Updates on adjuvant and neoadjuvant treatment strategies for surgically resectable and borderline resectable pancreatic ductal adenocarcinoma

Siddharth Iyengar, Christopher Nevala-Plagemann[iD] **and Ignacio Garrido-Laguna**

Abstract: Pancreatic cancer is the third leading cause of cancer-related mortality in the US. Outcomes for patients with pancreatic cancer are poor as curative approaches are only available to the minority of patients who have localized tumors for which surgery may be an option. The past decade has established fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as the new standard of care following resection for fit patients with resectable pancreatic tumors. However, most patients will relapse and a large number of patients treated with upfront resection are unable to receive or complete adjuvant chemotherapy. There is therefore considerable interest in neoadjuvant treatment strategies for patients with resectable and borderline resectable pancreatic cancer as a way to provide early systemic treatment of micrometastatic disease, facilitate lymph node downstaging, and increase the likelihood of negative resection margins (R0). This review will focus on key aspects of completed trials evaluating adjuvant therapy in resectable pancreatic cancer and will provide an overview of emerging evidence supporting the use of neoadjuvant treatment strategies for both resectable and borderline resectable pancreatic cancer.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), which accounts for the vast majority (93%) of cancer cases arising from the pancreas, is projected to affect 60,430 Americans and cause 48,220 deaths in 2021.[1] PDAC will become the second leading cause of cancer-related deaths in the United States by 2040.[2] The 5-year overall survival (OS) rate of PDAC patients in the US remains poor, with only slight improvement from 3% during the years 1975–1977 to 10% during the years 2009–2015.[3]

Surgery continues to offer the only possibility of cure for PDAC; however, just 10–20% of PDAC patients have tumors amenable to upfront resection, either *via* a pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy.[4] Another 30–40% of patients will present with tumors that are considered locally advanced unresectable or borderline resectable.[4–6] In these cases, while the tumor remains localized to the pancreas and regional lymph nodes, invasion of nearby vasculature may decrease the likelihood of attaining a margin-negative (R0) resection.[7] While several guidelines have been proposed, the exact criteria by which patients are categorized as having resectable, borderline resectable, or locally advanced unresectable disease varies based on institution and surgical expertise.[5,6] To harmonize the definition of borderline resectable disease, a group of investigators published consensus guidelines. According to this group of investigators, patients with borderline resectable disease

Correspondence to:
Siddharth Iyengar
Department of Internal
Medicine, University of
Utah School of Medicine,
50 Medical Dr N, Salt Lake
City, UT 84132-0002, USA
**siddharth.iyengar@hsc.
utah.edu**

**Christopher
Nevala-Plagemann
Ignacio Garrido-Laguna**
Division of Oncology,
Huntsman Cancer
Institute, University of
Utah, Salt Lake City, UT,
USA

must meet one of the following criteria.[8] Firstly, anatomical criteria (A); in these patients upfront resection has a high likelihood of a microscopic margin-positive (R1) resection. Next, biological criteria (B); these are patients in which more advanced disease is suspected than can be seen on imaging studies, for instance an elevated carbohydrate antigen 19-9 (CA19-9) in the absence of biliary obstruction or equivocal findings on imaging studies. Finally, patients can be considered borderline resectable based on conditional factors (C); these are patients with poor performance status in which a trial of neoadjuvant chemotherapy is favored as a fitness test prior to resection.

In patients who undergo surgery with curative intent, disease recurrence unfortunately remains common. Studies attempting to explain this finding have demonstrated that early on in the course of the disease, pancreatic cancer cells can metastasize to other organs.[9,10] In genetically engineered mice, cancer cells were shown to seed the liver even before detectable tumors developed in the pancreas.[9] This concept of pancreatic cancer being a systemic disease at the time of diagnosis may explain the high recurrence rate following resection and thus provides the biological rationale for adjuvant or neoadjuvant systemic therapy.

Randomized trials have established the survival benefit of adjuvant chemotherapy in patients with resected PDAC.[11,12] Despite these improvements in outcomes with adjuvant therapy many issues remain. It is estimated that approximately 30–40% of patients are unable to receive adjuvant chemotherapy mainly due to postoperative complications, and in those who do receive adjuvant treatment, delays and dose modifications are common.[13–15] Furthermore, in those treated with surgical resection and the most active available adjuvant chemotherapy, approximately 50% will still relapse within 2 years.[12]

These issues with adjuvant therapy have led to increasing interest in neoadjuvant treatment strategies. In studies evaluating outcomes of PDAC patients treated surgically, lymph node metastases and positive margins have been associated with worse survival.[7] In addition, it is not uncommon for patients without any identifiable foci of distant cancer spread on imaging to have evidence of metastatic disease on surgical exploration.[16,17] Thus in addition to potentially being more tolerable, neoadjuvant chemotherapy in theory may improve outcomes by decreasing the rate of

positive surgical margins and pathological node positivity following surgery.[7] In addition, although the safety of pancreatic surgery has greatly improved, postoperative mortality rates even at high volume centers are still 3–5%.[7,18] Neoadjuvant chemotherapy thus has the potential to make surgery a viable option for many patients with borderline resectable or initial locally advanced unresectable disease who previously would not have had a chance for curative intent treatment. While not yet standard of care, evidence is rapidly accumulating to support the use of neoadjuvant therapy in this disease.

In this review we will start by providing an overview of the clinical trials that led to the establishment of adjuvant therapy as the current standard of care in resectable pancreatic cancer (Table 1). We will then discuss more recent trials investigating neoadjuvant approaches to this disease and where appropriate we will also discuss any relevant preclinical or observational studies that have helped inform the design of the ongoing and completed trials discussed in this review.

Review of milestones in the adjuvant setting

In 1985, results from the GITSG trial were published. In this trial 43 patients with resected PDAC were randomly assigned to observation *versus* chemoradiation (CRT) with 5-fluorouracil (5-FU) followed by maintenance 5-FU for 2 years or until recurrence.[19] Median OS was higher for patients in the treatment arm *versus* observation arm (20 months *versus* 11 months; $p = 0.03$). This was the first trial to demonstrate an OS benefit with adjuvant therapy in PDAC patients. However, it had several limitations, including poor accrual leading to the study being closed early as well as likely suboptimal dose of radiation (40 Gray (Gy)). While some have referenced this study to support the benefit of adjuvant radiation, it is likely that the survival benefit was driven by prolonged exposure to systemic 5-FU.

Nearly two decades later, the ESPAC-1 trial failed to show a benefit from adjuvant chemoradiation. In that trial, 289 patients with resected PDAC were randomly assigned to one of four groups: adjuvant chemotherapy, CRT, CRT followed by chemotherapy, or observation.[20] Chemotherapy consisted of leucovorin modulated 5-FU for 6 months while CRT consisted of a total of 20 Gy plus 5-FU. Median OS was best in the chemotherapy-alone arm (21.6 months), followed by CRT

Table 1. Selected completed and ongoing adjuvant trials in resected PDAC.

Trial	Design	N	Primary outcome	Population	Arms	Median DFS (months)	Median OS (months)	OS rate (%)	Notes
GITSG (1985)		43	OS	R0	Observation	9	11.0	NR	
					CRT (5-FU based) followed by 5-FU maintenance therapy	11 ($p=0.01$)	20.0 ($p=0.03$)	NR	
ESPAC-1 (2004)	Phase III	289	Two-year OS	R0/R1	Observation	NR	16.9	10.7	
					Chemotherapy (5-FU)	NR	21.6	29.0	
					CRT (5-FU based)	NR	13.9	7.3	
					CRT (5-FU based) followed by chemotherapy (5-FU)	NR	19.9	13.2 5-year OS rate	
CONKO-001 (2013)	Phase III open-label	368	DFS	R0/R1	Observation	6.7	20.2	10.4	
					Gemcitabine	13.4 ($p<0.001$)	22.8 ($p=0.01$)	20.7 ($p=0.01$) 5-year OS rate	
ESPAC-3 (2010)	Phase III open-label	1088	OS	R0/R1	5-FU	14.1	23.0	15.9	
					Gemcitabine	14.3 ($p=0.53$) PFS	23.6 ($p=0.39$)	17.5 ($p=0.39$) 5-year OS rate	
JASPAC 01 (2016)	Phase III open-label	385	OS	R0 (13% had R1)	Gemcitabine	11.3	22.5	24.4	
					S-1	22.9 ($p<0.0001$)	46.5 ($p<0.0001$)	44.1 ($p<0.0001$) 5-year OS rate	
ESPAC-4* (2017)	Phase III open-label	732	OS	R0/R1	Gemcitabine	13.1	26.0	20	
					Gemcitabine and capecitabine	13.9 ($p=0.082$)	27.7 ($p=0.049$)	28 ($p=0.049$) 5-year OS rate	
PRODIGE-24 (2018)	Phase III open-label	493	DFS	R0/R1	Gemcitabine	12.8	34.8	48.6	
					mFOLFIRINOX	21.6 ($p<0.0001$)	54.4 ($p=0.003$)	63.4 3-year OS rate	
APACT (2019)	Phase III open-label	866	DFS	R0/R1	Gemcitabine	18.8 Independent review / 13.7	36.2	NR	
					Gemcitabine plus nab-paclitaxel	19.4 ($p=0.18$) Independent review / 16.6 ($p=0.016$) Investigator review	40.5 ($p=0.045$)	NR	
RTOG 0848	Phase III open-label	950	OS	R0/R1	Adjuvant chemotherapy Adjuvant CRT				Identifier: NCT01013649 Start date: 2009 Expected completion: 2022

*ESPAC-4 data updated with final results presented at 2020 ASCO Annual Meeting.
CRT, chemoradiotherapy; DFS, disease-free survival; 5-FU, 5-fluorouracil; NR, not reported; OS, overall survival; PFS, progression-free survival.

and subsequent chemotherapy (19.9 months), then observation (16.9 months), and worst with CRT alone (13.9 months). Patients who received chemotherapy showed improved survival compared to those who did not [median OS 20.1 *versus* 15.5 months, 5-year survival rate was 21% *versus* 8%, hazard ratio (HR) = 0.71; *p* = 0.009]. In addition, patients who underwent adjuvant CRT demonstrated worse survival than those who did not (median OS 15.9 *versus* 17.9 months, 5-year survival rate was 10% *versus* 20%, HR = 1.28; *p* = 0.05). Limitations to this study included poor quality control of radiation therapy and poor experimental design as the 2×2 factorial design allowed clinicians to administer 'background' chemotherapy or CRT based on clinician or patient preference, and patients and clinicians were allowed to select which study arm to enter.[21] Despite this, the study was interpreted as failing to show benefit from adjuvant radiation therapy, which led to a shift in practice standards away from radiation therapy, especially in Europe.

In addition, in 2007, long-term results from the multicenter phase III EORTC trial 40891 were published. In this trial, 218 patients with resected cancer of the pancreatic head or periampullary region were randomly assigned to observation *versus* postoperative CRT (total of 40 Gy plus 5-FU). No difference was found between the observation group compared to the adjuvant CRT group (median OS was 1.6 years for observation group *versus* 1.8 years for CRT group, 5-year survival rate was 22% *versus* 25%, HR = 0.91; *p* = 0.540).[22]

While the GITSG and ESPAC-1 trials suggested a benefit with adjuvant therapy, due to their limitations they did not lead to widespread adoption of adjuvant treatment in the management of PDAC. This changed in 2007 with publication of the CONKO-001 trial which randomly assigned 368 patients with resected PDAC to either 6 months of adjuvant gemcitabine or observation.[11] In updated results published in 2013, both median disease-free survival (DFS) (13.4 *versus* 6.7 months; *p* < 0.001) and OS (22.8 *versus* 20.2 months; *p* = 0.01) were significantly greater in the adjuvant gemcitabine arm compared to observation.[23] That study established adjuvant gemcitabine as standard of care at the time for resected PDAC.

In 2010, results from the ESPAC-3 trial were published, which randomly assigned 1088 patients with resected PDAC to either 6 months of adjuvant gemcitabine or 6 months of adjuvant 5-FU plus leucovorin.[24] Median OS was not different between the two arms (23.6 months with gemcitabine *versus* 23.0 months with 5-FU, HR = 0.94; *p* = 0.39). Toxicity from 5-FU was found to be slightly worse as there was a higher incidence of grade 3/4 gastrointestinal adverse events in this arm. Both therapies are currently listed as recommended regimens in the adjuvant setting by the National Comprehensive Cancer Network (NCCN) with a category 1 level of evidence although gemcitabine is viewed as a superior option due to its better toxicity profile.[25]

In a similar Japanese study (JASPAC-01), 385 patients with resected PDAC were randomly assigned to 6 months of gemcitabine or 6 months of S-1.[26] S-1 is an oral combination (tegafur/gimeracil/oteracil) fluoropyrimidine that functions as an anti-metabolite and inhibitor of dihydropyrimidine dehydrogenase (DPD).[26] Longer median OS was seen in the S-1 arm *versus* the gemcitabine arm (46.5 *versus* 25.5 months, HR = 0.57; *p* < 0.0001). The frequency of adverse events was higher with gemcitabine than with S-1. However, due to pharmacodynamic and pharmacokinetic differences that have been observed in S-1 metabolism between East Asians and Caucasians, S-1 has not been approved for use in the US.[27]

Recent trials in the adjuvant setting

In 2017, results from the ESPAC-4 trial were published, which randomly assigned 732 patients with resected PDAC to adjuvant gemcitabine or combination gemcitabine/capecitabine.[28] A modest improvement in the primary outcome, median OS, was seen with combination gemcitabine/capecitabine compared to gemcitabine alone (27.7 *versus* 26.0 months, HR = 0.84; *p* = 0.049).[29] The estimated 5-year OS rate was also found to be higher in the combination arm compared to gemcitabine alone (28% *versus* 20%).[29] On subgroup analysis, the benefit with gemcitabine/capecitabine over gemcitabine seems mainly to have been driven by those with a R0 (margin-negative) resection (median OS 39.5 *versus* 27.9 months, HR = 0.68; *p* < 0.001) compared to R1 resections (23.7 *versus* 23.0 months, HR = 0.90; *p* > 0.05). Multivariate analysis confirmed that R1 resection, positive lymph nodes, elevated postoperative CA19-9, and preoperative C-reactive protein were associated with worse survival. Dose modifications were common and 46% of patients

in the gemcitabine/capecitabine arm discontinued treatment before finishing six cycles due to treatment toxicity compared to 35% in the gemcitabine arm. This study provides high-level evidence to support gemcitabine plus capecitabine following resection in patients who are not fit for modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX).

Following publication of PRODIGE-4, which established fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as standard of care for fit patients with metastatic PDAC,[30] the PRODIGE-24 trial was conducted to examine the efficacy of FOLFIRINOX in the adjuvant setting.[12] Due to difficulty tolerating systemic therapy following surgery, dose modifications to the treatment regimen of FOLFIRINOX were made in the PRODIGE-24 trial to decrease adverse events of neutropenia and diarrhea. Notably, bolus fluorouracil was not used, and the dose of irinotecan was reduced from $180\,mg/m^2$ to $150\,mg/m^2$ after 162 patients were enrolled, in accordance with a prespecified toxicity analysis. In 2018, results from the PRODIGE-24 study were published, in which 493 patients with resected PDAC were randomly assigned to 6 months of adjuvant gemcitabine or to mFOLFIRINOX. With a median follow-up of 30.5 months, the primary endpoint of median DFS was improved with mFOLFIRINOX compared to gemcitabine (21.6 *versus* 12.8 months; $p < 0.001$). Median OS was also improved in the mFOLFIRINOX arm (54.4 *versus* 34.8 months, HR = 0.64; $p = 0.003$). Importantly, on subgroup analysis of patients 70 years of age or older, no benefit was seen in DFS with mFOLFIRINOX as compared to gemcitabine.[31] The dose adjustments of fluorouracil and irinotecan from the FOLFIRINOX regimen seemed to reduce the occurrence of grade 3 or 4 neutropenia and diarrhea in patients in the PRODIGE-24 trial. Despite this, a higher incidence of adverse events was seen with mFOLFIRINOX compared to gemcitabine, with 75.9% of patients in the mFOLFIRINOX group reporting a grade 3 or 4 adverse event compared to 52.9% of patients in the gemcitabine group. Based on the results of this study, mFOLFIRINOX is seen as standard of care for adjuvant treatment of resected PDAC with favorable performance status [Eastern Cooperative Oncology Group (ECOG) 0–1]. Based on exploratory subgroup analysis it is unclear whether elderly patients (70–75 years old) derive the same benefit compared to those less than 70 years of age.

The MPACT trial showed improved survival with gemcitabine plus nab-paclitaxel *versus* gemcitabine monotherapy in patients with metastatic pancreatic cancer.[32] Therefore, this combination was studied in the adjuvant setting. At the 2019 American Society of Clinical Oncolocy (ASCO) Annual Meeting, early data from the APACT trial was presented, which randomly assigned patients with resected PDAC to gemcitabine monotherapy or gemcitabine plus nab-paclitaxel for 6 months.[33] This is the largest trial assessing the efficacy of adjuvant therapy in PDAC to date, with 866 patients enrolled at around 179 sites globally. Notably, this study was open-label and postoperative computed tomography (CT) scans were required prior to study entry (in contrast to ESPAC-4). Patients from the US and Europe comprised 82% of the study population. Patient characteristics were well balanced across geographical regions, with the exception of a lower rate of microscopic margin-positive (R1) resections in the US (although this did not translate into longer survival when compared to Europe). Of note, this study used a different definition of R1 resection status as compared to the ESPAC-4 and PRODIGE-24 studies, which defined R1 status according to NCCN criteria. Whereas ESPAC-4 and PRODIGE-24 defined R1 as any tumor cell within 1 ml of any surface of the specimen, APACT defined R1 as direct margin involvement. The study was negative for its primary endpoint of disease-free survival (DFS) per independent radiology review (18.8 months for gemcitabine monotherapy *versus* 19.4 months for gemcitabine/nab-paclitaxel, HR = 0.88; $p = 0.18$). However, when the analysis was done by investigator review, a benefit in DFS was seen in the combination arm compared to the gemcitabine monotherapy group (16.6 *versus* 13.7 months, HR = 0.82; $p = 0.016$). A benefit in OS, a secondary endpoint, was seen in the combination arm compared to the gemcitabine monotherapy group (40.5 *versus* 36.2 months, HR = 0.82; $p = 0.045$). Notably, on subgroup analysis, the benefit in OS was only statistically significant in North American patients, despite larger numbers of patients being enrolled in Europe. Unpublished data shared by the study team suggests a higher percentage of patients in the experimental arm in the US received salvage 5-FU and irinotecan. An analysis of salvage therapy by region is needed to understand the impact of treatment beyond progression in overall survival.

The difference seen in DFS between independent radiology review and investigator review suggests

Table 2. Estimated cost of gemcitabine-capecitabine regimen (ESPAC-4 trial) *versus* gemcitabine/nab-paclitaxel regimen (APACT trial) based on wholesale acquisition cost and comparative hazard ratios.

Trial	APACT	ESPAC4
Regimen	Nab-paclitaxel 125 mg/m^2 d1, 8, 15 q28 d	Capecitabine 830 mg/m^2 BID d1–21 q28 d
	Gemcitabine 1000 mg/m^2 d1, 8, 15	
Estimated cost of 1 cycle of treatment	$13,127	$195
Estimated cost of 6 cycles of treatment	$78,762	$1,170
OS HR	0.82	0.84

Data from Huntsman Cancer Institute Pharmacy. Wholesale acquisition cost of gemcitabine 1000 mg vial: $17.50, nab-paclitaxel 100 mg vial: $1446.91, capecitabine 150 mg (#60): $20.51, capecitabine 500 mg (#120): $84.15.

that this study may have benefited from blinding and with DFS being assessed by investigators. Independent assessment of DFS is complex as radiologists are blinded to information that clinical investigators have access to which may suggest progression of disease (pain, increasing tumor markers, etc.). Another consideration when taking into the account the results of this study is that using OS as an endpoint in the adjuvant setting presents a unique challenge as imbalances in the use of salvage chemotherapy may impact OS. Finally, financial toxicity of the experimental regimen is a significant consideration as the cost of six cycles of gemcitabine/nab-paclitaxel is estimated to be 67 times higher than gemcitabine/capecitabine (Table 2). Based on these data, current evidence does not support using nab-paclitaxel in the adjuvant setting in patients who did not receive preoperative chemotherapy.

Key differences in trial design and enrolled patient population

Although cross-trial comparisons should be made with caution, a few key differences in the design and results of these adjuvant therapy trials are worth noting. One key finding in trials of adjuvant therapy in PDAC is the importance of resection margin status as a prognostic and potentially predictive marker. As noted above, in ESPAC-4 an improvement in overall survival with adjuvant gemcitabine/capecitabine was only observed in those with a R0 resection. This finding is consistent with results from other adjuvant trials with the exception of PRODIGE-24 and CONKO-01 which also showed benefit in patients with R1 resection. The median OS in the control arm with

gemcitabine was substantially shorter in ESPAC-4 (25 months) compared to the gemcitabine arm in PRODIGE-24 and APACT (35 and 37 months, respectively). Differences in patient characteristics and disease biology at baseline may have contributed to this. Notably, APACT and PRODIGE-24 excluded patients with a CA19-9 level greater than 100 U/mL and 180 U/mL, respectively, while ESPAC-4 did not place a restriction on patient inclusion based on CA19-9 levels. In addition, a mandatory postoperative CT scan was required in both PRODIGE-24 and APACT that likely contributed to enriching these study populations with patients with better disease biology. It is also important to note that in ESPAC-4, surveillance CT scans were not mandatory and only requested by the treating physician if clinically indicated. We can hypothesize that lack of a mandatory CT scan during surveillance in ESPAC-4 likely led to more patients in this trial being diagnosed with symptomatic recurrence who may have been too frail for salvage chemotherapy. Indeed, only 33% of patients in ESPAC-4 got salvage chemotherapy *versus* 76% in PRODIGE-24. Although limited by potential for lead time bias, retrospective data also suggest that patients diagnosed with symptom-free recurrence have longer post-recurrence survival compared to those who present with symptoms.[34] Interestingly, a study evaluating the role of surveillance CT scans in PDAC failed to show that they are cost-effective. However, this study was done before FOLFIRINOX and gemcitabine plus nab-paclitaxel were standard of care in this disease.[35] While early detection of relapse may be associated with receipt of more intensive chemotherapy, whether early detection has an impact on overall survival remains to be proved.

Neoadjuvant strategies

There are several potential advantages of neoadjuvant chemotherapy, including assessment of chemotherapy response, early treatment of micrometastatic disease, downstaging of disease, and greater likelihood of margin-negative (R0) resections. The use of neoadjuvant treatment strategies in borderline resectable PDAC seems intuitive as these patients traditionally have had lower resection rates and worse survival than those with resectable PDAC. Recent evidence has shown that neoadjuvant chemotherapy increases the R0 resection rate in patients with resectable and borderline resectable PDAC.[36–38] R0 resection status has been shown to be an important prognostic factor in the adjuvant setting as it is associated with delayed recurrence and improved survival as compared to those with R1 resection status.[20,28,38] Interestingly, a recent retrospective analysis from a single institution database of patients with PDAC who received neoadjuvant treatment prior to resection did not confirm R1 resection was an independent prognostic factor in overall survival.[39] However, most patients included in the study had locally advanced unresectable or even metastatic disease. A second reason to consider preoperative chemotherapy is improved chemotherapy compliance as shown in the SWOG-1505 study in patients with resectable PDAC. In that study, a greater percentage of patients who started neoadjuvant treatment (88%) were able to complete it *versus* those in the PRODIGE trial (66% of patients able to complete adjuvant treatment).[40] Retrospective cohort data also support the use of neoadjuvant therapy over upfront surgery in patients with resectable PDAC.[41] Furthermore, a recent meta-analysis found that neoadjuvant therapy improves OS compared to an upfront surgery approach in patients with resectable and borderline resectable PDAC.[42] Currently, either FOLFIRINOX, mFOLFIRINOX, or gemcitabine/nab-paclitaxel with or without subsequent CRT are listed as preferred regimens for perioperative chemotherapy in resectable or borderline resectable PDAC by the NCCN.[25] A criticism to the neoadjuvant approach is early tumor progression that may preclude resection. However, patient selection is indeed one of the advantages of the neoadjuvant strategy as patients with poor disease biology who will not benefit from surgery are spared from the morbidity of a futile intervention.

Caveats comparing survival outcomes of adjuvant and neoadjuvant trials

It is important to keep in mind that the median OS reported in trials evaluating neoadjuvant and perioperative chemotherapy strategies cannot be directly compared to median OS from trials evaluating adjuvant chemotherapy. In adjuvant trials, the survival analysis includes only those who have undergone surgery and have a performance status favorable enough to be randomly assigned to receive adjuvant therapy. Patients who have disease progression prior to surgery are found to have occult metastases or locally advanced disease at the time of surgery, develop postoperative complications leading to poor recovery from surgery, or relapse prior to starting adjuvant therapy are not eligible for adjuvant trials. This leads to a significant selection bias enriching adjuvant trials with patients who have the most favorable disease biology, rather than taking into account the entire patient population being considered for the adjuvant treatment strategy (Figure 1). Due to this, the median OS in trials evaluating neoadjuvant or perioperative treatment strategies can be expected to be inferior to those reported in adjuvant trials. Therefore, it is critical that randomized studies that compare neoadjuvant to adjuvant studies use an intention-to-treat (ITT) analysis.

Notable neoadjuvant trials

Evidence from several randomized trials evaluating neoadjuvant treatment in resectable and borderline resectable PDAC has recently come to light, which will be summarized below.[36–38,43]

In 2018, Jang *et al.*[36] published results from a phase II/III trial comparing the efficacy of neoadjuvant CRT *versus* upfront surgery followed by adjuvant CRT in patients with borderline resectable pancreatic cancer. CRT in both arms consisted of 54 Gy delivered with concurrent weekly gemcitabine ($400\,mg/m^2$), followed by four cycles of gemcitabine ($1000\,mg/m^2$ on days 1, 8, and 15). The study was designed to enroll 110 patients. However, the study was discontinued due to early findings of survival differences between treatment arms. A total of 58 patients underwent randomization. In the ITT analysis, 2-year survival rate was significantly worse in the upfront surgery group compared to the neoadjuvant CRT group (26.1% *versus* 40.7%; HR = 1.495; $p = 0.028$). The R0 resection rate was also significantly higher in the neoadjuvant
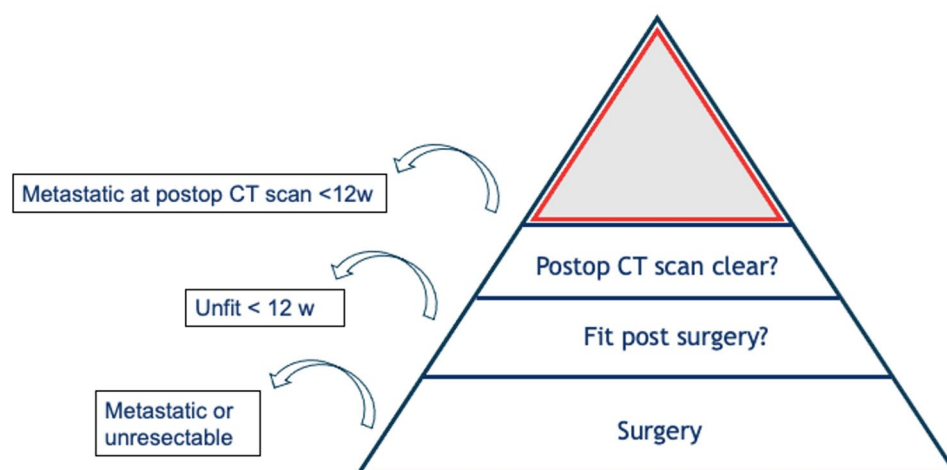
Figure 1. Selection bias in adjuvant trials.
In adjuvant trials patients are selected through different steps, each of them leading to patient drop off and enriching the study sample with patients who have favorable disease biology. The median survival reported in adjuvant trials is that of selected patients in the red triangle at the top rather than the overall survival (OS) for the entire patient population being considered for this strategy at the base.

CRT group (51.8% *versus* 26.1%; $p = 0.004$). A significant limitation to interpreting the results of this study is that only eight patients (26.7%) in the neoadjuvant CRT group and six patients (21.4%) in the upfront surgery group completed the entire per-protocol treatment. In addition, as this trial was conducted entirely in Korea, the applicability of these results to a broader population is limited. Finally, eight patients who withdrew consent could not be included in the ITT analysis.

In 2018, results of the phase II portion of the PACT-15 trial were published in which 93 patients with resectable PDAC were randomly assigned to one of three arms: perioperative cisplatin, epirubicin, gemcitabine and capecitabine (PEGX), upfront surgery followed by PEGX, or upfront surgery followed by gemcitabine.[37] In the per-protocol analysis, the primary endpoint of 1-year event-free survival was highest in the perioperative PEGX arm (66%), followed by the upfront surgery followed by PEGX arm (50%) and upfront surgery followed by gemcitabine arm (23%). The R0 resection rate was 63% in the perioperative PEGX arm compared to 37% in the upfront surgery followed by PEGX arm (37%). Unfortunately, analyses in the study were per-protocol rather than ITT and no statistical analysis was performed among the arms. In addition, this study is limited by the use of PEGX which is a non-standard chemotherapy regimen in this disease.

At the 2019 ASCO Gastrointestinal Cancers Symposium, preliminary results were presented from the randomized phase II/III Prep-02/JSAP-05 trial which was conducted in Japan. In that trial, 364 patients with resectable PDAC were randomly assigned to receive either upfront surgery followed by adjuvant S-1 for 6 months or neoadjuvant gemcitabine plus S-1 followed by resection and adjuvant S-1.[43] The primary endpoint was OS and an improvement was seen in the perioperative chemotherapy arm (median OS 36.6 *versus* 26.6 months; HR = 0.72; $p = 0.015$). The main limitation regarding this study is that the use of S-1 outside of East Asian populations may be limited by pharmacokinetic and pharmacodynamic differences affecting S-1 dosing.

PREOPANC was a phase III trial that randomly assigned 248 patients with resectable or borderline resectable PDAC to either immediate surgery followed by adjuvant gemcitabine for six cycles or neoadjuvant CRT (gemcitabine-based) followed by surgery and adjuvant gemcitabine.[38] Neoadjuvant CRT consisted of a total of 36 Gy alongside 1000 mg/m^2 of gemcitabine for 4 weeks (given on days 1, 8, and 15), preceded and followed by a modified cycle of gemcitabine for 3 weeks (1000 mg/m^2 on days 1 and 8). After resection, four cycles of gemcitabine were administered (1000 mg/m^2 on days 1, 8, and 15) for patients in the neoadjuvant CRT arm. The primary endpoint was OS and no difference was

found between the preoperative CRT arm and immediate surgery arm (median OS 16.0 *versus* 14.3 months; HR = 0.78; *p* = 0.096). A modest improvement in DFS was seen in the preoperative CRT arm (8.1 *versus* 7.7 months; HR = 0.73; *p* = 0.032). In addition, a higher R0 resection rate was seen in the preoperative CRT arm (72% *versus* 40%; *p* < 0.001) and there was a significantly decreased rate of patients who were found to have had pathological lymph nodes, perineural invasion, or venous invasion in the preoperative CRT arm. Patients who underwent R0 resection had a better OS than patients with non-R0 resection. Notably, on subgroup analysis, the benefit in DFS and R0 resection rate was driven by the group of patients with borderline resectable PDAC, and a benefit in OS was seen in this group as well. No benefit in any of these three outcomes was observed in the resectable PDAC group. Limitations to this study include the limited amount of systemic treatment delivered prior to starting radiation, the use of single agent gemcitabine, a suboptimal systemic treatment per current standard, and poor survival outcomes compared with historical data in both arms.

Recent neoadjuvant trials

Given these limitations, none of the four aforementioned studies established a new standard of care. However, these randomized studies consistently showed an increase in the rate of R0 resection when neoadjuvant chemotherapy is administered. In addition, two of these studies showed improved survival.[36,43] Results from three additional neoadjuvant studies that were reported recently will be summarized below.

The ESPAC-5F study was a multicenter international randomized phase II trial that compared immediate surgery to neoadjuvant strategies for borderline resectable PDAC. The study randomly assigned 90 patients to one of four arms: immediate surgery, two cycles of neoadjuvant gemcitabine/capecitabine followed by surgery, four cycles of neoadjuvant FOLFIRINOX followed by surgery, or neoadjuvant CRT (capecitabine based, 50.4 Gy) followed by surgery.[44] This was a feasibility study with the primary endpoint being recruitment and resection rate. Adjuvant therapy was administered to all resected patients per the treating physician's choice. Median dose intensities were high in all arms (>90% of planned). 25% of patients in both the gemcitabine/capecitabine and FOLFIRINOX arms completed neoadjuvant chemotherapy as planned, while 38% of patients completed all planned neoadjuvant CRT. In this small study, no difference was seen in the primary outcome (R0 + R1 resection rate) or in the R0 resection rate between the immediate surgery group and neoadjuvant therapy groups (62% *versus* 55%, *p* = 0.668 and 15% *versus* 23%, *p* = 0.721, respectively). However, the CRT arm had a higher proportion of patients who underwent R0 resections (37%), compared to the gemcitabine/capecitabine (17%) and FOLFIRINOX (18%) arms. Greater downstaging was accomplished in the CRT arm, with a higher percentage of patients having stage pT1–2 tumors in the CRT arm (50%) compared to the surgery-alone arm (19%), gemcitabine/capecitabine arm (33%), or FOLFIRINOX arm (27%), although no formal statistical analysis was done. In addition, 75% of patients in the CRT arm were lymph node negative, compared to 42% and 27% of patients in the gemcitabine/capecitabine and FOLFIRINOX arms, respectively. Serious adverse events (SAEs) were reported in 26% of patients in the FOLFIRINOX arm, 21% of patients in the CRT arm, and 6% of patients in the gemcitabine/capecitabine arm. Notably, 21.9% of patients in the immediate surgery group died within the first 4 months after surgery. The enrollment of patients with more locally advanced disease including arterial involvement may have influenced this high rate of early mortality and suggests that upfront resection is a suboptimal strategy in these patients. Patients in the neoadjuvant therapy groups showed better survival at one year compared to the immediate surgery group (77% *versus* 42%, HR = 0.27; *p* < 0.001). One-year survival was highest in the FOLFIRINOX arm (84%), followed by the gemcitabine/capecitabine (79%) and CRT (64%) arms. The main limitation of this study is that it was designed to assess recruitment and feasibility for neoadjuvant therapy rather than efficacy, and therefore was not powered appropriately for survival. Taken together, these results are encouraging and further support the use of neoadjuvant therapy in patients with borderline resectable pancreatic cancer.

SWOG-1505 was a randomized phase II trial of perioperative chemotherapy (12 weeks preoperative, 12 weeks postoperative) with either mFOLFIRINOX or gemcitabine/nab-paclitaxel in patients with resectable PDAC.[40] Resectable disease was defined per Intergroup criteria.[25] Primary

outcome was 2-year overall survival (OS); if 2-year survival reached 58% or more, investigators planned to compare the two arms to determine the better treatment. This was a small study with 147 patients enrolled. Notably, 44 patients (29.9%) were deemed ineligible (43 by central radiology review). A total of 102 patients were included in the analysis (not ITT). The study did not meet its primary endpoint and therefore no formal comparison was done between the two arms. Resection rate was 73% in the mFOLFIRINOX arm compared to 70% in the gemcitabine/nab-paclitaxel arm, with R0 resection rate 85% in both groups. Notably, 84% and 85% of patients completed neoadjuvant chemotherapy in the mFOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively. In addition, 56% and 55% of patients started adjuvant chemotherapy in the mFOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively, with more patients in the mFOLFIRINOX arm completing adjuvant chemotherapy (49% *versus* 40%). Among those patients unable to undergo surgery, progression of disease was more frequently seen in the gemcitabine/nab-paclitaxel arm, 50% (7/14) *versus* 13% (2/15) in the mFOLFIRINOX arm. A higher proportion of patients in the mFOLFIRINOX arm reported grade 3/4 diarrhea while a higher proportion of patients in the gemcitabine/nab-paclitaxel arm reported grade 3/4 neutropenia. Interestingly, a higher percentage of patients showed a complete pathological response at surgery in the gemcitabine/nab-paclitaxel arm ($N=14$, 42%) compared to the mFOLFIRINOX arm ($N=10$, 25%). We hypothesize this may simply reflect patient selection, as more patients in the nab-paclitaxel plus gemcitabine arm were not able to undergo resection due to progression of disease, therefore effectively excluding patients with worse disease biology from the analysis of complete pathological response. Median OS and 2-year OS rate were similar between the mFOLFIRINOX and gemcitabine/nab-paclitaxel arms (23.2 months, 47.0% *versus* 23.6 months, 48.0%, respectively). Notably, DFS after resection was numerically longer with gemcitabine/nab-paclitaxel (14.2 months) compared to mFOLFIRINOX (10.9 months). Overall, these results seem to suggest similar efficacy between mFOLFIRINOX and gemcitabine/nab-paclitaxel. The SWOG-1505 trial is limited by multiple factors including its small sample size, high percentage of ineligible patients, lack of ITT analysis, lack of formal statistical comparison between arms, and non-standardized definition of resectable PDAC. A recent retrospective cohort study compared neoadjuvant FOLFIRINOX and gemcitabine/nab-paclitaxel in localized PDAC.[45] Patients in the FOLFIRINOX arm were younger, had more advanced disease and were more likely to have a response to therapy based on response evaluation criteria in solid tumors (RECIST). The authors did a propensity score-matching analysis. No statistically significant difference in survival was seen; however, the authors seemed to disregard an obvious trend towards improved survival with neoadjuvant FOLFIRINOX compared to gemcitabine/nab-paclitaxel [HR = 1.48, 95% confidence interval (CI) 0.97–2.26, $p=0.07$]. Their analysis included only 280 matched patients. By contrast, adjuvant studies that established current standard of care enrolled twice as many patients.[12,28] It is our opinion that a FOLFIRINOX-based regimen would continue to be favored for fit patients who are younger than 70 years. This is also supported by indirect evidence including the fact that the best survival outcomes in the adjuvant setting were attained with mFOLFIRINOX in the PRODIGE-24 trial while the APACT trial failed to show superiority of nab-paclitaxel plus gemcitabine compared to single agent gemcitabine.

Only a randomized trial that compares both treatment strategies (neoadjuvant *versus* adjuvant) with an ITT analysis of both arms will be able to provide definitive evidence to select the best strategy. The ongoing ALLIANCE A021806 trial is a randomized phase III trial evaluating the role of neoadjuvant *versus* adjuvant FOLFIRINOX in patients with resectable pancreatic cancer.

Finally, the role of neoadjuvant radiation remains controversial. The Alliance 021501 study randomly assigned patients with borderline resectable PDAC to neoadjuvant FOLFIRINOX with or without stereotactic body or hypofractionated radiation therapy.[46] The primary endpoint was 18-month overall survival rate. The study failed to show any benefit from adding stereotactic body or hypofractionated radiation in this setting. In this non-comparative design, patients who received radiation seemed to have worse outcomes (18-month overall survival rate 66% *versus* 47%). The lack of benefit of stereotactic body radiation therapy is likely to be a consequence of the systemic nature of PDAC.

Summary and future perspectives

Despite these recent advances, outcomes for patients with resectable and borderline resectable PDAC remain suboptimal. The best survival

outcomes following resection are attained with adjuvant mFOLFIRINOX. Unfortunately, a large percentage of patients are not fit enough to receive mFOLFIRINOX. For these unfit patients, adjuvant gemcitabine plus capecitabine can be considered after a R0 resection. The added benefit from capecitabine after a R1 resection is less clear and for these patients perhaps single agent gemcitabine or a clinical trial can be considered. Studies are needed to define the best treatment strategy in patients 75 years of age and older as they are generally underrepresented in clinical trials (less than 5% of trial population). For patients with resectable disease, perioperative chemotherapy with mFOLFIRINOX or nab-paclitaxel plus gemcitabine can be considered based on data from the SWOG-1505 trial. The ongoing A021806 trial will address the role of neoadjuvant treatment *versus* upfront resection in patients with resectable disease. For patients with borderline resectable PDAC, neoadjuvant chemotherapy is preferred in the NCCN guidelines.[25] This recommendation is supported by several randomized trials that have consistently shown an increased rate of R0 resection, lymph node downstaging and improved outcome with neoadjuvant treatment despite some limitations in the study design in all of these studies (Table 3).

We have reached a plateau in the benefit we can gain from cytotoxic therapies in early stages of disease. Therefore, some changes to drug development paradigms as well as novel treatment strategies are urgently needed. It is critical that we implement universal germline testing, as well as improve turnaround times, as the presence of germline *BRCA* (*gBRCA*) mutations can potentially influence the choice of chemotherapy backbone. Currently, for patients in whom family history points towards a *gBRCA* mutation possibly running in the family (family history of breast or ovarian cancer, etc.) regimens that include a platinum agent are favored. The APOLLO trial (NCT04858384) will also elucidate the role of maintenance olaparib in patients with pathogenic (germline or somatic) mutations in *BRCA* or *PALB2* following resection and completion of adjuvant treatment. It is plausible that genomic signatures may inform treatment decisions in the future. The COMPASS trial provided some early evidence of this in patients with stage IV PDAC.[47] In that study, patients with a classic-like signature

attained longest progression-free survival when treated with mFOLFIRINOX. Studies to evaluate the predictive role of this signature, or surrogates of this signature such as high GATA6 expression in the perioperative setting are warranted.[48]

The paradigm of testing novel agents in patients with early stage disease only after they have shown benefit in advanced disease also needs to be re-evaluated. This is especially important with targeted agents in which data in other cancers suggest that the greatest benefit can be achieved if targeted treatment is initiated early in the course of the disease before transformation occurs.[49] There is an emerging pipeline of agents targeting the Ras pathway, including SHP2 (Src homology region 2-containing protein tyrosine phosphatase 2), SOS1 (son of sevenless 1), and direct Ras inhibitors that are currently being evaluated in clinical trials or are about to enter clinical development. Given the high prevalence of *KRAS* mutations in this disease, the high risk of relapse, and expected favorable safety profile of some of these agents, it is imperative we design trials to evaluate some of the most promising candidates as maintenance treatment following resection while also evaluating them in the advanced setting.

Finally, there is a clear need to improve accrual of PDAC patients into clinical trials. The percentage of patients with this disease who are enrolled into clinical trials remains low at approximately 5%.[50] This is particularly true in the adjuvant setting where there is also a paucity of clinical trials. To this end, expanding eligibility criteria can improve accrual as well as increase the likelihood for study results to be extrapolated to real-world patients.[51]

In conclusion, it is unlikely that we will improve outcomes of patients with resectable or borderline resectable PDAC with available cytotoxic therapies beyond what can be attained with mFOLFIRINOX. Therefore, testing novel agents in earlier stages of disease through umbrella trials that incorporate adaptive designs which spare patients from entering less efficacious arms, in addition to incorporating comprehensive pharmacodynamic analysis and improved patient selection, will be critical.

Table 3. Selected completed and ongoing neoadjuvant trials in resectable and borderline resectable PDAC.

Trial	Design	N	Primary outcome	Population	Arms	R0 Resection rate (%)	Median DFS (months)	Median OS (months)	OS rate (%)	Notes
Jang et al.[36]	Phase II/III open-label	58	2-year survival rate	Borderline resectable	Upfront surgery followed by adjuvant CRT (gemcitabine-based)	26	NR	11	26.1	
					Neoadjuvant CRT (gemcitabine-based) followed by surgery	52 ($p=0.004$)	NR	21 ($p=0.028$)	40.7 ($p=0.028$) 2-year OS rate	
PACT-15 (2018)	Phase II open-label	93	1 year event-free survival	Resectable	Upfront surgery followed by adjuvant gemcitabine	27	4.7	20.4	13	
					Upfront surgery followed by adjuvant PEXG (cisplatin epirubicin, gemcitabine, capecitabine)	37	12.4	26.4	24	
					Perioperative PEGX	63	16.9 EFS	38.2	49 5-year OS rate	
JSAP-05 (2019)	Phase II/III open-label	364	OS	Resectable	Upfront surgery followed by adjuvant S-1	NR		26.6		
					Neoadjuvant gemcitabine/S-1 followed by surgery and adjuvant S-1	NR		36.6 ($p=0.015$)		
SWOG-1505 (2021)	Phase II open-label	147 (102 eligible)	2-year OS	Resectable	Perioperative mFOLFIRINOX	85	10.9	23.2	47.0	
					Perioperative gemcitabine/nab-paclitaxel	85	14.2	23.6	48.0 2-year OS rate	
PREOPANC (2020)	Phase III open-label	248	OS	Borderline resectable/Resectable	Immediate surgery followed by adjuvant gemcitabine	31	7.7	14.3	NR	
					Neoadjuvant CRT (gemcitabine-based) followed by surgery and adjuvant gemcitabine	63 ($p<0.001$)	8.1 ($p=0.032$)	16.0 ($p=0.096$)	NR	
ESPAC-5F (2020)	Phase II open-label	90	Resection rate (R0 + R1 resections)	Borderline resectable	Immediate surgery	14	NR	NR	42	
					Neoadjuvant gemcitabine/capecitabine	17	NR	NR	79	
					Neoadjuvant FOLFIRINOX	18	NR	NR	84	
					Neoadjuvant XRT	37	NR	NR	64 1-year OS rate	
					Neoadjuvant FOLFIRINOX followed by surgery and adjuvant FOLFIRINOX					
NEPAFOX (2021)	Phase II/III open-label	40	OS	Borderline resectable/resectable	Surgery followed by adjuvant gemcitabine	NR	9.8	25.7	NR	Identifier: NCT02172976 Study discontinued due to poor accrual
					Neoadjuvant FOLFIRINOX followed by surgery and adjuvant FOLFIRINOX	NR	6.6 ($p=0.41$) PFS	10.0 ($p=0.034$)	NR	
NEONAX	Phase II open-label	162	18-month DFS	Resectable	Surgery followed by adjuvant gemcitabine/nab-paclitaxel					Identifier: NCT02047513 Start date: 2015 Expected completion: 2022
					Neoadjuvant gemcitabine/nab-paclitaxel followed by surgery and adjuvant nab-paclitaxel					
PREOPANC-2	Phase III	368	OS	Borderline resectable/resectable	Neoadjuvant CRT (gemcitabine-based) followed by surgery and adjuvant gemcitabine Neoadjuvant FOLFIRINOX followed by surgery					Identifier: NTR7292 Start date: 2018 Expected completion: 2021

CRT, chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival.

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