Original Investigation

Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer
The CONKO-001 Randomized Trial

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IMPORTANCE The prognosis for patients with pancreatic cancer is poor, even after resection with curative intent. Gemcitabine-based chemotherapy is standard treatment for advanced pancreatic cancer, but its effect on survival in the adjuvant setting has not been demonstrated.

OBJECTIVE To analyze whether previously reported improvement in disease-free survival with adjuvant gemcitabine therapy translates into improved overall survival.

DESIGN, SETTING, AND PATIENTS CONKO-001 (Charité Onkologie 001), a multicenter, open-label, phase 3 randomized trial to evaluate the efficacy and toxicity of gemcitabine in patients with pancreatic cancer after complete tumor resection. Patients with macroscopically completely removed pancreatic cancer entered the study between July 1998 and December 2004 in 88 hospitals in Germany and Austria. Follow-up ended in September 2012.

INTERVENTIONS After stratification for tumor stage, nodal status, and resection status, patients were randomly assigned to either adjuvant gemcitabine treatment (1g/m^2 d 1, 8, 15, q 4 weeks) for 6 months or to observation alone.

MAIN OUTCOMES AND MEASURES The primary end point was disease-free survival. Secondary end points included treatment safety and overall survival, with overall survival defined as the time from date of randomization to death. Patients lost to follow-up were censored on the date of their last follow-up.

RESULTS A total of 368 patients were randomized, and 354 were eligible for intention-to-treat-analysis. By September 2012, 308 patients (87.0% [95% CI, 83.1%-90.1%]) had relapsed and 316 patients (89.3% [95% CI, 85.6%-92.1%]) had died. The median follow-up time was 136 months. The median disease-free survival was 13.4 (95% CI, 11.6-15.3) months in the treatment group compared with 6.7 (95% CI, 6.0-7.5) months in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]; $P < .001$). Patients randomized to adjuvant gemcitabine treatment had prolonged overall survival compared with those randomized to observation alone (hazard ratio, 0.76 [95% CI, 0.61-0.95]; $P = .01$), with 5-year overall survival of 20.7% (95% CI, 14.7%-26.6%) vs 10.4% (95% CI, 5.9%-15.0%), respectively, and 10-year overall survival of 12.2% (95% CI, 7.3%-17.2%) vs 7.7% (95% CI, 3.6%-11.8%).

CONCLUSIONS AND RELEVANCE 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.

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Pancreatic cancer is a disease with a poor prognosis, mainly because of the inability to detect the tumor at an early stage, its high potential for early dissemination, and its relatively poor sensitivity to chemotherapy or radiation therapy. The ratio of overall mortality to incidence is almost 98%. Only a minority of patients present with localized disease allowing for resection of the tumor with curative intent. However, even after microscopically pathologically complete removal of the tumor (R0), the vast majority of the patients relapse within 2 years, leading to a 5-year survival rate of less than 25%.[1] No consensus has been reached on a standard treatment approach for adjuvant therapy, although controlled trials have been conducted in this area for almost 3 decades.[2] The CONKO-001 (Charité Onkologie 001) study was designed to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete, curative-intent resection of pancreatic cancer. Results for the primary end point of disease-free survival and adverse effects accompanying therapy have been published previously.[3] In this article we present the final, long-term results with a cutoff date of September 10, 2012.

Methods

Patients

The study details of the CONKO-001 trial have been reported previously.[3] Briefly, patients with stage T1-4N0-1M0, histologically proven, macroscopically completely resected pancreatic cancer were eligible. Main inclusion criteria included age 18 years or older, a Karnofsky Performance Status Scale score of 50% or higher, adequate bone marrow function (defined as white blood cell count ≥3500 cells/μL, platelet count ≥100 000 cells/μL, and hemoglobin level ≥80 g/L), anticipated patient adherence to treatment, and adherence to long-term follow-up for at least 2 years after surgery. Patients were excluded if they had received neoadjuvant therapy, had active infection, had impaired coagulation (international normalized ratio >1.5 times the upper limit of normal [ULN], activated partial thromboplastin time >1.5 times ULN, or both), had distinct organ dysfunction (transaminase levels >3 times ULN, serum creatinine level >1.5 times ULN, or a history of another malignant disease other than carcinoma in situ of the uterine cervix or adequately treated basal cell carcinoma of the skin). Postoperative tumor marker levels (carcinoembryonic antigen/cancer antigen [CEA/CA19-9]) had to be lower than 2.5 times ULN. Pregnant or breastfeeding women were also excluded from the study. All patients had to provide written informed consent before randomization.

Trial Design and Logistics

CONKO-001 was a multicenter, open-label, parallel-group study with centralized randomization to either an active treatment group (adjuvant gemcitabine) or a control group (observation with a similar follow-up schedule), stratified according to tumor stage, nodal status, and resection status.

The trial was initiated by the German Study Group for Pancreatic Cancer within the German Cancer Society (Deutsche Krebsgesellschaft), with data collection and trial coordination carried out by the Charité–Universitätsmedizin Berlin, Berlin, Germany. Because adjuvant chemotherapy with gemcitabine can be administered on an outpatient basis, the participating centers included oncology departments and oncology clinics within hospitals as well as private oncology practices in Germany and Austria. The study was conducted in accordance with the principles of good clinical practice (including regular educational and monitoring procedures), the provisions of the Declaration of Helsinki, and local regulatory requirements. The protocol was approved by the respective institutional review board of each study site. All patients provided written informed consent.

The primary objective of disease-free survival was defined as the time from the date of randomization to the date of first documentation of recurrence (with cytological or histological confirmation or with radiological evidence). Patients alive without recurrence were censored on the date of last follow-up. Secondary cancers were not considered events. Secondary objectives included treatment safety and overall survival, defined as the time from the date of randomization to death, censoring patients who were alive on the date of last follow-up.

Randomization

Patients were randomized between adjuvant chemotherapy and observation in a 1:1 ratio using computer-generated random numbers generated at the study coordination center at the Charité–Universitätsmedizin Berlin, Berlin, Germany. At randomization, the patients were stratified according to tumor stage (T1-2 vs T3-4), nodal status (N0 vs N1), and resection status (R0 vs R1), based on the TNM classification.

Procedures

Surgery was performed according to institutional standards and varied depending on the location and extent of tumor involvement. Histological examinations were performed in the pathology institutions of the recruiting centers without central pathological review. Between day 10 and day 42 following surgery and wound healing, patients in the adjuvant chemotherapy group began to receive 6 cycles of gemcitabine every 4 weeks, consisting of 3 weekly infusions of gemcitabine (1000 mg/m^2), followed by a 1-week break. Details on dose modifications, adverse events, treatment cessation, and quality-of-life data have been reported.[3] Patients in the observation group who experienced a relapse were offered palliative chemotherapy that consisted predominantly of gemcitabine therapy.

The baseline assessment of all patients included complete medical history, physical examination with routine laboratory studies, levels of tumor markers CEA and CA19-9, vital signs, and body weight. Tumor assessments included abdominal computed tomography or magnetic resonance imaging, ultrasound, and chest radiography. An abdominal ultrasound to detect recurrent disease was performed every 8 weeks. Computed tomography was repeated after completion of adjuvant chemotherapy in the gemcitabine group and after 6 months in the observation group. Patients then received fol-

low-up every 8 weeks for up to 5 years or until death to assess adverse events, performance status, quality of life, disease status, and survival. Disease-free survival was defined as the time from randomization to the date of local or distant recurrence. The date of recurrence was defined as the date of the first subjective symptom indicating relapse or the date of tumor detection by diagnostic imaging techniques, independent of site, whichever occurred first. Overall survival was defined as the time from randomization to either death from any cause or the date of last follow-up. Tumor histological diagnosis and risk stratification were based on the local pathology assessment.

Statistical Analysis

The sample size calculation was based on the assumption that median disease-free survival of patients with completely resected pancreatic cancer without adjuvant treatment would be less than 12 months.[4] A sample size of 184 patients in each group was required to detect an improvement in disease-free survival of 6 months using gemcitabine, with a bilateral 5% type I error and a power of 90%, and assuming (1) a 20% dropout rate attributable to ineligibility or early dropout; (2) a 3-year recruitment period; and (3) an additional follow-up period of at least 2 years. Premature termination of the study had to be considered at any time if unacceptable toxicity was reported for more than 10% of the patients in the treatment group. One formal interim analysis of efficacy was performed, using the O'Brien-Fleming adjustment for α error control.[5]

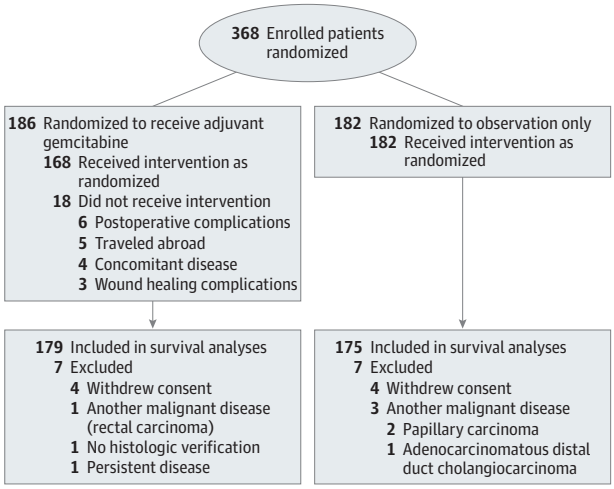
Data analysis was undertaken using SPSS, German version 19 (SPSS Inc, IBM). Disease-free and overall survival were estimated according to Kaplan and Meier, providing medians with 95% confidence intervals; the respective comparisons between the groups were performed using the log-rank test.[6] The latter methods were also applied in the bivariable analysis of other prognostic factors. The Cox model was used for the multivariable analysis,[7] initially including all bivariably significant parameters and implementing a backward selection procedure with a cutoff value of $P < .10$. All P values are 2-sided and of exploratory nature except for the primary analysis. Results were considered significant at $P \leq .05$. As defined in the protocol, all survival-type analyses presented were based on the intention-to-treat population, which included all eligible patients enrolled in the study. Patients lost to follow-up were censored on the date of last follow-up.

Results

Patients and Treatment

Between July 1998 and December 2004, a total of 368 patients were recruited into the study in 88 German and Austrian centers. Of these, 186 patients were assigned to the gemcitabine group and 182 to the observation group. A total of 179 patients from the gemcitabine group and 175 patients from the observation group were eligible for the intention-to-treat analyses of disease-free and overall survival (**Figure 1**). The major baseline characteristics of eligible patients were well balanced across study groups (**Table 1**). The majority of patients had T3N1 disease prior to surgery and had undergone an R0 resection. Of 186 patients in the chemotherapy group, 111 (62%) received all 6 gemcitabine cycles as specified in the protocol. Ninety percent of the patients received at least a single dose, and 87% received at least 1 full cycle of adjuvant therapy with gemcitabine. The mean weekly dose of gemcitabine was 700 mg/m^2; the median relative dose intensity was 86%. For 18 patients, treatment according to study protocol was never initiated, mainly because of wound healing and other postoperative complications or because of concomitant disease.

Figure 1. Study Flow



The number of patients screened for enrollment in the study was not documented.

Efficacy

The database was closed in September 2012, when 308 recurrence events had occurred in 354 patients (87% [95% CI, 83.1%-90.1%]), 145 (81% [95% CI, 74.6%-86.1%]) in the gemcitabine group and 163 (93% [95% CI, 88.4%-96.0%]) in the observation group. The median follow-up duration was 136 (interquartile range, 104-144) months. As reported previously, the median disease-free survival was 13.4 (95% CI, 11.6-15.3) months in the treatment group compared with 6.7 (95% CI, 6.0-7.5) months in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]; $P < .001$]) (**Figure 2**A). At 5 and 10 years, the rates of disease-free survival were 16.6% (95% CI, 11.0%-22.2%) and 14.3% (95% CI, 8.9%-19.8%), respectively, in the gemcitabine group and 7.0% (95% CI, 3.2%-10.8%) and 5.8% (95% CI, 2.3%-9.3%) in the observation group (Figure 2A). This treatment effect on disease-free survival was detected consistently across all subgroups as based on the prestratification criteria (tumor stage, nodal status, resection status) (**Table 2** and **Figure 3**A), with heterogeneity tests showing no treatment × subgroup interaction, except for a remarkably low hazard ratio in the (albeit small) subgroup with microscopic residual disease.

By September 2012, 316 patients (89.3% [95% CI, 85.6%-92.1%) had died and 38 patients were still alive, 23 in the treatment group and 15 in the observation group. There was a statistically significant difference in overall survival between the

study groups, with a median of 22.8 months in the gemcitabine group compared with 20.2 months in the observation group (HR, 0.76 [95% CI, 0.61-0.95]; *P* = .01) (Figure 2B).

Table 1. Baseline Demographic and Disease Characteristics (Intent-to-Treat Population)

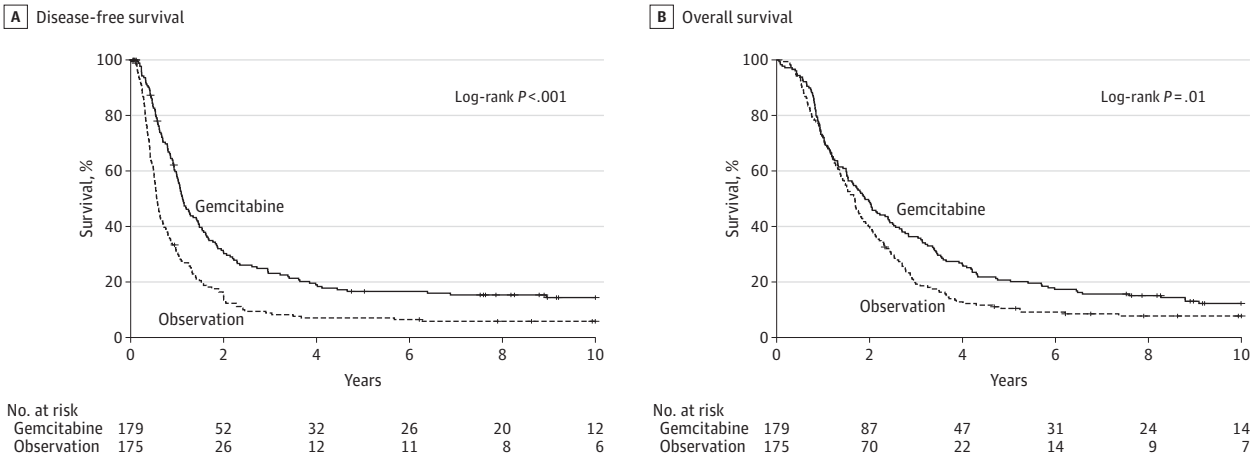
Characteristic	No. (%)	
	Gemcitabine	Observation
No. of patients	179	175
Age, median (range), y	62 (34-82)	62 (36-81)
Karnofsky Performance Status Scale, median (range), %	80 (60-100)	80 (50-100)
Sex		
Women	74 (41)	77 (44)
Men	105 (59)	98 (56)
Primary tumor stage		
T1	7 (4)	7 (4)
T2	18 (10)	17 (10)
T3	146 (82)	146 (83)
T4	8 (4)	5 (3)
Nodal status		
N0	52 (29)	48 (27)
N1	126 (70)	124 (71)
N2	1 (1)	3 (2)
Resection status		
R0	145 (81)	148 (85)
R1	34 (19)	27 (15)
Grading		
G1	10 (6)	9 (5)
G2	103 (58)	96 (55)
G3	63 (35)	67 (38)
Unknown	3 (2)	3 (2)
Histology		
Adenocarcinoma	175 (98)	168 (96)
Other	4 (2)	7 (4)

Survival rates at 5 and 10 years were 20.7% (95% CI, 14.7%-26.6%) and 12.2% (95% CI, 7.3%-17.2%), respectively, in the gemcitabine group and 10.4% (95% CI, 5.9%-15.0%) and 7.7% (95% CI, 3.6%-11.8%) in observation group. The multivariable analysis showed that, beside gemcitabine treatment, T and N stage remain the dominant prognostic factors in terms of survival (Table 2). Tests for heterogeneity did not indicate any major treatment × subgroup interaction with effects on the main conclusions of the trial (Figure 3B). Additional details of the statistical analyses have been reported.[3]

Discussion

CONKO-001 was the first phase 3 randomized trial in pancreatic cancer research that investigated the effects of adjuvant gemcitabine chemotherapy. The choice of chemotherapy was based on landmark trial data based on metastatic disease more than a decade ago.[8,9] The main result of this trial is that treatment with adjuvant gemcitabine for 6 months leads to a 24% improvement in overall survival, with a statistically significant absolute 10.3% improvement in the 5-year overall survival rate (20.7% vs 10.4%) and a 4.5% improvement in the 10-year survival rate (12.2% vs 7.7%), compared with observation alone. The study findings were robust with regard to observation duration, with a median follow-up of more than 11 years. Considering the high number of relapses within the first year of the study, and considering that gemcitabine-based therapy was the standard therapy in patients experiencing relapse after resection, the study design could be seen as a study of immediate vs delayed postoperative therapy with gemcitabine. The statistically significant differences in disease-free and overall survival between treatment groups support the use of gemcitabine as the backbone for future studies of adjuvant therapy following R0/R1 resection of pancreatic cancer. The treat-

Figure 2. Kaplan-Meier Estimates of Disease-Free and Overall Survival



A, Median disease-free survival was 13.4 months (95% CI, 11.6-15.3 months) in the gemcitabine group compared with 6.7 months (95% CI, 6.0-7.5 months) in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]). B, Median overall survival was 22.8 months (95% CI, 18.5-27.2 months) in the gemcitabine group compared with 20.2 months (95% CI, 17.7-22.8 months) in the observation group (hazard ratio, 0.76 [95% CI, 0.61-0.95]). Vertical lines on curves indicate patients censored on the date of their last follow-up.

Table 2. Bivariable and Multivariable Analyses of Prognostic Factors

		Survival							
		Disease-Free				Overall			
		Bivariable		Multivariable		Bivariable		Multivariable	
Prognostic Factor	No.	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Intervention									
Gemcitabine	179	0.55 (0.44-0.69)	<.001	0.54 (0.43-0.67)	<.001	0.76 (0.61-0.95)	.01	0.78 (0.62-0.97)	.03
Observation	175								
Age, y									
≥65	219	1.11 (0.88-1.40)	.37			1.28 (1.02-1.60)	.04	1.24 (0.99-1.56)	.06
<65	135								
Sex									
Women	151	1.11 (0.89-1.40)	.36			1.05 (0.84-1.32)	.65		
Men	203								
Karnofsky Performance Status Scale score, %									
≤80	168	1.13 (0.88-1.43)	.34			1.15 (0.90-1.46)	.26		
90-100	135								
Primary tumor stage									
T3-4	305	1.76 (1.25-2.47)	.001	1.60 (1.14-2.26)	.007	1.81 (1.28-2.55)	.001	1.68 (1.19-2.37)	.003
T1-2	49								
Nodal status									
N+	254	1.84 (1.42-2.38)	<.001	1.82 (1.40-2.36)	<.001	1.66 (1.29-2.14)	<.001	1.59 (1.23-2.05)	<.001
N0	100								
Resection status									
R1	61	1.19 (0.89-1.60)	.25			1.19 (0.89-1.59)	.25		
R0	293								

Abbreviation: HR, hazard ratio.

[a] A hazard ratio less than 1.0 indicates a favorable prognosis of the category mentioned first.

ment effects were consistent and uniform throughout all prognostic strata (ie, tumor stage, nodal status, resection status), as shown in predefined exploratory subgroup analyses and despite the limited power for these secondary end points.

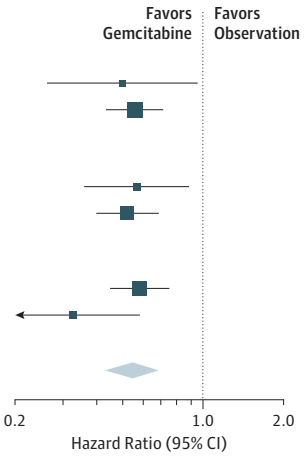
Because CONKO-001 was a community-based trial and designed to be applicable not only to academic centers but also to community-based oncologists without uniform standards for surgery and centralized pathology review, the trial results are likely to be representative of general clinical practice not only for Austria and Germany but for many other countries as well.

Results from several other trials in the adjuvant setting and with similar parallel-group designs of chemotherapy compared with observation alone have been published. Two of these trials included relatively small patient numbers and used a fluorouracil bolus regimen as the chemotherapy backbone. One trial was conducted in the early 1990s by a group from Norway[10] and compared adjuvant combination chemotherapy with doxorubicin, mitomycin C, and fluorouracil given every 3 weeks, with observation in 61 resected patients with either pancreatic cancer (47 patients) or tumors of the papilla of Vater (greater duodenal papilla) (14 patients). After 2 years of follow-up, there was a statistically nonsignificant difference in survival (43% vs 32%), but the 5-year survival rates of 4% in the chemotherapy group vs 8% in the control group did not reveal any increased curative potential for the adjuvant therapy. Similarly, the results of a Japanese randomized controlled trial[11] failed to substantiate the long-term efficacy of postoperative fluorouracil-based chemotherapy. Another recently published multicenter trial from Japan including 89 patients with R0-resected pancreatic cancer also did not detect a survival advantage following adjuvant administration of a cisplatin/fluorouracil combination chemotherapy.[12] The JSAP-02 (Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer 02) study design (119 patients, 58 gemcitabine vs 60 surgery only) basically resembled that of CONKO-001, except for the intended number of gemcitabine cycles (6 in CONKO-001, 3 in JSAP-02). The increase in disease-free survival of approximately 6 months (11.4 vs 5.0 months; $P = .01$) reported in JSAP-02 was similar to that of CONKO-001 (13.4 vs 6.9 months; $P < .001$), with a statistically nonsignificant difference in overall survival ($P = .19$).[13] The ESPAC-1 (European Study Group for Pancreatic Cancer 1) trial claimed an effect on overall survival for an adjuvant treatment consisting of bolus fluorouracil plus folinic acid, when compared with a mixed chemoradiotherapy and observation-only group.[14] The median survival times were 20.1 and 15.5 months, with a hazard ratio for death of 0.71 ($P = .009$). However, definite conclusions from that trial are hampered by the complicated factorial design of the study, which resulted in uncontrollable confounding and interactions as sources of bias, as has been widely discussed elsewhere.[15,16]

Figure 3. Disease-Free and Overall Survival

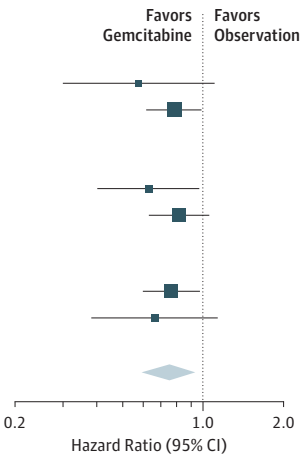
A Disease-free survival

Subcategory	Gemcitabine Events, No.	Gemcitabine Total Patients, No.	Observation Events, No.	Observation Total Patients, No.	Hazard Ratio (95% CI)
Primary tumor stage					
T1-2	18	25	20	24	0.50 (0.26-0.95)
T3-4	127	154	143	151	0.56 (0.44-0.71)
Test for heterogeneity: $\chi^2_1 = 0.10$; $P = .76$; $I^2 = 0\%$					
Nodal status					
N0	37	52	42	48	0.57 (0.36-0.89)
N1	108	127	121	127	0.53 (0.40-0.68)
Test for heterogeneity: $\chi^2_1 = .09$; $P = .77$; $I^2 = 0\%$					
Resection status					
R0	117	145	137	148	0.59 (0.46-0.76)
R1	28	34	26	27	0.33 (0.19-0.58)
Test for heterogeneity: $\chi^2_1 = 3.46$; $P = .06$; $I^2 = 71\%$					
Total (95% CI)	145	179	163	175	0.55 (0.44-0.69)
Test for overall effect: $z = 5.17$; $P < .001$					



B Overall survival

Subcategory	Gemcitabine Events, No.	Gemcitabine Total Patients, No.	Observation Events, No.	Observation Total Patients, No.	Hazard Ratio (95% CI)
Primary tumor stage					
T1-2	17	25	20	24	0.58 (0.30-1.10)
T3-4	139	154	140	151	0.78 (0.61-0.99)
Test for heterogeneity: $\chi^2_1 = 0.74$; $P = .39$; $I^2 = 0\%$					
Nodal status					
N0	40	52	41	48	0.63 (0.40-0.97)
N1	116	127	119	127	0.81 (0.63-1.06)
Test for heterogeneity: $\chi^2_1 = 1.02$; $P = .31$; $I^2 = 2\%$					
Resection status					
R0	125	145	135	148	0.76 (0.60-0.98)
R1	31	34	25	27	0.66 (0.39-1.13)
Test for heterogeneity: $\chi^2_1 = 0.23$; $P = .63$; $I^2 = 0\%$					
Total (95% CI)	156	179	160	175	0.75 (0.60-0.94)
Test for overall effect: $z = 2.54$; $P = .01$					



Size of data markers indicates the amount of statistical information in the respective subgroup.

However, the 5-FU chemotherapy data from the ESPAC-1 trial are being supported by the ESPAC-3 trial.[17] In this large, randomized phase 3 trial, 1088 patients with resected pancreatic ductal adenocarcinoma were randomized to receive either fluorouracil plus folinic acid (intravenous bolus injection given 1-5 days every 28 days) or gemcitabine (1 g/m^2, intravenous infusion, once a week for 3 of every 4 weeks) for 6 months. The primary outcome in the trial was overall survival. In an intention-to-treat analysis performed after a median of 34.2 months follow-up and 753 deaths (69%), median survival was 23.0 (95% CI, 21.1-25.0) months for patients treated with fluorouracil and 23.6 (95% CI, 21.4-26.4) months for those treated with gemcitabine. A total of 14% of patients receiving fluorouracil had 97 treatment-related serious adverse events, compared with 7.5% in the gemcitabine group ($P < .001$). No significant differences in either progression-free survival or global quality-of-life scores between the treatment groups were reported. Thus, median overall survival in this trial, as well as 3- and 5-year survival rates, was similar to the long-term follow-up results of CONKO-001 (median follow-up, 136 months).

The recently published Japanese JASPAC-01 (Japan Adjuvant Study Group of Pancreatic Cancer 01)[18] phase 3 study in patients with stages I-III pancreatic cancer compared treatment with S-1 (80/100/120 mg/d based on body surface area, by mouth, d1-28, q6w, for 4 courses) vs gemcitabine (similar to CONKO-001). Toxicities were comparable in both groups. Rates of disease-free survival at 2 years were 49% vs 29% for S-1 vs gemcitabine, respectively; corresponding rates of overall survival at 2 years were 70% vs 53%. A longer follow-up would be needed to find out if the disease-free survival advantage of S-1 vs gemcitabine translates into an overall survival advantage for S-1. Based on the study, S-1 seems to be an effective agent for Asian patients with pancreatic cancer.

The effectiveness of any gemcitabine-based therapy in pancreatic cancer is dependent on uptake of the drug into the tumor cells. The human equilibrative nucleoside transporter-1

(hENT1) has been identified as a potential predictor of overall survival in treatment with gemcitabine.[19] Multivariable analyses of the adjuvant ESPAC-1 and ESPAC-3 randomized trials confirmed increased intratumoral hENT1 expression as a predictive marker for response to gemcitabine (Wald $\chi^2 = 7.10$, $P = .008$) but not to fluorouracil (Wald $\chi^2 = 0.34$, $P = .56$).[20] However, contrary to these retrospective results, hENT1 status had no significant effect on survival for patients receiving gemcitabine in a phase 3 study in the metastatic setting with CO101, a modified gemcitabine.[21]

The role of radiotherapy or chemoradiation therapy in the adjuvant treatment of pancreatic cancer remains unclear. The favorable results of the GITSG (Gastrointestinal Tumor Study Group)[22] trial for adjuvant fluorouracil-based chemoradiation therapy in a small study could not be confirmed by a subsequent trial from the EORTC (European Organisation for Research and Treatment of Cancer)[23] that failed to show statistical significance for a trend toward prolonged survival in 114 patients with pancreatic cancer. Likewise, the contribution of irradiation could not be clarified definitively in the large (442 eligible patients) RTOG (Radiation Therapy Oncology Group) trial, which showed a median survival significantly prolonged by almost 4 months in the subgroup with pancreatic head tumors by the addition of gemcitabine, because chemoradiation therapy was used as a backbone in both groups.[24,25] The results of ESPAC-1 uniformly imply a detrimental effect of the concurrent modality approach in comparison with chemotherapy alone or observation only. Results from the large (442 patients) international phase 3 LAP 07 study[26] comparing chemoradiation therapy and chemotherapy in patients with locally advanced pancreatic cancer without disease progression after a 4-month course of gemcitabine induction chemotherapy demonstrated no beneficial effect on overall survival for chemoradiation therapy vs chemotherapy alone. Therefore, chemotherapy with gemcitabine should remain the standard of care following R0/R1 resections and for the treatment of locally advanced pancreatic cancer. Chemoradiation therapy should only be performed within clinical trials to acquire more reliable information about the benefit of this approach. Recently a randomized EORTC phase 2 study explored the feasibility and tolerability of a gemcitabine-based chemoradiation therapy regimen after R0 resection of pancreatic head cancer. Adjuvant gemcitabine-based chemoradiation therapy was feasible and not deleterious.[27] The ongoing RTOG 0848 phase 3 protocol (joined by the EORTC gastrointestinal group) is testing the addition of erlotinib to gemcitabine for 5 cycles (first randomization). In addition, in patients with no recurrence, a second randomization compares a cycle of chemotherapy with a cycle of chemotherapy followed by chemoradiation plus either capecitabine or fluorouracil in patients with resected pancreatic carcinoma.

Despite the increasing evidence for a survival benefit of gemcitabine-based chemotherapy in the adjuvant setting, the results are far from optimal. Our study group builds on the CONKO-001 results and is currently testing gemcitabine monotherapy against gemcitabine combination therapy in the adjuvant setting: CONKO-005 (EudraCT2007-003813-15) is testing gemcitabine vs gemcitabine plus erlotinib in patients with R0 resection and has completed enrollment of 450 patients. For patients with R1 resection, a study of gemcitabine vs gemcitabine plus sorafenib for 1 year (CONKO-006) (EudraCT2007-000718-35) is closing enrollment as well.

In the currently recruiting ESPAC-4 trial (EudraCT2007-004299-38), patients with resectable pancreatic cancer or periampullary cancer are being randomized to gemcitabine plus capecitabine or gemcitabine monotherapy. Completion of enrollment is scheduled for November 2014.

Because of the relatively high remission rates of approximately 30% and a significant prolongation of survival in metastatic pancreatic cancer, treatment with leucovorin calcium/fluorouracil/irinotecan hydrochloride/oxaliplatin (FOLFIRINOX)[28] or gemcitabine in combination with nab-paclitaxel,[29] compared with gemcitabine monotherapy, may also be of value in the adjuvant setting. Studies with these combinations are in the planning phase.

Conclusion

The CONKO-001 data show that among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 months compared with observation resulted in increased overall survival as well as disease-free survival. These findings support the use of gemcitabine in this setting.

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