



A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer

Masato Ozaka¹ · Hiroshi Ishii² · Tosiya Sato³ · Makoto Ueno⁴ · Masafumi Ikeda⁵ · Kazuhiro Uesugi² · Naohiro Sata⁶ · Kouichirou Miyashita⁷ · Nobumasa Mizuno⁸ · Kunihiro Tsuji⁹ · Takuji Okusaka¹⁰ · Junji Furuse¹¹

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Abstract

Background We evaluated the efficacy and safety of a modified FOLFIRINOX regimen for chemotherapy-naïve patients with metastatic pancreatic cancer.

Methods Patients with untreated metastatic pancreatic cancer (MPC) received modified FOLFIRINOX (intravenous oxaliplatin 85 mg/m², irinotecan 150 mg/m², 5-FU infusion 2400 mg/m² over 46 h, no bolus 5-FU). The primary endpoints were overall survival and the incidence of grade 3 or higher neutropenia. No patients received prophylactic pegfilgrastim.

Results Sixty-nine pts. were enrolled from 39 institutions in Japan. The median overall survival was 11.2 months [95% confidence interval (CI) 9.0–]. The median progression-free survival was 5.5 months (95% CI 4.1–6.7). The response rate was 37.7% (95% CI 26.3–50.2), and the disease control rate was 78.3% (95% CI 66.7–87.3). The incidence of grade 3 or higher neutropenia was 47.8%. Serious adverse events occurred in six patients (8.7%). All AE proportions were less than those in the previous Japanese full-dose phase II study. One patient died due to interstitial pneumonia related to treatment.

Conclusion This is the first prospective study of modified FOLFIRINOX in Asia. Modified FOLFIRINOX in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim.

Keywords Metastatic · Pancreatic cancer · Chemotherapy · FOLFIRINOX · Modified FOLFIRINOX

✉ Masato Ozaka
masato.ozaka@jfcrr.or.jp

¹ Department of Gastroenterology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

² National Hospital Organization Shikoku Cancer Center, 160 Kou, Minami Umemoto, Matsuyama 791-0280, Japan

³ Department of Biostatistics, Kyoto University School of Public Health, Yoshida-honmachi, Sakyo-ku, Kyoto 606-8501, Japan

⁴ Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, 2-3-2 Nakao, Asahi-ku, Yokohama, Kanagawa 241-8515, Japan

⁵ Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

⁶ Department of Surgery, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

⁷ Internal Medicine of Gastroenterology, Showa University Northern Yokohama Hospital, Tsudukiku, Chigasakiyuo 35-1, Yokohama, Kanagawa 224-8503, Japan

⁸ Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

⁹ Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kuratsukihigashi 2-1, Kanazawa, Ishikawa 920-8530, Japan

¹⁰ Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

¹¹ Department of Medical Oncology, Kyorin University School of Medicine, 6-20-2, Shinkawa, Mitaka, Tokyo 181-8611, Japan

Introduction

Pancreatic cancer is a highly lethal cancer with a 2–3% 5-year survival rate and is the fourth leading cause of cancer-related mortality in Japan. In the phase III study (ACCORD11 trial) conducted by Conroy et al., FOLFIRINOX (FFX: oxaliplatin, irinotecan, 5-FU and leucovorin) showed a significant improvement in overall survival, progression-free survival and quality of life compared with gemcitabine [1]. From the results of the ACCORD11 trial, FFX is currently acknowledged as one of the standard therapies for chemotherapy-naïve patients with metastatic pancreatic cancer (MPC), with good performance status. However, in the ACCORD11 trial, the incidence rates of neutropenia and febrile neutropenia in the FFX arm were reported as 45.3 and 5.4%, respectively. This was significantly higher than in the gemcitabine arm. Furthermore, it was found to be more toxic when used in real clinical situations than previously indicated by the ACCORD11 trial, so regimens with a reduced dosage have been used at many hospitals [2]. Many of the recent FFX-related clinical trials were conducted using a modified regimen by omitting the 5FU bolus.

In Japan, a phase II trial of FFX was conducted for 36 patients with metastatic pancreatic cancer [3]. The efficacy in the Japanese phase II study was similar to that reported in the ACCORD11 trial, and the incidences of grade 3 or 4 toxicities, especially neutropenia (77.8%) and febrile neutropenia (22.2%), were higher. Although the standard FFX has a greater effectiveness based on the data of the Japanese/ACCORD11 trial, it is considered that the management of adverse events could still be difficult. The trial was planned because we considered it necessary upfront to perform dose reductions for the 5FU bolus and irinotecan in patients with MPC to develop a safer FFX therapy while maintaining its efficacy. We report the analysis of the efficacy and toxicity of modified FFX in MPC.

Materials and methods

Patients

The inclusion criteria were as follows: 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 haematological, liver, and renal function (haemoglobin ≥ 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 ≤ 2.5 upper limit of normal, creatinine ≤ 1.2 mg/dL, and C-reactive protein ≤ 2.0 mg/dL). Patients were excluded if they had the following: prior chemotherapy or radiation therapy; grade 2 or higher peripheral sensory neuropathy; blood transfusion, blood products, or haematopoietic 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 cancer dissemination; diarrhoea 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.

Study design

This study was an open-label, multicentre, single-arm phase II study.

The primary endpoints were overall survival (OS) and the incidence of grade 3 or higher neutropenia, and the secondary endpoints were progression-free survival (PFS), response rate and safety for all of the patients. This clinical trial was conducted with the approval of the review board of each participating institution and in accordance with the Declaration of Helsinki. This trial is registered with UMIN-CTR (<http://www.umin.ac.jp/ctr/index-j.htm>), identification number (UMIN000013301).

Treatment

Patients were treated with modified FFX every 2 weeks, as follows: 2-h i.v. infusion of oxaliplatin at 85 mg/m^2 and 2-h i.v. infusion of l-leucovorin at 200 mg/m^2 . Irinotecan was also i.v. infused over 90 min at 150 mg/m^2 , followed by continuous i.v. infusion of 5-FU over 46 h at 2400 mg/m^2 . Bolus 5-FU was omitted. All patients routinely received palonosetron, aprepitant and dexamethasone for emesis prophylaxis. 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 $< 1500/\text{mm}^3$, platelet count $< 75,000/\text{mm}^3$, total bilirubin > 1.5 mg/dL, grade 3 or higher peripheral sensory neuropathy, grade 2 or higher diarrhoea, and watery stools.

When the predefined toxic events in the protocol occurred, dose adjustment was required. The reduced dose was set at 120 and 100 mg/m^2 for irinotecan, 65 and 50 mg/

m² for oxaliplatin, and 1800 and 1200 mg/m² for infusional 5-FU.

Assessment

Patients were evaluated for toxicities at the start of each cycle. Complete blood counts, blood chemical tests, and physical examinations were carried out every 2 weeks. Computed tomography was carried out at least every 6 weeks. Tumour response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OS was measured from the date of enrolment to the date of death or the date of the last follow-up. PFS was defined as the time from the date of enrolment to the first documentation of disease progression or death. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

The expected and threshold OS times for the modified FFX regimen were set as 11 and 7 months, respectively, on the basis of the OS associated with gemcitabine and FFX (6.8 and 11.1 months, respectively) in the ACCORD11 trial. Assuming an exponential distribution for OS, we calculated 60 participants required to provide the trial with 80% power to detect a 36% improvement in median OS at a one-sided significance level of 2.5%. Accordingly, the target sample size was set at 65 subjects to account for the exclusion of patients. The median survival time and corresponding 95% CIs for OS and PFS were estimated using the Kaplan–Meier method.

Results

Patient characteristics

Between February 2014 and December 2014, 69 patients were enrolled (Fig. 1). The patient characteristics at baseline are shown in Table 1. The median age was 62.6 years (range 42–74), 68.1% of the patients had a PS 0, the primary site of the tumour was the head of the pancreas in 44.9% of patients, 20.3% 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 69 patients received the study drugs and met the eligibility criteria.

Treatment

The median number of treatment cycles was eight (range 1–25). The median relative dose intensities of oxaliplatin,

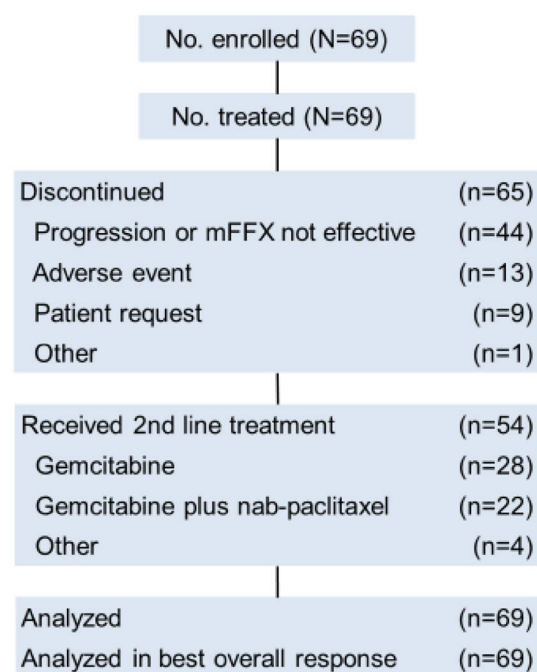


Fig. 1 Patient disposition

irinotecan, infusional 5-FU, and l-leucovorin were 76.1, 91.4, 95.4 and 99.1%, respectively. Dose reduction and treatment delay occurred in 54 patients (79.7%). Neutropenia was the most frequent cause of both dose reduction and treatment delay. The major reasons for discontinuation of the treatment were disease progression (67.7%) and adverse event (20%). Of the 69 enrolled patients, 54 received second-line treatment. The most common treatment comprised gemcitabine, which was given to 28 patients. The other regimen was gemcitabine + nab-paclitaxel, which was given to 22 patients. There was no significant difference between the gemcitabine group and the gemcitabine + nab-paclitaxel group in PFS from the secondary treatment.

Efficacy

The objective RR and disease control rate in all patients were 37.7% (95% CI 26.3–50.2) and 78.3% (95% CI 66.7–87.3), respectively (Table 2). They were not significantly different from the response rate in patients in the FFX-treated historical control group.

Partial response, stable disease, and progressive disease were observed in 26, 28, and 10 patients, respectively. The median time to partial response was 76 days (range 35–252 days), and the median duration of response was 167 days (range 152–196 days).

Table 3 and Fig. 2 show the results for OS and PFS, respectively. The median OS was 11.2 months (95% CI 9.0–), and the 1-year survival rate was 48.1% (95% CI 36.1–60.1).

Table 1 Baseline characteristics of treated patients

Characteristics	N = 69	
	No. of patients	%
Age (years)		
Median	62.6	
Range	42.4–74.2	
Sex		
Female	26	37.7
Male	43	62.3
ECOG PS		
0	47	68.1
1	22	31.9
Pancreatic tumor cell type		
Adenocarcinoma	68	98.6
Squamous cell carcinoma	1	0.1
Pancreatic tumor location		
Head	31	44.9
Body	22	31.9
Tail	16	23.2
Measurable metastatic sites		
Liver	49	71.0
Lymph node	11	15.9
Lung	5	7.2
Other	3	4.3
Prior surgery		
Yes	4	5.8
No	65	94.2
Biliary stent		
Yes	14	20.3
No	55	79.7
CA19-9		
Median	1183.3	
Range	0.6–127,436	
1000 U/mg and less	33	47.8
Over 1000 U/mg	36	52.2

The median PFS was 5.5 months (95% CI 4.1–6.7) and the 1-year PFS rate was 21% (95% CI 11.2–30.7).

Adverse events

Grade 3 or 4 toxicities occurred in 49 patients (71%). The major grade 3 and 4 toxicities are summarized in Table 4. The major grade 3 or 4 haematological toxicities were neutropenia (47.8%), leucopenia (29%), and anaemia (4.3%). The incidence of febrile neutropenia was 8.7%. The incidences of grade 3 or 4 neutropenia (47.8 vs 77.8%) and febrile neutropenia (8.7 vs 22.2%) were significantly decreased in our study compared with the historical Japanese trial treated with standard FFX. Patients with severe neutropenia and febrile neutropenia were treated with G-CSF

Table 2 Summary of best response by RECIST criteria

Best response	n = 69	
	No. of patients	%
CR	0	
PR	26	37.7
SD	28	40.6
PD	10	14.5
Not evaluable	5	7.2
ORR (CR + PR)	26	37.7
Exact 95% CI		26.3–50.2
DCR (CR + PR + SD)	54	78.3
Exact 95% CI		66.7–87.3

CI confidence interval, CR complete response, DCR disease control rate, ORR overall response rate, PD progressive disease, PR partial response, SD stable disease

Table 3 Results of overall survival (OS) and progression-free survival (PFS)

N = 69	
OS	
No of events	38
Person-months	729.7
Median OS (months)	11.2
95% CI	9.0– ^a
1 year survival proportion	0.481
95% CI	0.361–0.601
Estimated hazard ^b	0.62
Exact 95% CI ^b	0.44–0.86
PFS	
No of events	59
Person-months	450.8
Median PFS (months)	5.5
95% CI	4.1–6.7
1 year PFS proportion	0.210
95% CI	0.112–0.307
Estimated hazard ^b	1.57
Exact 95% CI ^b	1.20–2.03

^a Upper limit was not calculated

^b per 12 person-months (1 person-year)

to control these toxicities, but only 18% of patients were treated with G-CSF. The major grade 3 and 4 non-haematological toxicities were as follows: anorexia (15.9%), diarrhoea (10.1%), fatigue (4.3%), nausea (8.7%), cholangitis (8.7%), thromboembolism (4.1%), and peripheral neuropathy (5.8%). Serious adverse events occurred in six patients (two duodenal perforation, two venous thromboembolisms, tumour haemorrhage and pneumonitis). There was one treatment-related death due to pneumonitis.

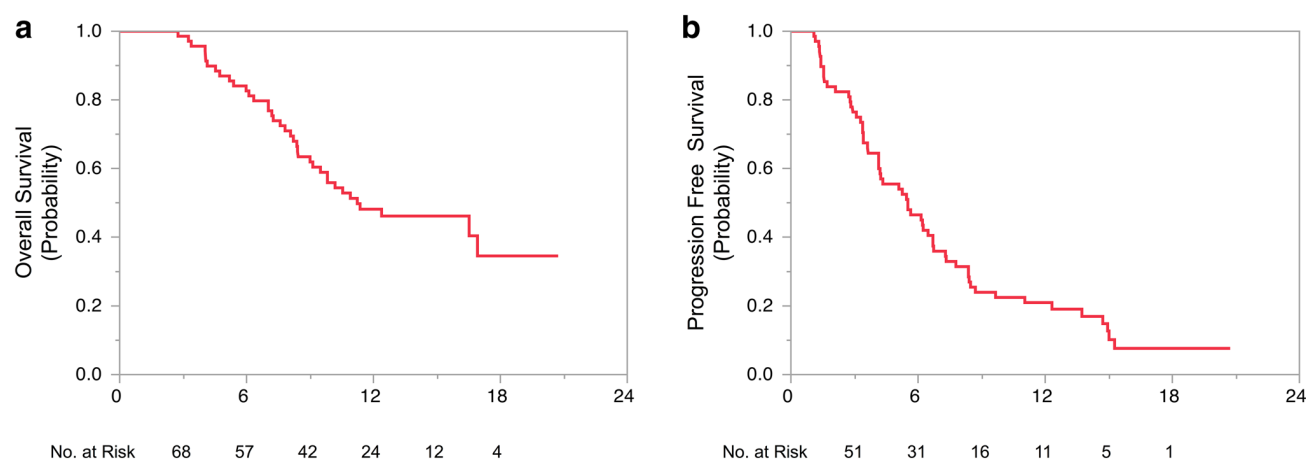


Fig. 2 **a** is Kaplan–Meier analysis of overall survival and **b** is progression-free survival

Table 4 Adverse events in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with modified FOLFIRINOX ($n = 69$)

	≥ Grade 3	
	<i>n</i>	%
Hematological toxicities		
Neutropenia	33	47.8
Leukopenia	20	29
Thrombocytopenia	2	2.9
Anemia	3	4.3
Non-hematological toxicities		
Febrile neutropenia	6	8.7
Anorexia	11	15.9
Diarrhoea	7	10.1
Nausea	6	8.7
Cholangitis	6	8.7
Fatigue	4	5.8
Peripheral sensory neuropathy	4	5.8
Infusion reaction	1	1.4

Discussion

This phase II trial was conducted to evaluate the efficacy and safety of reduced doses of FFX to mitigate adverse events.

In particular, in a Japanese phase II trial, febrile neutropenia was observed with a high frequency. To evaluate the efficacy and safety of modified FFX in this study, we needed to align the background with that of the Japanese phase II trial [3]. The demographics of the participants in the two trials were generally similar.

The features of the regimen in this study included the omission of the bolus 5FU and the reduced dose of

CPT-11 (to 150 mg). We omitted the bolus 5FU because of the results of the phase III trial to evaluate the efficacy of FOLFOXIRI (a regimen of FFX without a 5FU bolus, which was developed in Italy) for advanced colorectal cancer patients in comparison with FOLFIRI, which were presented by the Hellenic Oncology Research Group (HORG) in 2006 [4] and the Gruppo Oncologico Ovest (GONO) in 2007 [5], respectively. In the HORG trial, the median overall survival period in the FOLFOXIRI group was 21.5 months, and efficacy was not proven statistically when compared to the FOLFIRI group, whose survival period was 19.5 months ($p = 0.337$). However, the GONO trial showed significantly longer survival periods; the median overall survival period in the FOLFOXIRI group was 22.6 months, whereas it was 16.7 months in the FOLFIRI group. The reason that the GONO trial showed positive results was due to the omission of the 5FU bolus and the administered dose of the key drugs CPT-11 and L-OHP (L-OHP: 85 mg, CPT-11: 165 mg) (in the HORG regimen, L-OHP: 65 mg and CPT-11: 150 mg). In FFX for pancreatic cancer patients, CPT-11 and L-OHP were considered key drugs, and maintaining their dosages was very important. Furthermore, the median relative dose intensity of the 5FU bolus in the Japanese phase II trial was 15.9%. Thus, combined with the results of the phase III trial on colon cancer patients described above, we determined that the 5FU bolus had less significance in FFX therapy.

Moreover, the reason for reducing the dosage of CPT-11 was as follows: A phase I trial on FOLFOXIRI (GONO regimen) in the treatment of colon cancer patients was conducted in Japan [6]. For ten advanced colorectal cancer patients, the plan was to use the dose titration method and to increase the dosage level of L-OHP/CPT-11/5FU to 85/165/2400, 85/165/3200 and 85/185/3200 (mg/m²). However, dose-limiting toxicity (DLT) emerged due to a haematologic

toxicity of level 0, so the MTD was determined to be 85/165/2400 mg/m² and the RD was 85/150/2400 mg/m².

Furthermore, in a Japanese phase II trial on pancreatic cancer patients, the dosage of CPT-11 was reduced to 150 mg in 66.7% of patients after the second course, and only 10% of patients did not require reduction. We, therefore, believed that the reduction in CPT-11 in the modified FFX therapy was reasonable. Based on the Japanese phase I trial on colon cancer patients described above, we considered 150 mg to be appropriate for an initial dosage.

There is a risk that the efficacy could weaken due to the reduction in the initial dosage. However, the overall survival, which was the primary endpoint of this study, was almost the same as those in the ACCORD11 trial and the Japanese phase II trial. The other efficacy results were also similar to those of the previous standard FFX studies.

There are concerns that tumour shrinkage might be delayed by lowering the dosage at the start of therapy; however, tumour shrinkage was observed promptly after the start of therapy. Thus, there was no observable impact of reducing the dosage. We believe that the impact on the efficacy of the regimen when reducing the dose is minimal.

Furthermore, in this trial, we set the following provision: if a patient was determined to have sufficient tolerance in this modified regimen, they could return to their original regimen. In accordance with this provision, the dosage was increased for three patients; however, they showed obvious signs of haematologic toxicity with the increased dosage cycle, so we returned them to the reduced dosage regimen. This also indicates that the dosage used in this therapy has validity.

On the other hand, with respect to adverse events, a reduction in haematologic toxicity was observed due to the modified regimen. In particular, febrile neutropenia, which was frequently observed in the Japanese phase II trial, was suppressed and occurred at only a significantly low frequency. It should be noted that in this study, the rate of GCSF use during the study was only 18% among all patients, which was a low rate; however, the rate of occurrence of febrile neutropenia was suppressed.

The other modified FFX treatment showed favourable results in a previous report [7], but in that report, GCSF was used in all the cases. In this study, only 18% patients were treated with GCSF. Our modified FFX regimen is medico-economically very viable because the additional cost of GCSF is approximately \$1000.

When compared to the Japanese phase II trial, the results showed that satisfactory management of adverse events was possible while ensuring efficacy, but when compared to the ACCORD trial, the incidence of haematologic toxicity seemed to be higher. However, there were big differences between the ACCORD11 trial and the Japanese phase II trial in haematologic toxicity (the incidence of febrile

neutropenia: ACCORD; 5.4% and Japanese trial; 22.2%). In other carcinoma trials, it has been reported that the incidence of haematologic toxicity (especially febrile neutropenia) in non-Japanese trials is very different from that in the results of the Japanese trial. Most cases showed a higher febrile neutropenia incidence among Japanese patients breast cancer TC <DTX 75 + CPA 600 4 courses>: non-Japanese; 5%, Japanese; 68.8% [8, 9]; prostate cancer cabazitaxel 25 mg: non-Japanese; 8%, Japanese; 54.5% [10, 11], so there might be ethnic disparities in febrile neutropenia. Patients with the UGT1A1 mutation, which is deeply involved in the development of blood toxicity, were excluded both in the Japanese phase II trial and this trial. In these cases, the frequency of occurrence of blood toxicity was higher than in non-Japanese data. We assume that inter-ethnic differences might contribute to this difference, as non-Japanese subjects were included in other carcinoma cases, so adverse events should be compared between the Japanese data.

The limitations of this trial were that it was a single-arm phase II trial and we only had data on Japanese people. However, the efficacy of this modified regimen was similar to other global studies, and we found that the adverse events were well controlled compared to other Japanese groups, which have the same demographic balance of adverse events. Therefore, we believe this modified regimen to be one of the more effective FFX regimens.

One of the standard therapies for metastatic pancreatic cancer is gemcitabine + nab-paclitaxel (GnP). Compared to the original FFX, GnP is likely to be used because its adverse events are slightly mitigated [12]. However, if our modified FFX regimen is used, the same level of treatment can be expected with the same level of adverse events, so comparative trials between these two therapies are awaited in the future.

In conclusion, this is the first prospective study of modified FOLFIRINOX in Asia. The modified FOLFIRINOX regimen in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim.

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Compliance with ethical standards

Conflict of interest Masato Ozaka received the honoraria from Taiho Pharmaceutical, Yakult, Bayer, Pfizer and Novartis. Hiroshi Ishii is a member of a Data and safety Monitoring Board of Ono, and received the honoraria from Eisai, Taiho, Chugai and Astellas. Makoto Ueno

received honoraria from Abbott, Eli Lilly, Yakult and AstraZeneca and research funding from Eli Lilly, Kowa, Taiho, Yakult, Daiichi-Sankyo, Kyowa Hakko Kirin, Zeria, Merck Serono and AstraZeneca. Masafumi Ikeda received research funding from received research funding from GlaxoSmithKline, AstraZeneca, Yakult, Ono Pharmaceutical, and Eisai. Nobumasa Mizuno has received research grants from AstraZeneca, Eisai, Merck Serono, MSD, NanoCarrier, Taiho Pharmaceutical, and Zeria Pharmaceutical, and speakers bureau honoraria from Kyowa Hakko Kirin, Novartis, Pfizer, Taiho Pharmaceutical, and Yakult Honsha. Takuji Okusaka has had an editor role, research grant, and honoraria from Novartis; reports research grants and honoraria from Pfizer, Taiho, Bayer, Chugai, Eli Lilly and Company, Yakuruto Honsha, Ono Pharmaceutical, AstraZeneca, Merck Serono, Baxter, Nobelpharma Co.; and research grants from Nippon Boehringer Ingelheim, Dainippon Simitomo Pharma, Eisai Co., OncoTherapy Science Inc., Kyowa Hakko Kirin Co., Shizuoka Industry, Nano Carrier Co., Zeria Pharmaceutical Co. and Glaxo Smith Kline. Junji Furuse received has received honoraria from Taiho Pharmaceutical, Fujifilm, Eisai, Astellas, Yakult, Sumitomo Dainippon, Eli Lilly Japan, and Kyowa Hakko Kirin, and research funding from J-Pharma, Taiho Pharmaceutical, Ono Pharmaceutical, MSD, Janssen and Daiichi Sankyo. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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