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Current Standards of Chemotherapy for Pancreatic Cancer

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Abstract

Purpose—Pancreatic cancer has a dismal prognosis due to the early development of systemic metastatic disease. Chemotherapeutics are the only systemic therapies that offer a meaningful benefit to the patients.

Methods—We reviewed the literature for recently published phase III clinical trials whose results have guided the current standards of chemotherapy for pancreatic cancer.

Findings—Although combination chemotherapy regimens are shown to be superior to gemcitabine monotherapy for both metastatic pancreatic cancer and adjuvant chemotherapy following surgical resection, it should be recognized that all the combination chemotherapy regimens only offer limited benefits. In addition, there is a paucity of clinical trials that directly compare the various combination chemotherapy regimens.

Implications—With the advancement of systemic cancer treatment beyond chemotherapy, it is important to devote more investigation into better understanding the biology of these chemotherapy regimens, such that we combine them with targeted therapeutics and immunotherapeutics in a rational and scientific manner. For the current treatment of pancreatic cancer, the available chemotherapy regimens have shown modest but statistically significant improvements in survival. However, it is important to avoid cross-comparisons of trials and choose regimens based on patient characteristics and side effect profiles of the regimen.

Keywords

pancreatic cancer; metastatic; adjuvant; FOLFIRINOX; gemcitabine; nab-paclitaxel; capecitabine; liposomal irinotecan

Pancreatic cancer is the tenth most common cancer among men, and eleventh in women, and yet it is the fourth leading cause of cancer death in the United States.[1] Its incidence is also

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increasing. Over a span of five years, from 2009 to 2013, the average annual percentage change in incidence increased by 1% among men and by 1.1% among women. There has been very limited progress in treatment of pancreatic cancer over the past few decades, with its 5-year survival rate increasing from 2.5% (95% CI, 2.0–3.0) in 1975–1977 to 8.5% (95% CI, 8.0–9.0) in 2006–2012. Therefore, it is projected to become the second leading cause of cancer mortality before 2030 due to improving therapies for other cancers than those for pancreatic cancer.[2] One of the major reasons for the dismal prognosis of pancreatic cancer is its early development of systemic metastatic disease. Although enormous efforts have been placed in developing innovative therapies, chemotherapeutics are essentially the only systemic treatment that are proven to be effective and also offer a meaningful, albeit limited, prolongation of the patients' lives. Therefore, in this review, we will discuss the current standards of chemotherapy for pancreatic adenocarcinoma.

First-line systemic treatment for advanced pancreatic cancer

Most patients diagnosed with pancreatic cancer have advanced disease, and their estimated 5-year survival rate is dismal. For the 29% who are diagnosed with regional disease (i.e. regional lymph nodes are involved),[3] the 5-year survival is 10%.[4] 52% have distant metastases at diagnosis,[3] and their 5-year survival plummets to 2%.[4]

The single agent gemcitabine had been a standard of care first-line treatment for advanced pancreatic cancer for more than two decades[5] until the PRODIGE[6] and MPACT[7] clinical trials demonstrated that two combination chemotherapy regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, respectively, achieved higher response rates and longer median overall survival than gemcitabine (Table 1). Now, these two combination chemotherapy regimens are the two current standard of care first-line treatment regimens for advanced pancreatic cancer. They have also become the chemotherapy regimens of choice for neoadjuvant therapy for borderline resectable pancreatic cancer or locally advanced pancreatic cancer.

FOLFIRINOX

The 5-FU, leucovorin, irinotecan and oxaliplatin combination was chosen based on preclinical[8,9,10,11,12] and clinical studies[13,14,15] suggesting synergy between the different therapies and non-overlapping toxic effects of the drugs. PRODIGE[6] was a phase II-III, open-label trial that compared FOLFIRINOX to gemcitabine (171 evaluable patients in each arm) for patients with advanced pancreatic cancer. FOLFIRINOX increased the median overall survival by 4.3 months [11.1 vs. 6.8 months; hazard ratio (HR) 0.57, 95% CI, 0.45–0.73, $p < 0.001$]. This was in contrast to the modest improvement in overall survival of 0.33 months with the gemcitabine/erlotinib combination, the only regimen prior to FOLFIRINOX that improved survival compared to gemcitabine (median overall survival of 6.24 months with gemcitabine/erlotinib and 5.91 months with gemcitabine).[16,17] Analysis indicated that the survival benefit of FOLFIRINOX was not due to use of subsequent second-line therapy. All subgroups favored FOLFIRINOX for improved survival, except for those with metachronous metastases, 3 or more metastatic sites or a biliary stent, who favored gemcitabine monotherapy.

FOLFIRINOX is notable for its higher incidence of grade 3–4 adverse events including neutropenia (45.7 vs. 21.0%), febrile neutropenia (5.4 vs. 1.2%), thrombocytopenia (9.1 vs 3.6%), diarrhea (12.7 vs. 1.8%) and peripheral neuropathy (9 vs 0%) compared to gemcitabine. However, despite higher rates of grade 3–4 toxicity, the initial analysis[6] showed that the quality of life was not statistically different during the first 8 cycles of FOLFIRINOX. At 6 months, 31% of the patients in the FOLFIRINOX arm had decrease in quality of life scores, whereas it was 66% in the gemcitabine arm (HR 0.47, 95% CI, 0.3–0.7, $p < .001$). Subsequent analysis indicated that there was a statistically significant improvement in quality of life with FOLFIRINOX compared to Gemcitabine.[18] This result suggested that disease progression affected the quality of life in the advanced pancreatic cancer patients more than the toxicity of chemotherapy.

Gemcitabine/nab-Paclitaxel

MPACT was a phase III, open-label trial where 431 patients were randomized to gemcitabine/nab-paclitaxel and 430 were randomized to gemcitabine alone.[7] The median overall survival was 8.5 months (95% CI, 7.89–9.53) with gemcitabine/nab-paclitaxel compared to 6.7 months (95% CI, 6.01–7.23) with gemcitabine with a HR for death of 0.72 (95% CI, 0.62–0.83, $p < .001$). Analysis also demonstrated that the survival benefit of gemcitabine/abraxane was not due to use of subsequent second line therapy. Patients with more advanced disease benefited from the combination treatment (i.e. those with metastatic disease at initial diagnosis, liver metastasis, more than 3 metastatic sites, CA 19−9 at or greater than 59 times the upper limit of normal). There was a trend towards improvement in survival with gemcitabine/nab-paclitaxel compared to gemcitabine alone for those who were 65 years or older.

Amongst the common grade 3 or higher adverse events, the gemcitabine/nab-paclitaxel arm experienced more neutropenia (38 vs. 27%), febrile neutropenia (3 vs. 1%), fatigue (17 vs. 7%), peripheral neuropathy (17 vs. 1%) and diarrhea (6 vs. 1%) than the gemcitabine arm. However, there were no grade 4 neuropathies in either arm. Neuropathy was cumulative and reversible for most after temporary discontinuation and some could restart at a reduced dose of nab-paclitaxel. Thus, neuropathy caused by gemcitabine/nab-paclitaxel appears to be better tolerated than that caused by FOLFIRINOX.

FOLFIRINOX vs. Gemcitabine/nab-paclitaxel

FOLFIRINOX and gemcitabine/nab-paclitaxel have not been compared head-to-head. FOLFIRINOX achieved higher response rates and longer median overall survival than gemcitabine in PRODIGE[6] compared to gemcitabine/nab-paclitaxel against gemcitabine in MPACT.[7] However, without a randomized trial comparing the two regimens, we cannot conclude which is more efficacious. Cross comparisons of trials should be done with caution. The two trials differed in terms of baseline patient characteristics, diversity of study sites involved and inclusion of an independent review of results.

The patients in PRODIGE had better prognostic factors than those in MPACT with respect to age, performance status, CA 19−9 level and exposure to prior therapy. PRODIGE had a more restrictive enrollment criterion than MPACT with an age cut off at 75 years old and

restriction of performance status to an ECOG score of 0 to 1, whereas MPACT had no age cut off and allowed patients with ECOG performance score from 0 to 2. In IMPACT, 10% of the patients were older than 75 years old, and the oldest patient was 88 years old. PRODIGE pooled data from phase II and III portions, so it potentially influenced the characteristics of the patients who were enrolled. Additionally, PRODIGE was carried out in 48 centers in a single country (France), and MPACT was carried out across 151 community and academic centers in 11 countries across 3 continents (North America, Europe and Australia). This difference in diversity of sites also limits the utility of comparing the two trials. Finally, MPACT had both investigator assessment and independent radiographic review for determination of secondary endpoints (progression-free survival and response rate); their conclusions were similar. PRODIGE had independent review of the CT scans only at the end of phase II of the study. According to investigator assessment, the objective response rate was essentially identical between FOLFIRINOX and gemcitabine/nab-paclitaxel.[19]

It has become consensus that for patients with good performance status and metastatic disease, both FOLFIRINOX and gemcitabine/nab-paclitaxel are acceptable treatment options. The differences in eligibility criteria, including age and performance status, between PRODIGE and MPACT has led to the current belief that gemcitabine/nab-paclitaxel should be preferred for those patients older than 75 years old or with poor performance status. Nevertheless, a retrospective study reported that elderly patients tolerate FOLFIRINOX with a similar side effect profile and efficacy as long as the doses are adjusted as needed. In this retrospective analysis, 17.3% of the patients had ECOG performance score of 2 or above.[20] There is currently an ongoing phase II trial, PAMELA-70, to prospectively evaluate the efficacy and tolerance of dose-adjusted FOLFIRINOX (irinotecan and continuous 5-FU infusion are dose-reduced compared to the doses used in PRODIGE) in patients who are 70 years old or older.[21] Also notably, the subgroup analysis in MPACT showed that patients with more metastatic disease burden significantly benefited from the combination of gemcitabine/nab-paclitaxel whereas, in the PRODIGE study, this feature was not demonstrated by FOLFIRINOX. This result has led to the notion that gemcitabine/nab-paclitaxel may have a stronger effect in treating metastatic disease than FOLFIRINOX; however, such a notion would still need to be further validated.

Taken together, there may be misconceptions that guide the selection of FOLFIRINOX and gemcitabine/nab-paclitaxel for advanced pancreatic cancer. It should also be recognized that even though chemotherapy is the only systemic therapy that offers meaningful benefit to patients, neither chemotherapy regimen offers durable response. Increased efforts into investigating the biology of these chemotherapy regimens could lead to better understanding on how to select the appropriate chemotherapy regimen and how to improve upon their efficacy when combining them with targeted therapeutics and immunotherapeutics.

Second-line systemic treatment for advanced pancreatic cancer

There is no standardization for the treatment of advanced pancreatic cancer after progression through FOLFIRINOX or gemcitabine/nab-paclitaxel. The current clinical practice is to transition to a fluorouracil-based regimen if the patient was on a gemcitabine-based regimen or visa-versa as long as the patient can tolerate more treatment. Although there is no data

from randomized, controlled studies to support this strategy, multiple single-institution, retrospective analyses suggest that gemcitabine/nab-paclitaxel is a reasonable second-line option following FOLFIRINOX.[22,23,24]

5-FU/oxaliplatin

Despite several phase III trials investigating the role of second-line treatment for advanced pancreatic cancer, they have not standardized our current management (Table 2). The phase III CONKO-003 trial tested the combination of oxaliplatin/5-FU/folinic acid (OFF) as second-line therapy for advanced pancreatic cancer.[25] OFF differs from FOLFOX (folinic acid, fluorouracil, oxaliplatin) in that flourouracil is administered weekly for the first 4 weeks and oxaliplatin is administered on day 8 and 22 of a 6-week cycle, whereas FOLFOX includes infusional 5-FU and is given every 2 weeks. The median overall survival improved with OFF (5.9 months; 95% CI, 4.1 to 7.4) compared to the folinic acid/5-FU (FF) arm (3.3 months; 95% CI, 2.7 to 4.0) with a HR of 0.66 (95% CI, 0.48 to 0.91; log-rank $P = .01$). Time to progression also improved with OFF (2.9 months; 95% CI, 2.4 to 3.2) compared to FF (2.0 months; 95% CI, 1.6 to 2.3) with a HR of 0.68 (95% CI, 0.50 to 0.94; log-rank $P = .019$). There were several issues with this clinical trial. Best supportive care was initially the comparison arm, but the trial was terminated due to insufficient accrual and reopened with change of comparison arm to FF. This modification left the trial with a small sample size of 76 patients analyzed in the OFF arm and 84 in the FF arm. The benefit of the 5-FU/oxaliplatin combination as second-line therapy was not validated in the subsequent phase III PANCREOX trial evaluating FOLFOX.[26] Again, PANCREOX only enrolled a small sample size of 54 patients in each arm and closed before its target enrollment of 128 patients per arm because of slow accrual due to a decrease in eligible patients after FOLFIRINOX became available as first-line therapy. PANCREOX showed no difference in median progression-free survival between 3.1 months for mFOLFOX6 and 2.9 months for 5-FU/LV (leucovorin) ($p = 0.989$). Median overall survival was inferior in the mFOLFOX6 arm compared to the 5-FU/LV arm (6.1 vs. 9.9 months; $p = 0.024$). Before making conclusions on the role of 5FU/oxaliplatin as second-line therapy, one should realize several note-worthy differences between CONKO-003 and PANCREOX that may explain the difference in outcome between the two trials. PANCREOX included patients up to ECOG performance status of 2, whereas CONKO limited enrolment to patients with KPS score of 70% or higher. More patients in PANCREOX had alterations and/or discontinuation of the treatment, which could be attributed to poor performance status or more intense dosing of oxaliplatin in the FOLFOX regimen. The eligibility in CONKO-003 required progression while on gemcitabine, but PANCREOX allowed progression whether on or off gemcitabine as long as the patient had been treated with it before. Moreover, there was more use of post-progression therapy in the 5-FU/LV arm vs. the FOLFOX arm (25% vs 7%, $p = .015$) in PANCREOX. Therefore, it remains inconclusive whether 5-FU/oxaliplatin should or should not be used as a second-line therapy.

5-FU/liposomal irinotecan

5FU/liposomal irinotecan as a standard of care second-line therapy is supported by level-one evidence from the NAPOLI-1 trial.[27] In NAPOLI-1, an international phase III study, patients with metastatic pancreatic cancer who progressed on previous gemcitabine therapy were

randomized to receive either nano-liposomal irinotecan, 5-FU/LV or nano-liposomal irinotecan/5-FU/LV. Median overall survival improved with the nano-liposomal irinotecan/5-FU/LV combination to 6.1 months (95% CI, 4.8–8.9) compared to nano-liposomal irinotecan (4.9 months) and 5-FU/LV (4.2 months). Objective response was 16% with nano-liposomal irinotecan/5-FU/LV ($p < .0001$ compared to 5-FU/LV), 6% with nano-liposomal irinotecan ($p = .02$ compared to 5-FU/LV) and 1% with 5-FU/lV. Even though grade 3–4 adverse events were more common with the nano-liposomal irinotecan/5-FU/LV (27% neutropenia vs. 15% with nano-liposomal irinotecan monotherapy vs. 1% with 5-FU/LV, 13% diarrhea vs. 21% vs. 4%, 11% vomiting vs. 14% vs. 3%, 14% fatigue vs. 6% vs. 4%), there was no decrease in quality of life at 6 weeks and 12 weeks from baseline.

5-FU/liposomal irinotecan vs. 5-FU/oxaliplatin vs. FOLFIRINOX

Currently, 5-FU/liposomal irinotecan is the regimen that is supported by the strongest level of evidence for second-line treatment, but there is still no consensus on how to select treatment for pancreatic cancer upon progression of disease. As FOLFIRINOX is one of the standard of care first-line options, it would be reasonable to consider gemcitabine/nab-paclitaxel as the second-line therapy after progression on FOLFIRINOX. Since the components of FOLFIRINOX do not overlap with gemcitabine/nab-paclitaxel, it would be reasonable to choose FOLFIRINOX as the next line after progression on gemcitabine-based therapy for patients who can tolerate aggressive therapy. Nevertheless, one cannot assume that FOLFIRINOX is superior to 5-FU/liposomal irinotecan in efficacy. As all the potential second-line options offer limited survival benefit, the selection of second-line therapies should be individualized with an emphasis on minimizing side effects and maximizing quality of life. The preferable option is to refer the patients to a clinical trial for second-line therapy.

Systemic adjuvant treatment

Surgical resection of localized disease is the only hope for a cure in patients with pancreatic cancer. However, only approximately 20% of patients have resectable disease at diagnosis, and the median overall survival still is only about 22 to 26 months due to the high recurrence rated despite adjuvant treatment.[19]

Gemcitabine monotherapy has been the stalwart for adjuvant chemotherapy in the US for several decades, but evidence to support it as standard of care was only established in 2007 by the CONKO-001 study.[28] In subsequent years, notable phase III randomized trials were ESPAC-3[29] and JASPAC-1[30], which compared gemcitabine to bolus 5-FU/leucovorin and S-1 (contains an oral prodrug of fluorouracil), respectively (Table 3). ESPAC-3 demonstrated that there was no statistically significant difference in median overall survival between gemcitabine (23.6 months, 95% CI, 21.4–26.4) and bolus 5-FU/leucovorin (23.0 months, 95% CI, 21.1–25.0) with HR 0.94 (95% CI, 0.81–1.08). JASPAC-1 was a non-inferiority trial where S-1 was not only non-inferior ($p < .001$), but also superior to gemcitabine ($p < .001$) with median overall survival of 25.5 months (95% CI, 22.5–29.6) with gemcitabine compared to 46.5 months (37.8–63.7) with S-1. In East Asia, S-1 subsequently became the standard of care adjuvant chemotherapy. In Europe, the results of

ESPAC-3 were intriguing enough to pursue investigation into the combination of gemcitabine and an orally available pro-drug of 5-FU in ESPAC-4.[31] In this phase III trial, patients were randomized to adjuvant gemcitabine or to the combination of gemcitabine and capecitabine (GemCap) following R0 or R1 surgical resections. The combination arm improved the median survival by 2.5 months compared to gemcitabine alone (28 vs. 25.5 months respectively, HR 0.82, p = 0.032). The estimated 5-year survival in the combination arm was 28.8% compared to 16.3% in the gemcitabine alone arm. This improvement in survival with GemCap did not come with an increase in serious adverse events (26% for gemcitabine vs. 24% for GemCap, p > .05). Thus, ESPAC-4 has established a new standard of care adjuvant chemotherapy in Europe and North America.

Ongoing phase III trials testing innovative therapeutic agents

Chemotherapeutic agents, even in combination, only offer limited benefit to the patients. Therefore, investigational agents are being combined with the chemotherapy regimens discussed above (Table 4). Current phase III trials include the addition of STAT3 inhibitor (Napabucasin), EGFR-inhibitor (Nimotuzumab), PARP-inhibitor (Olaparib), and stroma targeting agent (PEGPH20-pegylated hyaluronidase) to chemotherapy. Chemotherapy agents are also being altered to increase efficacy, such a nanoparticle-based cisplatin (N-6004) and liposomal paclitaxel (EndoTAG-1) or a next-generation version of ifosfomide (glufosfamide). Immune-based therapeutic agents such as vaccines (GV1001, which contains fragments of telomerase) and cytokines (pegylated-IL10) are also being combined with chemotherapy in phase III clinical trials.

Many prior phase III studies have failed, and inappropriate combination of experimental agents without strong biological rationale and lack of biomarkers to select proper candidates for experimental therapeutics are often the two main reasons for the failure. Thus, the design of future phase III trials should be based on in-depth analysis of mechanism of action of the experimental therapeutics. Clinical trials testing innovative agents should actively search for prognostic and predictive biomarkers.

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Table 1

Selected randomized phase III clinical trials investigating first-line systemic treatment for advanced pancreatic cancer

Study characteristics	Drug studied	Comparison drug	Indication for treatment	Primary outcome
Burris et al. JCO. 1997.[5]	Gemcitabine	Bolus 5-FU	First line for advanced stage (locally advanced or metastatic)	Clinical benefit response (Pain, KPS, weight) – 23.8% gemcitabine vs. 4.8% 5-FU (p = 0.0022)
Cunningham D et al. JCO. 2009.[27]	Gemcitabine/Capecitabine (GemCap)	Gemcitabine	First line for advanced stage (locally advanced or metastatic)	Overall survival, median – 7.1 months GemCap vs. 6.2 months gemcitabine (p = 0.008)
NCIC CTG PA.3 (Moore et al. JCO. 2007.[16])	Gemcitabine/Erlotinib	Gemcitabine/Placebo	First line for advanced stage (locally advanced or metastatic)	Overall survival, median – 6.24 months gemcitabine/erlotinib vs. 5.91 months gemcitabine (p = 0.038)
AIO group (Boeck et al. Anticancer Drugs. 2010.[26] & Heinemann V et al. Gut. 2013.[17])	Capecitabine/Erlotinib followed by Capecitabine	Gemcitabine/ Erlotirib followed by Gemcitabine	Treatment-naïve advanced stage (trial to investigate sequencing of drugs upon failure with first-line)	Time to treatment failure of second-line therapy – 4.2 months for both arms
PRODIGE (Conroy T et al. NEJM. 2011.[6])	FOLFIRINOX	Gemcitabine	First-line for metastatic	Overall survival, median – 11.1 months FOLFIRINOX vs. 6.8 months gemcitabine (p < 0.001)
MPACT (von Hoff D et al. NEJM. 2013.[7])	Gemcitabine/Nab-paclitaxel	Gemcitabine	First line for metastatic	Overall survival, median – 8.5 months gemcitabine/ nab-paclitaxel vs. 6.7 months gemcitabine (p < 0.001)
GEST (Ueno H et al. JCO. 2013.[29]) Non-inferiority trial.	S-1 monotherapy or Gemcitabine/S-1	Gemcitabine	First line for advanced stage (locally advanced or metastatic)	Overall survival, median – 8.8 months for gemcitabine, 9.7 months for S-1, 10.1 months for gemcitabine/S-1. S-1 non-inferior to gemcitabine (p < 0.001).

Table 2

Selected randomized phase III clinical trials investigating systemic treatment for progressive advanced pancreatic cancer

Study characteristics	Drug studied	Comparison drug	Indication for treatment	Primary outcome
CONKO-003 (Pelzer U et al. Eur J Cancer. 2011.[20] & Oettle H et al. JCO.2014.[30])	Oxaliplatin/5-FU/ Leucovorin (OFF)	5-FU/Leucovorin (LV)	Second-line for advanced stage after progression while receiving first-line gemcitabine	Overall survival, median – 5.9 months OFF vs. 3.3 months 5-FU/LV (p = 0.01)
PANCREOX (Gill et al. JCO. 2016.[21])	mFOLFOX6 (infusional Fluorouracil, LV, Oxaliplatin)	Infusional 5-FU/LV	Second-line for progressive advanced stage, must have had gemcitabine as first-line therapy	Progression-free survival, median – 3.1 months mFOLFOX6 vs. 2.9 months 5-FU/LV pP = 0.989)
NAPOLI-1 (Wang-Gillam A et al. Lancet. 2016.[22]	5-FU/LV	Nanoliposomal Irinotecan (NPiri) monotherapy or NPiri/ 5-FU/LV	Subsequent-line treatment for metastatic disease, must have had prior gemcitabine	Overall survival, median – 6.1 months NPiri/5-FU/LV vs. 4.2 months 5-FU/LV (p = 0.012) – 4.9 months NPiri vs. 4.2 months 5-FU/LV (p = 0.94)

Table 3

Selected randomized phase III clinical trials investigating adjuvant systemic treatment for pancreatic cancer

Study characteristics	Drug studied	Comparison drug	Indication for treatment	Primary outcome
CONKO-001 (Oettle et al. JAMA. 2007[31] & 2013.[32])	Gemcitabine	Observation	First-line adjuvant	Disease-free survival, median – 13.4 months gemcitabine vs. 6.9 months observation (p <. 001)
ESPAC-3 (Neoptolemos JP et al. JAMA. 2010.[24])	Gemcitabine	Bolus 5-FU/Leucovorin (LV)	First-line adjuvant	Overall survival, median – 23 months 5-FU/LV vs. 23.6m for gemcitabine (p = 0.39)
JASPAC-01 (Uesaka et al. Lancet. 2016.[25]) Non-inferiority trial.	S-1	Gemcitabine	First-line adjuvant	Overall survival, median – 46.1 months S-1 vs. 25.5 months gemcitabine. S-1 is non-inferior to gemcitabine (p< 0.0001), and p<0.0001 for superiority.
ESPAC-4 (Neoptolemos JP et al. Lancet. 2017.[26])	Gemcitabine/capecitabine (GemCap)	Gemcitabine	First-line adjuvant	Overall survival, median – 28 months GemCap vs. 25.5 months gemcitabine (p = 0.032)

Table 4

selected ongoing randomized phase III clinical trials investigating systemic therapy

Disease state	Indication for treatment	Intervention
Metastatic pancreatic cancer	First-line metastatic therapy	Napabucasin plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine
Metastatic pancreatic cancer	First-line metastatic therapy	PEGPH20 plus nab-paclitaxel/gemcitabine versus placebo plus nab-paclitaxel/gemcitabine
Locally advanced or metastatic pancreatic cancer	First-line advanced therapy	NC-6004 with Gemcitabine versus Gemcitabine alone
gBRCA-mutated metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy	Patients are on treatment with a first line platinum-based metastatic therapy without progression	Maintenance Olaparib monotherapy versus Placebo
K-RAS wild-type locally advanced and metastatic pancreatic cancer	Must have had no anti-tumor palliative chemotherapy or molecularly targeted therapy. Adjuvant therapy must have been more than 6 months prior.	Nimotuzumab with Gemcitabine versus Placebo with Gemcitabine
Locally advanced and/or metastatic pancreas cancer that failed FOLFIRINOX	Secord-line metastatic therapy	Endo TAG-1 plus Gemcitabine versus Gemcitabine alone
Metastatic pancreatic cancer previously treated with gemcitabine	Second-line metastatic therapy	Glufosfamide versus Fluorouracil
Metastatic pancreatic cancer that has progressed during or following a first-line gemcitabine containing regimen	Second-line metastatic therapy	AM0010 with FOLFOX versus FOLFOX alone
Locally advanced or metastatic pancreatic cancer	Second-line therapy for progressive advanced pancreatic cancer or progression after resection	GV1001 with Gemcitabine/Capecitabine versus gemcitabine/Capecitabine alone