# Evolving Standards of Care for Resected Pancreatic Cancer

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**Abstract:** Pancreatic cancer is a devastating illness, and surgical resection offers the only chance of a cure for patients with the disease. Relatively few patients have resectable disease at diagnosis, however, and the cancer frequently recurs even after complete surgical resection. This review discusses clinical trials in which adjuvant therapy with chemotherapy or chemoradiation has prolonged survival in patients following surgery. It also highlights new data from the ESPAC-4 and JASPAC 01 studies that may change the current treatment paradigm for adjuvant therapy. The ESPAC-4 results support the use of adjuvant gemcitabine plus capecitabine in preference to the previous standard of gemcitabine alone, demonstrating that in this instance, more may be better. Finally, the review discusses ongoing trials and new approaches that aim to improve outcomes further for patients with resectable pancreatic cancer.

## Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, and death rates from pancreatic cancer are increasing by 0.4% annually.[1] Approximately 9% of patients have localized disease at diagnosis and undergo surgical resection, but the 5-year overall survival (OS) rate in these patients is only 29%.[2] Because resection alone is associated with a median OS (mOS) of just 11 to 19 months, numerous studies have evaluated the use of adjuvant therapies in an effort to improve outcomes.[3-6] These approaches include adjuvant gemcitabine- or 5-fluorouracil (5-FU)–based chemotherapy with or without concurrent chemoradiation (Table 1 and Figure).

## Adjuvant Chemotherapy Trials

The 2007 phase 3 CONKO-001 (Charité Onkologie 001) trial (Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer) compared adjuvant gemcitabine vs observation following resection in 368 patients with pancreatic ductal adenocarcinoma (PDA).[6] After being stratified by tumor stage, nodal status, and resection margin status, patients were randomly assigned 1:1 to gemcitabine (1000 mg/m$^2$

**Table 1.** Summary of Trials of Adjuvant Therapy in PDA

| Trial | Year | N | Population (n) | R0 Resection, % | Regimens | Outcomes |
|---|---|---|---|---|---|---|
| GITSG[3] | 1985 | 43 | PDA | 100 | chemoXRT vs observation | mOS, 20 vs 11 mo (*P*=.03) |
| Norwegian Pancreatic Cancer Trial[10] | 1993 | 61 | PDA (47), ampullary (14) | 100 | 5-FU/Doxo/MMC (AMF) vs observation | mOS, 23 vs 11 mo (*P*=.02) |
| EORTC[4] | 1999 | 218 | T1-2 N0-1a M0 pancreatic head or T1-3 N0-1a M0 periampullary | 77 | chemoXRT vs observation | mOS, 24.5 vs 19.0 mo (*P*=.208) |
| Takada et al[11] | 2002 | 508 | PDA (173), ampullary (56), biliary (279) | 58 (PDA) | MMC/5-FU vs observation | 5-y survival in PDA group, 11.5% vs 18.0% (*P*>.05) |
| ESPAC-1[5] | 2004 | 289 | PDA | 82 | chemoXRT vs chemo vs both vs observation | mOS, 13.9 vs 21.6 vs 19.9 vs 16.9 mo (*P*=.05 for no chemoXRT; *P*=.0009 for chemo) |
| CONKO-001[6] | 2007 | 368 | T1-4 N0-1 M0 PDA | 83 | Gem vs observation | mDFS, 13.4 vs 6.7 mo (*P*<.001); mOS, 22.8 vs 20.2 mo (*P*=.01) |
| RTOG 97-04[15] | 2008 | 451 | T1-4 N0-1 M0 PDA | 42 | Gem vs 5-FU before/after chemoXRT | mOS, 20.5 (Gem) vs 17.1 (5-FU) mo (*P*=.51) |
| ESPAC-3[8] | 2010 | 1088 | PDA or ampullary | 65 | Gem vs 5-FU | mOS, 23.6 (Gem) vs 23.0 (5-FU) mo (*P*=.39) |
| Schmidt et al[14] | 2012 | 132 | PDA | 61 | 5-FU/Cis/IFN alfa + XRT vs leucovorin/5-FU | mOS, 26.5 vs 28.5 mo (*P*=.99) |
| CAP-002[12] | 2013 | 96 | PDA | 67 | Gem vs S-1 vs Gem + S-1 | 2-y DFS, 25.1% vs 28.1% vs 34.4% (*P*=.47); mOS, 21.4 vs 26.2 vs 27.9 mo (*P*=.48) |
| IMPRESS[21] | 2016 | 722 | PDA | NA | Gem +/– chemoXRT + algenpantucel-L vs Gem +/– chemoXRT | mOS, 27.3 vs 30.4 mo (*P* not reported) |
| ESPAC-4[22] | 2016 | 732 | PDA | 40 | Gem vs Gem/Cape | mOS, 25.5 vs 28.0 mo (*P*=.032) |
| JASPAC 01[23] | 2016 | 385 | PDA, Japan only | 87 | Gem vs S-1 | mOS, 25.5 vs 46.5 mo (*P*<.0001) |

Cape, capecitabine; chemo, chemotherapy; chemoXRT, chemoradiation; Cis, cisplatin; DFS, disease-free survival; Doxo, doxorubicin; 5-FU, 5-fluorouracil; Gem, gemcitabine; IFN, interferon; mDFS, median disease-free survival; MMC, mitomycin-C; mo, months; mOS, median overall survival; N, number of patients; NA, not available; PDA, pancreatic ductal adenocarcinoma; R0, microscopic tumor clearance; XRT, radiation therapy; y, year.

intravenously [IV] on days 1, 8, and 15 every 28 days for 6 months) or to observation. Median disease-free survival (mDFS) was significantly longer in the gemcitabine group (13.4 vs. 6.7 months; hazard ratio [HR], 0.55; 95% CI, 0.44-0.69; *P*<.001), as was mOS (22.8 vs. 20.2 months; HR, 0.76; 95% CI, 0.61-0.95; *P*=.01). Gemcitabine was well tolerated, with rare grade 3/4 adverse events (leukopenia in 2.4%, nausea/vomiting in 1.3%, and diarrhea in 0.9%).[7] Thus, gemcitabine monotherapy is an effective and a well-tolerated adjuvant treatment option.

Chemotherapy regimens based on 5-FU have long been used as another option since the first adjuvant study by the Gastrointestinal Tumor Study Group (GITSG; see later section on adjuvant chemoradiation trials). The

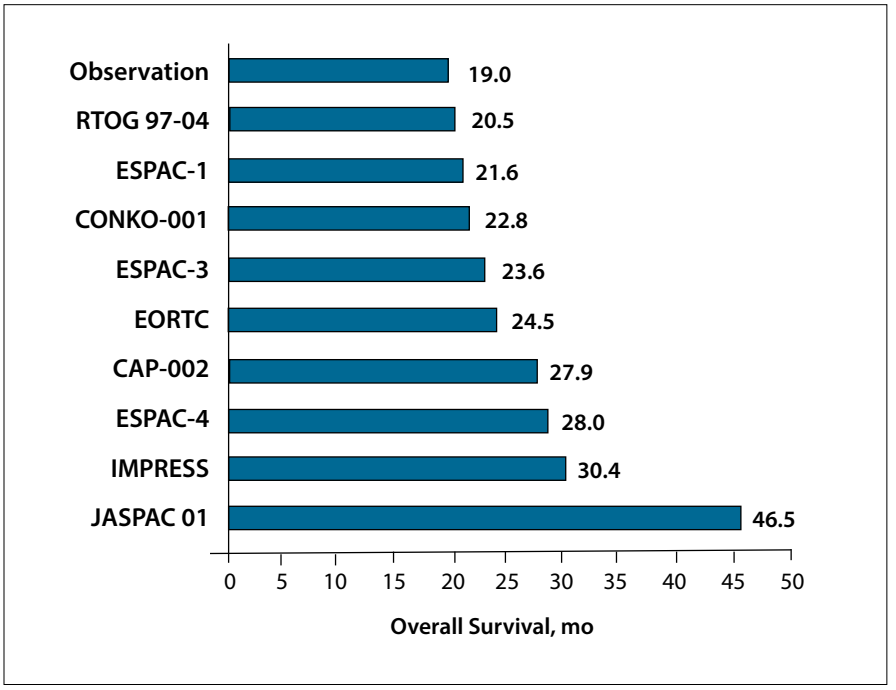


**Figure.** Best median overall survival outcomes in trials of adjuvant therapy for pancreatic cancer.[4-6,8,12,15,21-23]

2010 phase 3 ESPAC (European Study Group for Pancreatic Cancer)-3 study (European Study of Adjuvant Chemotherapies in Resectable Pancreatic Cancer) compared 6 months of adjuvant gemcitabine vs 6 months of adjuvant 5-FU (leucovorin 20-mg/m$^2$ IV bolus, followed by 5-FU 425-mg/m$^2$ IV bolus on days 1-5 every 28 days).[8] A total of 1088 patients were randomly assigned 1:1 and stratified by country and resection status. The mOS was similar in the 2 groups (23.6 months with gemcitabine vs 23.0 months with 5-FU; HR, 0.94; 95% CI, 0.8-1.08, *P*=.39). However, the rates of grade 3/4 adverse events differed significantly (7.5% of patients with gemcitabine vs 14% of patients with 5-FU; *P*<.001), including higher rates of grade 3/4 stomatitis (10% vs 0%; *P*<.001) and diarrhea (13% vs 2%; *P*<.001) in the 5-FU group. A small but significantly higher rate of leukopenia was observed in the gemcitabine group (10% vs 6%; *P*=.01). Overall, gemcitabine was better tolerated than 5-FU and led to similar survival outcomes. Gemcitabine for 6 months became the preferred adjuvant treatment option, although the National Comprehensive Cancer Network has given category 1 recommendations to both adjuvant gemcitabine and adjuvant bolus 5-FU.[9]

Earlier studies looked at the addition of mitomycin-C (MMC) to 5-FU–based adjuvant chemotherapy regimens. In 1993, Bakkevold and colleagues published the results of a Norwegian trial that randomly assigned 61 patients (47 with PDA and 14 with ampullary cancer) 1:1 to adjuvant AMF (doxorubicin 40 mg/m$^2$ IV, MMC 6 mg/m$^2$ IV, and 5-FU 500 mg/m$^2$ IV every 3 weeks for 6 cycles) or to observation.[10] The AMF group had a significantly prolonged mOS compared with the observation group (23 vs 11 months; *P*=.02), although the 5-year survival rates were similar (24% vs 19%; *P*=.10). The AMF regimen was toxic; only 45% of patients completed all 6 cycles, 73% were hospitalized during the first cycle, and 17% stopped treatment owing to adverse events.

In a 2002 study of 508 patients, including 158 patients with PDA and 48 patients with ampullary cancer, Takada and colleagues randomly assigned patients 1:1 to adjuvant MMC plus 5-FU (MF) or observation.[11] Patients in the MF group received MMC 6 mg/m$^2$ IV on the day of surgery and infusional 5-FU 310 mg/m$^2$ IV for 5 consecutive days on postoperative weeks 1 and 3, followed by oral 5-FU 100 mg/m$^2$ daily from postoperative week 5 until disease recurrence. The 5-year survival rates were similar in the MF group and the observation group for patients with PDA (11.5% vs 18.0%; *P*>.05) and for those with ampullary cancer (28.1% vs 34.3%; *P*>.05). Treatment was generally well tolerated, although significantly higher rates of grades 2 to 4 leukopenia (12.9% vs 3.0%), anorexia (22.4% vs 13.9%), and nausea/vomiting (12.9% vs 6.9%) were observed in the MF group (*P*<.05). No further studies of adjuvant regimens that include MMC have been published.

In Japan in 2013, Yoshitomi and colleagues evaluated the addition of S-1, an oral fluoropyrimidine, to adjuvant gemcitabine in a phase 2 trial of patients with resected pancreatic cancer (CAP-002).[12] They randomly assigned 96 patients 1:1:1 to gemcitabine, to S-1 (80/100/120 mg

daily on the basis of body surface area [BSA] orally on days 1-14 every 21 days), or to a combination of gemcitabine and S-1 (GS; same gemcitabine dosing, with S-1 60/80/100 mg daily on the basis of BSA). Patients were stratified by resection margin status, stage, and institution. No significant differences were found among the 3 groups in 2-year DFS (25.1% with gemcitabine, 28.1% with S-1, and 34.4% with GS; *P*>.05) or in mOS (21.4 vs 26.2 vs 27.9 months; *P*>.05). Although there was a trend toward improved survival with the combination, the rate of grade 3/4 adverse events was greater in the combination group (90.3% vs 70.0%; *P* not reported). Thus, although S-1 was not inferior to gemcitabine, the combination was more toxic than gemcitabine alone.

## Adjuvant Chemoradiation Trials

Adjuvant chemoradiation was shown to be beneficial compared with observation in the 1985 GITSG trial, but its use in addition to adjuvant chemotherapy is often debated. The GITSG trial randomly assigned 43 patients with resected PDA to chemoradiation or to observation.[3] Patients in the chemoradiation arm received a total of 40 Gy of external beam radiation therapy (weeks 1-2 and 5-6) and concurrent bolus 5-FU (during weeks 1 and 5), then maintenance 5-FU weekly for 2 years or until disease progression. The mOS was 20 months for patients in the treatment arm vs 11 months for those in the observation arm (*P*=.03). Only 14% of the treated patients had grade 3 leukopenia, and otherwise the treatment was well tolerated. These findings were confirmed after 30 additional patients were registered, received the same adjuvant regimen, and had an mOS of 18 months.[13]

Klinkenbijl and colleagues in 1999 reported the results of a phase 3 EORTC (European Organisation for Research and Treatment of Cancer) trial that randomly assigned 218 patients with resected pancreatic head or periampullary adenocarcinoma 1:1 to chemoradiation (40 Gy split into 2 courses with concurrent infusional 5-FU, without maintenance 5-FU) or to observation.[4] The mOS was 24.5 months for patients in the chemoradiation arm vs 19.0 months for those managed with observation alone, but this finding was not statistically significant (relative risk [RR], 0.8; 95% CI, 0.6-1.1; *P*=.208). Interestingly, there was no difference between the local recurrence rates of the 2 arms. Treatment was well tolerated overall, with only 1 severe event (persistent duodenal ulcer that limited 1 patient to a single radiation course).

The 2004 phase 3 ESPAC-1 trial went further by using a 2 × 2 factorial design and randomly assigning 289 patients to 1 of 4 groups: chemoradiation, chemotherapy alone, chemoradiation followed by chemotherapy, or observation.[5] Chemoradiation consisted of 20 Gy administered in 10 daily fractions over 2 weeks with concurrent bolus 5-FU (500 mg/m$^2$ IV on days 1-3), repeated after a 2-week break. In the chemotherapy arm, patients received leucovorin 20 mg/m$^2$ IV followed by bolus 5-FU 425 mg/m$^2$ IV on days 1 to 5 every 28 days for 6 cycles. The mOS was 15.9 months for the patients who received chemoradiation vs 17.9 months for the patients who did not receive chemoradiation (HR, 1.28; 95% CI, 0.99-1.66; *P*=.05), indicating a trend toward lack of benefit from chemoradiation. Patients did benefit from chemotherapy; mOS was 20.1 months with chemotherapy vs 15.5 months without chemotherapy (HR, 0.71; 95% CI, 0.55-0.92; *P*=.009). In fact, the chemotherapy-alone arm had the best survival outcome (mOS, 21.6 months), better than the outcomes for chemoradiation followed by chemotherapy (19.9 months), observation (16.9 months), and chemoradiation alone (13.9 months). It is possible that delaying chemotherapy had a negative effect in the combination arm and that the best sequence may be chemotherapy followed by chemoradiation.

In a 2012 phase 3 trial, Schmidt and colleagues randomly assigned 132 patients with PDA 1:1 to chemoradiation with cisplatin, 5-FU, and interferon (IFN) alfa-2b or to leucovorin/5-FU.[14] In the chemoradiation arm, patients received 5.5 weeks of external beam radiation (50.4 Gy in 28 fractions) combined with a concurrent infusion of 5-FU 200 mg/m$^2$ IV daily, cisplatin 30 mg/m$^2$ IV per week, and 3 million units of IFN alfa-2b three times weekly, followed by 2 cycles of daily 5-FU. The other arm received bolus leucovorin 20 mg/m$^2$ IV and 5-FU 425 mg/m$^2$ IV on days 1 to 5 every 28 days for 6 cycles. mOS was essentially the same in the 2 arms (26.5 months with chemoradiation vs 28.5 months with leucovorin/5-FU; HR, 1.04; 95% CI, 0.66-1.53; *P*=.99). Patients in the chemoradiation arm had significantly more toxicity; 29% had grade 4 adverse events vs 2% in the leucovorin/5-FU arm. Therefore, further trials of this chemoradiation regimen have not been performed.

Finally, in 2008 the Radiation Therapy Oncology Group (RTOG) randomly assigned 451 patients 1:1 to infusional 5-FU or gemcitabine for 3 weeks before and 12 weeks after chemoradiation (50.4 Gy with daily concurrent infusional 5-FU 250 mg/m$^2$ IV) in RTOG 97-04 (A Phase III Study of Pre and Post Chemoradiation 5-FU vs. Pre and Post Chemoradiation Gemcitabine for Postoperative Adjuvant Treatment of Resected Pancreatic Adenocarcinoma).[15] Patients were stratified by tumor size (<3 cm or ≥3 cm), nodal status, and resection margin status. The 5-FU arm received a 250-mg/m$^2$ IV continuous infusion of 5-FU daily for 3 weeks before chemoradiation, then daily for 3 additional months

starting 3 to 5 weeks after chemoradiation (4 weeks on, 2 weeks off). The gemcitabine arm received gemcitabine 1000 mg/m$^2$ IV over 30 minutes weekly for 2 weeks before chemoradiation, then for 3 additional months after chemoradiation (3 weeks on, 1 week off). No significant difference in mOS was observed between the 2 arms (20.6 months with gemcitabine vs 16.9 months with 5-FU; *P*=.34). In a multivariate analysis, there was a trend toward improved survival in the patients with pancreatic head tumors treated with gemcitabine (20.5 months with gemcitabine vs 16.9 months with 5-FU; HR, 0.80; 95% CI, 0.63-1.00; *P*=.05). The incidence of grade 3/4 hematologic toxicities was higher in the gemcitabine arm (58% vs 9%; *P*<.001). In a 5-year analysis of the study, there was still no significant difference in mOS between the 2 study arms (HR, 0.933; 95% CI, 0.760-1.145; *P*=.51).[16] In patients with pancreatic head tumors, there again was a trend toward improved OS for those who received gemcitabine, but this result also was not statistically significant (20.5 vs 17.1 months with 5-FU; HR, 0.838; 95% CI, 0.671-1.045; *P*=.12).[16]

Although the use of chemoradiation in the adjuvant treatment of PDA remains controversial overall, some studies describe a benefit in patients with margin-positive resections and nodal disease. As discussed previously, the ESPAC-1 trial demonstrated the benefit of adjuvant chemotherapy and the detrimental effect of adjuvant chemoradiation. A meta-analysis of 875 patients from 5 randomly assigned trials showed an OS benefit with chemotherapy overall, but chemoradiation was more effective in patients with R1 (microscopic margin positive) resections.[17] In a retrospective analysis of more than 6000 patients in the National Cancer Data Base, there was an mOS benefit of chemoradiation compared with chemotherapy alone, irrespective of resection margin and nodal status (22.3 vs 20.0 months; *P*<.001).[18] There appeared to be an even more pronounced benefit in the R1 population (HR, 0.842; 95% CI, 0.722-0.983; *P*=.030) vs the R0 (microscopic margin negative) population (HR, 0.901; 95% CI, 0.839-0.969; *P*=.005), and in the N1 population (HR, 0.856; 95% CI, 0.793-0.924; *P*<.001) vs the N0 population (HR, 0.957; 95% CI, 0.845-1.084; *P*=.493).[18] Thus, chemoradiation could play a role after therapy for patients with R1 resections, and this sequence is currently being evaluated in the RTOG 0848 trial (Table 2). In this phase 3 trial, 950 patients with resected PDA (pancreatic head only) and no progression of disease after 5 months of adjuvant chemotherapy will be randomly assigned 1:1 to 1 more cycle of chemotherapy or to 1 more cycle plus chemoradiation with either 5-FU or capecitabine.[19] It is hoped that the results of this trial will determine the role of adjuvant chemoradiation following chemotherapy.

The 2016 phase 3 IMPRESS (Immunotherapy for Pancreatic Resectable Cancer Study) aimed to demonstrate a survival benefit from the addition of algenpantucel-L immunotherapy to standard adjuvant therapy (gemcitabine with or without 5-FU–based chemoradiation). Algenpantucel-L is an allogeneic vaccine composed of 2 irradiated PDA cell lines that are reengineered to express the murine α-1,3-galactosyltransferase gene.[20] This vaccine is designed to facilitate hyperacute rejection and antibody-dependent cell-mediated cytotoxicity of PDA cells. In a previous phase 2 study, Hardacre and colleagues treated 70 patients with resected PDA with gemcitabine and 5-FU–based chemoradiation (per the RTOG 97-04 study; see above) and algenpantucel-L.[20] In this study, 12-month OS was 86%, compared with 69% in the RTOG 97-04 study.[15] In IMPRESS, 722 patients with resected PDA were randomly assigned 1:1 to gemcitabine with or without 5-FU–based chemoradiation or the same plus algenpantucel-L (300 million cells every 2 weeks for 6 months, then monthly for 6 more months). No statistically significant difference in mOS was found between the 2 groups, and the algenpantucel-L group actually had shorter survival (27.3 vs 30.4 months; *P*>.05).[21] Thus, algenpantucel-L does not appear to play a role in the adjuvant treatment of PDA.

## New Standards in Adjuvant Chemotherapy: ESPAC-4 and JASPAC 01

The standard of care of 6 months of adjuvant gemcitabine as a single agent has been challenged by the results of the multinational, open-label ESPAC-4 trial. In this 2016 study, 732 patients with resected PDA were randomly assigned 1:1 to receive adjuvant gemcitabine or gemcitabine plus capecitabine for 6 cycles (830 mg/m$^2$ orally twice daily on days 1-21 of a 28-day cycle).[22] Patients were also stratified by resection margin status and country of origin. The mOS was 28.0 months for the combination arm vs 22.5 months for the gemcitabine-only arm (HR, 0.82; 95% CI, 0.68-0.98; *P*=.032). The 5-year OS rate also was longer in the combination arm (28.8% vs 16.3%). Patients with R0 resections benefited the most from the combination (mOS, 39.5 vs 27.9 months; *P*<.001), although a trend toward a smaller benefit was noted in patients with R1 resections (23.7 vs 23.0 months; *P*>.05). In general, the rates of grade 3/4 adverse events were similar in the 2 arms (24% of patients in the combination arm vs 26% of patients in the gemcitabine-only arm; *P*>.05). In the combination arm, there were higher rates of grade 3/4 diarrhea (5% vs 2%; *P*=.008), neutropenia (38% vs 24%; *P*<.001), and hand-foot syndrome (7% vs 0%; *P*<.001), and there was a slightly higher rate of infections in the gemcitabine-only

**Table 2.** Ongoing Trials of Adjuvant and Neoadjuvant Therapy in PDA Trials

| Trial | N | Phase | Regimens | Primary Outcome | Clinical Trial Number |
|---|---|---|---|---|---|
| **Adjuvant** | | | | | |
| PRODIGE 24/ ACCORD 24 (UNICANCER)[26] | 490 | 3 | mFOLFIRINOX vs Gem | PFS | NCT01526135 |
| APACT[27] | 846 | 3 | Gem/nab-P vs Gem | DFS | NCT01964430 |
| RTOG 0848[19] | 950 | 3 | Gem + chemoXRT vs Gem | OS | NCT01013649 |
| **Neoadjuvant** | | | | | |
| NEOPAC[33] | 310 | 3 | neoadj Gem/Ox and adj Gem or adj Gem (PDA head only) | PFS | NCT01521702 |
| NEOPANC[35] | 46 | 1/2 | neoadj IMRT and intraop XRT | Local recurrence rate | NCT01372735 |
| NEOPA[34] | 410 | 3 | neoadj Gem/XRT and adj Gem vs adj Gem | 3-y OS | NCT01900327 |
| NEONAX[39] | 162 | 2 | neoadj (2) and adj (4) Gem/nab-P vs adj Gem/nab-P (6) | 18-mo DFS | NCT02047513 |
| Prep-02/JSAP05[40] | 280 | 2/3 | neoadj Gem/S-1 and adj S-1 vs adj S-1 | OS | UMIN000009634 |
| NEPAFOX[36] | 126 | 2/3 | neoadj (6) and adj (6) FOLFIRINOX vs adj Gem | OS | NCT02172976 |
| ESPAC-5F[42] | 100 | 2 | adj Gem or 5-FU vs neoadj Gem/Cape vs neoadj FOLFIRINOX vs chemoXRT (Cape) (borderline resectable PDA only) | Recruitment rate, resection rate | ISRCTN89500674 |
| SWOG S1505[43] | 112 | 2 | neoadj (3) and adj (3) Gem/nab-P vs neoadj (3) and adj (3) mFOLFIRINOX | OS | NCT02562716 |

adj, adjuvant; Cape, capecitabine; chemoXRT, chemoradiation; DFS, disease-free survival; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; Gem, gemcitabine; IMRT, intensity-modulated radiation therapy; intraop, intraoperative; mFOLFIRINOX, modified FOLFIRINOX; MMC, mitomycin-C; mo, months; mOS, median overall survival; N, number of patients; nab-P, nab-paclitaxel; neoadj, neoadjuvant; OS, overall survival; Ox, oxaliplatin; PDA, pancreatic ductal adenocarcinoma; PFS, progression-free survival; XRT, radiation; y, year.

arm (7% vs 3%; *P*=.012). Given the survival outcomes in the adjuvant setting and tolerability of the regimen, 6 months of gemcitabine plus capecitabine should be considered a new standard of care.

The JASPAC 01 study (Japan Adjuvant Study Group of Pancreatic Cancer) also has effectively changed the standard of care for patients with resected pancreatic cancer, at least within the Japanese patient population. In this 2016 open-label, multicenter, phase 3 trial, 385 patients were randomly assigned 1:1 to receive 6 months of gemcitabine or S-1 (40, 50, or 60 mg on the basis of BSA orally twice daily, 4 weeks on and 2 weeks off).[23] The mOS was significantly longer in the S-1 group (46.5 vs 25.5 months; HR, 0.57; 95% CI, 0.44-0.72; *P*<.0001). S-1 was generally well tolerated. Patients in the gemcitabine group had significantly higher rates of grade 3/4 leukopenia (39% vs 9%; *P*<.0001), neutropenia (73% vs 13%; *P*<.0001), aspartate aminotransferase elevation (5% vs 1%; *P*=.0211), and alanine aminotransferase elevation (4% vs 1%; *P*=.0200). Rates of grade 3/4 febrile neutropenia were low and similar in the 2 groups (2% vs 1%; *P*=.3231). Although the generalizability of this study is limited because it enrolled only Japanese patients, the clear choice of adjuvant therapy for Japanese patients is now 6 months of S-1. It is also noteworthy that neither the ESPAC-4 nor the JASPAC 01 trial design included adjuvant radiotherapy.

## Forthcoming Adjuvant Chemotherapy Trials

FOLFIRINOX and gemcitabine plus nab-paclitaxel (Abraxane, Celgene) are effective first-line regimens for patients with metastatic PDA,[24,25] and they are now being studied for use as adjuvant therapies for patients with resectable PDA (Table 2). From the results of the 2011 PRODIGE 4 (Partenariat de Recherche en Oncologie Digestive)/ACCORD 11 (Actions Concertées dans les Cancers Colo-Rectaux et Digestifs) trial, FOLFIRINOX (oxaliplatin 85 mg/m$^2$ IV, leucovorin 400 mg/m$^2$ IV, irinotecan 180 mg/m$^2$ IV, 5-FU 400-mg/m$^2$ IV bolus,

and 5-FU 2400-mg/m$^2$ continuous IV infusion over 46 hours every 14 days) has an OS benefit over gemcitabine monotherapy in patients with metastatic PDA (11.1 vs 6.8 months; HR, 0.57; 95% CI, 0.45-0.73; *P*<.001).[24] The ongoing phase 3 PRODIGE 24/ACCORD 24 trial (Trial Comparing Adjuvant Chemotherapy With Gemcitabine Versus mFOLFIRINOX to Treat Resected Pancreatic Adenocarcinoma) plans to enroll 490 patients with resected PDA and randomize them 1:1 to modified FOLFIRINOX (mFOLFIRINOX, irinotecan reduced to 150 mg/m$^2$ and 5-FU bolus omitted) or gemcitabine for 24 weeks; the primary endpoint is progression-free survival (PFS).[26] The 2013 MPACT trial (A Randomized Phase III Study of Weekly ABI-007 Plus Gemcitabine Versus Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas) demonstrated an OS benefit of gemcitabine plus nab-paclitaxel over gemcitabine monotherapy in metastatic PDA (8.5 vs 6.7 months; HR, 0.72; 95% CI, 0.62-0.83; *P*<.001).[25] The ongoing phase 3 APACT trial (Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer) aims to demonstrate this benefit in the adjuvant setting, randomly assigning 846 patients with resected PDA 1:1 to gemcitabine plus nab-paclitaxel or gemcitabine monotherapy for 24 weeks; the primary endpoint is DFS.[27]

## Neoadjuvant Therapy

Despite the recent advances made by the ESPAC-4 and JASPAC 01 studies, more work is clearly necessary to improve outcomes in this patient population. Several new avenues of research are being evaluated, including neoadjuvant approaches, novel chemotherapy combinations, predictive biomarkers, and maintenance therapy.

Neoadjuvant therapy for patients with resectable disease remains controversial and should be offered only in the context of a clinical trial. Nevertheless, neoadjuvant chemotherapy may help identify patients with occult metastatic disease and spare them unnecessary surgery. In addition, the chance of an R0 resection may be increased. Better delivery of systemic therapy can be expected in patients who are unable to tolerate therapy after surgery. Prior neoadjuvant studies have generally used gemcitabine-based regimens and evaluated the addition of chemoradiation and platinum-based chemotherapies. One exception was the 1998 ECOG study by Hoffman and colleagues, in which 53 patients received MMC (10 mg/m$^2$ IV on day 2), 5-FU (continuous infusion of 1000 mg/m$^2$ per day IV on days 2-5 and 29-32), and concurrent radiation (50.4 Gy in 1.8-Gy fractions).[28] A total of 15% of patients had an R0 resection, and those patients had an mOS of 15.5 months. The treatment was toxic; 37% of the patients were hospitalized for cholangitis. Other studies evaluated neoadjuvant gemcitabine alone or in combination with platinum-based chemotherapies, chemoradiation, or adjuvant gemcitabine. R0 resection rates ranged from 36% to 64%, and mOS was as high as 34 months in patients who underwent resection following neoadjuvant therapy (Table 3).[29-32]

Multiple studies are ongoing that may definitively answer whether neoadjuvant therapy provides a benefit (Table 2). The NEOPAC study (Adjuvant Versus Neoadjuvant Plus Adjuvant Chemotherapy in Resectable Pancreatic Cancer) plans to randomly assign 310 patients with PDA in the head of the pancreas to neoadjuvant gemcitabine/oxaliplatin followed by adjuvant gemcitabine, or to adjuvant gemcitabine alone.[33] The NEOPA trial (Neoadjuvant Treatment in Resectable Pancreatic Cancer) will randomly assign 410 patients

**Table 3.** Summary of Trials of Neoadjuvant Therapy in PDA Trials

| Trial | Year | N | R0 Resection Achieved, % | Regimens | Outcomes |
|---|---|---|---|---|---|
| ECOG[28] | 1998 | 53 | 15 | MMC/5-FU/XRT | mOS, 15.5 mo with R0 resection |
| Palmer et al[29] | 2007 | 50 | 36 | Gem vs Gem/Cis | R0 resection, 25% vs 46%; mOS, 9.9 vs 15.6 mo |
| Varadhachary et al[30] | 2008 | 90 | 61 | Gem/Cis, then Gem/XRT | mOS, 17.4 mo (31 mo if resected) |
| Evans et al[31] | 2008 | 86 | 64 | Gem/XRT | mOS, 22.7 mo (34 mo if resected) |
| O'Reilly et al[32] | 2014 | 38 | 53 | Gem/Ox, adj Gem | mOS, 27.2 mo |
| AGITG GAP[38] | 2016 | 42 | 38 | neoadj (2) and adj (4) Gem/nab-P | mRFS, 12.3 mo |

adj, adjuvant; Cis, cisplatin; 5-FU, 5-fluorouracil; Gem, gemcitabine; MMC, mitomycin-C; mo, months; mOS, median overall survival; mRFS, median recurrence-free survival; N, number of patients; nab-P, nab-paclitaxel; neoadj, neoadjuvant; Ox, oxaliplatin; R0, microscopic tumor clearance; XRT, radiation.

to gemcitabine/chemoradiation followed by adjuvant gemcitabine, or to adjuvant gemcitabine alone.[34] The single-arm NEOPANC trial (Trial of Neoadjuvant Short Course IMRT Followed by Surgery and IORT for Resectable Pancreatic Cancer) will study the use of intensity-modulated short-term radiation therapy (IMRT; 5 × 5 Gy) and intraoperative radiation therapy (IORT; 15 Gy; goal accrual, 46 patients).[35]

Neoadjuvant FOLFIRINOX is a potentially excellent choice for patients with borderline resectable or even locally advanced unresectable PDA who are in need of a rapid clinical response, and it is also being studied in patients with resectable PDA.[36] In a pilot study of 21 patients with resectable disease treated with neoadjuvant FOLFIRINOX, 76% of patients had an R0 resection.[37] Gemcitabine with nab-paclitaxel is another potentially viable option in the neoadjuvant setting. In the 2016 single-arm, phase 2 AGITG GAP study (Phase II Study of Perioperative Nab-Paclitaxel and Gemcitabine for Resectable Pancreatic Ductal Adenocarcinoma), 42 patients received 2 cycles of neoadjuvant therapy and 4 cycles of adjuvant therapy consisting of gemcitabine plus nab-paclitaxel.[38] A total of 38% of patients had an R0 resection, and their median recurrence-free survival was 17.7 months. The ongoing NEONAX trial (Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer) is randomly assigning patients to 2 cycles of neoadjuvant gemcitabine plus nab-paclitaxel followed by 4 adjuvant cycles, or to 6 adjuvant cycles alone.[39] The Prep-02/JSAP05 trial (Randomized Phase II/III Trial of Neoadjuvant Chemotherapy With Gemcitabine and S-1 Versus Surgery-First For Resectable Pancreatic Cancer) is randomly assigning Japanese patients to neoadjuvant gemcitabine plus S-1 followed by adjuvant S-1, or to adjuvant S-1 alone.[40] ESPAC-5F (European Study Group for Pancreatic Cancer - Trial 5F) is an ongoing phase 2 feasibility study that is randomly assigning 100 patients with borderline resectable PDA to 1 of 4 arms (all followed by 6 months of adjuvant 5-FU/leucovorin or gemcitabine, physician's choice): surgery, neoadjuvant gemcitabine plus capecitabine for 8 weeks, neoadjuvant FOLFIRINOX for 8 weeks, or chemoradiation with capecitabine.[41,42] Finally, the ongoing SWOG S1505 trial aims to establish the optimal neoadjuvant/adjuvant treatment regimen for resectable PDA by randomly assigning 112 patients with resectable PDA 1:1 to 3 cycles of neoadjuvant mFOLFIRINOX followed by 3 cycles of adjuvant mFOLFIRINOX, or to 3 cycles of neoadjuvant gemcitabine plus nab-paclitaxel followed by 3 cycles of adjuvant gemcitabine plus nab-paclitaxel.[43] The results of these trials will be vital in determining what are the best neoadjuvant and adjuvant options for patients with resectable disease.

## Biomarkers

Given the statistically equivalent survival outcomes for adjuvant gemcitabine and bolus 5-FU in the ESPAC-3 trial, novel biomarkers could play a role in therapeutic selection. Human equilibrative nucleoside transporter 1 (hENT-1) has been thought to be a predictive biomarker of response to gemcitabine, and several retrospective studies have examined this (hENT-1 expression has not been evaluated prospectively).

Tumors from 388 patients in the ESPAC-3 trial were classified as having low or high hENT-1 expression, and the outcomes of patients treated with gemcitabine who had tumors with low hENT-1 expression were worse than the outcomes of patients who had tumors with high hENT-1 expression (17.1 vs 26.2 months; $P$=.002). This was not true for patients who received 5-FU (25.6 vs 21.9 months; $P$=.54).[44] Deoxycytidine kinase (dCK) metabolically activates gemcitabine via phosphorylation, and a high dCK level also may predict response to gemcitabine.

Another retrospective study examined 434 patients, including 243 who received adjuvant gemcitabine. The mOS of patients who were treated with gemcitabine and who had high hENT-1 and dCK levels was better than the mOS of patients who had low levels, which did not hold true for patients who did not receive gemcitabine.[45] However, yet another retrospective analysis showed that low hENT-1 expression in resected PDA was a poor prognostic factor independently of whether patients received gemcitabine.[46] In the RTOG 97-04 trial, patients who had tumors with high rather than low dCK expression had improved OS with 5-FU (HR, 0.56; 95% CI, 0.35-0.88; $P$=.012), but not with gemcitabine (HR, 0.83; 95% CI, 0.51-1.36; $P$=.45).[47] The OS of patients who were treated with gemcitabine and who had tumors expressing hENT-1 was superior to the OS of those who had hENT-1–negative tumors (HR, 0.51; 95% CI, 0.29-0.91; $P$=.02), a finding that did not hold true for 5-FU.[48]

Ribonucleotide reductase regulatory subunit M1 (RRM1) is also thought to be a biomarker for gemcitabine, and combining it with hENT-1 expression may further augment the predictive value of hENT-1 expression.[49] Finally, Hu protein antigen R (HuR) is an mRNA-binding protein that may predict response to gemcitabine, but this also has not been confirmed prospectively.[50]

Although many potential biomarkers exist, large clinical trials are needed to evaluate them prospectively. One potential trial design could include randomly assigning patients to adjuvant therapy based on their expression profile (eg, hENT-1, dCK, RRM1, and HuR).

## Maintenance Therapy

Maintenance chemotherapy may be a promising method to further improve survival in the subset of patients who tolerate and complete adjuvant therapy with no evidence of disease recurrence. Pancreatic cancer cells likely remain locally and systemically despite complete surgical resection. Studies in animal models demonstrate the potential for widely disseminated disease to occur before a visible primary tumor is first detected.[51] Residual PDA cells may lie dormant in G0 arrest and only infrequently enter the G1/S phase, so maintenance chemotherapy may be necessary to maintain pressure on these cells.

The original GITSG study effectively used a maintenance approach by continuing bolus 5-FU for up to 2 years.[3] Several trials have evaluated maintenance chemotherapy in advanced PDA,[52-57] but no prospective studies have been done following adjuvant therapy for patients with resected PDA. We conducted a retrospective analysis comparing patients who received maintenance capecitabine following adjuvant gemcitabine with patients who did not, and a clear survival benefit was noted for patients who received maintenance capecitabine (mOS >48 vs 22 months; $P<.001$).[58] Maintenance capecitabine also needs to be validated in a prospective clinical trial, potentially following the new standard of 6 months of adjuvant gemcitabine plus capecitabine.

## Conclusion

Treatment for patients with resected PDA has come a long way, but there clearly is still a long way to go. Gemcitabine or a fluoropyrimidine for 6 months after resection remains a standard treatment. Newer therapies include gemcitabine/capecitabine and S-1, both of which show superiority to gemcitabine and should be considered new standards of treatment. The role of chemoradiation and its place in the sequence of adjuvant therapy remain debatable. Neoadjuvant options that are commonly used in borderline resectable and locally advanced unresectable disease are intriguing, but they are not yet established for use in resectable disease outside clinical trials. Finally, maintenance chemotherapy may be another effective method for prolonging survival, although this also needs to be validated prospectively. For now, it appears that more is better for patients with resected PDA. Enrollment in a clinical trial must be considered for all patients with resectable disease.

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