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FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

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ABSTRACT

BACKGROUND

Among patients with metastatic pancreatic cancer, combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) leads to longer overall survival than gemcitabine therapy. We compared the efficacy and safety of a modified FOLFIRINOX regimen with gemcitabine as adjuvant therapy in patients with resected pancreatic cancer.

METHODS

We randomly assigned 493 patients with resected pancreatic ductal adenocarcinoma to receive a modified FOLFIRINOX regimen (oxaliplatin [85 mg per square meter of body-surface area], irinotecan [180 mg per square meter, reduced to 150 mg per square meter after a protocol-specified safety analysis], leucovorin [400 mg per square meter], and fluorouracil [2400 mg per square meter] every 2 weeks) or gemcitabine (1000 mg per square meter on days 1, 8, and 15 every 4 weeks) for 24 weeks. The primary end point was disease-free survival. Secondary end points included overall survival and safety.

RESULTS

At a median follow-up of 33.6 months, the median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group (stratified hazard ratio for cancer-related event, second cancer, or death, 0.58; 95% confidence interval [CI], 0.46 to 0.73; P<0.001). The disease-free survival rate at 3 years was 39.7% in the modified-FOLFIRINOX group and 21.4% in the gemcitabine group. The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (stratified hazard ratio for death, 0.64; 95% CI, 0.48 to 0.86; P=0.003). The overall survival rate at 3 years was 63.4% in the modified-FOLFIRINOX group and 48.6% in the gemcitabine group. Adverse events of grade 3 or 4 occurred in 75.9% of the patients in the modified-FOLFIRINOX group and in 52.9% of those in the gemcitabine group. One patient in the gemcitabine group died from toxic effects (interstitial pneumonitis).

CONCLUSIONS

Adjuvant therapy with a modified FOLFIRINOX regimen led to significantly longer survival than gemcitabine among patients with resected pancreatic cancer, at the expense of a higher incidence of toxic effects. (Funded by R&D Unicancer and others; ClinicalTrials.gov number, NCT01526135; EudraCT number, 2011-002026-52.)

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Pancreatic adenocarcinoma is a major cause of cancer-related death in Western countries and is anticipated to emerge as the second leading cause of cancer-related death in the United States by 2030.[1] The prognosis of patients with pancreatic cancer has changed little over the past two decades,[2] and according to recent studies, it is estimated that almost 44,000 persons in the United States[3] and 89,000 in Europe[4] will die from this disease in 2018.

Surgery offers the only chance of cure, but 5-year survival rates after surgical resection alone are low (approximately 10%).[5,6] A 6-month regimen of adjuvant therapy with gemcitabine[6,7] or a fluoropyrimidine (fluorouracil plus leucovorin[5,8] or S-1 in Japan[9]) has been shown to significantly improve outcomes and is recognized as standard care in patients with resected pancreatic cancer.[2,10] However, recurrence rates remain high despite adjuvant treatment, with 69 to 75% of patients having a relapse within 2 years.[7,8,11]

The combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has resulted in longer overall survival than gemcitabine when administered as first-line treatment in patients with metastatic pancreatic cancer.[12] On the basis of these results, we initiated a phase 3 trial to explore the efficacy of FOLFIRINOX, as compared with gemcitabine, as adjuvant therapy after resection of pancreatic cancer. A modified version of the FOLFIRINOX regimen, without bolus fluorouracil, was used to decrease the incidence and severity of hematologic toxic effects and diarrhea and has been shown to not reduce treatment efficacy in patients with advanced disease.[13]

Methods

Trial Oversight

The trial was designed under the auspices of the PRODIGE (Partenariat de Recherche en Oncologie Digestive) intergroup and the Canadian Cancer Trials Group. An independent data and safety monitoring committee was established to review all the trial data and to ensure the ethical conduct of the trial. A central review of surgical reports, postsurgical computed tomographic (CT) and magnetic resonance imaging (MRI) scans, and pathology reports was performed to confirm the eligibility of the patients and to check major prognostic factors. R&D Unicancer (one of the trial sponsors) and its representatives collected and analyzed the data. All the versions of the manuscript were prepared by the authors (two of whom are employees of R&D Unicancer), with editorial and writing assistance funded by R&D Unicancer. The investigators agreed to keep all the aspects of the trial confidential. All the authors reviewed the manuscript and made the decision to submit it for publication. All the authors vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol, available with the full text of this article at NEJM.org. Oxaliplatin was supplied to the Canadian centers by Sanofi-Aventis Canada, which had no role in the trial design, the data collection or analysis, or the manuscript preparation or review.

Patients

Patients 18 to 79 years of age who had histologically confirmed pancreatic ductal adenocarcinoma, who had undergone complete macroscopic (R0 [no cancer cells within 1 mm of all resection margins] or R1 [cancer cells present within 1 mm of one or more resection margins]) resection within 3 to 12 weeks before randomization, and who had no evidence of metastatic disease, malignant ascites, or pleural effusion were eligible for inclusion. Other inclusion criteria were full recovery from surgery, a World Health Organization (WHO) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability), and adequate hematologic function (absolute neutrophil count, ≥1500 per cubic millimeter; platelet count, ≥100,000 per cubic millimeter; and hemoglobin level, ≥10 g per deciliter), liver function (serum total bilirubin level, ≤1.5 times the upper limit of the normal range), and renal function (creatinine clearance, ≥50 ml per minute). Patients with nonductal pancreatic tumors, incomplete (R2) resection, a serum CA 19-9 level of more than 180 U per milliliter within 21 days before randomization, receipt of previous chemotherapy or radiotherapy, or symptomatic heart failure or coronary heart disease were ineligible.

Trial Design

This multicenter, randomized, open-label, phase 3 trial (PRODIGE 24–ACCORD [Actions Concertées dans les Cancers Colorectaux et Digestifs] 24 and CCTG PA [Canadian Cancer Trials Group Pancre-

atic Adenocarcinoma] 6) was conducted at 77 hospitals in France and Canada. Patients were randomly assigned to start receiving the modified FOLFIRINOX regimen or gemcitabine within 1 week after enrollment. Randomization at a 1:1 ratio was performed centrally with the use of an independent Web-based system, with stratification according to trial center, lymph-node status (pN0 [no lymph-node involvement] or pN1 [lymph-node involvement]), resection status (R0 vs. R1), and CA 19-9 level (≤90 U per milliliter vs. 91 to 180 U per milliliter). Randomization of patients with pN0 status was also stratified according to the number of lymph nodes examined (<12 vs. ≥12).

The trial protocol was approved by an independent ethics committee in France (Comité de Protection des Personnes Est III) and by ethics committees at participating centers in Canada. All the patients provided written informed consent. The trial was conducted in accordance with the latest version of the Declaration of Helsinki, with the Good Clinical Practice guidelines of the International Conference on Harmonisation, and with relevant French, European, and Canadian laws and directives.

TREATMENT REGIMENS

Gemcitabine at a dose of 1000 mg per square meter of body-surface area was delivered by means of a 30-minute intravenous infusion on days 1, 8, and 15 every 28 days for 24 weeks (6 cycles). The modified FOLFIRINOX regimen consisted of oxaliplatin, at a dose of 85 mg per square meter delivered as a 2-hour intravenous infusion, followed by leucovorin, at a dose of 400 mg per square meter given as a 2-hour intravenous infusion, and after 30 minutes, the addition of irinotecan at a dose of 180 mg per square meter administered as a 90-minute intravenous infusion, immediately followed by fluorouracil at a dose of 2400 mg per square meter administered by continuous intravenous infusion over a period of 46 hours, every 14 days for 24 weeks (12 cycles). The dose of irinotecan was reduced to 150 mg per square meter after the enrollment of 162 patients, in accordance with a protocol-specified safety analysis. In cases of febrile neutropenia or delay in treatment administration due to neutropenia, the use of granulocyte colony-stimulating factor (G-CSF) was advised for the following cycles. Protocol-specified treatment modifications were allowed when prespecified toxic effects occurred (see the Supplementary Appendix, available at NEJM.org).

END POINTS AND ASSESSMENTS

The primary end point was disease-free survival. Secondary end points were overall survival, metastasis-free survival, cancer-specific survival, and safety. Disease-free survival was calculated from the date of randomization until the date of the first cancer-related event, second cancer, or death from any cause. Overall survival was calculated from the date of randomization until death from any cause. Metastasis-free survival was calculated from the date of randomization until the date of the first detectable distant disease or death. Cancer-specific survival was calculated from the date of randomization until death due to the treated cancer or a treatment-related complication. Patients without events at the time of analysis had their data censored on the date of last informative follow-up.

Evaluations at baseline included a postoperative abdominal, thoracic, and pelvic CT scan (or MRI if the patient could not receive a contrast agent) and the assessment of postoperative serum CA 19-9 levels. At the start of every cycle, the status of the patient was assessed by means of a complete physical examination, WHO performance-status assessment, complete blood counts, and blood biochemical testing. Follow-up assessments included CT scans or MRI, serum CA 19-9 levels, and clinical examinations repeated every 3 months for 2 years and then every 6 months for 3 years. Patients with disease recurrence were monitored every 6 months for survival and long-term toxic effects. Safety assessments were performed before each cycle and until the end of follow-up. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[14]

STATISTICAL ANALYSIS

On the basis of a median overall survival benefit of 4.3 months with FOLFIRINOX among patients with metastatic pancreatic cancer,[12] we anticipated that the 3-year disease-free survival rate would be 10 percentage points higher with the modified FOLFIRINOX regimen than with gemcitabine therapy, which would correspond to a hazard ratio for cancer-related event, second

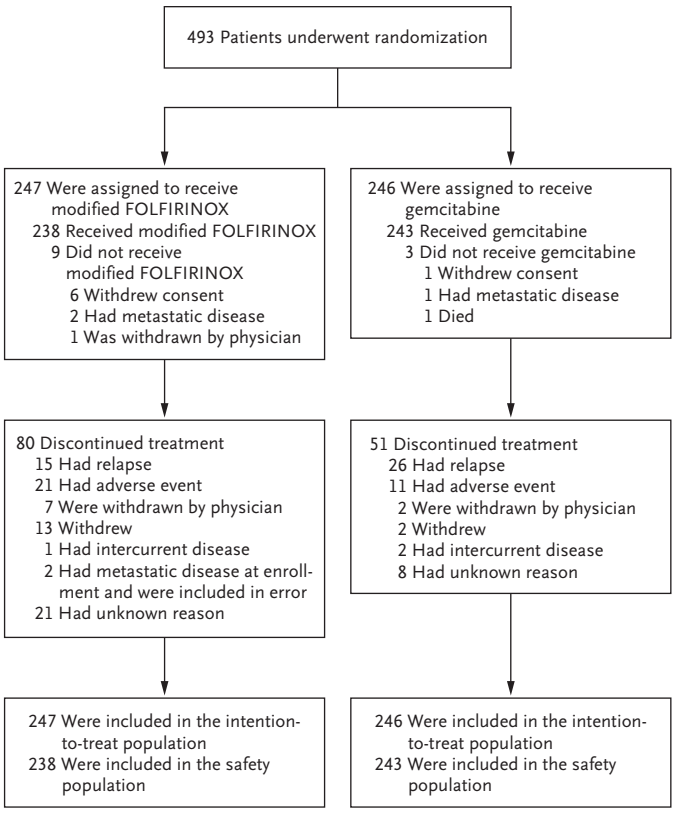


Figure 1. Randomization and Treatment of the Patients.

The modified FOLFIRINOX regimen consisted of fluorouracil (without bolus), leucovorin, irinotecan, and oxaliplatin.

cancer, or death of 0.74. We calculated that the inclusion of 490 patients (with 342 events required for the analyses) would provide the trial with 80% power to detect a difference of 10 percentage points in the 3-year disease-free survival rate at a two-sided significance level of 5%.

On February 5, 2018, for ethical reasons, the independent data and safety monitoring committee recommended early analysis and publication of the findings. The database was locked on April 13, 2018, at which time 314 cancer-related events, second cancers, or deaths from any cause (91.8% of the expected events regarding disease-free survival) had occurred. The findings from this analysis are presented here.

All the analyses were performed on an intention-to-treat basis, except for the safety analyses, which included only the treated patients. Qualitative variables were compared by the chi-square test or Fisher's exact test, and quantitative variables by the Kruskal–Wallis test. Survival rate estimates were calculated with the use of the Kaplan–Meier method[15] and compared with the use of a stratified log-rank test. A Cox proportional-hazards model (stratified according to the stratification factors, except for trial center) was used to estimate hazard ratios with 95% confidence intervals. The proportional-hazards assumption was verified by the Schoenfeld residual method.[16] All the tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

A Cox proportional-hazards model was used to evaluate the effects of prognostic factors on disease-free survival in univariate and multivariate analyses, including the effect size of treatment. Clinically relevant factors or variables with P values of less than 0.20 were explored further in a multivariate analysis with the use of ascending or descending selection techniques. Hazard ratios indicating the effects of prognostic factors were calculated and displayed in a forest plot.[17] The interaction test was used to assess the heterogeneity of treatment effects for subgroup analyses.[18] Exploratory analyses to identify risk factors for the occurrence of diarrhea were performed with the use of a logistic-regression model. All the analyses were performed with the use of Stata software, version 13.0 (StataCorp).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From April 2012 through October 2016, a total of 493 patients at 58 centers in France and 19 centers in Canada were randomly assigned to receive the modified FOLFIRINOX regimen (247 patients) or gemcitabine (246 patients); these patients constituted the intention-to-treat population (Fig. 1). A total of 9 patients in the modified-FOLFIRINOX group and 6 in the gemcitabine group had major violations of eligibility criteria, primarily because some patients were found to have metastatic disease (8 and 5 patients, respectively). The demographic and disease characteristics of the patients at baseline were similar in the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix), except for lymphovascular invasion, which was significantly more common in the modified-FOLFIRINOX group than in the gemcitabine group (73.7% vs. 63.1%, P=0.02).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)
Age		
Median (range) — yr	63 (30–79)	64 (30–81)
≥70 yr — no. (%)	47 (19.0)	54 (22.0)
Male sex — no. (%)	142 (57.5)	135 (54.9)
WHO performance-status score — no./total no. (%)†		
0	122/245 (49.8)	127/242 (52.5)
1	123/245 (50.2)	115/242 (47.5)
Status of surgical margins — no. (%)‡		
R0	148 (59.9)	134 (54.5)
R1	99 (40.1)	112 (45.5)
Tumor histologic findings — no./total no. (%)		
Ductal adenocarcinoma	244/247 (98.8)	242/245 (98.8)
Nonductal carcinoma	3/247 (1.2)	3/245 (1.2)
Tumor stage — no. (%)§		
I	12 (4.9)	14 (5.7)
IIA	43 (17.4)	47 (19.1)
IIB	183 (74.1)	179 (72.8)
III	1 (0.4)	1 (0.4)
IV	8 (3.2)	5 (2.0)
Lymphovascular invasion — no./total no. (%)	154/209 (73.7)	135/214 (63.1)
Perineural invasion — no. (%)	205/221 (92.8)	207/231 (89.6)
Surgery		
Venous resection — no./total no. (%)	53/245 (21.6)	69/245 (28.2)
Portal-vein resection — no. (%)	32 (13.0)	42 (17.1)
Superior-mesenteric-vein resection — no. (%)	19 (7.7)	25 (10.2)
Arterial resection — no./total no. (%)	8/247 (3.2)	7/245 (2.9)

* Patients in the modified-FOLFIRINOX group received fluorouracil (without bolus), leucovorin, irinotecan, and oxaliplatin. There were no significant differences between the two treatment groups, except for lymphovascular invasion (P=0.02).
† Scores for the World Health Organization (WHO) performance status are assessed on a 5-point scale, with higher numbers indicating greater disability; a score of 0 indicates that the patient is fully active and able to carry on activities without restriction, and a score of 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out light work.
‡ A surgical margin of R0 indicates that no cancer cells were present within 1 mm of all resection margins, and R1 the presence of cancer cells within 1 mm of one or more resection margins.
§ Tumor stage was assessed according to the 2009 tumor–node–metastasis (TNM) classification, 7th edition.[19]

TREATMENT

The median number of cycles was 12 (range, 1 to 12) in the modified-FOLFIRINOX group and 6 (range, 1 to 6) in the gemcitabine group (Table S2 in the Supplementary Appendix). The median duration of treatment was 24.6 weeks (range, 2.0 to 36.6) in the modified-FOLFIRINOX group and 24.0 weeks (range, 3.0 to 36.0) in the gemcitabine group. A total of 158 patients (66.4%) in the modified-FOLFIRINOX group and 192 patients (79.0%) in the gemcitabine group received all the planned cycles of chemotherapy (P=0.002). The relative dose intensity (i.e., the proportion of administered doses per time unit relative to planned doses) was 0.70 or higher in 116 patients (48.7%) in the modified-FOLFIRINOX group and in 222 patients (91.4%) in the gemcitabine group (P<0.001).

EFFICACY

The median duration of follow-up in the intention-to-treat population was 33.6 months (95% confidence interval [CI], 30.3 to 36.0). A cancer-related event, second cancer, or death occurred in 134 patients (54.3%) in the modified-FOLFIRINOX group and in 180 (73.2%) in the gemcitabine group (Table S3 in the Supplementary Appendix). The median disease-free survival was 21.6 months (95% CI, 17.7 to 27.6) in the modified-FOLFIRINOX group, as compared with 12.8 months (95% CI, 11.7 to 15.2) in the gemcitabine group (stratified hazard ratio for cancer-related event, second cancer, or death, 0.58; 95% CI, 0.46 to 0.73; P<0.001) (Fig. 2A). Disease-free survival rates at 1 year, 2 years, and 3 years were 69.0% (95% CI, 62.6 to 74.6), 47.0% (95% CI, 40.2 to 53.5), and 39.7% (95% CI, 32.8 to 46.6), respectively, in the modified-FOLFIRINOX group, as compared with 53.7% (95% CI, 47.2 to 59.8), 30.7% (95% CI, 24.8 to 36.8), and 21.4% (95% CI, 15.8 to 27.5), respectively, in the gemcitabine group. The pattern of recurrence was similar in the two groups (Table S3 in the Supplementary Appendix).

Tumor grade indicating moderately or poorly differentiated or undifferentiated tumor, pN1 nodal status, higher tumor stage (IIB, III, or IV), R1 resection status, superior-mesenteric-vein resection, and portal-vein resection were identified as adverse prognostic factors for disease-free survival in the univariate analysis. Tumor grade and portal-vein resection were the only adverse prognostic factors that were identified in the multivariate analysis. The beneficial effect of the modified FOLFIRINOX regimen as compared with gemcitabine therapy on disease-free survival remained significant after adjustment for these factors (adjusted hazard ratio for cancer-related event, second cancer, or death, 0.60; 95% CI, 0.48 to 0.76; P<0.001). Details are provided in Tables S4 and S5 in the Supplementary Appendix.

The subgroup analysis showed no evidence of heterogeneity of the effect size of treatment on disease-free survival (Fig. 3). In particular, the benefit of the modified FOLFIRINOX regimen as compared with gemcitabine therapy was similar in patients younger than 65 years of age and those 65 years of age or older. In the 101 patients who were 70 years of age or older (20.5% of the trial population), however, the benefit of the modified FOLFIRINOX regimen as compared with gemcitabine therapy did not reach significance (hazard ratio for cancer-related event, second cancer, or death, 0.86; 95% CI, 0.53 to 1.39). The reduction in the irinotecan dose from 180 mg per square meter (90 patients at this level) to 150 mg per square meter (124 patients at this level) after a prespecified toxicity analysis did not significantly affect disease-free survival (hazard ratio in the subgroup with the reduced dose, 0.97; 95% CI, 0.67 to 1.40; P=0.87). A total of 24 patients received a maximum dose of irinotecan between 155 and 175 mg per square meter.

The median overall survival was 54.4 months (95% CI, 41.8 to not reached) in the modified-FOLFIRINOX group, as compared with 35.0 months (95% CI, 28.7 to 43.9) in the gemcitabine group (stratified hazard ratio for death, 0.64; 95% CI, 0.48 to 0.86; P=0.003) (Fig. 2B). The overall survival rate at 3 years was 63.4% (95% CI, 55.7 to 70.1) in the modified-FOLFIRINOX group and 48.6% (95% CI, 40.9 to 55.8) in the gemcitabine group.

The median metastasis-free survival was 30.4 months (95% CI, 21.7 to not reached) in the modified-FOLFIRINOX group, as compared with 17.7 months (95% CI, 14.2 to 21.5) in the gemcitabine group (stratified hazard ratio for detectable distant disease or death, 0.59; 95% CI, 0.46 to 0.75; P<0.001) (Fig. S1A in the Supplementary Appendix). The metastasis-free survival rate at 3 years was 48.2% (95% CI, 41.0 to 55.0) in the modified-FOLFIRINOX group and 30.9% (95% CI, 24.4 to 37.6) in the gemcitabine group.

The median cancer-specific survival was not reached (95% CI, 47.3 to not reached) in the modified-FOLFIRINOX group, as compared with 36.4 months (95% CI, 30.9 to 46.2) in the gemcitabine group (stratified hazard ratio for death due to the treated cancer or a treatment-related complication, 0.63; 95% CI, 0.47 to 0.85; P=0.003) (Fig. S1B in the Supplementary Appendix). The cancer-specific survival rate at 3 years was 66.2% (95% CI, 58.7 to 72.7) in the modified-FOLFIRINOX group and 51.2% (95% CI, 43.5 to 58.4) in the gemcitabine group.

All the secondary end points remained significant after Bonferroni adjustment. Treatments that were administered after tumor relapse were chemotherapy (in 63.0% of the patients in the modified-FOLFIRINOX group [with gemcitabine-based therapy used in 78.8% of these patients] and in 75.7% of the patients in the gemcitabine

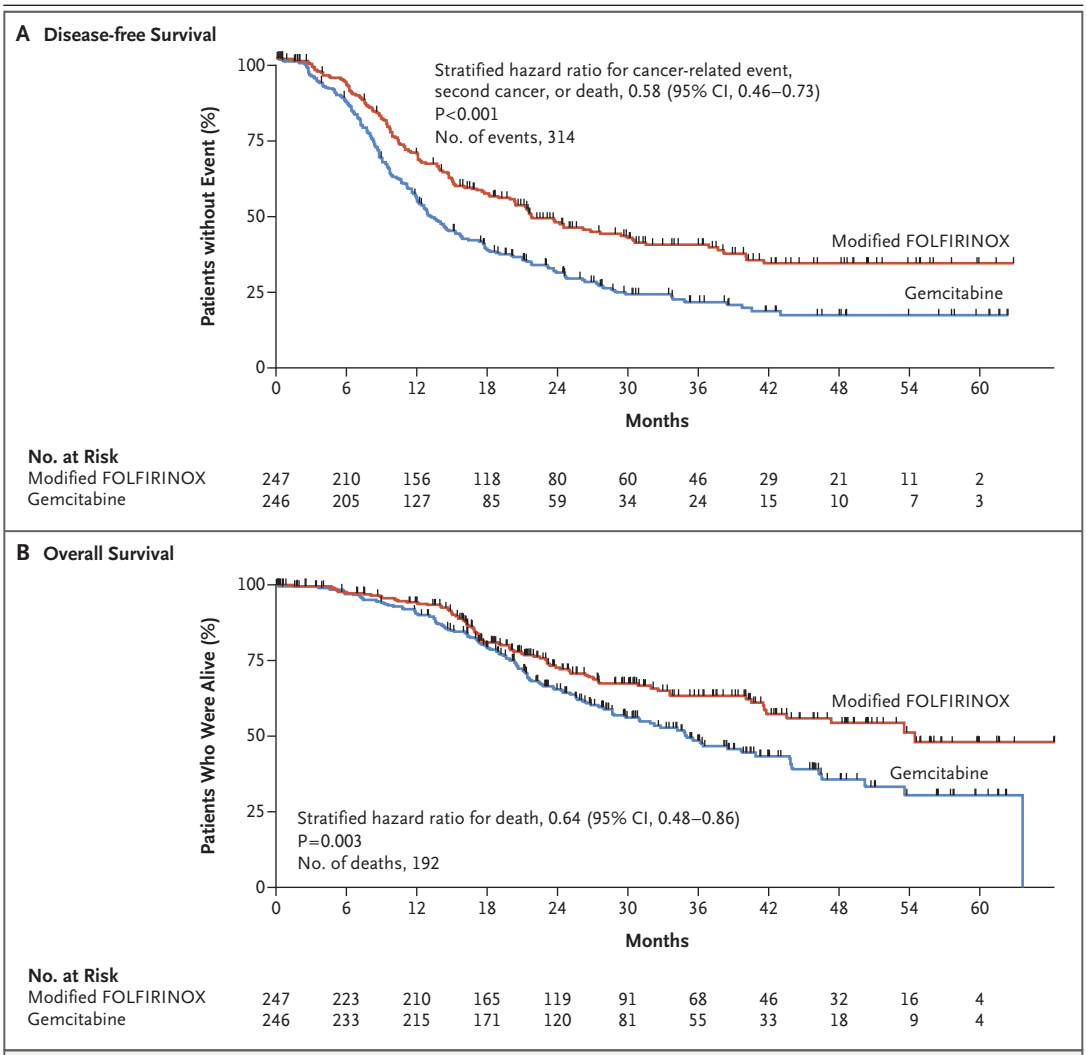


Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival in the Intention-to-Treat Population, According to Treatment Group.

The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group, as compared with 12.8 months in the gemcitabine group (Panel A). The median overall survival was 54.4 months in the modified-FOLFIRINOX group, as compared with 35.0 months in the gemcitabine group (Panel B). Tick marks indicate censored data.

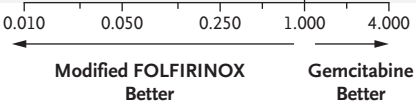
group [with FOLFIRINOX therapy used in 75.8%]), radiotherapy with or without chemotherapy (in 12.6% and 5.9%, respectively), and surgery (in 4.7% and 4.7%) (Table S6 in the Supplementary Appendix).

ADVERSE EVENTS

Adverse events of grade 3 or 4 were reported in 180 of 237 patients (75.9%) in the modified-FOLFIRINOX group and in 128 of 242 (52.9%) in the gemcitabine group, and grade 4 events were reported in 29 patients (12.2%) and 29 patients (12.0%), respectively (Table 2). One patient in the gemcitabine group died because of treatment-related toxic effects (interstitial pneumonitis). All the toxic effects were reversible, except for oxaliplatin-induced peripheral neurotoxic effect, which was persistent at 3 years in 2 patients in the modified-FOLFIRINOX group.

The incidence of grade 3 or 4 events of diarrhea, increase in the γ-glutamyltransferase level, paresthesia, fatigue, sensory peripheral neuropathy, nausea, vomiting, abdominal pain, and mucositis was significantly higher in the modified-

Subgroup	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)	Unstratified Hazard Ratio (95% CI)	P Value
	no. of events/total no. of patients			
Sex				0.42
Male	78/142	96/135	0.68 (0.50–0.92)	
Female	56/105	84/111	0.56 (0.40–0.78)	
Age				0.88
<65 yr	83/152	103/140	0.61 (0.46–0.82)	
≥65 yr	51/95	77/106	0.63 (0.44–0.90)	
WHO performance-status score				0.10
0	61/122	96/127	0.51 (0.37–0.71)	
1	73/123	80/115	0.77 (0.56–1.06)	
Diabetes				0.59
No	100/183	123/177	0.66 (0.50–0.86)	
Yes	33/62	52/64	0.55 (0.35–0.85)	
Tumor location				0.89
Head	105/193	129/175	0.62 (0.48–0.80)	
Other	28/53	47/67	0.62 (0.39–0.98)	
Tumor grade				0.69
Well differentiated	32/70	58/79	0.52 (0.34–0.81)	
Moderately differentiated	75/124	91/125	0.69 (0.51–0.93)	
Poorly differentiated or undifferentiated	21/35	23/29	0.62 (0.34–1.13)	
Primary tumor status				0.82
pT1 or pT2	16/31	16/25	0.67 (0.34–1.34)	
pT3 or pT4	118/216	164/221	0.62 (0.49–0.79)	
Nodal status				0.10
pN0	25/55	33/61	0.89 (0.53–1.49)	
pN1	109/192	147/185	0.54 (0.42–0.69)	
Tumor stage				0.31
IA or IB	3/12	8/14	0.36 (0.10–1.38)	
IIA or IIB	127/226	167/226	0.64 (0.50–0.80)	
III or IV	4/9	5/6	0.07 (0.01–0.61)	
Status of surgical margins				0.15
R0	73/148	88/134	0.72 (0.53–0.98)	
R1	61/99	92/112	0.52 (0.37–0.72)	
Superior-mesenteric-vein resection				0.29
No	122/228	161/221	0.61 (0.48–0.77)	
Yes	12/19	19/25	0.92 (0.44–1.91)	
Portal-vein resection				0.86
No	112/215	145/204	0.62 (0.49–0.80)	
Yes	22/32	35/42	0.64 (0.37–1.11)	
Postoperative CA 19-9 level				0.85
≤90 U/ml	123/231	166/226	0.61 (0.48–0.77)	
>90 U/ml	11/16	14/20	0.74 (0.33–1.64)	
Early stopping of treatment				0.49
No	83/158	137/192	0.56 (0.42–0.73)	
Yes	51/80	42/51	0.53 (0.35–0.81)	
Overall	134/247	180/246	0.62 (0.49–0.77)	



FOLFIRINOX group, whereas thrombocytopenia of grade 3 or 4 was significantly more common in the gemcitabine group. The occurrence of neutropenia was similar in the two groups, but G-CSF was administered to 148 patients (62.2% [41.8% of cycles administered in this group]) in the modified-FOLFIRINOX group and to only 9 patients (3.7% [1.1% of cycles]) in the gemcitabine group (P<0.001). In the modified-FOLFIRINOX group, 84 of 148 patients (56.8%)

Figure 3 (facing page). Forest Plot of the Treatment Effect on Disease-free Survival in Subgroup Analyses.

In the analysis of disease-free survival, the hazard ratio is for the first cancer-related event, second cancer, or death. The position of each square represents the point estimate of the treatment effect, and error bars represent 95% confidence intervals. The sizes of the squares are proportional to the precision of the estimates. The diamond represents the overall point estimate of the treatment effect, with the lateral points indicating the 95% confidence interval. The vertical line indicates a hazard ratio of 1.0, which was the null hypothesis value. Scores for the World Health Organization (WHO) performance status are on a 5-point scale, with higher numbers indicating greater disability; a score of 0 indicates that the patient is fully active and able to carry on activities without restriction, and a score of 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out light work. Primary tumor status was assessed as pT1 (tumor limited to the pancreas and ≤2 cm in the greatest dimension), pT2 (tumor limited to pancreas and >2 cm in the greatest dimension), pT3 (tumor extends beyond pancreas but without involvement of celiac axis or superior mesenteric artery), or pT4 (tumor involves celiac axis or superior mesenteric artery). Nodal status was assessed as pN0 (no lymph-node involvement) and pN1 (lymph-node involvement). Tumor stage was assessed according to the 2009 tumor–node–metastasis (TNM) classification, 7th edition.[19] A surgical margin of R0 indicates that no cancer cells were present within 1 mm of all resection margins, and R1 the presence of cancer cells within 1 mm of one or more resection margins.

received G-CSF as primary prophylaxis or for uncomplicated neutropenia without cycle delay.

In the modified-FOLFIRINOX group, diarrhea of grade 3 or 4 occurred in 18 of 90 patients (20.0%) who received at least one cycle with irinotecan at a dose of more than 175 mg per square meter and in 21 of 123 patients (17.1%) who received irinotecan at a dose of 150 mg or less per square meter, with diarrhea occurring in significantly fewer cycles at the lower doses (35.3% vs. 40.2% of the cycles, P=0.02). Diarrhea of grade 3 or 4 was more likely to occur during the first two cycles of the modified FOLFIRINOX regimen than during later cycles (Fig. S2 in the Supplementary Appendix). Significant predictors for the occurrence of diarrhea of grade 3 or 4 were treatment with the modified FOLFIRINOX regimen rather than with gemcitabine (adjusted odds ratio, 6.0; 95% CI, 2.9 to 12.8; P<0.001) and a higher number of lymph nodes retrieved during surgery (≥20 vs. <20; adjusted odds ratio, 2.4; 95% CI, 1.3 to 4.4; P<0.001). No significant differences in the incidence of toxic effects of grade 3 or 4, either as the most common events or overall, were seen between the two treatment groups regardless of the age of the patients (<70 or ≥70 years).

DISCUSSION

In this trial involving patients with resected pancreatic adenocarcinoma, adjuvant chemotherapy with a modified FOLFIRINOX regimen led to significantly longer disease-free survival, overall survival, metastasis-free survival, and cancer-specific survival than treatment with gemcitabine. The median disease-free survival (primary end point) was significantly longer, by 8.8 months, in the modified-FOLFIRINOX group than in the gemcitabine group. The disease-free survival benefit with modified FOLFIRINOX was significant in the majority of subgroups, including subgroups of patients with adverse prognostic factors (i.e., T3 or T4 tumor status, positive lymph nodes, or R1 resection).

The median disease-free survival in the gemcitabine group (12.8 months) was similar to that reported in previous phase 3 trials of adjuvant therapy (11.3 to 15.3 months), although the median overall survival was longer in our trial (35.0 months vs. 20.1 to 26.5 months).[5,7,9,11,20] This may be due to the high use of FOLFIRINOX after relapse in the gemcitabine group (in 76% of the patients). Nevertheless, overall survival was significantly longer, by 19.4 months, in the modified-FOLFIRINOX group than in the gemcitabine group, with a similar duration of follow-up in each group. However, the data remain immature, with 61% of all the patients being alive at the time of analysis.

As expected, the safety profile of the modified FOLFIRINOX regimen was less favorable than that of gemcitabine but appeared to be manageable. The occurrence of neutropenia of grade 3 or 4 was efficiently reduced by the deletion of bolus fluorouracil (and a reduction in the irinotecan dose) from the FOLFIRINOX regimen — from 46% of the patients with metastatic disease who received the unmodified regimen in the previous PRODIGE trial[12] to 28% of the patients who received the modified FOLFIRINOX regimen in the current trial — although the use of G-CSF with the modified FOLFIRINOX regimen remained high (62% of the patients). Both the protocol-

Table 2. Adverse Events during Treatment (Safety Population).*

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—
Biochemical event¶							
Increased alanine aminotransferase level	151 (64.0)	10 (4.2)	0	178 (73.6)	12 (5.0)	0	0.71
Increased aspartate aminotransferase level	158 (66.9)	9 (3.8)	1 (0.4)	167 (69.0)	8 (3.3)	0	0.76
Increased alkaline phosphatase level	173 (73.6)	5 (2.1)	0	111 (45.9)	5 (2.1)	0	1.00
Increased γ-glutamyltransferase level	150 (65.2)	42 (18.3)	6 (2.6)	110 (46.0)	20 (8.4)	3 (1.3)	0.002
Hyperglycemia	59 (24.9)	7 (3.0)	0	59 (24.4)	5 (2.1)	0	0.53

* Per the protocol, in the modified-FOLFIRINOX group, 90 patients (37.8%) received irinotecan at a dose of more than 175 mg per square meter of body-surface area, 24 (10.1%) received irinotecan at a dose of 155 to 175 mg per square meter, and 124 (52.1%) received irinotecan at a dose of less than 155 mg per square meter. Data do not include one patient in each group who did not have safety data; these patients received one cycle of treatment and then withdrew consent. Safety data were calculated on the basis of the available data (see below). P values are for the between-group comparisons of rates of events of grade 3 or 4.

† Data regarding the hemoglobin level, neutrophil or granulocyte counts, hyperleukocytosis, platelet count, and lymphocyte count were missing for two patients in the modified-FOLFIRINOX group and for one in the gemcitabine group, and data regarding febrile neutropenia for one in each group.

‡ Data regarding nonhematologic events were missing for one patient in the modified-FOLFIRINOX group and for two in the gemcitabine group.

§ There is no grade 4 classification for alopecia.

¶ Data regarding the alanine aminotransferase and aspartate aminotransferase levels were missing for two patients in the modified-FOLFIRINOX group and for one in the gemcitabine group; data regarding the alkaline phosphatase level for three and one, respectively; data regarding the γ-glutamyltransferase level for eight and four, respectively; and data regarding hyperglycemia for one in each group.

specified irinotecan-dose modifications and the per-protocol dose reduction of irinotecan to 150 mg per square meter significantly reduced the incidence of grade 3 or 4 diarrhea. The occurrence of grade 3 or 4 diarrhea in the overall population and in the modified-FOLFIRINOX group was significantly associated with the number of lymph nodes retrieved, as described previously by others.[21,22]

The selection of patients in this trial required that patients had to be eligible to receive the modified FOLFIRINOX regimen, and all the patients were required to undergo postsurgical CT or MRI and to have postoperative serum CA 19-9 levels of less than 180 U per milliliter in order to minimize the risk of incorrect inclusion of patients with metastatic disease. A central review of surgical reports, postsurgical CT and MRI scans, and pathology reports was performed to check prognostic factors. Disease-free survival rather than overall survival was chosen as the primary end point because it provides an earlier assessment of efficacy, requires fewer patients for evaluation, and avoids any bias that may result from the crossover of patients between groups. Although disease-free survival is not validated as a surrogate end point for overall survival in trials of adjuvant therapy for pancreatic cancer, this criterion was robust and correlated with overall survival. Disease-free survival was also used as the primary end point and correlated with overall survival in the Charité Onkologie (CONKO) trials, including a trial that compared adjuvant gemcitabine therapy with surgery alone (CONKO-001) and two trials that compared gemcitabine therapy with the use of gemcitabine plus targeted agents (CONKO-005 and CONKO-006).[7,11,23] Our trial is ongoing, with 3 years of follow-up currently.

In conclusion, among patients who underwent complete resection of pancreatic cancer, adjuvant chemotherapy with a modified FOLFIRINOX regimen led to significantly longer disease-free survival and overall survival than adjuvant chemotherapy with gemcitabine. The incidence of toxic effects was higher with the modified FOLFIRINOX regimen than with gemcitabine therapy.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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