Systemic therapy for metastatic pancreatic adenocarcinoma

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***Abstract*:** Systemic treatment of metastatic pancreatic adenocarcinoma achieves only modest benefits, with evidence indicating a survival advantage with 5-fluorouracil (5-FU) over best supportive care alone, and further advantage of single-agent gemcitabine over 5-FU. There are very few regimens better than single-agent gemcitabine despite multiple trials of cytotoxic and targeted agents. The addition of a platinum agent has improved response rate but not survival. The addition of erlotinib has improved survival but only by a small margin. The use of gemcitabine in multidrug regimens containing one or more of: a platinum agent; fluoropyrimidine; anthracycline; and taxane has demonstrated advantages in response rate, progression-free survival and, in one randomized study, overall survival. After gemcitabine failure, second-line therapy with oxaliplatin and 5-FU provides a further survival advantage. Further advances depend upon the current and future clinical trials investigating enhanced delivery of current agents, new agents and novel modalities, improved supportive care, and treatment more tailored to the individual patient and tumour.

***Keywords*:** adenocarcinoma, antineoplastic agents, chemotherapy, metastatic therapeutics, pancreas, pancreatic neoplasms

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Background

Pancreatic adenocarcinoma (PAC) is unresectable at diagnosis in 80% of patients, and if not already metastatic will usually become so. Conventional measures to modify the natural history of this disseminated disease are only modestly helpful with small survival advances in the palliative setting. With current treatments, 41% of patients with local or regional disease survive to 1 year, but only 13% of patients with metastatic disease achieve this milestone [SEER, 1996–2004]. The aim of this review is to provide the clinician with an up-to-date summary of current evidence for the treatment of metastatic PAC and provide insights into future research directions.

Method

A systematic search of published trials and recent abstracts was conducted using Medline, Embase, The Cochrane Database of Systematic Reviews, and the abstracts lists from the past 4 years of the American Society of Clinical Oncology (ASCO) and ASCO Gastrointestinal congress, and the European Society of Medical Oncology (ESMO) congress. The Medline search (including Medline in process) was conducted using the strategy [*pancreatic neoplasms/dt AND *adenocarcinoma /dt AND metast$.mp NOT (radio$ or adjuv$).mp] LIMIT TO [(clinical trial, all OR clinical trial, phase I OR clinical trial phase II OR clinical trial phase III, OR clinical trial, phase IV OR clinical trial OR controlled clinical trial OR meta analysis OR randomized controlled trial)]. Embase was searched using the strategy [(*Pancreas Adenocarcinoma/dt OR metastatic pancreatic adenocarcinoma.mp) AND exp evidence based medicine]. The Cochrane Database of Systematic Reviews was searched for any reviews regarding advanced or metastatic pancreatic cancer. Trials with at least some patients with metastatic PAC were included. Studies were excluded if they were phase I only, involved radiotherapy, if doses could not be obtained from an English language abstract or article, and if groups included both previously treated and nontreated participants.

Chemotherapy in addition to best supportive care

Some clinicians remain uncertain whether chemotherapy offers added benefit over best

supportive care (BSC) alone for patients with metastatic PAC. Interpreting trial data is complicated by a variety of factors such as a wide variation in response rate and survival between phase II trials; subsequent phase III trials are usually negative; the participant groups are a mixture of locally advanced and metastatic disease; the effect sizes are usually small; multiple regimens have been tested; study size is sometimes too small to detect differences. Registry data from patients with metastatic PAC in Veterans Affairs Hospitals between 1995 and 2005 showed that patients who received chemotherapy lived longer than untreated patients, at 5.3 *versus* 1.5 months median overall survival (OS), respectively [Mekan *et al.* 2007]. These data are retrospective and might only reflect the performance status of patients at the time of consideration for chemotherapy.

A Cochrane review compared fluorouracil (5-FU)-based chemotherapy with BSC in seven randomized controlled trials (RCTs) [Yip *et al.* 2006]. The meta-analysis showed that 5-FU-based regimens reduced 12-month mortality when compared to BSC [odds ratio (OR) 0.37, confidence interval (CI) 0.25–0.57, $p < 0.00001$]. There were some limitations in generalizability. Firstly, two of the trials trended towards supporting BSC over chemotherapy, and the study that most favoured chemotherapy had not required a histological diagnosis. Secondly, although five of the studies attempted to measure some aspect of quality of life, only two showed any improvement with chemotherapy.

Three further randomized phase II trials have compared chemotherapy to best supportive care. No survival benefit was obtained from gemcitabine (after biliary stenting) [Xinopoulos *et al.* 2008], a combination of cisplatin and 5-FU [Huguier *et al.* 2001], or the hormonal agent, flutamide [Negi *et al.* 2006].

Single-agent chemotherapy

Fluoropyrimidines

The modest activity of 5-FU-containing regimens in the Cochrane review has some support from nonrandomized phase II studies using 5-FU as a single agent. Both bolus and infusional 5-FU regimens have achieved radiological response rates up to 15% and median OS up to 5 months [Van Rijswijk *et al.* 2004; Di Costanzo *et al.* 1996; Weinerman and MacCormick, 1994]. Two oral 5-FU pro-drugs have shown similar results. Capecitabine alone (1250 mg/m^2 bd, d1–14 q3w) achieved a 10% response rate, but a 24% clinical benefit response rate [Cartwright *et al.* 2002]. S1 (30 mg/m^2 bd, d1–14 q3w) showed a 21% response rate and median OS of 5.6 months in one trial [Ueno *et al.* 2005], but only 9% response rate in another [Strumberg *et al.* 2009]. Fluorodeoxyuridine [Ardalan and Lima, 2004] and the oral agents dFUR [Di Bartolomeo *et al.* 1996], and uracil-tegafur [Ueno *et al.* 2002] were not effective.

Platinum drugs

Platinum drugs might have some single-agent activity in metastatic PAC. In a nonrandomized phase II trial, cisplatin alone (100 mg/m^2 q4w) achieved a response rate of 21% [Wils *et al.* 1993], but platinum drugs have not been tested as single agents in a RCT.

Other single agents

Many other cytotoxic and biological agents have been tested in phase II trials and have shown no single-agent activity. These include mitoxantrone [Taylor *et al.* 1990], Mitomycin Natural Killer [Tuinmann *et al.* 2008], paclitaxel [Gebbia and Gebbia, 1996], topotecan [Stevenson *et al.* 1998], fludarabine [Kilton *et al.* 1992], glufosfamide [Briasoulis *et al.* 2003], dihydroxyanthracenedione [Asbury *et al.* 1994; Bukowski *et al.* 1993], aziridinylbenzoquinone [Bukowski *et al.* 1993], lithium gamolenate [Johnson *et al.* 2001], etoposide [Asbury *et al.* 1994], aclacinomycin, spirogermanium [Asbury *et al.* 1994], maytansine, chlorozotocin [GITSG, 1985], octreotide [Burch *et al.* 2000], lantreotide [Raderer *et al.* 1999], gastrazole [Chau *et al.* 2006], goserilin [Philip *et al.* 1993], and tamoxifen [Bakkevold *et al.* 1990]. Ralitrexed achieved no response in one trial [Pazdur *et al.* 1996] and a low response in another [Francois *et al.* 2005]. Limited single-agent response was achieved using curcumin [Dhillon *et al.* 2006]. A complete response was noted in a randomized phase II trial of a semisynthetic version of an extract of the plant chelodium majus called NSC-631570 [Gansauge *et al.* 2002].

Gemcitabine as a single agent

Gemcitabine is currently the most active cytotoxic agent in metastatic PAC. The original phase II trials of gemcitabine achieved modest response rates of 11% [Casper *et al.* 1994] and 6% [Carmichael *et al.* 1996], but the favourable

toxicity profile enabled notable relief of cancer-related symptoms in responders. In one of these studies, 17% of patients noted improved performance status, 29% experienced reduced pain, and 28% described reduced nausea [Carmichael *et al.* 1996]. These observations provided the rationale for evaluation in a phase III trial (see Table 1).

Burris and colleagues compared single-agent gemcitabine to single-agent 5-FU in a phase III study with the endpoints of median OS and clinical benefit [Burris *et al.* 1997]. Clinical benefit response occurred if the patient experienced an improvement in one of three areas – pain (either by analgesia use or on a rating scale), performance status, or weight – that lasted at least 4 weeks, and without deterioration in the remaining areas. One hundred and twenty-six patients were randomized to receive gemcitabine (1000 mg/m^2 q7/8w, then q3/4w) or 5-FU (600 mg/m^2 q1w). Median OS was slightly but significantly longer in the gemcitabine group (5.7 months) than the 5-FU group (4.4 months), but more importantly gemcitabine achieved a higher clinical benefit response of 24%, compared to 5% for 5-FU. Critics of the study point out that the control arm did not receive an optimal 5-FU regimen. However, on the basis of this small benefit – one quarter of patients receiving a month or more of symptomatic improvement – gemcitabine became the standard of care in metastatic PAC.

There is further randomized evidence that gemcitabine is more useful than an inactive agent (see Table 1). In a phase III trial of 277 patients, gemcitabine achieved better survival and quality of life than the matrix metalloproteinase inhibitor, BAY 12-9566 (Tanomastat) [Moore *et al.* 2003]. A retrospective review of 82 patients with advanced PAC also suggested that gemcitabine achieved greater clinical benefit (48%) than 5-FU with folinic acid (19%) [Klein *et al.* 2000].

Gemcitabine regimen

The gemcitabine regimen in the original phase II studies was 800 mg/m^2 q3/4w, but in later studies the dose was increased to 900 and then 1000 mg/m^2 because of the low side-effect profile. The Burris regimen has been described above, but many institutions use an abridged 1000 mg/m^2 q3/4w regimen. Three modified regimens bear some discussion – low-dose, dose-dense, and fixed-dose rate infusions.

A very small randomized trial ($n = 25$) found that low-dose gemcitabine delivered weekly (250 mg/m^2 q1w) achieved a similar median OS of 7.2 months when compared to standard gemcitabine, but with less haematologic toxicity in the low-dose group [Sakamoto *et al.* 2006]. This study is too small to draw any firm conclusions; however, it provides some support for a future trial examining the balance of toxicity and efficacy.

Dose-dense gemcitabine (2200 mg/m^2 q2w) has achieved similar results to standard gemcitabine in uncontrolled trials, with a response rate of 21% and a median OS of 8.8 months [Ulrich-Pur *et al.* 2000], and in a second trial at the same dose a median OS of 8.2 months [Scheithauer *et al.* 2003]. Nearly half of patients experienced effective palliation, and the regimen was well tolerated.

Fixed-dose rate (FDR) infusions have pharmacokinetic advantages in the laboratory, where they maximize the intracellular concentration of gemcitabine by avoiding saturation of the enzyme that

Table 1. Randomized controlled trials of single-agent gemcitabine compared to non-gemcitabine regimens in metastatic pancreatic adenocarcinoma.

Author	Sample size	Interventions	Radiological response	*p* value	Clinical benefit response	*p* value	Median overall survival (months)	*p* value
Burris *et al.* 1997	126	Gemcitabine Weekly 5-FU	– –	–	24%* 5%	0.002	5.7* 4.4	0.003
Moore *et al.* 2003	277	Gemcitabine BAY 12-9566	5% <1%	np	–	–	6.6* 3.7	<0.001

*$p < 0.05$; np, not provided.

Table 2. Randomized controlled trials of combined cytotoxic therapy in metastatic pancreatic adenocarcinoma.

Author	Sample size	Interventions	Radiological response	*p* value	Clinical benefit response	*p* value	Median overall survival (months)	*p* value
Colucci *et al.* 2002	107	Gem + Cis Gem	26%* 9%	0.02	53% 49%	np	6.9 4.6	0.43
Colucci *et al.* 2009	400	Gem + Cis Gem	13% 10%	0.37	15% 23%	0.057	7.2 8.3	0.38
Louvet *et al.* 2005	326	Gem + Oxa Gem	27%* 17%	0.04	38%* 27%	0.03	9.0 7.1	0.13
Heinemann *et al.* 2006	195	Gem + Cis Gem	12% 9%	np$^{\$}$	—	—	7.5 6.0	0.15
Poplin *et al.* 2009	832	Gem + Oxa FDR Gem Gem	21% 21% 16%	0.11	—	—	5.7 6.2 4.7	0.15
Hermann *et al.* 2007	319	Gem + Cap Gem	10% 8%	np	—	—	8.4 7.2	0.23
Bernhard *et al.* 2008	319	Gem + Cap Gem	—	—	19% 20%	np	—	—
Scheithauer *et al.* 2003	83	Gem + Cap Gem	17% 14%	np	33% 48%	np	8.2 9.5	np
Riess *et al.* 2005	473	Gem + 5-FU Gem	—	—	—	—	5.9 6.2	0.68
Ducreux *et al.* 2002	207	5-FU + Cis 5-FU	12%* 0%	< 0.01	—	—	3.7 3.4	0.10
Reni *et al.* 2005	99	Gem + Cis + 5-FU +Epi Gem	39%* 9%	0.0008	—	—	12% 2 year* 2% 2 year	0.03
Ychou *et al.* 2007	88	FOLFIRINOX Gem	41% 12%	np	—	—	—	—

Cap, capecitabine; Cis, cisplatin; Epi, epirubicin; FDR, fixed dose rate; FOLFIRINOX, folinic acid, 5-fluorouracil (5-FU), irinotecan, oxaliplatin; Gem, gemcitabine; np, not provided; Oxa, oxaliplatin; *$p < 0.05$; $^{\$}p < 0.001$ for 'assessable' patients but intention-to-treat analysis not significant.

transforms the drug into the active metabolites. FDR appeared promising in retrospective and phase II work [Cessot *et al.* 2009]. Indeed, a randomized phase II study of 92 patients showed that patients who received FDR gemcitabine (1500 mg/m^2 over 150 min q3/4w) had higher 1 year, 2 year and OS than patients who received high-dose gemcitabine (2200 mg/m^2 q3/4w over 30 min) [Tempero *et al.* 2003]. The cost for this benefit was increased haematological toxicity in the FDR group, and statistical significance was lost when only metastatic patients were included. Therefore, FDR gemcitabine (1500 mg/m^2 over 150 min q3/4w) was compared to standard gemcitabine (Burris regimen) in a multicentre RCT with over 800 patients [Poplin *et al.* 2009]. FDR gemcitabine acheived an improvement in 1-year survival from 16% to 21% (in pairwise comparison), but this did not meet the prespecified significance level. Median OS was not significantly different, and there was more myelosuppression in the FDR group. The authors concluded that FDR gemcitabine did not offer substantial benefit.

Gemcitabine in combination

Gemcitabine as a single agent is only modestly effective but is relatively well tolerated. Gemcitabine in combination with other agents such as platinum drugs, fluoropyrimidines and taxanes have therefore been explored, but with mixed results (see Table 2).

Platinum drugs

Platinum agents have activity when added to gemcitabine, but have not produced a survival advantage in randomized trials. Fortnightly oxaliplatin (100 mg/m^2 d2) and gemcitabine (1000 mg/m^2 d1) improved response rate and 'clinical benefit' more than gemcitabine alone (1000 mg/m^2 q1w), but did not improve survival [Louvet *et al.* 2005]. Adding cisplatin (25 mg/m^2 q3/4w) to gemcitabine (Burris regimen) improved response rate in a mixed group

[Colucci *et al.* 2002], but the effect was not sustained in the phase III study that followed [Colucci *et al.* 2009] (see Table 2). In another randomized study, cisplatin and gemcitabine (50 mg/m^2 and 1000 mg/m^2, respectively, q2w) did not improve response rate or median OS compared to gemcitabine alone [Heinemann *et al.* 2006].

Several uncontrolled phase II trials support mild activity of gemcitabine–platinum schedules, with consistent response rates above 10% and median OS of more than 7 months [Ferrari *et al.* 2008; Lee *et al.* 2008a; Ueno *et al.* 2007a; Ko *et al.* 2006; Alberts *et al.* 2003]. A single-centre retrospective review of gemcitabine and oxaliplatin showed an objective response in 16% of patients, and a median OS of 9 months [Di Marco *et al.* 2007].

Fluoropyrimidines

The addition of an oral fluoropyrimidine to gemcitabine has not produced an improvement in response or survival in RCTs, despite initial positive phase II results. In phase II studies, capecitabine combined with standard gemcitabine [Park *et al.* 2006], FDR gemcitabine [Tonini *et al.* 2009], and intermediate-dose gemcitabine (800 mg/m^2 q2/3w) [Reza *et al.* 2007] achieved response rates above 20%. But in a phase III study, the addition of capecitabine (650 mg/m^2 bd d1–14, q3w) to gemcitabine (1000 mg/m^2 q2/3w) did not improve survival [Bernhard *et al.* 2008], except in a posthoc analysis in patients with good performance status [Herrmann *et al.* 2007]. Similarly, adding capecitabine (2500 mg/m^2 d1–7 q2w) to dose-dense gemcitabine (2200 mg/m^2 d1 q2w) in a second randomized study gave a trend towards clinical benefit but did not increase any measures of survival [Scheithauer *et al.* 2003].

The oral 5-FU pro-drug, S1, combined with gemcitabine has achieved response rates above 40% in four phase II trials in Japanese patients [Lee *et al.* 2008b; Sudo *et al.* 2008; Ueno *et al.* 2007b; Nakamura *et al.* 2006], and 17% in a fifth trial [Ohkawa *et al.* 2007]. Phase III studies are underway.

The combination of intravenous 5-FU and gemcitabine has been examined in a phase III trial [Riess *et al.* 2005] where 473 patients were randomized to receive GFF (gemcitabine 1000 mg/m^2 q4/6w, 5-FU 750 mg/m^2 24 h-infusion plus folinic acid 200 mg/m^2 q4/6w) or single-agent gemcitabine (Burris regimen). There was no difference in any survival endpoint. This result occurred despite uncontrolled phase II trials supporting the addition of 5-FU to gemcitabine. Gemcitabine, 5-FU and folinic acid (GEMFUFOL) [Oztop *et al.* 2004], (FOLFUGEM2) [Andre *et al.* 2004], oxaliplatin, 5-FU and folinic acid (FOLFOX-6) with gemcitabine sequentially [Ghosn *et al.* 2009], sequential 5-FU and gemcitabine [Nakamori *et al.* 2009], weekly 5-FU and gemcitabine boluses [Gennatas *et al.* 2006] all achieved response rates of over 20% or median OS beyond 11 months. Gemcitabine and 5-FU boluses administered q3/4w were tested in two trials, one positive [Kurtz *et al.* 2000] and one negative [Berlin *et al.* 2000].

Other doublet combinations with gemcitabine

Perhaps the most promising drug now in phase III trials is nab-paclitaxel, a formulation where paclitaxel is bound to albumin nanoparticles. Early results from a phase I/II study recently reported in abstract described a 26% response rate including one complete response [Von Hoff *et al.* 2009]. Phase II trials also suggest activity when gemcitabine is combined in doublets with epirubicin [Neri *et al.* 2002; Scheithauer *et al.* 1999], docetaxel [Des Guetz *et al.* 2007], mitomycin [Tuinmann *et al.* 2008], etoposide [Lange *et al.* 2006], lipid-complexed paclitaxel (EndoTAG-1) [Löhr *et al.* 2008; 2009] and paclitaxel GPM [Podoltsev *et al.* 2008]. Agents with little activity in doublet combination with gemcitabine include exatecan [Abou-Alfa et al. 2006], irinotecan [Stathopoulos *et al.* 2006; Rocha Lima *et al.* 2004], celecoxib [Dragovich *et al.* 2008] and curcumin [Epelbaum *et al.* 2008].

Doublet combinations without gemcitabine

Combinations without gemcitabine have little activity, including 5-FU and irinotecan [Di Costanzo *et al.* 1996], 5-FU with 13-cis-retinoic acid [Michael *et al.* 2007], irinotecan and docetaxel [Burtness *et al.* 2008], and cisplatin and 5-FU (despite infusional dosing and folinic acid modulation) [Wagener *et al.* 2002; Huguier *et al.* 2001; Nose *et al.* 1999]. The addition of cisplatin (100 mg/m^2 d1,2) to 5-FU (infusional 1000 mg/m^2 d1–5) increased response rate in one randomized trial with 12% response in patients receiving the doublet, compared to no responses from single agent 5-FU [Ducreux *et al.* 2002]. However, as when platinum agents are added to gemcitabine, there was no survival difference (see Table 2).

Multiagent cytotoxic combinations

Multidrug combinations covering multiple targets in the tumour cell cycle have the potential for multiple or overlapping toxicities. This may be offset by the use of low and frequent dosing, and by the choice of agents. The trials in single agent and doublet chemotherapy provided the rationale for the inclusion of gemcitabine, platinum agents, fluoropyrimidines, taxanes and epirubicin in multiagent regimens.

A randomized multicentre phase III trial comparing PEFG (cisplatin 40 mg/m^2 d1, epirubicin 40 mg/m^2 d1, gemcitabine 600 mg/m^2 d1 and 8, 5-FU 200 mg/m^2 d1-28 by continuous infusion; q4w) *versus* gemcitabine alone (Burris regimen) showed an improved response rate and survival with the combined regimen [Reni *et al.* 2005]. The 99 patients were randomized to PEFG or gemcitabine. More patients in the PEFG group responded (see Table 2). Analysis of secondary endpoints showed that survival at 1 year was not significantly improved (39% *versus* 21%, $p = 0.11$), but survival at 2 years was improved (12% *versus* 2%, $p = 0.03$) [Reni *et al.* 2005]. Data from the same trial suggested that the PEFG regimen more often provided improved quality of life than gemcitabine alone, despite an increased rate of grade 3 and 4 neutropenia (43%) and thrombocytopenia (29%) [Reni *et al.* 2006a].

Variations of PEFG have been described. A fortnightly variant of PEFG called 'dose-intense' PEFG (DI-PEFG, using the same 5-FU schedule but with cisplatin 30 mg/m^2 d1 and 15, epirubicin 30 mg/m^2 d1 and 15, gemcitabine 800 mg/m^2 d1 and 15; q4w) achieved comparable survival to standard PEFG with a 1-year survival rate of 46% [Reni *et al.* 2006b]. Although this was an uncontrolled phase II trial with inter-trial comparison to the original PEFG study the relative efficacy combined with the low rates of grade 3 and 4 neutropenia (9%) and thrombocytopenia (1%) suggests this may be a useful schedule for further consideration. A subsequent study of another variation of PEFG suggests that substitution of capecitabine (1250 mg/m^2/day d1–28) for infusional 5-FU, and docetaxel (25 mg/m^2 d1 and 15) for epirubicin were both feasible manoeuvres and worthy of further investigation [Cereda *et al.* 2009].

Further multidrug combinations have been explored in uncontrolled phase II studies. GTX (gemcitabine 750 mg/m^2 over 75 minutes, d4 and 11, docetaxel 30 mg/m^2 d4 and 11 and capecitabine 750 mg/m^2 bd d1–14, q3w) achieved a response rate of around 20% and median OS of 15 months [Fine *et al.* 2009]. The combination of gemcitabine, cisplatin and infusional 5-FU achieved survival median OS of 9.0 months [Novarino *et al.* 2004] and 10 months [Kim *et al.* 2009]. Gemcitabine, 5-FU and cisplatin (GFP) and gemcitabine, oxaliplatin and infusional 5-FU both achieved an OS of 7.5 months in a mixed group [Wagner *et al.* 2007]. A retrospective audit of gemcitabine, cisplatin, folinic acid then bolus and infusional 5-FU described a 16% response rate and median OS of 11.8 months [Araneo *et al.* 2003]. These multidrug combinations await randomized testing.

Multidrug combinations without gemcitabine

First-line multidrug combinations without gemcitabine have had mixed results, with any effect tending to be offset by significant toxicity. An interim analysis (presented as an abstract) of a randomized trial of FOLFIRINOX (oxaliplatin 85 mg/m^2 d1, irinotecan 180 mg/m^2 d1, leucovorin 400 mg/m^2 d1, 5-FU 400 mg/m^2 bolus d1 and 2, 400 mg/m^2 46 h continuous infusion q2w) showed a better response rate than gemcitabine (41% *versus* 12%) [Ychou *et al.* 2007]. Survival data were not provided. Also, a very small phase II study of POLF (paclitaxel 60 mg/m^2 q1w, oxaliplatin 50 mg/m^2 q1w, leucovorin 20 mg/m^2 q1w and 5-FU 425 mg/m^2 q1w) achieved symptomatic improvement in seven of nine participants [Chue, 2007].

Combinations with limited effect include streptozocin, mitomycin and 5-FU [Kelsen *et al.* 1991; GITSG, 1986; Oster *et al.* 1986], doxorubicin, mitomycin and 5-FU [GITSG, 1986; Oster *et al.* 1986], cisplatin, ara-c and caffeine [Kelsen *et al.* 1991], 5-FU, doxorubicin and cisplatin [Cullinan *et al.* 1990], 5-FU, doxorubicin, mitomycin-C and streptozocin [Bukowski *et al.* 1993], etoposide, folinic acid, 5-FU, interferon α-2b [MacDonald *et al.* 2000], etoposide, folinic acid, 5-FU, epirubicin [Maiello *et al.* 1998], and 5-FU, cyclophosphamide, vincristine, methotrexate and mitomycin [Cullinan *et al.* 1990].

Targeted therapy

All cancers acquire six hallmark abilities to function as invasive tumours, including self sufficiency of growth signalling, insensitivity to antigrowth signals, evasion of apoptosis, limitless

Table 3. Randomized controlled trials of first line targeted therapy in metastatic pancreatic adenocarcinoma.

Author	Sample size	Interventions	Radiological response	*p* value	Median overall survival (months)	*p* value
Moore *et al.* 2007	569	Gem + Erl	9%	np	6.2*	0.04
		Gem	8%		5.9	
Philip *et al.* 2007	766	Gem + Cet	7%	np	6.5	0.14
		Gem	7%		6.0	
Burtness *et al.* 2008	87	Irino + Docet + Cet	7%	np	5.3	np
		Irino + Docet	5%		6.5	
Kindler *et al.* 2009a	632	Gem + Axi	—	—	8.2	(HR 1.06)
		Gem	—		7.4	
Vervenne *et al.* 2008	607	Gem + Erl	8.6%	np	6.0	(HR 0.89)
		Gem + Erl + Bev	13.5%		7.1	
Kindler *et al.* 2008	139	Gem + Bev + Cet	23%	np	7.8	np
		Gem + Bev + Erl	18%		7.2	
Bramhall *et al.* 2002	239	Gem + Mar	11%	0.07	5.4	0.95
		Gem	16%		5.4	
Wright *et al.* 2006	434	Gem + Vir	—	—	6.3	np
		Gem			6.0	

Axi, axitinib; Bev, bevacizumab; Cet, cetuximab; Erl, erlotinib; Gem, gemcitabine; HR, hazard ratio; Irino, irinotecan; Docet, docetaxel; Mar, marimastat; np, not provided; Vir, virulizin; * = $p<.05$.

reproduction, the ability to invade and metastasize, and to develop a blood supply [Hanahan *et al.* 2000]. Mutations, deletions, and amplifications of genes that encode proteins that regulate cellular pathways are known to be present in metastatic PAC [Jones *et al.* 2008]. For example, PAC tumour cells achieve self sufficiency in growth signalling by epidermal growth factor receptor (EGFR) overexpression and activating k-RAS mutations, become insensitive to anti-growth signals through permissive cyclin-D mutations, and facilitate angiogenesis by vascular endothelial growth factor (VEGF) overexpression. These and other factors should, in theory, provide multiple targets for molecular therapy. Unfortunately, as with cytotoxic agents, the targeted agents have seen limited success so far (see Table 3).

Preventing self sufficiency in growth signalling

Small-molecule EGFR tyrosine kinase inhibitors (TKIs) are the only targeted agents to show a survival advantage in RCTs, and have become the standard of care in some jurisdictions that can fund them. The addition of the oral EGFR TKI erlotinib (100 or 150 mg/day) to gemcitabine increases survival [Moore *et al.* 2007], but some argue not in a clinically significant way (see Table 3). Median OS increased from 5.9 to 6.2 months, an improvement of about 10 days, despite no difference in objective response rate. More patients in the combined arm developed an interstitial lung disease-like syndrome. There was more diarrhoea in the combined group, but no other difference in the quality-of-life measures.

Erlotinib has also shown activity with gemcitabine in a small nonrandomized phase II study in a Japanese cohort, with a response rate of 20%, although a quarter of patients discontinued the drug due to adverse effects [Nakachi et al. 2009]. Erlotinib with FDR gemcitabine achieved response rates of 24% [Espinosa *et al.* 2007] and 8% [Milella *et al.* 2009]. The efficacy of the EGFR TKI, gefitinib, compared to erlotinib may not be clear, however when coupled with gemcitabine it achieved a response rate of 7% and a median OS of 7.4 months [Fountzilas *et al.* 2007].

EGFR inhibitors have been combined with gemcitibine and a third agent in uncontrolled phase II trials. Erlotinib (100 mg/day) added to gemcitabine (1000 mg/m^2 q3/4w) and capecitabine (1660 mg/m^2/day q3/4w) achieved a response rate of 32% and a median OS of 12 months [Oh *et al.* 2009], although EGFR overexpression was associated with a shorter response. Erlotinib with gemcitabine and docetaxel achieved a response rate of 22%, improvement in pain or quality of life in 50%, and a median OS of 5.3 months, although the regimen was reasonably toxic [Samelis *et al.* 2008]. Previous failure of regimens as they move from phase II to III trials suggests caution in interpreting these results.

The anti-EGFR monoclonal antibodies have not been as effective as the TKIs (see Table 3). A phase III trial of gemcitabine plus cetuximab (400 mg/m^2 w1, then 250 mg/m^2 q1w) showed no improvement in median OS over gemcitabine alone (Burris regimen) [Philip *et al.* 2007]. Cetuximab did not improve response rate or median OS when added to irinotecan and docetaxel [Burtness *et al.* 2008]. These disappointing results in randomized trials occurred despite promising phase II results when cetuximab was added to a gemcitabine/oxaliplatin combination [Merchan *et al.* 2008; Kullmann *et al.* 2007], and from retrospective review of addition to oxaliplatin and irinotecan [Lee *et al.* 2007]. Perhaps the lack of response to EGFR monoclonals in PAC is not surprising given the k-RAS story in colorectal cancer. Cetuximab is not effective in colorectal cancer in the presence of an activating mutation in downstream k-RAS, presumably because inhibiting an upstream target no longer inhibits the EGFR pathway [Karapetis *et al.* 2008]. Unfortunately in PAC, an activating k-RAS mutation occurs in more than three-quarters of tumours [Pellegata *et al.* 1994].

Some hope for inhibiting pro-proliferation pathways remains. Talabostat, a small-molecule inhibitor of fibroblast activation protein achieved a complete response in one patient when coupled with gemcitabine a small phase II trial [Nugent *et al.* 2007]. The TGF-B2 inhibitor, AP12009, has achieved a complete response in a patient in a phase I/II trial [Oettle *et al.* 2007].

Inhibition of other targets in the EGFR pathway has been largely disappointing. As with cetuximab, the HER2 monolclonal receptor blocker, trastuzumab, has not been effective, even with tumours that overexpress HER2 on immunohistochemical (IHC) testing [Harder *et al.* 2009; Safran *et al.* 2004]. The latter study found that only 11% showed IHC3+ HER2 staining, suggesting that few PACs express an appropriate target for this agent. Perhaps not surprisingly then, lapatinib, a TKI that targets HER2, was also ineffective [Safran *et al.* 2009].

Other agents with little efficacy include the anti H-Ras agent, ISIS-2503 [Alberts *et al.* 2004], and the selective farnesyltransferase inhibitor, R115777, did not achieve significant response rates in combination with gemcitabine [Van Cutsem *et al.* 2004; Cohen *et al.* 2003]. Zoledronic acid is thought to inhibit p21 ras/raf-1/MEK1/ERKL signalling but also showed little activity combined with gemcitabine [Cox *et al.* 2006].

Inhibiting sustained angiogenesis

A growing tumour must develop a blood supply to enable its growth. The VEGF inhibitor, bevacizumab, has only been tested as the sole targeted agent in addition to cytotoxic agents. All trials are uncontrolled and phase II, but response rates are promising. With fortnightly gemcitabine and docetaxel, bevacizumab (10 mg/m^2 q2w) achieved a response rate approaching 50% [Picozzi *et al.* 2009]. With gemcitabine and capecitabine, or with gemcitabine and cisplatin, bevacizumab (15 mg/m^2 q3w) achieved response rates over 20% and with median OS above 8 months [Iyer *et al.* 2008; Ko *et al.* 2007a]. With fortnightly gemcitabine and oxaliplatin, bevacizumab (10 mg/kg q2w) showed a promising response rate of 39%, but a high grade 3 and 4 toxicity rate of 86%, mostly fatigue, nausea, pain and shortness of breath [Fogelman *et al.* 2009]. Similar results had been achieved in another phase II trial with the same protocol, but there were 4% treatment-related fatalities [Kim *et al.* 2007].

Other antiangiogenic agents have been trialled. The oral VEGF receptor (VEGFR) inhibitor, axitinib (5 mg bd ongoing), added to gemcitabine, gave a trend toward increase in OS in a randomized phase II trial [Spano *et al.* 2008], but the subsequent phase III trial was discontinued after an interim analysis showed no survival benefit [Kindler *et al.* 2009a] (see Table 3). The metalloproteinase inhibitor marimastat is also expected to have antiangiogenic properties, but did not have clinical efficacy in PAC [Bramhall *et al.* 2001, 2002]. The antiangiogenic monoclonal antibody, volocixumab, blocks fibronectin binding to a5β1 integrin and induces apoptosis of endothelial cells, and is being further evaluated after showing activity in early phase trials [Evans *et al.* 2007; Valle *et al.* 2006].

Combined growth factor and angiogenesis inhibition

Given the minimal reponse achieved from targeting a proliferative or an angiogenic pathway separately, researchers have attempted to block more than one pathway at a time. Reflecting this, the VEGF inhibitor, bevacizumab, has only moved through to randomized trials in combination with a second targeted agent (see Table 3).

Adding bevacizumab to concurrent gemcitabine and erlotinib, saw a nonsignificant trend towards improved median OS in a phase III trial of 7.1 *versus* 6.0 months [Vervenne *et al.* 2008]. In this study, participants who did not develop a rash had a median OS of less than 5 months, whereas those who developed a grade 2 or higher rash achieved a median OS of more than 8 months [Van Cutsem *et al.* 2009].

Other studies of dual pathway inhibition have been only modestly effective. The addition of either cetuximab or erlotinib to gemcitabine and bevacizumab achieved a response rate of around 20% and a median OS of over 7 months [Kindler *et al.* 2008]. The combination of dual monoclonal antibodies cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 q1w) and bevacizumab (10 mg/m^2 q2w) without a cytotoxic agent showed no objective responses in a phase II trial, but a response rate of 10% when added to FDR gemcitabine [Ko *et al.* 2009]. It seems that a cytotoxic agent is still required as part of a successful regimen.

Preventing evasion of apoptosis

All cancers successfully evade cellular mechanisms of programmed cell death [Hanahan and Weinberg, 2000]. Some pro-apoptotic agents have shown promise in nonrandomized phase II trials. AMG655 (conatumumab) is a humanized monoclonal antibody that binds to human death receptor, and achieved a 23% response rate combined with gemcitabine [Kindler *et al.* 2009b]. Survival data are pending. The DNA pathway checkpoint activator, ARQ 501, probably activates a proapoptotic protein and has been associated with objective responses in a phase II trial [Khong *et al.* 2007]. A combination of gemcitabine, cisplatin and the supporter of apoptosis, RP101, achieved a response rate of 33% in a small phase II trial of 13 patients [Fahrig *et al.* 2006].

Some other pro-apoptotic agents have not appeared effective. Proteosome inhibitors might reduce the effect of 26S proteasomes that break down proapoptotic proteins such as p53, but the proteasome inhibitor, bortezomib, has not been effective in PAC [Alberts *et al.* 2005]. The protein kinases of the AKT gene family are thought to promote survival of antiapoptotic genes, overcome cell cycle arrest, and have a role in tumour angiogenesis. The PKCβ and PI3K/AKT inhibitor, enzastaurin [Richards *et al.* 2009], and the AKT inhibitor, perifosine [Marsh Rde *et al.* 2007], have not shown clinical utility.

Reducing insensitivity to antigrowth signals

Effective tumours must also become resistant to signals causing arrest of growth [Hanahan and Weinberg, 2000]. For example, histone deacetylase inhibitors might downregulate the Rb pathway in cell cycle control and downregulate p21 gene expression, thereby reducing inhibition of p53. Unfortunately, the oral histone deacetylase inhibitor, CI-994, was not effective [Richards *et al.* 2006].

Targeting multiple pathways

Tyrosine kinase inhibitors that target multiple pathways (multi-TKIs) are theoretically promising, but not yet tested beyond nonrandomized phase II trials. Masitinib (9 mg/kg/day), a multi-TKI targeting c-Kit, PDGFR, Fibroblast Growth Factor Receptor 3 and affecting the Focal Adhesion Kinase pathway, added to gemcitabine achieved a response rate of 23% in metastatic PAC and a median OS of 6.8 months [Mitry *et al.* 2009], and a clinical benefit rate of only 16% with a median OS of 7.1 months in another [Hammel *et al.* 2009]. The multi-TKI, sorafenib, targets b-Raf and VEGF among other targets, but had little impact in combination with gemcitabine [Wallace *et al.* 2007], or in combination with gemcitabine or erlotinib [Cohen *et al.* 2009].

Other targets

Triapine is a small molecule inhibitor of the DNA repair enzyme, ribonucleotide reductase, and had mild activity in PAC in one phase II trial [Greeno *et al.* 2006].

Anticoagulation

Patients with PAC experience high rates of venous thromboembolic disease (VTE). The low molecular weight heparins (LMWH) were initially thought to have inherent antitumour activity, but have more recently been trialled to reduce 'early death burden' from thrombosis. There is solid RCT evidence that prophylactic 'chemo-anticoagulation' in metastatic PAC reduces rate of VTE. In the CONKO 004 trial, the LMWH enoxaparin (1 mg/kg/day), reduced venous thromboembolic events from 15% to 5% without an increase in bleeding complications [Pelzer *et al.* 2009]. Similarly, the phase IIb UK-FRAGEM study compared gemcitabine with or without 100 days of weight adjusted dalteparin, with a significant reduction in VTE from

31% to 12% [Maraveyas *et al.* 2009]. Survival data for both trials are maturing, but interim analyses look unlikely to show an overall benefit. In contrast, the LMWH nadroparin, was not effective [Voorthuizen *et al.* 2006].

Other modalities

Modalities beyond cytotoxics and cell-pathway targeted agents have also been tested in metastatic PAC, including immune agents, gene therapy and hyperthermia.

Immune agents have not proved effective to date. The telemorase peptide vaccine, GV-1001, did not improve survival in combination with gemcitabine resulting in early stopping of this phase III trial [Buanes *et al.* 2009]. Virulizin is an intramuscular immune modulator that induces macrophage IL-12 production, which leads to Natural Killer cell-mediated antitumour activity. Virulizin combined with gemcitabine did not improve survival in a randomized phase III study [Wright *et al.* 2006]. Other immune agents in trial include the vaccine, panvac-VF G17DT, an immune stimulant that raises antibodies to growth factor gastrin-17 called immunogen, a vaccination therapy using degraded dendritic cells [Bauer *et al.* 2007], and a peptide vaccine matched to circulating IgG antibodies and cytotoxic T cells [Yanagimoto *et al.* 2006].

Gene therapy has been tested in a phase I/II trial, where intravenous rexin-G, a dominant negative analogue of the cyclin-G1 gene, was safe and achieved one partial response [Chawla *et al.* 2009].

Transdermal regional 'heating' of the tumour immediately after gemcitabine infusion has been reported to increase mean survival from 8 to 12 months in a multigroup phase II study, although this study was presented in abstract form, and it is not clear whether the groups were randomized [Yasuda *et al.* 2008]. The same process was applied to a small metastatic group ($n = 12$) in second-line treatment with a gemcitabine and cisplatin doublet, and although there were no radiological responses, 1-year survival was 30% [Tschoep *et al.* 2006]. The value of localizing this heating in a disseminated disease awaits clarification.

Second-line treatment

An audit at a single centre showed that less than half of patients were given second-line chemotherapy [Schrag *et al.* 2007]. This may change after announcement of the first positive randomized phase III trial in second-line treatment of metastatic PAC.

Second-line cytotoxic therapy

The CONKO 003 investigators randomized 168 patients to receive 5-FU and folinic acid with or without oxaliplatin (OFF, oxaliplatin 85 mg/m^2 days 8, 22; folinic acid 500 mg/m^2 then 5-FU 2600 mg/m^2 days 1, 8, 15, 22 q6w) [Pelzer *et al.* 2008]. The group who received OFF had a significantly higher median OS of 6 months *versus* 3 months in the 5-FU group.

Oxaliplatin had shown mild activity in previous phase II studies before CONKO 003. The combination of 5-FU, folinic acid and oxaliplatin had resulted in one positive [Tsavaris *et al.* 2005] and one negative [Mitry *et al.* 2006] trial. Oxaliplatin had also been combined with 3-weekly ralitrexed and shown some improvement in quality of life [Reni *et al.* 2006c]. Capecitabine and oxaliplatin (Xelox) achieved a response in one of 15 patients in one study [Gasent Blesa *et al.* 2009] and one response in 39 patients in another [Xiong *et al.* 2006]. Patients randomized to FOLFOX (or FOLFIRI3) acheived combined partial response or stable disease of less than 30% [Hwang *et al.* 2009]. Pemitrexed and oxaliplatin achieved partial responses in three of 15 patients [Mazzer *et al.* 2009].

Phase II studies of other second-line cytotoxic agents have found a few with modest activity. S1 acheived response rates of 18% [Morizane *et al.* 2009] and 15% [Sudo *et al.* 2008] in phase II trials, and 17% in a single-institution audit [Nakai *et al.* 2009]. Irinotecan monotherapy acheived 14% response rate [Boeck *et al.* 2007], and 16% in combination with ralitrexed [Ulrich-Pur *et al.* 2003]. Capecitabine and docetaxel achieved a 13% response rate in good performance status patients [Blaya *et al.* 2007], but no responses in a small trial in patients with poorer performance status [Lopes *et al.* 2006]. Ralitrexed alone achieved a 4% response rate [Boeck *et al.* 2006]. No objective responses were achieved by single-agent capecitabine (1250 mg/m^2 bd d1–14 q3w), docetaxel and irinotecan [Ko *et al.* 2008], mitomycin, docetaxel and irinotecan [Reni *et al.* 2004], and mitomycin and ifosfamide [Cereda *et al.* 2008].

Second-line targeted therapy

Molecular targeted therapies have some activity in gemcitabine-refractory metastatic PAC, but are

yet to be examined in randomized trials. Single-agent erlotinib achieved a 23% response rate in a heavily pretreated phase II mixed group [Epelbaum *et al.* 2007], and erlotinib titrated to induce rash achieved stable disease for longer than 8 weeks in one-quarter of 40 patients who had previously received gemcitabine [Tang *et al.* 2009]. A combined VEGF and PDGF inhibitor, valatinib, might have activity with 31% of patients alive at 6 months when given to a predominantly metastatic group [Dragovich *et al.* 2009].

Several single-agent, second-line targeted therapy trials have been negative. No second-line responses were achieved by the mammalian target of rapamycin inhibitor, everolimus [Shroff *et al.* 2009; Wolpin *et al.* 2008], the multi-TKI sunitinib [O'Reilly *et al.* 2008], the microtubule assembly inhibitors dolastatin-10 [Kindler *et al.* 2005] and ARC-100 [Reeves *et al.* 2009], the halichondrin B analogue eribulin [Moore *et al.* 2009], or the ribonucleotide reductase inhibitor, triapine [Groteluschen *et al.* 2006].

Several combinations of targeted agents and/or cytotoxic agents have also been ineffective to date in second-line treatment. This includes erlotinib and bevacizumab [Ko *et al.* 2007b], docetaxel and gefitinib [Shadad *et al.* 2006], docetaxel and the cyclin-dependent-kinase inhibitor flavopiridol [Carvajal *et al.* 2008], gefitinib and docetaxel [Blaszkowsky *et al.* 2007; Brell *et al.* 2007], and bevacizumab with docetaxel [Astsaturov *et al.* 2007].

In general, good performance status is the most important predictor of response to second-line therapy, and this clinical observation is supported by a retrospective multivariate analysis of a variety of cytotoxic schedules [Mancuso *et al.* 2007]. Gemcitabine is effective as second-line treatment in the event that the first-line regimen that did not contain gemcitabine, with a clinical benefit in 27% of patients that lasted for a median of 3 months [Rothenberg *et al.* 1996].

The future

There are 747 active trials on the US government clinical trials registry in PAC alone, including 41 phase III trials involving patients with metastatic PAC. Registered phase III trials will test gemcitabine with a second cytotoxic (5-FU, capecitabine, cisplatin, oxaliplatin, mitomycin, pemetrexed) or targeted agent (erlotinib, ccetuximab, bevicuzumab). Most of these trials have had initial reports. Several novel agents are currently in phase III trial, including newer cytotoxics nab-paclitaxel, S1, rubitecan, exatecan, and irofulven. These trials offer hope for improved responses through enhanced delivery of current agents or new regimens.

Improved delivery of current agents

Small gains may be made by maximizing the effectiveness of current chemotherapeutic agents. With respect to gemcitabine, there may be better ways to deliver this drug other than bolus or FDR dosing, and these might be guided by patient biology. For example, retrospective analysis of the RTOG 9704 trial showed that levels of hENT1, the protein that transports gemcitabine into cells, were correlated with survival after gemcitabine chemotherapy [Farrell *et al.* 2009]. In another example, studies in mouse models suggest that drug delivery to the tumour is reduced by desmoplastic stroma that is produced by these tumours [Olive *et al.* 2009]. They used an inhibitor of the Hedgehog pathway to reduce tumour stroma, improve intratumoural chemotherapy concentration and tumour response. This approach awaits clinical trial. Finally, multidrug regimens might provide further improvement in survival and clinical benefit.

Personalized medicine

Perhaps the greatest hope in the treatment of metastatic PAC lies with rational use of molecular targeted agents (or cytotoxics) in tumours where they are likely to be effective. This is no small feat in PAC, where analysis of the genome of 24 pancreatic tumours suggested an average of 63 mutations in PAC grouped into 12 key pathways [Jones *et al.* 2008]. The authors suggest that irrespective of the individual mutations, we might achieve more by targeting a point in each pathway downstream from the potential raft of mutation sites.

Rational use of therapies requires biomarkers that predict a subsequent response, and these are so far uncommon in pancreatic cancer. Pancreatic tumours known to overexpress SPARC (secreted protein acidic and rich in cysteine) have been more effectively targeted with nab-paclitaxel than tumours that do not express this protein [Von Hoff et al. 2009], and so might provide just such a marker. Some translational centres have trialled assessment of biomarkers of each individual tumour and attempted to predict a

drug combination based on this profile. Trial results are pending.

It is also likely that epigenetic control of gene expression by methylation or noncoding RNA (eg microRNA) has a role in the pathogenesis of PAC, and therefore might be suitable for biomarkers.

Improvements in trial design

Trials in metastatic pancreatic cancer have been hampered by the short natural history of the disease, difficulty recruiting patients with a tissue diagnosis and appropriate performance status, and a relatively inactive standard of care. Trials are therefore small and recruitment slow, and researchers sometimes introduce further variance by including patients with unresectable but nonmetastatic disease. These patients typically have a longer survival, so including these patients in metastatic PAC trials adds noise to the data, making detection of a statistically signicant difference between groups more difficult.

Palliation is an important consideration when drugs have a limited impact on the natural history of PAC. Researchers use a variety of methods to measure quality of life from none, to clinical benefit surrogates, to formal inventories; but the lack of a sensitive tool makes detecting an improvement in quality of life difficult. Nonetheless, measurement of quality of life should be an expected part of all trials in metastatic PAC, as it is a key aim of treatment.

Finally, given that only one-quarter of patients will benefit from gemcitiabine, we need biomarkers to predict which 75% of patients should not receive chemotherapy unnecessarily. MicroRNA has shown predictive value in other tumour types, and candidate biomarkers should be included prospectively in all clinical trials in PAC. Recent examples in PAC include DPC4 gene status as a prognostic marker [Iacobuzio-Donahue *et al.* 2009], and certain mismatch repair gene polymorphisms as predictive markers [Dong *et al.* 2009]. Tumour tissue sample should also be collected from subjects in trials to also allow retrospective biomarker validation when new technologies arrive. It is difficult for many jurisdictions to offer established agents such as erlotinib due to cost, but the cost benefit improves markedly if we could predict which patients will respond.

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Conflict of interest statement

None declared.

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