Reviews

Current Standards of Chemotherapy for Pancreatic Cancer

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ABSTRACT

Purpose: Pancreatic cancer has a dismal prognosis due to the early development of systemic metastatic disease. Chemotherapeutic agents are the only systemic therapy that offers patients meaningful benefit.

Methods: This study reviewed the literature for recently published Phase III clinical trials whose results have guided the current standards of chemotherapy for pancreatic cancer.

Findings: Although combination chemotherapy regimens are shown to be superior to gemcitabine monotherapy for both metastatic pancreatic cancer and adjuvant chemotherapy after surgical resection, it should be recognized that all combination chemotherapy regimens offer only limited benefits. In addition, there is a paucity of clinical trials that directly compare the various combination chemotherapy regimens.

Implications: With the advancement of systemic cancer treatment beyond chemotherapy, it is important to devote more investigation into better understanding the biology of these chemotherapy regimens, such that we combine them with targeted therapeutics and immunotherapeutics in a rational and scientific manner. For the current treatment of pancreatic cancer, the available chemotherapy regimens have shown modest but statistically significant improvements in survival. However, it is important to avoid cross-comparisons of trials and choose regimens based on patient characteristics and the side-effect profiles of the regimen. (Clin Ther. 2017;39:2125–2134) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: adjuvant, capecitabine, FOLFIRINOX, gemcitabine, liposomal irinotecan metastatic, nab-paclitaxel, pancreatic cancer.

INTRODUCTION

Although pancreatic cancer is the tenth most common cancer among men and eleventh in women, it is the fourth leading cause of cancer death in the United States. Its incidence is also increasing. Over a span of 5 years, from 2009 to 2013, the average annual percentage change in incidence increased by 1% among men and by 1.1% among women. There has been very limited progress in the treatment of pancreatic cancer over the last few decades, with its 5-year survival rate increasing from 2.5% (95% CI, 2.0–3.0) in 1975–1977 to 8.5% (95% CI, 8.0–9.0) in 2006–2012. It is therefore projected to become the second leading cause of cancer mortality before 2030 due to improving therapies for other cancers compared with those for pancreatic cancer. One of the major reasons for the dismal prognosis of pancreatic cancer is its early development of systemic metastatic disease. Although enormous efforts have been enlisted in developing innovative therapies, chemotherapeutic agents are essentially the only systemic treatment that is proven to be effective and also offers a meaningful, albeit limited, prolongation of patients’ lives.

The goal of the present review was to discuss the current standards of chemotherapy for pancreatic adenocarcinoma.

FIRST-LINE SYSTEMIC TREATMENT FOR ADVANCED Pancreatic CANCER

Most patients diagnosed with pancreatic cancer have advanced disease, and their estimated 5-year survival rate is dismal. For the 29% who are diagnosed with regional disease (ie, regional lymph node involvement), the 5-year survival is 10%. Fifty-two...
percent have distant metastases at diagnosis, and their 5-year survival plummets to 2%.

The single agent gemcitabine had been a standard-of-care first-line treatment for advanced pancreatic cancer for 2 decades until the PRODIGE and MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) clinical trials showed that 2 combination chemotherapy regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, respectively, achieved higher response rates and longer median overall survival than gemcitabine (Table I). These 2 combination chemotherapy regimens are the 2 current standard-of-care first-line treatment regimens for advanced pancreatic cancer. They have also become the chemotherapy regimens of choice for neoadjuvant therapy for borderline resectable pancreatic cancer or locally advanced pancreatic cancer.

**FOLFIRINOX**

FOLFIRINOX, the 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin combination, was chosen based on preclinical and clinical studies, suggesting synergy between the different therapies and nonoverlapping toxic effects of the drugs. PRODIGE was a Phase II/III, open-label trial that compared FOLFIRINOX with gemcitabine (171 evaluable patients in each arm) for the treatment of patients with advanced pancreatic cancer. FOLFIRINOX increased the median overall survival by 4.3 months (11.1 vs 6.8 months; hazard ratio [HR], 0.57 [95% CI, 0.45–0.73]; P < 0.001). This outcome was in contrast to the modest improvement in overall survival of 0.33 month with the gemcitabine/erlotinib combination, the only regimen before FOLFIRINOX that improved survival compared with gemcitabine (median overall survival of 6.24 months with gemcitabine/erlotinib and 5.91 months with gemcitabine). Analysis indicated that the survival benefit of FOLFIRINOX was not due to use of subsequent second-line therapy. All subgroups favored FOLFIRINOX for improved survival, except for those with metachronous metastases, ≥ 3 metastatic sites, or a biliary stent, which favored gemcitabine monotherapy.

FOLFIRINOX is notable for its higher incidence of grade 3 to 4 adverse events, including neutropenia (45.7% vs 21.0%), febrile neutropenia (5.4% vs 1.2%), thrombocytopenia (9.1% vs 3.6%), diarrhea (12.7% vs 1.8%), and peripheral neuropathy (9% vs 0%) compared with gemcitabine. However, despite higher rates of grade 3 to 4 toxicity, the initial analysis found that the quality of life was not statistically different during the first 8 cycles of FOLFIRINOX treatment. At 6 months, 31% of patients in the FOLFIRINOX arm had a decrease in quality of life scores compared with 66% in the gemcitabine arm (HR, 0.47 [95% CI, 0.3–0.7]; P < 0.001). Subsequent analysis indicated that there was a statistically significant improvement in quality of life with FOLFIRINOX compared with gemcitabine. This result suggested that disease progression affected the quality of life in patients with advanced pancreatic cancer more than the toxicity of chemotherapy.

**Gemcitabine/Nab-paclitaxel**

MPACT was a Phase III, open-label trial in which 431 patients were randomized to receive gemcitabine/nab-paclitaxel, and 430 were randomized to receive gemcitabine alone. The median overall survival was 8.5 months (95% CI, 7.89–9.53) with gemcitabine/nab-paclitaxel compared with 6.7 months (95% CI, 6.01–7.23) with gemcitabine, with an HR for death of 0.72 (95% CI, 0.62–0.83; P < 0.001). Analysis also showed that the survival benefit of gemcitabine/nab-paclitaxel was not due to use of subsequent second-line therapy. Patients with more advanced disease benefited from the combination treatment (ie, those with metastatic disease at initial diagnosis, liver metastasis, > 3 metastatic sites, carbohydrate antigen 19-9 concentration at or > 59 times the upper limit of normal). There was a trend toward improvement in survival with gemcitabine/nab-paclitaxel compared with gemcitabine alone for those patients aged ≥65 years.

Among the common grade 3 or higher adverse events, the gemcitabine/nab-paclitaxel arm experienced more neutropenia (38% vs 27%), febrile neutropenia (3% vs 1%), fatigue (17% vs 7%), peripheral neuropathy (17% vs 1%), and diarrhea (6% vs 1%) than the gemcitabine arm. However, there were no grade 4 neuropathies in either arm. Neuropathy was cumulative and reversible for most patients after temporary discontinuation of treatment, and some patients could restart therapy at a reduced dose of nab-paclitaxel. Thus, neuropathy caused by gemcitabine/nab-paclitaxel seems to be better tolerated than that caused by FOLFIRINOX.
Table I. Selected randomized Phase III clinical trials investigating first-line systemic treatment for advanced pancreatic cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Studied</th>
<th>Comparison Drug</th>
<th>Indication for Treatment</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burris et al, 1997</td>
<td>Gemcitabine</td>
<td>Bolus 5-FU</td>
<td>First line for advanced stage (locally advanced or metastatic)</td>
<td>Clinical benefit response (pain, KPS, weight), 23.8% gemcitabine vs 4.8% 5-FU (P = 0.0022)</td>
</tr>
<tr>
<td>Cunningham et al, 2009</td>
<td>Gemcitabine/capecitabine</td>
<td>Gemcitabine</td>
<td>First line for advanced stage (locally advanced or metastatic)</td>
<td>Overall survival, median, 7.1 mo gemcitabine/capecitabine vs 6.2 mo gemcitabine (P = 0.08)</td>
</tr>
<tr>
<td>Moore et al, 2007 (NCIC-CTG PA.3)</td>
<td>Gemcitabine/erlotinib</td>
<td>Gemcitabine/placebo</td>
<td>First line for advanced stage (locally advanced or metastatic)</td>
<td>Overall survival, median, 6.24 mo gemcitabine/erlotinib vs 5.91 mo gemcitabine (P = 0.038)</td>
</tr>
<tr>
<td>AIO group (Heinemann et al, 2013)</td>
<td>Capecitabine/erlotinib followed by capecitabine</td>
<td>Gemcitabine/erlotinib followed by gemcitabine</td>
<td>Treatment-naive advanced stage (trial to investigate sequencing of drugs upon failure with first-line)</td>
<td>Time to treatment failure of second-line therapy, 4.2 mo for both arms</td>
</tr>
<tr>
<td>Conroy et al (PRODIGE)</td>
<td>FOLFIRINOX</td>
<td>Gemcitabine</td>
<td>First line for metastatic</td>
<td>Overall survival, median, 11.1 mo FOLFIRINOX vs 6.8 mo gemcitabine (P &lt; 0.001)</td>
</tr>
<tr>
<td>von Hoff et al, 2013 (MPACT)</td>
<td>Gemcitabine/nab-paclitaxel</td>
<td>Gemcitabine</td>
<td>First line for metastatic</td>
<td>Overall survival, median, 8.5 mo gemcitabine/nab-paclitaxel vs 6.7 mo gemcitabine (P &lt; 0.001)</td>
</tr>
<tr>
<td>Ueno et al, 2013 (GEST noninferiority trial)</td>
<td>S-1 monotherapy or gemcitabine/S-1</td>
<td>Gemcitabine</td>
<td>First line for advanced stage (locally advanced or metastatic)</td>
<td>Overall survival, median, 8.8 mo for gemcitabine, 9.7 months for S-1, 10.1 mo for gemcitabine/S-1. S-1 was noninferior to gemcitabine (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

*S-FU = 5-fluorouracil; MPACT = Metastatic Pancreatic Adenocarcinoma Clinical Trial; KPS = Karnofsky Performance Status; NCIC-CTG PA.3 = National Cancer Institute of Canada Clinical Trials Group PA.3.*
FOLFIRINOX Versus Gemcitabine/Nab-paclitaxel

FOLFIRINOX and gemcitabine/nab-paclitaxel have not been compared head-to-head. FOLFIRINOX achieved higher response rates and longer median overall survival than gemcitabine in PRODIGE compared with gemcitabine/nab-paclitaxel against gemcitabine in MPACT. However, without a randomized trial comparing the 2 regimens, we cannot conclude which is more efficacious. Cross-comparisons of trials should be conducted with caution. The 2 trials differed in terms of baseline patient characteristics, diversity of study sites involved, and inclusion of an independent review of results.

The patients in PRODIGE had better prognostic factors than those in MPACT with respect to age, performance status, carbohydrate antigen 19-9 level, and exposure to previous therapy. PRODIGE had a more restrictive enrollment criterion than MPACT, with an age cut-off at 75 years and restriction of performance status to an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1; MPACT had no age cut-off and allowed patients with ECOG performance scores from 0 to 2. In IMPACT, 10% of the patients were aged >75 years, and the oldest patient was 88 years old. PRODIGE pooled data from the Phase II and III portions, and it thus potentially influenced the characteristics of the patients who were enrolled. In addition, PRODIGE was conducted in 48 centers in a single country (France), and MPACT was performed across 151 community and academic centers in 11 countries across 3 continents (North America, Europe, and Australia). This difference in diversity of sites also limits the utility of comparing the 2 trials. Finally, MPACT had both investigator assessment and independent radiographic review for determination of secondary end points (progression-free survival and response rate); their conclusions were similar. PRODIGE had independent review of the CT scans only at the end of Phase II of the study. According to investigator assessment, the objective response rate was essentially identical between FOLFIRINOX and gemcitabine/nab-paclitaxel.

It has become consensus that for patients with good performance status and metastatic disease, both FOLFIRINOX and gemcitabine/nab-paclitaxel are acceptable treatment options. The differences in eligibility criteria (including age and performance status) between PRODIGE and MPACT has led to the current belief that gemcitabine/nab-paclitaxel should be preferred for those patients aged >75 years or with poor performance status. Nevertheless, a retrospective study reported that elderly patients tolerate FOLFIRINOX with a similar side-effect profile and efficacy as long as the doses are adjusted as needed. In this retrospective analysis, 17.3% of the patients had an ECOG performance score ≥2. There is currently an ongoing Phase II trial (PAMELA-70 [Efficacy and Tolerance Evaluation in FOLFIRINOX Dose Adjusted in Elderly Patients with a Metastatic Pancreatic Cancer]) to prospectively evaluate the efficacy and tolerance of dose-adjusted FOLFIRINOX (irinotecan and continuous 5-FU infusion are dose reduced compared with the doses used in PRODIGE) in patients who are aged ≥70 years. It is noteworthy that in a subgroup analysis in MPACT, patients with more metastatic disease burden significantly benefited from the combination of gemcitabine/nab-paclitaxel, whereas in the PRODIGE study, this feature was not shown by FOLFIRINOX. This outcome has led to the notion that gemcitabine/nab-paclitaxel may have a stronger effect in treating metastatic disease than FOLFIRINOX; however, such a notion would need further validation.

Taken together, there may be misconceptions that guide the selection of FOLFIRINOX and gemcitabine/nab-paclitaxel for advanced pancreatic cancer. It should also be recognized that even though chemotherapy is the only systemic therapy that offers meaningful benefit to patients, neither chemotherapy regimen offers durable response. Increased efforts into investigating the biology of these chemotherapy regimens could lead to better understanding how to select the appropriate chemotherapy regimen and how to improve their efficacy when combining these regimens with targeted therapeutics and immunotherapeutics.

SECOND-LINE SYSTEMIC TREATMENT FOR ADVANCED PANCREATIC CANCER

There is no standardization for the treatment of advanced pancreatic cancer after progression through FOLFIRINOX or gemcitabine/nab-paclitaxel. The current clinical practice is to transition to a 5-FU–based regimen if the patient was on a gemcitabine-based regimen or vice versa as long as the patient can tolerate more treatment. Although there are no data
from randomized controlled studies to support this strategy, multiple single-institution, retrospective analyses suggest that gemcitabine/nab-paclitaxel is a reasonable second-line option after FOLFIRINOX.\textsuperscript{22–24}

\textbf{5-FU/Oxaliplatin}

Despite several Phase III trials investigating the role of second-line treatment for advanced pancreatic cancer, they have not standardized current management options (Table II). The Phase III CONKO-003 trial tested the combination of oxaliplatin/5-FU/folinic acid (OFF) as second-line therapy for advanced pancreatic cancer.\textsuperscript{25} OFF differs from FOLFOX (folinic acid, 5-FU, oxaliplatin) in that 5-FU is administered weekly for the first 4 weeks and oxaliplatin is administered on days 8 and 22 of a 6-week cycle, whereas FOLFOX includes infusional 5-FU and is given every 2 weeks. The median overall survival improved with OFF (5.9 months; 95% CI, 4.1–7.4) compared with the folinic acid/5-FU (FF) arm (3.3 months; 95% CI, 2.7–4.0) with an HR of 0.66 (95% CI, 0.48–0.91; log-rank test, \( P = 0.01 \)). Time to progression also improved with OFF (2.9 months; 95% CI, 2.4–3.2) compared with FF (2.0 months; 95% CI, 1.6–2.3) with an HR of 0.68 (95% CI, 0.50 to 0.94; log-rank test, \( P = 0.019 \)). There were several issues with this clinical trial. Best supportive care was initially the comparison arm, but the trial was terminated due to insufficient accrual and was reopened with change of comparison arm to FF. This modification left the trial with a small sample size of 76 patients analyzed in the OFF arm and 84 in the FF arm. The benefit of the 5-FU/oxaliplatin combination as second-line therapy was not validated in the subsequent Phase III PANCREOX (A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy) trial evaluating FOLFOX.\textsuperscript{26} Again, PANCREOX only enrolled a small sample size of 54 patients in each arm and closed before its target enrollment of 128 patients per arm because of slow accrual (there was a decrease in eligible patients after FOLFIRINOX became available as first-line therapy). PANCREOX found no difference in median progression-free survival between 3.1 months for mFOLFOX6 (modified FOLFIRINOX) and 2.9 months for 5-FU/leucovorin (5-FU/LV) (\( P = 0.989 \)). Median overall survival was inferior in the mFOLFOX6 arm compared with the 5-FU/LV arm (6.1 vs 9.9 months; \( P = 0.024 \)). Before making conclusions regarding the role of 5-FU/oxaliplatin as second-line therapy, one should note several differences between CONKO-003 and PANCREOX that may explain the difference in outcome between the 2 trials. PANCREOX included patients up to an ECOG performance status of 2, whereas CONKO limited enrollment to patients with a Karnofsky Performance Status score \( \geq 70\% \). More patients in PANCREOX had alterations and/or discontinuation of treatment, which could be attributed to poor performance status or more intense dosing of oxaliplatin in the FOLFOX regimen. The eligibility in CONKO-003 required progression while on gemcitabine, but PANCREOX allowed progression whether on or off gemcitabine as long as the patient had been treated with it before. Moreover, there was more use of post-progression therapy in the 5-FU/LV arm versus the FOLFOX arm (25% vs 7%; \( P = 0.015 \)) in PANCREOX. Therefore, it remains inconclusive whether 5-FU/oxaliplatin should be used as a second-line therapy.

\textbf{5-FU/Liposomal Irinotecan}

The regimen of 5-FU/liposomal irinotecan as a standard-of-care second-line therapy is supported by Level I evidence from the NAPOLI-1 trial.\textsuperscript{27} In NAPOLI-1, an international Phase III study, patients with metastatic pancreatic cancer whose disease progressed on previous gemcitabine therapy were randomized to receive either nanoliposomal irinotecan, 5-FU/LV, or nanoliposomal irinotecan/5-FU/LV. Median overall survival improved with the nanoliposomal irinotecan/5-FU/LV combination to 6.1 months (95% CI, 4.8–8.9) compared with nanoliposomal irinotecan (4.9 months) and 5-FU/LV (4.2 months). Objective response was 16% with nanoliposomal irinotecan/5-FU/LV (\( P < 0.0001 \) compared with 5-FU/LV), 6% with nanoliposomal irinotecan (\( P = 0.02 \) compared with 5-FU/LV), and 1% with 5-FU/LV. Even though grade 3 to 4 adverse events were more common with nanoliposomal irinotecan/5-FU/LV (27% neutropenia vs 15% with nanoliposomal irinotecan monotherapy vs 1% with 5-FU/LV; 13% diarrhea vs 21% vs 4%; 11% vomiting vs 14% vs 3%; 14% fatigue vs 6% vs 4%), there was no decrease in quality of life at 6 weeks and 12 weeks from baseline.
Table II. Selected randomized Phase III clinical trials investigating systemic treatment for progressive advanced pancreatic cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Studied</th>
<th>Comparison Drug</th>
<th>Indication for Treatment</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO-003</td>
<td>Oxaliplatin/5-FU/</td>
<td>S-FU/LV</td>
<td>Second line for advanced stage after progression while receiving first-line gemcitabine</td>
<td>Overall survival, median, 5.9 mo OFF vs 3.3 mo 5-FU/LV ($P = 0.01$)</td>
</tr>
<tr>
<td>(Pelzer U et al, 2011)</td>
<td>Folinic Acid (OFF)</td>
<td></td>
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<tr>
<td>PANCREOX (Gill et al, 2016)</td>
<td>mFOLFOX6 (infusional S-FU, LV, oxaliplatin)</td>
<td>Infusional S-FU/LV</td>
<td>Second line for progressive advanced stage, must have had gemcitabine as first-line therapy</td>
<td>Progression-free survival, median, 3.1 mo mFOLFOX6 vs 2.9 mo S-FU/LV ($P = 0.989$)</td>
</tr>
<tr>
<td>NAPOLI-1</td>
<td>5-FU/LV</td>
<td>NPiri monotherapy or NPiri/5-FU/LV</td>
<td>Subsequent-line treatment for metastatic disease, must have had prior gemcitabine</td>
<td>Overall survival, median, 6.1 mo NPiri/5-FU/LV vs 4.2 months 5-FU/LV ($P = 0.012$); 4.9 mo NPiri vs 4.2 mo 5-FU/LV ($P = 0.94$)</td>
</tr>
<tr>
<td>(Wang-Gillam et al, 2016)</td>
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</tbody>
</table>

5-FU = 5-fluorouracil; NPiri = nanoliposomal irinotecan; LV = leucovorin; PANCREOX = A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy.
5-FU/Liposomal Irinotecan Versus 5-FU/Oxaliplatin Versus FOLFIRINOX

Currently, 5-FU/liposomal irinotecan is the regimen supported by the strongest level of evidence for second-line treatment, but there is still no consensus on how to select treatment for pancreatic cancer upon progression of disease. Because FOLFIRINOX is one of the standard-of-care first-line options, it would be reasonable to consider gemcitabine/nab-paclitaxel as the second-line therapy after progression on FOLFIRINOX. Because the components of FOLFIRINOX do not overlap with gemcitabine/nab-paclitaxel, it would be reasonable to choose FOLFIRINOX as the next line after progression on gemcitabine-based therapy for patients who can tolerate aggressive therapy. Nevertheless, one cannot assume that FOLFIRINOX is superior to 5-FU/liposomal irinotecan in efficacy. All the potential second-line options offer limited survival benefit; thus, the selection of second-line therapies should be individualized with an emphasis on minimizing side effects and maximizing quality of life. The preferable option is to refer the patients to a clinical trial for second-line therapy.

SYSTEMIC ADJUVANT TREATMENT

Surgical resection of localized disease is the only hope for a cure in patients with pancreatic cancer. However, only ~20% of patients have resectable disease at diagnosis, and the median overall survival is still only ~22 to 26 months due to the high recurrence rate despite adjuvant treatment.19 Gemcitabine monotherapy has been the stalwart for adjuvant chemotherapy in the United States for several decades, but evidence to support it as standard of care was only established in 2007 by the CONKO-001 study.28 In subsequent years, notable Phase III randomized trials included ESPAC (European Study Group for Pancreatic Cancer)-329 and JASPAC-01 (Japan Adjuvant Study Group of Pancreatic Cancer),30 which compared gemcitabine versus bolus 5-FU/LV and S-1 (contains an oral prodrug of 5-FU), respectively (Table III). ESPAC-3 showed that there was no statistically significant difference in median overall survival between gemcitabine (23.6 months [95% CI, 21.4–26.4]) and bolus 5-FU/LV (23.0 months [95% CI, 21.1–25.0]) with an HR of 0.94 (95% CI, 0.81–1.08). JASPAC-01 was a noninferiority trial in which S-1 was not only

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Studied</th>
<th>Comparison</th>
<th>Drug</th>
<th>Indication for Treatment</th>
<th>Primary Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO-001 (Oettle et al,28 2007)</td>
<td>Gemcitabine</td>
<td>Observation</td>
<td>Gemcitabine vs observation</td>
<td>Disease-free survival, median, 13.4 mo</td>
<td>gemcitabine vs observation (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>ESPAC-3 (Neoptolemos et al,29 2010)</td>
<td>Gemcitabine</td>
<td>Gemcitabine vs bolus 5-FU/leucovorin</td>
<td>Overall survival, median, 23 mo</td>
<td>5-FU/leucovorin vs gemcitabine (P = 0.39)</td>
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</tr>
<tr>
<td>JASPAC-01 (Uesaka et al,30 2016; noninferiority trial)</td>
<td>Gemcitabine vs S-1</td>
<td>First-line adjuvant vs first-line adjuvant</td>
<td>Overall survival, median, 46.1 mo</td>
<td>S-1 vs 25.5 mo gemcitabine</td>
<td>S-1 is noninferior to gemcitabine for overall survival (P = 0.001; noninferiority P &lt; 0.001 for superiority)</td>
<td></td>
</tr>
<tr>
<td>ESPAC-4 (Neoptolemos et al,31 2017)</td>
<td>Gemcitabine vs capecitabine</td>
<td>Gemcitabine vs capecitabine</td>
<td>Overall survival, median, 28 mo</td>
<td>Gemcitabine vs capecitabine (P = 0.032)</td>
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</table>

ESPAC = European Study Group for Pancreatic Cancer; JASPAC-01 = Japan Adjuvant Study Group of Pancreatic Cancer.
noninferior ($P < 0.001$) but also superior ($P < 0.001$) to gemcitabine, with a median overall survival of 25.5 months (95% CI, 22.5–29.6) with gemcitabine compared with 46.5 months (95% CI, 37.8–63.7) with S-1. In East Asia, S-1 subsequently became the standard-of-care adjuvant chemotherapy.

In Europe, the results of ESPAC-3 were intriguing enough to pursue investigation into the combination of gemcitabine and an orally available prodrug of 5-FU in ESPAC-4.\textsuperscript{31} In this Phase III trial, patients were randomized to receive adjuvant gemcitabine or to the combination of gemcitabine and capecitabine (GemCap) after R0 or R1 surgical resections. The combination arm improved median survival by 2.5 months compared with gemcitabine alone (28 vs 25.5 months, respectively; HR, 0.82; $P = 0.032$). The estimated 5-year survival in the combination arm was 28.8% compared with 16.3% in the gemcitabine alone arm. This improvement in survival with GemCap did not come with an increase in serious adverse events (26% for gemcitabine vs 24% for GemCap; $P > 0.05$). Thus, ESPAC-4 has established a new standard-of-care adjuvant chemotherapy in Europe and North America.

### Table IV. Selected ongoing randomized Phase III clinical trials investigating systemic therapy.

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Indication for treatment</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic pancreatic cancer</td>
<td>First-line metastatic therapy</td>
<td>Napabucasin plus nab-paclitaxel/gemcitabine vs nab-paclitaxel/gemcitabine</td>
</tr>
<tr>
<td>Metastatic pancreatic cancer</td>
<td>First-line metastatic therapy</td>
<td>PEGPH20 plus nab-paclitaxel/gemcitabine vs placebo plus nab-paclitaxel/gemcitabine</td>
</tr>
<tr>
<td>Locally advanced or metastatic pancreatic cancer</td>
<td>First-line advanced therapy</td>
<td>NC-6004 with gemcitabine vs gemcitabine alone</td>
</tr>
<tr>
<td>gBRCA-mutated metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy</td>
<td>Patients are on treatment with a first-line platinum-based metastatic therapy without progression</td>
<td>Maintenance olaparib monotherapy vs placebo</td>
</tr>
<tr>
<td>K-RAS wild-type locally advanced and metastatic pancreatic cancer</td>
<td>Must have had no antitumor palliative chemotherapy or molecularly targeted therapy. Adjuvant therapy must have been &gt;6 mo prior</td>
<td>Nimotuzumab with gemcitabine vs placebo with gemcitabine</td>
</tr>
<tr>
<td>Locally advanced and/or metastatic pancreatic cancer that failed FOLFIRINOX</td>
<td>Second-line metastatic therapy</td>
<td>EndoTAG-1 plus gemcitabine vs gemcitabine alone</td>
</tr>
<tr>
<td>Metastatic pancreatic cancer previously treated with gemcitabine</td>
<td>Second-line metastatic therapy</td>
<td>Glufosfamide vs fluorouracil</td>
</tr>
<tr>
<td>Metastatic pancreatic cancer whose disease has progressed during or after a first-line gemcitabine-containing regimen</td>
<td>Second-line metastatic therapy</td>
<td>AM0010 with FOLFOX vs FOLFOX alone</td>
</tr>
<tr>
<td>Locally advanced or metastatic pancreatic cancer</td>
<td>Second-line therapy for progressive advanced pancreatic cancer or progression after resection</td>
<td>GV1001 with gemcitabine/capecitabine vs gemcitabine/capecitabine alone</td>
</tr>
</tbody>
</table>
ONGOING PHASE III TRIALS TESTING INNOVATIVE THERAPEUTIC AGENTS

Chemotherapeutic agents, even in combination, offer only limited benefit to patients. Therefore, investigational agents are being combined with the chemotherapy regimens discussed earlier (Table IV). Current Phase III trials include the addition of a STAT3 inhibitor (napabucasin), an epidermal growth factor receptor inhibitor (nimotuzumab), a poly(ADP-ribose) polymerase inhibitor (olaparib), and a stroma-targeting agent (PEGPH20-pegylated hyaluronidase) to chemotherapy. Chemotherapy agents are also being altered to increase efficacy, such as nanoparticle-based cisplatin (N-6004) and liposomal paclitaxel (EndoTAG-1) or a next-generation version of ifosfamide (glufosfamide). Immune-based therapeutic agents such as vaccines (GV1001, which contains fragments of telomerase) and cytokines (pegylated interleukin-10) are also being combined with chemotherapy in Phase III clinical trials.

Many previous Phase III studies have failed, and the inappropriate combination of experimental agents without strong biological rationale and lack of biomarkers to select proper candidates for experimental therapeutics are often the 2 main reasons for the failure. Thus, the design of future Phase III trials should be based on in-depth analysis of mechanism of action of the experimental therapeutics. Clinical trials testing innovative agents should actively search for prognostic and predictive biomarkers.

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AUTHOR CONTRIBUTIONS

M.T.S. reviewed the literature and wrote the manuscript; L.Z. designed the concept, wrote and revised the manuscripts.

CONFLICTS OF INTEREST

Under a licensing agreement between Aduro Biotech and Johns Hopkins University, the University and Dr. Zheng are entitled to milestone payments and royalty on sales of the granulocyte macrophage-colony stimulating factor–secrating tumor vaccine product GVAX. Dr. Zheng receives grant supports from Bristol-Myers Squibb, Merck, iTeos, Amgen, Gardasil, and Halozyme; and also served on the advisory board for Merrimack. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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