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A Phase 2 study of nivolumab in combination with modified FOLFIRINOX for metastatic pancreatic cancer

Chigusa Morizane¹✉, Makoto Ueno², Masafumi Ikeda³, Kentaro Sudo⁴, Yoshinori Hirashima⁵, Masataka Kuroda⁵, Shinji Ueno⁵, Takuji Okusaka¹ and Junji Furuse^{6,7}

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BACKGROUND: Nivolumab with modified FOLFIRINOX (mFOLFIRINOX) may have additive antitumour effects while minimising chemotherapy cytotoxicity. We assessed the efficacy and safety of nivolumab+mFOLFIRINOX in metastatic pancreatic cancer.

METHODS: Thirty-one treatment-naïve patients aged ≥ 20 years with metastatic unresectable/recurrent pancreatic cancer (≥ 1 measurable lesion per Response Evaluation Criteria in Solid Tumours version 1.1) and Eastern Cooperative Oncology Group 0/1 score and life expectancy ≥ 90 days received nivolumab (480 mg, every 4 weeks) plus mFOLFIRINOX. The primary endpoint was objective response rate (ORR). Secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety.

RESULTS: At the median follow-up of 13.4 months, the ORR was 32.3% (complete response 0%; partial response 32.3%) and the median duration of response was 7.4 (range: 3.5–21.9) months; the primary endpoint was not met. Median OS and PFS were 13.4 (95% confidence interval [CI]: 10.6–16.6) months and 7.4 (95% CI: 3.9–9.2) months, respectively. The 1-year survival rate was 54.8% (95% CI: 36.0%–70.3%). Drug-related serious adverse events were reported in 29.0% of the patients; 3.2% drug-related adverse events led to discontinuation, and none led to death within 30-day safety window.

CONCLUSION: Nivolumab+mFOLFIRINOX was tolerable in patients with metastatic pancreatic cancer. ORR and survival were comparable to previously reported data. (JapicCTI-184230)

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BACKGROUND

Pancreatic cancer ranks among the top five gastrointestinal cancers [1]. The majority of pancreatic cancers are adenocarcinomas, accounting for approximately 85%–95% of all pancreatic tumours [2]. Unfortunately, owing to lack or non-specificity of symptoms in early stages, most patients with pancreatic cancer present clinically at an advanced stage and have grim prognoses [3]. It is one of the most lethal cancers despite the advances in cancer therapeutics. In fact, pancreatic cancer is predicted to become the third leading cause of death from cancer in Europe by 2025 [4] and second leading cause of death from cancer in the United States by 2030 [5].

Both FOLFIRINOX and gemcitabine + nab-paclitaxel regimens are considered standard of care worldwide and also in Japan for unresectable metastatic pancreatic cancer [6–9]. However, these regimens have not greatly influenced overall survival (OS; median survival being <1 year) in these patients, with no substantial improvement in survival in the last 10 years [10, 11], despite the high costs as well as toxicity [10, 12].

Recently, in a randomised, open-label, Phase 3 trial, first-line NALIRIFOX (liposomal irinotecan, fluorouracil, leucovorin and oxaliplatin) demonstrated significant improvement in OS and progression-free survival (PFS) over gemcitabine + nab-paclitaxel

in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma [13]. However, the median OS was still <1 year (11.1 months) in NALIRIFOX arm, suggesting a limited impact on the therapeutic landscape.

Nivolumab, a monoclonal antibody, binds to programmed death-1 receptor (PD-1), preventing binding of ligands to PD-1. Thus, nivolumab prevents downstream immune suppression and elicits an immune response [14]. It has shown efficacy in multiple cancer types both as monotherapy and in combination with other therapies [15–19]. Understanding of the cancer–immunity cycle is useful in elucidating how the combined use of nivolumab and FOLFIRINOX could have a synergistic antitumour effect owing to their different yet complementary mechanisms of action. The development of cancer immunity is a self-propagating and self-amplifying virtuous cycle that includes cancer cell antigen release, T cell activation, infiltration of T cells into tumours, and the killing of cancer cells [20]. Chemotherapy has been described to not only directly inhibit the proliferation of cancer cells but also restore the immune surveillance mechanism for cancer cells and thus provide better immune environment for subsequent immunotherapy [21–23]. As chemotherapy with drugs such as oxaliplatin induces cancer cell death, exposure of the tumour antigen to antigen-presenting cells increases, thereby potentiating the cancer

¹Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan. ²Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan. ³Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan. ⁴Department of Gastroenterology, Chiba Cancer Center, Chiba, Japan. ⁵Clinical Development Headquarters, Ono Pharmaceutical Co., Ltd., Osaka, Japan. ⁶Department of Medical Oncology, Kyorin University Faculty of Medicine, Mitaka, Japan. ⁷Present address: Kanagawa Cancer Center, Yokohama, Japan. ✉email: cmorizan@ncc.go.jp

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elimination mechanism [24, 25]. 5-fluorouracil and oxaliplatin have been reported to eliminate myeloid-derived suppressor cells and other immune-related cells [26, 27]. At the same time, irinotecan enhances the effect of T cell activation caused by anti-programmed death-ligand 1 (PD-L1) treatment; irinotecan leads to depletion of regulatory T cells, with restoration of the cancer immune surveillance mechanism [28]. Thus, chemotherapy can expand the response of the cancer–immunity cycle improving the efficacy of nivolumab.

Therefore, we evaluated the combined antitumour efficacy and safety of nivolumab, an immune checkpoint inhibitor, and a standard chemotherapeutic regimen of modified FOLFIRINOX (mFOLFIRINOX) vs. current standard of care in patients with chemotherapy-naïve metastatic pancreatic carcinoma.

METHODS

Study design and treatment

This was a multicentre, open-label, Phase 2 study (JapicCTI-184230) conducted at five centres; the first and the last patients were enrolled on 10 January 2019, and 09 July 2019, respectively. The study (JapicCTI-184230) was conducted in compliance with the protocol, the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines and other applicable laws and regulations. It was also approved by the Institutional Review Board of each study site. All participants gave their written informed consent for study participation.

Patients

Patients aged ≥ 20 years with life expectancy ≥ 90 days at the time of enrolment were eligible for inclusion if they had histologically or cytologically diagnosed pancreatic adenocarcinoma with distant metastases without prior treatment for pancreatic cancer (except surgical resection) and ≥ 1 measurable lesion as per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) guideline at imaging within 14 days before enrolment. Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 [29]; adequate haemogram (neutrophil count $\geq 2000/\text{mm}^3$; platelet count $\geq 100,000/\text{mm}^3$; haemoglobin ≥ 9.0 g/dL) without receiving blood transfusion or a granulocyte colony stimulating factor within the past 14 days; adequate liver function (aspartate aminotransferase and alanine aminotransferase ≤ 100 U/L; total bilirubin ≤ 1.2 mg/dL); and adequate renal function (creatinine ≤ 1.2 mg/dL). Each patient voluntarily provided written consent.

Key exclusion criteria were current or past history of severe hypersensitivity reactions to antibody drugs; contraindicated use of FOLFIRINOX drugs; UDP-glucuronosyltransferase 1A1 (UGT1A1) homozygous (UGT1A1*6/*6, UGT1A1*28/*28) or double heterozygous (UGT1A1*6/*28) genotype; concurrent, chronic or recurrent autoimmune disease (Supplementary Material); multiple primary cancers; any symptomatic metastatic lesion in the brain or meninges requiring treatment; peripheral motor or sensory neuropathy; clinically relevant diarrhoea, diverticulitis or gastrointestinal ulcer disease; prior nivolumab or T cell suppression therapies; and vaccinations within 28 days before enrolment.

Treatment

Treatment-naïve patients with metastatic unresectable/recurrent pancreatic cancer received nivolumab (480 mg, infused intravenously [IV] over 30 min every 4 weeks) plus mFOLFIRINOX. The mFOLFIRINOX regimen included oxaliplatin 85 mg/m² infused IV over 2 h, followed by levofolinate 200 mg/m² infused IV over 2 h. Irinotecan 150 mg/m² was infused IV over 1.5 h, starting 30 min after the start of levofolinate infusion. After the end of levofolinate infusion, fluorouracil 2400 mg/m² was infused IV over 46 h. The treatment cycle of mFOLFIRINOX was repeated every 2 weeks.

No dose modification of nivolumab was permitted. If nivolumab and the mFOLFIRINOX regimen were given on the same day, nivolumab was administered first, and mFOLFIRINOX administration was started at least 30 min after the end of nivolumab infusion.

Treatment was repeated until the patient met any of the predetermined discontinuation criteria, which included intolerable adverse events (AEs), progressive disease as assessed by the investigator or sub-investigator (RECIST v1.1), worsened clinical symptoms judged to be due to disease

Table 1. Baseline demographics and clinical characteristics.

Characteristics	Nivolumab + mFOLFIRINOX (N = 31)
Sex, male, n (%)	18 (58.1)
Age, median (range), years	59.0 (39–75)
ECOG performance status, n (%)	
0	21 (67.7)
1	10 (32.3)
Primary tumour site, n (%)	
Head	9 (29.0)
Body	14 (45.2)
Tail	11 (35.5)
Number of organs with metastases, n (%)	
1	20 (64.5)
≥ 2	11 (35.5)
Site of metastasis, n (%)	
Liver	20 (64.5)
Lung	5 (16.1)
Lymph node	14 (45.2)
Peritoneum	6 (19.4)
Pleura	1 (3.2)
CA19-9 (U/mL) ^a	
Mean (SD)	8125.5 (23,883.9)
Median [Minimum–Maximum]	1000.0 [1–113,900]
Any biliary drainage, n (%)	
No	24 (77.4)
Yes	7 (22.6)
PD-L1 (CPS), n (%)	
<1	23 (74.2)
≥ 1	7 (22.6)
Not quantifiable	1 (3.2)
Tumour mutation burden: (Muts/Mbp), n (%)	
<5	20 (64.5)
≥ 5	4 (12.9)
Missing	7 (22.6)

CA carbohydrate antigen, CPS combined positive score, ECOG Eastern Cooperative Oncology Group, mFOLFIRINOX modified FOLFIRINOX, PD-L1 programmed death-ligand 1, SD standard deviation.

^aAssessed in $n = 23$.

progression and continuation of intervention judged to be inappropriate by the investigator or sub-investigator from efficacy or safety viewpoints.

Assessments

At the beginning of a treatment cycle, the patients were evaluated based on medical history, complete physical examination by a physician, ECOG performance status and laboratory tests (haemogram, blood chemistry, qualitative urinalysis). Imaging was performed every 2 cycles (8 weeks). Patients were followed at 3-month intervals until death.

During the screening period, tumour tissue samples for analysis of PD-L1 expression status and tumour mutation burden (TMB; number of genetic mutations in tumour tissue) were collected. Tumour tissue samples were stained for PD-L1 and assessed by a pathologist at the central laboratory. PD-L1 expression was analysed with the pharmDx 28–8 assay (Dako, Carpinteria, CA, USA). The combined positive score (CPS) is the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100. TMB was assessed using the Foundation Medicine's solid tumour assay (Foundation Medicine, Cambridge, MA, USA).

Endpoints

Progression was assessed according to RECIST v 1.1. The primary efficacy endpoint was the objective response rate (ORR) by central assessment and secondary efficacy endpoints included maximum percentage change in tumour diameter from baseline, OS, PFS by central assessment, duration of response, time to response, best overall response, disease control rate, percentage change and maximum percentage change in the sum of diameters of target lesions. Safety endpoints were AEs, clinical laboratory test results (haematology, blood chemistry, qualitative urinalysis, immunology tests, hormone tests) and vital signs (systolic and diastolic blood pressure, pulse rate, body temperature).

Statistical analysis

All analyses were performed in the full analysis set. For each quantitative variable, the mean (standard deviation [SD]) was reported. For each qualitative variable, the number (%) was reported. The relative dose intensity was calculated as described in the Supplementary Material. For primary endpoints, 90% confidence intervals (CIs) were estimated using the Clopper-Pearson method. For secondary endpoints, the Kaplan-Meier method was used for time-to-event analysis. Specifically, for OS and PFS, Kaplan-Meier curves were prepared. The Kaplan-Meier method was used to calculate the median (95% CI) and the OS and PFS rates (95% CI) at 6, 12,

18 and 24 months. Exploratory analyses included efficacy assessments by PD-L1 status and by TMB.

For this study, assuming $\alpha = 0.10$, a power of 80%, a threshold ORR of 31.6% (as per ACCORD 11 trial results [30]) and an expected ORR of 56.0% (based on clinical meaningfulness expectation), the minimum sample size required for the lower limit of the 90% CI of the ORR by the Clopper-Pearson method to exceed the threshold ORR was estimated to be 30 patients.

RESULTS

From five study sites, 31 patients were included in the study and in both the safety analysis and full analysis sets (Table 1).

The median (range) of duration for treatment with nivolumab and mFOLFIRINOX regimen was 7.6 (0.1–31.1) months, and the follow-up duration was 13.4 (1.0–34.3) months. The mean (SD) relative dose intensity (%) was 98.7 (2.9), 76.8 (15.2), 85.0 (10.8), 71.4 (15.4) and 81.6 (12.9) for nivolumab, oxaliplatin, leovorin, irinotecan and fluorouracil, respectively. Only one (3.2%) patient received <50% relative dose intensity of oxaliplatin while two (6.5%) patients received <50% relative dose intensity of irinotecan. The majority ($n = 5$, 80.6%) of patients discontinued as they had progressive disease as assessed by the investigator or sub-investigator according to RECIST v1.1. Data were available for subsequent anticancer therapy in 28 patients; of these, 19 (67.8%) received gemcitabine + nab-paclitaxel, four (14.3%) received gemcitabine, one (3.6%) received S-1 and one (3.6%) underwent a surgery, while three (10.7%) did not receive subsequent anticancer therapy.

Efficacy

ORR (90% CI) by central assessment was 32.3% (18.7%–48.5%; Table 2) and the median duration of response was 7.4 (range: 3.5–21.9) months. The primary endpoint was not met as the lower limit of the 90% CI for the ORR was lower than the threshold ORR of 31.6%. ORR by PD-L1 status was 30.4% at CPS <1 and 42.9% at CPS ≥ 1 (Supplementary Table 1). ORR by TMB analysis showed that 45.0% (9/20) patients with TMB <5 achieved objective response while 0.0% (0/4) patients with TMB ≥ 5 achieved objective response (Supplementary Table 1).

Maximum percentage change in tumour diameter from baseline showed an increase in six patients and a reduction in 23 patients (Fig. 1). Among patients with CPS <1, 86.4% (19/22) showed a decrease in tumour diameter, while among those with CPS ≥ 1 , 66.7% (4/6) showed a decrease in tumour diameter.

Table 2. Best overall response by central assessment (total study population, $N = 31$).

Outcome	No. of patients with response	Rate, % (90% CI)
Objective response ^a	10	32.3 (18.7–48.5)
Complete response ^b	0	0 (0–9.2)
Partial response ^c	10	32.3 (18.7–48.5)
Stable disease	12	38.7 (24.1–55.0)
Progressive disease ^d	7	22.6
Not evaluable	2	6.5

^aComprises patients whose best overall response was complete or partial.

^bDefined as disappearance of all non-nodal target lesions. Any nodal lesions must have reduction in short axis to <10 mm.

^cDefined as at least a 30% decrease from baseline in the sum of diameters of target lesions.

^dDefined as at least a 20% increase in the sum of diameters of target lesions relative to the smallest sum observed in the study and with an absolute increase of ≥ 5 mm in the sum.

CI confidence interval.

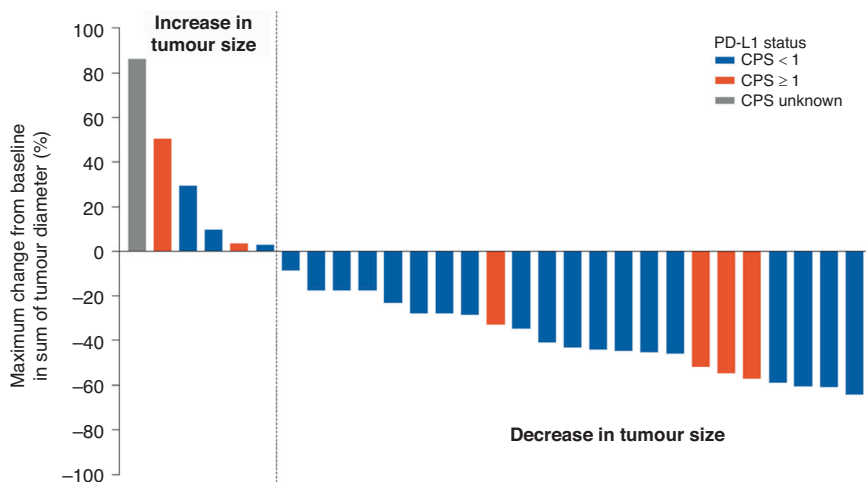


Fig. 1 Maximum percentage change in tumour diameter from baseline. CPS combined positive score, PD-L1 programmed death-ligand 1. Represented here are 29 evaluable patients with target lesion at baseline and at least one follow-up after the first administration of study treatment.

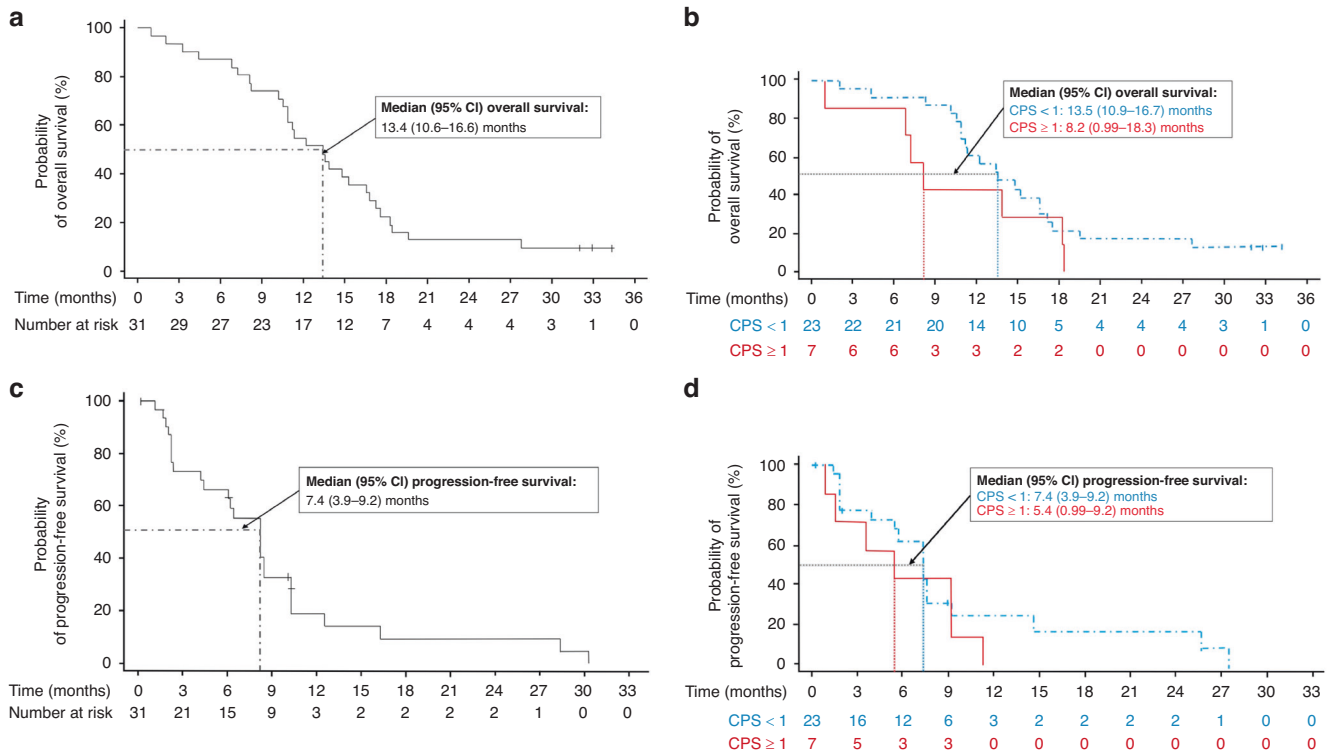


Fig. 2 Survival plots. **a** Overall survival in the study population, **b** Overall survival by PD-L1 status, **c** Progression-free survival in the study population, **d** Progression-free survival by PD-L1 status. Analysis set: Full analysis set. 1 month = 30.4375 days. CI confidence interval, CPS combined positive score, PDL-1 programmed death-ligand 1. The analysis by PD-L1 status was done for 30 patients whose CPS data were available. The 95% CIs were estimated using the Kaplan–Meier method.

Table 3. Summary of adverse events by preferred terms (30-day safety window).

Adverse event preferred term	Any grade	Grade 3/4
Nausea	25 (80.6)	3 (9.7)
Diarrhoea	19 (61.3)	1 (3.2)
Neutrophil count decreased	19 (61.3)	12 (38.7)
Peripheral sensory neuropathy	19 (61.3)	0
Decreased appetite	18 (58.1)	5 (16.1)
Stomatitis	15 (48.4)	0
Constipation	13 (41.9)	0
Dysgeusia	12 (38.7)	0
Malaise	14 (45.2)	1 (3.2)
Rash	10 (32.3)	1 (3.2)
White blood cell count decreased	9 (29.0)	3 (9.7)
Platelet count decreased	8 (25.8)	0
Alopecia	7 (22.6)	0
Fatigue	7 (22.6)	0
Hiccups	7 (22.6)	0
Pyrexia	7 (22.6)	0

Data are presented as *n* (%) for adverse events observed in ≥20% of the patients between the first day of the regimen and 30 days after the last dose.

There were no Grade 5 adverse events.

The 1-year survival rate was 54.8% (95% CI: 36.0%–70.3%) (Supplementary Table 2), and the median OS was 13.4 (95% CI: 10.6–16.6) months in the study population (Fig. 2a). Median OS was 13.5 months in PD-L1 CPS < 1 and 8.2 months in PD-L1 CPS ≥ 1 subgroups (Fig. 2b). The 6-month PFS rate was 55.5% (95%

CI: 35.8%–71.3%) (Supplementary Table 2), and the median PFS was 7.4 (95% CI: 3.9–9.2) months in the study population (Fig. 2c). Median PFS was 7.4 months in PD-L1 CPS < 1 and 5.4 months in PD-L1 CPS ≥ 1 subgroups (Fig. 2d). The OS and PFS rates at 6, 12, 18 and 24 months are presented in Supplementary Table 2.

Safety

Major reason for discontinuation of nivolumab was progressive disease as assessed by the investigator or sub-investigator according to RECIST v1.1 (*n* = 25, 80.6%). Drug-related serious AEs were reported in 29.0% of the patients; 3.2% drug-related AEs led to discontinuation, and none led to death within 30-day safety window (Supplementary Table 3). Nausea (80.6%), diarrhoea (61.3%), neutrophil count decreased (61.3%) and peripheral sensory neuropathy (61.3%) were the most common AEs within 30-day safety window (Table 3). Diarrhoea (22.6%), rash (12.9%) and hypothyroidism (12.9%) were the most common treatment-emergent AEs of interest for nivolumab within 100-day safety window (Table 4).

DISCUSSION

The abysmally poor prognosis in advanced pancreatic cancer continues to drive the research for therapeutic options with better efficacy and/or safety. We assessed the efficacy and safety of nivolumab in combination with mFOLFIRINOX in 31 Japanese patients with chemotherapy-naïve pancreatic cancer with distant metastasis over a median follow-up of 13.4 months. The primary efficacy endpoint was not met; ORR was 32.3% (complete response 0.0%; partial response 32.3%). Median OS, however, was longer than a year (13.4 [95% CI: 10.6–16.6] months) with a 1-year survival of 54.8% (95% CI: 36.0%–70.3%), a median PFS of 7.4 (95% CI: 3.9–9.2) months, and a median duration of response

Table 4. Treatment-emergent adverse events of interest for nivolumab (100-day safety window).

Adverse events preferred term	Any grade	Grade 3/4
Diarrhoea	7 (22.6)	0
Rash	4 (12.9)	0
Hypothyroidism	4 (12.9)	0
Interstitial lung disease ^a	2 (6.5)	1 (3.2)
Gamma-glutamyltransferase increased	2 (6.5)	0
Alanine aminotransferase increased	1 (3.2)	0
Aspartate aminotransferase increased	1 (3.2)	0
Blood alkaline phosphatase increased	1 (3.2)	0
Adrenal disorder	1 (3.2)	0

Data are presented as *n* (%) for adverse events observed between the first day of the regimen and 100 days after the last dose.

There were no Grade 5 adverse events.

^aBoth events were serious drug-related adverse events.

of 7.4 (range: 3.5–21.9) months. The safety profile demonstrated that this combination was tolerable with no new safety signals.

Immunotherapy in combination with chemotherapy for pancreatic cancer is expected to improve efficacy, similar to that observed in other solid tumours [23, 31]. However, the combined efficacy of mFOLFIRINOX with nivolumab has not been assessed previously.

In our study, the median OS was 13.4 months and 54.8% individuals survived longer than a year. Median PFS was 7.4 months. The median OS and PFS in our study were numerically though not statistically better than the median OS and PFS reported in previous Phase 2 studies in Japanese patients with untreated metastatic pancreatic cancer (excluding patients with peritoneal dissemination): 10.7 and 5.6 months, respectively, with FOLFIRINOX treatment [32] and 11.2 and 5.5 months, respectively, with the mFOLFIRINOX regimen [33]. The safety profile in our study was favourable compared to these previous studies. Nevertheless, the ORR observed in the present study was comparable to that reported in previous studies [32, 33]. Further studies with larger sample sizes are needed to evaluate the efficacy and safety results of the combination with immune checkpoint inhibitor.

Similarly, comparisons can be drawn between our study with the previous open-label, Phase 1 study of nivolumab + nab-paclitaxel + gemcitabine in 50 patients with locally advanced/metastatic pancreatic cancer [34]. The baseline characteristics in that study were comparable to those in our study, except for some differences in ECOG performance status (0, 38% vs. 68%; 1, 62% vs. 32%) and probably for PD-L1 status (<1%: 56% vs. 74%; ≥1%, 24% vs. 23%; missing, 20% vs. 3%). With a median OS of 9.9 months (95% CI: 6.74–12.16 months) and a median PFS of 5.5 months (95% CI: 3.3–7.2 months), the authors concluded that the combination therapy with nivolumab did not lead to survival benefit. Though the OS and PFS in our study were numerically better than those reported by Wainberg et al. [34], our conclusion of no statistically significant efficacy benefit was similar. Also, in both trials, PD-L1 positivity was not associated with substantially better efficacy and the relative dose intensity was comparable. Further studies with larger sample sizes are warranted.

The use of valid biomarkers for individualised targeted treatment selection could improve outcomes [31]. Although we also evaluated the potential effects of PD-L1 expression and TMB on efficacy, there was no correlation between either PD-L1 expression or TMB and efficacy. Those with CPS ≥1 had lower numerical values for OS, PFS and the proportion demonstrating a decrease in tumour diameter, though they had higher ORR than

those with CPS <1. A meta-analysis evaluating the effect of PD-L1 positive status on the prognosis of patients with pancreatic ductal adenocarcinoma demonstrated that high PD-L1 expression levels were associated with a poor prognosis [35]. Thus, even though this combination showed higher ORR in PD-L1 positive patients, it was not sufficient to prolong the OS. In terms of TMB, although high TMB values potentially predict response to immunotherapy [36], ORR was 0.0% at TMB ≥5 vs. 45.0% at TMB <5. It must be clarified that no patients having 10 or more mut/mb were observed amongst patients enrolled in this study, thus the cutoff of 5 mut/mb was used for TMB instead of the commonly used 10 mut/mb cutoff. Overall, the results must be interpreted with caution given the small number of patients in the study and unequal distribution across subgroups.

Some limitations of this study should be discussed. This was a single-arm study limiting comparison with other treatment regimens, except from historical cohorts. Considering the small cohort size, we could not compare responders vs. non-responders to identify factors associated with combination therapy response. Also, the small sample size may have led to unreliable results for subgroup analyses based on biomarkers. Nevertheless, this study provides initial encouraging results of prolonged survival with nivolumab plus mFOLFIRINOX immunochemotherapy in advanced pancreatic carcinoma.

CONCLUSIONS

Our results demonstrated that nivolumab in combination with modified FOLFIRINOX had a manageable safety profile in patients with metastatic pancreatic cancer. The primary endpoint for ORR was not met and the study failed to show meaningful increase in efficacy with nivolumab added to mFOLFIRINOX. Nevertheless, the ORR observed in this study was comparable to previously reported data. We found no correlation between PD-L1 expression and efficacy. In the late stages of pancreatic cancer, single immunotherapy with chemotherapy may have limited benefit and multiple immunotherapeutic options in combination with chemotherapy may improve efficacy. Further research is needed to determine the patient subpopulations which can benefit from this combination therapy.

DATA AVAILABILITY

Qualified researchers may request Ono Pharma to disclose individual patient-level data from clinical studies through the following website: <https://www.clinicalstudydatarequest.com/>. For more information on Ono Pharma's Policy for the disclosure of clinical study data, please see the following website: <https://www.ono.co.jp/eng/rd/policy.html>.

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CM, MU, MI, and TO contributed to conception, investigation, drafting and revising the manuscript critically for important content. KS contributed to investigation, drafting and revising the manuscript critically for important content. YH and MK contributed to conception, methodology, drafting and revising the manuscript critically for important content. SU contributed to curation, formal analysis, drafting and revising the manuscript critically for important content. JF contributed to conception, investigation, methodology, project administration, supervision, drafting and revising the manuscript critically for important content. All the authors have given the final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study (JapicCTI-184230) was conducted in compliance with the protocol, the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice Guidelines, and other applicable laws and regulations. It was also approved by the Institutional Review Board of each study site. All participants gave their written informed consent for study participation.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Chigusa Morizane.

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