Adjuvant and Neoadjuvant Therapy for Pancreatic Cancer

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KEYWORDS

• Pancreas adenocarcinoma • Adjuvant therapy • Neoadjuvant therapy • Clinical trials

KEY POINTS

- Current international standards of care for adjuvant therapy for pancreas adenocarcinoma consist of 6 months of gemcitabine or 5-fluorouracil with leucovorin.
- Erlotinib does not provide additional benefit in the treatment of patients with resected or locally advanced pancreas adenocarcinoma.
- Neoadjuvant therapy provides theoretic advantages over standard adjuvant therapy including treatment of distant micrometastases, assessment of tumor response to treatment, and better selection of patients most appropriate for surgery.
- The use of combination cytotoxic therapy, targeted agents, incorporation of chemoradiation, and immunotherapy all represent approaches under active investigation for adjuvant and neoadjuvant treatment of pancreas adenocarcinoma.

INTRODUCTION

Patients diagnosed with pancreas adenocarcinoma have a poor prognosis with 5-year overall survival (OS) rates estimated to be 6%.[1] Although surgery for patients with localized resectable pancreas adenocarcinoma remains a potential curative modality, the risk of relapse remains substantial with local-regional recurrence rates from 50% to 80% and systemic recurrence rates of greater than 70%.[2] The value of adjuvant systemic therapy has been clearly established in terms of reducing the risk of recurrence and prolonging survival, albeit the risk of recurrence remains significant. The

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determination of optimal adjuvant treatment modalities between the types of systemic therapy used, combined chemotherapy and radiation, and chemoradiation plus chemotherapy along with whether to pursue an adjuvant or neoadjuvant strategy remain areas of active investigation. Furthermore, neoadjuvant therapy provides an emerging paradigm with several theoretic advantages over adjuvant therapy. Although not based on randomized data but rather consensus opinion, neoadjuvant therapy before surgery is an emerging paradigm for patients with borderline resectable pancreas cancer.

HISTORIC ADJUVANT SYSTEMIC TRIALS

The major historic phase III trials of adjuvant therapy in pancreas adenocarcinoma are listed in **Table 1**. One of the earliest phase III trials was the Gastrointestinal Tumor Study Group (GITSG) trial.[3] Forty-three evaluable patients with surgically resected pancreas adenocarcinoma were randomized to receive adjuvant treatment with 5-fluorouracil (5-FU) concurrent with a split-course of radiation versus observation. Median survival was found to be significantly longer for the adjuvant treatment group at 20 months compared with 11 months for the observation group ($P = .035$). Although the GITSG study has been used by some as a basis for 5-FU-based chemoradiation in the adjuvant setting, other studies have challenged the value of chemoradiation inferring the benefit observed came from prolonged systemic therapy. The EORTC 40891 (European Organization for Research and Treatment of Cancer) trial was a large multicenter phase III study of patients with resected pancreatic head cancer and periampullary tumors.[4] Patients were randomized to either observation or postoperative chemoradiation with short-course infusional 5-FU with concurrent split-course radiation. A total of 120 patients (approximately >50% of the total study population) with resected pancreatic head cancer were evaluated as part of this study and the long-term follow-up analysis showed no significant difference in survival between the treatment and observation groups even when only the pancreatic head cancer group was evaluated, although a nonstatistically significant trend was in favor of adjuvant therapy.[5]

Along with EORTC 40891, the ESPAC-1 (European Study Group of Pancreatic Cancer) trial[6,7] further challenged the value of chemoradiation and rather suggested that chemotherapy alone provided a survival benefit in the adjuvant setting. This study used a complex 2×2 factorial study design to randomize patients undergoing curative resection for pancreas adenocarcinoma into four treatment arms: (1) chemoradiation consisting of an intravenous bolus of 5-FU with split-course radiation, (2) chemotherapy consisting of an intravenous bolus of leucovorin followed by intravenous bolus of 5-FU for a total of 6 months of therapy, (3) combination therapy consisting of chemoradiation followed by chemotherapy as described previously, or (4) observation. A total of 289 patients underwent randomization with results showing the 5-year survival rate was 21% among patients treated with chemotherapy versus 8% among patients not treated with chemotherapy ($P = .009$). In addition, the estimated 5-year survival rate was 10% for patients treated with chemoradiation compared with 20% for patients who did not receive chemoradiation ($P = .05$). These results ultimately lead to a path away from using chemoradiation in Europe and beyond in favor of systemic chemotherapy alone as the main adjuvant treatment choice for resected pancreas adenocarcinoma. However, in North America, debate over the radiation techniques used in the EORTC 40891 and ESPAC-1 studies underpin the ongoing controversies over the value of chemoradiation in the adjuvant setting, which continues to remain an area of ongoing investigation and is being evaluated as part of RTOG 0848 (NCT01013549; Radiation Therapy Oncology Group).

Table 1
Historic randomized phase III trials of adjuvant therapy in pancreas adenocarcinoma

Trial	Patients	Treatment Arms	Median Disease-Free Survival (Months)	Median Overall Survival (Months)
GITSG-9173[3]	43	1. 5-FU-based CRT with bolus 5-FU 500 mg/m^2 on Days 1–3 of Weeks 1 and 5 of radiation, given as a split course of 50 Gy with 2-wk break in the middle Maintenance 5-FU given weekly for 2 y or until recurrence 2. Observation	2 y survival: 48% vs 14%	21 vs 11 (P = .035)
EORTC-40891[4]	218	1. 5-FU-based CRT with infusional 5-FU at a dose of 25 mg/kg/d on Days 1–5 on Weeks 1 and 5 with concurrent split-course radiation totaling 40 Gy with 2-wk break between radiation blocks 2. Observation	17.4 vs 16 (P = .643)	24.5 vs 19 (P = .208)
ESPAC-1[7]	289	1. 5-FU chemotherapy consisting of intravenous bolus of leucovorin 20 mg/m^2 followed by intravenous bolus of 5-FU at 425 mg/m^2 Days 1–5 every 28 d for total of 6 mo 2. 5-FU-based CRT with intravenous bolus of 5-FU at 500 mg/m^2 on Days 1–3 of Weeks 1 and 5 of radiation, given as split course of 40 Gy with 2-wk break in the middle 3. 5-FU-based CRT followed by chemotherapy as described in treatment arms (1) and (2) 4. Observation	Chemo vs no chemo: 15.3 vs 9.4 (P = .02) CRT vs no CRT: 10.7 vs 15.2 (P = .04)	Chemo vs no chemo: 20.1 vs 15.5 (P = .009) CRT vs no CRT: 15.9 vs 17.9 (P = .05)
CONKO-001[8]	368	1. Gemcitabine given Days 1, 8, 15 q 4 wk of 1000 mg/m^2, for total of 6 cycles 2. Observation	13.4 vs 6.9 (P < .001)	22.8 vs 20.2 (P = .005)
RTOG 9704[10]	451	1. Gemcitabine (1000 mg/m^2) for 3 wk -> CRT -> gemcitabine for 12 wk postradiation 2. 5-FU (continuous infusion of 250 mg/m^2 per day) -> CRT ->5-FU	No difference, NA	20.5 vs 16.9 (P = .09)
ESPAC-3 (v2)[12]	1088	1. Gemcitabine (1000 mg/m^2) Days 1, 8, 15 q 4 wk for 6 mo 2. 5-FU (leucovorin 20 mg/m^2 intravenous bolus followed by 5-FU 425 mg/m^2 intravenous bolus given on Days 1–5 every 28 d) for 6 mo	14.3 vs 14.1 (P = .53)	23.6 vs 23.0 (P = .39)
JASPAC-01[14]	385	1. Gemcitabine (1000 mg/m^2 intravenous infusion once a week for 3 of every 4 wk) for 6 mo 2. S-1 (80–120 mg/day based on BSA for 4 wk followed by 2 wk of rest) for total of 6 mo	Relapse-free survival: 11.2 vs 23.2 (P < .0001)	25.5 vs 46.3 (P < .0001)

Abbreviations: 5-FU, 5-fluorouracil; BSA, body surface area; CRT, chemoradiation therapy.

Although ESPAC-1 demonstrated the benefit of adjuvant systemic chemotherapy alone in pancreas adenocarcinoma with intravenous 5-FU, the CONKO-001 (Charite Onkologie 001) trial was designed to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing curative resection for pancreatic cancer.[8,9] A total of 368 patients were randomized to either observation or to receive 6 months of gemcitabine. The primary end point was disease-free survival (DFS) and the key result of the study was a significant DFS advantage of 13.4 months in the treatment group versus 6.7 months in the observation group ($P < .001$). In addition, patients in the treatment group were found to have significantly prolonged OS compared with those being observed ($P = .01$).[9] These findings from the CONKO-001 therefore provided strong level 1 evidence supporting the use of gemcitabine as a standard chemotherapy agent in the adjuvant setting.

In addition to CONKO-001, the RTOG 9704 study[10] was a US-based phase III trial to determine if the addition of gemcitabine to adjuvant fluorouracil-based chemoradiation improved survival in patients with resected pancreatic adenocarcinoma. A total of 451 patients were enrolled and randomized to chemotherapy with either 5-FU or gemcitabine for 3 weeks before chemoradiation therapy and for 12 weeks following chemoradiation therapy. With a key primary end point of OS for patients with pancreatic head tumors, the investigators reported a median survival of 20.5 months in the gemcitabine group versus a median survival of 16.9 months in the 5-FU group ($P = .09$). Although not statistically significant, the authors concluded that the addition of gemcitabine given before and after chemoradiation was associated with a survival trend in the adjuvant setting. Furthermore, stratification of postresctional carbohydrate antigen (CA) 19-9 demonstrated the use of CA 19-9 as a significant predictor of survival in patients treated with adjuvant chemoradiation.[11] As a result, CA 19-9 is now frequently being used as a key eligibility criteria or stratification factor in many pancreas cancer clinical trials.

The ESPAC investigators also began to build on results from their ESPAC-1 trial. The ESPAC-3 (v2) trial ultimately accrued a total of 1088 patients who received either 5-FU plus leucovorin or gemcitabine chemotherapy for 6 months in the adjuvant setting.[12] The final results revealed equivalency between the two different chemotherapy agents with a median survival of 23.0 months for patients treated with 5-FU plus leucovorin and 23.6 months for those patients treated with gemcitabine ($P = .39$). The study also reported that 14% of patients treated with 5-FU plus leucovorin developed serious (> grade 3) treatment-related adverse events compared with 7.5% of patients treated with gemcitabine ($P < .001$). Based on these results, the use of gemcitabine chemotherapy alone became favored as the predominant therapy in the adjuvant setting. However, these data also provide support for the use of 5-FU/leucovorin in settings where patients may be at risk or develop serious complications to gemcitabine.

Although gemcitabine chemotherapy alone is often recommended as a current standard adjuvant chemotherapy for resected pancreas adenocarcinoma, many trials under investigation are focused on adding either different chemotherapy or biologic agents to gemcitabine or the use of other agents. Recently, preliminary results of the 385-patient JASPAC-01 (Japan Adjuvant Study Group of Pancreatic Cancer) trial suggested that S-1 (an oral fluoropyrimidine)[13] seems to be not only noninferior to gemcitabine but was also superior to gemcitabine in the adjuvant setting for the Japanese patient subpopulation.[14] Although the initial results are impressive, it is unclear if the survival benefit with adjuvant S-1 will translate to a broader population because white persons receiving S-1 have been known to develop more severe gastrointestinal toxicities and therefore lower doses of S-1 may be required in a

broader patient population, which may diminish the overall efficacy of the drug. Future results and publication of this trial are awaited.

CURRENT AND FUTURE AREAS OF INVESTIGATION IN ADJUVANT THERAPY

Currently, several approaches being explored in the adjuvant setting to improve outcomes include evaluating (1) the role of combination cytotoxic therapy, (2) the role of the addition of a targeted agent, (3) the role of chemoradiation therapy, and (4) the role of immunotherapeutic approaches. These selected areas of investigation are listed in **Table 2** and are described next.

In terms of combination cytotoxic therapies, ESPAC-4 (ISRCTN96397434) is a large randomized phase III trial comparing the addition of capecitabine plus gemcitabine to gemcitabine. The study is powered for OS with a target of 1080 patients. The study completed recruitment in late 2014 and results are awaited. In addition to capecitabine being added to gemcitabine, combination cytotoxic regimens with significant benefit in metastatic pancreas adenocarcinoma, such as FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin)[15] and the combination of gemcitabine plus nab-paclitaxel,[16] are now currently under investigation in the adjuvant setting. For example, investigators from the PRODIGE group, which conducted the prior FOLFIRINOX study[15] in the metastatic setting, have now developed PRODIGE 24/ACCORD 24 (NCT01526135), which is a phase III trial comparing adjuvant chemotherapy with gemcitabine versus modified FOLFIRINOX (omission of bolus 5-FU) to treat resected pancreatic adenocarcinoma. The estimated enrollment will be 490 patients with the primary outcome being DFS at 3 years. Another key study, ABI-007-PANC-003

Table 2
Selected ongoing adjuvant phase III trials in pancreas adenocarcinoma

Trial	Patients	Trial Design	Primary End Point
ESPAC-4 (ISRCTN96397434)	1080	Gemcitabine + capecitabine vs gemcitabine	Overall survival
CONKO-005 (DRKS00000247)	436	Gemcitabine + erlotinib vs gemcitabine	Equivalent median 11.6 mo disease-free survival between groups reported (P = .291)
RTOG 0848 (NCT01013649)	952	First randomization: gemcitabine + erlotinib vs gemcitabine (now discontinued) Second randomization: chemoradiation vs no chemoradiation	Overall survival
PRODIGE/ACCORD 24 (NCT01526135)	490	Gemcitabine vs FOLFIRINOX	Disease-free survival at 3 y
APACT ABI-007-PANC-003 (NCT01964430)	800	Gemcitabine vs gemcitabine + nab-paclitaxel	Disease-free survival
NewLink Genetics Corporation (NCT01072981)	722	Gemcitabine (+/- chemoradiation) +/- hyperacute immunotherapy	Overall survival

Abbreviation: FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, oxaliplatin.

(NCT01964430), the APACT trial, will compare the efficacy of nab-paclitaxel in combination with gemcitabine with gemcitabine alone as adjuvant treatment in patients with surgically resected pancreatic adenocarcinoma. This study will recruit 800 patients to evaluate the primary outcome of DFS.

Regarding targeted therapy, erlotinib is the agent that has been most extensively investigated in the adjuvant setting based on positive results reported in the locally advanced and metastatic treatment settings for pancreas adenocarcinoma.[17] The CONKO-005 (DRKS00000247) trial recently reported on the role of gemcitabine plus erlotinib compared with gemcitabine alone in patients with R0 resected pancreas cancer. The primary end point of the study was DFS. A total of 436 patients were accrued and results of this study were just recently presented at a median follow-up of 41 months; there was no significant difference between the two treatment groups in terms of median DFS (11.6 months for both groups; $P = .291$) and OS (24.6 months for gemcitabine plus erlotinib vs 26.5 months for gemcitabine; $P = .406$).[18] In addition to CONKO-005, RTOG 0848 (NCT01013549) is an active North American phase III trial also originally designed to evaluate the role of the addition of erlotinib in the adjuvant setting while also attempting to address the value of chemoradiation in the adjuvant setting. The study was originally designed for a target of 952 patients to be randomized to receive gemcitabine or gemcitabine plus erlotinib to complete a total of 6 months of adjuvant systemic therapy. Patients in this study will also undergo restaging after 5 months of chemotherapy and if found to have no recurrence, they will undergo a second randomization to the addition of chemoradiation versus no added therapy. In 2013, results from the LAP-07 phase III trial[19] were presented demonstrating that the addition of radiation did not improve outcomes following 4 months of systemic therapy in patients with locally advanced pancreas adenocarcinoma. In addition, there was no change in survival outcomes for patients in the LAP-07 study who were first randomized to receive gemcitabine alone versus gemcitabine plus erlotinib. Given these findings the RTOG 0848 study has since been amended, where patients will now only undergo one randomization to plus or minus the addition of fluoropyrimidine-based radiation to a single-agent gemcitabine cytotoxic backbone and the randomization to include erlotinib has been discontinued. Based on all of the previously mentioned studies, erlotinib seems to have no significant benefit in the treatment of patients with resected and locally advanced pancreas cancer.

Another area of increasing research interest in the adjuvant treatment of pancreas adenocarcinoma has been the development of the use of vaccinations and broad immunotherapeutic approaches. Although vaccinations targeting KRAS mutations,[20,21] the telomerase peptide vaccine GV1001,[22,23] and the allogenic whole cell vaccine GVAX (granulocyte-macrophage colony–stimulating factor gene-transfected tumor cell vaccine)[24,25] have yielded mixed results from prior studies, vaccine development using the concept of hyperacute rejection may have potential promise moving forward. A vaccine (algenpantucel-L) has been developed using genetically modified pancreas cancer cells with a mouse gene leading to foreign protein expression of α (1,3)-galactosyl (αGal). Pre-existing anti-αGal antibodies then trigger a significant immune response leading to proposed cell destruction of any tumor cells in patients undergoing treatment with this form of immunotherapy.[26,27] A phase II study evaluating the role of this form of algenpantucel-L immunotherapy in addition to therapy with gemcitabine with 5-FU-based chemoradiation in patients with resected pancreas adenocarcinoma showed a significant 1-year DFS of 63% and OS of 86%, which compares favorably with historical control subjects.[28] As a result, a phase III trial of chemotherapy and chemoradiotherapy with or without algenpatnucel-L immunotherapy in

722 subjects with surgically resected pancreatic cancer has recently completed recruitment and results are eagerly awaited (NCT01072981).

NEOADJUVANT THERAPY: AN EMERGING PARADIGM IN PANCREAS ADENOCARCINOMA

Neoadjuvant therapy has not yet been widely established or accepted as a standard of care for patients with borderline resectable pancreatic adenocarcinoma. However, it does offer an alternative to traditional upfront surgery and adjuvant therapy with several theoretic advantages including treating distant micrometastases not seen on initial staging radiographs, assessing tumor response to treatment, selecting patients most appropriate for surgery, and including radiation to improve margin negative resection (R0) rates.[29,30] In addition, up to an estimated 25% to 30% of patients are unable to receive adjuvant systemic therapy following surgical resection. Neoadjuvant therapy could potentially increase the overall exposure to systemic therapy for many patients by decreasing time off treatment during recovery after surgical resection.[31]

The National Comprehensive Cancer Network guidelines currently recommend neoadjuvant therapy for borderline resectable disease.[29,32] Although tumors have been typically classified as either resectable or unresectable, the concept of "borderline resectable disease" has recently emerged as a category clinically distinct from "resectable" or "locally advanced disease." However, consensus over the standardization of these individual categories remains a major challenge.[33] Furthermore, prior randomized studies exploring the role of neoadjuvant treatment in pancreas adenocarcinoma have been limited primarily to single institution patients often with various disease settings (resectable, borderline resectable, and locally advanced pancreas cancer).[34,35] Therefore, questions of when to administer neoadjuvant systemic therapy, what is the optimal therapy (systemic, systemic and chemoradiation, or chemoradiation), and duration of treatment remain unanswered and are areas of intense investigation.

NEOADJUVANT RADIATION THERAPY TRIALS

Ishikawa and colleagues[36] was one of the early investigators in a retrospective study to compare preoperative and postoperative radiation alone in resectable disease patients before a Whipple surgery. Although preoperative radiation significantly decreased local recurrence with a 1-year survival rate of 75% in the preoperative group, and 43% in the postoperative group ($P < .05$), the overall 5-year survival rates were not significant between the two groups (22% vs 26%). Similarly, studies using 5-FU-based chemoradiation performed by Staley and colleagues[37] and Spitz and colleagues[38] also showed a decrease in local recurrence for patients who received preoperative compared with postoperative chemoradiation. Interestingly, the Spitz study also found no difference in OS between the preoperative and postoperative treatment groups, whereas the Staley study found no incidences of pathologic complete response for those receiving preoperative chemoradiation.

Neoadjuvant gemcitabine-based radiation has also been studied (**Table 3**). Two phase II nonrandomized studies[39,40] found that patients with potentially resectable disease treated with neoadjuvant gemcitabine-based radiation had higher rates of R0 resection compared with previous studies using 5-FU-based therapy. However, the true beneficial value of chemoradiation in the neoadjuvant setting remains unclear, because Xu and colleagues[41] performed a meta-analysis with a total of 3088 patients

Table 3
Selected neoadjuvant trials in pancreas adenocarcinoma

Trial	Type	Patients	Initial Disease Stage	Therapy	Results
Talamonti et al,[40] 2006	Phase II	20	Resectable	Gemcitabine + RT	Resection rate 85% R0 rate 94% Median OS 26 mo (resected)
Evans et al,[39] 2008	Phase II	86	Resectable	Gemcitabine + RT	Resection rate 71% Median PFS 28.6 mo (resected) Median OS 34 mo (resected) vs OS 7 mo (unresectable)
Heinrich et al,[42] 2008	Phase II	28	Resectable	Gemcitabine + cisplatin	Resection rate 89% R0 rate 80% Median PFS 9.2 mo (resected) Median OS 26.5 mo (resected
Sahora et al,[44] 2011	Phase II	33	Borderline resectable + locally advanced unresectable	Gemcitabine + oxaliplatin	Resection rate 39% R0 rate 69% Median PFS 10 mo (resected) Median OS 22 mo (resected) vs 12 mo (unresectable)
Sahora et al,[45] 2011	Phase II	25	Borderline resectable + locally advanced unresectable	Gemcitabine + docetaxel	Resection rate 32% R0 rate 87% Median PFS 12 mo (resected) Median OS 16.3 mo (resected) vs 12.2 mo (unresectable)
Motoi et al,[43] 2013	Phase II	35	Resectable + borderline resectable	Gemcitabine + S1	Resection rate 86% R0 rate 87% Median OS 34.7 mo (resected) vs OS 10 mo (unresectable)
Leone et al,[46] 2013	Phase II	39	Borderline resectable + locally advanced unresectable	Gemcitabine + oxaliplatin + gemcitabine-based RT	Resection rate 28% R0 rate 82% Median PFS 19.9 mo (resected) vs 7.6 mo (unresectable)
O'Reilly et al,[47] 2014	Phase II	38	Resectable	Gemcitabine + oxaliplatin	Resection rate 71% 18 mo OS 63% Median overall survival 27.2 mo

Abbreviations: PFS, progression free survival; R0, margin negative surgical resection; RT, radiation therapy.

with resectable pancreatic adenocarcinoma and found no significant difference in progression-free survival (PFS) and OS for patients who received either presurgical or postsurgical chemoradiation.

GEMCITABINE-BASED NEOADJUVANT SYSTEMIC THERAPY TRIALS

As gemcitabine-based regimens became widely accepted in the treatment of metastatic pancreas adenocarcinoma, numerous gemcitabine systemic combinations have been investigated preoperatively (see **Table 3**). Heinrich and colleagues[42] performed a phase II study using neoadjuvant gemcitabine and cisplatin systemic therapy in patients initially with resectable disease and found that 25 of 28 patients ultimately underwent surgery, of which 80% attained an R0 resection. Overall survival for the patients undergoing resection was 26.5 months, which was higher than the OS previously reported in 5-FU-based neoadjuvant studies.[37,38] The role of S1 in the neoadjuvant setting has also been explored. Motoi and colleagues[43] performed a phase II study with neoadjuvant gemcitabine plus S1 in 35 patients with resectable and borderline resectable disease. A total of 30 of 35 (85.7%) patients underwent resection with a median OS of 34.7 months for patients who had an R0 resection compared with 10 months for patients who could not undergo surgery or had resection with evidence of distant metastases.

Two prospective phase II trials by Sahora and colleagues[44,45] also examined the roles of neoadjuvant gemcitabine-based regimens with gemcitabine plus oxaliplatin and gemcitabine plus docetaxel in patients initially with borderline resectable and locally advanced disease. In the neoadjuvant trial with gemcitabine plus oxaliplatin, 13 of 33 (39%) patients underwent surgical resection after 6 weeks of neoadjuvant gemcitabine plus oxaliplatin. Median OS was 22 months for those who had surgical resection compared with 12 months for those without resection. Similarly, in the trial with neoadjuvant gemcitabine plus docetaxel, 8 of 25 (32%) patients underwent surgical resection after 8 weeks of neoadjuvant gemcitabine plus docetaxel. Median OS was 16.3 and 12.2 months for patients who did and did not undergo surgical resection, respectively. In addition to the Sahora studies, another prospective trial[46] explored the role of neoadjuvant gemcitabine plus oxaliplatin with gemcitabine-based chemoradiation for patients with borderline resectable and locally advanced unresectable disease, reporting similar results (28% patients ultimately underwent surgical resection with PFS advantage of 19.7 months compared with 7.6 months in favor of patients completing surgical resection). Furthermore, for patients with resectable disease, O'Reilly and colleagues[47] performed a single-arm prospective study with neoadjuvant gemcitabine plus oxaliplatin followed by adjuvant gemcitabine. A total of 27 of 38 (71%) patients underwent resection and an overall 18-month survival rate of 63% and a median OS of 27.2 months were observed. The American College of Surgeons Co-operative Oncology Group evaluated neoadjuvant gemcitabine and erlotinib in a single-arm nonrandomized design in resectable pancreas adenocarcinoma (NCT00773746). This trial, Z5041, used real-time central radiology review to adjudicate eligibility. This study was completed several years ago and results are awaited. Ultimately, although the number of patients in many neoadjuvant studies has been small to date, the potential benefit with respect to PFS and OS even for patients initially with borderline resectable or locally advanced disease has been encouraging. Investigation into the use of newer and more active systemic regimens in the neoadjuvant setting for the treatment of pancreas adenocarcinoma could potentially improve outcomes even further moving forward.

NEOADJUVANT THERAPY WITH FOLFIRINOX

FOLFIRINOX is an example of a multiagent cytotoxic systemic therapy currently established as a standard of care in the treatment of metastatic pancreas adenocarcinoma.[15] However, reports of its use in the neoadjuvant setting have currently been limited mainly to single institution experiences. One retrospective study of neoadjuvant FOLFIRINOX[48] in patients with both borderline resectable and locally advanced pancreas adenocarcinoma found that 11 of 21 (52%) patients underwent surgical resection. The authors also reported a 5% complete pathologic response and a 19% partial response rate following FOLFIRINOX treatment alone. Similarly, another retrospective study of neoadjuvant FOLFIRINOX[49] in patients with borderline resectable pancreas adenocarcinoma found that 12 of 18 (67%) patients undergoing treatment with FOLFIRINOX followed by gemcitabine- or capecitabine-based radiation therapy were able to undergo R0 resection. Even for locally advanced, unresectable disease, a retrospective single-institution study from the Massachusetts General Hospital noted that up to 20% of patients who received neoadjuvant FOLFIRINOX followed by 5-FU or capecitabine-based radiation therapy were converted from unresectable to resectable disease.[50] Given these findings, several ongoing prospective studies are examining the role of FOLFIRINOX in a neoadjuvant setting for resectable disease (**Table 4**). These include a single-arm nonrandomized trial evaluating preoperative and postoperative FOLFIRINOX in patients with resectable disease (NCT01660711) and the multicenter German randomized trial investigating adjuvant gemcitabine compared with neoadjuvant and adjuvant FOLFIRINOX (NCT02172976). For borderline resectable disease, the Alliance pilot trial A021101 (NCT01821612) represents an important study examining the role of neoadjuvant FOLFIRINOX and chemoradiation followed by surgery and adjuvant gemcitabine. The primary end points are R0/R1 resection rates, radiographic and pathologic response rates, time to local and distant recurrence, and OS. Initial results were recently presented showing 15 of 22 (68%) patients underwent successful R0/R1 resections after neoadjuvant treatment and 2 of 22 (9%) patients even achieved a pathologic complete response at time of resection.[51] Further follow-up is planned for this study and ongoing discussions are underway regarding designing a randomized phase II trial. This study also aims to further standardize the definition of borderline resectable disease, which will provide a better foundation and reference for future neoadjuvant trials involving patients with locally advanced disease.[52,53]

CURRENT AND EMERGING AREAS OF NEOADJUVANT INVESTIGATION

Given the dearth of randomized neoadjuvant trials, questions regarding neoadjuvant therapy strictly in resectable disease along with determination of the optimal therapeutic regimen remain areas of active investigation. Several emerging studies aimed to address these questions are summarized in **Table 4**.

The NEOPAC trial (NCT01521702) is a prospective randomized phase III trial comparing adjuvant gemcitabine with neoadjuvant gemcitabine and oxaliplatin in conjunction with surgery followed by adjuvant gemcitabine in patients with resectable head of pancreas adenocarcinoma. The study was initiated in 2011[54] with a target accrual of 310 patients and represents one of the largest randomized trials examining adjuvant and neoadjuvant gemcitabine-based therapy to date. The primary end point is PFS at 1 year and secondary end points are pathologic response to neoadjuvant therapy, OS, and postoperative complications. In addition to the NEOPAC trial, several other gemcitabine-based combination regimens are being explored with particular

Table 4
Select ongoing neoadjuvant trials for resectable pancreas adenocarcinoma

Trial	Type	Patients	Therapy	Primary Outcome
NEOPAC NCT01521702	Phase III	310	Neoadjuvant FOLFIRINOX - > surgery - > adjuvant gemcitabine vs adjuvant gemcitabine	5 y PFS
NCT01900327	Phase III	410	Neoadjuvant gemcitabine-based CRT - > surgery - > adjuvant gemcitabine vs adjuvant gemcitabine	3 y OS
NCT01771146	Phase II	100	Neoadjuvant FOLFIRINOX	PFS
NEONAX NCT02047513	Randomized phase II	166	Neoadjuvant gemcitabine + nab-paclitaxel - > surgery - > adjuvant gemcitabine + nab-paclitaxel vs adjuvant gemcitabine + nab-paclitaxel	18 mo DFS
NCT02172976	Randomized phase II/III	126	Adjuvant gemcitabine vs neoadjuvant FOLFIRINOX - > surgery - > adjuvant FOLFIRINOX	Median OS
NCT01150630	Randomized phase II/III	370	Adjuvant PEXG vs adjuvant gemcitabine vs neoadjuvant PEXG - > surgery - > adjuvant PEXG	1 y event-free survival
ACOSOG-Z5041 NCT00733746	Phase II	123	Neoadjuvant gemcitabine + erlotinib (completed; results pending)	2 y OS
NCT00727441	Phase II	87	GVAX +/- IV or oral cyclophosphamide - > surgery - > adjuvant gemcitabine + CRT	Safety, feasibility, and immune response
NCT02178709	Phase II	48	Neoadjuvant FOLFIRINOX	Pathologic complete response
GEMCAD1003 NCT01389440	Phase II	24	Neoadjuvant gemcitabine + erlotinib	R0 resection rate
NCT02243007	Randomized phase II	112	Neoadjuvant FOLFIRINOX vs gemcitabine + nab-paclitaxel	18 mo OS
NCT02030860	Pilot	15	Neoadjuvant gemcitabine + nab-paclitaxel +/- paricalcitol	Number of adverse events
NCT02305186	Randomized phase Ib/II	56	Neoadjuvant capecitabine based CRT +/- pembrolizumab (MK-3745)	Safety and immune response

Abbreviations: CRT, chemoradiation therapy; GVAX, granulocyte-macrophage colony–stimulating factor gene-transfected tumor cell vaccine; PEXG, cisplatin, epirubicin, capecitabine, gemcitabine; R0, margin-negative surgical resection.

interest with the combination of gemcitabine and nab-paclitaxel given its success in the metastatic setting. For example, several phase II trials investigating the neoadjuvant role of gemcitabine plus nab-paclitaxel in resectable (NCT02047513) and borderline/locally advanced disease (GAIN-1 study [NCT01470417] and trial [NCT02210559]) are currently under evaluation. Furthermore, neoadjuvant gemcitabine plus nab-paclitaxel are also being evaluated with oral hedgehog inhibitors, such as LDE-225 targeting the stroma (NCT01431794) or with paricalcitol targeting the vitamin D metabolic program (NCT02030860). These studies illustrate the opportunity for neoadjuvant trials to incorporate additional correlative and tissue evaluation that may ultimately provide a better understanding of the entire disease process.

IMMUNOTHERAPY TRIALS

The value of immunotherapeutic approaches is also an area of focused research in the neoadjuvant setting. Although the role of GVAX in metastatic pancreas adenocarcinoma has yet to be established, trial NCT00727441 is a randomized three-arm neoadjuvant study that has been completed and was designed to explore the role of neoadjuvant GVAX with and without cyclophosphamide for neoadjuvant and adjuvant treatment of 87 patients with resectable pancreatic adenocarcinoma. All patients in this study received standard adjuvant gemcitabine with chemoradiation. The primary end points are evaluating safety, immune infiltrate levels postvaccination, and changes in specific regulatory T-cell levels status-post GVAX and surgical resection. Secondary end points consist of disease-free and OS in those patients treated with GVAX. In addition to GVAX, algenpantucel-L is also being investigated in the adjuvant setting as previously discussed. In the neoadjuvant setting, the PILLAR trial (NCT01836432) is a phase III study developed to examine the effect of algenpantucel-L administered with either FOLFIRINOX or gemcitabine plus nab-paclitaxel in patients with borderline resectable or locally advanced pancreas adenocarcinoma. Neoadjuvant algenpantucel-L with stereotactic body radiation therapy following FOLFIRINOX will also be investigated in an upcoming phase II study in patients with borderline resectable pancreatic cancer (NCT02405585).

In addition to vaccines, modulating T-cell signaling through PD-1 (NCT02305186) or targeting the cell-surface CD40 cosignaling molecules using monoclonal ligands to affect an immune response against tumor antigens are additional areas of interesting investigation. For instance, Beatty and colleagues[55] reported a partial tumor response in 4 of 22 (18%) patients with advanced pancreas adenocarcinoma after the use of a CD40 agonist, CP-870893, combined with gemcitabine. Results from a follow-up phase I study (NCT01456585) examining the efficacy of neoadjuvant CP-870893 plus gemcitabine followed by postoperative 5-FU-based chemoradiation in 10 patients with resectable disease are pending. Further study evaluating the addition of CP-870893 to combinations, such as gemcitabine and nab-paclitaxel, in the neoadjuvant setting are being considered.

SUMMARY

The value of adjuvant systemic therapy in pancreas adenocarcinoma has been clearly established in terms of its ability to delay recurrence and enhance OS. Current international standards of care for adjuvant therapy consist of either 6 months of gemcitabine or 5-FU and leucovorin. The role of adjuvant chemoradiation has not yet been firmly established in the United States. Although not yet widely accepted as a standard of care for patients with resectable pancreatic adenocarcinoma, neoadjuvant

chemotherapy provides theoretic advantages including most importantly selection of patients most appropriate for surgery. The roles of multiagent chemotherapy combinations, targeted agents, and immunotherapeutic approaches in the adjuvant and neoadjuvant settings remain areas of active investigation and represent opportunities for improved care in the treatment of pancreas adenocarcinoma.

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