Randomized Clinical Trials in Pancreatic Cancer

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KEYWORDS

• Randomized trials • Pancreatic cancer • Chemotherapy • Chemoradiation
• Randomized control trails

KEY POINTS

- To gain a thorough understanding of the evolution of pancreatic cancer management.
- To discuss the most recent level 1a evidence for management of pancreatic cancer.
- To discuss the future of pancreatic cancer management and ongoing clinical trials.

REVIEW OF OLDER ADJUVANT TRIALS

Adjuvant Chemotherapy

The CONKO-001 (Charite Onkologie 001) trial was designed to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete curative resection for pancreatic cancer.[1] Three-hundred and sixty-eight patients without prior chemotherapy or radiation were randomized to 6 cycles of standard-dose gemcitabine or observation, following complete resection. More than 80% of patients had an R0 resection. During median follow-up of 53 months, 133 patients (74%) in the gemcitabine group and 161 patients (92%) in the control group developed recurrent disease. Median disease-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group ($P<.001$). Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. There was no difference in overall survival between the gemcitabine group and the control group (median, 22.1 months and 20.2 months, respectively; $P = .06$). However, there were differences in estimated 3-year and 5-year survival. In the gemcitabine group, the estimated survivals were 34% at 3 years and 22.5% at 5 years compared with the control group, in which estimated survivals were 20.5% at 3 years and 11.5% at 5 years. This study has been criticized for its high local failure rate (92% in

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observation arm). Nevertheless, this study further strengthened the efficacy of gemcitabine-based chemotherapy for patients in the adjuvant setting.

Long-term outcomes analyzing whether the previously reported improvement in disease-free survival with adjuvant gemcitabine therapy translated into improved overall survival were published in *JAMA* in 2013. With a median follow-up of 136 months, long-term follow-up of the CONKO-001 study showed a significant improvement in overall survival that favors gemcitabine (median survival, 22.8 months vs 20.2 months; $P = .01$). The median disease-free survival was 13.4 months in the treatment group compared with 6.7 months in the observation group ($P<.001$). Gemcitabine compared with observation alone yielded improved survival rates at 5 years of 20.7% for the gemcitabine arm versus 10.4% for the observation-alone arm, and at 10 years the survival rates were 12.2% for the gemcitabine arm versus 7.7% for the observation-alone arm. Thus, among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 months compared with observation alone resulted in increased overall survival as well as disease-free survival. These findings provide strong support for the use of gemcitabine in this setting.[2]

Adjuvant Chemoradiation

The Gastrointestinal Tumor Study Group (GITSG) trial published in 1985 was one of the first phase III trials exploring the role of adjuvant therapy in pancreas adenocarcinoma. The GITSG trial reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold with adjuvant chemoradiation.[3] Patients were randomly assigned to either observation or radiation therapy (RT) combined with an intermittent bolus of 5-fluorouracil (5-FU) postresection. A standard split course of 4000 cGy was used. 5-FU, 500 mg/m^2 daily for 3 days, was given concurrently with each 2000-cGy segment of RT. The 5-FU regimen was then continued weekly for 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group. Criticisms of this study include having a small patient population and inadequate quality assurance of RT. Furthermore, although patients in this study derived a survival benefit with adjuvant treatment, it is unclear whether the benefit was from the systemic chemotherapy or the chemoradiation or both. 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.[4]

The European Organisation for Research and Treatment of Cancer (EORTC) 40891 trial was a large multicenter phase III study of patients with resected pancreatic head cancer and periampullary tumors performed to investigate the results of the GITSG trial from 1985, and reported their 5-year and 10-year follow-up. Two-hundred and eighty patients with resected cancers of the pancreatic head or periampullary region were randomized to surgery alone or surgery and chemoradiation (5-FU and 40 Gy). Subgroup analysis of 114 patients with pancreatic head cancers revealed a trend toward improved overall survival for those who received adjuvant therapy compared with the surgery-only arm (median, 17.1 months vs 12.6 months), but this difference was not statistically significant ($P = .99$). Long-term results in the patients with pancreatic head cancer over a greater than 10-year follow-up period reported median survivals of 1.3 and 1 year, which were not statistically significant. Overall, unlike the previous, much smaller 43-patient GITSG trial, EORTC-40891 did not support the benefit of 5-FU-based chemoradiation.[5]

The European Study Group of Pancreatic Cancer (ESPAC)-1 trial further investigated the impact of chemoradiation and suggested that chemotherapy alone

provided a survival benefit in the adjuvant setting. ESPAC-1 enrolled 541 patients who were randomized to one of 4 arms: observation, chemotherapy with bolus 5-FU and leucovorin, radiation (20 Gy) plus bolus 5-FU during the first 3 days of split-course external beam RT (EBRT), or radiation followed by 6 months of chemotherapy with bolus 5-FU and leucovorin. The study analyzed the survival outcomes using a 2 × 2 factorial design, pooling survival data based on randomization to chemotherapy (yes or no) or chemoradiation (yes or no). Median follow-up of the 227 patients (42%) still alive was 10 months (range, 0–62). Results showed no benefit for adjuvant chemoradiotherapy (median survival, 15.5 months in 175 patients with chemoradiotherapy vs 16.1 months in 178 patients without; $P = .24$). There was evidence of a survival benefit for adjuvant chemotherapy (median survival, 19.7 months in 238 patients with chemotherapy vs 14.0 months in 235 patients without; $P = .0005$). The investigators concluded that this study showed no survival benefit for adjuvant chemoradiotherapy but revealed a potential benefit for adjuvant chemotherapy.[6]

Final results of this study published in 2004 showed an estimated 5-year survival rate of 10% among patients assigned to receive chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy ($P = .05$). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy ($P = .009$). This study further supported the previously described significant survival benefit of chemotherapy, and deleterious effect of chemoradiation, in the adjuvant setting.[7]

The ESPAC-1 trial has been criticized for lack of standardized trial methodology, the large number of patients who did not receive the intended therapy (31% to receive chemotherapy and 19% to receive chemoradiation did not receive it), and its high local recurrence rate >60%.[4] Despite the various limitations of the study, ESPAC-1 led to a trend away from chemoradiation in Europe and beyond in favor of systemic chemotherapy alone as the main adjuvant treatment choice for resected pancreas adenocarcinoma. Regardless, ESPAC-1 remains the first randomized controlled trial (RCT) to show a statistically significant benefit of adjuvant systemic therapy alone in resected pancreas cancer.[6]

At approximately the same time as the CONKO-001 study was being conducted in Germany and Austria, investigators in North America conducted the Radiation Therapy Oncology Group (RTOG) 9704 study. RTOG 9704 was a phase III trial to determine whether the addition of gemcitabine to adjuvant 5-FU chemoradiation improved survival in patients with resected pancreatic adenocarcinoma. RTOG 9704 was a phase III study that evaluated postoperative adjuvant treatment of resected pancreatic adenocarcinoma using either gemcitabine or 5-FU for 3 weeks before and 12 weeks after 5-FU–based chemoradiation for both groups.[8] This trial, which used daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative computed tomography imaging and radiation fields. For patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non–statistically significant increase in overall survival in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months vs 16.9 months; $P = .05$).[8]

The 5-year analysis of RTOG 9704 showed that there was no difference in overall survival between the two groups, although patients with tumors in the head of the pancreas showed a trend toward improved overall survival with gemcitabine ($P = .08$) on multivariate analysis.[9] Although not statistically significant, the investigators concluded that the addition of gemcitabine given before and after chemoradiation was associated with a survival benefit in the adjuvant setting. The major

criticisms of this trial included the lack of a radiation-only arm and that at least 50% of patients had an unknown or positive margin.[4] A follow-up study by Abrams and colleagues[10] on the RTOG 9704 in 2010 noted that, on multivariate analysis for patients with pancreatic head tumors, adherence to RT per protocol and gemcitabine treatment were both correlated with improved median survival ($P = .016$ and $P = .043$, respectively). Therefore, the investigators further concluded that it was a failure to adhere to specified RT guidelines during the trial that was associated with reduced survival (**Table 1**).

RECENT ERA OF ADJUVANT THERAPY

Adjuvant Chemotherapy

In more recent years, the ESPAC investigators began to build on results from their ESPAC-1 trial. The ESPAC-3(v1) trial was developed as an initial 3-arm study randomizing patients with resected pancreas adenocarcinoma to adjuvant 5-FU and leucovorin versus gemcitabine versus observation. Chemoradiation was not evaluated in this study. As the ESPAC-1 trial results were finalized showing a benefit to adjuvant 5-FU, the observation arm for ESPAC-3(v1) was removed, and ESPAC-3 (v2) accrued a total of 1088 patients from 2000 to 2007. The ESPAC-3 (NCT00058201) trial randomly assigned 1088 patients who had undergone complete macroscopic resection to either 6 months of 5-FU and leucovorin or 6 months of gemcitabine. The primary end point of the study was 2-year overall survival. The final analysis was performed after a median follow-up of 34.2 months and revealed equivalency between the 2 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 only 7.5% of patients treated with gemcitabine ($P<.001$). Based on these results, the ESPAC-3 trial argued that adjuvant gemcitabine should be the

Table 1
Overall survival data from older prospective, randomized trials of adjuvant therapy in resected pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
CONKO-001	368	Chemotherapy (gemcitabine) vs observation	22.1 vs 20.1 Long follow-up: 22.8 vs 20.2	.06 .01	1a
GITSG	43	Observation or radiation/bolus 5-FU	20 vs 11	Not reported	1a
ESPAC-1	541	Chemoradiation (5-FU, 20 Gy) vs no chemoradiation Chemotherapy vs observation	15.5 vs 16.1 19.7 vs 14.0	.24 .0005	1a
EORTC 40,891	114	Chemoradiation (5-FU 1 40 Gy EBRT) vs observation	17.1 vs 12.6	.99	1a
RTOG 9704	451	Gemcitabine and 5-FU 1 50.4 Gy EBRT vs 5-FU 1 50.4 Gy EBRT	20.5 vs 16.9	.05	1a

standard of care based on similar survival to, and less toxicity than, adjuvant 5-FU/leucovorin.[11] Nevertheless, this study also supported the use of 5-FU/leucovorin when gemcitabine cannot be safely continued or administered, such as in patients with a history of gemcitabine-related pneumonitis, hemolytic uremic syndrome, or idiopathic pulmonary fibrosis in which there is a high risk of gemcitabine-related pneumonitis.[11]

In March of 2017, the results of the ESPAC-4 phase III, multicenter, randomized trial in which gemcitabine combined with capecitabine was compared with gemcitabine monotherapy for the adjuvant setting were published. Patients were randomly, within 12 weeks of surgery, to receive 6 cycles of either gemcitabine alone administered once a week for 3 of every 4 weeks (1 cycle) or oral capecitabine administered for 21 days followed by 7 days' rest (1 cycle). The primary end point was overall survival, measured as the time from randomization until death from any cause, and assessed in the intention-to-treat population. Of 732 patients enrolled, 730 were included in the final analysis. Of these, 366 were randomly assigned to receive gemcitabine and 364 to gemcitabine plus capecitabine. The median overall survival for patients in the gemcitabine plus capecitabine group was 28.0 months compared with 25.5 months in the gemcitabine group ($P = .032$). Six-hundred and eight grade 3 to 4 adverse events were reported by 226 of 359 patients in the gemcitabine plus capecitabine group compared with 481 grade 3 to 4 adverse events in 196 of 366 patients in the gemcitabine group. This study concluded that the adjuvant combination of gemcitabine and capecitabine should be the new standard of care following resection for pancreatic ductal adenocarcinoma.[12]

In July 2016 the results of the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01 trial suggested that S-1, an oral fluoropyrimidine designed with the aim of improving antitumor activity and reducing the toxicity of 5-FU, seems to be not only noninferior to gemcitabine but also superior to gemcitabine in the adjuvant setting for the Japanese patient subpopulation. This study investigated the noninferiority of S-1 to gemcitabine as adjuvant chemotherapy for pancreatic cancer in terms of overall survival. Three-hundred and eighty-five patients with resected pancreas adenocarcinoma from 2007 to 2010 were randomized to 6 cycles of intravenous gemcitabine or 4 cycles of oral S-1. The study was a noninferiority study with 80% power with the primary end point of overall survival. Median overall survival was greater for S-1 at 46.5 months compared with gemcitabine at 25.5 months. Three-year and 5-year survival rates were 59.7% and 44.1%, respectively, for S-1, and 38.8% and 24.4%, respectively, for gemcitabine. S-1 was generally well tolerated, and the treatment of patients randomized to receive gemcitabine was more likely to be discontinued, relative to the treatment of patients randomized to receive S-1 ($P = .005$). Although the results are impressive, it is unclear whether the survival benefit with adjuvant S-1 will translate to a broader population. Specifically, white people receiving S-1 have been known to develop more severe gastrointestinal toxicities compared with Asian people, possibly because of metabolic and pharmacogenomic differences between the populations. Therefore, lower doses of S-1 may be required if S-1 is introduced to a broader patient population, which could affect the overall efficacy of the drug in the adjuvant setting.[13]

Adjuvant Chemoradiation

The role of adjuvant chemoradiation therapy (CRT) in resectable pancreatic cancer is still debated. The EORTC-40013-22012/FFCD-9203/GERCOR randomized phase II intergroup study explores the feasibility and tolerability of a gemcitabine-based CRT regimen after R0 resection of pancreatic head cancer. Within 8 weeks after surgery, patients were randomly assigned to receive either 4 cycles of gemcitabine (control

arm) or gemcitabine for 2 cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to exclude a less than 60% treatment completion and a greater than 40% rate of grade 4 hematologic or gastrointestinal toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival, and overall survival. Between September 2004 and January 2007, 90 patients were randomly assigned. No differences were seen in overall survival (24.4 months vs 24.3 months) or disease-free survival (10.9 months vs 11.8 months) between the groups, but, with only 45 patients in each arm, no *P* values were reported. The investigators concluded that adjuvant gemcitabine-based CRT is feasible, well tolerated, and not deleterious. Adding this treatment to full-dose adjuvant gemcitabine after resection of pancreatic cancer should be evaluated in a phase III trial.[14]

In addition, the multicenter, open-label, randomized, phase III CapRI trial evaluated adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b (IFN α-2b) followed by 5-FU chemotherapy compared with 5-FU alone. Between 2004 and 2007, 132 R0/R1 resected patients received FU, cisplatin, and IFN α-2b plus radiotherapy followed by 2 cycles of FU (arm A, n = 64) or 6 cycles of FU monotherapy (arm B, n = 68). One-hundred and ten patients (arm A, n = 53; arm B, n = 57) received at least 1 dose of the study medication, and these patients composed the per-protocol (PP) population. Biomarkers were analyzed longitudinally for their predictive value. Median survival for all randomly assigned patients was 26.5 months in arm A and 28.5 months in arm B. Median survival for the PP population was 32.1 months in arm A and 28.5 months in arm B ($P = .49$). Eighty-five percent of patients in arm A and 16% of patients in arm B experienced grade 3 or 4 toxicity. The quality of life was temporarily negatively affected in arm A. This study concluded that the 5-FU, cisplatin, and IFN α-2b plus radiotherapy regimen did not improve the survival compared with 5-FU monotherapy.[15]

Adjuvant Targeted Therapy

The CONKO-005 (DRKS00000247) phase III randomized trial has completed recruitment and is currently in the follow-up phase. This study evaluated gemcitabine plus erlotinib compared with gemcitabine alone in patients with R0 resected pancreas cancer. The primary end point of the study was relapse-free survival based on 436 patients. Two-hundred and nineteen patients were randomized to gemcitabine/erlotinib and 217 to gemcitabine. Preliminary results presented at American Society of Clinical Oncology (ASCO) in 2015 revealed that this combination regimen did not significantly improve overall survival or disease-free survival, compared with gemcitabine monotherapy. Median disease-free survival for gemcitabine/erlotinib was 11.6 months versus 11.6 months for gemcitabine alone. Median overall survival for gemcitabine/erlotinib was24.6 months compared with 26.5 months for gemcitabine alone. Based on the data discussed earlier, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time.[16]

Adjuvant Immunotherapy

An area of increasing research in the adjuvant setting for pancreas adenocarcinoma has been the development of the use of vaccinations and immunotherapy. A vaccine composed of long synthetic mutant ras peptides designed mainly to elicit T-helper responses was developed for KRAS mutated pancreatic adenocarcinomas. A small phase I/II trial of 23 patients treated with a KRAS vaccine in the adjuvant setting showed an immune response to the vaccine in 85% of patients with a median survival of 28 months. The 5-year survival was 22% for all patients and 29% for responders.

The 10-year survival was 20% (4 out of 20) versus 0% (0 out of 87) in a cohort of non-vaccinated patients treated in the same period. The present observation of long-term immune response together with 10-year survival following surgical resection indicates that KRAS vaccination may consolidate the effect of surgery and represent an adjuvant treatment option for the future.[17]

Another target besides KRAS has been telomerase. A recent phase III randomized trial of 1062 patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine and capecitabine with or without the telomerase vaccination (GV1001) found that there was no significant overall survival benefit with the addition of GV1001 to chemotherapy, compared with chemotherapy alone.[18]

Allogeneic granulocyte-macrophage colony-stimulating factor (GM-CSF)–secreting pancreatic tumor vaccines have also been studied. Investigators at the Johns Hopkins University developed an allogeneic whole-cell GM-CSF vaccine (GVAX). A phase I trial studying adjuvant GVAX revealed that 3 of 14 patients treated with the vaccine and chemoradiation developed specific immunity. Mean disease-free survival for this vaccine study was 13 months, although 3 patients were still disease free at 25 to 30 months. The investigators concluded that this vaccine approach seems to induce dose-dependent systemic antitumor immunity as measured by increased postvaccination delayed-type hypersensitivity responses against autologous tumors.[19] A follow-up single-arm phase II trial of approximately 60 patients treated with GVAX in the adjuvant setting found that there was no improvement in survival compared with a contemporary patient cohort treated without the vaccine at the same institution.[20]

Overall, no vaccines or immunotherapies have shown significant improvements in overall survival in phase III clinical trials of patients with resected pancreas adenocarcinoma. However, new agents are continually being developed and studied. Using the concept of hyperacute rejection, a vaccine (algenpantucel-L) has been developed using genetically modified pancreas cancer cells with a mouse gene leading to foreign protein expression of alpha (1,3)-galactosyl (αGal). Preexisting anti-αGal antibodies then trigger a significant immune response leading to cell destruction of any tumor cells in patients undergoing treatment with this form of immunotherapy.[21,22] 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 the adjuvant setting showed an impressive 1-year disease-free survival of 63% and overall survival of 86%, which is encouraging based on historical controls.[23]

Ongoing Adjuvant Trials

Ongoing clinical trials in the adjuvant setting include RTOG 0848 (NCT01013649), which is assessing gemcitabine with or without subsequent chemoradiation; a phase II study comparing FOLFIRINOX with albumin-bound paclitaxel (NCT02243007); the Advanced Pancreatic Adenocarcinoma Clinical Trial study (NCT01964430), comparing albumin-bound paclitaxel with gemcitabine; and the Immunotherapy for Pancreatic Resectable cancer Study trial, which is comparing gemcitabine (with or without chemoradiation) with and without algenpantucel-L immunotherapy (NCT01072981). A phase III trial of chemotherapy and chemoradiotherapy with or without algenpantucel-L immunotherapy in 722 subjects with surgically resected pancreatic cancer recently completed recruitment in May 2016 with pending results (**Table 2**) (NCT01072981).

NEOADJUVANT THERAPY IN BORDERLINE RESECTABLE DISEASE

Patients with borderline resectable disease should be considered for neoadjuvant therapy, followed by restaging and resection in patients without disease progression.

Table 2
Overall survival data from recent prospective, randomized trials of adjuvant therapy in resected pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
ESPAC-3	1088	5-FU and leucovorin or gemcitabine	23 vs 23.6	.39	1a
ESPAC-4	732	Gemcitabine/capecitabine or gemcitabine	28.0 vs 25.5	.032	1a
JASPAC-01	385	Gemcitabine or S-1	25.2 vs 46.5	.005	1b
EORTC-40013-22012/ FFCD-9203/ GERCOR	90	Gemcitabine or gemcitabine/50.4 Gy	24.4 vs 24.3	Not reported	1b
CapRI trial	132	Chemoradiation with 5-FU, cisplatin, and IFN α-2b followed by 5-FU chemotherapy or 5-FU alone	26.5 vs 28.5	.49	1b

The use of neoadjuvant therapy in the setting of borderline resectable disease has been highly debated and is supported mainly by trials at the phase I and phase II levels. Nevertheless, according to the 2016 National Comprehensive Cancer Network (NCCN) guidelines, up-front resection in patients with borderline resectable disease is no longer recommended because it is becoming clear that patients with borderline resectable pancreatic cancer, especially those at high risk for R1 resections, need a different management strategy. More recent approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving overall survival. The theoretic benefits of neoadjuvant therapy include a higher chance of patients completing chemotherapy and/or radiation in the preoperative setting given they are not debilitated after surgery. In addition, there is the potential benefit of downsizing tumors or shrinking them away from vasculature, allowing an R0 resection. Neoadjuvant chemotherapy also has the potential to select for those patients with more stable disease or disease that is responsive to therapy. There is the potential benefit of treating micrometastases at an earlier stage. Surgery following neoadjuvant treatment seems to be safe.[24,25]

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well tolerated. E1200, a randomized phase I/II trial of neoadjuvant therapy in borderline resectable disease, eventually allowed 5 of 21 patients to be resected posttherapy. This trial was designed to assess toxicities and surgical resection rates in 2 neoadjuvant gemcitabine–based chemoradiation regimens in patients with borderline resectable pancreatic cancer. Arm A patients (n = 10) received gemcitabine weekly for 6 weeks, with radiation followed by surgical resection. Arm B patients (n = 11) received preoperative gemcitabine, cisplatin, and 5-FU, followed by radiation with a continuous infusion of 5-FU for 6 weeks. Three patients in arm A and 2 patients in arm B were resected.[26]

A recent multi-institutional phase II trial found that full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n = 23), borderline resectable (n = 39), or unresectable disease (n = 6) resulted in a high percentage of R0 resections. Forty-three patients underwent resection (63%), and complete (R0)

resection was achieved in 36 of those 43 patients (84%). The median overall survival was18.2 months for all patients, 27.1 months for those who underwent resection, and 10.9 months for those who did not undergo resection.[27]

A multicenter nonrandomized phase II trial evaluating neoadjuvant/adjuvant gemcitabine and erlotinib (American College of Surgeons Oncology Group [ACOSOG] Z5041; NCT003733746) has completed recruitment and may provide additional valuable results regarding the delivery of systemic therapy in the neoadjuvant setting. This study has proved the feasibility of multicenter participation in a neoadjuvant study. A phase III trial of 310 patients exploring the role of neoadjuvant gemcitabine with oxaliplatin in addition to adjuvant gemcitabine compared with adjuvant gemcitabine alone in resectable pancreatic cancer with the primary end point of progression-free survival (NEOPAC [Neoadjuvant Gemcitabine/Oxaliplatin Plus Adjuvant Gemcitabine in Resectable Pancreatic Cancer]; NCT01521702) is projected to be completed by December 2015. Several phase II clinical trials are currently underway to determine the R0 resection rate following neoadjuvant chemotherapy in patients with borderline resectable or unresectable locally advanced disease (NCT00557492). In addition, the Alliance A021101 trial (NCT01821612) is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population (**Table 3**).

NEOADJUVANT THERAPY IN RESECTABLE DISEASE

The standard approach to therapy in patients with resectable disease has been (and remains) adjuvant therapy, with median survivals in the range of 20.1 to 23.6 months under the most optimal phase III trials.[1,6–8] Neoadjuvant chemotherapy in resectable patients has yet to be fully defined with regard to value because results from prior phase II studies have been limited and mostly are based on single-institution experiences. Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.[25]

In a randomized phase II trial of 50 patients evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients

Table 3
Neoadjuvant therapy in borderline resectable pancreatic cancer

Trial	N	Treatment	Significance	Classification
Kim et al,[27] 2013	68	Full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n = 23), borderline resectable (n = 39), or unresectable disease (n = 6)	Preoperative therapy with full-dose gemcitabine, oxaliplatin, and RT was feasible and resulted in a high percentage of R0 resections	IIa
E1200	21	Gemcitabine/XRT (arm A) vs gemcitabine, cisplatin, 5-FU, followed by XRT with a continuous infusion 5-FU (arm B)	3 out of 10 (A) and 2 out of 11 (B) were resectable. Both regimens were tolerable, and resectability was comparable with previous studies	Ia

Abbreviation: XRT, Radiation.

with resectable pancreatic cancer, 9 patients (38%) in the gemcitabine-only arm and 18 patients (70%) in the gemcitabine and cisplatin arm were able to undergo resection compared with those in the gemcitabine-only arm.[28]

A single 28-patient phase II prospective trial evaluating neoadjuvant gemcitabine and cisplatin for resectable head of pancreas adenocarcinoma showed feasibility with favorable overall and disease-free survival. Patients received 4 biweekly cycles of gemcitabine and cisplatin, and were then restaged before surgery. Twenty-six patients (93%) had resectable cancer on restaging, and the R0 resection rate was 80%. On intention-to-treat analysis, the actuarial overall survival was 26.5 months, which did not change after exclusion of the patient without invasive cancer (n = 27). Those with resected ductal adenocarcinoma had a median overall survival of 19.1 months. Twenty patients developed disease recurrence, resulting in an actuarial recurrence-free survival of 9.2 months on an intention-to-treat analysis, which did not change after excluding the patient without proof of invasive cancer. Patients with resected ductal adenocarcinoma had a median recurrence-free survival of 9 months. The investigators concluded that neoadjuvant chemotherapy with gemcitabine and cisplatin is well tolerated and does not impair the resectability of pancreatic cancer.[29]

Another phase II trial studied the outcomes of patients who received preoperative gemcitabine-based chemoradiation and resection for stage I/II pancreatic adenocarcinoma.[30] Preoperative radiation and gemcitabine was administered to 86 patients with resectable disease, and patients were restaged 4 to 6 weeks following completion. Those without progression of disease were taken to surgery for a pancreatoduodenectomy. Although all patients were able to complete neoadjuvant therapy, at the time of restaging, only 73 patients (85%) were able to undergo surgery, and at the time of surgery 9 patients were had extrapancreatic disease. Median overall survival was 22.7 months with a 27% 5-year survival. The investigators concluded that preoperative gemcitabine-based chemoradiation followed by restaging and evaluation for surgery separated the study population into 2 different subsets: those patients likely to benefit from resection (n = 64) and those in whom surgery would be unlikely to provide clinical benefit (n = 22).[30]

Similar results were observed in another phase II trial involving preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation.[31] Of the 90 patients enrolled in this study, 79 patients (88%) were able to complete neoadjuvant therapy, and 52 patients (66%) underwent surgery. The median overall survival of all 90 patients was 17.4 months. Median survival for the 79 patients who completed chemotherapy-chemoradiation was 18.7 months, with a median survival of 31 months for the 52 patients who underwent resection and 10.5 months for the 27 patients who did not undergo resection of their primary tumors ($P<.001$). Preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation did not improve survival beyond that achieved with preoperative gemcitabine-based chemoradiation alone. The longer preoperative interval was not associated with local tumor progression.[31]

A recent randomized phase II trial, which was terminated early because of slow accrual, compared gemcitabine/cisplatin neoadjuvant chemoradiation with up-front surgery. Both arms received adjuvant chemotherapy.[32] With only 66 patients eligible for analysis, no significant differences were seen in the R0 resection rate, which was 52% in patients who had neoadjuvant chemoradiation and 48% in up-front surgery group. The (y)pN0 rate was 39% in the neoadjuvant chemoradiation arm and 30% in the up-front surgery arm. Overall survival was not statistically significant at 25 months in the neoadjuvant chemoradiation arm versus 18.9 months in the up-front surgery arm. Nevertheless, all results favored the neoadjuvant arm and no safety issues were noted.[32]

At this time, the NCCN does not recommend neoadjuvant therapy for clearly resectable patients without high-risk features, except in a clinical trial. Ongoing trials include the phase III NEOPA trial, which is comparing neoadjuvant gemcitabine CRT with up-front surgery in patients with clearly resectable pancreatic cancer. The primary end point is overall survival (ClinicalTrials.gov, NCT01900327).[33] A phase II trial with R0 resection as the primary end point is also ongoing (**Table 4**) (ClinicalTrials.gov, NCT01389440).[34,35]

CHEMOTHERAPY IN LOCALLY ADVANCED OR METASTATIC DISEASE

The BAYPAN study was a multicenter, placebo-controlled, double-blind, randomized phase III trial comparing gemcitabine/sorafenib and gemcitabine/placebo in the

Table 4
Neoadjuvant therapy in resectable pancreatic cancer

Trial	N	Treatment	Significance	Classification
Palmer et al,[28] 2007	50	Gemcitabine or gemcitabine/cisplatin	27 (54%) underwent pancreatic resection, 9 (38%) in the gemcitabine arm and 18 (70%) in the combination arm, with no increase in surgical complications	Ib
Heinrich et al,[29] 2008	28	Gemcitabine and cisplatin	26 patients (93%) had resectable cancer on restaging, and the R0 resection rate was 80%	IIa
Evans et al,[30] 2008	86	Gemcitabine-based chemoradiation	Preoperative gemcitabine-based chemoradiation followed by restaging and evaluation for surgery separated the study population into 2 different subsets: those patients likely to benefit from resection (n = 64) and those in whom surgery would be unlikely to provide clinical benefit (n = 22)	IIa
Varadhachary et al,[31] 2008	90	Gemcitabine/cisplatin followed by gemcitabine-based chemoradiation	Preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation did not improve survival beyond that achieved with preoperative gemcitabine-based chemoradiation alone	IIa
Golcher et al,[32] 2015	66	Gemcitabine/cisplatin neoadjuvant chemoradiation or up-front surgery	Overall survival was not statistically significant at 25 mo in the neoadjuvant chemoradiation arm vs 18.9 mo in the up-front surgery arm. Nevertheless, all results favored the neoadjuvant arm and no safety issues were noted	Ib

treatment of chemotherapy-naive patients with advanced or metastatic disease. Between December 2006 and September 2009, 104 patients were enrolled on the study (52 patients in each arm) and 102 patients were treated. The median and 6-month progression-free survival were 5.7 months and 48% for gemcitabine/placebo and 3.8 months and 33% for gemcitabine/sorafenib ($P = .902$). The median overall survivals were 9.2 and 8 months, respectively ($P = .231$). The investigators concluded that the addition of sorafenib to gemcitabine does not improve progression-free survival.[36]

Gemcitabine plus Albumin-bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a publication of a phase I/II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients showing stable disease for greater than 16 weeks. The median overall survival at this dose was 12.2 months.[37]

Based on these results, the large, open-label, international, randomized phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) trial was initiated in 861 patients with metastatic pancreatic cancer and no prior chemotherapy.[38] Patients were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary end point of overall survival (8.7 months vs 6.6 months; $P<.0001$).[38] The addition of albumin-bound paclitaxel also improved other end points, including 1-year survival, 2-year survival, response rate, and progression-free survival. Overall survival was associated with a decrease in cancer antigen (CA) 19-9 ($P = .001$).[39] Tumor response was validated with PET imaging.[40] The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel. Three percent of patients from that arm were alive at 42 months, whereas no patients were alive from the control arm at that time.[41] This combination of gemcitabine plus albumin-bound paclitaxel is a preferred treatment option for patients with metastatic disease and good performance status.

Gemcitabine plus Erlotinib and Other Targeted Therapeutics

Although early phase II trial results of gemcitabine combined with new targeted drugs such as bevacizumab [42] and cetuximab[43] were encouraging, results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only gemcitabine plus erlotinib is associated with a statistically significant increase in survival compared with gemcitabine alone. This finding was described in the phase III, double-blind, placebo-controlled National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) trial, in which 569 patients were randomized to receive standard gemcitabine plus erlotinib or gemcitabine plus placebo. Patients in the erlotinib arm showed statistically significant improvements in overall survival ($P = .038$) and progression-free survival ($P = .004$) compared with patients receiving gemcitabine alone. Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm.[44]

Adding to the previous study that reported that gemcitabine plus erlotinib shows a small but significant improvement in overall survival versus gemcitabine alone, a double-blind, phase III trial was developed of 607 patients with metastatic pancreatic adenocarcinoma studying gemcitabine, erlotinib, and bevacizumab compared with gemcitabine, erlotinib, and placebo. A total of 301 patients were randomly assigned

to the placebo group and 306 to the bevacizumab group. Median overall survival was 7.1 and 6.0 months in the bevacizumab and placebo arms, respectively (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.74–1.07; $P = .2087$); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved progression-free survival (HR, 0.73; 95% CI, 0.61–0.86; $P = .0002$). Treatment with bevacizumab plus gemcitabine-erlotinib was well tolerated and safe.[45]

Another phase III trial of 745 patients evaluating the addition of cetuximab to standard gemcitabine therapy revealed no significant difference in median survival between the gemcitabine plus cetuximab arm and the gemcitabine-alone arm (6.3 months vs 5.9 months; $P = .23$).[46]

Given the initial encouraging results of gemcitabine plus bevacizumab with a 21% response rate and a median survival of 8.8 months in a multicenter phase II trial in patients with metastatic pancreatic cancer, the Cancer and Leukemia Group B (CALGB) conducted a double-blind, placebo-controlled, randomized phase III trial of gemcitabine/bevacizumab versus gemcitabine/placebo in patients with advanced pancreatic cancer.[42] Five-hundred and thirty-five patients were treated and the median overall survival was 5.8 months for gemcitabine/bevacizumab and 5.9 months for gemcitabine/placebo ($P = .95$). Median progression-free survival was 3.8 and 2.9 months for gemcitabine/bevacizumab and gemcitabine/placebo, respectively ($P = .07$). Overall response rates were 13% and 10% for gemcitabine/bevacizumab and gemcitabine/placebo, respectively. The investigators concluded that the addition of bevacizumab to gemcitabine does not improve survival in patients with advanced pancreatic cancer.[42]

Targeted therapies in addition to erlotinib have been assessed in combination with gemcitabine but none have been shown to significantly improve outcomes. For example, axitinib, a potent selective inhibitor of vascular endothelial growth factor (VEGF) receptors, was studied in a randomized phase II trial studying gemcitabine alone or with axitinib in advanced pancreatic cancer. Results suggested increased overall survival in axitinib-treated patients. From these results, Kindler and colleagues[47] assessed the effect of treatment with gemcitabine plus axitinib on overall survival in a phase III trial. Six-hundred and thirty-two patients were enrolled and assigned to 2 treatment groups. Three-hundred and sixteen patients were in the gemcitabine/axitinib group compared with 316 patients in the gemcitabine/placebo group. An interim analysis in January 2009 revealed that the addition of axitinib to gemcitabine does not improve overall survival in advanced pancreatic cancer.[46]

Other phase II/III trials of gemcitabine plus ziv-aflibercept,[48] a VEGF inhibitor; rigosertib,[49] a Ras mimetic and small-molecule inhibitor of multiple signaling pathways; ganitumab,[50] an insulinlike growth factor 1 receptor monoclonal antibody; and sunitinib,[51] an angiogenesis inhibitor showed no improved overall survival, compared with gemcitabine alone, in patients with metastatic pancreatic cancer.

Poly (ADP-ribose) polymerase (PARP) inhibitors are another avenue of research for cancers associated with breast cancer antigen gene (BRCA)1/2 mutations. In a phase II trial assessing the efficacy and safety of olaparib, an oral PARP, the tumor response rate for patients with metastatic pancreatic cancer and a germline BRCA1/2 mutation (n = 23) was 21.7%.[52] The PARP inhibitor rucaparib is being assessed in the ongoing RUCAPANC trial, targeting patients with a BRCA1/2 mutation.[53] Preliminary data from this phase II trial presented at ASCO in 2016 revealed that 19 patients with a BRCA1/2 mutation and relapsed disease showed an objective response rate of 11% with rucaparib, a PARP inhibitor, in patients with pancreatic cancer and a known deleterious germline or somatic BRCA mutation.[53] The phase III randomized POLO trial

(NCT02184195), in which the effectiveness of maintenance olaparib monotherapy following cisplatin, carboplatin, or oxaliplatin is being assessed, is currently in progress.[54]

Gemcitabine plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting and results of RCTs have not provided support for the use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for combination therapy compared with gemcitabine monotherapy.[55–57]

Gemcitabine plus Capecitabine

Several randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer. A randomized study of 533 patients with advanced disease found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine compared with gemcitabine alone. There was also a trend toward an improvement in overall survival in the combination arm; however, it did not reach statistical significance.[58] Results from another, smaller phase III trial evaluating gemcitabine and capecitabine did not show an overall survival advantage, although a post-hoc analysis showed overall survival to be significantly increased in the subgroup of patients with good performance status.[59]

Gemcitabine and Other Fluoropyrimidine-based Therapies

FU-based, irinotecan–based, and gemcitabine-based regimens are the standard of care as first-line treatment of patients with metastatic pancreatic cancer. Whether a sequential approach alternating irinotecan, FU, and gemcitabine may be effective and tolerable in patients with metastatic pancreatic cancer is unknown. In a phase II randomized trial, the effects of the FIRGEM regimen (irinotecan delivered before and after infusion of 5-FU/leucovorin [FOLFIRI.3], alternating with fixed-dose-rate gemcitabine) were assessed in 98 patients with metastatic pancreatic cancer.[60] Patients were randomized to receive the FIRGEM regimen or fixed-dose-rate gemcitabine monotherapy. The primary objective of a 45% progression-free survival rate at 6 months was reached, and progression-free survival was a median of 5 months in those randomized to receive the FIRGEM regimen, whereas those randomized to receive only gemcitabine had a median progression-free survival of 3.4 months. Study investigators deemed FIRGEM to be effective and feasible in the metastatic setting.[60]

A recent randomized trial from Asia showed that gemcitabine combined with the oral fluoropyrimidine S-1 may improve response and survival in patients with locally advanced pancreatic cancer, although trial results are inconsistent regarding whether outcomes are improved compared with gemcitabine monotherapy.[61]

FOLFIRINOX

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free

survival (6.4 months vs 3.3 months; $P<.001$) and median overall survival (11.1 months vs 6.8 months; $P<.001$), in favor of the group receiving FOLFIRINOX.[62] However, the eligibility criteria for this trial were stringent, limiting ability to generalize to real-world settings. For example, patients with abnormal bilirubin levels were excluded from participating. There are also some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3 to 4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.[63] Despite the high levels of toxicity, no toxic deaths have been reported.[62,63] Furthermore, the PRODIGE trial determined that, despite this toxicity, fewer patients in the FOLFIRINOX group than in the gemcitabine group experienced a degradation in their quality of life at 6 months (31% vs 66%, $P<.01$).[63]

The efficacy and toxicity of a modified FOLFIRINOX regimen in which the initial dosings of bolus 5-FU and irinotecan were each reduced by 25% were assessed in a phase II single-arm prospective trial of 75 patients.[64] In patients with metastatic disease, the efficacy of the modified regimen was comparable with that of the standard regimen, with a median overall survival of 10.2 months. In patients with locally advanced disease, the median overall survival was 26.6 months. Patients who received the modified regimen experienced significantly less neutropenia, fatigue, and vomiting, relative to patients who received the standard FOLFIRINOX regimen.

Capecitabine and Continuous-infusion 5-Fluorouracil

Capecitabine monotherapy and continuous-infusion 5-FU is also considered a first-line treatment option for patients with locally advanced unresectable or metastatic disease. The capecitabine recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which overall survival was similar in patients with advanced pancreatic cancer receiving capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.[65] Two-hundred and eighty-one treatment-naive patients were randomly assigned to either the capecitabine plus erlotinib arm (A) or the gemcitabine plus erlotinib arm (B). Interim analysis of toxicity evaluated data from the first 127 randomized patients. Grade 3 to 4 hematological toxicity was less than 10% in both the arms. Major grade 3 to 4 toxicities in arms A and B were diarrhea (9% vs 7%), skin rash (4% vs 12%), and hand-foot syndrome (7% vs 0%). No treatment-related death was observed. This interim safety analysis suggests that treatment with erlotinib 150 mg/d is feasible in combination with capecitabine or gemcitabine.[65]

Possible Role of Maintenance Therapy in Advanced Disease

Given the success of more effective regimens in patients with advanced disease, clinicians are now determining how best to manage the treatment-free interval before disease progression. Options include stopping treatment, eliminating the most toxic agents, and switching to an alternative agent for maintenance therapy. A recent randomized phase II trial (PACT-12) had interesting results, suggesting that maintenance therapy with sunitinib after a full course of first-line treatment may have a benefit in some patients with metastatic disease.[66] In this trial, 55 patients with pathologic diagnosis of metastatic pancreatic adenocarcinoma, performance status greater than 50%, and no progression after 6 months of chemotherapy (mostly gemcitabine combinations) were randomized to observation (arm A) or sunitinib until

progression or a maximum of 6 months (arm B). The primary outcome measure was the probability of being progression free at 6 months from randomization. Median overall survival was 9.2 months in the observation group versus 10.6 months in the sunitinib group ($P = .11$). A criticism of this study is the small sample size. However, the 1-year and 2-year survival rates were 36% and 7% in the observation arm compared with 41% and 23% in the sunitinib arm, suggesting that a subset of patients may derive significant benefit. Overall, results of the PACT-12 trial suggest that there may be a role for antiangiogenic agents after more effective first-line treatments.[66]

Second-line Systemic Therapy in the Advanced Setting

Final results of the 160-patient phase III CONKO-003 trial initially presented in 2008 were published in 2014. This study assessed the efficacy of a second-line regimen of oxaliplatin and folinic acid–modulated FU (OFF) in patients with advanced pancreatic cancer who experienced progression while receiving gemcitabine monotherapy. The median overall survival in the OFF arm was 5.9 months and was 3.3 months in the 5-FU/leucovorin arm, for a significant improvement in the HR ($P = .01$).[67]

However, results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/leucovorin in second-line treatment may be detrimental.[68] In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line FOLFOX or infusional 5-FU/leucovorin. No difference was seen in median progression-free survival (3.1 vs 2.9 months; $P = .99$), but median overall survival was worse in those in the FOLFOX arm (6.1 vs 9.9 months; $P = .02$). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3 to 4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/leucovorin arm.[68]

In the recent NAPOLI-1 phase III randomized trial, the effects of nanoliposomal irinotecan were examined in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy. Four-hundred and seventeen patients were randomized to receive the nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both. Median progression-free survival was 3.1 months versus 1.5 months, which was statistically significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin compared with patients who did not receive irinotecan ($P<.001$). Updated analyses showed that median overall survival was 6.2 months versus 4.2 months and was also significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin compared with patients who received 5-FU/leucovorin without irinotecan ($P = .042$). Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[69] Irinotecan liposomal injection, combined with 5-FU/leucovorin, was recently approved by the US Food and Drug Administration to be used as second-line treatment following gemcitabine-based therapy in patients with metastatic disease.[69]

The AIO-PK0104 trial also assessed second-line therapy in a randomized crossover trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.[70] Gemcitabine/erlotinib followed by second-line capecitabine was compared with a reverse experimental sequence of capecitabine/erlotinib followed by gemcitabine. Two-hundred and seventy-four patients were randomly assigned to first-line treatment with either gemcitabine plus erlotinib or capecitabine plus erlotinib. In case of treatment failure such as progression of disease or toxicity, patients were allocated to second-line treatment with the comparator cytostatic drug without erlotinib. Forty-three patients had locally advanced

disease and 231 had metastatic disease. One-hundred and forty (51%) received second-line chemotherapy. Median time to treatment failure after second-line therapy was estimated as 4.2 months in both arms; median overall survival was 6.2 months with gemcitabine/erlotinib followed by capecitabine and 6.9 months with capecitabine/erlotinib followed by gemcitabine, respectively ($P = .90$). Time to treatment failure for first-line therapy was significantly prolonged with gemcitabine/erlotinib compared with capecitabine/erlotinib (3.2 vs 2.2 months; $P = .0034$). The investigators concluded that both treatment strategies are feasible and showed comparable efficacy (**Table 5**).

CHEMORADIATION IN LOCALLY ADVANCED DISEASE

Results of 2 early randomized trials comparing up-front chemoradiation with chemotherapy in locally advanced disease were contradictory.[71,72] Three phase II

Table 5
Overall survival data from prospective, randomized trials of chemotherapy in locally advanced or metastatic pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
BAYPAN	104	Gemcitabine/sorafenib or gemcitabine/placebo	9.2 vs 8	.23	Ia
MPACT	861	Gemcitabine plus albumin-bound paclitaxel or gemcitabine alone	8.7 vs 6.6	.0001	Ia
NCIC CTG	569	Gemcitabine + erlotinib or gemcitabine + placebo	6.24 vs 5.91	.038	Ia
CALGB	535	Gemcitabine + bevacizumab or gemcitabine + placebo	5.8 vs 5.9	.95	Ia
Cunningham et al,[58] 2009	533	Gemcitabine + capecitabine or gemcitabine alone	6.2 vs 7.1	.08	Ib
PRODIGE	342	FOLFIRINOX vs gemcitabine in patients with metastatic pancreatic cancer	11.1 vs 6.8	.001	Ia
CONKO-003	160	OFF or 5-FU/LV in patients with advanced pancreatic cancer who progressed on gemcitabine	5.9 vs 3.3	.01	Ia
PANCREOX	108	FOLFOX or infusional 5-FU/LV in patients with advanced pancreatic cancer who progressed on gemcitabine	6.1 vs 9.9	.02	Ib
NAPOLI-1	417	Nanoliposomal irinotecan monotherapy + 5-FU/LV or 5-FU/LV	6.2 vs 4.2	.042	Ib
AIO-PK0104	274	Gemcitabine/erlotinib followed by second-line capecitabine was compared with a reverse experimental sequence of capecitabine/erlotinib followed by gemcitabine	6.2 vs 6.9	.9	Ib

Abbreviation: LV, leucovorin.

trials also assessed the up-front chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.[73–76]

The phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus radiation followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer was closed early because of poor accrual. However, an intention-to-treat analysis of data for the 74 patients enrolled in this study showed that median overall survival was significantly longer in the CRT arm of the study (11.1 months vs 9.2 months; $P = .017$).[77] However, the poor accrual rate decreased its statistical power. There was no difference in progression-free survival, and the CIs for overall survival overlapped between the two groups of patients, leading claims that the results do not achieve the level of evidence required to determine standard of care.

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III Francophone de Cancerologie Digestive (FFCD)/Société Française de. Radiothérapie Oncologie (SFRO) study from France in 2008, in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment. Gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs 32%; $P = .006$).[78] This study was stopped before the planned accrual because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this chemoradiation regimen. Thus, the role of up-front chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. If patients present with poorly controlled pain or local invasion with bleeding, then starting with up-front CRT is an option.

Chemoradiation Following Chemotherapy in Locally Advanced Disease

In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown. In the international phase III LAP07 RCT, 269 patients with locally advanced pancreatic cancer received chemoradiation with capecitabine following 4 months of induction chemotherapy with either gemcitabine monotherapy or gemcitabine and erlotinib.[79] The goal was to assess whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy and to assess the effect of erlotinib on survival. Chemoradiation in this setting provided no survival benefit compared with chemotherapy only ($P = .83$).[79]

In a recent single-arm phase II trial examining stereotactic body radiotherapy (SBRT) following gemcitabine monotherapy in 49 patients with locally advanced pancreatic cancer, this regimen showed low toxicity and favorable freedom from local disease progression.[80] The median overall survival was 13.9 months (95% CI, 10.2–16.7 months). Patients reported a significant improvement in pancreatic pain ($P = .001$) 4 weeks after SBRT. The investigators concluded that fractionated SBRT with gemcitabine results in minimal acute and late gastrointestinal toxicity and that future studies should incorporate SBRT with more aggressive multiagent chemotherapy compared with gemcitabine monotherapy alone (**Table 6**).

Table 6
Overall survival data from prospective, randomized trials of chemoradiation in locally advanced or metastatic pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
ECOG-4201	74	Gemcitabine or gemcitabine + radiation followed by gemcitabine	9.2 vs 11.1	.17	Ib
FFCD-SFRO	119	Gemcitabine alone or chemoradiation with 5-FU + cisplatin followed by gemcitabine maintenance	13 vs 8.6	.03	Ib
LAP07	269	In the second randomization involving patients with progression-free disease after 4 mo, 136 patients received 2 mo of the same chemotherapy (gemcitabine or gemcitabine + erlotinib) and 133 received chemoradiation + capecitabine	16.5 vs 15.2	.83	Ib

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