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Systemic Therapy in Metastatic Pancreatic Cancer: A Review

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Abstract

The prognosis for pancreatic cancer is still poor, because it is typically identified at an advanced, frequently metastatic stage. Recently, a sequential treatment for metastatic pancreatic ductal adenocarcinoma (mPDAC) has been developed. When the performance status is good, combination chemotherapy regimens such FOLFIRINOX and gemcitabine plus nab-paclitaxel are options for first-line treatment. Gemcitabine monotherapy is a viable choice for patients with lower performance status. Recently, olaparib, a PARP inhibitor, was showed to enhance the amount of time patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) and a BRCA1/-2 germ line mutation can live without their disease worsening. If the initial treatment is unsuccessful, patients should be provided with an alternative treatment option if their ECOG score allows for continued treatment. The combination of 5-FU/FA with nanoliposomal irinotecan has demonstrated better overall survival compared to 5-FU/FA alone. Immune checkpoint drugs like PD1/PD-L1 mAbs are particularly efficacious in malignancies with high microsatellite instability (MSI-h). Limited data in mPDACs suggests that only a part of the already tiny subgroup of MSI-H mPDACs (frequency approximately 1%) appears to benefit substantially from a checkpoint inhibitor treatment. The identification of other subgroups, may further increase therapeutic efficacy.

Keywords: Pancreatic Cancer, Metastatic, Chemotherapy, Systemic Therapy, Review

Introduction

Most patients with pancreatic cancer are diagnosed when the disease has progressed or in metastatic scondition, which contributes to the disease's still very poor prognosis. Surgery should only be performed in cases where a resection R0 is possible. In contrast to other cancers, resection of metastasis is not recommended in pancreatic cancer outside of a clinical trial even in the event of isolated liver metastasis since there is no data that surgery improves overall survival in this condition [1-5]. Also, radiation therapy has largely a supporting role in metastatic disease, e.g., in case of bone metastases and as a strategy to relieve tumor-related pain. Therefore, systemic treatment plays an essential role in the treatment of metastatic pancreatic adenocarcinoma (mPDAC). All patients with mPDAC and an ECOG performance status of 0–2 should be offered systemic therapy since it improves both overall survival and quality of life [5-11]. Additionally, systemic treatment can postpone weight loss, lessen the need for painkillers, and delay the point at which quality of life finally declines [12]. Systemic treatment should be started soon following the identification of metastases. Theperformance status is predictive for mPDAC. When a patient has an ECOG score of more than 2, systemic treatment is only beneficial if the tumor disease is the cause of their poor performance status, which will likely improve if the treatment results in tumor remission. There is also no recommended length of systemic treatment in mPDAC, and maintenance regimens are only defined for particular subgroups. Thus, the duration of treatment in mPDAC depends on its efficacy as well as tolerability and, of course, on the patient requirements. Here, we present the current state of systemic treatment of mPDAC.

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2024, using the keywords Pancreatic cancer, Metastatic, Chemotherapy, Systemic therapy, Review. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and June 2024 were examined.

First-Line Treatment of mPDAC

Gemcitabine monotherapy, gemcitabine plus nab-paclitaxel, and the FOLFIRINOX strategy are the three well-researched choices for first-line treatment of mPDAC (see Table 1). The choice of the relevant treatment depends on the patient's ECOG performance status, comorbidities, and patient's preferences.

Table 1: Metastatic pancreatic ductal adenocarcinoma: Palliative first-line regimens

Regiment	Phase	*n*	mPFS (months)	mOS (months)	DCR (%)	References
First-line therapy	III	342	6.4	11.1	70	[6]
FOLFIRINOX (Prodige-4 Intergroup trial) Gemcitabine			3.3	6.8	51	
Gemcitabine/Nab-Paclitaxel (MPACT trial) Gemcitabine	III	861	5.5	8.7	48	[15]
Gemcitabine/erlotinib Gemcitabine Gemcitabine			3.7	6.6	33	
5-FU	III	569	3.8	6.2 (RASH 2 +: 10.5)	58	[29, 30]
Maintenance therapy after first-line therapy Olaparib (POLO trial),						
only pat. with germline BRCA 1 or BRCA			3.6	5.9	49	
2 mutation and	III	126	2.3	5.7	n.a	[7]
disease control after at least 16 weeks of platinum-based induction			0.9	4.4		
therapy	III	154	7.4	19.0	n.a	[31, 32]
Placebo			3.8	19.2		

mPFS median progression-free survival, *mOS* median overall survival, ***DCR*** disease control rate, *FOLFIRINOX* 5-FU, leucovorin, irinotecan, oxaliplatin

The performance status for the choice of treatment

Patients with an ECOG of 0–1 respond well to combination chemotherapy, whereas single-agent treatment is preferable for those with an ECOG of ≥2 and significant comorbidities. This assertion is based on findings from a meta-analysis that has evaluated gemcitabine or gemcitabine-based combination therapies. Patients with a good performance status (ECOG 0–1) benefited from combined treatment in terms of survival (HR 0.76). However, when the ECOG was > 1, patients did not benefit from combined treatment (HR 1.08) [13]. There is a restriction to this statement: If tumor-related symptoms are predominantly responsible for the poor ECOG and if the ECOG may be improved by tumor remission, combination treatment, e.g., gemcitabine + nab-paclitaxel, can be given. In this scenario, smaller dosages of nab-paclitaxel have been employed [14].

Disregarding the ECOG status, it is vital that supportive measures such as proper pain treatment and nutritional support after examination of the nutritional status are also implemented as early as possible.

Treatment Intensity of mPDAC and age

There is no sufficient data supporting chronological age as a factor for the decision of systemic treatment of mPDAC. The biological age of patients appears significantly more important to decide on the proper treatment in the metastatic setting. However, several studies did include an age limit for inclusion of patients into the trial (e.g., the PRODIGE 4 Intergroup research evaluating FOLFIRINOX vs. gemcitabine only included individuals up 75 years of age [6], and in general, there are little data on patients of advanced age.

Specific treatment protocols: Gemcitabine monotherapy

Patients with an ECOG of ≥2 or with comorbidities that prohibit combination treatment should get a single-agent treatment. Gemcitabine is preferable over 5-FU in this case [7]. There are multiple phase III trials that demonstrate the efficacy of gemcitabine with 1-year overall survival rates of 18–20% and a median OS of around 6 months [6, 15]. Gemcitabine also displayed a clinical benefit response compared to 5-FU (although the latter was utilized at a suboptimal dose in the study) [7]. Gemcitabine is generally well tolerated. Its most frequent grade 3/4 side effect is hematologic toxicity with leuko-/neutropenia, thrombopenia, and anemia. Other consequences such as interstitial pneumonitis are infrequent, but physicians should be aware of this adverse event to commence quick treatment.

Gemcitabine-based combinations

The combination of gemcitabine and albumin-nanoparticle bound paclitaxel, or nab-paclitaxel, was compared to gemcitabine as a single agent in the phase III MPACT trial. The trial demonstrated a significantly improved mOS compared to the monotherapy (8.5 months compared to 6.7 months, HR 0.72; $p < 0.001$). The combination also significantly enhanced mPFS (5.5 months vs. 3.7 months, HR 0.69, $p < 0.001$) and response rate (23% vs. 7%, $p < 0.001$). The combination has a greater risk of grade 3/4 side effects with increased neutropenia, neuropathy, and diarrhea. The trial enrolled patients with a Karnofsky performance level of ≥70 such that patients with an ECOG of 0–2 can be treated with this regimen [8, 15, 16]. A phase 2 trial could demonstrate the safety and efficacy of gemcitabine + nab-paclitaxel in patients with mPDAC and an ECOG of 2 [14]. As a result, compared to FOLFIRINOX, the combination of gemcitabine and nab-paclitaxel can be used in a broader range of patients with mPDAC (ECOG 0–2). In addition, the study included elderly patients up to the age of 88 years [15]. The subgroup study showed that patients ≥65 years of age also benefit from the combination. There is no independent examination of the group of patients above 75 years or even 80 years of age from this trial.

The MPACT study involved recruiting centers across the globe. The results from the experiment may be confirmed in a real-world scenario with even superior outcome data when just Western countries were included. For example, mOS was 10.9 months with gemcitabine plus nab-paclitaxel in retrospective Swedish research [17].

In more recent clinical trials, gemcitabine plus nab-paclitaxel was utilized as a control arm and also showed good efficiency, for example, a mOS of 11.5 months in phase III HALO-301 trial (gem/nab-paclitaxel vs. gem/nab-paclitaxel + PegPH20 for patients with hyaluronan-high mPDAC) [18]. This could be related to the therapy in further lines, although, notably in this study, patient selection by the

inclusion criterion "hyaluronan-high mPDAC" should be considered.

Gemcitabine has been coupled with numerous different drugs such as irinotecan, capecitabine, oxaliplatin, cisplatin, cisplatin/epirubicin, and 5-FU plus docetaxel or exatecan. None of these combinations could show a substantial increase in OS compared to gemcitabine alone in phase III trials in the whole study populations. Patients with an ECOG of 0–1 are one example of a subgroup of patients who might benefit from some of these combinations. A significant survival benefit, e.g., of the combination of gemcitabine with oxaliplatin or cisplatin, could only be proven in meta-analyses. However, the combination of gemcitabine with cisplatin may be an attractive alternative for patients with genetic BRCA1/2 mutations.

5-FU-Based Combinations: FOLFIRINOX

The combination of 5-FU, irinotecan, and oxaliplatin in the FOLFIRINOX protocol represents a landmark in the treatment of mPDAC. In the PRODIGE 4 Intergroup study, this combination treatment achieved a median OS (mOS) of 11.1 months and a median PFS (mPFS) of 6.4 months compared to gemcitabine alone with a mOS of 6.8 months (HR 0.57; $p < 0.001$) and a mPFS of 3.3 months, respectively (HR 0.47; $p < 0.001$) [6]. The data of the initial study may be verified in multiple later phase II trials and cohort studies [19].

Patients with an ECOG of 0–1, a bilirubin value of ≤ 1.5 × ULIN, and a good comorbidity profile could be administered FOLFIRINOX. About 30% of mPDAC patients fit this description [20]. In comparison to gemcitabine, the FOLFIRINOX treatment causes greater grade 3/4 neutropenia (45.7% vs. 21%), febrile neutropenia (5.4% vs. 1.2%), and diarrhea (12.7% vs. 1.8%). About 42% of patients treated with FOLFIRINOX also received G-CSF compared to only 5.3% in the gemcitabine group. This greater toxicity rate is the reason why this regimen is commonly adjusted with eliminating the 5-FU bolus, lowering irinotecan and the 5-FU bolus, or reducing oxaliplatin. Interestingly, despite lesser toxicity, survival benefits are comparable with the initial FOLFIRINOX treatment in a meta-analysis [21, 22]. In addition, modified FOLFIRINOX (here, modified by eliminating the 5-FU bolus) exhibited an remarkable mOS of 14.4 months in the control arm of the SWOG 1313 study (mFOLFIRINOX vs. mFOLFIRINOX + PEGPH20) [23]. This could be related to the therapy in further lines.

Notably, in the FOLFIRINOX group of the phase III PRODIGE 4 Intergroup trial, the decline in quality of life was markedly postponed, even despite the protocol's greater rate of toxicity [12].

The PRODIGE 4 included patients up to the age of 75 years. Thus, there are no results from this prospective randomized trial for this group of patients regarding FOLFIRINOX effectiveness and tolerability. Retrospective results reveal that adjusted FOLFIRINOX treatments had similar toxicity but also similar efficacy when compared to younger individuals [22].

Other 5-FU-Based Combination Treatments

Several phase III trials explored the effect of other 5-FU-based combination chemotherapies. Neither 5-FU plus mitomycin C [24] nor the combination of 5-FU, gemcitabine, epirubicin, and cisplatin [25, 26] has shown adequate efficacy to qualify as a treatment standard.

A randomized phase II trial using the FIRGEM regime compared fixed-dose-rate gemcitabine alone to FOLFIRI.3 alternating with gemcitabine [27]. The combination was superior to gemcitabine alone with respect to mOS (11 months vs. 8.2 months; HR = 0.71). However, due to a lack of phase III data, this combination cannot be recognized as a clinical standard. Another phase II trial assessed the combination of 5-FU/leucovorin with nab-paclitaxel compared to gemcitabine plus nab-paclitaxel. The 4-month PFS as the primary endpoint of the trial was 56% for 5-FU/leucovorin plus nab-paclitaxel compared to 54% in the gemcitabine plus nab-paclitaxel group. The respective values for mOS were 11.4 months vs. 9.2 months, respectively [28]. Thus, this procedure may be implemented when gemcitabine cannot be used, e.g., in the case of gemcitabine intolerance.

Targeted therapies

The combination of gemcitabine with targeted therapies, has not proven a clinically relevant survival benefit for patients with mPDAC. An exemption is the combination of gemcitabine plus erlotinib, an EGFR tyrosine kinase inhibitor. There was a substantial improvement in overall survival in favor of the combination (HR 0.82, $p = 0.038$). But in the overall population, there was only a 10-day difference in mOS between the groups. Unplanned subgroup analysis revealed that only the subgroup of individuals experiencing a skin rash ≥ grade 2 in response to erlotinib had a greater difference in mOS (mOS 10.5 months vs. 5.8 months). Thus, if employed, this combination should not be continued when there is no rash during the first 8 weeks of treatment [29, 30].

Second and later lines

If a patient's ECOG is less than 2, a second-line treatment should be administered after progression disease with a first-line treatment. Many second-line treatments have been investigated in individuals receiving only gemcitabine as a first-line treatment (see Table 2).

Table 2: Metastatic pancreatic ductal adenocarcinoma: Palliative second-line regimens

Regiment	Phase	*n*	mPFS (months)	mOS (months)	DCR (%)	Refer- ences
Second-line therapy (mostly after gemcitabine mono in first-line treatment)						
Nal-Iri/5-FU/LV (NAPOLI-1 trial)	III	236	3.1	6.1	n.a	[33]
5-FU/LV		1.5		4.2		
OFF (CONKO-003 trial)	III	160	2.9	5.9	n.a	[35]
5-FU/LV			2.0	3.3		
mFOLFOX6, (PANCREOX trial)	III	108	3.1	6.1	44.7	[37]
5-FU/LV			2.9	9.9	55.3	
Gemcitabine/nab-paclitaxel (after Cohort FOLFIRINOX)		57	5.1	8.8	58	[39]

mPFS median progression-free survival, ***mOS*** median overall survival, *DCR* disease control rate, ***OFF*** oxaliplatin, leucovorin, 5-FU, *LV* leucovorin, ***5-FU*** 5-FU, *nal-Iri* nanoliposomal irinotecan, ***FOLFIRI*** 5-FU, leucovorin, irinotecan, *FOLFOX* 5-FU, leucovorin, oxaliplatin

The three-arm, phase III NAPOLI study assessed the combination of nanoliposomal irinotecan (nal-Iri) plus 5-FU/FA, nal-Iri alone, and 5-FU/FA alone in gemcitabine-pretreated patients with mPDAC and a Karnofsky performance level of ≥ 70%. The combination of nal-iri/5-FU/FA significantly increased overall survival compared to 5-FU/FA alone (6.2 months vs. 4.2 months; HR 0.75; p = 0.039) [33]. Nal-Iri alone was not superior to 5-FU/FA. The most frequent ≥ grade 3 adverse effects of the combination were neutropenia (27%), diarrhea (13%), emesis (11%), and weariness (14%). Health-related quality of life was comparable between the combination and 5-FU/FA [34].

Another alternative in the second-line scenario is the OFF regimen consisting of 5-FU/LV and oxaliplatin. Patients who demonstrate improvement while on gemcitabine and have an ECOG of ≤ 2 and polyneuropathy ≤ 2 may benefit from this regimen. This regimen increased OS (5.9 vs. 3.3 months; HR 0.66; p = 0.010) and time to tumor progression (2.9 months vs. 2 months; HR 0.68; p = 0.019) compared to 5-FU/LV alone [35, 36]. The PANCREOX trial evaluated a modified FOLFOX6 (mFOLFOX6) regimen with 5-FU/LV. mFOLFOX6 has a higher-dose intensity and inferior tolerability compared to OFF; 20% of patients in the mFOLFOX6 arm compared to 2% in the 5-FU/LV arm quit the treatment due to side effects. The combination did not increase mPFS as the primary endpoint of the experiment (mFOLFOX6: 3.1 months, 5-FU/LV: 2.9 months; p = 0.99). OS was even shorter in the mFOLFOX6 arm (6.1 months vs. 9.9 months; p = 0.02). This may be explained by the increased rate of post-progression therapy in the 5-FU/LV group (FU/LV: 25% vs. mFOLFOX6: 7%; p = 0.015) [37]. However, even with a high incidence of post-progression therapy, a mOS of 9.9 months attained with only 5-FU/LV in a second-line context is difficult to explain given the ideal mOS with FOLFIRIOX in the first line is only 11 months.

As its components have not been used in the first line, 5-FU/FA plus nal-Iri, or OFF, is a therapeutic option in the second-line setting even though there are no data from prospective, randomized trials for the second-line treatment following gemcitabine plus nab-paclitaxel in the first line. However, oxaliplatin should only be administered when there is no ≥ 2 grade residual polyneuropathy after nab-paclitaxel.

The circumstances after FOLFIRINOX are more complicated because the FOLFIRINOX protocol includes elements of both the NAPOLI-1 trial (nal-Iri, %-FU, LV) and the OFF protocol (oxaliplatin, 5-FU, LV). There are no prospective, randomized trials testing a second-line treatment following first-line FOLFIRINOX. In the PRODIGE 4 Intergroup study, 47% of patients received second-line therapy with gemcitabine (82.5%) or gemcitabine-based combinations (12.5%). The combination of gemcitabine with nab-paclitaxel as second-line treatment after FOLFIRONOX has only been investigated in retrospective analysis and small cohort studies [38]. The efficacy of gemcitabine with nab-paclitaxel in the second-line context may be high with a mOS of 8.8 months and a mPFS of 5.1 months in a small cohort study. However, the toxicity of the combination was equally considerable, with a grade 3/4 toxicity of almost 40% of the patients consisting of neutropenia (12.5%), neurotoxicity (12.5%), asthenia (9%), and thrombocytopenia (6.5%) [39]. Thus, if adopted, this medication should only be administered to individuals with an ECOG of 0–1.

Few evidence suggests that a third-line treatment is beneficial if second-line therapy fails, and there are no sizable randomized trials available. In the NAPOLI trial, roughly 30% of patients had received more than one prior treatment. The combination of 5-FU/FA with nal-Iri proved efficacious also in this context, assuming the patients had not received irinotecan previously (no previous irinotecan: HR 0.62; previous irinotecan: HR 1.25). Thus, this combination can even be employed in lines beyond the second line when irinotecan has not been used during the preceding lines of treatment [33].

Therapeutic options in molecular subgroups

The genetic heterogeneity of pancreatic cancer is substantial. There are few subgroups that allow specific therapies. According to recent research, 4-7% of an unselected Caucasian population carries germline mutations in the BRCA1 or -2 gene, even in the absence of a distinct family history [31, 40]. These cancers display a not working DNA homologous recombination leading to inadequate repair of DNA double strand breaks. The tumors appear to be particularly vulnerable to DNA crosslinking drugs such as cisplatin or DNA repair inhibitors such as gemcitabine. This could be demonstrated in preclinical investigations, but also in phase II trials assessing the effect of gemcitabine plus cisplatin in mPDAC patients with a genetic BRCA or PALB2 mutation [41].

In patients with mPDAC and a hereditary mutation in BRCA1 or -2, the phase III POLO study [31] compared maintenance treatment with the PARP inhibitor olaparib to placebo. Patients required to be on a platinum-based first-line therapy for at least 16 weeks with at least stable illness; 81% of trial participants got FOLFIRINOX. In the entire population, mOS was roughly 19 months, underlining the favorable impact of a platinum-based treatment in patients with germ line BRCA1/2 mutations. Olaparib maintenance treatment significantly prolonged PFS, the primary endpoint of the study, compared to placebo (7.4 months vs. 3.8 months; HR 0.53; p = 0.004). The two therapy groups did not vary in overall survival (19 months vs. 19.2 months; HR 0.83, 95% CI 0.56–1.22; p = 0.3487) (see Table 1) [32]. Olaparib was well tolerated with anemia and fatigue as the most frequent ≥ grade 3 adverse effects.

As a result, patients with mPDAC should be tested for a germline BRCA1/2 mutation as soon as possible after diagnosis, as platinum-based treatment seems to work quite well in these people. The question of whether regimens based on oxaliplatin, or cisplatin is superior in this case is not yet directly compared [42]. For these patients, olaparib maintenance is an intriguing possibility. Genetic counseling has to be made available to people who have documentation of a BRCA-1/-2 germ line mutation.

Immunotherapy in PDAC

A phase 2 trial by Royal *et al*., published in 2010, evaluated ipilimumab monotherapy in 27 patients with advanced PDAC [43]. While two patients with locally advanced disease reportedl had minor responses, the overall response rate (ORR) by RECIST was unimpressive at 0%, and there was no improvement in OS. Of note, there was one patient who initially progressed but continued ipilimumab with an

eventual clinically significant delayed response. Biomarker correlates were not reported. In 2012, a phase 1 study evaluated an anti-PD-L1 therapeutic agent (BMS-936559) in advanced PDAC patients who progressed on at least one prior line of therapy and similarly reported no responses. In addition, the median OS (mOS) was dismal at four months when tremelimumab (anti-CTLA-4) was used in the second line setting in 20 advanced PDAC patients after prior 5-fluorouracil (5-FU) or gemcitabine-based therapy [44]. In fact, all 18 evaluable patients in this trial had progression of disease.

In the KEYNOTE-158 phase 2 study, which only included patients with advanced MSI-H/dMMR PDAC that had progressed on prior standard-of-care (SOC) therapy (22 patients in total), the ORR was 18.2% with pembrolizumab (anti-PD-1) monotherapy [46]. This included one complete response (CR), three partial responses (PR), and a promising median duration of response (mDOR) of 13.4 months (range, 8.1 months to over 16 months). Durable responses have also been reported with ICI in an MSI-H/dMMR subgroup in a small retrospective study of 10 patients where mDOR was not reached after a median follow-up of 22.6 months [50]. Emerging studies also suggest that blood-based testing of MSI-H status may be accurate and predictive of ICI responses [51]. This may be important to consider, especially if obtaining tumor tissue for profiling is not feasible.

Together, while ICI monotherapy has been ineffective in microsatellite stable (MSS) PDAC to date, the clinical benefit with durable responses seen in previously treated MSI-H/dMMR PDAC patients supports our current National Comprehensive Cancer Network (NCCN) guidelines, which recommend MSI/MMR testing in advanced disease and ICI therapy for advanced treatment-refractory or treatment-intolerant patients with PDAC that has MSI-H/dMMR but not microsatellite stable (MSS) or proficient mismatch repair (pMMR) status [52].

Understanding the tumor immune microenvironment in MSS PDAC to elucidate mechanisms of IO resistance is a major area of research. Many studies across cancer types have demonstrated that higher levels of CD8+ TILs are associated with clinical benefit from ICI [53]. In PDAC, immunosuppressive microenvironments have lower T-cell densities in tumor epithelial compartments compared to stromal compartments. Additionally, juxta-tumoral sites have more regulatory T cells (T-reg) and macrophages that suppress effector T-cell function, and these activities likely contribute to immune evasion and IO inefficacy [54, 55]. PDAC itself modulates the immune milieu through cytokines like TGF-β, chemokine receptor 5, and IL-10, which are involved in inhibiting T-cell activation and promoting T-reg differentiation, activation, and homing [56, 57]. PDACs also tend to have an increased presence of myeloid-derived suppressor cells (MDSC), tumor-associated macrophage (TAM) signaling, and immunosuppressive cytokine signaling, all of which facilitate tumor growth and metastases [58, 59]. Studies suggest that the microenvironment may vary between the primary pancreatic tumor and metastatic sites. For example, studies have found lower CD8+ T-cell densities and higher CD4+/CD8+ ratios in pre-treatment metastatic PDAC tumor samples compared to primary tumor samples [54]. In addition, TMB frequencies vary across cancer types. PDACs tend to have lower rates of somatic mutations, which may partly explain their low immunogenicity and responses to ICI [60]. In a retrospective analysis of over 4000 PDAC tumor samples, mutant KRAS was seen in 81% of PDAC and was associated with higher M1 macrophages and cancer-associated fibroblast infiltration and lower CD4+/CD8+, natural killer (NK) cells, MSI-H status, and TMB compared to KRAS wild-type samples. With these potential reasons for primary ICI resistance in mind, strategies combining ICI with other drugs to enhance immunogenicity and overcome these barriers have been explored.

Dual ICI Therapy in PDAC

One strategy tested to improve ICI efficacy and overcome primary resistance is combining multiple ICIs in treatment. In the first phase 2 study evaluating dual ICI therapy, 65 patients with metastatic PDAC (mPDAC) were randomized to either durvalumab (anti-PD-L1) monotherapy or durvalumab plus tremelimumab combination therapy in the second line setting [48]. The ORR was 3.1% and 0% in the combination and durvalumab monotherapy arms, respectively. The median PFS (mPFS) was 1.5 months in both arms, and mOS was also similar at 3.1 months and 3.6 months in each arm, respectively. The only one patient with a confirmed PR in the combination arm had metastatic disease with low PD-L1 expression but MSI-H/dMMR status. This patient achieved a PR by week 6 and then PD at week 24, but was still alive by week 61 at the time of data cut-off. Interestingly, in another patient with PD-L1 low and MSS status randomized to the combination arm, after achieving stable disease (SD) following four doses of tremelimumab followed by durvalumab monotherapy, the patient progressed at week 43, was retreated with tremelimumab, and was alive at week 67 at the time of data cut-off. Another patient with unknown PD-L1 and microsatellite status had an unconfirmed PR at week 18 in the monotherapy arm, and although their disease had progressed by week 24, the patient was alive at week 65. There were about 12% of patients with PD-L1 expression scores $\geq$ 25 in each arm, but there were not enough responders in this study to establish associations between biomarkers and clinical outcomes. The authors did report that out of 12 patients with SD, nine had tumors evaluable for PD-L1 expression, and all of these had low/negative PD-L1 status. While the objective response in the study was limited to one MSI-H patient, the observation that other patients may have still benefited by way of longer disease control highlights the need to identify biomarkers that predict benefit.

Conclusions

Pancreatic cancer remains a tough therapy area. However, finding relevant subsets of pancreatic cancer may offer the possibility to dramatically improve outcomes. Such subgroups are cancers with somatic DNA damage repair deficits such as ATM. Also, the subset of KRAS wild-type tumors is noteworthy, demonstrating targetable fusions such as NRG1 fusions. Another however very small subgroup PDACs with NTRK fusions that are also targetable. In addition, novel predictive screening methodologies such as tumor–organoid pharmacotyping and therapy selection may potentially help to pick a more efficacious treatment for an individual tumor]. Finally, the future probable availability of specific inhibitors of mutant KRAS could also represent major improvement in PDAC treatment.

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Conflicts of Interest
The authors declare no conflict of interest.

References
1. Agalianos C, Gouvas N, Papaparaskeva K, Dervenis C. Positive para-aortic lymph nodes following pancreatectomy for pancreatic cancer. Systematic review and meta-analysis of impact on short term survival and association with clinicopathologic features. HPB. 2016; 18(8):633-641. [PMC free article] [PubMed] [Google Scholar]
2. Cao F, Li J, Li A, Li F. Prognostic significance of positive peritoneal cytology in resectable pancreatic cancer: A systemic review and metaanalysis. Oncotarget. 2017; 8(9):15004-15013. [PMC free article] [PubMed] [Google Scholar]
3. Gebauer F, Damanakis AI, Bruns C. Oligometastasis in pancreatic cancer: Current state of knowledge and spectrum of local therapy. Chirurg. 2018; 89(7):510-515. [PubMed] [Google Scholar]
4. Michalski CW, Erkan M, Huser N, Muller MW, Hartel M, Friess H, *et al*. Resection of primary pancreatic cancer and liver metastasis: A systematic review. Dig Surg. 2008; 25(6):473-480. [PubMed] [Google Scholar]
5. National Comprehensive Cancer N: Pancreatic Adenocarcinoma, Version 1.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Fort Washington: NCCN, 2020.
6. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, *et al*. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19):1817-1825. [PubMed] [Google Scholar]
7. Burris HA, 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, *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. [PubMed] [Google Scholar]
8. National Institute for H, Care E: Pancreatic cancer in adults: diagnosis and management. NICE Guideline NG85. London: NICE, 2018.
9. Mallinson CN, Rake MO, Cocking JB, Fox CA, Cwynarski MT, Diffey BL, *et al*. Chemotherapy in pancreatic cancer: Results of a controlled, prospective, randomised, multicentre trial. Br Med J. 1980; 281(6255):1589-1591. [PMC free article] [PubMed] [Google Scholar]
10. Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard RC. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. Br J Surg. 1994; 81(6):882-885. [PubMed] [Google Scholar]
11. Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, *et al*. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol. 1996; 7(6):593-600. [PubMed] [Google Scholar]
12. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, *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. [PubMed] [Google Scholar]
13. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: Evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer. 2008; 8:82. [PMC free article] [PubMed] [Google Scholar]
14. Macarulla T, Pazo-Cid R, Guillén-Ponce C, López R, Vera R, Reboredo M, *et al*. Phase I/II trial to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with pancreatic cancer and an ECOG performance status of 2. J Clin Oncol. 2019; 37(3):230-238. [PubMed] [Google Scholar]
15. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, *et al*. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med, 2013. [PMC free article] [PubMed]
16. Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, *et al*. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. J Natl Cancer Inst. 2015; 107(2). [PubMed]
17. Blomstrand H, Scheibling U, Bratthäll C, Green H, Elander NO. Real world evidence on gemcitabine and nab-paclitaxel combination chemotherapy in advanced pancreatic cancer. BMC Cancer. 2019; 19(1):40. [PMC free article] [PubMed] [Google Scholar]
18. Cutsem EV, Tempero MA, Sigal D, Oh D-Y, Fazio N, Macarulla T, *et al*. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. J Clin Oncol. 2020; 38(27):3185-3194. [PMC free article] [PubMed] [Google Scholar]
19. Thibodeau S, Voutsadakis IA. FOLFIRINOX chemotherapy in metastatic pancreatic cancer: A systematic review and meta-analysis of retrospective and phase II studies. J Clin Med. 2018; 7(1):7. [PMC free article] [PubMed] [Google Scholar]
20. Hegewisch-Becker S, Aldaoud A, Wolf T, Krammer-Steiner B, Linde H, Scheiner-Sparna R, *et al*. Group TPK Results from the prospective German TPK clinical cohort study: Treatment algorithms and survival of 1,174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. Int J Cancer. 2019; 144(5):981-990. [PMC free article] [PubMed] [Google Scholar]
21. Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: A systematic review and meta-analysis. Sci Rep. 2018; 8(1):8666. [PMC free article] [PubMed] [Google Scholar]
22. Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, *et al*. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer. 2016; 114(7):737-743. [PMC free article] [PubMed] [Google Scholar]
23. Ramanathan RK, McDonough SL, Philip PA, Hingorani SR, Lacy J, Kortmansky JS, *et al*. Phase IB/II randomized study of FOLFIRINOX plus pegylated recombinant human hyaluronidase versus

FOLFIRINOX alone in patients with metastatic pancreatic adenocarcinoma: SWOG S1313. J Clin Oncol. 2019; 37(13):1062-1069. [PMC free article] [PubMed] [Google Scholar]
24. Maisey N, Chau I, Cunningham D, Norman A, Seymour M, Hickish T, *et al*. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. J Clin Oncol. 2002; 20(14):3130-3136. [PubMed] [Google Scholar]
25. Ducreux M, Rougier P, Pignon JP, Douillard JY, Seitz JF, Bugat R, *et al*. A randomised trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. Ann Oncol. 2002; 13(8):1185-1191. [PubMed] [Google Scholar]
26. Dahan L, Bonnetain F, Ychou M, Mitry E, Gasmi M, Raoul JL, *et al*. Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: Final results of a randomised strategic phase III trial (FFCD 0301) Gut. 2010; 59(11):1527-1534. [PMC free article] [PubMed] [Google Scholar]
27. Trouilloud I, Dupont-Gossard A-C, Malka D, Artru P, Gauthier M, Lecomte T, *et al*. Fixed-dose rate gemcitabine alone or alternating with FOLFIRI.3 (irinotecan, leucovorin and fluorouracil) in the first-line treatment of patients with metastatic pancreatic adenocarcinoma: An AGEO randomised phase II study (FIRGEM) Eur J Cancer. 2014; 50(18):3116-3124. [PubMed] [Google Scholar]
28. Bachet JB, Hammel P, Desramé J, Meurisse A, Chibaudel B, André T, *et al*. Nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil as first-line therapy for metastatic pancreatic adenocarcinoma (AFUGEM GERCOR): A non-comparative, multicentre, open-label, randomised phase 2 trial. Lancet Gastroenterol Hepatol. 2017; 2(5):337-346. [PubMed] [Google Scholar]
29. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, *et al*. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25(15):1960-1966. [PubMed] [Google Scholar]
30. Heinemann V, Vehling-Kaiser U, Waldschmidt D, Kettner E, Marten A, Winkelmann C, *et al*. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: Final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104) Gut. 2013; 62(5):751-759. [PMC free article] [PubMed] [Google Scholar]
31. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, *et al*. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med, 2019. [PMC free article] [PubMed]
32. Golan T, Hammel P, Reni M, Cutsem EV, Macarulla T, Hall MJ, *et al*. Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol. 2021; 39:378-378. [Google Scholar]
33. Wang-Gillam A, Chung-Pin L, Bodoky G, Dean A, Yan-Shen S, Jameson G, *et al*. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. Lancet. 2016; 387(10018):545-557. [PubMed] [Google Scholar]
34. Hubner RA, Cubillo A, Blanc JF, Melisi D, Von Hoff DD, Wang-Gillam A, *et al*. Quality of life in metastatic pancreatic cancer patients receiving liposomal irinotecan plus 5-fluorouracil and leucovorin. Eur J Cancer. 2019; 106:24-33. [PubMed] [Google Scholar]
35. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, *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. [PubMed] [Google Scholar]
36. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dorken B, *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. [PubMed] [Google Scholar]
37. Gill S, Ko YJ, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfiqar M, *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. [PubMed] [Google Scholar]
38. de Jesus VHF, Camandaroba MPG, Calsavara VF, Riechelmann RP. Systematic review and meta-analysis of gemcitabine-based chemotherapy after FOLFIRINOX in advanced pancreatic cancer. Ther Adv Med Oncol. 2020; 12:1758835920905408. [PMC free article] [PubMed] [Google Scholar]
39. Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardière C, *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. [PMC free article] [PubMed] [Google Scholar]
40. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, *et al*. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015; 33(28):3124-3129. [PubMed] [Google Scholar]
41. O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, *et al*. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. J Clin Oncol. 2020; 38(13):1378-1388. [PMC free article] [PubMed] [Google Scholar]
42. Pokataev I, Fedyanin M, Polyanskaya E, Popova A, Agafonova J, Menshikova S, *et al*. Efficacy of platinum-based chemotherapy and prognosis of patients with pancreatic cancer with homologous recombination deficiency: Comparative analysis of published clinical

studies. ESMO Open. 2020; 5(1):e000578. [PMC free article] [PubMed] [Google Scholar]
43. Ribas A. Releasing the brakes on cancer immunotherapy. N Engl J Med. 2015; 373(16):1490-1492. [PubMed] [Google Scholar]
44. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, *et al*. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J. Immunother. 2010; 33:828-833. Doi: 10.1097/CJI.0b013e3181eec14c. [DOI] [PMC free article] [PubMed] [Google Scholar]
45. Sharma P, Dirix L, De Vos FYFL, Allison JP, Decoster L, Zaucha R, *et al*. Efficacy and tolerability of tremelimumab in patients with metastatic pancreatic ductal adenocarcinoma. J. Clin. Oncol. 2018; 36:470. Doi: 10.1200/JCO.2018.36.4_suppl.470. [DOI] [Google Scholar]
46. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord J-P, *et al*. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J. Clin. Oncol. 2020; 38:1-10. Doi: 10.1200/JCO.19.02105. [DOI] [PMC free article] [PubMed] [Google Scholar]
47. Hong DS, Rasco DW, Veeder MH, Luke JJ, Chandler J, Balmanoukian AS, *et al*. A multicenter study of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib plus durvalumab in patients with relapsed/refractory (R/R) solid tumors. J. Clin. Oncol. 2018; 36:2578. Doi: 10.1200/JCO.2018.36.15_suppl.2578. [DOI] [PubMed] [Google Scholar]
48. O'Reilly EM, Oh D-Y, Dhani N, Renouf DJ, Lee MA, Sun W, *et al*. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019; 5:1431-1438. Doi: 10.1001/jamaoncol.2019.1588. [DOI] [PMC free article] [PubMed] [Google Scholar]