

# Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer

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## Key words

Chemotherapy, FOLFIRINOX, irinotecan, oxaliplatin, pancreatic cancer

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The FOLFIRINOX combination of chemotherapy drugs had not been fully evaluated for Japanese pancreatic cancer patients. Therefore, we carried out a phase II study to examine the efficacy and safety of FOLFIRINOX in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. FOLFIRINOX (i.v. infusion of 85 mg/m<sup>2</sup> oxaliplatin, 180 mg/m<sup>2</sup> irinotecan, and 200 mg/m<sup>2</sup> l-leucovorin, followed by a bolus of 400 mg/m<sup>2</sup> fluorouracil and a 46-h continuous infusion of 2400 mg/m<sup>2</sup> fluorouracil) was given every 2 weeks. The primary endpoint was the response rate. The 36 enrolled patients received a median of eight (range, 1–25) treatment cycles. The response rate was 38.9% (95% confidence interval [CI], 23.1–56.5); median overall survival, 10.7 months (95% CI, 6.9–13.2); and median progression-free survival, 5.6 months (95% CI, 3.0–7.8). Major grade 3 or 4 toxicities included neutropenia (77.8%), febrile neutropenia (22.2%), thrombocytopenia (11.1%), anemia (11.1%), anorexia (11.1%), diarrhea (8.3%), nausea (8.3%), elevated alanine aminotransferase levels (8.3%), and peripheral sensory neuropathy (5.6%). Febrile neutropenia occurred only during the first cycle. There were no treatment-related deaths. FOLFIRINOX can be a standard regimen showing favorable efficacy and acceptable toxicity profile in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer.

Pancreatic cancer is the eighth leading cause of cancer-related deaths worldwide, with approximately 266 000 deaths reported in 2008.<sup>(1)</sup> In Japan, approximately 30 000 people die of pancreatic cancer annually, accounting for 8.3% of all malignant neoplasm-related deaths.<sup>(2)</sup> Pancreatic cancer is associated with an extremely poor prognosis, with the reported 5-year survival rates in male and female patients being only 7.1% and 6.9%, respectively, in Japan.<sup>(3)</sup>

In a randomized study, GEM monotherapy showed significant improvements in OS and clinical benefit response compared to 5-FU.<sup>(4)</sup> Thereafter, it has been recognized as the standard regimen for pancreatic cancer. Various GEM-based combination regimens have been investigated, without any evidence of additional survival benefits. The only exception is erlotinib, which, when combined with GEM, has been shown to provide a statistically significant improvement in OS,<sup>(5)</sup> although the absolute difference at median survival time was only marginal (0.3 months). Gemcitabine monotherapy has remained the standard therapy. Accordingly, more effective treatment options are urgently needed.

In a phase II/III study in 2011, Conroy *et al.*<sup>(6)</sup> showed a significant improvement in OS and quality of life with FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and leucovorin) compared to GEM in patients with MPC. Since then, FOLFIRINOX has become the standard treatment for patients with pancreatic

cancer with a good PS in North America and Europe. However, the safety and efficacy of this regimen in Japanese patients has not been evaluated. Accordingly, we carried out a phase II study of FOLFIRINOX in Japanese patients with MPC.

## Materials and Methods

**Patients.** The inclusion criteria were: histologically or cytologically confirmed pancreatic adenocarcinoma or adenosquamous carcinoma; an Eastern Cooperative Oncology Group PS of 0 or 1; age 20–75 years; MPC with at least one measurable lesion; and adequate hematological, liver, and renal function (hemoglobin  $\geq 9.0$  g/dL, white blood cell count  $\leq 10\ 000/\text{mm}^3$ , neutrophil count  $\geq 2000/\text{mm}^3$ , platelet count  $\geq 100\ 000/\text{mm}^3$ , total bilirubin  $\leq$  upper limit of normal, aspartate transaminase and alanine transaminase  $\leq 2.5 \times$  upper limit of normal, creatinine  $\leq 1.2$  mg/dL, and C-reactive protein  $\leq 2.0$  mg/dL).

Patients were excluded if they had: received prior chemotherapy or radiation therapy; grade 2 or higher peripheral sensory neuropathy; blood transfusion, blood products, or hematopoietic growth factor preparations such as G-CSF within 7 days before enrolment; UGT genetic polymorphisms of homozygous *UGT1A1\*28* or *UGT1A1\*6* or heterozygous *UGT1A1\*6* and *UGT1A1\*28*; apparent coelomic fluid (pleural effusion, ascites, or pericardial fluid) or peritoneal

dissemination; diarrhea including watery stools within 3 days before enrolment; poorly controlled diabetes; synchronous or metachronous double cancer, excluding carcinoma *in situ* or intramucosal carcinoma cured by local treatment; active infection; or other serious concomitant diseases.

The study was carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The protocol was approved by the ethics committees of all participating institutions, and informed consent was obtained from all patients before their enrolment in the study.

**Study design.** This study was an open-label, multicenter, single-arm phase II study. To ensure the safety of the patients, the study consisted of two stages. In the first stage, the IDMC evaluated the feasibility of the regimen during the initial two cycles in the first 10 patients to determine proceeding to the next stage or not. For careful safety evaluation, the first 10 patients were required to be hospitalized until the end of the third cycle of treatment. If more than half of the patients withdrew from the study treatment because of toxicities by the completion of the second cycle or if the IDMC decided that the study had to be discontinued, the trial would be terminated. If feasibility was confirmed in the first stage, an additional 25 patients would be enrolled in the second stage. The decision as to whether these additional patients would be treated as inpatients or outpatients was made by the investigators. The final analysis would be carried out 12 months after enrolment of the last patient.

The primary endpoint was the RR, and the secondary endpoints were OS PFS, and safety for all of the patients including those in the first stage.

**Treatment.** Treatment with FOLFIRINOX was given as follows: 2-h i.v. infusion of oxaliplatin at 85 mg/m<sup>2</sup> and 2-h i.v. infusion of *l*-leucovorin at 200 mg/m<sup>2</sup> (during which irinotecan was also i.v. infused over 90 min at 180 mg/m<sup>2</sup>), followed by an i.v. bolus of 5-FU at 400 mg/m<sup>2</sup> and continuous i.v. infusion of 5-FU over 46 h at 2400 mg/m<sup>2</sup>. This regimen was repeated every 2 weeks. Prior to the study treatment, a 5-HT<sub>3</sub> receptor antagonist and dexamethasone were given. Selective neurokinin 1 receptor antagonistic antiemetics were recommended to alleviate nausea and vomiting; G-CSF was not allowed as primary prophylaxis. The treatment was continued until disease progression, unacceptable toxicity, discontinuation as decided by the investigators, or patient refusal.

Chemotherapy was delayed until recovery from the following criteria: neutrophil count <1500/mm<sup>3</sup>, platelet count <75 000/mm<sup>3</sup>, total bilirubin >1.5 mg/dL, grade 3 or higher peripheral sensory neuropathy, grade 2 or higher diarrhea, and watery stools.

When the predefined toxic events in the protocol occurred, dose adjustment was required. The reduced dose were set at 150 mg/m<sup>2</sup> and 120 mg/m<sup>2</sup> for irinotecan, 65 mg/m<sup>2</sup> and 50 mg/m<sup>2</sup> for oxaliplatin, and 1800 mg/m<sup>2</sup> and 1200 mg/m<sup>2</sup> for infusional 5-FU (for more detail, see Tables S1–S3).

**Assessment.** Complete blood counts, blood chemical tests, and physical examinations were carried out at least once a week until the end of the fifth cycle and every 2 weeks thereafter. In cases of grade 4 hematological toxicity, re-examination within 4 days was required. Computed tomography was carried out at least every 6 weeks. Tumor response was independently reviewed extramurally in accordance with Response Evaluation Criteria in Solid Tumors version 1.0. Safety was evaluated in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

**Statistical analysis.** Patients who received the study drugs at least once and did not considerably violate the Good Clinical

Practice guidelines were included in the safety analysis population. Of these patients, those who met the eligibility criteria were included in the FAS. Efficacy was analyzed in the FAS population.

The expected and threshold RRs for the FOLFIRINOX regimen were set as 30% and 10%, respectively, on the basis of the RRs associated with GEM and FOLFIRINOX (9.4% and 31.6%, respectively) in the phase II/III study of FOLFIRINOX by Conroy *et al.*<sup>(6)</sup> If an exact binomial test was carried out at a one-sided significance level of 2.5%, according to the binomial distribution for the null hypothesis that the threshold RR was 10%, a sample size of 29 subjects would result in a power of 81.2%. Accordingly, the target sample size was set at 35 subjects, to account for exclusion of patients from the FAS. The median survival time and corresponding 95% CIs for OS and PFS were estimated using the Kaplan–Meier method. Progression-free survival was defined as the time from Day 1 of Cycle 1 until the first event (progressive disease or death due to any cause). If no such event occurred in a patient, data for that patient were censored on the day of the last imaging procedure. Overall survival was defined as the time from Day 1 of Cycle 1 until death due to any cause. In the absence of an event, data were censored on the last day of survival confirmation.

## Results

**Patient characteristics.** Between June 2011 and September 2012, 36 patients were enrolled from seven institutions. In January 2012, the IDMC evaluated the safety data of the first 10 patients who underwent two cycles of treatment and determined that the study could be continued. The patient characteristics at baseline are shown in Table 1. The median age was 61.5 years (range, 27–71), 58.3% of the patients had a PS 0, the primary site of the tumor was the head of the pancreas in 19.4% of patients, 16.7% of patients had a biliary stent, and 2.8% of patients experienced recurrence after resection. The major sites of metastasis were the liver and lymph nodes.

All 36 patients received the study drugs and met the eligibility criteria; thus, all 36 patients were included in both the safety analysis and the FAS.

**Treatment exposure.** The median number of treatment cycles was eight (range, 1–25). The median relative dose intensities of oxaliplatin, irinotecan, bolus 5-FU, infusional 5-FU, and *l*-leucovorin were 71.0%, 69.6%, 15.9%, 80.3%, and 82.7%, respectively (Table 2). Dose reduction and treatment delay occurred in 32 patients (88.9%). Neutropenia was the most frequent cause for both dose reduction and treatment delay (75.0% and 75.0%, respectively). The major reasons for discontinuation of the treatment were disease progression (75.0%) and adverse event (19.4%).

**Efficacy.** Partial response, SD, and progressive disease were observed in 14, 11, and 10 patients, respectively, and 1 patient was not evaluated because the patient came off the study before SD confirmation. The RR was 38.9% (95% CI, 23.1–56.5), and the disease control rate was 69.4% (95% CI, 51.9–83.7; Table 3). The median time to partial response was 49 days (range, 35–129), and the median duration of response was 170 days (range, 156–196).

The median follow-up time was 12.6 months. The median OS was 10.7 months (95% CI, 6.9–13.2; Fig. 1), and the median PFS was 5.6 months (95% CI, 3.0–7.8; Fig. 2). The 6-month and 1-year survival probabilities were 72.2% (95% CI, 54.5–84.0) and 41.5% (95% CI, 25.4–56.8), respectively.

**Table 1. Characteristics of chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX (n = 36)**

	n	%
Sex		
Male	24	66.7
Female	12	33.3
Age, years		
Median	61.5	
Range	27–71	
<65	29	80.6
≥65	7	19.4
ECOG performance status		
0	21	58.3
1	15	41.7
Body surface area (m <sup>2</sup> )		
Median	1.68	
Range	1.32–1.96	
Type of tumor		
Adenocarcinoma	33	91.7
Adenosquamous carcinoma	3	8.3
Primary tumor location		
Head	7	19.4
Others	28	77.8
None (recurrence)	1	2.8
Metastatic sites		
Liver	31	86.1
Lymph node	20	55.6
Spleen	1	2.8
Stent or drainage		
No	30	83.3
Yes	6	16.7
UGT1A1(*6/*28)		
Wild/wild	25	69.4
Wild/heterozygous	6	16.7
Heterozygous/wild	5	13.9

ECOG, Eastern Cooperative Oncology Group; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

At the time of analysis, 27 patients had died, 9 patients were alive, and no patients were lost to follow-up.

Of the 36 enrolled patients, 33 received secondary treatment. The most common treatment comprised GEM-based regimens, which were given to 28 patients (GEM, n = 23; GEM plus erlotinib, n = 4; GEM + S-1, n = 1). The other regimens included S-1 alone in two patients, and S-1 plus radiation, and FOLFOX in one patient each. Following the FOLFIRINOX treatment, R0 resection of pathology by distal pancreatectomy and splenectomy was achieved in one patient.

**Safety.** Grade 3 or 4 toxicities occurred in 31 patients (86.1%). There were no treatment-related deaths. The major grade 3 and 4 toxicities are listed in Table 4. The major grade 3 or 4 hematological toxicities were neutropenia (77.8%), leucopenia (44.4%), febrile neutropenia (22.2%), thrombocytopenia (11.1%), and anemia (11.1%). Neutropenia and febrile neutropenia occurred frequently, and 52.8% of the patients were treated with G-CSF to control these toxicities. The incidence of neutropenia decreased as the number of cycles increased (Table 5), and febrile neutropenia occurred only during the first cycle.

The major grade 3 and 4 non-hematological toxicities were anorexia (11.1%), diarrhea (8.3%), nausea (8.3%), an increased alanine transaminase level (8.3%), and peripheral

**Table 2. Drug delivery in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX (n = 36)**

	Values	Range
Total no. of cycles	325	–
Median cycle of treatment	8	1–25
Median relative dose-intensity per patient	%	Range
Oxaliplatin	70.98	24.1–100.0
Irinotecan	69.62	17.4–100.0
Fluorouracil bolus	15.86	4.40–100.0
Continuous fluorouracil	80.33	49.6–100.0
/-Leucovorin	82.71	62.2–100.0
	Per patient	Per cycle
	n	%
Dose reductions	n	%
Total	32	88.9
Main reason for reduction	n	%
Neutropenia	27	75.0
Febrile neutropenia	5	13.9
Thrombocytopenia	6	16.7
Diarrhea with fever (≥38°C)	3	8.3
Mucositis (≥Grade 3)	1	2.8
Anaphylaxis	1	2.8
Peripheral sensory neuropathy	2	5.6
Investigator decision	7	19.4
	n	%
Delayed cycles	n	%
Total	32	88.9
Main reason for delay	n	%
Neutropenia	27	75.0
Thrombocytopenia	5	13.9
Diarrhea (≥Grade 2 or watery stool)	2	5.6
Total bilirubin (>1.5 mg/dL)	1	2.8
Peripheral sensory neuropathy	1	2.8
Investigator decision	12	33.3
Patient conveniences	7	19.4
Other	5	13.9

†After two cycles.

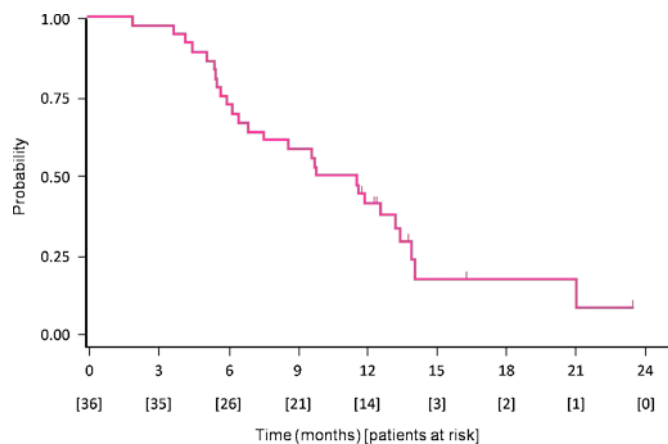
sensory neuropathy (5.6%). No grade 3 or 4 fatigue or vomiting was reported. Cholinergic syndrome, an irinotecan-specific toxicity, was observed in 33% of the patients, but was resolved immediately after treatment with atropine or butylscopolamine.

Serious adverse events occurred in 12 patients (33.3%), and treatment-related toxicity occurred in nine patients (25.0%), including febrile neutropenia in three patients (8.3%) and infection in two patients (5.6%). Severe infection identified as sepsis was observed in two patients, during the 10th and 17th cycle of the treatment, respectively. The infection recovered to grade 1 by the end of the cycle in one patient, however, the treatment had to be discontinued due to concurrent liver abscess. The infection recovered to grade 0 in the other patient by the end of the cycle, however, the treatment was discontinued due to concurrent cholangitis. In terms of SAEs, biliary tract-related events were reported in five patients, including cholangitis, obstructive jaundice, biliary tract infection, and an increased level of blood bilirubin in two, one, one, and two

**Table 3. Efficacy results in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX (n = 36)**

Best overall response	N	%
CR	0	0
PR	14	38.9
SD	11	30.6
Progressive disease	10	27.8
Not evaluated	1	2.8
Response rate (CR+PR)	14	38.9
Disease control rate (CR+PR+SD)	25	69.4
Median time to PR, days†	49	
n†	16	
95% confidence interval†	42.0–77.0	
Range†	35–129	
Median duration of overall response, days‡	170	
n‡	14	
95% confidence interval‡	156.0–196.0	
Range‡	42–287	

†Including patients with partial response (PR). ‡Including patients with PR as best response. CR, complete response; SD, stable disease.



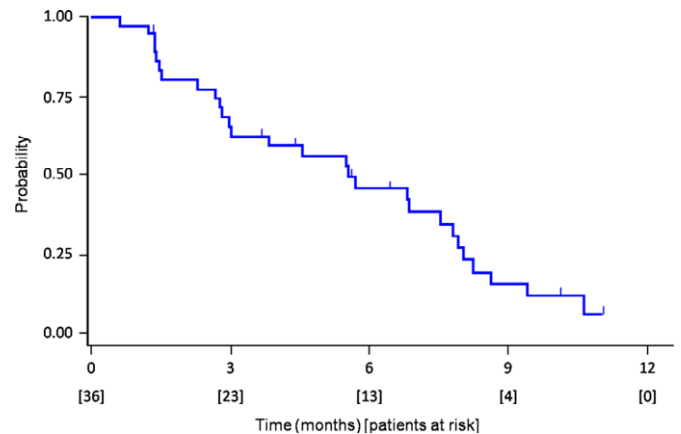
**Fig. 1.** Kaplan–Meier analysis of overall survival in a phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. The median survival was 10.7 months (95% confidence interval, 6.9–13.2). One-year overall survival was 41.5% (95% confidence interval, 25.4–56.8). Data on nine patients were censored.

patients, respectively, all of which were unrelated to the study treatment.

For patients with or without a biliary stent, febrile neutropenia was observed in 50.0% and 16.7%, biliary tract-related events were observed in 50.0% and 6.7%, and sepsis was observed in 33.3% and 0.0%, respectively.

## Discussion

This study was carried out to investigate the efficacy and safety of the FOLFIRINOX regimen in chemotherapy-naïve Japanese patients with MPC. Compared to the FOLFIRINOX phase II/III study by Conroy *et al.*<sup>(6)</sup> in 2011, the proportion of patients with a PS 0 was high (58.3% vs 37.4%) and the proportion of patients in whom the primary site was the pancreatic head was low (19.4% vs 39.2%) in this study. How-



**Fig. 2.** Kaplan–Meier analysis of progression-free survival in a phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. The median progression-free survival was 5.6 months (95% confidence interval, 3.0–7.8). Data on eight patients were censored.

**Table 4. Toxicities in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX (n = 36)**

	Any grade		≥Grade 3	
	n	%	n	%
<b>Hematological toxicities</b>				
Neutropenia	34	94.4	28	77.8
Febrile neutropenia	8	22.2	8	22.2
Leukopenia	33	91.7	16	44.4
Thrombocytopenia	32	88.9	4	11.1
Anemia	31	86.1	4	11.1
<b>Non-hematological toxicities</b>				
Anorexia	31	86.1	4	11.1
Diarrhea	31	86.1	3	8.3
Nausea	32	88.9	3	8.3
Elevated ALT	20	55.6	3	8.3
Elevated ALP	15	41.7	3	8.3
Elevated GGT	5	13.9	3	8.3
Peripheral sensory neuropathy	27	75.0	2	5.6
Elevated C-reactive protein	24	66.7	2	5.6
Elevated AST	20	55.6	2	5.6
Hypoalbuminaemia	23	63.9	2	5.6
Hypokalaemia	9	25.0	2	5.6
Sepsis	2	5.6	2	5.6

Events listed are those in which grade 3–4 toxicities occurred in more than 5% of patients. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, galactolipid galactosyltransferase.

ever, the proportion of patients with stents at baseline was similar in the two studies (16.7% in this study and 15.8% in the FOLFIRINOX phase II/III study),<sup>(6)</sup> with no particular differences in other demographic or clinical variables. It is not considered that these small differences in patients' background might compromise comparability in the RR, the primary endpoint of this study, between these two studies.

In the present study, RR, which was the primary endpoint, was 38.9% (95% CI, 23.1–56.5), with the lower limit of the 95% CI being above the threshold RR of 10%. Other efficacy endpoints (PFS, 5.6 months; OS, 10.7 months) were also favorable and were similar to the findings of the FOLFIRINOX



**Table 5. Neutropenia by cycle in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX (n = 36)**

Cycle	Total patients per cycle (n)	≥Grade 3 neutropenia	
		n	%
Total	36	28	77.8
1	36	24	66.7
2	33	13	39.4
3	30	5	16.7
4	28	5	17.9
5	27	6	22.2
6	24	4	16.7
7	19	1	5.3
8	19	1	5.3

phase II/III study (PFS, 6.4 months; OS, 11.1 months).<sup>(6)</sup> The results of this study were also favorable compared to those of previous studies of first-line treatment in patients with MPC, including Japanese patients, wherein the OS was 7.0–9.4 months.<sup>(7–10)</sup> Accordingly, we consider the FOLFIRINOX regimen to be very effective in Japanese patients with pancreatic cancer.

Grade 3–4 neutropenia and febrile neutropenia were more common in this study than those in the FOLFIRINOX phase II/III study (77.8% and 22.2% vs 45.7% and 5.4%, respectively).<sup>(6)</sup> We hypothesize that these discrepancies are due to differences in the laboratory testing frequency, with weekly testing in this study versus testing every 2 weeks in the phase II/III study.

Despite the high incidence of severe neutropenia, febrile neutropenia and infections identified as SAEs were noted in only three and two patients, respectively, in this study. Although febrile neutropenia was observed in eight patients, all of these patients recovered quickly (median recovery time, 2.5 days; range, 2–4) under the appropriate supportive care. In addition, the incidence of neutropenia decreased along with the number of cycles, and febrile neutropenia occurred only in the first cycle. On the basis of these findings, it is considered that active management, including hospitalization, frequent laboratory testing, supportive care for toxicity, and appropriate dose modifications during the treatment period is important, especially during the initial period.

With regard to non-hematological toxicities, the incidences of grade 3 or higher fatigue, vomiting, diarrhea, and peripheral sensory neuropathy were lower in this study than in the FOLFIRINOX phase II/III study (0.0%, 0.0%, 8.3%, and 5.6% vs 23.6%, 14.5%, 12.7% and 9.0%, respectively).<sup>(6)</sup> It is speculated that the lower incidence of vomiting might be associated with the implementation of active prophylactic supportive therapy, including the use of selective neurokinin 1 receptor antagonistic antiemetics in 34 patients in this study.

As anticipated, biliary tract-related events, severe infection, and febrile neutropenia frequently occurred in patients with biliary stents at baseline, indicating that careful management is required in these patients to avoid the development of cholangitis or infection.

In this study, patients homozygous for *UGT1A1*\*28 or *UGT1A1*\*6 or heterozygous for both *UGT1A1*\*6 and *UGT1A1*\*28 were excluded. *UGT1A1* is involved in the metabolism of SN-38, an active metabolite of irinotecan, and variants of

*UGT1A1* have been reported to intensify myelosuppression, such as severe neutropenia.<sup>(11–13)</sup> The efficacy and safety of FOLFIRINOX have not yet been evaluated in patients homozygous for *UGT1A1*\*28 or *UGT1A1*\*6 or heterozygous for both *UGT1A1*\*6 and *UGT1A1*\*28 in Japan; genetic polymorphism was not included in the eligibility of the phase III trial of FOLFIRINOX. Considering the high incidence of neutropenia in this study, indication of FOLFIRINOX and intensive follow-up for these patients should be considered carefully, especially in Japan.

In 2013, combination therapy of nab-paclitaxel and GEM was found to prolong the survival of patients with MPC compared to GEM alone (the MPACT study).<sup>(14)</sup> The RR, median OS, and median PFS associated with nab-paclitaxel plus GEM were 23%, 8.5, and 5.5 months, respectively, indicating that this may represent another prospective regimen for patients with MPC. However, no randomized controlled study has yet been carried out to compare FOLFIRINOX and nab-paclitaxel plus GEM.

Because of the severe toxicity of FOLFIRINOX, it cannot be applied to all patients with metastatic pancreatic cancer as a standard of care. At present, the choice of regimen, whether FOLFIRINOX or GEM-based chemotherapy, depends on general conditions in each patient, and FOLFIRINOX is generally recommended to the patients who fulfill the eligibility criteria of this study. Recently, several clinical studies of a modified FOLFIRINOX regimen have been carried out to reduce its toxicities.<sup>(15,16)</sup> The FOLFIRINOX regimen is also investigated in patients with genetic polymorphisms of *UGT1A1*\*28 or \*6, which were excluded in this study.<sup>(17)</sup> As it is important to select the most appropriate treatment regimen based on the clinical information of the patients, these results may provide a guide to selection for each individual patient.

In conclusion, on the basis of our findings in this study, the FOLFIRINOX regimen appears to be effective in Japanese patients, and the associated toxicity can be adequately controlled by careful observation and appropriate supportive care. Thus, FOLFIRINOX can be the standard treatment for Japanese patients with MPC with good performance status (ECOG PS 0 or 1) and normal bilirubin level.

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## Abbreviations

5-FU	fluorouracil
CI	confidence interval
FAS	full analysis set
FOLFIRINOX	oxaliplatin, irinotecan, fluorouracil, and leucovorin
G-CSF	granulocyte-colony stimulating factor
GEM	gemcitabine

IDMC Independent Data Monitoring Committee  
MPC metastatic pancreatic cancer  
nab-paclitaxel albumin-bound paclitaxel  
OS overall survival  
PFS progression-free survival

PS performance status  
RR response rate  
SAE serious adverse events  
SD stable disease  
UGT uridine diphosphate-glucuronosyltransferase

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## Supporting Information

Additional supporting information may be found in the online version of this article:

**Table S1.** Dose level at dose adjustment in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX ( $n = 36$ ).

**Table S2.** Dose adjustment criteria in hematological toxicity in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with FOLFIRINOX ( $n = 36$ ).

**Table S3.** Dose adjustment criteria in non-hematological toxicity in chemotherapy-naïve.