ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

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ABSTRACT

BACKGROUND

Data are lacking on the efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer.

METHODS

We randomly assigned 342 patients with an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating a greater severity of illness) to receive FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at a dose of 1000 mg per square meter weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks. Six months of chemotherapy were recommended in both groups in patients who had a response. The primary end point was overall survival.

RESULTS

The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001).

CONCLUSIONS

As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status. (Funded by the French government and others; ClinicalTrials.gov number, NCT00112658.)

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Pancreatic adenocarcinoma was the fourth leading cause of death from cancer in the United States in 2010,[1] and it carries a grim prognosis: the 5-year survival rate is 6% in Europe and the United States.[1,2] Gemcitabine became the reference regimen for advanced pancreatic cancer after a randomized trial showed significant improvement in the median overall survival as compared with fluorouracil administered as an intravenous bolus (5.6 vs. 4.4 months, P=0.002).[3] In the subsequent phase 3 trials of single-agent gemcitabine,[4] the median overall survival ranged from 5.0 to 7.2 months. The combination of gemcitabine with a variety of cytotoxic and targeted agents has generally shown no significant survival advantage as compared with gemcitabine alone.[4] Some studies have suggested a significant benefit associated with gemcitabine-based cytotoxic combinations in patients with good performance status.[5-7]

Irinotecan has some clinical activity against advanced pancreatic cancer.[8,9] Preclinical studies have indicated that irinotecan has synergistic activity when it is administered before fluorouracil and leucovorin.[10-13] Oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil.[14] Oxaliplatin and irinotecan show synergistic activity in vitro.[15] Given the relative absence of overlapping toxic effects among fluorouracil, leucovorin, irinotecan, and oxaliplatin, a regimen combining these agents was studied in a phase 1 trial and showed responses in patients with advanced pancreatic cancer.[16] Accordingly, we conducted a phase 2 study of the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil, and leucovorin) involving 46 patients with good performance status and advanced pancreatic cancer; this regimen was associated with encouraging efficacy and grade 3 or 4 neutropenia in half the patients.[17] These results prompted the initiation of a phase 2-3 trial to further explore FOLFIRINOX as compared with single-agent gemcitabine as first-line treatment in patients with metastatic pancreatic cancer.

Methods

Patients

Patients were eligible to be included in the study if they were 18 years of age or older and had histologically and cytologically confirmed, measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature [e.g., light housework or office work])[18] and adequate bone marrow (granulocyte count, ≥1500 per cubic millimeter; and platelet count, ≥100,000 per cubic millimeter), liver function (bilirubin ≤1.5 times the upper limit of the normal range), and renal function.

Exclusion criteria were an age of 76 years or older, endocrine or acinar pancreatic carcinoma, previous radiotherapy for measurable lesions, cerebral metastases, a history of another major cancer, active infection, chronic diarrhea, a clinically significant history of cardiac disease, and pregnancy or breast-feeding.

Study Design and Oversight

This multicenter, randomized, phase 2–3 trial was conducted at 15 centers during phase 2 and expanded to 48 centers during phase 3. Patients were randomly assigned to receive FOLFIRINOX or gemcitabine within 1 week after enrollment. Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization (the head vs. the body or tail of the pancreas).

The study was approved by the Lorraine ethics committee. All patients provided written informed consent. An independent data and safety monitoring committee supervised the collation of efficacy and safety data. The trial was conducted according the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and relevant French and European laws and directives. The study was designed and the first draft of the manuscript was prepared by the first author, with writing assistance from an employee of the sponsor, Unicancer, and in cooperation with the other authors. Data were collected at the headquarters of the French anticancer centers (Unicancer, the study sponsor) and analyzed by the statistician, who vouches for the accuracy of the data. Oxaliplatin and irinotecan were donated by Sanofi-Aventis and Pfizer, respectively; these drug manufacturers had no role in the design of the study, in the accrual or analysis of the data, or in the preparation of the manuscript.

The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The first author vouches for the fidelity of the study to the protocol.

TREATMENT

Gemcitabine, at a dose of 1000 mg per square meter of body-surface area, was delivered by 30-minute intravenous infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3 weeks in subsequent 4-week courses. FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg per square meter over a 46-hour period every 2 weeks. In the gemcitabine group, a cycle was also defined as a 2-week interval. Six months of chemotherapy was recommended for patients who had a response. Patients were followed every 3 months until death.

In the event of predefined toxic events, protocol-specified treatment modifications were permitted (see the Supplementary Appendix, available at NEJM.org). Doses of gemcitabine were reduced by 25% if the granulocyte count decreased to 500 to 999 per cubic millimeter or if the platelet count was 50,000 to 100,000 per cubic millimeter. In case of grade 2, 3, or 4 neutropenia or thrombocytopenia, FOLFIRINOX administration was delayed until recovery and doses were reduced. Filgrastim was not recommended as primary prophylaxis, but it could be considered for high-risk patients.

ASSESSMENTS

At the start of every cycle, the patient's status was assessed according to his or her medical history, complete physical examination by a physician, ECOG performance status, and complete blood counts and blood chemical tests. Baseline evaluations also included measurement of the serum carbohydrate antigen 19-9 level, a computed tomographic (CT) evaluation, and assessment of the patient's quality of life with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30, version 3.0).[19]

EORTC QLQ-C30 questionnaires were to be completed every 2 weeks. Safety assessments were performed before each cycle with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[20] Tumors were measured every 2 months.

Patients discontinued the study in the event of unacceptable toxic effects or evidence of progressive disease, or at their request. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (see the Supplementary Appendix).[21] Independent review of CT scans was performed at the end of phase 2 of the study. Overall survival and progression-free survival were calculated from the date of randomization until the date of death and the date of documentation of disease progression or death in patients without disease progression, respectively.

STATISTICAL ANALYSIS

The primary efficacy end point for the phase 2 analysis was tumor response, and the secondary end point was safety. The trial was planned to continue as a phase 3 study if more than 11 responses were observed in the first 40 patients who were randomly assigned to the FOLFIRINOX group. Patients from the phase 2 analysis were included in the phase 3 analysis. The primary end point for the phase 3 analysis was overall survival. Secondary end points were progression-free survival, tumor response, safety, and quality of life. The statistical considerations are detailed in the Sample Size Determination section in the Supplementary Appendix.

All analyses were performed on an intention-to-treat basis. Qualitative variables were compared with the use of the chi-square test or Fisher's test, quantitative variables with the use of Student's t-test or a nonparametric (Wilcoxon) test, and survival data with the use of a stratified log-rank test. All these comparisons were adjusted for stratification factors. All tests were two-sided, with a P value of less than 0.05 considered to indicate statistical significance. Data are presented with 95% confidence intervals, calculated with the use of standard methods based on a binomial distribution. All analyses were performed with the use of Stata software, version 10.

Overall survival and progression-free survival were estimated with the use of the Kaplan–Meier method.[22] A Cox proportional-hazards model was

Table 1. Demographic and Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	FOLFIRINOX (N=171)	Gemcitabine (N=171)
Age — yr		
Median	61	61
Range	25–76	34–75
Sex — no. (%)		
Male	106 (62.0)	105 (61.4)
Female	65 (38.0)	66 (38.6)
ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
Pancreatic tumor location — no. (%)		
Head	67 (39.2)	63 (36.8)
Body	53 (31.0)	58 (33.9)
Tail	45 (26.3)	45 (26.3)
Multicentric	6 (3.5)	5 (2.9)
Biliary stent — no. (%)		
Yes	27 (15.8)	22 (12.9)
No	144 (84.2)	149 (87.1)
No. of metastatic sites involved		
Median	2	2
Range	1–6	1–6
Level of carbohydrate antigen 19-9 — no./total no. (%)		
Normal	24/164 (14.6)	23/165 (13.9)
Elevated, <59×ULN	72/164 (43.9)	65/165 (39.4)
Elevated, ≥59×ULN	68/164 (41.5)	77/165 (46.7)
Unknown	7/171 (4.1)	6/171 (3.5)
No. of measurable metastatic sites — no. of patients/total no. (%)		
Liver	149/170 (87.6)	150/171 (87.7)
Pancreas	90/170 (52.9)	91/171 (53.2)
Lymph node	49/170 (28.8)	39/171 (22.8)
Lung	33/170 (19.4)	49/171 (28.7)
Peritoneal	33/170 (19.4)	32/171 (18.7)
Other	18/170 (10.6)	29/171 (17.0)

* ECOG denotes Eastern Cooperative Oncology Group; FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin; and ULN upper limit of the normal range.

used to estimate the hazard ratios. Hazard ratios indicating the effects of prognostic factors on the risk of death were calculated and are shown in a forest plot.[23] The interaction test was used to assess the heterogeneity of treatment effects for subgroup analyses.[24]

Analysis of the QLQ-C30 questionnaires was performed in accordance with the EORTC guidelines.[25] The preplanned analysis centered on the scales that are usually most affected in patients with pancreatic cancer: the Global Health Status and Quality of Life scale and scales for fatigue, pain, physical functioning, emotional functioning, and role functioning.[26] The other QLQ-C30 domains were only examined in an exploratory manner. Time to definitive deterioration in quality of life, with the use of a 10-point minimal clinically important difference,[27,28] was analyzed with the use of the Kaplan–Meier method and the log-rank test.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between December 2005 and October 2009, a total of 342 patients from 48 French centers were enrolled in the study. The database was closed for final analysis on April 16, 2010. The intention-to-treat population included 171 patients in each group, and the safety population (all patients who received treatment) included 167 patients in the FOLFIRINOX group and 169 patients in the gemcitabine group (Fig. I in the Supplementary Appendix). There were similar numbers of patients with minor violations of eligibility criteria in the FOLFIRINOX and gemcitabine groups (8 and 7, respectively).

Demographic and baseline disease characteristics of the patients were similar in the two treatment groups (Table 1), but there were fewer measurable target lung metastases in the FOLFIRINOX group than in the gemcitabine group (19.5% vs. 28.7%, P=0.05).

The median number of treatment cycles administered was 10 (range, 1 to 47) in the FOLFIRINOX group and 6 (range, 1 to 26) in the gemcitabine group (P<0.001). More patients in the gemcitabine group had disease progression before 12 cycles (6 months) (79.9%, vs. 54.6% in the FOLFIRINOX group; P<0.001). The median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.

EFFICACY

Response to Therapy

A total of 88 patients were recruited between January 2005 and November 2006 during phase 2 of this study. The confirmed response rate, according to the investigators, was 31.8% (14 of 44 pa-

tients) in the FOLFIRINOX group and 11.3% (5 of 44 patients) in the gemcitabine group. Independent review confirmed an objective response rate of 34.1% (in 15 patients) in the FOLFIRINOX group. Since the primary objective of phase 2 was met, the trial proceeded to phase 3. All patients in phase 2 continued treatment, and data on these patients are fully reported in the phase 3 efficacy and safety results.

The response to therapy in the phase 3 trial is summarized in Table 2. The objective response rate was 31.6% (95% confidence interval [CI], 24.7 to 39.1) in the FOLFIRINOX group and 9.4% (95% CI, 5.4 to 14.7) in the gemcitabine group (P<0.001). In both groups, after 12 cycles, chemotherapy could be discontinued in patients with a response or stable disease; in 7.6% of the patients in the FOLFIRINOX group and 7.0% of those in the gemcitabine group, the same regimen was reintroduced with the use of a stop-and-go strategy.

Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

* CI denotes confidence interval, and FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin.
† The rate of objective response was defined as the percentage of patients who had a complete response or partial response.
‡ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease.

Survival

The median duration of follow-up was 26.6 months (95% CI, 20.5 to 44.9). The overall survival analysis was based on 273 deaths among the 342 patients (79.8%). The median overall survival was 11.1 months (95% CI, 9.0 to 13.1) in the FOLFIRINOX group as compared with 6.8 months (95% CI, 5.5 to 7.6) in the gemcitabine group (hazard ratio for death, 0.57; 95% CI, 0.45 to 0.73; P<0.001) (Fig. 1A). Overall survival rates at 6, 12, and 18 months were 75.9%, 48.4%, and 18.6%, respectively, in the FOLFIRINOX group as compared with 57.6%, 20.6%, and 6.0%, respectively, in the gemcitabine group.

Synchronous metastases, a low baseline albumin level (<3.5 g per deciliter), hepatic metastases, and an age of more than 65 years were identified as independent adverse prognostic factors for overall survival (see the Supplementary Appendix). The hazard ratio for death with FOLFIRINOX treatment, adjusted for these variables, was significant (adjusted hazard ratio, 0.54; 95% CI, 0.41 to 0.73; P<0.001). Results were similar when adjusted according to the presence or absence of pulmonary metastases. The effect of FOLFIRINOX was homogeneous in all subgroups (Fig. 2).

The analysis of progression-free survival was based on 317 events among 342 patients (92.7%). The median progression-free survival was 6.4 months (95% CI, 5.5 to 7.2) in the FOLFIRINOX group as compared with 3.3 months (95% CI, 2.2 to 3.6) in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001) (Fig. 1B). Progression-free survival rates at 6, 12, and 18 months were 52.8%, 12.1%, and 3.3%, respectively, in the FOLFIRINOX group as compared with 17.2%, 3.5%, and 0%, respectively, in the gemcitabine group.

SECOND-LINE THERAPY

Second-line therapy was administered in 80 patients in the FOLFIRINOX group and in 85 patients in the gemcitabine group. No difference in median survival was noted between the groups (4.4 months in each group) from the introduction of second-line therapy. The most common second-line regimens were as follows: in the FOLFIRINOX group, gemcitabine (in 82.5% of the patients) or a gemcitabine-based combination (in 12.5%), and in the gemcitabine group, a combination of fluorouracil, leucovorin, and oxaliplatin (FOLFOX) (in 49.4%); gemcitabine plus oxaliplatin (in 17.6%); a regimen of fluorouracil and leucovorin plus cisplatin every 2 weeks (in 16.5%); and FOLFIRINOX (in 4.7%).

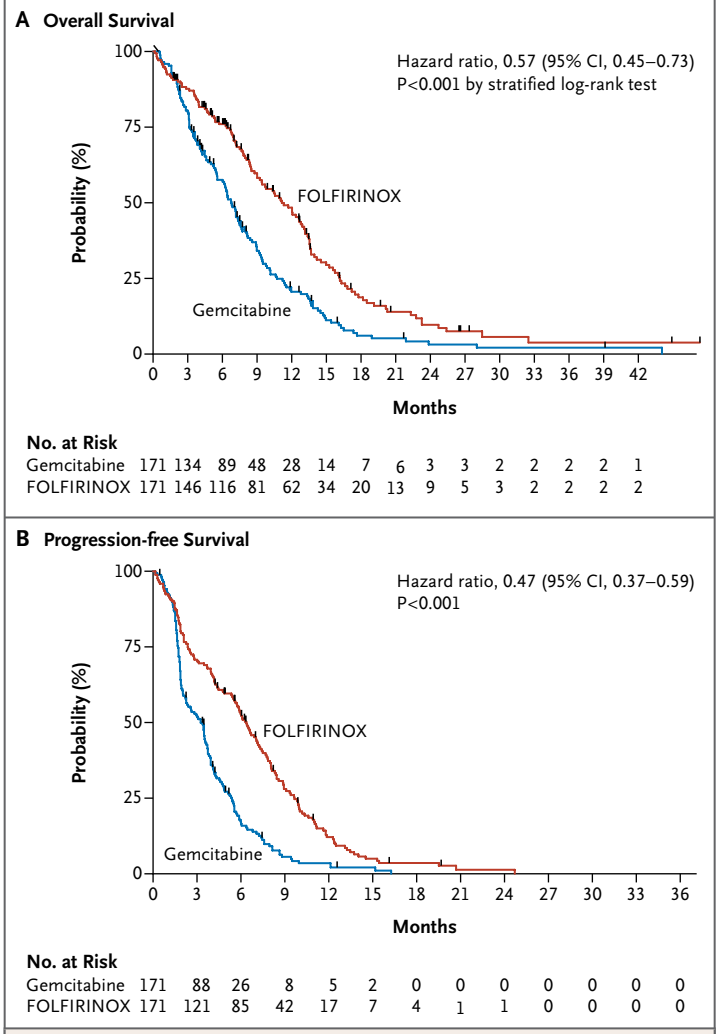

Figure 1. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival, According to Treatment Group.

Panel A shows overall survival; the median was 11.1 months in the group receiving FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). Panel B shows progression-free survival; the median was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group.

ADVERSE EVENTS

Two patients died from treatment-related cause: one from febrile neutropenia in the FOLFIRINOX group and one from cardiac decompensation in the gemcitabine group. Treatment-related grade 3 or 4 adverse events occurring in more than 5% of patients in either treatment group are summarized in Table 3. Incidences of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were significantly higher in the FOLFIRINOX group, whereas the incidence of grade 3 or 4 elevated alanine aminotransferase levels was significantly higher in the gemcitabine group. Grade 2 alopecia occurred in 11.4% of patients in the FOLFIRINOX group and in 1.2% of patients in the gemcitabine group (P<0.001). No cholangitis was observed. In both groups, the hematologic toxicity and the risk of infection were similar with or without placement of a biliary stent. Filgrastim was administered in 42.5% of patients who received FOLFIRINOX and in 5.3% of patients who received gemcitabine (P<0.001).

QUALITY OF LIFE

The proportion of patients with QLQ-C30 questionnaires that could be evaluated at baseline was 95.3% in the FOLFIRINOX group and 95.9% in the gemcitabine group. No significant differences between the groups were noted at baseline in the QLQ-C30 scales or single items. Subsequently, the rate of compliance with completion of the QLQ-C30 questionnaire was high: 78.2% in the FOLFIRINOX group and 77.4% in the gemcitabine group. No significant differences were noted between the groups in the Global Health Status and Quality of Life scale or in the individual domains, except that the FOLFIRINOX group had higher scores for diarrhea during the first eight cycles.

At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive decrease in the scores on the Global Health Status and Quality of Life scale versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001) (Fig. II in the Supplementary Appendix). Significant increases in the time until definitive deterioration in the quality of life were also noted in the FOLFIRINOX group for all functional and symptom scales and with respect to appetite loss, dyspnea, and constipation. Time to a definitive decrease in the scores that were associated with diarrhea, insomnia, or financial difficulties caused by a physical condition or medical treatment did not differ significantly between regimens.

DISCUSSION

In this study, FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status. The median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months).

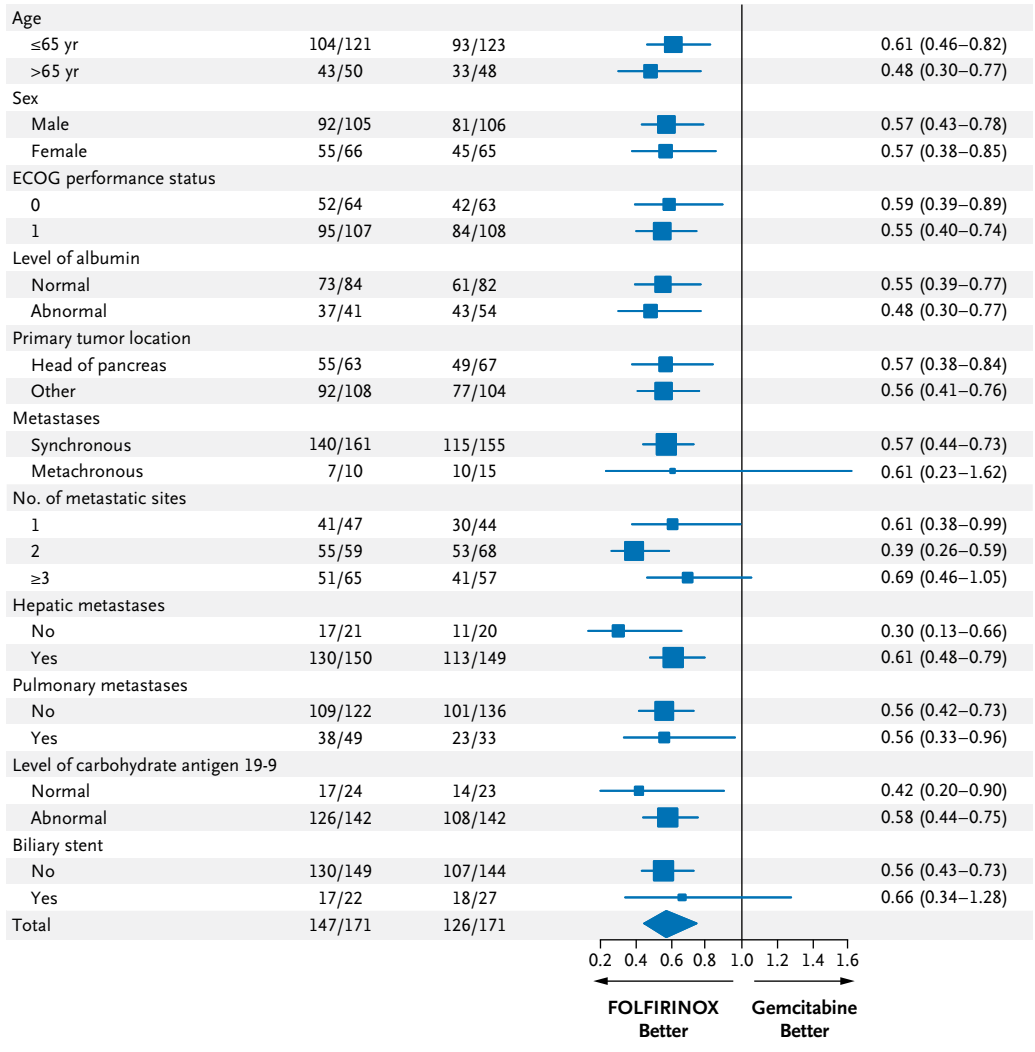

Figure 2. Forest Plot of the Treatment Effect on Overall Survival in Subgroup Analyses.

The Eastern Cooperative Oncology Group (ECOG) grades the status of patients with respect to activities of daily living, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work). The sizes of the squares are proportional to the sizes of the subgroups. Horizontal lines represent 95% confidence intervals. The position of each square represents the point estimate of the treatment effect.

Single-agent gemcitabine is the current standard of care,[4,29] but the addition of cytotoxic and targeted agents to gemcitabine has almost invariably provided no significant survival improvement,[4] despite an improvement in response rates in some trials.[30-34] Conversely, one phase 3 trial involving 569 patients with locally advanced or metastatic cancer showed a significant prolongation of overall survival with the combination of erlotinib and gemcitabine as compared with gemcitabine alone (hazard ratio for death, 0.82; 95% CI, 0.69 to 0.99; P=0.04). However, the magnitude of the improvement in median overall survival was modest, at 0.33 months (6.24 vs. 5.91 months).[35]

Recently, a phase 3 trial involving 543 patients with advanced pancreatic cancer showed that the combination of capecitabine and gemcitabine as

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

compared with gemcitabine alone resulted in an increased response rate (19.1% vs. 12.4%, P=0.03) and improved progression-free survival (hazard ratio for disease progression, 0.78; 95% CI, 0.66 to 0.93; P=0.04), as well as a trend toward improvement in overall survival (hazard ratio for death, 0.86; 95% CI, 0.72 to 1.02; P=0.08).[31] The median survival among patients who received capecitabine plus gemcitabine was 7.1 months, versus 6.2 months among patients who received gemcitabine alone. The authors performed a meta-analysis of their study and two similar but smaller studies. These results showed a significant survival benefit with gemcitabine plus capecitabine as compared with gemcitabine alone (hazard ratio, 0.86; 95% CI, 0.75 to 0.98; P=0.02). The efficacy results obtained with gemcitabine in our study are in line with the results of these studies, as well as the findings in other trials of single-agent gemcitabine in patients with advanced pancreatic cancer.[4,29]

The patient-selection criteria in our study were more rigorous than those in previous studies. Patients had to have metastatic disease and a good performance status (ECOG status score of 0 or 1). Only 38% of our patients had carcinoma of the pancreatic head — a lower rate than in previous trials (52 to 70%).[6,31,32] This difference may be related to the exclusion of patients with a high bilirubin level, because of the increased risk of irinotecan-induced toxicity.[8] As a result of this exclusion criterion, the proportion of enrolled patients with biliary stents was low (14.3%). Cholangitis is a common complication of biliary stenting, and although it did not occur in any of the patients in our study, careful monitoring of the bilirubin level is required when irinotecan is administered in patients with biliary drainage.

The safety profile of FOLFIRINOX was less favorable than that of gemcitabine. FOLFIRINOX was associated with a higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia. Despite the higher incidence of adverse events associated with the FOLFIRINOX regimen, a significant increase in the time to definitive deterioration of the quality of life was observed in the FOLFIRINOX group as compared with the gemcitabine group.

In conclusion, our findings suggest that FOLFIRINOX is a first-line option for patients with metastatic pancreatic cancer who are younger than 76 years and who have a good performance status (ECOG 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels.

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