PANCREATIC CANCER

An assessment of the total cost of pancreatic cancer using real-world evidence.

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Abstract Disclosures

Abstract

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Background: 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). 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. 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. The individual patient level ratios of prescription drug cost to other medical expenses was also computed. All expenditures are adjusted for inflation using 2017 US dollars. 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:**Between 1997 and 2017 inflation adjusted first and second year non-medication spending on pancreatic cancer care averaged $66,999.96 and $105,308.60 respectively. However, inflation-adjusted first and second year charges for hospitalizations and emergency visits fell between 2007-2017. Prescription drug as a

proportion of total spending prescription drugs increased during the same time period. Lost work/school days declined between 2007 and 2017. **Conclusions:** Total inflation adjusted pancreatic cancer care expenses declined over the past decade even as drug costs increased. Quality of life costs declined as well. Further analysis is needed to evaluate the relationship between drug spending, total cost of care and quality of life.

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Capecitabine and Celecoxib as Second-Line Treatment of Advanced Pancreatic and Biliary Tract Cancers

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Key Words
Advanced pancreatic carcinoma · Biliary tract cancer · Capecitabine · Celecoxib · Oral chemotherapy

Abstract
Objective: An increasing number of patients with advanced pancreatic or biliary tract cancer who progress after a gemcitabine-containing regimen are candidates for further chemotherapy. We therefore evaluated a fully oral regimen of capecitabine and celecoxib (CapCel) as second-line treatment in these patients. ***Methods:*** Thirty-five patients with documented progressive disease after first-line treatment were enrolled. Capecitabine was administered at a dose of 1,000 mg/m^2 b.i.d. for 2 consecutive weeks followed by 1 week of rest; celecoxib was given continuously at 200 mg b.i.d. Progression-free survival at 3 months was the primary study endpoint. ***Results:*** The CapCel combination was associated with an overall response rate of 9% and median survival duration of 19 weeks. Sixty percent of patients were free from progression 3 months after the start of treatment. Multivariate analysis identified a positive clinical benefit response and a decline in CA 19.9 serum levels >25% compared with baseline levels as independent predictors of prolonged survival. The treatment protocol was well tolerated with negligible hematological toxicity. The most common grade 3 non-hematological toxicities were hypertransaminasemia, diarrhea and asthenia. ***Conclusions:*** The CapCel combination is a safe treatment option with moderate activity in patients with pancreatic/biliary tract cancer after failure of a previous gemcitabine-containing regimen.

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Introduction

Pancreatic cancer (particularly pancreatic ductal adenocarcinoma, PDAC) is arguably one of the deadliest solid tumors, with mortality closely approaching its incidence (e.g. 37,000 estimated new cases and 33,370 estimated deaths in the US in 2007) [1]. In advanced, inoperable disease, the aims of systemic treatment are palliative, and in this context weekly treatment with gemcitabine (Gemzar™; Eli Lilly, Indianapolis, Ind., USA) has been shown to provide some degree of symptomatic improve-

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ment with a modest survival benefit [2]. Despite intensive clinical research efforts (>20 randomized trials over the past 10 years), improvements over single-agent gemcitabine have been modest at best and no significant improvement in 5- and 10-year relative survival has been observed for patients diagnosed with advanced pancreatic cancer from 1998 to 2003 [3–8]. Thus, with only two agents formally approved for this patient population, gemcitabine and erlotinib, new treatment options are urgently needed. Biliary tract carcinomas (BTC) are relatively rare tumors associated with a poor prognosis and high mortality [9]. At present, there is no established palliative standard of care for advanced disease. Different treatments including gemcitabine as single agent or in combination with mitomycin, a platinum compound, or a fluoropyrimidine have yielded response rates of 10–35%, and median overall survival (OS) ranged from 5 to 12 months [10–17].

Cyclooxygenase-2 (COX-2), the inducible enzyme catalyzing the rate-limiting step in the conversion of arachidonic acid into prostaglandins and other eicosanoids, has recently emerged as a potential pharmacological target for inhibiting tumor growth [18]. Indeed, overexpression of COX-2 is frequently observed in human malignancies, including PDAC and BTC, where it stimulates tumor growth and progression, inhibits apoptosis and induces the production of a variety of proangiogenic factors [19–24]. In addition, the main product of COX-2 enzymatic activity, prostaglandin E_2, transactivates the epidermal growth factor receptor, rendering therapeutic COX-2 targeting especially interesting for malignancies such as PDAC, in which the epidermal growth factor receptor pathway is thought to play a relevant pathogenetic role [25–27]. Indeed, in preclinical models of PDAC, selective COX-2 inhibitors, such as celecoxib (Celebrex; Pfizer, New York, N.Y., USA), reduce in vitro and in vivo cell growth, induce apoptosis and suppress expression of vascular endothelial growth factor, thus inhibiting tumor progression and metastases [28, 29].

Capecitabine (Xeloda; Roche Laboratories, Nutley, N.J., USA) is an orally administered fluoropyrimidine, currently approved for the treatment of colorectal and breast cancer. In advanced PDAC, capecitabine has shown single-agent activity, with a 7% objective response rate (ORR), a 24% positive clinical benefit response (CBR) and a median survival of approximately 6 months [30, 31]. Moreover, ORR of 6 and 50% have been reported with single-agent capecitabine in the treatment of patients with cholangiocarcinoma and gallbladder carcinoma, respectively [32]. In addition, capecitabine has been successfully combined with gemcitabine (and more recently erlotinib), although randomized trials against single-agent gemcitabine have yielded conflicting results [33, 34].

Recent preclinical and clinical evidence suggests that the addition of celecoxib may increase the anti-tumor activity of capecitabine and attenuate characteristic toxicities (e.g. hand-foot syndrome, HFS, and diarrhea) in different tumor models, including PDAC [35–38]. Moreover, we have recently reported on the promising activity and tolerability of the celecoxib-5-fluorouracil (FU) combination in advanced, pretreated PDAC patients [39].

Based on this rationale, we designed an open-label, prospective, phase II study to explore the safety and activity of a fully oral CapCel combination regimen in the second-line treatment of patients with advanced PDAC and BTC who had failed first-line therapy with a gemcitabine-containing regimen.

Patients and Methods

Study Design and Eligibility Criteria

The study was designed as an open-label, prospective, phase II trial. Patients with a histologically or cytologically confirmed locally advanced or metastatic PDAC or BTC and documented progressive disease (PD) after first-line chemotherapy were considered eligible. Additional eligibility criteria included: age ≥18 years; measurable and/or evaluable disease according to standard WHO criteria; ECOG performance status (PS) ≤2; adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and hemoglobin ≥10 g/dl), hepatic (total serum bilirubin <2 × upper normal limit, UNL; serum transaminases <2.5 × UNL or <5 × UNL in the absence or presence of liver metastases, respectively) and renal (serum creatinine ≤1.5 mg/dl or a calculated creatinine clearance ≥ 60 ml/min) function; life expectancy of at least 12 weeks, and the ability to swallow treatment medications. Previous radiation therapy, completed at least 4 weeks before enrollment, was allowed provided that other, non-irradiated sites of measurable/evaluable disease were present. Patients with unstable cardiovascular disease, active infections, documented active gastric/duodenal ulcer or known or suspected allergy to sulfa drugs were considered ineligible, as were pregnant or lactating women or women of childbearing potential not undergoing adequate contraception. All patients gave written informed consent before study entry. The study was approved by the local ethics committee and institutional review board, and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the guidelines on good clinical practice.

Treatment Plan and Dose Adjustments

Treatment consisted of oral celecoxib (200 mg b.i.d.), given continuously without scheduled interruptions starting on the 1st day of chemotherapy, in combination with oral capecitabine 1,000 mg/m^2 b.i.d. administered with food for 14 consecutive days followed by 1 week of rest for every 3-week cycle. Prophylactic proton

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Table 1. Patient characteristics (n = 35)

	n	%
Age, years		
Median	62	
Range	40–76	
Gender		
Male	17	49
Female	18	51
Tumor type		
PDAC	30	86
BTC	5	14
ECOG PS		
0	17	48
1	9	26
2	9	26
Disease status		
Locally advanced	2	6
Metastatic	33	94
Pretreatment		
Single-agent gemcitabine	24	69
Gemcitabine-based chemotherapy	5	14
Gemcitabine/radiotherapy	6	17

pump inhibitors (20 mg/day orally) were routinely administered starting on the 1st day of chemotherapy. Adverse events were graded on a five-point scale (grades 1–5, G1–G5), according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (available online at http://ctep.cancer.gov/forms/CTCAEv3.pdf). A capecitabine dose reduction to 750 mg/m^2 b.i.d. and/or treatment delay for a maximum of 2 weeks was allowed in the event of significant (>G2) hematological and non-hematological toxicity. Celecoxib was to be discontinued in the event of any gastrointestinal (GI) bleeding, documented upper GI ulcer or any cardiovascular event >G2.

Assessment of Response

All patients underwent complete medical history and physical examination, including assessment of ECOG PS, concurrent medications and measures of any clinically assessable tumor lesions at baseline and before each subsequent treatment cycle. Complete blood cell counts and serum chemistries were obtained at baseline and before each subsequent cycle. Tumor markers were assessed, and ECG and complete tumor staging by total body CT scan were performed at baseline and every three cycles thereafter. Other imaging methods, e.g. ultrasound, X-ray or MRI, were used whenever required either by the radiologist or for specific clinical purposes. Using standard WHO criteria, tumor response was evaluated every three cycles and confirmed after at least 4 weeks in the event of a complete (CR) or partial response (PR) [40]. Patients with documented PD were withdrawn from the study, while patients with CR, PR or stable disease (SD) were allowed to continue treatment until disease progression or unacceptable toxicity, for a maximum of 9 cycles.

Statistical Methods

The primary endpoint of the study was progression-free survival (PFS) at 3 months in the intent-to-treat population (ITT). Toxicity, ORR, CBR (according to Burris criteria), tumor marker response and OS (measured from the date of the first administration of chemotherapy to the date of death or last follow-up) were secondary endpoints. Sample size was calculated according to the exact, one-stage, phase II design described by A'Hern [41]; with 35 evaluable patients, the study was powered to detect a 3-month PFS rate of interest of 40% and discard the alternative hypothesis of a 3-month PFS rate of 20%, with an 80% power ($1 - \beta = 0.8$) at a significance level of 5% ($\alpha = 0.05$). With this hypothesis, at least 12 patients had to be free from progression at 3 months in order to declare the study positive. All patients enrolled were considered in the ITT and evaluated for efficacy and safety. Cox proportional hazards models were used to compare survival among different patient/disease characteristics, and treatment response groups and hazard ratios were appropriately derived from these models. The Kaplan-Meier method was used to estimate PFS and OS. Statistical analyses were performed using the SPSS package for Windows (version 11).

Results

Patient Characteristics

A total of 35 patients were enrolled between January 2003 and October 2006. Baseline patient characteristics are shown in table 1. Seventeen (49%) patients were male and 18 (51%) were female, with a median age of 62 years (range: 40–76 years). Seventeen patients (48%) were asymptomatic with an ECOG PS of 0, while 18 patients (52%) had an ECOG PS of 1 or 2. The majority of patients had PDAC (86%) and 5 patients (14%) had BTC. Two patients had locally advanced disease and 33 patients had metastatic disease. All patients had been pretreated with either single-agent gemcitabine (24 patients), or gemcitabine-based chemotherapy and radiotherapy combinations (5 and 6 patients, respectively), and all had confirmed PD at the time of inclusion. All patients received at least one treatment cycle (median: 3 cycles; range, 1–9 cycles) and were included in the ITT analysis. Treatment-unrelated early death occurred in 1 patient, who was considered as progressive at the time of death for all subsequent analyses.

Responses and Survival

All 35 patients were evaluable for response and survival (table 2). Three patients had a confirmed PR (ORR: 9%; 95% CI: 0–18%) lasting 34, 24 and 16 weeks, respectively. Disease remained stable in 10 patients (29%) for a median duration of 33 weeks (95% CI: 13–73 weeks). Twenty-two patients experienced PD as their best re-

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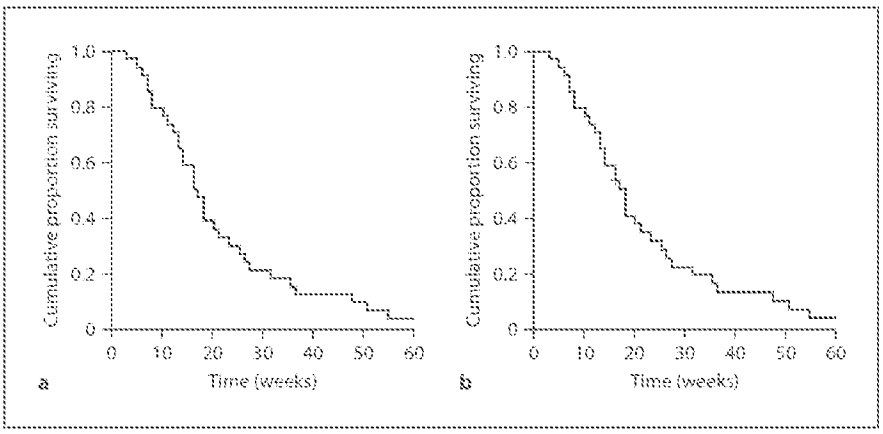


Fig. 1. Kaplan-Meier plots of PFS (**a**) and OS (**b**).

sponse. The composite endpoint of clinical benefit improved in 11 of 33 evaluable patients (CBR: 33%; 95% CI: 17–49%). Variations in serum CA 19.9 levels during treatment were evaluable in 26 patients showing elevated levels at baseline and were monitored serially every 4 weeks. A decrease >25% from baseline was observed in 9 patients, while CA 19.9 remained stable in 3 patients and increased in 14 patients. At the time of this analysis, all patients had progressed. The median PFS was 17 weeks (95% CI: 14–20 weeks; fig. 1a). With 60% of patients being progression free 3 months after the start of treatment, we reached our primary endpoint. When the PFS analysis was restricted to the cohort of 30 PDAC patients, 20 patients (66%) were free of progression at 3 months. The median OS in the entire population was 19 weeks (95% CI: 14–22 weeks; fig. 1b). Univariate Cox regression analysis identified baseline ECOG PS, CBR and tumor marker response as patient/treatment variables significantly associated with OS; of these, a positive CBR and a decline in CA 19.9 serum levels >25% from baseline remained significant, independent predictors of longer survival at multivariate analysis (table 3). These findings were further confirmed by Kaplan-Meier analysis of survival curves (log-rank p = 0.0003 and 0.006 for CBR and tumor marker response, respectively; fig. 2).

Table 2. Response to treatment

Response	n	%	95% CI
Clinical response			
Evaluable	35		
PR	3	9	0–18
SD	10	29	13–43
PD	22	63	47–79
Clinical benefit			
Evaluable	33		
Improvement	11	33	17–49
Tumor marker response			
Evaluable	26		
Decrease (>25%)	9	35	16–53
Stability	3	11	0–24
Increase	14	54	34–73

Toxicity

All patients and 132 cycles were evaluable for toxicity (table 4). Treatment protocol was well tolerated and there were no toxic deaths; only 1 patient was hospitalized due to G3 GI bleeding. Hematological toxicity was negligible, with G1 anemia and G2 thrombocytopenia observed in 3 and 1 of 132 cycles, respectively, and no episodes of neutropenia. Only 4 patients experienced G3 non-hematological toxicities: diarrhea (2 patients, 2 cycles), skin toxicity (1 patient, resolved with treatment delay), asthenia (2 patients, 2 cycles) and GI bleeding (1 patient). Serum transaminase elevation was the most common clinical laboratory alteration observed and reached G3 in 19/132 cycles (14%). All patients promptly recovered from toxicity upon treatment interruption and appropriate medical treatment, and only 1 patient discontinued treatment due to G3 GI bleeding after cycle 1. No patient discontinued treatment because of abnormal laboratory values. Four patients (7 cycles) required dose modification of capecitabine to 750 mg/m^2 b.i.d. and retreatment was delayed in 7 cycles mainly due to HFS, rash/desquamation, diarrhea and serum transaminase elevation.

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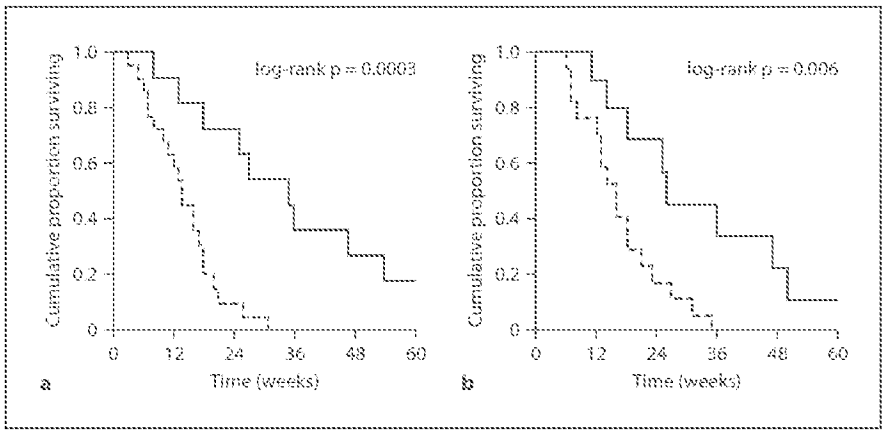


Fig. 2. Kaplan-Meier analysis of survival curves for CBR (**a**; ——— = positive CBR; ------ = negative CBR) and tumor marker response (**b**; ——— = CA 19.9 decrease >25% from baseline; ------ = no change or increase).

Table 3. Univariate and multivariate analysis of factors influencing OS

Factors	Univariate		Multivariate	
	hazard ratio (95% CI)	p	hazard ratio (95% CI)	p
Sex (male vs. female)	1.05 (0.52–2.11)	0.895		
Age (>62 vs. ≤62 years)	1.81 (0.85–3.86)	0.123		
ECOG PS (≥1 vs. 0)	3.04 (1.34–6.74)	0.006		
CA 19.9 ⇓ (no vs. yes)	3.70 (1.33–10.27)	0.012	2.57 (0.91–7.26)	0.074
CBR (– vs. +)	5.61 (1.99–15.83)	0.001	3.05 (1.05–8.84)	0.040

Discussion

This is the first report describing the activity and tolerability of CapCel as second-line therapy in patients with gemcitabine-refractory PDAC and BTC. Relatively few studies have evaluated second-line treatments in these patients. In a recently published phase II study, single-agent capecitabine showed a modest activity with no objective tumor response reported and a median time to progression and OS of 2.3 and 7.6 months, respectively [31]. In studies investigating new agents combined with capecitabine, the results obtained with capecitabine/erlotinib in the study by Kulke et al. [34] and those obtained in the present study with the CapCel combination convey the common message that capecitabine-based combinations do have sizeable, albeit modest, activity in second-line treatment (ORR: 10 and 9%, respectively; CA 19.9 response: 17 and 35%, respectively). In this context, promising activity with a median OS and a median PFS of 23 and 9.9 weeks, respectively, has recently been reported by Xiong et al. [42] with the capecitabine-oxaliplatin combination (XELOX).

Table 4. Treatment-related toxicities (per cycle, 132 evaluable cycles)

Toxicity	G1	G2	G3	G4
Anemia	3 (2)	–	–	–
Thrombocytopenia	–	1 (0.7)	–	–
Lenkopenia/neutropenia	–	–	–	–
Hypertransaminasemia	5 (4)	3 (2)	19 (14)	–
Diarrhea	12 (9)	6 (4)	2 (1)	–
Astenia	1 (0.7)	9 (7)	2 (1)	–
Rash/desquamation	2 (1)	3 (2)	1 (0.7)	
HFS	6 (4)	7 (5)	–	–
Nausea/vomiting	7 (5)	6 (4)	–	–
Fever	4 (3)	–	–	–
Heartburn/dispepsia	3 (2)	–	–	–
GI bleeding	–	–	1 (0.7)	–

Figures in parentheses are percentages.

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Response to chemotherapy, however, is not necessarily a primary treatment goal, particularly in patients with advanced PDAC where it does not correlate with survival endpoints [3]. We therefore selected the 3-month PFS rate as our primary endpoint: the median PFS in the entire population was 17 weeks (95% CI: 14–20 weeks) with 60% of patients being progression free 3 months after the start of treatment; the median OS was 19 weeks (95% CI: 14–22 weeks). Although comparisons between different studies are limited by the small size of the patient cohorts studied and heavily biased by selection issues, our data are consistent with those reported in other studies investigating the role of second-line chemotherapy in advanced PDAC after gemcitabine failure, with median PFS ranging from 1.7 to 5.5 months and median OS ranging from 3.4 to 10.3 months, and compare favorably with our previous experience with celecoxib/infusional 5-FU (median PFS: 8 weeks; median OS: 15 weeks) [39]. More positive efficacy data were reported only recently at ASCO 2008 with a platinum-based combination. Indeed, in the CONKO 003 trial, the combination of oxaliplatin, folinic acid and 5-FU led to a clinically and statistically significant improvement in survival (26 vs. 13 weeks, $p = 0.014$) compared to the folinic acid-5-FU combination, establishing a new reference standard in the second-line setting [43].

The CapCel combination appears particularly attractive for its remarkably mild toxicity profile, in addition to the convenience of oral administration of both drugs, without the need for indwelling vascular devices and infusion pumps: indeed, only 4 of 35 patients required capecitabine dose modifications (7 cycles) or treatment interruptions for treatment-related toxicity (GI bleeding in 1 patient). In this respect, several reports, including our previous experience with the very same regimen in advanced, pretreated breast cancer, suggest that the addition of celecoxib may actually decrease the incidence and severity of two common toxicities associated with capecitabine treatment, namely HFS and diarrhea [35–38]. In contrast, as expected, the capecitabine-erlotinib combination was associated with a high incidence of severe diarrhea, HFS and skin rash, leading to capecitabine or erlotinib dose modifications in 21 and 20 of 30 patients, respectively [34]. Importantly, similar to other recently reported trials employing celecoxib combinations for chemotherapy, cardiovascular events potentially related to celecoxib were not observed in our study. Contradictory results were recently reported with the CapCel combination in patients with metastatic colorectal cancer in the EORTC 40015 study [44]. This study had aimed at demonstrating the non-inferiority of irinotecan in addition to either capecitabine or infusional 5-FU/folinic acid, as well as the benefit of adding celecoxib to irinotecan/fluoropyrimidine regimens compared with placebo. Although the small sample size and safety issues that caused early study termination do not allow valid conclusions to be drawn, no benefit was seen from adding celecoxib to irinotecan/fluoropyrimidine regimens, and celecoxib did not appear to modulate the toxicity of chemotherapy.

Finally, survival analysis suggests that, even within the limits imposed by the small number of patients studied, surrogate clinical endpoints such as CBR and CA 19.9 decrease display a good correlation with more relevant survival endpoints such as OS. This may be important in the routine clinical management of advanced, pretreated PDAC/BTC patients, in whom objective response is neither frequent nor necessarily clinically meaningful; in this context, alternative means of detecting a clinical effect of treatment may be more convenient for the patient and more cost-effective than frequent imaging procedures.

Collectively, the data presented here suggest that the CapCel combination has detectable activity in advanced PDAC refractory or resistant to gemcitabine. However, given the small number of BTC patients enrolled, no formal definitive conclusions can be drawn from the study data in this specific setting. Nevertheless, in both PDAC and BTC patients, treatment was very well tolerated, making this combination very attractive in such an essentially palliative setting and a reasonable second-line treatment option that warrants further investigation. Future studies should incorporate the immunohistochemical assessment of COX-2 expression in order to identify patients that may potentially benefit most from the addition of celecoxib, as recently suggested by studies performed in breast cancer and non-small cell lung cancer [38, 45].

References

1 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ: Cancer Statistics, 2007. CA Cancer J Clin 2007;57:43–66.

2 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–2413.

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3 Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, Carlini P, Nistico C, Terzoli E, Cognetti F, Giannarelli D: Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? Cancer 2007;110:525–533.
4 Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P: Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007;25:2607–2615.
5 Xie DR, Liang HL, Wang Y, Guo SS, Yang Q: Meta-analysis on inoperable pancreatic cancer: a comparison between gemcitabine-based combination therapy and gemcitabine alone. World J Gastroenterol 2006;12:6973–6981.
6 Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. Cochrane Database Syst Rev 2006;19:CD002093.
7 Banu E, Banu A, Fodor A, Landi B, Rougier P, Chatellier G, Andrieu JM, Oudard S: Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs Aging 2007;24:865–879.
8 Brenner H, Gondos A, Arndt V: Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. J Clin Oncol 2007;25:3274–3280.
9 deGroen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM: Biliary tract cancers. N Engl J Med 1999;341:1368–1378.
10 Gebbia V, Giuliani F, Maiello E, Colucci G, Verderame F, Borsellino N, Mauceri G, Caruso M, Tirrito ML, Valdesi M: Treatment of inoperable and/or metastatic biliary tree carcinomas with single-agent gemcitabine or in combination with levofolinic acid and infusional fluorouracil: results of a multicenter phase II study. J Clin Oncol 2001;19:4089–4091.
11 Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W: Phase II of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 2001;12:183–186.
12 Polyzos A, Nikou G, Giannopoulos A, Toskas A, Kalahanis N, Papargyriou J, Michail P, Papachristodoulou A: Chemotherapy of biliary tract cancer with mitomycin C and 5-fluorouracil biochemically modulated by folinic acid: a phase II study. Ann Oncol 1996;7:644–645.
13 Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinländer GS, Bareck E, Lenauer J, Brodowicz T, Lang F, Scheithauer W: Two consecutive phase II studies of 5-FU/leucovorin/mitomycin and of gemcitabine in patients with advanced biliary cancer. Oncology 1999;56:177–180.
14 Ducreux M, Van Cutsem E, Van Laethem JL, Gress TM, Jeziorski K, Rougier P, Wagener T, Anak O, Baron B, Nordlinger B; EORTC Gastro Intestinal Tract Cancer Group: A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. Eur J Cancer 2005;41:398–403.
15 André T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, Selle F, Paye F, Hannoun L, Houry S, Gayet B, Lotz JP, de Gramont A, Louvet C; GERCOR Group: Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 2004;15:1339–1343.
16 Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR, Zhang I, Moore MJ: Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332–2338.
17 Cho JY, Paik YH, Chang YS, Lee SJ, Lee DK, Song SY, Chung JB, Park MS, Yu JS, Yoon DS: Capecitabine combined with gemcitabine (GemCap) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. Cancer 2005;104:2753–2758.
18 Cascinu S, Verdecchia L, Valeri N, Berardi R, Scartozzi M: New target therapies in advanced pancreatic cancer. Ann Oncol 2006;17:148–152.
19 Maitra A, Ashfaq R, Gunn CR, Rahman A, Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Wilentz RE: Cyclooxygenase 2 expression in pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia: an immunohistochemical analysis with automated cellular imaging. Am J Clin Pathol 2002;118:194–201.
20 Tucker ON, Dannenberg AJ, Yang EK, Zhang F, Teng L, Daly JM, Soslow RA, Masferrer JL, Woerner BM, Koki AT, Fahey TJ 3rd: Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer. Cancer Res 1999;59:987–990.
21 Yip-Schneider MT, Barnard DS, Billings SD, Cheng L, Heilman DK, Lin A, Marshall SJ, Crowell PL, Marshall MS, Sweeney CJ: Cyclooxygenase-2 expression in human pancreatic adenocarcinomas. Carcinogenesis 2000;21:139–146.
22 Koshiba T, Hosotani R, Miyamoto Y, Wada M, Lee JU, Fujimoto K, Tsuji S, Nakajima S, Doi R, Imamura M: Immunohistochemical analysis of cyclooxygenase-2 expression in pancreatic tumors. Int J Pancreatol 1999;26:69–76.
23 El-Rayes BF, Ali S, Sarkar FH, Philip PA: Cyclooxygenase-2-dependent and -independent effects of celecoxib in pancreatic cancer cell lines. Mol Cancer Ther 2004;3:1421–1426.
24 Yip-Schneider MT, Sweeney CJ, Jung SH, Crowell PL, Marshall MS: Cell cycle effects of nonsteroidal anti-inflammatory drugs and enhanced growth inhibition in combination with gemcitabine in pancreatic carcinoma cells. J Pharmacol Exp Ther 2001;298:976–985.
25 Smith JJ, Derynck R, Korc M: Production of transforming growth factor alpha in human pancreatic cancer cells: evidence for a superagonist autocrine cycle. Proc Natl Acad Sci USA 1987;84:7567–7570.
26 Ebert M, Yokoyama M, Kobrin MS, Friess H, Lopez ME, Büchler MW, Johnson GR, Korc M: Induction and expression of amphiregulin in human pancreatic cancer. Cancer Res 1994;54:3959–3962.
27 Yamanaka Y, Friess H, Kobrin MS, Buchler M, Beger HG, Korc M: Coexpression of epidermal growth factor receptor and ligands in human pancreatic cancer is associated with enhanced tumor aggressiveness. Anticancer Res 1993;13:565–569.
28 Ding XZ, Tong WG, Adrian TE: Blockade of cyclooxygenase-2 inhibits proliferation and induces apoptosis in human pancreatic cancer cells. Anticancer Res 2000;20:2625–2631.
29 Wei D, Wang L, He Y, Xiong HQ, Abbruzzese JL, Xie K: Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res 2004;64:2030–2038.
30 Cartwright TH, Cohn A, Varkey JA, Chen YM, Szatrowski TP, Cox JV, Schulz JJ: Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002;20:160–164.
31 Boeck S, Wilkowski R, Bruns CJ, Issels RD, Schulz C, Moosmann N, Laessig D, Haas M, Golf A, Heinemann V: Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. Oncology 2007;73:221–227.
32 Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, Vauthey JN, Ellis LM, Schnirer II, Wolff RA, Charnsangavej C, Brown TD: Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 2004;101:578–586.
33 Smith DB, Neoptolemos JP: Capecitabine in carcinoma of the pancreas. Expert Opin Pharmacother 2006;7:1633–1639.
34 Kulke MH, Blaszkowsky LS, Ryan DP, Clark JW, Meyerhardt JA, Zhu AX, Enzinger PC, Kwak EL, Muzikansky A, Lawrence C, Fuchs CS: Capecitabine plus erlotinib in gemcitabine-refractory advanced pancreatic cancer. J Clin Oncol 2007;25:4787–4792.

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35 Blanquicett C, Saif MW, Buchsbaum DJ, Eloubeidi M, Vickers SM, Chhieng DC, Carpenter MD, Sellers JC, Russo S, Diasio RB, Johnson MR: Antitumor efficacy of capecitabine and celecoxib in irradiated and lead-shielded, contralateral human BxPC-3 pancreatic cancer xenografts: clinical implications of abscopal effects. Clin Cancer Res 2005;11:8773–8781.
36 Lin EH, Curley SA, Crane CC, Feig B, Skibber J, Delcos M, Vadhan SR, Morris J, Ayers GD, Ross A, Brown T, Rodriguez-Bigas MA, Janjan N: Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? Am J Clin Oncol 2006;29:232–239.
37 Lin E, Morris JS, Ayers GD: Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. Oncology 2002;16:31–37.
38 Fabi A, Metro G, Papaldo P, Mottolese M, Melucci E, Carlini P, Sperduti I, Russillo M, Gelibter A, Ferretti G, Tomao S, Milella M, Cognetti F: Impact of celecoxib on capecitabine tolerability and activity in pretreated metastatic breast cancer: results of a phase II study with biomarker evaluation. Cancer Chemother Pharmacol 2008;62:717–725.
39 Milella M, Gelibter A, Di Cosimo S, Bria E, Ruggeri EM, Carlini P, Malaguti P, Pellicciotta M, Terzoli E, Cognetti F: Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. Cancer 2004;101:133–138.
40 Miller AB, Hoogstraten B, Staquet M, Winkler A: Reporting results of cancer treatment. Cancer 1981;47:207–214.
41 A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 2001;20:859–866.
42 Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA: Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008;113:2046–2052.
43 Pelzer U, Kubica K, Stieler J, Schwaner I, Heil G, Görner M, Mölle M, Hilbig A, Dörken B, Riess H, Oettle H: A randomized trial in patients with gemcitabine-refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 2008, abstr 4508.
44 Köhne CH, De Greve J, Hartmann JT, Lang I, Vergauwe P, Becker K, Braumann D, Joosens E, Müller L, Janssens J, Bokemeyer C, Reimer P, Link H, Späth-Schwalbe E, Wilke HJ, Bleiberg H, Van Den Brande J, Debois M, Bethe U, Van Cutsem E: Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. Ann Oncol 2008;19:920–926.
45 Edelman MJ, Watson D, Wang X, Morrison C, Kratzke RA, Jewell S, Hodgson L, Mauer AM, Gajra A, Masters GA, Bedor M, Vokes EE, Green MJ: Eicosanoid modulation in advanced lung cancer: cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy – Cancer and Leukemia Group B Trial 30203. J Clin Oncol 2008;26:848–855.

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ORIGINAL REPORT

Phase III, Randomized Study of Gemcitabine and Oxaliplatin Versus Gemcitabine (fixed-dose rate infusion) Compared With Gemcitabine (30-minute infusion) in Patients With Pancreatic Carcinoma E6201: A Trial of the Eastern Cooperative Oncology Group

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ABSTRACT

Purpose
Single-agent gemcitabine (GEM) is standard treatment of metastatic pancreatic cancer. Fixed-dose rate (FDR) GEM and GEM plus oxaliplatin have shown promise in early clinical trials. E6201 was designed to compare overall survival (OS) of standard weekly GEM 1,000 mg/m^2/30 minutes versus GEM FDR 1,500 mg/m^2/150 minutes or GEM 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days (GEMOX).

Methods
This trial included patients with metastatic or locally advanced pancreatic cancer, normal organ function, and performance status of 0 to 2. The study was designed to detect a 33% difference in median survival (hazard ratio [HR] ≤ 0.75 for either of the experimental arms) with 81% power while maintaining a significance level of 2.5% in a two-sided test for each of the two primary comparisons.

Results
Eight hundred thirty-two patients were enrolled. The median survival and 1-year survival were 4.9 months (95% CI, 4.5 to 5.6) and 16% for GEM, 6.2 months (95% CI, 5.4 to 6.9), and 21% for GEM FDR (HR, 0.83; stratified log-rank $P = .04$), and 5.7 months (95% CI, 4.9 to 6.5) and 21% for GEMOX (HR, 0.88; stratified log-rank $P = .22$). Neither of these differences met the prespecified criteria for significance. Survival was 9.2 months for patients with locally advanced disease, and 5.4 months for those with metastatic disease. Grade 3/4 neutropenia and thrombocytopenia were greatest with GEM FDR. GEMOX caused higher rates of nausea, vomiting, and neuropathy.

Conclusion
Neither GEM FDR nor GEMOX resulted in substantially improved survival or symptom benefit over standard GEM in patients with advanced pancreatic cancer.

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INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States with an anticipated 37,700 new patients and 34,300 deaths in 2008.[1] It is the eighth most common cause of death from cancer worldwide.[2]

Gemcitabine (GEM) is the currently accepted standard treatment for pancreatic cancer,[3] as no chemotherapy combination has demonstrated statistical improvement in survival, when compared to GEM alone. However, two recent trials did suggest benefit.

A randomized phase II for patients with pancreatic cancer showed improved time to treatment failure for fixed-dose rate GEM (FDR) at 10 mg/m^2/min compared to GEM 30 minute infusion.[4] The second, a phase III of the combination GEM FDR and oxaliplatin (GEMOX), demonstrated a higher response rate, and progression-free survival (PFS), but not overall survival (OS) compared to GEM.[5]

Eastern Cooperative Oncology Group (ECOG) 6201 was developed to compare standard GEM, GEM FDR, and GEMOX. Different than the prior two studies, the primary end point was overall survival.

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PATIENTS

Eligibility Criteria

Patients age ≥ 18 years were required to have locally advanced or metastatic pancreatic adenocarcinoma with measurable or assessable disease. Patients could not have had prior chemotherapy for metastatic disease but could have had prior adjuvant chemotherapy. Any prior radiation must have been completed at least 4 weeks previously, and there had to be evidence of disease outside the radiation fields or radiologically confirmed progression of disease within the radiation fields. ECOG performance status of 0 to 2 was required. Patients had to have adequate baseline organ function including WBC ≥ 3,500/mm^3, absolute neutrophil count ≥ 1,500/mm^3, platelets ≥ 125,000/mm^3, bilirubin lower than 2.0 mg/dL, AST lower than 3.0× upper limit of normal, creatinine ≤ 1.5× upper limit of normal. Women could be neither pregnant nor breast feeding. Patients could not have had another malignancy within the prior 5 years except for nonmetastatic, nonmelanoma skin cancers, carcinoma in situ of cervix, or cancer cured by surgery or small field radiotherapy. Patients with other active illnesses were excluded as well as those with symptomatic peripheral neuropathy ≥ grade 2. Institutional review board approval was required, and all patients signed informed consent.

Treatment

Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified for performance status, 0 to 1 and versus 2, and for locally advanced versus metastatic disease. Patients were randomly assigned to either GEM (the first cycle of GEM at 1,000 mg/m^2 as a 30-minute infusion weekly for 7 weeks followed by 1 week of rest; for the subsequent cycles, patients received cycles of GEM 1,000 mg/m^2/30 minutes weekly for 3 weeks followed by 1 week rest), GEM FDR (1,500 mg/m^2 administered as a 150-minute infusion [10 mg/m^2/min] days 1, 8, and 15 every 28 days cycle), or GEMOX (GEM 1,000 mg/m^2 over 100 minutes [10 mg/m^2/min] day 1 and oxaliplatin 100 mg/m^2 day 2 over 120 minutes every 14 days cycle).

All patients completed a symptom assessment before therapy, and after 8 and 16 weeks.

Treatment modifications were mandated for myelosuppression or grade 3/4 toxicity. Patients requiring doses to be withheld on two or more consecutive occasions were removed from study. Patients requiring a decrease in GEM dose to lower than 500 mg/m^2 were removed from study. Oxaliplatin was held for patients with persistent grade 3 or 4 neuropathy or other oxaliplatin-related symptoms, and such patients then could continue to receive 30-minute infusion GEM alone weekly for 3 weeks followed by 1 rest week.

All patients who received a single dose of assigned chemotherapy were assessable for efficacy and toxicity. Patients who progressed during the first 8 weeks of study were considered nonresponders. Patients were removed from study at the time of progressive disease. Patients could withdraw or be removed from study at the discretion of the treating physician for unacceptable toxicity. Patients removed from study for any reason were observed for 4 weeks after the last dose of chemotherapy for toxicity assessment and until death for survival duration. Patients with stable disease, or partial or complete remission were eligible to continue therapy on study until disease progression or intolerable toxicity occurred.

National Cancer Institute Common Toxicity Criteria version 2.0 was used initially during the study and, later, version 3.0 was used for toxicity reporting. Version 2.0 toxicities were mapped to version 3.0 toxicities according to Cancer Therapy Evaluation Program specifications.

Response Evaluation Criteria in Solid Tumors were utilized for response assessment at 8-week intervals.[6] All responses had to be confirmed by repeat assessment at ≥ 4 weeks. Patients who had global deterioration of health status but without imaging evidence of disease progression were classified as symptomatic deterioration.

Symptom Assessment

Assessment of patient-reported pancreatic cancer symptoms was a secondary end point in the trial. Symptom severity was measured using the 8-item Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index,[7] which queried pain (three items), fatigue (two items), nausea, weight loss and jaundice. The study investigators added four questions to the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index to include appetite, malaise, everyday functional ability, and bother with treatment adverse effects.

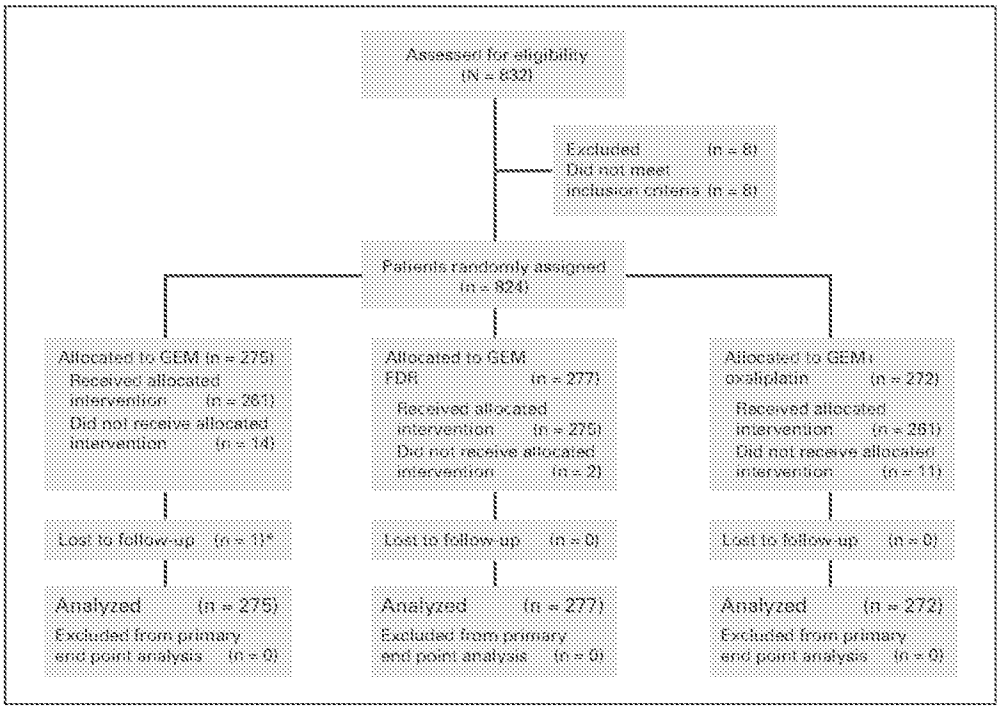


Fig 1. CONSORT diagram. (*) One patient, case 62256, withdrew consent, did not receive allocated intervention, and was lost to follow-up. GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate.

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Table 1. Baseline Characteristics Among Eligible Patients

Characteristic	Treatment					
	GEM (n = 275)		GEM FDR (n = 277)		GEMOX (n = 272)	
	No.	%	No.	%	No.	%
Mean age, years*	63		62		63	
Standard deviation	11		11		11	
Median	64		61		63	
Range	31-88		36-87		29-86	
Under 55	57	20.7	88	31.8	59	21.7
55-69	141	51.3	123	44.4	136	50.0
70+	77	28.0	66	23.8	77	28.3
Sex†						
Male	155	56.4	160	57.8	124	45.6
Female	120	43.6	117	42.2	148	54.4
Race						
Hispanic	9	3.3	12	4.4	12	4.4
Non-Hispanic white	235	85.8	236	86.1	231	85.6
Non-Hispanic black	24	8.8	22	8.0	23	8.5
Other	6	2.2	4	1.5	4	1.5
Previous 6-month weight loss						
< 5% of body weight	100	36.6	100	36.8	107	39.6
5-< 10% of body weight	71	26.0	64	23.5	65	24.2
10-< 20% of body weight	78	28.6	79	29.0	65	24.2
20% or more of body weight	24	8.8	29	10.7	32	11.9
Histology grade						
Well differentiated	14	5	16	6	22	8
Moderately differentiated	82	30	71	26	56	21
Poorly differentiated/undifferentiated	76	28	77	28	76	29
Missing/unknown	103	38	113	41	118	43
Prior RT						
No	254	92.4	253	91.3	250	91.9
Yes	21	7.6	23	8.3	21	7.7
Prior adjuvant chemotherapy						
No	260	94.5	259	93.5	261	96.0
Yes	15	5.5	17	6.1	10	3.7
Prior surgery						
No	230	83.6	234	84.5	239	87.9
Yes	43	15.6	42	15.2	32	11.8
History of DVT or prior embolus						
No	236	85.8	240	86.6	243	89.3
Yes	39	14.2	36	13.0	28	10.3
Disease measurable or not						
Measurable only	70	25.5	67	24.2	84	30.9
Nonmeasurable only	13	4.7	13	4.7	16	5.9
Both	192	69.8	194	70.0	172	63.2
PS on study						
0	94	34.2	86	31.0	73	26.8
1	147	53.5	157	56.7	168	61.8
2	34	12.4	33	11.9	30	11.0
Disease status on study						
Locally advanced	27	9.8	30	10.8	29	10.7
Metastatic	248	90.2	246	88.8	243	89.3
Median CA19-9, U/mL	1,961		1,148		1,077	
25%-75% quantile	167-12,024		136-9,651		90-9,301	
Median CEA, ng/dL	5.7		5.9		6.3	
25%-75% quantile	2.3-30.9		2.4-30.1		2.4-35.5	

Abbreviations: GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days; RT, radiotherapy; DVT, deep vein thrombosis; PS, performance status.

*Age different among three treatment arms, $P = .03$ (Pearson's χ^2 test).

†Sex different among three treatment arms, $P < .01$ (Pearson's χ^2 test).

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Pharmacokinetics

Investigators from 18 centers contributed 23 sample sets after the first dose of GEM. Five time points over 4 hours were sampled from start of infusion. GEM and its metabolite difluorodeoxyuridine were quantified from acetonitrile-deproteinized plasma after perchloric acid extraction by gradient elution reverse phase high-performance liquid chromatography.[8,9] Gemcitabine triphosphate was quantified by gradient elution ion-exchange high-performance liquid chromatography in neutralized peripheral mononuclear cells after removal of ribonucleotide triphosphates. Data were fit to nonlinear models (WiNNonlin pro version 4.1; Scientific Consultant, Apex, NC) and comparisons among dosing groups employed the nonparametric, one-sided Mann-Whitney U-test.[10]

Statistical Considerations

The primary objective of this study was to compare survival of GEM FDR and GEMOX each to GEM using pair-wise comparisons. Secondary end points were the comparison of survival between the two experimental regimens and the assessment of toxicity, objective response to therapy, patterns of failure, PFS, and symptom severity across the three regimens.

Due to rapid accrual, the data monitoring committee approved the accrual expansion from 666 to 789 patients. This expanded trial was designed to be able to detect a 33% difference in median survival with 81% power while maintaining a significance level of 2.5% in a two-sided test for each of the two primary comparisons, assuming exponential failure and a median survival of 6 months for the GEM and 8 months for the GEM FDR or GEMOX.

OS and PFS curves were obtained using the Kaplan-Meier method.[11] OS was defined as the time from random assignment to death, or censored at last known date of survival. PFS was defined as the time from random assignment to progression, or death without evidence of progression. For patients without documentation of progression, follow-up was censored at the date of last disease assessment without progression. Patients dying within 4 months of last disease assessment were considered to have treatment failure, with date of death the date utilized for PFS. Cox regression models[12] of OS and PFS were utilized to provide adjusted treatment comparisons and identify simultaneous significant prognostic factors. Comparisons were made by fitting Cox models with the use of a stratified two-sided Wald test.[13] (stratified by ECOG performance status and locally advanced versus metastatic disease). Objective tumor response rates, categoric patient characteristics, as well as toxicity, were compared among the three arms using χ^2 tests with a two-sided significance level of .05. Where cell frequencies were small, Fisher's exact tests[14] were used. Baseline lab and continuous patient characteristic were compared among the three arms using Kruskall-Wallis[15] tests with a two-sided significance level of .05.

Baseline Patient Characteristics

This study accrued 832 patients between March 2003 and March 2005 (Fig 1) of whom 784 patients have died. There were 30 people who never started assigned therapy, most often because of early progression or death or withdrawal from study. There was no pattern to the reasons for patients' not receiving their assigned therapy across three treatment arms ($P = .35$). Eight ineligible patients were excluded, leaving an analyzable set of 824 patients.

Table 1 presents patient demographics and basic patient characteristics at entry onto the study by treatment arms.

Treatment

Table 2 provides a summary of treatment administered by study arm. Of the 824 eligible patients, 96% of them received at least one cycle of chemotherapy. Patients came off treatment primarily for progressive disease, but also for toxicity, the distribution of which varied significantly among the three arms ($P = .03$). On GEMOX, a lower proportion of patients discontinued treatment due to disease progression (48%), but a higher proportion of patients experienced treatment-terminating toxicity/adverse effects (26%). Fifty-four patients (7%) were categorized as off study for death occurring before the first assessment, presumably disease related.

Toxicity

Results are presented by treatment arm for all randomly assigned patients who received any treatment (Table 3). The most significant toxicity was myelosuppression, which was worse for GEM FDR. Grade 3 sensory neuropathy occurred in 10% of patients receiving GEMOX ($P = .001$).

Response

Two patients experienced a complete response, one receiving GEM FDR and the other on GEMOX. Partial responses were noted in 6% of patients on GEM, 10% on GEM FDR and 9% on GEMOX. There was a higher proportion

Table 2. No. of Cycles Received and Off Treatment Reason by Arm

Parameter	Treatment					
	GEM (n = 275)		GEM FDR (n = 277)		GEMOX (n = 272)	
	No.	%	No.	%	No.	%
Mean No. of total cycles*	3		3		5	
Standard deviation	3		4		6	
Median	2		3		4	
Range	0-21		0-18		0-32	
Mean duration on treatment, days	87		99		79	
Standard deviation	94		105		88	
Median	43		63		43	
Range	0-607		0-883		0-434	
Off treatment reason						
Disease progression/symptom deterioration	161	59	157	57	131	48
Toxicity/adverse effects/complications	42	15	52	19	70	26
Death ≤ 4 weeks after beginning protocol therapy	19	7	18	7	17	6
Physician/patient withdrawal	26	10	33	12	42	15
Alternative therapy/other complicating disease/ treatment delay or cancelled/other/unknown	27	10	17	6	12	4

NOTE. GEM, first cycle 8 weeks; subsequent cycles 4 weeks. GEM FDR, 4-week cycles. GEMOX, 2-week cycles.
Abbreviations: GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days.

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Table 3. Toxicity by Arm

Toxicity Type	Treatment by Grade (%)					
	GEM (n = 264)		GEM FDR (n = 275)		GEMOX (n = 263)	
	3	4	3	4	3	4
Allergic reaction	—	—	—	—	2	—
Hemoglobin	8	2	16	3	5	< 1
Leukocytes*	15	1	32	7	11	1
Neutrophils*	19	14	29	30	11	11
Platelets*	12	1	29	4	10	1
Fatigue	18	1	18	1	15	2
Anorexia	8	—	6	—	7	< 1
Dehydration	5	—	3	< 1	4	—
Diarrhea without prior colostomy	3	< 1	1	< 1	6	—
Nausea and vomiting	7	—	10	1	15	1
Infection w/grade 3-4 neutropenia	1	< 1	—	—	< 1	< 1
AST	3	—	5	—	5	< 1
Bilirubin	6	2	7	2	5	2
Neuropathy, sensory*	0	—	1	—	25	—

Abbreviations: GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days.
*Grade 3 and 4 toxicities different among three treatment arms ($P < .001$).

of partial responses in patients with baseline PS 0 (11%) than for patients with baseline PS of 1 to 2 (7%; $P < .01$).

There were no significant differences in the objective response rates (complete response plus partial response) among the three arms ($P = .11$, χ^2 test). Two hundred ninety-six patients (36%) had a best response of stable disease, and 222 patients (27%) experienced progressive disease at the time of first tumor reevaluation. An additional 222 patients (27%) were unassessable for RECIST-defined response: 89 who died within 4 months of random assignment and were coded as progression; and an additional 100 who had no response coded but had physician-determined progression. Often, rapid clinical deterioration or logistic impediments confounded the acquisition of mandated imaging studies. An additional 33 had insufficient information provided to assess response and date of progression.

OS and PFS

For all eligible patients, median OS was 5.6 months (95% CI, 5.2 to 6.0; Fig 2). Median survival was 4.9 months for GEM (95% CI, 4.5 to 5.6), 6.2 months for GEM FDR (95% CI, 5.4 to 6.9), and 5.7 months for GEMOX (95% CI, 4.9 to 6.5). The 1-year survival rates were 16% for GEM (SE, 2%), 22% for GEM FDR (SE, 3%); and 21% for GEMOX (SE, 3%). The 2-year survival rates were 4% (SE, 1%), 6% (SE, 2%), and 6% (SE, 2%) for GEM, GEM FDR, and GEMOX, respectively (Fig 2). The death HR for GEM FDR versus GEM was 0.83 (95% CI, 0.69 to 1.00) and 0.88 for GEMOX versus GEM (95% CI, 0.73 to 1.05). Stratified log-rank P values for GEM versus GEM FDR and for GEM versus GEM FDR were .04 and .22, respectively. Neither is statistically significant given the parameters of the study ($P < .025$ for statistical significance).

The median PFS for all eligible patients was 2.9 months (95% CI, 2.5 to 3.4; Fig 3). Median PFS for GEM, GEM FDR, and GEMOX were 2.6, 3.5, and 2.7 months, respectively. Stratified log-rank P values for GEM versus GEM FDR and for GEM versus GEMOX were .04 and .10, respectively. Neither comparison demonstrates a statistically significant difference.

Median survival was 9.2 months for patients presenting with locally advanced disease and 5.4 months for those with metastatic disease ($P < .01$). Similarly, median survival was better for patients with better baseline performance status (PS 0; 6.8 months) than it was for patients with PS 1 (5.3 months) and PS 2 (3.9 months; $P < .01$). PFS followed a similar pattern, better for patients with locally advanced and for those with better performance status. Median CA19-9 was 1,313 U/mL. Elevated CA19-9 was a significant predictor for poor OS and PFS ($P < .001$; data not shown).

By univariate analysis, the two experimental regimens were not found to be statistically significantly different from the control arm in terms of OS or PFS (Table 4). Multivariable proportional hazards regression models were fit to OS and PFS to confirm the univariate results after adjusting for prognostic demographic and clinical features. No substantive differences in treatment comparisons resulted from the covariate adjusted models. No statistically significant interactions with regard to PFS or survival between treatment and age, sex, or race were noted.

Symptom Severity

There were 787 questionnaires completed at baseline, but only 501 at 8 weeks and 276 at 16 weeks. At baseline, lack of energy, loss of appetite, fatigue, and inability to do usual activities were the most prominent symptoms noted by 85% to 90% of patients. Pain was present at baseline in 81% of patients. There were no differences in symptom severity between groups observed at baseline. The severity of fatigue, loss of appetite loss, and weight loss did not change with time for patients remaining on study, although pain severity lessened.

Pharmacokinetics

For GEM, GEM FDR, and GEMOX the plasma GEM (mean ± standard deviation) area under the time-concentration curves (AUCs) were: 4,678 ± 2,472 (n = 9), 9,720 ± 2,608 (n = 8), and 11,276 ± 8,788 (n = 6) ng/mL/hr, respectively. The difference between GEM and GEM FDR ($P = .0008$) and GEM and GEMOX ($P = .025$) were statistically different. PBMC intracellular dFdCTP AUCs for GEM, GEM FDR, and GEMOX were: 1,958.7 ± 794

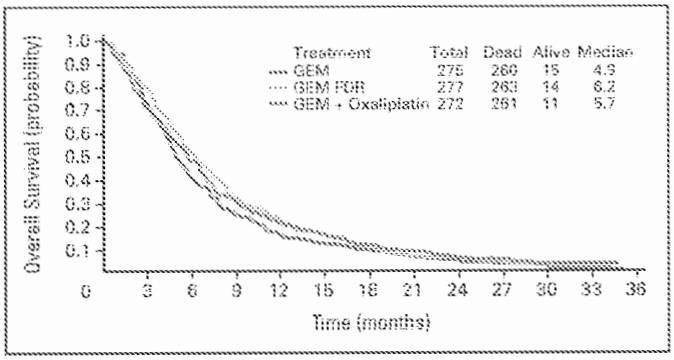


Fig 2. Overall survival. GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days.

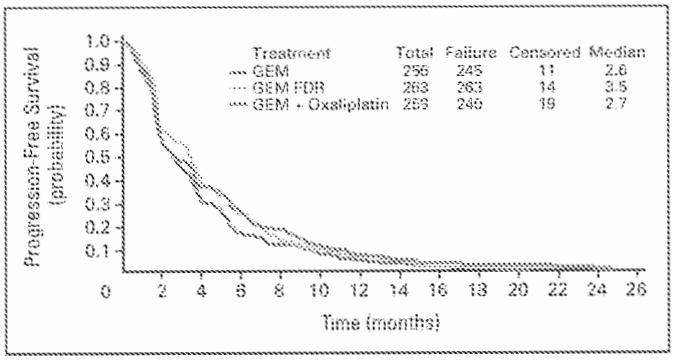


Fig 3. Progression-free survival. GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days.

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Table 4. Univariate Analyses of Progression-Free and Overall Survival Among Eligible Patients

Parameter	Progression-Free Survival		Overall Survival	
	Median (months)	Log-Rank *P*	Median (months)	Log-Rank *P*
All eligible patients	2.9	—	5.6	—
Treatment*				
GEM	2.6	.09	4.9	.15
GEM FDR	3.5		6.2	
GEM + oxaliplatin	2.7		5.7	
Age, years				
55-69	2.8	.65	5.6	.63
70+	3.0		5.5	
Under 55	3.3		5.7	
Sex				
Female	2.7	.40	5.6	.40
Male	3.3		5.7	
Race				
Hispanic	2.6	.69	6.0	.80
Non-Hispanic black	2.2		4.8	
Non-Hispanic white	3.2		5.7	
Other	2.9		4.3	
ECOG performance status				
0	3.6	< .01	6.8	< .01
1	2.8		5.3	
2	2.1		3.9	
Disease status				
Locally advanced	5.4	< .01	9.2	< .01
Metastatic	2.7		5.4	
Previous 6-month weight loss				
< 5%	2.4	.02	5.3	.27
5-< 10%	3.4		6.1	
10-< 20%	3.4		5.5	
20% or more	2.8		6.0	
Prior RT				
No	5.5	0.52	2.9	.53
Yes	6.9		3.1	
Prior adjuvant chemotherapy				
No	5.5	.10	3.0	.14
Yes	7.3		2.9	
Prior surgery				
No	5.5	< .01	2.8	.06
Yes	7.2		3.4	
History of DVT or prior embolus				
No	5.8	< .01	3.1	.02
Yes	4.5		2.5	
Disease measurable or not				
Both	5.3	< .01	2.7	.12
Measurable	6.8		3.6	
Nonmeasurable	5.4		2.8	

Abbreviations: GEM, gemcitabine; GEM FDR, gemcitabine fixed-dose rate; GEMOX, gemcitabine 1,000 mg/m^2/100 minutes/day 1 plus oxaliplatin 100 mg/m^2/day 2 every 14 days; ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; DVT, deep vein thrombosis.
*Stratified by strata at random assignment.

(n = 8); 6,804 ± 7,763 (n = 8), and 4,501 ± 2,113 μM/L, and significantly different for both GEM versus GEM FDR (P = .025) and GEM versus GEMOX (P = .033). These data support the finding that GEM FDR yields higher plasma GEM and PBMC dFdCTP levels than those achieved with 30-minute GEM infusion.

DISCUSSION

GEM has been the only cytotoxic drug with proven and consistent activity against advanced pancreatic cancer. Tempero and colleagues[4] administered EM at 10 mg/m^2/min to maximize the phosphorylation of GEM and the incorporation of dFdCTP into newly synthesized DNA, with the goal of improving response for patients. In that randomized phase II trial of GEM 2,200 mg/m^2/30 minutes versus GEM FDR 1,500 mg/m^2/150 minutes, the median times to failure (primary end point) were 1.8 months and 2.1 months, respectively. Median survival times for all patients were 5.0 months for GEM and 8.0 months for GEM FDR (P = .013). The phase III Groupe Cooperateur Multidisciplinaire en Oncologie/Gruppo italiano per lo studio dei carcinomi dell' apparato digerente study conducted by Louvet et al compared the combination of GEMOX to GEM alone in 313 eligible patients with advanced pancreatic cancer.[5] The median OSs were 9.0 and 7.1 months, respectively (P = .13). However, whether any advantage of GEMOX was provided by the slower FDR infusion of GEM or the addition of oxaliplatin could not be determined in this smaller study.

E6201 was designed to test these two promising approaches against standard single-agent GEM in a sufficiently sized trial using a unequivocal end point of survival. Although GEM FDR was associated with the longest OS (6.2 months), this outcome did not satisfy the protocol-specified criteria for superiority. There was less evidence for superiority of the GEMOX arm over standard GEM, with OS of 5.7 months for GEMOX-treated patients. Our findings indicate that neither GEM FDR, nor GEMOX significantly increases OS or PFS in patients with advanced pancreatic carcinoma when compared to GEM by 30-minute infusion.

Survival for patients in all three arms was shorter than anticipated, perhaps because of some differences in baseline characteristics and study conduct. E6201 had fewer patients with locally advanced disease (10%) compared to Louvet et al's study (30%). This difference, along with the use of radiation therapy for some patients with locally advanced disease in the Louvet et al study, could have contributed to the differing outcomes with GEMOX in the two studies. While E6201 allowed entry of patients with measurable and assessable disease, 95% had measurable disease. In Tempero et al's study of GEM FDR, only 46% of patients had measurable metastatic disease at the time of enrollment. This difference, suggesting higher tumor burden in E6201, may have contributed to the shorter OS for patients in both the GEM as well as the GEM FDR arms of E6201 compared to those observed in the Tempero et al study.

There were differences in dose modification strategies between Tempero's study and E6201. In E6201, patients did not receive chemotherapy if grade 3 neutropenia or grade 2 thrombocytopenia was present on a midcourse treatment day, while in Tempero's study, reduced-dose GEM was given to patients with grade 3 neutropenia or grade 2 thrombocytopenia. Thus, it is possible that patients receiving GEM FDR in Tempero's study received more dose-intense treatment compared to FDR-treated patients in E6201. It is noteworthy that FDR-treated patients in the Tempero study had an 8.0-month survival compared to E6201's FDR patients, with a survival of 6.2 months.

There was a shorter median duration of treatment for GEMOX in the ECOG study compared to that in the GECOR (6 versus 17 weeks). Twenty-six percent of patients came off the GEMOX arm of

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E6201 for toxicity, adverse effects, or complications whereas only 10% of patients came off GEMOX for these reasons in the GERCOR study (C. Louvet, personal communication, August 2008). ECOG 6201 was initiated in 2003, shortly before oxaliplatin entered the United States market (early 2004). Toxicity concerns with this new drug may have prompted some physicians to stop oxaliplatin earlier than physicians with more experience with the drug.

Finally, the E6201 was conducted in more than 100 centers throughout the ECOG network and the United States. Results of limited institution studies often are not duplicated in large studies, with more investigators and a wide variety of patients.

There are several important observations and implications of the results of E6201. The first is the failure of this and other recent phase III trials to confirm promising results generated by smaller trials. Phase III trials of GEM plus bevacizumab (CALGB 80303)[16] and GEM plus cetuximab (SO205)[17] did not confirm the efficacy results obtained in earlier trials.[18,19] Therefore, perhaps, different or more stringent benchmarks for promising regimens or different trial design could be developed more predictive of benefit for new regimens. In addition, only a minority of patients appear to benefit from GEM treatment. In several recent trials, specific polymorphisms in the deoxycytidine kinase, cytidine deaminase, and/or GEM transporter genes correlated with therapeutic response to GEM.[20-22] To substantially improve outcome with GEM, we should consider selecting patients based on these pharmacogenomic criteria, who may be more likely to benefit from this drug. Finally, although GEM plus erlotinib resulted in longer survival in advanced pancreatic cancer patients than GEM plus placebo, the median survival for the combination arm was only 6.4 months.[23] While the result was statistically significant, our goals for our patients should be substantially longer.

A decade after the Burris trial of GEM,[3] we have made little progress in the treatment of advanced pancreatic cancer. Recent genetic analysis of multiple pancreatic cancers demonstrates that each cancer has large numbers of genetic alterations, likely causing disregulation of multiple pathways.[24] Additional data point to the active role of pancreatic cancer stroma.[25] Perhaps, the best hope for real progress in this disease will be through the coordinated use of multiple therapeutic agents or modalities that attack the most critical of these pathways.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Provision of study materials or patients: Peter O'Dwyer, Daniel Haller
Collection and assembly of data: Yang Feng, Howard Hochster
Data analysis and interpretation: Elizabeth Poplin, Yang Feng, Mace L. Rothenberg, Howard Hochster, Peter O'Dwyer, David Cella
Manuscript writing: Elizabeth Poplin, Yang Feng, Jordan Berlin, Mace L. Rothenberg, Howard Hochster, Daniel Haller, David Cella
Final approval of manuscript: Elizabeth Poplin, Yang Feng, Jordan Berlin, Mace L. Rothenberg, Howard Hochster, Edith Mitchell, Steven Alberts, Peter O'Dwyer, Daniel Haller, Paul Catalano, David Cella, Al Bowen Benson III

REFERENCES

1. American Cancer Society: Facts and Figures 2008. Atlanta, GA, American Cancer Society, 2008
2. Parkin M, Bray FJ, Ferlay J, et al: Global Cancer Statistics 2002. CA: Cancer J for Clinicians 55:74-108, 2005
3. Burris HA III, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997
4. Tempero M, Plunkett W, Ruiz van Haperen V, et al: Randomized phase II comparison of dose-intense gemcitabine: Thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402-3408, 2003
5. Louvet C, Labianca R, Hammel P, et al: Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23:3509-3516, 2005
6. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000
7. Yount S, Cella D, Webster K, et al: Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: The FACT Hepatobiliary Symptom Index. J Pain Symptom Management 24:32-44 S, 2002
8. Blackstock AW, Lightfoot H, Case LD, et al: Tumor uptake and elimination of 2',2'-deoxycytidine (gemcitabine) after deoxycytidine kinase gene transfer: Correlation with in vivo tumor response. Clin Cancer Res 7:3263-3268, 2001
9. Venook AP, Egorin MJ, Rosner GL, et al: Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol 18:2780-2787, 2000
10. Mann HB, Whitney DR: On a test of whether one of two random variables is stochastically larger than the other. Annals of Mathematical Statistics 18:50-60, 1947
11. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. American Statistical Association 53:457-481, 1958
12. Cox DR: Regression models and life tables. Journal Royal Statistical Society B 34:187-220, 1972
13. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966
14. Fisher RA: Statistical Methods for Research Workers (ed 11). New York, NY, Hafner Publishing Company, 1950, pp 107
15. Walpole RE, Meyers RH: Probability and Statistics for Engineers and Scientists (ed 2). New York, NY, MacMillan, 1978
16. Kindler HL, Niedzwiecki D, Hollis D et al: A double-blind, placebo-controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients with advanced pancreatic cancer (PC): A preliminary analysis of Cancer and Leukemia Group B (CALGB). J Clin Oncol 25:199s, 2007 (suppl; abstr 4508)
17. Philip PA, Benedetti J, Fenoglio-Preiser C et al: Phase III study of gemcitabine (G) plus cetuximab

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(C) versus gemcitabine in patients (pts) with locally advanced or metastatic pancreatic adenocarcinoma (Pca). SWOG S0205 study. J Clin Oncol 25:199s, 2007 (suppl; abstr LBA4509)

18. Xiong HQ, Rosenberg A, LoBuglio A, et al: Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: A multicenter phase II trial. J Clin Oncol 22:2610-2616, 2004

19. Kindler HL, Friberg G, Singh D, et al: Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 23: 8033-8040, 2005

20. Giovannetti E, Del Tacca M, Mey V, et al: Transcription analysis of human equilibrative nucleoside transporter-1 predicts survival in pancreas cancer patients treated with gemcitabine. Cancer Res 66:3928-3935, 2006

21. Ueno H, Kiyosawa K, Kaniwa N: Pharmacogenomics of gemcitabine: Can genetics lead to tailor made therapy? Br J Cancer 97:145-151, 2007

22. Javle MM, Okazaki T, Evans DB, et al: Polymorphisms of genes involved in gemcitabine metabolism correlate with prognosis in patients receiving neoadjuvant therapy for pancreatic cancer. J Clin Oncol 26:213s, 2008 (suppl; abstr 4501)

23. Moore MJ, Goldstein D, Hamm J, et al: National Cancer Institute of Canada Clinical Trials Group: 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. J Clin Oncol 25:1960-1966, 2007

24. Jones S, Zhang X, Williams Parsons D, et al: Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 321:1801-1806, 2008

25. Chu GC, Kimmelman AC, Hezel AF, et al: Stromal biology of pancreatic cancer. J Cellular Biochemistry 101:887-907, 2008

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JAMA Oncology | Review

Evaluation of Pancreatic Cancer Clinical Trials and Benchmarks for Clinically Meaningful Future Trials
A Systematic Review

Lola Rahib, PhD; Julie M. Fleshman, JD, MBA; Lynn M. Matrisian, PhD, MBA; Jordan D. Berlin, MD

IMPORTANCE Progress in the treatment of pancreatic adenocarcinoma has been minimal; it remains the only major cancer type with a 5-year survival rate of less than 10%.

OBJECTIVE To explore why a large proportion of advanced pancreatic cancer clinical trials executed over the past 25 years have had negative results and to identify benchmarks that could have predicted success.

EVIDENCE REVIEW Phase 3 studies of patients with advanced pancreatic cancer were identified by searching clinicaltrials.gov and the scientific literature.

FINDINGS Thirty-two phase 3 studies in 13 675 chemotherapy-naive patients resulted in 3 agents or combinations being considered clinically meaningful. Nineteen agents or combinations (70%) were tested in phase 2 trials preceding the phase 3 trial. In cases with paired phase 2 and 3 results, meeting the primary end point of the phase 2 trial predicted the outcome of the phase 3 trial 76% of the time but proceeded despite phase 2 negative results in 10 cases. We applied criteria for a clinically meaningful result identified by the American Society of Clinical Oncology (ASCO) Cancer Research Committee to these historical cases. Overall, progression-free and 1-year survival of experimental arms was compared with time period–controlled median values of control arms to normalize for the observed increase in response to gemcitabine over time.

CONCLUSIONS AND RELEVANCE Applying the benchmark of a 50% improvement in overall survival as the primary end point to phase 2 data, or secondary end points of a 90% increase in 1-year survival or an 80% to 100% increase in progression-free survival, showed the greatest ability to predict a clinically meaningful phase 3 trial. Had these criteria been applied to these trials over the past 25 years, more than 11 571 patients enrolled in phase 3 trials that did not meet the primary end point could theoretically have been diverted to earlier-stage trials in an attempt to more rapidly advance the field.

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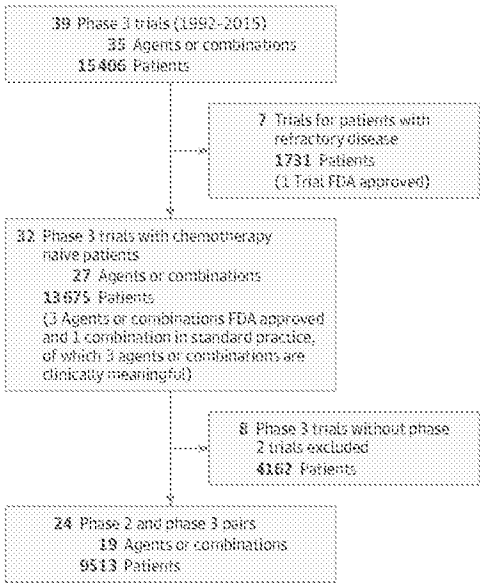
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Pancreatic cancer is the third leading cause of cancer deaths in the United States, and is projected to surpass colorectal cancer around 2020 to become the second leading cause of cancer death.[1,2] The number of pancreatic cancer cases, like most cancers, will undergo a substantial increase as a result of population growth, a change in the ratio of minorities with a higher incidence rate, and an increase in the percentage of the population that is 65 years or older.[3] However, despite the increase in the number of cases, the number of deaths from most of the major cancers is decreasing as a result of prevention and/or treatment advances that lower the death rate.[4] Pancreatic cancer stands in stark contrast to other major cancers in that both the incidence rate and death rate are increasing.[4] The medical advances that have changed the trajectory of the "big 4" cancer types: breast, prostate, colorectal, and to a lesser extent, lung, have yet to be realized in pancreatic cancer.

The lack of clinical progress in pancreatic cancer treatment was recognized by the National Cancer Institute's (NCI's) Gastrointestinal (GI) Cancer Steering Committee in a 2007 State of the Science meeting Consensus Report[5] and a 2011 international expert panel discussion.[6] Both concluded that a strong signal from a phase 2 trial should be identified before proceeding to a phase 3 trial. The American Society of Clinical Oncology (ASCO) convened disease-specific working groups, including 1 on pancreatic cancer, to consider the design of future clinical trials that would produce results that are clinically meaningful for patients.[7] The European Society for Medical Oncology (ESMO) devised a standardized approach to stratify the magnitude of clinical benefit of anticancer therapies that

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Figure 1. Flow Diagram Outlining the Methodology



Phase 3 clinical trials for advanced pancreatic adenocarcinoma (PAC) were considered for analysis. Corresponding phase 2 trials for each of the phase 3 trials were then examined. Phase 3 trials without published phase 2 trials and phase 3 trials for second line treatment of patients with advanced or metastatic PAC were excluded from the analysis to identify characteristics to predict a successful phase 3 trial.

incorporates hazard ratio (HR) and toxicity considerations.[8] Recently, Halperin et al[9] assessed the predictive value of phase 2 trials in GI cancers and showed that evaluation of prior probability of phase 2 clinical trials may increase the success rate of phase 2 studies. The purpose of this analysis was to use historical data in an attempt to identify characteristics that predicted a successful phase 3 trial with clinically meaningful benefit to patients with advanced pancreatic adenocarcinoma (PAC).

Methods

Papers and abstracts reporting phase 3 clinical trials for advanced PAC were collected by searching clinicaltrials.gov, PubMed, and abstracts from meetings of ASCO, including ASCO GI, and ESMO, including the EMSO GI World Congress (**Figure 1**). The corresponding phase 2 trials for each of the phase 3 trials were then examined. Phase 3 trials without published phase 2 trials are reported but were excluded from the analysis to identify characteristics to predict a successful phase 3 trial. An additional 7 phase 3 trials for second-line treatment of patients with advanced or metastatic PAC were identified but were excluded from the analysis owing to the small numbers and inability to compare end points with first-line trials.[10-16]

Computations were determined using Microsoft Excel and R programming environment (version 3.2.2, R Core Team).[17] The Pearson correlation coefficient was used to determine the linear associations between various parameters. Clustering was carried out by K-means analysis using the fpc package in the R programming environment.

Key Points

Question Why have a large proportion of advanced pancreatic adenocarcinoma phase 3 clinical trials performed over the past 25 years had negative results and what can we do to improve on them for the future?

Finding Phase 2 trials preceded phase 3 trials 70% of the time, and the result of the primary end point of a phase 2 trial predicted the outcome of the phase 3 trial 76% of the time. Setting aggressive benchmarks of a 50% increase in overall survival, 90% increase in 1-year survival, and 80% to 100% increase in progression-free survival in historical phase 2 trials would have most accurately predicted clinically meaningful phase 3 trials.

Meaning Placing more emphasis on robust phase 2 results to make go/no-go decisions on phase 3 pancreatic adenocarcinoma clinical trials may improve the success rate and allocation of patients willing to participate in studies that are more likely to achieve clinically meaningful results.

Results

A total of 27 different agents or combinations were reported in 32 phase 3 clinical trials for treatment-naïve patients with advanced-stage PAC between 1997 and 2015. Of these, 19 had phase 2 data[18-43] that influenced the decision to proceed to phase 3 trials.[44-67] 8 went to a phase 3 trial without a prior phase 2 trial,[68-75] and 1 had prior phase 2 data but included a third arm in the phase 3 trial that did not have prior phase 2 data and is included in both categories[55] (eTable 1 in the Supplement). Six of a total of 32 phase 3 studies were considered to have positive results by virtue of meeting the primary end point, and 4 agents or combinations (15%) were US Food and Drug Administration (FDA) approved or used as standard of care: gemcitabine, gemcitabine plus erlotinib, FOLFIRINOX, and gemcitabine plus nab-paclitaxel. One clinical trial[47] of gemcitabine plus cisplatin met the primary end points of time to progression (TTP) and clinical benefit rate, but 2 additional trials[46,48] failed to meet the overall survival (OS) end point. The combination of gemcitabine plus erlotinib was FDA approved in 2005 based on the HR of 0.82 for OS.[72] However, clinicians focused on the modest improvement in median survival (6.2 months vs 5.9 months) as being insufficient to warrant exposing participants to the additional toxic effects of erlotinib. For purposes of this analysis, the results of clinical trials leading to treatment with gemcitabine, FOLFIRINOX, and gemcitabine plus nab-paclitaxel are considered clinically meaningful to patients because these treatments represent the current first-line standard of care for advanced PAC in the United States.

It is assumed to be obvious that strong signals in phase 2 studies are necessary to expect clinically meaningful outcomes in subsequent phase 3 studies.[7] We examined the results of paired phase 2 and phase 3 trials that used treatment-naïve patients with advanced PAC for criteria that predict a clinically meaningful advance for patients with PAC.

End Point Concordance

Most phase 3 studies with corresponding phase 2 trials employed a median OS end point (83%, eTable 1 in the Supplement). In contrast, only 2 of 26 corresponding phase 2 trials used OS as the

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primary end point, and 9 did not specify a primary end point. Of 14 agents or combinations with phase 2 trials for which primary end points were prespecified, the primary end points for the phase 2 and phase 3 trials differed in the majority of cases (93%).

For 17 cases, the primary end point was reported for the phase 2 trial and we were able to determine whether meeting the primary end point criteria of the phase 2 trial set by the authors in advance predicted the outcome of the corresponding phase 3 trial. Meeting the primary end point of the phase 2 trial was concordant with meeting the primary end point of the phase 3 trial for 13 (76%) of the phase 2 trials. This included 2 sets in which both results were positive, and 11 sets in which both results were negative. The 4 trial sets that were discordant had primary end points of OS for the phase 3 trial, and response rate (RR) or TTP for the phase 2 trials. For the 10 phase 3 trials that were executed despite not meeting the stated primary end point for the phase 2 trial, the reasons included at least 1 phase 2 trial with positive results, being close to being positive, and an encouraging secondary end point or subset analysis.

Increase in OS

Improving OS by a specified percentage in a phase 2 trial seems an obvious predictor of OS in a subsequent phase 3 trial. This benchmark is complicated by the lack of a control arm in most of the phase 2 trials. Overall survival following treatment with gemcitabine alone has steadily increased since the first clinical trial (Figure 2; eTable 2 in the Supplement). A cluster analysis reveals 3 distinct groups: those trials that finished in 2000 or before have a median OS of 5.5 months (early time period), those that finished between 2001 and 2006 had a median OS of 6.2 months (middle time period), and from 2007 to 2012, median OS was 8.1 months (late time period).

To explore the reason behind the increase in OS with gemcitabine treatment over time, correlations between trial parameters such as size, the Eastern Cooperative Oncology Group eligibility score, age, percent of locally advanced and/or metastatic patients, liver metastasis, prior surgery, and prior radiation were performed. Of these, the only parameter showing a linear correlation with OS was the percentage of patients that went on to receive a secondary therapy (Pearson $r = 0.73$) (Figure 3A). In general, a higher percentage of patients went on to receive second-line therapy in trials that were completed in the late period compared with the early period. We reasoned that if receiving a second line of therapy was responsible for the trend in increased OS following gemcitabine treatment, that the PFS end point should show less change over time than the increase in OS. In support of this conclusion, PFS showed a lower rate of change over time than OS, with a slope that indicates a median of 0.08 months (2.4 days) increase per year compared with a median of 0.34 months (4.3 days) increase per year for OS (Figure 3B).

Inclusion of Patients With Locally Advanced Disease

PAC clinical trials over the past several decades have at times been restricted to patients with metastatic disease, and in other cases have enrolled patients with advanced disease that include those with nonresectable locally advanced disease. Trials that enrolled patients with metastatic disease only, or those that reported subanalysis data on patients with metastatic and locally advanced disease, independently demonstrated an upward trend and correlation between OS with gemcitabine alone and the date of the completion of the trial for both subgroups of patients (Pearson $r = 0.72$ for locally advanced, and $r = 0.74$ for metastatic) (Figure 3C). These trials are disbursed throughout the 3 periods and do not account for the increase in OS in later vs earlier periods. There is no correlation between the percent of patients with locally advanced disease in the trial and OS (Pearson $r = 0.2$) (data not shown). However, the percent of patients with locally advanced disease enrolled in the trials correlated with PFS (Pearson $r = 0.47$) (Figure 3D).

Figure 2. Overall Survival of Gemcitabine Treatment From Pancreatic Cancer Clinical Trials Over Time



Median overall survival after treatment with gemcitabine reported in phase 3 (25) and corresponding phase 2 (2) trials. Clinical trials that did not report a completion date were excluded. Data from the phase 2 trial reported by Scheithauer et al[50] was also excluded from the analysis because the gemcitabine regimen differed.

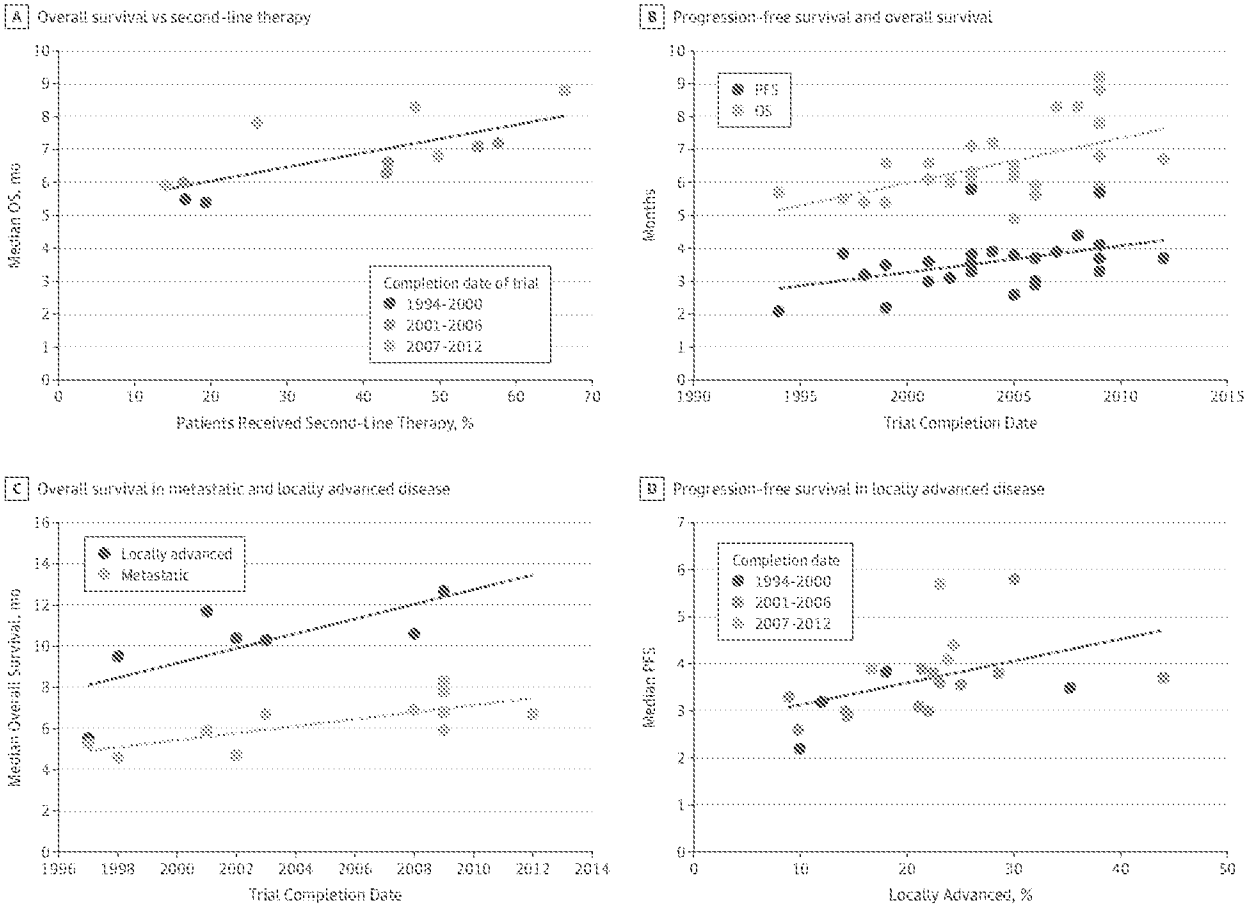
Benchmarks for Clinically Meaningful Improvements

The Pancreatic Cancer Working Group of the ASCO Cancer Research Committee recommended 4 target goals for future phase 3 clinical trials to be considered clinically meaningful. For patients who would be considered for treatment with gemcitabine or gemcitabine plus nab-paclitaxel, goals include improvement over the current 8- to 9-month median OS by 3 to 4 months as the primary end point with a target HR of 0.6 to 0.75, and as secondary end points, improvement in 1-year survival rate from 35% to 50% and in PFS from 3 to 4 months. We considered whether using similar criteria for the assessment of phase 2 trials would predict clinically meaningful outcomes in subsequent phase 3 trials.

The recommendation of an improvement of 3 to 4 months over the current 8- to 9-month OS following treatment with gemcitabine or gemcitabine plus nab-paclitaxel is an approximately 40% increase. In this study, the comparator gemcitabine only value was established for each phase 2 trial based on the date of trial completion and the median value of the range was used (5.5, 6.2, and 8.1 months for trials in the early, mid, and late periods, respectively). One phase 2 trial[56] did not report the finish date and was excluded from this analysis. Using this value as the baseline, the percent increase in 10 percentage point increments between 40% and 100% was determined, and the increment at which OS from the phase 2 trial became predictive of a clinically meaningful phase 3 trial is indicated in eTable 1 in the Supplement. Using a 40% increase in OS in a phase 2 trial as the benchmark predicts the result of the phase 3 trial in 16 of 23 trials (70%) (Table). Increasing the benchmark to a 50% improvement resulted in 18 (78%) of the 23 phase 2 trials accurately

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Figure 3. Correlations of Outcomes of Gemcitabine Treatment From Pancreatic Cancer Clinical Trials Over Time



A, Median overall survival plotted against the percent of patients that received second line therapy in randomized phase 2 (1) and phase 3 (11) clinical trials. B, Median progression-free survival after treatment with gemcitabine reported in phase 3 (24) and phase 2 (1) trials compared to median overall survival as reported in Figure 2. C, Median overall survival after treatment with gemcitabine in metastatic and locally advanced patients reported in phase 3 (10 metastatic, 7 locally advanced) and phase 2 (1 metastatic) trials. D, Median progression-free survival after treatment with gemcitabine plotted against the percent of locally advanced patients included in phase 2 (1) and phase 3 (21) trials.

Table. Predictive Benchmarks for Advanced Pancreatic Cancer Clinical Trials

	Phase 2 Trials That Met Benchmark, No. (%)				
Benchmark, %	OS	1-Year Survival	PFS	TTP	TTP or PFS
40	16 (69.6)	8 (42.1)	6 (60)[a]	4 (44.4)	10 (52.6)
50	18 (78.3)	12 (63.2)	7 (70)[a]	5 (55.6)	12 (63.2)
60	18 (78.3)[b]	15 (78.9)	7 (70)[a]	5 (55.6)	12 (63.2)
70	19 (82.6)[b]	17 (89.5)	9 (90)[a]	5 (55.6)	14 (73.7)
80	19 (82.6)[b]	17 (89.5)	10 (100)[a]	5 (55.6)	15 (78.9)
90	20 (87)[b]	18 (94.7)	10 (100)[a]	7 (77.8)	17 (89.5)
100	21 (91.3)[b]	17 (89.5)[a]	10 (100)[a]	8 (88.9)	18 (94.7)
Total No. of trials	23	19	10	9	19

Abbreviations: OS, overall survival; PFS, progression-free survival; TTP, time to progression.

[a] One clinically meaningful clinical trial excluded.

[b] Both clinically meaningful clinical trials excluded.

predicting whether the corresponding phase 3 trial was clinically meaningful or not. An increase to 60% to 70% also resulted in a 78% predictive value, but eliminated the phase 2 trial for gemcitabine plus nab-paclitaxel which is considered to be a clinically meaningful combination. Further increases in the benchmark eliminate both the gemcitabine plus nab-paclitaxel and the FOLFIRINOX clinically meaningful clinical trials.

The ASCO Pancreatic Cancer Working Group recommended a 25% increase in the HR, from 0.6 to 0.75, as another primary end point to define a clinically meaningful trial. We are unable to apply retrospective clinical trial information to determine the usefulness of the HR as the predictor of phase 3 success since only 4 phase 2 trials were randomized. This also precluded the application of the benchmarks recommended by the ESMO Magnitude of Clinical Benefit Scale.[17]

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The ASCO Pancreatic Cancer Working Group recommended the secondary end point of an improvement in 1-year overall survival values from 35% to 50% or greater as a benchmark for proceeding from phase 2 to phase 3 trials from 2014 forward. We applied benchmarks of 40% to 100% improvement to the 1-year survival rate for historical phase 2 trials using the median 1-year survival of 18% for the control gemcitabine-only arm for phase 2 trials that ended in the early time period (before 2000), 22% for those in the middle period (2001-2006), and 24% for the late time period (2007-2012). Using the 40% increase benchmark, 8 of 19 (42.1%) phase 2 trials for which 1-year survival data were available would have been predictive of a clinically meaningful phase 3 trial (Table). The predictive value reached 94.7% if a benchmark of a 90% increase in 1-year survival rate is applied.

Progression-free survival information was available for 10 phase 2 trials. Progression-free survival was either not stated in other trials, or time to progression (TTP) was an alternative end point. We applied the same benchmarks of 40% to 100% improvement using the median PFS of 3.2, 3.6, and 4.0 months for trials that ended in the early, middle, and late time periods, respectively. Using the 40% increase benchmark, 6 of 10 (60%) of the phase 2 trials for which PFS data were available would have been predictive of the results of the subsequent phase 3 trial (positive or negative) (Table). The predictive value reached 100% if the benchmark of an 80% to 100% increase in PFS was applied, but it is important to note that this data set includes only 1 phase 2 trial with a clinically meaningful phase 3 result. Time to progression was provided for 9 phase 2 trials. An evaluation of TTP relative to the benchmarks set for PFS demonstrate 88.9% predictive value at a 100% increase relative to the median PFS value for that time period (Table). If the assumption is made that a significant number of patients did not die before their disease progressed and TTP and PFS are roughly equivalent, the results include both treatment combinations considered clinically meaningful and suggest a doubling of PFS and/or TTP is the optimum benchmark to identify a therapy with a high probability of resulting in a clinically meaningful phase 3 trial (Table).

Discussion

In the purest sense of trial design, the phase 2 trial is written with the ultimate goal that, if the primary end point is positive, it will lead to a phase 3 trial, and if negative, the drug or regimen will not go further in that setting. Secondary end points are employed to yield leads that are hypothesis-generating and can guide further exploratory trials, but not generally phase 3 trials. Using a series of 15 pairs of phase 2/3 trials, we first focused on the primary end point as defining a positive or negative trial. The phase 2 trials were predictive of a clinically meaningful phase 3 trial 76% of the time, but in 11 of 13 cases, a phase 3 trial was pursued irrespective of the phase 2 not meeting its primary end point. The decision to proceed was based on encouraging secondary end points, subset analyses results, or a second phase 2 trial conducted elsewhere that showed promise. However, the statistics are most rigorous around the designed primary end point, which may explain why the primary end point is predictive regardless of which end point was selected. Additional factors that are not mentioned but contribute to corporate go/no-go decisions involve economic and logistical 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.[76] The concern that develops is that the trend of negative phase 3 trials continues.

In addition, the number of phase 3 trials developed without a phase 2 trial is disheartening. The fact that 1 of these trials, which combined gemcitabine with erlotinib, was positive does not justify the concept of moving forward without adequate data. In fact, its use remains low and is often dismissed for providing only a 2-week survival benefit. An evaluation of the literature associated with these trials indicates that the rationale used for conducting a phase 3 trial in the absence of phase 2 data included antitumor activity in a phase I trial, the assumption that the agent tested would be enhanced by combining it with a cytotoxic agent, decrease metastasis in human pancreatic tumor xenografts, and efficacy or synergy with a cytotoxic agent in preclinical models.[68-75]

Several consensus groups have made recommendations on guidelines to follow for further pancreatic cancer clinical trials.[5-8] Retrospectively, we determined if applying the ASCO Cancer Research Committee benchmarks to the phase 2 trials would have predicted a clinically meaningful response in the paired phase 3 trial. Applying the criteria of a 50% improvement in OS as the primary end point, or secondary end points of a 90% increase in 1-year survival rate, or an 80% to 100% increase in PFS, showed the greatest ability to predict a clinically meaningful phase 3 trial, but has the highest risk of missing potentially effective agents or regimens. Had this criteria been applied to the 27 different agents or combinations tested over the past 25 years, the 11 571 patients that enrolled in phase 3 trials that did not meet their primary end point or did not participate in a prior phase 2 could have at least theoretically been diverted to testing different agents or combinations in early stage trials in an attempt to more rapidly advance the field.

If a 50% increase in OS from a phase 2 trial would have been used as a standard for progressing to a phase 3 study, both combinations identified as clinically meaningful and 4 combinations with negative phase 3 studies would have met the criteria for continuation. The combination of gemcitabine plus fluorouracil and gemcitabine plus capecitabine were positive in 1 phase 2 trial but negative in 2 other trials, suggesting that there would have been strong evidence for discontinuation of clinical studies of these combinations. The combination of gemcitabine plus oxaliplatin would have reached the benchmark. A meta-analysis suggested a benefit from platinum-based therapies,[77,78] suggesting that further testing of these agents could be considered appropriate. Finally, the combination of gemcitabine plus S-1 would have exceeded the benchmark. S-1 is used particularly for some GI malignant diseases in Japan, but is not used in the United States owing to drug dosage issues associated with population differences in *CYP2A6* alleles and dietary levels of folic acid.[79] The results of trials in Asian populations for this class of drugs would have to be considered in the decision to proceed in Western populations.

It is interesting that OS following treatment with gemcitabine only has increased from a median of 5.5 months in the studies conducted prior to 2000 to a median of 8.1 months in those studies conducted in the latest time period. This increase correlates with the percentage of enrollees that received second-line treatment, and may suggest decreased nihilism and a willingness to try subsequent lines of therapy. This is supported by the recent FDA approval of nanoliposomal irinotecan in treatment of patients with

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gemcitabine refractory metastatic PAC.[10] The observation that PFS following treatment with gemcitabine alone showed a modest increase over time may point to better supportive care measures, another factor that could contribute to improved OS and the ability to tolerate subsequent lines of therapy.

There are limitations to this analysis. There were only 6 positive phase 3 trials to estimate the necessary outcome in phase 2 trials to predict positive phase 3 trials. Some phase 3 trials, in particular those with negative data, may not have been published or presented in a manner that would have been identified within our search parameters and skewed the correlation. However, these possibilities remain unlikely to have changed the results significantly.

Conclusions

The overoptimism of oncologists and pharmaceutical sponsors regarding the results of phase 2 trials has been previously recognized.[8,9] What has perhaps not been adequately recognized is the negative impact that has come from ignoring the basic tenet that phase 2 primary end point results should be the determinant of a go/no-go decision for a phase 3 trial. The 15% success rate of phase 3 clinical trials in advanced pancreatic cancer over a 20-year period involving a total of 13 675 patients who overcame the hurdles of enrolling in a clinical trial is a stark reminder of this impact. The efforts of the ASCO Cancer Research Committee in identifying quantitative measures to determine clinically meaningful outcomes in future phase 3 trials is commended. Applying these measures to historical phase 2 trials suggests the criteria should be even more stringent. In an era when only 4% to 5% of pancreatic cancer patients are enrolled in clinical trials,[81] the benefit of applying more stringent criteria in clinical trial design provides the opportunity to divert the precious resource of patients that enroll in clinical trials into phase 2 trials to test the rapidly growing number of new chemical entities and drug combinations. This is especially critical in a population of patients with desperate need for clinical advances.

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Study concept and design: All authors.
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Drafting of the manuscript: Rahib, Matrisian, Berlin.
Critical revision of the manuscript for important intellectual content: All authors
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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.

2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921.

3. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*. 2009;27(17):2758-2765.

4. Ryerson AB, Eheman CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer*. 2016;122(9):1312-1337.

5. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. *J Clin Oncol*. 2009;27(33):5660-5669.

6. Tempero MA, Berlin J, Ducreux M, et al. Pancreatic cancer treatment and research: an international expert panel discussion. *Ann Oncol*. 2011;22(7):1500-1506.

7. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014;32(12):1277-1280.

8. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol*. 2015;26(8):1547-1573.

9. Halperin DM, Lee JJ, Dagohoy CG, Yao JC. Rational Clinical Experiment: Assessing Prior Probability and Its Impact on the Success of Phase II Clinical Trials. *J Clin Oncol*. 2015;33(26):2914-2919.

10. Chen LT, Von Hoff D, Li CP, et al. Expanded analyses of napoli-1: Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, vs 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. *J Clin Oncol*. 2015;33, 2015 (Suppl 3; abstr 234).

11. Cluleanu TE, Pavlovsky AV, Bodoky G, et al. A randomised Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine. *Eur J Cancer*. 2003;45(9):1589-1596.

12. Dahan L, Bonnetain F, Ychou M, et al; Fédération Francophone de Cancérologie Digestive. Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301). *Gut*. 2010;59(11):1527-1534.

13. Gill S, Ko YJ, Cripps MC, et al. PANCREOX: A randomized phase 3 study of SFU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT). *J Clin Oncol*. 2014;32.5S(abstr 4022).

14. Heinemann V, Vehling-Kaiser U, Waldschmidt D, et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). *Gut*. 2013;62(5):751-759.

15. Jacobs AD, Burris HA, Rivkin S, Ritch PS, Eisenberg PD, Mettinger KL. A randomized phase III study of rubitecan (ORA) vs best choice (BC) in 409

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patients with refractory pancreatic cancer report from a North-American multi-center study. *J Clin Oncol*. 2004;22(14S).

16. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol*. 2014;32(23):2423-2429.

17. R: A language and environment for statistical computing. R Foundation for Statistical Computing; 2015. http://www.r-project.org. Accessed June 2015.

18. Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs*. 1994;12(1):29-34.

19. Evans J, Bramhall S, Carmichael J, et al. A phase II study of marimastat (BB-2516) in advanced pancreatic cancer. *Ann Oncol*. 1996;7 (suppl 5).

20. Heinemann V, Wilke H, Mergenthaler HG, et al. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol*. 2000;11(11):1399-1403.

21. Philip PA, Zalupski MM, Vaitkevicius VK, et al Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. *Cancer*. 2001;92(8):569-577.

22. Berlin JD, Adak S, Vaughn DJ, Flinker D, Blaszkowsky L, Harris JE, Benson IIIAB. A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Cooperative Oncology Group Study (E3296). *Oncology*. 2000;58(3):215-218.

23. Cascinu S, Silva RR, Barni S, et al. A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Br J Cancer*. 1999;80(10):1595-1598.

24. Jovtis S, Marantz A, Almira E, et al. Phase II trial of gemcitabine (GEM), 5-Fluorouracil (5-FU) and leucovorin (LV) in advanced pancreatic cancer (PC). *Eur J Cancer*. 1999;35:S157.

25. Rocha Lima CM, Savarese D, Bruckner H, et al. Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. *J Clin Oncol*. 2002;20(5):1182-1191.

26. Stathopoulos GP, Rigatos SK, Dimopoulos MA, et al; Greek Cooperative Group for Pancreatic Cancer. Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study by the Greek Cooperative Group for Pancreatic Cancer. *Ann Oncol*. 2003;14(3):388-394.

27. Louvet C, André T, Lledo G, et al. Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. *J Clin Oncol*. 2002;20(6):1512-1518.

28. Hess V, Salzberg M, Borner M, et al. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol*. 2003;21(1):66-68.

29. Stathopoulos GP, Syrigos K, Polyzos A, et al. Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. *Ann Oncol*. 2004;15(2):224-229.

30. Scheithauer W, Schüll B, Ulrich-Pur H, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol*. 2003;14(1):97-104.

31. Kindler HL. The pemetrexed/gemcitabine combination in pancreatic cancer. *Cancer*. 2002;95(4)(suppl):928-932.

32. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol*. 2003;21(18):3402-3408.

33. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. *J Clin Oncol*. 2004;22(13):2610-2616.

34. Reni M, Passoni P, Panucci MG, et al. Definitive results of a phase II trial of cisplatin, epirubicin, continuous-infusion fluorouracil, and gemcitabine in stage IV pancreatic adenocarcinoma. *J Clin Oncol*. 2001;19(10):2679-2686.

35. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2005;23(31):8033-8040.

36. Kindler HL, Bylow KA, Hochster HS, et al. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis. *J Clin Oncol*. 2006;24(18S).

37. Conroy T, Paillot B, François E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol*. 2005;23(6):1228-1236.

38. Wallace JA, Locker G, Nattam S, et al. Sorafenib (S) plus gemcitabine (G) for advanced pancreatic cancer (PC): A phse II trial of the University of Chicago Phase II Consortium. *J Clin Oncol*. 2007;25(18S).

39. Spano JP, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet*. 2008;371(9630):2101-2108.

40. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*. 2011;29(34):4548-4554.

41. Kindler HL, Richards DA, Garbo LE, et al. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. *Ann Oncol*. 2012;23(11):2834-2842.

42. Mitry E, Hammel P, Deplanque G, et al. Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2010;66(2):395-403.

43. Ueno H, Okusaka T, Furuse J, et al. Multicenter phase II study of gemcitabine and S-1 combination therapy (GS Therapy) in patients with metastatic pancreatic cancer. *Jpn J Clin Oncol*. 2011;41(8):953-958.

44. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413.

45. Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA; Marimastat Pancreatic Cancer Study Group. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol*. 2001;19(15):3447-3455.

46. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol*. 2006;24(24):3946-3952.

47. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer*. 2002;94(4):902-910.

48. Colucci G, Labianca R, Di Costanzo F, et al; Gruppo Oncologico Italia Meridionale (GOIM); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol*. 2010;28(10):1645-1651.

49. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB III. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002;20(15):3270-3275.

50. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol*. 2004;22(18):3776-3783.

51. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer*. 2006;95(5):587-592.

52. Louvet C, Labianca R, Hammel P, et al; GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23(15):3509-3516.

53. Herrmann R, Bodoky G, Ruhstaller T, et al; Swiss Group for Clinical Cancer Research; Central European Cooperative Oncology Group. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the

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Central European Cooperative Oncology Group. *J Clin Oncol*. 2007;25(16):2212-2217.

54. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009;27(33):5513-5518.

55. Oettle H, Richards D, Ramanathan RK, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol*. 2005;16(10):1639-1645.

56. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27(23):3778-3785.

57. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol*. 2010;28(22):3605-3610.

58. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol*. 2005;6(6):369-376.

59. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol*. 2010;28(22):3617-3622.

60. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009;27(13):2231-2237.

61. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.

62. Gonçalves A, Gilabert M, François E, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol*. 2012;23(11):2799-2805.

63. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol*. 2011;12(3):256-262.

64. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703.

65. Fuchs CS, Ikeda M, Bodoky G, et al. A phase III trial of ganitumab (GAN, AMG 479) with gemcitabine (G) as first-line treatment (tx) in patients (pts) with metastatic pancreatic cancer (MPC): An analysis of safety from the GAMMA trial (GEM and AMG 479 in Metastatic Adenocarcinoma of the Pancreas). *J Clin Oncol*. 2012.

66. Deplanque G, Demarchi M, Hebbar M, et al. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. *Ann Oncol*. 2015;26(6):1194-1200.

67. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*. 2013;31(13):1640-1648.

68. Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer*. 2002;87(2):161-167.

69. Moore MJ, Hamm J, Dancey J, et al; National Cancer Institute of Canada Clinical Trials Group. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2003;21(17):3296-3302.

70. Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol*. 2004;22(8):1430-1438.

71. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol*. 2006;24(27):4441-4447.

72. Moore MJ, Goldstein D, Hamm J, et al; National Cancer Institute of Canada Clinical Trials Group. 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. *J Clin Oncol*. 2007;25(15):1960-1966.

73. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2014;15(8):829-840.

74. O'Neil BH, Scott AJ, Ma WW, et al. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. *Ann Oncol*. 2015;26(9):1923-1929.

75. Rougier P, Riess H, Manges R, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer*. 2013;49(12):2633-2642.

76. Feuerstein A, Ratain MJ. Oncology micro-cap stocks: caveat emptor! *J Natl Cancer Inst*. 2011;103(20):1488-1489.

77. Cliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer*. 2013;49(3):593-603.

78. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol*. 2007;25(18):2607-2615.

79. Kobayakawa M, Kojima Y. Tegafur/gimeracil/oteracil (S-1) approved for the treatment of advanced gastric cancer in adults when given in combination with cisplatin: a review comparing it with other fluoropyrimidine-based therapies. *Onco Targets Ther*. 2011;4:193-201.

80. Maitland ML, Hudoba C, Snider KL, Ratain MJ. Analysis of the yield of phase II combination therapy trials in medical oncology. *Clin Cancer Res*. 2010;16(21):5296-5302.

81. Hoos WA, James PM, Rahib L, Talley AW, Fleshman JM, Matrisian LM. Pancreatic cancer clinical trials and accrual in the United States. *J Clin Oncol*. 2013;31(27):3432-3438.

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Poster Reception

CT13 | Impact of Treatment Sequence on Overall Survival in Metastatic Pancreatic Cancer Patients Treated with Irinotecan Liposomal in the Real-World Setting (Screen 9)

Thu, Mar 12 5:00 PM – 5:45 PM

Background/Rationale:
There is limited real-world evidence on the impact of treatment sequence on outcomes for patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in combination with fluorouracil and leucovorin.

Objective(s):
This study assessed clinical characteristics and overall survival in patients that received nal-IRI in the third-line (3L) setting or beyond (3L+) following treatment with fluorouracil and gemcitabine-based treatment (Sequence 1), and patients who received nal-IRI as second-line treatment following gemcitabine-based frontline treatment (Sequence 2).

Methods:
Using the Flatiron Health® longitudinal database, data were extracted and analyzed for adult patients with mPC treated with nal-IRI between November 2015 and October 2018. Lines of treatment were derived from structured medication administration and order data. Kaplan-Meier methods were used to estimate overall survival (OS) from nal-IRI initiation.

Results:
There were 121 Sequence 1 and 129 Sequence 2 patients included in this study. Sequence 1 patients had a median age of 66y (IQR 60 – 73) at nal-IRI initiation and Sequence 2 patients were 72y (IQR 65 – 77) at initiation. 65.1% of Sequence 2 patients (n=84) were initially diagnosed with Stage IV pancreatic cancer compared to 55.4% (N=67) of the Sequence 1 patients. ECOG scores were similar between the two cohorts; 52.1% (N=63) of Sequence 1 patients had a score of 0-1 compared to 52.7% (N=68) of Sequence 2 patients. Sequence 1 patients had a median OS of 4.1 months (95% CI, 3.5 – 5.4) from nal-IRI treatment initiation while Sequence 2 patients had a median OS of 6.3 months (95% CI 4.2 – 7.5).

Conclusions:
This real-world analysis showed similar results to a recent single center study of nal-IRI treated patients and the NAPOLI-1 trial. As expected, Sequence 2 patients had a longer overall survival than Sequence 1 patients. Further real-world studies are needed to understand the impact of treatment sequences on survival outcomes in nal-IRI treated patients.

Glassman DC, Palmaira RL, Covington CM, et al. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. BMC Cancer. 2018;18(1):693.

Wang-Gillam A, Li C-P, Bodoky G, 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):545-557.

Poster Presenter(s)

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clinical studies

Raltitrexed–eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer

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Limited information on salvage treatment in patients affected by pancreatic cancer is available. At failure, about half of the patients present good performance status (PS) and are candidate for further treatment. Patients >18 years, PS ⩾50, with metastatic pancreatic adenocarcinoma previously treated with gemcitabine-containing chemotherapy, and progression-free survival (PFS) <12 months received a combination of raltitrexed (3 mg m^{-2}) and oxaliplatin (130 mg m^{-2}) every 3 weeks until progression, toxicity, or a maximum of six cycles. A total of 41 patients received 137 cycles of chemotherapy. Dose intensity for both drugs was 92% of the intended dose. Main grade >2 toxicity was: neutropenia in five patients (12%), thrombocytopenia, liver and vomiting in three (7%), fatigue in two (5%). In total, 10 patients (24%) yielded a partial response, 11 a stable disease. Progression-free survival at 6 months was 14.6%. Median survival was 5.2 months. Survival was significantly longer in patients with previous PFS >6 months and in patients without pancreatic localisation. A clinically relevant improvement of quality of life was observed in numerous domains. Raltitrexed–oxaliplatin regimen may constitute a treatment opportunity in gemcitabine-resistant metastatic pancreatic cancer. Previous PFS interval may allow the identification of patients who are more likely to benefit from salvage treatment.
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Keywords: chemotherapy; metastatic disease; oxaliplatin; pancreatic cancer; raltitrexed; salvage therapy

Pancreatic adenocarcinoma has a dismal prognosis due to early metastatic dissemination even in patients submitted to surgery with radical intent. As a consequence, effective systemic treatment has a strategic role in the therapeutic management of this disease. Unfortunately, very few agents have demonstrated any activity with reproducible response rates greater than 15%. While randomised studies have suggested that chemotherapy is superior to best supportive care in prolonging survival and improving symptoms in patients with advanced disease (Glimelius *et al*, 1996), standard single agent gemcitabine yields a marginal impact on disease outcome. Median progression-free survival (PFS) with this agent is approximately 3 months (Burris *et al*, 1997; Bramhall *et al*, 2001, 2002; Berlin *et al*, 2002; Moore *et al*, 2003; Rocha Lima *et al*, 2004; Van Cutsem *et al*, 2004; Reni *et al*, 2005), and <15% of patients are PF at 6 months (PFS-6) from diagnosis (Reni *et al*, 2005). Approximately half of the patients failing previous treatment present good performance status (PS) and are willing to undergo further treatment. However, very limited information concerning the impact of salvage treatment upon survival and quality of life is available. This patient population represents the target for experimental trials aimed at broadening the chemotherapeutic armamentarium. Raltitrexed (Tomudex® AstraZeneca S.p.A., Ben Venue Laboratories Inc., Bedford, OH, USA) is a thymidylate synthase inhibitor that is easily transported in the cell, where it undergoes extensive polyglutamation within the cells, which extends the intracellular retention, increases concentration, and ultimately leads to increased cytotoxicity. Raltitrexed blocks the production of thymidine monophosphate from deoxyuridine monophosphate in a reaction-specific manner. Oxaliplatin (Eloxatin®, Sanofi-Synthelabo S.p.A, Milan, Italy), a third-generation platinum analogue, is a diaminocyclohexane platinum that forms interstrand DNA adducts, which differ from those formed by cisplatin or carboplatin in their capability to overcome resistance mechanisms. Preclinical studies suggested that pancreatic cancer cell lines are highly sensitive towards raltitrexed and oxaliplatin even in gemcitabine- and 5-fluorouracil-resistant cells (Kornmann *et al*, 2000; Monti *et al*, 2004), and that oxaliplatin yields an addictive antitumour activity when combined with raltitrexed or other thymidylate synthase inhibitors (Raymond *et al*, 1998), thus encouraging the use of these two drugs in experimental protocols as salvage treatment (Monti *et al*, 2004). Furthermore, raltitrexed and oxaliplatin have a noncrossresistant mode of action, differential toxicity profiles, and can be used in combination as outpatient therapy in the same doses as for single agent use (Fizazi *et al*, 2000).

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Raltitrexed-oxaliplatin (TOM-OX) combination has been assessed in colorectal cancer and mesothelioma yielding elevated tumour control rates in 5-fluorouracil or cisplatin pretreated patients (Cascinu *et al*, 2002; Seitz *et al*, 2002). Single agent raltitrexed obtained 5% partial response (PR) and 29% stable disease (SD) in 42 patients with pancreatic adenocarcinoma (Pazdur *et al*, 1996).

A multicentre phase II trial was undertaken to determine the activity and safety of TOM-OX combination as salvage treatment in gemcitabine-resistant metastatic pancreatic cancer.

PATIENTS AND METHODS

Patient population

Patients aged >18 years with histologically or cytologically proven metastatic pancreatic adenocarcinoma, with at least one bidimensionally measurable target lesion were eligible for this study. Patients were to have received previous gemcitabine-containing chemotherapy. No definition of gemcitabine resistance in pancreatic cancer exists and no other trial has used this eligibility criterion. Thus, in the absence of benchmarks to which to refer, it was arbitrarily decided to include only those patients in whom progression occurred <12 months from the start of treatment (i.e. <6 months from treatment conclusion) as it was deemed unlikely that these patients could achieve relevant benefit with further gemcitabine administration. Other inclusion criteria were: Karnofsky PS $\geqslant$50, adequate bone marrow (absolute neutrophil count (ANC) $\geqslant$1500 cells mm^{-3}, platelet count $\geqslant$100 000 cells mm^{-3}, and haemoglobin $\geqslant$10 g dl^{-1}); kidney function (creatinine clearance $\geqslant$65 ml min^{-1}) and liver function (serum total bilirubin $\leqslant$2 mg dl^{-1}, alkaline phosphatase and serum transaminases $\leqslant$three times the upper limit of normal (ULN)). Patients with prior malignancy were ineligible for the study, with the exception of those who had had basal-cell carcinoma of the skin, carcinoma *in situ* of the cervix, or other cancer for which the patient had been disease free for at least 5 years. Patients with ampullary tumours or other histologic variants of pancreatic carcinoma were ineligible. The study was reviewed and approved by each local Ethics Committee of the participating institutions and was conducted in accordance with the Declaration of Helsinki. All participating patients were required to provide written informed consent.

Treatment plan

Raltitrexed was diluted in 5% dextrose and given as 15 min intravenous (i.v.) infusion at 3 mg m^{-2}. After a 45 min interval, oxaliplatin was administered in at least 2 h i.v. infusion at 130 mg m^{-2}. Patients were systematically given prophylactic antiemetic treatment with 5-HT3 antagonists. Cycles were repeated every 3 weeks until PD, unacceptable toxicity, patient's or physician's decision, or a maximum of six cycles. Dose adjustments were made according to the greatest degree of toxicity. In the case of ANC <1500 cells mm^{-3}, of platelet count <100 000 cells mm^{-3}, or of $\geqslant$grade 3 nonhaematological toxicity, on the first day of the next cycle, the treatment was withheld until recovery and then restarted with dose for the drug responsible for nonhaematological toxicity reduced by 25%. If recovery was not evident within 2 weeks, the patient was discontinued from the study. If grade 3 or grade 4 haematological toxicity occurred, doses for both drugs were reduced by 25% or by 50%, respectively. Treatment was discontinued in cases of grade 4 haematological toxicity associated with grade 3 gastro-intestinal toxicity. If grade 2 or grade 3 gastro-intestinal toxicity occurred, raltitrexed dose was to be reduced by 25% or by 50%, respectively. Treatment was discontinued in cases of grade 4 gastro-intestinal toxicity. In cases of decreased creatinine clearance, raltitrexed was administered every 4 weeks at 75% (55–65 ml min^{-1}) or 50% (25–54 ml min^{-1}) of the original dose. Raltitrexed was discontinued if creatinine clearance fell below 25 ml min^{-1}. The oxaliplatin dose was to be reduced to 100 mg m^{-2} in cases of paraesthesia or dysesthesia with pain or functional impairment lasting >7 days, to 80 mg m^{-2} for persistent paraesthesia or dysesthesia between two cycles without functional impairment, or discontinued in cases with persistent paraesthesia or dysesthesia between two cycles with functional impairment.

Study evaluations

Pretreatment evaluation consisted of PS assessment, haematological and biochemical profiles, CA 19-9 analysis, spiral computed tomography (CT) scan of the abdomen, and the chest or magnetic resonance imaging (MRI). During treatment, blood chemistry, creatinine clearance, and CA 19-9 analysis was performed on day 14, whereas haematological profile was repeated on day 1 of every cycle. Imaging studies, employing the same method used to measure the initial target, were repeated every two treatment cycles to assess objective response. At the end of chemotherapy, CA 19-9 analysis was performed every 40–50 days, and imaging studies were repeated every 2–3 months, when an increase of CA 19-9 was observed, or when PD was suspected. The EORTC QLQ-C30 (Aaronson *et al*, 1993) and PAN26 (Fitzsimmons *et al*, 1999) questionnaires for quality of life (QOL) assessment were given to patients at study entry and every second cycle of chemotherapy, until PD.

Outcome measures

Side effects were graded according to the Common Toxicity Criteria defined by the NCI (US), extended by the NCIC (Canada) version 2.0 (Ajani *et al*, 1990). The objective tumour response to treatment was assessed according to the WHO criteria on the basis of a maximum of three 'target lesions' selected before the start of the treatment. All scans were centrally reviewed by one expert radiologist. The duration of complete response was defined as the time between the first documentation of complete disease resolution and the first documented observation of PD. The duration of PR was defined as the time between the initiation of treatment and the time of PD. The PFS was defined as the interval between the initiation of treatment and the occurrence of PD. Survival (OS) was measured from the initiation of treatment to the date of death for any reason or to the last follow-up assessment. The QOL was assessed using the EORTC QLQ-C30 questionnaire (Aaronson *et al*, 1993) supplemented by the pancreatic cancer module (EORTC QLQ-PAN-26) (Fitzsimmons *et al*, 1999). Differences >10 points on the transformed scales were regarded as clinically significant (Osoba *et al*, 1998). Mean scale and items scores were transformed to a 0–100 scale, as described in the EORTC scoring manual (Fayers *et al*, 2001). To be assessable for QOL, patients had to have a baseline QOL assessment and at least one subsequent QOL assessment. The numbers of patients in each analysis may differ from scale to scale as some patients may have had randomly missing scores on certain scales.

Statistical analysis

The primary end point of this trial was to assess the objective response rate of TOM-OX in gemcitabine-resistant metastatic pancreatic adenocarcinoma. Secondary end points were PFS, OS, toxicity, response duration, and QOL. The Simon Minimax two-stage design was used. The maximum response rate considered of low interest was 10% and the minimum response rate considered of interest was 25%. The sample size was calculated with a type I error of 10% and a test power of 90%. Early discontinuation of the

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study was planned in the case of <3 responses in the first 27 patients. Alternatively, the target enrollment was estimated to be 40 patients. TOM-OX would be considered an active regimen in this patient population if >6 responses were noted among the 40 enrolled patients. All the statistical analyses were performed on the intention-to-treat population. The survivor functions curves were estimated according to the Kaplan–Meier method and compared using the log-rank test. All the probability values were from two-sided tests. Analyses were carried out using the Statistica 4.0 statistical package for Windows (1993 Statsoft, Tulsa, OK, USA).

Funding source

Raltitrexed and oxaliplatin were supplied gratuitously by AstraZeneca, Italy and Sanofi-Synthelabo, Italy. No funding sources supported the work.

RESULTS

Patient population

Between December 2002 and March 2004, 41 patients were entered into this trial. The characteristics of the patient population are listed in Table 1. Previous PFS, which was calculated as the interval between the initiation of latest chemotherapy treatment and the occurrence of PD, was 1–11.5 months (median 6). With regard to previous treatment, 16 of 18 patients submitted to surgery with curative intent received postoperative chemotherapy, which was followed by radiotherapy in 10 cases, while two patients were submitted to postoperative chemoradiation and received gemcitabine at the time of first recurrence. Two of the 23 patients who did not receive prior surgery were irradiated. Among 35 patients receiving a single prior chemotherapy, treatment consisted of gemcitabine alone in 17 patients, PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen (Reni *et al*, 2005) in 16 patients, gemcitabine plus cisplatin or 5-fluorouracil in one case each. Among six patients receiving either two ($n=5$) or three ($n=1$) prior chemotherapy lines, first-line treatment consisted of gemcitabine in all cases and was followed as second-line treatment by PEFG regimen ($n=5$) or 5-fluorouracil and folinic acid ($n=1$); one patient also received mitomycin-C after gemcitabine and PEFG regimen, as third-line treatment. In total, 26 patients had PD during previous chemotherapy, and 15 had an interval <5 months between the end of previous therapy and PD.

Table 1 Patient characteristics at baseline

Characteristic	*n* (%)
Patients enrolled	41
Age (years)	
Median	61
Range	25–80
Sex	
Male	23 (56)
Female	18 (44)
Karnofsky PS	
70–80	16 (39)
90–100	25 (61)
Site of metastases	
Liver	33 (80)
Lymphnodes	8 (20)
Lung	12 (29)
Peritoneum	5 (12)
Number of metastatic lesions	
1	1 (2)
2–5	24 (59)
>5	16 (39)
Prior therapy	
Prior pancreatic surgery	18 (44)
Prior radiotherapy	14 (34)
Prior chemotherapy lines	
n = 1	35 (85)*
n > 1	6 (15)
*Gemcitabine alone	17 (49)
*Combination	18 (51)

PS = performance status; *n* = number. *In all, 35 patients received 1 prior chemotherapy line. Of those, 17 received Gemcitabine alone and 18 received a combination chemotherapy.

Treatment summary and toxicity

A total of 137 cycles were delivered. Total number of cycles per patient is reported in Table 2. In all, 13 (32%) patients received six cycles, while 28 discontinued treatment due to radiologically confirmed PD (16), clinical PD without radiological assessment (five), patient or medical decision (five), persistent thrombocytopenia (one), and death of heart failure (one). Dose intensity was 92% for both drugs. The mean interval between cycles was 22.8 days. The start of a new cycle was delayed by 7–14 days in 18 cycles (13%) due to persistent neutropenia ($n=6$) or thrombocytopenia ($n=1$), fever ($n=1$), liver toxicity ($n=2$), bowel subocclusive status ($n=1$), delay in CT scan reassessment ($n=2$), patient or medical decision ($n=5$). Raltitrexed dose was reduced in five (12%) patients either by 50% due to G3 vomiting ($n=1$) or by 25% due to grade 2 liver toxicity ($n=1$) or fatigue ($n=3$). Oxaliplatin dose was reduced in four (10%) patients by 25% due to G3 liver toxicity ($n=1$), G2 liver toxicity, or fatigue ($n=1$ each).

Table 3 summarises the main side effects observed. One patient died on day 1 of the third cycle due to heart failure. Febrile neutropenia, or non-neutropenic infections were not observed.

Response and survival

Table 4 summarises the outcome measures. The central radiology independent review showed 10 PR (24%; 95% confidence interval

Table 2 Treatment summary

Number of cycles	Number of patients
1	6
2	18
3	1
4	1
5	2
6	13

Table 3 Treatment-related toxicity per cycle (and worst ever by patient)

Toxicity	Grade 0	Grade 1/2	Grade 3	Grade 4	NA
Granulocytes	66 (63)	22 (22)	3 (5)	3 (7)	6 (2)
Platelets	70 (61)	22 (29)	2 (5)	1 (2)	6 (2)
Haemoglobin	39 (29)	54 (66)	1 (2)	0	6 (2)
Stomatitis	98 (93)	2 (7)	0	0	0
Nausea/vomiting	61 (46)	36 (46)	3 (5)	1 (2)	0
Diarrhoea	90 (76)	9 (22)	1 (2)	0	0
Neurologic	81 (68)	19 (32)	0	0	0
Fatigue	72 (49)	27 (46)	2 (5)	0	0
Liver (GOT/GPT)	62 (49)	30 (41)	2 (5)	1 (2)	6 (2)
Liver (GGT/Alk.P)	88 (83)	5 (12)	1 (2)	0	6 (2)
Fever	92 (80)	8 (20)	0	0	0
Kidney	98 (93)	2 (7)	0	0	0

Numbers are expressed as percentages. NA = not available.

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Table 4 Activity and efficacy analyses summary

	Best response		Outcome measures	
Previous treatment	**PR**	**SD**	**PFS-6**	**OS-12**
All patients ($n=41$)	10 (24.4%)	11 (26.8%)	6 (14.6%)	5 (12.2%)
PEFG ($n=16$)	3 (18.7%)	6 (37.5%)	3 (18.8%)	4 (25.0%)
G ($n=17$)	5 (29.4%)	4 (23.5%)	2 (11.8%)	0 (0.0%)
G⇒PEFG ($=5$)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)
F including				
y ($n=23$)	5 (21.7%)	7 (30.4%)	4 (17.4%)	5 (21.7%)
n ($n=18$)	5 (27.8%)	4 (22.2%)	2 (11.8%)	0 (0.0%)
P including				
y ($n=22$)	3 (13.6%)	7 (31.8%)	3 (13.6%)	4 (18.2%)
n ($n=19$)	7 (36.8%)	4 (21.1%)	3 (15.8%)	1 (5.3%)
n of lines				
1 ($n=35$)	9 (25.7%)	10 (28.6%)	6 (17.1%)	5 (14.3%)
>1 ($n=6$)	1 (16.6%)	1 (16.6%)	0 (0.0%)	0 (0.0%)

n = number; PR = partial response; SD = stable disease; PFS-6 = progression-free at 6 months; OS-12 = alive at 12 months; P = cisplatin; E = epirubicin; F = 5-fluorouracil; G = gemcitabine; y = yes; n = no; ⇒ = followed by.

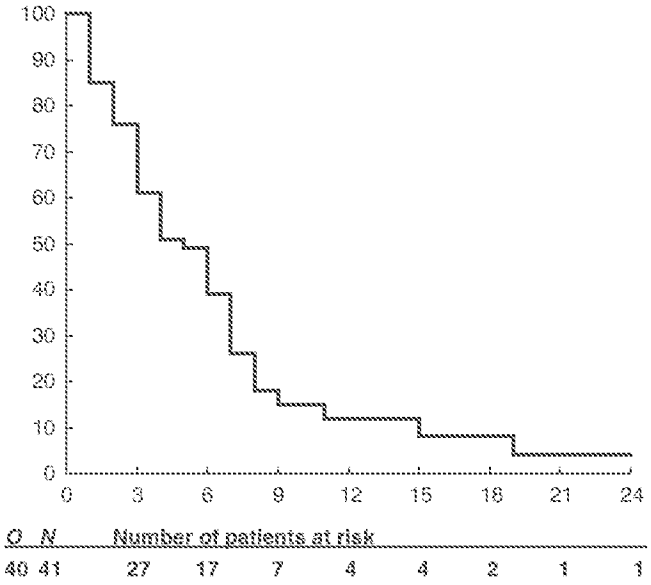


Figure 1 Overall survival. N = number of eligible patients. O = total number of events at the final analysis. Subsequent numbers are the number of patients at risk.

(95% CI) 11–37%), 11 SD (27%; 95% CI 13–41%), 15 PD (37%; 95% CI 22–52%), while five patients (12%; 95% CI 2–22%) discontinued chemotherapy before tumour assessment due to clinical PD. Median duration of PR was 5.6 months (interquartile range: 4.3–6.4 months) and five of 10 patients with PR were PF at 6 months. Median duration of SD was 4.0 months (interquartile range 3.1–4.5 months) and one of 11 patients with SD was PF at 6 months. Of 35 patients, 13 (37%; 95% CI 20–54%) with elevated CA19.9 basal value had a marker reduction of >50% during treatment.

All patients, apart from one dying from heart failure while PF, had PD. In the five patients without radiological documentation of PD, PFS was calculated as the interval between treatment initiation and death. Median and 6-month PFS was 1.8 months (interquartile range: 1.2–4.5 months) and 14.6% (95% CI 4.6–24.6%; Table 4). A total of 40 patients died. One is alive at 29 months. Median and 1-year OS was 5.2 months (interquartile range: 2.3–7.5 months) and 12.2% (95% CI 2.2–22.2%; Figure 1; Table 4), respectively. Median survival for patients with PR, SD, and PD was 7.4, 6.8, and 2.5 months, respectively. Median survival was 2.9 months for 22 patients without CA19.9 reduction and 7.4 months for 13 patients with CA19.9 reduction >50% ($P=0.006$).

Quality of life

At baseline, questionnaires were completed by 29 patients (71%). Two of those had PD after the first cycle, while three patients completed only baseline questionnaires. Thus, 24 patients (59%) were assessable for QOL analysis. In this subset of patients, a clinically significant improvement in QOL relative to baseline was observed in health-care satisfaction (50%), body image (42%), fear for future health (40%), pain (39%), sexuality, digestive symptoms (33%), QOL 1 and 2 (30–35%), altered bowel habit and cachexia (30%), cognitive functioning, hepatic symptoms, pancreatic pain (29%), physical functioning, fatigue (26%), nausea, and appetite loss (24%).

Exploratory analyses

As the aim of salvage treatment in metastatic pancreatic cancer is palliative, exploratory analyses of the impact of TOM-OX on OS in subgroups of patients were performed in an attempt to identify those who could receive the greatest benefit from treatment (significance level after multiple comparison adjustment: 0.0036). Previous chemotherapy including 5-fluorouracil or cisplatin did not reduce the probability to be PF at 6 months or alive at 12 months after TOM-OX (Table 4). When considering patients who received only one prior chemotherapy line, no significant difference in OS was observed among 16 patients previously treated by PEFG when compared to 17 patients treated by gemcitabine alone (1-year OS 25.0 *vs* 0%; $P=0.018$). A summary of univariate and multivariate analyses of the relationship between OS and patient-, treatment-, and tumour-related variables is reported in Table 5. Overall survival was significantly longer in patients with previous PFS ranging between 6.1 and 12 months relative to those with shorter PFS and in patients without pancreatic localisation. A trend towards longer OS was observed in patients submitted to previous surgery. A multivariate analysis by the Cox proportional hazard model confirmed that previous PFS and pancreatic localisation were significantly predictive of survival (Table 5).

DISCUSSION

The present trial showed that TOM-OX regimen was feasible, had limited toxicity and relevant activity in patients with gemcitabine-resistant metastatic pancreatic adenocarcinoma, and may constitute a treatment opportunity in this setting. It is noteworthy that this regimen was also active in patients with 5-fluorouracil- or cisplatin-resistant disease. Until a decade ago, the use of chemotherapy in pancreatic cancer was believed to have no role in the routine treatment of patients with advanced disease (Lionetto *et al*, 1995). A few options are currently available for first-line treatment (Burris *et al*, 1997; Moore *et al*, 2005; Reni *et al*, 2005). However, gemcitabine-based chemotherapy yields a very limited disease control, and progression usually occurs within a few months after starting first-line treatment. As no further standard therapeutic option exists and scarce information on the impact on outcome of salvage therapy is available, prospective trials attempting to widen the therapeutic armamentarium against this disease are warranted. So far, very few studies have investigated salvage chemotherapy after failure of gemcitabine or gemcitabine-containing chemotherapy (Stehlin *et al*, 1999; Oettle *et al*, 2000; Ulrich-Pur *et al*, 2003; Cantore *et al*, 2004; Milella *et al*,

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Table 5 Exploratory analyses summary

				Univariate		Multivariate	
Variable	**Subgroups**	**No. of patients**	**1 year OS (%)**	***P***	**HR**	**95% CI**	***P***
PFS	< 6 months	22	0.0				
	≥ 6 months	19	21.1	0.0035	4.27	1.56–11.67	0.007
Surgery	Yes	18	22.2				
	No	23	0.0	0.0049	2.26	0.48–10.79	0.31
CHT lines	1	6	11.4				
	> 1	35	0.0	0.1278	1.49	0.38–5.83	0.58
Age	≤ 60	19	15.8				
	> 60	22	4.5	0.3362	1.27	0.50–3.21	0.62
Gender	Male	23	17.4				
	Female	18	0.0	0.0296	0.52	0.23–1.19	0.13
PS	90–100	25	12.0				
	70–80	16	6.2	0.2882	1.29	0.49–3.38	0.61
Radiotherapy	Yes	14	11.1				
	No	27	7.1	0.3601	0.78	0.34–1.80	0.56
No. of lesions	2–5	24	4.2				
	> 5	16	18.8	0.4529	0.62	0.18–2.12	0.45
Site: liver	Yes	33	9.1				
	No	8	12.5	0.4891	0.96	0.32–2.88	0.94
Site: lung	Yes	12	16.7				
	No	29	6.9	0.4457	1.06	0.31–3.58	0.93
Site: pancreas	Yes	26	0.0				
	No	15	26.7	0.0011	3.46	1.34–53.4	0.03
Site: peritoneum	Yes	5	0.0				
	No	36	11.1	0.3860	0.37	0.03–1.76	0.22
No. of sites	1	7	42.9				
	> 1	34	2.9	0.0080	0.70	0.14–3.42	0.66

No = number; CHT = chemotherapy; PFS = progression-free survival; OS = overall survival; PS = performance status; HR = hazard ratio; CI = confidence interval.

Table 6 Results of salvage therapy for pancreatic adenocarcinoma

Ref	**No. of pts**	**Treatment**	**m. age**	**PS 0**	**M (%)**	**liver M (%)**	**> 1 CHT (%)**	**PPFS**	**ORR (%)**	**mPFS**	**PFS-6 (%)**	**1 year OS (%)**
7	30	I+E	60	30	100	60	23	Nr	10	4.1	Nr	23
15[a]	34	G-FLIP	64	Nr	100	85	29	Nr	24	3.9	20	20
17	17	F+celecoxib	60	35	82	Nr	0	Nr	35	1.9	6	20
21	18	T	59	Nr	100	Nr	22	7.9	5.5	3.3	Nr	Nr
26	15	MDI	61	26	100	60	20	Nr	0	1.7	0	0
29	33	Ru	62	0	73	57	Nr	Nr	9	Nr	Nr	6
30	19	R	60	21	100	74	0	Nr	0	2.5	Nr	0
30	19	R+I	63	21	100	63	0	Nr	16	4.0	Nr	22
cs	41	R+E	61	61	100	80	15	6.0	24	1.8	15	12

Ref = reference; No. of pts = number of patients; m. age = median age; PS 0 = performance status = 0 (ECOG) or 90–100 (Karnofsky); M = metastatic; CHT = % of patients with > 1 previous chemotherapy lines; PPFS = previous progression-free survival; ORR = objective response rate; m PFS = median progression-free survival; PFS-6 = progression-free survival at 6 months; 1 year OS = overall survival at 1 year; cs = current series; I = irinotecan; E = oloxatin; G = gemcitabine; F = 5-fluorouracil; L = leucovorin; P = cisplatin; T = paclitaxel; M = mitomycin; D = docetaxel; Ru = rubitecan; R = raltitrexed; Nr = not reported. [a]Retrospective.

2004; Reni *et al*, 2004), one of which was retrospective (Kozuch *et al*, 2001). The populations selected were different in terms of proportion of patients with PS > 80, which ranged from 0 to 61%, metastatic patients (73–100%), patients with liver metastases (57–85%), patients with > 1 prior chemotherapy lines (0–29%), and median PFS after previous treatment (6.0–7.9 months), which was rarely reported in other series, while in our exploratory analyses it resulted as an independent factor predicting the outcome of salvage therapy (Table 6). Furthermore, the sample size of most series is limited to < 20 patients per treatment arm (Oettle *et al*, 2000; Ulrich-Pur *et al*, 2003; Milella *et al*, 2004; Reni *et al*, 2004), thus producing data with very large CIs. Given these differences,

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the lack of information on important prognostic factors, and other potential bias related to phase II trial design, results are difficult to compare across trials, especially in terms of survival. Activity observed in the current trial (PR: 24%) was consistent with the response rate of 16–35% previously reported with other active regimens (Kozuch *et al*, 2001; Ulrich-Pur *et al*, 2003; Milella *et al*, 2004) and compares favourably with the 0–10% objective responses reported elsewhere (Stehlin *et al*, 1999; Oettle *et al*, 2000; Ulrich-Pur *et al*, 2003; Cantore *et al*, 2004; Reni *et al*, 2004). The median PFS of 1.8 months observed with TOM-OX regimen was slightly shorter than the median PFS of 1.7–4.1 months reported in other series (Stehlin *et al*, 1999; Oettle *et al*, 2000; Kozuch *et al*, 2001; Ulrich-Pur *et al*, 2003; Cantore *et al*, 2004; Milella *et al*, 2004; Reni *et al*, 2004). However, it is likely that this depended on the timing of radiographic assessment, which was performed more frequently in the current trial and was therefore more prone to intercept early PD. Consistently, PFS-6 was identical in our series and in the retrospective series which had previously obtained the longest median PFS among published series (Kozuch *et al*, 2001). With regard to grade 3–4 toxicity, neutropenia (12%), nausea/vomiting (7%), and liver enzymes increase (7%) observed in our series were within the range reported with other regimens (5–38, 3–14, and 5–13%, respectively). Fatigue (5%) was reported in a single series (10% (Reni *et al* 2004)). Diarrhoea (2%) was observed less often relative to other series (3–10%). Of note, less toxicity was observed in our series relative to TOM-OX when administered to patients with metastatic colorectal cancer (Cascinu *et al*, 2002; Seitz *et al*, 2002), namely, 17–33% liver toxicity, 10–30% neutropenia, 5–13% nausea-vomiting, 11–16% fatigue, and 7–17% diarrhoea were reported in metastatic colorectal cancer (Cascinu *et al*, 2002; Seitz *et al*, 2002). The differences in toxicity may reflect different selection of patients (e.g. in terms of PS) and may suggest that toxicity profile could be different in different tumour sites. As the aim of salvage therapy in patients with metastatic pancreatic cancer is purely palliative, some concern could be raised that the improvement in clinical outcome is not achieved at the cost of impaired QOL. Clinical benefit response was proposed to address this issue (Burris *et al*, 1997). However, this measure was not validated and has been criticised for using selected variables that do not reflect QOL (Hoffman and Glimelius, 1998). Thus, we preferred a more reliable and validated measure, such as the EORTC QLQ questionnaire. No data to which to compare the present findings are available in the literature. Raltitrexed–oxaliplatin regimen yielded a clinically significant improvement relative to baseline in a large proportion of patients in several QOL domains, including most of the important symptoms that are frequently associated with pancreatic cancer.

Altogether, a median overall survival of 3.5–10 months and median PFS of 2–4 months was achieved with active salvage therapy. It is of note that 12–23% patients with metastatic disease are alive at 1 year from salvage treatment start (current series, Kozuch *et al*, 2001; Ulrich-Pur *et al*, 2003; Cantore *et al*, 2004; Milella *et al*, 2004). These figures are similar to those observed after gemcitabine in the first-line setting. While a bias in favour of salvage therapy due to better selection of patients cannot be ruled out, these data suggest that an appropriately selected subset of patients, for example, on the basis of previous PFS, with gemcitabine-refractory disease may yield a relevant clinical and survival benefit from further treatment. This hypothesis should be tested in a phase III trial against best supportive care.

REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F on behalf of the EORTC Quality of Life Study Group (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* **2**: 319–325

Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH (1990) Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Invest* **8**: 147–159

Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson III AB (2002) Phase III study of gemcitabine in combination with fluorouracil *vs* gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* **20**: 3270–3275

Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA, for the Marimastat Pancreatic Cancer Study Group (2001) Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol* **19**: 3447–3455

Bramhall SR, Schultz J, Nemunaitis J, Brown PD, Baillet M, Buckels JAC (2002) A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* **87**: 161–167

Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* **15**: 2403–2413

Cantore M, Rabbi C, Fiorentini G, Oliani C, Zamagni D, Iacono C, Mambrini A, Del Freo A, Manni A (2004) Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. *Oncology* **67**: 93–97

Cascinu S, Graziano F, Ferraù F, Catalano V, Massacesi C, Santini D, Silva RR, Barni S, Zaniboni A, Battelli N, Siena S, Giordani P, Mari D, Baldelli AM, Antognoli S, Maisano R, Priolo D, Pessi MA, Tonini G, Rota S, Labianca R (2002) Raltitrexed plus oxaliplatin (TOMOX) as first-line chemotherapy for metastatic colorectal cancer. A phase II study of the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD). *Ann Oncol* **13**: 716–720

Fayers P, Aaronson N, Bjordal K, Curran D, Groenvold M (2001) *EORTC QLQ Scoring Manual*, 3rd edn. Brussels, Belgium: European Organization for Research and Treatment of Cancer

Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, Beger HG, Birk D, Buchler MW, Dervenis C, Fernandez Cruz L, Friess H, Grahm AL, Jeekel J, Laugier R, Meyer D, Singer MW, Tihanyi T (1999) Development of a disease specific Quality of Life questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. *Eur J Cancer* **35**: 939–941

Fizazi K, Ducreux M, Ruffie P, Bonnay M, Daniel C, Soria JC, Hill C, Fandi A, Poterre M, Smith M, Armand JP (2000) Phase I, dose-finding, and pharmacokinetic study of raltitrexed combined with oxaliplatin in patients with advanced cancer. *J Clin Oncol* **18**: 2293–2300

Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, Linne T, Svensson C (1996) Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* **7**: 593–600

Hoffman K, Glimelius B (1998) Evaluation of clinical benefit of chemotherapy in patients with upper gastrointestinal cancer. *Acta Oncol* **37**: 651–659

Kornmann M, Fakler H, Butzer U, Beger HG, Link KH (2000) Oxaliplatin exerts potent *in vitro* cytotoxicity in colorectal and pancreatic cancer cell lines and liver metastases. *Anticancer Res* **20**: 3259–3264

Kozuch P, Grossbard ML, Barzdins A, Araneo M, Robin A, Prager D, Homel P, Marino J, DeGregorio P, Brucner HW (2001) Irinotecan combined with gemcitabine, 5-fluorouracil, leucovorin, and cisplatin (G-FLIP) is an effective and non crossresistant treatment for chemotherapy refractory metastatic pancreatic cancer. *Oncologist* **6**: 488–495

Lionetto R, Pugliese V, Bruzzi P, Rosso R (1995) No standard treatment is available for advanced pancreatic cancer. *Eur J Cancer* **6**: 882–887

Milella M, Gelibter A, Di Cosimo S, Bria E, Ruggeri EM, Carlini P, Malaguti P, Pellicciotta M, Terzoli E, Cognetti F (2004) Pilot study of celecoxib and

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CSPC Exhibit 1101
Page 34 of 314

infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. *Cancer* **101:** 133 – 138

Monti P, Marchesi F, Reni M, Mercalli A, Sordi V, Allavena P, Piemonti L (2004) Pancreatic cancer *in vitro* biology: a comprehensive characterization of pancreatic ductal carcinoma cell line behaviour and chemosensitivity for translational research. *Virchow's Arch* **445:** 236 – 247

Moore MJ, Goldstein D, Hamm J, Kotecha J, Gallinger S, Au HJ, Nomikos D, Ding K, Ptaszynski M, Parulekar W (2005) Erlotinib improves survival when added to gemcitabine in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG). Proceedings of the Gastrointestinal Cancers Symposium; 27 – 29 January 2005; Hollywood, FL, USA, p 3: abstract 77

Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, Fields A, Hagan K, Greenberg B, Colwell B, Zee B, Tu D, Ottaway J, Humphrey R, Seymour L (2003) Comparison of gemcitabine *vs* the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* **21:** 3296 – 3302

Oettle H, Arnold D, Esser M, Huhn D, Riess H (2000) Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma. *Anti-Cancer Drugs* **11:** 635 – 638

Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* **16:** 139 – 144

Pazdur R, Meropol NJ, Casper ES, Fuchs C, Douglass Jr HO, Vincent M, Abbruzzese JL (1996) Phase II trial of ZD1694 (Tomudex) in patients with pancreatic cancer. *Invest New Drugs* **13:** 355 – 358

Raymond E, Chaney SG, Taamma A, Cvitkovic E (1998) Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* **9:** 1053 – 1071

Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V (2005) Gemcitabine *vs* cisplatin, epirubicin, 5-fluorouracil, gemcitabine in advanced pancreatic cancer: a phase III trial. *Lancet Oncol* **6:** 369 – 376

Reni M, Panucci MG, Passoni P, Bonetto E, Nicoletti R, Ronzoni M, Zerbi A, Staudacher C, Di Carlo V, Villa E (2004) Salvage chemotherapy with mitomycin, docetaxel, and irinotecan (MDI regimen) in metastatic pancreatic adenocarcinoma: a phase I and II trial. *Cancer Invest* **22:** 688 – 696

Rocha Lima CMS, Green MR, Rotche R, Miller Jr WH, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL (2004) Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* **22:** 3776 – 3783

Seitz JF, Bennouna J, Paillot B, Gamelin E, Francois E, Conroy T, Raoul JL, Becouarn Y, Bertheault-Cvitkovic F, Ychou M, Nasca S, Fandi A, Barthelemy P, Douillard JY (2002) Multicenter non-randomized phase II study of raltitrexed (Tomudex) and oxaliplatin in non-pretreated metastatic colorectal cancer patients. *Ann Oncol* **13:** 1072 – 1079

Stehlin JS, Giovanella BC, Natelson EA, Deipolyi PD, Coil D, Davis B, Wolk D, Wallace P, Trojacek A (1999) A study of 9-nitrocamptothecin (RFS-2000) in patients with advanced pancreatic cancer. *Int J Oncol* **14:** 821 – 831

Ulrich-Pur H, Raderer M, Kornek GV, Schull B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W (2003) Irinotecan plus raltitrexed *vs* raltitrexed alone in patients with gemcitabine-pretreated advanced adenocarcinoma. *Br J Cancer* **88:** 1180 – 1184

Van Cutsem E, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, Schoffski P, Post S, Verslype C, Neumann H, Safran H, Humblet Y, Perez Ruixo J, Ma Y, Von Hoff D (2004) Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* **22:** 1430 – 1438

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A phase II study of erlotinib in gemcitabine refractory advanced pancreatic cancer

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Abstract ***Background:*** Erlotinib induced skin toxicity has been associated with clinical benefit in several tumour types. This phase II study evaluated the efficacy of erlotinib, dose escalated to rash, in patients with advanced pancreatic cancer previously treated with gemcitabine.
Methods: Erlotinib was given at an initial dose of 150 mg/day, and the dose was escalated by 50 mg every 2 weeks (to a maximum of 300 mg/day) until >grade 1 rash or other dose limiting toxicities occurred. Erlotinib pharmacokinetics were performed, and baseline tumour tissue was collected for mutational analysis and epidermal growth factor receptor (EGFR) expression. The primary end-point was the disease control rate (objective response and stable disease >8 weeks).
Results: Fifty-one patients were accrued, and 49 received treatment. Dose-escalation to 200–300 mg of erlotinib was possible in 9/49 (18%) patients. The most common ⩾grade 3 adverse events included fatigue (6%), rash (4%) and diarrhoea (4%). Thirty-seven patients were evaluable for response, and the best response was stable disease in 12 patients (32% (95% confidence interval (CI) 17–47%)). Disease control was observed in nine patients (24% (95% CI: 10–38%)). Median survival was 3.8 months, and 6 month overall survival rate was 32% (95% CI 19–47%). Mutational analysis and EGFR expression were performed on 29 patients, with 93% having *KRAS* mutations, none having *EGFR* mutations, and 86% expressing EGFR. Neither *KRAS* mutational status nor EGFR expression was associated with survival.
Conclusions: Erlotinib dose escalated to rash was well tolerated but not associated with significant efficacy in non-selected patients with advanced pancreatic cancer.
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1. Introduction

Pancreatic cancer continues to be one of the leading causes of cancer related death [1]. Despite recent advances in therapy, median survival remains poor and the majority of patients survive for less than 1-year [2]. Gemcitabine has been regarded as the standard backbone of systemic therapy for advanced pancreatic cancer based upon a 1997 trial comparing gemcitabine versus fluorouracil that demonstrated an improvement in median and 1-year survival [3]. More recent data suggest that FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) or a combination of gemcitabine and nab-paclitaxel [33] may be a preferable first line options in patients with good performance status [2]. Once patients have progressed on gemcitabine-based chemotherapy, there is limited evidence that further systemic therapy provides meaningful benefit. Most phase II studies in this setting have noted median progression free survival in the range of 2 to 4 months, and few responses [4–12,14], although one trial demonstrated a modest survival benefit from treatment with fluorouracil and oxaliplatin [13]. Given the lack of effective therapies, new treatment options are urgently needed.

Erlotinib (Tarceva®) is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. EGFR is known to be frequently overexpressed in pancreatic tumours [15–17], and to be associated with worse prognosis [16,17]. There is pre-clinical evidence for an anti-tumour effect of erlotinib in pancreatic cancer [18,19]. A phase III study comparing gemcitabine and erlotinib versus gemcitabine alone (NCIC Clinical Trials Group (CTG) PA.3) demonstrated a modest but significant survival advantage for the combination [20]. A small phase II study was also conducted assessing the combination of capecitabine and erlotinib in the gemcitabine-refractory setting, and demonstrated a response rate of 10% and median survival of 6.5 months [4].

Subgroup analysis of the NCIC CTG PA.3 trial demonstrated that the presence of an erlotinib induced rash was associated with a significantly higher likelihood of achieving disease control, and appeared to be associated with improved survival (hazard ratio: 0.74) [20]. Studies of erlotinib in other tumour types have also demonstrated an association between rash and clinical benefit [21–23]. Chen and colleagues examined the correlation between erlotinib minimum steady state concentration (Cmin) and severity of skin rash and noted that patients without a rash had a significantly lower steady state concentration compared to patients with a rash [24]. Thus, intrapatient dose escalation to rash may be a strategy to increase erlotinib efficacy. It is also possible that molecular factors such as *KRAS* and *EGFR* mutational status may predict for EGFR tyrosine kinase efficacy in pancreatic cancer, as has been noted for non-small cell lung cancer [25,26].

To assess the safety, efficacy and feasibility of this treatment strategy, the Princess Margaret Hospital Phase II consortium undertook a phase II study of erlotinib dose escalated to rash in patients with advanced gemcitabine refractory pancreatic cancer. In addition, mutational profiling and EGFR expression were conducted in patients with archived tissue suitable for analysis to assess mutational profiles predictive of erlotinib efficacy.

2. Methods

2.1. Patient selection

Eligible patients had locally advanced or metastatic pancreatic cancer and had received prior treatment with gemcitabine. Patients were required to be Eastern Cooperative Oncology Group (ECOG) performance status 0–2, an absolute granulocyte count $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, normal serum creatinine and bilirubin $\leqslant 1.5 \times$ the upper limit of normal (ULN). Aspartate aminotransferase (AST) and alanine transaminase (ALT) were required to be $\leqslant 2.0 \times$ the ULN, unless liver metastases were present ($\leqslant 5 \times$ ULN). Patients were required to have measurable disease using Response Evaluation Criteria in Solid Tumours [RECIST 1.0] [27]. Exclusion criteria included concurrent other malignancies and serious medical conditions that would impair the ability of the patient to receive protocol treatment. The institutional review boards of the participating institutions approved the study, and all patients provided written informed consent.

2.2. Study design

This phase II study of erlotinib (NCT Registration ID: 00497224) was conducted using a two-stage Simon design, with the primary end-point being disease control rate (objective response plus prolonged stable disease >8 weeks). The study was funded by OSI pharmaceuticals.

Erlotinib was initially administered orally at 150 mg daily on a continuous basis. Study treatment was administered as 28-day cycles. Every 2 weeks for the first two cycles, patients were assessed for toxicity and the presence of rash. Patients who experienced adverse events necessitating dose reduction continued on the reduced dose of erlotinib with no dose escalation. Dose escalation was performed in patients who met all of the following criteria: absence of an erlotinib induced rash; ≤grade 1 diarrhoea; absence of a dose reduction during cycle 1 for toxicity. Patients that did not meet the criteria for dose reduction or dose escalation continued on the present dose of erlotinib. Patients who did not develop a rash had the erlotinib dose increased by 50 mg every 2 weeks as long as they met the criteria

for dose escalation. Once a patient developed a rash, dose escalation was stopped and they were to continue on the same dose of erlotinib unless they meet criteria for dose reduction.

Baseline radiological investigations were performed within 28 days prior to study treatment. Radiological assessments for tumour measurements were conducted every 8 weeks. Study treatment continued until unacceptable toxicity, patient request or progression.

2.3. Dose modifications

2.3.1. Non-haematological toxicity

For grade 2 toxicity not immediately resolving with symptomatic treatment, erlotinib was held until the toxicity improved to ⩽grade 1 and then resumed without dose reduction. On second occurrence, the dose was reduced by 50 mg. For grade 3 toxicity, erlotinib was withheld until ⩽grade 1 and then resumed at a 50 mg dose reduction. For grade 4 toxicity protocol, therapy was discontinued.

2.3.2. Haematological toxicity

For grade 4 neutropenia, grade 3 or 4 thrombocytopenia or febrile neutropenia, erlotinib was held until the adverse event resolved to ⩽grade 2. If that adverse event was felt by the investigator to be possibly, probably or definitely related to erlotinib, the dose was reduced by 50 mg/day. If it was thought to be unlikely to be related, or unrelated, no dose reduction was required. If the adverse event persisted for >14 days, therapy was discontinued.

2.4. Erlotinib steady state concentrations

Erlotinib pharmacokinetics were assessed on cycle 1 day 1 (prior to first dose), cycle 1 day 15 (prior to study dose) and cycle 2 day 1 (prior to study dose). In patients that underwent dose escalation, one addition sample was to be taken on cycle 2 day 22 (pre dose).

Plasma concentrations of erlotinib were quantitated with validated high-performance liquid chromatography (HPLC)-tandem mass spectrometry methods. Pharmacokinetic parameters were calculated by non-compartmental methods using the WinNonlin Version 5.1 (Pharsight Corp., Mountain View, CA). Pharmacokinetic variables were analysed with descriptive statistics. Post-hoc analyses of the relationships between smoking status (assessed by baseline questionnaire) and erlotinib pharmacokinetic levels, and toxicity were undertaken.

2.5. Mutational analysis and EGFR expression

Mutation assessment was performed on archived tissue using the Sequenom® system (using the OncoCarta panel v1.0). This a sequencing system that screens for mutations in genes commonly mutated in cancers including *KRAS*, *EGFR*, *BRAF*, *NRAS* and *HRAS*, and can detect *KRAS* mutations in codons 12, 13 and 61. In addition, sequencing analysis was also performed by Sanger sequencing® to detect *KRAS* mutations in codons 12 or 13. A post hoc analysis of the relationship between *KRAS* mutational status and survival was undertaken.

2.6. EGFR immunohistochemistry

Available archival formalin-fixed paraffin embedded tissue blocks were assessed for EGFR expression by immunohistochemistry. Staining was performed using the EGFR pharmDx kit (Dako Inc, Mississauga, ON, Canada) according to the manufacturer's protocols. Slide evaluation was performed independently by two pathologists using light microscopy and the final scores reflect a consensus score. Cases were considered positive if they showed any IHC staining of tumour cell membrane whether complete or incomplete above the background level [28]. Positive and negative control cell lines were included in each run. A post hoc analysis of the relationship between EGFR expression and survival was performed.

2.7. Statistical methods

The primary end-point was the disease control rate (objective response and prolonged stable disease >8 weeks). Secondary end-points included overall survival (defined as time from randomisation to death from any cause), time to progression (defined as time from randomisation to progression by RECIST 1.0), duration of response or stable disease, progression-free survival and toxicity. The optimal Simon two-stage phase II design was used [29], with the treatment determined to be inactive if the disease control rate was at most 10% and active if it was at least 30%. In stage I, 18 patients were to be accrued, and if three patients responded or had prolonged stable disease then the study would proceed to stage II. In stage II, 17 further patients were to be enrolled, and if seven or more patients of the total of 35 met the criteria for disease control the primary end-point would be met. The one-sided α was 0.05, and power 0.90. A minimum of 8 weeks of follow up was required for patients to be evaluable for disease control rate. Standard descriptive statistics were used to summarise the patient characteristics and toxicity. Kaplan–Meier method was performed to estimate time to progression and overall survival in the overall cohort, and also in subgroups based on mutational status and presence or absence or rash, with exploratory comparisons performed using the log-rank test.

2.8. Role of the funding source

OSI pharmaceutical had no role in the study design, data collection and interpretation or manuscript preparation.

3. Results

Fifty-one patients were accrued over 23 months from November 2006 until October 2008, and 49 received treatment (Table 1). Two patients never received treatment, one due to withdrawal of consent prior to treatment and one due to symptomatic deterioration prior to study enrolment. The median number of cycles administered was two (range of 1–15). Thirty-three patients came off study due to progressive disease, two patients died while on study, ten patients withdrew consent, three patients came off due to toxicity (diarrhoea; myocardial ischaemia and fracture; thrombosis and lower gastrointestinal haemorrhage) and one patient was non-compliant with study protocol. One patient was subsequently found to have a tumour more in keeping with neuroendocrine then ductal adenocarcinoma on further pathology review, therefore this patient was excluded from the efficacy analysis. The median follow up was 3.3 months, and as of the last follow up 35 patients had progressed and 40 patients had died.

Dose-escalation to 200–300 mg of erlotinib was possible in 10 (20%) patients. The best response was stable disease in 12/37 evaluable patients (32%). Disease control (stable disease >8 weeks) was observed in 9/37 evaluable patients (24%). The observed disease control rate surpassed the Simon criteria for a positive trial, but at 24% it was less than the 30% disease control rate that was pre-defined to represent relevant activity of the drug.

Table 1
Patient demographics.

Characteristic	Enrolled patients ($n = 51$)
Age, years	
Median	62
Range	37–79
Gender	
Male	25
Female	26
ECOG performance status	
0	3
1	38
2	10
Stage	
Locally advanced	6
Metastatic	45
Prior therapy	
Chemotherapy in adjuvant setting	23
Chemotherapy in metastatic setting	32
Radiation therapy	8
Histology	
Adenocarcinoma	50
Neuroendocrine*	1

* This patient was excluded from the efficacy analysis

All patients who received treatment, except for the one patient with neuroendocrine pathology, were included in the survival analysis. The median time to progression was 1.61 months (95% confidence interval (CI): 1.58–2.10) (Fig. 1), with a 6 month progression free rate of 10% (95% CI: 3–24%). Median overall survival was 3.78 months (Fig. 2), with a 6 month survival rate of 32% (95% CI: 19–47%).

All patients who received treatment were included in the toxicity analysis. Adverse events are listed in Table 2. The most common treatment related adverse events of any grade included rash (88%), diarrhoea (49%) and fatigue (49%). Grade 3 or greater treatment related adverse events at least possibly related to erlotinib included fatigue (6%), rash (4%) and diarrhoea (4%) (Table 2). There were no grade 4 or 5 toxicities noted. Dose reductions were required in two patients.

3.1. Mutational analysis and EGFR expression

Archived tissue suitable for analyses was available for 29 patients, and mutational analysis was performed using the Sequenom® OncoCarta panel v1.0. Ninety-three percent (27/29) of patients had *KRAS* mutations (one of which had a *KRAS* and *PI3K* mutation, and another that had a *KRAS* and *HRAS* mutation). *KRAS* mutations were confirmed using Sanger sequencing®. Seven percent (2/29) of patients were *KRAS* wild type. None of the patients had an *EGFR* mutation. EGFR expression was performed by immunohistochemistry, and 86% (25/29) of patients had EGFR expression.

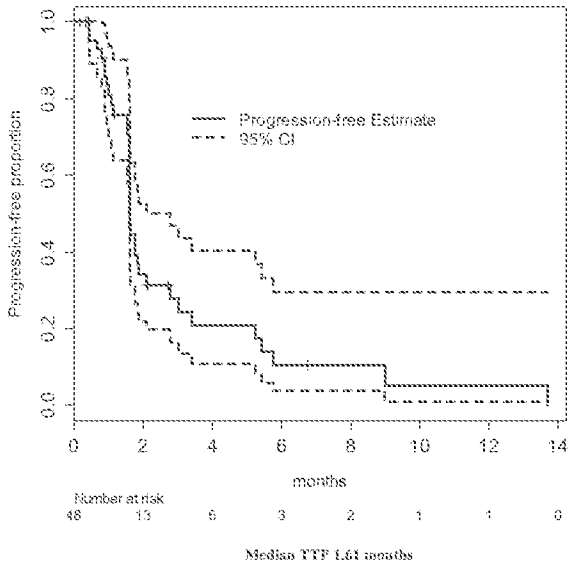


Fig. 1. Kaplan–Meier curve of time to progression (TTP).

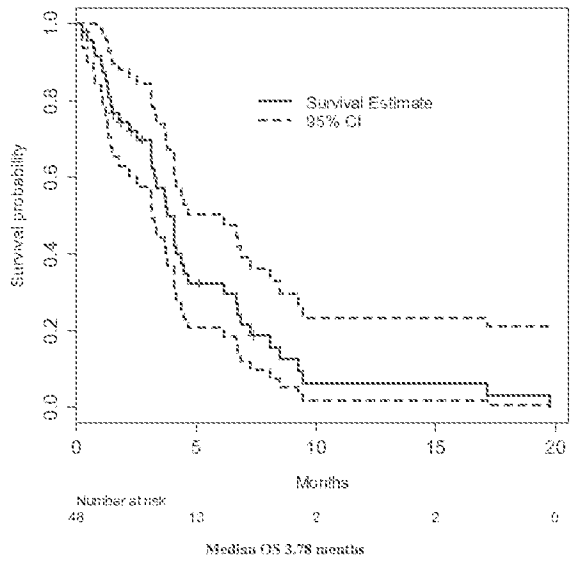


Fig. 2. Kaplan–Meier curve of overall survival (OS).

Table 2
Possibly related grade 3 adverse events.

Adverse event (grade 3)	Erlotinib ($n = 49$)* n (%)
Non-haematological	
Fatigue	3 (6)
Rash	2 (4)
Diarrhoea	2 (4)
Lower gastrointestinal haemorrhage	1 (2)
Cecal perforation	1 (2)
Renal failure	1 (2)
Haematological	
Anaemia	2 (4)
Lymphopenia	2 (4)
Decrease in albumin	2 (4)
Elevation in alkaline phosphatase (ALP)	1 (2)
Elevation in aspartate aminotransferase (AST)	1 (2)
Elevation in bilirubin	1 (2)
Hypokalaemia	1 (2)
Elevation in international normalized ratio (INR)	1 (2)

* Two patients were enrolled but did not receive treatment.

Survival data were available for 28/29 patients (one patient did not receive treatment). There was no difference in overall survival comparing *KRAS* mutant versus *KRAS* wild type patients ($p = 0.6$), nor for the EGFR positive versus negative patients ($p = 0.6$).

3.2. Skin rash

Of the patients evaluable for rash, 16 patients developed a grade 2 or 3 rash and 32 patients had a grade 0 or 1 rash. There was a correlation between rash and disease control, with 7/15 (47%) of evaluable patients with grade 2 or 3 rash having SD >8 weeks versus 2/22 (9%) of patients with grade 0 or 1 rash ($p = 0.017$). There was no difference in survival based on rash with a median overall survival of 3.9 months for patients who developed grade 2 or 3 rash versus 3.8 months for patients with grade 0 or 1 rash ($p = 0.12$). In addition no differences in median time to progression by degree of rash was noted ($p = 0.25$).

3.3. Steady state erlotinib concentrations

Pharmacokinetic data for erlotinib were available for 31 patients. The mean erlotinib Cmin on day 14 was 1179 ± 791 ng/ml. The mean day 14 Cmin of the main active metabolite or erlotinib (OSI-420) was 151 ± 166 ng/ml.

3.3.1. Erlotinib pharmacokinetics by smoking status

Smoking status was obtained in 46 patients, 16 were never smokers (NS), 25 were past smokers (PS) and five were current smokers (CS). Pharmacokinetic data were available for 30 patients with known smoking status. The mean erlotinib Cmin on day 14 in CS, PS and NS was 517, 1008 and 1862 ng/ml respectively ($p = 0.01$ for CS versus NS). The mean Cmin of OSI-420 on day 14 in CS, PS and NS was 55, 123, and 256 ng/ml respectively ($p = 0.01$ for CS versus NS). Cycle 1 ⩾grade 2 diarrhoea occurred in 0/5 (0%) CS, 5/25 (20%) PS and 3/16 (19%) NS ($p = 0.55$ for CS versus NS). Cycle 1 ⩾grade 2 rash occurred in 0/5 (0%) CS, 7/25 (28%) PS and 5/16 (31%) NS ($p = 0.28$ for CS versus NS).

4. Discussion

Improving survival with systemic therapy for metastatic pancreatic cancer remains a challenge, especially in the gemcitabine refractory setting. There is strong rationale, based on both pre-clinical and clinical data, that targeting the EGFR pathway with erlotinib may have an anti-tumour effect in pancreatic cancer [18–20]. The results of this multi-institutional phase II study reveal that erlotinib dose escalated to rash is feasible and generally well tolerated, but is associated with minimal efficacy in non-selected patients in the gemcitabine refractory setting.

Erlotinib as a single agent has been shown to be effective in non-small cell lung cancer (NSCLC), and recent work has demonstrated that this effect is limited to patients who possess *EGFR* mutations (exon 19 deletion or exon 21 L858R mutation) [25,26]. Data from NSCLC have also shown that patients with *KRAS* mutations, which are relatively uncommon in NSCLC compared with pancreatic cancer, have significantly decreased benefit from EGFR tyrosine kinase inhibitors [26]. In addition, evidence from the colorectal cancer literature has convincingly demonstrated that patients with *KRAS* mutations do not benefit from EGFR targeted therapy [30,31].

The frequency of *KRAS* mutations in pancreatic cancer is known to be high, while the frequency of *EGFR* mutations is low. In this study, mutational analysis was conducted on 29 patients, 27 (93%) of which were *KRAS* mutant. Of the 29 patients analysed, none possessed *EGFR* mutations. There was no difference in outcomes seen when comparing patients with *KRAS* mutations versus *KRAS* wild type, but given the small number of *KRAS* wild type patients the conclusions that can be made from this are limited. In addition, EGFR expression was not found to be associated with survival, but this analysis is also limited by the sample size.

The impact of *KRAS* mutations and *EGFR* gene copy number on erlotinib efficacy in pancreatic cancer was previously assessed in the NCIC CTG PA.3 study [32]. The role of *KRAS* mutational status on treatment effect was analysed for 117 patients, and the results indicated a non-significant trend toward a greater benefit from the erlotinib and gemcitabine combination in *KRAS* wild type patients (hazard ratio 0.66 versus 1.07, interaction $p = 0.38$). EGFR gene copy number using fluorescence in situ hybridisation was assessed for 100 patients and appeared to be of no predictive value. Whether *KRAS* wild type and/or *EGFR* mutant pancreatic cancers derive a greater benefit from erlotinib is yet to be determined, but given the high prevalence of *KRAS* mutations, and low prevalence of *EGFR* mutations in pancreatic cancer, patients with these tumour profiles represent a significant minority of all pancreatic cancer patients.

There are increasing data suggesting that rash may be a clinical predictive marker to EGFR inhibitor therapy [20–23,33]. This effect has been demonstrated with both EGFR tyrosine kinase inhibitors and anti-EGFR monoclonal antibodies. In this study we found that degree of rash did appear to correlate with rates of disease control, but this did not translate to differences in time to progression or overall survival. These comparisons were limited by the small sample size. In the phase II RACHEL (BO21128) study patients received 4 weeks of gemcitabine and erlotinib (100 mg/day), and after the run-in period if grade 2 or greater rash was not observed they were randomised to either ongoing treatment with gemcitabine and standard dose erlotinib, or erlotinib dose escalated to rash [34]. Consistent with the results of our study, the RACHEL results did not demonstrate an efficacy benefit from the erlotinib dose escalation to rash strategy.

We conducted a post hoc analysis to assess for a relationship between smoking status and erlotinib steady state levels, as previous studies performed in lung cancer [35–37] have demonstrated that cigarette smoking leads to lower erlotinib levels, possibly due to induction of the CYP1A1 pathway [35,37–39]. Our results also indicate this effect, as current smokers had significantly lower erlotinib and OSI-420 (the main active metabolite) levels then never smokers. In addition, current smokers had a trend toward less toxicity then never smokers. These results add to the body of literature demonstrating an effect of smoking of erlotinib levels, and the concept of alternate dosing of erlotinib in active smokers should be explored further.

This is the largest study to date of single agent erlotinib in advanced pancreatic cancer. The off label use of erlotinib in this setting is currently considered by some clinicians. The results of our study importantly show that in the unselected population the use of single agent erlotinib is of minimal clinical benefit. Whether other molecular markers can predict for a subset of patients that would benefit from single agent erlotinib is yet to be fully elucidated.

In summary, dose escalation of erlotinib to rash is feasible, but it is not associated with significant efficacy in non-selected patients with advanced pancreatic cancer resistant to gemcitabine.

Conflict of interest statement

Dr. Renouf has received honoraria and travel grants from Roche. Dr. Tsao has received research funding and honoraria from Roche. None of the other authors have any conflicts of interest to declare.

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References

[1] Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.

[2] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.

[3] Burris 3rd HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403–13.

[4] Kulke MH, Blaszkowsky LS, Ryan DP, et al. Capecitabine plus erlotinib in gemcitabine-refractory advanced pancreatic cancer. J Clin Oncol 2007;25:4787–92.

[5] Tang P, Gill S, Au HJ, et al. Phase II trial of erlotinib in advanced pancreatic cancer. J Clin Oncol 2009;27.

[6] Renouf D, Moore M. Evolution of systemic therapy for advanced pancreatic cancer. Expert Rev Anticancer Ther 2010;10:529–40.

[7] Cantore M, Rabbi C, Fiorentini G, et al. Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. Oncology 2004;67:93–7.

[8] Demols A, Peeters M, Polus M, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer 2006;94:481–5.

[9] Xiong HQ, Varadhachary GR, Binas JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008;113:2046–52.

[10] Sudo K, Yamaguchi T, Nakamura K, et al. Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer. Cancer Chemother Pharmacol 2011;67:249–54.
[11] Wolpin BM, Hezel AF, Abrams T, et al. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. J Clin Oncol 2009;27:193–8.
[12] Hosein PJ, de Lima Lopes Jr G, Pastorini VH, et al. A phase II trial of nab-Paclitaxel as second-line therapy in patients with advanced pancreatic cancer. Am J Clin Oncol 2013;36(2):141–56.
[13] Pelzer U, Kubica K, Stieler J, et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 2008;26 [Abstr 4508].
[14] Tempero MA, Arnoletti JP, Behrman S, et al. Pancreatic adenocarcinoma. J Natl Compr Canc Netw 2010;8:972–1017.
[15] Fjällskog ML, Lejonklou MH, Oberg KE, et al. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. Clin Cancer Res 2003;9:1469–73.
[16] Xiong HQ. Molecular targeting therapy for pancreatic cancer. Cancer Chemother Pharmacol 2004;54(Suppl. 1):s69–77.
[17] Ueda S, Ogata S, Tsuda H, et al. The correlation between cytoplasmic overexpression of epidermal growth factor receptor and tumor aggressiveness: Poor prognosis in patients with pancreatic ductal adenocarcinoma. Pancreas 2004;29:e1–8.
[18] Bruns CJ, Solorzano CC, Harbison MT, et al. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res 2000;60:2926–35.
[19] Ng SS, Tsao MS, Nicklee T, et al. Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Mol Cancer Ther 2002;1:777–83.
[20] Moore MJ, Goldstein D, Hamm J, et al. 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. J Clin Oncol 2007;25:1960–6.
[21] Perez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. J Clin Oncol 2004;22:3238–47.
[22] Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: Is there a silver lining? J Clin Oncol 2005;23:5235–46.
[23] Soulieres D, Senzer NN, Vokes EE, et al. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. J Clin Oncol 2004;22:77–85.
[24] Chen EX, Zhang W, Pond GR, et al. Correlation between erlotinib concentrations and severity of skin rash. In: AACR-NCI-EORTC international conference on molecular targets and cancer therapeutics; 2005.
[25] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[26] Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada clinical trials group study BR.21. J Clin Oncol 2008;26:4268–75.
[27] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[28] Atkins D, Reiffen KA, Tegtmeier CL, Winther H, Bonato MS, Storkel S. Immunohistochemical detection of EGFR in paraffin-embedded tumor tissues: variation in staining intensity due to choice of fixative and storage time of tissue sections. J Histochem Cytochem 2004;52(7):893–901.
[29] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;1–10.
[30] Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757–65.
[31] Peeters M, Siena S, Van Cutsem E, et al. Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. Cancer 2009;115:1544–54.
[32] da Cunha Santos G, Dhani N, Tu D, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada clinical trials group study PA.3. Cancer 2010;116:5559–607.
[33] PMID: 24356622.
[34] Van Cutsem E, Nowara E, Ciuleanu T, et al. Dose escalation to rash for erlotinib plus gemcitabine in patients with metastatic pancreatic cancer: the phase II RACHEL (B021128) study. Ann of Oncol 23(Suppl. 4) [abstr 0006].
[35] Hughes AN, O'Brien ME, Petty WJ, et al. Overcoming CYP1A1/1A2 mediated induction of metabolism by escalating erlotinib dose in current smokers. J Clin Oncol 2009;27:1226–6.
[36] Clark GM, Zborowski DM, Santabarbara P, et al. Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada clinical trials group study BR.21. Clin Lung Cancer 2006;7:389–94.
[37] Hamilton M, Wolf E, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166–71.
[38] Li J, Zhao M, He P, et al. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res 2007;13:3731–7.
[39] Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet 1999;36:425–38.

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14	Non Patent Literature	Melisi_AIOM_2016_abstract.pdf	40202 e4de2e3102936f9248be2df9b552f591099b8684	no	1
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Warnings:					
Information:					
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43	Non Patent Literature	Philip_2009.pdf	149049 8366111662a7ded46bff3db4c3c77e0c9a3e0a76	no	10
Warnings:					
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45	Non Patent Literature	Picozzi_ASCO_GI_2020_abstract.pdf	68932 e7e3114f1a1b86e8fcae7c33f9fa0312260fa3fb	no	2
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49	Non Patent Literature	Ramnani_HOPA_2020_abstract.pdf	73481 ce9a4191a701d56d727f6f6e3743b613c642ea35	no	2
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Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	1	ROCHA LIMA C, et al., "Irinotecan Plus Gemcitabine Results in No Survival Advantage Compared With Gemcitabine Monotherapy in Patients With Locally Advanced or Metastatic Pancreatic Cancer Despite Increased Tumor Response Rate," J Clin Oncol. 22(18):3776-83 (2004).
	2	SANCHO A, et. al., Abstract 15625. "Oxaliplatin and Capecitabine After Gemcitabine Failure in Patients With Advanced Pancreatic, Biliary, and Gallbladder Adenocarcinoma (APBC)," J Clin Oncol. 26(15_suppl):15625 (2008), 5 printed pages.
	3	SHI S, et al., "Combinational Therapy: New Hope for Pancreatic Cancer?" Cancer Lett. 317(2):127-35 (2012). Epub 2011.
	4	SIVEKE J, et al., "Subgroup Analysis by Measurable Metastatic Lesion (ML) Number and Selected Lesion Locations (LL) at Baseline (BL) in NAPOLI-1: A Phase 3 Study of Liposomal Irinotecan (nal-IRI)±5-Fluorouracil/Leucovorin (5-FU/LV) in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine-Based Therapy." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 18-20, 2018, 8 pages.
	5	SIVEKE J, et al., Abstract 460. "Subgroup Analysis by Measurable Metastatic Lesion (ML) Number and Selected Lesion Locations (LL) at Baseline (BL) 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):460 DOI: 10.1200/JCO.2018.36.4_suppl.460 (2018), 2 printed pages.
	6	SIVEKE J, et al., Abstract ID0596. "Expanded Analyses of NAPOLI-1: Phase 3 Study of nal-IRI (MM-398), With or Without 5-Fluorouracil (5FU) and Leucovorin (LV), Versus 5-Fluorouracil and Leucovorin (5FU/LV), in Metastatic Pancreatic Cancer (mPAC) Previously Treated With Gemcitabine-Based Therapy," Oncol Res Treat. 39(Suppl 1):170 (2016).
	7	SIVEKE J, et al., Abstract P863. "Effects of Nanoliposomal Irinotecan (nal-IRI;MM-398) ± 5-Fluorouracil und Leucavorin (5-FU/LV) on Quality of Life (QoL) in NAPOLI-1: A Phase 3 Study in Patients (pts) With Metastatic Pancreatic Adenocarcinoma (mPAC) Previously Treated With Gemcitabine-Based Therapy," Oncol Res Threat. 39 (Suppl 3):259 (2016).
	8	SOARES H, et. al., "A Phase II Study of Capecitabine Plus Docetaxel in Gemcitabine-Pretreated Metastatic Pancreatic Cancer Patients: CapTere," Cancer Chemother Pharmacol. 73(4):839-45 (2014).
	9	SOHAL D et. al., "Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update," J Clin Oncol. 36 (24):2545-2556 and appendix (2018).
	10	SOHAL D, et. al., "Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline," J Clin Oncol. 34(23):2784-96 and Appendix (2016).
	11	SOHAL D, et. al., "Reply to A. Wang-Gillam et al," J Clin Oncol. 35(6):690-1 (2017). Epub 2016.

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	12	SON J, et al., "Glutamine Supports Pancreatic Cancer Growth Through a Kras-Regulated Metabolic Pathway," Nature. 496(7443):101-5 (2013), author manuscript version, 16 pages.
	13	SOUSA C and KIMMELMAN A, "The Complex Landscape of Pancreatic Cancer Metabolism," Carcinogenesis. 35 (7):1441-50 (2014).
	14	STARLING N, et. al., "A Dose Escalation Study of Gemcitabine Plus Oxaliplatin in Combination With Imatinib for Gemcitabine-Refractory Advanced Pancreatic Adenocarcinoma," Ann Oncol. 23(4):942-7 (2012). Epub 2011.
	15	STATHIS A and MOORE M, "Advanced Pancreatic Carcinoma: Current Treatment and Future Challenges," Nat Rev Clin Oncol. 7(3):163-72 (2010).
	16	STATHOPOULOS G, et. al., "A Multicenter Phase III Trial Comparing Irinotecan-Gemcitabine (IG) With Gemcitabine (G) Monotherapy as First-Line Treatment in Patients With Locally Advanced or Metastatic Pancreatic Cancer," Br J Cancer. 95(5):587-92 (2006).
	17	STATHOPOULOS G, et. al., "Lipsomal Cisplatin Combined With Gemcitabine in Pretreated Advanced Pancreatic Cancer Patients: A phase I-II Study," Oncol Rep. 15(5):1201-4 (2006).
	18	TAKADA T et. al., "Comparison of 5-Fluorouracil, Doxorubicin and Mitomycin C with 5-Fluorouracil Alone in the Treatment of Pancreatic-Biliary Carcinomas," Oncology. 51(5):396-400 (1994).
	19	TAKAHARA N, et. al., "A Retrospective Study of S-1 and Oxaliplatin Combination Chemotherapy in Patients With Refractory Pancreatic Cancer," Cancer Chemother Pharmacol. 72(5):985-90 (2013).
	20	TEMPERO M, et. al., "NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma," Version 1.2012. National Comprehensive Cancer Network, Inc. (2011), 79 pages.
	21	TEMPERO M, et. al., "NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma," Version 2.2012. National Comprehensive Cancer Network, Inc. (2011), 94 pages.
	22	TEMPERO M, et. al., "NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma," Version 2.2014. National Comprehensive Cancer Network, Inc. (2014), 122 pages.

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	23	TEMPERO M, et. al., "Pancreatic Adenocarcinoma: Clinical Practice Guidelines in Oncology," J Natl Compr Canc Netw. 8(9):972-1017 (2010).	
	24	THOTA R, et. al., "Treatment of Metastatic Pancreatic Adenocarcinoma: A Review," Oncology. 28(1):70-4 (2014). Available at cancernetwork.com/view/treatment-metastatic-pancreatic-adenocarcinoma-review, 6 printed pages.	
	25	TODAKA A, et. al., "S-1 Monotherapy as Second-line Treatment for Advanced Pancreatic Cancer after Gemcitabine Failure," Jpn J Clin Oncol. 40(6):567-72 (2010).	
	26	TOGAWA A, et. al., "Treatment With an Oral Fluoropyrimidine, S-1, Plus Cisplatin in Patients Who Failed Postoperative Gemcitabine Treatment for Pancreatic Cancer: A Pilot Study," Int J Clin Oncol. 12(4):268-73 (2007).	
	27	TOMICKI S, et al., "Utilization of Hospital Inpatient Services Among Patients With Metastatic Pancreatic Cancer With Commercial and Medicare Insurance Treated With FDA-Approved/NCCN Category 1 Regimens." Poster presented at the Academy of Managed Care Pharmacy, Nexus (AMCP, Nexus): virtual meeting, week of October 19, 2020, 6 pages.	
	28	TSAVARIS N, et. al., "Second-Line Treatment With Oxaliplatin, Leucovorin and 5-Fluorouracil in Gemcitabine-Pretreated Advanced Pancreatic Cancer: A Phase II Study," Invest New Drugs. 23(4):369-75 (2005).	
	29	VAN CUTSEM E et. al., "Phase III Trial of Bevacizumab in Combination With Gemcitabine and Erlotinib in Patients With Metastatic Pancreatic Cancer," J Clin Oncol. 27(13):2231-7 (2009).	
	30	VAN RIJSWIJK R, et. al., "Weekly High-Dose 5-Fluorouracil and Folinic Acid in Metastatic Pancreatic Carcinoma: A Phase II Study of the EORTC GastroIntestinal Tract Cancer Cooperative Group," Eur J Cancer. 40(14):2077-81 (2004).	
	31	VENTURA M, et al., "Efficacy of nal-IRI and Hypoxia Modulation in Orthotopic Patient-Derived Pancreatic Tumor Models of High (OCIP51) and Low (OCIP19) Hypoxia," Presentation presented at the World Molecular Imaging Congress 2017, Philadelphia, Pennsylvania, September 13-16, 2017, 15 pages.	
	32	VENTURA M, et al., Abstract. "Efficacy of nal-IRI and Hypoxia Modulation in Orthotopic Patient-Derived Pancreatic Tumor Models of High (OCIP51) and Low (OCIP19) Hypoxia," The World Molecular Imaging Congress 2017, Philadelphia, Pennsylvania, September 13-16, 2017, 1 page.	
	33	VICKERS M, et. al., "Comorbidity, Age and Overall Survival in Patients With Advanced Pancreatic Cancer – Results from NCIC CTG PA.3: A Phase III Trial of Gemcitabine Plus Erlotinib or Placebo," Eur J Cancer. 48(10):1434-42 (2012). Epub 2011.	

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	34	VON HOFF D, et. al., "Gemcitabine Plus nab-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial," J Clin Oncol. 29(34):4548-54 (2011).
	35	VON HOFF D, et. al., "Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine," N Engl J Med. 369(18):1691-703 (2013).
	36	WAINBERG Z, et al., "First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study." Presentation presented at the ESMO World Congress on Gastrointestinal Cancer, July 1-4, 2020, 13 pages.
	37	WAINBERG Z, et al., "First-Line Liposomal Irinotecan + 5-Fluorouracil/Leucovorin + Oxaliplatin in Patients With Pancreatic Ductal Adenocarcinoma: Long-Term Follow-Up Results From a Phase 1/2 Study." Poster presented at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, virtual format, July 1-4, 2020, 7 pages.
	38	WAINBERG Z, et al., "NAPOLI-3: An Open-Label, Randomized, Phase 3 Study of First-Line Liposomal Irinotecan + 5 Fluorouracil/Leucovorin + Oxaliplatin Versus Nab-Paclitaxel + Gemcitabine in Patients With Metastatic Pancreatic Ductal Adenocarcinoma." Poster presented at the American Society of Clinical Oncology (ASCO) Annual Conference, virtual format, May 29-June 2, 2020, 6 pages.
	39	WAINBERG Z, et al., Abstract LBA-1. "First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study," Ann Oncol. 31(Suppl 3): S241 doi.org/10.1016/j.annonc.2020.04.076 (2020).
	40	WAINBERG Z, et al., Abstract TPS4661. "NAPOLI-3: An Open-Label, Randomized, Phase III Study of First-Line Liposomal Irinotecan + 5 Fluorouracil/Leucovorin + Oxaliplatin Versus Nab-Paclitaxel + Gemcitabine in Patients With Metastatic Pancreatic Ductal Adenocarcinoma," J Clin Oncol. 38(15_Suppl):TPS4461 DOI: 10.1200/ JCO.2020.38.15_suppl.TPS4661 (2020), 2 printed pages.
	41	WALKER E and KO A, "Beyond First-Line Chemotherapy for Advanced Pancreatic Cancer: An Expanding Array of Therapeutic Options?" World J Gastroenterol. 20(9):2224-36 (2014).
	42	WANG-GILLAM A, et al., "Characteristics of Long-Term Survivors in a Randomized Phase 3 Trial (NAPOLI-1) of Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mDPAC) Treated With Liposomal Irinotecan (nal-IRI; MM-398) + 5-FU/LV." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 19-21, 2017, 9 pages.
	43	WANG-GILLAM A, et al., "Dose Modifications of Liposomal Irinotecan (nal-IRI) + 5-Fluorouracil/Leucovorin (5-FU/LV) in NAPOLI-1: Impact on Efficacy." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 18-20, 2018, 8 pages.
	44	WANG-GILLAM A, et al., "Nomogram for Predicting Overall Survival in Patients Treated With Liposomal Irinotecan (nal-IRI) ± 5-Fluorouracil/Leucovorin (5-FU/LV) in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy in NAPOLI-1." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 18-20, 2018, 9 pages.

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	45	WANG-GILLAM A, et al., "Updated Overall Survival Analysis of NAPOLI-1: Phase 3 Study of Nanoliposomal Irinotecan (nal-IRI, MM-398), With or Without 5-Fluorouracil and Leucovorin (5-FU/LV), Versus 5-FU/LV in Metastatic Pancreatic Cancer (mPAC) Previously Treated With Gemcitabine-Based Therapy." Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, January 21-23, 2016, 11 pages.
	46	WANG-GILLAM A, et al., "Updated Overall Survival Analysis of NAPOLI-1: Phase 3 Study of Nanoliposomal Irinotecan (nal-IRI, MM-398), With or Without 5-Fluorouracil and Leucovorin, vs 5-Fluorouracil and Leucovorin in Metastatic Pancreatic Ductal Adenocarcinoma Previously Treated With Gemcitabine." Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, Illinois, June 3-7, 2016, 8 pages.
	47	WANG-GILLAM A, et al., Abstract 293. "Characteristics of Long-Term Survivors in a Randomized Phase III Trial (NAPOLI-1) of Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan (nal-IRI; MM-398) + 5-FU/LV," J Clin Oncol. 35(4_Suppl):293 DOI: 10.1200/JCO.2017.35.4_suppl.293 (2017), 2 printed pages.
	48	WANG-GILLAM A, et al., Abstract 388. "Dose Modifications of Liposomal Irinotecan (nal-IRI) + 5-Fluorouracil/ Leucovorin (5-FU/LV) in NAPOLI-1: Impact on Efficacy," J Clin Oncol. 36(4_Suppl):388 DOI: 10.1200/ JCO.2018.36.4_suppl.388 (2018), 2 printed pages.
	49	WANG-GILLAM A, et al., Abstract 4126. "Updated Overall Survival (OS) Analysis of NAPOLI-1: Phase 3 Study of Nanoliposomal Irinotecan (nal-IRI, MM-398), With or Without 5-Fluorouracil and Leucovorin (5-FU/LV), vs 5-FU/LV in Metastatic Pancreatic Cancer (mPAC) Previously Treated With Gemcitabine (Gem)-Based Therapy," J Clin Oncol. 34 (15_Suppl):4126 DOI: 10.1200/JCO.2016.34.15_suppl.4126 (2016), 5 printed pages.
	50	WANG-GILLAM A, et al., Abstract 417. "Updated Overall Survival Analysis of NAPOLI-1: Phase III Study of Nanoliposomal Irinotecan (nal-IRI, MM-398), With or Without 5-Fluorouracil and Leucovorin (5-FU/LV), Versus 5-FU/ LV in Metastatic Pancreatic Cancer (mPAC) Previously Rreated With Gemcitabine-Based Therapy," J Clin Oncol. 34 (4_Suppl):417 DOI: 10.1200/jco.2016.34.4_suppl.417 (2016), 2 printed pages.

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	Examiner Name	Celeste A. RONEY
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ORIGINAL REPORT

Irinotecan Plus Gemcitabine Results in No Survival Advantage Compared With Gemcitabine Monotherapy in Patients With Locally Advanced or Metastatic Pancreatic Cancer Despite Increased Tumor Response Rate

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ABSTRACT

Purpose
This phase III, randomized, open-label, multicenter study compared the overall survival associated with irinotecan plus gemcitabine (IRINOGEM) versus gemcitabine monotherapy (GEM) in patients with chemotherapy-naive, locally advanced or metastatic pancreatic cancer.

Patients and Methods
IRINOGEM patients received starting doses of gemcitabine 1,000 mg/m^2 and irinotecan 100 mg/m^2 given weekly for 2 weeks every 3-week cycle. GEM patients received gemcitabine 1,000 mg/m^2 weekly for 7 of 8 weeks (induction) and then weekly for 3 of 4 weeks. The primary end point of the trial was survival. Secondary end points included tumor response, time to tumor progression (TTP), changes in CA 19-9, and safety.

Results
In each arm, 180 randomly assigned patients comprised the intent-to-treat population evaluated for efficacy; 173 IRINOGEM and 169 GEM patients were treated. Median survival times were 6.3 months for IRINOGEM (95% CI, 4.7 to 7.5 months) and 6.6 months for GEM (95% CI, 5.2 to 7.8 months; log-rank $P = .789$). Tumor response rates were 16.1% (95% CI, 11.1% to 22.3%) for IRINOGEM and 4.4% (95% CI, 1.9% to 8.6%) for GEM (χ^2 $P < .001$). Median TTP was 3.5 months for IRINOGEM versus 3.0 months for GEM (log-rank $P = .352$). However, subset analyses in patients with locally advanced disease suggested a TTP advantage with IRINOGEM versus GEM (median, 7.7 *v* 3.9 months). CA 19-9 progression was positively correlated with tumor progression. The incidence of grade 3 diarrhea was higher in the IRINOGEM group but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were similar.

Conclusion
IRINOGEM safely improved the tumor response rate compared with GEM but did not alter overall survival.

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INTRODUCTION

Carcinoma of the pancreas is the fourth leading cause of cancer deaths in the United States.[1] The nonspecific nature of early symptoms of pancreatic cancer may result in delayed diagnosis such that 80% or more of patients present initially with locally advanced or metastatic disease that cannot be treated by surgical resection.[2-4] Median survival time is 6 to 10 months for patients with locally advanced disease, and 3 to 6 months for those with metastatic disease.[5]

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Chemotherapy options for advanced or metastatic pancreatic cancer are limited. Single-agent fluorouracil (FU) results in tumor response rates of 7% or less.[6-9] Combination chemotherapy with FU has resulted in increased toxicity without higher efficacy.[2-5]

Gemcitabine (Gemzar; Eli Lilly and Co, Indianapolis, IN) in weekly infusions has been shown to be superior to bolus FU as monotherapy for advanced disease in a randomized phase III study involving 126 patients.[8] A greater clinical benefit (22.2% *v* 4.8%; $P = .0022$), longer median survival time (5.7 *v* 4.4 months; $P = .0025$), and greater 12-month survival rate (18% *v* 2%) favoring gemcitabine were observed. A comprehensive experience reported in a large, multicenter, open-label study that enrolled more than 3,000 patients on a compassionate-need basis documented single-agent gemcitabine (GEM) to be reasonably safe and to offer a median overall survival of 4.8 months.[9]

Irinotecan (Camptosar; Pfizer Oncology, New York, NY), a camptothecin derivative, demonstrated efficacy results similar to those of gemcitabine in two phase II studies in chemotherapy-naive pancreatic cancer patients.[10,11] Complimentary toxicity profiles and different mechanisms of cytotoxicity provided the rationale for development of a gemcitabine and irinotecan (IRINOGEM) combination. Preclinical studies suggested dose-dependent synergistic interactions between gemcitabine and irinotecan.[8,11] In a phase I study with both drugs given on days 1 and 8 of repeated 3-week cycles, the maximum-tolerated doses were gemcitabine 1,000 mg/m^2 given during a 30-minute infusion immediately followed by irinotecan 100 mg/m^2 infused during 90 minutes.[12] A phase II study at the maximum-tolerated dose and schedule defined by the phase I experience showed that the combination was active and had an acceptable toxicity profile.[13] In this phase II trial, significant correlations between proportional changes in CA 19-9 and radiographically assessed tumor area were observed and CA 19-9 seemed to be a good indicator of response and progression. On the basis of these observations, a phase III study of the combination of IRINOGEM versus GEM was undertaken in patients with advanced or metastatic pancreatic cancer, with a primary end point of survival. To our knowledge this is also the first phase III study to examine CA 19-9 as a predictor of disease status in pancreatic cancer patients receiving chemotherapy.

PATIENTS AND METHODS

Patient Eligibility

The protocol was conducted according to the guidelines of the Declaration of Helsinki. All patients provided written informed consent before study enrollment. Male and female patients were eligible for the study if they were 18 years of age or older and had histologically or cytologically documented locally advanced or metastatic epithelial cancer (adenocarcinoma) of the exocrine pancreas. These patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and adequate hematologic, renal, and hepatic function as defined by the following: absolute neutrophil count $\geq 1{,}500/\mu L$; platelet count $\geq 100{,}000/\mu L$; creatinine and bilirubin levels $\leq 1.5\times$ central laboratory upper limit of normal; and alkaline phosphatase, AST, and lactate dehydrogenase levels $\leq 5\times$ upper limit of normal. In addition, all patients had to have measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST).[14] Patients were to have documented resolution (to National Cancer Institute Common Toxicity Criteria [Version 2.0] grade ≤ 1) of all acute toxic effects of any prior radiotherapy or FU given as a radiation sensitizer.

Patients were excluded if they had received prior systemic therapy given as adjuvant chemotherapy or as therapy for advanced pancreatic cancer, except FU used strictly as a radiation sensitizer. Patients were excluded if they had prior irradiation to the only site of measurable disease; were pregnant or breast-feeding; had active inflammatory bowel disease, significant bowel obstruction, chronic diarrhea, known brain or leptomeningeal disease (unless such lesions were previously irradiated, not currently being treated with corticosteroids, and showed no clinical symptoms), myocardial infarction within the previous 6 months, uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia, known HIV infection or an AIDS-related illness, currently active second malignancy other than nonmelanoma skin cancers (patients with other malignancies must have been disease free for 5 years or longer), mental incapacitation or psychiatric illness that prevented the patient from giving informed consent, or other severe concurrent disease that, in the judgment of the investigator, made the patient inappropriate for entry onto this study.

Study Design and Treatment

Patients were centrally randomly assigned and stratified by ECOG performance status (0, 1, or 2), extent of disease (locally advanced or metastatic), and previous radiotherapy for pancreatic cancer (yes or no). Patients treated with IRINOGEM received starting doses of gemcitabine 1,000 mg/m^2 given as a 30-minute intravenous infusion followed immediately by irinotecan 100 mg/m^2 given intravenously during 90 minutes, both administered on days 1 and 8 of each 3-week treatment cycle. Patients in the GEM arm received the single-agent starting dose of gemcitabine 1,000 mg/m^2 weekly for 7 weeks during an 8-week induction, then weekly treatment for 3 weeks in repeated 4-week cycles. Treatment was discontinued for disease progression, unacceptable toxicity, patient noncompliance, or withdrawal of patient consent. After discontinuation of study treatment, patients were observed (every month for 1 year and then every 3 months) for survival and additional antitumor therapies until the last patient treated with IRINOGEM discontinued therapy.

Supportive Care

Antiemetic agents were administered as prophylaxis or as needed for nausea or vomiting. Atropine was given as recommended for the treatment of the cholinergic syndrome that may occur shortly after irinotecan infusion. Loperamide was provided for treatment of delayed diarrhea or abdominal cramping; additional antidiarrheal measures were instituted at the discretion of the physician.

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Prophylactic administration of granulocyte colony-stimulating factor was allowed at the investigator's discretion for recurrent neutropenia or therapeutically for serious neutropenic complications.

Efficacy and Safety Evaluations

Standard efficacy end points of objective tumor response rates, time to progression (TTP), and survival times were assessed. Baseline tumor evaluations were performed within 14 days before the start of treatment. Postrandomization oncologic assessments were made every 6 weeks for patients in both treatment arms. To ensure consistency, the imaging method used to detect lesions in an individual patient at study entry was used for all subsequent evaluations. Objective tumor response was determined by comparison with baseline assessments using RECIST criteria. All responses were confirmed ≥ 4 weeks later.

Patients were defined as not assessable for response if there was no postrandomization oncologic assessment (and were considered as having experienced treatment failure in the intent-to-treat [ITT] response assessment). The objective tumor response rate was the proportion of the ITT population with a confirmed complete response (CR) or partial response.

Survival was defined as the time from random assignment to the date of death as a result of any cause. Patients lost to follow-up were censored at the date of last contact. TTP was defined as the time from random assignment to the first objective documentation of tumor progression or to the time of death as a result of progressive disease in the absence of previous documentation of objective progressive disease. TTP was censored for patients who did not have objective evidence of tumor progression and were removed from the study treatment, or died more than 30 days after last dose, or died as a result of causes unrelated to pancreatic cancer.

Assessments of serum tumor marker CA 19-9 were conducted at screening (≤ 14 days before random assignment); on days 1, 22, and 43; and every 3 weeks thereafter. To ensure consistency of results, CA 19-9 assays were performed by a central laboratory. Changes in CA 19-9 levels were not considered an objective measure of tumor response; however, an increasing CA 19-9 value did prompt a repeat radiographic evaluation to document whether objective tumor progression had occurred. Tumor marker response was defined as a reduction in the CA 19-9 value of ≥ 50% relative to the baseline measurement. Tumor marker progression was defined as a CA 19-9 value more than 37 U/mL and the occurrence of either an increase in the CA 19-9 value by more than 25% from a nadir level of more than 200 U/mL or an increase more than 50% from a nadir level of ≤ 200 U/mL. A patient was considered not assessable if an adequate tumor marker evaluation could not be obtained at baseline and at least once while on study.

Safety evaluation parameters included weekly assessments of adverse events, hematology values, and blood chemistry assays (albumin, creatinine, total bilirubin, alkaline phosphatase, AST, and lactate dehydrogenase). Safety was characterized in terms of the frequency and severity of adverse events and laboratory abnormalities. Severity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Quality of Life

Patients were asked to assess their quality of life using the Functional Assessment of Cancer Therapy-Hepatobiliary Quality of Life (QOL) survey (FACT-Hep, Version 4) instrument. This QOL tool has been designed for adults with hepatobiliary cancer. The FACT-Hep self-reporting scale comprises the FACT-G core (27 general items; Version 4), designed for adults with various cancer diagnoses, combined with the FACT-Hep subscale, which includes 18 additional items specific for hepatobiliary cancer. The FACT-G explores the domains of physical well-being, social and family well-being, emotional well-being, and functional well-being.[15,16] The FACT-Hep 45-item questionnaire has been validated in patients with pancreatic cancer and uses a question structure similar to that of the FACT-G.[17]

Patients completed the questionnaires at the start of each cycle of therapy and before termination from the study. Other quality-of-life parameters included maintenance of body weight and ECOG performance status, which were assessed at baseline and at the beginning of every cycle. A decline in weight of less than 5% from baseline and no worsening on the ECOG scale were defined as criteria of success for weight and performance status, respectively.

Statistical Methods

The study was event driven with a primary end point of survival; 306 deaths were anticipated in the planned sample size of 350 patients to detect a 40% improvement in median survival time, assuming an exponential distribution, a .05 level, two-sided log-rank test, and a power of 0.85. Survival status was updated on all patients at the time of the 306th death so that the analysis was actually based on 319 events. All efficacy analyses were conducted at the .05, two-sided, nominal type I error, and were based on the ITT population. Time-to-event end points were described by Kaplan-Meier methods, and were compared by log-rank testing. Confirmed and unconfirmed response rates were analyzed by the χ^2 test. The influence of the stratification factors on the primary and secondary end points was tested by proportional hazards techniques or logistic regression. Exploratory subgroup analyses by stratification factors were also performed. The agreement between CA 19-9 results and results of radiologic and clinical assessments were investigated in the subgroup of patients with baseline and ≥ 1 on study tumor marker assessment. Sensitivity, specificity, positive and negative predicted values, and the diagnostic accuracy of CA 19 NCI 9 were assessed. Treatment administration, safety, and quality-of-life variables were analyzed descriptively in the treated population. Quality of life was described considering best and worst scores and changes from baseline. Life-table methods and log-rank testing were used to evaluate the influence of treatment on declines in weight and performance status over time.

RESULTS

Patient Characteristics

A total of 360 patients were randomly assigned between February 10, 2000, and December 28, 2001: 180 each in the IRINOGEM and GEM arms. Of these, 173 patients and 169 patients were treated, respectively. The 18 patients who were randomly assigned but not treated discontinued because of withdrawal of consent (10 patients), progression of disease (three patients), protocol violations (four patients), and adverse events (one patient). Patient characteristics are listed in Table 1. The two treatment arms were well balanced with respect to age, sex, performance status, extent of disease, and prior radiotherapy. Approximately 80% of the patients had metastatic disease; 14% had locally advanced

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Table 1. Baseline Patient Characteristics

Characteristic	IRINOGEM (n = 180)		GEM (n = 180)	
	No. of Patients	%	No. of Patients	%
Age				
< 65 years	106	58.9	113	62.8
≥ 65 years	70	38.9	56	31.1
Missing	4	2.2	11	6.1
Median, years	63.2		60.2	
Range, years	38.7 to 81.2		32.3 to 82.9	
Sex				
Male	103	57.2	96	53.3
Female	73	40.6	73	40.6
Missing*	4	2.2	11	6.1
ECOG performance status				
0	51	28.3	42	23.3
1	90	50.0	91	50.6
2	34	18.9	36	20.0
3	1	0.6	0	0.0
Missing*	4	2.2	11	6.1
Extent of disease				
Locally advanced	27	15.0	24	13.3
Metastatic	148	82.2	145	80.6
Missing*	5	2.8	11	6.1
Liver metastases	78	43.3	83	46.1
Previous radiotherapy				
Yes	11	6.1	14	7.8

Abbreviations: IRINOGEM, irinotecan plus gemcitabine; GEM, gemcitabine alone; ECOG, Eastern Cooperative Oncology Group.
*There were seven patients in the IRINOGEM group and 11 patients in the GEM group who were randomly assigned but not treated. Baseline information was not routinely collected for these patients.

disease. Median baseline values of CA 19-9 were 1,798 and 1,766 U/mL, respectively.

Treatment Administration

Median duration of therapy for IRINOGEM patients was 12.1 weeks (range, 3.0 to 83.9 weeks) and median duration of therapy for GEM patients was 12.9 weeks (range, 6.6 to 88.0 weeks). The median dose intensities for IRINOGEM patients were 54.9 mg/m^2/wk (range, 25.2 to 72.3 mg/m^2/wk) and 548.2 mg/m^2/wk (range, 252.4 to 715.2 mg/m^2/wk) for irinotecan and gemcitabine, respectively. GEM-treated patients received a median dose of 626.8 mg/m^2/wk of gemcitabine (range, 123.3 to 929.2 mg/m^2/wk). The relative dose intensities were 82.4% (range, 37.9 to 108.5%) for irinotecan and 82.2% (range, 37.9 to 107.3%) for gemcitabine in the IRINOGEM arm, and 76.0% (range, 14.1 to 118.9%) for gemcitabine in the single-agent GEM arm.

Efficacy

There was no difference in survival between the two treatment arms (Fig 1). Median survival time was 6.3 months for IRINOGEM (95% CI, 4.7 to 7.5 months; range, 0.2 to 23.8 months) and 6.6 months for GEM (95% CI, 5.2 to 7.8 months; range, 0.03 to 22.8 months; log-rank $P = .789$). The probability of survival at 1 year was approximately 0.20 in both arms. Subset analyses by stratification factors did not reveal any differences in survival. Poststudy chemotherapy was given to 39% of IRINOGEM-treated patients and 46% of GEM-treated patients. Gemcitabine and FU were the most common agents used. Second-line irinotecan was given to 8% of patients who received first-line GEM.

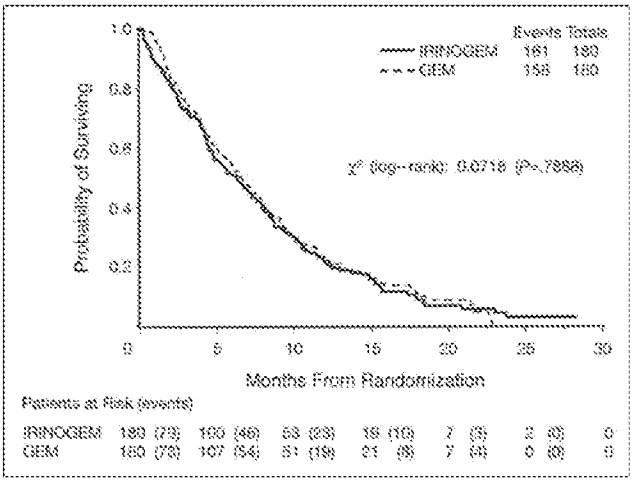


Fig 1. Kaplan-Meier estimates of overall survival. IRINOGEM, irinotecan and gemcitabine; GEM, gemcitabine alone.

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The best confirmed tumor response using RECIST criteria was 16.1% (29 of 180) for IRINOGEM patients versus 4.4% (eight of 180) for GEM patients (χ^2 $P < .001$; Table 2). Three IRINOGEM-treated patients with locally advanced disease had a confirmed CR; no GEM-treated patient had a CR.

Although no difference in TTP was observed (3.5 months [95% CI, 2.8 to 4.2 months] for IRINOGEM patients and 3.0 months [95% CI, 2.5 to 3.7 months] for GEM patients; log-rank $P = .352$; Fig 2 and Table 2;), exploratory analysis by extent of disease suggests that TTP may be longer in patients with locally advanced disease treated with IRINOGEM than in those treated with GEM (Fig 3). Median TTPs for patients with locally advanced disease were 7.7 months (95% CI, 5.3 to 12.1 months) and 3.9 months (95% CI, 2.4 to 5.9 months) for IRINOGEM and GEM, respectively. However, median survival in this small subset of patients numerically favored the GEM arm (11.7 months [95% CI, 8.7 to 15.2 months]) compared with the IRINOGEM arm (9.8 months [95% CI, 7.8 to 15.5 months]). The CIs overlapped significantly.

CA 19-9 Status

Only 238 patients (66% of randomly assigned patients) were considered assessable for the analysis of tumor marker versus radiologic and clinical assessment. As listed in Table 3, the overall diagnostic accuracy of CA 19-9 values in the prediction of tumor response and tumor progression from the radiologic evaluation was low: 57.6% and 59.0%, respectively. However a less than 50% decline in CA 19-9 values was predictive of a lack of response as determined by RECIST criteria (negative predictive value, 94.8%). Furthermore, progression of tumor marker values was predictive of disease progression (positive predicted value, 82.8%). Figure 4 shows the positive correlation of time to CA 19-9 progression with TTP in the subgroup of patients with both events.

Safety

In both treatment groups, similar incidences were seen for the most common adverse events such as nausea (67% and 65%), fatigue (56% and 60%), and vomiting (54% and

Table 2. Summary of Tumor Response Rate, Time to Tumor Progression, and Overall Survival

	IRINOGEM			GEM		
Tumor Response and Progression per RECIST	No. of Patients	%	95% CI	No. of Patients	%	95% CI
Tumor response						
ITT	180			180		
Confirmed* CR + PR ($P < .001$)†		16.1	11.1 to 22.3		4.4	1.9 to 8.6
CR		1.7			0	
PR		14.4			4.4	
Locally advanced disease	27			24		
Confirmed* CR + PR		25.9	11.1 to 46.3		4.2	0.1 to 21.1
Metastatic disease	148			145		
Confirmed* CR + PR		14.9	9.6 to 21.6		4.8	2.0 to 9.7
Tumor progression						
ITT	180			180		
Patients with tumor progression	131	72.8		136	75.6	
TTP						
ITT						
Median	3.5		2.8 to 4.2	3.0		2.5 to 3.7
Locally advanced disease						
Median	7.7		5.3 to 12.1	3.9		2.4 to 5.9
Metastatic disease‡						
Median	3.0		2.6 to 4.0	2.9		2.1 to 3.6
3-month probability of being progression free§		56			50	
Overall survival						
ITT						
Median	8.3		4.7 to 7.5	8.6		8.2 to 7.8
Locally advanced disease						
Median	9.8		7.8 to 15.5	11.7		8.7 to 15.2
Metastatic disease						
Median	5.4		4.4 to 6.7	5.9		4.6 to 7.1
1-year probability of survival§		21			22	

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; IRINOGEM, irinotecan plus gemcitabine; GEM, gemcitabine alone; ITT, intent-to-treat; CR, complete response; PR, partial response; TTP, time to tumor progression.
*Confirmed ≥ 4-6 weeks after initial objective response.
†χ^2 test.
‡Log-rank test.
§Kaplan-Meier estimate.

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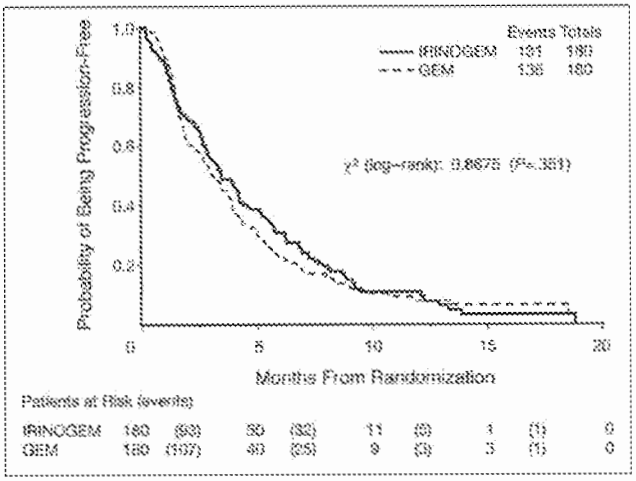


Fig 2. Kaplan-Meier estimates of tumor progression. IRINOGEM, irinotecan and gemcitabine; GEM, gemcitabine alone.

53%). Diarrhea was more common with IRINOGEM treatment (62%) than with GEM treatment (31%) and was more severe. Table 4 summarizes the most common grade 3 or 4 nonhematologic adverse events. Neutropenia, leukopenia, and thrombocytopenia were the most common grade 3 or 4 hematologic adverse events in both groups (Table 5). There were 64 (37%) IRINOGEM-treated patients and 54 (32%) GEM-treated patients who withdrew from treatment because of adverse events; approximately half of the patients in both groups had adverse events associated with progression of disease. Only five of the IRINOGEM patients discontinued therapy because of diarrhea.

Quality of Life

Compliance in completing the FACT-Hep questionnaires was 80% for IRINOGEM-treated patients and 73% for GEM-treated patients during the first 30 weeks of the study. The addition of irinotecan to gemcitabine did not influence quality of life as measured by the questionnaire. No differences were observed between the two treatment groups in the means of the best and worst scores for any of the functional scales.

In addition, the analysis of time to worsening of performance status and time to weight loss ≥ 5% did not demonstrate any statistically significant differences between the two treatment groups (data not shown).

Table 3. Sensitivity, Specificity, and Predictive Values of CA 19-9* Assay in Evaluating Tumor Response and Tumor Progression (RECIST)

Parameter	Tumor Response (%)	Tumor Progression (%)
Sensitivity	82.2	80.9
Specificity	53.4	51.9
Positive predictive value	22.8	32.5
Negative predictive value	94.8	26.0
Diagnostic accuracy	57.6	59.0

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors Group.
*Serum CA 19-9 levels were available for 158 patients in the irinotecan plus gemcitabine arm (median CA 19-9, 1,795 U/mL; range, 0-1,563,800 U/mL) and for 150 patients in the gemcitabine-alone arm (median CA 19-9, 1,766 U/mL; range, 0-710,780 U/mL).

DISCUSSION

This multicenter, phase III study evaluated the efficacy and safety of IRINOGEM when compared with GEM monotherapy with respect to survival, tumor response, TTP, and CA 19-9 response in patients with locally advanced or

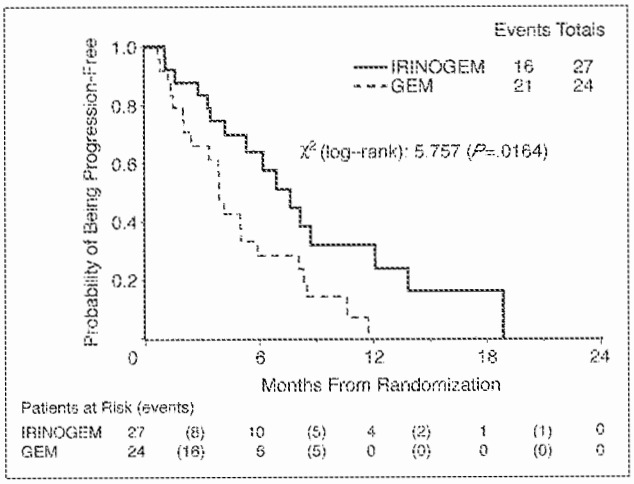


Fig 3. Kaplan-Meier estimates of time to tumor progression in patients with locally advanced disease. IRINOGEM, irinotecan and gemcitabine; GEM, gemcitabine alone.

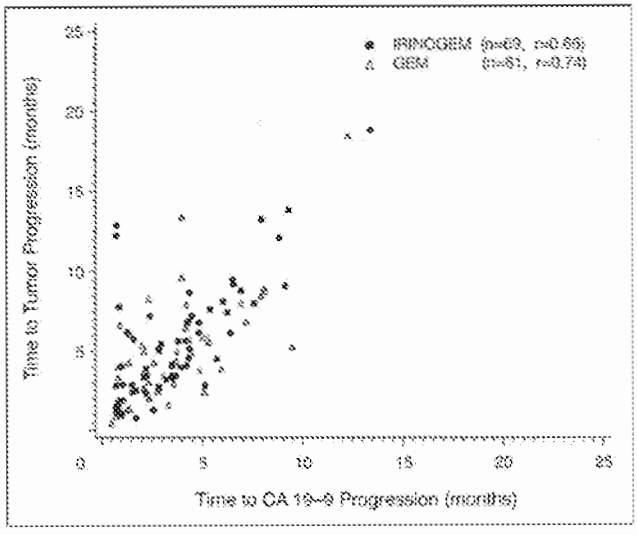


Fig 4. Time to tumor progression measured by radiologic and clinical assessment versus time to CA 19-9 progression (patients with tumor progression and CA 19-9 progression). IRINOGEM, irinotecan and gemcitabine; GEM, gemcitabine alone.

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Table 4. Selected Grade 3 or 4 Adverse Events by Treatment Arm (treated patients)

Adverse Event*	IRINOGEM (n = 173) No. of Patients	%	GEM (n = 169) No. of Patients	%
Diarrhea	32	18.5	3	1.8
Nausea	29	16.8	17	10.1
Fatigue	29	16.8	26	15.4
Abdominal pain	31	17.9	31	18.3
Vomiting	24	13.9	14	8.3
Dehydration	21	12.1	15	8.9
Deep vein thrombosis or pulmonary embolism	26	15	23	14

Abbreviations: IRINOGEM, irinotecan plus gemcitabine; GEM, gemcitabine alone.
*Ordered by frequency in IRINOGEM arm.

metastatic pancreatic cancer. The primary end point, improvement in survival, was not met and this phase III trial should be regarded as negative.

The design of the phase III study was based on preclinical data[18] and phase I and II data[12,13] assessing the combination of irinotecan and gemcitabine in pancreatic cancer. A small randomized phase II study in pancreatic cancer patients previously treated with gemcitabine suggests that irinotecan and gemcitabine are not cross-resistant.[19] In this trial, the combination of irinotecan and raltitrexed resulted in a higher response rate and longer median progression-free survival compared with raltitrexed alone. The trial was closed early because of the superiority of the two-drug combination.

The results of our phase III study corroborate the preliminary evidence of activity observed in phase I and II trials. For all patients, the confirmed tumor response rate was almost four-fold higher favoring IRINOGEM compared with GEM alone (16.1% *v* 4.4%; $P < .001$), and subset analyses suggest that the incremental tumor response with IRINOGEM compared with GEM may be higher in patients with locally advanced disease (25.9% *v* 4.2%, respectively).

Table 5. Hematologic Grade 3 or 4 Adverse Events (treated patients)

Grade 3 or 4 Adverse Event*	IRINOGEM (n = 173) No. of Patients	%	GEM (n = 169) No. of Patients	%
Neutropenia†	65	37.6	54	32.0
Leukopenia†	45	26.0	25	14.8
Thrombocytopenia†	34	19.7	24	14.2
Anemia†	28	16.2	22	13.0
Febrile neutropenia	6	3.5	0	0.0

Abbreviations: IRINOGEM, irinotecan plus gemcitabine; GEM, gemcitabine alone.
*Ordered by incidence in the IRINOGEM arm.
†Abnormality by laboratory assessment or from adverse event reporting.

The patients with locally advanced disease also had the longest median TTP (7.7 months). This last observation should be interpreted with caution because it represents only a small group of patients in this randomized trial.

Despite the higher response rate for the two-drug combination, no survival advantage was detected. This negative result cannot be explained by second-line therapy, which was similar between the two treatment groups. Moreover, demography, baseline disease characteristics and laboratory values, and other possible contributing factors (such as body-surface area and early withdrawal from the trial) were similar between the two groups and cannot explain the results. The 40% improvement in median survival as the primary end point was ambitious. However, had we designed this trial with a larger sample size it is unlikely that the results would have changed because the survival curves are almost identical.

Given that the serum tumor marker CA 19-9 is commonly increased in patients with pancreatic cancer and can change in association with tumor shrinkage or disease progression, CA 19-9 levels were assessed for potential use in determining the antitumor activity of the treatment regimens. In a phase II trial from our group, CA 19-9 had a significant correlation with the radiographically assessed tumor area with regard to extent of change from baseline ($r = 0.67$), timing of minimum on-study values ($r = 0.85$), and tumor progression ($r = 0.89$).[15] In this study, there was significant positive correlation between CA 19-9 progression and tumor progression as determined with RECIST criteria. These results suggest that CA 19-9 levels may provide an adjunct, not a substitute, to radiographic tumor evaluation for assessing treatment effect, notably disease progression, in patients with pancreatic cancer.

The IRINOGEM combination had no detrimental effects on QOL compared with GEM. Few randomized phase III trials in pancreatic cancer published to date have evaluated QOL and other functional outcomes in this group of patients. Compliance with completion of the questionnaire was good: 80% for the IRINOGEM patients and 73% for the GEM patients. However, there were no significant differences between the two treatment arms for any of the tested domains (social, emotional, physical, new symptoms, and functional). Given that the combination resulted in higher response rates, studying improvement on disease-related symptoms potentially dependent on tumor volume (such as biliary obstruction, pain, bowel obstruction, gastric outlet syndrome, and others) may have been of interest, but the study was not designed to collect this information systematically.

Patients receiving the IRINOGEM combination had a higher incidence of any grade of diarrhea (62%) than the GEM-treated patients (31%). This did not affect the start of new treatment cycles or the duration of treatment; only five patients discontinued treatment due to diarrhea. The most common toxicities in more than 50% of patients in both

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arms of the study were nausea, vomiting, and fatigue. Incidences of hematologic toxicities were similar in both arms. The median relative dose intensities of 82% for both irinotecan and gemcitabine over the entire study were not significantly different from that of gemcitabine monotherapy (76%).

The results of this study indicate that the IRINOGEM regimen, given on days 1 and 8 of repeated 3-week cycles, does not improve survival compared with GEM for patients with advanced and metastatic pancreatic cancer, despite higher response rates and manageable safety profile.

Acknowledgment

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Appendix

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

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have 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. Employment: Laura A. Cisar, Pfizer; Adele Morganti, Pfizer; Nicoletta Orlando, Pfizer; Gabriela Gruia, Pfizer; Langdon L. Miller, Pfizer. Consultant/Advisory Role: Caio M. Rocha Lima, Pfizer, Eli Lilly; Mark R. Green, Pfizer, Eli Lilly. Stock Ownership: Mark R. Green, Pfizer; Laura A. Cisar, Pfizer; Nicoletta Orlando, Pfizer; Gabriela Gruia, Pfizer; Langdon L. Miller, Pfizer. Honoraria: Caio M. Rocha Lima, Pfizer, Eli Lilly; Mark R. Green, Pfizer, Eli Lilly. Research Funding: Caio M. Rocha Lima, Eli Lilly. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration form and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

References

1. Greenlee RT, Hill-Harmon MB, Thun TM: Cancer statistics 2001. CA Cancer J Clin 51:15-36, 2001

2. Brennan MF, Kinsella TJ, Casper ES: Cancer of the pancreas, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 4). Philadelphia, PA, Lippincott, 1993, pp 849-882

3. Schnall SF, Macdonald JS: Chemotherapy of adenocarcinoma of the pancreas. Semin Oncol 23:220-228, 1996

4. Stephens CD: Gemcitabine: A new approach to treating pancreatic cancer. Oncol Nurs Forum 25:87-93, 1998

5. Evans DB, Abbruzzese JL, Tyvin AR: Cancer of the pancreas, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 4). Philadelphia, PA, Lippincott, 1997, pp 1054-1087

6. Casper ES: Pancreatic Cancer: How can we do better? Eur J Cancer 29A:171-172, 1993

7. Cullinan S, Moertel CG, Wieand HS, et al: A phase III trial on the therapy of advanced pancreatic carcinoma: Evaluations of the Malinson regimen and combined 5-fluorouracil, doxorubicin, and cisplatin. Cancer 65:2207-2212, 1990

8. Burris HA, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997

9. Storniolo AM, Enas NH, Brown CA, et al: An investigational new drug treatment program for patients with gemcitabine. Cancer 85:1261-1268, 1999

10. Sakata Y, Shimeda Y, Yoshino M, et al: A late phase II study of CPT-11, irinotecan hydrochloride, in patients with advanced pancreatic cancer: CPT-11 study group on gastrointestinal cancer. Jpn J Cancer Chemother 21:1039-1046, 1994

11. Wagener DJ, Verdonk HE, Dirix LY, et al: Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. Ann Oncol 6:129-132, 1995

12. Rocha Lima CM, Leong SS, Sherman CA, et al: Phase I study of CPT-11 and gemcitabine in patients with solid tumors. Cancer Ther 2:58-66, 1999

13. Rocha Lima CM, Savarese D, Bruckner H, et al: Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. J Clin Oncol 20: 1182-1191, 2002

14. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

15. Cella DF, Tulsky DS, Gray G, et al: The functional assessment of cancer therapy scale: Development and validation of the general measure. J Clin Oncol 11:570-579, 1993

16. Overcash J, Extermann M, Parr J, et al: Validity and reliability of the FACT-G scale use in the older person with cancer. Am J Clin Oncol 24:591-596, 2001

17. Heffernan N, Cella D, Webster K, et al: Measuring health-related quality of life in patients with hepatobiliary cancers: The functional assessment of cancer therapy-hepatobiliary questionnaire. J Clin Oncol 20:2229-2239, 2002

18. Bahadori HR, Rocha Lima CM, Green MR, et al: Synergistic effect of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. Anticancer Res 19:5423-5428, 1999

19. Ulrich-Pur H, Raderer M, Verena Kornek G, et al: Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer 88:1180-1184, 2003

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Oxaliplatin and capecitabine after gemcitabine failure in patients with advanced pancreatic, biliary, and gallbladder adenocarcinoma (APBC)

A. Sancho , G. López-Vivanco , I. Díaz de Corcuera , J. Ferreiro , A. Moreno , X. Mielgo ...

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Abstract

15625

Background: Patients (pts) with advanced pancreatic (P), biliary (B) and gallbladder (GB) adenocarcinoma have a poor prognosis. Gemcitabine (G) is the standard treatment for patients with APBC. There is no consensus about second line after progression disease.

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The aim of this study is to examine the efficacy and tolerability of Oxaliplatin (O) and Capecitabine (Cap) after G failure. **Methods:** From February 2005 to February 2007 18 pts with histologically proven unresectable or metastastic APBC, and refractory to G were included. Pts received CAPOX (O 130 mg/m^2 D1 and Cap 1000 mg/m^2 D2-14). Treatment cycles were repeated every 3 weeks and continued until progression or unacceptable toxicity. **Results:** Eighteen pts were evaluated: 12 male (66.7%); 6 female (33.3%), Median Age: 57 (range 4–72). PS 0/1/2: 6/9/3. Location: P: 9 (50%), B: 4 (22.2%), GB: 4 (22.2%), ampuloma: 1 (5.6%). Stages: III: 1 (5.6%), IV: 17 (94,6%). Median number of cycles: 3,5 (1-11). Grade 2/3 toxicity: Sensitive peripheral neurotoxicity 4/0; Hand-foot-syndrome 0/1, Diarrhea: 5/2, Nausea/vomiting: 4/0, Neutropenia: 1/1, Thrombocytopenia 2/0, Anemia 2/1: Fatigue: 6/4, Anorexia; 1/2. Overall response rate: Partial Response: 1/18 (5.6%), Stable Disease: 8/18 (44.4%), Progressive disease: 5/18 (27.8%). Four pts were not evaluated because early deaths. 27.7% of pts had a 50% or more decrease in Ca 19-9 levels. Median overall survival was 24.71 weeks (w) and median progression free survival was 16.71 w. The OS was higher in patients with PS0 and PS1 than pts with PS2 (p=0.001). **Conclusions:** Oxaliplatine and Capecitabine can be safely administered with tolerable safety profiles in pts with APBC previously treated with G. This study shows similar results in OS to infusional 5-Fiuorouracil and oxaliplatin in ABPC (CONKO 0003).

No significant financial relationships to disclose.

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Mini-review

Combinational therapy: New hope for pancreatic cancer?

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ABSTRACT

Pancreatic cancer is a devastating disease with a low overall survival rate. Chemotherapy is the most common treatment for patients presenting with advanced pancreatic cancer. Gemcitabine achieves a modest improvement in overall survival and is the gold standard for advanced pancreatic cancer treatment. Capecitabine and S-1, derivatives of 5-fluorouracil (5-FU), offers minimal clinical benefits. Folfirinox represents a new and aggressive regimen that might benefit patients of metastatic pancreatic cancer with good performance status. Other chemotherapy drugs such as platinums and irinotecan do not provide significant improvement in overall survival, but have been used as part of combinational therapies. Comparing to systemically delivered chemotherapy, regional intra-arterial chemotherapy achieves higher local drug concentration in tumors with lower systemic drug toxicity, and may serve as a better treatment regimen. Although there have been progress made in chemotherapeutic strategies against pancreatic cancer, the overall survival is not significantly improved in the last decade. Recently, development of chemotherapy in combination with molecular targeted therapies holds great promise in pancreatic cancer treatment, especially in patients with metastatic disease. Growing bodies of preclinical and clinical evidences indicate that the combination of conventional modalities with specific molecular targeted therapy increase the efficacy of the monotherapy without an increase in toxicity. In this review, we summarized the current regimens of chemotherapy and molecular targeted therapy for advanced pancreatic cancer and highlighted the novel combinational treatments tested in recent clinical trials.

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1. Introduction

Pancreatic cancer is an aggressive disease associated with an extremely poor prognosis. It is one of the most malignant tumors characterized by its insidious onset, late diagnosis and low survival rate. Pancreatic cancer is the fourth leading cause of cancer death in the United States in 2010 and the 5-year survival rate is only 6% [1]. Only 10–15% patients have disease amenable to surgical resection, and the recurrence rate remains high even with a radical surgery. Although some progress has been made in developing new diagnostic methods and novel targeted therapies, the overall survival rate has not improved over the last decade. The impairment of drug delivery pathways caused by the low density of vasculature within pancreatic tumors makes pancreatic tumors highly resistant to chemotherapy. Systemic treatment of pancreatic cancer thus has only modest benefits [2,3]. Patients with pancreatic cancer usually present with locally advanced, unresectable or metastatic diseases, and are often sensitive to the adverse effects of more intensive treatments. Therefore, postoperative chemo- or radiation therapy is still necessary for pancreatic cancer treatment. Although pancreatic cancer patients are largely resistant to radiation therapy, the results to date suggest that the use of induction chemotherapy can select patient populations without early metastatic disease who can benefit from consequent aggressive local therapy of chemoradiation, which provides local control for palliation of symptoms and improved survival. However, there is insufficient evidence to recommend chemoradiation in patients with locally advanced unresectable pancreatic cancer as a superior alternative to chemotherapy alone. Recent studies using regional intra-arterial chemotherapy which was expected to increase the local drug concentration has generated promising results, and clinical trials in pancreatic cancer have been focusing on developing more effective treatment regimens by combining cytotoxic chemotherapy agents with molecular targeted therapies. This review summarizes the classic and the current regimens of chemotherapy for advanced pancreatic cancer and highlights the combination of chemotherapy and molecular targeted therapies tested in recent clinical trials (Fig. 1).

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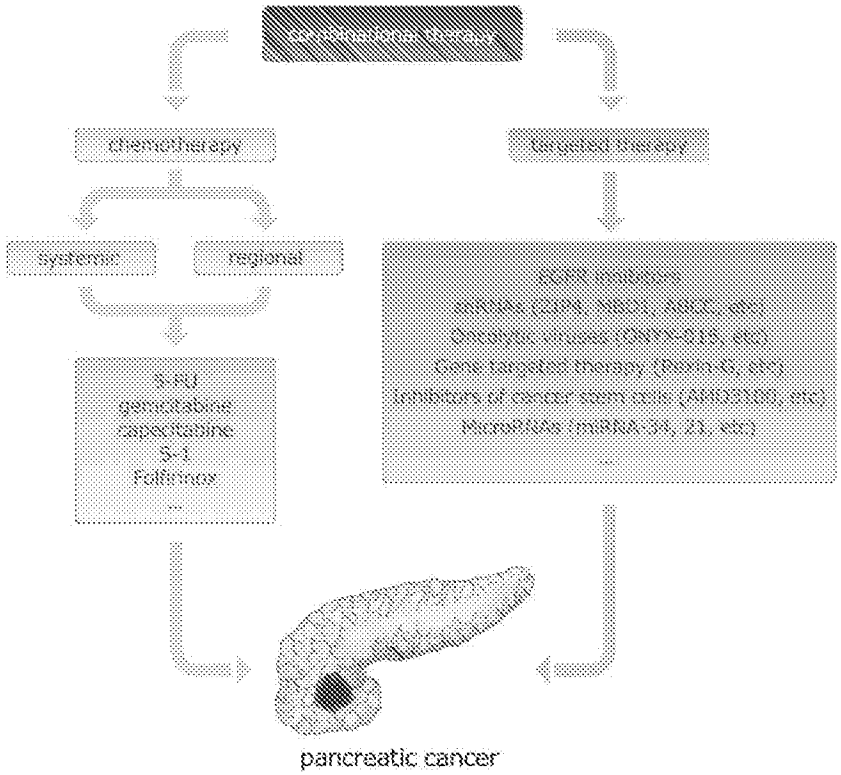


Fig. 1. Combinational therapy is a new hope for pancreatic cancer. Pancreatic cancer is a devastating disease. Surgical resection only applies to less than 15% of the patients diagnosed with pancreatic cancer, and the recurrence rate is high. Traditional chemotherapy is ineffective. Combination of chemotherapy and molecular targeted therapy holds great promise in pancreatic cancer treatment. As they have different pharmacological effects to kill tumor cells, the combinational therapy is believed to provide synergistic effect and is a new hope for pancreatic cancer treatment.

2. 5-Fluorouracil (5-FU) and its derivatives

2.1. 5-FU and 5-FU based therapies

5-Fluorouracil (5-FU), 5-fluoro-1H-pyrimidine-2,4-dione, is an antimetabolite pyrimidine analogue. Before 1995, 5-FU was the only drug with a response rate with an upper 95% confidence limit exceeding 20% before the CT was widely used. Prior to the approval of gemcitabine in 1996, 5-FU was considered the standard chemotherapeutic treatment for advanced pancreatic cancer, showing a wide range of response rates from 0% to 67% [4]. In trials using CT to precisely measure the tumor size and extent, the reported single-agent 5-FU response rates ranged from 0% to 19% [5]. Based on these findings, 5-FU was tested in combination with other chemotherapy agents such as doxorubicin and mitomycin [6], but none of the randomized trials showed a survival benefit for 5-FU-based combination regimens compared with 5-FU alone. However, a 5-FU and cisplatin combination treatment in a phase II trial involving patients with metastatic pancreatic cancer reached a response rate of 26% and median survival of 7 months [7]. Based on these promising results, a large randomized Phase III trial comparing single agent 5-FU vs. cisplatin plus 5-FU was conducted. In this trial involving 207 patients, 5-FU plus cisplatin was shown to be superior to 5-FU in terms of response and progression-free survival (PFS), but not in overall survival (OS) [8]. However, the combination therapy was more toxic, as 48% of the patients in the combination arm experienced World Health Organization (WHO) grade 3–4 toxic reactions compared to 20% in the 5-FU arm [9].

2.2. Capecitabine

Capecitabine is an oral prodrug of 5-FU which is rationally designed to generate 5-FU preferentially within tumors. It is converted to 5-FU by three sequential enzymatic reactions. The last enzyme, thymidine phosphorylase (TP), has a higher level in tumors than in healthy tissues and therefore makes capecitabine more effective and specific in targeting tumors than 5-FU [10]. Treatment with capecitabine showed promising clinical benefits on tumor-related symptoms and yielded objective response activity in patients with metastatic or locally advanced pancreatic cancer, suggesting capetabine might be a better option than 5-FU [11]. A recent study in xenograft animal models indicated that capecitabine was synergistic when used with gemcitabine together [12], two phase III trials were performed to test the combination therapy. In the first SAKK/CECOG trial, patients were randomly assigned to receive gemcitabine and capecitabine (oral capecitabine 650 mg/m^2 twice daily on days 1–14 plus gemcitabine 1000 mg/m^2 by 30-min infusion on days 1 and 8 every 3 weeks) or gemcitabine alone (1000 mg/m^2 by 30-min infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks). The trial failed to achieve statistical significance on OS as the median OS was 8.4 months for the combination and 7.3 months for gemcitabine ($P = 0.314$) [13]. There was no indication of a difference in clinical benefit response (CBR) and quality of life (QOL) between the two groups. Regardless of their initial condition, some patients experienced an improvement in QOL on chemotherapy, followed by a decline before treatment failed [14]. In the second trial conducted by the National Cancer Research Institute and Cancer Research at UK, the dose level and dosing frequency were more intense than the first trail. In the combination arm, gemcitabine was delivered 1000 mg/m^2/week and capecitabine 1660 mg/m^2/day for 3 out of every 4 weeks. The median OS for gemcitabine alone and the combination were 6 and 7.4 months and the 1-year survival rates were 19% and 26% ($P = 0.026$). The combination therapy showed statistically significant improvements than gemcitabine alone in the survival rate [15]. These

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two trials suggest that the addition of capecitabine to gemcitabine is particularly advantageous for patients with good performance status. Capecitabine was also studied in combination with radiotherapy for patients with locally advanced pancreatic cancer. The survival rate, response, and toxicity were comparable to infusional 5-FU and radiotherapy [16,17]. Further studies are warranted to investigate the mechanism of capecitabine in the chemoradiation therapy of pancreatic cancer.

2.3. S-1

S-1 is another oral fluoropyrimidine which has been used in pancreatic cancer treatment. S-1 was developed based on a biochemical modulation of 5-FU and contains TF (tegafur), CDHP (gimeracil) and OXO (potassium oxonate) in a molar radio of 1:0.4:1 [18]. A phase II trial has demonstrated that S-1, as a single agent, was effective and well tolerated in patients with metastatic pancreatic cancer and the median OS was 5.6 months with a 1-year survival rate of 15.8% [19]. S-1 monotherapy has also shown a marginal anti-tumor activity in patients with gemcitabine refractory metastatic pancreatic cancer [20], suggesting that S-1 may be a viable option for advanced pancreatic cancer [21]. A recent phase II trial using S-1 showed comparable effect on PFS and OS to gemcitabine [22], however, further studies are needed to confirm this result. After a preclinical study showed that S-1 and gemcitabine had synergistic effects on each other [23], many trials have been performed to determine whether combination therapy offers additional advantage. In one phase II trial, the overall response rate was 32% and the median OS was 8.4 months [24]. In a phase III trial named GEST study, 834 patients have been randomized to three groups receiving gemcitabine, S-1 or gemcitabine plus S-1. The result demonstrated that gemcitabine plus S-1 significantly improved PFS, but not OS and this combination might contribute to a better QOL, emerging as a treatment option in some cases [25]. Two recent phase II studies of the combination of S-1 and radiotherapy showed a promising result, and this well-tolerated regimen can be recommended as an effective treatment for locally advanced pancreatic cancer [26,27].

3. Gemcitabine and gemcitabine-based therapies

In 1996 the Food and Drug Administration (FDA) approved the first-line use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer [28]. Since then, monotherapy of gemcitabine has become the standard treatment for advanced pancreatic cancer in the USA. The approval was mainly based on a randomized phase III trial. The study compared gemcitabine with 5-FU and demonstrated that gemcitabine could provide better median OS (5.7 vs. 4.2 months), 1-year survival rate (18% vs. 2%) and CBR (22.2% vs. 4.8%) than 5-FU for patients with advanced, symptomatic pancreas cancer [2]. The results of this study suggest that gemcitabine is the first cytotoxic agent with a clinically meaningful impact on survival and disease-related symptoms in advanced pancreatic cancer. For patients with gross complete (R0 or R1) resection of pancreatic cancer, postoperative administration of gemcitabine improved 5-year OS compared to observation alone (21% vs. 9%) in a phase III trial (CONKO-001) [29]. Another phase III trial (ESPAC-3) compared Gemcitabine to bolus 5-FU/folinic acid following surgery showed no difference in median survival (23.6 vs. 23 months), but less toxicity [30]. These two studies supported the use of gemcitabine monotherapy as adjuvant chemotherapy in resectable pancreatic cancer.

A large number of studies have been conducted to test if combining other chemotherapy agents with gemcitabine can further improve the outcomes. A lot of phase II trials compared single-agent gemcitabine with the combination of gemcitabine plus 5-FU given by bolus or continuous intravenous injection and the results were disappointing [31–34]. Another phase III trial showed a trend toward improved survival with median OS (5.4 vs. 6.7 months, $P = 0.09$) and PFS (2.2 vs. 3.4 months), but more adverse reactions were observed in the combination therapy arm [35]. These studies suggest that the addition of 5-FU to gemcitabine did not offer significant benefit to the survival of patients with pancreatic cancer when compared with gemcitabine alone.

Regimens of gemcitabine plus platinums have been tested to improve the patient outcome. In a randomized trial, the addition of cisplatin to gemcitabine significantly improved the PFS (7 vs. 4.7 months) and the overall response rate (26.4% vs. 9.2%) compared with gemcitabine alone; however, the CBR was similar in both arms (49% vs. 52.5%) [36]. In a different randomized phase III trial, combination treatment was associated with a prolonged median OS (7.5 vs. 6.0 months) and PFS (5.3 vs. 3.1 months), however, no statistical significance was obtained [37]. The combination of gemcitabine and cisplatin currently may be considered as the optimal treatment for patients with locally advanced and/or metastatic pancreatic cancer.

Given the promising phase II results regarding to the efficacy of gemcitabine and oxaliplatin combination [38], Louvet et al. conducted a phase III study comparing gemcitabine and oxaliplatin with gemcitabine alone in advanced pancreatic cancer [39]. The combination arm was superior to gemcitabine alone arm in terms of response rate (26.8% vs. 17.3%, $P = 0.04$), PFS (5.8 vs. 3.7 months, $P = 0.04$) and CBR (38.2% vs. 26.9%, $P = 0.03$). Median OS of the combination therapy was also longer than the monotherapy (9.0 and 7.1 months) although it was not statistically significant ($P = 0.13$). This regimen was used for patients with advanced pancreatic cancer after progression following standard gemcitabine treatment and more than half of the patients reached a clinical benefit [40]. Gemcitabine plus oxaliplatin may benefit patients with untreated advanced pancreatic cancer or gemcitabine refractory patients.

4. Folfirinox: oxaliplatin, irinotecan, fluorouracil, and leucovorin

Folfirinox is a new and aggressive chemotherapy combination regimen for pancreatic cancer. Although the four components of Folfirinox are old drugs, this new combination regimen may hold potential in providing new therapy for pancreatic cancer. The result of the phase II trial was promising as the confirmed response rate was 26% and the median OS was 10.2 months [41]. Folfirinox was further assessed in a phase III trial and the result was similar to the phase II trial with a 11.1 months median OS in the Folfirinox arm while 6.8 months in the gemcitabine group ($P < 0.001$). The objective response rate in Folfirinox group was also significantly higher than the gemcitabine group (31.6% vs. 9.4%, $P < 0.001$). Though Folfirinox was associated with a higher survival rate, it had a corresponding increase in toxicity, such as severe neutropenia and febrile neutropenia, despite treating with granulocyte-colony stimulating factor [42,43]. In addition to the toxicity, the trial was criticized for being highly selective, with only 39% of the patients had a primary tumor in the head of pancreas compared to what's observed in the clinical practice (about 2/3) [44,45]. In spite of these controversies, the new regimen still holds great promise for patients of metastatic pancreatic cancer with good performance status. In order to alleviate the side effects, the simplified versions of Folfiri (5-FU, folinic acid, and irinotecan) or Folfox (folinic acid, 5-FU, and oxaliplatin) has been tested in a phase II study and both were tolerated with manageable toxicity, offering modest activities, while the curative effects were not as promising as the full version [46].

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5. Other drugs and regimens

5.1. Platinums: cisplatin and oxaliplatin

Wils et al. showed that cisplatin used as a single chemotherapy agent had a response rate of 21% and its reported median survival time was 4 months in pancreatic cancer [47]. No further studies had been carried on the monotherapy of cisplatin, however, it was tested in combination with 5-FU and gemcitabine in many trials. Oxaliplatin appears to have a slightly different spectrum of activity *in vitro* compared with other platinums. Currently, there has only been one small randomized trial comparing oxaliplatin as a single-agent therapy to 5-FU monotherapy, which showed a better PFS and OS than 5-FU (2.0 and 3.4 months vs. 1.5 and 2.4 months) [48]. Oxaliplatin plus infusional 5-FU as a second line salvage treatment for patients who received prior gemcitabine therapy had shown its better efficacy and doubling of survival time compared to 5-FU alone (CONKO-003 trial) [49]. The combination of platinums with other classes of chemotherapy agents may synergize the therapeutic effect and this needs to be further tested in a larger sample size.

5.2. Taxanes: paclitaxel, docetaxel, and nab-paclitaxel

Paclitaxel used as a single chemotherapy agent has been proved to have minimal effect on pancreatic cancer patients [50]. Safran and Rathore found paclitaxel could be used as a radiation sensitizer for locally advanced pancreatic cancer [51]. Docetaxel has also been used in combination with radiotherapy. But a significant rate (28%) of rehospitalization was observed in the trail because of adverse reactions such as vomiting and anorexia or progressive disease [52]. Paclitaxel or docetaxel treatment is still considered as salvage chemotherapy after gemcitabine failure in patients with good performance status [53,54]. Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. In a phase II trial studying Nab-paclitaxel plus gemcitabine, for patients who had tumor expressing secreted protein acidic and rich in cysteine (SPARC) protein, 23% of them achieved complete response, and 55% had partial response by Response Evaluation Criteria In Solid Tumors (RECIST) criteria [55].

5.3. Irinotecan

Irinotecan (CPT-11) monotherapy was tested in a phase II trial and the median survival duration was 5.2 months and the toxicities were mild [56]. Another trial tested irinotecan as a salvage single-agent chemotherapy for gemcitabine-pretreated patients. The median OS was 6.6 months and PFS was 2.0 months, which indicated that single-agent irinotecan as a second-line chemotherapy may be marginally effective [57]. Phase II trials of irinotecan plus gemcitabine were carried on and the combination therapy appeared to provide better clinical benefits as compared to the irinotecan montherapy. An early multicenter phase II study showed that the regimen was effective against pancreatic cancer with a 24.7% objective response rate [58]. And in a recent study, the combination of gemcitabine plus irinotecan was administered in a weekly schedule (more frequently than the previous one) and it offered an encouraging result that the PFS and OS were 9.2 and 11.8 months, respectively, with a 2-year survival rate of 22% [59]. Gemcitabine alone and gemcitabine plus irinotecan were compared in an international multi-center phase III trial. No statistically significant difference in overall or 1-year survival rate was observed between gemcitabine monotherapy and gemcitabine plus irinotecan in the treatment of advanced pancreatic cancer [60]. A pilot study of irinotecan/oxaliplitin combination chemotherapy for patients with gemcitabine- and 5-FU-refractory pancreatic cancer has been reported recently. The PFS and OS were 1.4 months and 4.1 months, respectively. The regimen appeared to be a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who had failed to respond to gemcitabine- and 5-FU-based chemotherapy [61]. Further studies of more regimens involving irinotecan should be tested in the future.

As a brief summary, gemcitabine and oral fluoropyrimidines may be the key drugs in the chemotherapy for pancreatic cancer. Although many other phase III trials (Table 1) have been conducted recently, no significant improvements were found.

6. Regional intra-arterial chemotherapy in pancreatic cancer

The responses to chemotherapeutic agents rely on not only the chemosensitivity of the tumors but also the local drug concentration. As the effects of systemic chemotherapy are limited, many attempts have been made on regional intra-arterial chemotherapy. Comparing to systemic chemotherapy, regional intra-arterial chemotherapy has advantages of achieving higher local drug concentration in tumor with lower systemic drug toxicity. The efficacy of regional intra-arterial chemotherapy has been proved by pharmacokinetic analysis and animal experiments [66,67]. Many trails have been conducted to confirm the validity of this approach in locally advanced and metastatic pancreatic cancer (Table 2). Numbers of chemotherapeutic agents such as 5-FU, gemcitabine, and cisplatin were used alone or in combinations in these studies. Some trials used celiac axis infusion (CAI) and others used selective arterial infusion (SAI) and hypoxic abdominal perfusion (HAP). The results indicated that regional intra-arterial chemotherapy was a tolerable and feasible treatment to improve the prognosis in patients of locally advanced and metastatic pancreatic cancer. This approach was tested in resectable pancreatic head adenocarcinoma in another trial. Although no statistical difference was observed in survival time, the alleviated pain and reduction of serum tumor markers in most patients suggested that regional intra-arterial chemotherapy could offer some clinical benefit [68].

Table 1
Recent phase III trials of chemotherapy for pancreatic cancer.

Series	Treatment	Number	OS	P	PFS	P
Pelzer et al. [62]	Oxaliplatin + folinic acid + 5-FU + BSC[a] (after gemcitabine)	23	9.09	0.031	–	–
	BSC (after gemcitabine)	23	7.90		–	–
Dahan et al. [63]	5-FU + folinic acid + cisplatin (followed by gemcitabine)	102	6.7	0.83	3.4	0.67
	Gemcibabine (followed by 5-FU + folinic acid + cisplatin)	100	8.03		3.5	
Ueno et al. [64]	Gemcitabine after surgery	58	22.3	0.19	11.4	0.01
	Surgery only	60	18.4		5.0	
Poplin et al. [65]	Gemcitabine	275	4.9	0.15	2.6	0.09
	Gemcitabine (fixed dose rate infusion)	277	6.2		3.5	
	Gemcitabine + oxaliplatin	272	5.7		2.7	

[a] BSC = Best supportive care.

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Table 2
Some studies on regional intra-arterial chemotherapy in locally advanced and metastatic pancreatic cancer.

Series	Regimen	Techniques	Number of cases	Median survival
Link et al. [70]	Mitoxantrone + folinic acid + 5-FU + cisplatin	CAI	32	8.3 mon
Cantore al. [71]	Folinic + 5-FU + carboplatin + epirubincin	SAI or CAI	96	9.9 mon
Bayer et al. [72]	5-FU + mitomycin + cispaltin	SAI	14	8 mon
Barletta et al. [73]	Folinic + 5-FU + carboplatin + epirubincin	SAI	32	11.8 mon
Pohlen et al. [74]	5-FU + mitomycin + cisplatin	HAP	8	12.7 mon

Regional Chemotherapy in Locally Advanced Pancreatic Cancer (RECLAP) trial is a phase I trial on evaluating super-selective intra-arterial administration of gemcitabine in patients with locally advanced and unresectable pancreatic adenocarcinoma and is the latest trial testing this approach in the USA. The priliminary results indicated that intra-arterial gemcitabine therapy was safe and feasible. The objectives included the determination of PFS and OS, as well as the conversion rate from unresectable to potentially resectable pancreatic cancer [69]. Regional intra-arterial chemotherapy is a promising approach to increase local drug concentration, relieve pain, reduce risk of liver metastasis, and turn unresectable patients into resectable status and finally can improve the prognosis. A large-scale, randomized, and well-controlled clinical trial is needed to further confirm the efficacy of regional intra-arterial chemotherapy in pancreatic cancer.

7. Molecular targeted therapy

Although the drugs such as 5-FU, gemcitabine and S1 remain the chemotherapeutic mainstay in the treatment of all setting of pancreatic adenocarcinoma for decades, recent advances in our understandings of the molecular abnormalities implicated in pancreatic cancer pathogenesis have led to the development of new targeted agents for pancreatic cancer therapy, which include small-molecule inhibitors, short-hairpin RNAs (shRNAs), oncolytic viruses, gene therapy, and immunotherapy. While many of these targeted therapies have only been assessed preclinically or in early clinical trials, they hold potential in combination with other chemotherapeutic drugs in improving clinical outcomes of pancreatic cancer.

8. Targeted therapies in clinical trials

The most successful molecular targeted therapy against pancreatic cancer is the inhibition of epidermal growth factor receptor (EGFR) [75]. The targeted EGFR inhibition, particularly erlotinib as a small-molecule inhibitor of EGFR tyrosine kinase, has been one of the few effective therapies and it was able to improve the overall survival of patients with advanced pancreatic cancer in combination with gemcitabine in a phase III randomized trial [76]. Cetuximab acting as a monoclonal antibody against EGFR, when combined with gemcitabine and oxaliplatin, also led to a statistically significant improvement of a median PFS and OS [77,78]. Combination treatment with gemcitabine and EGFR monoclonal anbodies, such as Matuzumab and Trastuzumab, is currently being tested in clinical trials showing a promising partial response.

A better understanding of the biology of pancreatic cancer also led to the development of other small molecules targeting vascular endothelial growth factor (VEGF) [79], Kirsten rat sarcoma oncogene (K-ras) [80], gastrin [81,82] and cholecystokinin receptor (CCK-BR) [83,84]. Due to lack of clinical benefit compared with gemcitabine alone in randomized phase III trials, the outcomes of the combination with the molecular targeted therapy and chemotherapy drugs in the clinical setting are still disappointing, even with intensive studies. Combination therapies with some other agents including PI3K/Akt/mTOR pathway inhibitor, TGFβ/Smad based therapeutic strategy, and telomerase inhibitor are also under investigation [85]. In addition to the studies that aim to design small molecule inhibitors or antibody-based antagonists targeted to specific molecular abnormality, gene therapy also offers other new opportunities for a variety of targeting strategies by using some plasmids or viral vectors. In a recent phase I/II trial, Chawla et al. showed that Rexin-G, a nonreplicative-targeted retroviral gene therapy vector, which can cause cell death by delivering a dominant negative cyclin-G1 gene to tumor cells, was well-tolerated and may prolong survival in chemotherapy-resistant pancreatic cancer patients [86]. Furthermore, oncolytic viruses can selectively target, replicate in, and kill tumor cells by a variety of mechanisms, including direct cell lysis and the expression of anticancer proteins within the cells [87,88]. Recently, a phase I/II clinical trial assessing an oncolytic virus, ONYX-015, showed favorable results (tumor reduction or stabilization) in about 50% of patients [89,90].

Combination therapies may be the ultimate hope to improve the bleak outlook for patients suffered from pancreatic cancer. However, up to the present, the outcomes of a number of phase III clinical trials are still unavailable, further studies are needed to test the efficacy of the combination therapy in pancreatic cancer.

9. Promising targeted therapies in preclinical trials

Recent progress on the better understanding of the molecular mechnism in the aggressive profile of pancreatic cancer have generated more promising molecular targets and therapeutic agents in pancreatic cancer treatment. These agents include small molecule inhibitors, short-hairpin RNAs (shRNA), gene targeted therapy, microRNAs, oncolytic virus, and interferes of cancer stem cells.

Administration of Gefitnib, another kind of EGFR tyrosine kinase inhibitor, led to an increase of cell death in pancreatic cancer cell lines, suggesting an additive inhibitory effect for pancreatic cancer cell *in vitro*. Other small-molecule antagonists, such as those targeting hedgehog [91], protein kinase D [92], and Bcl-2 [93] have not yet been studied in clinical trials but show great promise preclinically (Table 3).

ShRNAs are used to selectively silence gene expression and have shown some potential as a novel cancer therapy fashion. A recent study found that a zinc transporter (ZIP4) was overexpressed in human pancreatic cancer cell lines and clinical specimens, and silencing of ZIP4 by shRNA significantly inhibited pancreatic cancer growth and increases the survival of nude mice with pancreatic cancer xenografts [94,95]. Methyl-CpG-binding domain protein 1 (MBD1), a transcriptional regulator by coupling DNA methylation to transcriptional repression, has been found to be upregulated in human pancreatic adenocarcinoma which may be involved in inactivation of tumor suppressor genes during pancreatic tumorigenesis. Suppressive effect of MBD1 siRNA on cell growth *in vitro* indicates that it is a promising candidate for gene therapy of pancreatic cancer [96,97]. In addition, silencing of ATP-binding cassette sub-family C member 4 (ABCC) in pancreatic cancer cells by shRNA leads to inhibition of cell growth and represents a promising target for gene therapy [98]. These studies suggest that the shRNA therapy may provide specific knocking down of key

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Table 3
Outcomes of preclinical trials of molecular targets to hedgehog, K-RAS/MAPK, mTOR, NF-kappaB, PKD, Bcl-2 for pancreatic cancer treatment.

Single-agent drug arm	Targeting sites	Outcomes	Reference
Cyclopomine (HhAntag)	SHH (blocking the function of smoothened in hedgehog pathway)	HhAntag is under development	Taipale et al. [114] Kumar et al. [115]
Mutant KRAS–RNA interfere	*K-RAS* gene	A significantly potent clinical relevance	Fleming et al. [116]
BAY 43-9006/sorafenib	RAF gene	A phase I trial in combination with gemcitabine needs further evaluation	Siu et al. [117]
PD 0325901	MEK signaling pathway	Under development	Rinehart et al. [118]
Rapamycin (CCI-779, RAD001, AP23573)	mTOR	A putative therapeutic target and currently in clinical development	Adjei et al. [119]
Thalidomide (bortezomib, sulphasalazine)	NF-κB	In clinical study	Sebens et al. [120]
CRT0066101	Protein kinase D (PKD)	A novel therapeutic target	Harikumar et al. [92]
TW-37	Bcl-2	A novel therapeutic target	Wang et al. [94]

1. BAY 43-9006/sorafenib, an immediate downstream molecule of RAS in the RAS-MAPK pathway.
2. PD 0325901, a second-generation small molecule MEK inhibitor with a highly specific, superior biopharmaceutical and pharmacological properties.
3. CCI-779, RAD001, and AP23573 are compounds structurally related with Rapamycin.

molecules in pancreatic cancer pathogenesis, sensitize the efficacy of traditional chemotherapy, and offer additional therapeutic benefit to patients with advanced pancreatic cancer.

Oncolytic virus therapy represents another potent molecular targeted therapy for pancreatic cancer because of their selected replication in tumor cells. Fu et al. used a novel oncolytic virus (FusOn-H2) from the type 2 herpes simplex virus, which only replicates in K-ras activated cells, to treat established pancreatic cancer xenografts, and found that intraperitoneal delivery of FusOn-H2 completely eradicated established orthotopic tumors in 75% animals and completely prevented local metastases, indicating that FusOn-H2 had potent activity against human pancreatic cancer and may be a promising candidate for virotherapy of this malignancy [99]. Other virus therapies include adenovirus, reo virus and measles virus [100–102].

Angiotensin-converting enzyme 2 (ACE2), a target molecular to counterbalance the growth-promoting function of angiotensin converting enzyme, was also found to be widely down-regulated in pancreatic cancer tissues and cells. Restoration of ACE2 could strongly enhance the anti-tumor activity of gemcitabine in a pancreatic cancer xenografts model in vivo and significantly prolong the survival time of animals, indicating that ACE2 is a promising candidate for pancreatic cancer treatment [103]. Similarly, actin regulating protein Profilin1 (Pfn1) is found to be often significantly low-expressed in a variety of tumor tissues and cell lines from human malignancies, including breast cancer and pancreatic cancer. Overexpression of Pfn1 leads to inhibition of cell proliferation, failing to form tumors in vivo, and enhancement of chemo- or radioactive-sensitivity. Pfn1 has also been identified to stimulate anti-tumor immune responses and the rejection of established tumors in mice. All these researches indicate that perturbing Pfn1 may be as a good molecular strategy for pancreatic cancer [104,105]. PAR-4, an important apoptosis inducer which is down-regulated in pancreatic cancer, can also serve as a potential therapeutic target due to its association with k-ras status, along with the crosstalk with crucial resistance and survival molecules, NF-κB, and Bcl-2 [106].

The importance of eradicating pancreatic cancer stem/initiating cells has made it an attractive therapeutic strategy for cancer therapy. A specific inhibitor of hedgehog signaling pathway preferentially reduced pancreatic cancer cells expressing high levels of aldehyde dehydrogenase, a stem cell-like marker, suggesting its potential cytotoxic effect on the pancreatic tumor initiating/stem cells [107]. AMD3100, the non-peptidic antagonist of CXCR4 (CXC chemokine receptor 4), also reduced tumor metastasis established by the migrating $CD133^+/CXCR4^+$ L3.6pl cell fraction orthotopically injected into athymic mice [108]. Thus, the combination of treatment targeting the oncogenic elements in pancreatic cancer stem/initiating cells, with the conventional chemotherapeutic regimens, could represent promising therapeutic strategies. Also it is worth noting that, identification of unique patterns of deregulated microRNA expression in pancreatic cancer implicates the importance of microRNAs as therapeutic targets [109]. Although further studies are needed to understand the molecular mechanism of microRNA mediated pancreatic cancer pathogenesis and progression, many investigations have been performed to test the efficacy of microRNA-based therapies such as miRNA-34 [110], miRNA-3548 [111], miRNA-21, miRNA221 [112], and miRNA-10a [113], which may become a novel therapeutic target in pancreatic cancer.

10. Conclusion

At present, gemcitabine and gemcitabine based regimens are still the standard therapies for pancreatic cancer. Traditional 5-FU therapy has been proved to have minimal effects on the disease, however, new oral fluoropyrimidines, such as capecitabine and S-1 may provide more effective results. Folfirinox is a promising but toxic combination proposal that might be an option for patients with good physical status. Regional intra-arterial chemotherapy is a better approach to achieve higher local drug concentration than systemic chemotherapy. Pancreatic cancer still remains as a serious medical problem with poor prognosis and recently more efforts have been made on molecular targeted therapies. Large numbers of targeted therapeutic agents have been produced and many of them have been tested in preclinical and clinical trials. Personalized treatment holds great promise which will identify patient populations who are sensitive to a specific regimen. We believe the combination of chemotherapy and molecular targeted therapy can bring new hope to patients with advanced pancreatic cancer.

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References

[1] A. Jemal, R. Siegel, J. Xu, E. Ward, Cancer statistics, 2010, CA Cancer J. Clin. 60 (2010) (2010) 277–300.

[2] H.R. Burris, M.J. Moore, J. Andersen, M.R. Green, M.L. Rothenberg, M.R. Modiano, M.C. Cripps, R.K. Portenoy, A.M. Storniolo, P. Tarassoff, R. Nelson, F.A. Dorr, C.D. Stephens, D.D. Von Hoff, Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial, J. Clin. Oncol. 15 (1997) 2403–2413.

[3] R. Andersson, U. Aho, B.I. Nilsson, G.J. Peters, M. Pastor-Anglada, W. Rasch, M.L. Sandvold, Gemcitabine chemoresistance in pancreatic cancer: molecular mechanisms and potential solutions, Scand. J. Gastroenterol. 44 (2009) 782–786.

[4] S.K. Carter, R.L. Comis, The integration of chemotherapy into a combined modality approach for cancer treatment. VI. Pancreatic adenocarcinoma, Cancer Treat. Rev. 2 (1975) 193–214.

[5] D.G. Haller, Chemotherapy for advanced pancreatic cancer, Int. J. Radiat. Oncol. Biol. Phys. 56 (2003) 16–23.

[6] S.A. Cullinan, C.G. Moertel, T.R. Fleming, J.R. Rubin, J.E. Krook, L.K. Everson, H.E. Windschitl, D.I. Twito, R.F. Marschke, J.F. Foley, A. Et, A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin, JAMA 253 (1985) 2061–2067.

[7] P. Rougier, J.J. Zarba, M. Ducreux, M. Basile, J.P. Pignon, M. Mahjoubi, M. Benahmed, J.P. Droz, E. Cvitkovic, J.P. Armand, Phase II study of cisplatin and 120-hour continuous infusion of 5-fluorouracil in patients with advanced pancreatic adenocarcinoma, Ann. Oncol. 4 (1993) 333–336.

[8] M. Ducreux, P. Rougier, J.P. Pignon, J.Y. Douillard, J.F. Seitz, R. Bugat, J.F. Bosset, Y. Merrouche, J.L. Raoul, M. Ychou, A. Adenis, F. Berthault-Cvitkovic, M. Luboinski, A randomised trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma, Ann. Oncol. 13 (2002) 1185–1191.

[9] A. Strimpakos, M.W. Saif, K.N. Syrigos, Pancreatic cancer: from molecular pathogenesis to targeted therapy, Cancer Metastasis Rev. 27 (2008) 495–522.

[10] M. Miwa, M. Ura, M. Nishida, N. Sawada, T. Ishikawa, K. Mori, N. Shimma, I. Umeda, H. Ishitsuka, Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue, Eur. J. Cancer 34 (1998) 1274–1281.

[11] T.H. Cartwright, A. Cohn, J.A. Varkey, Y.M. Chen, T.P. Szatrowski, J.V. Cox, J.J. Schulz, Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer, J. Clin. Oncol. 20 (2002) 160–164.

[12] N. Sawada, K. Fujimoto-Ouchi, T. Ishikawa, Y. Tanaka, Antitumour activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumor xenograft models, Proc. Am. Assoc. Cancer Res. 21 (2002) 5388 (Abstracts).

[13] R. Herrmann, G. Bodoky, T. Ruhstaller, B. Glimelius, E. Bajetta, J. Schuller, P. Saletti, J. Bauer, A. Figer, B. Pestalozzi, C.H. Kohne, W. Mingrone, S.M. Stemmer, K. Tamas, G.V. Kornek, D. Koeberle, S. Cina, J. Bernhard, D. Dietrich, W. Scheithauer, Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group, J. Clin. Oncol. 25 (2007) 2212–2217.

[14] J. Bernhard, D. Dietrich, W. Scheithauer, D. Gerber, G. Bodoky, T. Ruhstaller, B. Glimelius, E. Bajetta, J. Schuller, P. Saletti, J. Bauer, A. Figer, B.C. Pestalozzi, C.H. Kohne, W. Mingrone, S.M. Stemmer, K. Tamas, G.V. Kornek, D. Koeberle, R. Herrmann, Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial – SAKK 44/00-CECOG/PAN.1.3.001, J. Clin. Oncol. 26 (2008) 3695–3701.

[15] D. Cunningham, I. Chau, D.D. Stocken, J.W. Valle, D. Smith, W. Steward, P.G. Harper, J. Dunn, C. Tudur-Smith, J. West, S. Falk, A. Crellin, F. Adab, J. Thompson, P. Leonard, J. Ostrowski, M. Eatock, W. Scheithauer, R. Herrmann, J.P. Neoptolemos, Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer, J. Clin. Oncol. 27 (2009) 5513–5518.

[16] M.W. Saif, M. Joseph, S. Tang, S. Vickers, B. Plants, S. Russo, Retrospective analysis of capecitabine and radiation therapy in the treatment of pancreatic cancer, J. Appl. Res. 4 (2004) 635–646.

[17] B.J. Schneider, E. Ben-Josef, C.J. McGinn, A.E. Chang, L.M. Colletti, D.P. Normolle, G.F. Hejna, T.S. Lawrence, M.M. Zalupski, Capecitabine and radiation therapy preceded and followed by combination chemotherapy in advanced pancreatic cancer, Int. J. Radiat. Oncol. Biol. Phys. 63 (2005) 1325–1330.

[18] T. Shirasaka, K. Nakano, T. Takechi, H. Satake, J. Uchida, A. Fujioka, H. Saito, H. Okabe, K. Oyama, S. Takeda, N. Unemi, M. Fukushima, Antitumor activity of 1 M tegafur–0.4 M 5-chloro-2,4-dihydroxypyridine–1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats, Cancer Res. 56 (1996) 2602–2606.

[19] H. Ueno, T. Okusaka, M. Ikeda, Y. Takezako, C. Morizane, An early phase II study of S-1 in patients with metastatic pancreatic cancer, Oncology 68 (2005) 171–178.

[20] C. Morizane, T. Okusaka, J. Furuse, H. Ishii, H. Ueno, M. Ikeda, K. Nakachi, M. Najima, T. Ogura, E. Suzuki, A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer, Cancer Chemother. Pharmacol. 63 (2009) 313–319.

[21] A. Todaka, A. Fukutomi, N. Boku, Y. Onozawa, S. Hironaka, H. Yasui, K. Yamazaki, K. Taku, N. Machida, T. Sakamoto, H. Tomita, S-1 monotherapy as second-line treatment for advanced pancreatic cancer after gemcitabine failure, Jpn. J. Clin. Oncol. 40 (2010) 567–572.

[22] B. Schultheis, D. Strumberg, L. Bergmann, U. Graeven, A.R. Hanauske, R. Lipp, J. Schuette, K. Saito, P. Scigalla, M.E. Scheulen, Results of a phase II trial of S-1 as first-line treatment of metastatic pancreatic cancer (CESAR-study group), Invest. New Drugs (2011) April 12 (Epub ahead of print).

[23] J. Yoshizawa, A. Takizawa, O. Takeuchi, O. Hiraku, K. Sasaki, Y. Morimoto, K. Atsuda, C. Inoue, Y. Suzuki, F. Asanuma, Y. Yamada, Experimental study of combination therapy with S-1 against pancreatic cancer, Cancer Chemother. Pharmacol. 64 (2009) 1211–1219.

[24] D.Y. Oh, Y. Cha, I.S. Choi, S.Y. Yoon, I.K. Choi, J.H. Kim, S.C. Oh, C.D. Kim, J.S. Kim, Y.J. Bang, Y.H. Kim, A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer, Cancer Chemother. Pharmacol. 65 (2010) 527–536.

[25] T. Ioka, M. Ikeda, S. Ohkawa, H. Yanagimoto, A. Fukutomi, K. Sugimori, H. Baba, K. Yamao, T. Shimamura, J. Chen, K. Mizumoto, J. Furuse, A. Funakoshi, T. Hatori, T. Yamaguchi, S. Egawa, A. Sato, Y. Ohashi, A. Cheng, T. Okusaka, Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (GEM) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study, J. Clin. Oncol. 29 (2011) 4007 (ASCO Meeting Abstracts).

[26] K. Sudo, T. Yamaguchi, T. Ishihara, K. Nakamura, T. Hara, T. Denda, K. Tawada, T. Imagumbai, H. Araki, M. Sakai, K. Hatano, H. Kawakami, T. Uno, H. Ito, O. Yokosuka, Phase II study of oral S-1 and concurrent radiotherapy in patients with unresectable locally advanced pancreatic cancer, Int. J. Radiat. Oncol. Biol. Phys. 80 (2011) 119–125.

[27] H. Shinchi, K. Maemura, Y. Mataki, H. Kurahara, M. Sakoda, S. Ueno, Y. Hiraki, M. Nakajo, S. Natsugoe, S. Takao, A phase II study of oral S-1 with concurrent radiotherapy followed by chemotherapy with S-1 alone for locally advanced pancreatic cancer, J. Hepatobiliary Pancreat. Sci. (2011) June 7 (Epub ahead of print).

[28] FDA expands access to gemcitabine for pancreatic cancer, Am. J. Health Syst. Pharm. 52 (1995) 931.

[29] H. Oettle, S. Post, P. Neuhaus, K. Gellert, J. Langrehr, K. Ridwelski, H. Schramm, J. Fahlke, C. Zuelke, C. Burkart, K. Gutberlet, B. Kettner, H. Schmalenberg, K. Weigang-Koehler, W.O. Bechstein, M. Niedergethmann, I. Schmidt-Wolf, L. Roll, B. Doerken, H. Riess, Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial, JAMA 297 (2007) 267–277.

[30] J.P. Neoptolemos, D.D. Stocken, C. Bassi, P. Ghaneh, D. Cunningham, D. Goldstein, R. Padbury, M.J. Moore, S. Gallinger, C. Mariette, M.N. Wente, J.R. Izbicki, H. Friess, M.M. Lerch, C. Dervenis, A. Olah, G. Butturini, R. Doi, P.A. Lind, D. Smith, J.W. Valle, D.H. Palmer, J.A. Buckels, J. Thompson, C.J. McKay, C.L. Rawcliffe, M.W. Buchler, Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial, JAMA 304 (2010) 1073–1081.

[31] S. Cascinu, R.R. Silva, S. Barni, R. Labianca, L. Frontini, E. Piazza, G. Pancera, P. Giordani, L. Giuliodori, M.A. Pessi, V. Fusco, G. Luporini, R. Cellerino, C. Catalano, A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD), Br. J. Cancer 80 (1999) 1595–1598.

[32] M. Hidalgo, D. Castellano, L. Paz-Ares, C. Gravalos, M. Diaz-Puente, R. Hitt, S. Alonso, H. Cortes-Funes, Phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer, J. Clin. Oncol. 17 (1999) 585–592.

[33] E. Matano, P. Tagliaferri, A. Libroia, V. Damiano, A. Fabbrocini, S. De Lorenzo, A.R. Bianco, Gemcitabine combined with continuous infusion 5-fluorouracil in advanced and symptomatic pancreatic cancer: a clinical benefit-oriented phase II study, Br. J. Cancer 82 (2000) 1772–1775.

[34] J.D. Berlin, S. Adak, D.J. Vaughn, D. Flinker, L. Blaszkowsky, J.E. Harris, I. Benson, A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Cooperative Oncology Group Study (E3296), Oncology 58 (2000) 215–218.

[35] J.D. Berlin, P. Catalano, J.P. Thomas, J.W. Kugler, D.G. Haller, A.R. Benson, Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297, J. Clin. Oncol. 20 (2002) 3270–3275.

[36] G. Colucci, F. Giuliani, V. Gebbia, M. Biglietto, P. Rabitti, G. Uomo, S. Cigolari, A. Testa, E. Maiello, M. Lopez, Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale, Cancer 94 (2002) 902–910.

[37] V. Heinemann, D. Quietzsch, F. Gieseler, M. Gonnermann, H. Schonekas, A. Rost, H. Neuhaus, C. Haag, M. Clemens, B. Heinrich, U. Vehling-Kaiser, M. Fuchs, D. Fleckenstein, W. Gesierich, D. Uthgenannt, H. Einsele, A. Holstege, A. Hinke, A. Schalhorn, R. Wilkowski, Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer, J. Clin. Oncol. 24 (2006) 3946–3952.

[38] C. Louvet, T. Andre, G. Lledo, F. Hammel, H. Bleiberg, C. Bouleuc, E. Gamelin, M. Flesch, E. Cvitkovic, A. de Gramont, Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study, J. Clin. Oncol. 20 (2002) 1512–1518.

[39] C. Louvet, R. Labianca, P. Hammel, G. Lledo, M.C. Zampino, T. Andre, A. Zaniboni, M. Ducreux, E. Aitini, J. Taieb, R. Faroux, C. Lepere, A. de Gramont,

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Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial, J. Clin. Oncol. 23 (2005) 3509–3516.
[40] A. Demols, M. Peeters, M. Polus, R. Marechal, F. Gay, E. Monsaert, A. Hendlisz, J.L. Van Laethem, Gemcitabine and oxaliplatin (GEMOX): in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study, Br. J. Cancer 94 (2006) 481–485.
[41] T. Conroy, B. Paillot, E. Francois, R. Bugat, J.H. Jacob, U. Stein, S. Nasca, J.P. Metges, O. Rixe, P. Michel, E. Maghrini, A. Hua, G. Deplanque, Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer – a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study, J. Clin. Oncol. 23 (2005) 1228–1236.
[42] T. Conroy, F. Desseigne, M. Ychou, O. Bouche, R. Guimbaud, Y. Becouarn, A. Adenis, J.L. Raoul, S. Gourgou-Bourgade, C. de la Fouchardiere, J. Bennouna, J.B. Bachet, F. Khemissa-Akouz, D. Pere-Verge, C. Delbaldo, E. Assenat, B. Chauffert, P. Michel, C. Montoto-Grillot, M. Ducreux, FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, N. Engl. J. Med. 364 (2011) 1817–1825.
[43] T. Conroy, C. Gavoille, A. Adenis, Metastatic pancreatic cancer: old drugs, new paradigms, Curr. Opin. Oncol. 23 (2011) 390–395.
[44] R. Kim, FOLFIRINOX: a new standard treatment for advanced pancreatic cancer?, Lancet Oncol 12 (2011) 8–9.
[45] M. Tada, Y. Nakai, T. Sasaki, T. Hamada, R. Nagano, D. Moiri, K. Miyabayashi, K. Yamamoto, H. Kogure, K. Kawakubo, Y. Ito, N. Yamamoto, N. Sasahira, K. Hirano, H. Ijichi, K. Tateishi, H. Isayama, M. Omata, K. Koike, Recent progress and limitations of chemotherapy for pancreatic and biliary tract cancers, World J. Clin. Oncol. 2 (2011) 158–163.
[46] C. Yoo, J.Y. Hwang, J.E. Kim, T.W. Kim, J.S. Lee, D.H. Park, S.S. Lee, D.W. Seo, S.K. Lee, M.H. Kim, D.J. Han, S.C. Kim, J.L. Lee, A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer, Br. J. Cancer 101 (2009) 1658–1663.
[47] J.A. Wils, T. Kok, D.J. Wagener, J. Selleslags, N. Duez, Activity of cisplatin in adenocarcinoma of the pancreas, Eur. J. Cancer 29A (1993) 203–204.
[48] M. Ducreux, E. Mitry, M. Ould-Kaci, V. Boige, J.F. Seitz, R. Bugat, J.L. Breau, O. Bouche, P.L. Etienne, J.M. Tigaud, F. Morvan, E. Cvitkovic, P. Rougier, Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients, Ann. Oncol. 15 (2004) 467–473.
[49] U. Pelzer, K. Kubica, J. Stieler, I. Schwaner, G. Heil, M. Görner, M. Mölle, A. Hilbig, B. Dörken, H. Riess, H. Oettle, A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study, J. Clin. Oncol. 26 (2008) 4508 (ASCO Meeting Abstracts).
[50] R.P. Whitehead, J. Jacobson, T.D. Brown, S.A. Taylor, G.R. Weiss, J.S. Macdonald, Phase II trial of paclitaxel and granulocyte colony-stimulating factor in patients with pancreatic carcinoma: a Southwest Oncology Group study, J. Clin. Oncol. 15 (1997) 2414–2419.
[51] H. Safran, R. Rathore, Paclitaxel as a radiation sensitizer for locally advanced pancreatic cancer, Crit. Rev. Oncol. Hematol. 43 (2002) 57–62.
[52] F. Viret, M. Ychou, A. Goncalves, V. Moutardier, V. Magnin, A.C. Braud, J.B. Dubois, E. Bories, G. Cravis, J. Camerlo, D. Genre, D. Maraninchi, P. Viens, M. Giovannini, Docetaxel and radiotherapy and pancreatic cancer, Pancreas 27 (2003) 214–219.
[53] S. Maeda, F. Motoi, T. Onogawa, T. Morikawa, O. Shigeru, N. Sakata, T. Takadate, T. Naitoh, T. Rikiyama, Y. Katayose, S. Egawa, M. Unno, Paclitaxel as second-line chemotherapy in patients with gemcitabine-refractory pancreatic cancer: a retrospective study, Int. J. Clin. Oncol. 16 (2011) 539–545.
[54] M.W. Saif, K. Syrigos, R. Penney, K. Kaley, Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study, Anticancer Res. 30 (2010) 2905–2909.
[55] D.D. Von Hoff, R. Ramanathan, M. Borad, D. Laheru, L. Smith, T. Wood, R. Korn, N. Desai, J. Iglesias, and M. Hidalgo, SPARC correlation with response to gemcitabine (G) plus nab-paclitaxel (nab-P) in patients with advanced metastatic pancreatic cancer: A phase I/II study, J. Clin. Oncol. 27 (2009) 4525 (ASCO Meeting Abstracts).
[56] D.J. Wagener, H.E. Verdonk, L.Y. Dirix, G. Catimel, P. Siegenthaler, M. Buitenhuis, A. Mathieu-Boue, J. Verweij, Phase II trial of CPT-11 in patients with advanced pancreatic cancer. an EORTC early clinical trials group study, Ann. Oncol. 6 (1995) 129–132.
[57] S.Y. Yi, Y.S. Park, H.S. Kim, H.J. Jun, K.H. Kim, M.H. Chang, M.J. Park, J.E. Uhm, J. Lee, S.H. Park, J.O. Park, J.K. Lee, K.T. Lee, H.Y. Lim, W.K. Kang, Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer, Cancer Chemother. Pharmacol. 63 (2009) 1141–1145.
[58] G.P. Stathopoulos, S.K. Rigatos, M.A. Dimopoulos, T. Giannakakis, G. Foutzilas, C. Kouroussis, D. Janninis, G. Aravantinos, N. Androulakis, S. Agelaki, J.G. Stathopoulos, V. Georgoulias, Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study by the Greek Cooperative Group for Pancreatic Cancer, Ann. Oncol. 14 (2003) 388–394.
[59] B. Neri, G. Cipriani, R. Griffoni, E. Molinara, P. Pantaleo, S. Kangan, A. Vannini, P. Tonelli, A. Valeri, D. Pantalone, A. Taddei, P. Bechi, Gemcitabine plus irinotecan as first-line weekly therapy in locally advanced and/or metastatic pancreatic cancer, Oncol. Res. 17 (2009) 559–564.
[60] G.P. Stathopoulos, K. Syrigos, G. Aravantinos, A. Polyzos, P. Papakotoulas, G. Fountzilas, A. Potamianou, N. Ziras, J. Boukovinas, J. Varthalitis, N. Androulakis, A. Kotsakis, G. Samonis, V. Georgoulias, A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer, Br. J. Cancer 95 (2006) 587–592.
[61] S.Y. Oh, H.J. Kim, T.H. Kim, G.W. Lee, H.G. Kim, C.Y. Jeong, H.C. Kwon, J.H. Kang, Pilot study of irinotecan/oxaliplatin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil-refractory pancreatic cancer, Invest. New Drugs 28 (2010) 343–349.
[62] U. Pelzer, I. Schwaner, J. Stieler, M. Adler, J. Seraphin, B. Dorken, H. Riess, H. Oettle, 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, Eur. J. Cancer 47 (2011) 1676–1681.
[63] L. Dahan, F. Bonnetain, M. Ychou, E. Mitry, M. Gasmi, J.L. Raoul, S. Cattan, J.M. Phelip, P. Hammel, B. Chauffert, P. Michel, J.L. Legoux, P. Rougier, L. Bedenne, J.F. Seitz, Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301), Gut 59 (2010) 1527–1534.
[64] H. Ueno, T. Kosuge, Y. Matsuyama, J. Yamamoto, A. Nakao, S. Egawa, R. Doi, M. Monden, T. Hatori, M. Tanaka, M. Shimada, K. Kanemitsu, A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer, Br. J. Cancer 101 (2009) 908–915.
[65] E. Poplin, Y. Feng, J. Berlin, M.L. Rothenberg, B. Hochster, E. Mitchell, S. Alberts, P. O'Dwyer, D. Haller, P. Catalano, D. Cella, A.B. Benson, Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group, J. Clin. Oncol. 27 (2009) 3778–3785.
[66] M. Mitsuyuji, Y. Suzuki, Y. Iwanaga, Y. Fujino, Y. Tanioka, T. Kamigaki, Y. Ku, Y. Kuroda, An experimental study on the pharmacokinetics of 5-fluorouracil regional chemotherapy for pancreatic cancer, Ann. Surg. Oncol. 10 (2003) 546–550.
[67] J.M. Collins, Pharmacologic rationale for regional drug delivery, J. Clin. Oncol. 2 (1984) 498–504.
[68] C. Jin, L. Yao, J. Long, D.L. Fu, X.J. Yu, J. Xu, F. Yang, Q.X. Ni, Effect of multiple-phase regional intra-arterial infusion chemotherapy on patients with resectable pancreatic head adenocarcinoma, Chin. Med. J. (Engl.) 122 (2009) 284–290.
[69] J.L. Davis, P. Pandalai, R.T. Ripley, R.C. Langan, S.M. Steinberg, M. Walker, M.A. Toomey, E. Levy, I. Avital, Regional chemotherapy in locally advanced pancreatic cancer: RECLAP trial, Trials 12 (2011) 129.
[70] K.H. Link, F. Gansauge, J. Gorich, G.H. Leder, N. Rilinger, H.G. Beger, Palliative and adjuvant regional chemotherapy in pancreatic cancer, Eur. J. Surg. Oncol. 23 (1997) 409–414.
[71] M. Cantore, P. Pederzoli, G. Cornalba, G. Fiorentini, S. Guadagni, L. Miserocchi, A. Frassoldati, C. Ceravolo, F. Smerieri, J.H. Muchmore, Intra-arterial chemotherapy for unresectable pancreatic cancer, Ann. Oncol. 11 (2000) 569–573.
[72] S. Bayar, E. Unal, M. Tez, H. Kocaoglu, S. Demirci, H. Akgul, Regional chemotherapy for advanced pancreatic carcinoma, Hepatogastroenterology 50 (2003) 550–552.
[73] E. Barletta, F. Fiore, B. Daniele, A. Ottaiano, R. D'Angelo, E. Ferrari, R. Formato, A. Tortoriello, G. Turitto, G.S. Bruni, S. Pignata, R.V. Iaffaioli, Second-line intra-arterial chemotherapy in advanced pancreatic adenocarcinoma, Front. Biosci. 11 (2006) 782–787.
[74] U. Pohlen, H. Rieger, S. Kunick-Pohlen, G. Berger, H.J. Buhr, Phase II study of regional chemotherapy using the hypoxic abdominal perfusion technique in advanced abdominal carcinoma. 5-FU pharmacokinetics, complications and outcome, Anticancer Res. 27 (2007) 667–674.
[75] B.A. Faller, B. Burtness, Treatment of pancreatic cancer with epidermal growth factor receptor-targeted therapy, Biologics 3 (2009) 419–428.
[76] M.J. Moore, D. Goldstein, J. Hamm, A. Figer, J.R. Hecht, S. Gallinger, H.J. Au, P. Murawa, D. Walde, R.A. Wolff, D. Campos, R. Lim, K. Ding, G. Clark, T. Voskoglou-Nomikos, M. Ptasynski, W. Parulekar, 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, J. Clin. Oncol. 25 (2007) 1960–1966.
[77] C.M. Rocha-Lima, New directions in the management of advanced pancreatic cancer: a review, Anticancer Drugs 19 (2008) 435–446.
[78] F. Rivera, M.E. Vega-Villegas, M.F. Lopez-Brea, Cetuximab, its clinical use and future perspectives, Anticancer Drugs 19 (2008) 99–113.
[79] H.G. Hotz, O.J. Hines, R. Masood, B. Hotz, T. Foitzik, H.J. Buhr, P.S. Gill, H.A. Reber, VEGF antisense therapy inhibits tumor growth and improves survival in experimental pancreatic cancer, Surgery 137 (2005) 192–199.
[80] S. Ohnami, K. Aoki, K. Yoshida, S. Ohnami, K. Hatanaka, K. Suzuki, H. Sasaki, T. Yoshida, Expression profiles of pancreatic cancer cell lines infected with antisense K-ras-expressing adenoviral vector, Biochem. Biophys. Res. Commun. 309 (2003) 798–803.
[81] I. Chau, D. Cunningham, C. Russell, A.R. Norman, T. Kurzawinski, P. Harper, P. Harrison, G. Middleton, F. Daniels, T. Hickish, J. Prendeville, P.J. Ross, B. Theis, R. Hull, M. Walker, N. Shankley, B. Kalindjian, G. Murray, A. Gillbanks, J. Black, Gastrazole (JB95008), a novel CCK2/gastrin receptor antagonist, in the treatment of advanced pancreatic cancer: results from two randomised controlled trials, Br. J. Cancer 94 (2006) 1107–1115.

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Page 80 of 314

[82] B.T. Brett, S.C. Smith, C.V. Bouvier, D. Michaeli, D. Hochhauser, E.R. Davidson, T.R. Kurzawinski, A.F. Watkinson, N. Van Someren, R.E. Pounder, M.E. Caplin, Phase II study of anti-gastrin-17 antibodies, raised to G17DT, in advanced pancreatic cancer, J. Clin. Oncol. 20 (2002) 4225–4231.
[83] R. Hassan, S. Bullock, A. Premkumar, R.J. Kreitman, H. Kindler, M.C. Willingham, I. Pastan, Phase I study of SS1P, a recombinant anti-mesothelin immunotoxin given as a bolus I.V. infusion to patients with mesothelin-expressing mesothelioma, ovarian, and pancreatic cancers, Clin. Cancer Res. 13 (2007) 5144–5149.
[84] R. Hassan, M. Ho, Mesothelin targeted cancer immunotherapy, Eur. J. Cancer 44 (2008) 46–53.
[85] S. Biswas, T.L. Criswell, S.E. Wang, C.L. Arteaga, Inhibition of transforming growth factor-beta signaling in human cancer: targeting a tumor suppressor network as a therapeutic strategy, Clin. Cancer Res. 12 (2006) 4142–4146.
[86] S.P. Chawla, V.S. Chua, L. Fernandez, D. Quon, W.C. Blackwelder, E.M. Gordon, F.L. Hall, Advanced phase I/II studies of targeted gene delivery in vivo: intravenous Rexin-G for gemcitabine-resistant metastatic pancreatic cancer, Mol. Ther. 18 (2010) 435–441.
[87] S. Varghese, S.D. Rabkin, G.P. Nielsen, U. MacGarvey, R. Liu, R.L. Martuza, Systemic therapy of spontaneous prostate cancer in transgenic mice with oncolytic herpes simplex viruses, Cancer Res. 67 (2007) 9371–9379.
[88] M.J. Vaha-Koskela, J.E. Heikkila, A.E. Hinkkanen, Oncolytic viruses in cancer therapy, Cancer Lett. 254 (2007) 178–216.
[89] J.R. Hecht, R. Bedford, J.L. Abbruzzese, S. Lahoti, T.R. Reid, R.M. Soetikno, D.H. Kirn, S.M. Freeman, A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma, Clin. Cancer Res. 9 (2003) 555–561.
[90] T. Nishimoto, K. Yoshida, Y. Miura, A. Kobayashi, H. Hara, S. Ohnami, K. Kurisu, T. Yoshida, K. Aoki, Oncolytic virus therapy for pancreatic cancer using the adenovirus library displaying random peptides on the fiber knob, Gene Ther. 16 (2009) 669–680.
[91] K.P. Olive, M.A. Jacobetz, C.J. Davidson, A. Gopinathan, D. McIntyre, D. Honess, B. Madhu, M.A. Goldgraben, M.E. Caldwell, D. Allard, K.K. Frese, G. Denicola, C. Feig, C. Combs, S.P. Winter, H. Ireland-Zecchini, S. Reichelt, W.J. Howat, A. Chang, M. Dhara, L. Wang, F. Ruckert, R. Grutzmann, C. Pilarsky, K. Izeradjene, S.R. Hingorani, P. Huang, S.E. Davies, W. Plunkett, M. Egorin, R.H. Hruban, N. Whitebread, K. McGovern, J. Adams, C. Iacobuzio-Donahue, J. Griffiths, D.A. Tuveson, Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324 (2009) 1457–1461.
[92] K.B. Harikumar, A.B. Kunnumakkara, N. Ochi, Z. Tong, A. Deorukhkar, B. Sung, L. Kelland, S. Jamieson, R. Sutherland, T. Raynham, M. Charles, A. Bagherzadeh, C. Foxton, A. Boakes, M. Farooq, D. Maru, P. Diagaradjane, Y. Matsuo, J. Sinnett-Smith, J. Gelovani, S. Krishnan, B.B. Aggarwal, E. Rozengurt, C.R. Ireson, S. Guha, A novel small-molecule inhibitor of protein kinase D blocks pancreatic cancer growth in vitro and in vivo, Mol. Cancer Ther. 9 (2010) 1136–1146.
[93] Z. Wang, A.S. Azmi, A. Ahmad, S. Banerjee, S. Wang, F.H. Sarkar, R.M. Mohammad, TW-37, a small-molecule inhibitor of Bcl-2, inhibits cell growth and induces apoptosis in pancreatic cancer: involvement of Notch-1 signaling pathway, Cancer Res. 69 (2009) 2757–2765.
[94] M. Li, Y. Zhang, U. Bharadwaj, Q.J. Zhai, C.H. Ahern, W.E. Fisher, F.C. Brunicardi, C.D. Logsdon, C. Chen, Q. Yao, Down-regulation of ZIP4 by RNA interference inhibits pancreatic cancer growth and increases the survival of nude mice with pancreatic cancer xenografts, Clin. Cancer Res. 15 (2009) 5993–6001.
[95] M. Li, Y. Zhang, Z. Liu, U. Bharadwaj, H. Wang, X. Wang, S. Zhang, J.P. Liuzzi, S.M. Chang, R.J. Cousins, W.E. Fisher, F.C. Brunicardi, C.D. Logsdon, C. Chen, Q. Yao, Aberrant expression of zinc transporter ZIP4 (SLC39A4) significantly contributes to human pancreatic cancer pathogenesis and progression, Proc. Natl. Acad. Sci. USA 104 (2007) 18636–18641.
[96] G. Luo, C. Jin, J. Long, D. Fu, F. Yang, J. Xu, X. Yu, W. Chen, Q. Ni, RNA interference of MBD1 in BxPC-3 human pancreatic cancer cells delivered by PLGA-poloxamer nanoparticles, Cancer Biol. Ther. 8 (2009) 594–598.
[97] C. Liu, Y. Chen, X. Yu, C. Jin, J. Xu, J. Long, Q. Ni, D. Fu, H. Jin, C. Bai, Proteomic analysis of differential proteins in pancreatic carcinomas: effects of MBD1 knock-down by stable RNA interference, BMC Cancer 8 (2008) 121.
[98] Z. Zhang, J. Wang, B. Shen, C. Peng, M. Zheng, The ABCC4 gene is a promising target for pancreatic cancer therapy, Gene (2011) October 2 (Epub ahead of print).
[99] X. Fu, L. Tao, M. Li, W.E. Fisher, X. Zhang, Effective treatment of pancreatic cancer xenografts with a conditionally replicating virus derived from type 2 herpes simplex virus, Clin. Cancer Res. 12 (2006) 3152–3157.
[100] H. Kasuya, S. Takeda, S. Nomoto, A. Nakao, The potential of oncolytic virus therapy for pancreatic cancer, Cancer Gene Ther. 12 (2005) 725–736.
[101] F. Motoi, S. Ottomo, N. Ohmura, H. Abe, S. Egawa, M. Sunamura, Therapeutics with replication – selective virus (RSV) for pancreatic cancer, Nihon. Rinsho. 64 (suppl. 1) (2006) 223–227.
[102] A. Nakao, H. Kasuya, T.T. Sahin, N. Nomura, A. Kanzaki, M. Misawa, T. Shirota, S. Yamada, T. Fujii, H. Sugimoto, T. Shikano, S. Nomoto, S. Takeda, Y. Kodera, Y. Nishiyama, A phase I dose-escalation clinical trial of intraoperative direct intratumoral injection of HF10 oncolytic virus in non-resectable patients with advanced pancreatic cancer, Cancer Gene Ther. 18 (2011) 167–175.
[103] L. Zhou, R. Zhang, L. Zhang, W. Yao, J. Li, Y. Yuan, Angiotensin-converting enzyme 2 acts as a potential molecular target for pancreatic cancer therapy, Cancer Lett. 307 (2011) 18–25.
[104] W. Yao, X. Yu, Z. Fang, P. Yin, C. Zhao, N. Li, L. Wang, Z. Li, X. Zha, Profilin1 facilitates staurosporine-triggered apoptosis by stabilizing the integrin beta1-actin complex in breast cancer cells, J. Cell. Mol. Med. (2011) June 21 (Epub ahead of print).
[105] M. Gronborg, T.Z. Kristiansen, A. Iwahori, R. Chang, R. Reddy, N. Sato, H. Molina, O.N. Jensen, R.H. Hruban, M.G. Goggins, A. Maitra, A. Pandey, Biomarker discovery from pancreatic cancer secretome using a differential proteomic approach, Mol. Cell. Proteomics 5 (2006) 157–171.
[106] A.S. Azmi, P.A. Philip, S.F. Zafar, F.H. Sarkar, R.M. Mohammad, PAR-4 as a possible new target for pancreatic cancer therapy, Expert Opin. Ther. Targets 14 (2010) 611–620.
[107] G. Feldmann, S. Dhara, V. Fendrich, D. Bedja, R. Beaty, M. Mullendore, C. Karikari, H. Alvarez, C. Iacobuzio-Donahue, A. Jimeno, K.L. Gabrielson, W. Matsui, A. Maitra, Blockade of hedgehog signaling inhibits pancreatic cancer invasion and metastases: a new paradigm for combination therapy in solid cancers, Cancer Res. 67 (2007) 2187–2196.
[108] P.C. Hermann, S.L. Huber, T. Herrler, A. Aicher, J.W. Ellwart, M. Guba, C.J. Bruns, C. Heeschen, Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer, Cell Stem Cell 1 (2007) 313–323.
[109] M. Bloomston, W.L. Frankel, F. Petrocca, S. Volinia, H. Alder, J.P. Hagan, C.G. Liu, D. Bhatt, C. Taccioli, C.M. Croce, MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis, JAMA 297 (2007) 1901–1908.
[110] Q. Ji, X. Hao, M. Zhang, W. Tang, M. Yang, L. Li, D. Xiang, J.T. Desano, G.T. Bommer, D. Fan, E.R. Fearon, T.S. Lawrence, L. Xu, MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells, PLoS One 4 (2009) e6816.
[111] N. Tsuda, T. Mine, C.G. Ioannides, D.Z. Chang, Synthetic microRNA targeting glioma-associated antigen-1 protein, Methods Mol. Biol. 487 (2009) 435–449.
[112] J.K. Park, E.J. Lee, C. Esau, T.D. Schmittgen, Antisense inhibition of microRNA-21 or -221 arrests cell cycle, induces apoptosis, and sensitizes the effects of gemcitabine in pancreatic adenocarcinoma, Pancreas 38 (2009). e190-9.
[113] F.U. Weiss, I.J. Marques, J.M. Woltering, D.H. Vlecken, A. Aghdassi, L.I. Partecke, C.D. Heidecke, M.M. Lerch, C.P. Bagowski, Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer, Gastroenterology 137 (2009). 2136-45.e1-7.
[114] J. Taipale, J.K. Chen, M.K. Cooper, B. Wang, R.K. Mann, L. Milenkovic, M.P. Scott, P.A. Beachy, Effects of oncogenic mutations in smoothened and patched can be reversed by cyclopamine, Nature 406 (2000) 1005–1009.
[115] S.K. Kumar, I. Roy, R.K. Anchoori, S. Fazli, A. Maitra, P.A. Beachy, S.R. Khan, Targeted inhibition of hedgehog signaling by cyclopamine prodrugs for advanced prostate cancer, Bioorg. Med. Chem. 16 (2008) 2764–2768.
[116] J.B. Fleming, G.L. Shen, S.E. Holloway, M. Davis, R.A. Brekken, Molecular consequences of silencing mutant K-ras in pancreatic cancer cells: justification for K-ras-directed therapy, Mol. Cancer Res. 3 (2005) 413–423.
[117] L.L. Siu, A. Awada, C.H. Takimoto, M. Piccart, B. Schwartz, T. Giannaris, C. Lathia, O. Petrenciuc, M.J. Moore, Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer, Clin. Cancer Res. 12 (2006) 144–151.
[118] J. Rinehart, A.A. Adjei, P.M. Lorusso, D. Waterhouse, J.R. Hecht, R.B. Natale, O. Hamid, M. Varterasian, P. Asbury, E.P. Kaldjian, S. Gulyas, D.Y. Mitchell, R. Herrera, J.S. Sebolt-Leopold, M.B. Meyer, Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer, J. Clin. Oncol. 22 (2004) 4456–4462.
[119] A.A. Adjei, M. Hidalgo, Intracellular signal transduction pathway proteins as targets for cancer therapy, J. Clin. Oncol. 23 (2005) 5386–5403.
[120] S. Sebens, A. Arlt, H. Schafer, NF-kappaB as a molecular target in the therapy of pancreatic carcinoma, Recent Results Cancer Res. 177 (2008) 151–164.

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Subgroup analysis by measurable metastatic lesion (ML) number and selected lesion locations (LL) at baseline in NAPOLI-1, a phase 3 study of liposomal irinotecan (nal-IRI)±5-fluorouracil/leucovorin (5-FU/LV) in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is an innovative liposomal formulation of irinotecan that exhibits extended circulation and enhanced intratumoral drug deposition vs. conventional irinotecan.[1–3]
- NAPOLI-1, a global, phase 3 study, demonstrated that nal-IRI (80 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 irinotecan free base; Q2W) in combination with 5-fluorouracil and leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR]=0.67; *P*=0.0122) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR=0.56; *P*=0.0001) compared with 5-FU/LV alone in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy.[4]
- Currently, nal-IRI is approved in combination with 5-FU/LV for the treatment of adult patients with mPDAC after disease progression following gemcitabine-based therapy.
  - NCCN guidelines recommend nal-IRI+5-FU/LV as a category 1 option for mPDAC patients previously treated with gemcitabine-based therapy, or a category 2 option for fluoropyrimidine-based therapy if no prior irinotecan.[5]
  - A 2017 update of the ESMO 2015 Clinical Practice Guidelines states that second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. For fit patients, nal-IRI+5-FU/LV may constitute an active and tolerable second-line treatment option.[6]
- Here, we present results from a post-hoc subgroup analysis by measureable metastatic lesion number (ML) and selected lesion locations (LL) at baseline from the NAPOLI-1 study.

METHODS

Objectives and subgroup analysis

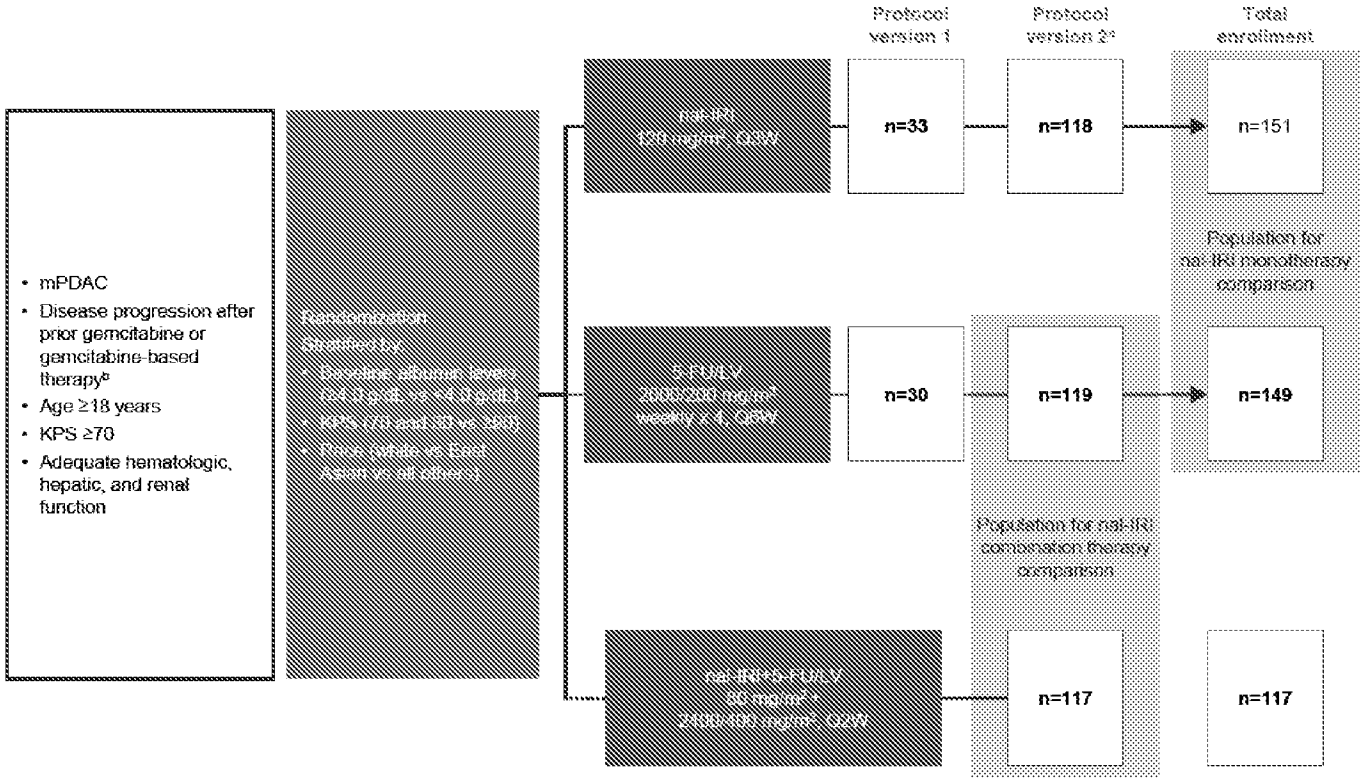
- This post-hoc subgroup analysis aimed to assess the impact of baseline ML and selected baseline LL on outcomes and efficacy within the overall NAPOLI-1 intent-to-treat (ITT) population and the nal-IRI+5-FU/LV treatment arm (Q2W, n=117). It also explored the benefit of nal-IRI+5-FU/LV compared with 5-FU/LV alone in subgroups of patients defined by lesion number and selected metastatic lesion locations.
- *P* values in this post-hoc analysis are descriptive.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

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Figure 1. Study design[a]



[a]Patients were initially randomized to nal-IRI monotherapy or 5-FU/LV. The protocol was amended to add a third arm (nal-IRI+5-FU/LV) after safety data on the combination became available from a concurrent study in metastatic colorectal cancer; 63 patients were enrolled under protocol version 1 before all sites switched to version 2. Only those patients enrolled in the 5-FU/LV arm after the amendment (n=119) were used as the control for the combination arm.
[b]In a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.

- The number of measurable metastatic lesions (ML; 1, 2, 3, or >3), and primary and metastatic lesion locations (LL; pancreas, liver, distant/regional lymph node, lung, peritoneal, other) were recorded at baseline in patients with measurable and non-measurable disease (per RECIST v1.1).
- Anatomical LL at baseline was investigator-reported using RECIST v1.1. Anatomical location included measurable, non-measurable, primary and metastatic lesions. Patients with more than one lesion location were counted once for each location.
- LL were investigated as various subgroups, i.e., patients with metastatic lesions in that location only (Location only), patients with metastatic lesions other than that location only (No location only), patients with lesions in that and other locations (Any location) and patients without lesions in that location (No location).
  - This analysis only includes data for liver, lung, and peritoneal locations.

RESULTS

Patient characteristics

- At baseline, 354 of 417 ITT patients had measurable metastatic lesions, and 1,080 lesion locations were recorded (Table 1).
- Numerical differences in patient demographics and baseline characteristics emerged between measurable baseline ML number and baseline LL subgroups, likely influenced by variable patient numbers per subgroup (Table 1).
- Gender, ethnicity and KPS score distribution varied across baseline metastatic ML and LL subgroups compared with the corresponding overall ITT populations. There was also a large variation in subgroup populations. Any differences should be taken into account when considering results (Table 1).

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

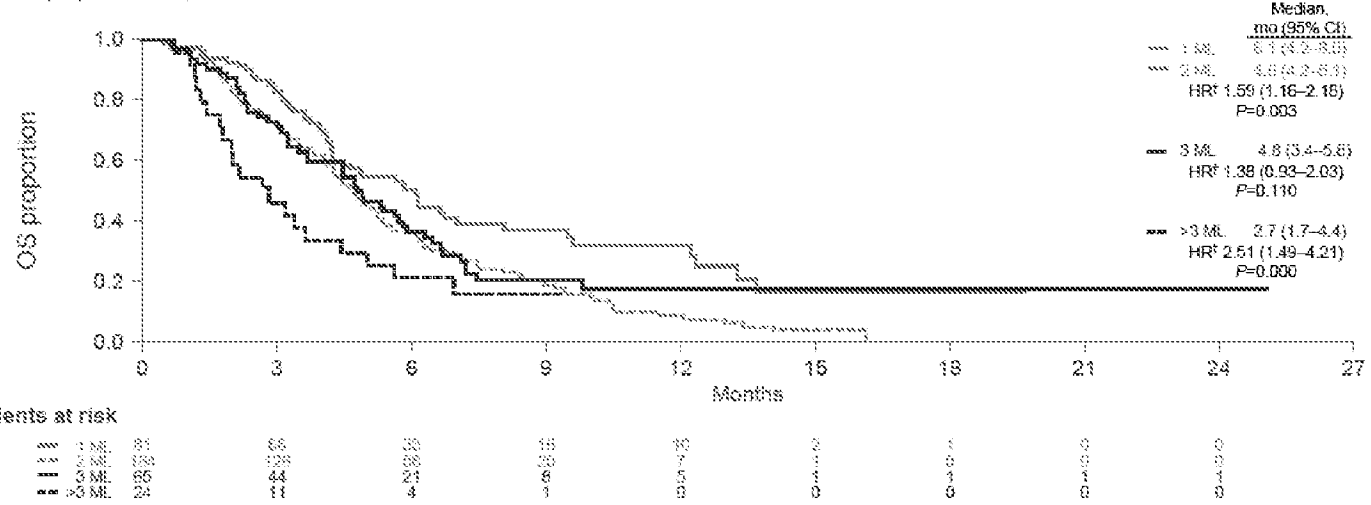
	Measurable metastatic lesion number								Location of baseline lesion*											
	Overall				nal-IRI+5-FU/LV				Overall						nal-IRI+5-FU/LV					
	1 (n=81)	2 (n=184)	3 (n=65)	>3 (n=24)	1 (n=19)	2 (n=49)	3 (n=22)	>3 (n=7)	Any liver (n=284)	No liver (n=133)	Any lung (n=129)	No lung (n=288)	Any peri (n=115)	No peri (n=302)	Any liver (n=75)	No liver (n=42)	Any lung (n=36)	No lung (n=81)	Any peri (n=28)	No peri (n=89)
Female, %	38	47	34	38	37	45	23	29	43	44	44	43	42	44	40	43	44	40	36	43
Male, %	62	53	66	63	63	55	77	71	57	56	56	57	58	56	60	57	56	61	64	57
Median age, years Min–Max	66 31–87	63 39–83	63 42–78	64 47–81	68 55–81	61 41–78	60 43–78	63 47–81	63 31–87	63 34–83	63 39–83	64 31–87	63 40–81	63 31–87	63 41–81	64 46–81	62 47–81	64 41–81	61 43–81	64 41–81
Race, %																				
White	58	61	62	71	53	63	68	71	64	53	61	60	50	65	64	57	69	58	43	67
Black or African American	4	2	3	4	0	4	5	14	2	4	4	2	3	2	4	2	6	3	0	5
Asian	37	33	29	17	47	27	14	14	30	38	32	33	40	30	24	38	22	32	46	24
Other	1	4	6	8	0	6	14	0	4	5	2	5	7	3	8	2	3	7	11	5
KPS score, %																				
90–100	59	53	63	42	53	65	59	43	56	53	50	58	50	57	60	58	50	63	64	57
70–80	41	46	34	58	47	33	32	57	42	47	50	41	50	41	36	42	47	35	36	39
Median baseline CA19-9, U/mL	1048	2897	2007	4199	1223	2381	2087	194	2427	478	2015	1487	2009	1526	1512	331	1874	556	2581	697
Liver metastases, %	52	86	80	96	47	84	73	100	100	N/A	54	74	49	76	100	N/A	44	73	39	72
Median baseline albumin, g/dL	4.0	4.1	4	3.9	4.0	4.2	4.0	3.9	4	3.9	4.0	4.0	4.0	4.0	4.1	3.9	4.1	4.0	4.1	4.0

Numbers may not add up to one hundred per cent due to rounding.
*Patients with lesions in multiple locations were included once for each location. Lesion location includes measurable, non-measurable, primary and metastatic lesions.
ITT, intent-to-treat; KPS, Karnofsky Performance Status; Max, maximum age; Min, minimum age; N/A, not applicable; Peri, peritoneal; SD, standard deviation.

Impact of measurable metastatic baseline lesion number on overall survival

- In the overall ITT population, patients with 1 selected ML at baseline had a lower risk of mortality. The hazard ratios for 2, 3, and >3 selected ML versus 1 selected ML at baseline were 1.59, 1.38, and 2.51, respectively (Table 2; Figure 2).
- This was also observed in the nal-IRI+5-FU/LV treatment arm (Table 2).

Figure 2. Overall survival in NAPOLI-1 by number of selected measurable metastatic lesions at baseline (ML ITT population*)



*Patients with ML data available (includes all treatment arms).
†Reference group for comparisons is '1 metastatic lesion'.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

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Table 2. Outcomes by number of selected measurable metastatic lesions at baseline (ITT population)

	Overall			
	1 (n=81)	2 (n=184)	3 (n=65)	>3 (n=24)
Median OS, months	6.1	4.6	4.6	2.7
95% CI	4.2,8.8	4.2,5.1	3.4,5.6	1.7,4.4
HR*		1.59	1.38	2.51
95% CI	–	1.16,2.18	0.93,2.03	1.49,4.21
P value†		*P*=0.003	*P*=0.110	*P*=0.000
Median PFS, months	2.9	1.6	2.3	1.4
95% CI	2.4,4.2	1.5,2.6	1.5,3.1	1.3,1.8
HR*		1.56	1.22	2.04
(95% CI)	–	1.2,2.1	0.84,1.78	1.25,3.33
P value††		*P*=0.003	*P*=0.302	*P*=0.004
Best overall response				
PR, %	9	8	5	8
SD, %	37	25	37	8
PD, %	33	48	32	33
NE, %	21	19	26	50
ORR, %	9	8	5	8
CBR, %	46	33	42	17

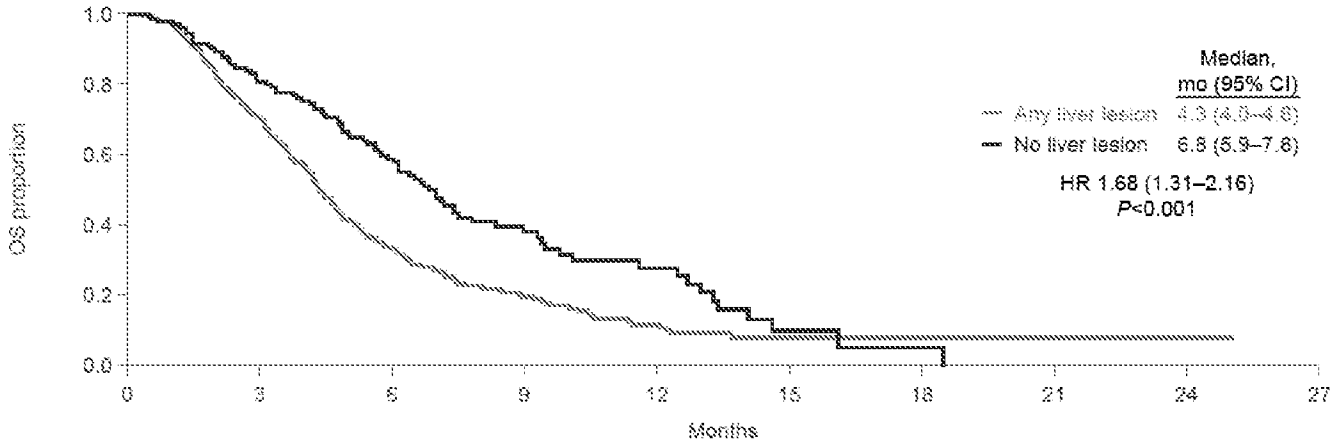
	nal-IRI+5-FU/LV			
	1 (n=19)	2 (n=49)	3 (n=22)	>3 (n=7)
Median OS, months	6.1	6.0	4.7	4.4
95% CI	3.6,NR	4.6,8.5	3.2,7.1	1.0,NR
HR*		1.31	1.42	1.36
95% CI	–	0.66,2.59	0.65,3.09	0.43,4.30
P value‡		*P*=0.441	*P*=0.380	*P*=0.598
Median PFS, months	4.2	2.8	3.1	2.0
95% CI	1.4,7.0	1.4,4.9	1.4,5.6	1.1,9.3
HR*		1.30	1.13	1.31
(95% CI)	–	0.70,2.41	0.55,2.34	0.47,3.67
P value‡‡		*P*=0.403	*P*=0.735	*P*=0.605
Best overall response				
PR, %	21	16	14	29
SD, %	42	31	32	0
PD, %	26	43	18	14
NE, %	11	10	36	57
ORR, %	21	16	14	29
CBR, %	63	47	45	29

*Reference group for comparisons is "1 metastatic lesion"; †Cox model analysis with multiple groups; ‡Two-sided *P* values from pairwise Fisher's exact test.
CBR, clinical benefit rate (CR + PR + SD); CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Impact of selected baseline lesion locations on overall survival

- Patients with a liver lesion at baseline (Any liver) had a significantly increased risk of mortality compared with patients without a liver lesion at baseline (No liver).
  (Overall ITT population: HR 1.68, *P*<0.001; nal-IRI+5-FU/LV arm: HR 1.68, *P*=0.015) (Figure 3; Table 3).
  - This was less evident when patients with only liver metastases (Liver only) were compared with all other patients (Overall ITT population [liver only, n=104 vs. all other patients, n=313]: HR 1.15, *P*=0.260; nal-IRI+5-FU/LV arm [liver only, n=27 vs. all other patients, n=90]: HR 1.53, *P*=0.091) (Table 3).
- No significant prognostic impact of lesion location on median OS was observed in lung or peritoneal lesion subgroups (Table 3).
  - Lung only (n=9) and Peritoneal only (n=18) groups contained too few patients to present as separate subgroups.

Figure 3. Overall survival in NAPOLI-1 by baseline liver lesions (LL ITT population*)



Patients at risk

Any liver	384	193	83	32	14	3	3	1	1
No liver	133	102	62	25	13	2	1	0	0

*Patients with LL data available (includes all treatment arms).
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Progression-free survival and tumor responses by lesion subgroups

- In the overall ITT population, patients with 1 ML at baseline had a lower risk of disease progression compared with other subgroups. The hazard ratios for 2, 3, and >3 ML versus 1 ML at baseline were 1.56, 1.22 and 2.04, respectively (Table 2).
  - This was also observed in patients receiving nal-IRI+5-FU/LV (Table 2).
- Similar to OS observations, patients with a liver lesion were at an increased risk of disease progression in the overall ITT population and nal-IRI+5-FU/LV arm compared with patients who did not have a liver lesion at baseline (Table 3).
  - This trend was not observed in the other lesion location subgroups (Table 3).
- There were no notable differences in objective response rate (ORR) across baseline LL subgroups in the overall ITT population or the nal-IRI+5-FU/LV arm (Table 3).

Table 3. Outcomes in selected baseline lesion location subgroups (ITT population)

	Overall							
	Liver only (n=104)	No liver only (n=313)	Any liver (n=284)	No Liver (n=133)	Any lung (n=129)	No lung (n=288)	Any peri (n=115)	No peri (n=302)
Median OS, months	4.4	5.0	4.3	6.8	5.6	4.8	4.8	5.2
95% CI	4.0,6.0	4.7,5.6	4.0,4.8	5.9,7.8	4.7,6.5	4.2,5.2	4.0,5.2	4.4,5.9
HR	1.15		1.68		0.80		1.16	
95% CI	0.90,1.48		1.31,2.16		0.62,1.02		0.91,1.48	
P value†	*P*=0.260		*P*<0.001		*P*=0.070		*P*=0.235	
Median PFS, months	2.0	2.6	1.6	4.2	2.6	2.4	2.4	2.6
95% CI	1.5,2.7	1.8,2.8	1.4,2.2	2.9,5.4	1.7,3.3	1.6,2.8	1.5,2.8	1.8,2.8
HR	1.21		1.83		0.86		1.09	
(95% CI)	0.94,1.55		1.50,2.47		0.68,1.09		0.86,1.40	
P value†	*P*=0.144		*P*<0.001		*P*=0.225		*P*=0.473	
Best overall response								
PR, %	8	7	7	7	9	6	4	8
SD, %	23	33	26	41	30	31	30	31
PD, %	45	35	45	26	35	39	37	37
NE, %	24	23	22	26	23	23	25	22
ORR, %	8	7	7	7	9	6	4	8
CBR, %	31	40	33	48	40	37	34	39

	nal-IRI+5-FU/LV							
	Liver only (n=27)	No liver only (n=90)	Any liver (n=75)	No Liver (n=42)	Any lung (n=36)	No lung (n=81)	Any peri (n=28)	No peri (n=89)
Median OS, months	6.1	6.1	5.2	9.3	6.0	6.2	9.8	6.1
95% CI	3.4,8.9	4.8,9.4	4.4,6.7	6.0,13.4	4.6,12.7	4.6,8.9	4.4,14.6	4.7,8.4
HR	1.53		1.88		0.87		0.72	
95% CI	0.93,2.50		1.12,3.14		0.52,1.46		0.41,1.26	
P value†	*P*=0.091		*P*=0.015		*P*=0.604		*P*=0.246	
Median PFS, months	2.7	4.0	2.8	5.6	4.1	3.0	2.8	3.3
95% CI	1.4,4.0	2.8,4.4	1.5,3.4	3.3,8.0	2.0,7.1	2.4,4.2	1.4,7.0	2.3,4.2
HR	1.53		1.87		0.79		0.89	
(95% CI)	0.93,2.52		1.15,3.03		0.48,1.30		0.53,1.49	
P value†	*P*=0.095		*P*=0.010		*P*=0.356		*P*=0.643	
Best overall response								
PR, %	19	16	17	14	17	16	11	18
SD, %	15	39	25	48	31	35	46	29
PD, %	44	24	39	12	22	32	25	30
NE, %	22	18	19	19	25	16	14	20
ORR, %	19	16	17	14	17	16	11	18
CBR, %	33	54	43	62	47	51	57	47

†Unstratified HR and log-rank *P* value; ‡Two-sided *P* values from pairwise Fisher's exact test. Subgroup analyses of "Lung only vs. no lung only" and "Peri only vs. no peri only" were not included due to very small patient numbers in these groups. CBR, clinical benefit rate (CR + PR + SD); CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; Peri, peritoneal; PD, progressive disease; PR, partial response; SD, stable disease.

Overall survival with nal-IRI+5-FU/LV compared with 5-FU/LV alone

- There was a reduction in mortality risk with nal-IRI+5-FU/LV compared with 5-FU/LV alone in patients with 2 and >3 metastatic lesions (HR 0.47 and 0.17) and for all LL subgroups (HR 0.39–0.83) (Tables 4 and 5).
- Patients receiving nal-IRI+5-FU/LV had a reduced risk for mortality across baseline LL subgroups compared with 5-FU/LV alone. This risk reduction reached statistical significance in the subgroups 'Any liver', 'No lung' and 'Any peritoneal' (Table 5).

Impact of treatment on progression-free survival and tumor responses within lesion subgroups

- There was a reduced risk of disease progression across baseline ML number and LL subgroups in patients receiving nal-IRI+5-FU/LV compared with 5-FU/LV alone.
  - This reached statistical significance in patients with 2 ML, and in all LL subgroups (Tables 4–5).
- The ORR was higher in patients receiving nal-IRI+5-FU/LV compared with 5-FU/LV alone across all baseline ML number and LL subgroups (Tables 4–5).
  - This was statistically significant in baseline ML subgroups with 2 and >3 lesions, and the baseline LL subgroups 'Any liver', 'No lung', and 'Any peritoneal' (Tables 4–5).

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Table 4. Efficacy of nal-IRI+5-FU/LV vs. 5-FU/LV in selected baseline measurable metastatic lesion number subgroups (ITT population)

	1		2		3		>3	
	Comb (n=18)	Ctrl (n=22)	Comb (n=49)	Ctrl (n=58)	Comb (n=22)	Ctrl (n=15)	Comb (n=7)	Ctrl (n=8)
Median OS, months	6.1	6.1	6.0	3.8	4.7	5.9	4.4	2.4
95% CI	3.6,NR	3.7,NR	4.6,8.5	2.2,4.3	3.2,7.1	2.1,7.4	1.1,NR	1.2,3.2
HR	1.08		0.52		1.02		0.17	
95% CI	0.47,2.49		0.33,0.82		0.45,2.34		0.03,0.85	
P value†	*P*=0.845		*P*=0.004		*P*=0.975		*P*=0.017	
Median PFS, months	4.2	1.9	2.8	1.4	3.1	1.5	2.0	1.4
95% CI	1.4,7.0	1.4,8.1	1.4,4.0	1.4,1.8	1.4,5.6	1.0,4.2	1.1,9.3	1.2,1.7
HR (95% CI)	0.88		0.48		0.51		0.35	
	0.42,1.87		0.31,0.73		0.23,1.11		0.09,1.38	
P value†	*P*=0.761		*P*<0.001		*P*=0.085		*P*=0.115	
Best overall response								
PR, %	21	5	16	0	14	0	29	0
SD, %	42	27	31	17	32	33	0	0
PD, %	26	50	43	55	18	33	14	50
NE, %	11	18	10	28	36	33	57	50
ORR, %	21	5	16	0	14	0	29	0
CBR, %	63	32	47	17	45	33	29	0

†Unstratified HR and log-rank *P* value. ‡Two-sided *P* values from pairwise Fisher's exact test.
CBR, clinical benefit rate (CR + PR + SD); CI, confidence interval; Comb, nal-IRI+5-FU/LV combination therapy; CR, complete response; Ctrl, 5-FU/LV control for combination arm; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 5. Efficacy of nal-IRI+5-FU/LV vs. 5-FU/LV in selected baseline lesion location subgroups (ITT population)

	Liver only		Any liver		No liver		Any lung		No lung		Any peri		No peri	
	Comb (n=27)	Ctrl (n=29)	Comb (n=75)	Ctrl (n=83)	Comb (n=42)	Ctrl (n=36)	Comb (n=36)	Ctrl (n=36)	Comb (n=81)	Ctrl (n=83)	Comb (n=28)	Ctrl (n=32)	Comb (n=89)	Ctrl (n=87)
Median OS, months	6.1	4.0	5.2	3.6	9.3	6.4	6.0	5.3	6.2	3.8	9.0	3.1	6.1	4.8
95% CI	3.6,8.9	2.1,7.4	4.4,6.7	2.9,4.3	6.0,13.4	3.1,NR	4.6,12.7	3.2,10.1	4.6,8.9	2.8,5.1	4.4,14.6	2.1,4.8	4.7,8.4	3.6,6.4
HR	0.84		0.64		0.73		0.81		0.59		0.37		0.82	
95% CI	0.46,1.56		0.45,0.93		0.39,1.37		0.44,1.47		0.41,0.86		0.20,0.71		0.56,1.18	
P value†	*P*=0.602		*P*=0.017		*P*=0.326		*P*=0.489		*P*=0.006		*P*=0.002		*P*=0.280	
Median PFS, months	2.7	1.8	2.8	1.4	5.6	2.7	4.1	1.5	3.1	1.4	2.8	1.4	3.3	1.8
95% CI	1.5,4.0	1.4,2.6	1.5,3.4	1.3,1.5	3.3,8.0	1.6,5.5	2.0,7.1	1.3,3.0	2.4,4.2	1.4,1.9	1.4,7.0	1.2,1.7	2.3,4.2	1.4,2.6
HR (95% CI)	0.83		0.55		0.55		0.46		0.58		0.39		0.64	
	0.44,1.56		0.38,0.78		0.30,1.00		0.26,0.83		0.40,0.83		0.21,0.72		0.45,0.90	
P value†	*P*=0.570		*P*<0.001		*P*=0.045		*P*=0.009		*P*=0.002		*P*=0.002		*P*=0.011	
Best overall response														
PR, %	19	0	17	0	14	3	17	0	16	1	11	0	18	1
SD, %	15	21	25	18	45	31	31	28	35	19	46	16	29	24
PD, %	44	48	39	55	12	28	22	50	32	46	25	50	30	46
NE, %	22	31	19	27	19	33	25	19	16	33	14	34	20	26
ORR, %	19	0	17	0	14	3	17	0	16	1	11	0	18	1
CBR, %	33	21	43	18	62	33	47	28	51	20	57	16	47	25

†Unstratified HR and log-rank *P* value. ‡Two-sided *P* values from pairwise Fisher's exact test.
CBR, clinical benefit rate (CR + PR + SD); CI, confidence interval; Comb, nal-IRI+5-FU/LV combination therapy; CR, complete response; Ctrl, 5-FU/LV control for combination arm; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; Peri, peritoneal; PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV in the NAPOLI-1 study has demonstrated clinical benefit (45% median OS increase) and predictable and manageable toxicity in patients with mPDAC previously treated with gemcitabine-based therapy.[4]
- The results of this post-hoc subgroup analysis suggest that the presence of lesions in the liver and, to some degree, the number of measurable metastatic lesions at baseline may be useful prognostic indicators for mortality and disease progression outcomes, regardless of treatment received.
- Treatment benefit with nal-IRI+5-FU/LV vs. 5-FU/LV alone was observed in most baseline measurable metastatic lesion number and all lesion location subgroups.
  - However, the differences did not reach statistical significance in all groups, and firm conclusions are precluded by small patient numbers in many subgroups.
- Overall, these data support the use of nal-IRI+5-FU/LV in patients with mPDAC previously treated with gemcitabine-based therapy, regardless of the number of measurable metastatic lesions or location of lesions at baseline.

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References

1. Roy AC, et al. Ann Oncol. 2013;24(6):1567-1573.
2. Kalra AV, et al. Cancer Res. 2014;72(23):7003-7013.
3. Ramanathan RK, et al. Annual Meeting AACR; April 5-9, 2014; San Diego, CA. abstract CT224 (and poster).
4. Wang-Gillam A, et al. Lancet 2016; 387(10018):545-557.
5. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Version 3.2017, September 11, 2017.
6. ESMO Guidelines Committee. Ann Oncol. 2017;28(suppl_4):iv157.

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CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Subgroup analysis by measurable metastatic lesion (ML) number and selected lesion locations (LL) at baseline (BL) 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.

Check for updates

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Abstract Disclosures

Abstract

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Background: We report a *post hoc*, exploratory analysis of pts with BL ML number and LL data who received nal-IRI+5-FU/LV, nal-IRI or 5-FU/LV in NAPOLI-1, a pivotal, phase 3 trial (NCT01494506). nal-IRI+5-FU/LV increased median OS (mOS) vs 5-FU/LV (6.1 vs 4.2 mo [HR=0.67; p=0.012]). **Methods:** ML (1, 2, 3, >3) and LL were recorded (local investigator) at BL. Pts with >1 LL were counted for each location. **Results:** 354 of 417 ITT pts had measurable BL ML and 1,080 LL were recorded. There was no clear trend in the percentage of pts with KPS ≥80 in 1- >3 ML (range 87%-95%) or LL (range 89%-94%) subgroups. ML 1 (n=81), 2 (n=65) and 3 (n=24) subgroups were small. nal-IRI+5-FU/LV significantly improved mOS vs. 5-FU/LV in pts with 2/>3 ML (n=184/24); nal-IRI+5-FU/LV had numerically higher mOS vs. 5-FU/LV for all LL (Table). nal-IRI+5-FU/LV had favourable median PFS (mPFS) vs. 5-FU/LV in pts with 1–>3 ML

(range 2.0-4.2 vs. 1.4-1.9 mo; HR range 0.35-0.88) and for all LL (range 2.8-4.2 vs. 1.4-2.0 mo; HR range 0.39-0.55). **Conclusions:** Low pt numbers across groups and repeat counting of pts in LL subgroups preclude firm conclusions on treatment efficacy, pending further analyses. Allowing for these limitations, we detected no clear prognostic effect on outcomes of higher BL ML number or LL in NAPOLI-1 ITT pts. nal-IRI+5-FU/LV improved mOS vs. 5-FU/LV in some ML groups and across LL groups; improvement in mPFS vs. 5-FU/LV in the ITT population was maintained in all subgroups. Clinical trial information: NCT01494506.

	mOS, mo(n)			
	nal-IRI+5-FU/LV	5-FU/LV	HR, p-value	Total ITT population
BL ML number				
1	6.1 (19)	6.1 (22)	1.08; ns	6.1 (81)
2	6.0 (49)	3.8 (58)	0.52; <0.01	4.6 (184)
3	4.7 (22)	5.9 (15)	1.02; ns	4.8 (65)
>3	4.4 (7)	2.4 (8)	0.17; <0.05	2.7 (24)
BL LL				
Distant lymph node (LN)	5.7 (32)	5.3 (31)	0.84; ns	5.3 (116)
Regional LN	13.4 (13)	4.0 (14)	0.44; ns	5.9 (52)
Liver	5.2 (75)	3.6 (83)	0.64; <0.05	4.3 (284)
Lung	6.0 (36)	5.3 (36)	0.81; ns	5.6 (129)
Pancreas	5.6 (75)	3.7 (72)	0.53; <0.01	4.6 (271)
Peritoneum	9.0 (28)	3.1 (32)	0.37; <0.01	4.8 (115)
Other	5.9 (27)	3.4 (39)	0.57; ns	4.7 (113)

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ID0596

Expanded analyses of NAPOLI-1: Phase 3 study of nal-IRI (MM-398), with or without 5-fluorouracil (5FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin (5FU/LV), in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy

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Question: Nal-IRI is a nanoliposomal encapsulated formulation of irinotecan. OS in the ITT population was significantly longer with nal-IRI+5FU/LV (n = 117) vs 5FU/LV (n = 119) (median OS was 6.1 m vs 4.2 m; unstratified HR = 0.67, log-rank test p = 0.012). Most frequent grade 3+ AEs included neutropenia, fatigue and GI-effects. These expanded, pre-specified analyses have been presented.
Methods: Patients with mPAC (n = 417) previously treated with gemcitabine-based therapy, were randomized 1:1:1 to receive: Nal-IRI (120 mg/m^2; IV 90 min) q3w; 5FU (2,000 mg/m^2; 24 h) + LV (200 mg/m^2; 30 min) ×4w followed by 2w rest; or combination of nal-IRI (80 mg/m^2; IV 90 min) prior to 5FU (2,400 mg/m^2; 46h) + LV (400 mg/m^2; 30min) q2w. Primary endpoint was OS. The ITT population included all randomized patients; the Per Protocol (PP) population included patients who received ≥80% of the target dose in the first 6 weeks and did not violate any in/exclusion criteria.
Results: Analysis of the PP populations confirmed the favorable OS of the combination nal-IRI+5FU/LV, which was also reflected by the PFS, ORR and CA19-9 levels. Median OS in the PP population for nal-IRI+5FU/LV-arm was 8.9 m (n = 66) vs 5.1 m (n = 71) for 5FU/LV (unstratified HR = 0.57, log-rank test p = 0.011). The nal-IRI monotherapy arm did not show a statistically significant OS improvement over 5FU/LV. Analysis of subgroups, based on pretreatment characteristics including stage at diagnosis, time since initial histological diagnosis, prior lines of therapy, time since last prior therapy, and CA19-9, favored OS for the nal-IRI+5FU/LV arm.
Conclusions: Expanded analysis of the PP population and sensitivity analyses support the favorability of nal-IRI+5FU/LV over 5FU/LV, with amanageable safety profile.

Gastrointestinal (Noncolorectal) Cancer

ID0592

A tumor protective role of Hemeoxygenase-1 in the Barrett's sequence?

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The esophageal adenocarcinoma (EAC) is characterized by an increasing incidence in the western population. An improvement in early diagnoses and advanced treatment options is needed because the overall survival is still poor due to early lymphatic metastasis. The redox status mediated by the hemeoxygenase-1 (HO-1) could play a potential therapeutic target in EAC.
To span the Barrett's sequence resulting in EAC, we used the epithelial (EPC1, EPC2), metaplastic (CP-A), dysplastic (CP-B) and adenocarcinoma (OE19, OE33) cell lines to investigate the redox status enzymes by RT- and qRT-PCR and the influence of 5-fluorouracil (5-FU) in OE33 and OE19 cells.
The detoxifying enzymes glyoxalase 1 (GLO1) and 2 (GLO2), HO-1 as well as their inductive transcription factor Nrf2 are increased with the Barrett's sequence from squamous epithelium to EAC. The EAC cell line OE33 is highly receptive for 5-FU with an IC50 of 0.74µM, however 5-FU has no significant proliferation inhibitory effect in the EAC cell line OE19. GLO1 is only slightly increased in 5-FU treated OE33 and OE19 cells (1.5fold) after 48h. Whereas HO-1 is increased in 1µM and 10µM 5-FU treated OE33 after 24h, 48h and 72h with a maximal induction by 5.4fold after 72h. 5-FU had no effect on HO-1 expression in OE19 cells. The transcription factor Nrf2 is only increased in 5-FU treated OE33 cell after 24h. Showing different expression levels in the cellular detoxifying enzymes GLO1, GLO2 and HO-1 in the EAC cell lines OE33 and OE19 as well as the defences in the responsiveness to 5-FU in OE33 and OE19 cells reflect a recently described heterogeneity in esophageal adenocarcinoma. Inhibition or reduction in GLO1/2, Nrf2 and HO-1 expression in 5-FU resistant tumor cells could represent a potentially therapeutically target in EAC treatment.

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ID0593

Aberrant expression levels of Wnt-signalling molecules in the Barrett's esophagus

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Lately the incidence of the esophageal adenocarcinoma (EAC) is increasing in the western population. Despite the currently available treatment options and the overall survival remains poor, due to late diagnosis and early lymphatic metastasis. The Wnt-signalling pathway has been studied in various malignancies, but its role in carcinogenesis of EAC remains illusive.
The epithelial (EPC1, EPC2), metaplastic (CP-A), dysplastic (CP-B) and adenocarcinoma (OE19, OE33) cell lines were utilized to cover the Barrett's sequence from squamous epithelium to EAC. Expression pattern of Wnt-signalling molecules were analysed by RT- and qRT-PCR.
While EPC1 and EPC2 cells show a high expression for Wnt3a and Wnt5a, whose expression is decreasing with the Barrett's sequence resulting in loss of expression in the EAC cells (OE33/OE19). We discovered an altered expression profile of all frizzled receptors (FZD 1–10) and the co-receptors LRP5 and LRP6 between the different cell lines. In OE33 cells the Wnt-inhibitory molecule Dkk1 is overexpressed consequently, while the Wnt-signalling target gene Axin2 is increasing within the Bar-

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study population nor in the stratified analysis according to treatment arm. The multivariable analysis including covariates treatment arm, resection status, grading, Karnofsky performance status, nodal involvement, tumor stage, and expression of CXCR4 did not show a significant correlation with disease-free survival (HR 0.92, CI 0.62–1.36).
Conclusion: Our data show neither a predictive nor a prognostic role of CXCR4, CXCR7, and CXCL12 in patients with pancreatic cancer. In contrast to previously reported studies, our results do not confirm an association between the expression of CXCR4, CXCR7, and their common ligand CXCL12 with the type of recurrence. Nevertheless, further studies are needed to validate their role in predicting recurrence patterns.

Disclosure: No conflict of interest disclosed.

P863

Effects of nanoliposomal irinotecan (nal-IRI;MM-398) ± 5-Fluorouracil und leucavorin (5-FU/LV) on quality of life (QoL) in NAPOLI-1: a phase 3 study in patients (pts) with metastatic pancreatic adenocarcinoma (mPAC) previously treated with gemcitabine-based therapy

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Introduction: Here we report QoL results from the NAPOLI-1 trial: a randomized phase 3 study of nal-IRI plus 5-FU/LV vs 5FU/LV in pts with mPDAC previously treated with gemcitabine-based therapy.
Methods: QoL was assessed using the EORTC-QLQ-C30, which includes functional and symptom scales, and a global health and QoL scale. Pts completed the questionnaire at treatment start, every 6 weeks (wks), and 30 days post-follow-up visit. Pts who provided baseline and ≥1 subsequent assessment were included. Linear transformations were applied to raw scores to produce reported scores in the 0-100 range. Pts were 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) for each subscale. Pairwise treatment group comparisons on response classification 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; 69% (49/71) in the nal-IRI+5-FU/LV group and 53% (44/83) in the 5-FU/LV group had evaluable data at 12 wks. At baseline, 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, with baseline values similar between groups. The observed median change in score at 12 wks was 0 for both treatment groups for Global Health Status and for 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 between-group differences were not substantial. There were no significant differences in the proportion of pts classified as improved, worsened, or stable between the treatment groups. Across subscales, adjusted P values for the comparisons were >0.05 (NS).
Conclusion: While limited by pt numbers, in this analysis nal-IRI+5-FU/LV-treated pts tended to maintain baseline QoL over 12 wks. There were no significant differences versus 5-FU/LV-treated pts in QoL response despite the addition of a second cytotoxic agent.

Disclosure: Jens T. Siveke: Advisory Role: Baxalta adivsory boards
Richard Hubner: Advisory Role: Baxalta advisory boards

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Nab-paclitaxel/Gemcitabine first line therapy in patients with metastatic pancreatic carcinoma and high-bilirubin values – data from the German QoliXane pancreatic cancer registry

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Introduction: Hyperbilirubinaemia is a common disease effect in patients (pts) with metastatic pancreatic cancer (mPC). As clinical trials often exclude them, data on management of these pts are rare. In the framework of a German observational multicenter study (QoliXane), quality of life and therapy data are currently being collected in pts with mPC receiving a combination of nab-paclitaxel and gemcitabine. This is an interim analysis on hyperbilirubinaemia management.
Methods: Pts were included to this analysis if they entered the trial with a bilirubin level ≥ 1.2 mg/dl and completed at least 2 cycles. Bilirubin levels were documented for up to 4 cycles and methods of hyperbilirubinaemia management have been assessed. A both descriptive and explorative analysis was performed using IBM SPSS V 23.
Results: 25 of 294 pts (8.5%) were included. Mean bilirubin level was 2.96 mg/dl (range 1.2-12.3) at baseline and dropped considerably by the 2nd cycle to 0.84 (range 0.29-3.9; p = 0.0001). Bilirubin levels decreased in 24 (96%) and increased in 1 (4%) pts upon treatment start. 18 (72%) pts started treatment with standard dosage, 7 (28%) with a reduced regime. 10 (40%) pts underwent additional intervention: either stenting (7 pts, 28%) or bile duct anastomosis (3 pts, 12%). Mean bilirubin values dropped from 4.59 to 1.09 in pts with and from 1.87 to 0.68 in pts without additional intervention. Grade 3/4 toxicity was seen in 60% of pts and most common 3/4 events were anemia, nausea, and fever.

Tab. 1. Mean Bilirubin Levels (1)

	Baseline	Cycle 2	Cycle 3	Cycle 4
All pts (n = 25)	2.96	0.84	0.83	0.53
no add. intervention (n = 15)	1.87	0.68	0.92	0.61
any add. intervention (n = 10)	4.59	1.09	0.68	0.46
add. stenting (n = 7)	4.52	1.19	0.84	0.35
add. bile duct anastomosis (n = 3)	4.80	0.87	0.47	0.53
p (all pts)(2)		0.0001	0.002	0.008

(1) n's indicate # of pts at baseline
(2) Wilcoxon test to baseline (related samples), level of significance p = 0.05

Conclusions: Data show that bilirubin levels drop considerably after start of nab-pac/gem therapy. The treatment seems to be feasible, although considerable frequencies of Grade 3/4 toxicities were observed.

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Salah-Eddin Al-Batran: Advisory Role: Merck, Roche, Celgene, Lilly, Nordic Pharma; Financing of Scientific Research: Merck, Roche, Celgene, Lilly, Nordic Pharma; Expert Testimony: Merck, Roche, Celgene, Vifor, Medac, Hospira, Lilly

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ORIGINAL ARTICLE

A phase II study of capecitabine plus docetaxel in gemcitabine-pretreated metastatic pancreatic cancer patients: CapTere

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Abstract
Purpose Docetaxel and capecitabine combination is synergistic in preclinical models. We investigated the efficacy and toxicity of this combination as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma (mPC), pretreated with gemcitabine-based chemotherapy.
Methods Eligible patients were treated with capecitabine 800 mg/m^2 orally PO bid on days 1–14 in combination with intravenous docetaxel 30 mg/m^2 on days 1 and 8 of each 21-day cycle. The primary end point was overall response rate. Using a three-stage sequential design, two interim analyses for early stopping due to lack of efficacy were planned and conducted after 13 and 26 patients were accrued. Secondary end points included time to treatment failure, progression-free survival (PFS), overall survival (OS) and 50 % drop in CA19-9 levels.
Results Forty-three patients were evaluable for toxicity and 42 evaluable for response, at a median age of 64 years. The majority of patients (74 %) had ECOG PS 0-1. Six patients (14 %) achieved a partial tumor response, and stable disease for ≥2 cycles was observed in 59 % of patients (n = 25). Thirty-five percent (n = 11/31) of patients had a ≥50 % decrease in CA19-9 levels. The median PFS was 3.7 months (95 % CI 2.1–4.3 months), and the median OS was 5.3 months (95 % CI 4.3–8.6 months). Treatment was generally well tolerated. Grade 3 toxicity and grade 4 toxicity were seen in 45 and 5 % of patients, respectively. One patient had a potential treatment-related mortality.
Conclusions The combination of capecitabine and docetaxel is active and well tolerated in mPC patients pretreated with gemcitabine-based therapy.

Keywords Pancreatic cancer · Gemcitabine pretreated · Second-line chemotherapy · Capecitabine · Docetaxel

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Introduction

Pancreatic cancer (PC) is the fourth most common cause of cancer-related death in the United States. The estimated incidence of PC is 45,220 cases with 38,460 deaths in the United States in 2013 [1]. Progress in first-line therapy for metastatic pancreas cancer (mPC) in good performance status patients has recently been made. Both FOLFIRINOX and the combination of gemcitabine and protein-bound paclitaxel improved survival compared to single-agent gemcitabine [2, 3]. Unfortunately, patients will eventually have cancer progression on first-line therapy.

Data for second-line chemotherapy in patients with advanced/metastatic PC are limited, and only one randomized trial to date reported a survival benefit in patients with gemcitabine-pretreated PC. In this trial, 5-FU, leucovorin and oxaliplatin (OFF) were superior to best supportive care, or to 5-FU alone [4–6]. However, median overall survival (OS) was still disappointing, only 4.8 months with OFF. Therefore, progress is clearly needed.

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Preclinical data demonstrated an increase in the thymidine phosphorylase levels in tumor cells following exposure to docetaxel [7]. Data particularly from the breast cancer literature suggested a synergistic interaction between docetaxel and capecitabine in patients with advanced disease [8–10]. Therefore, we conducted a phase II trial to study the efficacy and safety of the docetaxel/capecitabine combination (CapTere) in patients with gemcitabine-pretreated mPC. The activity of docetaxel has been investigated as a single agent in two phase II trials [11, 12] with an objective response rate (RR) of 6–15 % and stable disease (SD) rate of 38–58 % and median OS of 8–9 months. Capecitabine as a single agent [13] as well as in combination with erlotinib [14] and oxaliplatin [15] has been studied in gemcitabine-pretreated mPC patients, which offered a RR of 0, 10 and 28 % and a median OS of 7.6, 6.5 and 5.8 months, respectively.

Materials and methods

Patient selection

In this open-label, single-arm phase II trial, eligible patients had to meet the following criteria: histologic confirmation of metastatic adenocarcinoma of the pancreas, age >18 years, one prior gemcitabine-based chemotherapy regimen (with or without radiation) and had been at least 3 weeks or more beyond completion of prior chemotherapy (30 days beyond any experimental agent), ECOG (Eastern Cooperative Oncology Group) performance status of $\leq$2, at least one dimensionally measurable target lesion (i.e., lesions, $\geq$2 cm other than the primary or $\geq$1.5 cm in case of lung metastasis), adequate hematologic function (neutrophils >1,500/mm^3, platelets >100,000/mm^3, Hb > 8.0 mg/dl), adequate liver function [bilirubin levels $\leq$1.5 times the institutional upper normal limit (ULN), after biliary drainage if previously abnormal, and AST and alkaline phosphatase $\leq$2.5 times the UNL, or $\leq$5 times the UNL for patients with liver metastasis] and normal renal function (serum creatinine $\leq$2.0/dl, creatinine clearance >30 ml/min). Patients with metastatic disease to brain were eligible if prior brain radiation was given and were not receiving steroids or anticonvulsants. Radiation for palliation or for treatment of primary tumor, if completed at least 4 weeks prior to initiation of protocol, was also allowed.

Patients were excluded from the study if they were receiving an investigational agent, had received capecitabine or docetaxel as part of prior therapy and had pre-established peripheral neuropathy greater than grade 1 or presence of concurrent evidence of malignancy (excluding non-melanoma skin cancers, low-grade bladder carcinoma followed off therapy, treated in situ cervical cancer or lobular neoplasia of breast). Patients with known positive HIV serology, pregnant or breast-feeding women, history of severe hypersensitivity reaction to drugs formulated with polysorbate 80 or prior unanticipated reaction to fluoropyrimidine therapy, known sensitivity to 5-fluorouracil, clinically significant cardiac disease, and lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome were also excluded.

All patients have given their written informed consent before their enrollment to the study. The protocol has been approved by the ethics and the scientific committees of the participating institutions. This study was conducted according to the Helsinki's declaration and according to the guidelines on good clinical practice.

Treatment regimen and dose modifications

Capecitabine (Xeloda; Roche, Zurich, Switzerland) was given at a dose of 800 mg/m^2, orally, twice a day (1,600 mg/m^2/day in total), from day 1 through day 14 of a 21-day cycle, starting the first dose at least 1 h after the first dose of docetaxel. Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ, USA) was given at a dose of 30 mg/m^2, intravenously (IV), on days 1 and 8 of a 21-day cycle. At least two cycles of therapy were planned, and the chemotherapy regimen (CapTere) was continued until disease progression or unacceptable toxicity. After the cessation of therapy, patients continued to be followed at 3-month intervals up to a year after the end of the treatment.

Toxicity was monitored, and dose adjustments were allowed based on severity of adverse events including hematologic and liver function toxicity, diarrhea, stomatitis, hand and foot syndrome reaction, cutaneous erythema, nausea, vomiting and neurosensory symptoms. Capecitabine was allowed to be reduced to 1,200 mg/m^2/day (level 1) and 800 mg/m^2/day (level 2). Docetaxel could be decreased to 25 mg/m^2 (level 1) and 20 mg/m^2 (level 2).

There were three dose adjustment schedules: (1) adjustment at the beginning of a new course, based on laboratories on the scheduled day of treatment and on maximum toxicity encounter in the previous course; (2) adjustment of docetaxel on day 8 of treatment cycle based on toxicity observed since start of the course; and (3) adjustment of capecitabine throughout days 1–14 of each course. If an interim dose adjustment was made on day 8 of docetaxel or on days 1–14 of capecitabine, further additional dose adjustment was not made in the beginning of the subsequent cycle.

Response and toxicity evaluation

The primary end point of the study was objective tumor response rate, with responses defined by Response

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Evaluation Criteria in Solid Tumors criteria (RECIST version 1.1) [16]. Objective responses either complete (CR) or partial (PR) were to be confirmed at least after two cycles from the initial response. Secondary end points included time to treatment failure (TTF), progression-free survival (PFS), OS and 50 % drop in CA19-9 levels, when baseline CA19-9 level was >100 U/ml.

While on study, patients were assessed for adverse events at each protocol visit. Complete physical examination, ECOG performance status, vital signs, body weight and height were recorded at the beginning of each treatment cycle. Complete blood count was checked on days 1 and 8. Serum chemistry profile was tested on day 1 of each cycle. CA19-9 levels were measured every two cycles. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical analysis

All patients who received at least one dose of study drugs were included in the analyses of response (except for one patient who had imaging done outside and imaging was not recovered for assessment), progression, treatment failure and survival. PFS was defined as time from first dose of CapTere to first documentation of objective tumor progression or death from any cause. Patients who were removed from study due to toxicity (rather than progression) and were started on another antitumor therapy were censored at the date of subsequent treatment initiation. TTF was defined as time from first dose of CapTere until cessation of study treatment due to any cause. OS was defined as time from first dose of CapTere to date of death from any cause or last contact (censored). Time-to-event end points were estimated using the Kaplan–Meier method. All analyses were conducted using SAS, version 8.2.

A sample size of 40 patients was planned for 87 % power and one-sided 10 % significance to detect a target improvement in response rate from 10 to 25 % (considering 10 % rate of dropout). Using a three-stage sequential design, two interim analyses for early stopping due to lack of efficacy were planned and conducted after 13 and 26 patients were accrued. No early termination of the trial was necessary.

Results

Patient characteristics

A total of 45 patients were enrolled in the study between July 2007 and August 2008. Patient and disease characteristics of the 43 evaluable patients are summarized in Table 1. The patients' median age was 64 years, and 21 (49 %) patients were men. The majority of patients (74 %) had ECOG PS 0-1. Forty-two percent of patients had 2 or more co-morbidities (determined per physician's discretion).

Table 1 Demographic characteristics of the 43 evaluable patients

Age	
Median	64.4
(range)	(44–83)
Gender	
Male	21 (49 %)
Female	22 (51 %)
EGOG at baseline	
0	3 (7 %)
1	29 (67 %)
2	9 (21 %)
Missing	2 (5 %)
CA 19.9 level at baseline	
Median	1,812
(range)	(134–40,732.0)
Number of co-morbidities	
None	14 (32.5 %)
1	11 (25.5 %)
2	9 (21 %)
3 or more	9 (21 %)
Location of tumor	
Head of pancreas	20 (46.5 %)
Other	23 (53.5)
Prior first-line therapy	
Gemcitabine	4 (9 %)
Gemcitabine/oxaliplatin	14 (32 %)
Gemcitabine/oxaliplatin/erlotinib	11 (26 %)
Gemcitabine-based adjuvant treatment	6 (14 %)
Other	8 (19 %)

A total of 42 patients completed at least one cycle of treatment. The median number of treatment cycles was 4 (range 1–13 cycles). Subjects discontinued for multiple reasons and were counted once for each reported reason. The reasons for discontinuation were as follows: disease progression or death in 31 subjects (73 %); treatment-related toxicity in six subjects (14 %); treatment-related mortality in one subject (2 %); other clinical complications not related to progression or side effects in two subjects (4 %); and three subjects (7 %) discontinued for other reasons.

Tumor response and survival

Among 42 patients who were evaluable for response, the best overall tumor response was as follows: CR 0 (0 %); PR 6 (14.3 %; 95 % CI 5.4–24.9 %); SD 25 (59.5 %; 95 % CI 44.7–74.4 %); and progressive disease (PD) 11 (26.2 %; 95 % CI 12.9–39.5 %) (Table 2). The median number of

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Table 2 Tumor response rates of the 42 evaluable patients' response

Response	*N* (%)	95 % CI
Complete response	0	–
Partial response	6 (14.3)	(5.4–24.9)
Stable disease	25 (59.5)	(44.7–74.4)
Progression disease	11 (26.2)	(12.9–39.5)

cycles received was nine and four for patients who achieved PR and SD, respectively.

Thirty-nine patients had disease progression on study, while four others were taken off treatment due to toxicity and started subsequent treatment. Forty-two patients have died, and one patient was alive at 17.1 months following progression at 12.0 months. The estimated median PFS time was 3.7 months (95 % CI 2.1–4.3), and the proportion of progression-free survivors at 3, 6 and 12 months were 55.2 % (95 % CI 39.1–68.7 %), 26.2 % (95 % CI 14.0–40.1 %) and 7.9 % (95 % CI 2.1–18.9 %), respectively. Median TTF was 3.0 months (95 % CI 1.8–4.2), and the failure-free rates at 3, 6 and 12 months were 48.8 % (95 % CI 33.3–62.6 %), 23.3 % (95 % CI 12.0–36.6 %) and 2.3 % (95 % CI 0.2–10.6 %), respectively. Median OS was 5.3 months (95 % CI 4.3–8.6), and the 6, 12 and 24 months of OS rates were 46.5 % (95 % CI 31.2–60.4 %), 18.6 % (95 % CI 8.7–31.4 %) and 5.6 % (95 % CI 1.1–15.9 %), respectively (Fig. 1). OS was not affected by the number of co-morbidities or baseline performance status.

Seventy-nine percent ($N = 31/39$) of patients had available baseline CA19-9 levels above 100 U/ml. Of these patients, 11 (35 %) experienced a significant drop of at least 50 %. Among those 11 patients, three subjects had PR, seven had SD, and one patient had PD.

Toxicity

Toxicity data were available for all patients. Five (12 %) patients experienced no toxicity. A total of 175 events recorded were considered possibly associated with treatment. Out of these, 76.5 % were grade 1 or 2, 22 % were grade 3, 1 % were grade 4, and 0.5 % were grade 5.

Twenty-five percent of subjects experienced a maximum of grade 1 or 2 maximum toxicity. Forty-five percent of patients had their worst toxicity graded as 3. Two patients (5 %) had their worst toxicity considered life-threatening, and one patient (2 %) had a lethal toxicity (pneumonia) (Table 3). There was no significant difference in maximum grade of toxicity when comparing patients with baseline ECOG performance status of 0–1 versus 2.

Thirteen (31 %) and four (9 %) patients required level 1 and level 2 adjustments for capecitabine, respectively. Dose adjustment modifications for docetaxel were limited

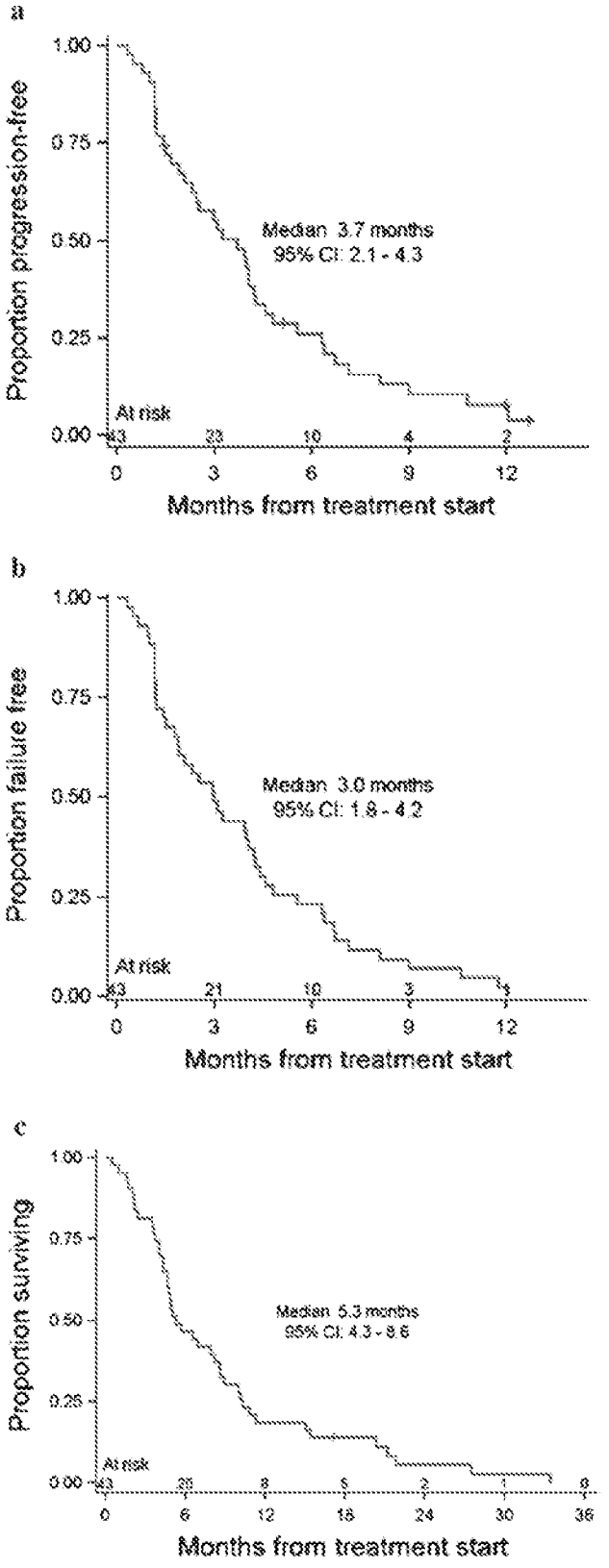


Fig. 1 Progression-free survival, time to treatment failure and overall survival for the 34 evaluable patients. **a** Progression-free survival. **b** Time to treatment failure. **c** Overall survival

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Table 3 Maximum toxicity per event

Toxicity	Grade 1	Grade 2	Grade 3	Grades 4/5
Nausea	5	1	3	–
Diarrhea	1	2	2	–
Hand and foot syndrome	1	4	6	–
Hepatotoxicity	1	–	–	–
Mucositis	1	1	2	–
Neuropathy	–	2	1	1
Fatigue	–	–	4	1
Pneumonitis	–	–	1	–
Pleural effusions	–	–	1	–
Vomiting	–	–	1	–
Infection	–	–	1	1
Alopecia	–	1	–	–
Anemia	–	–	1	–

Table 4 Frequency of dose adjustment of protocol drugs

Drug	*N* (%)
Capecitabine dose adjustment	
Level 0	25 (60 %)
Level 1	13 (31 %)
Level 2	4 (9 %)
Docetaxel dose adjustment	
Level 0	29 (69 %)
Level 1	13 (31 %)
Level 2	0

to 13 (31 %) patients that required level 1 dose reduction (Table 4).

Discussion

We carried out this single institution study to assess the safety and efficacy of combined therapy of capecitabine and docetaxel (CapTere) in mPC patients pretreated with gemcitabine-containing chemotherapy. The confirmed tumor RR was 14 %. Additionally, 60 % of the enrolled patients had SD. Secondary efficacy end points in our study included survival, safety and tolerability. The CapTere regimen had survival results with a median survival of 5 months, in range with other trials in this patient population (Table 5). With regard to safety, CapTere combination chemotherapy had acceptable toxicity without major additional toxicity over what is expected from single-agent docetaxel or capecitabine.

In a retrospective study, Saif et al. [17] showed mild activity of docetaxel as second-line therapy in patients with mPC pretreated with gemcitabine. Patients were treated with either weekly docetaxel at 25 mg/m^2 or 3-weekly docetaxel regimen (docetaxel at 75 mg/m^2 or docetaxel–gemcitabine–capecitabine or docetaxel–gemcitabine). Only one PR (6 %) was observed (docetaxel–gemcitabine), while five patients achieved SD (weekly docetaxel). Median progression-free survival (PFS) was 8 weeks (range 3–16 weeks), and median OS was 4.0 months (range 2.0–6.5 months).

Table 5 Randomized trials performed in pancreatic cancer patients after gemcitabine failure

References	Regimen	*N*	RR	TTP (mo)	OS (mo)
Ulrich-Pur et al. [21]	Irinotecan/raltitrexed	48	16	4.0	6.5
	Raltitrexed		0	2.5	4.3
Jacobs et al. [22]	Rubitecan	409	11[a]	1.9[a]	3.5
	Physician choice		1	1.6	3.1
Oettle et al. [4]	OFF	46	na	na	4.9[a]
	BSC				2.3
Astsaturov et al. [23]	Bevacizumab	30	0	1.4	5.9
	Bevacizumab and docetaxel		7	1.5	4.0
Pelzer et al. [5]	OFF	160	na	3.0[a]	6.0[a]
	FF			2.1	3.0
Hwang et al. [24]	FOLFOX	60	na	1.4	4.0
	FOLFIRI			1.9	4.0

RR response rate, *TTP* time to progression, *OS* overall survival, *mo* months

[a] Difference statistically significant

Another phase II trial combining docetaxel and capecitabine reported similar safety and efficacy results to CapTere in gemcitabine-pretreated, unresectable PC [18]. Thirty-one patients were enrolled in the study; 93.6 % of them had a performance status of 0–1. PR was observed in three (9.7 %) patients, SD in seven (22.6 %; 95 % CI 15.80–48.71 %) and PD in 21 (67.6 %). The median PFS was 2.4 months (95 % CI 1.6–3.13), and the median OS was 6.3 months (95 % CI 3.38–9.23).

There have been a few other phase II and phase III trials in the second-line setting mPC after gemcitabine failure (Table 5), and therefore, there is no consensus on the optimal treatment in the second-line setting. At present, oxaliplatin in combination with a fluoropyrimidine has become one of the preferred options based on the efficacy results of two randomized trials for patients that progress on gemcitabine-based therapy [4, 6, 19]. Moreover, FOLFIRINOX has emerged as an alternative to gemcitabine in the first-line setting for metastatic pancreatic cancer patients with good performance status and with good organ function. FOLFIRINOX showed superior survival (median OS 11.1 vs. 6.8 months, $P < 0.001$) in this patient population [2]. Despite the lack of randomized data, gemcitabine as a single agent or the combination of gemcitabine and

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nab-paclitaxel has become a second-line option. Whether gemcitabine is the appropriate choice and whether it should be used as a single agent or in combination with other agents after FOLFIRINOX failure remain to be determined. In addition, the MPACT trial [3] showed that adding *nab*-paclitaxel to gemcitabine in the first-line setting improves survival compared with gemcitabine alone in patients with mPC. This raises another question to the clinicians: Is there any cross-resistance between those nab-paclitaxel and docetaxel? The efficacy of CapTere in patients who are exposed to nab-paclitaxel plus gemcitabine in the first-line setting needs to be evaluated in appropriately designed trial. Another three-drug regimen of interest is a combination that relies on synergy between gemcitabine, capecitabine and docetaxel (GTX). A prospective phase II study [20] demonstrated response rates of 21.9 % and a median OS of 14.5 months ($n = 43$) in mPC. Given the accessibility of GTX, many oncologists are now using this regimen on a routine basis in the first-line setting. Furthermore, the MPACT trial [3] showed that adding *nab*-paclitaxel to gemcitabine in the first-line setting improves survival compared with gemcitabine alone in patients with mPC. These options raise other questions that need to be answered with well-designed second-line randomized trials: first, could GTX improve outcomes better than CapTere in the second-line setting without increasing the toxicities, and second, if Taxotere can be used in patients who previously are exposed to Abraxane.

In conclusion, the efficacy results and toxicity of CapTere make this combination an alternative in good performance status patients previously treated with gemcitabine-based therapy. However, better understanding of the resistance mechanism and the biology that drives cancer growth will lead to more effective therapies.

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Conflict of interest The manuscript has never been published and is not under consideration for publication elsewhere. Authors have no financial interest to declare.

References

1. http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-20132013. Accessed 4 Sept 2013
2. Conroy T, Desseigne F, Ychou M et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
3. Von Hoff DD, Ervin T, Arena FP, Gabriela Chiorean E, Infante JR, Moore MJ et al (2013) Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates. In: ASCO annual meeting, Chicago, IL. J Clin Oncol 31: abstract 4005
4. Oettle H, Pelzer U, Stieler J et al (2005) Oxaliplatin/folinic acid/5-fluorouracil [24 h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-pretreated advanced pancreatic cancer (CONKO 003). In: ASCO annual meeting proceedings 2005. J Clin Oncol 23: abstract 4031
5. Pelzer U, Kubica K, Stieler J et al (2008) A randomized trial in patients with gemcitabine pretreated pancreatic cancer. Final results of the CONKO 003 study. In: ASCO annual meeting proceedings. J Clin Oncol 26: abstract 4508
6. Pelzer U, Schwaner I, Stieler J et al (2011) 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. Eur J Cancer 47:1676–1681
7. Fujimoto-Ouchii K, Tanaka Y, Tominaga T (2001) Schedule dependency of antitumor activity in combination therapy with capecitabine/5′-deoxy-5-fluorouridine and docetaxel in breast cancer models. Clin Cancer Res 7:1079–1086
8. Maher JF, Villalona-Calero MA (2002) Taxanes and capecitabine in combination: rationale and clinical results. Clin Breast Cancer 2:287–293
9. O'Shaughnessy JA, Blum JL (2006) Capecitabine/taxane combination therapy: evolving clinical utility in breast cancer. Clin Breast Cancer 7:42–50
10. O'Shaughnessy J, Miles D, Vukelja S et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812–2823
11. Androulakis N, Kouroussis C, Dimopoulos MA et al (1999) Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II study. J Clin Oncol 17:1779–1785
12. Rougier P, Adenis A, Ducreux M et al (2000) A phase II study: docetaxel as first-line chemotherapy for advanced pancreatic adenocarcinoma. Eur J Cancer 36:1016–1025
13. Boeck S, Wilkowski R, Bruns CJ et al (2007) Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. Oncology 73:221–227
14. Kulke MH, Blaszkowsky LS, Ryan DP et al (2007) Capecitabine plus erlotinib in gemcitabine-pretreated advanced pancreatic cancer. J Clin Oncol 25:4787–4792
15. Xiong HQ, Varadhachary GR, Blais JC et al (2008) Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 113:2046–2052
16. van Meerten ELP, Gelderblom H, Bloem JL (2010) RECIST revised: implications for the radiologist. A review article on the modified RECIST guideline. Eur Radiol 20:1456–1467
17. Saif MW, Syrigos K, Penney R, Kaley K (2010) Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study. Anticancer Res 30:2905–2909
18. Katopodis O, Polyzos A, Kentepozidis N et al (2011) Second-line chemotherapy with capecitabine (Xeloda) and docetaxel (Taxotere) in previously treated, unresectable adenocarcinoma of pancreas: the final results of a phase II trial. Cancer Chemother Pharmacol 67:361–368
19. Chua YJ, Cunningham D (2006) Chemotherapy for advanced pancreatic cancer. Best Pract Res Clin Gastroenterol 20:327–348
20. Fine R, Moorer G, Sherman W, Chu, Maurer KM, Chabot J et al (2009) Phase II trial of GTX chemotherapy in metastatic pancreatic cancer. Clin Oncol 27(15 Suppl): abstract 4623
21. Ulrich-Pur H, Raderer M, Verena Kornek G et al (2003) Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. Br J Cancer 88:1180–1184

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22. Jacobs AD, Burris HA, Rivkin S et al (2004) A randomized phase III study of rubitecan (ORA) vs. best choice (BC) in 409 patients with refractory pancreatic cancer report from a North-American multi-center study. J Clin Oncol 22(Suppl):Abstr 4013
23. Astsaturov IA, Meropol NJ, Alpaugh RK et al (2007) A randomized phase II and coagulation study of bevacizumab alone or with docetaxel in patients with previously treated metastatic pancreatic adenocarcinoma. J Clin Oncol 25(18S):Abstr 4556
24. Hwang JY, Yoo C, Kim T et al (2009) A randomized phase II study of FOLFOX or FOLFIRI.3 as second-line therapy in patients with advanced pancreatic cancer previously treated with gemcitabine-based chemotherapy. J Clin Oncol 27(15S):Abstr 4618

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ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

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D.P.S.S. and D.L. were Expert Panel co-chairs.

Clinical Practice Guideline Committee approved: March 8, 2018.

Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

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ABSTRACT

Purpose

In 2016, ASCO published a guideline to assist in clinical decision making in metastatic pancreatic cancer for initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up. The purpose of this update is to incorporate new evidence related to second-line therapy for patients who have experienced disease progression or intolerable toxicity during first-line therapy.

Methods

ASCO convened an Expert Panel to conduct a systematic review of the literature on second-line therapy published between June 2015 and January 2018. Recommendations on other topics covered in the 2016 Metastatic Pancreatic Cancer Guideline were endorsed by the Expert Panel.

Results

Two new studies were found that met the inclusion criteria.

Recommendations

For second-line therapy, gemcitabine plus nanoparticle albumin-bound paclitaxel should be offered to patients with first-line treatment with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, and a favorable comorbidity profile; fluorouracil plus nanoliposomal irinotecan can be offered to patients with first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, and a favorable comorbidity profile; fluorouracil plus irinotecan or fluorouracil plus oxaliplatin may be offered when there is a lack of availability of fluorouracil plus nanoliposomal irinotecan; gemcitabine or fluorouracil should be offered to patients with either an ECOG PS of 2 or a comorbidity profile that precludes other regimens. Testing select patients for mismatch repair deficiency or microsatellite instability is recommended, and pembrolizumab is recommended for patients with mismatch repair deficiency or high microsatellite instability tumors. Endorsed recommendations from the 2016 version of this guideline for computed tomography, baseline performance status and comorbidity profile, defining goals of care, first-line therapy, and palliative care are also contained within the full guideline text. Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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INTRODUCTION

There were an estimated 55,440 new cases and 44,330 deaths as a result of pancreatic cancer in the United States in 2017, and an estimated 338,000 deaths worldwide in 2012.[1] A diagnosis of pancreatic ductal carcinoma is associated with poor prognosis due to early micrometastatic spread, and the 5-year survival rate for metastatic pancreatic cancer is approximately 2%.[2]

In 2016, ASCO published a guideline to assist in clinical decision making in metastatic pancreatic cancer. The guideline provided recommendations for initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up after treatment.[3]

ASCO guidelines are periodically assessed for currency using the signals approach,[4] which is designed to identify new, potentially practice-changing data that might translate into revised practice recommendations. This approach relies on targeted routine literature monitoring and regular review and assessment of the recommendations by ASCO Expert Panel members. Using this approach, new evidence was identified

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Guideline Question

The purpose of this focused update is to incorporate new evidence that is relevant to Clinical Question 3 from the previous version of this guideline[3]: What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens?

Target Population

Patients with metastatic pancreatic cancer

Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists

Methods

An Expert Panel was convened to develop updated clinical practice guideline recommendations based on a focused systematic review of the medical literature related to second-line therapy. This review resulted in additions or clarifications to recommendations 3.1, 3.2, 3.4, and 3.5. All other recommendations from the previous (2016) version of this guideline are endorsed for this 2018 update.

New recommendations or changes to the 2016 recommendations are denoted by ***bold, italicized text***. A comparison of the original 2016 recommendations and the updated 2018 recommendations can be found in the Data Supplement. See the full guideline text for definitions of favorable and relatively favorable comorbidity profiles.

RECOMMENDATIONS

1. Initial Assessment

Recommendation 1.1. A multiphase computed tomography scan of the chest, abdomen, and pelvis should be performed to assess extent of disease. Other staging studies should be performed only as dictated by symptoms (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2. The baseline PS, symptom burden, and comorbidity profile of a patient with metastatic pancreatic cancer should be evaluated carefully (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3. The goals of care (to include a discussion of an advance directive), patient preferences, as well as support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.4. Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with metastatic pancreatic cancer should be the standard of care (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5. Every patient with pancreatic cancer should be offered information about clinical trials, which include therapeutic trials in all lines of treatment as well as palliative care, biorepository/biomarker, and observational studies (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

2. First-Line Treatment

Recommendation 2.1. FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) is recommended for patients who meet all of the following criteria: an ECOG PS of 0 to 1, favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.2. Gemcitabine plus NAB-paclitaxel is recommended for patients who meet all of the following criteria: an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4. Patients with an ECOG PS $\geq$ 3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3. Second-Line Treatment

Recommendation 3.1. ***Routine testing for dMMR or MSI-H is recommended, using IHC, PCR, or NGS for patients who are considered to be candidates for checkpoint inhibitor therapy*** (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2. ***PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H*** (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with FOLFIRINOX, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.4. ***Fluorouracil plus nanoliposomal irinotecan, or fluorouracil plus irinotecan where the former combination is unavailable,*** is preferred as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.5. ***Fluorouracil plus oxaliplatin may be considered*** as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statement for recommendations 3.4 and 3.5. A recent phase III trial comparing mFOLFOX6 with FU + LV demonstrated a higher rate of grade 3 or 4 adverse events and significantly reduced OS within the mFOLFOX6 arm of the trial.[7] However, previous phase III data have demonstrated a benefit with the OFF regimen compared with FU + LV.[10] Considering the inconsistency of these results, although fluorouracil plus nanoliposomal irinotecan is preferred, the Expert Panel continues to support the use of fluorouracil plus oxaliplatin as an option where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where residual toxicity from first-line therapy or comorbidities preclude the use of fluorouracil plus nanoliposomal irinotecan.

Recommendation 3.6. Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 3.7. No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

4. Palliative Care

Recommendation 4.1. Patients with metastatic pancreatic cancer should have a full assessment of symptom burden, psychological status, and social supports as early as possible, preferably at the first visit. In most cases, this assessment will indicate a need for a formal palliative care consult and services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

5. Treatment of Pain and Symptoms

Recommendation 5.1. Patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

6. Follow-Up/Surveillance

Recommendation 6.1. For patients on active cancer-directed therapy outside a clinical trial, imaging to assess first response should be offered at 2 to 3 months from the initiation of therapy. Computed tomography scans with contrast are the preferred modality. Thereafter, clinical assessment, conducted frequently during visits for cancer-directed therapy, should supplant imaging assessment. The routine use of positron emission tomography scans for the management of patients with pancreatic cancer is not recommended. CA19-9 is not considered an optimal substitute for imaging for the assessment of treatment response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 6.2. No data exist on the duration of cancer-directed therapy. An ongoing discussion of goals of care and assessment of treatment response and tolerability should guide decisions to continue or to hold or terminate cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Additional Resources

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

in 2017 that could affect the Metastatic Pancreatic Cancer guidelines for second-line therapy for patients who had experienced disease progression or intolerable toxicity with first-line therapy.

The previous 2016 version of this guideline[3] included the following consensus-based, moderate-strength recommendations for second-line therapy, based on low-quality evidence:

- Gemcitabine plus nanoparticle albumin-bound paclitaxel (NAB-paclitaxel) can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy.
- Fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services.
- Gemcitabine or fluorouracil can be considered as second-line therapy to patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy.
- No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged.

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Based on the identification of two new studies related to these recommendations during the routine signals-based assessment, the Expert Panel for this guideline (Table A1, online only) chose to undertake a focused update of this guideline, including a systematic review for evidence related to the recommendations listed above for second- (or greater-) line therapy. Using the signals-based approach, no new studies were identified that were relevant to the remaining clinical questions; therefore, the Expert Panel continues to endorse the 2016 recommendations on those topics. A summary of the current recommendations is contained in the Bottom Line.

GUIDELINE QUESTION

This clinical practice guideline update addresses the following clinical question: What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens for metastatic pancreatic cancer?

METHODS

Guideline Update Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and a member of the ASCO guidelines staff with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of PubMed for studies published between June 2015 and January 2018. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- The population included patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens
- Studies of the efficacy of systematic treatment options for this patient population were considered for inclusion. Included systemic therapy options were chemotherapy or programmed cell death-1 (PD-1) immune checkpoint blockade.
- Study design was limited to phase III randomized controlled trials (RCTs) for studies of chemotherapy. There was no limitation placed on study design for studies of PD-1 immune checkpoint blockade.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (3) published in a non-English language. The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[5] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this guideline update, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (Guidelines Into Decision Support and BRIDGE-Wiz), and quality assessment, is available in the Methodology Supplement at www.asco.org/gastrointestinal-cancer-guidelines.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on a formal review of the emerging literature, ASCO will continue to determine the need to update these guideline recommendations.

This is the most recent information as of the publication date; to submit new evidence, visit www.asco.org/gastrointestinal-cancer-guidelines.

Definitions

A favorable comorbidity profile is loosely defined as hemoglobin $\geq$ 10 g/dL and platelet count $\geq$ 100,000/μL without transfusion support; absolute neutrophil count $\geq$ 1,500/μL; bilirubin and international normalized ratio $\leq$ 1.5 times the upper limit of normal; albumin $\geq$ 3 g/dL; creatinine clearance $\geq$ 60 mL/min/1.73 m^2; and absence of comorbid conditions that require ongoing active medical care, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders.

A relatively favorable comorbidity profile is loosely defined as hemoglobin $\geq$ 9 g/dL and platelet count $\geq$ 75,000/μL without transfusion support; absolute neutrophil count $\geq$ 1,500/μL; bilirubin and international normalized ratio $\leq$ 1.5 times the upper limit of normal; albumin $\geq$ 3 g/dL; creatinine clearance $\geq$ 60 mL/min/1.73 m^2; and absence of poorly controlled comorbid conditions, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert

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Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

QUALITY AND STRENGTH OF EVIDENCE AND RECOMMENDATIONS

Recommendation 3.1

Routine testing for deficiency in mismatch repair (dMMR) or high microsatellite instability (MSI-H) is recommended, using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS), for patients who are considered to be candidates for checkpoint inhibitor therapy (Type: informal-consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2

PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. **Study characteristics and quality assessment.** In Le et al,[6] dMMR was assessed using PCR or IHC. This study included 86 patients with 12 different cancer types (ampulla of vater, cholangiocarcinoma, colorectal, endometrial, gastroesophageal, neuroendocrine, osteosarcoma, pancreas (n = 8), prostate, small intestine, thyroid, and unknown primary), who had received at least one prior therapy and had evidence of progressive disease (Table 1). Median progression-free survival (PFS) and overall survival (OS) have not been reached yet in this study. A small, nonrandomized study such as that of Le at al[6] would generally be considered low quality due to the risk of bias associated with nonrandomized study designs and the indirectness resulting from the small number of patients with pancreatic cancer included in the study (n = 8). Nonetheless, the magnitude of the effect across disease sites in the population of patients with dMMR tumors is strong, and on this basis, the Expert Panel rated the study quality as intermediate.

Study outcomes. In the overall study population, Le et al[6] found a 21% rate of complete radiographic response, an objective response rate of 53% (46 of 86 patients; 95% CI, 42% to 64%), and a disease control rate (partial plus complete response or stable disease) of 77% (66 of 86 patients; 95% CI, 66% to 85%). Adverse events (AEs), which were mostly low grade, occurred in 74% of the study population. Twenty-one percent experienced endocrine-related AEs (mostly hypothyroidism) that could be controlled. Autoimmune phenomena were noted as a concern. Among the eight patients with pancreatic cancer included in this study, two (25%) experienced complete radiographic response, and the disease control rate was 75% (n = 6; Table 2).

Clinical interpretation. Immunotherapy has emerged as an option for metastatic pancreatic cancer since the previous version of this guideline was published in 2016. Le et al[6] have studied the effects of PD-1 blockade with pembrolizumab. dMMR cancers are predicted to have a large number of mutation-associated antigens that could potentially be recognized by the immune system. This study tests the hypothesis, established previously in a small study of patients with colorectal cancer, that PD-1 blockade is effective in dMMR tumors, regardless of their tissue of origin. In 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for dMMR that can lead to high levels of MSI-H in the tumors, regardless of disease site.[8] In pancreatic cancer, a recent study found that only approximately 0.8% of tumors had dMMR.[9]

Recommendation 3.4

Fluorouracil plus nanoliposomal irinotecan, or fluorouracil plus irinotecan where the former combination is unavailable, is preferred as second-line therapy, for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and

Table 1. Study Characteristics

First Author	Intervention or Comparison	No. of Patients Randomly Assigned	Median Age (years)	ECOG PS (%)	Median Follow-Up (months)	Disease Characteristics		
						Previous Treatment?	Eligibility Based on Timing of Disease Progression	Metastatic Disease (%)
Gill[7]	Biweekly mFOLFOX6 *v* FU + LV	108	mFOLFOX6: 65 (38-82) <70: 63% ≥ 70: 37% Infusional FU + LV: 67 (48-78) < 70: 67% ≥ 70: 33%	mFOLFOX6: 0: 13.0 1: 75.9 2: 11.1 Infusional FU + LV: 0: 18.9 1: 75.5 2: 5.7	8.8	Gemcitabine: Monotherapy: mFOLFOX6: 74.1% Infusional FU + LV: 77.8% Combination: mFOLFOX6: 25.9% Infusional FU + LV: 22.2%	Disease progression within 4 weeks of random assignment either during or after gemcitabine therapy	mFOLFOX6: 93 FU + LV: 94
Le[6]	PD-1 blockade (pembrolizumab)	86 (8 pancreatic)				Yes	Yes	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, infusional fluorouracil, leucovorin, and oxaliplatin; FU + LV, infusional fluorouracil and leucovorin; PD-1, programmed cell death-1.

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Table 2. Study Outcomes

First Author	Type of Study	No. of Patients	CRR	ORR	DC	Median PFS (months)	Median OS	Adverse Events
Gill[7]	Phase III multicenter trial	Biweekly mFOLFOX6 (54) *v* FU + LV (54); safety pop: 102; QOL pop: 83				3.1 *v* 2.9 (HR, 1.00; 95% CI, 0.66 to 1.53; log-rank $P = .989$)	6.1 *v* 9.9 (HR, 1.78; 95% CI, 1.08 to 2.93; log-rank $P = .024$)	Grade 3 or 4: mFOLFOX6: 63%, infusional FU + LV: 11% Treatment discontinuation: mFOLFOX6: 20%, infusional FU + LV: 2%
Le[8]	Prospective study of PD-1 blockade (pembrolizumab)	86 patients across 12 disease sites*	18 (21%; 95% CI not reported)	46 (53%; 95% CI, 42% to 64%)	66 (77%; 95% CI, 66% to 85%)	Not yet reached, study ongoing. PFS at 1 year: 64%; PFS at 2 years: 54%	Not yet reached, study ongoing	74%, mostly low grade; endocrine disorders (mostly hypothyroidism): 21%; autoimmune response is a concern.
Le[9]	Prospective study of PD-1 blockade (pembrolizumab)	Subset of 8 patients with pancreatic cancer	2 (25%)	62%	6 (75%)	Not yet reached, study ongoing	Not yet reached, study ongoing	Not reported

Abbreviations: CRR, complete radiographic response; DC, disease control rate; partial response plus complete response plus stable disease; FU + LV, fluorouracil and leucovorin; HR, hazard ratio; mFOLFOX6, infusional fluorouracil, leucovorin, and oxaliplatin; ORR, objective radiographic response (tumor size reduction according to RECIST criteria); OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; pop, population; QOL, quality of life.

*Ampulla of vater, cholangiocarcinoma, colorectal, endometrial, gastroesophageal, neuroendocrine, osteosarcoma, pancreas, prostate, small intestine, thyroid, unknown primary.

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access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.5

Fluorouracil plus oxaliplatin may be considered as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statement. A recent phase III trial comparing infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) with fluorouracil and leucovorin (FU + LV) demonstrated a higher rate of grade 3 or 4 AEs and significantly reduced OS within the mFOLFOX6 arm of the trial. However, previous phase III data have demonstrated a benefit with the OFF (oxaliplatin, folinic acid, and fluorouracil) regimen compared with FU + LV. Considering the inconsistency of these results, although fluorouracil plus nanoliposomal irinotecan is preferred, the Expert Panel continues to support the use of fluorouracil plus oxaliplatin as an option where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where residual toxicity from first-line therapy or comorbidities precludes the use of fluorouracil plus nanoliposomal irinotecan.

Literature review and analysis. **Study characteristics and quality assessment.** One phase III RCT, the PANCREOX study,[7] met the eligibility criteria for this focused guideline update. The PANCREOX study compared leucovorin 400 mg/m^2 administered as a 2-hour intravenous (IV) infusion on day 1 and fluorouracil administered as a bolus IV dose of 400 mg/m^2 on day 1 followed by a 2,400 mg/m^2 continuous infusion for 46 hours, administered every 14 days to the same regimen plus oxaliplatin 85 mg/m^2 given as a 2-hour IV infusion on day 1, administered every 14 days. Fifty-four patients with an ECOG PS of 0 to 2 were randomly assigned to each treatment arm. Approximately three quarters of the study population had been treated previously with gemcitabine monotherapy, and the remainder had received gemcitabine combination therapy. Metastatic disease was present in 93% of patients (Table 1).

Quality assessment was conducted for the important outcomes of OS, PFS, and incidence of grade 3 or 4 AEs. Quality assessment included risk of bias, indirectness, imprecision, and inconsistency for each outcome. Risk of bias may have been introduced with the open-label study design, and no information was provided on allocation concealment. Intention-to-treat analysis was used, and study characteristics were mostly well balanced, with the FU + LV group having more patients within ECOG PS 0. This study accrued only 108 of the planned 128 patients; however, the *P* value of .989 for the primary end point PFS would likely have not attained significance with the addition of 20 more patients to the study. Imprecision was not considered to be a major quality issue for the primary outcome of this study (PFS), or for other important outcomes. The majority of patients included in this study received first-line monotherapy with gemcitabine. Therefore, the results are less applicable to the population of patients who received previous treatment with first-line combination chemotherapy. In terms of inconsistency, the results of this study differ from the findings of the CONKO-003 study of fluorouracil and oxaliplatin compared with fluorouracil alone.[10] The authors of PANCREOX note that differences in dose intensities of oxaliplatin, eligibility criteria, and postprogression therapy could have contributed to this inconsistency; however, the comparison of the differences between the two studies is inconclusive.[7] Taking these factors into consideration, the quality of this study is rated as intermediate.

Study outcomes. There was no difference between arms in the PANCREOX study for the primary outcome, PFS (hazard ratio [HR], 1.00; 95% CI, 0.66 to 1.53; log-rank $P = .989$). Median OS was lower in the mFOLFOX6 group (6.1 *v* 9.9 months; HR, 1.78; 95% CI, 1.08 to 2.93; log-rank $P = .024$).[7] Grade 3 or 4 AEs were experienced by 63% of patients in the mFOLFOX6 group and by 11% of patients in the FU + LV group. Within these groups, 20% and 0% of patients discontinued treatment due to AEs, respectively. Dose reductions were more common in the mFOLFOX6 arm, most commonly due to hematologic toxicity (Table 2).[7]

Clinical interpretation. The authors of the previous version of this guideline noted that there is a lack of high-quality evidence to guide second-line therapy, and that previously, recommendations have been extrapolated from data for patients who have received gemcitabine monotherapy. The Expert Panel continues to recommend that the choice of therapy depend on performance status, comorbidities, organ function, residual toxicities from first-line therapy, and a support system for aggressive medical therapy.

The previous version of this guideline included a recommendation for the combination of fluorouracil and oxaliplatin, based on the results of CONKO-003, which compared folinic acid 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22 with oxaliplatin 85 mg/m^2 on days 8 and 22 (OFF regimen), with folinic acid and fluorouracil in patients with metastatic pancreatic cancer who had progressed on first-line gemcitabine.[10] This study demonstrated improved OS with the OFF regimen (5.9 *v* 3.3 months; HR, 0.66; 95% CI, 0.48 to 0.91; $P = .010$). New data from the PANCREOX trial, using the more commonly used mFOLFOX6 regimen, failed to find a benefit with the oxaliplatin combination.[7]

The Expert Panel continues to endorse the combination of fluorouracil and nanoliposomal irinotecan that was recommended in the previous version of this guideline for patients treated first line with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services. This recommendation is based on results from the NAPOLI-1 trial, which included a comparison of fluorouracil 2,400 mg/m^2 plus nanoliposomal irinotecan 80 mg/m^2 and leucovorin 400 mg/m^2 over 46 hours every 2 weeks, with fluorouracil in patients with metastatic pancreatic cancer who had progressed on first-line gemcitabine. This trial demonstrated improved OS with the combination (6.1 *v* 4.2 months; HR, 0.67; 95% CI, 0.49 to 0.92; $P = .01$).[33] Given the new data from the PANCREOX study, fluorouracil and nanoliposomal irinotecan are considered the preferred option for this patient population; however, fluorouracil and oxaliplatin may also be considered, as outlined in the qualifying statement to Recommendation 3.5.

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DISCUSSION

The purpose of this focused update is to incorporate new data related to second-line treatment options for metastatic pancreatic cancer. For the previous version of this guideline, the evidence base included studies of patients who had been treated with first-line gemcitabine monotherapy, rather than the current standard combination chemotherapy. Despite this limitation, the Expert Panel concluded that OS could be improved with second-line cytotoxic therapy, with the choice of agents depending on performance status, comorbidities, organ function, and residual toxicities from prior treatment (p.2791).[3]

This guideline update incorporates new evidence related to second-line treatment options, including results from the PANCREOX study, which compared treatment with mFOLFOX6 with treatment with FU + LV,[7] and a study of pembrolizumab in patients whose tumors had a dMMR.[6]

The Update Expert Panel continues to support the following options from the previous version of the guideline, depending on patient characteristics (Bottom Line): gemcitabine plus NAB-paclitaxel, gemcitabine monotherapy or fluorouracil monotherapy, and a recommendation for clinical trial participation in the setting of third-line therapy.[3] Fluourouracil plus nanoliposomal irinotecan also continues to be recommended; however, data from the recent PANCREOX trial showing a higher rate of AEs and a reduced duration of OS for patients treated with mFOLFOX6 compared with those who received FU + LV have resulted in a modification to the recommendation related to the second-line option of fluorouracil plus oxaliplatin. For this version, fluorouracil plus oxaliplatin may be recommended where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where the latter option is not preferred due to residual toxicities or comorbidities.

The Update Expert Panel noted that new results from the PANCREOX trial (2017)[7] differ from results of the CONKO-003 phase III RCT (2014),[10] which showed a benefit in the arm that included oxaliplatin. This may have been due to a difference in regimens; CONKO-003 used the OFF combination folinic acid 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22 with oxaliplatin 85 mg/m^2 on days 8 and 22) compared with folinic acid and fluorouracil, whereas the PANCREOX protocol called for the more common biweekly infusional FU + LV, and oxaliplatin (mFOLFOX6), with a higher dose intensity of oxaliplatin. In addition, all patients in CONKO-003 had first-line gemcitabine monotherapy, while in PANCREOX, approximately three quarters had first-line monotherapy. Eligibility criteria and rates of postprogression therapy also differed between the studies; however, it is difficult to determine a conclusive reason for the inconsistency in study results.

This update also incorporates new data from a study of PD-1 immune checkpoint inhibitor pembrolizumab. Recently, a unique FDA approval across disease sites was granted for pembrolizumab as a treatment option for patients with MSI-H status or dMMR solid tumors.[8] Although < 1% of patients in the target population for this guideline are expected to have tumors with this characteristic,[9] the potential for effectiveness is high. In formulating this recommendation, the Update Expert Panel considered the magnitude of the effect in the overall MSI-H population across pancreatic as well as other disease sites to be relevant. Although the key evidence for this recommendation included a nonrandomized study without a control group,[6] the evidence quality was graded as intermediate due to the magnitude of the effect and the opinion that future research would likely affirm the results of this study. To facilitate the implementation of the pembrolizumab recommendation, consensus-based recommendations have been included for testing for dMMR and MSI-H in this updated guideline. Other testing recommendations are considered outside the scope of this update, and a separate forthcoming ASCO guideline for germline testing in pancreatic cancer is currently under development.

Tumor mutation burden, as measured by NGS, has been hypothesized to indicate a potential for response to immunotherapy because it may be associated with a greater number of neoantigens. These, in turn, can be recognized by the immune system in response to checkpoint inhibition. Indeed, emerging data indicate that tumor mutation burden may be predictive of greater and more durable responses to immunotherapy in a variety of solid tumors.[12] It is possible that a high tumor mutation burden may also be a predictor of response to immunotherapy in metastatic pancreatic cancer, but until such data are available, the Panel felt it premature to recommend immunotherapy use for such tumors. Clear definitions of high tumor mutation burden and reduced variability among commercially available assays are also necessary for appropriate clinical implementation of this potential biomarker.

While developments in targeted therapy for this patient population are encouraging, there continues to be a need for more research and better therapy options. Poly (ADP-ribose) polymerase inhibitors are being studied in patients with advanced pancreatic cancer and a known BRCA mutation or a BRCAness genotype. Examples include the phase II open-label Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious *BRCA* Mutation (RUCAPANC) study of rucaparib in 19 patients,[13] as well as the ongoing Olaparib in *gBRCA*-Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO) phase III RCT.[14] Because the rate of BRCA positivity is approximately 4.6% in the advanced pancreatic cancer population,[15] these therapies are promising, and the Expert Panel will continue to monitor this literature for future guideline updates. Recent data published in an abstract from the Nab-paclitaxel in Combination With Gemcitabine in Fragile Patients With Advanced Pancreatic Cancer (FRAGRANCE) study showed that NAB-paclitaxel in combination with gemcitabine was well tolerated and showed acceptable survival outcomes and response rates in a patient population with ECOG PS 2 advanced pancreatic cancer.[16]

The Expert Panel is aware that additional data supporting the concept of referral to palliative care have been published since our original literature search. These new data support the previous recommendation for obtaining a palliative care consultation as early as possible.[17,18] The co-chairs and other members of the Expert Panel will also continue to monitor the literature on second-line therapy and on other aspects of the management of metastatic pancreatic cancer.

PATIENT AND CLINICIAN COMMUNICATION

Patients with pancreatic cancer face difficult treatment decisions while presented with complex medical information and a life-threatening diagnosis. Communication within a context of realistic hope and action between patients and clinicians can

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improve patients' ability to make sound, informed decisions within their own personal value set. Patients should fully understand the goals of care before making decisions about treatment and care.

Clear communication with patients with pancreatic cancer and their caregivers about the diagnosis, treatment options, and goals of care is key for patient understanding. The clinician is also responsible for offering ancillary support services, which include a referral to palliative care consultation and services.

For patients to make informed decisions, providers should describe the potential impact of the diagnosis of pancreatic cancer on the patient and his or her family. It is important to provide realistic hope within honest, yet supportive, discussions. Providers should ask patients about their personal goals and preferences. What do they hope for? What is important to them in their personal lives? What do they value more, an extension of life or maintenance of the best possible quality of life? An understanding of a patient's specific goals should shape conversations about goals of care and treatment recommendations.

Clinicians should clearly explain all potential treatment options, the specific biomarker testing needed to determine the appropriateness of those treatment options, the potential outcomes of each, and possible AEs so that patients understand the benefits and drawbacks of each option and can make an informed decision. Treatment discussions should include relevant clinical trials at every stage of treatment. Patients should have the opportunity to participate in trials for their own treatment as well as be given the opportunity to contribute to research.

Clinicians should also consider and proactively discuss quality-of-life issues. In patients with pancreatic cancer, dietary concerns, pain, and fatigue are major concerns. Dietary issues tend to be overlooked and yet are real problems, with a significant impact on daily life. Referral to a registered dietitian and/or gastroenterologist with early intervention can be of great benefit. Clinicians should also consider the use of, and discuss the possible need for, pancreatic enzyme replacement therapy.

Referral to palliative care services can facilitate the addressing of many non–treatment-related issues patients face, and this referral should be offered to all patients with pancreatic cancer, regardless of stage of disease or expected prognosis. Patients should understand that referral to a consultation for palliative care services is not synonymous with a referral to hospice care. This discussion is important because palliative care provides important support and can be part of an active cancer treatment paradigm.

Patients must feel comfortable in the choices they make, and the knowledge that they have explored their options can bring comfort. As such, clinicians should support a patient's desire to get a second opinion. Clinicians should address the costs of care and offer referrals to specialists within the health care system who can discuss in more detail what a patient should expect as well as resources and information about managing the costs related to cancer care.

The provision of realistic hope to patients with pancreatic cancer, although the prognosis may be short, is important. Patients deserve to know that their medical team is working to help them reach their goals. Even if a cure is not possible, hope for an extension of life or a good quality of life is powerful.

The provision of resources to help patients communicate better with their health care team is also advisable. Patients should be offered decision-making tools and be urged to write down questions in between and in advance of appointments. Patients can be referred to resources that will extend the support and information clinicians are able to provide. For pancreatic cancer, two such resources are the ASCO patient-facing Web site (www.Cancer.net) and the Pancreatic Cancer Action Network (www.pancan.org).

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than are other Americans.[19-22] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended

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care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[23,24] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[25,26]

Discussion of cost can be an important part of shared decision making.[27] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[27]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even within the same insurance plan, the price may vary among different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[27]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners, survivors of cancer, and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *JCO* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Related ASCO Guidelines

- Integration of Palliative Care into Standard Oncology Practice[18] (http://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Management of Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (http://ascopubs.org/doi/10.1200/JCO.2017.77.6385)[28]
- Metastatic Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2016.67.1412)[3]
- Locally Advanced, Unresectable Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2016.67.5561)[29]
- Potentially Curable Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2017.72.4948)[30]

ADDITIONAL RESOURCES

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA Cancer J Clin 68:7-30, 2018
2. Surveillance Epidemiology and End Results (SEER): Cancer stat facts: Pancreatic cancer. https://seer.cancer.gov/statfacts/html/pancreas.html
3. Sohal DP, Mangu PB, Khorana AA, et al: Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:2784-2796, 2016
4. Shojania KG, Sampson M, Ansari MT, et al: How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147:224-233, 2007
5. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
6. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017
7. Gill S, Ko YJ, Cripps C, et al: PANCREOX: A randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol 34:3914-3920, 2016
8. US Food and Drug Administration: FDA approves first cancer treatment for any solid tumor with a specific genetic feature. May 23, 2017 https://www.fda.gov/news-events/newsroom/pressannouncements/ucm560167.htm
9. Hu ZI, Shia J, Stadler ZK, et al: Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: Challenges and recommendations. Clin Cancer Res 24:1326-1336, 2018
10. Oettle H, Riess H, Stieler JM, et al: Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: Outcomes from the CONKO-003 trial. J Clin Oncol 32:2423-2429, 2014
11. Wang-Gillam A, Li CP, Bodoky G, et al: Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global,

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randomised, open-label, phase 3 trial. Lancet 387: 545-557, 2016

12. Rizvi H, Sanchez-Vega F, La K, et al: Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. J Clin Oncol 36:633-641, 2018

13. Domchek S, Hendifar AE, McWilliams RR, et al: RUCAPANCE: An open-label, phase 2 trial of the PARP inhibitor rucaparib in patients with pancreatic cancer and a known deleterious germline or somatic *BRCA* mutation. J Clin Oncol 34:4110, 2016 (suppl)

14. Golan T, Oh D, Reni M, et al: POLO: A randomized phase III trial of olaparib maintenance monotherapy in patients with metastatic pancreatic cancer who have a germline *BRCA* 1/2 mutation. J Clin Oncol 34, 2016 (suppl; abstr TPS4152)

15. Holter S, Borgida A, Dodd A, et al: Germline *BRCA* mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol 33:3124-3129, 2015

16. US National Library of Medicine: Nab-paclitaxel in combination with gemcitabine in fragile patients with advanced pancreatic cancer (FRAGANCE). ClinicalTrials.gov Identifier: NCT02382263. https://clinicaltrials.gov/ct2/show/NCT02382263

17. Temel JS, Greer JA, El-Jawahri A, et al: Effects of early integrated palliative care in patients with lung and GI cancer: A randomized clinical trial. J Clin Oncol 35:834-841, 2017

18. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

19. Mead H, Cartwright-Smith L, Jones K, et al: Racial and ethnic disparities in U.S. health care: A chartbook. New York, NY, The Commonwealth Fund, 2008.

20. US Cancer Statistics Working Group: United States Cancer Statistics: 1999-2012 Incidence and Mortality Web-Based Report. Atlanta, GA, US Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute, 2015. www.cdc.gov/uscs

21. Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute. https://seer.cancer.gov/csr/1975_2013/

22. American Cancer Society: Cancer Facts and Figures for African Americans 2016-2018. Atlanta, GA, American Cancer Society, 2016. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-047403.pdf

23. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34: 2925-2934, 2016

24. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A cnceptual framework to assess the value of cancer treatment options. J Clin Oncol 33:2563-2577, 2015

25. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32:306-311, 2014

26. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011

27. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27: 3868-3874, 2009

28. Brahmer JR, Lacchetti C, Schneider BJ, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology and National Comprehensive Cancer Network clinical practice guideline. J Clin Oncol [epub ahead of print on February 14, 2018]

29. Balaban EP, Mangu PB, Khorana AA, et al: Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:2654-2668, 2016

30. Khorana AA, Mangu PB, Berlin J, et al: Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:2541-2556, 2016

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

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Appendix

Table A1. Metastatic Pancreatic Cancer Update Expert Panel Membership

Name and Designation	Affiliation or Institution	Role or Area of Expertise
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Erin B. Kennedy, MHSc	ASCO, Alexandria, VA	Health research methodology
Alok Khorana, MD	Cleveland Clinic, Cleveland, OH	Medical oncology
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Eileen M. O'Reilly, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Internal medicine
Philip A. Philip, MD, PhD	Barbara Ann Karmanos Cancer Institute, Farmington Hills, MI	Medical oncology
Ramesh K. Ramanathan, MD	Mayo Clinic, Phoenix, AZ	Medical oncology
Joseph T. Ruggiero, MD	Weill Cornell Medicine, New York, NY	Hematology and medical oncology
Manish A. Shah, MD	Weill Cornell Medicine, New York, NY	Medical oncology
Susan Urba, MD	University of Michigan Health System Comprehensive Cancer Center, Ann Arbor, MI	Medical oncology
Hope E. Uronis, MD, MHS	Duke University, Durham, NC	Hematology and internal medicine
Michelle W. Lau, MD	Phoenix VA Medical Center, Phoenix, AZ	PGIN representative

Abbreviation: PGIN, Practice Guidelines Implementation Network.

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ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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D.P.S.S. and D.L. are co-chairs.

Clinical Practice Guidelines Committee approval: October 21, 2015.

Editor's note: This American Society of Clinical Oncology clinical practice guideline provides recommendations with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, which includes a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/guidelines/MetPC and www.asco.org/guidelineswiki.

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

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ABSTRACT

Purpose
To provide evidence-based recommendations to oncologists and others for the treatment of patients with metastatic pancreatic cancer.

Methods
American Society of Clinical Oncology convened an Expert Panel of medical oncology, radiation oncology, surgical oncology, gastroenterology, palliative care, and advocacy experts to conduct a systematic review of the literature from April 2004 to June 2015. Outcomes were overall survival, disease-free survival, progression-free survival, and adverse events.

Results
Twenty-four randomized controlled trials met the systematic review criteria.

Recommendations
A multiphase computed tomography scan of the chest, abdomen, and pelvis should be performed. Baseline performance status and comorbidity profile should be evaluated. Goals of care, patient preferences, treatment response, psychological status, support systems, and symptom burden should guide decisions for treatments. A palliative care referral should occur at first visit. FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin; favorable comorbidity profile) or gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel (adequate comorbidity profile) should be offered to patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 based on patient preference and support system available. Gemcitabine alone is recommended for patients with ECOG PS 2 or with a comorbidity profile that precludes other regimens; the addition of capecitabine or erlotinib may be offered. Patients with an ECOG PS ≥ 3 and poorly controlled comorbid conditions should be offered cancer-directed therapy only on a case-by-case basis; supportive care should be emphasized. For second-line therapy, gemcitabine plus NAB-paclitaxel should be offered to patients with first-line treatment with FOLFIRINOX, an ECOG PS 0 to 1, and a favorable comorbidity profile; fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan should be offered to patients with first-line treatment with gemcitabine plus NAB-paclitaxel, ECOG PS 0 to 1, and favorable comorbidity profile, and gemcitabine or fluorouracil should be offered to patients with either an ECOG PS 2 or a comorbidity profile that precludes other regimens. Additional information is available at www.asco.org/guidelines/MetPC and www.asco.org/guidelineswiki.

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INTRODUCTION

Pancreatic ductal adenocarcinoma is a disease associated with poor prognosis and an increasing impact on cancer-related mortality in the United States and around the world. There were an estimated 49,000 new diagnoses and 41,000 deaths from pancreatic cancer in the United States in 2015[1] and an estimated 338,000 deaths worldwide in 2012.[2] This disease remains an exception to the general trend of improvement in cancer-related mortality. One estimate suggests that pancreatic cancer will become the second leading cause of cancer-related death in the United States in the next decade.[3] The 5-year overall survival (OS) for metastatic pancreatic cancer remains at 2%,[4-6] with a median life expectancy of < 1 year with current

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THE BOTTOM LINE

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Question

What is the treatment of patients with metastatic pancreatic cancer?

Target Population

Patients with metastatic pancreatic cancer.

Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists, and other caregivers

Methods

An Expert Panel developed clinical practice guideline recommendations that are based on a systematic review of the medical literature.

Key Recommendations

Recommendation 1.1: A multiphase CT scan of the chest, abdomen, and pelvis should be performed to assess extent of disease. Other staging studies should be performed only as dictated by symptoms (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2: The baseline PS, symptom burden, and comorbidity profile of a patient with metastatic pancreatic cancer should be evaluated carefully (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3: The goals of care (to include a discussion of an advance directive), patient preferences, as well as support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.4: Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with metastatic pancreatic cancer should be the standard of care (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5: Every patient with pancreatic cancer should be offered information about clinical trials, which include therapeutic trials in all lines of treatment as well as palliative care, biorepository/biomarker, and observational studies (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.1: FOLFIRINOX is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2: Gemcitabine plus NAB-paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3: Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4: Patients with an ECOG PS $\geq$ 3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.1: Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy for patients who meet all of the following criteria: first-line treatment with FOLFIRINOX, ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for aggressive medical therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 3.2: Fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan can be offered as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, ECOG PS 0 to 1, relatively favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and chemotherapy port and infusion pump management (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.3: Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.4: No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.1: Patients with metastatic pancreatic cancer should have a full assessment of symptom burden, psychological status, and social supports as early as possible, preferably at the first visit. In most cases, this assessment will indicate a need for a formal palliative care consult and services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.1: Patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.1: For patients on active cancer-directed therapy outside a clinical trial, imaging to assess first response should be offered at 2 to 3 months from the initiation of therapy. CT scans with contrast are the preferred modality. Thereafter, clinical assessment, conducted frequently during visits for cancer-directed therapy, should supplant imaging assessment. The routine use of positron emission tomography scans for the management of patients with pancreatic cancer is not recommended. CA19-9 is not considered an optimal substitute for imaging for the assessment of treatment response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 6.2: No data exist on the duration of cancer-directed therapy. An ongoing discussion of goals of care and assessment of treatment response and tolerability should guide decisions to continue or hold/terminate cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Additional Resources

More information that includes a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources is available at www.asco.org/guidelines/MetPC and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

treatments.[7-9] Preclinical and clinical literature has established that pancreatic adenocarcinoma is a systemic disease from the outset, with early micrometastatic spread.[10,11] Current multiagent chemotherapy regimens afford some gains in OS, albeit with attendant treatment-emergent toxicities. The clinical course of pancreatic cancer usually is aggressive, with high symptom burden and potential for a substantial deterioration in quality of life. These symptoms often include abdominal pain and loss of appetite, weight, and functional status. Other symptoms include biliary tract obstruction issues and pancreatic insufficiency, which lead to nutritional depletion. Therefore, palliative care to focus on distressing symptoms and quality of life is an important adjunct in the management of this condition.

The focus of this clinical practice guideline is to help with clinical decision making, which includes the determination of the appropriate treatment of patients with metastatic pancreatic cancer and how to help patients and their families to access and use palliative care services.

GUIDELINE QUESTIONS

This clinical practice guideline addresses six overarching clinical questions: After a histopathologic confirmation of pancreatic adenocarcinoma diagnosis, what initial assessment is recommended before initiating any therapy for metastatic pancreatic cancer? What is the appropriate first-line treatment of patients with metastatic pancreatic cancer? What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens for

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metastatic pancreatic cancer? When should the concept of palliative care be introduced? For patients with metastatic pancreatic cancer, what are the recommended strategies for relief of pain and symptoms? What is the recommended frequency of follow-up care/surveillance for patients with metastatic pancreatic cancer?

METHODS

Guideline Development Process

The Expert Panel met through webinar and teleconference and corresponded through e-mail. With consideration of the evidence, the authors contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. Members of the Expert Panel (Appendix Table A1, online only) were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication.

The recommendations were developed by the multidisciplinary Expert Panel using a systematic review of articles in English (April 2002 to June 2015) of phase III randomized controlled trials (RCTs) of chemotherapy alone and/or chemoradiotherapy and/or compared with a control arm. Other peer-reviewed articles were used to inform the recommendations on palliative care, patients with metastatic pancreatic cancer, and clinician communication as well as the section on health disparities. Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; and published in a non-English language. The guideline recommendations were crafted, in part, by using the Guidelines Into Decision Support methodology and accompanying BRIDGE-Wiz software.[12] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided. In some selected cases where evidence is lacking but where there was a high level of agreement among the panel members, informal consensus was used (as noted in the recommendations).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/guidelines/MetPC, which includes an overview (eg, panel composition, development process, revisions), literature search terms, and a data extraction quorum diagram; the recommendation development process (Guidelines Into Decision Support and BRIDGE-Wiz); and information about quality assessment.

The ASCO Expert Panel co-chairs and guidelines staff keep abreast of newly published data that signal an update to this guideline. Based on formal review of the emerging literature, ASCO staff will determine the need to update and post updates on www.asco.org/guidelines when indicated. The Methodology Supplement provides additional information about the Signals update approach.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

Twenty-five RCTs met the eligibility criteria and form the evidentiary basis for the guideline recommendations.[8,9,13-35] The trials were generally of high quality, but few compared similar interventions. The primary outcome assessed for all included trials was therapeutic efficacy, which included OS and adverse events (AEs). Data Supplement 1, Table 1, lists the patient and disease characteristics of the studies pertinent to the development of the recommendations. Most studies were balanced for age and Eastern Cooperative Oncology Group performance status (ECOG PS). In all included trials, median age was younger (at least 5 years younger and for most, 10 years younger) than the median age of patients with pancreatic cancer in the general community. Previous treatments, if known, are also listed in the table.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were

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assessed and are shown in Data Supplement 1, Table 2. The study quality was high for this group of RCTs. Design aspects related to the individual study quality were assessed with respect to factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on, which generally indicated a low potential risk of bias for most of the identified evidence. Follow-up times varied among studies, which decreases the comparability of the results. Refer to Methodology Supplement for definitions of ratings for overall potential risk of bias.

Key Outcomes of Interest

Results for all outcomes of interest are response rates, OS, progression-free survival, disease-free survival, and AEs. Outcomes are included in Data Supplement 1, Table 3. The studies compared outcomes chemotherapy versus observation; chemotherapy versus chemoradiotherapy; and combination chemotherapy with or without radiotherapy for patients with metastatic pancreatic cancer.

Systematic Reviews and Meta-Analyses for Potentially Curable Pancreatic Cancer

Nine systematic reviews or meta-analyses of various rigor and quality were obtained. Because none were deemed suitable as the basis for recommendations, a formal assessment of quality was not performed. Data Supplement 2 is a summary table.

Data Supplements 3 and 4 include the literature review search terms and a quorum diagram of included and excluded articles. Data Supplement 5 contains information on the World Health Organization definition of palliative care, and Data Supplement 6 contains a pancreatic protocol for computerized tomography (CT).

RECOMMENDATIONS

Clinical Question 1: After a Histopathologic Confirmation of Pancreatic Adenocarcinoma Diagnosis, What Initial Assessment Is Recommended Before Initiating Any Therapy for Metastatic Pancreatic Cancer?

Recommendation 1.1. A multiphase CT scan of the chest, abdomen, and pelvis should be performed to assess extent of disease. Other staging studies should be performed only as dictated by symptoms (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2. The baseline PS, symptom burden, and comorbidity profile of a patient with metastatic pancreatic cancer should be evaluated carefully (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3. The goals of care (which include a discussion of an advance directive), patient preferences, and support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.4. Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with metastatic pancreatic cancer should be the standard of care (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5. Every patient with pancreatic cancer should be offered information about clinical trials, which include therapeutic trials in all lines of treatment as well as palliative care, biorepository/biomarker, and observational studies (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. Cross-sectional imaging with a CT scan of the abdomen and pelvis by using a pancreatic protocol (Data Supplement 6) should be performed to evaluate the extent of disease in all patients with metastatic pancreatic cancer. Magnetic resonance imaging (MRI) appears to be of equivalent sensitivity to CT scanning with respect to its ability to detect and stage pancreatic cancer, but CT scanning is preferred because it is more easily interpreted and is less operator dependent. Similarly, acquisition and interpretation of echoendoscopy images is operator dependent; therefore, endoscopic ultrasound is most often used to facilitate acquisition of a biopsy specimen but not as a primary staging modality. A CT scan of the chest should be performed to evaluate for intrathoracic metastases.

Among patients with metastatic pancreatic cancer, baseline PS and a comorbidity profile should be evaluated thoroughly because both have implications with regard to a patient's ability to tolerate therapy. PS has been consistently identified as a prognostic factor for patients with pancreatic cancer. PS and comorbidities should not be used simply to rule in or out patients for treatment. For example, a patient with controlled diabetes mellitus or low hemoglobin levels, once optimized, could still do well with treatment because these comorbid conditions may be considered issues related to pancreatic disease.

After a comprehensive staging evaluation, a discussion on goals of care is important. This discussion should include the patient and key caregivers. Their understanding of the disease as well as treatment options, personal preferences, and social support systems should be addressed. On the basis of this mutual understanding of the goals of care, management decisions should be established within the context of a coordinated multidisciplinary group. If referral to a high-volume pancreatic cancer treatment center is feasible in a timely fashion, a referral should be offered because care at high-volume pancreatic treatment centers may lead to a change in therapeutic recommendations.[36]

Furthermore, enrollment in pancreatic cancer clinical trials should be encouraged. Currently, the accrual to such trials is suboptimal. In 2011, only approximately 4.5% of patients with pancreatic cancer were enrolled onto a clinical trial, and only 14.9% of total anticipated enrollment in trials for patients with pancreatic cancer was achieved that year.[37] Barriers to enrollment were need for travel, prohibitive illness, and physician opposition.

Clinical interpretation. The focus of the initial work-up should be to identify clues about both the extent of systemic disease and the ability to tolerate available therapies. The goals of therapy should be discussed clearly, with a focus on the palliative nature of any treatment plan and risks and benefits thereof. The available therapies may then be understood on the basis of the

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perceived goals of care. Management decisions should be made, as much as possible, in a multidisciplinary team environment. Clinical trials (therapeutic and otherwise) should be discussed with all patients.

Clinical Question 2: What Is the Appropriate First-Line Treatment of Patients With Metastatic Pancreatic Cancer?

Recommendation 2.1. Leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2. Gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4. Patients with an ECOG PS ≥ 3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy on only a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. FOLFIRINOX (fluorouracil 400 mg/m^2 bolus, leucovorin 400 mg/m^2, fluorouracil 2,400 mg/m^2 over 46 hours, irinotecan 180 mg/m^2, oxaliplatin 85 mg/m^2, every 2 weeks) and gemcitabine plus NAB-paclitaxel (gemcitabine 1,000 mg/m^2, NAB-paclitaxel 125 mg/m^2, days 1, 8, 15, every 4 weeks) are the two frontline regimens for metastatic pancreatic cancer management. Each regimen has been compared with gemcitabine, the previous standard of care, in large RCTs.[8,9] However, no head-to-head comparisons of these two regimens exists. The FOLFIRINOX trial was conducted in France and enrolled 342 patients. The gemcitabine plus NAB-paclitaxel trial was conducted across many countries (North America, Europe, Australia) and enrolled 861 patients. Both trials had identical control arms: gemcitabine 1,000 mg/m^2 given weekly for 7 or 8 weeks followed by administration on days 1, 8, 15, every 4 weeks. Key eligibility criteria for the FOLFIRINOX trial were metastatic disease, no prior chemotherapy, ECOG PS 0 or 1, bilirubin ≤ 1.5 times the upper limit of normal, and age 18 to 75 years. Key eligibility criteria for the gemcitabine plus NAB-paclitaxel trial were metastatic disease, no prior chemotherapy (fluorouracil or gemcitabine as a radiation sensitizer > 6 months before enrollment was allowed), Karnofsky performance status (KPS) of ≥ 70%, bilirubin at or below the upper limit of normal, and no upper limit for age. Biliary stents were allowed in both trials if the bilirubin criterion was met. OS was the primary end point in each trial.

In the FOLFIRINOX trial, median OS with the experimental arm was 11.1 months compared with 6.8 months with gemcitabine (hazard ratio [HR], 0.57; 95% CI, 0.45 to 0.73; $P < .001$). Response rate with FOLFIRINOX was 32%. Major grade 3 or 4 toxicities with FOLFIRINOX were neutropenia (46%), febrile neutropenia (5%), fatigue (24%), vomiting (15%), diarrhea (13%), and peripheral neuropathy (9%). Growth factors were used in 43% of patients in the FOLFIRINOX arm.

In the gemcitabine plus NAB-paclitaxel trial, median OS with the experimental arm was 8.5 months compared with 6.7 months with gemcitabine (HR, 0.72; 95% CI, 0.62 to 0.83; $P < .001$). Response rate with gemcitabine plus NAB-paclitaxel was 23%. Major grade 3 or 4 toxicities with gemcitabine plus NAB-paclitaxel were neutropenia (38%), febrile neutropenia (3%), fatigue (17%), diarrhea (6%), and peripheral neuropathy (17%). Growth factors were used in 26% of patients in the gemcitabine plus NAB-paclitaxel arm.

In the absence of head-to-head comparisons of these two regimens in this setting, it is reasonable to offer either regimen. FOLFIRINOX is recommended in patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and chemotherapy port and infusion pump management. A favorable comorbidity profile is loosely defined as hemoglobin ≥ 10 g/dL and platelet count ≥ 100,000/μL without transfusion support; absolute neutrophil count ≥ 1,500/μL; bilirubin and international normalized ratio ≤ 1.5 times the upper limit of normal; albumin ≥ 3 g/dL; creatinine clearance ≥ 60 mL/min/1.73 m^2; and absence of comorbid conditions that require ongoing active medical care, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders. Because FOLFIRINOX was not tested in patients older than 75 years, a carefully considered clinical decision to administer this regimen to anyone older than 75 years should be made.

Gemcitabine plus NAB-paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy. A relatively favorable comorbidity profile is loosely defined as hemoglobin ≥ 9 g/dL and platelet count ≥ 75,000/μL without transfusion support; absolute neutrophil count ≥ 1,500/μL; bilirubin and international normalized ratio ≤ 1.5 times the upper limit of normal; albumin ≥ 3 g/dL; creatinine clearance ≥ 60 mL/min/1.73 m^2; and absence of poorly controlled comorbid conditions, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders. The gemcitabine plus NAB-paclitaxel trial allowed a KPS of 70%, and 7% of patients in the study had a KPS of 70%. Because the conversion of KPS and ECOG PS is not linear,[38] a careful functional and comorbidity evaluation should be performed in patients with an ECOG PS 2 before offering gemcitabine plus NAB-paclitaxel. The comorbidity parameters here are only suggestions, and the treating

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clinician's judgment along with patient preferences are key factors to guide the choice between these two regimens.

Dose modifications are an important component of the ongoing treatment of patients with metastatic pancreatic cancer. At each visit (usually every 2 weeks), patients should be evaluated carefully for treatment-related toxicities, and these should be separated from disease-related symptoms. For treatment-related toxicities, doses should be reduced appropriately, preferably when toxicities are grade 2 or 3, to prevent significant clinical worsening.

The following are suggestions based on dose-reduction schemes in the two clinical trials[6,9] and early reports from institutional series of modified approaches to FOLFIRINOX and gemcitabine plus NAB-paclitaxel use.[39,40] The treating physician's judgment remains paramount. For FOLFIRINOX, the omission of the fluorouracil bolus and leucovorin should be considered early (the omission of these from the first dose itself is not an unreasonable plan) in case of emerging toxicities. For hematologic toxicities, fatigue, nausea, and vomiting, dose reductions (usually by approximately 20%) of irinotecan and oxaliplatin should be considered next. Further dose reductions for all three drugs should be considered for such ongoing toxicities. For diarrhea, dose reductions for irinotecan and fluorouracil should be considered, and for neuropathy, oxaliplatin dose should be reduced. Growth factor use to maintain blood counts is not routinely recommended for all patients. If blood count decline precludes chemotherapy administration, dose and/or drug modification should be the main therapeutic maneuver.

For gemcitabine plus NAB-paclitaxel, hematologic toxicities, fatigue, nausea, and vomiting, dose reductions (usually by approximately 20%) for both drugs should be considered. For neuropathy, NAB-paclitaxel dose should be reduced. A commonly used maneuver with the use of this regimen is attenuation of schedule. Gemcitabine plus NAB-paclitaxel given at full doses but on days 1 and 15 of a 28-day cycle or on days 1 and 8 of a 21-day cycle are reasonable options to consider to mitigate treatment-related toxicities.

In patients who are not considered good candidates for FOLFIRINOX and gemcitabine plus NAB-paclitaxel due to comorbidities or who choose to pursue less-toxic therapies, gemcitabine (1,000 mg/m^2, days 1, 8, 15, every 4 weeks) is an appropriate option. Before data from the FOLFIRINOX and gemcitabine plus NAB-paclitaxel trials, this was the standard of care.[41] The addition of either erlotinib or capecitabine to gemcitabine also can be offered, although data to support these recommendations are limited. Gemcitabine with erlotinib (gemcitabine 1,000 mg/m^2, days 1, 8, 15, every 4 weeks, with erlotinib 100 to 150 mg/day orally) is approved in this setting. However, the added benefit of erlotinib is modest, with a nontrivial increase in treatment-associated toxicities and cost.[26] Gemcitabine with capecitabine was tested in a clinical trial that showed a trend toward improvement of OS but did not meet the primary outcome.[21]

Clinical interpretation. FOLFIRINOX and gemcitabine plus NAB-paclitaxel are the two frontline regimens for the treatment of metastatic pancreatic cancer. In the absence of head-to-head comparisons, the choice depends on clinician judgment that is based on the patient's PS and comorbidities. Because the treatment is palliative, dose, drug, and schedule modifications should be incorporated liberally to maintain an appropriate risk-benefit balance. Gemcitabine, either alone or with erlotinib, is another available option, albeit limited to patients who are assessed as having a PS that is not robust enough to handle multiagent cytotoxic regimens but who still wish to pursue cancer-directed therapy.

Clinical Question 3: What Is the Appropriate Therapy for Patients With Metastatic Pancreatic Cancer Who Experience Either Disease Progression or Intolerable Toxicity With Prior Regimens for Metastatic Pancreatic Cancer?

Recommendation 3.1. Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy for patients who meet all of the following criteria: first-line treatment with FOLFIRINOX, ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2. Fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan can be offered as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, ECOG PS 0 to 1, relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and chemotherapy port and infusion pump management (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.3. Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.4. No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. No prospective studies have evaluated second-line therapy for metastatic pancreatic cancer that has progressed on either FOLFIRINOX or gemcitabine plus NAB-paclitaxel. The only available second-line data are from trials where metastatic pancreatic cancer progressed on first-line gemcitabine. The CONKO-003 trial, which tested fluorouracil plus oxaliplatin (leucovorin 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22 with oxaliplatin 85 mg/m^2 on days 8 and 22) against fluorouracil in metastatic pancreatic cancer that had progressed on first-line gemcitabine,[43] showed improved OS with the combination (5.9 *v* 3.3 months; HR, 0.66; 95% CI, 0.48 to 0.91; $P = .01$). The NAPOLI-1 trial, which tested fluorouracil plus nanoliposomal irinotecan (nanoliposomal irinotecan 80 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2,400 mg/m^2 over 46 hours every 2 weeks) against fluorouracil in metastatic pancreatic cancer that had progressed on first-line gemcitabine, showed improved OS with the combination (6.1 *v* 4.2 months; HR, 0.67; 95% CI, 0.49 to 0.92; $P = .01$).[20] A meta-analysis of clinical trials comparing second-line chemotherapy with best supportive care alone showed that median OS was 6 months with chemotherapy compared with 2.8 months with best supportive care.[42] Because most patients now receive multiagent regimens instead of gemcitabine in the first-line setting, the CONKO-003 and

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NAPOLI-1 results do not apply to most clinical situations. However, the panel arrived at a consensus that after progression on (or intolerable toxicity from) a first-line regimen of FOLFIRINOX or gemcitabine plus NAB-paclitaxel, second-line chemotherapy should provide clinical benefit. The choice of a second-line regimen is not defined; it is reasonable to offer drugs that the patient has not been exposed to in the first-line regimen. Gemcitabine plus NAB-paclitaxel (gemcitabine 1,000 mg/m^2, NAB-paclitaxel 125 mg/m^2, days 1, 8, 15, every 4 weeks) can be offered as second-line therapy to persons who received FOLFIRINOX in the first-line setting and maintain a preserved comorbidity profile and a patient preference and support system for aggressive medical therapy. In case of residual toxicities from FOLFIRINOX, it is reasonable to start therapy at attenuated doses and/or schedules. Gemcitabine 800 mg/m^2, NAB-paclitaxel 100 mg/m^2 on days 1 and 8 every 3 weeks are some alternatives to consider. Similarly, fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan can be offered as second-line therapy to patients who received gemcitabine plus NAB-paclitaxel in the first-line setting and maintained a preserved comorbidity profile and who have a preference and support system for aggressive medical therapy. It is reasonable to omit fluorouracil bolus and leucovorin in this setting.

Clinical interpretation. 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 such as FOLFIRINOX and gemcitabine plus NAB-paclitaxel. Extrapolation from clinical trials in patients with metastatic pancreatic cancer that progressed on first-line gemcitabine leads to a reasonable conclusion that OS can be improved with second-line cytotoxic therapy. The choice of the agents depends on patient PS, comorbidities, organ function, and residual toxicities from the first-line regimen.

Clinical Question 4: When Should the Concept of Palliative Care Be Introduced?

Recommendation 4.1. Patients with metastatic pancreatic cancer should have a full assessment of symptom burden, psychological status, and social supports as early as possible, preferably at the first visit. In most cases, this assessment will indicate a need for a formal palliative care consult and services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. Patients with metastatic pancreatic cancer tend to have a high symptom burden at the time of diagnosis, although this varies with the extent of disease. A full assessment of symptoms to include psychological status is recommended. Social supports should be ascertained as well during the first visit. If available, a formal palliative care consult can introduce the patient to the full range of services available to assure that close attention will be paid to physical comfort, pain management, psychosocial concerns, and spiritual well-being throughout the trajectory of the illness. Palliative care, in its broadest definition, is the supportive care of a patient and family from diagnosis through treatment (either curative or noncurative) until death. Hospice care is a subset of palliative care focused on patients near the end of life. A survey showed that nearly 90% of adults in the United States had no knowledge or limited knowledge of palliative care services. When they were read a definition, > 90% of the respondents said that they would want palliative care for themselves or their family member and that it should be universally available.[43,44] If the patient presents with extensive disease, is too ill to tolerate treatment, or has progressive disease for which there is no reasonable further anticancer treatment, then a hospice discussion and possible referral should take place.

Clinical Question 5: For Patients With Metastatic Pancreatic Cancer, What Are the Recommended Strategies for Relief of Pain and Symptoms?

Recommendation 5.1. Patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. Patients with pancreatic cancer may experience various distressing symptoms and concerns that require ongoing supportive care.

Pain. The mainstay of pain management typically is opiate medication, and physicians must address the level of pain and the degree of pain relief from analgesics at every clinic visit. Initial pain management may involve nonopioid drugs, which includes paracetamol. Disease progression may require the use of stronger opioids (tramadol, morphine, or fentanyl).[45] Because of the proximity of the tumor to the celiac axis, the pain may be neuropathic in nature. This would warrant consideration of treatment with adjuvant medications such as gabapentin, pregabalin, nortriptyline, and duloxetine.

Adverse effects and decreased effectiveness may limit the use of medications, in which case, treatments to interrupt the neural pathways in the celiac plexus may be used to improve pain relief. The celiac plexus is a dense network of nerves that innervates the upper abdominal organs and varies in structure across individuals. Pain may be relieved by inhibiting these synaptic pathways without neuron destruction in celiac plexus block through surgery with thoracoscopic splanchnectomy, which interrupts the parasympathetic and sympathetic fibers in the celiac plexus, or chemical destruction of the pathways and ganglia with dehydrated alcohol through celiac plexus neurolysis.[45]

One hundred patients with unresectable pancreatic cancer who experienced pain were randomly assigned to receive either neurolytic celiac plexus block or systemic analgesic therapy.[46] The group treated with the neurolytic block had a larger initial decrease in pain ($P = .005$), and the improvement effect lasted over time. Another RCT was conducted in 109 patients with inoperable abdominal or pelvic cancer, 38 of whom had pancreatic cancer.[47] The trial evaluated the timing of neurolytic sympathectomy, performed either early after the diagnosis of the pain or later in the patient's course after not obtaining pain relief with strong opioids. Early sympathectomy led to better pain control, less opioid consumption, and better quality of life in these patients. Palliative radiotherapy or chemotherapy may be considered to augment pain management.

Anorexia, weight loss. Patients merit a consultation with a nutritionist and/or dietician if this service is available. Dietary intake can be assessed along with the possible need for nutritional

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supplements. Some patients experience exocrine pancreatic insufficiency and require pancreatic enzyme replacement. Pancrelipase replacement daily with meals can help to improve digestion and absorption of nutrients. A placebo-controlled, double-blind trial of enteric-coated pancreatin microspheres was conducted in patients with unresectable cancer in the pancreatic head. Patients on pancreatic enzymes along with dietary counseling gained 1.2% (0.7 kg) body weight, whereas patients on placebo lost 3.7% body weight (2.2 kg).[48,49] Appetite stimulant medications may be considered in severe cases.

Depression and anxiety. The diagnosis of cancer is unsettling to any patient, and the knowledge of the aggressive nature of metastatic pancreatic cancer may lead to depression or anxiety, even early in the course of the disease. All patients can benefit from a discussion of their psychosocial concerns and their available support system. Some may warrant treatment with antidepressants or anxiolytics, and others may need referral for ongoing formal support from a social worker or psychiatrist.

Biliary obstruction. A frequent complication of a pancreatic tumor is blockage of the biliary tree, which causes obstructive jaundice. The preferred treatment is endoscopic placement of a permanent self-expanding stent in the bile duct to re-establish drainage to achieve relief of jaundice and pruritus; normalization of bilirubin levels to allow palliative chemotherapy; and prevention of other adverse outcomes, such as cholangitis and frequent hospitalizations.[50] The choice of stent depends on patient prognosis and the relative costs of metal stents and repeat endoscopic retrograde cholangiopancreatographies. In general, metal stents are preferred. Plastic stents can be considered for patients expected to survive < 3 months.[51]

Gastric outlet/duodenal obstruction. Gastric outlet/duodenal obstruction occurs in up to 10% of patients with pancreatic cancer. Symptoms include early satiety, nausea, postprandial vomiting, and weight loss. Endoscopic duodenal stenting can be successful in the majority of these patients, and median duration of stent patency is 6 months.[52]

Ascites. Patients with malignant ascites from pancreatic cancer experience abdominal discomfort, nausea and vomiting, and dyspnea from pressure of the fluid against the diaphragm. Many will benefit from intermittent paracentesis for symptom relief, but unfortunately, the benefit often lasts only approximately 3 days and then must be repeated. Diuretics such as spironolactone are competitive antagonists to aldosterone; they decrease the reabsorption of water and sodium in the kidneys and provide some relief from ascites.

If ascites reaccumulate quickly, which requires frequent (more than once a week or so) paracentesis, placement of a long-term drainage catheter is suitable. Circulating blood volume is reduced and the renin-angiotensin-aldosterone system is activated, which lead to sodium retention.

Venous thromboembolism. The occurrence of deep venous thrombosis, pulmonary embolism, and visceral vein thrombi (eg, portal vein, superior mesenteric vein thrombus) is extremely prevalent in patients with pancreatic cancer. Indeed, in most epidemiologic studies, pancreatic cancer ranks as one of the malignancies with the highest incidence of venous thromboembolism (VTE). This may be driven by the early expression of tissue factor on preneoplastic and neoplastic pancreas.[53] The development of VTE is highly consequential to patients with cancer. It is associated with worsened short- and long-term mortality[54] and is the second leading cause of death in malignancy after the cancer itself.[55] Unfortunately, patients with cancer remain unaware of this complication and its treatments. As recommended by the ASCO guidelines on VTE, patients need to be educated on the warning signs and symptoms of VTE.[56] Primary prevention of VTE can be successfully achieved with the use of low-molecular-weight heparins (LMWHs). Two RCTs have addressed the utility of primary prophylaxis with LMWH in patients with advanced pancreatic cancer, and all have shown a substantial reduction of VTE.[57,58] Concordant with ASCO guidelines on VTE,[56] the panel recommends consideration of primary prophylaxis in select high-risk patients on a case-by-case basis while they undergo systemic therapy. Treatment of pancreatic cancer–associated VTE is best achieved with extended LMWH monotherapy. The utility of treatment of incidentally identified visceral vein thrombi is unclear; the decision to anticoagulate can be made on a case-by-case basis.

Clinical interpretation. Refer to other ASCO guidelines and other evidence-based guidelines (eg, VTE, peripheral neuropathy, fatigue, anxiety and depression, antiemetics, prophylaxis and management of fever and neutropenia, WBC growth factors) for more detailed information in the patient and survivor care and supportive care and treatment-related issues sections at www.asco.org/guidelines.

Clinical Question 6: What Is the Recommended Frequency of Follow-Up Care/Surveillance for Patients With Metastatic Pancreatic Cancer?

Recommendation 6.1. For patients on active cancer-directed therapy outside a clinical trial, imaging to assess first response should be offered at 2 to 3 months from the initiation of therapy. CT scans with contrast are the preferred modality. Thereafter, clinical assessment conducted frequently during visits for cancer-directed therapy should supplant imaging assessment. The routine use of positron emission tomography scans for the management of patients with pancreatic cancer is not recommended. CA19-9 is not considered an optimal substitute for imaging for assessing treatment response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 6.2. No data exist on the duration of cancer-directed therapy. An ongoing discussion of goals of care and assessment of treatment response and tolerability should guide decisions to continue or hold/terminate cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Literature review and analysis. At present, no evidence-based data exist to guide the frequency of imaging for patients with metastatic cancer. The two approved chemotherapy combinations of FOLFIRINOX (once every 2 weeks) and gemcitabine plus NAB-paclitaxel (days 1, 8, 15 every 4 weeks) lend themselves naturally to follow-up imaging after 8 or 12 weeks of chemotherapy. The clinical practice for physicians in this panel would be to reimage after 8 to 12 weeks of chemotherapy.

PANEL AND SAMPLING CONSIDERATIONS

This section is based on experience and selected literature but was not part of the systematic review of the literature. Patients with

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pancreatic cancer face difficult treatment decisions while presented with complex medical information and a life-threatening diagnosis. Communication within a context of realistic hope and action between patients and clinicians can improve patients' ability to make sound, informed decisions within their own personal value set.[59] Patients should fully understand goals of care before making decisions about treatment and care.

Clear communication with patients with pancreatic cancer and their caregivers about the diagnosis, treatment options, and goals of care is key for patient understanding. The clinician is also responsible for offering ancillary support services, which include a referral to a palliative care consultation and services.

For patients to make informed decisions, providers should describe the potential impact of the diagnosis of pancreatic cancer on the patient and family. It is important to provide realistic hope within honest, yet supportive discussions. Providers should ask patients about their personal goals and preferences. What do they hope for? What is important to them in their personal lives? What do they value more, an extension of life or maintenance of the best possible quality of life? An understanding of a patient's specific goals should shape conversations about goals of care and treatment recommendations.

Clinicians should clearly explain all potential treatment options, the potential outcomes of each, and possible AEs/adverse effects so that patients understand benefits and drawbacks of each and can make an informed decision. Treatment discussions should include relevant clinical trials at every stage of treatment. Patients should have the opportunity to participate in trials for their own treatment as well as be given the opportunity to contribute to research.

Clinicians should also consider and proactively discuss quality-of-life issues. In patients with pancreatic cancer, dietary concerns, pain, and fatigue are major concerns. Dietary issues tend to be overlooked and yet are real problems with a significant impact on daily life. Referral to a registered dietitian and/or gastroenterologist with early intervention can be of great benefit. Clinicians should also consider the use of and discuss the possible need for pancreatic enzyme replacement therapy.

Referral to palliative care services can facilitate the addressing of many non–treatment-related issues patients face and should be offered for all patients with pancreatic cancer, regardless of stage of disease or expected prognosis. Patients should understand that referral to a consultation for palliative care services is not synonymous with a referral to hospice care. This discussion is important because palliative care provides important support and can be part of an active cancer treatment paradigm.

Patients must feel comfortable in the choices they make, and the knowledge that they have explored their options can bring comfort.[59] As such, clinicians should support a patient's desire to get a second opinion. Clinicians should address the costs of care and offer referrals to specialists within the health care system who can discuss in more detail what a patient should expect as well as resources and information about managing the costs related to cancer care.

The provision of realistic hope to patients with pancreatic cancer, although the prognosis may be short, is important. Patients deserve to know that their medical team is working to help them reach their goals. Even if a cure is not possible, hope for an extension of life or good quality of life is powerful.

The provision of resources to help patients communicate better with their health care team is also advisable. Patients should be offered decision-making tools and urged to write down questions in between and in advance of appointments. Patients can be referred to resources that will extend the support and information clinicians are able to provide. For pancreatic cancer, two such resources are the ASCO patient-facing Web site (www.Cancer.net) and the Pancreatic Cancer Action Network (www.pancan.org).

Metastatic Pancreatic Cancer

- Explain all potential treatment options and possible AEs/adverse effects, which include clinical trials, so that the patient understands benefits and drawbacks of each and can make an informed decision.
- Discuss that a referral for a consultation with palliative care services does not mean hospice; it is in conjunction with active treatment.
- Ask about patient preferences and personal goals of care.
- Understand that patients may want active treatment to shrink or hold back cancer, extend life, and/or reduce pain and adverse effects
- Offer patients and their families a tool to discuss options (a decision aid to be used in conjunction with clinicians).
- Urge patients to write down questions to ask the clinician on follow-up visits. Support a second opinion by urging patients to consider high-volume centers for treatment of metastatic pancreatic cancer.
- List resources and support (ie, Pancreatic Cancer Action Network, Cancer.net).

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on best practices in disease management to provide the highest level of cancer care, many people have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. People with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor quality care than other Americans.[60] Many other people lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Such disparities may not exist in a more equal-access system. By using the Department of Defense tumor registry database from 1993 to 2007, patient, tumor, and treatment factors were analyzed to compare rates of therapy and survival between blacks and whites.[61] Of 1,008 patients with pancreatic cancer, 157 (15%) were black. Thirty-six percent of black and 37% of white patients presented with locoregional disease ($P = .85$). For example, among those with potentially curable cancers, the odds of black patients having received surgical resection (odds ratio [OR], 1.06; 95% CI, 0.60 to 1.89), chemotherapy (OR, 0.92; 95% CI, 0.49 to 1.73), and radiotherapy (OR, 1.14; 95% CI, 0.61 to 2.10) were not different

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from those of whites. Among those with distant disease, the odds of having received palliative chemotherapy were also similar (OR, 0.91; 95% CI, 0.55 to 1.51). In a multivariable analysis, black race compared with white race was not associated with shorter OS. These data suggest that improvement in the access to health care of minorities with pancreatic cancer may reduce disparities in oncologic outcomes. Thus, a significant proportion of patients with pancreatic cancer remain undertreated, possibly as a result of two nonclinical factors such as insurance status and access to care.

Multiple Chronic Conditions

The creation of evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which a person may have two or more such conditions (referred to as multiple chronic conditions [MCCs]), is challenging. Even in clinical trials that enroll highly selected patients with metastatic pancreatic cancer, tolerance and completion of adjuvant therapy are challenging due to AEs and toxicities.[62] Patients who have health status considerations that would have precluded them from participation in the clinical trials that establish the evidence may have uncertain benefit from interventions for their cancer, and this uncertainty should be discussed with the patient during the informed consent process for treatment. Older patients, for example, who have other health status conditions are at higher risk for chemotherapy toxicity.[62] In patients with metastatic pancreatic cancer, these risks should be assessed and discussed, especially given that first-line treatments have a high prevalence of toxicity, and clinical trials have not included patients with significant MCCs or those at advanced ages.

Patients with metastatic pancreatic cancer with MCCs are a complex and heterogeneous population, which makes it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials wherein study selection criteria may have excluded patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous population.

Because many patients with pancreatic cancer for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making with regard to guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in patients with metastatic pancreatic cancer and take those conditions into account when formulating the treatment and follow-up plan.

Cost Effectiveness

Limited cost-effectiveness analyses exist with regard to the various treatment modalities used in the multidisciplinary management of metastatic pancreatic cancer. However, the available data appear to support the recommendations in this guideline. One study assessed the cost-effectiveness of first-line FOLFIRINOX compared with first-line gemcitabine for public payers in Canada. Compared with first-line gemcitabine, first-line FOLFIRINOX resulted in more life-years and quality-adjusted life-years. Probabilistic sensitivity analysis results showed that for analyses 1 and 2, respectively, FOLFIRINOX has a > 85% probability and an approximately 80% probability of being cost-effective at the $100,000 threshold. Compared with gemcitabine, first-line FOLFIRINOX significantly prolongs median OS. Given the favorable cost per quality-adjusted life-year, the improvement in clinical efficacy, and the limited available treatment options, FOLFIRINOX represents an attractive cost-effective treatment.[64]

As reported at the 2014 Gastrointestinal Cancers Symposium, investigators compared the costs and clinical outcomes of gemcitabine plus NAB-paclitaxel versus erlotinib plus gemcitabine (E/G) by using drug cost per cycle multiplied by the median cycles delivered from clinical trials for gemcitabine plus NAB-paclitaxel and E/G. The comparison included the cost of the drugs as well as expenses related to the administration of the therapy and the management of AEs of grade 3/4 severity. These costs were based on 4 months of therapy for gemcitabine plus NAB-paclitaxel versus 3.9 months for E/G as administered at a large, multisite oncology clinic. The researchers found that the total cost for gemcitabine plus NAB paclitaxel was $24,984 versus $23,044 for E/G. However, the gemcitabine plus NAB-paclitaxel is expected to deliver a greater survival benefit based on clinical trial data, bringing the cost per life-year gained to $15,522.[65]

Moreover, health care experts have noted that the costs of treatment are high and increasing. The choice of therapy depends on a variety of clinical factors. More than 70% of cases are diagnosed in patients age 65 years and older. Thus, in the United States, Medicare pays for a substantial portion of associated costs. The costs of treating the malignancy are noteworthy when one considers that pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States.

External Review

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed that the guideline would be useful in practice. The Expert Panel reviewed the comments and integrated them into the final manuscript before approval by the Clinical Practice Guidelines Committee.

Guideline Implementation

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners, cancer survivors, and caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often

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published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND AREAS FOR FUTURE RESEARCH

Many research initiatives are aimed at improving the diagnosis and treatment of metastatic pancreatic cancer. Groups collaborate to find treatments and improve screening and diagnosis with biomarkers of pancreatic cancer, which could help physicians to diagnose the disease earlier and provide better treatment to patients with pancreatic cancer.

A prospective trial conducted through the National Cancer Institute National Clinical Trials Network that compares a treatment regimen that contains the novel agent NAB-paclitaxel with more established cytotoxic agents (fluorouracil, oxaliplatin, and irinotecan) may address the question of optimal first-line treatment of metastatic pancreatic cancer and determine the feasibility and impact of second-line therapy. A large phase III trial with smaller pilot and phase II trials to study novel interventions would be possible because of the large number of patients with pancreatic cancer. The question then remains about whether this large-scale study to determine superiority should be prioritized or whether resources would be better used toward another strategy, especially when many patients will receive both regimens throughout their treatment.[66]

Other strategies that would de-emphasize the treatment of all cases of metastatic pancreatic cancer with the same intervention should also be explored. An investigation of the molecular genetics and biology of pancreatic cancers would be more effective to identify subsets that would respond to single agents or combinations of targeted agents or a cytotoxic backbone. Also of value would be to explore immunologic approaches, such as CD40 agonists and T-cell engineering.[66] Each of these options recognizes the individual variation among patients with metastatic pancreatic cancer and allows for individualized treatments.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, which includes a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and other clinical tools and resources, are available at www.asco.org/guidelines/MetPC. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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REFERENCES

1. American Cancer Society: Cancer facts & figures 2015. www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf
2. World Cancer Research Fund International: Pancreatic cancer statistics. www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/pancreatic-cancer-statistics
3. Rahib L, Smith BD, Aizenberg R, et al: Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 74:2913-2921, 2014
4. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2006. CA Cancer J Clin 56:106-130, 2006
5. American Cancer Society: Cancer facts & figures 2013. www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013
6. Malvezzi M, Bertuccio P, Levi F, et al: European cancer mortality predictions for the year 2013. Ann Oncol 24:792-800, 2013
7. Hawes RH, Xiong Q, Waxman I, et al: A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol 95:17-31, 2000
8. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011
9. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691-1703, 2013
10. Sohal DP, Walsh RM, Ramanathan RK, et al: Pancreatic adenocarcinoma: Treating a systemic disease with systemic therapy. J Natl Cancer Inst 106:dju011, 2014
11. Rhim AD, Mirek ET, Aiello NM, et al: EMT and dissemination precede pancreatic tumor formation. Cell 148:349-361, 2012
12. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
13. Oettle H, Riess H, Stieler JM et al: Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: Outcomes from the CONKO-003 trial. J Clin Oncol 32:2423-2429, 2014
14. Rougier P, Riess H, Manges R, et al: Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer 49:2633-2642, 2013
15. Gonçalves A, Gilabert M, François E, et al: BAYPAN study: A double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. Ann Oncol 23:2799-2805, 2012
16. Kindler HL, Ioka T, Richel DJ, et al: Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: A double-blind randomised phase 3 study. Lancet Oncol 12:256-262, 2011
17. da Cunha Santos G, Dhani N, Tu D, et al: Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. Cancer 116:5599-5607, 2010
18. Moinpour CM, Vaught NL, Goldman B, et al: Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a phase III study comparing gemcitabine plus cetuximab versus gemcitabine as first-line therapy in patients with advanced pancreas cancer. J Clin Oncol 28:3611-3616, 2010
19. Colucci G, Labianca R, Di Costanzo F, et al: Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: The GIP-1 study. J Clin Oncol 28:1645-1651, 2010

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26. Dahan L, Bonnetain F, Ychou M, et al: Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: Final results of a randomised strategic phase III trial (FFCD 0301). Gut 59: 1527-1534, 2010

27. Cunningham D, Chau I, Stocken DD, et al: Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27: 5513-5518, 2009

28. Van Cutsem E, Vervenne WL, Bennouna J, et al: Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 27:2231-2237, 2009

29. Poplin E, Feng Y, Berlin J, et al: Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: A trial of the Eastern Cooperative Oncology Group. J Clin Oncol 27:3778-3785, 2009

30. Bernhard J, Dietrich D, Scheithauer W, et al: Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: A randomized multicenter phase III clinical trial—SAKK 44/00-CECOG/PAN.1.3.001. J Clin Oncol 26:3695-3701, 2008

31. Herrmann R, Bodoky G, Ruhstaller T, et al: Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: A randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 25:2212-2217, 2007

32. Moore MJ, Goldstein D, Hamm J, et al: 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. J Clin Oncol 25: 1960-1966, 2007

33. Abou-Alfa GK, Letourneau R, Harker G, et al: Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J Clin Oncol 24: 4441-4447, 2006

34. Stathopoulos GP, Syrigos K, Aravantinos G, et al: A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. Br J Cancer 95:587-592, 2006

35. Heinemann V, Quietzsch D, Gieseler F, et al: Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 24:3946-3952, 2006

36. Reni M, Cordio S, Milandri C, et al: Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: A randomised controlled multicentre phase III trial. Lancet Oncol 6: 369-376, 2005

37. Louvet C, Labianca R, Hammel P, et al: Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23: 3509-3516, 2005

38. Rocha Lima CM, Green MR, Rotche R, et al: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 22:3776-3783, 2004

39. Berlin JD, Catalano P, Thomas JP, et al: Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 20: 3270-3275, 2002

40. Maisey N, Chau I, Cunningham D, et al: Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. J Clin Oncol 20:3130-3136, 2002

41. Goldstein D, El-Maraghi RH, Hammel P, et al: nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. J Natl Cancer Inst 107:107, 2015

42. Pawlik TM, Laheru D, Hruban RH, et al: Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. Ann Surg Oncol 15:2081-2088, 2008

43. Hoos WA, James PM, Rahib L, et al: Pancreatic cancer clinical trials and accrual in the United States. J Clin Oncol 31:3432-3438, 2013

44. Ma C, Bandukwala S, Burman D, et al: Interconversion of three measures of performance status: An empirical analysis. Eur J Cancer 46:3175-3183, 2010

45. Mahaseth H, Brutcher E, Kauh J, et al: Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 42:1311-1315, 2013

46. Wang-Gillam A, Li CP, Bodoky G, 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 387: 545-557, 2016

47. Burris HA III, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997

48. Rahma OE, Duffy A, Liewehr DJ, et al: Second-line treatment in advanced pancreatic cancer: A comprehensive analysis of published clinical trials. Ann Oncol 24:1972-1979, 2013

49. Morrison RS, Augustin R, Souvanna P, et al: America's care of serious illness: a state-by-state report card on access to palliative care in our nation's hospitals. J Palliat Med 14:1094-1096, 2011

50. Kelley AS, Morrison RS: Palliative care for the seriously ill. N Engl J Med 373:747-755, 2015

51. Selcoan A: Celiac plexus neurolysis in pancreatic cancer: The endoscopic ultrasound approach. World J Gastroenterol 20:110-117, 2014

52. Wong GY, Schroeder DR, Carns PE, et al: Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: A randomized controlled trial. JAMA 291:1092-1099, 2004

53. Amr YM, Makhanta MY: Neurolytic sympathectomy in the management of cancer pain-time effect: A prospective, randomized multicenter study. J Pain Symptom Manage 48:944-956, 2014

54. Dameda V, Gotlieb V, Larson R, et al: Pancreatic enzyme supplementation in pancreatic cancer. J Support Oncol 6:393-396, 2008

55. Bruno MJ, Haverkort EB, Tijssen GP, et al: Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 42:92-96, 1998

56. Boulay BR, Parepally M: Managing malignant biliary obstruction in pancreas cancer: Choosing the appropriate strategy. World J Gastroenterol 20: 9345-9353, 2014

57. Baron TH: Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med 344:1681-1687, 2001

58. Maire F, Hammel P, Ponsot P, et al: Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. Am J Gastroenterol 101:735-742, 2006

59. Khorana AA, Ahrendt SA, Ryan CK, et al: Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 13: 2870-2875, 2007

60. Khorana AA: Venous thromboembolism and prognosis in cancer. Thromb Res 125:490-493, 2010

61. Khorana AA, Francis CW, Culakova E, et al: Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5:632-634, 2007

62. Lyman GH, Bohlke K, Khorana AA, et al: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol 33:654-656, 2015

63. Maraveyas A, Waters J, Roy R, et al: Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 48: 1283-1292, 2012

64. Vadhan-Raj S, Zhou X, Benjamin RS, et al: Incidence and risk factors predictive of recurrent venous thromboembolism in patients with cancer at a comprehensive cancer center. J Clin Oncol 29, 2011 (suppl, abstr 9059)

65. Epstein RMSR, Jr: Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering. Bethesda, MD, National Cancer Institute, 2007

66. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, Commonwealth Fund, 2008

67. Lee S, Reha JL, Tzeng CW, et al: Race does not impact pancreatic cancer treatment and survival in an equal access federal health care system. Ann Surg Oncol 20:4073-4079, 2013

68. Dias-Santos D, Ferrone CR, Zheng H, et al: The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Surgery 157: 881-887, 2015

69. Hurria A, Togawa K, Mohile SG, et al: Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. J Clin Oncol 29:3457-3465, 2011

70. Attard CL, Brown S, Alloul K, et al: Cost-effectiveness of FOLFIRINOX for first-line treatment of metastatic pancreatic cancer. Curr Oncol 21:e41-e51, 2014

71. Chorean EG, Whiting S, Binder G, et al: Cost-effectiveness of nab-paclitaxel plus gemcitabine versus erlotinib plus gemcitabine in metastatic pancreatic cancer. J Clin Oncol 32, 2014 (suppl, abstr 353)

72. Abbruzzese JL, Hess KR: New option for the initial management of metastatic pancreatic cancer? J Clin Oncol 32:2405-2407, 2014

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Metastatic Pancreatic Cancer Treatment Guideline Expert Panel Membership

Name (and Designation)	Affiliation/institution
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Michelle Lau (PGIN representative)	Private practice, Tempe, AZ
Susan Urba, MD	University of Michigan Cancer Center, Ann Arbor, MI

NOTE. ASCO staff: Pamela B. Mangu, MA. Abbreviation: PGIN, Practice Guideline Implementation Network.

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ASCO GUIDELINES

Data Supplement

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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Data Supplement 6: Pancreatic Protocol Computerized Tomography (CT)

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Table 1: Patient and Disease Characteristics

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
Oettle et al., 2014 CONKO-003	OFF	76	62	40	36	Karnofsky 70-80: 35 90-100: 41	NR	NR	NR
	FF	84	61	48	36	Karnofsky 70-80: 44 90-100: 40			
Von Hoff et al., 2013	nab-Paclitaxel plus Gemcitabine	431	62	245	186	Karnofsky 100: 69 (16%) 90: 179 (42%) 80: 149 (35%) 70: 30 (7%) 60: 2 (<1%)	Head: 191 (44%) Body: 132 (31%) Tail: 105 (24%) Unknown: 3 (1%)	Level of CA 19-9 Normal: 60 (16%) ULN to <59x ULN: 122 (32%) >/= 59x ULN: 197 (52%) CA 19-9 U/ml: 2293.7 range 1.9-6159	Chemo: 23 (5%) Radiation: 19 (4%) Whipple: 32 (7%) Stent: 80 (19%)

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine alone	430	63	257	173	Karnofsky 100: 69 (16%) 90: 199 (46%) 80: 128 (30%) 70: 33 (8%) 60: 0 (0%)	Head: 180 (42%) Body: 136 (32%) Tail: 110 (26%) Unknown: 4 (1%)	Level of CA 19-9 Normal: 56 (15%); ULN to <59x ULN 120 (32%); >/= 59x ULN 195 (53%) CA 19-9 U/ml: 2759 range 0.3-12,207	Chemo: 12 (3%) Radiation: 11 (3%) Whipple: 30 (7%) Stent: 68 (16%)
Rougier et al., 2013	Gemcitabine plus placebo	275	61	157	118	WHO 0: 102 1: 154 2: 19	Head: 117 Body: 41 Tail: 45 Entire pancreas: 72 Other: 0	NR	NR
	Gemcitabine plus aflibercept	271	62	160	111	WHO 0: 102 1: 152 2: 17	Head: 132 Body: 41 Tail: 46 Entire Pancreas: 50 Other: 2		

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Performance Status	Location	Markers	Previous Treatment
				Male	Female				
Goncalves et al., 2012 BAYPAN	Gemcitabine plus placebo	52	64	32	20	WHO 0: 18 1: 30 2: 3 NA: 1	NR	CA 19-9 Median 424 (1.3-3300)	NR
	Gemcitabine plus sorafenib	52	61	30	22	WHO 0: 16 1: 26 2: 5 NA: 5		CA 19-9 Median 471 (1.2-21500)	
Conroy et al., 2011	FOLFIRINOX	171	61	106	65	NR	Head: 67 Body: 53 Tail: 45 Multicentric: 6	NR	Stent: 27
	Gemcitabine	171	61	105	66		Head: 64 Body: 58 Tail: 45 Multicentric: 5/171		Stent: 22
Kindler et al., 2011	axitinib plus gemcitabine	314	61	191	123	WHO 0: 147 1: 162 Missing: 11	NR	NR	NR
	placebo plus gemcitabine	316	62	188	128	WHO 0: 158 1: 154 Missing: 4			

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
da Cunha Santos et al., 2010 NCIC CTG PA.3	Gemcitabine vs gemcitabine plus erlotinib in KRAS mutant patients	92	62.2	47	45	WHO 0:16 1:57 2:19 Unknown: 0	NR	NR	NR
	Gemcitabine vs gemcitabine plus erlotinib in KRAS wild type patients	25	65.6	17	8	WHO 0: 7 1: 14 2: 3 Unknown:1			
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH+ patients	50	61.0	32	18	WHO 0:11 1:24 2:14 Unknown:1			
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH- patients	57	64.7	30	27	WHO 0:12 1:35 2:10 Unknown:0			
Moinpour et al., 2010	Gemcitabine	359	65	197	162	WHO 0-1:312 2:47	NR	NR	Chemo: 14 Pancreatectomy: 36

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine plus cetuximab	361	64	188	173	WHO 0-1: 314 2: 47			Chemo: 21 Pancreatectomy: 32
Colucci et at., 2010 GIP-1	Gemcitabine	199	63	113	86	Karnofsky </=70:33 >/=80: 166	Head: 91 Body: 52 Tail: 26 Head + Body:10 Body + Tail:18 Head + Body + Tail:1 Unknown:1	NR	Surgery: 47
	Gemcitabine plus Cisplatin	201	63	125	73	Karnofsky </=70:36 >/=80: 165	Head: 101 Body: 34 Tail: 20 Head + Body: 6 Body + Tail: 39 Head + Body + Tail:1 Unknown:0		Surgery: 56
Dahan et al., 2010 FFCD 0301	LV5FU2-CDDP	102	62	65	37	WHO 0: 28 1: 51 2: 22 Not Determined : 1	Head: 57 Other: 44 Unknown: 1	CEA Median: 9 (0-2224) CA 19-9 Median: 565 (0-862200)	Chemo: 0 Radiation: 1 Resection: 13 Drainage: 4 Other Surgery: 6 Deudenal Stent: 10 Radiological/end oscopic drainage: 22
	Gemcitabine	100	65	65	35	WHO 0: 30 1: 53	Head: 49 Other: 50 Unknown: 1	CEA Median: 7 (1-3604)	Chemo: 3 Radiation: 2 Resection: 14

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Performance Status	Location	Markers	Previous Treatment
				Male	Female				
						2: 14 Not Determined: 3		CA 19-9 Median: 560 (1-156649)	Drainage: 8 Other Surgery: 6 Deudenal Stent: 5 Radiological/endoscopic drainage: 11
Cunningham et al., 2009	Gemcitabine	266	62	153	113	WHO 0: 56 1: 161 2: 49	Head: 185 Body: 36 Tail: 30 Head + Body: 7 Body + Tail: 7 Unknown: 5	NR	NR
	Gemcitabine plus Capecitabine	267	62	160	107	WHO 0: 66 1: 149 2: 52	Head: 190 Body: 29 Tail: 25 Head + Body: 10 Body + Tail: 10 Unknown: 4		
Van Cutsem et al., 2009	Gemcitabine-erlotinib plus placebo	301	61	188	113	NR	Head: 165 Body: 65 Tail: 67	NR	Radiation: 5 Antimetobolites: 14
	Gemcitabine-erlotinib plus Bevacizumab	306	62	174	132		Head: 157 Body: 79 Tail: 68		Radiation: 12 Antimetobolites: 12
Poplin et al., 2009 E6201	Gemcitabine	275	64	155	120	NR	NR	CA 19-9 Median 1961 (167-12024) CEA Median: 5.7 (2.3-30.9)	Chemo: 15 Radiation: 21 Surgery: 43

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine fixed-dose rate infusion	277	61	160	117			CA 19-9 Median: 1148 (136-9651) CEA Median: 5.9 (2.4-30.1)	Chemo: 17 Radiation: 23 Surgery: 42
	Gemcitabine plus oxaliplatin	272	63	124	148			CA 19-9 Median: 1077 (90-9301) CEA Median: 6.3 (2.4 -35.5)	Chemo: 10 Radiation: 21 Surgery: 32
Bernhard et al., 2008 SAKK 44/00-CECO/PAN.1.3.001	Capecitabine plus Gemcitabine	160	62	86	74	Karnofsky 90-100: 84 60-80: 76	NR	NR	NR
	Gemcitabine	159	62	85	74	Karnofsky 90-100: 84 60-80: 75			
Herrmann et al., 2007	Capecitabine plus Gemcitabine	160	NR	86	74	Karnofsky 90-100: 84 60-80: 76	NR	NR	NR
	Gemcitabine	159		85	74	Karnofsky 90-100: 84 60-80: 75			
Moore et al., 2007	Erlotinib plus Gemcitabine	285	63.7	136	149	WHO 0: 85 1: 145 2: 54	NR	NR	FU or Gem given concurrently as a radiosensatizer only: 20 Radiation: 22 Resection: 19

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Placebo plus Gemcitabine	284	64.0	162	122	WHO 0: 85 1: 174 2: 52			FU or Gem given concurrently as a radiosensatizer only: 25 Radiation: 25 Resection: 29
Abou-Alfa et al., 2006	Exatecan plus Gemcitabine	174	63.0	92	83	Karnofsky 90-100: 90 70-80: 81 60: 4	NR	CA 19-9 Median: 1053 (0.8-1237761)	NR
	Gemcitabine	174	62.3	99	99	Karnofsky 90-100: 90 70-80: 82 60: 2		CA 19-9 Median: 597 (1.3-304332)	
Stathopoulos et al., 2006	irinotecan plus gemcitabine	60	64	39	21	WHO 0-1: 52 2: 8	NR	NR	Surgery: 11 No Prior Treatment: 49
	gemcitabine	70	64	42	28	WHO 0-1: 8 2: 10			Surgery: 16 No Prior Treatment: 54
Heinemann et al., 2006	gemcitabine plus cisplatin	98	64	64	34	Karnofsky 100: 20 90: 24 80: 27 70: 8	Head: 55 Body: 19 Tail: 24	NR	NR
	gemcitabine	97	66	60	37	Karnofsky 100: 19 90: 21 80: 29 70: 13	Head: 55 Body: 24 Tail: 18		
Reni et al., 2005	PEFG	52	62	24	28	Karnofsky >70: 37 </= 70: 15	NR	NR	NR

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Perform-ance Status	Location	Markers	Previous Treatment
				Male	Female				
	Gemcitabine	47	59	24	23	Karnofsky >70: 35 </= 70: 12			
Louvet et al., 2005	Gemcitabine	156	60.1	53	47	WHO 0: 28 1: 54 2: 18	Head: 50 Body: 37 Tail: 13	Median: 1424	NR
	Gemcitibine plus oxaliplatin	157	61.3	60	40	WHO 0: 31 1: 52 2: 17	Head: 54 Body: 27 Tail: 19	Median: 965	
Rocha Lima et al., 2004	Gemcitabine plus Irinotecan	180	63.2	103	73	WHO 0:51 1:90 2:34 3:1 missing:4	NR	NR	Radiation: 11
	Gemcitabine	180	60.2	96	73	WHO 0:42 1:91 2:36 3:0 missing:11			Radiation: 14
Berlin et al., 2002 E2297	Gemcitabine	162	64.3	87	75	WHO 0:56 1:84 2:22	Head:81 Body: 19 Tail: 27 Unknown: 35	NR	NR
	Gemcitabine plus 5-FU	160	65.8	83	77	WHO 0:36 1:102 2:22	Head: 87 Body: 36 Tail: 21 Unknown: 17		
Maisey et al., 2002	PVI 5-FU	107	62	68	39	WHO 0:18 1:59	NR	NR	NR

Author Year Reference	Interventions [or] Comparisons	# of Pts	Patient Characteristics				Disease Characteristics		
			Median Age	Sex		Performance Status	Location	Markers	Previous Treatment
				Male	Female				
						2:28 3: 1			
	PVI 5-FU plus mitomycin	102	61	62	40	WHO 0:20 1:54 2:24 3:1			

Abbreviations: CONKO, Charité Onkologie; OFF, Oxaliplatin, fluoruracil, plus folinic acid; FF, fluoruracil, plus folinic acid; NR, not reported; CA, cancer antigen; ULN, upper limit of normal; Chemo, chemotherapy; WHO, World Health Organization; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; EGFR, Epidermal growth factor receptor; FISH, fluorescence in situ hybridization; GIP, Gruppo Italiano Pancreas; FFCD, Fédération Francophone de Cancérologie Digestive; LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination ; CEA, Carcinoembryonic antigen; SAKK, Swiss Group for Clinical Cancer Research; CECOG, Central European Cooperative Oncology Group; FU, fluorouracil; Gem, Gemcitabine; PEFG, cisplatin, epirubicin, 5-fluorouracil, gemcitabine; PVI, protracted venous infusion

Table 2: OUTCOMES: Survival (OS), progression free survival (PFS) and disease free survival (DFS) and adverse events (AEs)

Study	Intervention	# of patients	Outcome
Oettle et al., 2014 CONKO-003	OFF	76	The median overall survival 5.9 months; 95% CI, 4.1 to 7.4) (hazard ratio [HR], 0.66; 95% CI, 0.48 to 0.91; log-rank P .010). Time to progression (2.9 months; 95% CI, 2.4 to 3.2) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank P———————————.019). Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity, which were reported in 29 patients (38.2%) in the [(P ——————————— .001).
	FF	84	The median overall survival (3.3 months; 95% CI, 2.7 to 4.0) was significantly improved (hazard ratio [HR], 0.66; 95% CI, 0.48 to 0.91; log-rank P .010). Time to progression (2.0 months; 95% CI, 1.6 to 2.3) was significantly extended also (HR, 0.68; 95% CI, 0.50 to 0.94; log-rank P .019). Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity, which were reported in and six patients (7.1%) in the OFF and FF groups, (P ——————————— .001).
Von Hoff et al., 2013	nab-Paclitaxel plus Gemcitabine	431	The median overall survival was 8.5 months (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 35% at 1 year, and 9% at 2 years. The median progression-free survival was 5.5 months. (hazard ratio, 0.69; 95%

Study	Intervention	# of patients	Outcome
			CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were neutropenia (38%), fatigue (17%); and neuropathy (17% Febrile neutropenia occurred in 3% neuropathy of grade 3 or >r higher improved to grade 1 or lower in a median of 29 days
	Gemcitabine alone	430	The median overall survival was 6.7 months (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 22% at 1 year and 4% at 2 years. The median progression-free survival was 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); The response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were 27%; fatigue .7%, and neuropathy 1%). Febrile neutropenia occurred in 1% of the patients; neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 day
Rougier et al., 2013	Gemcitabine plus placebo	275	The study was stopped for futility following a planned interim analysis of OS in 427 randomized patients. With a median follow-up of 7.9 months, based on the 546 patients at study termination.

Study	Intervention	# of patients	Outcome
	Gemcitabine plus aflibercept	271	Median OS was 7.8 months in the gemcitabine plus placebo arm (n=275) versus 6.5 months in the gemcitabine plus aflibercept arm (n=271), which was not significant (hazard ratio 1.165, 95% confidence interval (CI) 0.921-1.473, p=0.2034). Median progression-free survival was 3.7 months in both arms. Treatment discontinuations due to adverse events were more frequent in the aflibercept than in the placebo-containing arm (23% versus 12%).
Goncalves et al., 2012 BAYPAN	Gemcitabine plus placebo	52	Median and the 6-month PFS were 5.7 months and 48%. (P = 0.902, stratified log-rank test) Median overall survivals was 9.2 (P = 0.231, log-rank test). Overall response rates were similar (19%).
	Gemcitabine plus sorafenib	52	The median and the 6 month PFS were 3.8 months and 33% (P = 0.902, stratified log-rank test), respectively The median overall survivals was 8 months (P = 0.231, log-rank test). The overall response rates were similar 23%.
Conroy et al., 2011	FOLFIRINOX	171	The median overall survival was 11.1 months, (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months , (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001) The objective response rate was 31.6%, (P<0.001).

Study	Intervention	# of patients	Outcome
			More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabinee group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001
	Gemcitabine	171	The median overall survival was 6.8 months, (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 3.3 months , (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 9.4, (P<0.001)
Kindler et al., 2011	Axitinib plus gemcitabine	314	At an interim analysis in January, 2009, the independent data monitoring committee concluded that the futility boundary had been crossed. Median overall survival was 8.5 months (95% CI 6.9-9.5) for gemcitabine plus axitinib (n=314, data missing for two patients; hazard ratio 1.014, 95% CI 0.786-1.309; one-sided p=0.5436).
	Placebo plus Gemcitabine	316	The most common grade 3 or higher adverse events for gemcitabine plus axitinib were hypertension (20 [7%] events, abdominal pain (20 [7%] ,fatigue (27 [9%] , and anorexia (19 [6%]/ Median overall survival was 8.3 months (6.9-10.3) (n=316; hazard ratio 1.014, 95% CI 0.786-1.309; one-sided p=0.5436). The most common grade 3 or higher adverse events for gemcitabine plus placebo were hypertension 5 [2%] events, abdominal pain (17 [6%]), fatigue and 21

Study	Intervention	# of patients	Outcome
			[7%]), and anorexia and 11 [4%]).
da Cunha Santos et al., 2010 NCIC CTG PA.3	Gemcitabine vs gemcitabine plus erlotinib in KRAS mutant patients	92	KRAS analysis was successful in 117 patients, and EGFR FISH analysis was successful in 107 patients. KRAS mutations were identified in 92 patients (78.6%), and EGFR amplification or high polysomy (FISH-positive results) was identified in 50 patients (46.7%). The hazard ratio of death between gemcitabine /erlotinib and gemcitabine /placebo was 0.66 (95% confidence interval [CI], 0.28-1.57) for patients with wild-type KRAS and 1.07 (95% CI, 0.68-1.66) for patients with mutant KRAS (P value for interaction = .38), and the hazard ratio was 0.6 (95% CI, 0.34-1.07) for FISH-negative patients and 0.90 (95% CI, 0.49-1.65) for FISH-positive patients (P value for interaction = .32).
	Gemcitabine vs gemcitabine plus erlotinib in KRAS wild type patients	25	
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH+ patients	50	
	Gemcitabine vs gemcitabine plus erlotinib in EGFR FISH- patients	57	

Study	Intervention	# of patients	Outcome
Moinpour et al., 2010	Gemcitabine	359	The two treatment arms did not differ statistically in the percentage of patients with successful worst pain palliation. Longitudinal analyses showed significantly improved emotional well-being for patients on both arms by weeks 13 and 17 (P < .01 and P < .001). An exploratory longitudinal analysis of worst pain showed significant decreases at all time points for both arms (P < .01 and P < .001). Significant treatment arm differences for either worst pain or emotional well-being were not observed at any of the assessment times.
	Gemcitabine plus cetuximab	361	
Colucci et at., 2010 GIP-1	Gemcitabine	199	Median overall survival was 8.3 months (HR, 1.10; 95% CI, 0.89 to 1.35; P = .38). Median progression-free survival was 3.9 months (HR, 0.97; 95% CI, 0.80 to 1.19; P = .80). The objective response rate was 10.1% in A (P = .37). Clinical benefit was experienced by 23.0% in (P = .057).
	Gemcitabine plus Cisplatin	201	Median overall survival was 7.2 months (HR, 1.10; 95% CI, 0.89 to 1.35; P = .38). Median progression-free survival was 3.8 months, (HR, 0.97; 95% CI, 0.80 to 1.19; P = .80). Clinical benefit was experienced by 15.1% in B (P = .057). The objective response rate was 12.9% (P = .37). Combination therapy produced more hematologic toxicity, without relevant differences in non-hematologic toxicity.

Study	Intervention	# of patients	Outcome
Dahan et al., 2010 FFCD 0301	LV5FU2-CDDP	102	Median OS in Arm A was 6.6 months. (p = 0.85). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when LV5FU2-CDDP was administered as a first-line treatment at 79% (p = 0.018)
	Gemcitabine	100	Median OS in 8.0 months (p = 0.85). Median progression-free survival was similar between Arms A and B. More grade 3/4 toxicities were observed when gemcitabine was administered as a first-line treatment 64% (p = 0.018).
Cunningham et al., 2009	Gemcitabine	266	Objective response rate with GEM was 12.4%; P = .034)
	Gemcitabine plus Capecitabine	267	Objective response rate with GEM-CAP was 19.1%; P = .034) Progression-free survival (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; P = .004) and was associated with a trend toward improved OS (HR, 0.86; 95% CI, 0.72 to 1.02; P = .08) compared with GEM alone. This trend for OS benefit for GEM-CAP was consistent across different prognostic subgroups according to baseline stratification factors (stage and performance status) and remained after adjusting for these stratification factors (P = .077).

Study	Intervention	# of patients	Outcome
Van Cutsem et al., 2009	Gemcitabine-erlotinib plus placebo	301	Median OS was 7.1 (hazard ratio [HR], 0.89; 95% CI, 0.74 to 1.07; P = .2087); this difference was not statistically significant.
	Gemcitabine-erlotinib plus Bevacizumab	306	Median OS was 6.0 months (hazard ratio [HR], 0.89; 95% CI, 0.74 to 1.07; P = .2087); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved PFS (HR, 0.73; 95% CI, 0.61 to 0.86; P = .0002). Treatment with bevacizumab plus gemcitabine-erlotinib was well tolerated: safety data did not differ from previously described safety profiles for individual drugs
Poplin et al., 2009 E6201	Gemcitabine	275	Median survival and 1-year survival were 4.9 months (95% CI, 4.5 to 5.6) and 16%, (95% CI, 5.4 to 6.9), (HR, 0.83; stratified log-rank P = .04.
	Gemcitabine fixed-dose rate infusion	277	The median survival and 1-year survival were 6.2 months (HR, 0.83; stratified log-rank P = .04), 21% and (95% CI, 4.9 to 6.5). Grade 3/4 neutropenia and thrombocytopenia were greatest with GEM FDR.
	Gemcitabine plus oxaliplatin	272	The median survival and 1-year survival were 5.7 months (95% CI, 4.9 to 6.5) and 21% (HR, 0.88; stratified log-rank P = .22). *None of these differences met the prespecified criteria for significance. Survival was 4 months for those with metastatic disease.

Study	Intervention	# of patients	Outcome
Bernhard et al., 2008 SAKK 44/00-CECO/PAN.1.3.001	Capecitabine plus Gemcitabine	160	Clinical benefit response of 19% treated with GemCap with a median duration of 9.5 weeks, respectively (P < .02). 54% of patients treated with GemCap had no Clinical benefit response.
	Gemcitabine	159	Clinical benefit response of 19% treated with Gem with a median duration of 9.5 weeks, (P < .02) 60% treated with Gem had no clinical benefit response (remaining patients were not assessable). There was no treatment difference in QOL (n = 311). QOL indicators were improving under chemotherapy (P < .05). These changes differed by the time to failure, with a worsening 1 to 2 months before treatment failure (all P < .05).
Herrmann et al., 2007	Capecitabine plus Gemcitabine	160	Median OS was 8.4 months, (P = .234). Post hoc analysis in patients with good KPS (score of 90 to 100) showed a significant prolongation of median OS of 10.1, P = .014).
	Gemcitabine	159	Median OS time was 7.2 months (P = .234). Post hoc analysis in patients with good KPS (score of 90 to 100) showed a significant reduction of median OS time of 7.4 months, P = .014). The overall frequency of grade 3 or 4 adverse events was similar in each arm. Neutropenia was the most frequent grade 3 or 4 adverse event in both arms

Study	Intervention	# of patients	Outcome
Moore et al., 2007	Erlotinib plus Gemcitabine	285	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). One-year survival was 23% 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).
	Placebo plus Gemcitabine	284	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; 5.91 months). One-year survival was 17%; P = .023). 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.
Abou-Alfa et al., 2006	Exatecan plus Gemcitabine	174	Median survival time was 6.7 months.and 6.2 months for gemcitabine alone (P = .52). One complete response (CR; < 1%) and 11 partial responses (PRs; 6.3%) were observed. Grade 3 and 4 toxicities neutropenia (30%); thrombocytopenia (15%).

Study	Intervention	# of patients	Outcome
	Gemcitabine	174	Median survival time was 6.2 months (P = .52). One CR (< 1%) and eight PRs (4.6%) were observed. Grade 3 and 4 toxicities neutropenia (15%); thrombocytopenia (4%).
Stathopoulos et al., 2006	Irinotecan plus Gemcitabine	60	The overall response rate was 15% (95% CI 5.96-24.04 and 95% CI 2.97-17.03, respectively; P=0.387). The median time to tumor progression was 2.8 months and median survival time was 6. One-year survival was 24.3%.
	Gemcitabine	70	The overall response rate was 10% (95% CI 5.96-24.04 and 95% CI 2.97-17.03, respectively; P=0.387). The median time to tumor progression was 2.9 months and median survival time was 6.5 months. One-year survival was 21.8%.
Heinemann et al., 2006	Gemcitabine plus Cisplatin	98	Median progression-free survival of 5.3 months; hazard ratio [HR] = 0.75; P = .053). Median overall survival was superior at 7.5 months), an advantage which did not, however, reach statistical significance (HR = 0.80; P = .15). Tumor response rate was 10.2%. Tumor response rates were comparable between treatment arms (10.2% v 8.2%).

Study	Intervention	# of patients	Outcome
			The rate of stable disease was, however, greater in the combination arm at 60.2% P < .001). Grade 3 to 4 hematologic toxicity did not exceed 15% in both treatment arms. Median progression-free survival of 3.1 months; hazard ratio [HR] = 0.75; P = .053). Median overall survival was 6.0 months, an advantage which did not, however, reach statistical significance (HR = 0.80; P = .15). Tumor response rate was 8.2%. The rate of stable disease was, however, greater in the combination arm was 40.2%; P < .001). Grade 3 to 4 hematologic toxicity did not exceed 15% in both treatment arms.
	Gemcitabine	97	
Reni et al., 2005	PEFG	52	The largest differences between arms favored PEFG. Expressed as improvement greater than or equal to 10 points from baseline (PEFG/gemcitabine), these were: emotional function (43/18%), fatigue (41/17%), QOL (55/29%), pain (64/41%), and flatulence (50/26%). Only change in sexual function favored gemcitabine (19/42%). Physical function, fatigue, appetite, and satisfaction with healthcare improved in 40-46% of partial responders compared with 0-12% of patients with stable disease.
	Gemcitabine	47	
Louvet et al., 2005	Gemcitabine plus oxaliplatin	157	Response rate (26.8%; P = .04) Progression-free survival (5.8; P = .04),] Clinical benefit (38.2%; P = .03).

Study	Intervention	# of patients	Outcome
			Median overall survival (OS) was 9.0 (P = .13). Higher incidence of National Cancer Institute Common Toxicity Criteria grade 3 and 4 toxicity per patient was observed for platelets (14.0%), vomiting (8.9%), and neurosensory symptoms (19.1%).
	Gemcitabine	157	Response rate (17.3%, P = .04) Progression-free survival (3.7 months; P = .04). Clinical benefit (26.9%, P = .03). Median overall survival (OS) for 7.1 months, respectively (P = .13). Grade 3 and 4 toxicity per patient was observed for platelets 3.2%, vomiting (3.2%), and neurosensory symptoms (0%).
Rocha Lima et al., 2004	Gemcitabine plus Irinotecan	180	Median survival times were 6.3 months for IRINOGEM (95% CI, 4.7 to 7.5 months) and 6.6 months for GEM (95% CI, 5.2 to 7.8 months; log-rank P =.789). Tumor response rates were 16.1% (95% CI, 11.1% to 22.3%) for IRINOGEM (chi2 P <.001). Median TTP was 3.5 months for IRINOGEM (log-rank P =.352). However, subset analyses in patients with locally advanced disease suggested a TTP disadvantage with IRINOGEM (median, 7.7 v 3.9 months). CA 19-9

Study	Intervention	# of patients	Outcome
			progression was positively correlated with tumor progression. The incidence of grade 3 diarrhea was higher in the IRINOGEM group but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were similar.
	Gemcitabine	180	Median survival times were 6.6 months (95% CI, 5.2 to 7.8 months; log-rank P =.789). Tumor response rates were and 4.4% (95% CI, 1.9% to 8.6%) (chi2 P <.001). Median TTP was 3.0 months (log-rank P =.352). Subset analyses in patients with locally advanced disease suggested a TTP disadvantage with GEM (median, 3.9 months). CA 19-9 progression was positively correlated with tumor progression. The incidence of grade 3 diarrheas was lower but grade 3 to 4 hematologic toxicities and quality-of-life outcomes were similar. .
Berlin et al., 2002 E2297	Gemcitabine	162	Median survival was 5.4 months (P =.09). Progression-free survival was 2.2 months, (P =.022). Objective responses were uncommon and were observed in only 5.6% of patients treated with gemcitabine. Most toxicities were hematologic or gastrointestinal; no significant differences were noted between the two treatment arms.

Study	Intervention	# of patients	Outcome
	Gemcitabine plus 5-FU	160	Median survival was 6.7 months (P =.09). Progression-free survival was 3.4 months (P =.022). Objective responses were uncommon and were observed in only 6.9%.. Most toxicities were hematologic or gastrointestinal; no significant differences were noted between the two treatment arms.
Maisey et al., 2002	PVI 5-FU	107	The overall response rate was 8.4% (95% confidence interval [CI]) 3.2% to 13.7% 95% (P =.04). Median failure-free survival was 2.8 months (P =.14). Median survival was 5.1 months (P =.34). Toxicities were mild. No differences in infection were seen. No patients developed hemolytic uremic syndrome.
	PVI 5-FU plus mitomycin	102	The overall response rate was 17.6%; (95% confidence interval [CI] 10.3% to 25.1%, (P =.04). Median failure-free survival was 2 3.8 months (P =.14). Median survival was 6.5 months (P =.34). Toxicities in both arms were mild. There was an increased incidence of neutropenia in the 5-FU plus MMC arm (P <.01), although no differences in infection were seen. No patients developed hemolytic uremic syndrome. Global QOL improved significantly after 24 weeks of treatment compared with

Study	Intervention	# of patients	Outcome
			baseline for patients receiving 5-FU plus MMC, although there was no statistically significant difference in QOL between arms.

Abbreviations: CONKO, Charité Onkologie; OFF, Oxaliplatin, fluoruracil, plus folinic acid; FF, fluoruracil, plus folinic acid; OS, overall survival; PFS, progression free survival; APC, advanced pancreatic cancer; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; EGFR, Epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HRQL, health-related quality of life; GIP, Gruppo Italiano Pancreas; FFCD, Fédération Francophone de Cancérologie Digestive; LV5FU2-CDDP, 5-fluorouracil, folinic acid and cisplatin combination; GEM, Gemcitabine; CAP, Capecitabine; FDR, fixed dose rate; GEMOX, gemcitabine and oxaliplatin; SAKK, Swiss Group for Clinical Cancer Research; CECOG, Central European Cooperative Oncology Group; CBR, clinical benefit response; QOL, quality of life; PEFG, cisplatin, epirubicin, 5-fluorouracil, gemcitabine; IRINOGEM, irinotecan plus gemcitabine; FU, fluorouracil; PVI, protracted venous infusion; MMC, mitomycin

Table 3: Systematic Reviews and Meta-analyses (Metastatic)

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
Sgouros J (1), Maraveyas A Excess premature (3-month) mortality in advanced pancreatic cancer could be related to fatal vascular thromboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer.	Acta Oncol. 2008;47(3):337-46.	A Medline and EMBASE search was done for chemotherapy or chemotherapy based phase III studies in advanced pancreatic cancer published since 1997. Similar search was done at the American Society of Clinical Oncology web site for abstracts presented since 2000. Three months mortality was based on the survival curves presented.	Fourteen papers and five abstracts met our criteria and are included in our review. Six thousand two hundred and twelve patients participated in these trials and 1,447 (23.3%) died in the first 3-month period. Figures were worse in patients with metastases and poorer performance status. Assuming that most deaths during treatment happened during the first 3-months, cause of death was reported in only 40 cases (2.8%). Progressive cancer was reported as cause of death in 21 of these cases. Less frequent causes of death were reported to be infections, 'complications of cancer', thromboembolic events and renal failure.	Overall treatment-related deaths represent a very small percentage of the deaths happening during the 3-month period, and are unlikely to be under-reported given the Good Clinical Practice oversight of these trials. Progressive cancer is likely to be an important cause of early mortality but given the very select nature of the trial-related population this cannot explain the phenomenon of 3-month early death burden of 23.3%. Our hypothesis, supported by multiple autopsy series, is that early death burden in advanced pancreatic cancer trial patients is likely to be due to under-reported vascular thromboembolic events. Thromboprophylaxis needs to be addressed in future trials.
Yang ZY (1), Yuan JQ, Di MY, Zheng DY, Chen JZ, Ding H, Wu	PLoS One. 2013;8(3):e57528. doi:	PubMed, EMBASE, The Cochrane Library and abstracts of recent major conferences were systematically searched	Sixteen studies containing 1,308 advanced pancreatic cancer patients treated with gemcitabine plus erlotinib were included. The reported	Gemcitabine plus erlotinib represent a new option for the treatment of advanced pancreatic cancer, with mild but clinically meaningful additive efficacy compared with gemcitabine alone. Its safety profile

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
XY, Huang YF, Mao C, Tang JL. Gemcitabine plus erlotinib for advanced pancreatic cancer: a systematic review with meta-analysis.	10.1371/journal.pone.0057528. Epub 2013 Mar 5.	to identify relevant publications. Studies that were conducted in advanced pancreatic cancer patients treated with gemcitabine plus erlotinib (with or without comparison with gemcitabine alone) and reporting objective response rate, disease control rate, progression-free survival, time-to-progression, overall survival, 1-year survival rate and/or adverse events were included. Data on objective response rate, disease control rate, 1-year survival rate and adverse events rate, respectively, were combined mainly by using Meta-Analyst software with a random-effects model. Data on progression-free survival, time-to-progression and overall	median progression-free survival (or time-to-progression), median overall survival, 1-year survival rates, objective response rates and disease control rates were 2-9.6 months, 5-12.5 months, 20%-51%, 0%-28.6% and 25.0%-83.3%, respectively. The weighted 1-year survival rate, objective response rate and disease control rate based on studies reporting robust results were 27.9%, 9.1% and 57.0%, respectively. According to the studies with relevant data, the incidences of total and severe adverse events were 96.3% and 62.9%, respectively. The most frequently reported adverse events were leucopenia, rash, diarrhea, vomiting, neutropenia, thrombocytopenia, anaemia, stomatitis, drug-induced liver injury, fatigue and fever. Compared with gemcitabine alone, the progression-free survival and overall survival with gemcitabine plus	is generally acceptable, although careful management is needed for some specific adverse events.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
		survival were summarized descriptively.	erlotinib were significantly longer, but there were also more deaths and interstitial lung disease-like syndrome related to this treatment.	
Li Y (1), Sun J, Jiang Z, Zhang L, Liu G. Gemcitabine and S-1 combination (GS) chemotherapy versus gemcitabine (GEM) alone for locally advanced and metastatic pancreatic cancer: a meta-analysis of randomized controlled trials in Asia.	J Chemother. 2015 Aug;27(4):227-34.	Relevant trials were identified by searching databases. Five trials were selected in this article. The indicators we used were overall response rate, disease control rate, 1-year survival rate and haematological toxicities.	Meta-analysis of the pooled data demonstrated that the overall response rate (risk ratio, RR = 2.52, 95% confidence interval, CI: 1.85-3.42, P < 0.00001) and disease control rate (RR = 1.24, 95% CI: 1.12-1.37, P < 0.0001) were significantly different for the GS and GEM alone chemotherapies. Among the group of patients, 43.4% in the GS group and 31.4% in the GEM group survived more than a year. According to this, patients who use the GS regiment may have a better prognosis than the GEM regiment (RR = 1.62, 95% CI: 1.12-2.33, P = 0.04). The combination chemotherapy with GEM and S-1 group had higher haematological toxicities including neutropaenia (RR = 1.58, 95% CI: 1.17-	Overall response rate and disease control rate as well as 1-year survival rate in patients who received GS were superior to those treated with GEM alone. Combination chemotherapy with GEM and S-1 may offer greater benefits in the treatment of pancreatic cancer than GEM alone, although the GS group had higher haematological toxicities. Combination chemotherapy with GEM and S-1 might be an option of first-line chemotherapy for pancreatic cancer patients, at least in Asia. Mini Abstract: This systematic review analysing randomized controlled trials (RCTs) comparing S-1 combination chemotherapy versus GEM alone for locally advanced and metastatic pancreatic cancer demonstrated greater efficacy for S-1 combination in term of response, disease control and 1-year survival proportion.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
			2.14, P = 0.003) and thrombocytopaenia (RR = 1.85, 95% CI: 1.28-2.67, P = 0.001). The incidence of anaemia was much the same in the two groups (RR = 1.22, 95% CI: 0.87-1.70, P = 0.24).	
Sultana A(1), Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer.	J Clin Oncol. 2007 Jun 20;25(18) :2607-15.	There are a large number of randomized controlled trials involving chemotherapy in the management of advanced pancreatic cancer. Several chemotherapeutic agents, either alone or in combination with other chemotherapy or novel agents, have been used. The aim of these meta-analyses was to examine the different therapeutic approaches, and the comparisons examined were as follows: chemotherapy versus best supportive care; fluorouracil (FU) versus FU combination	One hundred thirteen randomized controlled trials were identified, of which 51 trials involving 9,970 patients met the inclusion criteria. Chemotherapy improved survival compared with best supportive care (hazard ratio [HR] = 0.64; 95% CI, 0.42 to 0.98). FU-based combination chemotherapy did not result in better overall survival compared with FU alone (HR = 0.94; 95% CI, 0.82 to 1.08). There was insufficient evidence of a survival difference between gemcitabine and FU, but the wide CI includes clinically important differences in both directions, making a clear conclusion difficult (HR = 0.75; 95% CI, 0.42 to 1.31).	There was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone. This supports the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
		chemotherapy; gemcitabine versus FU; and gemcitabine versus gemcitabine combination chemotherapy. Relevant trials were identified by searching databases, trial registers, and conference proceedings. The primary end point was overall survival.	Survival was improved after gemcitabine combination chemotherapy compared with gemcitabine alone (HR = 0.91; 95% CI, 0.85 to 0.97).	
Ying JE(1), Zhu LM, Liu BX. Developments in metastatic pancreatic cancer: is gemcitabine still the standard?	World J Gastroenterol. 2012 Feb 28;18(8): 736-45.	In the past 15 years, we have seen few therapeutic advances for patients with pancreatic cancer, which is the fourth leading cause of cancer-related death in the United States.	Currently, only about 6% of patients with advanced disease respond to standard gemcitabine therapy, and median survival is only about 6 months. Moreover, phase III trials have shown that adding various cytotoxic and targeted chemotherapeutic agents to gemcitabine has failed to improve overall survival, except in cases in which gemcitabine combined with erlotinib show minimal survival benefit. Several meta-analyses have shown that the combination of	Strikingly, a phase III trial in 2010 showed that, in comparison to gemcitabine alone, the FOLFIRINOX regimen in patients with advanced disease and good performance status, produced better median overall survival, median progression-free survival, and objective response rates. This regimen also resulted in greater, albeit manageable toxicity.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
			gemcitabine with either a platinum analog or capecitabine may lead to clinically relevant survival prolongation, especially for patients with good performance status. Meanwhile, many studies have focused on the pharmacokinetic modulation of gemcitabine by fixed-dose administration, and metabolic or transport enzymes related to the response and toxicity of gemcitabine.	
Banu E(1), Banu A, Fodor A, Landi B, Rougier P, Chatellier G, Andrieu JM, Oudard S. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients	Drugs Aging. 2007;24(10):865-79.	We conducted a systematic review and meta-analysis of published data on the use of gemcitabine-based doublets compared with gemcitabine alone in chemotherapy-naive patients with advanced and metastatic pancreatic cancer treated in randomised controlled phase II-III trials with overall survival as the principal	Gemcitabine-based doublets were associated with small but significant reductions in the risk of death at 6, 12 and 18 months of 8% (95% CI 3, 13), 4% (95% CI 2, 7) and 3% (95% CI 1, 5), respectively ($p<0.005$ for all timepoints). No heterogeneity between studies was observed. Subgroup analyses showed an overall survival benefit for gemcitabine-based doublets in clinical trials testing the same planned dose intensity of gemcitabine in comparative	This meta-analysis of data obtained from randomised controlled phase II-III trials of patients with advanced pancreatic cancer showed a small but significant improvement in overall survival for patients receiving gemcitabine-based doublets compared with gemcitabine alone.

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
with advanced and metastatic pancreatic cancer.		or secondary endpoint. To this end, a literature search was performed using Cochrane methodology. The relative risks with 95% confidence intervals were estimated based on adjusted number of deaths and patients at risk according to the extent of follow-up and censoring. Twenty-three randomised clinical trials including 5886 patients met the inclusion criteria. In these trials, 2932 patients were randomly assigned to receive gemcitabine-based doublets and 2954 patients to receive gemcitabine alone.	arms, using platinum salt-based protocols and with survival as the primary endpoint.	
Zagouri F(1), Sergentanis TN, Chrysikos D, Zografos CG, Papadimitriou CA, Dimopoulos	Pancreas. 2013 Jul;42(5): 760-73.	This is the first systematic review of the literature to synthesize all available data coming from trials and evaluate the efficacy and safety of	The search strategy retrieved 439 articles. Of these articles, 237 were irrelevant, 113 were reviews, and 21 were case reports. After searching the references of all reviews and remaining articles, 29	Regarding the evaluation of molecular targeted therapies in pancreatic cancer, it should be stressed that although multiple agents have been tested, only 9 phase 3 trials have been conducted and one agent (erlotinib) has been approved by FDA for use in clinical practice. Nevertheless,

Author/Title	Journal	Patient and Study Characteristics	Results	Conclusion
MA, Filipits M, Bartsch R. Molecularly targeted therapies in metastatic pancreatic cancer: a systematic review.		molecular targeted drugs in unresectable and metastatic pancreatic cancer.	conference abstracts and 15 PubMed articles were also included. Overall, 112 studies were eligible for the systematic review.	erlotinib has exhibited modest results, as the gain in survival was only 0.4 months. However, molecularly targeted agents seem to mark the beginning of a new era in the context of unresectable and metastatic pancreatic cancer. It would be tempting to hypothesize an analogy in developments after the introduction of imatinib for the treatment of gastrointestinal stromal tumors. In any event, as molecular profiling surpasses the borders of morphological classifications, direct consequent molecularly targeted therapy may well contribute to the individualization of treatment in the challenging group of patients with metastatic/unresectable pancreatic cancer. It is thus anticipated that better selection of patients at the individual level will contribute to sizably better performance of the newly developed and explored molecularly targeted agents. Of great importance seems to be IGF1R monoclonal antibody inhibitors, which have entered phase 3 trials.

Data Supplement 3: Literature Search Strategy for Pancreatic Cancer (Potentially Curable, Locally Advanced, Unresectable and Metastatic) and Health Disparities for Pancreatic Cancer

Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature published from January 2000 to June 2015 combined pancreatic neoplasm terms and follow-up-related terms and MeSH headings. Results of the databases searches were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles, and contributions from Expert Panel members' personal files.

Disease and Treatments

Search: ("carcinoma, pancreas"[MeSH Terms] OR ((cancer[TIAB] OR neoplasm[TIAB] OR neoplasms[TIAB] OR tumor[TIAB] OR tumors[TIAB] OR tumour[TIAB] OR tumours[TIAB] OR malignant[TIAB] OR malignancy[TIAB] OR malignancies[TIAB] OR carcinoma[TIAB] OR carcinomas[TIAB] OR carcinomatosis[TIAB] OR carcinomatoses[TIAB] OR adenocarcinoma[TIAB] OR adenocarcinomas[TIAB] OR oncology[TIAB] AND ("pancreas"[MeSH Terms] OR "pancreatic"[TIAB])) AND "palliative care"[MeSH Terms] AND ("critical illness"[MeSH Terms] OR "home care services"[MeSH Terms] OR "hospitalization"[MeSH Terms] OR "hospices"[MeSH Terms] OR "terminal care"[MeSH Terms] OR "advance care planning"[MeSH Terms] OR "terminally ill"[MeSH Terms] OR "patient care team"[MeSH Terms] OR "quality of life"[MeSH Terms] OR ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms])) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR "randomized controlled trials as topic"[MeSH Terms] OR clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "clinical trials as topic"[MeSH Terms] OR "controlled clinical trials as topic"[MeSH Terms] OR "randomized controlled trials as topic"[MeSH Terms] OR "clinical trials, phase ii as topic"[MeSH Terms] OR "clinical trials, phase iii as topic"[MeSH Terms] OR "clinical trials, phase iv as topic"[MeSH Terms] OR clinical trial, phase II[pt] OR clinical trial, phase III[pt] OR clinical trial, phase IV[pt] OR "random allocation"[MeSH Terms] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR "double-blind method"[MeSH Terms] OR "single-blind method"[MeSH Terms]) OR ((random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab]) AND (clinical[tiab] OR control[tiab] OR controlled[tiab] OR "control groups"[MeSH Terms])) OR ((single[tiab] OR single-[tiab] OR double[tiab] OR double-[tiab] OR triple[tiab] OR triple-[tiab] OR multi[tiab] OR multi-[tiab] OR evaluator[tiab] OR assessor[tiab] OR interviewer[tiab]) AND (mask[tiab] OR masked[tiab] OR masking[tiab] OR blind[tiab] OR blinded[tiab] OR blinding[tiab])) OR (("placebos"[MeSH Terms] OR placebo[tiab] OR placebos[tiab] OR random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomization[tiab]) AND ("research design"[MeSH Terms] OR "comparative study"[tiab] OR comparative study[pt] OR "evaluation studies as topic"[MeSH Terms:noexp] OR evaluation studies[pt] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "validation studies as topic"[MeSH Terms] OR "follow-up studies"[MeSH Terms] OR "follow-up study"[tiab] OR "follow up study"[tiab] OR "follow-up studies"[tiab] OR "follow up studies"[tiab] OR "prospective studies"[MeSH Terms] OR prospective[tiab] OR "epidemiologic research design"[MeSH Terms] OR "epidemiologic

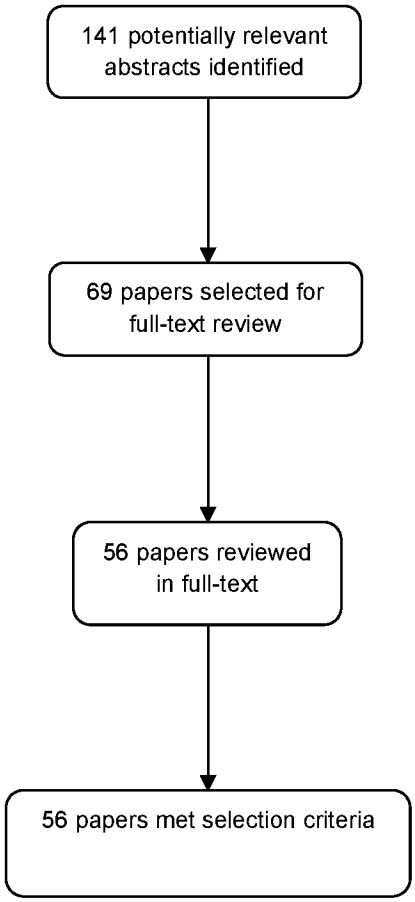
methods"[MeSH Terms] OR "epidemiologic study characteristics as topic"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms] OR "intervention studies"[MeSH Terms] OR "cross-over studies"[MeSH Terms])))) NOT (clinical trial, phase I[pt] OR "clinical trials, phase i as topic"[MeSH Terms]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) NOT review[pt] AND English[la] AND (2002/04/01[PDAT] : 2015/06/01[PDAT])

Health Disparities

(pancreatic cancer treatment) AND (((delivery of health care[MeSH:noexp] OR health behavior[MH] OR health knowledge, attitudes, practice[MH] OR health services accessibility[MH] OR health services, indigenous[MH] OR mass screening[MH] OR mass screening[TIAB] OR mass screenings[TIAB] OR health inequality[TIAB] OR health inequalities[TIAB] OR health inequities[TIAB] OR health inequity[TIAB] OR health services needs and demand[MH] OR patient acceptance of health care[MH] OR patient selection[MH] OR quality of health care[MAJR:noexp] OR quality of life[MH] OR quality of life[TIAB] OR social disparities[TIAB] OR social disparity[TIAB] OR social inequities[TIAB] OR social inequity[TIAB] OR Socioeconomic Factors[MAJR] OR socioeconomic factor[TIAB] OR socioeconomic factors[TIAB]) AND (African American[TIAB] OR African Americans[TIAB] OR African ancestry[TIAB] OR African Continental Ancestry Group[MH] OR AIAN[TIAB] OR American Native Continental Ancestry Group[MH] OR Asian continental ancestry group[MH] OR Asian[TIAB] OR Asians[TIAB] OR black[TIAB] OR blacks[TIAB] OR Caucasian[TIAB] OR Caucasians[TIAB] OR diverse population[TIAB] OR diverse populations[TIAB] OR environmental justice[TIAB] OR ethnic group[TIAB] OR ethnic groups[MH] OR ethnic groups[TIAB] OR ethnic population[TIAB] OR ethnic populations[TIAB] OR ghetto[TIAB] OR ghettos[TIAB] OR Hispanic[TIAB] OR Hispanics[TIAB] OR Indian[TIAB] OR Indians[TIAB] OR Latino[TIAB] OR Latinos[TIAB] OR Latina[TIAB] OR Latinas[TIAB] OR medically underserved area[MH] OR minority group[TIAB] OR minority groups[MH] OR minority groups[TIAB] OR minority population[TIAB] OR minority populations[TIAB] OR Native American[TIAB] OR Native Americans[TIAB] OR Oceanic Ancestry Group[MH] OR pacific islander[TIAB] OR pacific islanders[TIAB] OR people of color[TIAB] OR poverty area[MH] OR poverty area[TIAB] OR poverty areas[TIAB] OR rural health[MH] OR rural health[TIAB] OR rural health services[MH] OR rural population[MH] OR rural population[TIAB] OR rural populations[TIAB] OR slum[TIAB] OR slums[TIAB] OR urban health[MH] OR urban health services[MH] OR urban population[MH] OR urban population[TIAB] OR urban populations[TIAB] OR vulnerable populations[MH] OR vulnerable population[TIAB] OR vulnerable populations[TIAB] OR white[TIAB] OR whites[TIAB]) OR (ethnic disparities[TIAB] OR ethnic disparity[TIAB] OR health care disparities[TIAB] OR health care disparity[TIAB] OR health disparities[TIAB] OR health disparity[TIAB] OR health status disparities[MH] OR healthcare disparities[MH] OR healthcare disparities[TIAB] OR healthcare disparity[TIAB] OR minority health[MH] OR minority health[TIAB] OR racial disparities[TIAB] OR racial disparity[TIAB] OR racial equality[TIAB] OR racial equity[TIAB] OR racial inequities[TIAB] OR racial inequity[TIAB]))

OR sexual orientation[TIAB] OR sexual identity[TIAB] OR institutional racism[TIAB] OR disability[TIAB] OR special health care needs[TIAB] OR health differences[TIAB] OR social disadvantage[TIAB] OR economic disadvantage[TIAB] OR social obstacles to health[TIAB] OR economic obstacles to health[TIAB] OR social hierarchy[TIAB] OR unequal distribution[TIAB] OR ((ethnic*[tw] OR race[tw] OR racial[tw] OR disparity[tw] OR disparities[tw] OR blacks[tw] OR black[tw] OR Hispanic*[tw]) OR (population groups[mh] OR race relations[mh])))

Data Supplement 4: Quorum Diagram



Data Supplement 5: World Health Organization Definition of Palliative Care[1]

The World Health Organization has developed this definition of palliative care:

Palliative care is an approach that improves the quality of life of people with localized pancreatic cancer and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of people with localized pancreatic cancer care;
- offers a support system to help people with localized pancreatic cancer live as actively as possible until death;
- offers a support system to help the family cope during the people with localized pancreatic cancer illness and in their own bereavement;
- uses a team approach to address the needs of people with localized pancreatic cancer and their families, including bereavement counseling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as surgery and chemotherapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Data Supplement 6: Pancreatic Protocol Computerized Tomography (CT) [2,3]

To assess resectability and staging, a pancreatic protocol CT or CT angiography is performed. To perform the CT angiography:

- Bolus administration of iodinated nonionic contrast
- Imaging in arterial and venous phases
- First 30 seconds (arterial phase), maximizes attenuation of celiac axis, superior mesenteric artery, and peripancreatic arteries
- 60 to 70 seconds after start of the contrast injection (portal venous phase) provides enhancement for imaging of superior mesenteric vein, splenic and portal veins
- Portal venous phase also provides enhancement for imaging of pancreas and liver metastases
- 70 to 80 seconds after contrast injection (hepatic phase) provides enhancement for imaging of additional liver metastases

References

1. World Health Organization Definition of Palliative Care: Definition of Palliative Care, http://www.who.int/cancer/palliative/definition/en/, 2015
2. Tummala P, Junaidi O, Agarwal B: Imaging of pancreatic cancer: An overview. J Gastrointest Oncol 2:168-174, 2011
3. Wong JC, Lu DS: Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol 6:1301-1308, 2008

Reply to A. Wang-Gillam et al

Wang-Gillam et al[1] from the NAPOLI-1 Study Group[2] recently commented on our article in *Journal of Clinical Oncology* titled "Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline," (hereafter referred to as the Guideline).[3] We would like to take this opportunity to further clarify the issues raised by the NAPOLI-1 Study Group.

The Guideline was the result of the panel conducting a systematic review of all high-quality clinical trial literature in the field, and was up to date at the time of publication, as highlighted by the inclusion of the NAPOLI-1 results that were, in fact, published during the panel discussion conferences. A critical review of patient populations in each clinical trial was incorporated into the final decisions on the various recommendations.

The NAPOLI-1 Study Group comments highlight a common clinical situation: second-line treatment of patients with metastatic pancreatic cancer. Contemporary first-line regimens include fluorouracil, irinotecan, and oxaliplatin; and gemcitabine with nab-paclitaxel. There are currently no reported clinical trials on second-line therapies for these specific populations. The available data from the NAPOLI-1, CONKO-003, and, since the publication of the Guideline, PANCREOX trials are in patients who received gemcitabine, fluorouracil, or various combinations thereof, because the inception of these trials largely preceded the publication and subsequent widespread acceptance of fluorouracil, irinotecan, and oxaliplatin; and gemcitabine with nab-paclitaxel as frontline regimens. Therefore, data from these studies were extrapolated by the panel to arrive at consensus recommendations for the current therapeutic arena.

The NAPOLI-1 trial included a heterogeneous patient population in terms of prior therapies received: only 13% of patients had received gemcitabine with nab-paclitaxel as first-line therapy. Other patients in that trial had received single-agent gemcitabine, other gemcitabine combinations, and regimens that were based on flurouracil, irinotecan, and platinum (further details are not available via public sources). Therefore, a unanimous, high-quality conclusion cannot be drawn on the use of fluorouracil and nanoliposomal irinotecan in patients whose disease has progressed while receiving gemcitabine with nab-paclitaxel. This led to the panel's informal consensus on the use of fluorouracil and nanoliposomal irinotecan as a moderate-strength recommendation on the basis of low-quality evidence. (Evidence quality denotes the confidence that the available evidence reflects the true magnitude and direction of the net effect, and is a summary conclusion that is based on all aspects of the clinical trial, including applicability to clinical situations. It is not necessarily a judgment on the scientific quality of the study itself.)

We hope that future studies on second-line therapy will enroll patients treated with more contemporary regimens in the first-line setting to provide a better answer to this common clinical scenario. The panel will continue to review upcoming data and update the Guideline as appropriate.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

1. Wang-Gillam A, Von Hoff DD, Sivelis J, et al: Nanoliposomal irinotecan in the Clinical Practice Guideline for metastatic pancreatic cancer: Applicability to clinical situations. J Clin Oncol doi: 10.1200/JCO.2016.70.1607
2. Wang-Gillam A, Li CP, Bodoky G, 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 387:545-557, 2016
3. Sohal DP, Mangu PB, Khorana AA, et al: Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34: 2784-2796, 2016

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Reply to A. Wang-Gillam et al

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Glutamine supports pancreatic cancer growth through a Kras-regulated metabolic pathway

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Abstract

Cancer cells exhibit metabolic dependencies that distinguish them from their normal counterparts[1]. Among these addictions is an increased utilization of the amino acid glutamine (Gln) to fuel anabolic processes[2]. Indeed, the spectrum of Gln-dependent tumors and the mechanisms whereby Gln supports cancer metabolism remain areas of active investigation. Here we report the identification of a non-canonical pathway of Gln utilization in human pancreatic ductal adenocarcinoma (PDAC) cells that is required for tumor growth. While most cells utilize

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J.S., C.A.L., L.C.C., and A.C.K. designed the study, interpreted the data and wrote the manuscript. J.S., C.A.L., H.Y., and X.W. performed the experiments. J.M.A., E.M., and N.S. helped with the metabolomic studies and with S.H., M.C.H and R.A.D. assisted in data interpretation. M.L., R.M.P., C.R.F., Y.K., N.B. and J.B.F. developed essential reagents and resources.

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glutamate dehydrogenase (GLUD1) to convert Gln-derived glutamate (Glu) into α-ketoglutarate in the mitochondria to fuel the tricarboxylic acid (TCA) cycle, PDAC relies on a distinct pathway to fuel the TCA cycle such that Gln-derived aspartate is transported into the cytoplasm where it can be converted into oxaloacetate (OAA) by aspartate transaminase (GOT1). Subsequently, this OAA is converted into malate and then pyruvate, ostensibly increasing the $NADPH/NADP^+$ ratio which can potentially maintain the cellular redox state. Importantly, PDAC cells are strongly dependent on this series of reactions, as Gln deprivation or genetic inhibition of any enzyme in this pathway leads to an increase in reactive oxygen species and a reduction in reduced glutathione. Moreover, knockdown of any component enzyme in this series of reactions also results in a pronounced suppression of PDAC growth in vitro and in vivo. Furthermore, we establish that the reprogramming of Gln metabolism is mediated by oncogenic Kras, the signature genetic alteration in PDAC, via the transcriptional upregulation and repression of key metabolic enzymes in this pathway. The essentiality of this pathway in PDAC and the fact that it is dispensable in normal cells may provide novel therapeutic approaches to treat these refractory tumors.

The prognosis of patients with PDAC remains dismal. The disease is extremely aggressive and is profoundly resistant to all forms of therapy[3]. Thus, there is a strong impetus to identify new therapeutic targets for this cancer. In recent years, there has been renewed interest in understanding the altered metabolism in cancer, and how such dependencies can be targeted for therapeutic gain. However, achieving a successful therapeutic index remains a major challenge to the development of effective cancer therapies that target metabolic pathways.

Recent evidence demonstrates that some cancer cells utilize glutamine (Gln) to support anabolic processes that fuel proliferation[2]. However, the importance of Gln metabolism in pancreatic tumor maintenance is not known. Thus, we sought to explore the dependence of PDAC on Gln, and to examine the functional role of Gln in PDAC metabolism. As expected from our previous work[4], glucose was required for PDAC growth. Additionally, PDAC cells were also profoundly sensitive to Gln deprivation, indicating that Gln is also critical for PDAC growth (Fig. 1a and Supplementary Fig. 1).

Gln provides a carbon source to fuel the TCA cycle and nitrogen for nucleotide, nonessential amino acid (NEAA) and hexosamine biosynthesis[5,6]. To assess the role of Gln metabolism in PDAC growth, we first impaired glutaminase (GLS) activity using RNA interference (RNAi). Notably, GLS knockdown markedly reduced PDAC growth (Fig. 1b and Supplementary Fig. 2a, b). Consistent with this observation, Glutamate (Glu) was able to support growth in Gln-free conditions (Supplementary Fig. 2c).

Glu can be converted into α-ketoglutarate (αKG) to replenish the TCA cycle metabolites through two mechanisms[1]; either by glutamate dehydrogenase (GLUD1) or transaminases (Fig. 1c). Indeed, many cancer cells rely on GLUD1-mediated Glu deamination to fuel the TCA cycle[7], and αKG has been shown to be an essential metabolite in Gln metabolism[8]. Surprisingly, dimethyl αKG[9] did not restore growth upon Gln deprivation (Fig. 1d), whereas the combination of αKG and an NEAA mixture (the output of transaminase-mediated Glu metabolism) dramatically rescued proliferation in multiple PDAC lines (Fig. 1d and Supplementary Fig. 2d, e). Together, this data suggests that PDAC cells metabolize Gln in a

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manner that is different from canonical models[10] and that this class of enzymes may be critical for Gln metabolism in PDAC.

To confirm the importance of transaminases in PDAC Gln metabolism, we treated PDAC cells with either aminooxyacetate (AOA), a pan-inhibitor of transaminases[11], or epigallocatechin gallate (EGCG), an inhibitor of GLUD1[12]. While EGCG had no effect on PDAC growth, AOA treatment robustly inhibited the growth of multiple PDAC cell lines (Supplementary Fig. 3). Consistent with these results, GLUD1 knockdown also had no effect on PDAC growth (Fig. 2a). To identify the specific transaminase(s) involved in PDAC Gln metabolism, we inhibited a panel of Glu-dependent transaminases (aspartate, alanine and phosphoserine transaminase) individually using RNAi and examined the effect on PDAC growth. Interestingly, knockdown of the aspartate transaminase GOT1 significantly impaired PDAC growth in multiple PDAC cell lines and primary PDAC cells (Fig. 2a and Supplementary Fig. 4, 5).

We next explored the direct effects of GOT1 on Gln metabolism by performing targeted metabolomic analysis in GOT1 knockdown PDAC cells using uniformly ^{13}C-labeled Gln ([U-$^{13}C_5$]-Gln) as a tracer[4,13]. GOT1 catalyzes the conversion of aspartate (Asp) and αKG into OAA and Glu in the cytoplasm. Indeed, GOT1 knockdown led to increased Gln-derived Asp (and total Asp) and decreased OAA (Fig. 2b and Supplementary Fig. 6a). Interestingly, we also observed a significant decrease in the ratio of reduced-to-oxidized glutathione (GSH:GSSG; Fig. 2b and Supplementary Fig. 6b), suggesting that GOT1 may play a role in the maintenance of cellular redox homeostasis. It should be noted that the changes in metabolite abundance described in this experiment are representative of the total cellular metabolite pool, due to technical limitations associated with organelle-specific metabolite isolation. Importantly however, the results we obtained are consistent with what one would expect if flux through GOT1 was impaired.

In PDAC, we recently demonstrated that oncogenic Kras enhances the flux of glycolytic intermediates specifically through the non-oxidative arm of the pentose phosphate pathway (PPP) (for DNA/RNA biosynthesis) without effecting the NADPH-producing oxidative arm[4]. This decoupling of ribose biogenesis from NADPH production by Kras suggests that PDAC cells may rely on an alternative mechanism to maintain cellular redox balance. Indeed, inhibition of the oxidative PPP in PDAC by knockdown of the rate limiting enzyme G6PD had minimal effect on reactive oxygen species (ROS) levels, and, consistent with this, glucose deprivation had only a modest impact on ROS (Supplementary Fig. 6c). Therefore, we speculated that the GOT1-mediated conversion of Gln-derived Asp into OAA functions in a pathway that is used to generate the NADPH which could be used to maintain redox balance. To test this hypothesis, we assessed ROS levels upon Gln deprivation in the absence or presence of OAA. Indeed, Gln deprivation induced ROS and OAA could partially rescue the elevated ROS levels (Fig. 2c). GOT1 knockdown also increased ROS levels, which again were significantly restored upon supplementation with OAA (Fig. 2d).

Given that Gln-derived malate (and total malate) was significantly reduced upon GOT1 knockdown (Fig. 2b), we suspected that Gln-derived OAA is metabolized into malate, which is utilized by malic enzyme (ME1) to create NADPH, providing the reducing power to

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maintain reduced glutathione pools[14]. Indeed, malate was able to partially rescue the oxidative stress imposed by Gln-deprivation (Fig. 2e) or GOT1 knockdown (Fig. 2f). These data are consistent with a model whereby Gln-derived Asp is converted by GOT1 into OAA, then converted into malate by malate dehydrogenase (MDH1) and subsequently oxidized by ME1 into pyruvate and reducing power in the form of NADPH (Fig. 2g). Consistent with this pathway, metabolomic analysis of [U-$^{13}C_5$]-Gln tracing in ME1 knockdown cells revealed a significant increase in Asp, malate and OAA and decreased GSH (Fig. 2h and Supplementary Fig. 6d). Furthermore, knockdown of GOT1 and ME1 markedly increased the cellular $NADP^+$/NADPH ratio (Fig. 2i), whereas inhibition of other cytosolic sources of NADPH (G6PD or isocitrate dehydrogenase, IDH1) had no effect on $NADP^+$/NADPH ratios or ROS (Fig. 2i and Supplementary Fig. 6e). Together the data suggest that PDAC utilize Gln through the pathway depicted in Fig. 2g to increase the NADPH/$NADP^+$ ratio for maintenance of redox homeostasis. Lastly, Gln tracing kinetic flux experiments in GOT1 knockdown cells clearly demonstrate decreased flux through this pathway (Fig. 2j and Supplementary Fig. 7). Interestingly, lactate labeling in the ^{13}C-labeling experiments was typically at very low levels, indicating that the pyruvate produced by ME1 is not utilized to make lactate by lactate dehydrogenase and has a yet undetermined fate.

The majority of Asp in PDAC cells (50–75%) is derived from Gln, as evidenced by ^{13}C-labeling (Supplementary Fig. 6a, d and 8a). In principle, uniformly ^{13}C-labeled Asp can be derived from Gln following either (i) the GLUD1-mediated conversion of Glu to αKG (and its subsequent traversing through the TCA cycle) or (ii) the mitochondrial aspartate transaminase (GOT2)-mediated conversion of Glu and OAA to αKG and Asp. Of these two enzymes, only GOT2 knockdown significantly impacted PDAC growth (Fig. 2a and Supplementary Fig. 8b). Consistent with this observation, GLUD1 knockdown did not affect Asp biosynthesis from Gln, whereas GOT2 knockdown resulted in a significant decrease in Gln-derived Asp in PDAC cells (Supplementary Fig. 8a, c).

We next tested whether other components of this pathway are also necessary to support PDAC growth. Indeed, knockdown of either MDH1 or ME1 also dramatically inhibited clonogenic survival of PDAC cells (Fig. 3a, b and Supplementary Fig. 9) in a manner similar to GOT1 knockdown. As a further test of enzyme knockdown specificity, we investigated the ability of central metabolites in this pathway to rescue PDAC growth upon Gln deprivation. First, we confirmed that exogenously added metabolites permeated the cell and populated metabolite pools (Supplementary Fig. 10). Next, we demonstrated that the combination of GOT1 substrates, Asp and αKG, could rescue cell growth in Gln-free conditions (Supplementary Fig. 11a). Additionally, OAA permitted PDAC growth under Gln-free conditions in multiple PDAC cell lines (Fig. 3c and Supplementary Fig. 11a–d) as well as upon both GLS (Supplementary Fig. 12a) and GOT1 knockdown (Fig. 3d and Supplementary Fig. 13a, b). Lastly, the addition of dimethyl-malate[15] was able to partially rescue PDAC cell growth upon Gln deprivation (Supplementary Fig. 13c) or GOT1 knockdown (Supplementary Fig. 13d).

Next, to confirm that the OAA- or malate rescue of PDAC growth upon Gln deprivation was through maintenance of redox homeostasis, we treated cells grown in Gln-free conditions with a cell permeable GSH analog. Remarkably, GSH dramatically rescued clonogenic

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growth following Gln-deprivation (Fig. 3e and Supplementary Fig. 11c) or GOT1 knockdown (Fig. 3d and Supplementary Fig. 13a, b). GSH was also able to rescue either MDH1 or ME1 knockdown (Supplementary Fig. 14a). Near identical results were also seen with the antioxidant N-acetylcysteine (NAC) (Fig. 3e and f and Supplementary Fig. 14b, c). Together, these data support the idea that Gln is utilized by PDAC cells to maintain redox homeostasis, which is required to support continued tumor growth.

As further confirmation of the importance of this pathway in PDAC, we suppressed GOT1, MDH1, and ME1 expression using two lentiviral shRNAs in PDAC cells and assessed their ability to grow as xenografts. Consistent with our in vitro results, both GLUD1 shRNAs had no effect on tumor growth (Supplementary Fig. 15). In contrast, GOT1, MDH1, and ME1 knockdown each robustly diminished tumor growth (Fig. 3g). These data provide further support for the critical role of this pathway in Gln metabolism and PDAC tumor growth.

In contrast to PDAC, this pathway appears to be dispensable in normal cells. Indeed, treatment of non-transformed human pancreatic ductal cells (HPDE) and human diploid fibroblasts (IMR90) with AOA had only modest effects on growth (Supplementary Fig. 16a). HPDE cells, unlike PDAC cells, were significantly sensitive to EGCG, suggesting a greater reliance on the activity of GLUD1 (Supplementary Fig. 16b). Consistent with these results, GOT1 knockdown did not impair the growth of HPDE and IMR90 (Supplementary Fig. 16c). We also obtained similar results in mouse ductal epithelial cells (mPDE) and mouse PDAC cell lines, with the mPDEs being highly insensitive to AOA and GOT1 knockdown and two independently derived mouse PDAC lines exhibiting significant sensitivity to AOA and GOT1 knockdown (Supplementary Fig. 16d, e). Furthermore, using an inducible shGOT1 construct, we demonstrated that mouse PDAC rely on GOT1 to sustain tumor growth in vivo (Supplementary Fig. 17). Collectively, these data demonstrate that the GOT1-mediated utilization of the Gln carbon skeleton is a metabolic adaptation that PDAC, and not normal cells, have uniquely acquired to support growth.

Our previous work demonstrated that anabolic glucose metabolism in PDAC is controlled by oncogenic Kras, which leads to altered expression of a number of rate-limiting metabolic enzymes[4]. To investigate the role of Kras in the reprogramming of Gln metabolism, we assessed the expression of GOT1 and GLUD1 upon knockdown of Kras in PDAC cells. Interestingly, Kras knockdown resulted in a marked increase in GLUD1 and a decrease in GOT1 expression at the transcriptional level (Fig. 4a), as well as the protein level (Fig. 4b) in multiple PDAC lines (Supplementary Fig. 18a). Additionally, using five independent orthotopic tumors derived from our inducible Kras PDAC model[4], we show that expression of GOT1 increased and GLUD1 decreased in an oncogenic Kras-dependent manner in vivo (Supplementary Fig. 18b). These findings demonstrate that, in PDAC, oncogenic Kras plays a critical role in coordinating the shift in Gln metabolism to maintain tumor growth and survival.

We next assessed the sensitivity of PDAC cells to either AOA or EGCG upon Kras knockdown using 8988T cells, a cell line that is not dependent on Kras for survival[16]. Consistent with our previous results, AOA significantly inhibited clonogenic growth, whereas EGCG had minimal effects. Interestingly, Kras knockdown made the cells

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significantly more resistant to AOA and sensitive to EGCG (Fig. 4c and Supplementary Fig. 18c). To confirm the role of oncogenic Kras in the reprogramming of Gln metabolism, a targeted metabolomic analysis using [U-$^{13}C_5$]-Gln was performed upon Kras knockdown. Indeed, the changes observed were consistent with Kras-supporting the anabolic metabolism of Gln, where multiple metabolites in the GOT1-dependent pathway were significantly deregulated (Fig. 4d and Supplementary Fig. 19).

Given the importance of Gln metabolism in maintaining the redox state of PDAC, we speculated that inhibition of anabolic Gln metabolism may sensitize PDAC to oxidative stress. To test this concept, we inhibited Gln metabolism in PDAC cells using a GLS inhibitor and examined whether this would synergize with hydrogen peroxide (H_2O_2) treatment. Indeed, two chemically distinct GLS inhibitors[8,17] had a growth suppressive effect on both human and mouse PDAC cells (Supplementary Fig. 20a, b), consistent with the GLS knockdown data (Fig. 1b). Furthermore, when combined with H_2O_2, this effect was dramatically augmented, indicating that PDAC cells are markedly more sensitive to ROS when Gln metabolism is impaired (Fig. 4e and Supplementary Fig. 20c). This finding may have significant therapeutic implications, given that clinical grade GLS inhibitors are being developed[18] and that standard PDAC therapies (such as radiation) lead to the generation of ROS. Moreover, since this aspect of Gln metabolism does not appear as critical in normal cells, these data suggest an accessible therapeutic window.

Collectively, our data reveal a novel dependence on the transaminases GOT2 and GOT1 for metabolism of the Gln carbon skeleton in PDAC. These reactions lead to the cytosolic conversion of Asp into OAA, malate and then pyruvate and are required sustain PDAC growth, likely through maintaining redox balance. Importantly, our work also demonstrates that oncogenic Kras mediates this reprogramming of Gln metabolism (Fig. 4f). While this pathway is critical for redox balance and cell growth in PDAC, it does not preclude the involvement of other pathways that may contribute to redox balance such as glutathione synthesis[9,19,20] or an NRF2-dependent mechanism[21]. Furthermore, there may be cell-type specific differences, as Kras-transformed fibroblasts require both GLUD1 and transaminases for cell growth[22]. Lastly, these findings may have implications for future therapeutic approaches as inhibition of Gln metabolism in PDAC can potentially synergize with therapies that increase intracellular ROS such as chemotherapy and radiation.

Methods Summary

Proliferation and clonogenic assays were performed as previously described[23]. To characterize Gln metabolism, targeted liquid chromatography-tandem mass spectrometry was performed[4]. Briefly, cells were grown in complete media and transferred into Gln-free media supplemented with [U-$^{13}C_5$]-Gln overnight (steady state) or for the indicated timepoints (flux analyses). For subcutaneous xenografts, PDAC cells infected with lentivrial shRNAs to suppress target gene expression were suspended in 100 μl HBSS and injected subcutaneously into the lower flank of NCr nude mice. For mouse xenografts, murine PDAC cells stably infected with a doxycycline-inducible GOT1 shRNA construct were injected. Animals were fed with doxycycline water starting on the day of injection or when tumor

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volume reached ~50mm^3. Complete images of western blots are presented in Supplementary Fig. 21.

Methods

Cell culture

Cell lines were obtained from the American Type Culture Collection or the German Collection of Microorganisms and Cell Cultures. All cell lines were tested routinely, and prior to all metabolomic analyses, for mycoplasma contamination. RPMI-1640, fetal bovine serum and dialyzed fetal bovine serum (dFBS) were purchased from Invitrogen. Glucose free DMEM (containing 2 mM Gln), dimethyl αKG, Asp, GSH reduced ethyl ester, OAA, dimethyl malate and DMEM power (without glucose and Gln) were obtained from Sigma, and Gln-free RPMI 1640 was purchased from Cellgro. Cosmic calf serum (CCS) was obtained from Thermo Scientific. Cells were cultured in the following media: 8988T, Panc1, MPanc96, Miapaca2 and PL45 in DMEM supplemented with 10 mM glucose and 10% CCS; 8902 in RPMI with 10% CCS; IMR90 in MEM with 10% FBS; HPDE cells were cultured as described previously[24]. Primary human PDAC lines were generated from ascites fluid under IRB approved protocols 02--240 and 2007P001918. Lines were sequenced and confirmed to have Kras mutations.

Cell proliferation assay

Cells were plated in 24-well plates at 2,000 cells per well in 0.5 mL of media. To deprive Gln, cells were plated in complete culture media (10mM glucose and 2mM Gln) which was exchanged with Gln-free medium supplemented with 10% dFBS the following day. Media was not changed throughout the course of the experiment. At the indicated time points, cells were fixed in 10% formalin and stained with 0.1% crystal violet. Dye was extracted with 10% acetic acid and the relative proliferation was determined by OD at 595 nm.

Clonogenic assay

Cells were plated in 6-well plates at 300 cells per well in 2 mL of media. Media was not changed throughout the course of the experiment. After 7--10 days, colonies were fixed in 80% methanol and stained with 0.2% crystal violet.

Quantitative RT-PCR

Total RNA was extracted using TRIzol (Invitrogen) and reverse transcription was performed from 2 μg of total RNA using oligo-dT and MMLV HP reverse transcriptase (Epicentre), according to the manufacturer's instructions. Quantitative RT-PCR was performed with SYBR Green dye using an Mx3000PTM (Stratagene). PCR reactions were performed in triplicate and the relative amount of cDNA was calculated by the comparative CT method using the 18S ribosomal RNA sequences as a control. Primer sequences available upon request.

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Xenograft studies

For subcutaneous xenografts, 8988T cells were infected with lentiviral shRNAs targeting GLUD1 (n=2), GOT1 (n=2), MDH1 (n=2), ME1 (n=2) and GFP (control hairpin, n=1) and subjected to a short puromycin selection (2 μg/mL). shRNA sequences below. 1.5×10^6 cells, suspended in 100 μL Hanks Buffered Saline Solution (HBSS), were injected subcutaneously into the lower flank of NCr nude mice (Taconic). Tumor length and width were measured twice weekly and the volume was calculated according to the formula (length × width^2)/2. All xenograft experiments with human PDAC lines were approved by the HMS Institutional Animal Care and Use Committee (IACUC) under protocol number 04–605. For mouse xenografts, a doxycycline-inducible GOT1 shRNA construct was first generated. For generation of the construct, oligonucleotides to mouse GOT1 shRNA (forward : CCGGCCACATGAGAAGACGTTTCTTCTCGAGAAGAAACGTCTTCTCATGTGGTTTTTG; reverse : AATTCAAAAACCACATGAGAAGACGTTTCTTCTCGAGAAGAAACGTCTTCTCATGTGG) were digested to generate sticky ends (*AgeI* and *EcoRI*) and immediately subcloned into the *AgeI*-*EcoRI* sites of the pLKO-Tet-on vector. For subcutaneous xenograft, 10^6 stably infected murine PDAC cells were suspended in 100 μl Hanks Buffered Saline Solution and injected subcutaneously into the lower flank of NCr nude mice (Taconic). Animals were fed with doxycycline water (doxycycline 2g/L, sucrose 20g/L) starting on the day of injection or when tumor diameter reached 50mm. Tumor volumes were measured every third day starting from day 4 post-injection and calculated as above. These xenograft experiments were approved under MDACC IACUC protocol 11111393I.

Western blot analysis

After SDS-PAGE, proteins were transferred to Hybond-N Nitrocellulose (Amersham Biosciences). Membranes were blocked in Tris-buffered saline (TBS) containing 5% non-fat dry milk and 0.1% Tween 20 (TBS-T), prior to incubation with the primary antibody overnight at 4°. The membranes were then washed with TBS-T followed by exposure to the appropriate horseradish peroxidase-conjugated secondary antibody for 1h and visualized on Kodak X-ray film using the enhanced chemiluminescence (ECL) detection system (Thermo Scientific). The following antibodies were used: Kras (F234, Santa Cruz), GOT1 (NBP1-54778, Novus), GLUD1 (ab55061, Abcam) and β-Actin (A2066, Sigma).

ROS Quantification

DCFDA assay was performed 24hr after supplementing Gln-free media with either OAA (4mM) or dimethyl malate (4mM). Cells were incubated with 5μM 2',7'-dichlorodihydrofluorescein diacetate (DCFDA, Invitrogen) for 30 min. Excess DCFDA was removed by washing the cells twice with PBS, and labeled cells were then trypsinized, rinsed, and resuspended in PBS. Oxidation of DCFDA to the highly fluorescent 2',7'-dichloro-fluorescein (DCF) is proportionate to ROS generation and was analyzed by flow cytometry.

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Metabolomics

For steady state metabolomic analysis, PDAC cell lines were grown to ~50% confluence in growth media (DMEM, 2 mM Gln, 10 mM glucose, 10% CCS) on 10 cm dishes in biological quadruplicate. A complete media change was performed two hours prior to metabolite collection. To trace Gln metabolism, PDAC cell lines were grown as above and then transferred into Gln-free DMEM (with 10 mM glucose) containing 10% dialyzed FBS and 2 mM [U-$^{13}C_5$]-Gln (Cambridge Isotope Labs) overnight (for steady state labeling) or for the indicated timepoints in the flux analyses. Additionally, fresh media containing [U-$^{13}C_5$]-Gln was exchanged 2 hr prior to metabolite extraction for steady state analyses. The quantity of the metabolite fraction analyzed was adjusted to the corresponding protein concentration calculated upon processing a parallel 10cm dish. Metabolite fractions were collected and analyzed by targeted LC-MS/MS via selected reaction monitoring (SRM), as described[5,14]. Processed data was analyzed in Cluster 3.0 and TreeViewer.

Measurement of Sensitization of PDAC cells to ROS

PDAC cell lines were plated into 96-well plates at 10^3 cells/well in 200 μL of growth media. The following day, growth media was replaced with that containing GLS inhibitors and/or H_2O_2. Parallel plates were analyzed at 3, 6 and 9 days by Cell Titer Glo analysis (Promega), per the manufacturer's instruction. The GLS inhibitors 968 (active) and 365 (structurally similar, inactive) were provided as a kind gift from the Cerione laboratory[9]. BPTES was a kind gift from Jaime Escobedo (Forma Therapeutics).

Lentiviral-mediated shRNA Targets

All shRNA vectors were obtained from the RNA Interference Screening Facility of Dana Farber Cancer Institute. The sequences and RNAi Consortium clone IDs for each shRNA are as follows. shGLS-1 : GCACAGACATGGTTGGTATAT (TRCN0000051135), shGLS-2 : GCCCTGAAGCAGTTCGAAATA (TRCN0000051136), shMDH1-1 : CCCTGTTGTAATCAAGAATAA (TRCN0000221892), shMDH1-2 : GCAACAGATAAAGAAGACGTT (TRCN0000221893), shME1-1 : GCCTTCAATGAACGGCCTATT (TRCN0000064728), shME1-2 : CCAACAATATAGTTTGGTGTT (TRCN0000064729), shGLUD1-1, CCCAAGAACTATACTGATAAT (TRCN0000220878), shGLUD1-2 : GCAGAGTTCCAAGACAGGATA (TRCN0000220880), shGOT1-1 : GCGTTGGTACAATGGAACAAA (TRCN0000034784), shGOT1-2 : GCTAATGACAATAGCCTAAAT (TRCN0000034785), shGPT2-1 : CGGCATTTCTACGATCCTGAA (TRCN0000035024), shGPT2-2 : CCATCAAATGGCTCCAGACAT (TRCN0000035025), shPSAT1-1 : GCCAAGAAGTTTGGGACTATA (TRCN0000035264), shPSAT1-2 : CCAGACAACTATAAGGTGATT (TRCN0000035265), shKras-1 : CCTCGTTTCTACACAGAGAAA (TRCN0000040148), shKras-2 : GAGGGCTTTCTTTGTGTATTT (TRCN0000033260).

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Regents

$NADP^+$/NADPH ratios were determined using the NADP/NADPH assay kit (Abcam; ab65349) according to the manufacturer's instructions. Briefly, 10^5 cells (n=6 wells of a 6-well dish) were collected on ice in extraction buffer and subject to two rounds of freeze-thaw at −80°C. NADP+ and NADPH values were determined in biological sextuplet and concentration was obtained by comparison to standard curves. OAA was not analyzed by targeted LC/MS-MS due to its limited stability in aqueous solvents at room temperature[25]. As such, the abundance of this metabolite was determined using a quantification kit (Biovision), according the manufacturer's instruction. Briefly, 2×10^6 cells (n=4 10cm dishes) were collected during log-phase growth by trypsinization, re-suspended immediately in the buffers provided (on ice), analyzed and compared to standard curves. The signals obtained were normalized to the protein concentration calculated upon processing a parallel 10cm dish. NEAA mixture consisted of a mixture of 0.1 mM glycine, alanine, aspartate, asparagine, proline and serine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. Cancer Cell. 2012; 21:297–308. [PubMed: 22439925]
2. Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. Trends Biochem Sci. 2010; 35:427–433. [PubMed: 20570523]
3. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010; 362:1605–1617. [PubMed: 20427809]
4. Ying H, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell. 2012; 149:656–670. [PubMed: 22541435]
5. Dang CV. Links between metabolism and cancer. Genes Dev. 2012; 26:877–890. [PubMed: 22549953]
6. DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene. 2010; 29:313–324. [PubMed: 19881548]
7. Shanware NP, Mullen AR, DeBerardinis RJ, Abraham RT. Glutamine: pleiotropic roles in tumor growth and stress resistance. J Mol Med (Berl). 2011; 89:229–236. [PubMed: 21301794]
8. Wang JB, et al. Targeting mitochondrial glutaminase activity inhibits oncogenic transformation. Cancer Cell. 2010; 18:207–219. [PubMed: 20832749]
9. Weinberg F, et al. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proc Natl Acad Sci U S A. 2010; 107:8788–8793. [PubMed: 20421486]

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10. Jones RG, Thompson CB. Tumor suppressors and cell metabolism: a recipe for cancer growth. Genes Dev. 2009; 23:537–548. [PubMed: 19270154]

11. Wise DR, et al. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci U S A. 2008; 105:18782–18787. [PubMed: 19033189]

12. Choo AY, et al. Glucose addiction of TSC null cells is caused by failed mTORC1-dependent balancing of metabolic demand with supply. Mol Cell. 2010; 38:487–499. [PubMed: 20513425]

13. Yuan M, Breitkopf SB, Yang X, Asara JM. A positive/negative ion-switching, targeted mass spectrometry-based metabolomics platform for bodily fluids, cells, and fresh and fixed tissue. Nat Protoc. 2012; 7:872–881. [PubMed: 22498707]

14. Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. Nat Rev Cancer. 2011; 11:85–95. [PubMed: 21258394]

15. Huypens P, et al. The dicarboxylate carrier plays a role in mitochondrial malate transport and in the regulation of glucose-stimulated insulin secretion from rat pancreatic beta cells. Diabetologia. 2011; 54:135–145. [PubMed: 20949348]

16. Singh A, et al. A gene expression signature associated with "K-Ras addiction" reveals regulators of EMT and tumor cell survival. Cancer Cell. 2009; 15:489–500. [PubMed: 19477428]

17. DeLaBarre B, et al. Full-length human glutaminase in complex with an allosteric inhibitor. Biochemistry. 2011; 50:10764–10770. [PubMed: 22049910]

18. Vander Heiden MG. Targeting cancer metabolism: a therapeutic window opens. Nat Rev Drug Discov. 2011; 10:671–684. [PubMed: 21878982]

19. Trachootham D, et al. Selective killing of oncogenically transformed cells through a ROS-mediated mechanism by beta-phenylethyl isothiocyanate. Cancer Cell. 2006; 10:241–252. [PubMed: 16959615]

20. DeBerardinis RJ, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci U S A. 2007; 104:19345–19350. [PubMed: 18032601]

21. DeNicola GM, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature. 2011; 475:106–109. [PubMed: 21734707]

22. Gaglio D, et al. Oncogenic K-Ras decouples glucose and glutamine metabolism to support cancer cell growth. Mol Syst Biol. 2011; 7:523. [PubMed: 21847114]

23. Yang S, et al. Pancreatic cancers require autophagy for tumor growth. Genes Dev. 2011; 25:717–729. [PubMed: 21406549]

24. Ouyang H, et al. Immortal human pancreatic duct epithelial cell lines with near normal genotype and phenotype. Am J Pathol. 2000; 157:1623–1631. [PubMed: 11073822]

25. Bajad SU, et al. Separation and quantitation of water soluble cellular metabolites by hydrophilic interaction chromatography-tandem mass spectrometry. J Chromatogr A. 2006; 1125:76–88. [PubMed: 16759663]

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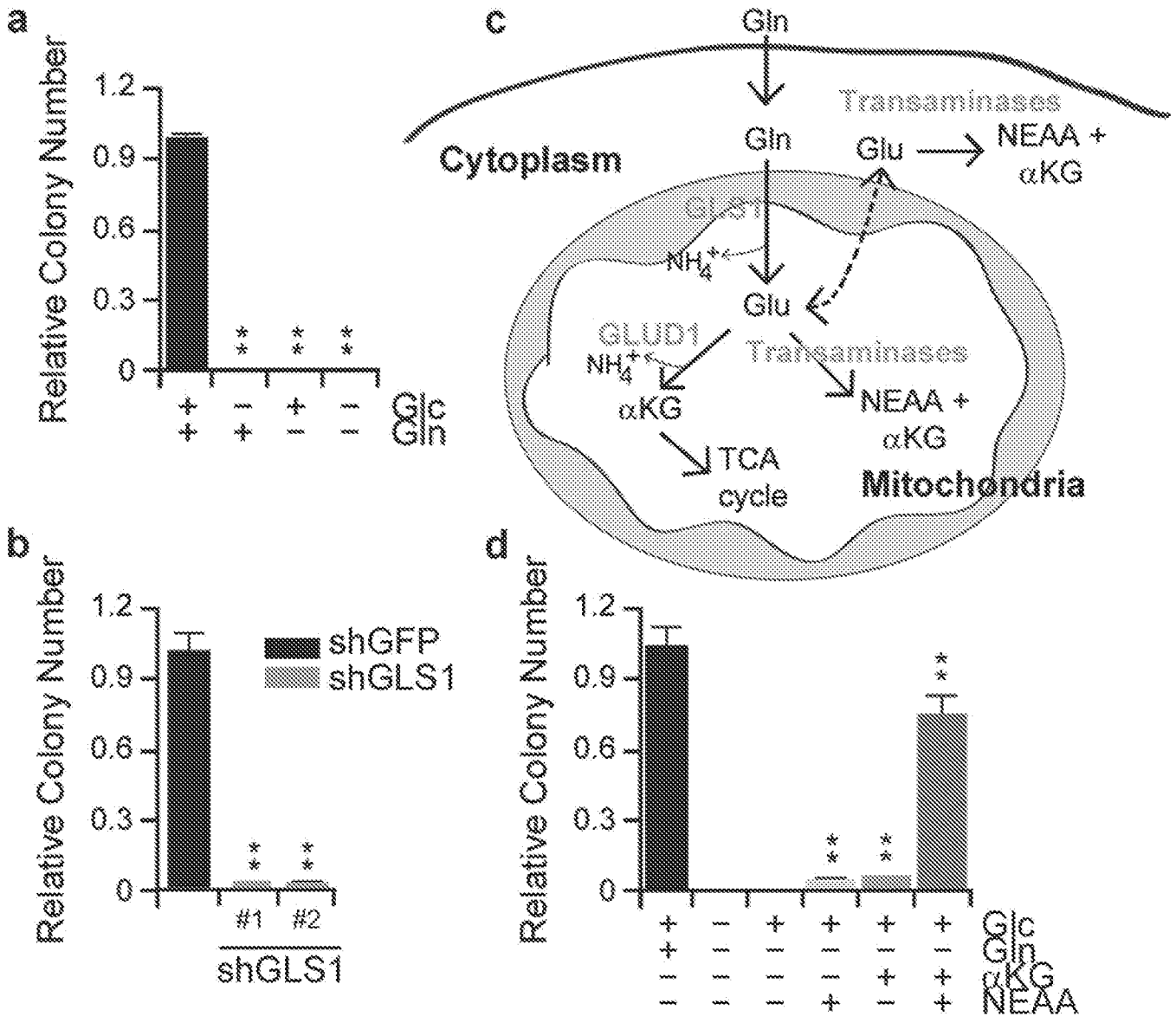


Figure 1. PDAC utilize a non-canonical glutamine metabolism pathway

a, PDAC proliferation requires both glucose and glutamine. Cells were plated in the complete media (10mM glucose and 2mM Gln) which was replaced the following day with glucose or Gln-free medium supplemented with 10% dialyzed FBS. **b,** Relative clonogenic growth of 8988T cells expressing a control shRNA (shGFP) or two independent shRNAs to GLS1. **c,** Schematic overview of GLUD1- or transaminase-mediated Glu metabolism. **d,** Relative clonogenic growth of 8988T cells. αKG (4mM), NEAA mixture (0.1 mM glycine, alanine, aspartate, asparagine, proline and serine) or the combination was added to media following Gln-withdrawal. αKG, α-ketoglutarate; Glc, glucose; Gln, glutamine; NEAA, non-essential amino acid. Error bars represent s.d. of triplicate wells from a representative experiment. **, $p < 0.01$.

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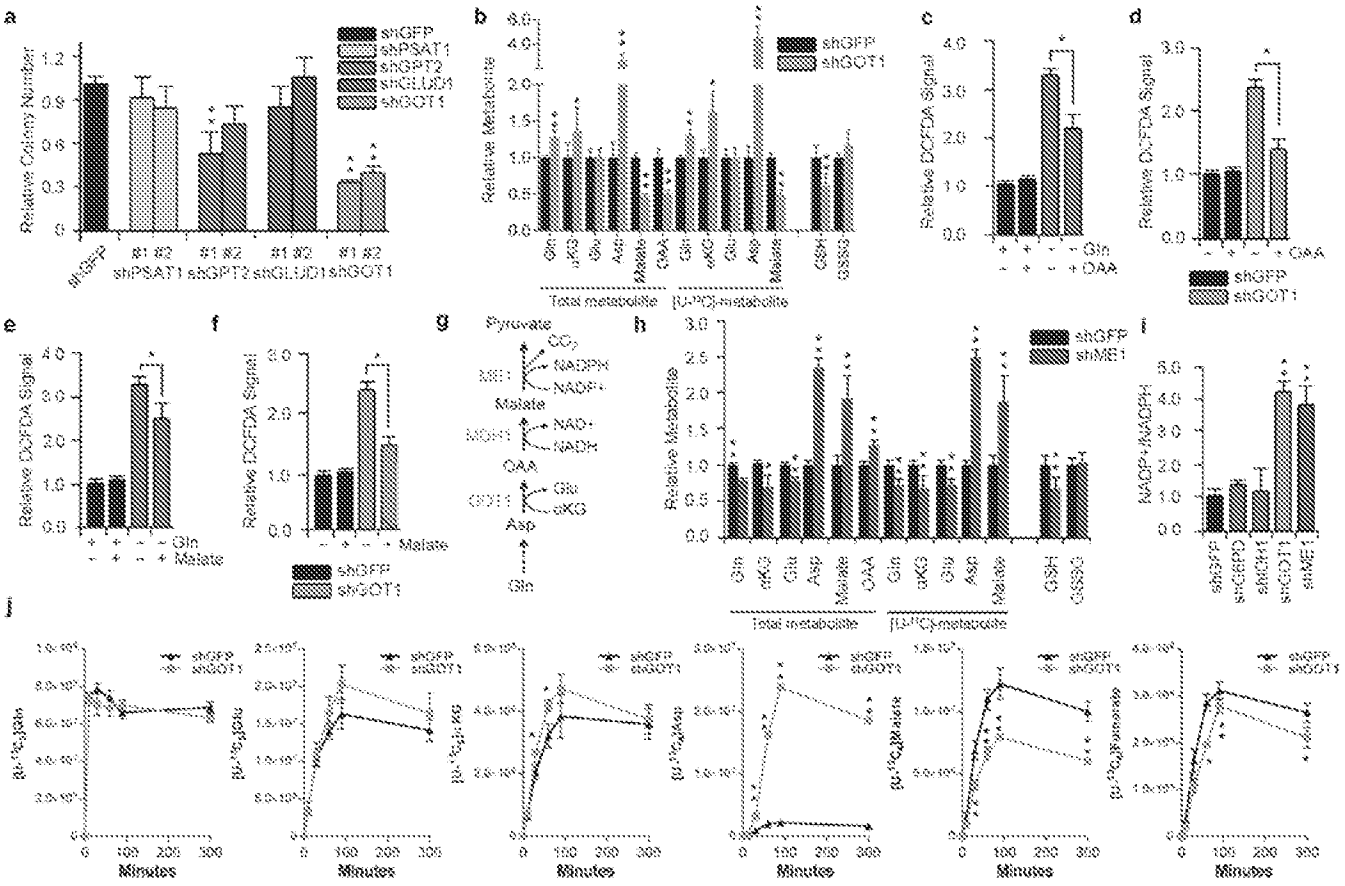


Figure 2. GOT1 is essential for redox balance and growth in PDAC

a, Relative clonogenic growth of 8988T cells expressing a control shRNA (shGFP) or two independent shRNAs targeting GLUD1, GOT1, GPT2 or PSAT1. Error bars represent s.d. of triplicate wells from a representative experiment. **b and h,** Relative metabolite abundance in 8988T cells grown in [U-$^{13}C_5$]-Gln upon GOT1 or ME1 knockdown. Data are presented as the total metabolite pool (encompassing both metabolite derived from Gln and that not Gln-derived, left) and the [U-^{13}C]-labeled and Gln-derived metabolite pool (right). Error bars represent the s.d. of three independently prepared samples. **c, d, e and f,** Relative ROS levels in 8988T cells under conditions indicated as determined by DCFDA staining. DCFDA assay was performed 24hr after supplementing Gln-free media with either OAA (4mM) or dimethyl malate (4mM). Each bar represents the mean of three independent experiments with error bars representing the s.d. **g,** Schematic depiction of the cytoplasmic reactions that convert Asp into pyruvate. **i,** NADP+/NADPH ratio in 8988T cells expressing a control shRNA (shGFP), or an shRNA to G6PD, IDH1, GOT1 or ME1. Error bars represent s.d. of five replicate wells from a representative experiment. **j,** Flux of the Gln carbon skeleton into downstream metabolites as a function of time. The reads for uniformly ^{13}C-labeled metabolites, presented in ion current, are plotted for cells expressing the shGFP control or shRNA to GOT1. Asp, aspartate; OAA, oxaloacetate; Glu, glutamate; GSH, reduced glutathione; GSSH, oxidized glutathione. *, $p < 0.05$; **, $p < 0.01$.

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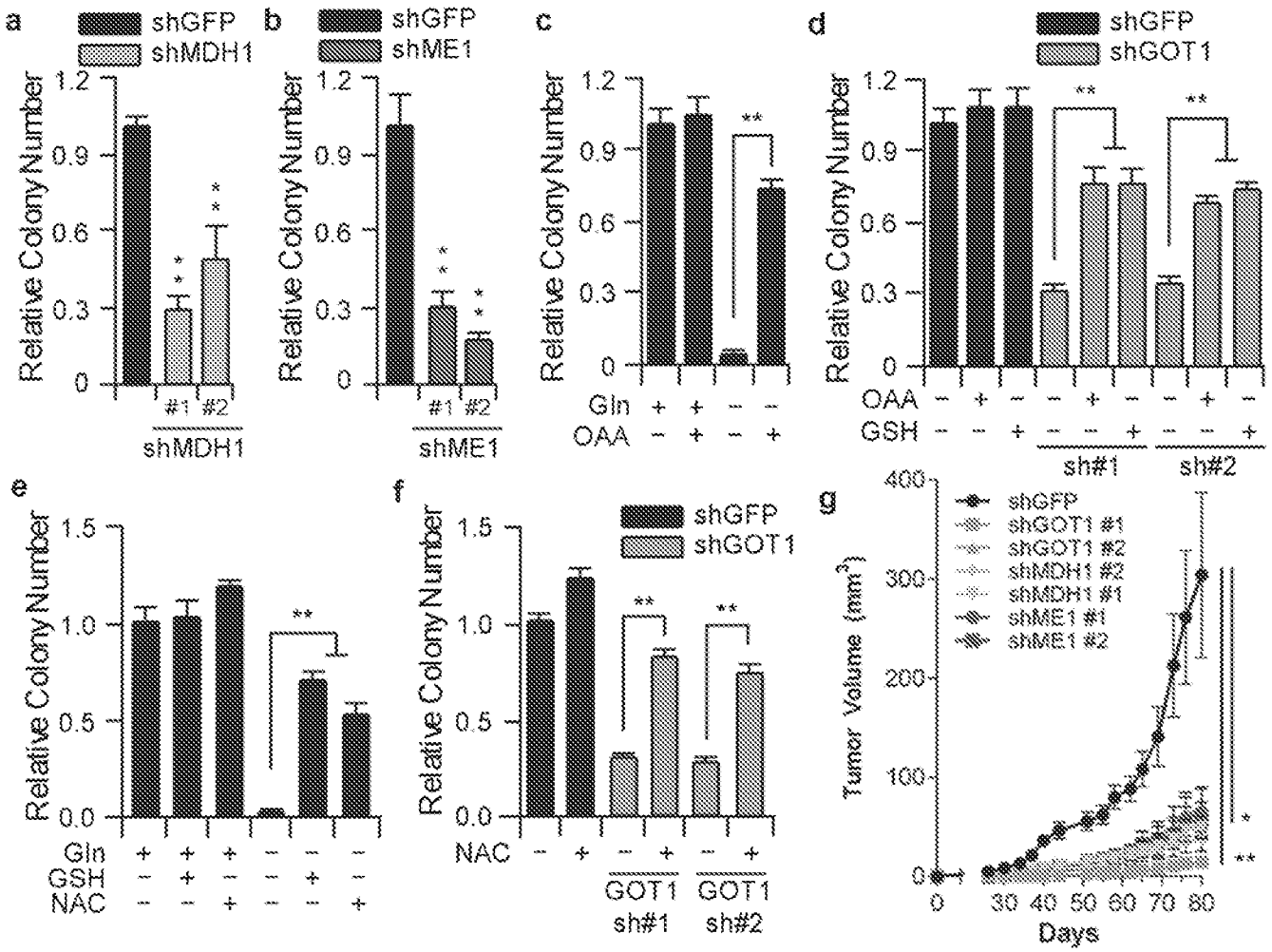


Figure 3. Metabolism of the Gln carbon skeleton through GOT1, MDH1 and ME1 supports PDAC growth by maintaining redox balance

a and b, Relative clonogenic growth of 8988T cells expressing a control shRNA (shGFP) or two independent shRNAs to MDH1 or ME1. **c and e**, Relative clonogenic growth of 8988T cells under conditions indicated. Cells were plated in complete culture media (10mM glucose and 2mM Gln), which was replaced the following day with Gln-free medium supplemented with OAA (4mM), GSH (4mM) or N-acetylcysteine (NAC) (4mM). **d and f**, Relative clonogenic growth of 8988T cells expressing a control shRNA (shGFP) or two independent shRNAs to GOT1 with or without OAA (4mM), GSH (4mM) or NAC (4mM). Error bars represent the s.d. of triplicate wells from a representative experiment. g, Xenograft growth of 8988T cells expressing a control shRNA (shGFP), shRNAs to GOT1 (#1 and #2), MDH1 (#1 and #2) or ME1 (#1 and #2) in mice. Error bars represent s.e.m (n=10). *, $p < 0.05$; **, $p < 0.01$.

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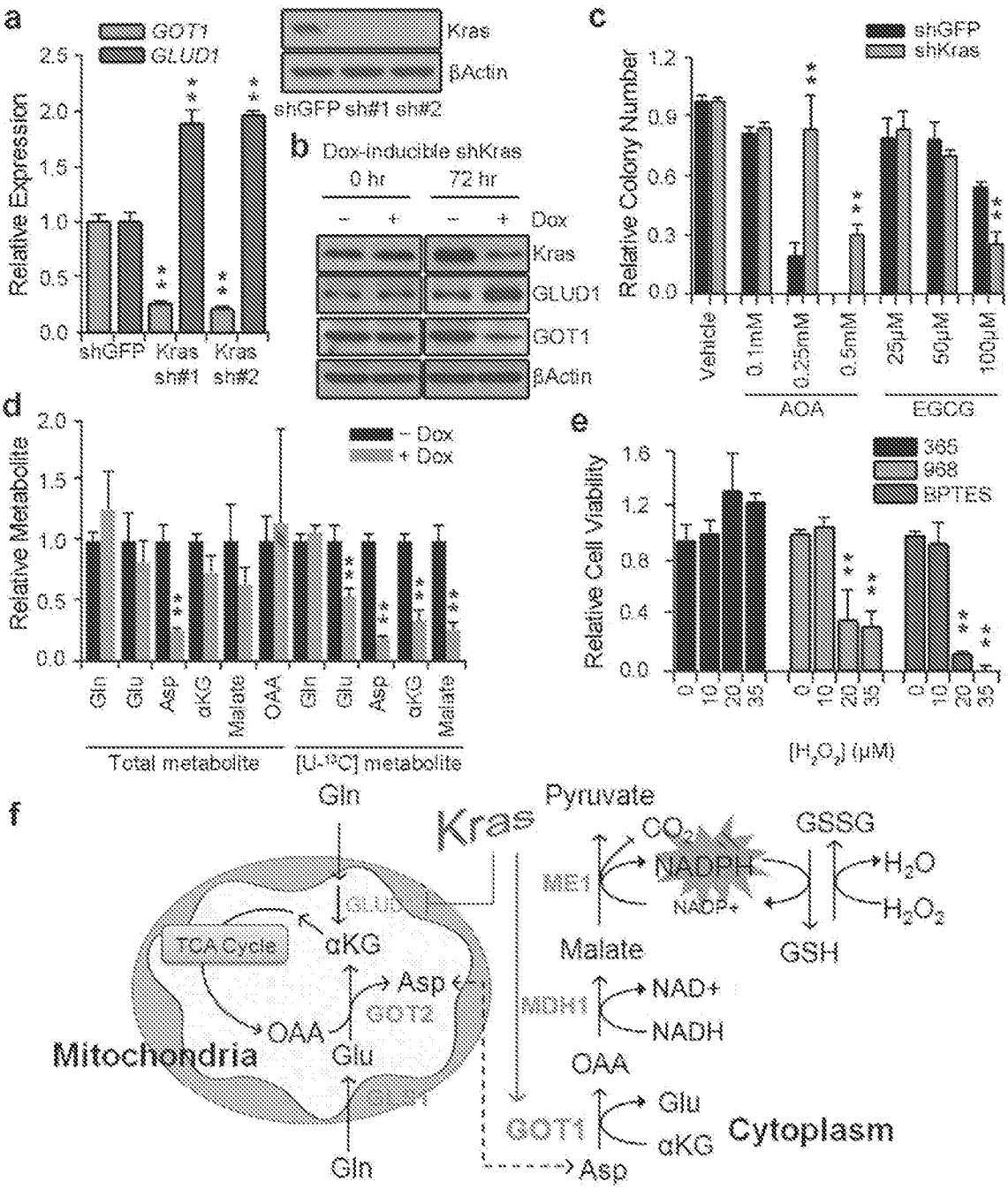


Figure 4. Oncogenic Kras mediates Gln reprogramming in PDAC

a, Expression of *GLUD1* and *GOT1* was determined by quantitative RT-PCR in 8988T cells expressing a control shRNA (shGFP) or two independent shRNAs targeting Kras. Western blot confirmed knockdown of Kras expression. **b,** The effect of Kras knockdown on GLUD1 or GOT1 protein levels in Panc1 cells expressing a doxycycline-inducible Kras shRNA. **c,** Relative clonogenic growth of 8988T cells expressing a control shRNA (shGFP) or shRNA to Kras following treatment with AOA or EGCG. Error bars represent the s.d. of triplicate wells from a representative experiment. **d,** Relative metabolite abundance in Miapaca2 cells

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grown in [U-$^{13}C_5$]-Gln upon doxycycline-inducible Kras knockdown. Data are presented as the total metabolite pool (encompassing both metabolite derived from Gln and that not Gln-derived, left) and the [U-^{13}C]-labeled and Gln-derived metabolite pool (right). Error bars represent the s.d. of three independently prepared samples. **e,** Relative cell viability of 8988T cells treated with GLS inhibitors 968 (active) (10μM), 365 (inactive analog) (50μM), or BPTES (100nM) with increasing concentrations of H_2O_2. . Error bars represent the s.d. of triplicate wells from a representative experiment. **f,** Model depicting the Kras-regulated Gln metabolic reprogramming in PDAC used to maintain redox and support growth. AOA, aminooxyacetate; EGCG, epigallocatechin gallate. *, $p< 0.05$; **, $p< 0.01$.

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REVIEW

The complex landscape of pancreatic cancer metabolism

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Pancreatic ductal adenocarcinomas (PDA) are extremely aggressive cancers and currently available therapies are only minimally effective in treating this disease. Tackling this devastating cancer has been a major challenge to the scientific and medical communities, in part due to its intense therapeutic resistance. One of the aspects of this tumor that contributes to its aggressive behavior is its altered cellular metabolism. Indeed, PDA cells seem to possess the ability to adapt their metabolism to the particular environment to which they are exposed, including utilizing diverse fuel sources depending on their availability. Moreover, PDA tumors are efficient at recycling various metabolic substrates through activation of different salvage pathways such as autophagy and macropinocytosis. Together, these diverse metabolic adaptations allow PDA cells to survive and thrive in harsh environments that may lack nutrients and oxygen. Not surprisingly, given its central role in the pathogenesis of this tumor, oncogenic Kras plays a critical role in much of the metabolic reprogramming seen in PDA. In this review, we discuss the metabolic landscape of PDA tumors, including the molecular underpinnings of the key regulatory nodes, and describe how such pathways can be exploited for future diagnostic and therapeutic approaches

Introduction

Pancreatic ductal adenocarcinomas epidemiology

With 45 220 new cases estimated for 2013 in the USA, pancreatic cancer is the 12th most common cancer, representing 2.7% of all the new cancer diagnoses in the USA (1,2). Despite not being one of the most prevalent cancers, it is by far one of the deadliest, with a 5 year survival of ~7% (2). It ranks fourth in cancer mortality and accounts for ~7% of all cancer-related deaths (1–3). With <10% of pancreatic cancers being diagnosed as localized disease (confined to primary site) (2), the majority of patients are not amenable to potentially curative surgical resection.

The normal pancreas is made up of two classes of cells: endocrine (hormone secreting) and exocrine (digestive enzyme producing). Depending on the cell of origin, pancreatic cancers can also be classified as endocrine or exocrine tumors. Roughly 90% of all pancreatic cancers are pancreatic ductal adenocarcinomas (PDA), an exocrine pancreatic tumor that resembles the cells lining the pancreatic duct (4,5). This tumor type will be the focus of this review.

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; HBP, hexosamine biosynthesis pathway; HIF, hypoxia inducible factor; LDHA, lactate dehydrogenase A; LKB1, liver kinase B1; MEK, mitogen-activated protein kinase kinase; NAD, nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; PDA, pancreatic ductal adenocarcinoma; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid.

Key characteristics of PDA

PDA have several defining features that influence its aggressive biology and resistance to multiple therapeutic modalities. These tumors are characterized by a distinct and exuberant stromal reaction (desmoplasia) (6,7), hypovascularization (8–11), genomic complexity (12–14) and an altered metabolism (15–17). This metabolic rewiring in PDA is critical to the growth of the tumor and is the subject of this review.

As mentioned above, PDA is characterized by a desmoplastic reaction, which often forms the bulk of the tumor mass (4,18). The PDA stroma is heterogeneous and is comprised of multiple cell types including pancreatic stellate cells, various leukocytes and endothelial cells, as well as a complex extracellular matrix (18–20). This dense fibrotic tissue, together with the poor vascularization limits access to the circulation, which has been shown to impair drug delivery (10,11,21). It also creates an hypoxic tumor microenvironment, known to negatively influence the response to radiotherapy in many cancer types (8,9,22). In addition, the PDA microenvironment is highly immunosuppressive (23–27), which has implications in immunotherapy for this disease (24).

The majority of PDA have Kras mutations, with 90% possessing activating mutations in this oncogene (28–31). In PDA, Kras is most commonly mutated at the G12 residue (G12D and G12V). This mutation affects the interaction site with GTPase activating proteins (GAPs), and therefore mutant proteins are guanosine triphosphate hydrolysis impaired, resulting in a constitutively active (guanosine triphosphate-bound) form of Kras. Like the other members of the RAS family of GTPases, Kras acts as a molecular switch, transducing signals from membrane-bound receptors to signaling pathways in the cell. By activating central signaling pathways in the cell such as mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) or PI3K/AKT pathways, Kras activity results in increased proliferation, cell growth, decreased apoptosis and increased invasiveness phenotypes (30,32,33). The Kras oncogene is considered a PDA driver mutation and, accordingly, it can be found mutated in early stages of tumor progression. Although rarely detectable in normal pancreas and chronic pancreatitis, the frequency of Kras mutation increases with the grade of the neoplasia to being nearly universal in advanced PDA (31). Consequently, its expression in the pancreas can drive the initiation of the disease in various mouse models (15,34–39).

In addition to Kras mutations, inactivating mutations or deletions are frequently seen in tumor suppressor genes, including p53, CDKN2A (INK4a/Arf) and Smad4 (21,40,41). Unfortunately, these recurrent genetic events have not provided any tractable therapeutic targets. Although there has been a significant effort to identify novel mutations in PDA tumors, such studies have not resulted in the identification of many recurrent driver events (42–44). However, it is now recognized that the PDA genomic landscape is highly complex with a particularly high rate of deletions and fold-back inversions (13), as well as frequent amplifications, deletions and complex rearrangements (12). In addition to a large amount of intertumoral heterogeneity, there is also significant intratumoral heterogeneity that may have implications on the intense therapeutic resistance (45).

Tumor metabolism

Normal, quiescent cells typically metabolize glucose to pyruvate, which can then enter the tricarboxylic acid (TCA) cycle where energy in the form of adenosine triphosphate (ATP) is efficiently produced by oxidative phosphorylation (46). Dividing cells, however, rely heavily on glycolysis, which allows for the production of energy along with building blocks required to generate a daughter cell (47). Similarly, metabolism in cancer cells is also altered to facilitate proliferation. An important distinction is that the metabolic networks in cancer cells are rewired to be independent of extracellular controls (46). In fact, the altered metabolism of tumor cells is now considered a hallmark of cancer (48). One of the main features of the metabolism of cancer cells is the emphasis on anabolic reactions required for *de novo* synthesis of proteins, nucleic acids and lipids (47,49,50). In order to fuel

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these processes, cancer cells may differ from normal cells in both the energy sources they utilize and how these fuel sources are metabolized (51–53). For example many cancer cells have developed a reliance on the amino acid glutamine in addition to glucose to help meet their biosynthetic needs (54,55). In this review, we will focus on the altered metabolism found in PDA, in particular those adaptations that are critical for the growth and maintenance of this aggressive tumor (Figure 1).

Kras-driven metabolic alterations in PDA

In addition to its well-studied roles in cancer cell proliferation, survival or metastasis, oncogenic Kras has been recently shown to have a key role in multiple aspects of PDA metabolism. In fact, it appears to have a prominent role in the metabolic rewiring of these tumors and this may be one of its critical roles in PDA pathogenesis.

Scavenging/recycling

Macroautophagy (hereafter referred to as autophagy) is a catabolic process that consists of the self-degradation of cellular organelles and molecular complexes (for review see ref. 56). In a cell, damaged or unnecessary organelles, proteins or protein aggregates are sequestered in a double membrane structure known as an autophagosome. The autophagosome eventually fuses with a lysosome creating an autolysosome, leading to the degradation and release of its contents. The degraded proteins (amino acids) and organelles (amino acids, lipids and nucleosides) are recycled back into the cytoplasm and used in the biosynthesis of proteins or nucleic acids, or for other anabolic or bioenergetic reactions. Because of its biological importance, the process is tightly controlled, with each step of autophagic progression being regulated by different complexes of proteins. Both the autophagic process and its regulation have been reviewed extensively elsewhere (57–62). There are three types of autophagy; macroautophagy, microautophagy and chaperone-mediated autophagy, which differ in terms of how cargo gets to the lysosome (63). Here, we will focus on macroautophagy.

Autophagy can act as a quality control mechanism in the cell by clearing damaged structures, including misfolded proteins, protein aggregates or dysfunctional organelles. Therefore, it is typically present at low levels in various tissues as a homeostatic mechanism. Different stimuli can trigger autophagy, thereby increasing it above baseline. One of the most well-studied and potent autophagy stimuli is starvation (lack of nutrients), which is regulated by the mammalian target of rapamycin (mTOR) complex (64). Other cellular stresses including protein damage, reactive oxygen species (ROS) or DNA damage are also known triggers of autophagy (58,65,66).

In cancer progression, autophagy has important but opposing roles (67,68). It has been demonstrated that autophagy can be both pro- and antitumorigenic. It is antitumorigenic due to the quality control function that it exerts: removing damaged organelles and protein aggregates, thereby mitigating oxidative stress, tissue damage and genomic instability; all protumorigenic factors that can promote tumor initiation. In established tumors, however, autophagy can fuel cellular proliferation in the nutrient-poor hypoxic regions in the tumor (68). Consistent with this, autophagy is found to be upregulated in tumors, particularly in nutrient-poor regions (69). It supports tumor cell survival via recycling cargo and generating substrates such as amino acids, fatty acids, nucleotides and ATP (70). Adding to this already complex role in cancer, autophagy is also linked with therapeutic resistance (71,72). In breast cancer for example autophagy upregulation increases resistance to hormonal therapy, playing a crucial role in the establishment of resistant tumors (73). Similarly, in lymphoma models, autophagy inhibition synergizes with cytotoxic chemotherapy (74). A recent study has shown that blocking autophagy in PDA cells via expression of a specific micro RNA enhances radiation response (75). However, it is important to note that there are some situations where inhibition of autophagy has been reported to mitigate the effect of a particular therapeutic agent in certain cancer types (71,76).

In Kras-driven tumors, autophagy has been shown to be required for tumor growth (77,78). Inhibiting autophagy also impairs Kras transformation of non-malignant breast cells (79). Similarly, transformation of mammary epithelial cells or immortalized mouse kidney cells by Hras also requires autophagy (80,81). Whereas in some cancer types, autophagy seems to be triggered as a reaction to various stressors (DNA damage, ROS, protein damage, lack of nutrients, etc.); in PDA, basal autophagy levels are unusually high (77). This appears to be cell autonomous, as high levels of autophagy are also observed in cell culture under nutrient-replete conditions. In PDA models, inhibition of autophagy both genetically (ATG5 depletion) or pharmacologically (chloroquine treatment) results in the inhibition of tumor growth in vitro and in vivo (77). The elevated basal autophagy appears to provide PDA cells with additional nutrients that can fuel the TCA cycle. Indeed, inhibition of autophagy resulted in decreased ATP production and impaired oxidative phosphorylation in PDA cells. Moreover, the impact of autophagy inhibition on PDA growth could be attenuated by adding back the metabolite pyruvate. Thus, autophagy appears to be a critical component of PDA metabolism. Similarly, autophagy inhibition in other tumor types has also been shown to impair mitochondrial metabolism (78) and in some contexts glycolysis (80,82).

In addition to utilizing intracellular substrates to recycle metabolites, PDA cells have the ability to take up and degrade extracellular macromolecules to fuel metabolism. Macropinocytosis is a form of endocytosis used by cells to engulf large portions of the extracellular space (83–85). Cells can extend their plasma membrane, folding it back onto the cell and creating a barrier around a portion of the extracellular fluid. This large, irregular, double membrane vesicle is known as a macropinosome. The macropinosome is internalized along with the extracellular fluid and associated molecules (proteins, bacteria, virus and even apoptotic bodies) (83–85) and then undergoes a step of maturation acquiring characteristics of an early endosome. It can then fuse with the lysosome, degrading its contents or, alternatively, it can be recycled back to the cell membrane, releasing the contents to the extracellular space.

It has been known for several decades that oncogenic Ras can promote macropinocytosis (86). Recently, PDA cell lines and tumors that possess activating Kras mutations were reported to show high levels of macropinocytosis (87). Macropinocytosis was shown to promote the uptake of extracellular albumin, which was then degraded in the lysosome. Interestingly, the amino acids that were produced by this degradation were shown to fuel cellular metabolism. In this elegant experiment, carbon-13 yeast protein was included in growth media. Kras-transformed cells consumed the protein and the liberated carbon-13 labeled amino acids were metabolized in the TCA cycle. Importantly, pharmacological inhibition of macropinocytosis showed significant antitumor responses in PDA xenografts (87).

In addition to recycling amino acids, Ras-transformed cells also appear to scavenge extracellular lipids as their primary source of fatty acids (88). Such lipids are hydrolyzed to form fatty acids and glycerol. The fatty acids can be used to fuel the TCA cycle, whereas the glycerol, the other product of lipid hydrolysis, can be converted into dihydroxyacetone, an intermediate of glycolysis (89). Alternatively, such fatty acids, which constitute a key component of the cellular membrane, can be used directly to make membranes in daughter cells (90).

Under normal conditions, the biosynthesis of fatty acids uses pyruvate, a product of glycolysis, which is converted to acetyl-CoA—a major precursor of fatty acids. These biosynthetic reactions require oxygen consumption and reduced nicotinamide adenine dinucleotide phosphate (NADPH). In cancer cells, scavenging substrates from the extracellular media to meet their fatty acid needs allows for the conservation of other rate-limiting molecules, such as NADPH, to be used for other functions such as redox balance (discussed below). Although this fatty acid scavenging appears to be a property of Ras-transformed cells, it has not yet been demonstrated specifically in PDA cells.

Together, the data from these studies illustrate that PDA cells are efficient in recycling and scavenging molecules to promote their own survival. Kras mutations appear to drive these mechanisms in the tumor, allowing tumor cells to adapt to environments where the access to nutrients can be diminished. Additionally, scavenging may allow for the conservation of energy and biomass so resources can be devoted to critical and rate-limiting processes such as NADPH biosynthesis,

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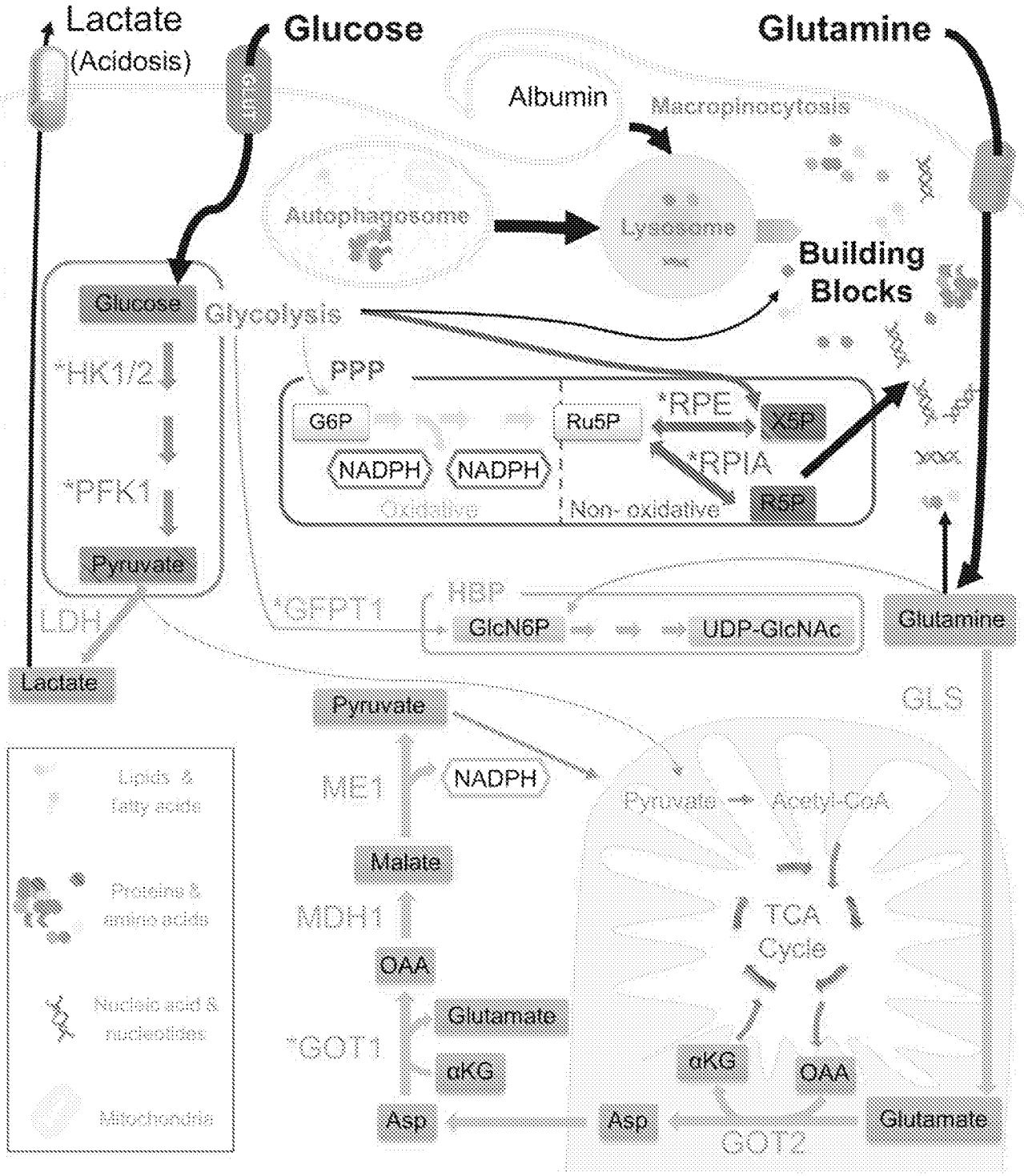


Fig. 1. A typical PDA cell is depicted showing schematics of representative metabolic pathways that are altered in the disease in response to oncogenic Kras. Enzymes whose expression is increased by Kras are indicated with an asterisk. Increased glucose uptake fuels glycolysis (leading to increased lactate production), anabolic pathways such as the non-oxidative arm of the PPP (producing ribose for nucleotide biosynthesis) and the HBP (producing precursors for glycosylation). Glutamine is a key metabolite that is utilized to fuel the TCA cycle and maintains redox homeostasis in PDA through a novel pathway (shown in orange) that leads to NADPH production. PDA are efficient metabolic scavengers and use autophagy (intracellular) and macropinocytosis (extracellular) to provide metabolic substrates through cargo degradation *via* the lysosome. Lipids are also taken up extracellularly to provide fatty acids. HK1/2, hexokinase 1 and 2; PFK1, phosphofructokinase 1; ME1, malic enzyme; GOT1/GOT2, aspartate aminotransferase 1 and 2; MDH1, malate dehydrogenase; GLS, glutaminase; GFPT1, glutamine fructose-6-phosphate amidotransferase; RPIA, ribose 5-phosphate isomerase A; RPE, ribulose-5-phosphate-3-epimerase; Asp, aspartate; OAA, oxaloacetate; G6P, glucose 6-phosphate; Ru5P, ribulose 5-phosphate; R5P, ribose 5-phosphate; X5P, xylulose 5-phosphate. LDH, lactate dehydrogenase; αKG, alpha keto-glutarate; GlcN6P, glucosamine-6-phosphate; UPD-GlcNAc, uridine diphosphate N-acetylglucosamine; MCT, monocarboxylate transporter; GLUT, glucose transporter.

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which will be discussed below. Importantly, these pathways have the potential for therapeutic targeting as chloroquine and its derivative hydroxychloroquine can inhibit autophagy through their interference with lysosomal acidification (71). Since autophagy and macropinocytosis converge at the level of the lysosome, these drugs would potentially attenuate both processes. Indeed, there are many clinical trials in various cancers, including PDA, incorporating hydroxychloroquine into the treatment regimen (http://clinicaltrials.gov/). Additionally, as macropinocytosis was shown to take up albumin in PDA, this could be used to help deliver drugs to the tumor. It is tempting to speculate that the recent success of the addition of nab-paclitaxel (an albumin bound paclitaxel) to gemcitabine in metastatic pancreatic cancer patients (91) was in part due to the increased delivery to the tumor by macropinocytosis. Lastly, as autophagy is often a reactive survival mechanism to metabolic stress, inhibiting this process using hydroxychloroquine, may increase the efficacy of inhibitors to other metabolic pathways.

Anabolic glucose metabolism

Like many other cancer types, PDA exhibit an elevated capacity for glucose uptake (15). Similar to the scavenging characteristics described previously, the metabolic changes involving glucose are also in part driven by oncogenic Kras. For example glycolysis is enhanced downstream of Kras in different and complementary ways. The glucose transporter GLUT1 is transcriptionally upregulated in response to Kras mutations in both PDA and other tumor types leading to increased glucose uptake (15,92). Additionally, key glycolysis enzymes such as HK1, HK2 and PFK1 are transcriptionally upregulated downstream of Kras activation (15,93,94). One of the fates of the glycolysis-derived pyruvate is its conversion to lactate by the enzyme lactate dehydrogenase. Oncogenic Kras has been shown to increase the expression of lactate dehydrogenase A (LDHA) through increasing its transcription (15,95). Additionally, PDA cells can upregulate LDHA levels and activity through posttranslational modification of the enzyme. Acetylation of LDHA at the lysine 5 residue reduces its activity and targets LDHA for lysosomal degradation. PDA cells and primary tumors were shown to have reduced levels of this particular acetylation, resulting in greater LDHA activity (96). Interestingly, a recent study suggested that lactate can be used as alternative fuel by certain PDA cells, thereby promoting proliferation (9). Given the elevated glycolysis in PDA, leading to increased lactate production, the ability to utilize lactate could provide an additional advantage to PDA cells. Indeed, the inhibition of glycolysis through suppressing LDHA expression by RNA interference decreased the growth of PDA cells (96).

Using a genetically engineered mouse model of PDA where $Kras^{G12D}$ expression is induced in the pancreas by feeding mice doxycycline, it was shown that oncogenic Kras is required for tumor maintenance, due in part to a Kras-specific rewiring of anabolic glucose metabolism (15). The metabolic rewiring by Kras is complex, and PDA metabolic pathways are divergent from normal cells in unique ways. In particular, the elevated glycolytic flux is shunted to various anabolic pathways. The pentose phosphate pathway (PPP) is a side branch of glycolysis that generates five carbon sugars (ribose-5-phosphate) from six carbon sugars, to be used in nucleotide biosynthesis. In parallel, it generates reducing equivalents in the form of NADPH for use in redox control and biosynthesis of different molecules such as fatty acids (47,97). The PPP can be visualized as having an oxidative and a non-oxidative arm. The oxidation steps use glucose-6-phosphate to generate two reducing equivalents in the form of NADPH. The non-oxidative reactions of the PPP are primarily used to produce ribose-5-phosphate. The non-oxidative reactions are also important to generate six carbon sugars from five carbon sugars, which can be used to support glycolysis. The oxidative and non-oxidative arm of PPP can be decoupled, and cells can regulate the relative contribution and output of the two arms of the PPP according to their needs (requiring more NADPH than ribose for example) (97).

In PDA, the PPP is important for tumor maintenance, again, as it generates the ribose moiety of DNA used to duplicate the genome during the generation of daughter cells. Unexpectedly, oncogenic Kras leads to an increase in flux specifically through the non-oxidative arm of PPP, resulting in the generation of more ribose 5-phosphate, which can be utilized for DNA/RNA biosynthesis. This occurs independently of the NADPH-generating oxidative arm. Kras activation leads to increased transcription of two non-oxidative PPP enzymes, ribose 5-phosphate isomerase A and ribulose-5-phosphate-3-epimerase, which lead to increased flux through the non-oxidative arm (15). Importantly, inhibition of this pathway through suppressing expression of either ribose 5-phosphate isomerase A or ribulose-5-phosphate-3-epimerase results in decreased PDA growth both *in vitro* and *in vivo*.

Another glucose-dependent pathway that is upregulated by oncogenic Kras in PDA is the hexosamine biosynthesis pathway (HBP). This pathway leads to production of uridine diphosphate–*N*-acetylglucosamine and other nucleotide hexosamines, which are the major substrates for glycosylation of proteins and lipids, including many cytoplasmic and nuclear proteins on their serine or threonine residues (98). The HBP uses glucose and glutamine to generate uridine diphosphate–*N*-acetylglucosamine, acting as a bridge between glycolysis and glutaminolysis. Glucose entry into the HBP is regulated by its first and rate-limiting enzyme, glutamine fructose-6-phosphate amidotransferase (GFPT1). This enzyme catalyzes the conversion of fructose-6-phosphate and glutamine to glucosamine-6-phosphate and glutamate, respectively (99). In a negative-feedback loop, the HBP final product, uridine diphosphate–*N*-acetylglucosamine, inhibits GFPT1 activity self-regulating this pathway (100).The HBP coordinates nutrient uptake, partially through modulating the glycosylation and membrane localization of growth factor receptors (101). Additionally, the HBP and protein glycosylation have been found to be increased in different cancers (98,102). In general, glycosylation is a pronumorigenic modification that triggers cancer-related phenotypes such as motility, proliferation and angiogenesis (103,104). In PDA, oncogenic Kras increases glucose flux through the HBP by upregulating GFPT1 expression (15). Consistent with this, suppression of Kras resulted in a decrease in total cellular O-linked glycosylation in PDA cells. Inhibition of the HBP in PDA cells by RNA interference-mediated suppression of GFPT1 resulted in a decrease in clonogenic growth and xenograft growth in mice (15).

One of the interesting aspects of many of the glucose metabolic changes seen in PDA is that they appear to be driven by the activation of the Raf/MEK/extracellular signal-regulated kinase pathway by oncogenic Kras (15). Indeed, pharmacological inhibition of MEK leads to a decrease in many of the rate-limiting enzymes that are upregulated by Kras and decreases in the respective downstream metabolites. This effect on transcription is mediated by the c-Myc oncogene as a significant fraction of the metabolic gene transcripts that were upregulated by oncogenic Kras have Myc binding elements in their promoters. Functionally, RNA interference-mediated suppression of c-Myc expression resulted in decreased expression of the same metabolic enzymes regulated by Kras and the corresponding downstream metabolites (15). Although there are no clinical grade inhibitors to most of the metabolic enzymes discussed above (GFPT1, ribose 5-phosphate isomerase A, ribulose-5-phosphate-3-epimerase), MEK inhibitors are being used in clinical trials for multiple tumor types (105). Therefore, utilizing MEK inhibitors based on their ability to inhibit anabolic glucose metabolism in PDA in combination with other therapeutic agents may be a useful strategy. In fact, the available data suggest potentially attractive therapeutic combinations. For example as MEK signaling pathways were shown to control expression of key enzymes of the non-oxidative arm of the PPP (15), a significant source of ribonucleotides for *de novo* DNA synthesis in the cell, combining DNA damaging therapies such as radiation with MEK inhibitors, could potentially achieve a synergetic effect.

Glutamine metabolism

Glutamine is the most abundant free amino acid in the blood (106). It has been studied for its role in cancer due to the fact that it appears to be required for the growth of many tumor types (107). It is a significant source of carbon in cancer cells, supporting anabolic processes through glutaminolysis (glutamine metabolism generating α-ketoglutarate) (54). Glutamine is also a precursor of glutathione (through its conversion to glutamate by glutaminase), a major cellular

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antioxidant. It is also the source of amino groups for non-essential amino acids such as alanine, aspartate, serine and glycine. The nitrogen group, released in the conversion of glutamine to glutamate also feeds the synthesis of nucleotides and the HBP. For a comprehensive review on glutamine metabolism see (54,108).

As discussed above, oncogenic Kras in PDA does not impact flux through the oxidative and NADPH-generating arm of PPP (15). Additionally, glucose deprivation, while impairing PDA growth, has minimal effects on cellular redox state in PDA cells (16). Together, this suggests that PDA utilize alternative mechanisms to maintain redox balance. Indeed, glutamine withdrawal results in a significant increase in ROS in PDA cells and it was shown that glutamine metabolism is critical for redox balance in PDA (16).

Canonical metabolism of the glutamine carbon skeleton generates α-ketoglutarate in the mitochondria to fuel the TCA cycle, and this relies on glutamate dehydrogenase (GLUD1) for the conversion of glutamate to α-ketoglutarate (54). The α-ketoglutarate can be used for anapleurosis, ultimately leading to the generation of intermediates used for biomass such as nucleic acids, proteins and lipids (109–111). In contrast, PDA cell lines do not rely on GLUD1. Instead they use the aspartate transaminase (GOT2) to generate anaplerotic α-ketoglutarate in the mitochondria. This reaction simultaneously creates aspartate from oxaloacetate, which is released into the cytoplasm. Cytosolic aspartate is then acted on by the cytosolic aspartate aminotransferase (GOT1) to convert glutamine-derived aspartate back into oxaloacetate. This oxaloacetate is subsequently converted into malate by malate dehydrogenase (MDH1) and then pyruvate and NADPH by malic enzyme. Indeed, this pathway appears to be a critical source of cytosolic NADPH in PDA cells (16). Importantly, this alternative branch of glutamine metabolism is required for PDA growth as depletion of any of the key enzymes of this pathway (GOT1, MDH1 or malic enzyme) suppressed *in vitro* growth and xenograft growth (16). Moreover, the NADPH produced by this pathway was critical to support PDA growth *via* its role in redox balance, as restoration of redox state by adding *N*-acetylcysteine or reduced glutathione could rescue growth upon suppression of any of these key enzymes. Moreover, this alternative glutamine metabolism was shown to be Kras dependent, as oncogenic Kras drives the expression of GOT1 while repressing GLUD1 in PDA cells (16). Interestingly, GOT1 was dispensable for the proliferation of normal cells, indicating that this pathway may be therapeutically tractable. Although no *bona fide* GOT1 inhibitors are currently available, other key enzymes in the glutamine metabolism have known inhibitors. One example is glutaminase and its inhibitor bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES), that decreases PDA cell viability *in vitro* (16). As seen in this same study, a major outcome of the unique glutamine metabolism in PDA is the production of NADPH, which results in an increased ability of PDA cells to cope with oxidative damage. One could think of a combined therapy targeting glutamine metabolism (such as glutaminase inhibition) along with classical ROS generating therapies such as radiation or chemotherapy. These therapies should synergize and effectively kill PDA cells.

Although the NADPH produced by this novel pathway is critical for PDA *via* its role in maintaining reduced glutathione pools, NADPH has many key roles in normal and particularly in tumor cells. NADPH is required for many aspects of biosynthesis and is thought to be limiting for tumor growth. A dividing cell for example requires significant pools of NADPH for the synthesis of fatty acids when compared with a normal cell in quiescence (47,97). Additionally, DNA synthesis, and particularly the conversion of ribonucleotides to deoxyribonucleotides (*via* ribonucleotide reductase), requires NADPH as the electron donor, explaining in part the large quantities of NADPH required by proliferating cells (97). Although the data suggest a critical role of NADPH production in PDA redox balance, NADPH is probably needed for all of these biosynthetic processes in PDA and detailed studies assessing the utilization of NADPH under different conditions during PDA pathogenesis are needed to define its precise roles.

ROS balance

ROS are produced during cellular metabolism. They can cause oxidative damage in cells (lipid, protein and DNA oxidation—the latter is a major cause of mutations), which in normal cells may lead to cell death through apoptosis when in excess (112–114). It is important to note that ROS are not simply toxic byproducts of cellular metabolism or damaged mitochondria. In fact, ROS are also important signaling molecules that have roles in such diverse processes as inflammation, immune response, adhesion or cellular migration (115–117).

Cancer cells often have higher levels of ROS than normal counter parts, as a result of either mitochondrial damage, increased metabolic rates or elevated expression of oxidizing enzymes (118–120). Indeed, ROS have been shown to act as signaling molecules in different cancer-related cellular behaviors. ROS generated by tumor cells can promote cell motility (and ultimately metastasis) in a cell autonomous or non-autonomous way by acting in the stroma and impairing stromal mobility-inhibitory activity (115,121,122). In fact, ROS have been shown to be critical for Kras transformation (123) and growth of Kras-transformed PDA (124). For example superoxide ($O2^-$), a byproduct of mitochondrial respiration, is a prosurvival factor in PDA as scavenging $O2^-$ inhibits cell growth (125,126). Moreover, oncogenic Kras promotes the production of superoxide by increasing levels of NADPH oxidase 2 (NOX2), an enzyme that transfers electrons from NADPH, coupling them to molecular oxygen. This activity appears to be important for PDA growth as inhibition of NOX2 in PDA cell lines impairs clonogenic growth (124). Similarly, the ROS produced by NOX4 appears to promote PDA survival as demonstrated by suppression of NOX4 expression (127).

Given the aforementioned roles of ROS in various cellular processes, it is not surprising that ROS would have both pro- and anti-tumorigenic effects. Indeed, this delicate balance is probably why PDA and other tumors have developed multiple mechanisms to balance the production and scavenging of these molecules. The redox state in a cell is determined by multiple factors including the balance of NADP+/NADPH to maintain pools of reduced glutathione (128). The reduced species (NADPH) allow for the maintenance of pools of reduced glutathione, which is critical for glutathione oxidation, a key pathway to reduce the levels of peroxide in the cell. As discussed above, one of the main roles of glutamine in PDA is to produce NADPH through a novel metabolic pathway to allow proper redox balance (16). Another way by which PDA can regulate the redox state is through NRF2, a transcription factor targeting genes in drug metabolism and ROS response (129,130). In the cell, NRF2 is stabilized upon different stresses. It then accumulates in the cell nucleus to promote transcription of multiple target genes involved in the ROS response including glutathione reductase, superoxide dismutase 3, NQO1 and thioredoxin (130). Recently, it was shown that the Kras oncogene, expressed at physiological levels, can upregulate NRF2, leading to decreased cellular ROS levels (131). Consistent with this, NRF2 is found overexpressed in PDA (132), and the higher availability of NRF2 in PDA could represent an increased potential of these cells to respond to ROS, thereby protecting PDA cells against their potentially detrimental effects. In addition to Kras, other oncogenes such as B-Raf and c-Myc can induce NRF2 expression to promote ROS detoxification. Importantly, NRF2 was shown to be critical for Kras-driven tumorigenisis in PDA models (131). Together, these data show that PDA have developed multiple mechanisms to control ROS levels and this has significant implications on tumor progression.

Hypoxia

As described above, areas within PDA tumors are hypoxic (8,9), which is probably a result of the hypovascular nature of the tissue. This hypoxic microenvironment has implications on its complex biology and in particular its cellular metabolism. Indeed, a recent study characterizing the hypoxic regions in PDA tumors suggested that hypoxia enhanced activity of the HBP (9).

The hypoxia inducible factor 1 alpha (HIF1α) is a central player in hypoxia response. At low oxygen concentrations in the cell, HIF1α is stabilized and translocates into the nucleus where it acts as a transcription factor triggering many hypoxic responses. The regulation of HIF1α stabilization is complex and very tightly regulated by ubiquitin-mediated proteosomal degradation (for review please see ref. 133).

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One of the consequences of HIF1α activation is the metabolic rewiring allowing a cell to subsist in low-oxygen environment. Namely, it leads to an increase in glycolysis by upregulating key genes such as HK, pyruvate kinase M2 and LDHA among others (133), as well as a shift to the non-oxidative arm of PPP by upregulation of transkelotases (TKT and TKTL2) expression (134). HIF1α also coordinates a decrease in the entry of glucose carbon into the TCA cycle, a beneficial adaptation under hypoxia due to the lack of oxygen, which acts as an electron acceptor during oxidative phosphorylation. One of the mechanisms by which HIF1α accomplishes this decrease in glucose flux through the TCA cycle is by increasing transcription of pyruvate dehydrogenase kinase (135). Pyruvate dehydrogenase kinase phosphorylates and inhibits pyruvate dehydrogenase, the enzyme that converts pyruvate to acetyl-CoA.

In colon cancers with Kras mutations, target genes of both HIF1α and HIF2α expression are induced downstream of oncogenic Kras (95), creating a state of 'aerobic-hypoxia'. This is consistent with the findings that Ras-transformed cells have similar metabolic profiles as hypoxic cells (55). In PDA, HIF1α has been shown to mediate metabolic changes downstream of MUC1 (136) and interference with HIF1α function has antitumor effects on PDA cells *in vitro* and *in vivo* (137,138). Another hypoxia response induced by HIF1α activity is the activation of autophagy (139,140). As autophagy is a critical mechanism for PDA cell metabolism under normoxic conditions, it may have additional roles in the setting of hypoxia. Indeed, autophagy appears to promote tumor-initiating cells in PDA cultures under hypoxic conditions (141).

PDA tumor suppressor genes are linked to metabolism

Oncogenic Kras, a key driver of PDA pathogenesis and a regulator of PDA metabolism, exists in the context of additional genetic alterations in tumor suppressor genes that in many cases have been shown to constrain malignant progression (142). Importantly, several of these genes have links to cellular metabolism (143). Thus, the metabolic consequences of Kras mutations in PDA or even Kras-independent metabolic changes are probably modulated by the constellation of tumor suppressor gene alterations. Additionally, these tumor suppressor mutations may alter the dependency of a tumor on particular metabolic pathways.

One such example is the tumor suppressor p53, which is well known for its roles in apoptosis and growth arrest. As a transcription factor, it can promote the transcription of genes that lead to growth arrest at G_1 phase, having a cell cycle 'check-point' function that guards cells against genotoxic insult coming from various sources such as irradiation, hypoxia or drug-induced genotoxic damage. Alternatively, it can promote apoptosis in response to certain stimuli (144–147). p53 is the most commonly mutated gene in cancer, with over half of all human tumors possessing mutations altering p53 function (144). In PDA, p53 is mutated in the majority of tumors (41), and its frequency increases with tumor progression (40,148,149). As further proof of its important role in PDA progression, deletion or mutation of p53 accelerates the development of PDA tumors in Kras-driven genetic mouse models of the disease (35,150).

p53 has been shown to regulate multiple aspects of cellular metabolism. Overall, the net effect of p53 expression appears to promote oxidative phosphorylation and attenuate glycolysis although there are certainly particular tissues and cellular contexts where this may differ. The reader is directed to several excellent reviews on this topic (151–155). Therefore, in cancers where p53 would be absent or mutated (such as the majority of PDA), one would expect to see increases in glycolysis and decreases in oxidative phosphorylation. For example p53 promotes expression of SCO2, a member of the COX-2 assembly involved in the electron transport chain that increases levels of mitochondrial respiration while decreasing glycolysis (156). Furthermore, glutamine is a major fuel source of the TCA cycle in many cancers as it can supply TCA cycle intermediates(105). p53 can upregulate glutaminase 2, which increases the conversion of glutamine to glutamate that can be ultimately used to make αKG (157,158). The net effect of this can lead to increased flux through the TCA cycle and increased oxidative phosphorylation.

There are multiple ways by which p53 can attenuate glycolysis, including promoting the inactivation of phosphoglycerate mutase (159) and repressing the glucose transporters GLUT1 and GLUT4 (160). p53 also upregulates TP53-induced glycolysis and apoptosis regulator, a fructose-2,6-bisphosphatase that lowers the intracellular concentration of fructose-2,6-bisphosphate resulting in a decrease in glycolysis and an increase in oxidative phosphorylation (161). Furthermore, p53 also influences the PPP, by binding to and inhibiting the activation of glucose-6-phosphate dehydrogenase, the first rate-limiting step enzyme of the PPP (162).

Additionally, recent data have suggested that p53 status may influence the role of autophagy in PDA progression using a PDA genetically engineered mouse model where Kras is activated concurrently with ATG5 or ATG7 loss and both copies of p53 are embryonically deleted. In the setting of combined loss of p53 and autophagy impairment, tumor formation may actually be accelerated. This is in contrast to tumors where Kras is activated and autophagy abrogated in the setting of an intact p53 locus. Here, tumor progression is completely inhibited (163). One issue not addressed in this study concerns the way p53 is mutated/lost in a physiological cancer setting. In this study, the homozygous deletion of p53 embryonically creates a situation where p53 is never present in the tissue prior to tumor development. Although these data are certainly of great interest, it would be valuable to study the role of autophagy in PDA progression in a more physiological setting, with p53 being lost as the tumor progresses. Indeed data from our group have shown that ATG5 loss in a PDA genetically engineered mouse model where p53 is lost stochastically by loss of heterozygosity significantly impairs PDA progression (unpublished data).

Other tumor suppressor genes involved in PDA also have roles in cellular metabolism. This includes the liver kinase B1 (LKB1), a serine threonine kinase that phosphorylates adenosine monophosphate-activated protein kinase (AMPK) (164). Patients with germline mutations of LKB1 (Peutz-Jeghers syndrome) have a significantly increased risk of developing PDA (165) and LKB1 haploinsufficiency cooperates with oncogenic Kras in a PDA mouse model (166). Although the metabolic consequences of LKB1 loss in PDA have not been well studied, downstream effectors of LKB1 such as AMPK have critical roles in metabolism, suggesting that PDA metabolism may be altered upon LKB1 loss. For example low energy levels result in stable AMPK phosphorylation and activation by LKB1 (164). In turn, AMPK stimulates ATP-producing catabolic pathways (glycolysis and fatty acid oxidation) and attenuates ATP-consuming anabolic pathways (lipogenesis, protein synthesis) (167,168). In fact, this switch to fatty acid oxidation has the net benefit of increasing NADPH levels in cells (169). Lastly, LKB1–AMPK signaling also positively regulates autophagy through activation of ULK1 and through inhibition of the mTOR pathway (168,170), suggesting that the LKB1 mutant tumors may have reduced autophagy, compared with tumors with LKB1 intact. Therefore, it would be interesting to understand how LKB1 mutant PDA tumors deal with energy or other metabolic stressors.

Other metabolic pathways

Lipids and fatty acids

Lipids and fatty acids are important for tumor cell growth and as mentioned previously, Ras-transformed cells have developed mechanisms to scavenge free fatty acids from the extracellular environment (85). The role of individual fatty acids in PDA metabolism has recently begun to be explored. Interestingly, there are both pro- and antitumorigenic properties of different fatty acid species described in various cancers making the biology complex (171,172).

Several recent studies have shown that PDA tumors have lower levels of fatty acids than corresponding normal tissues. For example in a proton magnetic resonance study (HNMR), lipids, choline-containing compounds and fatty acids were found decreased in pancreatic cancer

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compared with normal pancreatic tissue (173). Palmitoleic acid was found to be decreased in rat models of PDA (bearing oncogenic Kras), both in the tumor tissue and in the serum, compared with control animals (174). In another study that combined transcriptomic and proteomic approaches to compare PDA with matched non-tumor tissue from the same patients, fatty acids were shown to be consistently decreased in PDA (175). The proposed mechanism was that specific lipases (PNLOP, CLPS, PNLIPRP1 and PNLIPRP2) are downregulated in PDA, thereby resulting in a decrease in the content of free fatty acids. These include palmitic and stearic acids, two saturated fatty acids shown to induce apoptosis and inhibit proliferation of PDA cell lines (175). Along these lines, other fatty acids with antitumorigenic properties have been described such as N-3 polyunsaturated acids, which can impair PDA progression (176).

Lipids, however, can also be protumorigenic, with a high-fat diet promoting tumor growth in murine models of pancreatic cancer (177). Although this may not be due to direct effects of the lipids on the tumor cells themselves, there is evidence for direct protumorigenic effects of fatty acids in PDA. Indeed, lipid metabolism is likely to be an important source of energy in PDA and consistent with this, PDA cell lines treated with oleic and linoleic acid display increased proliferative rates (178). The metabolism of fatty acids can also generate ROS as it is the case with linoleic acid (179), a potentially pro- or antitumorigenic factor in PDA (depending on the levels of ROS), which could also explain why in some contexts fatty acids are growth suppressive and in others growth promoting.

Even if reducing the levels of certain fatty acids is apparently important for PDA, it remains to be determined which fatty acids are cytotoxic for tumor cells and which fatty acids provide the tumor with metabolic substrates. One possible explanation for the fatty acid level reduction in PDA could be that they are being rapidly metabolized by the tumor cells. It would therefore be of great interest to understand the complex role of lipids in PDA through detailed metabolic studies.

Nicotinamide adenine dinucleotide biosynthesis

Nicotinamide adenine dinucleotide (NAD) is a crucial cofactor in redox reactions in many metabolic pathways (180). NAD can be found in oxidized (NAD+) or reduced (NADH) forms. It is a crucial factor for both the TCA cycle and glycolysis, with NAD reduction being required for the conversion of glyceraldehyde-3-phosphate into 1,3-biphosphoglycerate. It also is used as an electron donor to make ATP *via* oxidative phosphorylation. NAD has other roles in the cell other than its oxidative potential. NAD regulates transcription factors involved in pathways linked to inflammation, cell cycle progression, apoptosis, metabolism or DNA repair. For a review see ref. 181.

There are two main pathways for NAD synthesis in a cell: *de novo* synthesis, from the amino acids tryptophan or aspartic acid or the salvage pathway, where NAD is recycled from compounds containing nicotinamide (180,182). The salvage synthesis pathway is essential to maintain NAD levels in mammals and is dependent on nicotinamide phosphoribosyltransferase, the rate-limiting enzyme that converts nicotinamide to nicotinamide mononucleotide. Blocking this enzyme with a specific chemical inhibitor (FK866) will lower NAD levels in cell, which can lead to cell death in many cancer types (183). As cancer cells rely on NAD availability, targeting NAD indirectly through nicotinamide phosphoribosyltransferase can be seen as a possible therapeutic target (184,185). A recent study demonstrated that PDA cells depend on NAD metabolism for their survival, with promising preclinical results when targeting nicotinamide phosphoribosyltransferase both genetically and with FK866 (184).

Conclusions

There has been much work done recently to define the spectrum of metabolic changes in PDA. Importantly, many of these metabolic changes appear to facilitate or be required for growth. Because tumor specific events, such as Kras mutations, play a critical role in driving much of the metabolic alterations in PDA and moreover because some of these alterations have been shown to be dispensable in normal cells, there is an exciting opportunity for therapeutic intervention. Indeed, the unique metabolism of PDA cells that allows their survival and proliferation could also be seen as their Achilles heel. As discussed in this review, our understanding of the complex metabolism of PDA suggests a number of rationally designed combination therapies that could be utilized in this deadly disease. Because metabolic enzymes are catalytic, they are potentially amenable to inhibition using small molecules and therefore we will probably see an increasing amount of metabolic-targeted therapies in the coming years. As metabolism is a complex and interconnected network, many unanswered questions still remain. However, as our disease models are improving and our capacity to measure complex metabolic reactions in aggregate are becoming more accessible and more robust, the future holds great promise.

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References

1. Siegel,R. *et al.* (2013) Cancer statistics, 2013. *CA. Cancer J. Clin.*, **63**, 11–30.
2. National Cancer Institute (2012). *SEER Cancer Statistics Factsheets: Pancreas Cancer*. National Cancer Institute, Bethesda, MD. http://seer.cancer.gov/statfacts/html/pancreas.html (6 May 2014, date last accessed).
3. Hidalgo,M. (2010) Pancreatic cancer. *N. Engl. J. Med.*, **362**, 1605–1617.
4. Vincent,A. *et al.* (2011) Pancreatic cancer. *Lancet*, **378**, 607–620.
5. Li,D. *et al.* (2004) Pancreatic cancer. *Lancet*, **363**, 1049–1057.
6. Erkan,M. *et al.* (2012) StellaTUM: current consensus and discussion on pancreatic stellate cell research. *Gut*, **61**, 172–178.
7. Chu,G.C. *et al.* (2007) Stromal biology of pancreatic cancer. *J. Cell. Biochem.*, **101**, 887–907.
8. Koong,A.C. *et al.* (2000) Pancreatic tumors show high levels of hypoxia. *Int. J. Radiat. Oncol. Biol. Phys.*, **48**, 919–922.
9. Guillaumond,F. *et al.* (2013) Strengthened glycolysis under hypoxia supports tumor symbiosis and hexosamine biosynthesis in pancreatic adenocarcinoma. *Proc. Natl. Acad. Sci. U. S. A.*, **110**, 3919–3924.
10. Olive,K.P. *et al.* (2009) Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science*, **324**, 1457–1461.
11. Provenzano,P.P. *et al.* (2012) Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell*, **21**, 418–429.
12. Kimmelman,A.C. *et al.* (2008) Genomic alterations link Rho family of GTPases to the highly invasive phenotype of pancreas cancer. *Proc. Natl. Acad. Sci. U. S. A.*, **105**, 19372–19377.
13. Campbell,P.J. *et al.* (2010) The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature*, **467**, 1109–1113.
14. Li,Y.H. *et al.* (2012) Inhibition of non-homologous end joining repair impairs pancreatic cancer growth and enhances radiation response. *PLoS One*, **7**, e39588.
15. Ying,H. *et al.* (2012) Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell*, **149**, 656–670.
16. Son,J. *et al.* (2013) Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature*, **496**, 101–105.
17. Lyssiotis,C.A. *et al.* (2013) Pancreatic cancers rely on a novel glutamine metabolism pathway to maintain redox balance. *Cell Cycle*, **12**, 1987–1988.
18. Feig,C. *et al.* (2012) The pancreas cancer microenvironment. *Clin. Cancer Res.*, **18**, 4266–4276.

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19. Neesse,A. *et al.* (2011) Stromal biology and therapy in pancreatic cancer. *Gut*, **60**, 861–868.
20. Apte,M.V. *et al.* (2012) Pancreatic stellate cells: a starring role in normal and diseased pancreas. *Front. Physiol.*, **3**, 344.
21. Oberstein,P.E. *et al.* (2013) Pancreatic cancer: why is it so hard to treat? *Therap. Adv. Gastroenterol.*, **6**, 321–337.
22. Milosevic,M. *et al.* (2012) Tumor hypoxia predicts biochemical failure following radiotherapy for clinically localized prostate cancer. *Clin. Cancer Res.*, **18**, 2108–2114.
23. Heller,A. *et al.* (2010) Immunogenicity of SEREX-identified antigens and disease outcome in pancreatic cancer. *Cancer Immunol. Immunother.*, **59**, 1389–1400.
24. Bazhin,A.V. *et al.* (2013) Overcoming immunosuppression as a new immunotherapeutic approach against pancreatic cancer. *Oncoimmunology*, **2**, e25736.
25. Bayne,L.J. *et al.* (2012) Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell*, **21**, 822–835.
26. Pylayeva-Gupta,Y. *et al.* (2012) Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. *Cancer Cell*, **21**, 836–847.
27. Clark,C.E. *et al.* (2007) Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res.*, **67**, 9518–9527.
28. Almoguera,C. *et al.* (1988) Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell*, **53**, 549–554.
29. Uemura,T. *et al.* (2004) Detection of K-ras mutations in the plasma DNA of pancreatic cancer patients. *J. Gastroenterol.*, **39**, 56–60.
30. Pylayeva-Gupta,Y. *et al.* (2011) RAS oncogenes: weaving a tumorigenic web. *Nat. Rev. Cancer*, **11**, 761–774.
31. Löhr,M. *et al.* (2005) Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. *Neoplasia*, **7**, 17–23.
32. Campbell,P.M. *et al.* (2004) Oncogenic Ras and its role in tumor cell invasion and metastasis. *Semin. Cancer Biol.*, **14**, 105–114.
33. Cox,A.D. *et al.* (2010) Ras history: The saga continues. *Small GTPases*, **1**, 2–27.
34. Aguirre,A.J. *et al.* (2003) Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. *Genes Dev.*, **17**, 3112–3126.
35. Hingorani,S.R. *et al.* (2005) Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. *Cancer Cell*, **7**, 469–483.
36. Ijichi,H. *et al.* (2006) Aggressive pancreatic ductal adenocarcinoma in mice caused by pancreas-specific blockade of transforming growth factor-beta signaling in cooperation with active Kras expression. *Genes Dev.*, **20**, 3147–3160.
37. Guerra,C. *et al.* (2007) Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. *Cancer Cell*, **11**, 291–302.
38. Gidekel Friedlander,S.Y. *et al.* (2009) Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras. *Cancer Cell*, **16**, 379–389.
39. Hingorani,S.R. *et al.* (2003) Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell*, **4**, 437–450.
40. Pellegata,N.S. *et al.* (1994) K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. *Cancer Res.*, **54**, 1556–1560.
41. Hezel,A.F. *et al.* (2006) Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev.*, **20**, 1218–1249.
42. Hudson,T.J. *et al.* (2010) International network of cancer genome projects. *Nature*, **464**, 993–998.
43. Cowley,M.J. *et al.* (2013) Understanding pancreatic cancer genomes. *J. Hepatobil. Pancreat. Sci*, **20**, 549–556.
44. Biankin,A.V. *et al.*; Australian Pancreatic Cancer Genome Initiative. (2012) Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature*, **491**, 399–405.
45. Yachida,S. *et al.* (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*, **467**, 1114–1117.
46. Vander Heiden,M.G. *et al.* (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*, **324**, 1029–1033.
47. Lunt,S.Y. *et al.* (2011) Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu. Rev. Cell Dev. Biol.*, **27**, 441–464.
48. Hanahan,D. *et al.* (2011) Hallmarks of cancer: the next generation. *Cell*, **144**, 646–674.
49. Vander Heiden,M.G. (2011) Targeting cancer metabolism: a therapeutic window opens. *Nat. Rev. Drug Discov.*, **10**, 671–684.
50. Ward,P.S. *et al.* (2012) Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer Cell*, **21**, 297–308.
51. Le,A. *et al.* (2012) Conceptual framework for cutting the pancreatic cancer fuel supply. *Clin. Cancer Res.*, **18**, 4285–4290.
52. White,E. (2013) Exploiting the bad eating habits of Ras-driven cancers. *Genes Dev.*, **27**, 2065–2071.
53. DeBerardinis,R.J. *et al.* (2008) The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.*, **7**, 11–20.
54. Hensley,C.T. *et al.* (2013) Glutamine and cancer: cell biology, physiology, and clinical opportunities. *J. Clin. Invest.*, **123**, 3678–3684.
55. Fan,J. *et al.* (2013) Glutamine-driven oxidative phosphorylation is a major ATP source in transformed mammalian cells in both normoxia and hypoxia. *Mol. Syst. Biol.*, **9**, 712.
56. Yang,Z. *et al.* (2010) Eaten alive: a history of macroautophagy. *Nat. Cell Biol.*, **12**, 814–822.
57. Levine,B. *et al.* (2008) Autophagy in the pathogenesis of disease. *Cell*, **132**, 27–42.
58. Kroemer,G. *et al.* (2010) Autophagy and the integrated stress response. *Mol. Cell*, **40**, 280–293.
59. Mizushima,N. *et al.* (2011) The role of Atg proteins in autophagosome formation. *Annu. Rev. Cell Dev. Biol.*, **27**, 107–132.
60. Boya,P. *et al.* (2013) Emerging regulation and functions of autophagy. *Nat. Cell Biol.*, **15**, 713–720.
61. Das,G. *et al.* (2012) Regulation and function of autophagy during cell survival and cell death. *Cold Spring Harb. Perspect. Biol.*, **4**,.
62. Klionsky,D.J. *et al.* (2011) A comprehensive glossary of autophagy-related molecules and processes (2nd edition). *Autophagy*, **7**, 1273–1294.
63. Yang,Z. *et al.* (2010) Mammalian autophagy: core molecular machinery and signaling regulation. *Curr. Opin. Cell Biol.*, **22**, 124–131.
64. Neufeld,T.P. (2010) TOR-dependent control of autophagy: biting the hand that feeds. *Curr. Opin. Cell Biol.*, **22**, 157–168.
65. Dodson,M. *et al.* (2013) Cellular metabolic and autophagic pathways: traffic control by redox signaling. *Free Radic. Biol. Med.*, **63**, 207–221.
66. Rodriguez-Rocha,H. *et al.* (2011) DNA damage and autophagy. *Mutat. Res.*, **711**, 158–166.
67. Kimmelman,A.C. (2011) The dynamic nature of autophagy in cancer. *Genes Dev.*, **25**, 1999–2010.
68. White,E. (2012) Deconvoluting the context-dependent role for autophagy in cancer. *Nat. Rev. Cancer*, **12**, 401–410.
69. Degenhardt,K. *et al.* (2006) Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell*, **10**, 51–64.
70. Rabinowitz,J.D. *et al.* (2010) Autophagy and metabolism. *Science*, **330**, 1344–1348.
71. Amaravadi,R.K. *et al.* (2011) Principles and current strategies for targeting autophagy for cancer treatment. *Clin. Cancer Res.*, **17**, 654–666.
72. Sui,X. *et al.* (2013) Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. *Cell Death Dis.*, **4**, e838.
73. Samaddar,J.S. *et al.* (2008) A role for macroautophagy in protection against 4-hydroxytamoxifen-induced cell death and the development of antiestrogen resistance. *Mol. Cancer Ther.*, **7**, 2977–2987.
74. Amaravadi,R.K. *et al.* (2007) Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma. *J. Clin. Invest.*, **117**, 326–336.
75. Wang,P. *et al.* (2013) MicroRNA 23b regulates autophagy associated with radioresistance of pancreatic cancer cells. *Gastroenterology*, **145**, 1133–1143.e12.
76. Liu,E.Y. *et al.* (2012) Autophagy and cancer–issues we need to digest. *J. Cell Sci.*, **125**(Pt 10), 2349–2358.
77. Yang,S. *et al.* (2011) Pancreatic cancers require autophagy for tumor growth. *Genes Dev.*, **25**, 717–729.
78. Guo,J.Y. *et al.* (2013) Autophagy is required for mitochondrial function, lipid metabolism, growth, and fate of KRAS(G12D)-driven lung tumors. *Autophagy*, **9**, 1636–1638.
79. Kim,M.J. *et al.* (2011) Involvement of autophagy in oncogenic K-Ras-induced malignant cell transformation. *J. Biol. Chem.*, **286**, 12924–12932.
80. Lock,R. *et al.* (2011) Autophagy facilitates glycolysis during Ras-mediated oncogenic transformation. *Mol. Biol. Cell*, **22**, 165–178.
81. Guo,J.Y. *et al.* (2011) Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. *Genes Dev.*, **25**, 460–470.
82. Wei,H. *et al.* (2011) Suppression of autophagy by FIP200 deletion inhibits mammary tumorigenesis. *Genes Dev.*, **25**, 1510–1527.
83. McMahon,H.T. *et al.* (2011) Molecular mechanism and physiological functions of clathrin-mediated endocytosis. *Nat. Rev. Mol. Cell Biol.*, **12**, 517–533.
84. Swanson,J.A. *et al.* (1995) Macropinocytosis. *Trends Cell Biol.*, **5**, 424–428.
85. Lim,J.P. *et al.* (2011) Macropinocytosis: an endocytic pathway for internalising large gulps. *Immunol. Cell Biol.*, **89**, 836–843.

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86. Bar-Sagi,D. *et al.* (1986) Induction of membrane ruffling and fluid-phase pinocytosis in quiescent fibroblasts by ras proteins. *Science*, **233**, 1061–1068.
87. Commisso,C. *et al.* (2013) Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. *Nature*, **497**, 633–637.
88. Kamphorst,J.J. *et al.* (2013) Hypoxic and Ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. *Proc. Natl. Acad. Sci. U. S. A.*, **110**, 8882–8887.
89. Berg,J.M. *et al.* (2002) *Biochemistry*. 5th edn. W.H. Freeman, New York, NY.
90. Vander Heiden,M.G. *et al.* (2011) Metabolic pathway alterations that support cell proliferation. *Cold Spring Harb. Symp. Quant. Biol.*, **76**, 325–334.
91. Von Hoff,D.D. *et al.* (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl. J. Med.*, **369**, 1691–1703.
92. Yun,J. *et al.* (2009) Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science*, **325**, 1555–1559.
93. Gaglio,D. *et al.* (2011) Oncogenic K-Ras decouples glucose and glutamine metabolism to support cancer cell growth. *Mol. Syst. Biol.*, **7**, 523.
94. Racker,E. *et al.* (1985) Glycolysis and methylaminoisobutyrate uptake in rat-1 cells transfected with ras or myc oncogenes. *Proc. Natl. Acad. Sci. U. S. A.*, **82**, 3535–3538.
95. Chun,S.Y. *et al.* (2010) Oncogenic KRAS modulates mitochondrial metabolism in human colon cancer cells by inducing HIF-1α and HIF-2α target genes. *Mol. Cancer*, **9**, 293.
96. Zhao,D. *et al.* (2013) Lysine-5 acetylation negatively regulates lactate dehydrogenase A and is decreased in pancreatic cancer. *Cancer Cell*, **23**, 464–476.
97. Icard,P. *et al.* (2012) A global view of the biochemical pathways involved in the regulation of the metabolism of cancer cells. *Biochim. Biophys. Acta*, **1826**, 423–433.
98. Slawson,C. *et al.* (2010) O-GlcNAc signaling: a metabolic link between diabetes and cancer? *Trends Biochem. Sci.*, **35**, 547–555.
99. Hanover,J.A. *et al.* (2010) The hexosamine signaling pathway: O-GlcNAc cycling in feast or famine. *Biochim. Biophys. Acta*, **1800**, 80–95.
100. Kornfeld,S. *et al.* (1964) The feedback control of sugar nucleotide biosynthesis in liver. *Proc. Natl. Acad. Sci. U. S. A.*, **52**, 371–379.
101. Wellen,K.E. *et al.* (2010) The hexosamine biosynthetic pathway couples growth factor-induced glutamine uptake to glucose metabolism. *Genes Dev.*, **24**, 2784–2799.
102. Mi,W. *et al.* (2011) O-GlcNAcylation is a novel regulator of lung and colon cancer malignancy. *Biochim. Biophys. Acta*, **1812**, 514–519.
103. Fuster,M.M. *et al.* (2005) The sweet and sour of cancer: glycans as novel therapeutic targets. *Nat. Rev. Cancer*, **5**, 526–542.
104. Hart,G.W. *et al.* (2010) Glycomics hits the big time. *Cell*, **143**, 672–676.
105. Jänne,P.A. *et al.* (2013) Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol.*, **14**, 38–47.
106. Ghadimi,H. *et al.* (1964) Free amino acids of cord plasma as compared with maternal plasma during pregnancy. *Pediatrics*, **33**, 500–506.
107. Wise,D.R. *et al.* (2010) Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem. Sci.*, **35**, 427–433.
108. DeBerardinis,R.J. *et al.* (2010) Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. *Oncogene*, **29**, 313–324.
109. Metallo,C.M. *et al.* (2012) Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature*, **481**, 380–384.
110. Wise,D.R. *et al.* (2011) Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of α-ketoglutarate to citrate to support cell growth and viability. *Proc. Natl. Acad. Sci. U. S. A.*, **108**, 19611–19616.
111. DeBerardinis,R.J. *et al.* (2007) Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc. Natl. Acad. Sci. U. S. A.*, **104**, 19345–19350.
112. Sinha,K. *et al.* (2013) Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis. *Arch. Toxicol.*, **87**, 1157–1180.
113. Imlay,J.A. *et al.* (1988) DNA damage and oxygen radical toxicity. *Science*, **240**, 1302–1309.
114. Sosa,V. *et al.* (2013) Oxidative stress and cancer: an overview. *Ageing Res. Rev.*, **12**, 376–390.
115. Hurd,T.R. *et al.* (2012) Redox regulation of cell migration and adhesion. *Trends Cell Biol.*, **22**, 107–115.
116. Iles,K.E. *et al.* (2002) Macrophage signaling and respiratory burst. *Immunol. Res.*, **26**, 95–105.
117. Sena,L.A. *et al.* (2012) Physiological roles of mitochondrial reactive oxygen species. *Mol. Cell*, **48**, 158–167.
118. Fruehauf,J.P. *et al.* (2007) Reactive oxygen species: a breath of life or death? *Clin. Cancer Res.*, **13**, 789–794.
119. Cui,X. (2012) Reactive oxygen species: the achilles' heel of cancer cells? *Antioxid. Redox Signal.*, **16**, 1212–1214.
120. Liou,G.Y. *et al.* (2010) Reactive oxygen species in cancer. *Free Radic. Res.*, **44**, 479–496.
121. Storz,P. (2005) Reactive oxygen species in tumor progression. *Front. Biosci.*, **10**, 1881–1896.
122. Pani,G. *et al.* (2010) Metastasis: cancer cell's escape from oxidative stress. *Cancer Metastasis Rev.*, **29**, 351–378.
123. Weinberg,F. *et al.* (2010) Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. *Proc. Natl. Acad. Sci. U. S. A.*, **107**, 8788–8793.
124. Du,J. *et al.* (2013) Regulation of pancreatic cancer growth by superoxide. *Mol. Carcinog.*, **52**, 555–567.
125. Romanowska,M. *et al.* (2007) DNA damage, superoxide, and mutant K-ras in human lung adenocarcinoma cells. *Free Radic. Biol. Med.*, **43**, 1145–1155.
126. Calvert,R.J. *et al.* (2013) K-ras 4A and 4B mRNA levels correlate with superoxide in lung adenocarcinoma cells, while at the protein level, only mutant K-ras 4A protein correlates with superoxide. *Lung Cancer*, **80**, 263–269.
127. Vaquero,E.C. *et al.* (2004) Reactive oxygen species produced by NAD(P)H oxidase inhibit apoptosis in pancreatic cancer cells. *J. Biol. Chem.*, **279**, 34643–34654.
128. Trachootham,D. *et al.* (2008) Redox regulation of cell survival. *Antioxid. Redox Signal.*, **10**, 1343–1374.
129. Shelton,P. *et al.* (2013) The transcription factor NF-E2-related factor 2 (Nrf2): a protooncogene? *FASEB J.*, **27**, 414–423.
130. Hayes,J.D. *et al.* (2009) NRF2 and KEAP1 mutations: permanent activation of an adaptive response in cancer. *Trends Biochem. Sci.*, **34**, 176–188.
131. DeNicola,G.M. *et al.* (2011) Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. *Nature*, **475**, 106–109.
132. Lister,A. *et al.* (2011) Nrf2 is overexpressed in pancreatic cancer: implications for cell proliferation and therapy. *Mol. Cancer*, **10**, 37.
133. Semenza,G.L. (2013) HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *J. Clin. Invest.*, **123**, 3664–3671.
134. Zhao,F. *et al.* (2010) Imatinib resistance associated with BCR-ABL upregulation is dependent on HIF-1alpha-induced metabolic reprograming. *Oncogene*, **29**, 2962–2972.
135. Dang,C. V. (2007) The interplay between MYC and HIF in the Warburg effect. *Ernst Schering Found. Symp. Proc.*, **4**, 35–53.
136. Chaika,N.V. *et al.* (2012) MUC1 mucin stabilizes and activates hypoxia-inducible factor 1 alpha to regulate metabolism in pancreatic cancer. *Proc. Natl. Acad. Sci. U. S. A.*, **109**, 13787–13792.
137. Chen,C. *et al.* (2009) siRNA targeting HIF-1alpha induces apoptosis of pancreatic cancer cells through NF-kappaB-independent and -dependent pathways under hypoxic conditions. *Anticancer Res.*, **29**, 1367–1372.
138. Chen,J. *et al.* (2003) Dominant-negative hypoxia-inducible factor-1 alpha reduces tumorigenicity of pancreatic cancer cells through the suppression of glucose metabolism. *Am. J. Pathol.*, **162**, 1283–1291.
139. Wilkinson,S. *et al.* (2009) Hypoxia-selective macroautophagy and cell survival signaled by autocrine PDGFR activity. *Genes Dev.*, **23**, 1283–1288.
140. Zhang,H. *et al.* (2008) Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia. *J. Biol. Chem.*, **283**, 10892–10903.
141. Rausch,V. *et al.* (2012) Autophagy mediates survival of pancreatic tumour-initiating cells in a hypoxic microenvironment. *J. Pathol.*, **227**, 325–335.
142. Guerra,C. *et al.* (2013) Genetically engineered mouse models of pancreatic adenocarcinoma. *Mol. Oncol.*, **7**, 232–247.
143. Levine,A.J. *et al.* (2010) The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. *Science*, **330**, 1340–1344.
144. Harris,C.C. (1996) p53 tumor suppressor gene: from the basic research laboratory to the clinic–an abridged historical perspective. *Carcinogenesis*, **17**, 1187–1198.
145. Kruse,J.P. *et al.* (2009) Modes of p53 regulation. *Cell*, **137**, 609–622.
146. Levine,A.J. *et al.* (1991) The p53 tumour suppressor gene. *Nature*, **351**, 453–456.
147. Aylon,Y. *et al.* (2007) Living with p53, dying of p53. *Cell*, **130**, 597–600.
148. Scarpa,A. *et al.* (1993) Pancreatic adenocarcinomas frequently show p53 gene mutations. *Am. J. Pathol.*, **142**, 1534–1543.
149. Oshima,M. *et al.* (2013) Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. *Ann. Surg.*, **258**, 336–346.

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150. Pérez-Mancera,P.A. *et al.* (2012) What we have learned about pancreatic cancer from mouse models. *Gastroenterology*, **142**, 1079–1092.
151. Gottlieb,E. *et al.* (2010) p53 regulation of metabolic pathways. *Cold Spring Harb. Perspect. Biol.*, **2**, a001040.
152. Shen,L. *et al.* (2012) The fundamental role of the p53 pathway in tumor metabolism and its implication in tumor therapy. *Clin. Cancer Res.*, **18**, 1561–1567.
153. Illuzzi,J.L. *et al.* (2011) Modifications of p53 and the DNA damage response in cells expressing mutant form of the protein huntingtin. *J. Mol. Neurosci.*, **45**, 256–268.
154. Johnson,R.F. *et al.* (2012) Nuclear factor-κB, p53, and mitochondria: regulation of cellular metabolism and the Warburg effect. *Trends Biochem. Sci.*, **37**, 317–324.
155. Madan,E. *et al.* (2011) Regulation of glucose metabolism by p53: emerging new roles for the tumor suppressor. *Oncotarget*, **2**, 948–957.
156. Matoba,S. *et al.* (2006) p53 regulates mitochondrial respiration. *Science*, **312**, 1650–1653.
157. Suzuki,S. *et al.* (2010) Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc. Natl. Acad. Sci. U. S. A.*, **107**, 7461–7466.
158. Hu,W. *et al.* (2010) Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. *Proc. Natl. Acad. Sci. U. S. A.*, **107**, 7455–7460.
159. Kondoh,H. *et al.* (2005) Glycolytic enzymes can modulate cellular life span. *Cancer Res.*, **65**, 177–185.
160. Schwartzenberg-Bar-Yoseph,F. *et al.* (2004) The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. *Cancer Res.*, **64**, 2627–2633.
161. Bensaad,K. *et al.* (2006) TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*, **126**, 107–120.
162. Jiang,P. *et al.* (2011) p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat. Cell Biol.*, **13**, 310–316.
163. Rosenfeldt,M.T. *et al.* (2013) p53 status determines the role of autophagy in pancreatic tumour development. *Nature*, **504**, 296–300.
164. Lizcano,J.M. *et al.* (2004) LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. *EMBO J.*, **23**, 833–843.
165. Lüttges,J. *et al.* (2004) Rare ductal adenocarcinoma of the pancreas in patients younger than age 40 years. *Cancer*, **100**, 173–182.
166. Morton,J.P. *et al.* (2010) LKB1 haploinsufficiency cooperates with Kras to promote pancreatic cancer through suppression of p21-dependent growth arrest. *Gastroenterology*, **139**, 586–97, 597.e1.
167. Yuan,H.X. *et al.* (2013) Nutrient sensing, metabolism, and cell growth control. *Mol. Cell*, **49**, 379–387.
168. Mihaylova,M.M. *et al.* (2011) The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. *Nat. Cell Biol.*, **13**, 1016–1023.
169. Jeon,S.M. *et al.* (2012) AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. *Nature*, **485**, 661–665.
170. Egan,D.F. *et al.* (2011) Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. *Science*, **331**, 456–461.
171. Guo,J.Y. *et al.* (2013) Autophagy suppresses progression of K-ras-induced lung tumors to oncocytomas and maintains lipid homeostasis. *Genes Dev.*, **27**, 1447–1461.
172. Zadra,G. *et al.* (2013) The fat side of prostate cancer. *Biochim. Biophys. Acta*, **1831**, 1518–1532.
173. Ma,X. *et al.* (2011) The metabolic features of normal pancreas and pancreatic adenocarcinoma: preliminary result of *in vivo* proton magnetic resonance spectroscopy at 3.0 T. *J. Comput. Assist. Tomogr.*, **35**, 539–543.
174. Yabushita,S. *et al.* (2013) Metabolomic and transcriptomic profiling of human K-ras oncogene transgenic rats with pancreatic ductal adenocarcinomas. *Carcinogenesis*, **34**, 1251–1259.
175. Zhang,G. *et al.* (2013) Integration of metabolomics and transcriptomics revealed a fatty acid network exerting growth inhibitory effects in human pancreatic cancer. *Clin. Cancer Res.*, **19**, 4983–4993.
176. Mohammed,A. *et al.* (2012) Endogenous n-3 polyunsaturated fatty acids delay progression of pancreatic ductal adenocarcinoma in Fat-1-p48(Cre/+)-LSL-Kras(G12D/+) mice. *Neoplasia*, **14**, 1249–1259.
177. Philip,B. *et al.* (2013) A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. *Gastroenterology*, **145**, 1449–1458.
178. Wang,F. *et al.* (2009) Increased lipid metabolism and cell turnover of MiaPaCa2 cells induced by high-fat diet in an orthotopic system. *Metabolism.*, **58**, 1131–1136.
179. Pierre,A.S. *et al.* (2013) Trans-10, cis-12 conjugated linoleic acid induced cell death in human colon cancer cells through reactive oxygen species-mediated ER stress. *Biochim. Biophys. Acta*, **1831**, 759–768.
180. Di Stefano,M. *et al.* (2013) Diversification of NAD biological role: the importance of location. *FEBS J.*, **280**, 4711–4728.
181. Chiarugi,A. *et al.* (2012) The NAD metabolome–a key determinant of cancer cell biology. *Nat. Rev. Cancer*, **12**, 741–752.
182. Garten,A. *et al.* (2009) Nampt: linking NAD biology, metabolism and cancer. *Trends Endocrinol. Metab.*, **20**, 130–138.
183. Billington,R.A. *et al.* (2008) NAD depletion by FK866 induces autophagy. *Autophagy*, **4**, 385–387.
184. Chini,C.C.S. *et al.* (2013) Targeting of NAD metabolism in pancreatic cancer cells: potential novel therapy for pancreatic tumors. *Clin. Cancer Res.*, **20**, 120–130.
185. von Heideman,A. *et al.* (2010) Safety and efficacy of NAD depleting cancer drugs: results of a phase I clinical trial of CHS 828 and overview of published data. *Cancer Chemother. Pharmacol.*, **65**, 1165–1172.

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A dose escalation study of gemcitabine plus oxaliplatin in combination with imatinib for gemcitabine-refractory advanced pancreatic adenocarcinoma

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Background: Targeting platelet-derived growth factor receptor-β (PDGFR-β) is a potential strategy to reduce tumour-related interstitial fluid pressure, enhance cytotoxic drug uptake and reduce chemoresistance. This study aimed to define safe doses of gemcitabine plus oxaliplatin when combined with imatinib (potent PDGFR-β inhibitor) in patients with advanced gemcitabine-refractory pancreatic cancer (PC).

Patients and methods: Using a 3 + 3 dose escalation design, patients of performance status zero or one were entered into five sequential dose levels (DLs) of gemcitabine [day 1, from 400 (DL1) to 1000 mg/m^2 (DL4)] and oxaliplatin [day 2, 85 (DL1–4) and 100 mg/m^2 (DL5)] two weekly. Imatinib 400 mg od was given for 7 days (day minus 2–5) each cycle.

Results: Twenty-seven patients received 168 cycles in total. Median age was 61 years (44–74 years). Dose-limiting toxicities occurred in two of two patients at DL5 (G4 thrombocytopenia, G3 lethargy), defined as the maximum tolerated dose and one of six patients at DL4 (G3 lethargy). DL4 was expanded. There were 2 of 27 partial responses and 14 of 27 stable disease [disease control 52%, 95% confidence interval (CI) 32% to 71%]. Median progression-free survival and overall survival were 4.6 (95% CI 2.1–7.0) and 5.6 months (95% CI 2.5–8.7), respectively.

Conclusion: In gemcitabine-refractory PC, gemcitabine (1000 mg/m^2) and oxaliplatin (85 mg/m^2) can be safely combined with imatinib given on a 7 days on and 7 days off intermittent schedule.

Key words: adenocarcinoma, gemcitabine, gemcitabine-refractory, imatinib, oxaliplatin, pancreatic

introduction

Pancreatic adenocarcinoma is a lethal chemoresistant disease associated with a dismal 5-year survival rate of 6% [1]. The majority of patients have documented or occult disseminated disease at presentation. Gemcitabine remains a standard of care for the treatment of chemonaive advanced pancreatic cancer (PC) [2]. For patients who develop resistance to gemcitabine but who remain of good performance status (PS), there is currently no standard of care owing to a paucity of level III data. A randomised trial of rubitecan against best supportive care (BSC) failed to show a survival benefit [3] and due to poor accrual, the CONKO-003 randomised trial of oxaliplatin/fluorouracil against BSC [4] was closed and redesigned with fluorouracil/folinic acid replacing the BSC arm, therein demonstrating superiority for oxaliplatin/fluorouracil over fluorouracil [5]. Other oxaliplatin-based combinations have been assessed and among these, the gemcitabine/oxaliplatin (GemOx) doublet has shown phase II activity associated with amelioration of symptoms in gemcitabine-refractory PC [6]. The notion that only a minority of pancreatic patients can tolerate second-line therapy was challenged by a recent randomised trial of erlotinib plus gemcitabine or capecitabine for untreated patients, in which 51% of patients received prespecified second-line therapy with capecitabine or gemcitabine [7].

Raised tumour interstitial fluid pressure (IFP) is one of several mechanisms that may contribute to chemoresistance in pancreatic and other solid tumours by impeding transcapillary transport and efficient uptake of therapeutic agents [8]. The pathogenesis of tumour-related raised IFP has not been fully elucidated but involves all tumour compartments including the stroma and supporting vasculature. Stromal platelet-derived growth factor receptor-β (PDGFR-β) may contribute to the modulation of IFP, governed primarily by the paracrine stimulation of stromal fibroblasts resulting in contracture of the interstitium [9]. Platelet-derived growth factor (PDGF)

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signalling is also implicated in the autocrine growth stimulation of tumour cells and promotion of angiogenesis [9].

Imatinib is a tyrosine kinase (TK) inhibitor with potent anti-PDGFR-B and anti-c-kit activity, and is licensed for the treatment of gastrointestinal (GI) stromal tumours and chronic myeloid leukaemia. In one body of preclinical experimentation, antagonism of PDGFR-β with imatinib mesylate reduced tumour-related IFP [10] and enhanced the uptake and efficacy of concomitantly administered chemotherapeutic drugs, while showing no activity for imatinib alone [11, 12] leading the authors to propose PDGFR-β targeting as a strategy to improve chemotherapeutic efficiency [13]. This may be particularly relevant in PC, which is often characterised by dense stromal reactions. In preclinical models of PC, imatinib showed limited single-agent antitumour activity [14, 15], enhanced the antitumour effect of gemcitabine [15] and increased the uptake of therapeutic agents including a radioimmunotherapy regimen [16].

Consistent with preclinical observations, imatinib does not appear to have single-agent clinical activity in PC [17, 18]. It has increasingly been evaluated in combination with chemotherapy in a range of solid tumours [19–22]. Early reports indicated considerable toxicity when imatinib was administered on a continuous daily schedule in combination with chemotherapy including dose-limiting myelotoxicity and fatigue when given with low doses of gemcitabine in chemorefractory solid tumours [23]. Intermittent imatinib dose scheduling may increase the feasibility of a combinatorial approach.

The primary objective of this dose escalation study was to determine the safety, feasibility, dose-limiting toxicities (DLTs) and thus, maximum tolerated doses (MTD) of the combination of GemOx chemotherapy with intermittently administered imatinib in patients with gemcitabine-refractory PC.

methods

patients

Eligibility criteria included age >18 years; locally advanced (LA) or metastatic gemcitabine-refractory PC (progression during or <6 months of previous gemcitabine treatment including adjuvant therapy); Eastern Cooperative Oncology Group PS of zero to one; adequate bone marrow/renal function; serum aspartate aminotransferase <2× upper limit of normal (ULN) (or <5× ULN if liver metastases present) and a life expectancy of >10 weeks. Measurable disease was not obligatory. Exclusion criteria included uncontrolled medical conditions; chemotherapy or investigational drugs within 4 weeks; prior radiation; peripheral neuropathy >grade 1 and known brain metastases. All patients provided written informed consent. The study was approved by the local Scientific Review and Research Ethics Committees (CCR 2731) and was conducted in accordance with International Conference on Harmonization and Good Clinical Practice guidelines.

study design and treatment

This single centre, open-label, phase I study employed a 3 + 3 dose escalation design [24] to determine the MTDs and overall safety/tolerability of gemcitabine and oxaliplatin in the GemOx doublet when combined with intermittently administered fixed-dose imatinib. Gemcitabine was administered i.v. over 30 min on day 1 and oxaliplatin was administered i.v. over 2 h on day 2 of a two weekly cycle. Standard antiemetics were given. Imatinib, at a fixed dose of 400 mg/day, was given orally on an intermittent 7 days on treatment and 7 days off treatment (7/7) schedule starting 2 days before day 1 gemcitabine and including days 1 and 2 of i.v. chemotherapy. Dose escalation in sequential dose levels (DLs) was mainly of gemcitabine with one dose escalation step for oxaliplatin (Table 1).

DL cohorts comprised three or more patients assessable for DLT in the first 4 weeks (2 cycles), expanding to six patients if one DLT occurred. Dose escalation proceeded to the subsequent DL in the absence of DLT in three patients or less than or equal to one DLT among six patients. The MTD of gemcitabine and oxaliplatin in the three-drug regimen was that which induced DLT in at least two of a maximum of six patients thereby terminating accrual to that DL. The DL below the MTD could be expanded by up to six patients and declared the recommended dose for possible further evaluation (if associated with less than or equal to one DLT among six patients). Patients not assessable for DLT in the first 4 weeks for reasons other than toxicity were replaced.

DLTs were febrile neutropenia, absolute neutrophil count (ANC) $<0.5 \times 10^9$/l lasting >7 days without fever; platelet count $<25 \times 10^9$/l; grade 3/4 diarrhoea despite aggressive antidiarrhoeal therapy; other non-haematological toxicity ≥grade 3 (excluding alopecia, nausea/vomiting and transient elevation of liver enzymes) and sensory neuropathy >grade 2 lasting >7 days. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Next cycle treatment required ANC $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l and resolution of any non-haematological toxicities to ≤grade 1, otherwise treatment was delayed with a maximum allowable delay of 4 weeks. Grade 3/4 toxic effects attributable to gemcitabine resulted in dose de-escalation to the next lower DL. Oxaliplatin was reduced from 85 to 65 mg/m^2 in the event of grade 2 sensory neuropathy >7 days and discontinued for grade 3 neuropathy. Oxaliplatin infusions were lengthened from 2 to 6 h if laryngeal dysaethesia occurred. Grade 3/4 toxic effects attributable to imatinib resulted in subsequent reduction of duration of dosing from 7 to 5 days (starting the day before gemcitabine). Treatment continued for 12 cycles (or longer in patients deriving clinical benefit) unless unacceptable toxicity, progressive disease or consent withdrawal occurred.

patient evaluation

Screening included a clinical history, physical examination, full blood count, biochemistry panel, coagulation and electrocardiogram. At every treatment visit, toxicity and standard laboratory panels were assessed, with additional full blood counts (FBCs) on days 4, 8 and 11 of cycles 1 and 2. CA 19-9 was recorded on day 1 of every other cycle. Tumour response was evaluated by computed tomography of the chest/abdomen/pelvis (RECIST guidelines [25]) at baseline (within 28 days of starting protocol therapy) and thereafter every 8 weeks. Responses were confirmed at least 4 weeks after responding scans.

study end points and objectives

The primary objective was to determine the MTD of gemcitabine and oxaliplatin in the GemOx doublet when combined with intermittently administered imatinib based on the end point of DLTs in the first

Table 1. Dose escalation schedule

DL	Gemcitabine dose (mg/m^2)	Oxaliplatin dose (mg/m^2)	Imatinib dose (mg)
1	200	85	400
1 (starting)	400	85	400
2	600	85	400
3	800	85	400
4	1000	85	400
5	1000	100	400

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2 cycles (4 weeks). Objective response rates, overall survival (OS) and progression-free survival (PFS) were secondary end points in the intention-to-treat (ITT) population. Survival was calculated from the date of study registration to the date of death (OS) or progression/death (PFS) using Kaplan–Meier with patients censored at the date of last follow-up if still alive.

results

patients

Twenty-seven patients were enrolled between June 2006 and March 2010. The database was analysed in May 2010 after the final patient had completed their DLT assessment period (4 weeks). Patient characteristics are shown in Table 2; 63% of patients were male and the majority of patients were of PS zero or one (96%) with metastatic disease (89%). All patients were gemcitabine-refractory, 40% having previously received gemcitabine in a cytotoxic doublet with capecitabine or cisplatin and 22% having received adjuvant gemcitabine-based therapy. Of the 27 patients, 4 were non-assessable for DLT (DL2 $n = 1$, DL4 $n = 3$) due to disease-related deterioration in cycles 1/2 and were replaced in their respective cohorts. All 27 patients were assessable for safety and efficacy in the ITT population. The median time from the final cycle of previous chemotherapy to study registration was 59 days (20–265 days).

Table 2. Patient characteristics

	All patients (ITT), $N = 27$[a] (%)
Median age in years (range)	61 (44–74)
Male:Female, *n* (%)	17:10 (63:27)
Site of primary, *n* (%)	
Body/tail	5 (18)
Complete pancreas	1 (4)
Head	21 (78)
Performance status, *n* (%)	
0/1	26 (96)
2	1 (4)[c]
Disease extent, *n* (%)	
Primary/locally advanced	3 (11)
Metastatic	24 (89)
Previous treatment[b], *n* (%)	
GEM alone	8 (30)
GEM-CAP or GEM-CIS[c]	11(40)
GEM or GEM-CAP + biological agent[d]	8 (30)

[a]Four patients were non-evaluable for DLT (DL2 $n = 1$, DL4 $n = 3$; disease-related deterioration in cycle 1).

[b]Six patients had progressed during/after adjuvant therapy (gemcitabine $n = 4$, gemcitabine + cisplatin $n = 1$, gemcitabine + erlotinib $n = 1$).

[c]Gemcitabine + capecitabine or gemcitabine + cisplatin.

[d]Biological agents included erlotinib, bevacizumab and telovac vaccine (in previous trial protocols).

[e]One PS 2 patient was entered and constituted a protocol violation.

ITT, intention-to-treat; CIS, cisplatin; CAP, capecitabine; DLT, dose-limiting toxicity; DL, dose level; GEM, gemcitabine; GEMCAP, gemcitabine+capecitabine; GEM-CIS, gemcitabine +cisplatin; PS, performance status.

DLT and MTD

No DLTs were observed in each of the three patients recruited to DLs 1, 2 or 3. One additional patient was recruited to DL2 ($n = 4$) to replace a patient non-assessable for DLT. At DL4, there was one DLT observed among six patients (G3 lethargy). At DL5, two DLTs occurred in the two recruited patients (G4 thrombocytopenia, G3 lethargy). DL5 was declared the MTD. DL4 was expanded to 15 patients in total including 3 replacement patients with no further DLTs. DL4 was therefore recommended as the dose for further evaluation.

safety

Thrombocytopenia (all grades) was the most frequent haematological toxicity across all DLs (Table 3). Grade 3/4 thrombocytopenia occurred in 1 of 2 patients at DL5 and was observed in 3 of 15 (20%) patients at the recommended DL4 (grade 1/2 = 80%). At DL4, grade 3/4 neutropenia was observed in only 13% of patients. Lethargy was one of the most frequent non-haematological toxicities across all DLs. Grade 3/4 lethargy was observed in 1 of 2 patients at DL5 and in 6 of 15 (40%) patients at DL4. At DL4, non-haematological grade 3/4 toxic effects with frequencies >10% included nausea/vomiting (20%), infection (13%) and lethargy (40%). Grade 2 peripheral neuropathy was seen in 2 of 15 (13%) patients with no cases of grade 3/4 peripheral neuropathy. One patient at each DL experienced oedema.

Treatment-related serious adverse events were observed in 10 patients including infection with normal ANC $n = 6$; febrile neutropenia $n = 2$; vomiting $n = 4$; fever $n = 3$; atrial flutter $n = 1$; abdominal pain $n = 1$; constipation $n = 1$ and hyperglycemia $n = 1$. There was one suspected unexpected serious adverse reaction (GI bleeding and renal failure secondary to disease-related thrombosis and anticoagulation) leading to death.

treatment delivery

A total of 168 cycles of treatment has been given to 27 patients. The median number of cycles administered was 4 (range 1–24). Two patients continue on protocol therapy. Four patients continued beyond 12 cycles. Reasons for discontinuing treatment included documented progressive disease ($n = 15$), clinical progressive disease ($n = 2$), patient request ($n = 4$), toxicity ($n = 3$) and treatment delay >4 weeks ($n = 1$).

efficacy

Twenty-four patients have died. Median follow-up for the three surviving patients is 7.3 months (range 1.9–8.4). Median OS (Figure 1) for all patients was 5.6 months [95% confidence interval (CI) 2.5–8.7] and 1-year survival was 28.1% (95% 12.1% to 46.6%). PFS (Figure 2) for all patients was 4.6 months (95% CI 2.1–7.0) with a 1-year PFS of 10.7% (95% CI 2.0% to 27.9%). For tumour response, six patients had died and/or were not evaluable. The objective response rate (unconfirmed) was 2 of 27 (7%, 95% CI 1% to 24%) with a disease control rate of 52% (95% CI 32 to 71%). Both partial responses were observed at DL4 and in patients with LA disease, one of which comprised a very bulky primary tumour (initially measuring 13.7 cm and reducing to 7.8 cm). Seven of 27 patients (27%) had progressive

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Table 3. Toxicity in all cycles (ITT).

	DL1 (n = 3)		DL2 (n = 3)		DL3 (n = 4)		DL4 (n = 12)		DL5 (n = 2)	
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Haematological										
Neutropenia	0	0	1	0	1	0	5	2	0	0
Thrombocytopenia	2	0	3	0	1	1	12	3	1	1[a]
Anaemia	3	0	3	0	2	1	14	1	1	1
Non-haematological										
Diarrhoea	1	0	3	0	3	0	8	1	0	0
Nausea/vomiting	2	0	1	0	3	0	10	3	1	0
Peripheral neuropathy	2	0	4	0	3	0	11[a]	0	1	0
Lethargy	3	0	3	1	3	0	8	6[a]	0	2[a]
Stomatitis	0	0	2	0	1	0	2	0	1	0
Infection	1	0	1	0	1	1	4	2	1	0
Rash	1	0	0	0	1	0	1	0	0	0
Oedema	1	0	1	0	1	0	1	0	1	0

[a]Dose limiting (in cycles 1/2) in one patient each in the cohort ± peripheral neuropathy: G1 $n = 9$, G2 $n = 2$.
ITT, intention-to-treat; DL, dose level.

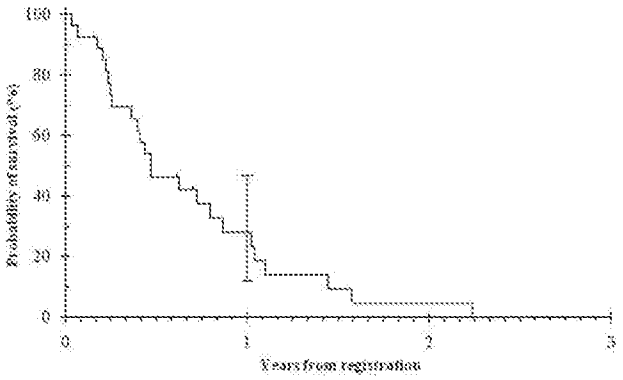


Figure 1. Overall survival (OS). The median OS was 5.6 months (95% confidence interval 2.5–8.7).

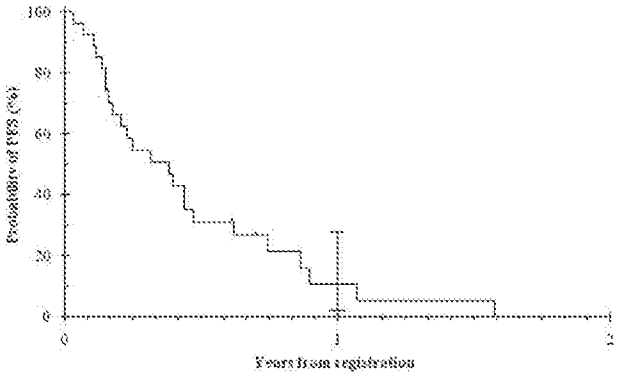


Figure 2. Progression-free survival (PFS). The median PFS was 4.6 months (95% confidence interval 2.1–7.0).

disease. In a prespecified analysis of CA 19-9 trends, no patients achieved a 50% reduction in CA 19-9 levels by 8 weeks.

discussion

Based on the hypothesis that PDGFR-β targeting lowers tumour-related IFP and improves chemotherapeutic uptake, our study was designed to examine the safety and feasibility of combining imatinib (400 mg/day) on an intermittent 7/7 schedule with gemcitabine and oxaliplatin in patients with chemorefractory PC. At the toxic DL5, the DLTs were thrombocytopenia and fatigue. At the recommended doses of gemcitabine 1000 mg/m^2 and oxaliplatin 85 mg/m^2, one DLT of lethargy was observed among 15 patients (12 assessable for DLT).

At study inception, GemOx appeared to be a promising regimen for the first-line treatment of PC and appeared to be active in the second-line setting [6] leading to its selection for this study, although gemcitabine was not given at a fixed-dose rate (greater potential for myelosuppression). Subsequently, however, a randomised trial failed to report a significant improvement in survival for first-line GemOx compared with gemcitabine alone [26]. Nonetheless, platinum-based combination treatments are often used for treating PC [27].

We chose not to investigate imatinib doses >400 mg/day because of the toxicity observed when this dose was given on a daily schedule. Hence, we sought to lessen toxicity and optimise chemotherapy doses with an intermittent 7/7 scheduling of the 400 mg/day imatinib dose. In a phase I study of patients with chemorefractory solid tumours treated with imatinib at doses of 300 or 400 mg/day continuously in combination with gemcitabine at doses of 700 or 800 mg/m^2 on days 1, 8 and 15, four of seven patients experienced DLTs (neutropenia $n = 2$, thrombocytopenia $n = 1$, fatigue $n = 1$) leading to early termination of the study [23]. Neutropenia was not dose limiting when imatinib was administered intermittently in our study but dose-limiting thrombocytopenia and lethargy were evident at the MTD (toxic dose) upon increasing the dose of oxaliplatin.

Since the initiation of our trial, two other phase I trials have been published examining the safety and feasibility of combining intermittent imatinib and chemotherapy [28, 29]. In these studies, imatinib was scheduled to straddle chemotherapy delivery to potentially optimise chemotherapy

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uptake and also because single-agent activity was not anticipated. In one study, 30 patients with GI malignancies (17 with PC) were assigned to escalating doses of imatinib (300–700 mg/day) for 8 days, starting 4 days before fixed-dose biweekly fluorouracil/leucovorin; DLTs of severe neutropenia, central fluid retention and nausea were observed at the 700 mg/day imatinib dose and there were no significant pharmacokinetic (PK) interactions [28]. In the other study, an intermittent imatinib schedule was employed after the demonstration of excessive toxicity when imatinib 300 mg/day was combined with gemcitabine 600 mg/m^2 on days 1, 8 and 15 in 54 patients with chemorefractory solid tumours (10 patients with PC) [29]. Imatinib 400 mg/day was given for 5 days, starting 2 days before every gemcitabine administration with no demonstration of DLT (maximum gemcitabine dose of 1500 mg/m^2) or PK drug–drug interactions.

In our study, the target dose of gemcitabine (1000 mg/m^2) was deliverable with intermittent imatinib but escalation to the target dose of oxaliplatin (100 mg/m^2) was not feasible. PK analysis was not carried out since the drugs assessed are not metabolised by common pathways and drug interactions were not anticipated as supported above. The decision to start imatinib at least 2 days before chemotherapy is supported by preclinical data; in a mouse model of anaplastic thyroid tumours treated with the epothilone EPO906 combined with imatinib, EPO906 uptake was maximal when imatinib was started 2 days before and continued on the day of chemotherapy [12].

The addition of imatinib to GemOx at the recommended DL was well tolerated. Importantly, the rate of grade 3/4 neutropenia was only 13% compared with 8%–12% with GemOx alone in studies of pretreated [6] and chemonaive PC patients [26]. No cases of grade 3 peripheral neuropathy were observed compared with 10% [26] to 12% [6] patients treated with GemOx alone and may reflect the lower dose of oxaliplatin used (85 mg/m^2) in our study. However, grade 3/4 nausea (20%) and lethargy (40%) are higher compared with the 0%–6% observed with GemOx alone [6, 26]. Fluid retention, particularly periorbital and leg oedema, is a well-recognised dose-dependent toxicity of imatinib [30, 31] thought to be mediated by PDGFR-β inhibition. In the study of 5-fluorouracil/leucovorin and imatinib in refractory GI tract tumours, fluid retention (all grades) was observed in 27% of patients including one patient (bile duct cancer) with dose-limiting non-cardiac fluid retention. However, dose escalation in that study encompassed higher doses of imatinib up to 700 mg/day, with a recommended dose of 600 mg/day in combination with chemotherapy. In our study, grade 1/2 fluid retention was observed in fewer patients (18.5% of all patients) using the 400 mg/day imatinib dose.

The assessment of efficacy was a secondary objective. The median OS and PFS were 5.6 and 4.6 months, respectively, with an overall response rate and disease control of 7% and 52%, respectively. The survival appears to be better than the median OS of 2.3 and 3.1 months associated with BSC in the two unpublished randomised trials in patients with chemorefractory PC [3, 4]. The results are also comparable to the efficacy associated with single-agent gemcitabine in the first-line treatment of PC, which is noteworthy given that patients were refractory to previous gemcitabine treatment (median time since completion of previous gemcitabine was 59 days). The patients in this study, however, represent a highly selected group with good PS, a well-recognised favourable prognostic variable [32–34] and a relatively uncommon scenario for pretreated PC. Any potential efficacy increment attributable to imatinib cannot be gauged from this single-arm study. Compared with a median OS and PFS of 6 and 4.5 months, respectively, in a phase II study of GemOx alone in patients with chemorefractory PC [6], and accepting the limitations of cross study comparison, the results of our study with the addition of imatinib appear to be similar and not superior.

The most marked responses to treatment were observed in patients with bulky LA tumours. This interesting observation may have a plausible biological basis; in a preclinical model of desmoplastic breast cancer, carcinoma-secreted PDGF appeared to be the main driver of tumour desmoplasia [35]. PC, particularly LA disease, is similarly characterised by dense stromal desmoplastic reactions with a complex composition, in which myofibroblastic pancreatic stellate cells appear to have a crucial role and are strongly stimulated by PDGF [36, 37]. The observations in our study may be a chance finding or could reflect an inhibitory effect of imatinib on PDGF signalling in LA tumours, which could potentially relate to reduction in stromal IFP and increased uptake of chemotherapy.

In summary, we explored a novel stromally targeted strategy for patients with chemorefractory PC and demonstrated the safety of administering full-dose gemcitabine but slightly reduced-dose oxaliplatin with intermittent imatinib straddling the chemotherapy administration period. This knowledge could be exploited for future experimental application given that gemcitabine forms the mainstay of treatment of PC. An important avenue for investigation would be to provide *in vivo* evidence of increased tumour cytotoxic drug uptake in the presence of imatinib in patients with LA PC, thereby potentially providing proof-of-principle validation for targeting PDGFR-β-mediated IFP regulation as a rational therapeutic approach in these patients. 19-F magnetic resonance spectroscopic imaging, suitable for fluorinated compounds such as gemcitabine, is a non-invasive modality used to evaluate tumour drug uptake in humans [38]. To our knowledge, limited clinical functional imaging studies have been published in relation to imatinib PDGFR-β targeting and would be of biological interest, particularly in LA pancreatic tumours.

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disclosures

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references

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60(5): 277–300.
2. Burris HA III, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15(6): 2403–2413.
3. Jacobs AD, Burris HA, Rivkin S et al. A randomized phase III study of rubitecan (ORA) vs. best choice (BC) in 409 patients with refractory pancreatic cancer report from a North-American multi-center study. ASCO Meeting Abstracts 2004; 22(14S): (Abstr 4013).
4. Oettle H, Pelzer U, Stieler J et al. Oxaliplatin/folinic acid/5-fluorouracil [24h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). ASCO Meeting Abstracts 2005; (Abstr 4031).
5. Pelzer U, Kubica K, Stieler J et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 2008; 26(20): (Abstr 4508).
6. Demols A, Peeters M, Polus M et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer 2006; 94(4): 481–485.
7. Boeck SH, Vehling-Kaiser U, Waldschmidt D et al. Gemcitabine plus erlotinib (GE) followed by capecitabine (C) versus capecitabine plus erlotinib (CE) followed by gemcitabine (G) in advanced pancreatic cancer (APC): a randomized, cross-over phase III trial of the Arbeitsgemeinschaft internistische Onkologie (AIO). ASCO Meeting Abstracts 2010; 28(18 Suppl): (Abstr LBA4011).
8. Heldin CH, Rubin K, Pietras K, Ostman A. High interstitial fluid pressure - an obstacle in cancer therapy. Nat Rev Cancer 2004; 4(10): 806–813.
9. Pietras K, Sjoblom T, Rubin K et al. PDGF receptors as cancer drug targets. Cancer Cell 2003; 3(5): 439–443.
10. Pietras K, Ostman A, Sjoquist M et al. Inhibition of platelet-derived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. Cancer Res 2001; 61(7): 2929–2934.
11. Pietras K, Rubin K, Sjoblom T et al. Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. Cancer Res 2002; 62(19): 5476–5484.
12. Pietras K, Stumm M, Hubert M et al. STI571 enhances the therapeutic index of epothilone B by a tumor-selective increase of drug uptake. Clin Cancer Res 2003; 9(10 Pt 1): 3779–3787
13. Pietras K. Increasing tumor uptake of anticancer drugs with imatinib. Semin Oncol 2004; 31(2 Suppl. 6): 18–23.
14. Li J, Kleeff J, Guo J et al. Effects of STI571 (gleevec) on pancreatic cancer cell growth. Mol Cancer 2003; 2: 32.
15. Hwang RF, Yokoi K, Bucana CD et al. Inhibition of platelet-derived growth factor receptor phosphorylation by STI571 (Gleevec) reduces growth and metastasis of human pancreatic carcinoma in an orthotopic nude mouse model. Clin Cancer Res 2003; 9(17): 6534–6544
16. Baranowska-Kortylewicz J, Abe M, Nearman J, Enke CA. Emerging role of platelet-derived growth factor receptor-beta inhibition in radioimmunotherapy of experimental pancreatic cancer. Clin Cancer Res 2007; 13(1): 299–306.
17. Chen J, Rocken C, Nitsche B et al. The tyrosine kinase inhibitor imatinib fails to inhibit pancreatic cancer progression. Cancer Lett 2006; 233(2): 328–337.
18. Gharibo M, Patrick-Miller L, Zheng L et al. A phase II trial of imatinib mesylate in patients with metastatic pancreatic cancer. Pancreas 2008; 36(4): 341–345.
19. Chew HK, Barlow WE, Albain K et al. A phase II study of imatinib mesylate and capecitabine in metastatic breast cancer: Southwest Oncology Group Study 0338. Clin Breast Cancer 2008; 8(6): 511–515.
20. Saraiya B, Chugh R, Karantza V et al. Phase I study of gemcitabine, docetaxel and imatinib in refractory and relapsed solid tumors. Invest New Drugs 2010
21. Spigel DR, Hainsworth JD, Simons L et al. Irinotecan, carboplatin, and imatinib in untreated extensive-stage small-cell lung cancer: a phase II trial of the Minnie Pearl Cancer Research Network. J Thorac Oncol 2007; 2(9): 854–861.
22. Yardley DA, Burris HA III, Markus T et al. Phase II trial of docetaxel plus imatinib mesylate in the treatment of patients with metastatic breast cancer. Clin Breast Cancer 2009; 9(4): 237–242.
23. George S, Desai J, Paul EJ et al. Selective kinase inhibition with daily imatinib intensifies toxicity of chemotherapy in patients with solid tumours. Eur J Cancer 2006; 42(7): 864–870.
24. Rabin MJ, Mick R, Schilsky RL, Siegler M. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. J Natl Cancer Inst 1993; 85(20): 1637–1643.
25. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92(3): 205–216.
26. Poplin E, Feng Y, Berlin J et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009; 27(23): 3778–3785.
27. Sultana A, Smith CT, Cunningham D et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007; 25(18): 2607–2615.
28. Al-Batran SE, Atmaca A, Schleyer E et al. Imatinib mesylate for targeting the platelet-derived growth factor beta receptor in combination with fluorouracil and leucovorin in patients with refractory pancreatic, bile duct, colorectal, or gastric cancer—a dose-escalation Phase I trial. Cancer 2007; 109(9): 1897–1904
29. Ali Y, Lin Y, Gharibo MM et al. Phase I and pharmacokinetic study of imatinib mesylate (Gleevec) and gemcitabine in patients with refractory solid tumors. Clin Cancer Res 2007; 13(19): 5876–5882.
30. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347(7): 472–480.
31. Cortes JE, Baccarani M, Guilhot F et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnoseri, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 2010; 28(3): 424–430.
32. Nakaizhi K, Furuse J, Ishii H et al. Prognostic factors in patients with gemcitabine-refractory pancreatic cancer. Jpn J Clin Oncol 2007; 37(2): 114–120
33. Marechal R, Demols A, Gay F et al. Prognostic factors and prognostic index for chemonaive and gemcitabine-refractory patients with advanced pancreatic cancer. Oncology 2007; 73(1–2): 41–51.
34. Boeck S, Hinke A, Wilkowski R, Heinemann V. Importance of performance status for treatment outcome in advanced pancreatic cancer. World J Gastroenterol 2007; 13(2): 224–227.
35. Shao ZM, Nguyen M, Barsky SH. Human breast carcinoma desmoplasia is PDGF initiated. Oncogene 2000; 19(36): 4337–4345.
36. Pandol S, Edderkaoui M, Gukovsky I et al. Desmoplasia of pancreatic ductal adenocarcinoma. Clin Gastroenterol Hepatol 2009; 7 (11 Suppl): S44–S47
37. Shimizu K. Pancreatic stellate cells: molecular mechanism of pancreatic fibrosis. J Gastroenterol Hepatol 2008; 23 (Suppl. 1): S119–S121.
38. Wolf W, Presant CA, Waluch V. 19F-MRS studies of fluorinated drugs in humans. Adv Drug Deliv Rev 2000; 41(1): 55–74.

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Advanced pancreatic carcinoma: current treatment and future challenges

Anastasios Stathis and Malcolm J. Moore

Abstract | Pancreatic adenocarcinoma is the most lethal of the solid tumors and the fourth leading cause of cancer-related death in North America. Most patients present with locally advanced or metastatic disease that precludes curative resection. These patients have an extremely poor prognosis. In the absence of effective screening methods, considerable efforts have been made during the past decade to identify better systemic treatments. Unfortunately most trials have not shown a survival advantage for most therapies. In tandem with this increased clinical research, there has also been an expansion of preclinical laboratory investigation. These preclinical studies revealed many of the molecular mechanisms involved in pancreatic cancer development, which has provided insights into why current therapies are ineffective. These new discoveries provide some optimism that new agents inhibiting specific targets will improve outcome and overcome the resistance of pancreatic cancer to most standard treatments. We review the current standards of care for patients with locally advanced and metastatic pancreatic carcinoma and outline some future directions for the development of new treatment strategies.

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Learning objectives

Upon completion of this activity, participants should be able to:

1. Describe the diagnosis and prognosis of pancreatic carcinoma
2. Identify the first line treatment for most patients with advanced pancreatic carcinoma.
3. Specify a combination treatment that has improved survival outcomes vs cytotoxic monotherapy among patients with advanced pancreatic carcinoma.
4. Describe the diagnosis and management of locally advanced pancreatic carcinoma.

Competing interests

The authors, the Journal Editor L. Hutchinson and the CME questions author C. P. Vega declare no competing interests.

Introduction

Pancreatic carcinoma is one of the most lethal solid malignancies and the fourth leading cause of cancer-related deaths in North America, where over 38,000 cases are diagnosed annually, with a similar number of patients dying from the disease.[1,2] Pancreatic ductal adenocarcinoma accounts for the majority (>90%) of pancreatic malignancies.[3] Approximately 60–70% of pancreatic adenocarcinomas arise in the head, neck or uncinate process, whereas presentations in the body (5–10%) or tail (10–15%) of the gland are less common.[4] At the microscopic level, stroma surrounds the tumor, which is largely composed of fibroblastic and inflammatory cells, and extracellular matrix.[5] There is a complex interplay between tumor and stromal cells, which leads to the activation of signaling pathways (such as TGF-b/SMAD, HGF/Met, matrix metalloproteinases, Hedgehog, Wnt) through autocrine and paracrine mechanisms and the establishment of a dynamic microenvironment that promotes tumor growth and invasion.[6]

Pancreatic adenocarcinoma has a high propensity for local invasion and distant metastases. Perineural, vascular and lymphatic invasion are commonly observed in resected tumor specimens; lymph-node metastases are present in 50–75% of resected cases.[7–9] The management of patients with pancreatic carcinoma depends on the extent of the disease at diagnosis. Surgical resection followed by adjuvant therapy is the standard of care for patients diagnosed with early-stage disease. The majority of patients, however, present with advanced-stage disease that precludes surgery. Prognosis for these patients is extremely poor and the impact of standard therapy is minimal.

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Key points

- Pancreatic adenocarcinoma has a high propensity for locoregional invasion and early development of distant metastases
- Approximately 80% of patients present with locally advanced or metastatic disease that precludes curative surgery, and long term survival is poor
- In 1997 gemcitabine was established as the standard first-line treatment for patients with advanced disease based on clinical benefit and survival improvement compared with 5-fluorouracil based chemotherapy
- During the past decade several clinical trials assessing different cytotoxic agents and combination chemotherapy failed to improve treatment outcomes
- The combination of a targeted agent, erlotinib, with gemcitabine resulted in a small but significant improvement in survival compared with gemcitabine alone
- A better understanding of the biology and molecular changes that occur in pancreatic cancer will permit the development of new agents to overcome resistance

Recent advances in the understanding of the molecular alterations that occur in pancreatic cancer have permitted the development of new agents that target components of specific pathways and provide optimism for better treatment strategies in the future.[10]

Clinical presentation

Most patients with pancreatic carcinoma present with symptoms that are related to the location of the cancer within the pancreas. Jaundice is a common symptom for tumors at the most common location—the head, neck or uncinate process. Many patients experience an antecedent period of nonspecific but persistent abdominal or back pain, followed by the development of obstructive jaundice. Other associated complications are the development of diabetes mellitus or pancreatitis. Anorexia, weight loss, gastric outlet obstruction and ascites are usually manifestations of more-advanced disease.[11] Left-sided pancreatic tumors may remain asymptomatic for long periods of time and can be diagnosed when they reach large dimensions (that is, 4–5 cm) following the development of symptoms of advanced disease.[8]

Thromboembolic disease including distal vein thrombosis, thrombophlebitis migrans and pulmonary embolism are common presentations. The incidence of thromboembolism among patients with pancreatic cancer is 17–57%, which is one of the highest among cancer patients.[12] Tumor location, impaired performance status and an increase in pro-thrombotic (for example, thrombin, fibrinogen) and proinflammatory factors that can promote thrombosis (for example, transforming growth factor), might explain the high incidence of thromboembolism in patients with advanced disease.[13] The development of thrombembolism is associated with a poor prognosis; several trials have been conducted in patients with advanced disease to determine the effect of prophylactic anticoagulation (mainly with low molecular weight heparin). There is some evidence that prophylactic anticoagulation reduces the incidence of thromboembolic events and is associated with improved response to chemotherapy and improved overall survival.[14,15] Several trials of prophylactic anticoagulation are currently ongoing and it is hoped that results from these studies will better define the role of prophylactic anticoagulation in patients with advanced pancreatic carcinoma (Table 1).[16]

Current management

Most patients have locally advanced unresectable disease due to local vascular invasion, or metastatic disease at diagnosis. It is estimated that only 10–15% of patients present with early-stage disease that permits curative surgery.[17] Adjuvant treatment with both chemotherapy and radiation therapy was investigated in large European and North American studies, which demonstrated improvements in disease-free survival and overall survival rates; therefore, on the basis of these findings, post-operative therapy is now considered the standard of care for patients with early-stage pancreatic cancer.[18–24] However, no universal consensus exists as to the type of adjuvant therapy. Gemcitabine or 5-fluorouracil (5-FU) chemotherapy without radiation, are the most common treatments outside North America, while chemoradiation plus systemic chemotherapy is still widely used in the US.

The results of the largest adjuvant trial of chemotherapy (ESPAC-3) in patients with resected pancreatic ductal adenocarcinoma were presented at ASCO 2009. Following surgical resection (R0/R1), 1,088 patients were randomly assigned to receive 5-FU and folinic acid or gemcitabine. There were no significant differences in survival rates between the two treatment arms (median survival from resection was 23 and 23.6 months, respectively), although adverse effects were less common with gemcitabine.[25]

Several reviews have discussed the role of surgery and the use of perioperative systemic therapy and radiation therapy for patients with pancreatic cancer.[17,26] In this article, we focus on the management of advanced disease and will discuss the results of recent clinical trials, the optimal management of both metastatic and locally advanced disease, and outline potential strategies of how the outcome of patients could be improved.

Management of metastatic disease

Approximately 50% of patients with pancreatic carcinoma present with advanced-stage disease that has extended beyond the pancreas and regional lymph nodes with metastases to the liver or other visceral organs. The median survival for patients with metastatic disease is 6 months based on data from recent clinical trials; patients who have impaired performance status or significant comorbidities, however, are not eligible to enter such trials. The survival for patients with untreated metastatic disease is about 2–3 months. Another 30–35% of patients present with locoregional disease that is considered unresectable, usually because of local vascular invasion. This disease is incurable and most patients succumb to both distant and local relapse. Although 15% of patients present with resectable disease, at least 80% of these individuals will develop local or distant relapse within 2 years of surgery. Since the majority of patients eventually develop advanced metastatic disease, improvements in systemic therapy are essential, together with the development of strategies for prevention and early detection in order to improve the outcome of patient with pancreatic cancer.

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Table 1 | Recent and ongoing trials of chemotherapy and prophylactic anticoagulation in patients with pancreatic cancer

Reference or trial	Study design	Study phase	Tumor type	Number of patients	Treatment	Status (estimated end date)
Ioli *et al.* (2007)[33]	Single arm	II	Pancreas	69	Gemcitabine + cisplatin + nadroparin	Closed
Riess *et al.* (2008)[16]	Randomized	II	Pancreas	540	Gemcitabine + cisplatin + 5-FU + leucovorin ± enoxaparin	Closed
NCT00462852*	Randomized	II	Pancreas	120	Gemcitabine ± dalteparin	Ongoing (NR)
NCT00662688*	Randomized; four arms	III	Pancreas	136	Gemcitabine ± capecitabine ± dalteparin	Ongoing (January 2012)
NCT00876915*	Single arm	III	Multiple solid tumors	NR	Dalteparin with chemotherapy	Ongoing (September 2013)
NCT00908960*	Randomized	III	Lung, colon, pancreas	NR	Chemotherapy ± enoxaparin	Ongoing (April 2011)
NCT00031837*	Randomized	III	Multiple solid tumors	400	Gemcitabine ± dalteparin	Closed
NCT00312013*	Single arm	III	Lung, prostate, pancreas	NR	Chemotherapy + nadroparin	Closed

*Trials registered at www.clinicaltrials.gov, the official National Cancer Institute website (last updated August 2009). Abbreviations: 5-FU, 5-fluorouracil; NR, not reported.

The modern era of chemotherapy for pancreatic cancer began in 1997 when Burris and colleagues reported the results of a phase III trial. Patients enrolled in earlier studies were treated with 5-FU alone or in combination with other cytotoxic agents, however, there was a lack of consistent evidence of the impact of chemotherapy on patient survival or quality of life. In the trial by Burris *et al.*,[27] 126 patients with locally advanced and metastatic pancreatic cancer were randomly assigned to receive gemcitabine or 5-FU, administered as a bi-weekly intravenous injection. More patients treated with gemcitabine had a clinical response compared with patients who received 5-FU (23.8% versus 4.8%, $P = 0.0022$). Moreover, patients in the gemcitabine arm also experienced significant improvements in median overall survival (5.65 months versus 4.41 months) and 1-year survival (18% versus 2%) compared with those in the 5-FU arm. The results of this study led to the approval of gemcitabine as the first cytotoxic agent for the treatment of pancreatic cancer. Moreover, gemcitabine also became the standard first-line palliative treatment worldwide for patients with advanced pancreatic adenocarcinoma.

Over the past decade, major efforts have been made to improve treatment outcomes in patients with metastatic disease. Cooperative groups and the pharmaceutical industry have conducted more than a dozen large randomized trials worldwide. The most common approach has been to use gemcitabine as the control arm and gemcitabine combined with a new or existing agent as the experimental arm. The experimental arms have consisted of the combination of gemcitabine with a second cytotoxic agent or, more recently, with a targeted agent. Large randomized phase III trials were performed to evaluate the combination of gemcitabine with cisplatin,[28,29] oxaliplatin,[30,31] 5-FU,[32,33] capecitabine,[34,35] irinotecan,[36,37] exatecan[38] and pemetrexed (Table 2).[39] The primary end point of overall survival was not improved in any of these trials. Combination chemotherapy resulted in an improved response rate and had some impact on progression-free survival in some of these trials; however, there was an absence of an overall survival benefit. The most recent randomized phase III trial of combination chemotherapy that compared gemcitabine with gemcitabine plus weekly cisplatin failed to demonstrate a significant improvement in overall survival, progression-free survival and overall response rates between the two arms.[40]

Some investigators believe that a subset of patients with advanced pancreatic carcinoma do benefit from first-line combination chemotherapy. In the study by Herrmann *et al.*,[34] 319 patients were randomly assigned to receive gemcitabine (1,000 mg/m^2 on days 1 and 8, every 3 weeks) plus capecitabine (650 mg/m^2 on days 1–14, twice daily) or gemcitabine alone. Combination treatment did not significantly improve median overall survival compared with gemcitabine alone (8.4 months versus 7.2 months, $P = 0.234$); however, patients in the combination arm with a good Karnofsky performance status (90–100) experienced a significant prolongation of median overall survival compared with gemcitabine (10.1 months versus 7.4 months, $P = 0.014$).

Heinemann and colleagues performed a meta-analysis of 15 randomized clinical trials that compared gemcitabine alone with gemcitabine plus a cytotoxic agent in over 4,000 patients with pancreatic cancer. The analysis revealed a significant survival benefit for patients when gemcitabine was combined with platinum analogs or fluoropyrimidines (hazard ratio [HR] = 0.91, 95% CI 0.85–0.97; $P = 0.004$).[41] A subset analysis showed that the benefit from combination chemotherapy was restricted to patients with a good performance status. Similar findings were reported in a meta-analysis by Sultana *et al.*,[42] which included almost 10,000 patients from 51 trials.[42] Of the studies that were assessed, 19 compared gemcitabine with gemcitabine-based combination chemotherapy. Overall survival was significantly improved in the gemcitabine-based combination treatment arm: with a 9% reduction in the risk of death (HR = 0.91%, 95% CI 0.85–0.97). In a subgroup analysis, this benefit was limited to patients who received gemcitabine combined with a platinum-based

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Table 2 | Phase III trials of chemotherapy in advanced pancreatic cancer patients

Reference*	Treatment	Number of patients	Median survival (months)
Heinemann *et al.* (2006)[38]	Gemcitabine vs gemcitabine + cisplatin	195	6 vs 7.5 (P=0.15)
Colucci *et al.* (2002)[39]	Gemcitabine vs gemcitabine + cisplatin	107	5 vs 7.5 (P=0.43)
Louvet *et al.* (2005)[40]	Gemcitabine vs gemcitabine + oxaliplatin	313	7.1 vs 9 (P=0.13)
Poplin *et al.* (2009)[41]	Gemcitabine vs gemcitabine FDR vs gemcitabine + oxaliplatin	832	4.9 vs 6.2 (P=0.04) vs 5.7 (P=0.22)
Berlin *et al.* (2002)[42]	Gemcitabine vs gemcitabine + 5-FU	322	5.7 vs 6.5 (P=0.09)
Herrmann *et al.* (2007)[34]	Gemcitabine vs gemcitabine + capecitabine	319	7.2 vs 8.4 (P=0.234)
Rocha Lima *et al.* (2004)[35]	Gemcitabine vs gemcitabine + irinotecan	342	6.3 vs 6.6 (P=0.789)
Stathopoulos *et al.* (2006)[37]	Gemcitabine vs gemcitabine + irinotecan	145	6.4 vs 6.5 (P=0.970)
Abou-Alfa *et al.* (2006)[36]	Gemcitabine vs gemcitabine + exatecan	349	6.2 vs 6.7 (P=0.52)
Oettle *et al.* (2005)[43]	Gemcitabine vs gemcitabine + pemetrexed	565	6.3 vs 6.2 (P=0.847)

*Articles shown are reported in complete form. Abbreviations: FDR, fixed dose rate; 5-FU, 5-fluorouracil.

agent (HR = 0.85, 95% CI 0.74–0.96) or capecitabine (HR = 0.83, 95% CI 0.72–0.96). Gemcitabine combined with 5-FU or irinotecan did not improve overall survival when compared with gemcitabine alone.[42]

These data provide some evidence of a benefit with gemcitabine-based combination chemotherapy as first-line treatment for patients with advanced pancreatic cancer who have a good performance status. This evidence, however, is based on data from meta-analyses, whereby all phase III trials to date failed to report an overall survival benefit; this outcome suggests that any true benefit is small. In a disease with a median survival of only 6 months, a hazard ratio of 0.9 is indicative of a modest absolute benefit, the increase in toxic effects and the risk of complications that might occur when agents are combined should be considered, particularly when treating a disease with the primary objective of symptomatic benefit.

It is possible that some patients who progress on single-agent gemcitabine may benefit from second-line chemotherapy. At present, there is no standard second-line treatment; therefore, more trials are needed in this population of patients to evaluate novel agents that might not be used in combination with gemcitabine.[43] Data from some trials with second-line salvage chemotherapy suggest some benefit for a select group of patients. 5-FU, capecitabine and oxaliplatin are the most commonly employed cytotoxic agents in patients who are refractory to gemcitabine.[44–47] In the CONKO-003 trial, patients who experienced disease progression after gemcitabine therapy, were randomly assigned to receive oxaliplatin (85 mg/m^2 on days 8 and 22) plus 5-FU (2 g/m^2 over 24 h) and leucovorin (200 mg/m^2 on days 1–8 and 15 to 22) or 5-FU and leucovorin. Patients in the oxaliplatin arm had a significant improvement in progression-free survival (13 weeks versus 9 weeks, P=0.012) and median overall survival (26 weeks versus 13 weeks, P=0.014).[48] The use of second-line chemotherapy might, therefore, provide equal benefit as an initial approach of front-line combination chemotherapy. More trials are needed in order to define the clinical significance of second-line chemotherapy in patients who have disease progression after first-line therapy, and this can represent an important setting for the evaluation of new drugs in pancreatic carcinoma.

New treatment strategies

The improvements achieved with cytotoxic chemotherapy combinations in patients with metastatic disease are modest,[49] and major advances might emerge from different approaches to treatment. Our improved knowledge of the genetic and molecular changes that occur in pancreatic cancer has allowed the identification of candidate pathways for novel 'targeted' approaches to therapy. Multiple signaling pathways involved in the regulation of apoptosis, DNA damage control, regulation of the cell cycle, and invasion, such as KRAS signaling, and developmental pathways such as Hedgehog and Notch, are affected by genetic alterations in the development of pancreatic cancer. Several drugs have been developed to influence many of these pathways and the efficacy of some of these agents has been tested in phase II and randomized phase III trials (Table 3).

Mutations in *KRAS* occur in up to 90% of pancreatic cancers,[50] providing a strong rationale for the evaluation of KRAS inhibition in pancreatic cancer. Tipifarnib, a farnesyltransferase inhibitor, was the first putative RAS inhibitor tested. Tipifarnib competitively inhibits the farnesyl protein transferase, which is an essential enzyme for the activity of a variety of intracellular proteins, including the RAS family of proteins. In a large phase III trial of 688 patients the combination of oral tipifarnib and gemcitabine was compared with gemcitabine alone; there were no significant differences in overall survival, objective disease response or progression-free survival.[51] A potential explanation for these results might be that *KRAS* mutations take place early in the development of pancreatic cancer and cancer cells might become less dependent on this pathway as disease progression occurs. Mechanisms other than farnesylation, such as prenylation by other enzymes including geranylgeranyl transferase, might be involved in the activation of RAS proteins.[52]

Matrix metalloproteinases (MMPs) are a large family of zinc-containing proteolytic enzymes involved in the degradation of extracellular matrix proteins in physiological and pathological conditions.[53] Increased MMP expression has been demonstrated in several solid tumors including pancreatic adenocarcinoma, and can result in excessive destruction of the extracellular matrix, neovascularization, tumor spread and metastases. Several synthetic inhibitors of MMPs have been developed based on the results from preclinical studies. Marimastat was the first compound tested in a large randomized phase III trial of 414 patients with advanced pancreatic cancer that compared three doses of marimastat (5 mg, 10 mg or 25 mg

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Table 3 | Phase III trials of targeted agents in advanced pancreatic carcinoma

Reference	Treatment	Class of targeted agent	Target of targeted agent	Number of patients
Bramhall *et al.* (2001)[54]	Gemcitabine vs marimastat	Broad-spectrum inhibitor of MMP	MMP	414
Bramhall *et al.* (2002)[55]	Gemcitabine vs gemcitabine + marimastat	Broad-spectrum inhibitor of MMP	MMP	313
Moore *et al.* (2003)[56]	Gemcitabine vs BAY 12-9566	Inhibitor of MMP-2, MMP-3, MMP-9, MMP-13	MMP	277
Van Cutsem *et al.* (2004)[61]	Gemcitabine vs gemcitabine + tipifarnib	Inhibitor of FT	FT	688
Moore *et al.* (2007)[58]	Gemcitabine vs gemcitabine + erlotinib	Tyrosine kinase inhibitor	EGFR	569
Kindler *et al.* (2007)[59]*	Gemcitabine vs gemcitabine + bevacizumab	Monoclonal antibody	VEGF	602
Philip *et al.* (2007)[60]*	Gemcitabine vs gemcitabine + cetuximab	Monoclonal antibody	EGFR	766
Vervenne *et al.* (2008)[62]*	Gemcitabine + erlotinib vs gemcitabine + erlotinib + bevacizumab	Tyrosine kinase inhibitor/ monoclonal antibody	EGFR/ VEGF	607

*Trials reported in abstract form. Abbreviations: FT, farnesyltransferase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor.

twice daily) with standard gemcitabine. A dose-response and a biological effect were postulated for patients treated with marimastat. Patients treated with the highest dose of marimastat had the best 1-year survival rate, which was similar to that of patients treated with gemcitabine.[54] A subsequent trial that evaluated the combination of marimastat and gemcitabine with gemcitabine and placebo, however, did not show any improvement in overall survival or tumor control for the combination arm.[55]

BAY 12-9566, a specific inhibitor of MMP-2, MMP-3, MMP-9 and MMP-13, which also has anti-angiogenic properties, was tested in a phase III trial. Patients with locally advanced or metastatic pancreatic carcinoma were treated with BAY 12-9566 or standard intravenous gemcitabine; patients who experienced tumor progression were allowed to crossover to gemcitabine. The study was closed to accrual after the completion of the second interim analysis showed that the new agent was significantly inferior to gemcitabine (median overall survival of 3.74 months and 6.59 months, respectively).[56] This study further affirmed the use of gemcitabine as the platform for drug development in the first-line setting.

Targeting angiogenesis is a validated strategy for cancer treatment. A wide variety of agents that interfere with angiogenesis have been developed, and some of these are now part of the standard of care for various solid tumors. Bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody, which is approved for the treatment of colon cancer, has also been investigated in pancreatic carcinoma. Overexpression of VEGF and its receptors (VEGFR-1, VEGFR-2 and VEGFR-3) in pancreatic cancer has been correlated with the development of metatases and poor prognosis.[57] On the basis of results from a phase II trial, which showed promising activity for bevacizumab in patients with metastatic pancreatic cancer,[58] a large phase III trial was conducted, which compared bevacizumab and gemcitabine with gemcitabine alone in 602 patients with pancreatic cancer.[59] The bevacizumab and gemcitabine combination, however, failed to improve survival in these patients when compared with gemcitabine alone.[59] The promising activity observed in the phase II trial might have been the result of the selection of patients with a good performance status without associated disease complications. These discrepancies have led to an initiative to standardize eligibility criteria within phase II trials for the purposes of result interpretation.

The combination of bevacizumab with gemcitabine and erlotinib has also been tested in the AVITA phase III trial.[60] In this study, patients were randomly assigned to receive gemcitabine and erlotinib (an oral small-molecule EGFR inhibitor) with or without bevacizumab, however, there were no significant differences in overall survival between the treatment arms.[60]

In another phase II study, 103 patients with pancreatic cancer were randomly assigned to receive gemcitabine or gemcitabine plus axitinib, which is an oral inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3. A small improvement in overall survival was observed for patients in the combination arm, but this was not statistically significant.[61] Following these results, a phase III trial was initiated in patients with advanced pancreatic carcinoma; however, based on an interim analysis showing that that there were no improvements in survival—the primary end point—with axitinib and gemcitabine compared with gemcitabine alone, the sponsor has recently announced the discontinuation of the study. The lack of survival benefit with antivascular agents in patients with pancreatic adenocarcinoma might be because of tumor biology—most tumors are fibrotic and are of a hypovascular nature, which might limit the efficacy of antivascular agents.

Overexpression of EGFR occurs in many pancreatic tumors and has been found to correlate with poor prognosis and disease progression.[62] Preclinical studies have shown that antagonizing EGFR signaling could inhibit growth and metastasis of pancreatic tumors in xenograft animal models.[63] In 2007, the National Cancer Institute of Canada (NCIC) Clinical Trials Group conducted a phase III randomized trial in 569 patients with advanced pancreatic carcinoma, which compared gemcitabine alone with gemcitabine and erlotinib.[64] Patients who received

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gemcitabine plus erlotinib had an improvement in median overall survival compared with those who received gemcitabine alone (6.24 months versus 5.91 months, HR = 0.82, 95% CI 0.69–0.99; $P = 0.038$); the respective 1-year survival rates were 23% versus 17% ($P = 0.023$). Although increased rates of diarrhea and skin rash were observed in patients who received erlotinib, these toxic effects were mostly of grade 1 and 2 and were not associated with any deterioration of quality of life. The development of a skin rash of grade 2 or greater was associated with a better outcome—respective median overall survival rates of 5.3, 5.8 and 10.5 months and a 1-year survival of 16%, 9% and 43% were observed for patients with rash grade 0, 1, 2 or higher. The outcome of patients treated with erlotinib was not related to EGFR status as assessed by immunohistochemistry and fluorescence *in situ* hybridization.[64,65]

Studies in colorectal cancer have shown that the effectiveness of EGFR signaling inhibition depends on the mutational status of *KRAS*. The KRAS protein functions downstream of the EGFR in the EGFR signaling pathway and if *KRAS* is mutated, the KRAS protein remains switched 'on' and signaling within the cancer cells continues regardless of the fact that the EGFR is blocked. The correlation between *KRAS* status and overall survival was studied in the population of patients in the previously reported randomized trial of erlotinib and gemcitabine versus gemcitabine alone in pancreatic cancer.[65] *KRAS* mutations were observed in 79% of cases and the HR for erlotinib in this group was 1.07, whereas in patients with wild-type *KRAS* (21%) the HR was 0.66. This difference did not reach statistical significance because of the small number of patients with wild-type *KRAS*. This finding, however, requires further study based on data showing that mutations in *KRAS* are a predictive marker for no benefit from EGFR inhibitors in colorectal and other cancers.[66]

Cetuximab is a monoclonal antibody that binds to the extracellular domain of EGFR. A phase II study suggested activity of the combination of cetuximab with gemcitabine in patients with advanced pancreatic cancer based on improved time to disease progression and median overall survival compared with historical data of single-agent gemcitabine;[67] based on the results of this study the Southwest Oncology Group carried out a randomized comparison of cetuximab and gemcitabine with gemcitabine alone in patients with advance pancreatic cancer; however, no survival benefit was observed in the combination arm.[68]

Management of locally advanced disease

Most of the phase II and phase III trials discussed earlier included patients with both metastatic and locally advanced disease. Patients with locally advanced disease represent almost 30% of newly diagnosed pancreatic carcinoma cases. These patients have a better outcome (median survival of 8–12 months) than patients with metastatic disease. The optimum treatment for patients with locally advanced disease has not yet been defined as data are limited; however, radiation combined with chemotherapy is often considered the standard treatment for these patients. Clinical trials should not include both patients with locally advanced disease and patients with metastatic disease—these groups of patients should be treated separately as they may have different outcomes.

A small randomized trial compared chemoradiotherapy with best supportive care in patients with locally advanced pancreatic cancer.[69] In total, 16 patients were treated with standard fractionation radiotherapy (up to 50.4 Gy) with concurrent 5-FU (200 mg/m^2/day continuous infusion) and 15 patients were assigned to best supportive care. A survival benefit was observed for patients in the chemoradiotherapy arm (median overall survival of 13.2 months versus 6.4 months, $P < 0.01$).[69]

A limited number of trials have compared chemoradiotherapy with radiation therapy alone,[70,71] or with chemotherapy alone.[72–76] The heterogeneity in the design and in the treatment regimens of these trials (some were performed in the 1980s with radiation or chemotherapy regimens that are no longer in use) make it difficult for comparisons to be made for the different treatment approaches; thus, definitive conclusions cannot be draw from these data. The results of the two most recent trials, which compared chemoradiotherapy with chemotherapy, also produced conflicting results.[75,76] In one of these trials, 119 patients with locally advanced pancreatic cancer were randomly assigned to receive gemcitabine until disease progression or chemoradiotherapy (split course of radiation therapy up to 60 Gy concurrently with continuous infusion of 5-FU and cisplatin, followed by gemcitabine until disease progression). The combined modality treatment was associated with increased grade 3 and grade 4 toxic effects and a significantly lower survival compared with patients who received chemotherapy only. The radiation dose and the mode of delivery could have accounted for the increase in toxic effects.[75] Another trial compared chemoradiotherapy (involved-field radiation up to 50.4 Gy combined with concurrent weekly gemcitabine, followed by maintenance gemcitabine) with gemcitabine only in 74 patients with locally advanced pancreatic cancer.[76] A survival benefit was observed for patients in the combined treatment modality arm (median overall survival of 11.2 months versus 9.2 months, $P = 0.044$). Higher rates of grade 4 gastrointestinal and hematological toxic effects were observed with chemoradiotherapy compared with chemotherapy alone (41.2% versus 5.7%, $P < 0.0001$). However, this study had to close prematurely because of the small number of patients accrued and, therefore, it is difficult to draw definitive conclusions.

First-line induction chemotherapy for 2–3 months and subsequent radiation therapy combined with chemotherapy is commonly used in patients with advanced pancreatic cancer who have stable disease following chemotherapy. This approach was recently investigated in two retrospective studies.[77,78] In the study by Krishnan and colleagues, the outcomes of 247 patients with locally advanced pancreatic cancer who had received chemoradiotherapy as initial treatment were compared with 76 patients who had received gemcitabine-based induction chemotherapy for a median of 2.5 months before chemoradiotherapy. Most patients (85%) received a radiation dose of 30 Gy in 10 fractions concurrently with infusion of 5-FU (41%), gemcitabine (39%), or capecitabine

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(20%). The median overall survival and progression-free survival rates were 8.5 months and 4.2 months, respectively, for patients who received chemoradiotherapy, and 11.9 months and 6.4 months, respectively, for patients who received chemotherapy followed by chemoradiotherapy ($P<0.001$ both for progression-free survival and overall survival). The authors concluded that induction chemotherapy used in patients with locally advanced pancreatic cancer might derive a benefit from consolidative chemoradiation by the exclusion of patients with rapid distant disease progression.[77]

In another trial, of 181 patients, 128 did not develop disease progression after induction chemotherapy (gemcitabine, gemcitabine and oxaliplatin, gemcitabine plus 5-FU and leucovorin) and received either chemoradiotherapy (up to 55 Gy with 5-FU) or continued on the same chemotherapy regimen.[78] Induction chemotherapy followed by chemoradiotherapy resulted in significantly prolonged median overall survival rates (15 months versus 11.7 months, $P=0.0009$).[78] Although these trials were retrospective and require validation in prospective studies, they provide an interesting treatment approach for patients with locally advanced disease. Some patients with locally advanced disease develop rapidly progressive metastatic disease and most likely will not benefit from local therapy, whereas those with less-aggressive disease might benefit from chemoradiotherapy.

Future directions

Pancreatic adenocarcinoma is characterized by the accumulation of a high number of gene deletions, mutations and amplifications, with deletions of tumor suppressor genes as the most prevalent alteration. The most common changes have been identified and characterized, and components of abnormal pathways that might be involved in pancreatic tumorigenesis have been proposed as possible treatment targets.[79] To date, with the exception of erlotinib and gemcitabine, current targeted agents tested in phase III trials have failed to improve survival of patients with pancreatic cancer. This finding highlights the need to better understand the molecular mechanisms that guide pancreatic tumorigenesis. The development of targeted agents was based on the ability of these agents to inhibit specific components (a cell receptor, a growth factor or an enzyme) of pathways that are believed to be involved in pancreatic cancer development. Targeting a single component of a pathway is not sufficient as pancreatic cancer has a complex biology (Box 1). The use of multitargeted agents or the combination of targeted agents that recognize various proteins that could simultaneously inhibit several pathways might be an appropriate strategy for the design of future clinical trials.

Future drug developments should aim to design agents that are able to target the physiologic effects of altered pathways by the inhibition of a broad number of downstream mediators or key nodal points. Sian and colleagues performed a genome analysis of 24 human pancreatic cancers and determined the sequences of 23,219 transcripts, which represented 20,611 different genes.[80] A total of 1,562 somatic mutations were detected in these genes and 1,327 of these genes had at least one mutation. Many of these mutations occurred in a group of genes involved in specific pathways and processes. The researchers were able to identify 69 gene sets that were genetically altered in the majority of the 24 cancers examined, and 31 of these sets could be incorporated into 12 core signaling pathways that were altered in 67–100% of the analyzed specimens. Pancreatic cancer development, therefore, seems to be related to alterations in a group of genes involved in specific pathways and processes.[80] However, for each individual case, the genes and pathways affected were varied, indicating that an individualized approach to therapy is likely to be required. The work by Sian and colleagues provides a possible explanation of why most targeted agents have failed to provide a benefit for patients with pancreatic cancer in clinical trials.

Box 1 | Pathways involved in pancreatic cancer

Signal transduction pathways via Ras and PI3K/Akt that cause cell proliferation and survival
- EGFR
- IGF-1R
- HGFR
- VEGFR

Developmental signaling pathways that can cause tumor progression and resistance to chemotherapy
- Hedgehog
- Notch
- Wnt

Tissue invasion and neovascularization
- MMP
- Other proteins

DNA damage control and impaired apoptosis
- p53
- p14 ARF/p16^{INK4A}
- SMAD4/TGF-b

In a xenograft model of human pancreatic adenocarcinoma in immunocompromised mice, Li *et al.*[81] identified a subset of cells that comprised about 0.2–0.8% of the tumor specimen that had a 100-fold increase in tumorigenic potential compared with other non-tumorigenic cells. This small subset of pancreatic cancer cells could self-renew, generate progeny that could differentiate and showed activation of the Hedgehog developmental signaling pathway. These findings are in agreement with previous research that has identified the presence of cancer stem cells in leukemia and in various solid tumors. The identification of pancreatic cancer stem cells is one of the major recent achievements in our knowledge of pancreatic cancer biology and could define new treatment strategies based on agents that target developmental pathways such as Hedgehog, Notch and Wnt signaling. These pathways are normally expressed during tissue development, and are quiescent in normal pancreas but have been found to be overexpressed in specimens of pancreatic cancer where it is believed they could sustain tumor growth and be responsible for the resistance to chemotherapy.[82]

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Table 4 | Ongoing phase III trials in patients with pancreatic carcinoma*

Trial ID	Treatment	Estimated number of patients	Disease stage
NCT00112658[†]	Gemcitabine vs oxaliplatin + irinotecan + 5-FU + folinic acid	348	IV
NCT00113256[‡]	Gemcitabine vs gemcitabine + rubitecan	NS	II–IV
NCT00051467	TNFerade™ + 5-FU + radiation	NS	II–III
NCT00425360[§]	Gemcitabine + capecitabine ± GV1001	1110	III–IV
NCT00440167	Capecitanib + erlotinib followed by gemcitabine if PD vs gemcitabine + erlotinib followed by capecitabine if PD	NS	II–IV
NCT00486460	Gemcitabine + curcumin + celecoxib	NS	II–IV
NCT00498225	Gemcitabine vs TS-1 vs gemcitabine + TS1	NS	II–IV
NCT00486460	Gemcitabine vs gemcitabine + sorafenib	104	II–IV
NCT00574275	Gemcitabine vs gemcitabine + aflibercept	NS	IV
NCT00634725	Gemcitabine ± capecitabine and/or radiotherapy vs gemcitabine ± erlotinib	820	III
NCT00662688	Gemcitabine ± capecitabine ± dalteparin	138	IV
NCT00789633	Gemcitabine vs gemcitabine + masitinib	NS	II–IV

*Data from the National Cancer Institute website (last updated August 2009) of ongoing and recently closed trials in patients with locally advanced and metastatic pancreatic cancer. [†]Phase II/III trials. [‡]Three treatment arms: only chemotherapy (gemcitabine plus capecitabine) vs the same chemotherapy regimen for two cycles followed by GV1001 until disease progression and switch to the same chemotherapy, versus the same chemotherapy plus GV1001. Abbreviations: 5-FU, 5-fluorouracil; NS, not specified; PD, progressive disease.

Box 2 | Agents and their mechanism of action for advanced pancreatic cancer

Rubitecan

Oral topoisomerase I inhibitor that blocks DNA and RNA synthesis in dividing cells.

TNF erade

Replication deficient adenovirus vector containing the gene for TNF-α controlled by a chemoradiation inducible promoter; used in combination with radiation therapy.

GV1001

Telomerase peptide vaccine; stimulates T cells to destroy the cancer cells by targeting the telomerase.

Curcumin

Natural compound with potent anti-inflammatory and antioxidative properties; inhibits cyclooxygenase-2 and blocks several pathways in cancer cells.

Celecoxib

Inhibits the enzyme cyclooxygenase-2 that is produced in response to inflammation and by precancerous and cancerous tissues.

TS-1

Prodrug of 5-fluorouracil (Tegafur) combined with two modulators to enhance its activity and reduce the gastrointestinal side effects of 5-FU.

Sorafenib

Tyrosine kinase inhibitor; blocks pathways involved in cell division and proliferation such as RAF/MEK/ERK; in addition blocks angiogenesis through inhibition of VEGFR-2/PDGFR-β signaling cascade.

Aflibercept

Fusion protein comprised of segments of the extracellular domains of human vascular endothelial growth factor receptors VEGFR-1 and VEGFR-2 and the constant region of human IgG1; binds to VEGF and prevents it from binding to its receptor.

Masitinib

Tyrosine kinase inhibitor that acts on several proteins in critical pathways, such as KIT, PDGFR, FGFR and, to a lesser extent, focal adhesion kinases.

The initiative by the International Cancer Genome Consortium aims to obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes that are of clinical and societal importance across the globe. One part of this project will involve the extensive analysis of the genetic changes that occur in pancreatic carcinoma and will aim to fully sequence 300–500 pancreatic cancer specimens.[82]

The development of effective treatments requires an improvement in preclinical studies (such as *in vitro* cell-based assays and tumor models) with identification of methods that could better predict the effectiveness of target inhibition in the clinic based on laboratory data. During the past decade thousands of patients with advanced pancreatic carcinoma were treated in phase II and phase III trials. It is a tragedy that 10 years of trials have added little to our overall knowledge of the disease and we are forced to speculate on why the intervention was unsuccessful. Routine examination of tumor and body fluids to assess predictive and prognostic biomarkers should be an essential component of future studies.

The majority of these trials had a reasonable accrual of patients with successful international multicenter collaborations. Over time, trials have become larger to allow the detection of smaller differences in outcome owing to patient subgroups that might benefit from treatment. A redesign of phase II and phase III trials in patients with advanced pancreatic cancer should be considered. Phase II trials should have standard entry criteria and set a high threshold for proceeding to phase III trials—for example, a minimum of a 2-month improvement in expected progression-free survival and overall survival. Phase III trials in advanced disease should also be relatively small and powered to detect hazard ratios of 0.75 or less, which would have clinical significance.[49] Future trials should probably make a distinction between patients with metastatic disease and patients with locally advanced disease, with separate treatment approaches employed for these two populations. Recently completed and ongoing phase III trials in patients with advanced pancreatic carcinoma registered with the National Cancer Institute are shown in Table 4 and the class of agent with the relative mechanism of action is reported in Box 2.

Conclusions

Approximately 80% of patients with pancreatic carcinoma are diagnosed with advanced disease, which precludes curative surgery. Following the establishment of gemcitabine as the standard first-line treatment, an international clinical research effort was undertaken. Thousands of patients were enrolled in large phase III trials, which investigated various cytotoxic agents or combination chemotherapy. This strategy has been largely unsuccessful and new approaches are required in the areas of clinical, translational and basic research for progress to be made. For patients with metastatic disease, gemcitabine remains the standard of care; a subset of patients with a good performance status might benefit from combination therapy. Gemcitabine plus erlotinib has demonstrated a benefit in some patients, although the molecular tumor phenotype of those individuals requires further definition. Patients with locally advanced

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disease should be considered as a different group to those with metastatic disease and may benefit from induction chemotherapy for 2–3 months followed by chemoradiation. The identification of pathways that might play a critical role in the development of pancreatic cancer and a better understanding of the underlying mechanisms of their activation could help in the development of new and more-active targeted agents that could overcome the resistance of pancreatic cancer cells to most of the current treatments.

Review criteria

The PubMed and Scopus Clinical Trials databases were searched for articles published before 30 July 2009. Only articles published in English were considered. The search terms used were "pancreatic cancer" in association with the search terms: "metastatic", "locally advanced", "clinical trials", "cytotoxic therapy", "targeted therapy" and "radiotherapy". Full articles were obtained and references were checked for additional material when appropriate.

1. Jemal, A. *et al.* Cancer statistics. *CA Cancer J. Clin.* **58**, 71–96 (2008).
2. Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2008, Toronto, Canada, 2008. April 2008, ISSN 0835–2976.
3. Cubilla, A. L. & Fitzgerald, P. J. Tumors of the exocrine pancreas. in *Atlas of Tumor Pathology* (Eds Hartmann, W. H. & Sobin, H.), 2nd series, fascicle 19 (Armed Forces Institute of Pathology, Washington, 1984).
4. Solcia, E., Capella, C. & Kloppel, G. Tumors of the exocrine pancreas. in *Tumors of the Pancreas* (Eds Rosai, J. & Sobin, L. H.) 145 (Armed Forces Institute of Pathology, Washington, 1997).
5. Chu, G. C., Kimmelman, A. C., Hezel, A. F. & DePinho, R. A. Stromal biology of pancreatic cancer. *J. Cell. Biochem.* **101**, 887–907 (2007).
6. Mahadevan, D. & Von Hoff, D. D. Tumor–stroma interactions in pancreatic ductal adenocarcinoma. *Mol. Cancer Ther.* **6**, 1186–1197 (2007).
7. Winter, J. M. *et al.* 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J. Gastrointest. Surg.* **10**, 1199–1211 (2006).
8. Sohn, T. A. *et al.* Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. *J. Gastrointest. Surg.* **4**, 567–579 (2000).
9. Yeo, C. J. *et al.* Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. *Ann. Surg.* **221**, 721–731 (1995).
10. Wong, H. H. & Lemoine, N. R. Pancreatic cancer: molecular pathogenesis and new therapeutic targets. *Nat. Rev. Gastroenterol. Hepatol.* **6**, 412–422 (2009).
11. Royal, R. E., Wolff, R. A. & Crane, C. H. in *Cancer Principles and Practice of Oncology* (Eds De Vita Jr, V. T., Lawrence, T. & Rosenberg, S. A.) 8th edition, 1, 1113–1120 (Lippincott Williams and Wilkins, Philadelphia, USA, 2008).
12. Khorana, A. A. & Fine, R. L. Pancreatic cancer and thromboembolic disease. *Lancet Oncol.* **5**, 655–663 (2004).
13. Sohail, M. A. & Saif, M. W. Role of anticoagulation in the management of pancreatic cancer. *JOP* **10**, 82–87 (2009).
14. Ioli, F. *et al.* Low molecular weight heparin (LMWH) increases the efficacy of cisplatinum plus gemcitabine combination in advanced pancreatic cancer. *J. Surg. Oncol.* **95**, 507–512 (2007).
15. von Delius, S. *et al.* Effect of low-molecular weight heparin on survival in patients with advanced pancreatic adenocarcinoma. *Thromb. Haemost.* **98**, 434–439 (2007).
16. Riess, H. *et al.* Rationale and design of PROSPECT CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy [abstract]. *BMC Cancer* **8**, a361 (2008).
17. Heinemann, V. & Boeck, S. Perioperative management of pancreatic cancer. *Ann. Oncol.* **19** (Suppl. 7), vii273–vii278 (2008).
18. Kaiser, M. H. & Ellenberg, S. S. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch. Surg.* **120**, 899–903 (1985).
19. Klinkenbijl, J. H. *et al.* Adjuvant radiotherapy and 5-fluorouracil after resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer group. *Ann. Surg.* **230**, 776–784 (1999).
20. Neoptolemos, J. P. *et al.* European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N. Engl. J. Med.* **350**, 1200–1210 (2004).
21. Crane, C. H., Ben-Josef, E. & Small, W. Jr. Chemotherapy for pancreatic cancer. *N. Engl. J. Med.* **350**, 2713–2715 (2004).
22. Oettle, H. *et al.* Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer. *JAMA* **297**, 267–277 (2007).
23. Neuhaus, P. *et al.* CONKO-001: final results of the randomized, prospective, multicentre phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer [abstract]. *J. Clin. Oncol.* **26** (Suppl. 18), a4504 (2008).
24. Regine, W. F. *et al.* Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma. *JAMA* **299**, 1019–1026 (2008).
25. Neoptolemos, J. *et al.* ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma [abstract]. *J. Clin. Oncol.* **27** (Suppl. 18), a4505 (2009).
26. Wolff, R. A., Varadhachary, G. R. & Evans, D. B. Adjuvant therapy for adenocarcinoma of the pancreas: Analysis of reported trials and recommendations for future progress. *Ann. Surg. Oncol.* **15**, 2773–2786 (2008).
27. Burris III, H. A. *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J. Clin. Oncol.* **15**, 2403–2413 (1997).
28. Heinemann, V. *et al.* Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J. Clin. Oncol.* **24**, 3946–3952 (2006).
29. Colucci, G. *et al.* Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: A prospective, randomized phase III study of the Gruppo Oncologico dell'Italia Meridionale. *Cancer* **94**, 902–910 (2002).
30. Louvet, C. *et al.* Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. *J. Clin. Oncol.* **23**, 3509–3516 (2005).
31. Poplin, E. *et al.* Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* **27**, 3778–3785 (2009).
32. Berlin, J. D. *et al.* Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern cooperative oncology group trial E2297. *J. Clin. Oncol.* **20**, 3270–3275 (2002).
33. Riess, H. *et al.* A randomised, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs gemcitabine alone in patients with advanced pancreatic cancer [abstract]. *J. Clin. Oncol.* **23** (Suppl. 16), a4009 (2005).
34. Herrmann, R. *et al.* Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J. Clin. Oncol.* **25**, 2212–2217 (2007).
35. Cunningham, D. *et al.* Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer [abstract]. *Eur. J. Cancer* **3** (Suppl. 3), a12 (2005).
36. Rocha Lima, C. M. *et al.* Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J. Clin. Oncol.* **22**, 3776–3783 (2004).
37. Stathopoulos, G. P. *et al.* A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br. J. Cancer* **95**, 587–592 (2006).
38. Abou-Alfa, G. K. *et al.* Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J. Clin. Oncol.* **24**, 4441–4447 (2006).
39. Oettle, H. *et al.* A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann. Oncol.* **16**, 1639–1645 (2005).
40. Colucci, G. *et al.* A randomized trial of gemcitabine (G) versus G plus cisplatin in chemotherapy-naive advanced pancreatic adenocarcinoma: The GIP-1 (*Gruppo Italiano Pancreas—GOIM/GISCAD/GOIRC*) study. *J. Clin. Oncol.* **27** (Suppl. 15), a4504 (2009).

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41. Heinemann, V., Boeck, S., Hinke, A., Labianca, R. & Louvet, C. Meta-analysis of randomized trials: Evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* **8**, 82 (2008).
42. Sultana, A. *et al.* Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br. J. Cancer* **96**, 1183–1190 (2007).
43. Boeck, S. & Heinemann, V. Second-line therapy in gemcitabine-pretreated patients with advanced pancreatic cancer. *J. Clin. Oncol.* **26**, 1178–1179 (2008).
44. Demols, A. *et al.* Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: A phase II study. *Br. J. Cancer* **94**, 481–485 (2006).
45. Tsavaris, N. *et al.* Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study. *Invest. New Drugs* **23**, 369–375 (2005).
46. Cantore, M. *et al.* Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. *Oncology* **67**, 93–97 (2004).
47. Xiong, H. Q. *et al.* Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* **113**, 2046–2052 (2008).
48. Petzer, U. *et al.* A randomized trial in patients with gemcitabine refractory pancreatic cancer.Final results of the CONKO 003 study [abstract]. *J. Clin. Oncol.* **26** (Suppl.), a4508 (2008).
49. Welch, S. A. & Moore, M. J. Combination chemotherapy in advanced pancreatic cancer: Time to raise the white flag? *J. Clin. Oncol.* **25**, 2159–2161 (2007).
50. Lemoine, N. R. *et al.* Ki-ras oncogene activation in preinvasive pancreatic cancer. *Gastroenterology* **102**, 230–236 (1992).
51. Van Cutsem, E. *et al.* Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J. Clin. Oncol.* **22**, 1430–1438 (2004).
52. Lobell, R. B. *et al.* Evaluation of farnesyl: protein transferase and geranylgeranyl: protein transferase inhibitor combinations in preclinical models. *Cancer Res.* **61**, 8758–8768 (2001).
53. Jones, L., Ghaneh, P., Humphreys, M. & Neoptolemos, J. P.The matrix metalloproteinases and their inhibitors in the treatment of pancreatic cancer. *Ann. NY Acad. Sci.* **880**, 288–307 (1999).
54. Bramhall, S. R., Rosemurgy, A., Brown, P. D., Bowry, C. & Buckels, J. A. Marimastat as first line therapy for patients with unresectable pancreatic cancer: A randomized trial. *J. Clin. Oncol.* **19**, 3447–3455 (2001).
55. Bramhall, S. R. *et al.* A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br. J. Cancer* **87**, 161–167 (2002).
56. Moore, M. J. *et al.* Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12–9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* **21**, 3296–3302 (2003).
57. Seo, Y., Baba, H., Fukuda, T., Takashima, M. & Sugimachi, K. High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. *Cancer* **88**, 2239–2245 (2000).
58. Kindler, H. L. *et al.* Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J. Clin. Oncol.* **23**, 8033–8040 (2005).
59. Kindler, H. L. *et al.* A double-blind, placebo controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine (G) plus placebo (P) in patients with advanced pancreatic cancer (PC). A preliminary analysis of cancer and Leukemia Group B (CALGB) 80303 [abstract]. *J. Clin. Oncol.* **25** (Suppl.), a4508 (2007).
60. Vervenne, W. *et al.* A randomized, double-blind, placebo controlled, multicenter phase III trial to evaluate the efficacy and safety of adding bevacizumab to erlotinib and gemcitabine in patients with metastatic pancreatic cancer [abstract]. *J. Clin. Oncol.* **26** (Suppl.), a4507 (2008).
61. Spano, J. P.*et al.* Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet* **371**, 2101–2108 (2008).
62. Ueda, S. *et al.* The correlation between cytoplasmic overexpression of epidermal growth factor receptor and tumor aggressiveness: Poor prognosis in patients with pancreatic ductal adenocarcinoma. *Pancreas* **29**, E1–E8 (2004).
63. Bruns, C. J. *et al.* Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. *Cancer Res.* **60**, 2926–2935 (2000).
64. Moore, M. J. *et al.* 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. *J. Clin. Oncol.* **25**, 1960–1966 (2007).
65. Moore, M. J. *et al.* The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with erlotinib on National Cancer Institute of Canada Clinical Trials Group trial study PA.3. *J. Clin. Oncol.* **25** (Suppl. 18), a4521 (2007).
66. Siena, S., Sartore-Bianchi, A., Di Nicolantonio, F., Balfour, J. & Bardelli, A. Biomarkers predicting clinical outcome of epidermal growth factor receptor-targeted therapy in metastatic colorectal cancer. *J. Natl Cancer Inst.* **101**, 1308–1324 (2009).
67. Xiong, H. Q. *et al.* Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. *J. Clin. Oncol.* **22**, 2610–2626 (2004).
68. Philip, P.et *al.* Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study [abstract]. *J. Clin. Oncol.* **25**, a4509 (2007).
69. Schinchi, H. *et al.* Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **53**, 146–150 (2002).
70. Moertel, C. G., Frytak, S. & Hahn, R. G. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5 fluorouracil), and high dose radiation + 5-fluorouracil. The Gastrointestinal Tumor Study Group. *Cancer* **48**, 1705–1710 (1981).
71. Cohen, S. J. *et al.* A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas. Eastern cooperative oncology group study E8282. *Int. J. Radiat. Oncol. Biol. Phys.* **62**, 1345–1350 (2005).
72. [No authors listed] Treatment of locally unresectable carcinoma of the pancreas: Comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumour Study Group. *J. Natl Cancer Inst.* **80**, 751–755 (1988).
73. Hazel, J. J., Thirlwell, M. P., Huggins, M., Maksymiuk, A. & MacFarlane, J. K. Multi-drug chemotherapy with and without radiation for carcinoma of the stomach and pancreas: a prospective randomized trial. *J. Can. Assoc. Radiol.* **32**, 164–165 (1981).
74. Klaassen, D. J., MacIntyre, J. M., Catton, G. E., Engstro, P. F. & Moertel, C. G. Treatment of locally unresectable cancer of the stomach and pancreas: A randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. *J. Clin. Oncol.* **3**, 373–378 (1985).
75. Chauffert, B. *et al.* Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study. *Ann. Oncol.* **19**, 1592–1599 (2008).
76. Loehrer, P. J. *et al.* A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201 [abstract]. *J. Clin. Oncol.* **26** (Suppl. 214), a4506 (2008).
77. Krishnan, S. *et al.* Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* **110**, 47–55 (2007).
78. Huguet, F. *et al.* Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J. Clin. Oncol.* **25**, 326–331 (2007).
79. Maitra, A. & Hruban, R. H. Pancreatic cancer. *Ann. Rev. Pathol. Mech. Dis.* **3**, 157–188 (2008).
80. Sjan, J. *et al.* Core signaling pathways in human pancreatic cancer revealed by global genomic analyses. *Science* **321**, 1801–1806 (2008).
81. Li, C. *et al.* Identification of pancreatic cancer stem cells. *Cancer Res.* **67**, 1030–1037 (2007).
82. Lee, C. J., Dosch, J. & Simeone, D. Pancreatic cancer stem cells. *J. Clin. Oncol.* **26**, 2806–2812 (2008).
83. Kern, S. *et al.* A white paper: the product of a pancreas cancer think tank. *Cancer Res.* **61**, 4923–4932 (2001).

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clinical studies

A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer

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Our purpose was to determine the response rate and median and overall survival of gemcitabine as monotherapy versus gemcitabine plus irinotecan in advanced or metastatic pancreatic cancer. Patients with histologically or cytologically confirmed adenocarcinoma who were chemotherapy and radiotherapy naive were enrolled. Patients were centrally randomised at a one-to-one ratio to receive either gemcitabine monotherapy (900 mg m^{-2} on days 1, 8 and 15 every 4 weeks (arm G), or gemcitabine (days 1 and 8) plus irinotecan (300 mg m^{-2} on day 8) (arm IG), repeated every 3 weeks. The total number of cycles administered was 255 in the IG arm and 245 in the G arm; the median number of cycles was 3. In all, 145 patients (71 in arm IG and 74 in arm G) were enrolled; 60 and 70 patients from arms IG and G, respectively, were evaluable. A complete clinical response was achieved in three (4.3%) arm G patients; nine (15%) patients in arm IG and four (5.7%) in arm G achieved a partial response. The overall response rate was: arm IG 15% and arm G 10% (95% CI 5.96–24.04 and 95% CI 2.97–17.03, respectively; $P = 0.387$). The median time to tumour progression was 2.8 months and 2.9 months and median survival time was 6.4 and 6.5 months for the IG and G arms, respectively. One-year survival was 24.3% for the IG arm and 21.8% for the G arm. No statistically significant difference was observed comparing gemcitabine monotherapy versus gemcitabine plus irinotecan in the treatment of advanced pancreatic cancer, with respect to overall and 1-year survival.

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Owing to the nonspecific symptoms of the disease or to its insidious evolution, pancreatic cancer is often diagnosed when the disease is at an advanced stage; as a result, fewer than 20% of newly diagnosed patients are able to have a radical excision of the tumour (Brenna *et al*, 1993; Schnall and Macdonald, 1996; Stephens, 1998). Chemotherapy is the treatment of choice in patients with locally advanced and metastatic disease. Gemcitabine as a single agent is considered to be the standard treatment for these patients since, in spite of the low overall objective response, studies have shown an improvement in overall survival and a statistically significant clinical benefit when compared to the best supportive care (Casper *et al*, 1994; Burris *et al*, 1997).

Other single agents have also been tested in advanced pancreatic cancer but the response rate and survival have remained low; moreover, the incidence of clinical benefit obtained with these drugs has been variable (Wagener *et al*, 1995; Scher *et al*, 1996; Androulakis *et al*, 1999; Rougier *et al*, 2000; Konstandoulakis *et al*, 2001; Cartwright *et al*, 2002). Several phase II studies have evaluated different combinations of cytotoxic agents in order to improve the proportion of objective responses and the duration of survival. Numerous phase II studies have investigated combinations of these active drugs with or without gemcitabine in patients with advanced/metastatic pancreatic cancer (Rothenberg *et al*, 1998; Bahadori *et al*, 1999; Hidalgo *et al*, 1999; Rocha-Lima *et al*, 1999; Heinemann *et al*, 2000; Stathopoulos *et al*, 2001; Alberts *et al*, 2002; Berlin *et al*, 2002; Hess *et al*, 2003; Stathopoulos *et al*, 2003; Ulrich-Pur *et al*, 2003). The combination of gemcitabine plus irinotecan has resulted in an objective response of 25% with a median overall survival ranging from 5.7 to 7 months (Rocha-Lima *et al*, 2002; Stathopoulos *et al*, 2004). As phase II studies of combinations of active anticancer drugs in patients with advanced/metastatic pancreatic cancer have been associated with a better survival (about 7 months) (Rocha-Lima *et al*, 2002; Stathopoulos *et al*, 2003; Stathopoulos *et al*, 2004) compared with gemcitabine monotherapy (about 5 months) (Miller *et al*, 1981), various randomised trials are ongoing in order to validate these observations.

Despite the fact that the achieved objective response rate with gemcitabine-based combinations is practically similar, there are

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controversial results concerning overall survival; the 1-year survival was reported to be 22% with the gemcitabine–irinotecan combination (objective response rate (ORR) 25%) whereas overall survival was found to be 34.8% with the gemcitabine–capecitabine combination (ORR 18.9%) (Stathopoulos *et al*, 2003; Ulrich-Pur *et al*, 2003).

The Gastrointestinal Working Parties of the Hellenic Oncology Research Group (HORG) and the Hellenic Cooperative Oncology Group (HeCOG) conducted this intergroup, multicenter, phase III randomised trial in order to evaluate the efficacy of the gemcitabine-irinotecan combination versus gemcitabine monotherapy, in previously untreated patients with inoperable locally advanced or metastatic pancreatic cancer.

PATIENTS AND METHODS

Patients >18 years of age with histologically or cytologically confirmed adenocarcinoma of the pancreas and bidimensionally measurable disease, who were chemotherapy and radiotherapy naive were enrolled in the study. Other eligibility criteria included a World Health Organization (WHO) performance status (PS) of 0–2, a life expectancy of at least 3 months, an adequate bone marrow reserve (granulocyte count $\geqslant 1500\,dl^{-1}$, platelet count $\geqslant 120\,000\,dl^{-1}$), adequate renal (serum creatinine concentration $<1.2\,mg\,dl^{-1}$) and liver function (total serum bilirubin concentration $<3\,mg\,dl^{-1}$) provided that serum transaminases and serum proteins were normal; normal cardiac function with no history of clinically unstable angina pectoris or myocardial infraction or congestive heart failure within the 6 months prior and no central nervous system involvement. Prior surgery was allowed provided that it had taken place at least 3 weeks before enrollment. Patients with active infection, malnutrition or a second primary tumour (except for a nonmelanoma skin epithelioma or *in situ* cervix carcinoma) were excluded from the study. All patients gave their written informed consent to participate in the study.

Treatment

All patients were treated on an outpatient basis. Patients were centrally randomised by computer at a one-to-one ratio to receive either monotherapy (arm G) with gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN, USA) at a dose of $900\,mg\,m^{-2}$ as a 60 min i.v. infusion on days 1, 8 and 15 every 4 weeks or the combination (arm IG) of gemcitabine (same dose on days 1 and 8) plus irinotecan (Campto; Sanofi-Aventis Collegeville, PA, USA) on day 8 at a dose of $300\,mg\,m^{-2}$ over a 90 min i.v. infusion every 3 weeks. Cycles were continued provided that patients had sufficiently recovered from drug-related side effects. The allocation to either regimen was done by stratified randomisation according to age, performance status and stage of the disease. Standard antiemetic treatment with ondansetron was administered to all patients. Prophylactic recombinant human granulocyte colony-stimulating factor (rhG-CSF; Granocyte, Sanofi-Aventis) was allowed only in patients with $\geqslant$ grade 3 granulocytopenia and given at a dose of $150\,\mu g\,m^{-2}$ subcutaneously. Patients with an objective response or stable disease received at least six chemotherapy cycles. The protocol was approved by the Ethics and Scientific Committees of the participating hospitals.

Dose adjustment criteria were based on haematological parameters. Irinotecan and gemcitabine doses were reduced by 25% in cases of febrile or grade 4 neutropenia or thrombocytopenia. In cases of grade 3 neutropenia and/or thrombocytopenia lasting for >5 days, the dose of both drugs was reduced by 15%. Toxicities were graded according to WHO guidelines (Miller *et al*, 1981).

Evaluation of patients

Pretreatment evaluation included a complete medical history and physical examination, a full blood cell count with differential and platelet count, a standard biochemical profile, serum carcinoembryonic antigen (CEA) and CA 19-9 determinations, electrocardiogram, chest X-rays, ultrasound of the upper abdomen and computed tomography scans of the chest and upper and lower abdomen. Additional imaging studies were performed on clinical indication; these studies were performed and analysed by the same radiologist. Full blood cell counts with differential were performed weekly; in cases of grade 3–4 neutropenia or grade 4 thrombocytopenia, full blood cell counts with differential were evaluated daily until the absolute granulocyte count was $\geqslant 1000\,dl^{-1}$ and the platelet count $\geqslant 75\,000\,dl^{-1}$. A detailed medical and physical examination was performed before each course of treatment in order to document disease symptoms and treatment toxicity. Biochemical tests, electrocardiogram (ECG), serum CEA and CA 19-9 determinations and chest X-rays were performed every 6 weeks. A neurological evaluation was performed by clinical examination every 6 weeks. Lesions were measured after each cycle if they were assessable by physical examination or by chest X-rays; lesions assessable by ultrasound or CT scan were measured after 3 cycles of chemotherapy.

Definition of response

A complete response (CR) was defined as the disappearance of all measurable or evaluable disease, signs and symptoms and biochemical changes related to the tumour for at least 4 weeks, during which time no new lesions may appear; partial response (PR), a >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements lasting $\geqslant$ 24 weeks, during which time no new lesions may appear and no existing lesions may enlarge. For hepatic lesions, a reduction of >30% in the sum of the measured distances from a costal margin at the midclavicular line and at the xiphoid process to the edge of the liver was required. Stable disease (s.d.) was defined as a <50% reduction or a <25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and the appearance of no new lesions for 8 weeks. Progression or relapse was defined as an increase in the product of the two perpendicular diameters of any measurable lesion by >25% over the size present at enrolment or for patients who responded, the size at the time of maximum regression and the appearance of new areas of malignant disease (usually excluding central nervous system metastases). A deterioration in performance status, loss of >10% pretreatment weight or worsening symptoms did not by themselves constitute progression; however, persistence of these complaints or the appearance of new symptoms required a repeat evaluation of the extent of the disease (Donehower *et al*, 1995). All responses had to be maintained for $\geqslant$4 weeks and had to be confirmed by an independent panel of radiologists.

Assessment of clinical benefit

The assessment of pain was based on both the consumption of analgesics (narcotics and non-narcotics) and the patient's own evaluation using a scale graded from 0 (no pain) to 10 (maximum pain necessitating narcotics for relief). A >50% decrease of analgesic consumption with no need for narcotics coupled with the patient's evaluation of a >50% decrease in pain intensity was characterised as 'pain improvement.' A >50% increase in the consumption of analgesics in combination with the patient's evaluation or a >50% increase in pain intensity was characterised as 'pain deterioration.' All other cases were characterised as 'no change.' Symptoms of vomiting and diarrhoea were assessed

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according to the number of daily episodes: a 50% decrease in number was characterised as 'improvement' whereas a >50% increase, as 'deterioration.' All other cases were characterised as 'no change.' In addition, patients were asked to grade their fatigue and anorexia using a scale of 0 (no fatigue or anorexia) to 10 (maximum fatigue or anorexia). A 50% decrease or increase in symptom intensity indicated 'improvement' or 'deterioration,' respectively.

Statistical analysis

The study was designed as a group-sequential clinical trial. An interim analysis based on the O'Brien/Fleming boundary values was performed when 50% of the endpoints had been reached (Rocha-Lima *et al*, 2004). The study would have ended prematurely if a significant difference in survival had been observed. The randomisation of patients into two treatment arms was performed according to the method of random permuted blocks within strata. Stratification factors comprised stage III or and IV disease. Dynamic balancing was performed by the hospital. Pearson's χ^2 test (or Fisher's exact test when appropriate) was used for the comparisons of categorical variables. The nonparametric Mann–Whitney test was used for comparisons of continuous variables. Time-to-event analyses were performed where survival distribution was estimated by the Kaplan–Meier curve, and treatment comparison was made using the log-rank test. All reported *P*-values are two-sided. A *P*-value of <0.05 was considered significant. The primary end point was median survival time and the secondary end points were response rate, median time to tumour progression and tolerance.

The randomisation was carried out at the University Hospital of Heraklion, Crete, in the Office of Clinical Trials. There were eight losses to follow-up (four per treatment group). The analysis of data was done on an intention-to-treat analysis basis. The accrual time was 36 months and the median follow-up time, 24 months.

RESULTS

Patient demographics

From November 2001 to February 2005, 145 patients (71 in the IG arm and 74 in the G arm) were enrolled. Eleven (15.5%) IG arm and 4 (5.4%) G arm patients were not evaluated for the following reasons: arm IG: a PS of 3 in three patients, protocol violation in two, consent withdrawn by six patients; arm G: renal failure in one patient, no measurable disease in one patient, protocol violation in one, and consent withdrawn by one patient. The patients' characteristics are shown in Table 1. The median age was 64 years in each arm and 78% arm IG and 86% arm G patients had stage IV disease. Although the difference in stage IV patients enrolled in the IG and G arms was about 8%, this difference was not statistically significant ($P=0.272$). The median number of involved organs was 2 (range, 1–4) in each arm; liver involvement was present in 34% and 37% IG and G patients, respectively; similarly, 10 and 11% patients enrolled in the IG and G arms, respectively, had abdominal lymph node involvement.

Compliance with treatment

The total number of administered chemotherapy cycles were 255 (median 3; range, 1–16) for patients treated with the IG regimen and 245 (median 3; range 1–8) for those treated with the G regimen. The median interval between cycles was 21 (range, 21–30.8) and 29 days (range 28–35) for the IG and G arms, respectively. The median dose intensity was 83 mg m^{-2} week^{-1} (range, 25–100) for irinotecan and 553 mg m^{-2} week^{-1} (range, 299–600) for gemcitabine (IG arm) and 591 mg m^{-2} week^{-1} (range, 179–675) for gemcitabine (G arm). Twelve (4.7%) of the IG arm and 13 (5.3%) of the G arm cycles were delayed. The reasons for treatment delay were: in arm IG, haematologic toxicity in five patients, nonhaematologic toxicity in one patient, and nonrelated to treatment or the disease (non-neutropenic infections) in six patients; in arm G, haematologic toxicity in four patients, nonhaematologic toxicity in two patients and nonrelated to treatment or the disease in six patients. Dose reduction was required in eight (13.3%) patients treated with IG and 17 (24.3%) patients treated with G ($P<0.001$). Dose reduction was required in 34 (13.3%) of the IG arm and 60 (24.5%) of the G arm cycles. Haematologic toxicity was the main reason for dose reduction in both groups; however, the incidence of haematologic toxicity was higher (35.3%) in patients treated with IG than in those treated with G (26.7%) ($P<0.001$) Table 2. In addition, the incidence of no drug administration on day 8 and/or day 15 was higher (46.7%) in patients enrolled in the G arm versus 29.4% in the IG arm ($P=0.002$). Treatment was completed as per protocol in 18 (30%) IG arm patients and in 12 (17.1%) G arm patients whereas it was

Table 1 Patients' characteristics

	Treatment groups	
	IG ($n=60$) *n* (%)	G ($n=70$) *n* (%)
Age (year)		
Median (range)	64 (31–84)	64 (44–83)
Gender		
Male	39 (65)	42 (60)
Female	21 (35)	28 (40)
Performance status (WHO)		
0–1	52 (87)	60 (86)
2	8 (13)	10 (14)
Stage		
III	13 (22)	10 (14)
IV	47 (78)	60 (86) ($P=0.272$)
No. of organs involved		
1	24 (40)	24 (34)
2	22 (37)	34 (49)
>3	14 (23)	12 (17)
Prior Surgery	11 (18)	16 (23)
No prior treatment	49 (82)	54 (77)

Table 2 Reasons for dose reduction

	Treatment groups	
	IG (255 cycles) *n* (%)	G (245 cycles) *n* (%)
Dose reduction	34 (13.3)	60 (24.5)
Due to:		
Haematologic toxicity	12 (35.3)*	16 (26.7)
Nonhaematologic toxicity	10 (29.4)	8 (13.3)
Haematologic and nonhaematologic toxicity	1 (2.9)	1 (1.7)
Day 8 and/or day 15 treatment not given (for reasons other than toxicity)	10 (29.4)	28 (46.7)†
Other	1 (2.9)	7 (11.7)

*$P<0.001$. †P 0.002.

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stopped because of disease progression in 29 (48.3%) IG arm patients and in 49 (70.9%) G arm ($P=0.027$).

The total number of deaths at the end of the study were 46 (76.7%) and 57 (81.4%) patients enrolled in the IG and G arms, respectively. Death was due to malignant disease in 84.8% and 84.2% of the G and IG patients, respectively. One patient in arm G died because of stroke.

Response to treatment

Responses were analysed on an intention-to-treat basis. There were no complete responses in the IG-arm patients; however, a complete clinical response was achieved in three (4.3%) patients treated with G. In addition, nine (15%) IG arm and four (5.7%) G arm patients achieved a partial response (overall response rate: IG arm, 15% and G arm 10%, 95% CI 5.96–24.04% and 2.97–17.03, respectively; $P=0.387$). Stable disease was achieved in 16 (26.7%) IG arm and 13 (18.6%) G arm patients, while disease progression was observed in 35 (58.3%) and 50 (71.4%) of the IG and G arm patients, respectively. Tumour disease control (CR + PR + SD) was achieved in 25 (41.7%; 95% CI: 29.19–54.14) and in 20 (28.6%; 95% CI 17.99–39.15) patients treated with IG and G, respectively, ($P=0.800$). The median time to tumour progression (TTP) was 2.8 months (range 1.0–17.3 months) and 2.9 months (range 1.0–17.4 months) for patients treated with IG and G, respectively ($P=0.795$).

After a median follow-up period 5.9 months (range, 1.0–24.4 months) for IG arm patients and 5.3 months (range, 1.0–27.4) for G arm patients, 46 (76.7%) and 57 (81.4%) patients, respectively, died. The median survival time was 6.4 months (range, 1.0–24.4 months) and 6.5 months (range, 1.0–27.4 months) in patients treated with IG and G, respectively ($P=0.970$). The 1-year survival was 24.3% in patients treated with IG and 21.8% in patients treated with G (Figure 1). In all, 21 (35%) in the IG and 22 (31.4%) in the G group received second-line chemotherapy. The difference was not statistically significant ($P=0.666$) with regard to survival benefit.

Effect of treatment on serum levels of CA 19-9

In 52 (86.7%) and 60 (85.7%) patients treated with the IG and G regimens, respectively, there were sufficient evaluable data on the serum levels of CA 19-9. In 24 (46.2%) IG arm and in 22 (36.7%) G arm patients, a >25% decrease of serum levels of CA 19-9 was observed ($P=0.308$). Similarly, 13 (25%) and 23 (38.3%) patients treated with the IG and G regimens, respectively, showed a >25% increase in the serum levels of CA 19-9 during treatment. There was no clear correlation between CA 19-9 measurements and radiological response ($P=0.226$).

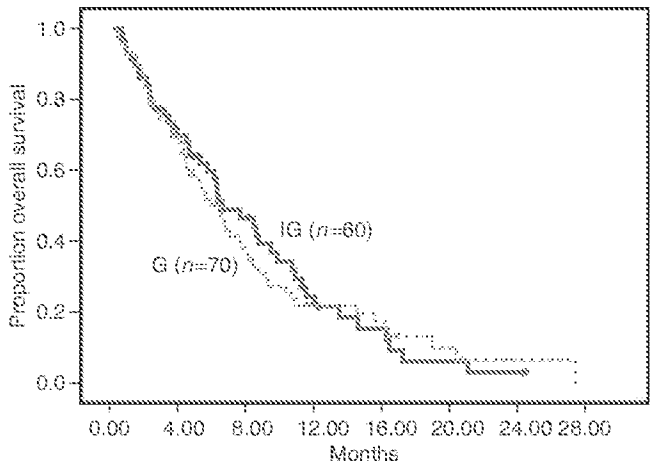


Figure 1 Kaplan–Meier overall survival.

Effect of treatment on tumour-related symptoms

Tumour-related symptoms were present at enrolment in 48 (80%) and 58 (82.9%) of patients treated with IG and G, respectively. There was no significant difference between the two chemotherapy regimens with regard to their effect on tumour-related symptoms.

Toxicity

Table 3 shows the incidence of severe (grade 3 and 4) haematologic and non-haematologic toxicity associated with the IG and G regimens. Grade 3 and 4 neutropenia occurred in 16 (26.7%) patients treated with IG and 11 (15.7%) patients treated with G ($P=0.125$). No patients developed febrile neutropenia. Grade 3 and 4 thrombocytopenia occurred in three (5.0%) patients treated with IG ($P=0.028$). Nonhaematologic toxicity was mild, usually <5%, regardless of the chemotherapy regimen administered.

DISCUSSION

Locally advanced or metastatic pancreatic cancer is an incurable disease and in this setting, only systemic chemotherapy may result in a small improvement in survival and clinical benefit. In an effort to improve the results obtained with gemcitabine, which is the standard treatment, several phase II studies have evaluated it in combination with other cytotoxic agents. Some of these studies have reported an improved median overall survival and 1-year survival rates. However, the question which concerns the superiority of gemcitabine-based chemotherapy regimens over gemcitabine monotherapy in terms of overall survival and quality of life can only be answered by comparative randomised studies.

The present study was based on the promising results of a previous phase II trial of irinotecan and gemcitabine in patients with advanced/metastatic pancreatic cancer, which reported an objective response rate of 25% (Stathopoulos *et al*, 2003). This efficacy of the irinotecan-gemcitabine combination was higher than that obtained with gemcitabine alone. Similar results have also been reported with the irinotecan-gemcitabine regimen by another research group (Rocha-Lima *et al*, 2002). The results of the present study demonstrate that although the ORR was higher with the IG regimen compared with that of the G regimen, this difference did not reach statistical significance. Moreover, there was no difference between the two treatment arms in terms of duration of response, TTP, overall survival and 1-year survival.

Table 3 Severe (grade 3 and 4) haematologic and nonhaematologic toxicity

	Grade 3 and 4 (WHO)		
	IG	G	
	n = 60	n = 70	
	n (%)	n (%)	P-value
Anemia	3 (5)	3 (4.3)	NS
Neutropenia	16 (26.7)	11 (15.7)	0.125
Thrombocytopenia	3 (5)	—	0.028
Nausea	1 (1.7)	2 (2.9)	NS
Vomiting	1 (1.7)	1 (1.4)	NS
Diarrhea	2 (3.3)	2 (2.9)	NS
Asthenia	—	4 (5.7)	—
Influenza-like syndrome	2 (3.3)	—	

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The results of a randomised trial comparing the irinotecan–gemcitabine combination with gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer have recently been reported (Rocha-Lima *et al*, 2004). This study demonstrated a significantly higher ORR of 16.1% with the combination versus that achieved with gemcitabine alone (ORR 4.4%); moreover, the ORR was also higher with the two-drug combination (25.9%) compared with gemcitabine monotherapy (ORR 4.2%). In addition, these authors (Rocha-Lima *et al*, 2004) reported that the TTP was significantly higher in patients with locally advanced disease treated with the irinotecan–gemcitabine combination compared with gemcitabine as a single agent. However, there was no difference between the two chemotherapy regimens in terms of overall and 1-year survival (Rocha-Lima *et al*, 2004). It is interesting to note that the above study (Rocha-Lima *et al*, 2004) and the present trial have documented a similar efficacy achieved with the irinotecan–gemcitabine combination; however, gemcitabine monotherapy resulted in a relatively low response rate (Rocha-Lima *et al*, 2004) which may account for the observed statistical difference.

These results were obtained with an acceptable toxicity profile for both regimens. Indeed, the incidence of severe grade 3 and 4 toxicity was practically similar in the two arms and only the incidence of severe thrombocytopenia was shown to be statistically higher in the combination arm compared with gemcitabine monotherapy. In addition, the incidence of severe asthenia was higher in the monotherapy arm compared to the combination arm.

It is difficult to explain why the combinations of gemcitabine with a second anticancer drug cannot significantly improve the overall survival of patients with locally advanced/metastatic pancreatic cancer. This may reflect the natural history of the tumour, which is characterised by its indolent onset and its inoperability at the time of diagnosis. The clinical characteristics of this disease are directly related to the biology of the tumour cell. Therapeutic approaches which target the specific biologic mechanisms involved in tumour cell proliferation and metastasis might be revealed to be more effective in these patients. The recently reported improvement of overall survival in patients with advanced and metastatic pancreatic cancer with the gemcitabine–erlotinib combination compared to single-agent gemcitabine supports this hypothesis (Moore *et al*, 2005). Additional studies evaluating novel agents against specific molecular targets alone or in combination with other cytotoxic agents are necessary.

clinical studies

REFERENCES

Alberts SR, Townley PM, Goldberg RM, Cha SS, Moore Jr DF, Krook JE, Pilot HC, Fitch TR, Wiesenfeld M, Maillard JA, Sargent DJ (2002) Gemcitabine and oxaliplatin for patients with advanced or pancreatic metastatic cancer: a North Central Cancer Treatment Group (NCCTG) phase I study. *Ann Oncol* **13**: 553–557

Androulakis N, Kouroussis CH, Dimopoulos MA, Samelis G, Kakolyris S, Tsavaris N, Genatas K, Aravantinos G, Papadimitriou CR, Karabekios S, Stathopoulos GP, Georgoulias V (1999) Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II study. *J Clin Oncol* **17**: 1779–1785

Bahadori HR, Rocha Lima CM, Green MR, Safa AR (1999) Synergistic effect of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. *Anticancer Res* **19**: 5423–5428

Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DJ, Benson AB (2002) Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma. Eastern Cooperative Oncology Group Trial E 2297. *J Clin Oncol* **20**: 3270–3275

Brenna MF, Kinsella TJ, Casper ES (1993) Cancer of the pancreas. In *Cancer: Principles and Practice of Oncology* DeVita VT jr Hellman S, Rosenberg SA (eds) 4th edition, pp 849–882. Philadelphia, PA: Lippincott

Burris III HA, Moore MJ, Anderson J, Green HR, Rothenberg HL, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer. A randomized trial. *J Clin Oncol* **15**: 2403–2413

Cartwright TH, Cohn A, Varkey JA, Chen Y-M, Szatrowski TP, Cox JV, Schulz J (2002) A phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol* **20**: 160–164

Casper ES, Green MR, Kelsen DP (1994) Phase II trial of gemcitabine (2,2 difluorodeoxytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* **12**: 29–34

Donehower RC, Abeloff MD, Perry MC (1995) Response criteria. In *Clinical Oncology* Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE (eds), pp 201–208. New York NY: Churchill Livingston

Heinemann V, Wilke H, Mergenthaler HG, Clemens M, König H, Illiger HL, Arning M, Schalhorn A, Possinger K, Fink V (2000) Gemcitabine and cisplatin in the treatment of advanced and metastatic pancreatic cancer. *Ann Oncol* **11**: 1399–1403

Hess V, Salzberg M, Borner M, Marant R, Roth AD, Ludwig C, Hermann R (2003) Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol* **21**: 66–68

Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, Alonso D, Cortes-Funes H (1999) Phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol* **17**: 585–592

Konstandoulakis MM, Antonakis PT, Tsiblioulis BG, Stathopoulos GP, Manouras AP, Mylonaki DB, Golematis BX (2001) A phase II study of 9-nitro-camptothecin in patients with advanced pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* **48**: 417–420

Miller AB, Hoogstraten BB, Staquet M, Winkler A (1981) Reporting results of cancer treatment. *Cancer* **47**: 207–217

Moore MJ, Goldstein D, Hamm J, Figer A, Hecht J, Gallinger S, Au H, Ding K, Christy-Bittel J, Parulekar W (2005) Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *Proceedings of Am Soc Clin Oncol* 1s, (abstract 1)

Rocha-Lima CM, Green MR, Rotche R, Miller Jr WH, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL (2004) Irinotecan plus gemcitabine, results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* **22**: 3776–3783

Rocha-Lima CM, Leong SS, Sherman CA, Perkel JA, Putman-Hair T, Safa AR, Green MR (1999) Phase I study of CPT-11 and gemcitabine in patients with solid tumors. *Cancer Ther* **2**: 58–66

Rocha-Lima CM, Savarese D, Bruckner H, Dudet A, Eckardt J, Hainsworth J, Yunus F, Lester E, Miller W, Saville W, Elfring GL, Locker PK, Compton LD, Miller LL, Green MR (2002) Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. *J Clin Oncol* **20**: 1182–1191

Rothenberg ML, Sharma A, Weiss GR, Villanova-Calero MA, Eckardt JR, Aylesworth C, Kraynak MA, Rinoldi DA, Rodriguez GI, BUrris III HA, Eckhardt SG, Stephens CD, Forral K, Nicol SJ, Von HOff DD (1998) A phase I trial of paclitaxel and gemcitabine administered every 2 weeks in patients with refractory solid tumors. *Ann Oncol* **9**: 733–738

Rougier PH, Adenis A, Ducreux M, de Forni M, Bonneterre J, Dembak M, Clouet P, Lebecq A, Baille P, Lefresne-Soulas F, Blanc C, Armand JP (2000) A Phase II study of docetaxel as first-line chemotherapy for advanced pancreatic carcinoma. *Eur J Cancer* **36**: 1016–1021

Scher RM, Kosierowski R, Lusch C, Alexander R, Fox S, Redei I, Green F, Raskay B, Amfoh K, Engstrom PF, O'Dwyer PJ (1996) Phase II trial of topotecan in advanced or metastatic adenocarcinoma of the pancreas. *Invest New Drugs* **13**: 347–351

Schnall SF, Macdonald JS (1996) Chemotherapy of adenocarcinoma of the pancreas. *Semin Oncol* **23**: 220–228

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Stathopoulos GP, Mavroudis D, Tsavaris N, Kouroussis C, Aravantinos G, Agelaki S, Kakolyris S, Rigatos SK, Karabekios S, Georgoulias V (2001) Treatment of pancreatic cancer with a combination of docetaxel, gemcitabine and granulocyte colony-stimulating factor: a phase II study of the Greek Cooperative Group for pancreatic cancer. *Ann Oncol* **12:** 101–103

Stathopoulos GP, Rigatos SK, Dimopoulos MA, Giannakakis T, Fountzilas G, Kouroussis C, Janninis D, Aravantinos G, Androulakis N, Agelaki S, Stathopoulos JG, Georgoulias V (2003) Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study of the Greek Cooperative Group for Pancreatic Cancer. *Ann Oncol* **14:** 388–394

Stathopoulos GP, Syrigos K, Polyzos A, Fountzilas G, Rigatos SK, Ziras N, Potamiannou A, Tsiakopoulos I, Androulakis N, Aravantinos G, Athanasiadis A, Papakotoulas P, Georgoulias V (2004) Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phases II study. *Ann Oncol* **15:** 224–229

Stephens CD (1998) Gemcitabine: A new approach to treating pancreatic cancer. *Oncol Nurs Forum* **25:** 87–93

Ulrich-Pur H, Raderer M, Verena Kornek G, Schull B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W (2003) Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* **88:** 1180–1184

Wagener DJ, Verdonk HE, Dirix LY, Catimel G, Siegenthaler P, Buitenhuis N, Mathieu-Boué A, Verweij J (1995) Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. *Ann Oncol* **6:** 129–132

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Liposomal cisplatin combined with gemcitabine in pretreated advanced pancreatic cancer patients: A phase I-II study

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Abstract. The present trial is a phase I-II study based on a new liposomal cisplatin (lipoplatin). Previous preclinical and clinical data (phase I pharmacokinetics) led to the investigation of a combined treatment modality involving lipoplatin and gemcitabine. The gemcitabine dose was kept standard at 1000 mg/m^2 and the lipoplatin dose was escalated from 25 mg/m^2 to 125 mg/m^2. The treatment was administered to advanced pretreated pancreatic cancer patients who were refractory to previous chemotherapy which included gemcitabine. Lipoplatin at 125 mg/m^2 was defined as dose limiting toxicity (DLT) and 100 mg/m^2 as the maximum tolerated dose (MTD) in combination with 1000 mg/m^2 of gemcitabine. Preliminary objective response rate data showed a partial response in 2/24 patients (8.3%), disease stability in 14 patients (58.3%) for a median duration of 3 months (range 2-7 months) and clinical benefit in 8 patients (33.3%). Liposomal cisplatin is a non-toxic alternative agent to bare cisplatin. In combination with gemcitabine, it has an MTD of 100 mg/m^2 and shows promising efficacy in refractory pancreatic cancer.

Introduction

Cisplatin, [cis-$PtCl_2(NH_3)_2$] is used world-wide for the treatment of testicular and ovarian cancer as well as for bladder, head, neck, lung, gastrointestinal and many other tumors (1-7). Although very effective against these tumors, cisplatin has been associated with severe side effects including nephrotoxicity (8) ototoxicity, neurotoxicity, nausea and vomiting (7-9). Carboplatin, a cisplatin analogue, is markedly less toxic to the kidneys and nervous system than cisplatin and causes less nausea and vomiting, while generally (and certainly for ovarian cancer and non- small cell lung cancer) retaining equivalent antitumor activity. However, hematological adverse effects are more frequent with carboplatin than with Cisplatin (10,11).

Gemcitabine (Gemzar®, Eli Lilly, Indianapolis, IN), a nucleoside analogue, is administered in combination with cisplatin as first-line treatment of patients with inoperable, locally advanced (stage IIIA or IIIB) or metastatic (stage IV) non-small cell lung cancer and as front-line treatment for patients with locally advanced (non-resectable stage III) or metastatic (stage IIIB, IV) adenocarcinoma of the pancreas (12-14). The main adverse reaction is myelotoxicity. The advantage of using combinations of gemcitabine with platinum has been attributed to the inhibition of the DNA synthetic pathways involved in the repair of platinum-DNA adducts. Gemcitabine and cisplatin act synergistically, increasing platinum-DNA adduct formation and inducing combination-dependent changes in ribonucleotide and deoxyribonucleotide pools in ovarian cancer cell lines (15).

A previous study on lipoplatin (Regulon Inc. Mountain View, CA) showed a low toxicity profile, an ability to concentrate in tumors and to escape immune cells and macrophages, a slow clearance rate from the kidneys, long circulation properties in body fluids, a half-life of 36 h in the blood, and promising therapeutic efficacy (16). In the present phase I-II study we attempted to explore the therapeutic efficacy and toxicity profile of the lipoplatin-gemcitabine combination, given every 14 days in advanced stage pretreated pancreatic cancer patients. Our primary objectives were to determine toxicity and the maximum tolerated dose (MTD) and our secondary aims, to determine the response rate and clinical benefit.

Patients and methods

Patient >18 years of age with histologically or cytologically confirmed adenocarcinoma of the pancreas and bidimensionally measurable disease, who had undergone chemotherapy pretreatment and had recurrent or non-responsive disease, were enrolled in the study. Other eligibility criteria included a World Health Organization (WHO) performance status (PS) of 0-2, life expectancy of at least 3 months, adequate bone marrow reserves (granulocyte count ≥1,500/dl, platelet count ≥120,000/dl), normal renal (serum creatine concentration <1.2 mg/dl) and liver function tests (total serum bilirubin concentration, <3 mg/dl, provided that serum transaminases and serum proteins were normal), normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction, or congestive heart failure within the 6 months prior, and no central nervous system involvement. Prior surgery was allowed

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provided that it had taken place at least 3 weeks before. Patients with active infection, malnutrition or a second primary tumor (except for a non-melanoma skin epithelioma or in situ cervix carcinoma) were excluded from the study. All patients gave their written informed consent to participate in the study.

Treatment plan. The plan was to combine lipoplatin with gemcitabine. Lipoplatin, supplied by Regulon Inc., was administered as an 8 h i.v. infusion on days 1 and 15; 8 h was chosen in order to be able (0 control possible adverse effects on the basis of our experience in the phase I trial. Gemcitabine was given as a 60 min i.v. infusion in 500 ml normal saline on days 1 and 15 at a dose of 1000 mg/m^2 and cycles were repeated every 4 weeks (28 days). The infusions on days 1 and 15 were considered to be 1 cycle. Provided that patients had recovered sufficiently from the drug-related side effects, standard ondansetron antiemetic treatment was to be administered to all patients. Prophylactic administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed. In cases of grade 3 neutropenia, these patients would receive subsequent infusions of pegfilgrastim 6 mg, on the 6th or 7th day and treatment would be postponed for one week. Treatment was administered for at least three cycles or until disease progression. The study was a phase I/II cohort, dose escalation trial of lipoplatin and gemcitabine. Its aims were to determine the dose limiting toxicity (DLT) of the combination and to define the MTD as a recommended dose for Phase II and to collect preliminary data on the efficacy of the drug in pretreated patients with pancreatic cancer. Myelotoxicity with lipoplatin as a single agent was considered very mild in a previous phase I study (16). We started with a low dose of lipoplatin combined with gemcitabine which is a myelotoxic agent, mainly to determine the extent of bone marrow adverse reaction. The starting dose of lipoplatin was 25 mg/m^2 and increased by 25 mg/m^2 per dose level (Table I). The protocol was approved by the Ethics and Scientific Committee of the Hospital.

Dose adjustment criteria were based on hematological parameters. In case of grade 3 or 4 febrile neutropenia, subsequent cycles were repeated with pegfilgrastim prophylactic administration, as described above. In cases of febrile neutropenia or grade 3 or 4 neutropenia, despite the administration of rhG-CSF, gemcitabine and lipoplatin doses were reduced by 25% in the following treatment infusion. In cases of grade 3 or 4 thrombocytopenia lasting for >5 days, the doses of both drugs were also reduced by 25%. Toxicities were graded according to WHO guidelines (17).

Pretreatment evaluation included complete medical history and physical examination, full blood cell count including differential leukocyte and platelet counts, a standard biochemical profile (and creatinine clearance when necessary), serum carcinoembryonic antigen (CEA), and CA 19-9 determinations, electrocardiogram, chest X-rays, ultrasound of the upper abdomen, and computed tomography (CT) scans of the chest, upper and lower abdomen. Additional imaging studies were performed upon clinical indication. Full blood counts with differential were performed weekly; in case of grade 3 or 4 neutropenia or grade 4 thrombocytopenia, full blood counts with differential were evaluated daily until the absolute granulocyte count was >1000/dl and the platelet count >75000/dl. A detailed medical and physical examination was completed before each course of treatment in order to document symptoms of the disease and treatment toxicities. Biochemical tests, ECG, serum CEA and CA 19-9 determinations, and chest X-rays were performed every 6 weeks and a neurologic evaluation was performed by clinical examination. Lesions were measured after each cycle if they were assessable by physical examination or by chest X-rays; lesions assessable by ultrasound or CT scans were evaluated after three chemotherapy cycles.

Definition of response. Complete response (CR) was defined as the disappearance of all measurable or evaluable disease, signs and symptoms and biochemical changes related to the tumor for at least 4 weeks, during which time no new lesions appeared. Partial response (PR) was defined as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements, lasting for at least 4 weeks, during which time no new lesions appeared and no existing lesions enlarged. For hepatic lesions, a reduction of >30% in the sum of the measured distances from the costal margin at the midclavicular line and at the xiphoid process to the edge of the liver, was required. Stable disease (SD) was defined as 50% reduction to a 25% increase in the sum of the products of the two perpendicular diameters of all measurable lesions and the appearance of no new lesions for 8 weeks. Progressive disease (PD) was defined as an increase in the product of the two perpendicular diameters of any measurable lesion by >25% over the size present at entry into the study, or, for patients who responded, the size at the time of maximum regression and the appearance of new areas of malignant disease. Bilirubin increase without recovery after endoscopic retrograde choledocho-pancreatography (ERCP) or stent set was considered as disease progression. A two-step deterioration in performance status, a >10% loss of pretreatment weight or increasing symptoms did not by themselves constitute progression of the disease; however, the appearance of these complaints was followed by a new evaluation of the extent of the disease. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists.

Results

Patient demographics. From January 2003 until December 2004, 24 patients (11 male, 13 female; median age 66 years, range 47-80 years) were enrolled in the study. The patient characteristics are shown in Table XI. WHO performance status was 0 in 4.2% of the patients, 1 in 45.8% and 2 in 50%. The great majority of the patients were stage IV (79.2%). All patients had undergone prior chemotherapy: eleven patients with gemcitabine as a single agent treatment and 13 with gemcitabine combined with irinotecan.

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Table I. Lipoplatin and gemcitabine dose escalation.

Dose level	No. of patients	Lipoplatin (mg/m^2 per week)	Gemcitabine (mg/m^2 per week)
First	4	25	1000
Second	4	50	1000
Third	4	75	1000
Fourth	4+4	100	1000
Fifth	4	125	1000

Table II. Patient characteristics at baseline.

		No.	%
No. of patients enrolled		24	100
Age (years)			
Median	66		
Range	47-80		
Gender			
Male		11	45.8
Female		13	54.2
Performance status (WHO)			
0		1	4.2
1		11	45.8
2		12	50.0
Disease stage			20.8
III		5	
IV		19	79.2
Histology			
Well-differentiated		3	12.5
Moderately differentiated		12	50.0
Low differentiation		9	37.5
Previous treatment			
Gemcitabine 1 mg/m^2	Days 1, 8, 15/ every 4 weeks	11	45.8
Gemcitabine 900 mg/m^2 + Irinotecan 300 mg/m^2	Days 1, 8/ every 3 weeks Days 8/ every 3 weeks	13	54.2

Dose intensity. The patients received 36 courses (108 infusion every two weeks) arid the median number of courses was 2 (range 1-5). Of the 24 patients, 10 patients completed 3 courses. There was no dose reduction for either drug and the patients received 99.5% of the planned dose intensity (range 93-100%) of each drug up to the fourth dosage level.

Toxicity. No neurotoxicity or renal toxicity was observed. Temporary abdominal pain which lasted for 2-4 min, and which righted itself, was observed in 10/24 patients at the beginning of the Lipoplatin™ infusion. Grade 3 myelotoxicity was observed in 2 out of 4 patients at the fifth dosage level. No febrile neutropenia was seen. Toxicity is shown in Tables III and IV. The level five dosage (125 mg/m^2 of Lipoplatin™ and 1000 mg/m^2 of gemcitabine) was considered as DLT and dosage level 4 as the MTD. Four additional patients were treated at the fourth dosage level.

Table III. Hematological toxicity by dose level.

Dose level	Lipoplatin mg/m^2	Gemcitabine mg/m^2	Toxicity no. of pts	Maximum Toxicity (grade)	Toxicity type
First	25	1000	-	-	-
Second	50	1000	-	-	-
Third	75	1000	-	-	-
Fourth	100	1000	2/4[a]	2-3	Neutropenia
Fifth	125	1000	2/4	3-4	Neutropenia

[a]Original 4 patients

Table IV. Non-hematologic toxicity.

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	5 (20.8)	-	-	-
Vomiting	2 (8.3)	-	-	-
Alopecia	14(58.3)	-	-	-
Fatigue	8 (33.3)	-	-	-
Diarrhea	2(8.3)	-	-	-
Cardiotoxicity	-	-	-	-
Neurotoxicity	3 (12.5)	-	-	-
Nephrotoxicity	-	-	-	-
Thrombotic episodes	4(16.7)	-	-	-

Response to treatment. The determination of measurable response on computed tomography was performed by two independent radiologists and two experienced oncologists. No complete responses were detected. PR was achieved in 2 patients (8.3%) with durations of 6 and 5 months. Stable disease was seen in 14 patients (58.3%) with a median duration of 3 months (range 2-7 months). Clinical benefit mainly due to pain reduction was seen in 8 patients (33.3%). At the end of the study 7 patients (29.2%) were still alive. Median survival from the beginning of second-line treatment was 4 months (range 2-8+ months).

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Discussion

This new liposomal cisplatin (lipoplatin) aims mainly at the avoidance of renal toxicity, which is often seen in cisplatin administration, while at the same time producing similar efficacy. The pharmacokinetics of lipoplatin are different from cisplatin, as has been shown in animal studies as well as in a clinical trial in patients (16). The lack of toxicity is a major advantage, which was shown when lipoplatin was administered as a single agent. In the present phase I-II trial, toxicity and efficacy were studied by administering lipoplatin in combination with gemcitabine, the toxicity of which is well defined, particularly when combined with other agents (5). The cisplatin-gemcitabine combination has been similarly used as treatment in non-small cell lung cancer, urothelial and pancreatic cancer (5,7,12). It seems that the data from the present trial indicate the advantage of very low toxicity. The every-two-week administration of the combination is very well tolerated up to the dose of 100 mg/m^2 of lipoplatin when gemcitabine is maintained at a standard dose of 1000 mg/m^2. At the dose of 125 mg/m^2 of lipoplatin, myelotoxicity reached grades 3 and 4 and therefore this dosage was considered as DLT. The 100 mg/m^2 of lipoplatin and 1 g/m^2 of gemcitabine were considered as the MTD. The combination achieved an objective response in 8.33% of the patients, disease stability in 58.3% and pain relief in 33.3%. Taking into account that all of the patients were refractory or in disease progression while on a prior treatment including gemcitabine, the response rate produced here should be attributed to the addition of lipoplatin.

Further testing of lipoplatin in combined schedules is needed in order to determine its role in treatment modalities for cancer patients.

Liposomal cisplatin combined with gemcitabine administered every two weeks in advanced pretreated pancreatic cancer patients, has an MTD of 100 mg/m^2 and 1000 mg/m^2, respectively. It is a well tolerated treatment with promising signs of efficacy.

References

1. Rosenberg B: Platinum complexes for the treatment of cancer: why the search goes on. In: Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug. Lippert B (ed). Zurich, Verlag Helvetica Chimica Acta, pp3-12, 1999.
2. Sorenson C and Eastman A: Mechanism of cis-diamminedichloroplatinum (II)-induced cytotoxicity: role of G_2 arrest and DNA double-strand breaks. Cancer Res 48: 4484-4488, 1988.
3. Einhorn LH, Williams SD, Loehrer PJ, Birch R, Drasga R and Omura G: Evaluation of optimal duration of chemotherapy in favorable prognosis disseminated germ cell tumors: a Southeastern Cancer Study group protocol. J Clin Oncol 7: 387-391, 1989.
4. Aabo K, Adams M, Adnitt P, Alberts DS, Athanazziou A, Barley V, Bell DR, Bianchi U, Bohs G, Brady MF, Brodovsky HS, Bruckner H, Buyse M, Canetta R, Chylak V, Cohen CJ, Colombo N, Conte PF, Crowther D, Edmonson JH, Gennatas C, Gilbey E, Gore M, Guthrie D, Yeap BY, et al: Chemotherapy in advanced ovarian cancer: four systematic meta-analysis of individual patient data from 37 randomized trials. Br J Cancer 78: 1749-148, 1998.
5. Kaufman D, Raghavan D, Carducci M, Carducci M, Levine EG, Murphy B, Aisner J, Kuzel T, Nicol S, Oh W and Stadler W: Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 18: 1921-1927, 2000.
6. Pignon JP, Bourhis J, Domenge C and Designe L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355: 949-955, 2000.
7. Non-Small-Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer, a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 311: 899-909, 1995.
8. Hayes D, Cvitkovic B, Golfey R, Golbey RB, Schemer B, Nelson L and Krakoff IH: High dose cis-platinum diammine-dichioride: amelioration of renal toxicity by mannitol diuresis. Cancer 39: 1372-1378, 1977.
9. Gandara DR, Nainhas NA, Adelson MD, Lichtman SM, Podosaslol ES, Yanovich S, Homesley HD, Braly P, Ritch PS and Weisberg SR: Randomized placebo-controlled multicenter evaluation of diethyldithocarbamate for chemoprotection against cisplatin-induced toxicities. J Clin Oncol 13: 490-496, 1995.
10. Sculier JP, Lafitte JJ, Lecomte J, Berghmans T, Thiriaux J, Florin MC, Efremidis A, Alexopoulos CG, Recloux P, Ninane V, Mommen P, Paesmans M and Klastersky J: Europefin Lung Cancer Working Party: a three-arm phase III randomized trial comparing combinations of platinum derivatives ifosfamide and/or gemcitabine in stage IV non-small cell lung cancer. Ann Oncol 13: 874-882, 2002.
11. Tognoni A, Pensa F, Vaira F, Vigani A, Caness P, Sinacejo G and Prontato P: A dose finding study of carboplatin and gemcitabine in advanced non-small cell lung cancer. J Chemother 14: 296-300, 2002.
12. Burns HA Iii, Moore MJ, Anderson J, Green MR, Rothernberg ML, Modieno MR, Crippa MC, Portenoy IRK, Stornlolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and van Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer; a randomized trial. J Clin Oncol 15: 240-2413, 1997.
13. Heinemann V, Wilke H, Mergenthaler HG, Clemens M, Konig H, Illiger HJ, Arning NI, Schalhorn A, Possinger K and Fink U: Gemcitabine and cisplatin in the treatment of advanced and metastatic pancreatic cancer. Ann Oncol 11: 1399-1403, 2000.
14. Stathopoulos GP, Rigatos SK, Dimopoulos MA, Giannakakis T, Fountzilas O, Kouroussis C, Janninis D, Aravantinos G, Androulakis N, Agelaid S, Stathopoulos JG and Cleorgoulias V: Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study of the Greek Cooperative Group for Pancreatic Cancer. Ann Oncol 14: 388-394, 2003.
15. Van Moorsel CJ, Smid K, Voom DA, Bergman AM, Pinedo HM and Peters GJ: Effect of gemcitabine and cis-platinum combinations on ribonucleotide and deoxyribonucleotide pools in ovarian cancer cell lines. Int J Oncol 22: 201-207, 2003.
16. Stathopoulos GP Boulikas T, Vougiouka M, Deliconstantinos O, Rigatos S, Darli E, Vilhoton V and Stathopoulos JG: Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): phase I study. Oncol Rep 13: 589-595, 2005.
17. Miller AB, Hoogarraten B, Staquet M and Winkler A: (WHO) Reporting results of cancer treatment. Cancer 47: 207-214, 1981.

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Original Paper

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Pancreatic carcinoma
Biliary tract carcinoma
Chemotherapy, combination

Comparison of 5-Fluorouracil, Doxorubicin and Mitomycin C with 5-Fluorouracil Alone in the Treatment of Pancreatic-Biliary Carcinomas

Abstract
In this multicenter randomized trial, the efficacy of combination chemotherapy using 5-fluorouracil, doxorubicin and mitomycin C (arm A) was compared with that of 5-fluorouracil alone (arm B) in 81 patients with nonresectable carcinomas of the pancreas or biliary tract. There were no significant differences between treatment arms regarding the median time to progressive disease, median survival time, palliative effects or toxicities. It was concluded that combination chemotherapy is feasible but cannot be recommended.

Introduction

The first choice of treatment of carcinomas of the pancreas and biliary tract is surgery. Recently, the prognosis for these diseases has been improved in association with the increased resection rate. However, there are many patients whose disease remains unresected because of the difficulty of early detection. Intensive combination chemotherapy is usually applied to these patients in order to suppress the disease progression and improve the clinical symptoms and survival.

Although combination chemotherapy using 5-fluorouracil (FU), doxorubicin (ADR) and mitomycin C (MMC) (FAM) initiated by Smith et al. [1] was once considered to be one of the standard therapies for carcinomas of the pancreas or biliary tract, it is doubtful whether FAM has any benefits in terms of duration of survival and cost [2, 3]. Since FAM had caused high toxicity in Japanese patients, clinical application of modified FAM, taking into account Japanese sensitivity to drugs, has been investigated. In the study reported here, we applied a modified FAM regimen, which was primarily based on tolerability in our pilot study, to patients with nonresectable carcinomas of the pancreas or biliary tract, and compared the efficacy of combination chemotherapy with that of FU alone.

Materials and Methods

Patient Selection

Patients with nonresectable carcinomas of the pancreas or biliary tract, who presented at 20 institutions between June 1988 and May 1989, fulfilling the following criteria were eligible for this study: (1) those aged less than 75 and histologically diagnosed as having carcinomas of the pancreas or biliary tract, whose major lesions were not resectable or who were not operable; (2) those without multicentric and double cancer (regardless of either synchronous or metachronous diseases); (3) those with performance status (PS) of 0–3 (graded by the Japan Society for Cancer Therapy, [4]) and no serious

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complications; (4) those with baseline laboratory test values of WBC $\geq 4{,}000\ mm^{-3}$, platelets $\geq 100{,}000\ mm^{-3}$, GOT-GPT ≤ 100 U and proteinuria (−); (5) for previously treated patients, a washout period of at least 4 weeks after their previous treatment with no carryover effects, and (6) those judged by the physicians in charge to be tolerant to chemotherapy. Prior to entry to the study, details of the chemotherapy including the possibility of toxicities were explained and informed consent was obtained from each patient.

Treatment Regimens and Randomization

Combination Chemotherapy with Three Drugs (Arm A). MMC 6 mg/m^2 was administered intravenously on day 1 (or during surgery to operable patients); FU 310 mg/m^2/day was administered intravenously for 5 days in week 1 (or after the surgery) and week 3; ADR 12 mg/m^2/day was administered intravenously in the 2nd week of treatment. Each drug administration was repeated every 6 weeks.

5-FU Alone (Arm B). FU was administered in the same way as for arm A. The treatment regimens were repeated until progressive disease was observed and the dosage was reduced when patients developed serious side effects.

Patients were randomly assigned to either arm A or arm B. A randomized design stratified according to institution and patient disease was used. Patients who underwent surgery were randomized during the operation.

Response Criteria

A complete response was defined as the disappearance of all measurable lesions without occurrence of new ones. A partial response (PR) was defined as a decrease of 50% in the product of the two largest perpendicular diameters of measurable lesions. If hepatomegaly was used, a decrease of at least 30% in the sum of measurements below the xyphoid process and costal margins at the midclavicular lines was used. There should be no increase in the size of other known areas of malignant disease and no new areas of malignant disease should appear. Response duration should be at least 4 weeks. No change was defined as a decrease of less than 50% in the size of measurable disease, or an increase of less than 25% in the size of measurable disease after 4 weeks. Progressive disease (PD) was defined as an increase of 25% or greater in the product of longest perpendicular diameters of measurements or hepatomegaly (for measurable patients), appearance of measurable areas of malignant disease (for nonmeasurable patients), decrease in PS by more than two grades or from 3 to 4, weight loss exceeding 10% of postoperative body weight.

Palliative Effects

Palliative effects were evaluated according to one of the following criteria: (1) improvement in PS by more than one grade, (2) body weight gain of more than 2 kg, and (3) relief of cancer pain and/or improvement of gastrointestinal symptoms.

Statistical Methods

Distribution comparisons of patient characteristics, response, palliative effects, and toxicities were done with the χ^2 test and Fisher's exact test. Survival and time to PD were estimated using the method of Kaplan and Meier [5] and were calculated from the data of randomization to death or last follow-up date. The log-rank test [6] was used to make survival comparisons between groups. Unless otherwise indicated significant p values were less than 0.05.

Table 1. Patient characteristics

Characteristics	Arm A	Arm B	p value[1]
Evaluable patients	35	36	
Sex			
Male	14 (40)	17 (47)	0.71
Female	21 (60)	19 (53)	
Age, years			
Mean	59.1	61.5	0.82
Range	38–73	31–74	
Primary site			
Pancreas	17 (49)	18 (50)	0.99
Bile duct	8 (23)	8 (22)	
Gallbladder	10 (29)	10 (28)	
Number with metastatic disease	27 (77)	31 (86)	0.50
Site of metastasis[2]			
Lymph nodes	18 (51)	16 (44)	00.12
Liver	12 (34)	19 (53)	
Peritoneum	11 (31)	4 (11)	
Lung	1 (3)	0 (0)	
Measurability			
Measurable	25 (71)	26 (72)	1.00
Nonmeasurable	10 (29)	10 (28)	
PS			
0–1	21 (60)	17 (47)	0.40
2–3	14 (40)	19 (53)	
Mean cycles of chemotherapy	2.3	2.2	0.87
Range	1–10	1–8	

Figures in parentheses represent percentage.

[1] χ^2 test with Yates correction factor and Student's t test were used.

[2] A patient may have had more than one site of metastasis.

Results

Of the 81 patients enrolled in this study, 3 were ineligible; 2 patients had PS of grade 4 and 1 patient had an insufficient washout period. Seventy-eight patients were considered to be eligible for the study, but 7 patients were excluded because of rapid aggravation of their general condition at the beginning of the study. Thus, 71 patients could be evaluated (35 in arm A group and 36 in arm B group). Patient characteristics are summarized in table 1.

All evaluable patients had primary carcinomas with no history of previous treatment including chemotherapy, surgery and radiotherapy. No statistical differences regarding background factors were seen between the two arms, although there were more hepatic metastases in arm B, more peritoneum metastases in arm A and more patients with PS of 2–3 in arm B.

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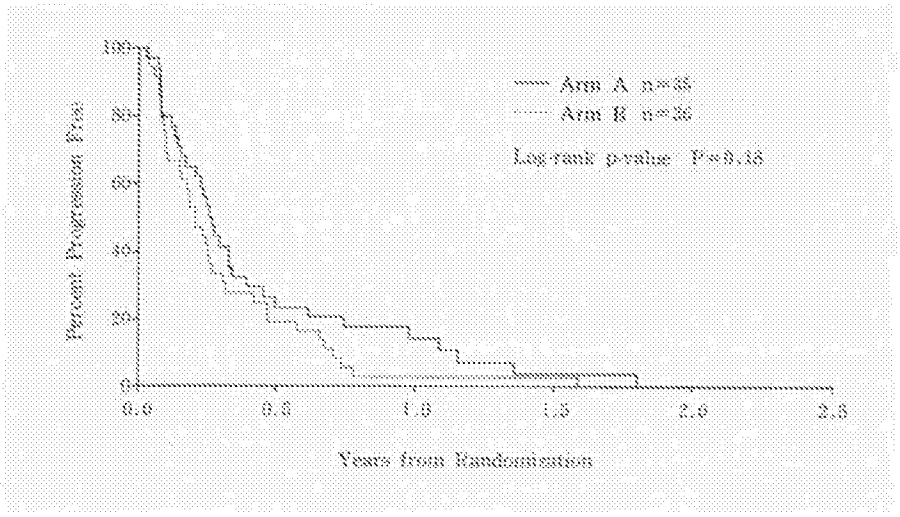


Fig. 1. Time to PD according to treatment regimen.

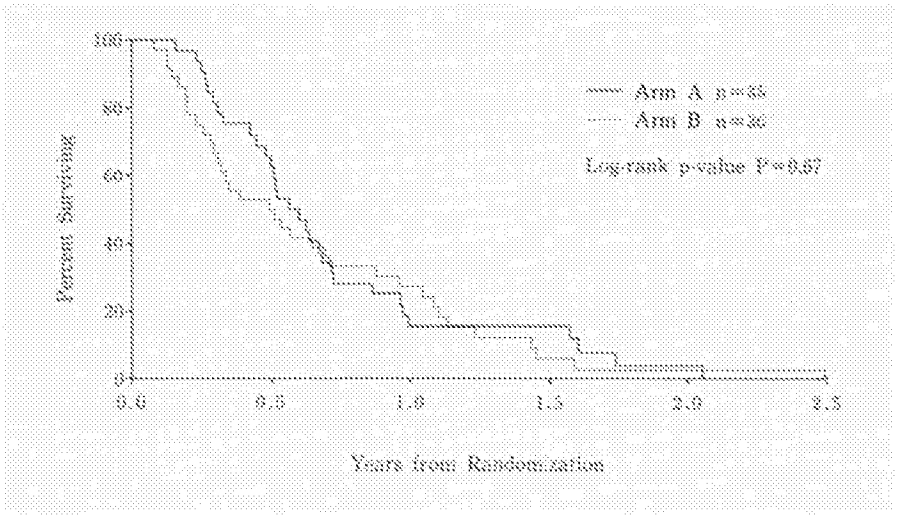


Fig. 2. Comparative survival measured from the date of randomization.

Eighteen patients in arm A completed 1 course, 11 patients completed 2 courses and 6 patients completed more than 3 courses of the chemotherapy (maximum 10 courses, mean 2.1 courses). In arm B, 19 patients completed 1 course, 8 patients completed 2 courses and 9 patients completed more than 3 courses (maximum 8 courses, mean 2.2 courses).

The total number of patients with measurable diseases was 51: 25 in arm A and 26 in arm B. PR was achieved in 1 patient (4%) in arm A, and no response was seen in arm B. No change and PD were observed in 10 (40%) and 14 (56%) in arm A, and 12 (46%) and 14 (54%) in arm B, respectively. One patient in arm A who achieved PR had carcinoma of the pancreas, with a response duration of 6 months.

Figure 1 shows time to PD. Median time to PD was 3.1 months [95% confidence intervals (CI): 6.9–3.3 months] in arm A and 2.5 months (CI: 4.9–2.5 months) in arm B, with no significant differences between the two arms (log-rank test, $p = 0.18$).

Figure 2 shows survival curves from the date of randomization. Of the 71 evaluable patients, 70 died of the carcinoma and the remaining patient died of other causes. Median survival time was 6.2 months (CI: 10.8–6.6 months) in arm A, and 6.0 months (CI: 10.1–5.8 months) in arm B, with no significant differences between the two arms (log-rank test, $p = 0.67$). One-year survival rate was 14.3% (CI: 4.8–30.3%) in arm A, and 25% (CI: 12.2–42.2%) in arm B. As most patients (83% of patients in arm A and 75% in arm B) completed only 1–2 courses of the

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chemotherapy, we could not analyze differences in clinical responses that might occur when treatment courses exceeded this period. When those patients who had measurable or nonmeasurable disease were analyzed separately, and when patients were analyzed according to their site of metastasis, no statistically significant difference was seen between the two arms.

Palliative effects of chemotherapy are shown in table 2 as improvement rates of PS, body weight and symptoms. The improvement rates were 17, 19 and 27% in arm A, and 25, 13 and 28% in arm B, respectively, with no apparent difference between treatment arms.

Table 3 shows the frequency of toxicities of grade 2 or more according to the criteria of the Japan Society for Cancer Therapy [4], which are modified according to WHO criteria. The most common toxicities were gastrointestinal symptoms, such as anorexia, nausea or vomiting, and hepatic dysfunction, with anorexia occurring in the majority of the patients: i.e. 51.4% in arm A and 52.8% in arm B. The only significant difference between the two arms was for alopecia, with a significantly higher incidence in arm A ($p = 0.02$). There was a tendency for increased incidence of leukopenia in arm A. No toxicities reported were serious (all of them ≤ grade 2), except for leukopenia of grade 3 in 1 patient in arm A.

Table 2. Palliative effects

Palliative effects	Arm A	Arm B	p value[1]
PS[2]			
Evaluable patients	30 (86)	24 (67)	0.78
Improved patients	5 (17)	6 (25)	
Body weight[3]			
Evaluable patients	31 (89)	31 (86)	0.81
Improved patients	6 (19)	4 (13)	
Symptoms[4]			
Evaluable patients	33 (94)	36 (100)	1.00
Improved patients	9 (27)	10 (28)	

Figures in parentheses represent percentage.
[1] χ^2 test with Yates correction factor was used.
[2] Improvement in PS by one grade or more after disappearance of operation influence.
[3] Increase in body weight exceeding 2 kg.
[4] Decreased pain and/or improvement of gastrointestinal symptoms.

Table 3. Toxicities

Toxicity[1]	Arm A	Arm B	p value[2]
Leukopenia	13 (36)	6 (17)	0.09
Thrombocytopenia	4 (11)	2 (6)	0.64
Hepatic	16 (46)	12 (33)	0.41
Anorexia	18 (51)	19 (53)	1.00
Nausea/vomiting	11 (31)	13 (36)	0.87
Diarrhea	3 (9)	2 (6)	0.97
Stomatitis	2 (6)	3 (8)	1.00
Alopecia	9 (26)	1 (3)	0.02*

Figures in parentheses represent percentage. * $p < 0.05$.
[1] Occurrence of toxicities of grade 2 or more according to the criteria of the Japan Society for Cancer Therapy [4].
[2] χ^2 test with Yates correction factor was used.

Discussion

Early clinical trials in advanced carcinoma of the pancreas, using streptozotocin (STZ), MMC and 5-FU [7], FAM [1] and FAM plus STZ [8], have reported relatively high response rates of 43, 37 and 48%, respectively. Mallinson et al. [9] reported that combination chemotherapy with 4 drugs (5-FU, cyclophosphamide, methotrexate and vincristine) followed by maintenance therapy with MMC and 5-FU (Mallinson regimen) led to a median survival time of 44 weeks, compared to 9 weeks in a supportive care group. Subsequent trials [2, 3, 10, 11] could not reproduce such high response rates and investigators suggested that combination chemotherapy considered to be effective in early trials had no advantages over monotherapy. Cullinan et al. [2, 3] failed to find any advantages of combination chemotherapy in their comparative studies between three regimens [comparison either between FAM, FA and FU alone, or between Mallinson regimen, FU + ADR + cisplatin (CDDP) and FU alone] in advanced carcinomas of the pancreas. This is true for the biliary tract carcinoma to which a combination chemotherapy for carcinoma of the pancreas is usually applied because the absolute number of patients is too small to establish its own treatment regimen. Falkson et al. [12] reported that the combination of FU and STZ or semustin in inoperable biliary tract cancer did not produce a greater response rate or survival time than FU alone. These reports may suggest that intensive combination chemotherapy is not useful in terms of survival time, toxicities or quality of life apart from tumor regression.

Recently, FU continuous infusion [13] to improve the efficacy of monotherapy, and FU plus leucovorin [14],

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FU plus CDDP [15] or FU plus interferon-α [16] to enhance the efficacy of FU by biochemical modulation were investigated in carcinomas of the pancreas or biliary tract; these results will be of interest. In Japan, combination chemotherapy based on the FAM regimen has been routine as various modes of action are seen and cumulative toxicity induced by a single drug may be avoided, and also because of the favorable early results from the USA in patient with pancreatic carcinoma. Indeed, the dosage schedule of each drug has been modified as it was dangerous to directly apply the original FAM to Japanese patients; e.g. ADR in particular, is, administered in lower doses over a longer interval. If chemotherapy for carcinomas of the pancreas and biliary tract can be used as palliative therapy, improvement of symptoms or quality of life rather than tumor remission should be emphasized in the evaluation of efficacy. Although the present study compares two treatment arms from this point of view, we could not prove that arm A was significantly superior to arm B. In this study, results are similar to those reported by Cullinan et al. [2, 3], with no differences in either survival time or time to PD between combination chemotherapy and monotherapy groups. When the palliative effects on pain and gastrointestinal symptoms obtained from our pilot study as well as toxicity results of the present study were considered, it was concluded that arm B was slightly more beneficial than arm A. Future studies should include the modification of dosage and administration regimen of FU or the introduction of biomedical modulation, but it is controversial whether such chemotherapy is useful or not compared with supportive care only. The validity of this requires further well-controlled trials comparing supportive care only in patients with nonresectable disease. Our trial in this area will be reported in the future.

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References

1 Smith FP, Hoth DF, Levin B, Karlin DA, Macdonald JS, Woodley PV, Schein PS: 5-Fluorouracil, adriamycin and mitomycin-C (FAM) chemotherapy for advanced adenocarcinomas of the pancreas. Cancer 1980;46:2014–2018.

2 Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF, Pfeifle DM, Barlow JF: A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. JAMA 1985; 253:2061–2067.

3 Cullinan SA, Moertel CG, Wieand HS, Schutt AJ, Krook JE, Foley JF, Norris BD, Kardinal CG, Tschetter LK, Barlow JF: A phase III trial on the therapy of advanced pancreatic carcinoma. Cancer 1990;65:2207–2212.

4 Japan Society for Cancer Therapy: Japanese criteria for the evaluation of the direct effects of cancer chemotherapy for solid tumors. J Jpn Soc Cancer Ther 1986;21:931–942.

5 Kaplan EL, Meier P: Nonparametric estimation from incomplete observation. J Am Stat Assoc 1985;53:457–481.

6 Pete R, Peto J: Asymptomatically efficient rank invariant test procedures. J R Stat Soc 1972;135:185–198.

7 Wiggans RG, Woolley PV, Macdonald JS, Smythe T, Ueno W, Schein PS: Phase II trial of streptozotocin, mitomycin C and 5-fluorouracil (SMF) in the treatment of advanced pancreatic cancer. Cancer 1978;41:387–391.

8 Bukowsky RM, Schacter LP, Groppe CW, Heswiett JS, Weick JK, Livingston RB: Phase II trial of 5-fluorouracil, adriamycin, mitomycin-C and streptozotocin (FAM-S) in pancreatic adenocarcinoma. Cancer 1982;50:197–200.

9 Mallinson CN, Rake MO, Cocking JB, Fox CA, Cwynarski MT, Diffey BL, Jackson GA, Hanley J, Wass VJ: Chemotherapy in pancreatic cancer: Results of a controlled, prospective, randomized, multicenter trial. Br Med J 1980; 281:1589–1591.

10 The Gastrointestinal Tumor Study Group: Phase II studies of drug combinations in advanced pancreatic carcinoma: Fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin C plus fluorouracil. J Clin Oncol 1986;4:1794–1798.

11 Oster MW, Gray R, Panasci L, Perry MC: Chemotherapy for advanced pancreatic cancer. Cancer 1986;57:29–33.

12 Falkson G, MacIntyre JM, Moertel CG: Eastern Cooperative Oncology Group experience with chemotherapy of inoperable gallbladder and bile duct cancer. Cancer 1984;54:965–969.

13 Hansen R, Quebbeman E, Rusch P, Chitambar C, Anderson T: 5-Fluorouracil (5FU) infusion in carcinoma of the pancreas: A phase II study. Am J Med Sci 1988;295:91–93.

14 DeCaprio JA, Mayer RJ, Gonin R, Arbuch SG: Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas: Results of phase II trial. J Clin Oncol 1991;9:2128–2133.

15 Rothman H, Cantrell JE Jr, Lokich J, Ostino S, Harvey J, Ahlgren J, Fryer J: Continuous infusion of 5-fluorouracil plus weekly cisplatin for pancreatic carcinoma. Cancer 1991;68:264–268.

16 Pavlov R, Ajani JJ, Abbruzzese JL, Belt RJ, Dakhil SR, Dubinsky D, Graham S, Pilat S, Wins R, Levin B: Phase II evaluation of fluorouracil and recombinant alpha-2a-interferon in previously untreated patients with pancreatic adenocarcinoma. Cancer 1992;70:2073–2076.

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ORIGINAL ARTICLE

A retrospective study of S-1 and oxaliplatin combination chemotherapy in patients with refractory pancreatic cancer

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Abstract
Purpose The aim of this study was to evaluate S-1 and oxaliplatin combination chemotherapy (SOX) in patients with refractory pancreatic cancer (PC).
Methods Consecutive patients with advanced PC refractory to gemcitabine who were treated with oral S-1 (80 mg/m^2) on days 1–14 and intravenous oxaliplatin (100 mg/m^2) on day 1 every 3 weeks were studied retrospectively. The primary end point was the objective response rate (ORR). The secondary end points were progression-free survival (PFS), overall survival (OS), the disease control rate (DCR), and safety.
Results Between March 2009 and October 2011, 30 patients were treated with SOX, with a median of two courses (range 1–8). The ORR and DCR were 10.0 and 50.0 %, respectively. Median PFS and OS were 3.4 months (95 % confidence interval [CI] 1.3–5.3) and 5.0 months (95 % CI 3.4–7.4), respectively. The median PFS and OS were 5.6 and 9.1 months in patients receiving S-1 and oxaliplatin as a second-line treatment. Major grade 3 or 4 adverse events included neutropenia (10.0 %), anemia (3.3 %), and diarrhea (6.7 %).
Conclusions SOX was well tolerated and moderately effective in patients with refractory PC.

Keywords Pancreatic cancer · Chemotherapy · Gemcitabine refractory · S-1 · Oxaliplatin

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Abbreviations

SOX	S-1 and oxaliplatin combination chemotherapy
PC	Pancreatic cancer
ORR	Objective response rate
DCR	Disease control rate
PFS	Progression-free survival
OS	Overall survival
CI	Confidence interval
5-FU	5-Fluorouracil
Lv	Leucovorin
CRC	Colorectal cancer

Introduction

Gemcitabine has been the standard chemotherapy for advanced pancreatic cancer (PC), based on a pivotal randomized controlled trial [1]. Attempts have been made to improve its efficacy as a front-line therapy in combination with other cytotoxic or molecularly targeted agents [2–6], but few trials have demonstrated superiority over single-agent gemcitabine [6]. Recently, FOLFIRINOX showed a significant survival benefit over gemcitabine in metastatic PC [7]. However, this multi-agent chemotherapy was also associated with a high incidence of adverse events [7].

Though almost all patients receiving chemotherapy for advanced PC experience disease progression, second-line chemotherapy in patients with advanced PC has not been investigated intensely. In the CONKO 003 study, combination chemotherapy with oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin (Lv) showed a significant survival benefit over the best supportive care alone in a second-line setting [8]. As a result, oxaliplatin plus fluoropyrimidine combination chemotherapy is recognized as an acceptable option for patients with advanced PC in the 2012 National

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Comprehensive Cancer Network (NCCN) Guidelines for Pancreatic Adenocarcinoma [9]. S-1, an oral fluoropyrimidine derivative, is commonly used to treat advanced PC instead of 5-FU or capecitabine in Japan, because of studies showing its activity against gemcitabine-refractory PC [10, 11]. Thus, we conducted this retrospective study of S-1 and oxaliplatin combination chemotherapy (SOX) in patients with gemcitabine-refractory PC.

Patients and methods

This was a retrospective analysis of consecutive patients with gemcitabine-refractory PC who received salvage chemotherapy with SOX at the University of Tokyo Hospital, Japan. All data were recorded prospectively and only the outcomes were updated at the time of analysis. The institutional review board approved the protocol, and informed consent was obtained from each participant.

Eligibility

Inclusion criteria were as follows: (1) histologically or cytologically proven adenocarcinoma of the pancreas; (2) refractory to gemcitabine-based chemotherapy and confirmed as progressive disease, as defined by response evaluation criteria in solid tumors (RECIST; ver. 1.0) [12]; (3) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, (4) capability of oral intake; and (5) adequate bone marrow function (white blood cell count $\geq$3,000/mm^3, hemoglobin $\geq$8.0 g/dL, platelet count $\geq$75,000/mm^3), liver function (total bilirubin $\leq$3 times the upper limit of normal [ULN] and aspartate/alanine transaminases $\leq$5 times the ULN), and renal function (creatinine $\leq$1.8 mg/dL). Exclusion criteria were as follows: (1) age <20 years; (2) severe complications, such as active infection, marked pleural effusion or ascites; (3) active gastrointestinal bleeding; (4) severe drug hypersensitivity; (5) active concomitant malignancy; (6) pregnancy or lactation.

Treatment

Patients received S-1 orally twice/day for 2 weeks, followed by 1-week rest, and oxaliplatin intravenously (100 mg/m^2) on day 1 of each 3-week cycle. Three doses of S-1 were established according to the body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; 1.25 m^2 $\leq$ BSA < 1.5 m^2, 100 mg/day; BSA $\geq$1.5 m^2, 120 mg/day. The efficacy and safety of this schedule were previously reported in advanced gastric cancer [13]. The treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent.

Response and toxicity assessment

The primary end point was objective response rate (ORR). Secondary end points were progression-free survival (PFS), overall survival (OS), and safety. Pretreatment evaluation using contrast-enhanced computed tomography was performed within 4 weeks before the patient's enrollment. Tumor responses were evaluated every two cycles using RECIST ver. 1.0 [12]. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were measured at the beginning of SOX and on day 1 of each cycle. All adverse events were evaluated at each cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 (see http://ctep.cancer.gov/default.htm).

Dose modification

Treatment was temporarily suspended in the case of grade 3/4 hematological toxicity or grade 2 or higher non-hematological toxicity. After recovery to grade 1 toxicity or lower, treatment was restarted at reduced doses. As this combination chemotherapy consisted of two drugs, doses were modified alternately. First, the S-1 dose was reduced to: BSA < 1.25 m^2, 50 mg/day; 1.25 m^2 $\leq$ BSA < 1.5 m^2, 80 mg/day; and BSA $\geq$1.5 m^2, 100 mg/day. When dose reduction was necessary after S-1 dose reduction, the oxaliplatin dose was reduced by 25 mg/m^2. In cases of neuropathy which is a characteristic adverse effect of oxaliplatin, oxaliplatin was discontinued and then resumed at a dose reduced by 25 mg/m^2. No dose escalation was allowed following dose reduction.

Statistics

PFS and OS were calculated using the Kaplan–Meier method. PFS was calculated from the start of the treatment to the first day of documented disease progression. OS was defined as the time from initiation of therapy to final follow-up or until death from any cause. The final analysis was based on follow-up information, which was received until June 2012. All analyses were conducted based on the intention-to-treat principle. The JMP statistical software program (ver. 8.0; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Between March 2009 and October 2011, 30 patients with advanced or recurrent PC received SOX. Patient characteristics are shown in Table 1. By the time of this analysis, all patients had experienced disease progression or had discontinued treatment due to adverse events, and no patient was

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Table 1 Patients' characteristics

Age (years), median (range)	64 (35–81)
Sex (male), *n* (%)	22 (73.3 %)
ECOG performance status, *n* (%)	
0	11 (36.7 %)
1	16 (53.3 %)
2	3 (10.0 %)
CA19-9 (mg/dL), median (range)	5,100 (1–288,000)
Site of metastasis, *n* (%)	
Liver	22 (73.3 %)
Lung	10 (33.3 %)
Lymph node	18 (60.0 %)
Peritoneal dissemination[a]	11 (36.7 %)
Previous surgery	4 (13.3 %)
Line of treatment, *n* (%)	
Second	11 (36.7 %)
Third	10 (33.3 %)
Fourth	9 (30.0 %)

All values are expressed as *n* (%) or median (range)

ECOG Eastern Cooperative Oncology Group, *RECIST* response evaluation criteria in solid tumors

[a] Peritoneal dissemination was evaluated based on CT scan

actively on SOX. One patient was still alive and the median follow-up was 7.4 months. Only one patient (3.3 %) had a locally advanced disease. Four patients (13.3 %) had previously undergone surgical resection. All patients had been treated with a gemcitabine-containing regimen prior to SOX. Eleven patients (36.7 %) who received SOX as a second-line treatment were naïve for S-1 and the remaining 19 patients (63.3 %) had prior S-1 exposure. The median interval from first-line chemotherapy to SOX treatment was 12.8 months (95 % confidence interval [CI] 10.7–19.2). After SOX treatment failure, seven patients (23.3 %) received chemotherapy: irinotecan in four patients, S-1 in two patients, and S-1 plus paclitaxel in one patient [14].

Efficacy

As shown in Table 2, a partial response was achieved in three patients, with an ORR of 10.0 %, and stable disease in 12 patients, with a DCR of 50.0 %. The median PFS and OS were 3.4 months (95 % CI, 1.3–5.3) and 5.0 months (95 % CI 3.4–7.4), respectively (Fig. 1). The median OS from first-line chemotherapy was 16.0 months (95 % CI 13.4–22.5). SOX showed greater efficacy in S-1-naïve patients; ORR 27.3 versus 0 % ($p = 0.04$), DCR 72.7 versus 36.8 % ($p = 0.12$), PFS 5.6 versus 2.8 months ($p = 0.01$), and OS 9.1 versus 3.9 months ($p < 0.01$) in S-1-naïve versus refractory patients.

Safety

A total of 95 cycles were delivered, with a median of two cycles per patient (range, 1–8). The relative dose intensities for S-1 and oxaliplatin were 89.0 and 96.7 %, respectively. All eligible patients were evaluated for toxicities. Treatment-related adverse events are shown in Table 3. The most frequently encountered grade 3 or 4 adverse events were neutropenia (10.0 %), diarrhea (6.7 %), and anemia (3.3 %). Although grade 2 peripheral neuropathy occurred in two patients (6.7 %) after three and six cycles, it improved after cessation of chemotherapy. No patient developed febrile neutropenia or died from toxicity during treatment. Reasons for discontinuing treatment were disease progression (66.7 %), deterioration of PS (16.7 %), and unacceptable toxicity (16.7 %).

Discussion

This retrospective study of SOX in patients with gemcitabine-refractory PC demonstrated an ORR of 10.0 %, a DCR of 50.0 %, and median PFS and OS of 3.4 and 5.0 months, respectively. SOX showed greater efficacy in

Table 2 Efficacy in all patients and in each treatment line

	Total ($N = 30$)	Second line ($N = 11$)	Third or fourth line ($N = 19$)
Prior S-1 use (%)	63.3	0	100
Complete response (%)	0	0	0
Partial response (%)	10.0	27.3	0
Stable disease (%)	40.0	45.5	36.8
Progressive disease (%)	23.3	9.1	31.6
Not evaluable[a] (%)	26.7	18.2	31.6
Response rate (%)	10.0	27.3	0
Disease control rate (%)	50.0	72.7	36.8
PFS (months)	3.4 (1.3–5.3)	5.6 (1.0–6.5)	2.8 (1.2–3.4)
OS (months)	5.0 (3.4–7.4)	9.1 (5.1–12.8)	3.9 (1.8–4.9)

PFS progression-free survival, *OS* overall survival

[a] Defined as individuals who could not complete the first two cycles for any reason

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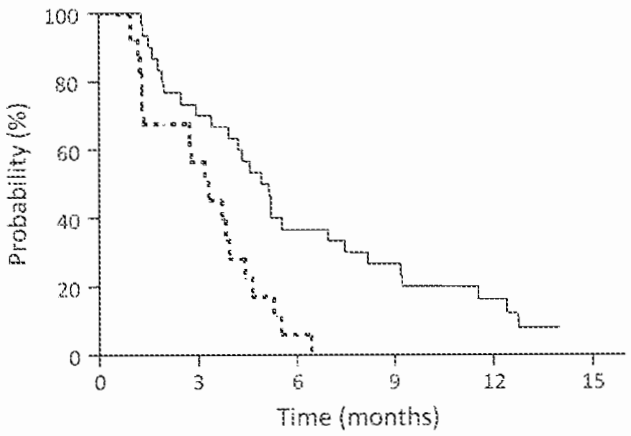


Fig. 1 Kaplan–Meier *curves* for overall survival (*black line*) and progression-free survival (*dotted line*). The median progression-free survival and overall survival were 3.4 months (95 % CI 1.3–5.3) and 5.0 months (95 % CI 3.4–7.4), respectively

Table 3 Adverse events

	Grades 1–4 (%)	Grades 3–4 (%)
Hematologic		
Leukopenia	36.7	6.7
Neutropenia	40.0	10.0
Anemia	46.7	3.3
Thrombocytopenia	50.0	0
Non-hematologic		
Nausea	3.3	0
Vomiting	23.3	0
Diarrhea	53.3	6.7
Constipation	16.7	0
Anorexia	60.0	0
Fatigue	56.7	0
Peripheral neuropathy	43.3	0

the 11 S-1-naïve patients: PFS was 5.6 versus 2.8 months and OS 9.1 versus 3.9 months in S-1-naïve versus refractory patients. The adverse events that exceeded grade 3 were neutropenia (10.0 %), diarrhea (6.7 %), and anemia (3.3 %), with no treatment-related deaths.

Recently, the NCCN stated that fluoropyrimidine plus oxaliplatin combination therapy can be an acceptable option for patients with gemcitabine-refractory PC [9]. Several studies have reported infused 5-FU/LV plus oxaliplatin as a second-line treatment, with an ORR of 0.0–14.0 %, PFS of 1.4–4.0 months, and OS of 3.4–6.7 months [8, 15–17]. Among them, the CONKO-003 study provided the first evidence for the benefit of second-line therapy, with significantly prolonged OS compared to BSC alone after failure of first-line therapy with gemcitabine (4.8 vs. 2.3 months). As for oxaliplatin-based therapy with oral fluoropyrimidine, capecitabine plus oxaliplatin (XELOX or CAPOX) was used in a second-line setting in PC patients, with an ORR of 2.6–13.0 %, PFS of 3.4–4.2 months, and OS of 5.2–8.1 months [18, 19]. No previous study of SOX in PC has been published, although SOX was demonstrated to be active as a first-line therapy in other malignancies, including gastric, colorectal, and bile duct cancers [13, 20–22]. In contrast, a phase 2 study of S-1 combined with cisplatin, instead of oxaliplatin, resulted in a high degree of toxicity and poor compliance, without promising antitumor activity [23]. Our results indicate that the effectiveness of the SOX regimen is similar to that of oxaliplatin combined with infused 5-FU/LV or capecitabine, and that it tends to be more feasible than S-1 plus cisplatin.

The treatment was generally well tolerated in this study. The median relative dose intensities of oxaliplatin and S-1 were 96.7 and 89.0 %, respectively, indicating that the treatment was carried out as scheduled in most patients. Although thrombocytopenia was one of the most common grade 3/4 adverse events (13–24 %) in previous studies with SOX in gastric and colorectal cancer (CRC) [13, 21, 22], thrombocytopenia, which developed in 50.0 % of our patients, was limited to grade 1/2. One possible reason for the low incidence of severe thrombocytopenia in this study is the lower dose of oxaliplatin in our regimen compared with some previous reports (100 vs. 130 mg/m^2). Another possible explanation is the different type of cancer, considering the similarly low occurrence of thrombocytopenia in biliary tract cancer [20].

Peripheral neuropathy is one of the principal dose-limiting toxic effects of oxaliplatin [24]. In patients with CRC, grade 3/4 oxaliplatin-induced peripheral neuropathy occurs in up to 30 % of patients treated with cumulative doses ranging from 765 to 1,020 mg/m^2, and in 50 % of patients treated with higher doses, thus impairing their functional capacity and compromising the treatment plan [25, 26]. In our study, nearly half of the patients had peripheral neuropathy, all of which was limited to grade 1/2, and the median cumulative dose of oxaliplatin was 200 mg/m^2 (range 100–800 mg/m^2). The reason for the lower cumulative dose was shorter PFS in patients with advanced PC.

We previously showed improvement of the prognosis in advanced PC after the introduction of S-1 [10, 27]. We subsequently showed that salvage chemotherapy with gemcitabine plus oxaliplatin (GEMOX) and irinotecan are tolerable but have limited activity: RR of 0.0–3.6 %, DCR of 44.6–59.0 %, PFS of 2.6–2.9 months, and OS of 5.3–6.8 months [28, 29]. In these studies, however, OS from first-line chemotherapy was of relatively long duration (19.5–22.7 months) in patients with advanced PC. Although few patients can receive salvage therapy, the availability of multiple drugs, including fluorouracil derivatives, platinum agents, and irinotecan, may prolong the survival of selected

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patients with advanced PC, similar to CRC [30]. Therefore, it is clearly essential to establish a method of selecting patients who will benefit from salvage therapy and to determine the order in which agents should be used. Several reports addressed the prognostic factors that may help select patients with advanced PC who will benefit most from second-line therapy [31–33]. According to these, good PS, previous response to first-line therapy, low CA19-9 level, low CRP level, high albumin level, and no peritoneal dissemination were the factors that could be used to select cases in which second-line therapy would be beneficial. However, only prospective randomized trials stratified for these prognostic factors can 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 PC.

In conclusion, SOX was moderately effective and well tolerated in patients with refractory PC. This regimen showed promising efficacy, especially as second-line chemotherapy in S-1-naïve patients. Further trials are expected to elucidate the role of salvage chemotherapy and a method of selecting patients who will benefit from salvage chemotherapy in terms of survival.

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Conflict of interest None.

References

1. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
2. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB III (2002) Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern cooperative oncology group trial e2297. J Clin Oncol 20:3270–3275
3. Oettle H, Richards D, Ramanathan RK, van Laethem JL, Peeters M, Fuchs M, Zimmermann A, John W, Von Hoff D, Arning M, Kindler HL (2005) A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. Ann Oncol 16:1639–1645
4. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, Zaniboni A, Ducreux M, Aitini E, Taieb J, Faroux R, Lepere C, de Gramont A (2005) Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a gercor and giscad phase III trial. J Clin Oncol 23:3509–3516
5. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP (2009) Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27:5513–5518
6. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W (2007) 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. J Clin Oncol 25:1960–1966
7. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M (2011) Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
8. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dorken B, Riess H, Oettle H (2011) 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. Eur J Cancer 47:1676–1681
9. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB III, Casper ES, Cohen SJ, Czito B, Ellenhorn JD, Hawkins WG, Herman J, Hoffman JP, Ko A, Komanduri S, Koong A, Ma WW, Malafa MP, Merchant NB, Mulvihill SJ, Muscarella P II, Nakakura EK, Obando J, Pitman MB, Sasson AR, Tally A, Thayer SP, Whiting S, Wolff RA, Wolpin BM, Freedman-Cass DA, Shead DA (2012) Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw 10:703–713
10. Nakai Y, Isayama H, Sasaki T, Sasahira N, Ito Y, Kogure H, Togawa O, Matsubara S, Arizumi T, Yagioka H, Yashima Y, Kawakubo K, Mizuno S, Yamamoto K, Hirano K, Tsujino T, Ijichi H, Tateishi K, Toda N, Tada M, Omata M, Koike K (2010) Impact of s-1 on the survival of patients with advanced pancreatic cancer. Pancreas 39:989–993
11. Morizane C, Okusaka T, Furuse J, Ishii H, Ueno H, Ikeda M, Nakachi K, Najima M, Ogura T, Suzuki E (2009) A phase II study of s-1 in gemcitabine-refractory metastatic pancreatic cancer. Cancer Chemother Pharmacol 63:313–319
12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
13. Koizumi W, Takiuchi H, Yamada Y, Boku N, Fuse N, Muro K, Komatsu Y, Tsuburaya A (2010) Phase II study of oxaliplatin plus s-1 as first-line treatment for advanced gastric cancer (g-sox study). Ann Oncol 21:1001–1005
14. Takahara N, Isayama H, Nakai Y, Sasaki T, Ishigami H, Yamaguchi H, Kogure H, Yamamoto N, Sasahira N, Hirano K, Tada M, Kitayama J, Watanabe T, Koike K (2013) Intravenous and intraperitoneal paclitaxel with s-1 for refractory pancreatic cancer with malignant ascites: an interim analysis. J Clin Oncol 31(4 suppl):267
15. Gebbia V, Maiello E, Giuliani F, Borsellino N, Caruso M, Di Maggio G, Ferrau F, Bordonaro R, Verderame F, Traiongo P, Di Cristina L, Agueli R, Russo P, Colucci G (2007) Second-line chemotherapy in advanced pancreatic carcinoma: a multicenter survey of the gruppo oncologico italia meridionale on the activity and safety of the folfox4 regimen in clinical practice. Ann Oncol 18(Suppl 6):vi124–vi127

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16. Novarino A, Saiolli MA, Chiappino I, Giacobino A, Bellone G, Rahimi F, Milanesi E, Berteotto O, Ciuffreda L (2009) Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. Am J Clin Oncol 32:44–48
17. Yoo C, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, Lee SS, Seo DW, Lee SK, Kim MH, Han DJ, Kim SC, Lee JL (2009) A randomised phase II study of modified folfiri.3 vs. modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. Br J Cancer 101:1658–1663
18. Boeck S, Weigang-Kohler K, Fuchs M, Kettner E, Quietzsch D, Trojan J, Stotzer O, Zeuzem S, Lordick F, Kohne CH, Kroning H, Steinmetz T, Depenbrock H, Heinemann V (2007) Second-line chemotherapy with pemetrexed after gemcitabine failure in patients with advanced pancreatic cancer: a multicenter phase II trial. Ann Oncol 18:745–751
19. Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA (2008) Phase II trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 113:2046–2052
20. Kim KP, Jang G, Hong YS, Lim HS, Bae KS, Kim HS, Lee SS, Shin JG, Lee JL, Ryu MH, Chang HM, Kang YK, Kim TW (2011) Phase II study of s-1 combined with oxaliplatin as therapy for patients with metastatic biliary tract cancer: influence of the cyp2a6 polymorphism on pharmacokinetics and clinical activity. Br J Cancer 104:605–612
21. Yamada Y, Takara M, Miya T, Satoh T, Shirao K, Shimada Y, Ohtsu A, Sasaki Y, Tanigawara Y (2008) Phase I/II study of oxaliplatin with oral s-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer 98:1034–1038
22. Zang DY, Lee BH, Park HC, Song HB, Kim HJ, Jang JY, Kim JH, Kim HY, Kwon JH, Hwang SW, Park SR, Park CH, Kim KO, Kim MJ, Jang KM (2009) Phase II study with oxaliplatin and s-1 for patients with metastatic colorectal cancer. Ann Oncol 20:892–896
23. Kim HJ, Yun J, Kim KH, Kim SH, Lee TH, Lee SC, Bae SB, Kim CK, Lee NS, Moon JH, Park SH, Lee KT, Park SK, Won JH, Park HS, Hong DS (2012) Phase II study of palliative s-1 in combination with cisplatin as second-line chemotherapy for gemcitabine-refractory pancreatic cancer patients. Oncol Lett 3:1314–1318
24. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP (2008) A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev 34:368–377
25. Kalofonos HP, Aravantinos G, Kosmidis P, Papakostas P, Economopoulos T, Dimopoulos M, Skarlos D, Bamias A, Pectasides D, Chalkidou S, Karina M, Kouras A, Samantas E, Bacoyiannis C, Samelis GF, Basdanis G, Kalfarentzos F, Fountzilas G (2005) Irinotecan or oxaliplatin combined with leucovorin and 5-fluorouracil as first-line treatment in advanced colorectal cancer: a multicenter, randomized, phase II study. Ann Oncol 16:869–877
26. Land SR, Kopec JA, Cecchini RS, Ganz PA, Wieand HS, Colangelo LH, Murphy K, Kneebier JP, Seay TE, Needles BM, Bearden JD III, Colman LK, Lanier KS, Pajon ER Jr, Cella D, Smith RE, O'Connell MJ, Costantino JP, Wolmark N (2007) Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J Clin Oncol 25:2205–2211
27. Nakai Y, Isayama H, Sasaki T, Sasahira N, Kogure H, Hirano K, Tsujino T, Ijichi H, Tateishi K, Tada M, Omata M, Koike K (2010) Impact of s-1 in patients with gemcitabine-refractory pancreatic cancer in Japan. Jpn J Clin Oncol 40:774–780
28. Isayama H, Nakai Y, Yamamoto K, Sasaki T, Mizuno S, Yagioka H, Yashima Y, Kawakubo K, Kogure H, Arizumi T, Togawa O, Ito Y, Matsubara S, Yamamoto N, Sasahira N, Hirano K, Tsujino T, Tada M, Omata M, Koike K (2011) Gemcitabine and oxaliplatin combination chemotherapy for patients with refractory pancreatic cancer. Oncology 80:97–101
29. Takahara N, Nakai Y, Isayama H, Sasaki T, Satoh Y, Takai D, Hamada T, Uchino R, Mizuno S, Miyabayashi K, Mohri D, Kawakubo K, Kogure H, Yamamoto N, Sasahira N, Hirano K, Ijichi H, Tada M, Yatomi Y, Koike K (2012) Uridine diphosphate glucuronosyl transferase 1 family polypeptide a1 gene (ugt1a1) polymorphisms are associated with toxicity and efficacy in irinotecan monotherapy for refractory pancreatic cancer. Cancer Chemother Pharmacol 71:85–92
30. Grothey A, Sargent D, Goldberg RM, Schmoll HJ (2004) Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 22:1209–1214
31. Nakachi K, Furuse J, Ishii H, Suzuki E, Yoshino M (2007) Prognostic factors in patients with gemcitabine-refractory pancreatic cancer. Jpn J Clin Oncol 37:114–120
32. Kim ST, Choi YJ, Park KH, Oh SC, Seo JH, Shin SW, Kim JS, Kim YH (2012) A prognostic model to identify patients with advanced pancreas adenocarcinoma who could benefit from second-line chemotherapy. Clin Oncol (R Coll Radiol) 24:105–111
33. Marechal R, Demols A, Gay F, De Maertelaere V, Arvanitaki M, Hendlisz A, Van Laethem JL (2007) Prognostic factors and prognostic index for chemonaive and gemcitabine-refractory patients with advanced pancreatic cancer. Oncology 73:41–51

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Metastatic Disease (PANC-9)
Recurrence After Resection (PANC-10)
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Criteria Defining Resectability Status (PANC-B)
Principles of Palliation and Supportive Care (PANC-C)
Principles of Radiation Therapy (PANC-D)
Principles of Chemotherapy (PANC-E)
American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010) (ST-1)

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 1.2012 Updates
Pancreatic Adenocarcinoma

Updates in Version 1.2012 of the NCCN Guidelines from Version 2.2011 include:

PANC-1
- Footnote a: Added "interventional endoscopy" to multidisciplinary team. "Multidisciplinary consultation should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology."
- Workup: Added MRI as an option to pancreatic protocol CT.
- Workup: Changed "chest imaging" to "chest CT."
- Workup: Changed "Biopsy confirmation, metastatic site preferred" to "Biopsy confirmation of metastatic site."

PANC-4
- Changed "biopsy negative" to "cancer not confirmed."
- Added "exclude autoimmune pancreatitis" to cancer not confirmed following repeat biopsy.
- Modified footnote h: "There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended."

PANC-7
- Changed "permanent metal stent" to "expandable metal stent."

PANC-8
- Locally advanced, unresectable, good performance status added: gemcitabine + erlotinib (category 1).
- Locally advanced, unresectable, good performance status removed (category 1) following FOLFIRINOX.
- Locally advanced, unresectable, good performance status, salvage therapy added: Chemoradiation if not previously given and if primary site is the sole site of progression.

PANC-9
- For good performance status, added gemcitabine + erlotinib (category 1).

PANC-A
- Changed #1: "radiographic studies" to "imaging studies."
- Added more details to #2: "Imaging should include specialized pancreatic CT or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3 mm) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients."
- Modified #5: "EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS FNA when compared with the percutaneous approach."

PANC-E
- Metastatic disease (page 1 of 3)
  - Monotherapy capecitabine was changed from category 2A to a category 2B recommendation (also noted on pages PANC-8 and -9).
  - Combination gemcitabine + cisplatin (especially for patients with possible hereditary cancers) was changed from a category 2B to a category 2A recommendation.
  - Added fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin or CapeOx)
- Adjuvant therapy (page 2 of 3)
  - Added: "For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine-based-combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx)[8] for patients previously treated with gemcitabine-based therapy."

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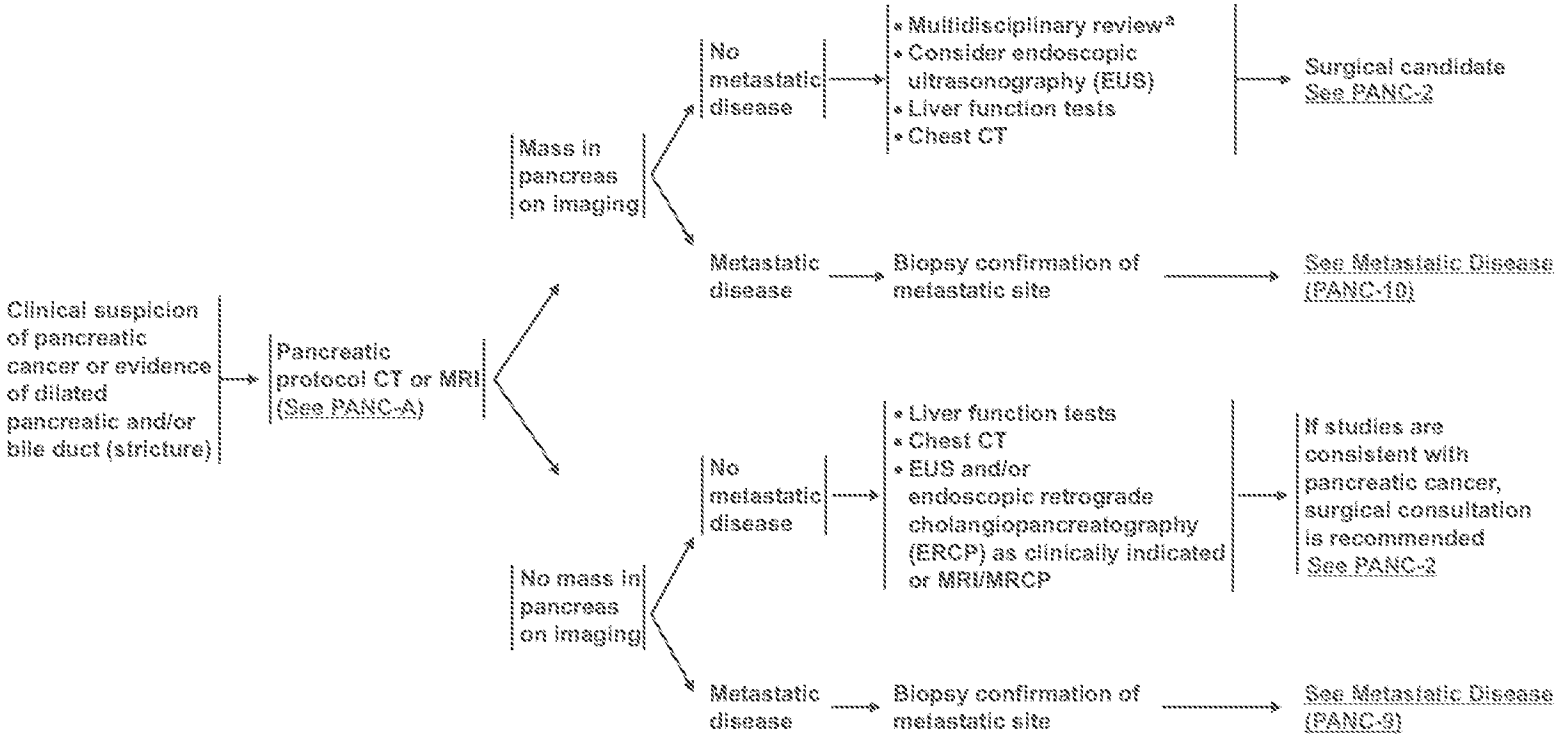
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NCCN Guidelines™ Version 1.2012
Pancreatic Adenocarcinoma

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CLINICAL PRESENTATION

WORKUP



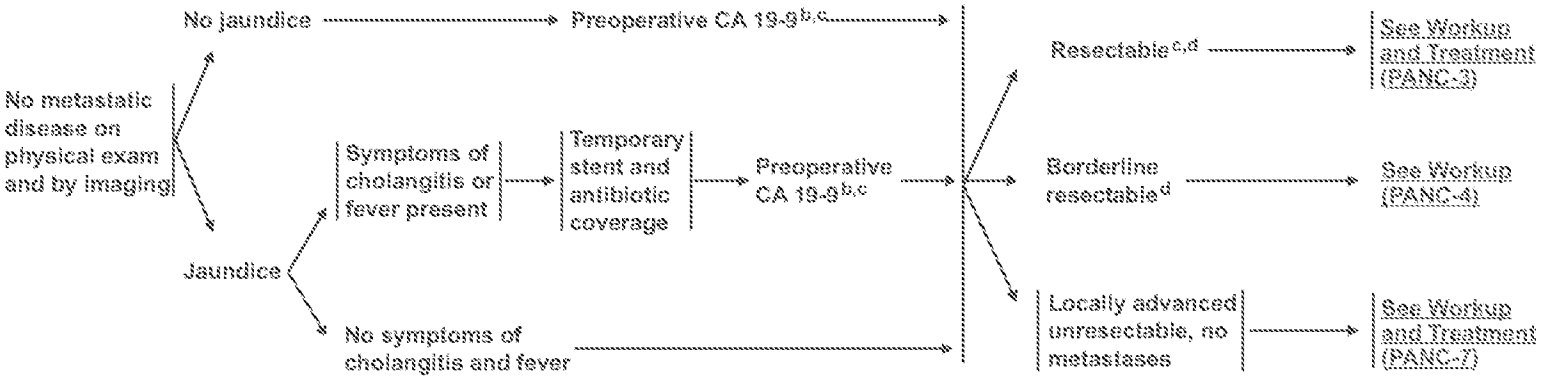
[a]Multidisciplinary review should ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

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CLINICAL PRESENTATION

WORKUP



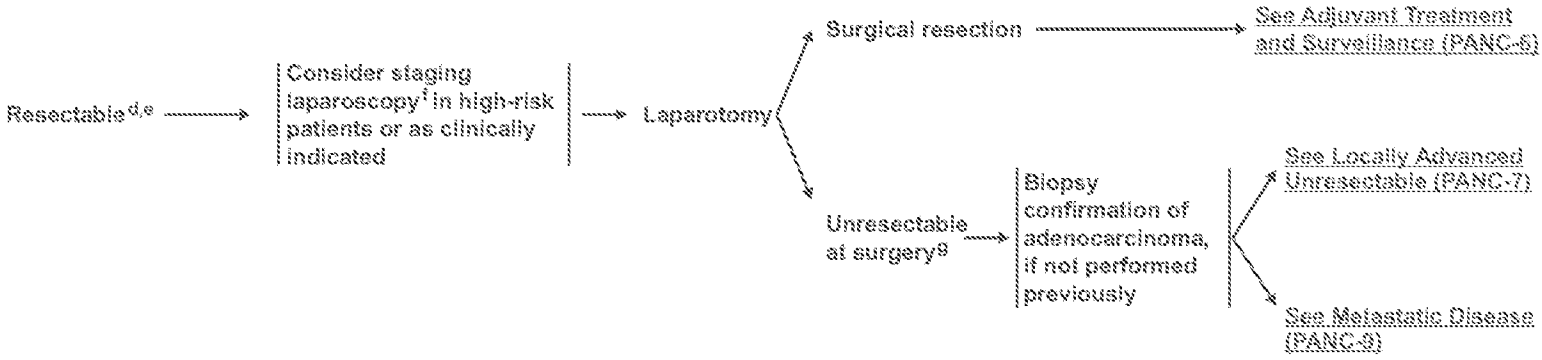
[b] CA 19-9 may be elevated in cases of benign biliary obstruction and does not represent an appropriate baseline until the biliary tree is adequately decompressed and the bilirubin is normal. In addition, CA 19-9 may be undetectable in Lewis antigen-negative individuals.

[c] See Principles of Diagnosis and Staging (PANC-A)

[d] See Criteria Defining Resectability Status (PANC-B)

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[d] See Criteria Defining Resectability Status (PANC-B).

[e] Consider neoadjuvant therapy on clinical trial, which requires biopsy confirmation of adenocarcinoma. For patients with biliary obstruction, durable biliary decompression is required.

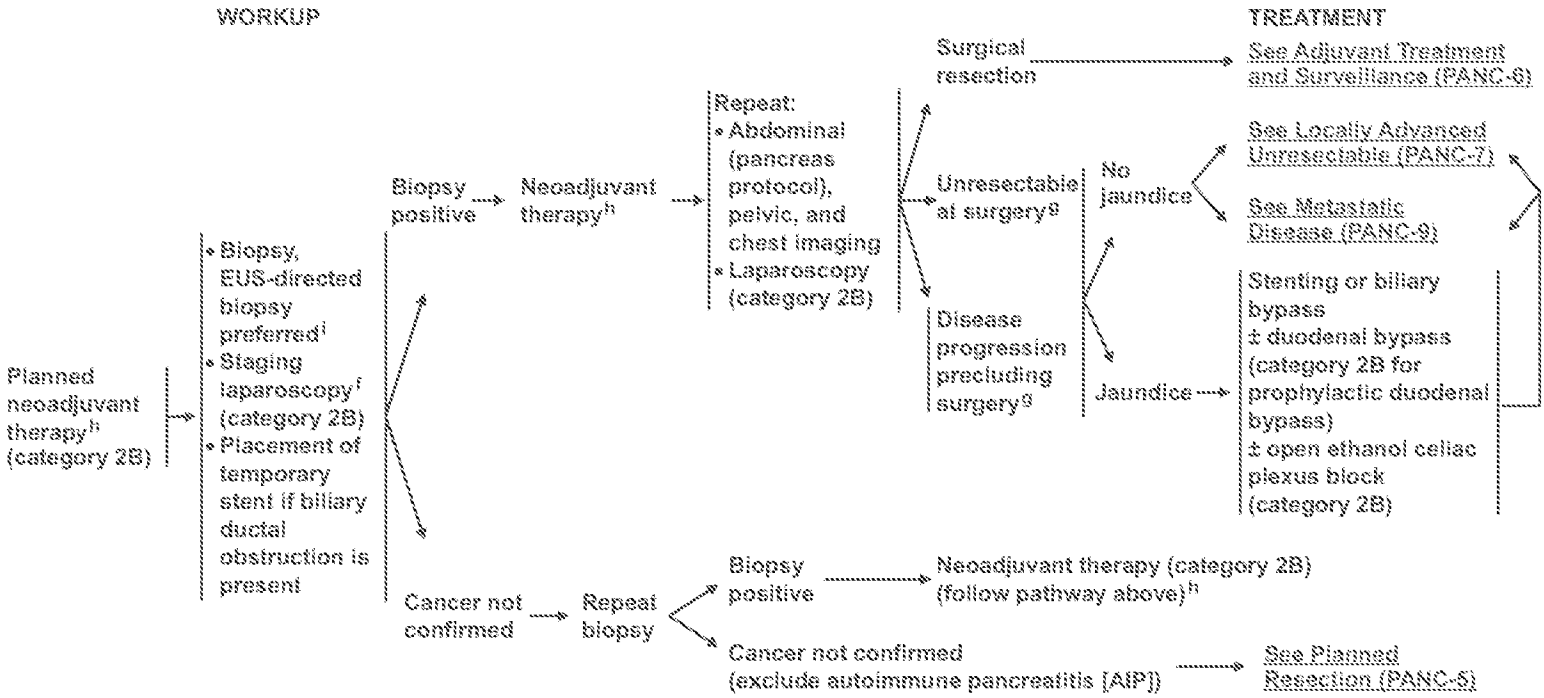
[f] See Principles of Diagnosis and Staging #6 (PANC-A).

[g] See Principles of Palliation and Supportive Care (PANC-C).

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BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED NEOADJUVANT THERAPY

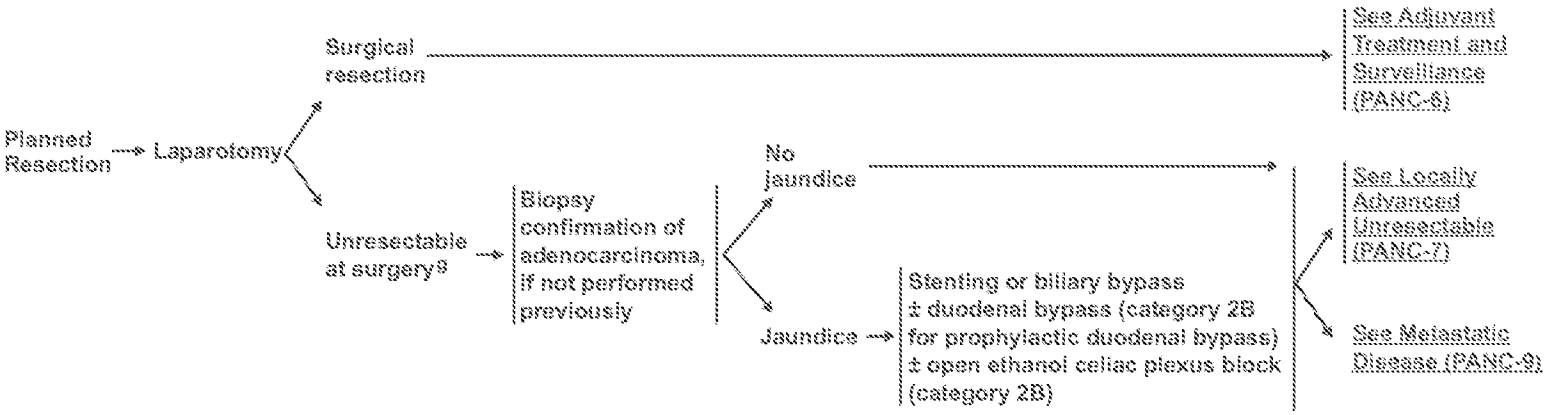


[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Diagnosis and Staging #6 (PANC-A).
[g] See Principles of Palliation and Supportive Care (PANC-C).
[h] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).

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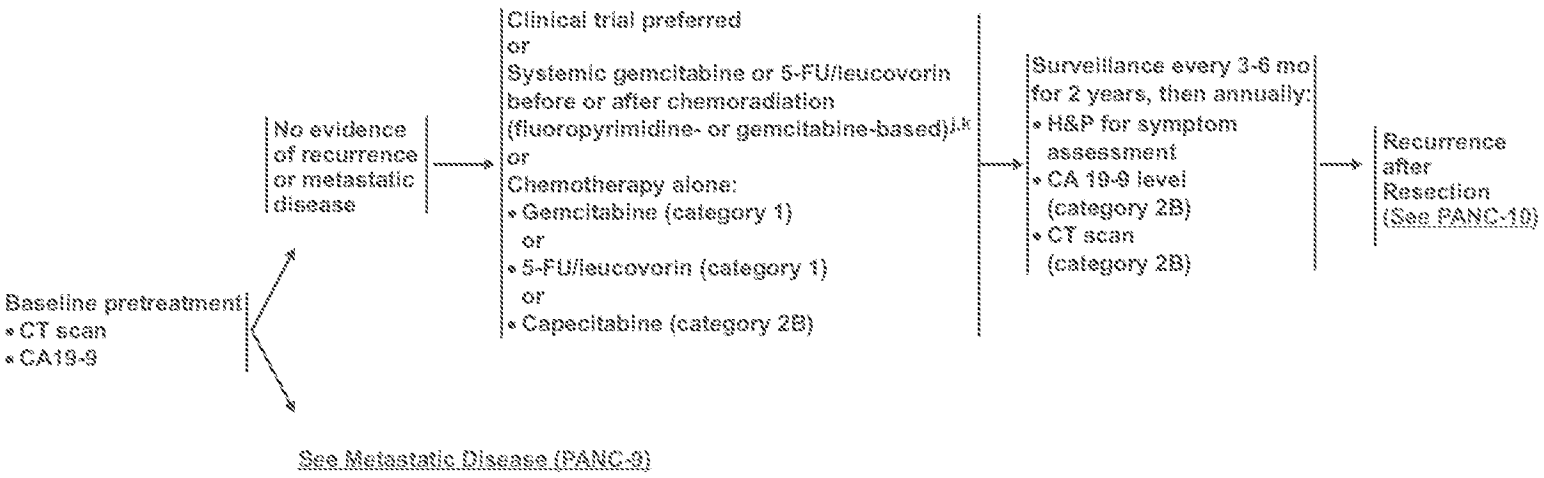
BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED RESECTION



[c] See Principles of Diagnosis and Staging (PANC-A)
[d] See Criteria Defining Resectability Status (PANC-B).
[g] See Principles of Palliation and Supportive Care (PANC-C).

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[j]See Principles of Radiation Therapy (PANC-D).

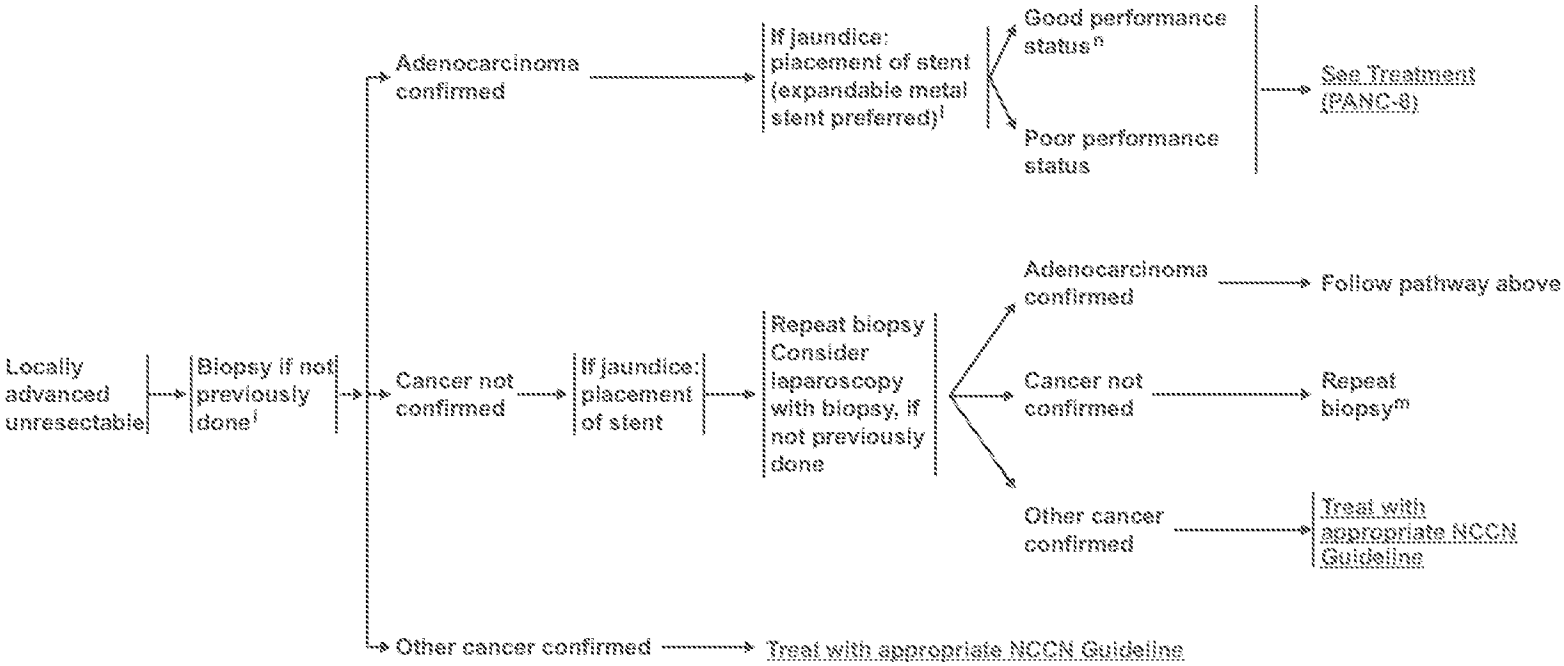
[k]Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, restaging with a CT scan should be done after each treatment modality.

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LOCALLY ADVANCED UNRESECTABLE

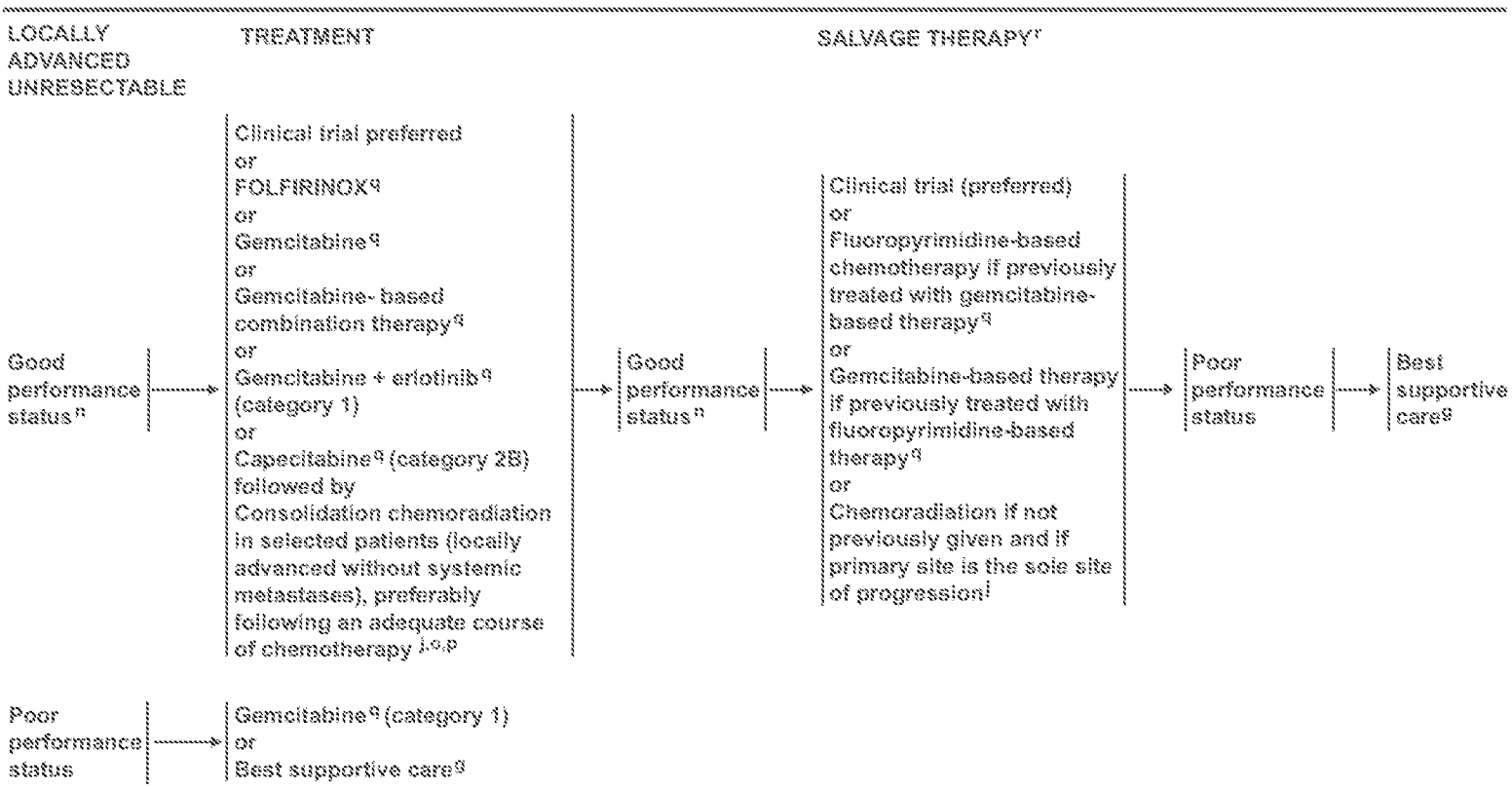
WORKUP



[l] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
[l] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[m] In this situation a laparscopic-directed biopsy may be useful.
[n] Defined as ECOG 0,1 with good pain management, patent biliary stent, and adequate nutritional intake.

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[q] See Principles of Palliation and Supportive Care (PANC-C).

[j] See Principles of Radiation Therapy (PANC-D).

[n] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.

[o] Laparoscopy as indicated to evaluate distant disease.

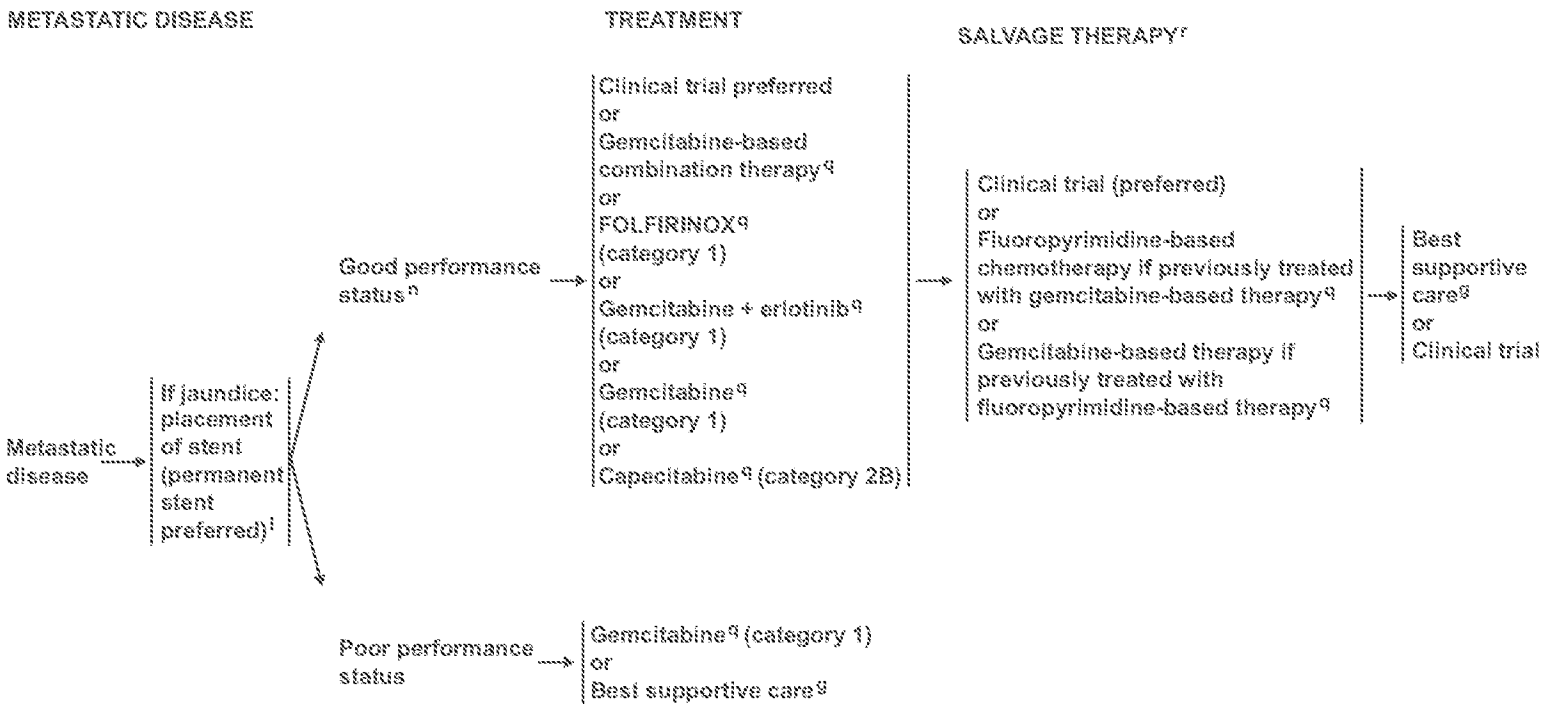
[p] Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy. Patients with a significant response to chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention.

[q] See Principles of Chemotherapy (PANC-E).

[r] Best reserved for patients who maintain a good performance status.

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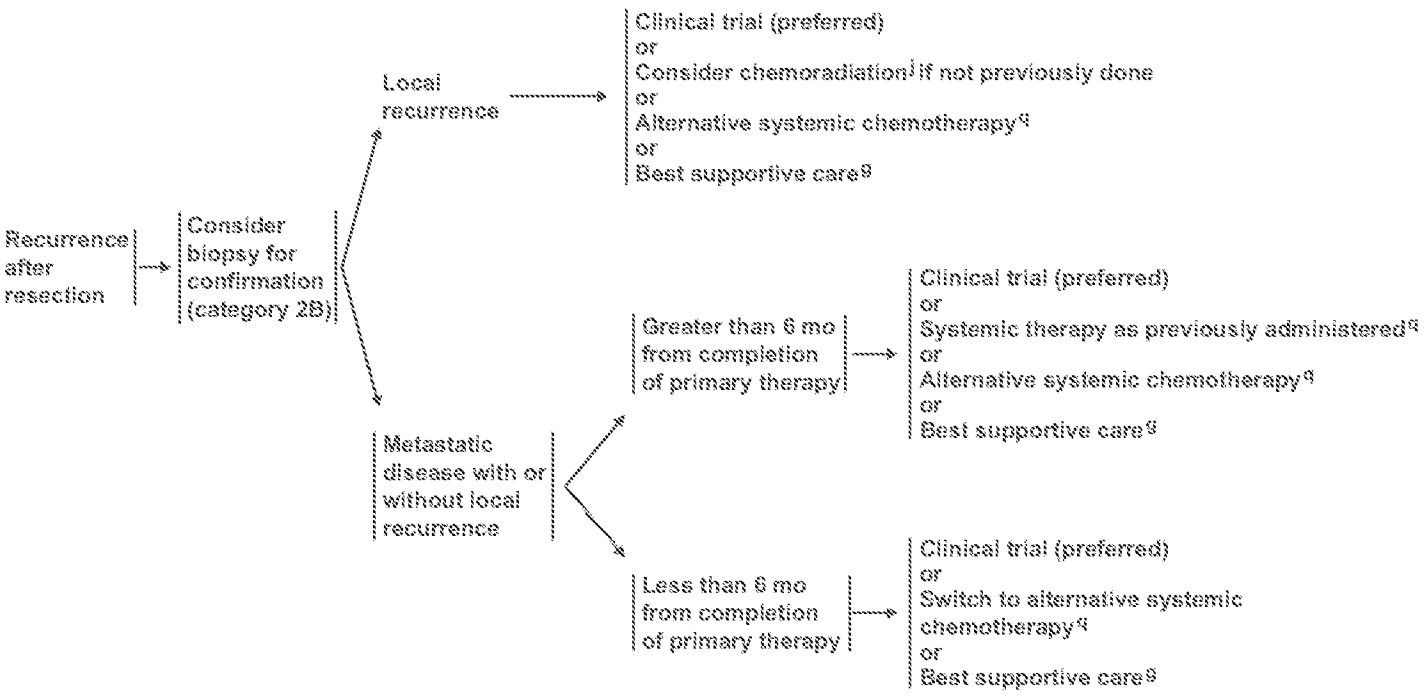
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[g] See Principles of Palliation and Supportive Care (PANC-C).
[i] Unless biliary bypass performed at time of laparoscopy or laparotomy.
[h] Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q] See Principles of Chemotherapy (PANC-E).
[r] Best reserved for patients who maintain a good performance status.

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[g] See Principles of Palliation and Supportive Care (PANC-C).
[i] See Principles of Radiation Therapy (PANC-D).
[q] See Principles of Chemotherapy (PANC-E).
[f] Best reserved for patients who maintain a good performance status.

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PRINCIPLES OF DIAGNOSIS AND STAGING

#1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation with reference to appropriate imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (15-20) of pancreatic resections annually.

#2 Imaging should include specialized pancreatic CT or MRI. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multi-phase imaging technique includes a non-contrast phase plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3mm) through the abdomen. This technique allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of metastatic deposits as small as 3-5 mm. Pancreas protocol MRI is emerging as an alternative to CT for patients.

#3 The role of PET/CT scan remains unclear. PET/CT scan may be considered after formal pancreatic CT protocol in "high-risk" patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast enhanced CT.

#4 Endoscopic ultrasound (EUS) may be complementary to CT for staging.

#5 EUS-directed FNA biopsy is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.

#6 Diagnostic staging laparoscopy to rule out subradiologic metastases (especially for body and tail lesions) is used routinely in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes).

#7 Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been done for such a patient, he or she should be treated for M1 disease.

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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement
- Clear fat planes around the celiac axis, hepatic artery, and SMA.

Tumors considered borderline resectable include the following:

- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short-segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:

- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- BODY
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE[2]

Objectives: Prevent and ameliorate suffering, while ensuring optimal quality of life

- Biliary obstruction
  - Endoscopic biliary stent (preferred method)
  - Percutaneous biliary drainage with subsequent internalization
  - Open biliary-enteric bypass

- Gastric outlet obstruction
  - Good performance status
    - Gastrojejunostomy (open or laparoscopic) ± J-tube
    - Consider enteral stent[1]
  - Poor performance status
    - Enteral stent[1]
    - Percutaneous endoscopic gastrostomy (PEG) tube

- Severe tumor-associated abdominal pain
  - EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
  - Consider palliative chemoradiation if not already given as part of primary therapy regimen

- Depression, pain, and malnutrition
  - Formal Palliative Medicine Service evaluation when appropriate (See NCCN Supportive Care Guidelines)

- Pancreatic insufficiency (inadequate production of digestive enzymes)
  - Pancreatic enzyme replacement

- Thrombembolic disease
  - Low-molecular-weight heparin preferred over warfarin

[1] Placement of an enteral stent is particularly important for patients with poor performance status.
[2] Palliative surgical procedures are best reserved for patients with a longer life expectancy.

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PRINCIPLES OF RADIATION THERAPY

General Principles:

- Patients with pancreatic cancer are best managed by a multi-disciplinary team.[1]
- Recommendations for radiation therapy (RT) for such patients are typically made based upon five typical clinical scenarios: 1) neoadjuvant/resectable, 2) borderline resectable, 3) locally advanced/unresectable, 4) adjuvant/resectable, and 5) palliative. For definitions of these scenarios, See Criteria Defining Resectability Status (PANC-B).
- Staging is optimally determined with modern contrast enhanced abdominal CT (3-D CT) and/or MRI imaging with thin cuts through the pancreas along with an EUS.
- If patients present with biliary obstruction (jaundice/elevated direct bilirubin), plastic or metal stents should be placed prior to initiation of RT. A percutaneous drain can also be used if ERCP stent placement is unsuccessful.
- The role of laparoscopic evaluation prior to chemoradiation is controversial, although standard at some institutions.
- Ideally, patients should be treated on clinical trials when available. Radiation is typically given concurrently with chemotherapy, except in the palliative setting, with intraoperative radiation therapy (IORT), or with stereotactic body radiation therapy (SBRT).

Standard Recommendations:

**Note: It is not known whether one regimen is necessarily more effective than another; hence, these are given as examples of commonly utilized regimens, however, others based on similar principles are acceptable.

Neoadjuvant resectable/borderline resectable:

- No standard treatment regimen currently exists for neoadjuvant resectable or borderline resectable pancreatic cancer. Neoadjuvant therapy for patients with resectable tumors should ideally be conducted on a clinical trial. Generally, use similar paradigms as for locally advanced unresectable disease.
  - Upfront flouropyrimidine- (CI-5-FU or capecitabine- based chemoradiation (CRT).[2,3]
  - Upfront gemcitabine-based CRT.[4]
  - Induction chemotherapy (2-4 cycles) followed by 5-FU- or gemcitabine-based CRT.[5]

  Options include RT 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.[6]
- Ideally, surgical resection should be attempted 6-8 weeks following CRT. Surgery can be performed >8 weeks following CRT; however radiation-induced fibrosis may potentially make surgery more difficult.

Continued on next page

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PRINCIPLES OF RADIATION THERAPY

Unresectable/Locally advanced (non-metastatic):
- Upfront fluoropyrimidine (CI 5-FU or capecitabine)-based chemoradiation (CRT) in select patients.
- Upfront gemcitabine- based CRT in select patients.[7,8]
- Induction chemotherapy (2-4 cycles) followed by 5-FU or gemcitabine-based CRT.[9,10]

Options include:
- RT 45-54 Gy in 1.8-2.5 Gy fractions or
- 36 Gy in 2.4 Gy fractions.[11]

- Following CRT, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.
- In cases where 1) it is highly unlikely that patients will become resectable (complete encasement of superior mesenteric/celiac arteries) 2) there are suspicious metastases, and 3) patients may not be able to tolerate CRT, then it may be reasonable to start with chemotherapy (2-6 cycles) followed by definitive CRT if no evidence of metastatic progression.
- If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront CRT.
- No standard total dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial.[12]

Adjuvant:
- Treatment options following pancreaticoduodenectomy or distal pancreatectomy include:
  - Upfront fluoropyrimidine- (CI 5-FU or capecitabine) or gemcitabine-based chemoradiation followed by maintenance 5-FU or gemcitabine.[13]
  - Gemcitabine or CI 5-FU (1 cycle) followed by CI 5-FU/RT followed by maintenance gemcitabine or CI 5-FU.[14]
  - Gemcitabine or bolus 5-FU/leucovorin [15]
  - Gemcitabine or bolus 5-FU/leucovorin for 2-6 cycles followed by fluoropyrimidine- (CI 5-FU or capecitabine) based CRT.[16]

  RT 45-46 Gy in 1.8-2 Gy fractions to the tumor bed, surgical anastomoses, and adjacent lymph, followed by an additional 5-9 Gy to the tumor bed and anastomoses.[17]

Palliative:
- See Principles of Palliation and Supportive Care (PANC-C).
  - RT alone to the primary tumor plus a margin (Typically 30-36 Gy in 2.4-3.0 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction or pain.[18]
  - Palliative RT can also be considered for patients who are elderly and/or not candidates for definitive therapy because of comorbidities.
  - Metastatic sites causing pain may also be palliated with RT.

Continued on next page

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PRINCIPLES OF RADIATION THERAPY

Radiation Therapy Treatment Planning Principles

- Patients should undergo a CT simulation (thin slices through the pancreas/bed and locoregional nodal basins) with IV (assuming adequate kidney function) and oral contrast. For resected cases, preoperative CT scans and strategically- placed surgical clips are used to determine the tumor bed, ideally with the surgeon's assistance. In the neoadjuvant, borderline, and locally advanced settings the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm and/or FDG-avid on PET) are contoured with assistance from structural (CT/MRI) and functional imaging (PET). [19,20]
- The PTV should be defined per the ICRU-62 guidelines.[21] A GTV should be defined for intact pancreatic tumors. For adjuvant cases, a CTV includes high risk peri-pancreatic lymph nodes, anastomoses, pancreatic tumor bed derived from pre-surgical imaging and strategically-placed surgical clips. CTV expansions are needed to include possible microscopic disease. Further expansion to PTV includes ITV for target/breathing motion and additional margin for patient set-up error (SM).[22-24] Organs at risk (OARs) should also be contoured and evaluated in the DVH.
- Elective nodal irradiation (ENI) is commonly used for adjuvant cases but is controversial for unresectable/neoadjuvant/borderline resectable cases.[11] Standard margin expansions for unresectable cases include the gross tumor and any pathologic lymph nodes (GTV) plus a 0.5-1.5 cm margin to target microscopic extension (CTV) and an additional 0.5-2 cm volume to account for tumor/breathing motion and patient set-up errors (PTV). With these expansions, peri-pancreatic nodes are generally included. 3D-conformal or intensity modulated radiation therapy (IMRT) with breathhold/gating techniques can result in improved PTV coverage with decreased dose to organs at risk (OARs). [25,26] With SBRT, smaller margins are used (0.2-0.5 cm) and the PTV does not cover locoregional elective nodal regions.[27] If small GTV margin expansions are used for CTV and PTV, breathing motion and set-up error should be evaluated or controlled per the AAPM task group 76 guidelines.[28]
- IORT is delivered with electron beam radiation (IOERT) or high dose rate brachytherapy (HDR-IORT). IORT is generally delivered in a single fraction and in combination with adjuvant or neoadjuvant CRT. The role of IORT for unresectable and resectable cases is controversial but is ideally used in cases where resection may result in close or involved margins.[29]
- It is imperative to evaluate the DVH of the PTV and critical normal structures such as liver, kidneys, spinal cord, liver and bowel. (See Table 1, Normal Tissue Dose Volume Constraints (PANC-D, 4 of 6)) While these limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/elective nodal irradiation, types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

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PRINCIPLES OF RADIATION THERAPY

- Fractionated RT is typically delivered as 30-60 Gy over ~3-6 weeks (1.8-3.0 Gy/fraction) with concurrent 5FU/capecitabine or gemcitabine as a radiosensitizer. For resected cases, 45 Gy is delivered to the tumor bed, surgical anastomosis, and regional lymph nodes. Additional radiation (~5-15 Gy) may be administered to the tumor bed/area of involved margins and anastomoses paying careful attention to dose to small bowel. For unresectable disease, 50-54 Gy in 1.8 to 2.0 cGy fractions is recommended. One must also use caution when multiple chemotherapeutic/targeted therapies are given concurrently with RT. For EBRT it is preferred that high energy photon beams are used. SBRT is often delivered in 1-5 fractions ranging from 5-25 Gy per fraction. IORT can be delivered in a single fraction alone (15-20 Gy) or in combination with EBRT (10-20 Gy).
- Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning (http://www.rtog.org/CoreLab/ContouringAtlases.aspx).

Table 1: Normal Tissue Dose Volume Constraints

Structure	Unresectable/Preoperative Constraints	Adjuvant/Resected Constraints
Kidney (L & R)	Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥18 Gy.	If two functioning kidneys present, not more than 50% of the right and 55% of the left kidney should receive >18 Gy. For IMRT planning mean dose to bilateral kidneys should be ≤18 Gy. If only one kidney is present not more than 15% should receive ≥18 Gy and no more than 30% should receive ≥14 Gy.
Stomach, duodenum, jejunum	Max dose ≤55 Gy; not more than 30% of the volume can be between 45 and 55 Gy.	Max dose ≤55 Gy; <10% of each organ volume can receive between 50-53.99 Gy. <15% of each organ volume can receive 45-49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean liver dose ≤25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.	Max dose ≤45 Gy.

*Adapted from RTOG 0936 (3-D conformal, 1.8-50.5) and RTOG 1102 (IMRT, 2.2 to 55 Gy)
**Adapted from RTOG 0848 (3-D or IMRT)

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Table 2. Commonly used radiation therapy abbreviations

3D-CRT	3-D Conformal Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SABR	Stereotactic Ablative Radiotherapy
EBRT	External Beam Radiation Therapy
ENI	Elective Nodal Irradiation
IORT	Intraoperative Radiation Therapy
DVH	Dose Volume Histogram
GTV	Gross Tumor Volume
CTV	Clinical Tumor Volume
IM	Internal Margin: Variations in shape/size of CTV due to respiration and adjacent structures
ITV	Internal Target Volume: encompasses the CTV and IM. (ITV = CTV + IM)
PTV	Planning Target Volume
BED	Biologically Effective Dose
OAR	Organ At Risk
ABC	Airway Breathing Control
IGRT	Image Guided Radiation Therapy
4DCT	Four Dimensional Computerized Tomography
CBCT	Cone Beam Computerized Tomography

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PRINCIPLES OF RADIATION THERAPY

References

1. Pawlik TM, Laheru D, Hruban RH, Coleman J, Wolfgang CL, Campbell K, Ali S, Fishman EK, Schulick RD, Herman JM, Johns Hopkins Multidisciplinary Pancreas Clinic Team. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. Ann Surg Oncol. 2008 Aug; 15(8): 2081-2088.
2. White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, McGrath KM, Clary BM, Pappas TN, Tyler DS. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol. 2001 Dec; 8(10): 758-765.
3. Le Scodan R, Mornex F, Girard N, Mercier C, Valette PJ, Ychou M, Bibeau F, Roy P, Scoazec JY, Partensky C. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: Feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. Ann Oncol. 2008 Aug; 20(8): 1387-1396.
4. Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerkel GA, Charnsangavej C, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008 Jul 20; 26(21): 3496-3502.
5. Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerkel GA, Lee JH, Ross WA, Tamm EP, Bhosale PR, Krishnan S, Das P, Ho L, Xiong H, Abbruzzese JL, Evans DB. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008 Jul 20; 26(21): 3487-3495.
6. Talamonti MS, Small W,Jr, Mulcahy MF, Wayne JD, Attiyeh V, Colletti LM, Zalupski MM, Hoffman JP, Freedman GM, Kinsella TJ, Philip PA, McGinn CJ. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol. 2006 Feb; 13(2): 150-158.
7. Blackstock AW, Tepper JE, Niedwiecki D, Hollis DR, Mayer RJ, Tempero MA. Cancer and leukemia group B (CALGB) 89805: Phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. Int J Gastrointest Cancer. 2003; 34(2-3): 107-116.
8. Loehrer PJ, Powell ME, Cardenes HR, Wagner L, Brell JM, Ramanathan RK, Crane CH, Alberts SR, Benson AB. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201. Journal of clinical oncology. 2008; 26(May 20 suppl). abst 4508.
9. Krishnan S, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, Das P, Delclos ME, Gould MS, Evans DB, Wolff RA, Crane CH. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer. 2007 Jul 1; 110(1): 47-55.
10. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: A qualitative systematic review. J Clin Oncol. 2009 May 1; 27(13): 2269-2277.
11. Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, Ben-Josef E. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2007 Jul 1; 68(3): 801-808.
12. Chang DT, Schellenberg D, Shen J, Kim J, Goodman KA, Fisher GA, Ford JM, Desser T, Quon A, Koong AC. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer. 2009 Feb 1; 115(3): 665-672.
13. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. gastrointestinal tumor study group. Cancer. 1987 Jun 15; 59(12): 2006-2010.
14. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Kudrimoti MR, Fromm ML, Haddock MG, Schaefer P, Willett CG, Pilch YA. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. JAMA. 2008 Mar 5; 299(9): 1019-1026.
15. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-1081.
16. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010 Oct 10; 28(23): 4450-4456. PMCID: PMC2988636.
17. Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, Robinson R, Laheru DA, Jaffee E, Hruban RH, Campbell KA, Wolfgang CL, Asrari F, Donehower R, Hidalgo M, Diaz LA,Jr, Yeo C, Cameron JL, Schulick RD, Abrams R. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the johns hopkins hospital. J Clin Oncol. 2006 Jul 20; 24(21): 3503-3510.
18. Zimmermann FB, Jeremic B, Lersch C, Gelmitz H, Hennig M, Molls M. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU-chemotherapy in advanced adenocarcinoma of the pancreas. Hepatogastroenterology. 2005 Jan-Feb; 52(61): 246-250.
19. Ford EC, Herman J, Yorke E, Wahl RL. 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. J Nucl Med. 2009 Oct; 50(10): 1655-1665.
20. Schellenberg D, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, Fisher GA, Goodman KA, Koong AC, Chang DT. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. Int J Radiat Oncol Biol Phys. 2010 Aug 1; 77(5): 1420-1425.
21. Chavaudra J, Bridier A. Definition of volumes in external radiotherapy: ICRU reports 50 and 62]. Cancer Radiother. 2001 Oct; 5(5): 472-478.
22. Minn AY, Schellenberg D, Maxim P, Suh Y, McKenna S, Cox B, Diederich S, Xing L, Graves E, Goodman KA, Chang D, Koong AC. Pancreatic tumor motion on a single planning 4D-CT does not correlate with intrafraction tumor motion during treatment. Am J Clin Oncol. 2009 Apr 24.
23. Goldstein SD, Ford EC, Duhon M, McNutt T, Wong J, Herman JM. Use of respiratory-correlated four-dimensional computed tomography to determine acceptable treatment margins for locally advanced pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2010 Feb 1; 76(2): 597-602.
24. Feng M, Balter JM, Normolle D, Adusumilli S, Cao Y, Chenevert TL, Ben-Josef E. Characterization of pancreatic tumor motion using cine MRI: Surrogates for tumor position should be used with caution. Int J Radiat Oncol Biol Phys. 2009 Jul 1; 74(3): 884-891. PMCID: PMC2691867.
25. Spalding AC, Jee KW, Vineberg K, Jablonowski M, Fraass BA, Pan CC, Lawrence TS, Haken RK, Ben-Josef E. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. Med Phys. 2007 Feb; 34(2): 521-529.
26. Yovino S, Poppe M, Jabbour S, David V, Bardalo M, Pandya N, Alexander R, Hanna N, Regine WF. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. Int J Radiat Oncol Biol Phys. 2011 Jan 1; 79(1): 158-162.
27. Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, Ford JM, Fisher GA, Greco R, Norton J, Yang GP. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2005 Oct 1; 63(2): 320-323.
28. Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, Kapatoes JM, Low DA, Murphy MJ, Murray BR, Ramsey CR, Van Herk MB, Vedam SS, Wong JW, Yorke E. The management of respiratory motion in radiation oncology report of AAPM task group 76. Med Phys. 2006 Oct; 33(10): 3874-3900.
29. Crane CH, Beddar AS, Evans DB. The role of intraoperative radiotherapy in pancreatic cancer. Surg Oncol Clin N Am. 2003 Oct; 12(4): 965-977.

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PRINCIPLES OF CHEMOTHERAPY (1 of 3)

Systemic therapy is used in the neoadjuvant or adjuvant setting and in the management of locally advanced unresectable and metastatic disease.

- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.

Close follow-up of patients undergoing chemotherapy is indicated.

Metastatic

- Acceptable monotherapy options include:
  - Gemcitabine at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1).
  - Fixed-dose rate gemcitabine (10 mg/m^2/minute) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B).
  - Capecitabine (category 2B)
- Acceptable chemotherapy combinations (for patients with good performance status):
  - Gemcitabine + erlotinib[1] (category 1)
  - FOLFIRINOX[2] (category 1)
  - Gemcitabine + capecitabine[3]
  - Gemcitabine + cisplatin (especially for patients with possible hereditary cancers)[4]
  - Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen) (category 2B)[5]
  - Gemcitabine + nab-paclitaxel[6] (category 2B)
  - Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx[8])
- Second-line therapy may consist of gemcitabine for those patients not previously treated with the drug. Other options include capecitabine (1000 mg/m^2 PO twice daily, days 1-14 every 21 days) or 5-FU/leucovorin/oxaliplatin[7] or CapeOx.[8] Results of the CONKO 003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU /leucovorin.[7]

Locally Advanced

- Depending on performance status, mono- or combination systemic chemotherapy, as noted above, may be considered as initial therapy prior to chemoradiation for appropriate patients with locally advanced, unresectable disease. Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. Patients who progress with metastatic disease are not candidates for chemoradiation unless required for palliative purposes.

See Adjuvant, Neoadjuvant, and Salvage on PANC-E 2 of 3

See References on PANC-E 3 of 3

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PRINCIPLES OF CHEMOTHERAPY (2 of 3)

Adjuvant

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of post-operative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[9]
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[10]
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post- chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for post-operative adjuvant treatment.[11]
- For patients who relapse after receiving adjuvant therapy, subsequent therapy may consist of gemcitabine or gemcitabine based-combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin[7] or CapeOx)[8] for patients previously treated with gemcitabine-based therapy.

Neoadjuvant

- Although there is insufficient evidence to recommend specific neoadjuvant regimens, most neoadjuvant regimens incorporate RT and chemoradiation is preferred in this setting.

See Metastatic and Locally Advanced on PANC-E 1 of 3

See References on PANC-E 3 of 3

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PRINCIPLES OF CHEMOTHERAPY (3 of 3)
References

[1] Moore MJ, Goldstein D, Hamm J, et al. 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. J Clin Oncol 2007;25:1960-1966.

[2] Conroy T, Desseigne F, Ychou M, et al. Randomized phase III trial comparing FOLFIRINOX versus gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma: Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial [abstract]. J Clin Oncol 2010;28(suppl_7s):Abstract 4010.

[3] Cunningham D, Chau I, Stocken D D, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. J Clin ONcol. 2009; 27:5513-5518.

[4] Oliver GR, Sugar E, Laheru D, et al. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Presented at: 2010 ASCO Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, Florida. Abstract 180.

[5] Fine RL, Fogelman DR, Schreibman SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 2008;61:167-175.

[6] Van Hoff DD, Ramanathan R, Borad M, et al. SPARC correlation with response to gemcitabine plus nab-paclitaxel in patients with advanced metastatic pancreatic cancer: A phase I/II study [abstract]. J Clin Oncol 2009;27(suppl_15s):Abstract 4525.

[7] Pelzer U, Kubica K, et al. A randomized trial in patients with gemcitiabine refractory pancreatic cancer. Final results of the CONKO 003 study. J Clin Oncol 26: 2008 (May 20 suppl) Abstract 4508.

[8] Xiong HQ, Varadhachary GR, Blais JC, et al. A phase II trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008; 113:2046-2052

[9] Neuhaus P, Riess H, et al. CONKO-001 Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer. J Clin Oncol26: 2008. (May 20 suppl) Abstract LBA 4504.

[10] Neoptolemos J, Buchler M, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-1081.

[11] Regine, WF Winter KA, Abrams RA et al. Fluorouracil vs. gemcitabine chemotherapy before and after fluorouracil-based chemoradiation after resection of pancreatic adenocarcinoma. A randomized controlled trial. JAMA. 2008; 299:1019-1026.

[12] Geissler M, Hofheinz R, Moehler MH, et al. Trastuzumab and capecitabine in patients with HER2-expressing metastatic pancreatic cancer: A multicenter phase II study of the German AIO pancreatic group (AIO PK-0204) J Clin Oncol 2010; 28 (suppl15s):Abstract 4070.

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Table 1

American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010)

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma *in situ**

T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension

T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension

T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

During the year 2010 in the United States, an estimated 43,140 people were diagnosed with pancreatic cancer, and approximately 36,800 people will die of pancreatic cancer.[1] This disease is the fourth most common cause of cancer-related death among U.S. men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).[1] Its peak incidence occurs in the seventh and eighth decades of life.[1] Although incidence is roughly equal in both sexes, African Americans appear to have a higher incidence of pancreatic cancer than white Americans.[2] Furthermore, the incidence and mortality rates of pancreatic cancer in the United States have remained approximately the same over the past 2 decades.[3] In these NCCN Pancreatic Adenocarcinoma guidelines, only tumors of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Neuroendocrine Tumors Guideline).

By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the Panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The Panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.[4-7] There is some evidence that increased consumption of red meat and dairy products is also associated with an elevation in pancreatic cancer risk,[8] although other studies have failed to identify dietary risk factors for the disease.[9] An increased body mass index is associated with increased risk of pancreatic cancer,[9-11] as are occupational exposure to chemicals such as beta-naphthylamine and benzidine[12] and heavy alcohol consumption.[4]

The relationship among diabetes mellitus, alcohol intake, and chronic pancreatitis with adenocarcinoma of the pancreas has been a topic of considerable debate. Numerous studies have shown an association between new-onset diabetes and the development of pancreatic cancer.[13-15] However, certain risk factors such as obesity and the use of diabetic medications can impact insulin resistance and blood glucose levels, thereby confounding these analyses.[16, 17] Chronic pancreatitis has also been identified as a risk factor for pancreatic

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cancer,[18, 19] and a more recent study demonstrated a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.[20] Nevertheless, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

True familial pancreatic cancer is rare; however, a genetic predisposition may be present in up to 5%-10% of patients,[21-23] and familial excess of pancreatic cancer is associated with high risk.[6, 23] For example, a germline mutation of the *CDKN2A* (p16) gene has been reported in families with pancreatic cancer and melanoma.[24, 25] An excess of pancreatic cancer is also seen in families harboring *BRCA2* (breast cancer susceptibility gene-2) mutations,[26, 27] and particular mutations in the *PALB2* gene have recently been identified as possibly increasing pancreatic cancer susceptibility.[28] Asymptomatic individuals at high risk for pancreatic cancer (ie, those with first-degree relatives with pancreatic cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project.[29] Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients suggesting that EUS may have a promising role in screening high-risk patients.[29] The diagnostic yield of pancreatic cancer screening with EUS or MRI in asymptomatic individuals at high risk of familial disease has also been investigated in 2 more recent studies, although the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are presently unclear.[30, 31]

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for over 90% of pancreatic malignancies. The presenting symptoms of this disease can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer.[32] Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss. All of the NCCN institutions represented on the Pancreatic Adenocarcinoma Panel agree that all patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should undergo initial evaluation by dynamic-phase helical or spiral CT performed according to a defined pancreas protocol.[33, 34] Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with reference to appropriate radiographic studies to evaluate the extent of disease.

Imaging Evaluations

CT is the most widely available and best-validated imaging modality for diagnosing and staging patients with pancreatic cancer.[35, 36] A pancreas CT protocol involves triphasic (ie, arterial phase, late arterial phase, and venous phase) cross-sectional imaging with thin slices using multidetector CT.[35, 37, 38] A rationale for triphasic CT is that the difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ.

In addition to providing a diagnosis of pancreatic cancer, CT is the modality of choice to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. Unlike many other cancers, CT imaging is the primary means

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through which the stage of pancreatic cancer is determined. The triphasic CT protocol allows for selective visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], and peripancreatic arteries) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, and portal vein), thereby providing an assessment of vascular invasion by the tumor. Software allowing for 3-D reconstruction of CT data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and the surrounding blood vessels and organs, although further development of this technology may be needed before it is routinely integrated into clinical practice.[39]

Studies have shown that 70%-85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.[36, 37, 39-42] The criteria for defining resectable disease by CT favor specificity over sensitivity to avoid denying surgery to patients with a potentially resectable tumor.[35] Furthermore, the sensitivity of CT for small hepatic and peritoneal metastases is limited.

In cases where CT is not possible or contraindicated (eg, contrast allergy), magnetic resonance imaging (MRI) with contrast can be used to diagnose and stage pancreatic cancer,[43] although MRI has not been shown to perform better than CT in this setting. MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for detecting the presence of extra-pancreatic disease in high-risk patients.[43]

NCCN institutions vary in the use of additional staging technologies, such as endoscopic ultrasound (EUS). The role of EUS in staging is felt to be complementary to CT, providing additional information for patients whose CT scans show no lesion or who have questionable involvement of blood vessels or lymph nodes.[38] Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise. The utility of PET/CT for upstaging patients with pancreatic cancer has also been evaluated. In a retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detection of metastatic disease when compared with the standard CT protocol or PET/CT alone.[44] The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT were 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established. PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. Non-contrast chest CT or chest X-ray (CXR) is recommended as part of the preoperative workup of patients without evidence of abdominal metastases to evaluate for the presence of pulmonary metastases.[45]

As previously mentioned, EUS may provide useful staging information in pancreatic cancer, particularly through assessment of certain types of vascular invasion.[46, 47] EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS may have a role in better characterizing cystic pancreatic lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be done with EUS (eg, celiac block, removal of ascites). It is the consensus of the Panel that whereas the accuracy of EUS in assessing involvement of certain veins (eg, portal vein) is high, this technique is less accurate in imaging tumor invasion of the SMA.[47, 48]

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Patients with a mass in the pancreas and evidence of metastatic disease should under biopsy confirmation, preferably at the metastatic site, before undergoing treatment.

Patients without a mass in the pancreas on cross-sectional imaging and without evidence of metastatic disease should undergo additional imaging with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP), as clinically indicated. It can be difficult to discriminate between benign and malignant strictures or stenosis; however, severe stenosis and marked proximal dilatation more often indicate malignancy.[49] EUS is usually the preferred approach, with ERCP reserved for patients requiring biliary decompression. Stent placement at the time of ERCP can be used to palliate biliary obstruction when surgery is not elected, or if surgery must be delayed. MRI/magnetic resonance cholangiopancreatography (MRCP) is considered to be equivalent to EUS/ERCP in this setting. Liver function tests and chest imaging are also recommended. If studies are consistent with pancreatic cancer, then multidisciplinary consultation is recommended.

Restaging with high quality abdominal and chest imaging is also recommended following surgery of resectable disease before initiation of adjuvant therapy. It should also be performed after administration of each treatment modality when systemic chemotherapy is followed by chemoradiation in the adjuvant setting. In addition, such restaging with abdominal (pancreas protocol), pelvic, and chest imaging is also recommended following administration of neoadjuvant therapy and prior to surgical resection for patients with borderline resectable disease.

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of metastatic tumor on the liver that may be missed even with the use of a pancreatic CT protocol.[50, 51] The yield of laparoscopy is dependent on the quality of preoperative imaging and the likelihood of metastatic disease. A key goal is to avoid unnecessary laparotomy, although routine use of staging laparoscopy is controversial. The Panel does not consider staging laparoscopy to be a substitute for poor quality preoperative imaging.

Some recent evidence provides support for a selective approach to staging laparoscopy (ie, it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).[52] For example, preoperative serum CA 19-9 levels >100 U/mL (see discussion on Tumor-Associated Antigens, below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.[53] In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.[54] Characteristics associated with an increased laparoscopic yield of unresectable disease include the location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out sub-radiologic metastases (especially for body and tail lesions) is used routinely in some NCCN institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk for disseminated disease (eg, borderline resectable disease; markedly elevated CA 19-9; large primary tumors). The value of a staging laparoscopy in patients with resectable or borderline resectable disease was debated by the Panel, and it is included as a category 2A recommendation for patients staged with

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resectable pancreatic cancer considered to be at increased risk of disseminated disease, and as a category 2B recommendation for patients with borderline resectable disease prior to and following administration of neoadjuvant therapy since it is not uniformly done at all NCCN institutions. The Panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.[55]

Tumor-Associated Antigens

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, cancer antigen (CA) 125, and carbohydrate antigen (CA) 19-9. A sialylated Lewis a blood group antigen, CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease, as well as in many malignancies; thus, it is not tumor specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas (see Differential Diagnoses, below).[56] CA 19-9 may be undetectable in Lewis antigen-negative individuals.[57] Furthermore, CA 19-9 may be falsely positive in cases of benign biliary obstruction,[58, 59] and thus does not represent an appropriate baseline. Preoperative measurement of CA19-9 levels should therefore be performed after biliary decompression is complete and bilirubin is normal.

A low postoperative serum CA 19-9 level and a decrease in serial CA 19-9 levels following surgery have been found to correlate with survival for patients undergoing resection for pancreatic cancer.[60-63] In a prospective study of patients undergoing surgery with curative intent, median survival for the group of patients with post-resectional CA 19-9 levels of <180 U/mL was significantly higher compared with the group with higher levels of CA 19-9 following surgery (hazard ratio=3.53; P<0.0001).[60] Similarly, in a prospective study of patients with advanced pancreatic cancer, a dichotomized pretreatment CA 19-9 serum level was shown to be an independent prognostic factor for survival.[64] However, data are conflicting regarding the predictive significance of CA 19-9 response following chemotherapy in patients with advanced disease.[64-68] The Panel recommends measurement of serum CA 19-9 level following surgery prior to administration of adjuvant therapy. Of note, a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

Differential Diagnoses

Chronic pancreatitis and other benign conditions (eg, autoimmune pancreatitis) are possible differential diagnoses of patients suspected of having pancreatic cancer.[69-73]

Autoimmune pancreatitis, a rare form of chronic pancreatitis also known as lymphoplasmacytic sclerosing pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.[71, 74-76] A benign disease that can be effectively treated with corticosteroids, autoimmune pancreatitis must be distinguished from pancreatic cancer to avoid unnecessary surgery and prevent delay in the initiation of appropriate treatment.

The finding of increased serum immunoglobulin (Ig) G levels is supportive of a diagnosis of autoimmune pancreatitis, although an elevated level of serum IgG4 specifically is the most sensitive and specific laboratory indicator.[77] The classic appearance of the pancreas

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on abdominal CT in patients with diffuse pancreatic involvement is a sausage-shaped enlargement of the organ with a capsule-like peripheral rim surrounding the pancreas, although focal enlargement of the pancreas is observed in some cases.[75] Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis. Jaundiced patients with locally advanced disease should be reviewed for autoimmune pancreatitis, and IgG4 levels should be assessed.

Autoimmune pancreatitis can also be negative for IgG4 and can present with a large pancreatic mass, thus closely mimicking pancreatic adenocarcinoma. For patients with borderline resectable disease and 2 or 3 negative biopsies, a second-opinion is recommended. Alternative diagnoses should be considered, especially autoimmune pancreatitis, and a short course of steroid treatment may be an appropriate first approach. If no response is seen, the patient should undergo laparotomy for removal of the mass.

Pathology

Biopsy

Although a histologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced and unresectable pancreatic cancer or metastatic disease. A histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either endoscopic ultrasonography (EUS) guidance (preferred) or CT. EUS-directed FNA biopsy is preferable to CT-guided FNA in patients with resectable disease because of the much lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach.[78] In rare cases when an EUS-directed biopsy cannot be obtained from a borderline resectable patients, there are other acceptable methods of biopsy. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy[79]; a percutaneous approach[78] or laparoscopic biopsy[80] are other alternatives.

A negative biopsy should be confirmed by at least 1 repeat EUS biopsy. However, in some cases (eg, borderline resectable disease), treatment (ie, laparotomy) may still be recommended for these patients following 2 negative biopsies, especially if there is clinical and radiographic evidence strongly suggestive of pancreatic cancer,[25] although alternative diagnoses should also be considered (see Differential Diagnoses, above). In situations where clinical and imaging findings indicate that locally advanced disease is present, laparoscopy with biopsy can be considered if repeat FNA biopsy is negative. In patients without obstructive jaundice at initial presentation, EUS-FNA is highly accurate and reliable for determining malignancy; in patients with obstructive jaundice and biliary stricture, EUS-FNA is less accurate.[30] It can be difficult to discriminate between non-neoplastic and neoplastic cystic pancreatic lesions radiographically; however, EUS-guided FNA of cystic pancreatic lesions can be useful in the differential diagnosis of these lesions.[81] Pancreatic ductal brushings or biopsies can also be obtained at the time of ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma.

It is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable patients and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The NCCN Pancreatic Adenocarcinoma Panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

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Specimen orientation, pathologic analysis, and reporting

A pathologic evaluation of the surgical specimen involves both the pathologist and the surgeon.[82, 83] For example, for an evaluation of resection margin status, surgical margins need to be inked appropriately and the surgeon must specify whether or not a complete resection was performed in order for the pathologist to be able to distinguish between an R1 and an R2 resection.[84] Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Pancreatic Adenocarcinoma Panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP).[85]

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The CAP protocols comply with the COC requirements, and the latest revisions to the CAP Pancreatic (Exocrine) protocol were issued in January, 2005. Therefore, pathologists should familiarize themselves with these documents.[85]

The American Joint Committee on Cancer (AJCC) has developed staging criteria for adenocarcinoma of the pancreas.[86] Recent validation of concordance between AJCC stage and overall survival has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma included in the National Cancer Database (NCDB).[87] Although the TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC Cancer Staging Manual have taken into account the fact that tumors of the pancreas are evaluated preoperatively by CT to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor.[86, 87] For clinical purposes, most NCCN centers use a clinical staging system based mainly on results of presurgical imaging studies. Following staging by CT (and EUS/ERCP in some cases), preoperative CA 19-9 testing, and evaluation for the presence of jaundice, disease is classified as: (1) resectable; (2) borderline resectable (ie, tumors which are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable); (3) locally advanced unresectable (ie, tumors which are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); or (4) disseminated (see section on Criteria for Resection, below), and this system is used throughout the guidelines.

Although not part of the TNM staging system criteria, it is recommended by the AJCC that the surgeon score the completeness of the resection as (1) R0 for complete tumor resection with all margins negative; (2) R1 for incomplete tumor resection with microscopic involvement of a margin; and (3) R2 for incomplete tumor resection with gross residual tumor that was not resected.[86] There is wide variation in the reported R1 rates of pancreatoduodenectomy specimens,[83] because there is no uniform definition of microscopic margin involvement. This is especially true for the vascular / uncinate / retroperitoneal / posterior margin, which seems to be an area of variability among pathologists. Although several methods of specimen orientation and pathologic analysis have been described, there is no uniform consensus on a standardized protocol for the gross pathological examination of these specimens (ie, en face margins or radial margins).[82, 83, 88]

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Surgical Management

Criteria for Resection

Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, more than 80% of patients present with disease that cannot be cured with surgical resection.[89] Early concerns about high mortality associated with various pancreatic resection procedures[90] have now been lessened by studies demonstrating an acceptably low (< 5%) mortality in experienced centers (see Effect of Clinical Volume, below).[91] Even under the most optimal conditions, however, the median survival of resected patients ranges from 15 to 19 months, and the actuarial 5-year survival rate is approximately 20%.[92] Negative margin status (ie, R0 resection), tumor DNA content, tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.[93-95] With respect to margin status, there is evidence for the converse statement -- the survival benefits of an R1 resection may be comparable to definitive chemoradiation without surgery.[96]

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions appear to differ in their approaches to patients with locoregional (pancreas and peripancreatic lymph node) disease involvement. Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group has developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection.[35] Using these criteria, tumors are classified as resectable; borderline resectable; or unresectable (eg, locally advanced or metastatic disease).

The absence of evidence of peritoneal or hepatic metastases following a thorough radiographic assessment is a criterion for both resectable and borderline resectable disease. Radiographic findings of tumor abutment on the portal vein or SMV with venous deformity, and limited encasement of the mesenteric vein and portal vein (ie, short segment occlusion with suitable vessel for anastomosis above and below) represent the extent of venous involvement that would categorize a tumor as borderline resectable. Radiographic findings suggesting borderline arterial involvement include encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the SMA involving ≤180 degrees of the artery circumference. Patients with resectable disease have clear fat planes around the celiac axis, hepatic artery, and SMA and no radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.[35]

An analysis of 9,559 patients diagnosed with early-stage disease from 1995-2004 revealed that a high percentage (71.4%) of these patients with potentially resectable disease were not treated surgically and that patients were less likely to receive surgery at a low-volume center.[97] The likelihood of attaining negative surgical margins (ie, R0 resection) is a key criterion for consideration when determining whether a patient is a potential candidate for resection.[98, 99] In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete (R1 or R2) resection. Unresectable tumors include those with distant metastases, nodal metastasis beyond the field of resection, SMA or celiac encasement greater than 180 degrees, unreconstructable SMV/portal occlusion, or aortic invasion or encasement.

The consensus of the Panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability

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of obtaining R0 resection margins. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection. Furthermore, the Panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Age of the patient, comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Senior Adult Oncology guidelines for further discussion of the treatment of older patients.

Primary Surgery for Pancreatic Cancer

The nature and the extent of the surgery for resectable tumors depend on the location and size of the tumor. If the tumor is found to be unresectable during surgery, the Panel recommends biopsy confirmation of adenocarcinoma at this time, if a biopsy was not performed previously.

Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. Patients with tumors in the head of the pancreas, who usually present because of jaundice, are treated with open or laparoscopic pancreatoduodenectomy.[100] A review of the biomedical literature indicates that there are no universally accepted surgical techniques for performing this procedure. This complex procedure has several controversial issues associated with it that are discussed in more detail in the following sections. Surgery should be performed only by surgeons capable of managing tumor-vessel involvement.

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis as well as to potentially make surgery less morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.[101-103] Stenting of the biliary system can improve symptoms and liver function, but it is not clear whether these changes can decrease the mortality rate of the Whipple procedure. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.[104-110] In 1999, a retrospective study from Memorial Sloan-Kettering Cancer Center examined 240 consecutive pancreaticoduodenectomies where 53% of patients underwent preoperative biliary decompression.[111] This study found a statistical relationship between the use of preoperative drainage (irrespective of the method used) and increased postoperative complications, including death, compared to patients who went straight to surgery.

In contrast, the University of Texas MD Anderson Cancer Center reported on their experience with more than 300 patients of whom 57% had preoperative biliary drainage as part of a neoadjuvant chemoradiation program.[112] It was found that wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. In addition, a recent multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed a nearly 2-fold increase in the rate of serious complications in the stented group (74% vs. 39%; relative risk in the surgery alone group = 0.54; 95% CI, 0.41-0.71; P<0.001), although no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.[113] Based on these reports, most groups who perform resection first advocate selective use of decompression only in patients who are

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symptomatic or septic or in whom surgical resection is significantly delayed.

Patients who present with jaundice and potentially resectable disease require placement of a temporary stent along with antibiotic coverage if symptoms of cholangitis or fever are present. Endoscopic placement of a temporary stent and normalization of bilirubin levels is recommended prior to CA 19-9 testing during the initial workup of patients with obstructed jaundice characterized by symptoms of cholangitis or fever when there is no evidence of metastatic disease. Most Panel members endorse use of a plastic stent in this case, since such a patient may undergo surgery shortly thereafter and not require the longer patency time of a metal stent. If metal stents are used, short stents are preferred by some Panel members because they may be less likely to interfere with the subsequent resection.

For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary before initiation of therapy and appears to be well tolerated with minimal increase in perioperative morbidity. Placement of a stent is thus required prior to administration of neoadjuvant therapy for patients with jaundice and borderline resectable disease that is biopsy-positive.[114-116]

The Panel pointed out that stents are an evolving technology. The choice of stents includes plastic and metal; fully covered, partially covered, or uncovered; rigid or self-expanding (also see the discussion on stents in Biliary Obstruction, below). While any stent can become occluded, several groups have reported better patency with metal stents.[114-116] Metal stents are generally viewed as more permanent than plastic stents. Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,[117] but the reported differences between covered and uncovered stents are not dramatic.[117, 118]

Furthermore, migration is more of an issue with covered stents.[118] This issue has lead to the introduction of partially covered stents [119], though these stents may still migrate in a substantial number of patients.[120, 121] Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.[119] Several Panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).[119] The Panel could not reach a consensus on which type of stent is best used in each preoperative circumstance, since level-1 evidence is lacking. A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov NCT01191814).

Pylorus Preservation

Reconstruction options for the stomach after pancreatoduodenectomy center on preservation of the pylorus. Traverso and Longmire[122] reported the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the benefits have been inconsistent to date. Yeo et al[123] reported no adverse affects of pylorus preservation; however, van Berge Henegouwen et al[124] reported longer nasogastric drainage times. In several randomized and nonrandomized studies,[125-129] the pylorus-preserving procedure seemed to be associated with shorter surgical duration. No consistent data suggest that pylorus preservation leads to a better quality of life or nutritional status in patients after resection. Thus, pylorus-preserving pancreatoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

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Pancreatic Anastomosis

Efforts in this area have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreatoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.[130] Furthermore, surgeons have examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.[131, 132] Results of a prospective trial show that pancreatic fistula can be almost entirely avoided by a technique that combines placement/tying of sutures under magnification with meticulous attention to blood supply.[133] Stents used in the 1930s and 1940s continue to be used today, but data suggests that they do not decrease leak rates.[134] Pancreatic fistula rates are similar among studies (ranging in most studies from 6% to 16%),[123, 152, 135] although the exact way to define a pancreatic leak in terms of volume and duration of drainage remains controversial.[136]

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in 2 prospective, randomized, double-blind, placebo-controlled studies (at the University of Texas MD Anderson Cancer Center and Johns Hopkins Hospital).[137, 138] Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.[139]

Portal Vein Resection

Vascular invasion has been a conventional contraindication to pancreatic resection. Early attempts at resection and reconstruction of the SMA and SMV in the 1970s were associated with poor results in a few patients who underwent "regional" pancreatectomy.[140] Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, in the 1990s, there was renewed interest in vein resection for complete resections. The group from the University of Texas MD Anderson Cancer Center has championed this approach, arguing that because overall mortality from pancreatoduodenectomy has decreased, vein resection and reconstruction allows for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection.[141] Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.[142] Although compelling, this approach has not been universally accepted. During the 1990s, several studies reported operative mortality of 0% to 16.5%, 3-year Kaplan-Meier survival of 12% to 23%, and median survival of 5 to 14 months in patients receiving vein resection.[143-146] A recent study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection (n = 141) had a median survival of approximately 2 years that did not differ from those having standard pancreatoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not receive surgical treatment.[147] Nevertheless, a few groups have recommended caution and only use vein resection for selected patients.

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Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreatoduodenectomy has been explored. In the 1970s and 1980s, pathology and autopsy studies demonstrated a high incidence of nodal metastasis (sometimes as high as 80%), leading some groups to propose a more aggressive lymphadenectomy in an attempt to regionally control disease.[148, 149] A standard lymphadenectomy in patients undergoing pancreatoduodenectomy entails removal of nodes at the duodenum and pancreas and on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreatoduodenal lymph nodes.[150] An extended lymphadenectomy is most commonly performed in the United States by removing not only the nodes removed in the standard procedure, but also the soft tissue in the retroperitoneum from the hilum of the right kidney to the left lateral border of the aorta on the right side, and from the portal vein to the origin of the inferior mesenteric artery on the left.[151]

Several prospective, randomized trials have addressed the role of lymphadenectomy in patients undergoing pancreatoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreatoduodenectomy with or without extended lymph node resection. Although the statistical power was low, this study did not support the concept that an extended lymphadenectomy was a good prognostic factor.[152] A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.[153] The group of patients who received the regional lymphadenectomy in addition to pancreatoduodenectomy had longer operation times, but overall median survival did not differ between the 2 groups at 1, 3, and 5 years.[153-155] Furthermore, a meta-analysis of randomized controlled trials comparing pancreatoduodenectomy with standard versus extended lymphadenectomy supports the conclusion that the extended procedure does not have any impact on survival.[156] In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.[157]

In summary, the information to date does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.[158] At this point in time, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter overall survival. One exception might be in the situation of an otherwise R0 resection with clinically positive adenopathy outside the standard field of dissection. Overall, outside of a clinical trial, a regional lymphadenectomy should not be considered as a routine part of the Whipple procedure, although consideration can be given to sampling of the aortocaval and common hepatic artery nodes, as those with positive nodes in these positions have inferior prognoses.[159, 160]

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large single institution experiences. Moreover, the concern was that if surgeons performed pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. In 1993, Edge and colleagues[161] assessed 223 pancreaticoduodenectomies from 26 U.S. hospitals, but they found that caseload did not correlate with mortality. However, surgeons who performed fewer than 4 resections over the 2-year period of the study had more complications. The group

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from Memorial Sloan-Kettering Cancer Center examined the issue in 1995 and found that in a cohort of 1,972 patients, high-volume centers in New York State had significantly less mortality than low-volume centers (4% versus 12.3%).[162] High volume was defined as more than 50 cases per year, and this relationship correlated in a regression analysis. Of note, 75% of the cases in New York State were performed in low-volume centers. Several other studies have assessed regional outcomes with pancreatoduodenectomy from U.S. hospitals.[163-167] These studies have reported decreased mortality, hospital length of stay, and overall cost at higher volume centers (or with surgeons who perform the resections frequently) when compared with low-volume centers. Interestingly, this effect was also seen in reports from Canada and the Netherlands.[168-170]

The definitions of high and low volume varied among all these studies. However, a striking difference is seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0-1 procedure/year) and in low-volume (1-2 procedures/year) hospitals are compared with rates in higher-volume hospitals (> 5 procedures/year).[171] In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, versus 4%; P < 0.001). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6-16 and >16 procedures per year were classified as "high" and "very-high" volume centers.[172] In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very-low-volume (16.3%) and high-volume (3.8%) centers is seen for pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can specifically have on pancreatic cancer outcomes.

A study involving 301,033 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB) evaluated the treatment patterns of 1,667 hospitals over a 19-year period.[173] During that time, the pancreatectomy rate as well as the use of multimodality adjuvant therapy (ie, surgery plus chemoradiation) for patients with stage I and II disease increased significantly (pancreatectomy rate increased from 36.9% to 49.3%, P<0.001; use of multimodality therapy increased from 26.8% to 38.7%, P<0.001). Further, patients were more likely to receive these treatments at academic institutions, particularly those considered to be high-volume hospitals.[173]

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (>15-20) of pancreatic resections annually.

Adjuvant Therapy

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that

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175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.[174] Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high dose (500 mg/m^2) or low dose (20 mg/m^2) leucovorin.[175] Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200 mg/m^2) or low (20 mg/m^2) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.[176] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Postoperative Therapy

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold by postoperative chemoradiation.[177, 178] In this study, patients were randomly assigned to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) after resection. A standard split course of 4,000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.[177]

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial (40891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery; however, they found the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.[179] At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to progression-free survival or overall survival for the subset of patients with pancreatic cancer.[180]

Provocative but controversial results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial have been reported by Neoptolemos and colleagues.[181] Results of this study suggested that 5-FU/leucovorin is superior to observation and that chemoradiation is unnecessary and perhaps harmful. However, the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.[182-184] Therefore, these latest results do not eliminate 5-FU-based chemoradiation as an acceptable choice in the adjuvant setting.

In the large phase III CONKO-001 trial in which 368 patients without prior chemotherapy or radiation therapy were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection, an intention-to-treat (ITT) analysis of the data showed that the primary endpoint of increased disease-free survival was met (median DFS 13.4 months vs. 6.9 months; P<0.001, log rank).[185] Final results from this study showed median overall survival to be improved significantly for patients in the gemcitabine arm (22.8 months vs. 20.2 months; P=0.005).[186] An absolute survival difference of 12.0% was observed between the two groups at 5 years (21% vs. 9%).[186]

The Radiation Therapy Oncology Group study RTOG 97-04 is a phase III study that evaluated post-operative adjuvant treatment of resected

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pancreatic adenocarcinoma using either gemcitabine or fluorouracil for 3 weeks before and 12 weeks after 5-FU-based chemoradiation for both groups.[187] This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.[188] Results of this study showed that, for patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non-statistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%; P=0.09); this benefit became more pronounced on multivariate analysis (hazard ratio = 0.80; 95% CI, 0.63-1.00; P=.05).

Whereas results from the RTOG trial suggest a possible small advantage for adjuvant therapy with gemcitabine over infusional 5-FU, results from the prospective randomized trial of bolus 5-FU/leucovorin versus gemcitabine following surgery (ESPAC-3) showed no difference in overall survival when the 2 groups were compared (median survival was 23.0 months and 23.6 months, respectively).[189]

Results of RTOG 97-04 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design, in timing of imaging, and in patient characteristics (eg, patients enrolled in CONKO-001 were more likely to be lymph node-negative and to have positive resection margins than those in RTOG 97-04, and CONKO-001 excluded patients with high postoperative CA19-9 or CEA levels[185]). However, it is interesting to note that median overall survival for patients in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 9704 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are remarkably similar.

Therefore, at this time, no definite standard has been established in the adjuvant treatment of pancreatic cancer. The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU based chemoradiation. Results of a recent randomized phase II trial suggest that gemcitabine-based chemoradiation may also be an effective adjuvant approach for patients with R0 resections.[190] Thus gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine or 5-FU/leucovorin[189] chemotherapy, as well as chemotherapy alone with gemcitabine (category 1) or 5-FU/leucovorin (category 1) are listed in the guidelines as options for adjuvant treatment. It was the consensus of the Panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over 5-FU/leucovorin for most patients due to its more favorable toxicity profile. In the adjuvant setting, capecitabine is also listed in the guidelines (category 2B). Capecitabine should only be used in this setting as a last choice in patients for whom other options are inappropriate or unacceptable. The Panel considered capecitabine a reasonable alternative to 5-FU/leucovorin in this setting.

Although the optimal combination and sequencing of adjuvant RT has yet to be defined, the NCCN Panel recommends that postoperative RT, when given, should be administered at a dose of 45 to 46 Gy (1.8-2.0 Gy/day) with high energy photons (>4 MV) to the tumor bed, surgical anastomoses, and adjacent lymph node regions, followed by an additional 5-15 Gy to the tumor bed while paying careful attention to dose to the small bowel.[191, 192] The Panel strongly recommends use of CT simulation and 3-D treatment planning (thin slices through the pancreas/bed and locoregional basin) with intravenous (assuming adequate kidney function) and oral contrast. Treatment volumes should be based on preoperative CT scans and surgical clips (when placed). Radiation is usually given in combination with continuous infusion 5-FU,

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capecitabine, or gemcitabine, and can be given before or after systemic chemotherapy in the adjuvant setting. While no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy, when patients have a margin-positive resection, upfront chemoradiation followed by systemic chemotherapy is an appropriate option.[187, 191, 193]

Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for patients who have adequately recovered from surgery; treatment should ideally be initiated within 4 to 8 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the Panel recommends restaging a patient with a CT scan following systemic chemotherapy, if it will precede chemoradiation.

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of pancreatic adenocarcinoma in the adjuvant setting with the aim of increasing radiation dose to the gross tumor/tumor bed while minimizing toxicity to surrounding tissues.[194] Results of a recent study demonstrated that IMRT resulted in reduced grade 3/4 toxicities when compared to patients who received a similar 5-FU-based regimen with 3-D conformal radiation in the RTOG 97-04 trial.[187, 195] Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% ($p = 0.024$) and of grade 3/4 diarrhea were 3% vs. 16% ($p = 0.017$),[195] suggesting that IMRT may be well tolerated and allow for higher radiation doses to the tumor.[195] There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Intraoperative radiation therapy (IORT) is sometimes used in resectable cases and may be best when resection may result is close or involved margins.[196] IORT is delivered with electron beam radiation (IOERT) or high dose rate brachytherapy (HDR-IORT). It is generally delivered in a single fraction of 15-20 Gy and in combination with adjuvant or neoadjuvant chemoradiation therapy. IORT can also be delivered in combination with external beam radiation therapy (EBRT, 10-20 Gy).

Preoperative (Neoadjuvant) Therapy

Novel contemporary approaches to adjuvant therapy have focused on preoperative (neoadjuvant) therapy for patients with borderline resectable disease with the goal of improving overall survival.[197, 198] The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation, the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie conversion of borderline resectable patients), the potential to select for surgery those patients with more stable disease or disease that is more responsive to therapy, and the treatment of micrometastases at an earlier stage.[36, 199-201]

Neoadjuvant therapy in resectable disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.[198, 199, 202-205] A retrospective review of the collective experience at the University of Texas MD Anderson Cancer Center suggested that the use of preoperative chemoradiation therapy in patients with resectable disease is advantageous.[202] The authors suggest that preoperative therapy gives a selection advantage, in that approximately 25% of patients who are restaged after therapy are found to have progressive disease and are therefore spared the morbidity of a surgical procedure

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that would not benefit them.[202] In this analysis of 132 consecutive patients, the University of Texas MD Anderson Cancer Center group reported that combined preoperative chemoradiation and pancreatoduodenectomy yielded a median survival of 21 months, and 32% of patients were alive without evidence of disease at a median follow-up of 14 months.[202]

Although most studies investigating the neoadjuvant experience in patients with pancreatic cancer are retrospective, several small phase II studies have been published. In a randomized phase II trial evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with resectable pancreatic cancer, more patients receiving combination therapy were able to undergo resection compared with those in the gemcitabine only arm.[205]

In a prospective trial, preoperative radiation with concurrent gemcitabine was administered to 86 patients with resectable disease, and patients were restaged 4 to 6 weeks following completion of neoadjuvant treatment.[210] Although all patients were able to complete neoadjuvant therapy, at the time of restaging, 73 (85%) patients were able to undergo surgery; the majority of the remaining patients were precluded from undergoing a pancreatoduodenectomy due to the presence of more advanced disease. Similar results were observed in another phase II trial involving preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation.[115] In this study, which enrolled 90 patients, 79 patients were able to complete neoadjuvant therapy and 52 patients underwent surgery. Again, the main reason patients were precluded from surgery was the finding of more advanced disease at restaging following completion of neoadjuvant therapy. A cross-study comparison of these results suggests that inclusion of preoperative chemotherapy prior to initiation of gemcitabine-based chemoradiation did not improve survival.[200] These results provide support for restaging patients with abdominal (pancreas protocol), pelvic, and chest imaging and diagnostic laparoscopy before committing them to laparotomy after neoadjuvant therapy.

Although evidence suggests that there may be a better chance of margin-negative resection with preoperative therapy,[211] results of randomized trials addressing this issue have yet to be reported. A randomized phase II trial comparing preoperative chemoradiation to postoperative chemotherapy in patients with resectable pancreatic cancer is currently recruiting patients (Clinicaltrials.gov NCT00335543). At this time, the Panel does not recommend neoadjuvant therapy for resectable patients, except on a clinical trial.

Neoadjuvant therapy in borderline resectable disease

The use of neoadjuvant therapy in the setting of borderline resectable disease is a highly debated topic. Although there is no high-level evidence supporting its use, many NCCN centers prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease, and the Panel recommends neoadjuvant therapy as an option (category 2B) to upfront resection following clinical staging of disease as borderline resectable (see Criteria for Resection, above, for definition of borderline resectable disease). Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated. A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.[212] A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease terminated early due to poor accrual, but 5 of 21 patients (24%) were resected.[213] In 2 recently published retrospective reviews, 31-35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections.[214, 215]

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It is important to note that no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease compared to the approach of taking these patients to surgery without initial therapy and that the best regimens to use in the borderline neoadjuvant setting are unknown. A phase II clinical trial is currently underway (clinicaltrials.gov NCT01268384) to determine the R0 resection rate following neoadjuvant chemotherapy with fixed dose rate (FDR) gemcitabine and capecitabine in patients with borderline resectable or unresectable locally advanced disease. Additional randomized trials are needed.

EUS-directed biopsy is the preferred method of obtaining histological confirmation of disease in these patients, and such confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed in cases where the initial biopsy results are negative. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, is also recommended (category 2B) before and after neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.[114-118]

Although there is insufficient evidence to recommend specific neoadjuvant regimens, most neoadjuvant regimens incorporate RT, and chemoradiation is preferred in this setting. Neoadjuvant therapy regimens are often similar to those used to treat locally advanced disease (see section on Chemoradiation for Locally Advanced Disease, below) and include upfront continuous infusion 5-FU- or capecitabine-based chemoradiation,[201, 218] upfront gemcitabine-based chemoradiation,[219] or 2 to 4 cycles of induction chemotherapy followed by 5-FU- or gemcitabine-based chemoradiation.[115] Options for radiation include 45-54 Gy in 1.8-2.5 Gy fractions or 36 Gy in 2.4 Gy fractions.[208] Abdominal (pancreas protocol), pelvic, and chest imaging should be repeated following neoadjuvant therapy, and surgical resection should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery should be performed 6 to 8 weeks following therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult.

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.[217] The role of chemoradiation was initially defined in a trial conducted by GITSG.[178] In this study, the combination of bolus 5-FU and split-course radiation (total dose, 4,000 cGy) was compared with radiation alone or with 6,000 cGy combined with 5-FU. A nearly 2-fold increase in median survival (42.2 versus 22.9 weeks) was observed with the regimen of bolus 5-FU and 4,000 cGy compared with radiation alone. Subsequent generations of studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation.

Gemcitabine has also been used as a radiation sensitizer.[115, 210, 219-220] There is evidence to suggest that concurrent gemcitabine and radiation can yield similar outcomes when compared with 5-FU-based chemoradiation,[219, 221] although no randomized trials have directly assessed whether any of these modifications are superior to the original trial results reported by GITSG. Results from a phase II study of patients with locally advanced pancreatic adenocarcinoma from the North Central Cancer Treatment Group (NCCTG) evaluated the safety and efficacy of RT in combination with gemcitabine and cisplatin. Although this regimen had acceptable toxicity, no survival benefit over other regimens was observed.[222]

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Some studies have addressed the use of chemoradiation with or without chemotherapy to convert selected patients with locally unresectable disease to a resectable status.[197-199, 201, 223] In some instances, patients are converted to what appears to be a resectable status by radiographic characterization after completing treatment. Following resection, these patients have similar survival rates as those initially determined to be resectable.[224]

Following biopsy confirmation of adenocarcinoma and treatment for jaundice if present (a permanent metal stent is preferred in this situation), the Panel recommends chemoradiation for patients with locally advanced unresectable disease and good performance status and with no metastases. For primary definitive chemoradiation therapy, the NCCN recommends one of two options: 1) 45-54 Gy in 1.8-2.5 Gy fractions for 5-FU-based chemoradiation regimens or 2) 36 Gy in 2.4 Gy fractions for gemcitabine-based chemoradiation regimens.[219] Use of CT simulation and 3-D treatment planning is strongly encouraged. Treatment volumes should be based on CT scans and surgical clips/fiducials (when placed). Radiation is given with concurrent gemcitabine,[219, 225, 226] capecitabine, or continuous infusion 5-FU.[221] Currently, upfront chemoradiation[225, 226] or, preferably, systemic chemotherapy followed by consolidation chemoradiation therapy[227-229] are recommended options for patients with unresectable disease and good performance status. When induction chemotherapy is administered, laparoscopy is sometimes performed to evaluate distant disease before chemoradiation therapy is initiated. If patients develop metastatic disease during systemic chemotherapy, chemoradiation is not given, as patients with metastatic disease are not candidates for chemoradiation unless required for palliation. Furthermore, patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. When systemic chemotherapy precedes administration of chemoradiation, the Panel also recommends restaging with a CT scan prior to radiation therapy. Patients with a significant response to chemoradiation may be considered for surgical resection, although there is no definitive evidence at this time to support this intervention. Following chemoradiation therapy, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.

The choice between upfront chemoradiation versus induction chemotherapy followed by consolidation chemoradiation is based on disease characteristics. If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation therapy. Three phase II trials have assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[225, 230-232]

Another option is to start with 2 to 6 cycles of chemotherapy in cases where 1) it is highly unlikely that the patient will become resectable (ie, complete encasement of superior mesenteric/celiac arteries), 2) there are suspicious metastases, or 3) the patient may not be able to tolerate chemoradiation. If there is no evidence of metastatic progression, definitive chemoradiation can follow. This treatment approach, employing an initial course of chemotherapy, may facilitate systemic disease control while simultaneously helping to uncover whether the disease is rapidly progressive. For example, a retrospective analysis of outcome from the GERCOR studies indicated that first-line treatment with chemotherapy may be a useful strategy for selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.[227] This approach is currently being evaluated in an ongoing phase III trial (GERCOR-LAP-07-D07-1; ClinicalTrials.gov NCT00634725), comparing gemcitabine with or

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without erlotinib followed by the same chemotherapy or capecitabine-based chemoradiation with or without erlotinib.

Intensity-modulated radiotherapy (IMRT) is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.[233-235] A retrospective treatment planning study evaluated the dose escalation that might have been possible in 15 patients with locally advanced unresectable pancreatic adenocarcinoma had IMRT been used instead of 3-D conformal planning.[235] While the authors concluded that the IMRT plans would allow for significant increase in target volume dose with substantial dose reductions to local organs at risk,[235] there is no clear consensus on the appropriate maximum dose of radiation when IMRT is used.

Stereotactic body radiotherapy (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue. Retrospective analysis of 77 patients with unresectable disease demonstrates that while SBRT gives effective local control, it lends no improvement to overall survival and is associated with significant toxicities.[236] There is also no standard total dose or dose per fraction established for SBRT, and the Panel currently recommends that SBRT only be utilized as part of a clinical trial.[236]

Chemotherapy without radiation therapy is also an option for patients with locally advanced pancreatic cancer, especially for patients with poor performance status (see Chemotherapy for Locally Advanced or Metastatic Disease, below, for a discussion of the different chemotherapy options). Results of 2 early randomized trials comparing chemoradiation to chemotherapy in locally advanced disease were contradictory.[237, 238] A phase III randomized trial (ECOG-4201) that assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median overall survival was significantly longer in the chemoradiation therapy arm of the study (11.0 months vs. 9.2 months; P=0.044).[238] The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[239] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs. 32%; HR = 0.54, 0.31–0.96; P = 0.006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this particular chemoradiation regimen.

It is important to reiterate that biopsy confirmation of pancreatic adenocarcinoma be obtained before treatment. At least 2 or 3 negative biopsies should be obtained before entertaining alternative diagnoses (see Differential Diagnoses, above). A second opinion should also be obtained in such a case. Occasionally, other cancer types are confirmed, and the patient should be treated according to the appropriate NCCN Guideline.

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Chemotherapy for Locally Advanced or Metastatic Disease

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. Please see the discussion in the section on Adjuvant Therapy, above, for a detailed discussion.

General Principles

Systemic therapy is used in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease. The primary goals of treatment for advanced pancreatic cancer are palliation and improved survival. Although some effect on survival may be achieved, these benefits are usually limited to patients with adequate performance status (ECOG 0-1, with good pain management, patent biliary stent, and adequate nutritional intake). Patients who present with very poor performance status may benefit from the administration of gemcitabine (category 1 recommendation), but comfort-directed measures are always paramount (see NCCN Supportive Care Guidelines). Before initiating cytotoxic therapy, an open dialogue regarding the goals of treatment should take place, and adjunctive strategies should be discussed including nonsurgical bypass and celiac block for pain (see Palliation of Locally Advanced and Metastatic Disease, below, and Principles of Palliation and Supportive Care in the guidelines). Of note, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, decreased oral intake, and constipation.

FOLFIRINOX

In 2003, a French group reported the results of an open phase I study to assess the feasibility of a combination therapy consisting of 5-FU/LV plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors.[240] Their study included 2 patients with pancreatic cancer and showed anti-tumor activity. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates.[241] A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.[242]

Results from the recently presented preplanned interim analysis of the randomized phase III PRODIGE 4/ACCORD 11 trial evaluating the regimen of FOLFIRINOX vs. gemcitabine alone in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free survival (6.4 months vs. 3.4 months; P<0.0001) and median overall survival (10.5 months vs. 6.9 months; P<0.001), in favor of the group receiving FOLFIRINOX.[243] Because of these strong results, the Panel has added FOLFIRINOX as a category 1 recommendation for first-line treatment of good performance status patients with either metastatic or locally advanced unresectable disease.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. The grade 3/4 toxicity rates were 12.3% for diarrhea, 15.6% for nausea, 17.2% for vomiting, 24% for fatigue, 47.9%

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for neutropenia, and 5.7% for febrile neutropenia.[243] Despite the high levels of toxicity, no toxic deaths have been reported.[241-243]

Role of Gemcitabine

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.[244] The NCCN Panel recommends gemcitabine monotherapy (1,000 mg/m^2 over 30 min, weekly for 3 weeks every 28 days) as one option for front-line therapy for patients with metastatic disease (category 1).[244] The NCCN Panel also recommends gemcitabine monotherapy as an option for patients with unresectable, locoregional disease and a good performance status (category 2A). For patients who derive clinical benefit from initial gemcitabine treatment in the setting of locally advanced disease, without developing distant disease, subsequent chemoradiation may enhance local control. Following disease progression, fluorinated pyrimidine-based therapy is an option for some patients (see Second-Line Therapy, below).

Because the approved indications for gemcitabine include the relief of symptoms, the Panel recommends gemcitabine as a reasonable option for symptomatic patients with metastatic or locally advanced unresectable disease with poor performance status (category 1). An alternative option for these patients is best supportive care.

Fixed-Dose Rate Gemcitabine

Recent studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed-dose rate ([FDR] 350 mg/m^2/minute) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.[245] In a randomized phase II trial, the infusion of gemcitabine at a FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.[246] In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine vs. standard gemcitabine (6.2 months vs. 4.9 months; P=0.04), although this outcome did not satisfy the protocol-specified criteria for superiority.[247] When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m^2/minute) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX; [gemcitabine, oxaliplatin] and GTX [gemcitabine, docetaxel, and capecitabine], see Gemcitabine Combinations, below).[248, 249]

Gemcitabine Combinations

The NCCN Panel also acknowledged that, historically, combination chemotherapy has not appeared to be superior to monotherapy in the era of 5-FU-based therapy. However, because gemcitabine is superior to bolus 5-FU when efficacy end points of survival and relief from symptoms are used, it is now often combined with other chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, and 5-FU).[247-280]

Recommended combinations are discussed below. However, the Panel does not consider the combination of gemcitabine plus docetaxel[261] or

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gemcitabine plus irinotecan[260-262] to meet criteria for inclusion in the guidelines.

Gemcitabine plus cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled trials have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.[251, 252, 255] Similarly, no survival benefit was observed in a phase III trial investigating the addition of oxaliplatin to gemcitabine compared with gemcitabine alone in this patient population, although the combination regimen was superior with respect to response rate, progression-free survival, and clinical benefit.[255] Furthermore, the addition of oxaliplatin to FDR gemcitabine in the ECOG-6201 study did not result in a significant improvement in survival over FDR gemcitabine.[247]

Nevertheless, selected patients may benefit from this regimen since patients with breast and ovarian cancers who are carriers of a *BRCA* mutation,[263, 264] and selected patients with inherited forms of pancreatic cancer[26] may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins University School of Medicine of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancers suggested that response to gemcitabine and cisplatin was superior even with one affected relative.[265] Patients with a family history of pancreatic cancer alone demonstrated a large survival advantage when treated with platinum-based chemotherapy (6.3 vs. 22.9 months, HR 0.34, 95% CI 0.15-0.74; $p < 0.01$).[265] Further, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The Panel recommends gemcitabine plus cisplatin for metastatic patients, especially those with possible hereditary cancers, as a category 2A recommendation.

Gemcitabine plus fluoropyrimidine

A number of randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.[256] A randomized study in 533 patients with advanced cancer found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although a trend toward an improvement in overall survival for the combination arm did not reach statistical significance.[253] Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an overall survival advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed overall survival to be significantly increased in the subgroup of patients with good performance status.[257] Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent phase I study suggest that a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.[266] Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.[254, 255, 257]

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The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial.

Gemcitabine plus erlotinib

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,[267, 268] results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival when compared to gemcitabine alone.[269-273] Results of the Cancer and Leukemia Group B (CALGB) phase III trial, which evaluated gemcitabine and bevacizumab (an anti-VEGF [vascular endothelial growth factor] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the Southwest Oncology Group (SWOG) phase III randomized trial, which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone did not reveal improvements in survival upon addition of the biologic agent.[270, 271, 273] A recent phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve overall survival, although a significant improvement in progression-free survival was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.[272]

However, in a phase III double-blind, placebo-controlled trial of patients (n = 569) with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (which is an inhibitor of EGFR tyrosine kinase) plus gemcitabine versus gemcitabine alone, patients in the erlotinib arm showed statistically significant improvements in overall survival (hazard ratio=0.82; P=0.038) and progression-free survival (hazard ratio=0.77; P=0.004) when compared to patients receiving gemcitabine alone.[269] Median survival was 6.24 months and 1-year survival was 23% compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib, but most were grade 1 or 2.[269]

Erlotinib in combination with gemcitabine has been approved by the Food and Drug Administration (FDA) for first-line treatment of patients with locally advanced unresectable or metastatic pancreatic cancer. The NCCN Panel recommends gemcitabine-erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status (category 1).

Gemcitabine plus nab-paclitaxel

The Panel includes the combination of gemcitabine plus nab-paclitaxel as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. In a recent report of a phase I/II trial in which 63 patients received gemcitabine plus nab-paclitaxel, 23% of patients had complete responses, 55% had partial responses, and 8% showed stable disease.[274] At the time of publication, the median survival had not been reached.

GTX regimen

The Panel included the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an overall response rate of 29% (all had partial responses), with an additional 31% of patients

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exhibiting a minor response or stable disease.[246] The median survival was 11.2 months for all patients and 13.5 months for patients exhibiting a partial response. This regimen demonstrated significant toxicities, however, with 14% of patients having grade 3/4 leukopenia, 14% having grade 3/4 thrombocytopenia, and 9% with grade 3/4 anemia.

Capecitabine

The Panel lists capecitabine monotherapy as a first-line treatment option for patients with locally advanced unresectable or metastatic disease (category 2B). This recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which overall survival was similar in patients with advanced pancreatic cancer receiving either capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.[275]

Second-Line Therapy

As cross-sectional body imaging has improved, small-volume metastatic disease is being detected in patients with pancreatic cancer who are otherwise maintaining good functional status. Such patients may initially benefit from gemcitabine-based therapy or from investigational therapy. However, these patients, as well as those with unresectable disease without detectable metastases, will ultimately progress. As many as 50% of them will continue to maintain a sufficiently good performance status to consider second-line therapy.[276] Enrollment in a clinical trial is the preferred course of action for these patients. For patients previously treated with fluoropyrimidine-based therapy, gemcitabine is an alternative that may offer palliative benefits in the second-line setting.[277] For patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable options.[278-280] The Panel includes capecitabine, 5-FU/LV/oxaliplatin[281], and CapeOx[280] as options. Note that the capecitabine dose (1,000 mg/m^2 PO twice daily) recommended in the guidelines is less than the dose described by Cartwright and colleagues, because the higher dose has been associated with increased toxicity (eg, diarrhea, hand and foot syndrome).[282] Of note, recent results from the phase III CONKO 003 trial showed significant improvements in both median progression-free survival (13 weeks vs. 9 weeks; P=0.012) and median overall survival (20 weeks vs. 13 weeks; P=0.014) when oxaliplatin was added to 5-FU/leucovorin,[281, 283] making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy.

Recurrent Disease

For patients experiencing a recurrence of disease following resection, the Panel recommends consideration of confirmatory biopsy (category 2B). Chemoradiation can be considered if not previously administered in those patients with local disease recurrence only. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the Panel recommends that an alternative chemotherapy option be administered. When this period is greater than 6 months, systemic therapy as previously administered or an alternative systemic regimen is recommended. Recommended regimens are as for second-line therapy in metastatic disease (also see Principles of Chemotherapy in the guidelines). In all cases of recurrent disease, a clinical trial is the preferred option; best supportive care without salvage therapy should also be an option, especially for patients with poor performance status.

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Future Clinical Trials: Recommendations for Design

In 2007, a meeting was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee in recognition of the failure of a number of recent phase III trials to show clinically significant benefit for patients with pancreatic cancer, and to address the importance of integrating basic and clinical knowledge in the design of clinical trials in pancreatic cancer. Meeting participants included representatives from industry, government, and the community, as well as academic researchers and patient advocates. Several important themes emerging from this meeting are summarized below, and the recommendations put forward by the committee are endorsed by the NCCN Pancreatic Adenocarcinoma Panel.[284]

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods as well as results from preclinical studies are important.
- For patients enrolled in clinical trials, banking of tumor tissue samples should be required along with paired blood and serum samples.
- Biomarkers which serve as surrogate markers of the anticancer effects of investigational agents should be sought, and assays to measure such biomarkers should be well validated.
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (ie, separate trials for patients with locally advanced disease and metastatic disease) and patient performance status; criteria for selecting study populations should take into account the putative differential efficacy of the agent (ie, vaccines in patients with early-stage disease).
- Phase III trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase II setting.
- Phase II and III clinical trials should have a primary endpoint of overall survival.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

Palliation of Locally Advanced and Metastatic Disease

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the disease. For patients with locally advanced unresectable and metastatic disease, the multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance. The main objective of palliative care is to prevent and ameliorate suffering, while ensuring optimal quality of life. Palliative surgical procedures are best reserved for patients with longer life expectancies.

Biliary Obstruction

Approximately 65%-75% of patients with pancreatic cancer develop symptomatic biliary obstruction.[285] For patients diagnosed with unresectable disease and biliary obstruction on initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent stent is

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recommended unless biliary bypass is performed (also see the discussion on stents in Preoperative Biliary Drainage, above). Stent occlusion that causes recurrent cholangitis is a well-know complication of plastic biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than temporary stents (ie, less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a recent randomized, controlled trial of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months (P=0.002), respectively.[286] A metaanalysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.[287] This study suggested that the risk of recurrent biliary obstruction was lower for the metal stents (RR = 0.52, 95% CI 0.39 - 0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality were found.

When a biliary stent cannot be placed (often because the endoscope cannot be advanced passed the neoplasm that is obstructing the gastric outlet), percutaneous biliary drainage with subsequent internalization may be necessary. An alternative is to sequentially dilate the duodenum endoscopically, place a metallic biliary stent, and then place an enteral stent.[288] Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.[288]

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The Panel recommends stenting or an open biliary-enteric bypass with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) since choledochojejunostomy / hepaticojejunostomy provide more durable and reliable palliation of biliary obstruction.[285] Furthermore, the Panel recommends biopsy confirmation of adenocarcinoma during surgery when the tumor is found to be unresectable, if a biopsy was not performed previously.

Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without duodenal bypass (category 2B for prophylactic duodenal bypass) and with or without open ethanol celiac plexus block (category 2B). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease. In this situation, a permanent metal stent is preferred, unless biliary bypass was performed at the time of laparoscopy or laparotomy. However, several Panel members reported that their institutions use plastic stents in patients with short life expectancies, due to the lack of concern about long-term patency.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10%-25% of patients with pancreatic cancer.[285] Patients with locally advanced or metastatic disease and a short life expectancy or poor performance status who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent.[288] An alternative for these patients

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with poor performance status is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (i.e., locally advanced disease) who develops gastric outlet obstruction, an open or laparoscopic gastrojejunostomy with or without a jejunostomy (J) tube should be considered since it may provide more durable and effective palliation of gastric outlet obstruction than an enteral stent.[289-291] Nevertheless, placement of an enteral stent is also an option for these patients.

For patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a palliative gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction. The role of prophylactic gastrojejunostomy in otherwise asymptomatic patients who are found to have unresectable cancers at the time of laparotomy has been evaluated. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer - the majority arising from the head of the pancreas.[292, 293] In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

If staging laparoscopy reveals unresectable disease, palliation of symptoms may be provided by a laparoscopic gastrojejunostomy, with or without laparoscopic biliary bypass, depending on life expectancy and surgical expertise.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.[294] General principles for cancer-related pain management can be found in the NCCN Adult Cancer Pain Guidelines. Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the upper abdomen, celiac plexus neurolysis should be considered. In 2 randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.[294, 295] Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are recommended, but laparoscopic, thoracoscopic, and open approaches can also be used. If staging laparoscopy reveals unresectable disease, palliation of tumor-associated abdominal pain may be provided by laparoscopic celiac plexus neurolysis, depending on life expectancy and surgical expertise. In selected patients with severe local back pain, palliative radiation therapy may be considered, even in the setting of metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin (typically 30-36 Gy in 2.4-3.0 Gy fractions) or radiation alone to the metastatic site.

Additional Palliative Interventions

Pancreatic Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the pancreatic duct, as well as by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.[296, 297] This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.[298] Oral pancreatic exocrine

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enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,[298, 300] therapy may be initiated without diagnostic tests. Enteric-coated mini-microspheres containing preparations of pancreatic enzymes are taken orally (25,000 to 75,000 units of lipase for a main meal and 10,000 to 25,000 units of lipase for a snack, depending on fat content), with half of the dose taken at the start of the meal and half taken in middle of the meal.[298] For patients failing this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.[298, 299] Patients with a clinical suspicion of pancreatic insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Treatment of thromboembolic disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.[301] The Panel recommends low molecular weight heparin (LMWH) as preferred therapy over warfarin for patients with pancreatic cancer who develop a venous thromboembolism (VTE). Support for this recommendation comes from results of 2 large prospective randomized clinical trials: CLOT and CONKO 004. In the CLOT study, an approximately 2-fold decrease in the incidence of recurrent VTE at 6 months was observed in patients with advanced or metastatic cancer diagnosed with a VTE who were treated with the LMWH, dalteparin, compared with those treated with an oral anticoagulant.[302] In the CONKO 004 trial, VTE- and chemotherapy-naive patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy with or without the LMWH, enoxaparin.[303] The risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study with no significant increase in bleeding observed in this group compared to those not receiving enoxaparin.

Depression, pain, malnutrition

The Panel recommends that patients with locally-advanced or metastatic pancreatic cancer receive a formal evaluation by a Palliative Medicine Service, when appropriate. Additional resources are detailed in the NCCN Palliative Care Guidelines; NCCN Adult Cancer Pain Guidelines; and the NCCN Distress Management Guidelines.

Surveillance

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The Panel recommends history and physical examination for symptom assessment every 3 to 6 months for 2 years, then annually. CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT scan, leads to better patient outcomes.

Summary

Resection remains the only chance for a cure of pancreatic adenocarcinoma, and resectable patients should under surgery without delay, followed by adjuvant therapy. Borderline resectable patients can undergo neoadjuvant therapy (category 2B) in the hopes of conversion to resectability. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with salvage therapy if performance status is

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maintained after progression. Good performance status patients presenting with metastatic disease can undergo palliative chemotherapy and can undergo salvage therapy if performance status is maintained after progression.

Overall, in view of the relatively high likelihood of a poor outcome for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

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References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610543.

2. Arnold LD, Patel AV, Yan Y, et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? Cancer Epidemiol Biomarkers Prev 2009;18:2397-2405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19723915.

3. StatBite. U.S. pancreatic cancer rates. J Natl Cancer Inst 2010;102:1822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21139097.

4. Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007;102:2696-2707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17764494.

5. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19561064.

6. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009;6:699-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19806144.

7. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;126:2394-2403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19790196.

8. Thiebaut AC, Jiao L, Silverman DT, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. J Natl Cancer Inst 2009;101:1001-1011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581318.

9. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer 2007;120:1993-1998. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17266034.

10. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. JAMA 2009;301:2553-2562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19549972.

11. Patel AV, Rodriguez C, Bernstein L, et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. Cancer Epidemiol Biomarkers Prev 2005;14:459-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15734973.

12. Mancuso TF, el-Attar AA. Cohort study of workers exposed to betanaphthylamine and benzidine. J Occup Med 1967;9:277-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6026374.

13. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology 2005;129:504-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16083707.

14. Gupta S, Vittinghoff E, Bertenthal D, et al. New-onset diabetes and pancreatic cancer. Clin Gastroenterol Hepatol 2006;4:1366-1372; quiz 1301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16945591.

15. Rosa JA, Van Linda BM, Abourizk NN. New-onset diabetes mellitus as a harbinger of pancreatic carcinoma. A case report and literature review. J Clin Gastroenterol 1989;11:211-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2661661.

16. Li D, Yeung S-CJ, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137:482-488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19375425.

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17. Pezzilli R, Casadei R, Morselli-Labate AM. Is type 2 diabetes a risk factor for pancreatic cancer? JOP 2009;10:705-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19890202.

18. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433-1437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8479461.

19. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. Gut 2002;51:849-852. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12427788.

20. Bracci PM, Wang F, Hassan MM, et al. Pancreatitis and pancreatic cancer in two large pooled case-control studies. Cancer Causes Control 2009;20:1723-1731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19760029.

21. Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Adv Surg 2010;44:293-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20919528.

22. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996;23:251-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8623061.

23. Wang W, Chen S, Brune KA, et al. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007;25:1417-1422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17416862.

24. Ghiorzo P, Gargiulo S, Nasti S, et al. Predicting the risk of pancreatic cancer: on CDKN2A mutations in the melanoma-pancreatic cancer syndrome in Italy. J Clin Oncol 2007;25:5336-5337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024887.

25. Whelan AJ, Bartsch D, Goodfellow PJ. Brief report: a familial syndrome of pancreatic cancer and melanoma with a mutation in the CDKN2 tumor-suppressor gene. N Engl J Med 1995;333:975-977. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7666917.

26. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 2009;27:433-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19064968.

27. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12569143.

28. Slater EP, Langer P, Niemczyk E, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet 2010;78:490-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20412113.

29. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol 2006;4:766-781; quiz 665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682259.

30. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. Gut 2009;58:1410-1418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19470496.

31. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol 2009;104:2175-2181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19491823.

32. Girelli CM, Reguzzoni G, Limido E, et al. Pancreatic carcinoma: differences between patients with or without diabetes mellitus. Recenti Prog Med 1995;86:143-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7617956.

33. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the

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diagnosis of pancreatic cancer. Am J Gastroenterol 2004;99:844-850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15128348.

34. Johnson CD. Pancreatic carcinoma: developing a protocol for multi-detector row CT. Radiology 2001;220:3-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11425965.

35. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16:1727-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19396496.

36. Wong JC, Lu DSK. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol 2008;6:1301-1308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18948228.

37. House MG, Yeo CJ, Cameron JL, et al. Predicting resectability of periampullary cancer with three-dimensional computed tomography. J Gastrointest Surg 2004;8:280-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15019924.

38. Olivie D, Lepanto L, Billiard JS, et al. Predicting resectability of pancreatic head cancer with multi-detector CT. Surgical and pathologic correlation. JOP 2007;8:753-758. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17993727.

39. Klauss M, Schobinger M, Wolf I, et al. Value of three-dimensional reconstructions in pancreatic carcinoma using multidetector CT: initial results. World J Gastroenterol 2009;15:5827-5832. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19998504.

40. Fuhrman GM, Charnsangavej C, Abbruzzese JL, et al. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. Am J Surg 1994;167:104-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7906097.

41. Horton KM, Fishman EK. Adenocarcinoma of the pancreas: CT imaging. Radiol Clin North Am 2002;40:1263-1272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12479710.

42. McNulty NJ, Francis IR, Platt JF, et al. Multi--detector row helical CT of the pancreas: effect of contrast-enhanced multiphasic imaging on enhancement of the pancreas, peripancreatic vasculature, and pancreatic adenocarcinoma. Radiology 2001;220:97-9102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11425979.

43. Schima W, Ba-Ssalamah A, Goetzinger P, et al. State-of-the-art magnetic resonance imaging of pancreatic cancer. Top Magn Reson Imaging 2007;18:421-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18303400.

44. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. Ann Surg Oncol 2008;15:2465-2471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18551347.

45. Panwalkar A, Grem J, Hauke R, et al. Imaging in pancreatic cancer [abstract]. ASCO Gastrointestinal Cancers Symposium 2007:125. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=45&abstractID=10573.

46. Rosch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. Gastroenterology 1992;102:188-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1727753.

47. Varadarajulu S, Wallace MB. Applications of endoscopic ultrasonography in pancreatic cancer. Cancer Control 2004;11:15-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14749619

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48. Santo E. Pancreatic cancer imaging: which method? Jop 2004;5:253-257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15254359.

49. Inoue K, Ohuchida J, Ohtsuka T, et al. Severe localized stenosis and marked dilatation of the main pancreatic duct are indicators of pancreatic cancer instead of chronic pancreatitis on endoscopic retrograde balloon pancreatography. Gastrointest Endosc 2003;58:510-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14520282.

50. Ahmed SI, Bochkarev V, Oleynikov D, Sasson AR. Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. J Laparoendosc Adv Surg Tech A 2006;16:458-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17004868.

51. Warshaw AL, Gu ZY, Wittenberg J, Waltman AC. Preoperative staging and assessment of resectability of pancreatic cancer. Arch Surg 1990;125:230-233. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2154172.

52. Andersson R, Vagianos CE, Williamson RCN. Preoperative staging and evaluation of resectability in pancreatic ductal adenocarcinoma. HPB (Oxford) 2004;6:5-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18333037.

53. Karachristos A, Scarmeas N, Hoffman JP. CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. J Gastrointest Surg 2005;9:1286-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16332484.

54. White R, Winston C, Gonen M, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. J Am Coll Surg 2008;206:445-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18308214.

55. Ferrone CR, Haas B, Tang L, et al. The influence of positive peritoneal cytology on survival in patients with pancreatic adenocarcinoma. J Gastrointest Surg 2006;10:1347-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17175453.

56. Safi F, Roscher R, Bittner R, et al. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis. Serological and immunohistochemical findings. Pancreas 1987;2:398-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3306867.

57. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res 1987;47:5501-5503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3308077.

58. Mann DV, Edwards R, Ho S, et al. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol 2000;26:474-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11016469.

59. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg 2009;198:333-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19375084.

60. Berger AC, Garcia M, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. J Clin Oncol 2008;26:5918-5922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19029412.

61. Ferrone CR, Finkelstein DM, Thayer SP, et al. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol 2006;24:2897-2902. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16782929.

62. Kondo N, Murakami Y, Uemura K, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol 2010;17:2321-2329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20336387.

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63. Montgomery RC, Hoffman JP, Riley LB, et al. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol 1997;4:551-556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9367020.

64. Hess V, Glimelius B, Grawe P, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. Lancet Oncol 2008;9:132-138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18249033.

65. Halm U, Schumann T, Schiefke I, et al. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. Br J Cancer 2000;82:1013-1016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10737382.

66. Ishii H, Okada S, Sato T, et al. CA 19-9 in evaluating the response to chemotherapy in advanced pancreatic cancer. Hepatogastroenterology 1997;44:279-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9058159.

67. Ko AH, Hwang J, Venook AP, et al. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. Br J Cancer 2005;93:195-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15999098.

68. Wong D, Ko AH, Hwang J, et al. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. Pancreas 2008;37:269-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18815548.

69. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. NIH Consens State Sci Statements 2002;19:1-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14768653.

70. Campisi A, Brancatelli G, Vuillerme MP, et al. Are pancreatic calcifications specific for the diagnosis of chronic pancreatitis? A multidetector-row CT analysis. Clin Radiol 2009;64:903-911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19664481.

71. Kajiwara M, Kojima M, Konishi M, et al. Autoimmune pancreatitis with multifocal lesions. J Hepatobiliary Pancreat Surg 2008;15:449-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18670850.

72. Kalady MF, Peterson B, Baillie J, et al. Pancreatic duct strictures: identifying risk of malignancy. Ann Surg Oncol 2004;11:581-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15150084.

73. Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. Gastrointest Endosc 2000;52:74-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10882966.

74. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med 2006;355:2670-2676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17182992.

75. Law R, Bronner M, Vogt D, Stevens T. Autoimmune pancreatitis: a mimic of pancreatic cancer. Cleve Clin J Med 2009;76:607-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797461.

76. Salla C, Chatzipantelis P, Konstantinou P, et al. EUS-FNA contribution in the identification of autoimmune pancreatitis: a case report. JOP 2007;8:598-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17873466.

77. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732-738. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11236777.

78. Micames C, Jowell PS, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc

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2003;58:690-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14595302.

79. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc 2007;65:832-841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17466202.

80. Strasberg SM, Middleton WD, Teefey SA, et al. Management of diagnostic dilemmas of the pancreas by ultrasonographically guided laparoscopic biopsy. Surgery 1999;126:736-741; discussion 741-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10520923.

81. Bhutani MS. Role of endoscopic ultrasonography in the diagnosis and treatment of cystic tumors of the pancreas. JOP 2004;5:266-272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15254381.

82. Luttges J, Zamboni G, Kloppel G. Recommendation for the examination of pancreaticoduodenectomy specimens removed from patients with carcinoma of the exocrine pancreas. A proposal for a standardized pathological staging of pancreaticoduodenectomy specimens including a checklist. Dig Surg 1999;16:291-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10449973.

83. Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? Histopathology 2008;52:787-796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18081813.

84. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg 2007;246:52-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17592291.

85. Pancreas (Exocrine). College of American Pathologists; 2005. Available at: http://www.cap.org/apps/docs/cancer_protocols/2005/pancreasexo05_ckw.doc. Accessed January 2011.

86. Edge SBB, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A., ed AJCC Cancer Staging Manual (ed 7th Edition). New York: Springer; 2010.

87. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer 2007;110:738-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17580363.

88. Staley CA, Cleary KR, Abbruzzese JL, et al. The need for standardized pathologic staging of pancreaticoduodenectomy specimens. Pancreas 1996;12:373-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8740405.

89. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004;363:1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051286.

90. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. Cancer 1987;60:2284-2303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3326653.

91. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987;206:358-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3632096.

92. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg 1997;225:621-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9193188.

93. Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. J Surg Oncol 1998;67:151-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9530884.

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94. Howard TJ, Krug JE, Yu J, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006;10:1338-1345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17175452.

95. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11307091.

96. Zervos EE, Rosemurgy AS, Al-Saif O, Durkin AJ. Surgical management of early-stage pancreatic cancer. Cancer Control 2004;11:23-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14749620.

97. Bilimoria KY, Bentrem DJ, Ko CY, et al. National failure to operate on early stage pancreatic cancer. Ann Surg 2007;246:173-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17667493.

98. Talamonti M. Borderline resectable pancreatic cancer: a new classification for an old challenge. Ann Surg Oncol 2006;13:1019-1020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16865593.

99. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006;13:1035-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16865597.

100. Gumbs AA, Rodriguez Rivera AM, Milone L, Hoffman JP. Laparoscopic Pancreatoduodenectomy: A Review of 285 Published Cases. Ann Surg Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21207166.

101. Boitger TC, Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: critical analysis of 221 resections. World J Surg 1999;23:164-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9880426.

102. Braasch JW, Gray BN. Considerations that lower pancreatoduodenectomy mortality. Am J Surg 1977;133:460-464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/848582.

103. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection. Surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199:432-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6712319.

104. Gundry SR, Strodel WE, Knol JA, et al. Efficacy of preoperative biliary tract decompression in patients with obstructive jaundice. Arch Surg 1984;119:703-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6428360.

105. Hatfield AR, Tobias R, Terblanche J, et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet 1982;2:896-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6126752.

106. Heslin MJ, Brooks AD, Hochwald SN, et al. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 1998;133:149-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9484726.

107. Lai EC, Mok FP, Fan ST, et al. Preoperative endoscopic drainage for malignant obstructive jaundice. Br J Surg 1994;81:1195-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7741850.

108. McPherson GA, Benjamin IS, Hodgson HJ, et al. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. Br J Surg 1984;71:371-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6372935.

109. Pitt HA, Gomes AS, Lois JF, et al. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg 1985;201:545-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2986552.

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110. Thomas JH, Connor CS, Pierce GE, et al. Effect of biliary decompression on morbidity and mortality of pancreatoduodenectomy. Am J Surg 1984;148:727-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6439064.

111. Povoski SP, Karpeh MS, Jr., Conlon KC, et al. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg 1999;230:131-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10450725.

112. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001;234:47-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11420482.

113. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362:129-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20071702.

114. Mullen JT, Lee JH, Gomez HF, et al. Pancreaticoduodenectomy after placement of endobiliary metal stents. J Gastrointest Surg 2005;9:1094-1104; discussion 1104-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16269380.

115. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3487-3495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640929.

116. Varadhachary GR, Wolff RA. The War on Pancreatic Cancer: Are We Gaining Ground? . Oncology 2011;24. Available at: http://www.cancernetwork.com/pancreatic-cancer/content/article/10165/1771371?GUID=85987554-CEFC-48ED-833F-6D33D7CE52E6&rememberme=1.

117. Krokidis M, Fanelli F, Orgera G, et al. Percutaneous Palliation of Pancreatic Head Cancer: Randomized Comparison of ePTFE/FEP-Covered Versus Uncovered Nitinol Biliary Stents. Cardiovasc Intervent Radiol 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20467870.

118. Kullman E, Frozanpor F, Soderlund C, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc 2010;72:915-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21034892.

119. Chun HJ, Kim ES, Hyun JJ, et al. Gastrointestinal and biliary stents. J Gastroenterol Hepatol 2010;25:234-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20136988.

120. Ho H, Mahajan A, Gosain S, et al. Management of complications associated with partially covered biliary metal stents. Dig Dis Sci 2010;55:516-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19267200.

121. Telford JJ, Carr-Locke DL, Baron TH, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc 2010;72:907-914. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21034891.

122. Traverso LW, Longmire WP, Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978;146:959-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/653575.

123. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248-257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9339931.

124. van Berge Henegouwen MI, van Gulik TM, DeWit LT, et al. Delayed gastric emptying after standard pancreaticoduodenectomy

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versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients. J Am Coll Surg 1997;185:373-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9328386.

125. Kozuschek W, Reith HB, Waleczek H, et al. A comparison of long term results of the standard Whipple procedure and the pylorus preserving pancreatoduodenectomy. J Am Coll Surg 1994;178:443-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7909485.

126. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg 1999;86:603-607. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10361177.

127. Morel P, Mathey P, Corboud H, et al. Pylorus-preserving duodenopancreatectomy: long-term complications and comparison with the Whipple procedure. World J Surg 1990;14:642-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2238665.

128. Roder JD, Stein HJ, Hutfl W, Siewert JR. Pylorus-preserving versus standard pancreatico-duodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 1992;79:152-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1348201.

129. Seiler CA, Wagner M, Sadowski C, et al. Randomized prospective trial of pylorus-preserving vs. Classic duodenopancreatectomy (Whipple procedure): initial clinical results. J Gastrointest Surg 2000;4:443-452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11077317.

130. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7574936.

131. Bassi C, Falconi M, Molinari E, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery 2003;134:766-771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14639354.

132. Sikora SS, Posner MC. Management of the pancreatic stump following pancreaticoduodenectomy. Br J Surg 1995;82:1590-1597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8548218.

133. Strasberg SM, Drebin JA, Mokadam NA, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194:746-758. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12081085.

134. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2006;10:1280-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17114014.

135. Balcom JH, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11296108.

136. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16003309.

137. Lowy AM, Lee JE, Pisters PW, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997;226:632-641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9389397.

138. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a

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prospective randomized placebo-controlled trial. Ann Surg 2000;232:419-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10973392.

139. Lillemoe KD, Cameron JL, Kim MP, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2004;8:766-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15531229.

140. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. Ann Surg 1984;199:418-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6712317.

141. Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8597509.

142. Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. Br J Surg 1996;83:611-617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8696805.

143. Clavien PA, Rudiger HA. A simple technique of portal vein resection and reconstruction during pancreaticoduodenectomy. J Am Coll Surg 1999;189:629-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10589601.

144. Launois B, Stasik C, Bardaxoglou E, et al. Who benefits from portal vein resection during pancreaticoduodenectomy for pancreatic cancer? World J Surg 1999;23:926-929. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10449822.

145. Taschieri AM, Elli M, Rovati M, et al. Surgical treatment of pancreatic tumors invading the spleno-mesenteric-portal vessels. An Italian Multicenter Survey. Hepatogastroenterology 1999;46:492-497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10228849.

146. van Geenen RC, ten Kate FJ, de Wit LT, et al. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129:158-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11174708.

147. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8:935-949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15585381.

148. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas area. Cancer 1978;41:880-887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/638975.

149. Nagai H, Kuroda A, Morioka Y. Lymphatic and local spread of T1 and T2 pancreatic cancer. A study of autopsy material. Ann Surg 1986;204:65-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3015059.

150. Glanemann M, Shi B, Liang F, et al. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? World J Surg Oncol 2006;6:123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19014474.

151. Pisters P, Brennan M. Regional lymph node dissection for pancreatic adenocarcinoma. In: Evans D, Pisters P, Abbruzzese J, eds., eds. Pancreatic Cancer. New York: Springer-Verlag; 2002:139-151.

152. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study.

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Lymphadenectomy Study Group. Ann Surg 1998;228:508-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9790340.

153. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999;229:613-622; discussion 622-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235519.

154. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma--part 3: update on 5-year survival. J Gastrointest Surg 2005;9:1191-1204; discussion 1204-1196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16332474.

155. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355-366; discussion 366-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12192322.

156. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007;94:265-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17318801.

157. Farnell MB, Aranha GV, Nimura Y, Michelassi F. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence. J Gastrointest Surg 2008;12:651-656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18085343.

158. Shrikhande SV, Barreto SG. Extended pancreatic resections and lymphadenectomy: An appraisal of the current evidence. World J Gastrointest Surg 2010;2:39-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21160848.

159. Cordera F, Arciero CA, Li T, et al. Significance of common hepatic artery lymph node metastases during pancreaticoduodenectomy for pancreatic head adenocarcinoma. Ann Surg Oncol 2007;14:2330-2336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17492334.

160. Shimada K, Sakamoto Y, Sano T, Kosuge T. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. J Am Coll Surg 2006;203:345-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16931307.

161. Edge SB, Schmieg RE, Rosenlof LK, Wilhelm MC. Pancreas cancer resection outcome in American University centers in 1989-1990. Cancer 1993;71:3502-3508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8098265.

162. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7487211.

163. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7826160.

164. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237:509-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12677147.

165. Imperato PJ, Nenner RP, Starr HA, et al. The effects of regionalization on clinical outcomes for a high risk surgical procedure: a study of the Whipple procedure in New York State. Am J Med Qual 1996;11:193-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8972336.

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166. Rosemurgy AS, Bloomston M, Serafini FM, et al. Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. J Gastrointest Surg 2001;5:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11309644.

167. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998;228:429-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9742926.

168. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11088073.

169. Simunovic M, To T, Theriault M, Langer B. Relation between hospital surgical volume and outcome for pancreatic resection for neoplasm in a publicly funded health care system. CMAJ 1999;160:643-648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10101998.

170. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. Ann Surg 2005;242:781-788, discussion 788-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327488.

171. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999;125:250-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10076608.

172. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-1137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11948273.

173. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S. : utilization, outcomes, and the effect of hospital volume. Cancer 2007;110:1227-1234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17654662.

174. Comparison of flourouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. Lancet 2000;355:1588-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10821362.

175. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol 1996;14:2274-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8708717.

176. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. Cancer 1989;63:1026-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2465076.

177. Kaiser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4015380.

178. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705-1710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7284971.

179. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract

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cancer cooperative group. Ann Surg 1999;230:776-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10615932.

180. Smeenk HG, van Eijck CHJ, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg 2007;246:734-740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17968163.

181. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15028824.

182. Crane CH, Ben-Josef E, Small W. Chemotherapy for pancreatic cancer. N Engl J Med 2004;350:2713-2715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15218575.

183. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. Int J Radiat Oncol Biol Phys 2005;61:965-966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15752874.

184. Morris SL, Beasley M, Leslie M. Chemotherapy for pancreatic cancer. N Engl J Med 2004;350:2713-2715; author reply 2713-2715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15215490.

185. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17227978.

186. Neuhaus P, Riess H, Post S, et al. CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC) [abstract]. J Clin Oncol 2008;26 (May 20 suppl):LBA4504. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34749.

187. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 2008;299:1019-1026. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18319412.

188. Garofalo MC, Abrams RA, Regine WF. Adjuvant therapy for pancreatic cancer: no 'definite' standard. Oncology 2007;21:726-730. Available at: http://www.cancernetwork.com/display/article/10165/61708.

189. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-1081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20823433.

190. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol 2010;28:4450-4456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20837946.

191. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol 2008;26:3503-3510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640931.

192. Mehta VK, Poen JC, Ford JM, et al. Protracted venous infusion 5-fluorouracil with concomitant radiotherapy compared with bolus 5-fluorouracil for unresectable pancreatic cancer. Am J Clin Oncol

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2001;24:155-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11319291.

193. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). J Clin Oncol 2008;26:3511-3516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640932.

194. Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2004;59:445-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15145161.

195. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. Int J Radiat Oncol Biol Phys 2011;79:158-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20399035.

196. Crane CH, Beddar AS, Evans DB. The role of intraoperative radiotherapy in pancreatic cancer. Surg Oncol Clin N Am 2003;12:965-977. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14658127.

197. Massucco P, Capussotti L, Magnino A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol 2006;13:1201-1208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16855382.

198. Quiros RM, Brown KM, Hoffman JP. Neoadjuvant therapy in pancreatic cancer. Cancer Invest 2007;25:267-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17612937.

199. Mornex F, Girard N, Delpero J-R, Partensky C. Radiochemotherapy in the management of pancreatic cancer--part I: neoadjuvant treatment. Semin Radiat Oncol 2005;15:226-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16183476.

200. Reni M. Neoadjuvant treatment for resectable pancreatic cancer: time for phase III testing? World J Gastroenterol 2010;16:4883-4887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20954273.

201. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol 2001;8:758-765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11776488.

202. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol 2001;8:123-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11258778.

203. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1359851.

204. Hoffman JP, Weese JL, Solin LJ, et al. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. Am J Surg 1995;169:71-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7818001.

205. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1998;16:317-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9440758.

206. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol 2007;14:2088-2096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17453298.

207. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with

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pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15:928-937. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9060530.

208. Talamonti MS, Small W, Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol 2006;13:150-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418882.

209. Wolff RA, Evans DB, Crane CH, et al. Initial results of preoperative gemcitabine (GEM)-based chemoradiation for resectable pancreatic adenocarcinoma [abstract]. Proc Am Soc Clin Oncol. 2002;21:516. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=16&abstractID=516.

210. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3496-3502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640930.

211. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. J Gastrointest Surg 2001;5:121-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11331473.

212. Marti JL, Hochster HS, Hiotis SP, et al. Phase I/II trial of induction chemotherapy followed by concurrent chemoradiotherapy and surgery for locoregionally advanced pancreatic cancer. Ann Surg Oncol 2008;15:3521-3531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18830756.

213. Landry J, Catalano PJ, Staley C, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol 2010;101:587-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20461795.

214. McClaine RJ, Lowy AM, Sussman JJ, et al. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. HPB (Oxford) 2010;12:73-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20495649.

215. Stokes JB, Nolan NJ, Stelow EB, et al. Preoperative Capecitabine and Concurrent Radiation for Borderline Resectable Pancreatic Cancer. Ann Surg Oncol 2011. Available at:

216. Le Scodan R, Mornex F, Girard N, et al. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. Ann Oncol 2009;20:1387-1396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19502533.

217. Kim R, Saif MW. Is there an optimal neoadjuvant therapy for locally advanced pancreatic cancer? JOP 2007;8:279-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17495356.

218. Girard N, Mornex F, Bossard N, et al. Estimating optimal dose of twice-weekly gemcitabine for concurrent chemoradiotherapy in unresectable pancreatic carcinoma: mature results of GEMRT-01 Phase I trial. Int J Radiat Oncol Biol Phys 2010;77:1426-1432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20056351.

219. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2007;68:801-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17379445.

220. Shibuya K, Oya N, Fujii T, et al. Phase II Study of Radiation Therapy Combined With Weekly Low-Dose Gemcitabine for Locally

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Advanced, Unresectable Pancreatic Cancer. Am J Clin Oncol 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20065850.

221. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? Int J Radiat Oncol Biol Phys 2002;52:1293-1302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11955742.

222. Haddock MG, Swaminathan R, Fosier NR, et al. Gemcitabine, cisplatin, and radiotherapy for patients with locally advanced pancreatic adenocarcinoma: results of the North Central Cancer Treatment Group Phase II Study N9942. J Clin Oncol 2007;25:2567-2572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17577035.

223. Ammori JB, Colletti LM, Zalupski MM, et al. Surgical resection following radiation therapy with concurrent gemcitabine in patients with previously unresectable adenocarcinoma of the pancreas. J Gastrointest Surg 2003;7:766-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13129554.

224. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010;7:e1000267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20422030.

225. Blackstock AW, Tepper JE, Niedwiecki D, et al. Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. Int J Gastrointest Cancer 2003;34:107-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15361643.

226. Loehrer PJ, Powell ME, Cardenes HR, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201 [abstract]. J Clin Oncol 2008;26 (May 20 suppl):4506. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=30957.

227. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007;25:326-331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17235048.

228. Huguet F, Girard N, Guerche CS-E, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009;27:2269-2277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19307501.

229. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007;110:47-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17538975.

230. Brunner TB, Grabenbauer GG, Kastl S, et al. Preoperative Chemoradiation in Locally Advanced Pancreatic Carcinoma: A Phase II Study. Onkologie 2000;23:436-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11441238.

231. Macchia G, Valentini V, Mattiucci GC, et al. Preoperative chemoradiation and intra-operative radiotherapy for pancreatic carcinoma. Tumori 2007;93:53-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17455872.

232. Thomas CR, Jr., Welden PL, Traverso LW, Thompson T. Concomitant intraarterial cisplatin, intravenous 5-flourouracil, and split-course radiation therapy for locally advanced unresectable pancreatic adenocarcinoma: a phase II study of the Puget Sound Oncology Consortium (PSOC-703). Am J Clin Oncol 1997;20:161-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9124192.

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233. Bai YR, Wu GH, Guo WJ, et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: results of feasibility study. World J Gastroenterol 2003;9:2561-2564. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14606097.

234. Crane CH, Antolak JA, Rosen, II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. Int J Gastrointest Cancer 2001;30:123-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12540024.

235. Spalding AC, Jee K-W, Vineberg K, et al. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. Med Phys 2007;34:521-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17388169.

236. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer 2009;115:665-672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117351.

237. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. J Natl Cancer Inst 1988;80:751-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2898536.

238. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. J Clin Oncol 1985;3:373-378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3973648.

239. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol 2008;19:1592-1599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18467316.

240. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/ 5-fluorouracil every 2 weeks in patients with advanced solid tumors. Ann Oncol 2003;14:481-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12598357.

241. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 2005;23:1228-1236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718320.

242. Ychou M, Desseigne F, Guimbaud R, et al. Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial [abstract]. J Clin Oncol 2007;25 (June 20 Suppl):4516. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=33280.

243. Conroy T, Desseigne F, Ychou M, et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial [abstract]. J Clin Oncol 2010;28 (15s suppl):4010. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=41582.

244. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin

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Oncol 1997;15:2403-2413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9196156.

245. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2',2'-difluorodeoxycytidine 5'-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. Cancer Chemother Pharmacol 1991;27:258-262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1998982.

246. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003;21:3402-3408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12885837.

247. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:3778-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581537.

248. Demols A, Peeters M, Polus M, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer 2006;94:481-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16434988.

249. Fine RL, Fogelman DR, Schreibman SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 2008;61:167-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17440727.

250. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002;20:3270-3275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149301.

251. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. Cancer 2002;94:902-910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920457.

252. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol 2010;28:1645-1651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194854.

253. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009;27:5513-5518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858379.

254. Heinemann V, Boeck S, Hinke A, et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 2008;8:82-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18373843.

255. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006;24:3946-3952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921047.

256. Heinemann V, Labianca R, Hinke A, Louvet C. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. Ann Oncol 2007;18:1652-1659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17580491.

257. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic

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cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007;25:2212-2217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17538165.

258. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23:3509-3516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15908661.

259. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol 2005;6:369-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15925814.

260. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004;22:3776-3783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15365074.

261. Kulke MH, Tempero MA, Niedzwiecki D, et al. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. J Clin Oncol 2009;27:5506-5512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858396.

262. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. Br J Cancer 2006;95:587-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16909140.

263. Majdak EJ, Debniak J, Milczek T, et al. Prognostic impact of BRCA1 pathogenic and BRCA1/BRCA2 unclassified variant mutations in patients with ovarian carcinoma. Cancer 2005;104:1004-1012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16047333.

264. Stefansson OA, Jonasson JG, Johannsson OT, et al. Genomic profiling of breast tumours in relation to BRCA abnormalities and phenotypes. Breast Cancer Res 2009;11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589159.

265. Oliver GR, Sugar E, Laheru D, Diaz LA. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Gastrointestinal Cancers Symposium 2010:180. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=72&abstractID=2395.

266. Espinoza AM, Ko AH, Venook AP, et al. A phase I study, with expanded cohort, of biweekly fixed-dose rate gemcitabine (FDR GEM) plus capecitabine (CAP) in patients with advanced pancreatic (APC) and biliary carcinomas (ABC) [abstract]. Gastrointestinal Cancers Symposium 2010:202. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=72&abstractID=1235.

267. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2005;23:8033-8040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16258101.

268. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. J Clin Oncol 2004;22:2610-2616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15226328.

269. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada

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Clinical Trials Group. J Clin Oncol 2007;25:1960-1966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17452677.

270. Philip PA, Benedetti J, Fenoglio-Preiser C, et al. Phase III study of gemcitabine plus cetuximab versus gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma: SWOG S0205 study [abstract]. J Clin Oncol 2007;25 (June 20 suppl):LBA4509. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=32920.

271. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 2010;28:3617-3622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20606091.

272. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009;27:2231-2237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19307500.

273. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010;28:3605-3610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20606093.

274. Von Hoff DD, Ramanathan R, Borad M, et al. SPARC correlation with response to gemcitabine (G) plus nab-paclitaxel (nab-P) in patients with advanced metastatic pancreatic cancer: A phase I/II study [abstract]. J Clin Oncol 2009;27 (suppl):4525. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=35180.

275. Boeck SH, Vehling-Kaiser U, Waldschmidt D, et al. Gemcitabine plus erlotinib (GE) followed by capecitabine (C) versus capecitabine plus erlotinib (CE) followed by gemcitabine (G) in advanced pancreatic cancer (APC): A randomized, cross-over phase III trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO) [abstract]. J Clin Oncol 2010;28 (18s suppl):LBA4011. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=41201.

276. Tempero MA, Berlin J, Ducreux M, et al. Pancreatic cancer treatment and research: an international expert panel discussion. Ann Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21199884.

277. Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 1996;7:347-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8805925.

278. Maisey N, Chau I, Cunningham D, et al. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. J Clin Oncol 2002;20:3130-3136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12118027.

279. Pelzer U, Stieler J, Roll L, et al. Second-line therapy in refractory pancreatic cancer: results of a phase II study. Onkologie 2009;32:99-9102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19295247.

280. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer 2008;113:2046-2052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18756532.

281. Pelzer U, Kubica K, Stieler J, et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study [abstract]. J Clin Oncol 2008;26 (May 20 suppl):4508. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34587.

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282. Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 2002;20:160-164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11773165.

283. Saif MW. New developments in the treatment of pancreatic cancer. Highlights from the "44th ASCO Annual Meeting". Chicago, IL, USA. May 30 - June 3, 2008. JOP 2008;9:391-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18648128.

284. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. J Clin Oncol 2009;27:5660-5669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858397.

285. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. Surg Clin North Am 2005;85:359-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15833477.

286. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63:986-995. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16733114.

287. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006:CD004200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625598.

288. Maire F, Hammel P, Ponsot P, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. Am J Gastroenterol 2006;101:735-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16635221.

289. Jeurnink SM, Polinder S, Steyerberg EW, et al. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. J Gastroenterol 2010;45:537-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20033227.

290. Jeurnink SM, Steyerberg EW, Hof G, et al. Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients. J Surg Oncol 2007;96:389-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17474082.

291. Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17559659.

292. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg 1999;230:322-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10493479.

293. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. Ann Surg 2003;238:894-902; discussion 902-895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14631226.

294. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004;291:1092-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14996778.

295. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993;217:447-455; discussion 456-447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7683868.

296. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep 2007;9:116-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17418056.

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297. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut 2005;54 Suppl 6:vi1-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15951527.

298. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. Best Pract Res Clin Gastroenterol 2010;24:337-347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20510833.

299. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol 2011;26 Suppl 2:12-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21323992.

300. Lemaire E, O'Toole D, Sauvanet A, et al. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. Br J Surg 2000;87:434-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10759738.

301. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol 2006;24:484-490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421425.

302. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12853587.

303. Riess H, Pelzer U, Deutschinoff G, et al. A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial [abstract]. J Clin Oncol 2009;27(suppl):LBA4506. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=32978.

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