microenvironment (stromal cells, vasculature, and immune cells) to the biology of PDAC is not well understood.[29] It has been suggested that stromal cells, including pancreatic stellate cells might be critical in the activation of pancreas CSCs.[30] There is evidence for a role for hepatocyte growth factor secreted by stromal cells in the activation of CSCs through its receptor C-Met.[31,32] However, the details of the interactions between pancreatic cancer cells and pancreatic stellate cells are just beginning to be investigated.

Even the role of vascular endothelial cells in pancreatic cancer primary tumors and metastases remains uncertain. In light of limited understanding of tumor-endothelial interactions in human pancreatic cancer, the potential benefit of blocking the VEGF-VEGFR pathway was debated with mixed opinion on its importance as a therapeutic target especially with the failure of a recent phase III trial using bevacizumab to demonstrate a prolongation of survival in patients with advanced PDAC.[33] Preclinical studies and ongoing clinical trials of VEGF and VEGFR inhibitors should clarify this issue in the near future.

Also discussed was the probability that the tumor-stromal interactions in metastatic deposits are different from those in the primary tumor.[34] This highlights the ability of metastatic tumor cells to grow independently of the original pancreatic stroma. Understanding these interactions may identify new targets for antimetastatic therapies. The consensus was that tumor-stromal interactions have been underappreciated in pancreatic cancer and greater emphasis needs to be placed on this area of research. New transgenic models of pancreatic cancer appear to reproduce the desmoplastic reaction of human pancreatic cancer with greater fidelity than orthotopic models and may allow for a better understanding of the biology of PDAC.[34,35]

Preclinical Models and Validation Systems

The transition to clinical testing may require multiple models to improve the predictive value of preclinical target identification. Models should be used both for the validation of sensitivity to targeted agents and to identify drug-resistance markers. Use of appropriate preclinical models may shorten the pathway to clinical trials and effective therapies by avoiding testing of ineffective strategies in patients. However, there has been no consistency in the use of preclinical models for drug development in PDAC. Although standardization would benefit the collective effort, no clearly superior model system to predict clinical behavior of human PDAC has yet emerged.

In vitro cell-based assays. Preclinical testing in cell systems, though helpful in determining the mechanism of action of drugs, ignores or minimizes the stromal and CSC contributions to tumor biology and drug response. However, response profiles in molecularly characterized cells from different cell lines may help to identify beneficial new therapies based on molecular markers. Three-dimensional in vitro models may further improve the predictive role of these systems.[36] Another strategy is to more fully characterize available cell lines and to compare these to primary tumors and xenografts using gene expression, comparative genomic hybridization, and methylation arrays. Major challenges include that no single cell line can mimic the heterogeneity of PDAC and it is not clear whether cell lines can mimic differences between primary and metastatic tumors. Taking data directly from in vitro cell lines to clinical testing without additional preclinical validation in vivo is considered inappropriate.

Tumor models. PDAC tumor models are valuable to screen for new drugs and drug combinations, characterize mechanism(s) of action of drugs, and validate biomarkers.[37] Models of preinvasive disease enable exploration of risk factors for disease progression, markers for early detection and strategies for chemoprevention. The major challenge heretofore with many preclinical models has been that they do not faithfully recapitulate human PDAC. Subcutaneous xenograft models using cloned cell lines are not sufficient to study the complex biology of pancreas cancers and metastases. Local factors within the pancreas (eg, very high levels of insulin, interactions with other cellular compartments and elements, including adaptive immunity, neovasculature) may not be replicated in subcutaneous tumor xenograft systems. Although orthotopic xenograft tumor models are considered more useful than subcutaneous xenograft models, both are limited by the lack of heterogeneity in cloned cell lines and the artificial microenvironment in an immune incompetent cohost.

Genetically engineered mouse models. One of the most significant advances in PDAC research has been the development of genetically engineered mouse models.[38] The presence of genetic heterogeneity in human cancers can be simulated by the use of multiple genetically engineered tumor models for drug testing. The defined genetic alterations in these animals allow investigators to study the biology of selected pathways of therapeutic interest and to search for biomarkers of clinical value. Many of these models appear to recapitulate the clinical, histopathologic, and molecular features of the human disease, and have the advantage of generating the disease in the native organ and in the setting of an intact immune system. The role of the host microenvironment in the biology of pancreas cancer can be explored in a number of genetically engineered models of human pancreas cancer.[38]

Primary tumor xenografts. Emerging data supports the potential of primary patient-derived tumor xenografts as a platform for drug screening, biomarker development, and to expand knowledge of the

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CSPC Exhibit 1100
Page 320 of 333

biology of pancreas cancer.[39,40] Such a system offers advantages over xenografts from cell lines and may recapitulate the heterogeneity seen in patients. The use of pancreas cancer explants may offer a better chance to predict the clinical activity of new drugs, particularly if the mechanism of drug action is confined to the tumor cell and does not involve the stroma. However, the development of primary human tumors for preclinical modeling is limited by the poor availability of fresh tumor tissues. Early evidence suggests that gene expression profiles and drug sensitivity patterns are retained through several generations of primary tumor xenografts.

Available data on primary tumor xenografts, though encouraging, needs to be validated with respect to long-term stability and the accuracy of assessment of antitumor effect. At this time, there is no knowledge of the biologic differences that might exist between xenografts obtained from primary and metastatic tumor sites. The failure of some tumors to engraft may introduce a selection bias in that the tumors that engraft may not identify agents that are active in those patients. Efforts are underway to improve the engraftment rates from the current rate of 50%. An increased effort to develop primary pancreatic cancer xenografts programs would increase access to this preclinical model system to test promising therapeutic agents.

Translation from Preclinical to Clinical Testing

Rational Selection of Target(s)

Empiricism has dominated the identification of new agents for clinical trials. The customary approach to test novel agents in PDAC has been to combine them with gemcitabine. However, these combinations have rarely added benefit over gemcitabine alone and the recent failure of major phase III trials in advanced disease[33,41] challenges the wisdom of this approach. There was strong consensus for the need to develop new strategies based on a rational choice of agents based on better understanding of signaling pathways in PDAC and using agents or combinations that have been previously tested in preclinical models as described above. Other cytotoxic drugs should continue to be evaluated preclinically and clinically especially those that may offer a better platform to combine with targeted agents. Ixabepilone, oxaliplatin/FU, nab-paclitaxel, and S-1 are examples of cytotoxic drugs currently being tested in patients with advanced PDAC. There was no consensus on the importance of assessing the activity of a single agent before inclusion in a combination strategy, but novel approaches to avoid single-agent testing should receive high priority. Clinical testing of combination of agents also presents significant logistic challenges. In particular, cooperation among sponsors in a single study is a major issue that is particularly problematic when testing non-US Food and Drug Administration–approved drugs that are in early development.

Target Validation and Monitoring in Patients

There was a strong consensus that early clinical trials of targeted drugs can be significantly more informative if molecular correlates using validated assays are included. Unless the drug has a major clinical anticancer effect, lack of an assay for assessing drug-target interaction in vivo can make it difficult to devise an efficient strategy for drug development. Phase I trials rarely establish an optimal biologic dose of a drug. Therefore, biospecimens (serum, blood, or tumor tissue) should be obtained from patients treated in phase II trials and tested for pharmacodynamic effects.

Measuring target modulation in patients can be facilitated by an understanding of biomarker(s) that may be affected by intended target modulation. Where the target, the relationship between target and biomarker, and the relationship between biomarker and anticancer effects are known, if a surrogate biomarker cannot be inhibited then the tumor would be unlikely to be affected by that agent. There was a consensus that researchers need to achieve a more comprehensive understanding of the biologic basis why certain drugs do not work in PDAC. With well-validated assays in hand, serial biopsies to evaluate the modulation of specific targets by novel agents could be very informative. Biopsy of liver metastases may be preferred over biopsy of the primary site because of demonstrated safety and acquisition of sufficient cancer cells for histologic examination and molecular studies. However, practical and ethical considerations limit multiple biopsies in a clinical trial. In addition, we need to develop reproducible assays and improve tissue sampling technologies to improve the yield of useful tissue. Surrogates for tumor tissue (normal tissue, blood, and serum) should be explored but have their own limitations. Since there is no universal consensus on what constitutes an effective in vivo inhibition of a target, each target will require separate validation.

Target identification and validation in patients is only one consideration in successful drug development. Effective inhibition of the target by a drug may not be clinically effective because of poor drug delivery to tumor cells (eg, dense stroma in PDAC) or reduced active metabolite concentration. This could also explain differential drug effects between primary and secondary deposits whose stromal content varies.

Role of Functional Imaging

For PDAC, functional imaging will require novel approaches and extensive validation. Current techniques, such as imaging with either positron emission tomography or dynamic contrast-enhanced magnetic resonance imaging, cannot be recommended as surrogates for treatment benefit, but deserve continued investigation. As imaging develops to demonstrate target modulation or predict response to therapy, it will be a critical part of evaluating novel rationally designed therapies.

Design of Trials

Developing phase II trials that have a high chance of success in subsequent phase III testing is a major priority. If suspected predictive biomarkers are available to select patients, clinical trial designs employing enrichment must be considered whenever possible. Given gemcitabine's limited ability to impact the natural history of PDAC, patient advocates and many investigators indicated the feasibility of performing studies that do not include gemcitabine as initial therapy. Some of the successes of therapy for pediatric cancer were based on the introduction of new therapies before exposure to agents with known clinical activity. Some agents, such as vaccines, may show differential efficacy based on the stage of disease and tumor burden. Therefore clinical trials of these agents should be focused on patients with minimal tumor burden. Assessing the clinical and biologic effects of novel interventions in the preoperative setting (neoadjuvant treatment) carries the advantage of allowing direct examination of the changes in the tumor compartment and microenvironment.

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CSPC Exhibit 1100
Page 321 of 333

Selection of Patients and Clinicopathologic Parameters

Heterogeneity between studies with respect to patient populations makes it difficult to translate results from one study to another. Reducing this variability will improve the ability to interpret results of clinical trials in PDAC. Patients with unfavorable Eastern Cooperative Oncology Group performance status (≥ 2) should be studied in separate clinical trials from patients with good performance status (zero or one). More emphasis should be placed on describing patient characteristics using additional parameters such as extent of weight loss and nutritional status. In addition early withdrawals from study (eg, within 4 weeks) because of worsening disease and/or overall health and without receiving meaningful treatment should be considered in the analysis of study outcome. Patients with locally advanced and metastatic disease should similarly be separately studied in clinical trials. Eligibility criteria should be uniform across phase II clinical trials and should be similar between phase II and phase III trials of the same agent(s).

The ability to select patients based on predictive biomarkers may reduce the number of patients required in subsequent phase III trials.

Study End Points

Because of the relatively short survival time for patients with pancreatic cancer, overall survival must remain the primary end point for phase II and phase III clinical trials. In addition, tumor shrinkage by either Response Evaluation Criteria in Solid Tumors (RECIST) or WHO criteria is a poor surrogate for survival in this disease and its use as a primary end point is discouraged. Progression-free survival suffers from similar limitations as objective response and can introduce additional biases in the phase III setting, where timing of disease assessment may vary by type of treatment. At this time, changes in serum CA 19-9 levels on therapy have not been established as surrogate for survival.

Statistical Designs

The failure of recent phase III trials to demonstrate clinically meaningful treatment benefit for patients with advanced pancreatic cancer despite the suggestion of benefit in single-arm phase II studies (eg, cetuximab, bevacizumab) has led to much discussion of the reasons for the failure. Possible reasons include phase II population selection bias, inadequate interpretation of historical data, compromises in error rates, overly optimistic interpretation of phase II results inadequate phase II designs, wrong end points, lack of understanding of the target, inadequate agents, and bad luck.

There has been much recent discussion over the relative merits of single arm phase II trials versus randomized phase II trials. In a disease such as pancreatic cancer, where there has been a large body of historical data, it has traditionally been felt that a single-arm trial can be conducted with little concern that the comparison with historic information is biased.[42] Where this is the case, single-arm trials require a smaller sample size, can achieve better error rates, and are easier to conduct, whereas a randomized phase II trial typically requires three to four times as many patients in order to achieve the same error rates (due to the need to account for increased statistical variability in the comparisons between the two treatment groups). However, where there are no reliable historical data, or the study population differs dramatically from patients used in previous studies, randomized trials typically offer the better option.[43]

Current work is ongoing to establish a database of prior phase II and phase III trial results in PDAC that will be analyzed to provide a prognostic model based on baseline covariates. This work is analogous to that performed by Korn et al[44] for melanoma, and is expected to provide a means to assess treatment effect in a single-arm trial, by adjusting patient outcome by what would have historically been expected in patients with a similar baseline profile. Other phase II designs may be appropriate in selected situations and should be explored for feasibility (eg, single-arm estimation with larger sample sizes, selection designs, targeted subgroup trials, and Bayesian designs).

Specific Considerations for Trials in Resectable Pancreas Cancer

Resectable Pancreas Cancer

The interpretation of results of adjuvant trials in resectable PDAC would be improved by a greater attention to quality control and generally agreed on standards for reporting. Historically, there has been inconsistent reporting of surgical margins that can unintentionally bias treatment arms. Patients with either R0 or R1 resections should be included in clinical trials of adjuvant therapies; however, those with gross residual disease (R2 resections) must be excluded. The use of laparoscopic staging was considered unnecessary for the selection of patients for clinical trials. However, postoperative staging with CT scanning and measurement of CA 19-9 should be done before study entry to exclude patients with known residual or metastatic disease. The primary end point of adjuvant trials should be overall survival.

There was consensus that improvement of overall cure rates and long-term survival after surgical resection are most likely to be achieved by the introduction of novel systemic agents. The testing of new agents should be moved to the resectable population in an expedited fashion after demonstration of activity in advanced disease although certain therapeutics may be selectively cytotoxic to micrometastatic disease (eg, vaccines). Well-conceived correlative studies must be included in adjuvant trials, including obtaining samples from patients at the time of recurrence when possible.

The study of neoadjuvant therapies in pancreas cancer should be encouraged. The safety and feasibility of this approach has been demonstrated in several tertiary referral centers.[45] Borderline resectable patients[46] should ideally be studied in separate clinical trials rather than mixed with the resectable (or the locally advanced) population. The role of radiation in the adjuvant setting remains controversial and warrants further evaluation.

Clinical Trials in Localized Unresectable Disease

Localized unresectable PDAC must be studied in trials that do not include patients with metastatic disease because of the differences in natural history and the potential impact of radiation therapy on survival in patients with localized disease. The treatment schema could consider initial systemic therapy of 3 to 4 months followed by chemoradiation in nonprogressing patients with survival as the primary end point.

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CSPC Exhibit 1100
Page 322 of 333

VACCINES AND IMMUNE THERAPIES

Molecular Targets

Relevant immune responses can be generated even in the context of advanced PDAC, which has traditionally been considered poorly immunogenic.[47] However, the challenges remain very high for a vaccination strategy to be successful in PDAC. Strategies are needed to manipulate immune check points at both the systemic and tumor microenvironment levels. At the systemic level, regulatory T cells are thought to represent the primary barrier to effective antitumor immunity, and distinct strategies for abrogating their negative influence are under active clinical investigation. Additional targets for immune checkpoint modulation under investigation include CTLA-4,[48] OX-40,[49] and PD-1.[50] Importantly, more focus on regulation within the local tumor microenvironment is needed because multiple immunosuppressive networks map to the local tumor environment. These include intratumoral regulatory T cells and myeloid derived suppressor cells, immunosuppression due to local production of VEGF, and negative signaling through B7-H1/B7-H4 pathways. Tumor biology itself, including signaling through the epidermal growth factor receptor, HER2, cyclooxygenase 2, transforming growth factor β, and STAT pathways, can also antagonize effective antitumor immunity. Advances in molecular and cellular immunology support the use of multitargeted vaccination strategies in the treatment of pancreas cancer.[47]

Clinical Vaccine Trial Designs

Vaccine therapies as a sole intervention are unlikely to have a significant impact on this disease and will need to be integrated with standard therapies. All standard therapies have potential to be combined with vaccines. Emerging data supports the inherent immunogenicity of some chemotherapeutic and targeted agents, suggesting that integrating tumor vaccines with standard cancer therapeutics may be possible. There is also a concern that cytotoxic drugs may depress immune function, thus having a negative impact on vaccine therapy.[51] The infrastructure for vaccine trials should be established to include a select group of specialized centers. Early immunotherapy trials should focus on the optimum biologic dose. Although there are preliminary data in this regard, it is unclear what measures of the immune response would be most likely to correlate with clinical activity. A consensus on appropriate measurements to determine the most effective dose and schedule of vaccines is needed using standardized methods and recording of immune responses.

The tumor cell itself is probably the best source of antigen. This approach has been most fully developed in the context of the GVAX allogeneic whole cell vaccine that has completed phase II assessments and is poised for further development.[52,53] While most of the current work focuses on advanced disease, earlier stage disease or tumors in the locally advanced stage III setting after initial cytoreduction may provide the best opportunity for meaningful intervention with immune-based therapy. Some published data suggest that the extent of tumor burden relative to the level of vaccine-induced T cells may be predictive for the success of cancer vaccines.[54]

BIOSPECIMEN REPOSITORIES

Sample Sets

One of the biggest barriers to conducting translational research in PDAC is the lack of appropriately collected, clinically and molecularly annotated, and properly stored biologic material. Tumor biopsies are the most common source of specimens, but biologic material is limited and often difficult to reserve for research purposes because of diagnostic needs. Unfortunately, a proportion of tissue samples obtained for diagnostic purposes in patients with advanced PDAC are unsuitable for research assays because of poor quality or small sample size or samples that are composed predominantly of stroma. Many available samples are biased toward earlier stage disease.

Ideal sample sets should include tumor tissue plus normal tissue, blood, serum, and serial samples when possible. Surgical resections provide a useful source of biospecimen material, but logistics are crucial. Good quality depends on speed, and immediate processing requires a responsive infrastructure. Autopsy material could be a source of abundant material, but preservation of high-quality tissue is difficult, given the rapid degradation of pancreatic tissue. Rapid autopsy protocols (eg, University of Nebraska, Johns Hopkins) are useful, but expensive. Exfoliated secreted biospecimens have the advantage of easy access, but this material is extremely limited, and distinguishing tumor cells in this type of specimen is sometimes difficult. Circulating tumor cells can be captured with some tumor types, such as breast and colorectal cancer, but so far only in advanced and metastatic pancreas cancer, and even then only in a small percentage of patients.[55] Initiatives to address standards in biospecimen quality should involve exploring surrogates for frozen tissue, such as formalin-fixed, paraffin-embedded tissue, and circulating DNA.

Committed Infrastructure

A committed infrastructure and leadership is critical to establish and maintain a system of specimen collection with the tasks of managing the consent process and following standard operating procedures to acquire and preserve high quality tissue. Experienced pathologists are especially important to the analysis of pancreatic tissue, as it may be difficult to distinguish cancer from pancreatitis, subtleties that are only exaggerated in the context of frozen sections. Complexities also extend to discerning islet cell neoplasms and other nonpancreas cancers that have metastasized to the pancreas.

Strategies to Improve Biorepositories

The adherence to good standards of practice (eg, NCI Harmonization Guidelines and Best Practices) must be in place at all institutions with biorepositories. Storage and tracking mechanisms are key elements of biorepositories and clinical annotation is essential in developing a reference set of biospecimens that will improve and expand the utilization of specimens for research purposes. Work should continue on developing common interinstitution consent forms and intellectual property agreements that facilitate sharing of biospecimens, and move toward the goal of an ideal pancreatic cancer reference set that contains high-quality tissue which is clinically and molecularly annotated and paired with genotype data and serum. The ideal number of high-quality and diverse samples that would be needed for a biorepository could be as high as 300, but 100 may be adequate for

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CSPC Exhibit 1100
Page 323 of 333

most research purposes. A biorepository could potentially be developed using specimens from patients participating in phase III adjuvant trials. Cooperative groups may play an important role in establishing biorepositories because specimens are best collected under the aegis of a focused scientific question and where clinical annotation is carefully performed.

DEVELOPMENT OF BIOMARKERS

Discovery and Validation of Biomarkers

Biomarkers are powerful tools that can improve PDAC diagnosis and its accuracy, improve clinical trial design, and aid in the identification of patient subsets for clinical management. There is, at this time, no robust surrogate biomarker for an antitumor effect in pancreas cancer. Accordingly, biomarker discovery in PDAC must be accelerated. Molecular profiles that predict response or resistance to therapy with targeted agents may be derived from preclinical models and applied prospectively in clinical trials for the selection of subjects. Appropriate methodology in clinical trial design must be implemented in biomarker validation to distinguish a predictive from a prognostic marker. Uniformity of clinical trial design and adherence to standard operating procedures (eg, standardized acquisition and storage procedures) are essential in studies including biomarkers. It is hoped that ongoing work using proteomics and new platforms such as antibody arrays will provide novel biomarkers that can be validated in therapeutic clinical trials. With incorporation of appropriate biomarker studies larger phase II trials may identify subsets of patients more likely to respond to a targeted agent or regimen and may provide a better estimate of clinical activity. However, the statistical power to identify such a subset of patients is extremely low. Therefore, any observed associations can only be considered as hypothesis generating, requiring validation in a phase III trial. Investing in studies designed to identify specific biomarkers associated with favorable outcomes provides justification to further study a given pathway(s) and to consider subsequent studies in enriched populations. Challenges to such an approach include the requirement for a large number of patients and possibly longer time to develop an agent.

Rather than imposing a strict hierarchy of processes for preclinical biomarker validation, the series of opportunities/methodologies that can be used preclinically (eg, xenograft, genetic models) should be employed in a flexible manner using various models as appropriate for the agent under study. There is no consensus on the value of high throughput systems in the development of biomarkers. One approach suggested for the development of biomarkers and their validation is based on the preclinical platform. The first step would involve a search in human pancreas cancer cell lines (cell-based targets) using expression profiling. Response in these cells to various drugs would be determined and correlated with gene expression profiles. Positive findings would then be validated in a primary cohort maintained as xenografts or genetically engineered mouse models. This approach is based on extensive experience in breast cancer (eg, in the model that developed lapatinib). Another approach is to determine the molecular profiles of patients at the extreme ends of the selected reported outcome to discern differences in selected biomarkers.

Two potential markers were discussed in some detail; serum CA19-9 and tissue markers that characterize the cellular phenomenon of epithelial mesenchymal transition (EMT). There is a suggestion that baseline level of CA 19-9 is a predictor for survival in patients with resected pancreas cancer.[56] Preliminary cell line-based studies are underway to determine whether EMT markers such as vimentin, E-cadherin, nuclear β-catenin, and upregulation of specific nuclear transcription factors such as Zeb-1[57] and Twist[58] may identify cells that are likely to be resistant to certain drugs (eg, anti-EGFR agents).[59-61]

Communication Within the Pancreas Cancer Research Community to Enhance Biomarker Development

Cell lines, pancreatic tissue, and other biospecimens that are important resources for research in pancreatic cancer exist in many locations but are often restricted by cumbersome intellectual property restrictions and are of varying quality. Communication among researchers and clinicians who would benefit from sharing of existing biospecimens is fractured and incomplete. A database of all biospecimens that could be made available to investigators should be generated to maximize use of these materials. Many laboratories have their own libraries of cell lines. However, lab-to-lab differences exist, and some of the biologic characteristics of original cell lines have changed with time. A recommendation was made that notice of grant awards should include a requirement for sharing tissue/mouse models and other biospecimens with other qualified investigators. It was suggested that investigators submit tissue to ATCC via the NCI as a liaison or that the NCI provide money to Specialized Programs of Research Excellence to establish and maintain pancreas cell lines and tissue cores. The Pancreas Cancer Map supported by the NCI (www.cancermap.org) is a resource that is underutilized by the pancreas cancer research community. The majority of pancreas cancer grants are listed on the map. Available pancreatic cancer cell lines could also be posted on this site for easier access.

EXECUTIVE SUMMARY

The NCI and other public and private agencies and organizations must increase funding for basic, clinical and translational research in pancreatic cancer relative to priorities as defined by the community and include methods to evaluate and refine the process in a dynamic manner. Communication between the academic community and the pharmaceutical industry must be improved to benefit patients with this deadly disease. Developing research partnerships that involve academic investigators, pharmaceutical industry, and patient advocacy will best accomplish the goals of decreasing the morbidity and mortality from this disease. There is a need for coordinated and collective effort to implement and ensure progress in the recommendations that were made in this meeting. The GI Steering Committee under the auspices of the NCI is structured to try to maximize collaborations between laboratory investigators, SPORE investigators, early phase clinical trialists as well as the cooperative groups in therapy and imaging. Active involvement by patient advocates and community physicians as well as the ongoing efforts within the NCI to simplify the protocol development process, will hopefully facilitate the necessary advances in this deadly disease. Specific recommendations were as follows:

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CSPC Exhibit 1100
Page 324 of 333

New Targets for Drug Development (Table 1)

- Enhance research in the identification and validation of relevant targets and molecular pathways in pancreatic cancer, CSCs, and the microenvironment, including the role of angiogenesis in earlier stage disease and as part of multitargeted therapy.
- Establish high-throughput assays systems to accelerate target identification and validation.

Utility of Preclinical Models

- Preclinical tumor models of pancreas cancer may improve the ability to rationally design therapies.
- The development, availability, standardization, and utility of preclinical models for rational drug therapy design and the establishment of predictive biomarkers should be expanded and supported. An infrastructure for developing, validating, and using genetically engineered mice or primary tumor explants should be established and supported.
- A better understanding of the relative strengths of primary tumor xenografts and genetically engineered mouse models is required before recommending widespread adoption by the scientific community. Nevertheless, it is recognized that both model systems will be complementary.
- The model systems should be made freely available to investigators. Some of these models are provided by the NCI via the Mouse Models of Human Cancer Consortium (http://mouse.ncifcrf.gov/).

Future Clinical Trials (Table 2)

- Phase III clinical trials in advanced disease should be implemented only if there is a meaningful clinical signal of efficacy and safety in the phase II setting. The emphasis therefore must be on performing well-designed phase II studies to help define strategies likely to succeed in a phase III setting with survival as the primary end point.
- All high-priority phase III trials must be conducted as intergroup trials without competition and should be designed to include a scientifically appropriate biorepository. The clinical research community in collaboration with the US Food and Drug Administration, industry, and cooperative groups should adopt a consistent set of basic entry and evaluation criteria for phase II trials.
- Emphasis in designing clinical trials should be on rational combinations of targeted agents and the development of predictive biomarkers to assist selection of patient subsets. Government agencies such as the NCI and US Food and Drug Administration should review policies to facilitate, or at least allow the practice of interrogating combinations of unapproved agents that show significant promise in preclinical models. This requires a clinical trial mechanism with intimate planning and coordination between pharmaceutical industry, Cancer Therapy Evaluation Program, US Food and Drug Administration, and the investigators.
- Recent advances in cancer immunology and the development of newer approaches in immune therapy justify the testing of such therapies in patients with pancreatic adenocarcinoma, especially those with earlier stage disease.
- Government agencies, pharmaceutical industry, and clinical investigators should readily provide information on clinical trials outcome, including negative trials to all investigators.

Table 2. Summary of Recommendations for the Conduct of Pilot Trials in Advanced Pancreas Cancer

Parameter	Recommendation
Patient selection	Restrict studies to patients with Eastern Cooperative Oncology Group performance status 0-1
	Study patients with localized unresectable disease separately from those with metastatic disease
	Establish uniform eligibility criteria
	Use of predictive biomarkers for enrichment
Agents to be tested	Maximize input from preclinical data
	Adopt multitargeted approaches based on scientific rationale
	Consider non-gemcitabine-based combinations
Statistical designs	Survival preferred primary end point
	Single arm and multiarm randomized studies each have their place
Correlative science	Incorporate hypothesis-driven correlative research in pilot trials
	Report negative as well as positive study outcomes
	Consider prospective patient selection in pilot study setting based on data relating outcome with a specific molecular profile
Transition to phase III	Consider input from multiple studies
	Implement phase III testing only after a robust signal from pilot study(s)

Establishing Biorepositories

- Clinically and molecularly annotated biorepositories of high quality material will provide a rich source of information and clinical samples that should be utilized by pancreas cancer researchers.
- All randomized and selected single-arm trials should consider inclusion of a related biorepository (eg, serum, blood, tumor tissue) and the infrastructure to allow easy and shared use of this material must be established. Alternate sources for tumor genomic material (eg, blood) should also be developed.
- Access to and sharing of existing biorepositories must be mandated and supported by public-private partnership.

Development of Biomarkers

- The biomarker should be tested preclinically in animal models as part of the process of moving a drug to the clinic.
- Whenever possible, prospective biomarker evaluation should be an integral part of clinical trials in pancreas cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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CSPC Exhibit 1100
Page 325 of 333

Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Philip A. Philip, sanofi-aventis (C), Bristol-Myers Squibb (C), OSI Pharmaceuticals (C); Neal Meropol, sanofi-aventis (C), Biogen Idec (C), Genomic Health (C), Genentech (C), Pfizer (C); Leisha Emens, Genentech (C); Lee Ellis, Schering-Plough (C); Margaret Tempero, Abraxas Bioscience (C), Celgene (C), Elsevier (C), F. Hoffmann-La Roche (C), Merck (C), Myriad Genetics (C), Centocor Ortho Biotech (C), Raven Biotechnologies (C), sanofi-aventis (C); Jordan Berlin, Genentech (C), Bayer Pharmaceuticals (C), AstraZeneca (C), ImClone Systems (C), Bristol-Myers Squibb (C), Abbott Laboratories (C), sanofi-aventis (C), Roche (C), Pfizer (C), Amgen (U), Cephalon (U) **Stock Ownership:** None **Honoraria:** Philip A. Philip, sanofi-aventis, OSI Pharmaceuticals; Malcolm Moore, OSI Pharmaceuticals; Leisha Emens, American Society of Clinical Oncology; Lee Ellis, Genentech **Research Funding:** Philip A. Philip, sanofi-aventis, Bristol-Myers Squibb, Pfizer; Malcolm Moore, OSI Pharmaceuticals; Leisha Emens, Genentech; Lee Ellis, sanofi-aventis; Margaret Tempero, Response Genetics; Diane Simeone, OncoMed Pharmaceuticals **Expert Testimony:** None **Other Remuneration:** Jordan Berlin, Pfizer

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Final approval of manuscript: Philip A. Philip, Margaret Mooney, Neal Meropol, Leisha Emens, Eileen O'Reilly, Jacqueline Benedetti, Mace Rothenberg, Margaret Tempero, Andrew Lowy, James Abbruzzese, Jordan Berlin

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CSPC Exhibit 1100
Page 326 of 333

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CSPC Exhibit 1100
Page 327 of 333

An Assessment of the Total Cost of Pancreatic Cancer Using Real-World Evidence

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BACKGROUND

- Over 55,000 patients are diagnosed with pancreatic cancer each year in the U.S. The prognosis is very poor, with 5-year survival at 9% (ACS, 2019).
- The aggregate health economic implications of pancreatic cancer are poorly understood, especially from the patient perspective.
- As a preliminary effort, we sought to better understand changes in type and quantity of medical expenditures over time, along with quality of life related costs, from this perspective.
- This preliminary research is part of a larger effort to understand how the introduction of new treatments affect both the outcome and costs of pancreatic cancer associated with care, patients, survivors, their families, and their communities.

METHODS

- We analyzed patient-level data from the Medical Expenditure Panel Survey (MEPS, 1996 – 2017). MEPS data are derived from a set of large-scale surveys of families and individuals, medical providers and employers across the US on the type, frequency and cost of health services used. All analyses were performed using R version 3.6.1 on Ubuntu 19.04.
- Averages were computed for the total health care costs, including prescription drug costs for the period between 2009 – 2016 to include approval and use of (nab)-paclitaxel (Abraxane), FOLFIRINOX and erlotinib.

CSPC Exhibit 1100
Page 328 of 333

- Average individual annual cost estimates for the second year excluded individuals that were identified as having died prior to the first round of data collection in the second year.
- Interpretation of results may be limited by a relatively small sample size and may not be generalizable to specific demographic groups.
- The individual patient level ratios of prescription drug cost to other medical expenses was also computed.
- All expenditures are adjusted for inflation using 2012 USD.
- Included subjects (n=80) had a diagnosis of pancreatic cancer and available prescription data. Individual age and employment status were accounted for as covariates.

RESULTS

TABLE 1
DEMOGRAPHICS AND DESCRIPTIVE CHARACTERISTICS

Sex	Female	41 (51.25%)
	Male	39 (48.75%)
Race	Asian	7 (8.75%)
	Black	10 (12.50%)
	White	59 (73.75%)
	Not Available	4 (5.00%)

CSPC Exhibit 1100
Page 329 of 333

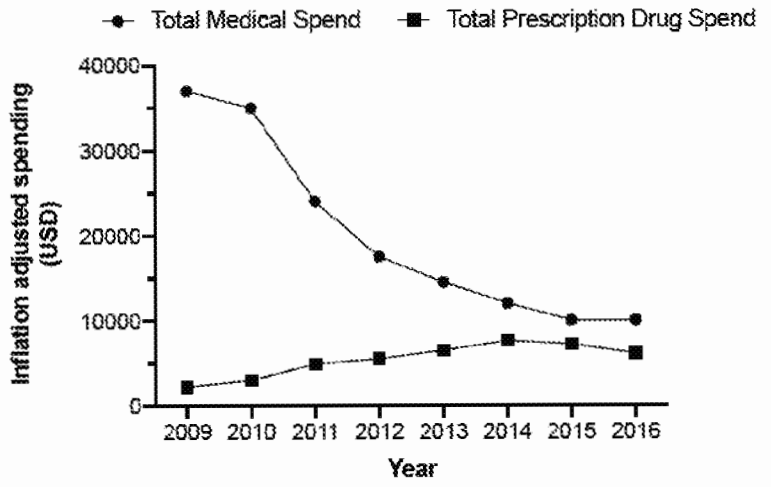
Employment Status	Employed	25 (31.25%)
	Will Return to Work	1 (1.25%)
	Not Employed	54 (67.50%)
Received Social Security Income	Yes	10 (12.50%)
	No	70 (87.50%)
Insurance Status	Any Private Insurance	43 (53.75%)
	Public Insurance Only	33 (41.25%)
	No Insurance	4 (5.00%)

TABLE 2: **PER PATIENT HEALTHCARE COSTS**

ENROLLMENT YEAR	MEAN (SD)	MINIMUM	MAXIMUM
1st Year (inflation-adjusted)	$25,957.55 ($41,054.70)	$0.00	$280,443.46
2nd Year (inflation-adjusted)	$40,547.85 ($62,938.41)	$0.00	$312,077.40

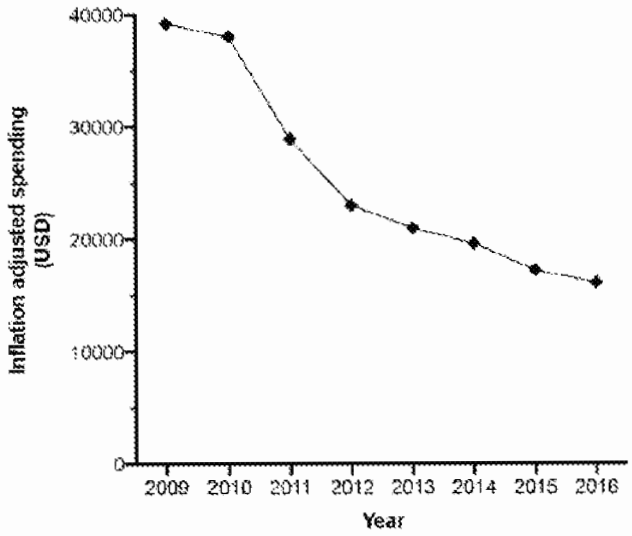
- Table 2 (above) shows mean inflation-adjusted patient level healthcare costs for patients with pancreatic cancer in the MEPS database.
- The few previous studies about the total cost of pancreatic cancer care have looked at the average dollars spent during a specific period of time. We replicated this approach and found that total pancreatic cancer costs averaged about $67,000 during the 1996-2017 time period, which is consistent with the findings of other analyses (Bao et al., 2018; O'Neill et al., 2012).
- However, such analyses are skewed by the fact that a small percentage of patients generate most of the cost. In this study, we attempt to capture statistically significant changes in spending and identify factors associated with such shifts.

FIGURE 1: AS PRESCRIPTION DRUG SPENDING ROSE, OTHER MEDICAL SPENDING FOR PANCREATIC CANCER DECLINED



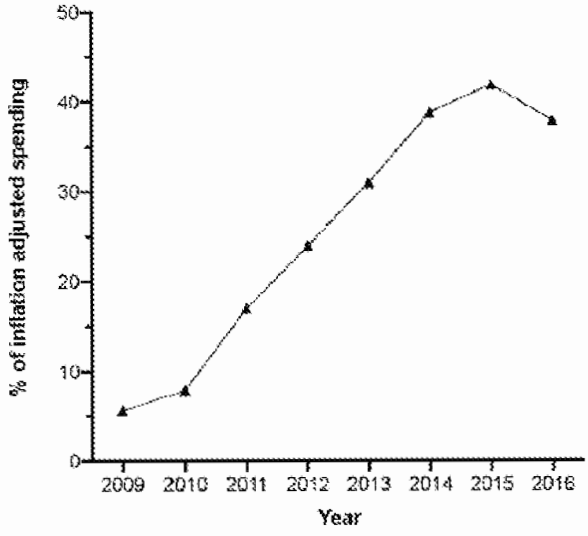
Between 2009 and 2016, inflation adjusted first- and second-year non-medication average per patient spending on pancreatic cancer care declined from $37,000 to $10,000. Prescription drug spending increased during the same time period.

FIGURE 2: THE TOTAL COST OF PANCREATIC CARE (INFLATION ADJUSTED $) FELL FROM 2009 TO 2016



The combined effect of decreased overall healthcare expenses and increased prescription drug expenses means that as a proportion of expense, prescription drugs have increased markedly in the last decade.

FIGURE 3: PRESCRIPTION DRUG SPENDING AS A PERCENTAGE OF TOTAL SPENDING (INFLATION ADJUSTED $) INCREASED



Specifically, between 2009 and 2016 prescription drug spending (not including the cost of administration) rose from approximately 6 percent to approximately 35 percent of inflation adjusted year 1 and year 2 total cost of care. At the same time, total inflation adjusted pancreatic cancer treatment costs declined by 73 percent per person.

DISCUSSION

- As noted, this preliminary study suggests that the therapeutic benefit of increasing the use of prescription drugs is so great that it is driving a decrease in the actual cost of healthcare. This study period corresponds to the introduction of more effective, multi-agent chemotherapies for pancreatic cancer, such as gemcitabine/Abraxane and FOLFIRINOX. The introduction of these prescription drug-based therapies may have contributed to decreasing the overall costs of care.
- Further analysis of a larger, longitudinal set of patient-level data is needed to more fully explore the relationship between drug spending, total cost of care as well as improvements in quality of life.
- 42.5% of patients in this study were under the age of 65 and not receiving Social Security Income, indicating a high societal burden from lost productivity. This patient and societal impact is worthy of future study.

CONCLUSIONS

- For every additional dollar spent on drugs for pancreatic cancer between 2009 and 2016, there was a reduction in non-drug spending of $8 – $9. This relationship is consistent with several other studies that have examined the impact of new medicines on total cost of care (Lichtenberg, 2018). The decline is directly related to a reduction in hospitalizations and emergency visits between 2009 and 2016.
- This preliminary study suggests that frequency or cost of necessary procedures is markedly reduced by allotting budget towards better pharmacotherapy.
- Development of more effective, better tolerated therapies for pancreatic cancer could lead to further decreases in the total cost of care and will also address the urgent patient need for additional treatment options.
- As even more therapies for pancreatic cancer have been developed in the past few years, it would be beneficial to conduct an update to this research periodically.

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Center for Medicine in the Public Interest
Introduction
Methods
Results
Discussion
Conclusions
References