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

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### Abstract

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

incorporating predictive biomarkers and quality of life measures whenever possible into study design.

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

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

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### INTRODUCTION

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

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

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

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

## GEMCITABINE-CONTAINING REGIMENS

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

Kozuch *et al*<sup>[4]</sup> first demonstrated the feasibility of this approach in a retrospective analysis of 34 consecutive patients with metastatic pancreatic cancer receiving irinotecan/gemcitabine/5-FU/leucovorin/cisplatin (G-FLIP), 32 of whom had previously progressed on gemcitabine and 31 who had progressed specifically on gemcitabine/5-FU/cisplatin (GFP). Of these 31 patients, whose regimen was altered only by the addition of irinotecan, 7 (23%) achieved partial responses (PR) and 7

(23%) achieved stable disease (SD). Notably, 8 of these 14 patients demonstrating disease control had previously experienced progressive disease as a best response to GFP alone. Median progression-free and overall survival (OS) for all 34 patients receiving second-line G-FLIP was 3.9 and 10.3 mo, respectively.

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

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

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

## NOVEL MONOTHERAPEUTIC REGIMENS

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

**Table 1 Clinical studies of second-line gemcitabine-containing regimens**

Ref.	Regimen	Sample size	RR <sup>1</sup>	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Kozuch <i>et al</i> <sup>[4]</sup> , 2001	G-FLIP	34	24%	3.9	10.3	47%
Reni <i>et al</i> <sup>[6]</sup> , 2008	PEFG	46	24%	5.0	8.3	26%
Demols <i>et al</i> <sup>[9]</sup> , 2006	GEMOX	33	21%	4.2	6.0	NR
Fortune <i>et al</i> <sup>[76]</sup> , 2009	GEMOX	17	24%	2.6	6.4	29%
Stathopoulos <i>et al</i> <sup>[77]</sup> , 2006	Gem, Lipoplatin	24	8.3%	NR	4.0	NR
Tschoep <i>et al</i> <sup>[11]</sup> , 2013	Gem, Cisplatin, RHT	23	4.3%	4.3	NR	NR
Morizane <i>et al</i> <sup>[12]</sup> , 2012	Gem, S-1	40	18%	2.8	7.0	18%
Ernani <i>et al</i> <sup>[13]</sup> , 2012	Gem, <i>nab</i> -Paclitaxel	10	20%	3.2	NR	NR

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

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

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

Inhibitors of microtubule dynamics, including taxanes (docetaxel, paclitaxel, *nab*-paclitaxel) and eribulin mesylate, have also been investigated in small retrospective and single-arm phase II studies<sup>[18-22]</sup>. Given the unique formulation of *nab*-paclitaxel that may allow it to more successfully traverse the blood-stroma barrier, in addition to the positive results from the phase III MPACT trial es-

tablishing the combination of *nab*-paclitaxel/gemcitabine as a viable option for first-line therapy<sup>[23]</sup>, there has been natural interest in evaluating this agent in the salvage setting. To date, we only have results from a small phase II study of *nab*-paclitaxel as a single agent for refractory pancreatic cancer, in which there was a single objective response (with an additional 6 achieving disease stabilization) amongst 19 patients, with a median PFS of 1.7 mo. Estimated median OS in this cohort was 7.3 mo<sup>[22]</sup>.

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

## CYTOTOXIC COMBINATION REGIMENS (NON-GEMCITABINE-BASED)

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

### Platinum-based combinations

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

**Table 2 Clinical studies of second-line monotherapeutic regimens**

Ref.	Regimen	Sample size	RR <sup>1</sup>	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Jacobs <i>et al</i> <sup>[16]</sup> , 2004	Rubitecan	198	11%	1.9	3.5	NR
Burris <i>et al</i> <sup>[15]</sup> , 2005	Rubitecan	58	5.2%	2.0	3.1	9%
Yi <i>et al</i> <sup>[78]</sup> , 2009	Irinotecan	33	9%	2.0	6.6	NR
Takahara <i>et al</i> <sup>[79]</sup> , 2013	Irinotecan	56	3.6%	2.9	5.3	NR
Ko <i>et al</i> <sup>[17]</sup> , 2013	Nanoliposomal irinotecan	40	7.5%	2.4	5.2	25%
Oettle <i>et al</i> <sup>[18]</sup> , 2000	Paclitaxel	18	5.6%	NR	4.1	NR
Maeda <i>et al</i> <sup>[19]</sup> , 2011	Paclitaxel	30	10%	NR	6.7	NR
Cereda <i>et al</i> <sup>[20]</sup> , 2008	Docetaxel	10	0%	1.5	4.0	0%
Hosein <i>et al</i> <sup>[22]</sup> , 2013	<i>Nab</i> -Paclitaxel	19	5%	1.7	7.3	37%
Boeck <i>et al</i> <sup>[24]</sup> , 2007	Capecitabine	39	0%	2.3	7.6	NR
Bodoky <i>et al</i> <sup>[59]</sup> , 2012	Capecitabine	38	7.9%	2.2	5.0	NR
Morizane <i>et al</i> <sup>[25]</sup> , 2009	S-1	40	15%	2.0	4.5	14%
Todaka <i>et al</i> <sup>[26]</sup> , 2010	S-1	52	3.8%	2.1	5.8	12%
Mizuno <i>et al</i> <sup>[28]</sup> , 2013	S-1	67	6%	1.9	5.9	NR
Ioka <i>et al</i> <sup>[27]</sup> , 2013	Best fluoropyrimidine <sup>2</sup>	40	10%	3.8	7.5	NR
Fukahori <i>et al</i> <sup>[80]</sup> , 2012	Gemcitabine <sup>3</sup>	27	14%	2.6	8.0	NR
Androulakis <i>et al</i> <sup>[81]</sup> , 2005	Oxaliplatin	18	0%	NR	3.5	NR
Boeck <i>et al</i> <sup>[82]</sup> , 2007	Pemetrexed	52	3.8%	1.6	4.7	NR
Ulrich-Pur <i>et al</i> <sup>[48]</sup> , 2003	Raltitrexed	19	0%	2.5	4.3	0%
Kindler <i>et al</i> <sup>[83]</sup> , 2008	Arsenic trioxide	13	0%	1.6	3.8	0%

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

times similar to that given in colorectal cancer, have also been examined with demonstrable evidence of activity in this setting. Yoo *et al*<sup>[30]</sup> conducted a randomized phase II trial comparing modified versions of FOLFOX and FOLFIRI (5-FU, leucovorin, irinotecan) for gemcitabine-refractory advanced pancreatic cancer. However, in this study, response rates to both regimens were low (7% and 0%) with associated PFS times of 6.0 and 8.3 wk, respectively. A more recent phase II trial of FOLFOX4 from Korea reported modestly better results, with an objective response rate of 11%, a tumor stabilization rate of 41%, and a median time to progression of 9.9 wk<sup>[31]</sup>. Single-arm studies of capecitabine plus oxaliplatin (CapOx) have also been performed by several Asian groups, with fairly comparable results<sup>[32-35]</sup>.

The most convincing evidence supporting a fluoropyrimidine/platinum-based combination comes from Germany, using a regimen termed OFF, in which 5-FU (given as a 24-h infusion) plus folinic acid are given weekly x 4 in 6-wk cycles, with the addition of oxaliplatin during weeks 2 and 4. Prompted by promising results from a phase II trial using this regimen (disease control rate lasting 12 wk or better in 43% of study patients), a phase III randomized trial was designed by Charité Onkologie (CONKO-003) in which patients were randomized to receive either the OFF regimen or best supportive care (BSC). A sample size of 165 was planned, but the study was stopped due to poor accrual (likely from the possibility of randomization to a BSC arm) after enrolling 46 patients<sup>[36]</sup>. Even with the limited sample size, overall survival in patients receiving OFF was 4.8 mo compared to 2.3 mo in those receiving BSC ( $P = 0.008$ )<sup>[37]</sup>. The investigators sought to build on these results with another randomized phase III trial comparing OFF to weekly 5-FU/folinic acid (FF) alone. The results of this

168-patient trial were presented in abstract form at the 2008 ASCO meeting<sup>[38]</sup>. As compared to the FF regimen, patients receiving OFF demonstrated improved PFS (13 wk *vs* 9 wk,  $P = 0.012$ ) and median OS (26 wk *vs* 13 wk,  $P = 0.014$ ). This trial marks the largest phase III study to date showing a survival benefit of second-line therapy for pancreatic cancer; as such, the OFF regimen (or iterations thereof) has become accepted as the de facto standard treatment of refractory disease.

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

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

### Non-platinum-based combinations

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

**Table 3** Clinical studies of second-line cytotoxic combination regimens

Ref.	Regimen	Sample size	RR <sup>1</sup>	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Platinum based regimens						
Tsavaris <i>et al</i> <sup>[29]</sup> , 2005	FOLFOX	30	23%	5.1	5.8	NR
Mitry <i>et al</i> <sup>[84]</sup> , 2006	FOLFOX	18	0%	0.9	1.3	NR
Gebbia <i>et al</i> <sup>[85]</sup> , 2007	FOLFOX	42	14%	4	6.7	NR
Novarino <i>et al</i> <sup>[86]</sup> , 2009	FOLFOX	23	0%	2.7	4.0	NR
Yoo <i>et al</i> <sup>[30]</sup> , 2009	FOLFOX	30	6.7%	1.4	3.5	NR
Chung <i>et al</i> <sup>[31]</sup> , 2013	FOLFOX	44	11%	2.3	7.3	NR
Berk <i>et al</i> <sup>[35]</sup> , 2012	FOLFOX	46	17%	3.7	5.8	NR
Sancho <i>et al</i> <sup>[32]</sup> , 2008	CapOx <sup>2</sup>	18	5.6%	3.9	5.8	NR
Xiong <i>et al</i> <sup>[33]</sup> , 2008	CapOx	41	2.4%	2.3	5.4	21%
Gasent-Blesa <i>et al</i> <sup>[34]</sup> , 2009	CapOx	15	6.7%	NR	5.3	NR
Berk <i>et al</i> <sup>[35]</sup> , 2012	CapOx	39	18%	3.7	4.9	NR
Pelzer <i>et al</i> <sup>[87]</sup> , 2009	OFF	37	5.4%	2.8	5.1	NR
Pelzer <i>et al</i> <sup>[37]</sup> , 2011	OFF	23	0%	NR	4.8	NR
Pelzer <i>et al</i> <sup>[38]</sup> , 2008	OFF	76	NR	3	6.1	NR
Assaf <i>et al</i> <sup>[40]</sup> , 2011	FOLFIRINOX	27	19%	5.4	8.5	NR
Togawa <i>et al</i> <sup>[88]</sup> , 2007	Cisplatin, S-1	17	29%	NR	10	32%
Kim <i>et al</i> <sup>[89]</sup> , 2012	Cisplatin, S-1	11	0%	1.5	2.7	NR
Takahara <i>et al</i> <sup>[90]</sup> , 2013	Oxaliplatin, S-1	30	10%	3.4	5.0	NR
Cantore <i>et al</i> <sup>[41]</sup> , 2004	Oxaliplatin, irinotecan	30	10%	4.1	5.9	23%
Oh <i>et al</i> <sup>[42]</sup> , 2010	Oxaliplatin, irinotecan	14	21%	1.4	4.1	7.1%
Reni <i>et al</i> <sup>[43]</sup> , 2006	Oxaliplatin, raltitrexed	41	24%	1.8	5.2	12%
Mazzer <i>et al</i> <sup>[44]</sup> , 2009	Oxaliplatin, pemetrexed	16	56%	3.3	NR	NR
Non-platinum based regimens						
Yoo <i>et al</i> <sup>[30]</sup> , 2009	FOLFIRI	31	0%	1.9	3.9	NR
Gebbia <i>et al</i> <sup>[45]</sup> , 2010	FOLFIRI	40	15%	3.7	6.0	0%
Cereda <i>et al</i> <sup>[91]</sup> , 2010	FOLFIRI or XELIRI	34	0%	2.0	4.2	5.6%
Zaniboni <i>et al</i> <sup>[46]</sup> , 2012	FOLFIRI	50	8%	3.2	5.0	NR
Neuzillet <i>et al</i> <sup>[47]</sup> , 2012	FOLFIRI	63	7.9%	3.0	6.6	NR
Mizuno <i>et al</i> <sup>[28]</sup> , 2013	S-1, irinotecan	60	18%	3.6	6.9	NR
Blaya <i>et al</i> <sup>[49]</sup> , 2007	Capecitabine, docetaxel	24	13%	NR	NR	NR
Katopodis <i>et al</i> <sup>[50]</sup> , 2011	Capecitabine, docetaxel	31	9.7%	2.4	6.4	15%
Kim <i>et al</i> <sup>[51]</sup> , 2009	5-FU, paclitaxel	28	10%	2.5	7.6	NR
Lee <i>et al</i> <sup>[92]</sup> , 2009	Conti-FAM <sup>3</sup>	31	12%	2.3	6.7	NR
Shi <i>et al</i> <sup>[93]</sup> , 2012	Capecitabine, thalidomide	31	6.5%	2.7	6.1	NR
Saif <i>et al</i> <sup>[94]</sup> , 2009	Capecitabine, PHY906	25	5.3%	NR	NR	NR
Ulrich-Pur <i>et al</i> <sup>[48]</sup> , 2003	Irinotecan, raltitrexed	19	16%	4.0	6.5	NR
Reni <i>et al</i> <sup>[95]</sup> , 2004	MDI	15	0%	1.7	6.1	0%
Cereda <i>et al</i> <sup>[96]</sup> , 2011	Mitomycin, ifosfamide	21	4.8%	1.7	3.7	9.5%
Ko <i>et al</i> <sup>[52]</sup> , 2008	Irinotecan, docetaxel	14	0%	1.2	4.5	21%

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

with response rates ranging between 8%-15% and median progression-free survival in the 3-4 mo range<sup>[45-47]</sup>. Another fluoropyrimidine/irinotecan combination termed IRIS (irinotecan plus S-1) was compared to S-1 alone in a randomized phase II trial from Japan of 127 patients who had progressed on gemcitabine<sup>[28]</sup>. The combination produced a response rate of 18%, compared to 6% with S-1 alone ( $P = 0.03$ ). Median PFS and OS also favored the IRIS combination, although these improvements did not reach statistical significance (107 and 208 d, compared to 58 and 176 d for S-1, respectively). Irinotecan has also been tested in combination with the folate antimetabolite raltitrexed in a randomized phase II trial *vs* raltitrexed monotherapy<sup>[48]</sup>. In this 38-patient study, the doublet was associated with a higher rate of objective response (16% *vs* 0%) and prolonged PFS (4.0 mo *vs* 2.5

mo) and OS (6.5 mo *vs* 4.3 mo), albeit with higher rates of clinically relevant toxicities including gastrointestinal symptoms and alopecia.

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

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

Clinical trial	Design	Study arms	Goal enrollment	Primary measure	Previous therapy	Status
NCT00674973	Phase II	Erlotinib <i>vs</i> placebo	207	PFS, biomarkers	1 prior CT regimen	Active, not recruiting
NCT01074996	Phase II	S-1 <i>vs</i> S-1, leucovorin	96	OS	Gem-based	Recruiting
NCT01417000	Phase II	GVAX pancreas, cyclophosphamide, CRS-207 <i>vs</i> GVAX pancreas, cyclophosphamide	90	OS	≥ 1 prior CT regimen	Active, not recruiting
NCT01423604	Phase II	Capecitabine, ruxolitinib <i>vs</i> capecitabine, placebo	138	OS	Gem-based	Active, not recruiting
NCT01658943	Phase II	Selumetinib, MK2206 <i>vs</i> FOLFOX	133	OS, PFS	Gem-based	Recruiting
NCT01796782	Phase II	QYHJ granules <i>vs</i> Capecitabine	60	OS	Non-capecitabine containing CT	Active, not recruiting
NCT01121848	Phase III	Capecitabine or 5-FU, leucovorin <i>vs</i> XELOX or mFOLFOX-6	128	PFS	Gem-based	Active, not recruiting
NCT01494506	Phase III	MM-398 <i>vs</i> MM-398, 5-FU, leucovorin <i>vs</i> 5-FU, leucovorin	405	OS	Gem-based	Active, not recruiting
NCT01954992	Phase III	Glufosfamide <i>vs</i> 5-FU	480	OS	Gem-based	Recruiting
NCT01956812	Phase III	Gemcitabine, IMMU-107 <i>vs</i> Gemcitabine, placebo	440	OS	2 prior CT regimens, ≥ 1 Gem-based	Not yet open for recruitment

GVAX pancreas: Allogeneic pancreatic cancer cell vaccine, induces GM-CSF production; CRS-207: Attenuated listeria monocytogenes vaccine, induces immune response to mesothelin; MK2206: Akt inhibitor; FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin; QYHJ: Qingyihuaiji formulation; 5-FU: 5-Fluorouracil; XELOX: Capecitabine, oxaliplatin; mFOLFOX-6: Modified schedule 5-fluorouracil, leucovorin, oxaliplatin; MM-398: Liposomal irinotecan; IMMU-07: Yttrium-90 radiolabeled humanized monoclonal antibody against mucin1 (CD227); PFS: Progression free survival; OS: Overall survival; CT: Chemotherapy; Gem-based: Gemcitabine-containing chemotherapy regimen.

## TARGETED THERAPIES

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

Small molecule inhibitors that bind the intracellular tyrosine kinase (TK) domain of the human epidermal growth factor receptor (HER1/EGFR) block signaling through this pathway that controls aspects of DNA synthesis, cell proliferation, adhesion, and migration. Erlotinib, one such anti-EGFR TK inhibitor (TKI), was approved in the front-line setting for advanced pancreatic cancer based on a small but statistically significant improvement in median survival when added to gemcitabine in a randomized phase III trial led by the National Cancer Institute of Canada<sup>[53]</sup>. When tested as monotherapy in the setting of gemcitabine-refractory disease in a (non-published) phase II trial, erlotinib produced prolonged disease control (greater than 8 wk) in 10/40 evaluable patients, with a median time to progression of 1.6 mo and a median survival of 4.1 mo<sup>[54]</sup>. A randomized trial of erlotinib *vs* placebo (NCT00674973) has completed accrual with the goal of identifying biomarkers predictive of benefit to this agent (Table 4); data are not yet available. Another phase II study tested erlotinib in combination with capecitabine in the refractory setting and pro-

duced somewhat better results, including a 10% objective response rate, a median PFS of 3.4 mo, and a median OS of 6.5 mo, with no associated grade 4 toxicities<sup>[55]</sup>.

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

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

Table 5 Clinical studies of second-line targeted therapies

Ref.	Regimen	Sample size	RR <sup>1</sup>	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Ignatiadis <i>et al</i> <sup>[97]</sup> , 2006	Gefitinib, docetaxel	26	0%	2.1	2.9	NR
Brell <i>et al</i> <sup>[98]</sup> , 2009	Gefitinib, docetaxel	41	2.4%	1.8	4.5	0%
Kulke <i>et al</i> <sup>[55]</sup> , 2007	Erlotinib, capecitabine	30	10%	3.4	6.5	26%
Tang <i>et al</i> <sup>[54]</sup> , 2009	Erlotinib	50	0%	1.6	4.1	6 m = 39% <sup>3</sup>
Iyer <i>et al</i> <sup>[99]</sup> , 2010	Erlotinib	18	0%	1.4	3.1	NR
Bodoky <i>et al</i> <sup>[39]</sup> , 2012	Selumetinib	32	6.3%	2.1	5.4	NR
Ko <i>et al</i> <sup>[61]</sup> , 2013	Selumetinib, erlotinib	46	0%	2.6	7.5	NR
Wolpin <i>et al</i> <sup>[62]</sup> , 2009	Everolimus	33	0%	1.8	4.5	NR
Garrido-Laguna <i>et al</i> <sup>[63]</sup> , 2010	Sirolimus	31	0%	NR	NR	6 m = 26% <sup>3</sup>
Javle <i>et al</i> <sup>[64]</sup> , 2010	Everolimus, erlotinib	16	0%	1.6	2.9	NR
Javle <i>et al</i> <sup>[64]</sup> , 2010	Temsirolimus	5	0%	0.6	1.5	NR
Dragovich <i>et al</i> <sup>[68]</sup> , 2008	Vatalinib	65	NR%	6 m = 14% <sup>3</sup>	6 m = 31% <sup>3</sup>	NR
O'Reilly <i>et al</i> <sup>[69]</sup> , 2010	Sunitinib	77	1.4%	1.3	3.7	NR
Ko <i>et al</i> <sup>[67]</sup> , 2010	Bevacizumab, erlotinib	36	2.8%	1.3	3.4	6 m = 22% <sup>3</sup>
Astsaturuv <i>et al</i> <sup>[100]</sup> , 2011	Bevacizumab	16	0%	1.4	5.5	NR
Astsaturuv <i>et al</i> <sup>[100]</sup> , 2011	Bevacizumab, docetaxel	16	0%	1.6	4.2	NR
Milella <i>et al</i> <sup>[73]</sup> , 2004	Celecoxib, 5-FU	17	12%	1.9	3.5	NR
Pino <i>et al</i> <sup>[74]</sup> , 2009	Celecoxib, capecitabine <sup>2</sup>	35	8.6%	4.0	4.4	NR
Starling <i>et al</i> <sup>[101]</sup> , 2012	Imatinib, gem, oxaliplatin	27	7.4%	4.6	5.6	28%
Carvajal <i>et al</i> <sup>[102]</sup> , 2009	Flavopiridol, docetaxel	10	0%	1.9	4.2	0%
Nallapareddy <i>et al</i> <sup>[103]</sup> , 2010	Sarcatinib	19	0%	1.6	2.5	NR

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

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

In a separate (but not unrelated) category, anti-angiogenic strategies, primarily targeting vascular endothelial growth factor (VEGF) and its corresponding receptor (VEGFR), have been extensively studied in pancreatic cancer in both the front-line and salvage settings. The anti-VEGF monoclonal antibody bevacizumab, which did not improve survival when added to either gemcitabine<sup>[65]</sup> or erlotinib/gemcitabine<sup>[66]</sup> as first-line therapy in two large randomized phase III studies, has also been explored in the refractory setting, with fairly minimal activity. A phase II trial by Ko *et al*<sup>[67]</sup> examined the combination of bevacizumab and erlotinib in gemcitabine-refractory patients and reported a progression-free survival rate of 1.3 mo, with a median OS of only 3.4 mo. Oral TKIs directed against VEGFR have also been explored, including fairly large single-arm phase II studies of vatalinib<sup>[68]</sup> and sunitinib<sup>[69]</sup>. Sunitinib, tested in the context of a cooperative group study (CALGB

80603), reported a single objective response amongst 77 patients (1.3%), a disease control rate of 22%, and progression-free and overall survival times of 1.3 and 3.7 mo, respectively. Interestingly, recent evidence suggests that pancreatic cancer, despite VEGF/VEGFR upregulation, is poorly vascularized relative to other tumors<sup>[70]</sup>. These data may help explain the minimal efficacy of anti-angiogenic therapy in pancreatic cancer.

Several other potential oncogenic pathways have been targeted in the second-line setting. Cyclooxygenase-2 (COX-2) is upregulated in pancreatic cancer<sup>[71]</sup>, and its product prostaglandin-E can transactivate EGFR and promote tumor survival<sup>[72]</sup>. Celecoxib, a selective COX-2 inhibitor, has been tested in combination with fluoropyrimidines (5-FU or capecitabine) in second-line regimens and found to produce response rates of 9%-12% with very mild side effect profiles<sup>[73,74]</sup>. Ruxolitinib, an oral inhibitor of Janus kinase (JAK) signaling that is approved for use in myelofibrosis, has been evaluated as second-line therapy in combination with capecitabine in a randomized phase II trial in patients with refractory pancreatic cancer (NCT01423604); this study has completed accrual as of mid-2013 and results are currently being awaited (Table 4). Data from other studies of targeted therapies are shown in Table 5.

## DISCUSSION

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

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

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

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

These conundrums highlight only some of the challenges in designing clinical trials in this refractory setting for pancreatic cancer. The other major obstacle hindering progress is the lack of validated predictive biomarkers for this disease that could help inform treatment decisions, whether for conventional cytotoxics or for targeted agents. The track record for targeted agents in chemo-refractory pancreatic cancer is particularly dismal, bringing to light the fact that, in the future, we need to be superselective in identifying the patients most likely to

benefit from a particular novel therapy, and to develop patient enrichment schemes in clinical trial design accordingly. However, obtaining adequate tumor tissue in this patient population for identifying and validating predictive molecular markers represents a substantial ongoing challenge.

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

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

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