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TOPIC HIGHLIGHT

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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.

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[1], 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[2]. 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[3]. 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*[4] 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*[5], 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[6]. 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[7,8], a similar strategy has also been explored in the gemcitabine-refractory setting in a variety of contexts. Demols *et al*[9] 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[10], by which basis Tschoep-Lechner *et al*[11] 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[12] and gemcitabine plus *nab*-paclitaxel[13] 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[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Kozuch *et al*[4], 2001	G-FLIP	34	24%	3.9	10.3	47%
Reni *et al*[6], 2008	PEFG	46	24%	5.0	8.3	26%
Demols *et al*[9], 2006	GEMOX	33	21%	4.2	6.0	NR
Fortune *et al*[76], 2009	GEMOX	17	24%	2.6	6.4	29%
Stathopoulos *et al*[77], 2006	Gem, Lipoplatin	24	8.3%	NR	4.0	NR
Tschoep *et al*[11], 2013	Gem, Cisplatin, RHT	23	4.3%	4.3	NR	NR
Morizane *et al*[12], 2012	Gem, S-1	40	18%	2.8	7.0	18%
Ernani *et al*[13], 2012	Gem, *nab*-Paclitaxel	10	20%	3.2	NR	NR

[1]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[14,15] to warrant a randomized phase Ⅲ trial in which 409 pretreated 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%, $P = 0.01$)[16].

More recently, a phase Ⅱ study of liposomal irinotecan sucrosofate (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[17]. Ko *et al*[17] 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[18-22]. 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 establishing the combination of *nab*-paclitaxel/gemcitabine as a viable option for first-line therapy[23], 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[22].

Fluoropyrimidines have also been studied in the advanced refractory disease setting. Boeck *et al*[24] 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[25-28]. 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*[29], 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[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Jacobs *et al*[16], 2004	Rubitecan	198	11%	1.9	3.5	NR
Burris *et al*[15], 2005	Rubitecan	58	5.2%	2.0	3.1	9%
Yi *et al*[78], 2009	Irinotecan	33	9%	2.0	6.6	NR
Takahara *et al*[79], 2013	Irinotecan	56	3.6%	2.9	5.3	NR
Ko *et al*[17], 2013	Nanoliposomal irinotecan	40	7.5%	2.4	5.2	25%
Oettle *et al*[18], 2000	Paclitaxel	18	5.6%	NR	4.1	NR
Maeda *et al*[19], 2011	Paclitaxel	30	10%	NR	6.7	NR
Cereda *et al*[20], 2008	Docetaxel	10	0%	1.5	4.0	0%
Hosein *et al*[22], 2013	*Nab*-Paclitaxel	19	5%	1.7	7.3	37%
Boeck *et al*[24], 2007	Capecitabine	39	0%	2.3	7.6	NR
Bodoky *et al*[59], 2012	Capecitabine	38	7.9%	2.2	5.0	NR
Morizane *et al*[25], 2009	S-1	40	15%	2.0	4.5	14%
Todaka *et al*[26], 2010	S-1	52	3.8%	2.1	5.8	12%
Mizuno *et al*[28], 2013	S-1	67	6%	1.9	5.9	NR
Ioka *et al*[27], 2013	Best fluoropyrimidine[2]	40	10%	3.8	7.5	NR
Fukahori *et al*[80], 2012	Gemcitabine[3]	27	14%	2.6	8.0	NR
Androulakis *et al*[81], 2005	Oxaliplatin	18	0%	NR	3.5	NR
Boeck *et al*[82], 2007	Pemetrexed	52	3.8%	1.6	4.7	NR
Ulrich-Pur *et al*[48], 2003	Raltitrexed	19	0%	2.5	4.3	0%
Kindler *et al*[83], 2008	Arsenic trioxide	13	0%	1.6	3.8	0%

[1]Intent-to-treat analysis; [2]S-1 (67.5%), uracil-tegafur (20%), or 5-fluorouracil (12.5%); [3]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*[30] 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[31]. Single-arm studies of capecitabine plus oxaliplatin (CapOx) have also been performed by several Asian groups, with fairly comparable results[32-35].

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[36]. 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)[37]. 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[38]. 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[39], 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[40]. 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[41,42], raltitrexed[43], and pemetrexed[44], 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*[30] 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[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
	Platinum based regimens					
Tsavaris *et al*[29], 2005	FOLFOX	30	23%	5.1	5.8	NR
Mitry *et al*[84], 2006	FOLFOX	18	0%	0.9	1.3	NR
Gebbia *et al*[85], 2007	FOLFOX	42	14%	4	6.7	NR
Novarino *et al*[86], 2009	FOLFOX	23	0%	2.7	4.0	NR
Yoo *et al*[30], 2009	FOLFOX	30	6.7%	1.4	3.5	NR
Chung *et al*[31], 2013	FOLFOX	44	11%	2.3	7.3	NR
Berk *et al*[35], 2012	FOLFOX	46	17%	3.7	5.8	NR
Sancho *et al*[32], 2008	CapOx[2]	18	5.6%	3.9	5.8	NR
Xiong *et al*[33], 2008	CapOx	41	2.4%	2.3	5.4	21%
Gasent-Blesa *et al*[34], 2009	CapOx	15	6.7%	NR	5.3	NR
Berk *et al*[35], 2012	CapOx	39	18%	3.7	4.9	NR
Pelzer *et al*[87], 2009	OFF	37	5.4%	2.8	5.1	NR
Pelzer *et al*[37], 2011	OFF	23	0%	NR	4.8	NR
Pelzer *et al*[38], 2008	OFF	76	NR	3	6.1	NR
Assaf *et al*[40], 2011	FOLFIRINOX	27	19%	5.4	8.5	NR
Togawa *et al*[88], 2007	Cisplatin, S-1	17	29%	NR	10	32%
Kim *et al*[89], 2012	Cisplatin, S-1	11	0%	1.5	2.7	NR
Takahara *et al*[90], 2013	Oxaliplatin, S-1	30	10%	3.4	5.0	NR
Cantore *et al*[41], 2004	Oxaliplatin, irinotecan	30	10%	4.1	5.9	23%
Oh *et al*[42], 2010	Oxaliplatin, irinotecan	14	21%	1.4	4.1	7.1%
Reni *et al*[43], 2006	Oxaliplatin, raltitrexed	41	24%	1.8	5.2	12%
Mazzer *et al*[44], 2009	Oxaliplatin, pemetrexed	16	56%	3.3	NR	NR
	Non-platinum based regimens					
Yoo *et al*[30], 2009	FOLFIRI	31	0%	1.9	3.9	NR
Gebbia *et al*[45], 2010	FOLFIRI	40	15%	3.7	6.0	0%
Cereda *et al*[91], 2010	FOLFIRI or XELIRI	34	0%	2.0	4.2	5.6%
Zaniboni *et al*[46], 2012	FOLFIRI	50	8%	3.2	5.0	NR
Neuzillet *et al*[47], 2012	FOLFIRI	63	7.9%	3.0	6.6	NR
Mizuno *et al*[28], 2013	S-1, irinotecan	60	18%	3.6	6.9	NR
Blaya *et al*[49], 2007	Capecitabine, docetaxel	24	13%	NR	NR	NR
Katopodis *et al*[50], 2011	Capecitabine, docetaxel	31	9.7%	2.4	6.4	15%
Kim *et al*[51], 2009	5-FU, paclitaxel	28	10%	2.5	7.6	NR
Lee *et al*[92], 2009	Conti-FAM[3]	31	12%	2.3	6.7	NR
Shi *et al*[93], 2012	Capecitabine, thalidomide	31	6.5%	2.7	6.1	NR
Saif *et al*[94], 2009	Capecitabine, PHY906	25	5.3%	NR	NR	NR
Ulrich-Pur *et al*[48], 2003	Irinotecan, raltitrexed	19	16%	4.0	6.5	NR
Reni *et al*[95], 2004	MDI	15	0%	1.7	6.1	0%
Cereda *et al*[96], 2011	Mitomycin, ifosfamide	21	4.8%	1.7	3.7	9.5%
Ko *et al*[52], 2008	Irinotecan, docetaxel	14	0%	1.2	4.5	21%

[1]Intent-to-treat analysis; [2]Pooled analysis of pancreatic (50%), biliary (22%), gallbladder (22%) and ampullary (6%) cancer; [3]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[45-47]. 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[28]. 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[48]. 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[49,50] and 5-FU/paclitaxel[51] 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[52]. 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 *vs* placebo	207	PFS, biomarkers	1 prior CT regimen	Active, not recruiting
NCT01074996	Phase Ⅱ	S-1 *vs* S-1, leucovorin	96	OS	Gem-based	Recruiting
NCT01417000	Phase Ⅱ	GVAX pancreas, cyclophosphamide, CRS-207 *vs* GVAX pancreas, cyclophosphamide	90	OS	≥ 1 prior CT regimen	Active, not recruiting
NCT01423604	Phase Ⅱ	Capecitabine, ruxolitinib *vs* capecitabine, placebo	138	OS	Gem-based	Active, not recruiting
NCT01658943	Phase Ⅱ	Selumetinib, MK2206 *vs* FOLFOX	133	OS, PFS	Gem-based	Recruiting
NCT01796782	Phase Ⅱ	QYHJ granules *vs* Capecitabine	60	OS	Non-capecitabine containing CT	Active, not recruiting
NCT01121848	Phase Ⅲ	Capecitabine or 5-FU, leucovorin *vs* XELOX or mFOLFOX-6	128	PFS	Gem-based	Active, not recruiting
NCT01494506	Phase Ⅲ	MM-398 *vs* MM-398, 5-FU, leucovorin *vs* 5-FU, leucovorin	405	OS	Gem-based	Active, not recruiting
NCT01954992	Phase Ⅲ	Glufosfamide *vs* 5-FU	480	OS	Gem-based	Recruiting
NCT01956812	Phase Ⅲ	Gemcitabine, IMMU-107 *vs* 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: Qingyihuaji 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[53]. 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[54]. 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 produced 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[55].

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[56-58]. 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. Bodoky *et al*[59] 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[60], and that simultaneous blockade of multiple nodes leads to better anti-tumor activity. Ko *et al*[61] 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[1]	PFS/TTP (mo)	Med OS (mo)	1 yr survival
Ignatiadis *et al*[97], 2006	Gefitinib, docetaxel	26	0%	2.1	2.9	NR
Brell *et al*[98], 2009	Gefitinib, docetaxel	41	2.4%	1.8	4.5	0%
Kulke *et al*[55], 2007	Erlotinib, capecitabine	30	10%	3.4	6.5	26%
Tang *et al*[54], 2009	Erlotinib	50	0%	1.6	4.1	6 m = 39%[3]
Iyer *et al*[99], 2010	Erlotinib	18	0%	1.4	3.1	NR
Bodoky *et al*[59], 2012	Selumetinib	32	6.3%	2.1	5.4	NR
Ko *et al*[61], 2013	Selumetinib, erlotinib	46	0%	2.6	7.5	NR
Wolpin *et al*[62], 2009	Everolimus	33	0%	1.8	4.5	NR
Garrido-Laguna *et al*[63], 2010	Sirolimus	31	0%	NR	NR	6 m = 26%[3]
Javle *et al*[64], 2010	Everolimus, erlotinib	16	0%	1.6	2.9	NR
Javle *et al*[64], 2010	Temsirolimus	5	0%	0.6	1.5	NR
Dragovich *et al*[68], 2008	Vatalinib	65	NR%	6 m = 14%[3]	6 m = 31%[3]	NR
O'Reilly *et al*[69], 2010	Sunitinib	77	1.4%	1.3	3.7	NR
Ko *et al*[67], 2010	Bevacizumab, erlotinib	36	2.8%	1.3	3.4	6 m = 22%[3]
Astsaturov *et al*[100], 2011	Bevacizumab	16	0%	1.4	5.5	NR
Astsaturov *et al*[100], 2011	Bevacizumab, docetaxel	16	0%	1.6	4.2	NR
Milella *et al*[73], 2004	Celecoxib, 5-FU	17	12%	1.9	3.5	NR
Pino *et al*[74], 2009	Celecoxib, capecitabine[2]	35	8.6%	4.0	4.4	NR
Starling *et al*[101], 2012	Imatinib, gem, oxaliplatin	27	7.4%	4.6	5.6	28%
Carvajal *et al*[102], 2009	Flavopiridol, docetaxel	10	0%	1.9	4.2	0%
Nallapareddy *et al*[103], 2010	Sarcatinib	19	0%	1.6	2.5	NR

[1]Intent-to-treat analysis; [2]Pooled analysis of pancreatic (86%) and biliary (14%) cancer; [3]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*[62] 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[63]. Javle *et al*[64] 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[65] or erlotinib/gemcitabine[66] 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*[67] 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[68] and sunitinib[69]. 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[70]. 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[71], and its product prostaglandin-E can transactivate EGFR and promote tumor survival[72]. 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[73,74]. 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 chemorefractory 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[75]. 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.

REFERENCES

1 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]

2 **Schrag D**, Archer L, Wang X, Romanus D, Mulcahy M, Goldberg R, Kindler H. A patterns-of-care study of post-progression treatment (Rx) among patients (pts) with advanced pancreas cancer (APC) after gemcitabine therapy on Cancer and Leukemia Group B (CALGB) study #80303. *J Clin Oncol* 2007; **25** Suppl 18: Abstract 4524

3 **Burris HA**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413 [PMID: 9196156]

4 **Kozuch P**, Grossbard ML, Barzdins A, Araneo M, Robin A, Frager D, Homel P, Marino J, DeGregorio P, Bruckner HW. Irinotecan combined with gemcitabine, 5-fluorouracil, leucovorin, and cisplatin (G-FLIP) is an effective and non-crossresistant treatment for chemotherapy refractory metastatic pancreatic cancer. *Oncologist* 2001; **6**: 488-495 [PMID: 11743211 DOI: 10.1634/theoncologist.6-6-488]

5 **Reni M**, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; **6**: 369-376 [PMID: 15925814 DOI: 10.1016/S1470-2045(05)70175-3]

6 **Reni M**, Cereda S, Mazza E, Passoni P, Nicoletti R, Balzano G, Zerbi A, Arcidiacono PG, Staudacher C, Di Carlo V. PEFG

(cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen as second-line therapy in patients with progressive or recurrent pancreatic cancer after gemcitabine-containing chemotherapy. *Am J Clin Oncol* 2008; **31**: 145-150 [PMID: 18391598 DOI: 10.1097/COC.0b013e31814688f7]

7 **Colucci G**, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, Cigolari S, Testa A, Maiello E, Lopez M. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002; **94**: 902-910 [PMID: 11920457]

8 **Louvet C**, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; **23**: 3509-3516 [PMID: 15908661 DOI: 10.1200/JCO.2005.06.023]

9 **Demols A**, Peeters M, Polus M, Marechal R, Gay F, Monsaert E, Hendlisz A, Van Laethem JL. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 2006; **94**: 481-485 [PMID: 16434988 DOI: 10.1038/sj.bjc.6602966]

10 **Wust P**, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. *Lancet Oncol* 2002; **3**: 487-497 [PMID: 12147435 DOI: 10.1016/S1470-2045(02)00818-5]

11 **Tschoep-Lechner KE**, Milani V, Berger F, Dieterle N, Abdel-Rahman S, Salat C, Issels RD. Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer. *Int J Hyperthermia* 2013; **29**: 8-16 [PMID: 23245336 DOI: 10.3109/02656736.2012.740764]

12 **Morizane C**, Okusaka T, Ueno H, Kondo S, Ikeda M, Furuse J, Shinichi O, Nakachi K, Mitsunaga S, Kojima Y, Suzuki E, Ueno M, Yamaguchi T. Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients. *Cancer Chemother Pharmacol* 2012; **69**: 957-964 [PMID: 22120961 DOI: 10.1007/s00280-011-1786-6]

13 **Ernani V**, Akunyili II, Hosein PJ, Macintyre J, Rocha Lima CM. Gemcitabine (G) and nab-paclitaxel (nab-P) in patients with refractory advanced pancreatic cancer (PC). *J Clin Oncol* 2012; **30** Suppl 4: Abstract 373

14 **Stehlin JS**, Giovanella BC, Natelson EA, De Ipolyi PD, Coil D, Davis B, Wolk D, Wallace P, Trojacek A. A study of 9-nitrocamptothecin (RFS-2000) in patients with advanced pancreatic cancer. *Int J Oncol* 1999; **14**: 821-831 [PMID: 10200331]

15 **Burris HA**, Rivkin S, Reynolds R, Harris J, Wax A, Gerstein H, Mettinger KL, Staddon A. Phase II trial of oral rubitecan in previously treated pancreatic cancer patients. *Oncologist* 2005; **10**: 183-190 [PMID: 15793221 DOI: 10.1634/theoncologist.10-3-183]

16 **Jacobs AD**, Burris HA, Rivkin S, Ritch PS, Eisenberg PD, Mettinger KL. A randomized phase III study of rubitecan (ORA) vs. best choice (BC) in 409 patients with refractory pancreatic cancer report from a North-American multicenter study. *J Clin Oncol* 2004; **22** Suppl 14: Abstract 4013

17 **Ko AH**, Tempero MA, Shan YS, Su WC, Lin YL, Dito E, Ong A, Wang YW, Yeh CG, Chen LT. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. *Br J Cancer* 2013; **109**: 920-925 [PMID: 23880820 DOI: 10.1038/bjc.2013.408]

18 **Oettle H**, Arnold D, Esser M, Huhn D, Riess H. Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma. *Anticancer Drugs* 2000; **11**: 635-638 [PMID: 11081455 DOI: 10.1097/00001813-200009000-00006]

19 **Maeda S**, Motoi F, Onogawa T, Morikawa T, Shigeru O, Sakata N, Takadate T, Naitoh T, Rikiyama T, Katayose Y, Egawa S, Unno M. Paclitaxel as second-line chemotherapy in patients with gemcitabine-refractory pancreatic cancer: a retrospective study. *Int J Clin Oncol* 2011; **16**: 539-545 [PMID: 21455624 DOI: 10.1007/s10147-011-0220-8]

20 **Cereda S**, Reni M. Weekly docetaxel as salvage therapy in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Chemother* 2008; **20**: 509-512 [PMID: 18676234]

21 **Renouf DJ**, Tang PA, Major P, Krzyzanowska MK, Dhesy-Thind B, Goffin JR, Hedley D, Wang L, Doyle L, Moore MJ. A phase II study of the halichondrin B analog eribulin mesylate in gemcitabine refractory advanced pancreatic cancer. *Invest New Drugs* 2012; **30**: 1203-1207 [PMID: 21526355 DOI: 10.1007/s10637-011-9673-x]

22 **Hosein PJ**, de Lima Lopes G, Pastorini VH, Gomez C, Macintyre J, Zayas G, Reis I, Montero AJ, Merchan JR, Rocha Lima CM. A phase II trial of nab-Paclitaxel as second-line therapy in patients with advanced pancreatic cancer. *Am J Clin Oncol* 2013; **36**: 151-156 [PMID: 22307213 DOI: 10.1097/COC.0b013e3182436e8c]

23 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

24 **Boeck S**, Wilkowski R, Bruns CJ, Issels RD, Schulz C, Moosmann N, Laessig D, Haas M, Golf A, Heinemann V. Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. *Oncology* 2007; **73**: 221-227 [PMID: 18424886 DOI: 10.1159/000127413]

25 **Morizane C**, Okusaka T, Furuse J, Ishii H, Ueno H, Ikeda M, Nakachi K, Najima M, Ogura T, Suzuki E. A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2009; **63**: 313-319 [PMID: 18398614 DOI: 10.1007/s00280-008-0741-7]

26 **Todaka A**, Fukutomi A, Boku N, Onozawa Y, Hironaka S, Yasui H, Yamazaki K, Taku K, Machida N, Sakamoto T, Tomita H. S-1 monotherapy as second-line treatment for advanced pancreatic cancer after gemcitabine failure. *Jpn J Clin Oncol* 2010; **40**: 567-572 [PMID: 20189975 DOI: 10.1093/jjco/hyq005]

27 **Ioka T**, Katayama K, Ishida N, Takada R, Yamai T, Fukutake N, Ashida R, Uehara H, Ohigashi H, Takahashi H, Ishikawa O. Randomized phase II study of best available fluoropyrimidine compared with continuation of gemcitabine (Gem) monotherapy in patients with Gem-refractory pancreatic cancer. *J Clin Oncol* 2012; **30** Suppl 34: Abstract 287

28 **Mizuno N**, Yamao K, Komatsu Y, Munakata M, Ishiguro A, Yamaguchi T, Ohkawa S, Kida M, Ioka T, Takeda K, Kudo T, Kitano M, Iguchi H, Tsuji A, Ito T, Tanaka M, Furuse J, Hamada C, Sakata Y. Randomized phase II trial of S-1 versus S-1 plus irinotecan (IRIS) in patients with gemcitabine-refractory pancreatic cancer. *J Clin Oncol* 2012; **30** Suppl 34: Abstract 263

29 **Tsavaris N**, Kosmas C, Skopelitis H, Gouveris P, Kopterides P, Loukeris D, Sigala F, Zorbala-Sypsa A, Felekouras E, Papalambros E. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study. *Invest New Drugs* 2005; **23**: 369-375 [PMID: 16012797 DOI: 10.1007/s10637-005-1446-y]

30 **Yoo C**, Hwang JY, Kim JE, Kim TW, Lee JS, Park DH, Lee SS, Seo DW, Lee SK, Kim MH, Han DJ, Kim SC, Lee JL. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer* 2009; **101**: 1658-1663 [PMID: 19826418 DOI: 10.1038/sj.bjc.6605374]

31 **Chung JW**, Jang HW, Chung MJ, Park JY, Park SW, Chung JB, Song SY, Bang S. Folfox4 as a rescue chemotherapy for gemcitabine-refractory pancreatic cancer. *Hepatogastroenterology* 2013; **60**: 363-367 [PMID: 23858557]

32 **Sancho A,** López-Vivanco G, Diaz de Corcuera I, Ferreiro J, Moreno A, Mielgo X, Fernandez R, Ancizar N, Iruarrizaga E, Mañe JM. Oxaliplatin and capecitabine after gemcitabine failure in patients with advanced pancreatic, biliary, and gallbladder adenocarcinoma (APBC). *J Clin Oncol* 2008; **26** Suppl 15: Abstract 15625

33 **Xiong HQ**, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008; **113**: 2046-2052 [PMID: 18756532 DOI: 10.1002/cncr.23810]

34 **Gasent Blesa J**, Candel VA, Marco VG, Juan O, Pulla MP, Llorca C, Gravalos C. Phase II trial of second-line chemotherapy in metastatic pancreas cancer with the combination of oxaliplatin (Ox) and capecitabine (Cp). *J Clin Oncol* 2009; **27** Suppl 15: Abstract e15561

35 **Berk V**, Ozdemir N, Ozkan M, Aksoy S, Turan N, Inal A, Balakan O, Yasar N, Unal OU, Benekli M, Durnali A, Colak D, Sonmez OU. XELOX vs. FOLFOX4 as second line chemotherapy in advanced pancreatic cancer. *Hepatogastroenterology* 2012; **59**: 2635-2639 [PMID: 22534542 DOI: 10.5754/hge12181]

36 **Oettle H**, Pelzer U, Stieler J, Hilbig A, Roll L, Schwaner I, Adler M, Detken S, Dörken B, Riess H. Oxaliplatin/folinic acid/5-fluorouracil [24h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). *J Clin Oncol* 2005; **23** Suppl 16: Abstract 4031

37 **Pelzer U**, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H, Oettle H. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011; **47**: 1676-1681 [PMID: 21565490 DOI: 10.1016/j.ejca.2011.04.011]

38 **Pelzer U**, Kubica K, Stieler J, Schwaner I, Heil G, Görner M, Mölle M, Hilbig A, Dörken B, Riess H, Oettle H. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study. *J Clin Oncol* 2008; **26** Suppl 15: Abstract 4508

39 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

40 **Assaf E**, Verlinde-Carvalho M, Delbaldo C, Grenier J, Sellam Z, Pouessel D, Bouaita L, Baumgaertner I, Sobhani I, Tayar C, Paul M, Culine S. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. *Oncology* 2011; **80**: 301-306 [PMID: 21778770 DOI: 10.1159/000329803]

41 **Cantore M**, Rabbi C, Fiorentini G, Oliani C, Zamagni D, Iacono C, Mambrini A, Del Freo A, Manni A. Combined irinotecan and oxaliplatin in patients with advanced pretreated pancreatic cancer. *Oncology* 2004; **67**: 93-97 [PMID: 15539911 DOI: 10.1159/000080993]

42 **Oh SY**, Kim HJ, Kim TH, Lee GW, Kim HG, Jeong CY, Kwon HC, Kang JH. Pilot study of irinotecan/oxalipltin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil- refractory pancreatic cancer. *Invest New Drugs* 2010; **28**: 343-349 [PMID: 19444385 DOI: 10.1007/s10637-009-9265-1]

43 **Reni M**, Pasetto L, Aprile G, Cordio S, Bonetto E, Dell'Oro S, Passoni P, Piemonti L, Fugazza C, Luppi G, Milandri C, Nicoletti R, Zerbi A, Balzano G, Di Carlo V, Brandes AA. Raltitrexed-eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer. *Br J Cancer* 2006; **94**: 785-791 [PMID: 16508631 DOI: 10.1038/sj.bjc.6603026]

44 **Mazzer M**, Zanon E, Foltran L, De Pauli F, Cardellino G, Iaiza E, Ermacora P, Aprile G, Fasola G. Second-line pemetrexed-oxaliplatin combination for advanced pancreatic adenocarcinoma. *J Clin Oncol* 2009; **27** Suppl: Abstract e15597

45 **Gebbia V**, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-Fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. *Am J Clin Oncol* 2010; **33**: 461-464 [PMID: 20142727 DOI: 10.1097/COC.0b013e3181b4e3b0]

46 **Zaniboni A**, Aitini E, Barni S, Ferrari D, Cascinu S, Catalano V, Valmadre G, Ferrara D, Veltri E, Codignola C, Labianca R. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol* 2012; **69**: 1641-1645 [PMID: 22576338 DOI: 10.1007/s00280-012-1875-1]

47 **Neuzillet C**, Hentic O, Rousseau B, Rebours V, Bengrine-Lefèvre L, Bonnetain F, Lévy P, Raymond E, Ruszniewski P, Louvet C, Hammel P. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. *World J Gastroenterol* 2012; **18**: 4533-4541 [PMID: 22969226 DOI: 10.3748/wjg.v18.i33.4533]

48 **Ulrich-Pur H**, Raderer M, Verena Kornek G, Schüll B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W. Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* 2003; **88**: 1180-1184 [PMID: 12698181 DOI: 10.1038/sj.bjc.6600883]

49 **Blaya M**, Lopes Jr. GL, Roman E, Ahn E, Macintyre J, Quesada J, Levi J, Walker G, Green M, Rocha Lima CM. Phase II trial of capecitabine and docetaxel as second line therapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; **25** Suppl 18: Abstract 15029

50 **Katopodis O**, Polyzos A, Kentepozidis N, Giassas S, Rovithi M, Bozionelou V, Kalbakis K, Vamvakas L, Mavroudis D, Georgoulias V. Second-line chemotherapy with capecitabine (Xeloda) and docetaxel (Taxotere) in previously treated, unresectable adenocarcinoma of pancreas: the final results of a phase II trial. *Cancer Chemother Pharmacol* 2011; **67**: 361-368 [PMID: 20428874 DOI: 10.1007/s00280-010-1329-6]

51 **Kim YJ**, Bang S, Park JY, Park SW, Chung JB, Song SY. Phase II study of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer. *Cancer Chemother Pharmacol* 2009; **63**: 529-533 [PMID: 18766341 DOI: 10.1007/s00280-008-0822-7]

52 **Ko AH**, Dito E, Schillinger B, Venook AP, Bergsland EK, Tempero MA. Excess toxicity associated with docetaxel and irinotecan in patients with metastatic, gemcitabine-refractory pancreatic cancer: results of a phase II study. *Cancer Invest* 2008; **26**: 47-52 [PMID: 18181045 DOI: 10.1080/07357900701681483]

53 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]

54 **Tang P**, Gill S, Au HJ, Chen EX, Hedley D, Leroux M, Wang L, Moore MJ. Phase II trial of erlotinib in advanced pancreatic cancer (PC). *J Clin Oncol* 2009; **27** Suppl 15: Abstract 4609

55 **Kulke MH**, Blaszkowsky LS, Ryan DP, Clark JW, Meyer-

hardt JA, Zhu AX, Enzinger PC, Kwak EL, Muzikansky A, Lawrence C, Fuchs CS. Capecitabine plus erlotinib in gemcitabine-refractory advanced pancreatic cancer. *J Clin Oncol* 2007; **25**: 4787-4792 [PMID: 17947726 DOI: 10.1200/JCO.2007.11.852]

56 **Almoguera C**, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell* 1988; **53**: 549-554 [PMID: 2453289 DOI: 10.1016/0092-8674(88)90571-5]

57 **Smit VT**, Boot AJ, Smits AM, Fleuren GJ, Cornelisse CJ, Bos JL. KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. *Nucleic Acids Res* 1988; **16**: 7773-7782 [PMID: 3047672 DOI: 10.1093/nar/16.16.7773]

58 **Moskaluk CA**, Hruban RH, Kern SE. p16 and K-ras gene mutations in the intraductal precursors of human pancreatic adenocarcinoma. *Cancer Res* 1997; **57**: 2140-2143 [PMID: 9187111]

59 **Bodoky G**, Timcheva C, Spigel DR, La Stella PJ, Ciuleanu TE, Pover G, Tebbutt NC. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. *Invest New Drugs* 2012; **30**: 1216-1223 [PMID: 21594619 DOI: 10.1007/s10637-011-9687-4]

60 **De Luca A**, Maiello MR, D'Alessio A, Pergameno M, Normanno N. The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. *Expert Opin Ther Targets* 2012; **16** Suppl 2: S17-S27 [PMID: 22443084 DOI: 10.1517/14728222.2011.639361]

61 **Ko AH**, Tempero MA, Bekaii-Saab TB, Kuhn P, Courtin R, Ziyeh S, Tahiri S, Kelley RK, Dito E, Ong A, Linetskaya R, Mirzoeva OK, Wu CS, Venook AP, Korn WM. Dual MEK/EGFR inhibition for advanced, chemotherapy-refractory pancreatic cancer: A multicenter phase II trial of selumetinib (AZD6244; ARRY-142886) plus erlotinib. *J Clin Oncol* 2013; **31** Suppl: Abstract 4014

62 **Wolpin BM**, Hezel AF, Abrams T, Blaszkowsky LS, Meyerhardt JA, Chan JA, Enzinger PC, Allen B, Clark JW, Ryan DP, Fuchs CS. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol* 2009; **27**: 193-198 [PMID: 19047305 DOI: 10.1200/JCO.2008.18.9514]

63 **Garrido-Laguna I**, Tan AC, Uson M, Angenendt M, Ma WW, Villaroel MC, Zhao M, Rajeshkumar NV, Jimeno A, Donehower R, Iacobuzio-Donahue C, Barrett M, Rudek MA, Rubio-Viqueira B, Laheru D, Hidalgo M. Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer. *Br J Cancer* 2010; **103**: 649-655 [PMID: 20664591 DOI: 10.1038/sj.bjc.6605819]

64 **Javle MM**, Shroff RT, Xiong H, Varadhachary GA, Fogelman D, Reddy SA, Davis D, Zhang Y, Wolff RA, Abbruzzese JL. Inhibition of the mammalian target of rapamycin (mTOR) in advanced pancreatic cancer: results of two phase II studies. *BMC Cancer* 2010; **10**: 368 [PMID: 20630061 DOI: 10.1186/1471-2407-10-368]

65 **Kindler HL**, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; **28**: 3617-3622 [PMID: 20606091 DOI: 10.1200/JCO.2010.28.1386]

66 **Van Cutsem E**, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem JL, Verslype C, Scheithauer W, Shang A, Cosaert J, Moore MJ. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 2009; **27**: 2231-2237 [PMID: 19307500 DOI: 10.1200/JCO.2008.20.0238]

67 **Ko AH**, Venook AP, Bergsland EK, Kelley RK, Korn WM, Dito E, Schillinger B, Scott J, Hwang J, Tempero MA. A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2010; **66**: 1051-1057 [PMID: 20130876 DOI: 10.1007/s00280-010-1257-5]

68 **Dragovich T**, Laheru DA, Crowley JJ, Smith LS, Seng J, Burris HA, Rosen PJ, Von Hoff DD, Bolejack V, Hidalgo M. Phase II trial of vatalinib in patients with advanced or metastatic pancreatic adenocarcinoma who failed gemcitabine therapy. *J Clin Oncol* 2008; **26** Suppl 15: Abstract 4615

69 **O'Reilly EM**, Niedzwiecki D, Hall M, Hollis D, Bekaii-Saab T, Pluard T, Douglas K, Abou-Alfa GK, Kindler HL, Schilsky RL, Goldberg RM. A Cancer and Leukemia Group B phase II study of sunitinib malate in patients with previously treated metastatic pancreatic adenocarcinoma (CALGB 80603). *Oncologist* 2010; **15**: 1310-1319 [PMID: 21148613 DOI: 10.1634/theoncologist.2010-0152]

70 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461 [PMID: 19460966 DOI: 10.1126/science.1171362]

71 **Okami J**, Yamamoto H, Fujiwara Y, Tsujie M, Kondo M, Noura S, Oshima S, Nagano H, Dono K, Umeshita K, Ishikawa O, Sakon M, Matsuura N, Nakamori S, Monden M. Overexpression of cyclooxygenase-2 in carcinoma of the pancreas. *Clin Cancer Res* 1999; **5**: 2018-2024 [PMID: 10473081]

72 **Pai R**, Soreghan B, Szabo IL, Pavelka M, Baatar D, Tarnawski AS. Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy. *Nat Med* 2002; **8**: 289-293 [PMID: 11875501 DOI: 10.1038/nm0302-289]

73 **Milella M**, Gelibter A, Di Cosimo S, Bria E, Ruggeri EM, Carlini P, Malaguti P, Pellicciotta M, Terzoli E, Cognetti F. Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma. *Cancer* 2004; **101**: 133-138 [PMID: 15221998 DOI: 10.1002/cncr.20338]

74 **Pino MS**, Milella M, Gelibter A, Sperduti I, De Marco S, Nuzzo C, Bria E, Carpanese L, Ruggeri EM, Carlini P, Cognetti F. Capecitabine and celecoxib as second-line treatment of advanced pancreatic and biliary tract cancers. *Oncology* 2009; **76**: 254-261 [PMID: 19246950 DOI: 10.1159/000205388]

75 **Rahma OE**, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. *Ann Oncol* 2013; **24**: 1972-1979 [PMID: 23670093 DOI: 10.1093/annonc/mdt166]

76 **Fortune BE**, Li X, Kosuri KV, Weatherby LM, Thomas JP, Bekaii-Saab TS. Fixed-dose-rate gemcitabine in combination with oxaliplatin in patients with metastatic pancreatic cancer refractory to standard-dose-rate gemcitabine: a single-institute study. *Oncology* 2009; **76**: 333-337 [PMID: 19307739 DOI: 10.1159/000209962]

77 **Stathopoulos GP**, Boulikas T, Vougiouka M, Rigatos SK, Stathopoulos JG. Liposomal cisplatin combined with gemcitabine in pretreated advanced pancreatic cancer patients: a phase I-II study. *Oncol Rep* 2006; **15**: 1201-1204 [PMID: 16596187]

78 **Yi SY**, Park YS, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Lee JK, Lee KT, Lim HY, Kang WK. Irinotecan monotherapy as second-line treat-

ment in advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2009; **63**: 1141-1145 [PMID: 18839175 DOI: 10.1007/s00280-008-0839-y]
79 **Takahara N**, Nakai Y, Isayama H, Sasaki T, Satoh Y, Takai D, Hamada T, Uchino R, Mizuno S, Miyabayashi K, Mohri D, Kawakubo K, Kogure H, Yamamoto N, Sasahira N, Hirano K, Ijichi H, Tada M, Yatomi Y, Koike K. Uridine diphosphate glucuronosyl transferase 1 family polypeptide A1 gene (UGT1A1) polymorphisms are associated with toxicity and efficacy in irinotecan monotherapy for refractory pancreatic cancer. *Cancer Chemother Pharmacol* 2013; **71**: 85-92 [PMID: 23053265 DOI: 10.1007/s00280-012-1981-0]
80 **Fukahori M**. Efficacy of gemcitabine as second-line therapy after S-1 therapy failure in advanced pancreatic carcinoma. *J Clin Oncol* 2012; **30** Suppl 4: Abstract 248
81 **Androulakis N**, Syrigos K, Polyzos A, Aravantinos G, Stathopoulos GP, Ziras N, Mallas K, Vamvakas L, Georgoulis V. Oxaliplatin for pretreated patients with advanced or metastatic pancreatic cancer: a multicenter phase II study. *Cancer Invest* 2005; **23**: 9-12 [PMID: 15779862 DOI: 10.1081/CNV-46502]
82 **Boeck S**, Weigang-Köhler K, Fuchs M, Kettner E, Quietzsch D, Trojan J, Stötzer O, Zeuzem S, Lordick F, Köhne CH, Kröning H, Steinmetz T, Depenbrock H, Heinemann V. Second-line chemotherapy with pemetrexed after gemcitabine failure in patients with advanced pancreatic cancer: a multicenter phase II trial. *Ann Oncol* 2007; **18**: 745-751 [PMID: 17229775 DOI: 10.1093/annonc/mdl463]
83 **Kindler HL**, Aklilu M, Nattam S, Vokes EE. Arsenic trioxide in patients with adenocarcinoma of the pancreas refractory to gemcitabine: a phase II trial of the University of Chicago Phase II Consortium. *Am J Clin Oncol* 2008; **31**: 553-556 [PMID: 19060586 DOI: 10.1097/COC.0b013e318178e4cd]
84 **Mitry E**, Ducreux M, Ould-Kaci M, Boige V, Seitz JF, Bugat R, Breau JL, Bouché O, Etienne PL, Tigaud JM, Morvan F, Cvitkovic E, Rougier P. Oxaliplatin combined with 5-FU in second line treatment of advanced pancreatic adenocarcinoma. Results of a phase II trial. *Gastroenterol Clin Biol* 2006; **30**: 357-363 [PMID: 16633299 DOI: 10.1016/S0399-8320(06)73188-8]
85 **Gebbia V**, Maiello E, Giuliani F, Borsellino N, Caruso M, Di Maggio G, Ferraù F, Bordonaro R, Verderame F, Tralongo P, Di Cristina L, Agueli R, Russo P, Colucci G. Second-line chemotherapy in advanced pancreatic carcinoma: a multicenter survey of the Gruppo Oncologico Italia Meridionale on the activity and safety of the FOLFOX4 regimen in clinical practice. *Ann Oncol* 2007; **18** Suppl 6: vi124-vi127 [PMID: 17591805 DOI: 10.1093/annonc/mdm240]
86 **Novarino A**, Satolli MA, Chiappino I, Giacobino A, Bellone G, Rahimi F, Milanesi E, Bertetto O, Ciuffreda L. Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. *Am J Clin Oncol* 2009; **32**: 44-48 [PMID: 19194124 DOI: 10.1097/COC.0b013e31817be5a9]
87 **Pelzer U**, Stieler J, Roll L, Hilbig A, Dörken B, Riess H, Oettle H. Second-line therapy in refractory pancreatic cancer. results of a phase II study. *Onkologie* 2009; **32**: 99-102 [PMID: 19295247 DOI: 10.1159/000197769]
88 **Togawa A**, Yoshitomi H, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Kato A, Sawada S, Miyazaki M. Treatment with an oral fluoropyrimidine, S-1, plus cisplatin in patients who failed postoperative gemcitabine treatment for pancreatic cancer: a pilot study. *Int J Clin Oncol* 2007; **12**: 268-273 [PMID: 17701005 DOI: 10.1007/s10147-007-0674-x]
89 **Kim HJ**, Yun J, Kim HJ, Kim KH, Kim SH, Lee TH, Lee SC, Bae SB, Kim CK, Lee NS, Moon JH, Park SH, Lee KT, Park SK, Won JH, Park HS, Hong DS. Phase II study of palliative S-1 in combination with cisplatin as second-line chemotherapy for gemcitabine-refractory pancreatic cancer patients. *Oncol Lett* 2012; **3**: 1314-1318 [PMID: 22783441 DOI: 10.3892/ol.2012.637]
90 **Takahara N**, Isayama H, Nakai Y, Sasaki T, Hamada T, Uchino R, Mizuno S, Miyabayashi K, Kogure H, Yamamoto N, Sasahira N, Hirano K, Ijichi H, Tateishi K, Tada M, Koike K. A retrospective study of S-1 and oxaliplatin combination chemotherapy in patients with refractory pancreatic cancer. *Cancer Chemother Pharmacol* 2013; **72**: 985-990 [PMID: 23995699 DOI: 10.1007/s00280-013-2278-7]
91 **Cereda S**, Reni M, Rognone A, Ghidini M, Belli C, Longoni S, Fugazza C, Brioschi M, Nicoletti R, Balzano G, Passoni P, Villa E. XELIRI or FOLFIRI as salvage therapy in advanced pancreatic cancer. *Anticancer Res* 2010; **30**: 4785-4790 [PMID: 21115942]
92 **Lee S**, Oh SY, Kim BG, Kwon HC, Kim SH, Rho MH, Kim YH, Rho MS, Jeong JS, Kim HJ. Second-line treatment with a combination of continuous 5-fluorouracil, doxorubicin, and mitomycin-C (conti-FAM) in gemcitabine-pretreated pancreatic and biliary tract cancer. *Am J Clin Oncol* 2009; **32**: 348-352 [PMID: 19363436 DOI: 10.1097/COC.0b013e31818c08ff]
93 **Shi SB**, Wang M, Niu ZX, Tang XY, Liu QY. Phase II trial of capecitabine combined with thalidomide in second-line treatment of advanced pancreatic cancer. *Pancreatology* 2012; **12**: 475-479 [PMID: 23217281 DOI: 10.1016/j.pan.2012.09.007]
94 **Saif MW**, Li J, Lamb L, Rosenberg A, Elligers K, Ruta S, Mezes M, Grant N, Liu SH, Chu E, Cheng Y. A phase II study of capecitabine (CAP) plus PHY906 in patients (pts) with advanced pancreatic cancer (APC). *J Clin Oncol* 2009; **27** Suppl 15: Abstract e15508
95 **Reni M**, Panucci MG, Passoni P, Bonetto E, Nicoletti R, Ronzoni M, Zerbi A, Staudacher C, Di Carlo V, Villa E. Salvage chemotherapy with mitomycin, docetaxel, and irinotecan (MDI regimen) in metastatic pancreatic adenocarcinoma: a phase I and II trial. *Cancer Invest* 2004; **22**: 688-696 [PMID: 15581049 DOI: 10.1081/CNV-200032929]
96 **Cereda S**, Reni M, Rognone A, Fugazza C, Ghidini M, Ceraulo D, Brioschi M, Nicoletti R, Villa E. Salvage therapy with mitomycin and ifosfamide in patients with gemcitabine-resistant metastatic pancreatic cancer: a phase II trial. *Chemotherapy* 2011; **57**: 156-161 [PMID: 21454973 DOI: 10.1159/000324865]
97 **Ignatiadis M**, Polyzos A, Stathopoulos GP, Tselepatiotis E, Christophylakis C, Kalbakis K, Vamvakas L, Kotsakis A, Potamianou A, Georgoulias V. A multicenter phase II study of docetaxel in combination with gefitinib in gemcitabine-pretreated patients with advanced/metastatic pancreatic cancer. *Oncology* 2006; **71**: 159-163 [PMID: 17646699 DOI: 10.1159/000106064]
98 **Brell JM**, Matin K, Evans T, Volkin RL, Kiefer GJ, Schlesselman JJ, Dranko S, Rath L, Schmotzer A, Lenzner D, Ramanathan RK. Phase II study of docetaxel and gefitinib as second-line therapy in gemcitabine pretreated patients with advanced pancreatic cancer. *Oncology* 2009; **76**: 270-274 [PMID: 19258727 DOI: 10.1159/000206141]
99 **Iyer RV**, Khushalani NI,Tan W, Litwin A, Starostik P, Levea C, Tucker C, Ma W, Fakih M, Adjei AA. A phase II study of erlotinib in patients (pts) with advanced pancreatic cancer (APC) who are refractory to gemcitabine (G). Presented at: 2010 ASCO Gastrointestinal Cancers Symposium; Orlando, FL, January 22-24, 2010
100 **Astsaturov IA**, Meropol NJ, Alpaugh RK, Burtness BA, Cheng JD, McLaughlin S, Rogatko A, Xu Z, Watson JC, Weiner LM, Cohen SJ. Phase II and coagulation cascade biomarker study of bevacizumab with or without docetaxel in patients with previously treated metastatic pancreatic adenocarcinoma. *Am J Clin Oncol* 2011; **34**: 70-75 [PMID: 20458210 DOI: 10.1097/COC.0b013e3181d2734a]
101 **Starling N**, Hawkes EA, Chau I, Watkins D, Thomas J, Webb J, Brown G, Thomas K, Barbachano Y, Oates J, Cunningham D. A dose escalation study of gemcitabine plus oxaliplatin in combination with imatinib for gemcitabine-refractory advanced pancreatic adenocarcinoma. *Ann Oncol* 2012; **23**: 942-947 [PMID: 21750117 DOI: 10.1093/annonc/mdr317]
102 **Carvajal RD**, Tse A, Shah MA, Lefkowitz RA, Gonen M,

Gilman-Rosen L, Kortmansky J, Kelsen DP, Schwartz GK, O'Reilly EM. A phase II study of flavopiridol (Alvocidib) in combination with docetaxel in refractory, metastatic pancreatic cancer. *Pancreatology* 2009; **9**: 404-409 [PMID: 19451750 DOI: 10.1159/000187135]

103 **Nallapareddy S**, Arcaroli J, Touban B, Tan A, Foster NR, Erlichman C, Wright JJ, Picus J, Hidalgo M, Messersmith WA. A phase II trial of saracatinib (AZD0530), an oral Src inhibitor, in previously treated metastatic pancreatic cancer. *J Clin Oncol* 2010; **28** Suppl: Abstract e14515

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