Second-Line Treatment for Metastatic Pancreatic Cancer

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Abstract: Pancreatic cancer is the fourth-leading cause of cancer-related death. It is commonly diagnosed at an advanced stage, when no curative options exist. Over the last decade, combination chemotherapy has shown a survival benefit compared with single-agent gemcitabine and has become established as first-line therapy in metastatic pancreatic cancer. The choice of frontline regimen, which is based on clinical factors, plays an important role in subsequent management. Limited second-line standard therapeutic options are available. Studies have not definitively established that chemotherapy with a fluoropyramidine (5-fluorouracil or capecitabine), gemcitabine, oxaliplatin, irinotecan, or a combination of oxaliplatin and irinotecan improves patient survival after the failure of first-line chemotherapy. Nanoliposomal irinotecan has been approved for use in patients who have progressive disease while on gemcitabine-based treatment. Although combination chemotherapy is associated with a modest survival benefit, this comes at the expense of increased toxicity and costs. Furthermore, the optimal sequencing of these agents in subsequent lines of treatment is unknown. Randomized controlled trials provide little evidence of greater benefit from second-line therapy compared with best supportive care alone. Therefore, treatment decisions should be patient-centered and based on functional status, medical comorbidities, and anticipated adverse effects. The clinical context and prior treatment-related toxicities have a significant influence on the choice of optimal salvage treatment. We review the published data focused on second-line treatment for advanced pancreatic cancer.

Introduction

Pancreatic cancer is among the 10 most commonly diagnosed cancers (9th in women and 10th in men) in the United States, with approximately 56,770 new cases and 45,750 deaths in 2019. This disease accounts for approximately 3% of new cancer cases and 7% of all cancer deaths. The incidence is approximately 25% higher in blacks than in whites.[1] Pancreatic cancer is the fourth-leading cause

of cancer death and is projected to be the second-leading cause in a decade. The 5-year survival rate for people with pancreatic cancer is 9%.[1] Because this disease is often asymptomatic early on, in more than 50% of patients it is diagnosed at an advanced stage, when no curative potential exists. Surgical resection offers the only chance of cure, but only 15% to 20% of patients have potentially resectable disease at presentation.[2] Even with surgery, systemic disease develops over the next 5 years in the majority of patients who have early-stage cancers. Therefore, systemic treatment becomes indispensable in the management of these patients, especially those with good performance status. The paradigm for managing metastatic pancreatic cancer has not changed over the past few decades because cytotoxic chemotherapy continues to be the mainstay of treatment. Despite the fact that precision medicine represents a potential shift in how cancers are treated, its use is limited in pancreatic cancer by the low frequency of associated actionable targets.

Drug development in pancreatic cancers is challenging. The overall success rate for drugs in phase 3 clinical trials of patients with solid tumors is approximately 40%. The success rate in pancreatic cancer is the lowest of the success rates for all solid tumors, at approximately 10%.[3] In this context, the National Cancer Institute Gastrointestinal Cancer Steering Committee organized a meeting to discuss the strategies for drug development in pancreatic cancer, with an emphasis on conducting well-designed phase 2 studies.[4] Although the pharmaceutical industry continues to sponsor phase 3 randomized trials, many of these have not met their endpoint and remain unpublished.[5-8]

Patients who have metastatic pancreatic cancer often present with poor functional status and a significant symptom burden, so a combination cytotoxic chemotherapeutic approach may not be suitable for most patients in the salvage setting. The emerging role for and increasing interest in evaluating second-line chemotherapy need to be further defined. In this setting, the nonspecific cytotoxic agents may have antitumor activity, but not necessarily a better toxicity profile. This information is critical because a considerable proportion of the patients will receive second-line treatment. Most of the randomized trials did not compare active treatment with best supportive care. There remains an unmet need for therapeutic strategies that can extend survival while allowing patients to maintain a reasonable quality of life. In the following review, we assess the armamentarium of current approaches to the second-line treatment of metastatic pancreatic cancer and discuss the implications and challenges involved in establishing the optimal sequence of therapies.

Overview of First-Line Treatment

A first-line chemotherapy regimen with a combination of either 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine and nab-paclitaxel (GEM/nab-P) is commonly selected after assessment of the patient's performance status and medical comorbidities, as well as the toxicity profile of the therapeutic regimen.[9,10] For the first-line treatment of metastatic pancreatic cancer, initial randomized controlled trials demonstrated that systemic chemotherapy was associated with a greater clinical benefit compared with best supportive care.[11] More than 2 decades ago, GEM was approved as standard therapy for metastatic pancreatic cancer, with improved overall survival (OS) and clinical benefit (local pain control and a favorable safety profile) relative to 5-FU.[12] In principle, the combination regimens have achieved better survival outcomes compared with monotherapy, leading to the assessment of experimental drug combinations plus GEM vs GEM monotherapy. In 2007, a combination of GEM and the endothelial growth factor receptor inhibitor erlotinib (Tarceva, Genentech/Astellas) enhanced survival by just 2 weeks.[13] Despite the minimal benefit, the combination was approved as a therapeutic option because of a lack of drugs providing greater benefit. Although erlotinib was not a fruitful choice, it was used more commonly starting in 2011, when the treatment landscape changed with the introduction of FOLFIRINOX as a regimen for patients younger than 76 years with good performance status. This change was based on the ACCORD 11 trial (Combination Chemotherapy as First-Line Therapy in Treating Patients With Metastatic Pancreatic Cancer), in which FOLFIRINOX was superior to GEM alone (response rate, 31.6% vs 9.4%; median survival, 11.1 vs 6.8 months; 1-year survival rate, 48.4% vs 20.6%), although at the expense of increased toxicity. In comparison with patients in the GEM arm, those in the FOLFIRINOX arm showed improved global health status, with a prolonged response time, until a decrease in quality-of-life measures (the time to definitive deterioration) occurred.[14] A phase 3 trial called MPACT (Phase III Study of ABI-007 [Albumin-bound Paclitaxel] Plus Gemcitabine Versus Gemcitabine in Metastatic Adenocarcinoma of the Pancreas), which was published in 2013, demonstrated an OS benefit for the combination of GEM plus nab-P vs GEM alone, with a significant improvement in median OS from 6.7 to 8.5 months and in response rate from 7% to 23%.[15] So far, the therapeutic development has occurred in the area of cytotoxic drugs. In these studies, chemotherapy has been associated with improvement in outcomes related to survival and quality of life. As a result, the National Comprehensive Cancer Network (NCCN) guidelines began to recommend FOLFIRINOX or GEM/nab-P in patients with good performance status (category 1).[16] Therefore, a treating oncologist might choose a treatment regimen based on the toxic effects involved and clinical experience.

Overview of Second-Line Treatment

The use of subsequent lines of treatment has increased over the past decade. Patients who maintain good performance status despite progression of disease on frontline treatment are considered for second-line therapy. This practice can be attributed to the availability of relatively better cytotoxic regimens for frontline treatment and improved supportive care strategies for those with advanced cancers.[17,18] The median OS for patients with metastatic pancreatic cancer has remained at approximately 1 year over the last decade, despite all the scientific progress that has occurred with cytotoxic agents.[10] In the past, there was no established single standard therapy in the second-line setting for patients whose disease progressed after GEM-based therapy despite the availability of more effective frontline treatments. However, emerging evidence indicates that cytotoxic chemotherapy in the second-line setting improves survival outcomes.[19] Several trials have evaluated monotherapy as second-line treatment and demonstrated increased OS.[20-22] A combination of LV, 5-FU, and oxaliplatin (FOLFOX) or of LV, 5-FU, and irinotecan (FOLFIRI) was commonly used for salvage.[23] However, high-quality data to support the use of standard therapeutic regimens in the second-line setting were limited until the recent approval of nanoliposomal irinotecan (nal-IRI).

Table 1 summarizes key trials of cytotoxic therapy in the second-line setting. Nal-IRI is a liposomal encapsulated form of irinotecan; the release of irinotecan is regulated to improve the therapeutic index by prolonging the duration of circulation (half-life of ~26 hours). The data related to this approval were extracted primarily from NAPOLI-1 (Study of MM-398 With or Without 5-FU/LV, Versus 5-FU/LV in Patients With Metastatic Pancreatic Cancer), a large global phase 3 clinical trial of patients with metastatic pancreatic cancer and good performance status following treatment with GEM.[19] The median OS benefit was 6.1 months for the combination of nal-IRI and 5-FU/LV compared with 4.2 months for the control arm of 5-FU/LV, with a hazard ratio of 0.68 that translated to 32% reduction in risk for mortality. The combination demonstrated a 45% reduction in the risk for progression, with doubled median progression-free survival (3.1 vs 1.5 months). Nal-IRI was associated with adverse effects, primarily neutropenia, diarrhea, and fatigue, which led to dose reduction in 33%, dose delay in 62%, and dose discontinuation in 11% of the patients.[19] However, these dose managements were not associated with worse outcomes.[24] Nal-IRI in combination with 5-FU and LV received US Food and Drug Administration approval for the treatment of patients with metastatic pancreatic cancer after progression on GEM-based treatment. The real-world experience with nal-IRI in unselected patients is encouraging.[25]

A limited number of randomized phase 3 trials have evaluated the role of second-line therapy. The first German CONKO (Charité Onkologie) trial showed that the combination of oxaliplatin, LV, and 5-FU (OFF) was better than best supportive care in terms of OS (4.8 vs 2.3 months).[22] The evidence was not substantial because the trial had to be discontinued for low accrual (46 patients). The benefit of oxaliplatin was further evaluated in the German CONKO 003 trial (A Phase III Second Line Trial in Advanced Pancreatic Cancer) of 160 patients, which compared OFF with 5-FU/LV in patients who had undergone prior GEM treatment.[21] The trial met its primary endpoint, and the patients who received OFF had a significantly longer median OS (by 2.6 months) and longer time to progression (approximately 1 month) compared with those who received 5-FU/LV. However, the subsequent Canadian phase 3 PANCREOX trial (Randomized Study With Oxaliplatin in 2nd Line Pancreatic Cancer) did not show survival benefit for modified FOLFOX-6 vs infusion 5-FU/LV.[26] Surprisingly, the median OS was worse in the modified FOLFOX-6 group (6.1 months) than in the 5-FU/LV group (9.9 months). The 3.8-month difference was attributed to the increased proportion of continued treatments in the 5-FU/LV group compared with the modified FOLFOX-6 group (25% vs 7%) and the higher proportion of grade 3/4 adverse events with modified FOLFOX-6 than with 5-FU/LV (63% vs 11%), which resulted in a 10-fold higher withdrawal rate (20% vs 2%). The study was prematurely closed to accrual after enrollment of approximately 80% of the accrual target, and the researchers concluded that the addition of oxaliplatin conferred no survival benefit.[26] Interestingly, OS in the 5-FU/LV arm was better in PANCREOX than it was in the corresponding arm in CONKO 003 and NAPOLI-1.

The addition of irinotecan hydrochloride (CPT-11) to 5-FU/LV (FOLFIRI) is relatively less well examined. Several small and single-arm prospective and retrospective studies assessed FOLFIRI-based regimens in the setting of refractory disease and yielded no definitive conclusion regarding survival benefit.[27-30] Evidence regarding the superiority of one regimen over the other (oxaliplatin or irinotecan) is limited. In a comprehensive indirect comparison that used pooled analysis, no significant differences in grade 3/4 toxicity and efficacy were noted.[31] Although this was a cross-trial assessment, only one randomized phase 2 study compared FOLFOX and FOLFIRI in the second-line setting.[32] The primary endpoint, 6-month survival rate, was similar in the 2 regimens: 27% with FOLFIRI and 30% with FOLFOX.[32] A meta-analysis evaluating more than 1000 patients with metastatic

Table 1. Selected Trials in Patients With Previously Treated Advanced Pancreatic Cancer

First Author	Phase	Treatment Arms	Patients, N	ORR, %	PFS, mo	OS, mo	Primary Endpoint	Grade 3/4 Toxicity (per CTCAE), % (>5%)
Tsavaris[52]	2	FOLFOX	30	23.3	5.5	6.2	OS	Leukopenia (16), diarrhea (14.2)
Xiong[53]	2	XELOX	41	2.6	2.47	5.75	6-mo OS	Fatigue (13)
Pelzer[54]	2	OFF	37	6	4	5	OS	Nausea (11), neurotoxicity (13.5)
Novarino[55]	2	FOLFOX	23	0	2.9	11	ORR	None
Yoo[32]	2	FOLFIRI	31	0	2	4	6-mo OS	Neutropenia (23)
		FOLFOX	30	2	1.5	3.7		Neutropenia (20)
Pelzer[22]	3	OFF	23	0	NR	4.82	OS	None
		BSC	23	0	NR	2.3		None
Azmy[56]	2	FOLFOX[a]	24	12.5	3.9	8	ORR	Diarrhea (20), nausea (16)
		FOLFOX[b]	24	8	4	9		Diarrhea (16), nausea (12)
El-Hadaad[57]	2	OFF	30	6.7	NR	5.5	6-mo OS	Neutropenia (23.2)
Oettle[21]	3	OFF	77	NR	2.9	5.9	OS	Pain (31)
		5-FU/LV	83	NR	2	3.3		Pain (24)
Chung[58]	3	Selumetinib + MK-2206	58	2	1.9	3.9	OS	Fatigue (12.1), hyperglycemia (12), rash (12)
		modified FOLFOX	62	7	2	6.7		Lymphopenia (12.9), fatigue (12.9)
Gill[26]	3	modified FOLFOX-6	54	13.2	3.1	6.1	PFS	Neutropenia (32.7), fatigue (14.2)
		5-FU/LV	54	18.5	2.9	9.9		Neutropenia (5)
Zaniboni[30]	2	FOLFIRI	50	8	3.3	5	ORR	None
Wang-Gillam[19]	3	Nal-IRI + 5-FU + LV	117	16	3.1	6.1	OS	Neutropenia (27), diarrhea (20), nausea (11)
		Nal-IRI	151	6	2.7	4.9		Neutropenia (15), diarrhea (20), vomiting (14), appetite loss (19), anemia (11)
		5-FU + LV	149	1	1.5	4.2		Anemia (7)
Ko[59]	2	Nal-IRI	40	7.5	2.4	5.2	3-mo OS	Neutropenia (30), fatigue (20), anemia (15), hyponatremia (15), diarrhea (15), nausea (10)
Portal[43]	2	Gemcitabine + nab-paclitaxel	57	17.5	5.1	8.8	6-mo PFS	Neutropenia (12.5), neurotoxicity (12.5), asthenia (9), thrombocytopenia (6.5)
Ettrich[60]	2	Docetaxel + oxaliplatin	44	15.9	1.82	10.1	ORR	Neutropenia (63), diarrhea (11), nausea (9)
Ioka[61]	3	TAS-118	300	20.6	3.9	7.6	OS	Appetite loss (9.3)
		S-1	301	15	2.8	7.9		Anemia (9), appetite loss (7)
Ueno[62]	2	S-1 + oral LV	69	27.5	3.8	6.3	PFS	Lymphopenia (13), decreased appetite (14)
		S-1	71	19.7	2.7	6.1		Lymphopenia (11), anemia (11)
Ciuleanu[63]	3	Glufosfamide	148	2	1.5	2.8	OS	Fatigue (8.5)
		BSC	155	0.5	1.4	3.5		Abdominal pain (9)

(Table continues on next page)

Table 1. *(Continued)* Selected Trials in Patients With Previously Treated Advanced Pancreatic Cancer

First Author	Phase	Treatment Arms	Patients, N	ORR, %	PFS, mo	OS, mo	Primary Endpoint	Grade 3/4 Toxicity (per CTCAE), % (>5%)
Hurwitz[64]	3	Ruxolitinib + capecitabine	204	6	1.4	3.0	OS	Anemia (15), fatigue (10), abdominal pain (10)
		Placebo + capecitabine	203	3	1.5	3.1		Abdominal pain (13.3), fatigue (11), nausea (33)
Kordes[65]	2	Everolimus + capecitabine	31	6	3.6	8.9	ORR	HFS (16), hyperglycemia (45), hypokalemia (16), GGT (29)
Ko[66]	2	Selumetinib + erlotinib	46	0	1.9	7.3	OS	Rash (22), diarrhea (13), anemia (11), HTN (13)
Chung[67]	2	Adoptive immunotherapy	20	NR	2.75	6.65	DCR	Fatigue (5), abdominal pain (5)
Kauffman[39]	2	Olaparib	23	21.7	4.6	9.8	ORR	Fatigue (13), anemia (17)
Schroff[68]	2	Rucaparib	19	15.8	NR	NR	ORR	Anemia (31), fatigue (15), nausea (10), thrombocytopenia (10), vomiting (10)
Lowery[69]	2	Veliparib	16	6	1.7	3.1	ORR	Fatigue (25), thrombocytopenia (13), hyponatremia (13)
O'Reilly[70]	2	Durvalumab + tremelimumab	65	3	1.5	3.1	ORR	Fatigue (13), diarrhea (13), hypothyroidism (13)
Le[47]	2	Pembrolizumab	8	53	NR	NR	ORR	NR for pancreatic cohort
Overman[71]	2	Acalabrutinib	26	0	NR	NR	ORR	Dehydration (12), anemia (12), and hypotension (8)
		Pembrolizumab + acalabrutinib	32	9	NR	NR	ORR	Anemia (9), abdominal pain (9)

[a] Oxaliplatin at 85 mg/m^2.

[b] Oxaliplatin at 40 mg/m^2.

5-FU, 5-fluorouracil; BSC, best supportive care; CTCAE, Common Terminology Criteria for Adverse Events; GGT, elevated gamma glutamyl transferases; HFS, hand-foot syndrome; HTN, hypertension; LV, leucovorin; mo, months; nal-IRI, nanoliposomal irinotecan; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

pancreatic cancer enrolled in randomized trials reported feasibility and comparable efficacy in terms of response, survival, and toxicity for oxaliplatin- and irinotecan-based regimens.[33] These studies were fundamentally different in terms of study design, outcomes, patients, and treatment characteristics. For instance, the conclusions were discordant in CONKO 003 (improved survival) and PANCREOX (lack of benefit) even though both trials compared oxaliplatin-based regimens with 5-FU/LV. The dosing and schedule of 5-FU in PANCREOX were different from those in CONKO 003. Indeed, the comparator arm (5-FU/LV, 9.9 months) in PANCREOX demonstrated significantly better survival compared with the experimental arm (modified FOLFOX-6, 6.1 months). There was uncertainty regarding oxaliplatin in the post-GEM setting.[33] A head-to-head comparison of the newer nal-IRI regimen vs FOLFOX or irinotecan hydrochloride is lacking.

In the phase 3 MPACT study of GEM/nab-P vs GEM, both as second-line therapy, the combination was significantly associated with improved and comparable survival (5.3 months with GEM/nab-P vs 4.5 months with GEM) beyond first progression.[34] Evidence in the form of retrospective or small single-arm phase 2 studies for using modified FOLFIRINOX as salvage treatment is limited.[35,36] Although the toxicity profile is manageable, even in pretreated patients, safety is still of some concern when unselected patients undergo second-line treatment in routine clinical practice, especially in the context of GEM/nab-P after FOLFIRINOX or vice versa. The potential superiority of the 3-drug combination over 2-drug regimens or 5-FU alone (OS reported for 5-FU alone in PANCREOX is comparable with OS for FOLFIRINOX) needs to be confirmed in larger trials, given that head-to-head comparative trials are lacking.[26]

Few targeted therapeutic agents are approved for use in patients with pancreatic cancer.[37] Several small molecules and antibodies targeting angiogenesis, cancer stem cells, stroma, and JAK-STAT pathways were evaluated in the second-line setting and resulted in unsatisfactory outcomes.[38] Clinical evidence suggests that patients with germline *BRCA* mutations may have improved outcomes when treated with platinum-based chemotherapy. Encouraging activity was reported for the oral poly(ADP-ribose) polymerase (PARP) inhibitors in patients having *BRCA1/2* mutations, with a response rate of 21% in those with disease refractory to GEM-based regimens.[39] Recently, olaparib (Lynparza, AstraZeneca) was evaluated in a phase 3 trial as maintenance therapy in patients with a germline *BRCA1* or *BRCA2* mutation and disease that had not progressed during at least 4 months of continuous first-line platinum-based chemotherapy. This study showed that median progression-free survival was significantly longer in the olaparib group than in the placebo group (7.4 vs 3.8 months).[37] Further investigation of PARP inhibitors is ongoing, comparing FOLFIRI alone vs FOLFIRI plus veliparib in second-line treatment after a period of improvement (NCT02890355, Table 2).

Immunotherapy options—including vaccines, single-agent immune checkpoint inhibitors, and oncolytic viral therapy—have been tested in patients with treatment-refractory disease, but outcomes have not been encouraging. This is likely because of the immunosuppressive tumor microenvironment associated with pancreatic cancer. A critical requirement for the efficacy of an immunotherapeutic approach is the local presence of cancer-specific T cells, which are lacking in most pancreatic tumors.[40] Nevertheless, with the advent of chimeric antigen receptor T-cell (CAR-T) therapy, pancreatic cancer–specific T cells that are able to produce efficient T-cell responses against cancer cells can now be generated ex vivo.[40] Research in this area is gaining momentum. Several ongoing early- and late-phase clinical trials are under way that are investigating the role of immunotherapy in combination with targeted agents, and the combination of 2 checkpoint inhibitors and CAR-T cells. Selected ongoing clinical trials in the second-line setting are listed in Table 2.

The evidence amassed over the last decade suggests that second-line treatments can lead to a modest improvement in survival outcomes, a finding that has enlivened the debate about the optimal sequencing strategy for these treatments. The definitive role of first-line FOLFIRINOX or GEM/nab-P in subsequent lines of therapy is not currently known. Also, large randomized trials are needed to determine whether irinotecan- or oxaliplatin-containing regimens are the better option. Because of conflicting results in studies evaluating oxaliplatin, along with the results of NAPOLI-1, nal-IRI can be considered the immediate second-line option.[16] In the absence of head-to-head trials, clinicians are advised to decipher these studies independently within the context of each patient's goals.

Discussion

FOLFIRINOX and GEM/nab-P have revolutionized treatment in pancreatic cancer, improving OS in treatment-naive patients. Several attempts to improve long-term survival outcomes with targeted treatments, alone or in combination, did not show benefit beyond cytotoxic chemotherapy. Survival has not increased significantly despite several phase 2 and phase 3 trials. Novel agents, such as lapatinib (Tykerb, Novartis)[41] and ruxolitinib (Jakafi, Incyte),[42] provided some hope in early-phase trials but failed in the phase 3 setting. So far, the current targeted and immunotherapeutic agents that have been used alone or in combination with chemotherapy have failed to improve clinical outcomes (Table 1). This problem is attributed to the heterogeneous molecular pathogenesis of pancreatic cancers, which involves several oncogenic pathways and a large spectrum of nonactionable genetic mutations. The disease of most of the patients who receive first-line treatment ultimately progresses, with 1-year failure rates of 60% to 80%.[9,10] In addition, many patients are poor responders owing to refractory primary disease. The management of patients whose disease fails to respond to first-line treatment is challenging. Although few randomized trials exist to help clinicians in this setting, and those that do have variable findings, the activity of second-line treatments (Table 3) has been reported in terms of progression-free survival (1.5-5.5 months), OS (2.3-10.2 months), and response rate (0-31%).

Second-line treatment options in pancreatic cancer include GEM/nab-P, FOLFIRINOX, GEM alone, 5-FU, nal-IRI, FOLFIRI, or FOLFOX, depending on the therapies previously given in the first-line setting and the patient's level of tolerance and performance status.[43] Targeted therapies are considered for a limited subset of patients with predictive biomarkers, such as germline *BRCA* mutations, neurotrophic tyrosine receptor kinase (NTRK) fusions, and microsatellite instability. These include immunotherapy, NTRK inhibitors, and PARP inhibitors.[44-47] Second-line treatment with nal-IRI, an "old drug in a new bottle," has only a modest effect on survival, with unknown effects on quality of life. The combination of nal-IRI plus 5-FU/LV has an NCCN category 1 indication as potential second-line therapy for patients whose disease progressed on prior GEM-based treatment and who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a favorable

Table 2. Selected Ongoing Clinical Trials for Previously Treated Advanced Pancreatic Cancer

Identifier	Phase	Clinical Trial
NCT03854110	1/2	Trial to Evaluate Safety and Tolerability of GP-2250 in Combination With Gemcitabine
NCT03553004	2	Niraparib in Metastatic Pancreatic Cancer After Previous Chemotherapy (NIRA-PANC): a Phase 2 Trial
NCT02498613	2	A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors
NCT03193190	1b/2	A Study of Multiple Immunotherapy-Based Treatment Combinations in Participants With Metastatic Pancreatic Ductal Adenocarcinoma (Morpheus-Pancreatic Cancer)
NCT02923921	3	Study of Pegilodecakin (LY3500518) With FOLFOX Compared to FOLFOX Alone Second-line Tx in Participants With Metastatic Breast Cancer (Sequoia)
NCT01489865	1/2	ABT-888 With Modified FOLFOX6 in Patients With Metastatic Pancreatic Cancer
NCT02890355	2	FOLFIRI or Modified FOLFIRI and Veliparib as Second Line Therapy in Treating Patients With Metastatic Breast Cancer
NCT02243371	2	GVAX Pancreas Vaccine (With CY) and CRS-207 With or Without Nivolumab
NCT03023722	2	Phase II Anetumab Ravtansine in Pre-treated Mesothelin-expressing Pancreatic Cancer
NCT02810418	1b/2	Mesothelin-Targeted Immunotoxin LMB-100 Alone or in Combination with Nab-Paclitaxel in People With Previously Treated Metastatic or Locally Advanced Pancreatic Ductal Adenocarcinoma and Mesothelin Expressing Solid Tumors
NCT01834235	2	QUILT-3.010: A Study of Gemcitabine and Nab-paclitaxel With or Without NPC-1C to Treat Patients With Pancreatic Cancer
NCT01585805	2	Gemcitabine and Cisplatin With or Without Veliparib or Veliparib Alone in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer
NCT03512756	2	A Multi-Center Study of SM-88 in Subjects With Pancreatic Cancer
NCT03264404	2	Azacitidine and Pembrolizumab in Pancreatic Cancer
NCT02777710	1	Evaluation of Safety and Activity of an Anti-PDL1 Antibody (DURVALUMAB) Combined With CSF-1R TKI (PEXIDARTINIB) in Patients With Metastatic/Advanced Pancreatic or Colorectal Cancers
NCT01583686	1	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer
NCT03323944	1	CAR T Cell Immunotherapy for Pancreatic Cancer
NCT02850536	1	CAR-T Hepatic Artery Infusions or Pancreatic Venous Infusions for CEA-Expressing Liver Metastases or Pancreas Cancer
NCT02830724	1	Administering Peripheral Blood Lymphocytes Transduced With a CD70-Binding Chimeric Antigen Receptor to People With CD70 Expressing Cancers
NCT02660034	1/1b	The Safety, Pharmacokinetics and Antitumor Activity of BGB-A317 in Combination With BGB-290 in Subjects With Advanced Solid Tumors
NCT02983578	2	AZD9150 With MEDI4736 in Patients With Advanced Pancreatic, Non-Small Lung and Colorectal Cancer
NCT02826486	2	Study Assessing Safety and Efficacy of Combination of BL-8040 and Pembrolizumab in Metastatic Pancreatic Cancer Patients (COMBAT/KEYNOTE-202)
NCT03611556	1/2	MEDI9447 (Oleclumab) Pancreatic Chemotherapy Combination Study
NCT03192462	1	TAA-Specific Cytotoxic T Lymphocytes in Patients With Pancreatic Cancer (TACTOPS)

comorbidity profile, and a support system for aggressive medical therapy.[48] GEM plus nab-P can be offered as second-line therapy to patients who meet these criteria and have been treated with first-line FOLFIRINOX. Monotherapy with GEM or 5-FU is an option in the second-line setting for patients who have a relatively poor performance status (ECOG 2) or medical comorbidities, or who are elderly.[48] Despite various combinations and doses of FOLFOX and FOLFIRI, no single regimen has shown superiority over another in the second-line setting,

Table 3. Treatment Efficacy Across the Continuum of Care in Advanced Pancreatic Cancer

Outcome	First-Line Therapy[34]	Second-Line Therapy[22,26,27,29,31,35,59,72]
ORR, %	27-39	0-31
PFS, mo	8.5-11.7	1.5-5.5
OS, mo	14.4-15.9	2.3-10.2

mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

and the optimal regimen after first-line treatment remains to be confirmed in randomized controlled trials. Therefore, clinical trial participation is highly encouraged for those with good functional status upon failure of frontline treatment. Finally, at this point, no data are emerging regarding a definitive third-line therapy.

The evaluation of sequential strategies in a clinical trial setting is challenged by the fact that treatment until progression, with no dose delays or interruptions, appears not to be feasible in a major proportion of patients receiving first-line agents. PARP inhibitor–based maintenance following stabilization of disease has been explored in selected patients.[49] Also, a considerable degree of heterogeneity exists in previous clinical trials owing to variability in response and choice of first-line chemotherapy. Drawing definitive conclusions from the available data is further challenged by the small number of participants in trials, premature closure due to limited accrual, and publication bias. These factors cripple the ability to select those patients who are most likely to benefit from second-line therapy.

The choice of frontline therapy has become increasingly critical in light of the use of second-line treatment because it has the potential to dictate the treatment sequence. The decision to treat beyond the front line should depend on a careful selection of patients according to their functional status, response to treatment, and overall tumor burden, as well as the type of drugs used in the front line. Poor responders with worsened performance status and a high degree of tumor burden are unlikely to benefit from additional treatment, and they may experience more harm than benefit. Clinical benefits in second-line treatment are not substantial and are associated with an increase in adverse events. The patient is considered to be a critical protagonist in subsequent therapeutic decisions because only a small subset of patients derive benefit from second-line therapy. Other factors that affect treatment selection include the potential for cumulative toxicity and lack of cross-resistance to prior drugs. Drugs that have not been used in prior lines of treatment and have tolerable safety profiles are prioritized during treatment selection, with quality of life an important factor in treatment decisions.

Owing to limited randomized studies with placebo, it is unclear whether any of these treatments are substantially better than best supportive care alone in the second-line setting. Phase 3 randomized trials comparing second-line chemotherapy vs best supportive care in patients with advanced pancreatic cancer would be able to assess the benefit; however, given the lethality of this disease, such trials may not be feasible. Evidence is now emerging that survival benefit can be improved with optimal monitoring and the management of symptoms in timely fashion by the integration of patient-reported outcomes into routine practice.[50] Greater emphasis in therapeutic clinical trials in oncology is being placed on measuring quality of life and other patient-reported outcomes. A recent study found that incorporating patient-reported outcomes into treatment improved survival in lung cancer.[51] No large trials in pancreatic cancer have assessed patient-reported outcomes, which include control of symptoms and the maintenance of performance status and quality of life. Ongoing clinical trials are limited by a lack of prognostic and predictive markers that can be used to select the most appropriate patients for second-line treatment.

Conclusion

Survival rates in pancreatic cancer remain very low. Determination of the sequencing of therapeutic options for patients with metastatic pancreatic cancer in the second-line setting continues to be a significant unmet need. The clinical outcomes for second-line treatment beyond nal-IRI are unsatisfactory, with poor survival and objective response rates. Discrepant results have been reported in randomized studies of combinations of oxaliplatin and irinotecan. The optimal sequencing of second or subsequent lines of treatment relies on up-front treatment decisions. Second-line treatment decisions should be made jointly by the patient and the provider after a thorough assessment of the oncologic value of treatment in terms of survival, therapeutic toxicity, and quality-of-life effects. Little progress has been made in survival over the past 5 years, leaving the door open for clinical trials of novel combinations. The valuable role of multiply targeted molecular therapies (targeting both the tumor cells and the stromal microenvironment) continues to evolve. It is hoped that ongoing studies incorporating biomarkers as a component of their design will be able to reshape the concept of therapeutic sequence in the near future.

Disclosures

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300.
3. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32(1):40-51.
4. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. *J Clin Oncol*. 2009;27(33):5660-5669.
5. Hurwitz H, Cutsem EV, Bendell JC, et al. Two randomized, placebo-controlled phase 3 studies of ruxolitinib (Rux) + capecitabine (C) in patients (pts) with advanced/metastatic pancreatic cancer (mPC) after failure/intolerance of first-line chemotherapy: JANUS 1 (J1) and JANUS 2 (J2) [ASCO abstract 343]. *J Clin Oncol.* 2017;35(4)(suppl).
6. Keown A. Celgene's Abraxane fails to hit the mark in a phase III pancreatic cancer study. *BioSpace*. March 13, 2019. https://www.biospace.com/article/celgene-s-abraxane-fails-to-hit-the-mark-in-a-phase-iii-pancreatic-cancer-study. Accessed January 3, 2020.
7. AbbVie provides update on phase 3 study of ibrutinib (IMBRUVICA®) in metastatic pancreatic cancer. AbbVie. January 18, 2019. https://bit.ly/2DslQY8?rel=0". Accessed January 3, 2020.
8. Lilly announces phase 3 study in patients with metastatic pancreatic cancer did not meet primary endpoint of overall survival [press release]. Eli Lilly ; October 16, 2019. https://www.prnewswire.com/news-releases/lilly-announces-phase-3-study-in-patients-with-metastatic-pancreatic-cancer-did-not-meet-primary-endpoint-of-overall-survival-300939319.html. Accessed January 3, 2020.
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703.
10. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
11. Moertel CG. Chemotherapy of gastrointestinal cancer. *N Engl J Med*. 1978;299(19):1049-1052.
12. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413.
13. Moore MJ, Goldstein D, Hamm J, et al; National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(15):1960-1966.
14. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013;31(1):23-29.
15. Peddi PF, Cho M, Wang J, Gao F, Wang-Gillam A. Nab-paclitaxel monotherapy in refractory pancreatic adenocarcinoma. *J Gastrointest Oncol*. 2013;4(4):370-373.
16. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic Adenocarcinoma, Version 1.2019. *J Natl Compr Canc Netw*. 2019;17(3):202-210.
17. Schrag D, Archer L, Wang X, et al. 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 [ASCO abstract 4524]. *J Clin Oncol.* 2007;25(18)(suppl).
18. Nagrial AM, Chin VT, Sjoquist KM, et al. Second-line treatment in inoperable pancreatic adenocarcinoma: A systematic review and synthesis of all clinical trials. *Crit Rev Oncol Hematol*. 2015;96(3):483-497.
19. Wang-Gillam A, Li CP, Bodoky G, et al; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10018):545-557.
20. Blanc J-F, Hubner R, Li C-P, et al. PD-018 subgroup analysis by prior non-liposomal irinotecan therapy in NAPOLI-1: a phase 3 study of nal-IRI±5-fluorouracil/leucovorin in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy [ESMO GI]. *Ann Oncol.* 2017;28(suppl)(3).
21. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol.* 2014;32(23):2423-2429.
22. Pelzer U, Schwaner I, Stieler J, et al. 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(11):1676-1681.
23. 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(8):1972-1979.
24. Glassman DC, Palmaira RL, Covington CM, et al. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. *BMC Cancer*. 2018;18(1):693.
25. Kieler M, Unseld M, Bianconi D, Scheithauer W, Prager GW. A real-world analysis of second-line treatment options in pancreatic cancer: liposomal-irinotecan plus 5-fluorouracil and folinic acid. *Ther Adv Med Oncol.* 2019;11:1758835919853196.
26. Gill S, Ko YJ, Cripps C, et al. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. *J Clin Oncol*. 2016;34(32):3914-3920.
27. Cereda S, Reni M, Rognone A, et al. XELIRI or FOLFIRI as salvage therapy in advanced pancreatic cancer. *Anticancer Res*. 2010;30(11):4785-4790.
28. 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(5):461-464.
29. Neuzillet C, Hentic O, Rousseau B, et al. FOLFIRI regimen in metastatic pancreatic adenocarcinoma resistant to gemcitabine and platinum-salts. *World J Gastroenterol*. 2012;18(33):4533-4541.
30. Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol*. 2012;69(6):1641-1645.
31. Petrelli F, Inno A, Ghidini A, et al; GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente) and Cremona Hospital. Second line with oxaliplatin- or irinotecan-based chemotherapy for gemcitabine-pretreated pancreatic cancer: a systematic review. *Eur J Cancer*. 2017;81:174-182.
32. Yoo C, Hwang JY, Kim JE, et al. 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(10):1658-1663.
33. Vogel A, Ciardiello F, Hubner RA, et al. Post-gemcitabine therapy for patients with advanced pancreatic cancer - a comparative review of randomized trials evaluating oxaliplatin- and/or irinotecan-containing regimens. *Cancer Treat Rev*. 2016;50:142-147.
34. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703.
35. Kobayashi N, Tokuhisa M, Goto A, Endo I, Ichikawa Y. Second-line chemotherapy by FOLFIRINOX with unresectable pancreatic cancer (phase I, II study) [ASCO abstract 297]. *J Clin Oncol.* 2016;34(4)(suppl).
36. Lee MG, Lee SH, Lee SJ, et al. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with advanced pancreatic cancer who have progressed on gemcitabine-based therapy. *Chemotherapy*. 2013;59(4):273-279.
37. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317-327.
38. Aroldi F, Bertocchi P, Savelli G, Rosso E, Zaniboni A. Pancreatic cancer: new hopes after first line treatment. *World J Gastrointest Oncol*. 2016;8(9):682-687.
39. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33(3):244-250.
40. Ali AI, Oliver AJ, Samiei T, Chan JD, Kershaw MH, Slaney CY. Genetic redirection of T cells for the treatment of pancreatic cancer. *Front Oncol*. 2019;9:56.
41. Wu Z, Gabrielson A, Hwang JJ, et al. Phase II study of lapatinib and capecitabine in second-line treatment for metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2015;76(6):1309-1314.

42. Hurwitz HI, Uppal N, Wagner SA, et al. Randomized, double-blind, phase II study of ruxolitinib or placebo in combination with capecitabine in patients with metastatic pancreatic cancer for whom therapy with gemcitabine has failed. *J Clin Oncol*. 2015;33(34):4039-4047.
43. Portal A, Pernot S, Tougeron D, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after FOLFIRINOX failure: an AGEO prospective multicentre cohort. *Br J Cancer*. 2015;113(7):989-995.
44. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747.
45. Doebele RC, Davis LE, Vaishnavi A, et al. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. *Cancer Discov*. 2015;5(10):1049-1057.
46. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.
47. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409-413.
48. Tempero MA. NCCN Guidelines Updates: pancreatic cancer. *J Natl Compr Canc Netw.* 2019;17(5.5):603-605.
49. Golan T, Oh D-Y, Reni M, et al. POLO: a randomized phase III trial of olaparib maintenance monotherapy in patients (pts) with metastatic pancreatic cancer (mPC) who have a germline BRCA1/2 mutation (gBRCAm) [ASCO abstract TPS4152]. *J Clin Oncol.* 2016;34(15)(suppl).
50. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017;318(2):197-198.
51. Denis F, Basch EM, Lethrosne C, et al. Randomized trial comparing a web-mediated follow-up via patient-reported outcomes (PRO) vs. routine surveillance in lung cancer patients: final results [ASCO abstract 6500]. *J Clin Oncol.* 2018;36(15)(suppl).
52. Tsavaris N, Kosmas C, Skopelitis H, et al. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study. *Invest New Drugs*. 2005;23(4):369-375.
53. 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(8):2046-2052.
54. Pelzer U, Stieler J, Roll L, et al. Second-line therapy in refractory pancreatic cancer. results of a phase II study. *Onkologie*. 2009;32(3):99-102.
55. Novarino A, Satolli MA, Chiappino I, et al. Oxaliplatin, 5-fluorouracil, and leucovorin as second-line treatment for advanced pancreatic cancer. *Am J Clin Oncol*. 2009;32(1):44-48.
56. Azmy A, Abdelwahab S, Yassen M. Oxaliplatin and bolus-modulated 5-fluorouracil as a second-line treatment for advanced pancreatic cancer: can bolus regimens replace FOLFOX when considered for second line [published online February 24, 2013]? *ISRN Oncol*. doi: 10.1155/2013/358538.
57. El-Hadaad HA, Wahba HA. Oxaliplatin plus 5-fluorouracil and folinic acid (OFF) in gemcitabine-pretreated advanced pancreatic cancer: a phase II study. *J Gastrointest Cancer*. 2013;44(3):313-317.
58. Chung V, McDonough S, Philip PA, et al. Effect of selumetinib and MK-2206 vs oxaliplatin and fluorouracil in patients with metastatic pancreatic cancer after prior therapy: SWOG S1115 study randomized clinical trial. *JAMA Oncol*. 2017;3(4):516-522.
59. Ko AH, Tempero MA, Shan YS, et al. 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(4):920-925.
60. Ettrich TJ, Perkhofer L, von Wichert G, et al. DocOx (AIO-PK0106): a phase II trial of docetaxel and oxaliplatin as a second line systemic therapy in patients with advanced pancreatic ductal adenocarcinoma. *BMC Cancer*. 2016;16:21-21.
61. Ioka T, Ueno M, Ueno H, et al. TAS-118 (S-1 plus leucovorin) versus S-1 in patients with gemcitabine-refractory advanced pancreatic cancer: a randomised, open-label, phase 3 study (GRAPE trial). *Eur J Cancer*. 2019;106:78-88.
62. Ueno M, Okusaka T, Omuro Y, et al. A randomized phase II study of S-1 plus oral leucovorin versus S-1 monotherapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Ann Oncol*. 2016;27(3):502-508.
63. Ciuleanu TE, Pavlovsky AV, Bodoky G, et al. A randomised phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine. *Eur J Cancer*. 2009;45(9):1589-1596.
64. Hurwitz H, Van Cutsem E, Bendell J, et al. Ruxolitinib + capecitabine in advanced/metastatic pancreatic cancer after disease progression/intolerance to first-line therapy: JANUS 1 and 2 randomized phase III studies. *Invest New Drugs*. 2018;36(4):683-695.
65. Kordes S, Klümpen HJ, Weterman MJ, Schellens JHM, Richel DJ, Wilmink JW. Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2015;75(6):1135-1141.
66. Ko AH, Bekaii-Saab T, Van Ziffle J, et al. A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. *Clin Cancer Res.* 2016;22(1):61-68.
67. Chung MJ, Park JY, Bang S, Park SW, Song SY. Phase II clinical trial of ex vivo-expanded cytokine-induced killer cells therapy in advanced pancreatic cancer. *Cancer Immunol Immunother*. 2014;63(9):939-946.
68. Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation [published online May 26, 2018]. *JCO Precis Oncol.* doi:10.1200/PO.17.00316.
69. Lowery MA, Kelsen DP, Capanu M, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. *Eur J Cancer*. 2018;89:19-26.
70. O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma: a phase 2 randomized clinical trial [published online July 18, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.1588.
71. Overman MJ, Lopez CD, Benson AB, et al. A randomized phase 2 study of the Bruton tyrosine kinase (Btk) inhibitor acalabrutinib alone or with pembrolizumab for metastatic pancreatic cancer (mPC) [ASCO abstract 4130]. *J Clin Oncol.* 2016;34(15)(suppl).
72. Chiorean EG, Cheung WY, Giordano G, Kim G, Al-Batran S-E. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review [published online May 19, 2019]. *Ther Adv Med Oncol*. doi:10.1177/1758835919850367.