

Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial

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ABSTRACT

Purpose

To compare the quality of life (QoL) of patients receiving oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) or gemcitabine as first-line chemotherapy and to assess whether pretreatment QoL predicts survival in patients with metastatic pancreatic cancer.

Patients and Methods

Three hundred forty-two patients with performance status 0 or 1 were randomly assigned to receive FOLFIRINOX (oxaliplatin, 85 mg/m²; irinotecan, 180 mg/m²; leucovorin, 400 mg/m²; and fluorouracil, 400 mg/m² bolus followed by 2,400 mg/m² 46-hour continuous infusion, once every 2 weeks) or gemcitabine 1,000 mg/m² weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks. QoL was assessed using European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 every 2 weeks.

Results

Improvement in global health status (GHS; $P < .001$) was observed in the FOLFIRINOX arm and improvement in emotional functioning ($P < .001$) was observed in both arms, along with a decrease in pain, insomnia, anorexia, and constipation in both arms. A significant increase in diarrhea was observed in the FOLFIRINOX arm during the first 2 months of chemotherapy. Time until definitive deterioration ≥ 20 points was significantly longer for FOLFIRINOX compared with gemcitabine for GHS, physical, role, cognitive, and social functioning, and six symptom domains (fatigue, nausea/vomiting, pain, dyspnea, anorexia, and constipation). Physical functioning, constipation, and dyspnea were independent significant prognostic factors for survival with treatment arm, age older than 65 years, and low serum albumin.

Conclusion

FOLFIRINOX significantly reduces QoL impairment compared with gemcitabine in patients with metastatic pancreatic cancer. Furthermore, baseline QoL scores improved estimation of survival probability when added to baseline clinical and demographic variables.

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INTRODUCTION

We have previously reported the efficacy and safety of the oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) regimen versus gemcitabine as first-line therapy among patients with metastatic pancreatic adenocarcinoma (mPAC).¹ The results showed significantly longer overall survival (OS) but increased toxicity with FOLFIRINOX. Health-related quality of life (QoL) is paramount to patients with mPAC because most have high levels of symptoms when diagnosed

and because life expectancy is usually short. Using a validated instrument, the European Organization for the Research and Treatment of Cancer QoL Questionnaire C30 (EORTC QLQ-C30) version 3.0,² we prospectively assessed longitudinal QoL as a secondary end point of the PRODIGE (Partenariat de Recherche en Oncologie Digestive) /ACCORD (Actions Concertées dans les Cancers Colo-Rectaux et Digestifs) phase III trial.

We have, in part, previously reported the results of the QoL analysis based on EORTC QLQ-C30 scales that are usually most affected in

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patients with pancreatic cancer (global health status [GHS], fatigue, pain, physical functioning (PF), emotional functioning, and role functioning); other domains were examined in an exploratory manner.¹ Time until definitive deterioration (TUDD) of the QoL domains was analyzed for a 10-point minimal clinically important difference (MCID).

The aim of our article is to provide detailed analysis of QoL data for all domains. We extended the analysis to include TUDD using a more stringent and clinically relevant 20-point MCID cutoff.³ Furthermore, we performed a multivariate analysis to determine the prognostic value of baseline QoL measures for survival.

PATIENTS AND METHODS

Trial Design

Adult patients with measurable mPAC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1, and no prior chemotherapy were eligible for inclusion in this open-label, multicenter, randomized, phase II/III trial. Detailed inclusion and exclusion criteria, study design, and protocol have been published previously.¹

Gemcitabine 1,000 mg/m² was infused weekly for 7 weeks, followed by a 1-week rest period, and then once per week for 3 weeks of a 4-week cycle. FOLFIRINOX consisted of oxaliplatin 85 mg/m² as a 2-hour intravenous infusion immediately followed by leucovorin 400 mg/m² administered as a 2-hour intravenous infusion and, after 30 minutes, with irinotecan 180 mg/m² as a 90-minute intravenous infusion; this was followed by a fluorouracil 400 mg/m² intravenous bolus and then continuous intravenous infusion of 2,400 mg/m² over 46 hours once every 2 weeks. Six months of chemotherapy was recommended for patients who had a response. Details of treatment have been published previously.¹

The cutoff date for the current QoL analysis was April 16, 2010, the date used for the original efficacy and safety assessment.¹

QoL Measurement

QoL was measured using EORTC QLQ-C30, version 3.0,² which is a validated, cancer-specific instrument designed for prospective clinical trials. The EORTC QLQ-C30 questionnaire evaluates five functions (physical, role, cognitive, emotional, and social), nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties) and the GHS/QoL. This questionnaire adequately covers the main problems and symptoms presented by patients with mPAC. Its psychometric properties and high acceptability rate in the French language have been confirmed.⁴

Questionnaires were to be completed at baseline before random assignment and every 2 weeks until progression. Questionnaires were completed in the clinic before interaction with health care personnel. Because of the multitude of QoL evaluations, we simplified the number of observations to calculate compliance to include baseline, day 15, day 30, and months 2, 4, 6, 8, and 10.

The description of QoL scores are therefore reported for these respective time points, whereas all QoL questionnaires were used for longitudinal analyses. Responses to the questionnaire were transformed into 0 to 100 scores, with a high score implying a high level of symptoms or a high level of functioning or global QoL.

Statistical Analysis

Analysis of findings from the EORTC QLQ-C30 questionnaires followed EORTC guidelines.⁵ All analyses were performed in the intent-to-treat population. Comparison of the scores between treatment arms was performed with the Kruskal-Wallis test. Comparison between the baseline and the end of treatment was performed using the Sign rank test. Internal consistency of the questionnaire was estimated by using Cronbach's alpha for each dimension and visit. Values greater than .7 are generally regarded as acceptable, greater than .8 as good, and greater than .9 as excellent.⁶ An additional longitudinal analysis was performed based on a survival analysis method.⁷ This involves survival methods in which the definitive deterioration of QoL score is considered as an event.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Intent-to-Treat Population

Characteristic	FOLFIRINOX (n = 171)		Gemcitabine (n = 171)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	61		61	
Range	25-76		34-75	
Sex				
Male	106	62	105	61
Female	65	38	66	39
ECOG performance status				
0	64	37	66	39
1	106	62	105	61
2	1	< 1	0	0
Pancreatic tumor location				
Head	67	39	63	37
Body	53	31	58	34
Tail	45	26	45	26
Multicentric	6	4	5	3
Metastatic sites involved				
Median	2		2	
Range	1-6		1-6	
Measurable metastatic sites*				
Liver	149	88	150	88
Pancreas	90	53	91	53
Lymph node	49	29	39	23
Lung	33	19	49	29
Peritoneal	33	19	32	19
Other	18	11	29	17

NOTE. Reproduced with permission from Conroy et al.¹

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin.

*Denominator 170 for the FOLFIRINOX arm.

Osoba et al³ showed that a mean change of 5 to 10 points in a QLQ-C30 score corresponds to a "little" change in QoL, a change of 10 to 20 points corresponds to a "moderate" change, and a change of more than 20 points corresponds to a "large" change. We used this definition when appropriate to indicate the clinical relevance of any differences observed. For a given baseline score, QLQ-C30 score was considered definitive deterioration if this score decreased by more than 10 points (or 20 points) as compared with the score at baseline, without later improvement superior to 10 points (or 20 points) as compared with baseline or without any available score. Thus, TUDD for QoL scores was defined as the time from randomization to the first observation of a definitive deterioration of QLQ-C30 score. Similarly, TUDD was reanalyzed by integrating death as an event. TUDD was analyzed with the use of the Kaplan-Meier method; the log-rank test was used to compare treatment arms.

Multivariate analysis was performed to determine baseline prognostic factors for OS, following the method previously published in an EORTC meta-analysis.⁸ OS was calculated from the date of random assignment to the date of death, with living patients censored at the last date of follow-up before the cutoff for analysis. We investigated the prognostic value of QoL scores in complementing the prognostic model based on clinical data. Synchronous metastases, a low baseline albumin (< 3.5 g/dL), liver metastases, age older than 65 years, and treatment arm were previously identified as independent prognostic factors for OS.¹ Initially, each baseline QLQ-C30 dimension was tested in a univariate model to identify prognostic variables for OS ($P < .05$) and was added to a Cox model stratified by ECOG score (0 v 1) and primary tumor localization (head v other sites) containing clinical data. A proportional hazards assumption was verified using Schoenfeld residuals. The predictive power of the models identified was assessed according to Harrell's discrimination C-index.⁹ The Harrell's C-index is a probability of concordance between

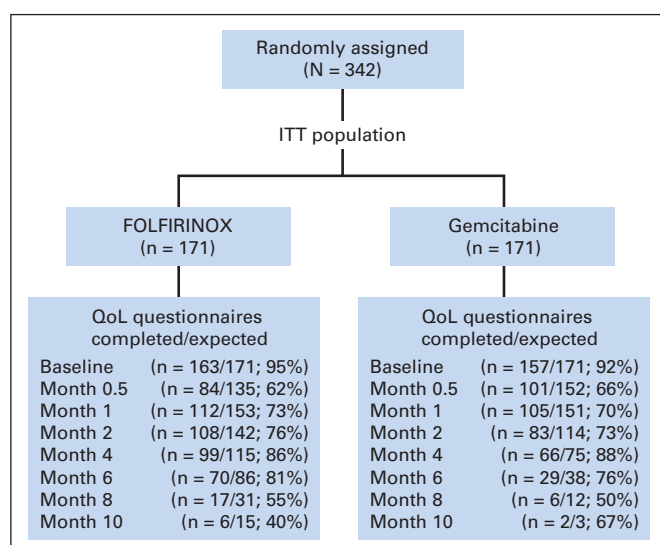


Fig 1. CONSORT diagram for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires C30 completed for the total number of eligible patients at different time points in each treatment group. FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin; ITT, intent to treat; QoL, quality of life.

predicted and observed survival, a value of 1 indicates perfect concordance of the score and outcome, whereas a value of .5 indicates only chance agreement.¹⁰ All analyses were performed with STATA software, version 11.0 (STATA, College Station, TX).

RESULTS

Patient Characteristics

A total of 342 patients were enrolled between December 2005 and October 2009; the intent-to-treat population comprised 171 patients

in each arm. The median follow-up was 26.6 months (95% CI, 20.5 to 44.9). Baseline demographic and disease characteristics were similar for both treatment arms (Table 1), except there were fewer measurable lung metastases in the FOLFIRINOX arm compared with the gemcitabine arm.

Baseline compliance with completion of QLQ-C30 questionnaires was high: 163 questionnaires (95%) and 157 questionnaires (92%) in the FOLFIRINOX and gemcitabine arms, respectively, and there was no difference between the patients who completed baseline QoL forms and those who did not (Figure 1). Despite the fact that ECOG PS was 0 or 1 at inclusion according to the physician, 30 patients (18.4%) in the FOLFIRINOX arm and 26 patients (16.6%) in the gemcitabine arm answered “quite a bit” (11.6%) or “very much” (6%) at the baseline item “Do you need to stay in bed or a chair during the day?”. These patients had a worse prognosis than the overall population with a median OS of 6.7 months and 4.6 months in the FOLFIRINOX and the gemcitabine arms, respectively. In the FOLFIRINOX group, the survival difference between patients who answered they have no need to rest and those who needed to rest is significant, with median survival of 12.6 months and 6.7 months, respectively ($P = .03$). In the gemcitabine arm, the median survival in these groups is not significantly different, 6.7 versus 4.6 months.

Compliance for questionnaire completion over time in surviving patients varied between 40% to 95%. The rate of assessable questionnaires decreased after the 6-month treatment period, as expected. The rates of missing questionnaires were comparable between both treatments during follow-up.

There was no statistically significant difference between treatment arms with respect to baseline QLQ-C30 QoL domains or single items (Appendix Table A1 [online-only]). Functional scores were high and the most marked symptoms were anorexia, fatigue, pain, insomnia, and constipation.

Table 2. Univariate Cox Analysis According to 10-Point and 20-Point MCID to Calculation of TUDD for QLQ-C30 Domain Scores

Domain	10-Point Deterioration					20-Point Deterioration				
	No. of Events		HR	95% CI	P	No. of Events		HR	95% CI	P
	FOLFIRINOX (n = 163)	Gemcitabine (n = 157)				FOLFIRINOX (n = 163)	Gemcitabine (n = 157)			
Global health status	32	42	2.3	1.4 to 3.7	< .001	13	32	4.7	2.3 to 9.5	< .001
Physical functioning	47	59	1.9	1.3 to 2.8	.001	27	37	2.2	1.3 to 3.6	.001
Role functioning	44	59	2.2	1.5 to 3.4	< .001	27	43	2.7	1.6 to 4.4	< .001
Emotional functioning	18	26	2.9	1.6 to 5.6	< .001	14	14	2.1	1.0 to 4.5	.057
Cognitive functioning	30	49	3.0	1.9 to 4.8	< .001	11	16	2.6	1.2 to 5.6	.015
Social functioning	42	54	2.1	1.4 to 3.1	< .001	23	40	2.7	1.6 to 4.7	< .001
Fatigue	52	62	1.9	1.3 to 2.7	.001	36	49	2.4	1.5 to 3.8	< .001
Nausea/vomiting	40	53	2.1	1.4 to 3.2	< .001	19	30	2.8	1.5 to 5.0	< .001
Pain	27	36	2.7	1.6 to 4.6	< .001	12	22	3.7	1.7 to 7.7	< .001
Dyspnea	32	38	2.3	1.4 to 3.8	< .001	32	38	2.3	1.4 to 3.8	< .001
Insomnia	20	15	1.4	0.7 to 2.9	.300	20	15	1.4	0.7 to 2.9	.300
Loss of appetite	24	28	1.9	1.1 to 3.4	.022	24	28	1.9	1.1 to 3.4	.022
Constipation	18	21	2.0	1.0 to 3.8	.033	18	21	2.0	1.0 to 3.8	.033
Diarrhea	37	32	1.5	0.9 to 2.5	.086	37	32	1.5	0.9 to 2.5	.086
Financial difficulties	22	8	0.6	0.2 to 1.4	.214	22	8	0.6	0.2 to 1.4	.214

NOTE. For global health status and functional scales, a high score indicates a better function. For symptoms and financial difficulties, a high score indicates more symptoms or more difficulties.

Abbreviations: FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin; HR, hazard ratio; MCID, minimal clinically important difference; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; TUDD, time until definitive deterioration.

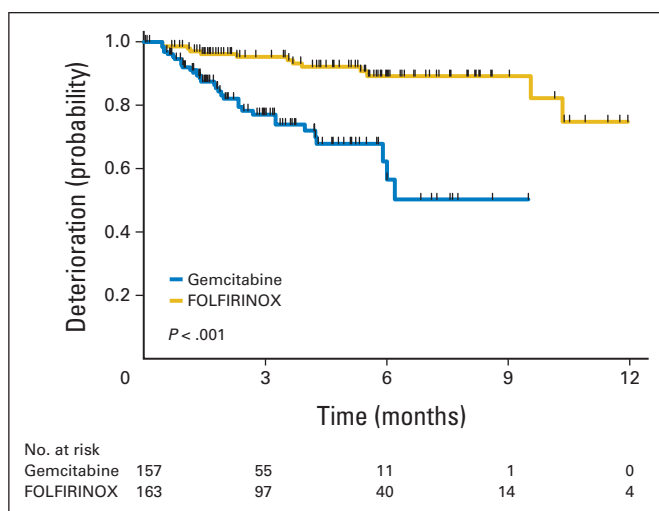


Fig 2. Kaplan-Meier plot for time until definitive deterioration more than 20 points for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 global health status/quality of life. FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin.

Longitudinal Analysis

Cronbach's alpha of all domains was calculated and was more than .85, confirming the internal consistency of the questionnaire in this population. When comparing the treatment arms, there did not appear to be any difference in the change in QLQ-C30 domains over time, except for diarrhea. The change in GHS over time was similar when comparing the treatment arms (Appendix Fig A1A [online-only]). GHS scores improved ($P < .001$) in the FOLFIRINOX arm and emotional functioning scores improved ($P < .001$) in both arms between baseline and the end of treatment (6 months). Similarly, a decrease in four symptom scores (pain: FOLFIRINOX, $P < .001$; gemcitabine, $P = .01$; insomnia: FOLFIRINOX, $P < .001$; gemcitabine, $P = .005$; anorexia: FOLFIRINOX, $P < .001$; gemcit-

abine $P = .02$; and constipation: FOLFIRINOX, $P = .002$; gemcitabine, $P = .02$) was found for both treatments. Patients experienced more diarrhea on the FOLFIRINOX arm than on the gemcitabine arm during the first 2 months of treatment (Appendix Fig A1N; $P = .009$). The other functional and symptom domains are presented in Appendix Figure A1. The percentage of patients with a worsening or improvement of ≥ 10 points each scores are also listed in Appendix Table A2. A moderate improvement of GHS score (≥ 10 points) was found in 30.1% and 18.5% of the patients, in the FOLFIRINOX and gemcitabine arms, respectively. Improvement in fatigue and dyspnea scores was significantly associated with treatment response in both arms, as were the scores for GHS, pain, and insomnia in the FOLFIRINOX arm.

Time Until Definitive Deterioration Analysis

TUDD was determined according to a MCID of at least 10 or 20 points in QLQ-C30 scores for the different domains in both arms (Table 2). TUDD ≥ 10 points was significantly longer for the FOLFIRINOX versus the gemcitabine arm for GHS/QoL, all five functional domains, and six symptom domains (fatigue, nausea/vomiting, pain, dyspnea, anorexia, and constipation). In general, significance was maintained for TUDD ≥ 20 points, except for the emotional functioning domain. The TUDD ≥ 10 points (hazard ratio [HR], 2.3; 95% CI, 1.4 to 3.7; $P < .001$) and ≥ 20 points (HR, 4.7; 95% CI, 2.3 to 9.5; $P < .001$) for GHS score were longer in the FOLFIRINOX arm. Median TUDD of GHS/QoL score was not reached in the FOLFIRINOX arm unlike the gemcitabine arm (Fig 2). Similar results were observed with the TUDD including death as an event (results not shown).

Prognostic Factors for Survival

Univariate Cox analysis revealed the following QLQ-C30 domains as significant prognostic factors for OS for the intent-to-treat population including both treatment arms: PF (HR, 0.88; 95% CI, 0.82 to 0.94; $P < .001$); role functioning (HR, 0.94; 95% CI, 0.90 to

Table 3. Multivariate Analysis of Overall Survival

Variable	Model 0*			Model 1†			Model 2‡			Model 3§		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Baseline clinical and demographic characteristics												
Treatment arm	0.54	0.41 to 0.72	< .001	0.49	0.36 to 0.66	< .001	0.45	0.33 to 0.62	< .001	0.50	0.37 to 0.68	< .001
Age > 65 years	1.45	1.06 to 1.99	.023	1.51	1.09 to 2.09	.012	1.63	1.16 to 2.27	.018	1.55	1.12 to 2.15	.009
Low serum albumin	1.85	1.38 to 2.49	< .001	1.71	1.25 to 2.34	< .001	1.62	1.17 to 2.23	< .001	1.68	1.23 to 2.29	< .001
Synchronous metastases	0.41	0.21 to 0.77	.002							0.69	0.35 to 1.37	.277
Liver metastases	1.62	1.03 to 2.55	.028	1.69	1.05 to 2.71	.022	1.94	1.19 to 3.16	.010	1.60	0.99 to 2.59	.045
Baseline QLQ-C30 domain score												
Physical functioning				0.91	0.84 to 0.99	.039	0.88	0.81 to 0.96	.010	0.91	0.84 to 0.99	.040
Constipation				1.06	1.01 to 1.11	< .001	1.06	1.01 to 1.12	< .001	1.06	1.01 to 1.11	< .001
Dyspnea				1.07	1.00 to 1.14	.001	1.10	1.02 to 1.18	< .001	1.06	1.00 to 1.14	.001
Pain							0.93	0.87 to 0.99	.063			

Abbreviations: HR, hazard ratio; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.

*Model 0: Base model includes only clinical and demographic characteristics.

†Model 1: Final model for backward selection using the five significant clinical and demographic variables (Model 0) plus the six QLQ-C30 domains that were significant on univariate analysis (physical functioning, role functioning, fatigue, constipation, dyspnea, and loss of appetite).

‡Model 2: Final model for forward selection using the variables selected by backward selection (Model 1) plus the nine QLQ-C30 domains that were not significant on univariate analysis (global health status, emotional functioning, cognitive functioning, social functioning, nausea/vomiting, pain, insomnia, diarrhea, and financial difficulties).

§Model 3: Final model excluding pain because of interaction and forcing the variable of the time of appearance of hepatic metastases.

0.98; $P = .005$); fatigue (HR, 1.07; 95% CI, 1.02 to 1.13; $P = .007$); constipation (HR, 1.06; 95% CI, 1.02 to 1.11; $P = .001$); dyspnea (HR, 1.08; 95% CI, 1.03 to 1.13; $P = .004$); and anorexia (HR, 1.06; 95% CI, 1.02 to 1.11; $P = .001$). These six univariate QLQ-C30 domains were added to the base model (model 0) that included the significant clinical and demographic prognostic variables for OS (treatment arm, age > 65 years, low serum albumin, synchronous metastases, and liver metastases) for backward selection (model 1) and forward selection (model 2; Table 3). Only PF, constipation, and dyspnea remained significant after the backward and forward selection procedures. The presence of liver metastases no longer remained significant after the addition of QLQ-C30 domains in the model. However, the presence of liver metastases was forced as a prognostic factor in the final model (model 3) to better measure the contribution of QoL to the clinical model as prognostic factors.

To complete the analysis of prognostic factors for QLQ-C30 data, we determined the Harrell predictive C-index. Two models were compared: a model with the five significant clinical and demographic prognostic variables and another model with the same variables plus the significant QLQ-C30 domains (PF, constipation, and dyspnea). The predictive value added to the three QLQ-C30 domains to the clinical model improved the predictive power by 7.5%, as the predictive power changed from 0.66 to 0.71. Survival curves in different subgroups for baseline QLQ-C30 scores by tercile for PF, constipation, and dyspnea are shown in Figure 3. Severely compromised baseline PF in the lower tercile (ie, less than 33.3 points) seemed to have the most dramatic negative impact on OS, with a median OS of 2.1 months versus 9 months for patients with PF score of more than 66.6 (Fig 3A). The GHS score at baseline and the early improvement of GHS score (within the first 1 or 2 months) are not predictive of a better OS (data not shown).

DISCUSSION

In our original trial, we demonstrated that the FOLFIRINOX regimen is an effective first-line treatment option for patients with mPAC with good PS.¹ Median OS (11.1 v 6.8 months; HR, 0.57; 95% CI, 0.45 to 0.73; $P < .001$) and progression-free survival (6.4 v 3.3 months; HR, 0.47; 95% CI, 0.37 to 0.59; $P < .001$) were significantly prolonged in patients receiving FOLFIRINOX compared with those receiving gemcitabine, which was considered to be a clinically meaningful improvement.¹¹⁻¹⁵ However, the safety of FOLFIRINOX was less favorable than gemcitabine, producing higher incidences of neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy. It is therefore important to analyze the impact of treatment on QoL in relation to patient outcome.

A potential source of bias is the proportion of missing QoL forms over the assessment period. However, there was no difference in the rate of missing data between the two arms with a good compliance rate until 6 months. After 6 months, the population was reduced as a result of progressive disease and end of treatment period.

As expected, there were no notable differences between treatment arms over time for EORTC QLQ-30 domains with the exception of diarrhea, which seemed to be negatively affected in the FOLFIRINOX arm during the first 2 months of treatment. However, TUDD ≥ 10 points was significantly longer in the FOLFIRINOX arm for all QLQ-C30 domains (except insomnia, diarrhea, and financial difficulties). Significance was maintained for a TUDD ≥ 20 points for the

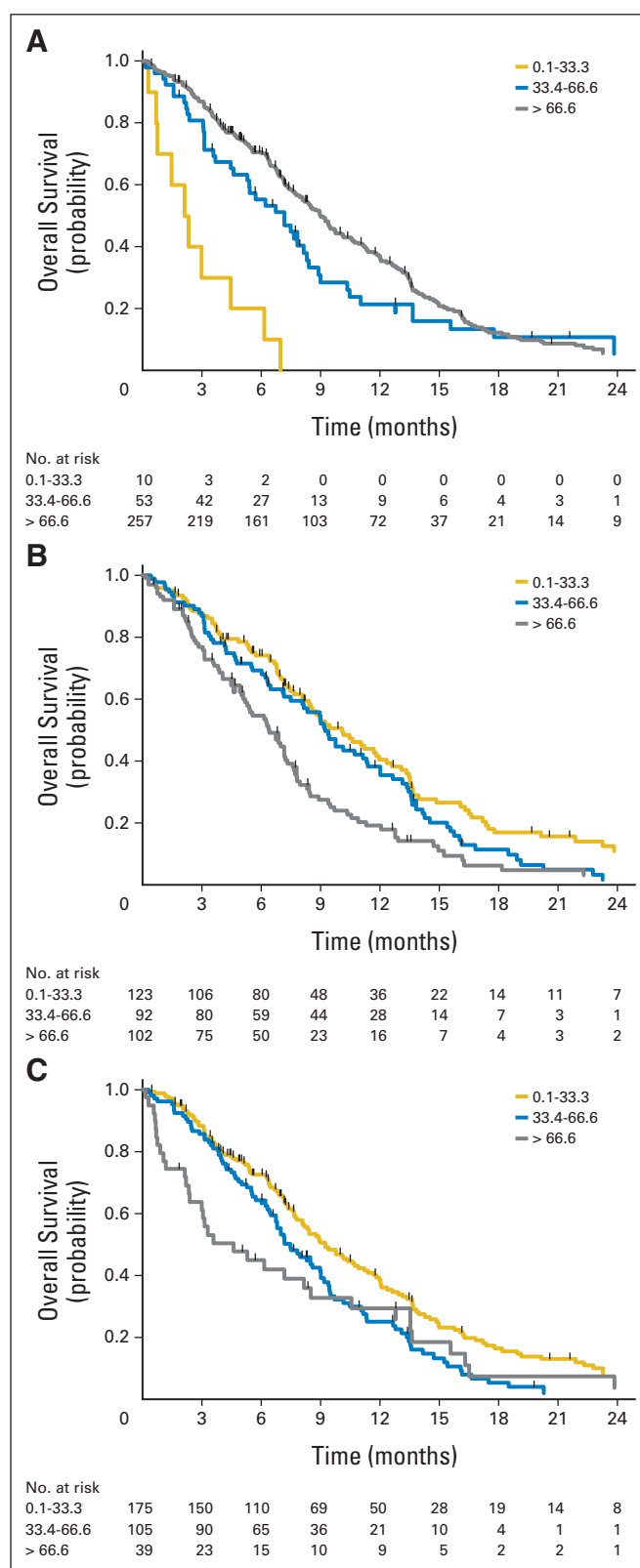


Fig 3. Kaplan-Meier overall survival plots according to baseline tercile point score of significant prognostic European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 domains (A) physical functioning, (B) constipation, and (C) dyspnea.

aforementioned QLQ-C30 domains except emotional functioning. The longer TUDD ≥ 10 points (HR, 2.3; 95% CI, 1.4 to 3.7; $P < .001$) and ≥ 20 points (HR, 4.7; 95% CI, 2.3 to 9.5; $P < .001$) for GHS score in the FOLFIRINOX arm versus the gemcitabine arm showed a more powerful result when using the more stringent MCID cutoff. The results for a TUDD ≥ 20 points confirm a clinically meaningful prolongation of QoL in patients treated with FOLFIRINOX as compared with gemcitabine despite its less favorable safety.

Another aim of this study was to determine the prognostic value of baseline QLQ-C30 domain scores with respect to survival. This analysis revealed three significant QLQ-C30 domains (PF, constipation, and dyspnea) when added to a model including significant clinical and demographic prognostic variables (treatment arm, age > 65 years, low serum albumin, synchronous metastases, and hepatic metastases). Severely impaired baseline PF seemed to impart the strongest negative impact on OS. This result is particularly important considering that this population was selected on good PS (ECOG 0 or 1) according to the physician's assessment. However, 56 patients (17.4%) wrote in their baseline QoL questionnaire that they needed to stay in bed or a chair during the day. These patients had a worse prognosis, and this result suggests that the PF score of the EORTC QLQ-C30 is a more comprehensive measure of QoL than PS and has a strong prognostic value. The highest prognostic value of patient self-assessment of QoL compared with physician rating of PS has been reported in other studies.^{8,16-17}

To our knowledge, there have been no other studies that have determined the impact of baseline QLQ-C30 QoL measures on survival outcome specifically in mPAC, although other QoL measures have been analyzed occasionally in smaller and/or less homogeneous populations. In a meta-analysis of randomized trials including 7,417 patients with cancer who filled out baseline QLQ-C30 questionnaires,⁸ multivariate analysis revealed that PF, pain, and anorexia were significant prognostic variables in addition to age, gender, and distant metastases, but not WHO PS. A literature review¹⁸ detailed the relationship between QoL and survival in cancer. Global QoL, functional domains, appetite loss, fatigue, and pain scores were the most prognostic indicators for OS. However, none of the studies identified in this review or our own review of the literature involved homogeneous populations with pancreatic cancer with baseline EORTC QLQ-C30 evaluation. The prognostic values of other QoL scales have been studied in patients with pancreatic cancer. In 55 patients,¹⁹ the health and physical subscale of the Ferrans and Powers QoL Index was shown to be a marginally significant predictor of survival after controlling for the stage at diagnosis. In 86 patients with cachexia,²⁰ baseline fatigue and PF scores predicted OS using various QoL measures, but multivariate analysis was not performed. The prognostic value of various

QoL indicators (including global linear-analog self-assessment indicators) was recently reported in 319 patients with advanced pancreatic cancer; baseline pain and tiredness were independent prognostic factors for OS but less so than baseline carbohydrate antigen 19-9.²¹

In conclusion, our analysis confirms that FOLFIRINOX significantly reduces QoL impairment compared with gemcitabine in patients with mPAC. Furthermore, multivariate analysis showed the additional prognostic value of baseline EORTC QLQ-C30 measures when added to clinical and demographic variables to predict survival among patients with mPAC. Whether or not baseline PF QoL score should be used as a stratification factor in further clinical trials has to be assessed prospectively.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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