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

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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.

Keywords: adjuvant therapy, chemotherapy, neoadjuvant therapy, pancreatic cancer, radiotherapy

Received: 28 May 2021; revised manuscript accepted: 25 August 2021.

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. PDAC will become the second leading cause of cancer-related deaths in the United States by 2040. 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.

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. Another 30–40% of patients will present with tumors that are considered locally advanced unresectable or borderline resectable. 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. 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. 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...
must meet one of the following criteria. 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. In genetically engineered mice, cancer cells were shown to seed the liver even before detectable tumors developed in the pancreas. 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. 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. Furthermore, in those treated with surgical resection and the most active available adjuvant chemotherapy, approximately 50% will still relapse within 2 years.

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. 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. 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. In addition, although the safety of pancreatic surgery has greatly improved, postoperative mortality rates even at high volume centers are still 3–5%. 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. 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. 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 S-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               |
| ESPAC-3 [2010]| Phase III  | 1088  | OS              | R0/R1      | Gemcitabine                                | 14.1               | 23.0               | 15.9        |                            |
|                |            |       |                 |            | Gemcitabine                                | 14.3 [p=0.53]      | 23.6               | 17.5        | 5-year OS rate               |
|                |            |       |                 |            | PFS                                        | [p=0.39]           |                    |             |                            |
| JASPAC 01 [2016]| Phase III | 385   | OS              | R0 [13% had R1] | Gemcitabine                                | 11.3               | 22.5               | 24.4        |                            |
|                | open-label |       |                 |            | Gemcitabine                                | 22.9 [p<0.001]     | 46.5               | 44.1        | 5-year OS rate               |
|                | open-label |       |                 |            | S-1                                        | [p<0.0001]         |                    |             |                            |
| ESPAC-4* [2017]| Phase III  | 732   | OS              | R0/R1      | Gemcitabine                                | 13.1               | 26.0               | 20          |                            |
|                | open-label |       |                 |            | Gemcitabine and capecitabine               | 13.9 [p=0.082]     | 27.7               | 28          | 5-year OS rate               |
|                |            |       |                 |            | [p=0.049]                                  |                    |                    |             |                            |
| PRODIGE-24 [2018]| Phase III | 493   | DFS             | R0/R1      | Gemcitabine                                | 12.8               | 34.8               | 48.6        |                            |
|                | open-label |       |                 |            | mFOLFIRINOX                                 | 21.6 [p<0.001]     | 54.4               | 63.4        | 3-year OS rate               |
|                |            |       |                 |            | [p=0.003]                                  |                    |                    |             |                            |
| APACT [2019]  | Phase III  | 866   | DFS             | R0/R1      | Gemcitabine                                | 18.8               | 13.7               | 36.2        |                            |
|                | open-label |       |                 |            | Gemcitabine plus nab-paclitaxel            | 19.4 [p=0.18] Independent review | 16.6 [p=0.016] Investigator review | 40.5        | 40.5 | 0.045 |                            |
| RTOG 0848     | Phase III  | 950   | OS              | R0/R1      | Adjuvant chemotherapy                       |                    |                    |             |                            |
|                | open-label |       |                 |            | Adjuvant CRT                                |                    |                    |             |                            |

*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 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/m² to 150 mg/m² 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 Oncology (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
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. 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. 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.

**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/m² d1, 8, 15 q28 d | Capecitabine 830 mg/m² BID d1–21 q28 d |
|        | Gemcitabine 1000 mg/m² 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.
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. 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. 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. 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). Retrospective cohort data also support the use of neoadjuvant therapy over upfront surgery 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). 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. In 2018, Jang et al. 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. 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
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. 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. The primary endpoint was OS and an improvement was seen in the perioperative chemotherapy arm (median OS 36.6 months 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. Neoadjuvant CRT consisted of a total of 36 Gy alongside 1000 mg/m² 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/m² on days 1 and 8). After resection, four cycles of gemcitabine were administered (1000 mg/m² 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. 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. 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 mFOLFIROINOX or gemcitabine/nab-paclitaxel in patients with resectable PDAC. Resectable disease was defined per Intergroup criteria.
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 arm were 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. 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. 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. 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.

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. 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%. 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.

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.
| Trial | Design | N | Primary outcome | Population | Arms | R0 Resection rate (%) | Median DFS (months) | Median OS (months) | OS rate (%) | Notes |
|-------|--------|---|-----------------|------------|------|----------------------|-------------------|-------------------|-------------|-------|
| Jang et al. (2018) | Phase II/III open-label | 36 | Borderline resectable | NR | 58 | 2-year survival rate | 26 | NR | 26.1 | |
| JSAP-05 (2018) | Phase II open-label | 93 | Resectable | NR | 364 | OS | 36 | NR | 23.6 | |
| PACT-15 (2018) | Phase II open-label | 147 (102 eligible) | Resectable | NR | 142 | 18-month DFS | 14 | NR | 9.8 | |
| SWOG-1505 (2021) | Phase II open-label | 37 | Resectable | NR | 238 | OS | 37 | NR | 18.0 | |
| ESPAC-5F (2020) | Phase II open-label | 18 | Resectable | NR | 182 | OS | 18 | NR | 10.0 | |
| PREOPANC-2 (2020) | Phase III open-label | 142 | Resectable | NR | 388 | OS | 388 | NR | 6.6 | |
| NEONAX (2021) | Phase II/III open-label | 162 | Resectable | NR | 142 | DFS | 142 | NR | 6.6 | |
| PREOPANC-2 (2020) | Phase III open-label | 368 | Resectable | NR | 368 | OS | 368 | NR | 6.6 | |
| Jang et al. (2018) | Phase II/III open-label | 36 | Borderline resectable | NR | 36 | OS | 36 | NR | 26.1 | |
| JSAP-05 (2018) | Phase II open-label | 93 | Resectable | NR | 364 | OS | 36 | NR | 23.6 | |
| PACT-15 (2018) | Phase II open-label | 147 (102 eligible) | Resectable | NR | 142 | 18-month DFS | 14 | NR | 9.8 | |
| SWOG-1505 (2021) | Phase II open-label | 37 | Resectable | NR | 238 | OS | 37 | NR | 18.0 | |
| ESPAC-5F (2020) | Phase II open-label | 18 | Resectable | NR | 182 | OS | 18 | NR | 10.0 | |
| PREOPANC-2 (2020) | Phase III open-label | 142 | Resectable | NR | 388 | OS | 388 | NR | 6.6 | |
| NEONAX (2021) | Phase II/III open-label | 162 | Resectable | NR | 142 | DFS | 142 | NR | 6.6 | |
| PREOPANC-2 (2020) | Phase III open-label | 368 | Resectable | NR | 368 | OS | 368 | NR | 6.6 | |

CRT: chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival.
Conflict of interest statement
The authors declare that there is no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

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References
1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7–33.
2. Rahib L, Wehner MR, Matrisian LM, et al. Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open 2021; 4: e214708.
3. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7–30.
4. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 2010; 7: e1000267.
5. Soweid AM. The borderline resectable and locally advanced pancreatic ductal adenocarcinoma: definition. Endosc Ultrasound 2017; 6 (Suppl. 3): S76–S78.
6. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol 2006; 13: 1035–1046.
7. Strobel O, Neoptolemos J, Jager D, et al. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol 2019; 16: 11–26.
8. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 2018; 18: 2–11.
9. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. Cell 2012; 148: 349–361.
10. Tuveson DA and Neoptolemos JP. Understanding metastasis in pancreatic cancer: a call for new clinical approaches. Cell 2012; 148: 21–23.
11. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007; 297: 267–277.
12. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018; 379: 2395–2406.
13. Merkow RP, Blimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 2014; 260: 372–377.
14. Akerberg D, Bjornsson B and Ansari D. Factors influencing receipt of adjuvant chemotherapy after surgery for pancreatic cancer: a two-center retrospective cohort study. Scand J Gastroenterol 2017; 52: 56–60.
15. Wu W, He J, Cameron JL, et al. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol 2014; 21: 2873–2881.
16. Contreras CM, Stanelle EJ, Mansour J, et al. Staging laparoscopy enhances the detection of occult metastases in patients with pancreatic adenocarcinoma. J Surg Oncol 2009; 100: 663–669.
17. Warshaw AL, Gu ZY, Wittenberg J, et al. Preoperative staging and assessment of resectability of pancreatic cancer. Arch Surg 1990; 125: 230–233.
18. Hartwig W, Werner J, Jager D, et al. Improvement of surgical results for pancreatic cancer. Lancet Oncol 2013; 14: e476–e485.
19. Kalser MH and Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985; 120: 899–903.
20. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004; 350: 1200–1210.
21. Abrams RA, Lillemoe KD and Piantadosi S. Continuing controversy over adjuvant therapy of pancreatic cancer. Lancet 2001; 358: 1565–1566.
22. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg 2007; 246: 734–740.
23. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013; 310: 1473–1481.

24. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010; 304: 1073–1081.

25. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Pancreatic Adenocarcinoma. v.1.2021. Plymouth Meeting (PA): NCCN, 2020.

26. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet 2016; 388: 248–257.

27. Chuah B, Goh BC, Lee SC, et al. Comparison of the pharmacokinetics and pharmacodynamics of S-1 between Caucasian and East Asian patients. Cancer Sci 2011; 102: 478–483.

28. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capcitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389: 1011–1024.

29. Neoptolemos J, Palmer D, Ghaneh P, et al. ESPAC-4: a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of Gemcitabine (GEM) and Capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma: five year follow-up. J Clin Oncol 2020; 38: 4516–4516.

30. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817–1825.

31. Conroy T, Hammel P, Hebbard M, et al. Unicancer GI PRODIGE 24/CCTG PA.6 trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. J Clin Oncol 2018; 36 (Suppl. 18): LBA4001.

32. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369: 1691–1703.

33. Tempero MA, Reni M, Riess H, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol 2019; 37 (Suppl. 15): 4000.

34. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. HPB (Oxford) 2012; 14: 365–372.

35. Tzeng CW, Abbott DE, Cantor SB, et al. Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis. Ann Surg Oncol 2013; 20: 2197–2203.

36. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, open-label, multicenter phase 2/3 trial. Ann Surg 2018; 268: 215–222.

37. Reni M, Balzano G, Zanon S, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. Lancet Gastroenterol Hepatol 2018; 3: 413–423.

38. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol 2020; 38: 1763–1773.

39. Klaiber U, Schmaitz ES, Hinz U, et al. Prognostic factors of survival after neoadjuvant treatment and resection for initially unresectable pancreatic cancer. Ann Surg 2021; 273: 154–162.

40. Sohal DPS, Duong M, Ahmad SA, et al. Efficacy of perioperative chemotherapy for resectable pancreatic adenocarcinoma: a phase 2 randomized clinical trial. JAMA Oncol 2021; 7: 421–427.

41. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. J Clin Oncol 2017; 35: 515–522.

42. Cloyd JM, Heh V, Pawlik TM, et al. Neoadjuvant therapy for resectable and borderline resectable pancreatic cancer: a meta-analysis of randomized controlled trials. J Clin Med 2020; 9: 1129.

43. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus...
upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). *J Clin Oncol* 2019; 37 (Suppl. 4): 189.

44. Ghaneh P, Palmer DH, Cicconi S, *et al.* ESPAC-5F: four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. *J Clin Oncol* 2020; 38 (Suppl. 15): 4505.

45. Perri G, Prakash L, Qiao W, *et al.* Response and survival associated with first-line FOLFIRINOX vs gemcitabine and nab-paclitaxel chemotherapy for localized pancreatic ductal adenocarcinoma. *JAMA Surg* 2020; 155: 832–839.

46. Katz MH, Shi Q, Meyers JP, *et al.* Alliance A021501: preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. *J Clin Oncol* 2021; 39 (Suppl. 3): 377.

47. O’Kane GM, Fischer S, Denroche R, *et al.* Integrative molecular profiling and response to chemotherapy on the COMPASS trial. *J Clin Oncol* 2019; 37 (Suppl. 4): 188.

48. Aung KL, Fischer SE, Denroche RE, *et al.* Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. *Clin Cancer Res* 2018; 24: 1344–1354.

49. Westin JR and Kurzrock R. It’s about time: lessons for solid tumors from chronic myelogenous leukemia therapy. *Mol Cancer Ther* 2012; 11: 2549–2555.

50. Hoos WA, James PM, Rahib L, *et al.* Pancreatic cancer clinical trials and accrual in the United States. *J Clin Oncol* 2013; 31: 3432–3438.

51. Kim ES, Bruinooge SS, Roberts S, *et al.* Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. *J Clin Oncol* 2017; 35: 3737–3744.