Editorial Commentary

Optimizing the treatment sequence for localized pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is often a lethal malignancy. The incidence is rising worldwide, and for all stages of disease the 5-year overall survival (OS) is only 9% (1). In the last decade modest improvements in outcomes have been achieved for advanced PDAC. FOLFIRINOX chemotherapy (a combination of 5-fluorouracil, oxaliplatin and irinotecan) extended median OS (mOS) to 11 months (2), nab-paclitaxel and gemcitabine prolonged mOS to 8.5 months, while nanoliposomal irinotecan and infusional fluorouracil showed benefit in the second line setting for metastatic PDAC (3). A minority of patients, approximately 20%, present with resectable disease. Among this population, outcomes are still discouraging with median 5-year OS 15–20 months and with up to 80% of patients developing systemic relapse after curative surgery (4-7). Considerable debate surrounds the optimal treatment sequence for patients with resectable and borderline resectable disease, with a standard approach being upfront resection followed by adjuvant chemotherapy (6,8,9).

The strategy for immediate surgery followed by adjuvant chemotherapy was adopted based on results from the CONKO-001 trial published in 2007, which demonstrated superior disease free survival (DFS) following 6 months of adjuvant post-operative gemcitabine over surgery alone (6). The median disease-free survival (mDFS) was 13.4 months in the adjuvant gemcitabine arm, comparing favorably with mDFS 6.9 months in the surgery alone arm (6). Subsequent adjuvant trials have further improved OS in pancreatic cancer patients by combining chemotherapy agents. The ESPAC-4 trial showed that adjuvant gemcitabine combined with capecitabine was superior to gemcitabine alone, prolonging mOS from 25.5 to 28 months (8). More recently, a modified FOLFIRINOX (mFOLFIRINOX) regimen has demonstrated substantial efficacy in the adjuvant setting compared to single-agent gemcitabine with mOS 54.4 months versus 35 months, and mDFS 21.6 months compared to 12.8 months (9). The mFOLFIRINOX arm was superior to gemcitabine in virtually all subgroups analyzed including patients with node positive status, T3/4 tumors, R1 resection and poorly differentiated tumors. The trial, however, enrolled a rather select patient population with ECOG 0-1 and median age 63 years, and excluded those with R2 resection and post-operative CA19-9 >180 U/mL. In contrast, the APACT trial, which compared combination gemcitabine and nab-paclitaxel to gemcitabine alone in the adjuvant setting, was a negative study with regards to the primary endpoint of DFS by independent reviewer, although a modest survival benefit was found with the combination (10).

Emerging efforts to increase the number of long-term survivors after pancreatic cancer resection include the use neoadjuvant therapy to extend potentially curative treatment to patients with borderline resectable tumors, defined as having primary involvement of venous vasculature with only focal abutment of visceral arteries (11). The experience acquired with neoadjuvant treatment for other gastrointestinal malignancies such as esophageal, gastric and rectal cancers, has demonstrated potential advantages of upfront systemic therapy (12-15). These include early delivery of chemotherapy to address micrometastatic disease along with treating visible tumor, improving the R0 resection rate, and using both biology and time to select

patients who are more likely to benefit from surgery while sparing those who develop early metastasis from a morbid operation. In addition, the neoadjuvant approach ensures that systemic therapy is delivered to more patients, which is particularly relevant for pancreatic cancer in which 40% of patients never receive adjuvant treatment due to perioperative morbidity as demonstrated in real-world experience (16,17).

Thus far, experience with preoperative treatment has been drawn from single arm studies (18,19), early-terminated randomized trials (20), and meta-analyses (21,22). The Japanese Prep-02/JSAP-05 trial was preliminarily presented in 2019 by Unno *et al.* (23). In this phase II/III trial, patients with resectable PDAC were randomized to receive neoadjuvant gemcitabine and S-1 followed by surgery and 6 months of adjuvant S-1 versus immediate surgery followed by 6 months of adjuvant S-1 (24). A significant benefit was observed in the neoadjuvant arm with mOS 36.7 months as compared to 26.6 months in the upfront surgery arm (HR, 0.72; 95% CI, 0.55 to 0.94; P=0.015). The final results are yet to be published; nonetheless this study indicates a potential superiority of the preoperative treatment over immediate surgery. More recently, a single arm study utilizing a total neoadjuvant approach with eight 2-week cycles of FOLFIRINOX followed by a short-course of capecitabine-based chemoradiation for borderline resectable patients was associated with a high R0 resection rate (65%) and mOS 37.7 months, suggesting that a more active combination chemotherapy regimen administered for a greater number of cycles prior to surgery may improve outcomes (18).

In this editorial, we discuss the findings of the recently reported PREOPANC trial by Versteijne *et al.* (25), which represents the first completed randomized phase III trial of neoadjuvant treatment for PDAC. We further provide a literature review on the evolving role of neoadjuvant treatment in pancreatic cancer.

The PREOPANC trial was a randomized controlled phase III trial conducted by the Dutch Pancreatic Cancer Group at 16 sites in the Netherlands with the aim of investigating whether preoperative chemoradiotherapy improved OS as compared to immediate surgery in patients with resectable or borderline resectable PDAC. Patients were randomized in a 1:1 ratio to receive preoperative chemoradiotherapy with 3 cycles of gemcitabine, the second combined with 2.4 Gy radiotherapy in 15 fractions, followed by surgery and 4 additional cycles of adjuvant gemcitabine or to immediate surgery followed by 6 cycles of adjuvant gemcitabine. Gemcitabine was dosed at 1,000 mg/m^2 on days 1, 8, and 15 of 28-day cycles when administered alone, and on days 1 and 8 of 21-day cycles when combined with radiation. The primary end point was OS by intention-to-treat analysis. The secondary end points were DFS, locoregional failure–free interval, distant metastasis-free interval, resection rate, R0 resection rate and toxicity. Between 2013 and 2017, a total of 246 patients were randomized, 119 to neoadjuvant therapy and 127 to upfront surgery. The study did not meet its primary endpoint. The mOS was 16 months in the neoadjuvant group and 14.3 months for immediate surgery (HR, 0.78; 95% CI, 0.58 to 1.05; P=0.096). Benefits of preoperative treatment were observed in secondary endpoints and pre-planned subgroup analyses. Neoadjuvant treatment was associated with an improved R0 resection rate (71% versus 40%, P<0.001), significantly longer DFS (8.1 versus 7.7 months, HR, 0.73; 95% CI, 0.55 to 0.96; P=0.0320), as well as locoregional failure–free interval (not reached *vs.* 13.4 months; HR, 0.56; 95% CI, 0.38 to 0.83; P=0.0034). No significant differences in toxicities were observed between the two arms. In a predefined subgroup analysis evaluating outcomes in subjects with borderline resectable disease (N=113), there was a significant OS benefit for the neoadjuvant approach over immediate surgery (mOS 17.6 versus 13.2 months, P=0.029). Furthermore, in the subgroup with borderline resectable disease, while the resection rate was equivalent between the two arms (52% versus 64%, P=0.19), there was a marked difference in the rate of R0 resection with 79% of neoadjuvant treatment achieving negative margins versus only 13% in the immediate surgery group (HR, 24.20; 95% CI, 6.57 to 89.12; P<0.001). No significant difference in OS and R0 resection rate were seen in the subgroup with resectable disease (N=133), suggesting that the neoadjuvant treatment was more beneficial for those with borderline resectable disease.

The authors concluded that preoperative chemoradiotherapy for resectable or borderline resectable pancreatic cancer was not associated with a significant OS benefit. While data from secondary endpoints and predefined subgroup analyses are provocative suggesting an advantage of the neoadjuvant approach, additional evidence is required to confirm the optimal treatment sequence for early stage pancreatic cancer. The PREOPANC study utilized single-agent gemcitabine, which based on ESPAC-4 and PRODIGE24, is considered a suboptimal regimen in the adjuvant setting. The theoretical advantage of preoperative treatment on improved compliance and increased delivery

of chemotherapy was underexplored in the neoadjuvant arm, in which less than half of the chemotherapy was given prior to surgery. In addition, no conclusions can be derived on the role of radiation to preoperative chemotherapy in the absence of an arm with preoperative chemotherapy alone. Preplanned analysis showed that patients with borderline resectable disease appeared to have benefited more from the preoperatory strategy with improved local control and prolonged survival. However, the study was not powered to establish definitive conclusions in this subpopulation, and the interaction test of hazard rates showed no significant difference between the resectable and borderline resectable subgroups.

While questions remain, the investigators of the PREOPANC trial are to be praised for this landmark study that provides key benchmark data for future neoadjuvant trials in PDAC. Ongoing studies (*Table 1*) will hopefully clarify which patient population is best served by neoadjuvant chemotherapy, those with resectable and/or borderline resectable disease, and whether there is benefit to combination chemotherapy and the optimal duration of chemotherapy in the neoadjuvant setting (26-28).

Several randomized controlled trials with contemporary chemotherapy regimens are ongoing (*Table 1*). The PREOPANC-2 trial compares the same neoadjuvant gemcitabine-based chemoradiation plus adjuvant gemcitabine used in the PREOPANC-1 study with eight 2-week cycles of neoadjuvant FOLFIRINOX followed by

Table 1 Summary of select ongoing randomized neoadjuvant trials for resectable and borderline resectable pancreatic cancer

Trial	Disease stage	Criteria	Treatment regimens	Primary outcome	Planned accrual	Status*
PREOPANC-2 (NTR7292)	Borderline resectable	DPCG	Neoadj. FOLFIRINOX ×8; Neoadj. Gem-based CRT ×3 + Adj. gemcitabine ×4	OS	368	Recruiting
ESPAC-5F (2013-003932-56)	Borderline resectable	NA	Immediate surgery + Adj. gemcitabine ×6 or 5-FU ×6; Neoadj. Gem-Cape ×8; Neoadj. FOLFIRINOX ×4; Neoadj. Cape-based CRT ×5.5 weeks	Recruitment rate; R0 resection rate	100	Accrual completed; results pending
NEPAFOX (NCT02172976)	Resectable and borderline resectable	No contact to SMA, CA; venous reconstructable	Immediate surgery + Adj. gemcitabine ×6; Periop. FOLFIRINOX (4/6+4/6)	OS	126	Accrual completed
SWOG S1505 (NCT02562716)	Resectable	No contact to SMA, CA, CHA; <180° venous contact	Periop. FOLFIRINOX (3+3); Periop. Gem-NabPlaclitaxel (3+3)	OS	112	Accrual completed
ALLIANCE A021501 (NCT02839343)	Borderline resectable	Intergroup	Neoadj. FOLFIRINOX ×8 + Adj. mFOLFOX6 ×4; Neoadj. mFOLFIRINOX ×7 and SBRT + Adj. mFOLFOX6 ×4	OS	134	Active, not recruiting
ALLIANCE A021806 (NCT04340141)	Resectable	No arterial involvement, limited venous contact (180°)	Neoadj. mFOLFIRINOX ×8 + Adj. mFOLFIRINOX ×4; immediate surgery + Adj. mFOLFIRINOX ×12	OS	344	Anticipated to start accrual in 2020
NorPACT-1 (NCT02919787)	Resectable	NCCN	Neoadj. FOLFIRINOX ×4 + Adj. Gem-Cape ×4; immediate surgery + Adj. Gem-Cape ×6	1-year OS	90	Recruiting
PANDAS-PRODIGE 44 (NCT02676349)	Borderline resectable	NCCN	Neoadj. mFOLFIRINOX + Cape-CRT + Adj. Gem or mLV5FU; Neoadj. mFOLFIRINOX + Adj. Gem or mLV5FU	R0 resection rate	90	Recruiting

Table 1 (*continued*)

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Trial	Disease stage	Criteria	Treatment regimens	Primary outcome	Planned accrual	Status*
PANACHE01-PRODIGE48 (NCT02959879)	Resectable	NCCN	Neoadj. mFOLFOX ×4 + Adj. Chemo ×8 (investigator's choice); Neoadj. mFOLFIRINOX ×4 + Adj. Chemo ×8 (investigator's choice); immediate surgery + Adj. Chemo ×12 (investigator's choice)	1-year OS	160	Recruiting
NEONAX (NCT02047513)	Resectable	No contact to SMA, CA, CHA	Neoadj. Gem-NabPaclitaxel ×2 + Adj. Gem-NabPaclitaxel ×4; immediate surgery + Adj. Gem-NabPaclitaxel ×6	DFS	166	Active, not recruiting
UVA-PC-PD101 (NCT02305186)	Resectable and borderline resectable	NA	Neoadj. Cape-based CRT + pembrolizumab during CRT; Neoadj. Cape-based CRT	Safety number of TILs	56	Active, not recruiting

*, status was assessed on April 15, 2020 in the following register databases, clinicaltrials.gov, clinicaltrialsregister.eu, trialregister.nl. Adj., adjuvant; CA, celiac axis; CHA, common hepatic artery; Cape, capecitabine; CRT, chemoradiation; DFS, disease free survival; DPCG, Dutch Pancreatic Cancer Group; FOLFOX, fluorouracil, folinic acid, oxaliplatin; FOLFIRINOX, fluorouracil, folinic acid, irinotecan, oxaliplatin; Gem, gemcitabine; mLV5FU, modified folinic acid, bolus fluorouracil and infusional fluorouracil; NA, not available; Neoadj., neoadjuvant; NCCN, National Comprehensive Cancer Network; OS, overall survival; Periop, perioperative; SBRT, stereotactic body radiation therapy; SMA, superior mesenteric artery; TILs, tumor infiltrating lymphocytes.

surgery. The Alliance trial A021806, a key study expected to begin accruing in 2020, will compare immediate surgery and adjuvant mFOLFIRINOX, arguably the standard of care for fit patients, with perioperative mFOLFIRINOX (eight 2-week cycles before and four 2-week cycles after surgery). With a gemcitabine backbone, the NEONAX trial will compare perioperative gemcitabine and nab-paclitaxel (two 4-week cycles before and four 4-week cycles after surgery) with immediate surgery followed by six 4-week cycles of adjuvant gemcitabine and nab-paclitaxel.

In conclusion, the PREOPANC study showed that preoperative chemoradiation is a safe and tolerable strategy for resectable and borderline resectable PDAC. While the primary survival endpoint was not met, the consistent benefits for most secondary endpoints, as well as in the borderline resectable subpopulation, suggest a potential advantage for the neoadjuvant strategy. At this time, preoperative treatment cannot be considered a practice changing approach, but undoubtedly the field is moving forward. The forthcoming results of over 10 neoadjuvant trials will pave the way to optimize treatment sequence for resectable and borderline resectable pancreatic cancer.

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Footnote

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