Table 3 Drug-related adverse events reported in ≥1 patients overall, by preferred term

Drug-related adverse event	Number of patients[a]		
	MEDI-573 5 mg/kg (n=4)	MEDI-573 15 mg/kg (n=3)	MEDI-573 45 mg/kg (n=3)
Diarrhoea	2	0	0
Pyrexia	1	1	0
Electrocardiogram QT prolonged	0	1	1
Fatigue	0	1	1
Alanine aminotransferase increased	1	0	0
Aspartate aminotransferase increased	1	0	0
Hyperglycaemia	1	0	0
Hypertension	1	0	0
Pain in extremity	1	0	0
Palmar-plantar erythrodysaesthesia syndrome	1	0	0
Vomiting	1	0	0
Constipation	0	1	0
Hepatic function abnormal	0	1	0
Neuropathy peripheral	0	1	0
Ulcerative keratitis	0	1	0
Anaemia	0	0	1
Hyperuricaemia	0	0	1
Infusion-related reactions	0	0	1
Malaise	0	0	1
Proteinuria	0	0	1
Rash	0	0	1

[a] A patient experiencing more than one adverse event within a preferred term was counted only once

patients completed the study and were evaluable up to 90 days after last dose of MEDI-573 was received (safety follow-up period; three in the 5 mg/kg group, three in the 15 mg/kg group and two in the 45 mg/kg group); two patients discontinued the study due to death caused by disease progression (one in the 5 mg/kg group and one in the 45 mg/kg group). All 10 patients were included in the safety, PK, PD and efficacy analysis sets. Nine patients were included in the MTD analysis set (one patient was excluded due to early discontinuation attributable to progressive disease before completing the safety follow up).

Safety and tolerability

The median number of treatment cycles was 2.0 (range 1–6) and the median number of MEDI-573 doses received was 4.0 (range 1–17).

Table 4 MEDI-573 PK parameters after the first dose (PK analysis set)

Dose (mg/kg)	Dosing frequency	n	T_{max}[a] (day)	C_{max}[b] (μg/mL)	C_{max}/dose[b] (μg/mL)	C_{trough}[b] (μg/mL)	AUC τ[b] (μg.mL)
5	Weekly	4	0.092 (0.051–0.307)	94.3 (30.2)	0.357 (0.0704)	4.27 (4.60)	177 (73.7)
15	Weekly	3	0.051 (0.050–0.294)	231 (64.6)	0.268 (0.0672)	48.8 (21.8)	708 (220)
45	Every 3 weeks	3	0.074 (0.072–0.318)	880 (289)	0.367 (0.0916)	14.5 (12.1)	4900 (1940)

[a] Median (range); [b] mean (standard deviation)

AUC, area under the concentration-time curve within a dosing interval (τ); C_{max}, maximum observed plasma concentration; C_{trough}, trough plasma concentration; PK, pharmacokinetic; T_{max}, time to C_{max}

In total, 48 AEs were reported in all the patients in the study: 23 in the 5 mg/kg group, 11 in the 15 mg/kg group, and 14 in the 45 mg/kg group. Overall, the most common AE was pyrexia (three patients; Table 2). Twenty-seven drug-related AEs were reported for nine out of 10 patients (Table 3). The most commonly reported drug-related AEs were diarrhoea (n=2 Grade 1 [5 mg/kg group], no action taken and patients recovered), pyrexia (n=2 Grade 1 [5 and 15 mg/kg groups], no action taken and patients recovered), fatigue (n=2 Grade 1 [15 and 45 mg/kg groups], no action taken, one patient recovered [15 mg/kg group] and one patient had an ongoing event of fatigue [45 mg/kg group]) and electrocardiogram QT prolongation (n=1 Grade 1 [45 mg/kg group], n=1 Grade 2 [15 mg/kg group]). The onset of the Grade 1 QT prolongation occurred 22 days following the start of MEDI-573 treatment and lasted for 23 days; no action was taken and the patient recovered. The QTcB values for this patient pre-dose, maximum value and 30 days post-dose were 414, 476 and 446 ms, respectively. The onset of the Grade 2 QT prolongation occurred 43 days following the start of MEDI-573 treatment and lasted for 8 days; there was a dose delay of MEDI-573 and the patient recovered. The QTcB values for this patient pre-dose, maximum value and 30 days post-dose were 428, 484 and 445 ms, respectively.

There were no AEs leading to discontinuation of investigational product or death, SAEs or other significant AEs. One AE of CTCAE grade 3 was reported for abnormal hepatic function in one patient. Hepatic function test values returned to normal levels at 30 days after the last dose. The investigator deemed the event to be related to the study drug. None of the patients experienced a DLT; MEDI-573 5 and 15 mg/kg IV infusion once weekly or 45 mg/kg IV infusion once every 3 weeks were tolerated. The MTD was not determined in this study.

Pharmacokinetics

After the first dose, maximum concentration (C_{max}) of free MEDI-573 in serum increased approximately dose proportionally from 94 μg/mL after 5 mg/kg to 880 μg/mL after 45 mg/kg (Table 4). The mean serum concentration-time profiles of free MEDI-573 following once weekly (5 or 15 mg/kg dose) and once every 3 weeks (45 mg/kg dose) dosing regimens are shown in Fig. 1. After multiple doses, trough levels were ~30 μg/mL following 5 mg/kg once weekly (cohort 1), ~150 μg/mL following 15 mg/kg once weekly (cohort 2). Following 45 mg/kg once every 3 weeks (cohort 3), the trough level was ~30 μg/mL, indicating that once every 3 weeks dosing resulted in a lower trough concentration compared to 15 mg/kg once weekly. The PK sampling period from dosing to final measurable point was not long enough to extrapolate after final measurable point; therefore, elimination half-life at terminal phase, area under the concentration-time curve, from zero to infinity, clearance and volume of distribution, were not calculated.

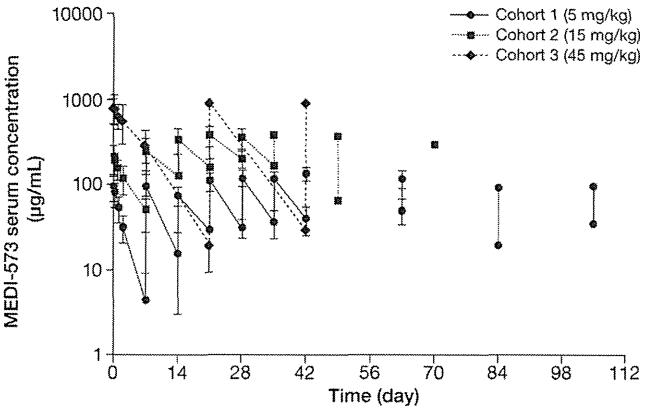

Fig. 1 Mean free MEDI-573 serum concentration-time profiles following once weekly and once every 3 weeks dose of MEDI-573 (PK analysis set)

Pharmacodynamics

Following the first dose of MEDI-573, 5, 15 or 45 mg/kg, plasma concentrations of free IGF-I and IGF-II rapidly

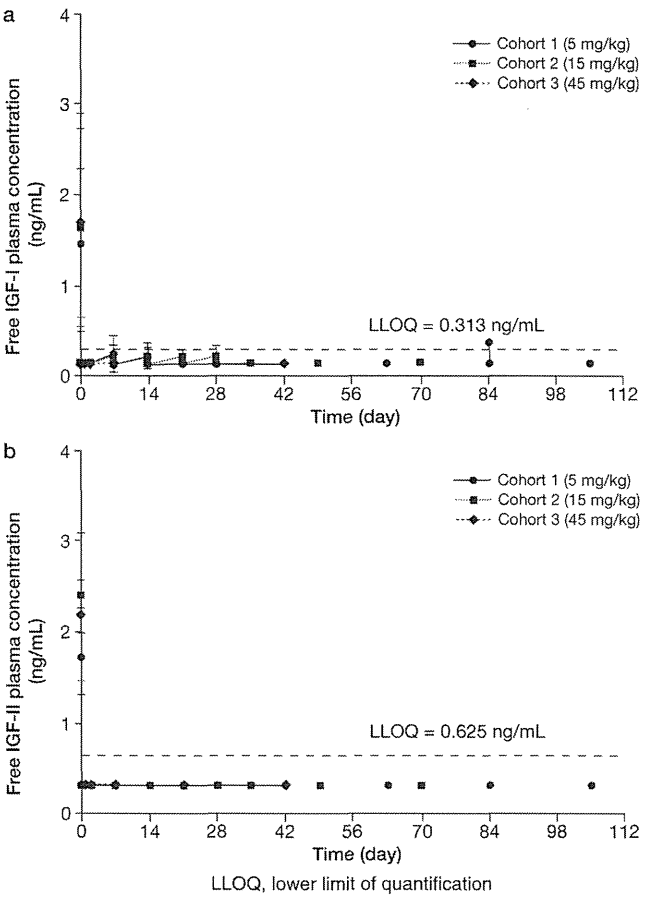

Fig. 2 Mean free **a** IGF-I and **b** IGF-II plasma concentration-time profiles following once weekly and once every 3 weeks dose of MEDI-573 (PD analysis set)

decreased to below the limit of quantitation (BLQ). At baseline, mean (range) IGF-I and IGF-II plasma concentrations were 1.60 (0.64–3.00) ng/mL and 2.07 (1.24–2.98) ng/mL, respectively. Free IGF-I and IGF-II remained BLQ throughout each dosing interval after all once-weekly doses of MEDI-573, 5 or 15 mg/kg, or once every 3 weeks' dose of MEDI-573, 45 mg/kg (Fig. 2).

Efficacy

There were no complete or partial responses in this study. Four patients (two patients in the 5 mg/kg group and one patient each in the 15 and 45 mg/kg groups) had an overall best response of stable disease which ranged from 64 to 125 days following the first dose of study treatment.

Immunogenicity

Anti-drug antibody was negative in all patients following infusion of MEDI-573.

Discussion

The IGF signalling pathway has become increasingly recognized as having a driving role in the development of malignancy [9]. Accordingly, targeted disruption of IGF signalling pathways by neutralizing IGF-I and IGF-II ligands with the novel anticancer therapy, MEDI-573, offers the potential to suppress the IGF system.

MEDI-573 was tolerated at doses of 5 or 15 mg/kg IV infusions, once weekly, or following 45 mg/kg IV infusion, once every 3 weeks, in Japanese patients with advanced solid tumours. All AEs were CTCAE grade 2 or less, except for one grade 3 abnormal hepatic function, which was reported as drug related but returned to normal levels at 30 days after the last dose of MEDI-573. There were no AEs leading to death, SAEs, AEs leading to discontinuation of investigational product or other significant AEs. No DLTs were observed, therefore the MTD has not been determined, as has been reported in many Phase I trials of anti-IGF-1R monoclonal antibodies [10].

The PK of MEDI-573 appeared approximately linear with a dose-dependent increase in MEDI-573 concentration. Following 5 or 15 mg/kg once-weekly dosing, trough levels of free MEDI-573 in serum increased with each dose, indicating that reticuloendothelial elimination prevailed within the investigated dose range. Following multiple doses of 5 or 15 mg/kg once weekly, C_{max} was approximately 50 % higher than C_{max} after the first dose, while no increase in C_{max} was seen upon repeated administrations of 45 mg/kg once every 3 weeks compared to the first dose. In addition, no patients were positive for anti-drug antibody following infusion of MEDI-573, which corresponded with no patients showing low exposures of MEDI-573 compared with others within the same cohort and suggests that there were no potential issues with immunogenicity. Furthermore, plasma concentrations of free IGF-I and IGF-II were rapidly decreased to BLQ at all three doses and remained lowered for the duration of the study.

One of the secondary objectives of this study was to observe any antitumour activity of MEDI-573. Although four of 10 patients experienced stable disease, no RECIST responses were observed. Thus, further investigation is needed to confirm the antitumour activity of MEDI-573.

The results presented here in Japanese patients are largely in line with those recently reported in a larger (n=43) Phase I dose-expansion study of MEDI-573 dosed weekly (0.5–15 mg/kg) or every 3 weeks (30 or 45 mg/kg) in a Western population of patients with advanced solid tumours [8]; no DLTs were observed. In our study, pyrexia was the most common AE, however, this was only observed in one patient (3 %) in the western population. Other AEs, PK and efficacy evaluations were consistent between the two study populations. The optimal biological dose of MEDI-573 in the Western population was reported to be 5 mg/kg weekly or 30 or 45 mg/kg every 3 weeks.

In conclusion, the results of this study in Japanese patients suggest that MEDI-573 is tolerated at the doses investigated, and further investigation of its antitumour activity is warranted.

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Conflicts of interest Tomohiro Nishina, Naoyuki Nogami, Yumiko Yamagiwa and Haruo Iguchi have no conflicts of interest to declare. Toshiyuki Kozuki has received honoraria from AstraZeneca KK. Katsuro Yagawa is an employee of AstraZeneca KK.

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Review Article

EBM-based Clinical Guidelines for Pancreatic Cancer (2013) Issued by the Japan Pancreas Society: A Synopsis

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Clinical practice guidelines for pancreatic cancer based on evidence-based medicine (2006) were published by the Japan Pancreas Society (Committee for revision of clinical guidelines for pancreatic cancer) in March 2009 in Japanese, revised to Clinical Practice Guidelines for Pancreatic Cancer based on evidence-based medicine (2009) in July 2009 in Japanese and further revised to Clinical Practice Guidelines for Pancreatic Cancer (2013) in October 2013 in Japanese. These guidelines were established according to evidence-based medicine. A total of 629 papers were collected from among 4612 reports concerning pancreatic cancer listed in PubMed and Igakuchuo Zasshi between May 2007 and January 2011. This new set of guidelines was written by members of the Committee for the Revision of Clinical Practice Guidelines for Pancreatic Cancer in the Japan Pancreas Society. The guidelines provide an algorithm for the diagnosis (Fig. 1) and treatment (Fig. 2) of pancreatic cancer and address six subjects (Diagnosis, Surgery, Adjuvant therapy, Radiation therapy, Chemotherapy and stent therapy), with 35 clinical questions and 57 recommendations.

Key words: EBM-based guidelines – pancreatic cancer

The corresponding clinical question (CQ) numbers are inserted in the algorithms.

There are five degrees of recommendation:

A. Strongly recommended because there is strong scientific evidence
B. Recommended because there is scientific evidence
C1. Recommended although there is no scientific evidence
C2. Not recommended because there is no scientific evidence
D. Not recommended because there is evidence showing the treatment to be ineffective or harmful

This article presents a synopsis of the guidelines in English[1].

DIAGNOSIS

CQ1-1 What are risk factors for pancreatic cancer?

Recommendation 1–1

(1) The following risk factors have been reported to have evidence supporting their relationship with pancreatic cancer.

(1) Family history: pancreatic cancer, hereditary pancreatic cancer syndrome
(2) Accompanying diseases: diabetes mellitus, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm (IPMN), pancreatic cysts, obesity.
(3) Habits: tobacco use, heavy drinking

(2) Patients with more than one risk factor (family history, accompanying diseases, relevant habits and so on) are recommended to undergo further examinations to detect pancreatic cancer (Grade B).
(3) IPMN and pancreatic cysts should be carefully followed as premalignant diseases of pancreatic cancer (Grade B).

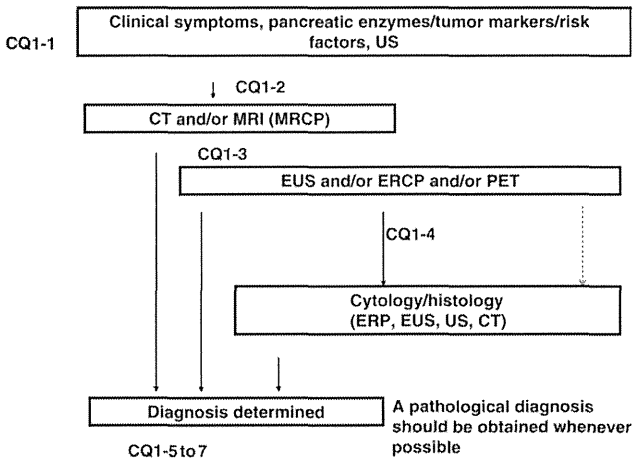

Figure 1. Algorithm for the Diagnosis.

CQ1-2 How to detect pancreatic cancer?

Recommendation 1–2

(1) Patients with unexplainable abdominal pain, back pain, jaundice and/or body weight loss should undergo further examinations for pancreatic cancer (Grade B). Early-onset diabetes mellitus (poor glycogen metabolism) and deterioration of diabetes mellitus suggest the presence of pancreatic cancer and necessitate further examinations for pancreatic cancer (Grade B).
(2) The serum pancreatic enzyme level is not specific for pancreatic cancer, although it is useful for diagnosing early pancreatic cancer (Grade B).
(3) Measuring serum tumor markers is recommended for the diagnosis and follow-up of pancreatic cancer (Grade B), although it is not useful for diagnosing early pancreatic cancer (Grade C1).
(4) US is recommended as the first screening examination for pancreatic cancer (Grade B), although it has a low value in detecting pancreatic cancer (Grade C1). Dilatation of the main pancreatic duct and/or the presence of a pancreatic cyst are important indirect signs of the presence of pancreatic cancer (Grade B). When such signs are evident, physicians should rapidly proceed to the next step for the diagnosis of pancreatic cancer.

CQ1-3 What is the second step when pancreatic cancer is suspected?

Recommendation 1–3

(1) Computed tomography (CT) (preferably enhancing) and/or magnetic resonance imaging (MRI) (MRCP)

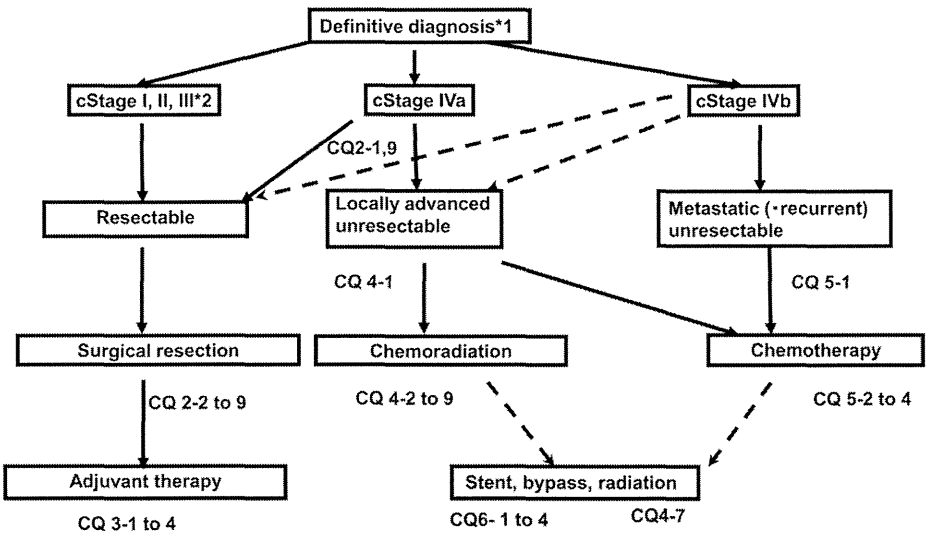

Figure 2. Algorithm for the Treatment.

(preferably enhancing and more than three cycles thereof) is strongly recommended to diagnose pancreatic cancer (Grade A).
(2) If a definitive diagnosis of pancreatic cancer is not obtained, although there are abnormal findings on the above-mentioned examinations, further examinations (CQ1-4) are preferable in order to obtain a definitive diagnosis of pancreatic cancer (Grade B).

CQ1-4 What is the next step to make a definitive diagnosis of pancreatic cancer?

Recommendation 1–4

(1) If a definitive diagnosis of pancreatic cancer is not obtained using CT and/or MRI (MRCP), EUS or ERCP (if necessary positron emission tomography) should be performed. (Grade B) EUS is useful for detecting lesions that cannot be detected on US and/or CT.
(2) Either a histological or cytological diagnosis is recommended prior to treatment if no qualitative diagnosis of a pancreatic mass is obtained with various imaging modalities (Grade B).
(3) Either a histological or cytological diagnosis is recommended before chemo(radiation)therapy is started for unresectable pancreatic cancer proven on imaging modalities (Grade B).
(4) A genetic analysis is an important adjuvant to cytology or histology (Grade C1).
(5) If a definitive diagnosis of pancreatic cancer is not obtained although there are abnormal findings on the above-mentioned examinations, periodic examinations and careful follow-up are recommended (Grade B).

CQ1-5 How do you determine the clinical stage of pancreatic cancer?

Recommendation 1–5

MDCT and/or EUS are recommended for staging the diagnosis (TNM) of pancreatic cancer (Grade B).

CQ1-6 Diagnosis of borderline resectable pancreatic cancer: What is the definition of borderline resectable pancreatic cancer in Japan?

Recommendation 1–6

(1) The definition of borderline resectable pancreatic cancer proposed in the NCCN guidelines is widely used in the USA; however, the management of portal vein invasion differs between Japan and the USA. Therefore, a unique definition of 'borderline resectable' should be proposed in Japan.
(2) In order to make the diagnosis of borderline resectable pancreatic cancer, MD-CT should be performed, including plain CT as well as three-phase-CT (arterial phase, pancreatic parenchymal phase and portal phase) with thin slices under 3 mm in thickness (Grade B).

CQ1-7 How to detect early pancreatic cancer associated with long-term survival?

Recommendation 1–7

(1) Dilatation of the main pancreatic duct and the presence of cysts are important indirect signs. MRCP and EUS are recommended, even when US and CT fail to directly detect a mass lesion (Grade C1).
(2) When localized stenosis of the main pancreatic duct is observed on the above-mentioned imaging work-up, ERCP with repeated cytology of the pancreatic juice is recommended (Grade C1).

SURGICAL THERAPY

CQ2-1 Is surgical resection useful for treating Stage IVa pancreatic cancer?

Recommendation 2–1

Surgical resection with intended curative resection is recommended for pancreatic cancer up to Stage IVa* (Grade B).

Stage IVa*: Stage IVa proposed by the Japan Pancreas Society Classification of pancreatic cancer, sixth edition showing no invasion of the superior mesenteric or celiac artery.

CQ2-2 Is pancreatectomy significant in cases of peritoneal lavage cytology-positive pancreatic cancer?

Recommendation 2–2

It is unclear whether pancreatectomy should be performed in patients with peritoneal lavage cytology-positive pancreatic cancer. Therefore, clinical trials and/or analyses of relevant results are required to address this issue (Grade C1).

CQ2-3 Is preservation of the stomach useful in pancreatoduodenectomy for treating pancreatic head cancer?

Recommendation 2–3

Preservation of the stomach decreases the operative time and amount of blood loss during pancreatoduodenectomy, although it does not decrease the survival rate after surgical resection (Grade C1).

It is unclear whether preservation of the stomach improves the rate of post-operative complications, quality of life, post-operative pancreatic function or nutritional status of patients with pancreatic cancer (Grade C1).

CQ2-4 Does combined portal vein resection improve the clinical outcomes of patients with pancreatic head cancer?

Recommendation 2–4

The effects of prophylactic portal vein resection intended to increase curability during the clinical course of pancreatic cancer are unclear. Portal vein resection is indicated when surgical and dissection margins free from cancer cells can be obtained with portal vein resection (Grade C1).

CQ2-5 Is radical resection with extended lymph node dissection useful for treating pancreatic cancer?

Recommendation 2–5

The contribution of extended lymph node and nerve plexus dissection to improving the clinical course of patients with pancreatic cancer is unclear, and there is no evidence to support the use of such extended radical resection procedures (Grade C2).

CQ2-6 Are surgical bypass and/or biliary stenting significant in cases of unresectable pancreatic cancer which was first judged unresectable after laparotomy intended to curative resection?

Recommendation 2–6

Hepaticojejunostomy for obstructive jaundice and prophylactic gastrojejunostomy are recommended in patients with unresectable pancreatic cancer harboring obstructive jaundice after laparotomy intended to curative resection (Grade B).

CQ2-7 Is laparoscopic pancreatectomy significant in cases of pancreatic cancer?

Recommendation 2–7

Laparoscopic pancreatectomy can be safely performed in selected patients with pancreatic cancer. The accumulation of results from high-volume centers would clarify whether laparoscopic pancreatectomy improves long-term clinical outcomes (Grade C1).

CQ2-8 Is the incidence of complications after pancreatic resection low in high-volume centers?

Recommendation 2–8

The incidence of complications tends to be low among patients undergoing pancreatic surgery, including pancreatoduodenectomy, and the management of complications tends to be superior in institutions with a high volume of pancreatic procedures (Grade B).

CQ2-9 Treatment of borderline pancreatic cancer: is pancreatectomy significant in Japan?

Recommendation 2–9

The accumulation of results from high-volume centers would clarify whether neoadjuvant (pre-operative) therapy for borderline resectable pancreatic cancer improves the clinical outcomes of surgical resection (Grade C1).

ADJUVANT THERAPY

CQ 3-1 Does pre-operative therapy (1. chemoradiation therapy, 2. chemotherapy) improve the clinical outcomes of patients with pancreatic cancer?

Recommendation 3–1

There is increasing evidence supporting the efficacy of pre-operative treatment (1. chemoradiation and 2. chemotherapy). However, clinical trials and/or analyses of long-term outcomes are required to determine whether such therapy improves clinical outcomes (Grade C1).

CQ3-2 Is intraoperative radiation therapy recommended at the time of resection of pancreatic cancer?

Recommendation 3–2

It is unclear whether intraoperative radiotherapy is usefulness for treating pancreatic cancer. To date, one randomized clinical trial performed in Japan does not demonstrate the efficacy of intraoperative radiation therapy alone (Grade C2).

CQ3-3 Is post-operative chemoradiation therapy recommended for pancreatic cancer?

Recommendation 3–3

The usefulness of post-operative chemoradiation therapy for treating pancreatic cancer is unclear, and post-operative chemoradiation therapy should be administered as an experimental treatment (Grade C1).

CQ3-4 Is post-operative adjuvant therapy recommended for pancreatic cancer?

Recommendation 3–4

Post-operative chemotherapy results in better clinical outcomes than surgery alone and is therefore recommended (Grade A). S-1 alone is recommended as post-operative adjuvant therapy (Grade A), while gemcitabine alone is recommended in cases of low S-1 tolerance (Grade B).

RADIOTHERAPY

CQ4-1 What is the recommended first-line treatment for locally advanced unresectable pancreatic cancer?

Recommendation 4–1

Chemoradiation or chemotherapy alone is recommended as the first-line treatment for locally advanced unresectable pancreatic cancer (Grade A) (refer to recommendations CQ4-2 and CQ5-2 concerning concrete regimens).

CQ4-2 What chemoradiation therapy is recommended for locally advanced unresectable pancreatic cancer?

Recommendation 4-2

Fluoropyrimidine or gemcitabine is recommended as combination chemotherapy for radiation therapy for locally advanced pancreatic cancer (Grade B). Concerning radiation therapy, three-dimensional radiation is recommended for precise irradiation of pancreatic cancer and to decrease irradiation to normal organs.

CQ4-3 How is the standard clinical target volume of external beam radiation therapy planned for locally advanced unresectable pancreatic cancer?

Recommendation 4–3

Radiation including the tumor and highly positive lymph nodes in the standard clinical volume is recommended as

external radiation therapy for locally advanced unresectable pancreatic cancer (Grade C1).

CQ4-4 Is induction chemotherapy followed by chemoradiation therapy significant in cases of locally advanced unresectable pancreatic cancer?

Recommendation 4–4

Induction chemotherapy followed by chemoradiation therapy is effective in selected patients with locally advanced unresectable pancreatic cancer. Induction chemotherapy followed by chemoradiation therapy can be considered as an alternative treatment option.

CQ4-5 Is intraoperative radiation therapy effective for locally advanced pancreatic cancer?

Recommendation 5–4

There are some reports concerning the efficacy of intraoperative radiation therapy for locally advanced unresectable pancreatic cancer. However, there is no scientific evidence showing that intraoperative radiation therapy improves the clinical course of locally advanced unresectable pancreatic cancer (Grade C1).

CQ4-6 Does chemoradiation therapy improve the quality of life of patients with locally advanced unresectable pancreatic cancer?

Recommendation 4–6

Chemoradiation therapy (Grade B) and/or radiation therapy (Grade C1) are recommended to improve the quality of life in patients with locally advanced unresectable pancreatic cancer.

CQ4-7 Is radiation therapy effective for treating bone metastasis of pancreatic cancer?

Radiation therapy is effective for pain control due to bone metastasis of pancreatic cancer (Grade A).

CHEMOTHERAPY

CQ5-1 Is chemotherapy recommended for treating metastatic pancreatic cancer?

Recommendation 5–1

Chemotherapy improves the clinical outcomes of metastatic pancreatic cancer compared with best supportive care and is recommended for metastatic pancreatic cancer (Grade A).

CQ5-2 What is the first-line chemotherapy for locally advanced unresectable and metastatic pancreatic cancer?

Recommendation 5–2

Gemcitabine alone, S-1 alone and combined gemcitabine and erlotinib are recommended as first-line treatments for locally advanced unresectable and metastatic pancreatic cancer (Grade A).

CQ5-3 How long should gemcitabine be continued for unresectable pancreatic cancer?

Recommendation 5–3

Chemotherapy is continuously administered for unresectable pancreatic cancer until clear progression becomes evident, if there are no adverse effects causing interruption of treatment (Grade B).

CQ5-4 Is second-line chemotherapy recommended for unresectable pancreatic cancer?

Recommendation 6–4

Recent randomized clinical trials in other countries showed the efficacy of second-line chemotherapy compared with best supportive care (Grade B). The regimen for second-line chemotherapy, S-1 or gemcitabine, is chosen based on the first-line chemotherapy regimen.

STENT THERAPY

CQ6-1 Is biliary drainage recommended for unresectable pancreatic cancer associated with obstructive jaundice?

Recommendation 6–1

Biliary drainage is recommended for unresectable pancreatic cancer (Grade B). Concerning biliary drainage, endoscopic biliary drainage is recommended rather than surgical biliary drainage after laparotomy in patients with unresectable pancreatic cancer (Grade B).

CQ6-2 What is the appropriate route for biliary drainage in patients with unresectable pancreatic cancer, percutaneous or endoscopic?

Recommendation 6–2

Endoscopic biliary drainage is recommended for biliary drainage of unresectable pancreatic cancer (Grade B).

CQ6-3 Which type of stent is recommended in patients with pancreatic cancer with obstructive jaundice?

Recommendation 6–3

Self-expandable metallic stents (SEMSs) of long patency are recommended rather than plastic stents (PSs) for treating obstructive jaundice in patients with unresectable pancreatic cancer (Grade C1). Of the types of SEMS, a longer patency is reported for the covered type than for the uncovered type (Grade C1). SEMSs of the uncovered type and PSs can be considered based on the technique applied in the institution, the treatment system of the hospital and the patient's condition.

CQ6-4 Which type of treatment is recommended for unresectable pancreatic cancer associated with gastroduodenal stenosis?

Recommendation 6–4

Surgical gastrojejunostomy is recommended in patients with a good PS who can expect a relatively long clinical course, while endoscopic duodenal stenting is recommended in the remaining patients.

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Conflict of interest statement

Takuji Okusaka is a member of the Board of Eli Lilly Japan Co., Ltd, Novartis Pharma Co., Ltd, Bayer Yakuhin, Ltd, Taiho Pharmaceutical Co., Ltd. Takuji Okusaka received research funding from Taiho Pharmaceutical Co., Ltd, Yakult Pharmaceutical Industry Co., Ltd, Chugai Pharmaceutical Co., Ltd, Novartis Pharma Co., Ltd, Shizuoka Industrial Fundation, Takeda Bio Development Center Ltd, Ono Pharmaceutical Co., Ltd, Otsuka Pharmaceutical Co., Ltd. Junji Furuse received research funding from Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Eli Lilly Japan Co., Ltd.

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Appendix

Structures of Committee for the Revision of the Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society were as follows;

Chairman: K. Yamaguchi (University of Occupational and Environmental Health)

Vice-chairman: T. Okusaka (National Cancer Center Hospital)

Diagnosis
K. Shimizu (Tokyo Women's Medical University)
A. Nakaizumi (Soka University)
T. Itoi (Tokyo Medical University)
N. Mizuno (Aichi Cancer Center)
T. Hatori (Tokyo Women's Medical University)
Y. Yamaue (Wakayama Medical University)
K. Hanada (JA Onomichi General Hospital)

Surgical therapy
K. Yamaguchi (University of Occupational and Environmental Health)
T. Fujii (Nagoya University)
W. Endo (Yokohama City University)
S. Egawa (Tohoku University)
Y. Yamaue (Wakayama Medical University)
Y. Yokoyama (Nagoya University)

Adjuvant therapy
J. Furuse (Kyorin University)
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T. Nagaori (Tokai University)
S. Kanno (Tohoku University)
K. Uesaka (Shizuoka Cancer Center)
T. Okusaka (National Cancer Center Hospital)
S. Nakamura (Kyoto Prefectural University of Medicine)

Radiotherapy
Y. Ito (National Cancer Center Hospital)
K. Shibuya (Yamaguchi University)
S. Nakamura (Kyoto Prefectural University of Medicine)
T. Ohguri (University of Occupational and Environmental Health)
H. Nagakura (KKR Sapporo Medical Center)

Chemotherapy
T. Okusaka (National Cancer Center Hospital)
K. Uesaka (Shizuoka Cancer Center)
Y. Kihara (Kitakyushu General Hospital)
T. Ito (Kyushu University)
J. Furuse (Kyorin University)

Stent therapy
K. Hanada (JA Onomichi General Hospital)
T. Itoi (Tokyo Medical University)
N. Mizuno (Aichi Cancer Center)
H. Isayama (Tokyo University)
A. Kanno (Tohoku University)

Patient representative
Y. Majima (PanCAN Japan)

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Safety, Tolerability, Pharmacokinetics and Antitumor Activity of Ganitumab, an Investigational Fully Human Monoclonal Antibody to Insulin-like Growth Factor Type 1 Receptor, Combined with Gemcitabine as First-line Therapy in Patients with Metastatic Pancreatic Cancer: A Phase 1b Study

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Objective: Previous Phase 1 studies have shown the acceptable safety profile of ganitumab—a fully human monoclonal antibody to insulin-like growth factor Type 1 receptor—in patients with advanced solid tumors. However, ganitumab 20 mg/kg in combination with gemcitabine had not been administered to patients with metastatic pancreatic cancer. To evaluate the safety, tolerability, pharmacokinetics and antitumor activity of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2 as first-line therapy in patients with metastatic pancreatic cancer, we conducted a Phase 1b study.

Methods: Eligible patients were adults with previously untreated metastatic adenocarcinoma of the pancreas. Patients received gemcitabine 1000 mg/m^2 on Days 1, 8 and 15 plus ganitumab 20 mg/kg on Days 1 and 15 of each 28-day cycle. Gemcitabine was administered intravenously over 30–60 min. Ganitumab was administered intravenously over 60 min after completing gemcitabine infusion.

Results: Six patients were enrolled and received the study treatment. All patients had thrombocytopenia and leukopenia. Other most common adverse events were neutropenia and nausea. One patient had a dose-limiting toxicity defined as Grade 3 neutropenia with fever. Exposure to ganitumab 20 mg/kg was not affected by the administration of gemcitabine. No apparent pharmacokinetic drug–drug interaction was observed. No anti-ganitumab antibodies were detected. Five patients had a measurable tumor region at baseline. Of these, four patients had a best response of stable disease.

Conclusions: Ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2 was tolerable and showed an acceptable safety profile in patients with untreated metastatic pancreatic cancer.

Key words: clinical trial Phase 1 – ganitumab – gemcitabine – pancreatic neoplasms – receptor, insulin-like growth factor type 1

INTRODUCTION

The insulin-like growth factor (IGF) system—the circulating ligands (insulin, IGF-1 and IGF-2), multiple receptors and binding proteins—plays a major role in cancer cell proliferation (1–3). In this system, IGF-1 acts as the primary regulator of growth, whereas IGF-2 has metabolic and mitogenic effects (4). Furthermore, a recent review has shown that the IGF Type 1 receptor (IGF-1R) plays a role in maintaining the malignant phenotype and disruption of IGF-1R activation leads to inhibited growth and motility of cancer cells (3). Thus, this family of growth factors, especially the IGF-1R, may present an excellent target for new therapeutic agents for anticancer treatment (5,6).

Ganitumab (previously known as AMG 479) is a fully human monoclonal antibody directed to IGF-1R. As a single agent, it inhibited the interaction of IGF-1R with IGF-1 and IGF-2 without cross-reacting to insulin receptor in IGF-1R-expressing pancreatic carcinoma cell lines (7). In addition, the combination of ganitumab with gemcitabine resulted in additive inhibitory activity both *in vitro* and *in vivo* (7). These results indicate that ganitumab is a clinical candidate for the treatment of patients with pancreatic cancer (PC).

Previous Phase 1 studies have shown that ganitumab can be administered safely to patients with advanced solid tumors at doses up to 20 mg/kg intravenously every 2 weeks (8,9). In a randomized Phase 2 study, ganitumab 12 mg/kg combined with gemcitabine 1000 mg/m^2 has shown evidence of activity with improved 6-month overall survival rates compared with gemcitabine alone in patients with metastatic PC (mPC) (10).

However, it is uncertain whether a higher dose level of ganitumab is needed to treat patients with mPC. A recent analysis using the data of the randomized Phase 2 study assessed the effect of ganitumab exposure on survival, and its results revealed that the progression-free survival and overall survival were longer in the high-exposure group than in the low-exposure group (11). According to this finding, a pharmacokinetic (PK) analysis was performed to determine a sufficient dose level, and the results showed that >90% of patients with mPC would reach high exposures when administered ganitumab 20 mg/kg (11).

Considering that ganitumab 20 mg/kg in combination with gemcitabine has not been administered in patients with mPC, we conducted a Phase 1b study to evaluate the safety, tolerability, PKs and antitumor activity of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2 as first-line therapy in this population.

PATIENTS AND METHODS

Study Design and Ethical Considerations

This Phase 1b, open-label study was conducted from August 2010 to February 2011 at three institutions in Japan. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Its protocol was reviewed and approved by the institutional review board of the participating institutions. All patients provided their written informed consent.

Patient Population

Patients aged at least 20 years were eligible for the study if they had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and adequate hematologic, renal and hepatic functions. Adequate functions were defined as follows: hemoglobin $\geq$9 g/dl; absolute neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l; activated partial thromboplastin time $\leq$1.3 $\times$ the upper limit of normal (ULN) and international normalized ratio (INR) $\leq$1.5 (for patients who did not receive anticoagulation therapy); creatinine clearance >60 ml/min; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with liver metastases); total bilirubin $\leq 1.5 \times$ ULN; and fasting blood glucose level $\leq$160 mg/dl.

Patients were excluded if they had received or were receiving any treatment for PC. Other exclusion criteria included the following: islet cell carcinoma, acinar cell carcinoma, non-adenocarcinoma, or adenocarcinoma originated from biliary tree or cystadenocarcinoma; a history of central nervous system metastases; internal or external biliary drain; a history of other malignancies; and myocardial infarction or uncontrolled cardiovascular disease including acute coronary syndrome or congestive heart failure within 6 months before enrollment. Pregnant women, breastfeeding women or patients who did not use adequate contraceptive precautions despite having a partner were also excluded.

Study Treatment

Initially, six patients received the study treatment (i.e. gemcitabine plus ganitumab), and three additional patients were to be enrolled if additional data for the safety or PK analysis were needed. Patients received gemcitabine 1000 mg/m^2 on Days 1, 8 and 15 as well as ganitumab 20 mg/kg on Days 1 and 15 of each 28-day cycle. Gemcitabine was administered intravenously over 30–60 min. Ganitumab was administered intravenously over 60 ($\pm$ 10) min after the completion of gemcitabine infusion. The infusion rate of ganitumab was slowed down (up to 120 min infusion) if patients could not tolerate the first infusion.

The dose of gemcitabine was reduced to Level 1 (750 mg/m^2) or Level 2 (563 mg/m^2) if patients had treatment-related neutropenia, thrombocytopenia or Grade 3 or greater non-hematologic toxicities that required dose reduction. The dose of ganitumab was reduced by 50% if patients had treatment-related Grade 3 or greater thrombocytopenia without Grade 2 or greater bleeding; febrile neutropenia; Grade 4 neutropenia; or Grade 3 neutropenia lasting 8 days or more. Antiemetic premedication for prophylaxis of nausea/vomiting associated with gemcitabine was allowed if necessary. Premedication with antihistamines,

corticosteroids or both was also allowed if patients had an infusion reaction. Patients continued the study treatment until the disease progression if they wished to receive it and had no unacceptable toxicities.

Outcome Measures

Medical history was collected within 14 days before enrollment. Patients were hospitalized at least 5 days from Day 1 of treatment. Adverse events were monitored throughout the study and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Dose-limiting toxicity (DLT) was defined as any Grade 3 or greater toxicity that related to ganitumab during the first 28 days. DLTs did not include lymphopenia and infusion reaction. Fatigue, nausea, diarrhea, vomiting, leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, hemoglobin decrease, increased AST or ALT, hyperglycemia and pulmonary embolism were included in DLTs if they met any of the following criteria: Grade 3 or greater neutropenia with fever (body temperature $>38.5°C$); Grade 4 leukopenia or neutropenia lasting 8 days or more; Grade 4 thrombocytopenia lasting 8 days or more; Grade 3 or greater thrombocytopenia (for patients who were receiving anticoagulation therapy); Grade 3 or greater thrombocytopenia accompanied by Grade 2 or greater bleeding; Grade 3 or greater thrombocytopenia requiring platelet transfusion; Grade 4 hemoglobin decrease; Grade 3 fatigue lasting 8 days or more; Grade 4 fatigue; Grade 3 or greater nausea, diarrhea or vomiting despite maximum supportive care; AST or ALT $>8 \times$ ULN; AST or ALT $>5 \times$ ULN and $\leq 8 \times$ ULN lasting 15 days or more (for patients with baseline values $\leq 2.5 \times$ ULN); AST or ALT $>2 \times$ baseline value and $\leq 8 \times$ ULN lasting 15 days or more (for patients with baseline values $>2.5 \times$ ULN and $\leq 4 \times$ ULN); AST or ALT $>3 \times$ ULN accompanied by total bilirubin $>2 \times$ ULN or INR >1.5; any pulmonary embolism that required full-dose anticoagulation therapy (except for deep vein thrombosis); or Grade 4 hyperglycemia with ketoacidosis or hyperosmolar non-ketotic coma.

Blood pressure, pulse rate, body temperature and body weight were measured on Days 1, 8 and 15 of each treatment cycle. ECOG performance status was assessed on Day 1 of each cycle. Electrocardiograms were recorded before starting gemcitabine infusion and after completing ganitumab infusion on Days 1 and 15 of Cycle 1, Day 15 of Cycle 2 and Day 15 of every 3 cycles thereafter. Laboratory tests were performed periodically throughout the study.

Serum samples for PK analysis of ganitumab were collected before starting gemcitabine infusion, within 5 min before completing ganitumab infusion, and 3 and 24 h after completing ganitumab infusion on Day 1 of Cycle 1; and before starting gemcitabine infusion on Days 8 and 15 of Cycle 1. Serum concentration of ganitumab was determined by using a validated double anti-idiotypic antibody sandwich immunoassay (8).

Plasma samples for PK analysis of gemcitabine were collected before starting gemcitabine infusion, within 5 min before completing gemcitabine infusion, and at 15, 30 and 90 min as well as 24 h (Day 1 only) after completing gemcitabine infusion on Days 1 and 8 of Cycle 1. Plasma concentration of gemcitabine was determined by using a validated method developed by Covance Bioanalytical Services, LLC. (Indianapolis, IN, USA).

Furthermore, serum samples for assessment of anti-ganitumab antibodies were collected pre-dose of gemcitabine on Day 1 of Cycles 1, 2 and 3, and every 2 cycles thereafter. Anti-ganitumab binding antibodies were detected by using a validated bridging immunoassay. Samples positive for anti-ganitumab binding antibodies were to be evaluated additionally for potential neutralizing capabilities in a cell-based assay.

Tumor response was evaluated at screening and every 8 weeks after starting the treatment by using computed tomography or magnetic resonance imaging and was classified according to the response evaluation criteria in solid tumors (12).

Statistical Considerations

All data were summarized descriptively. The PK parameters of ganitumab and gemcitabine were estimated by using non-compartmental methods with Phoenix WinNonlin software Version 6.1 (Pharsight Corporation, Mountain View, CA, USA). Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as the mean or the median combined with the standard deviation (SD) or the range. All data were analyzed by using SAS® System Version 9.1.3 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Disposition, Demographics and Baseline Characteristics

A total of six patients were enrolled into the study. All patients received at least one dose of ganitumab and gemcitabine and were included in the safety and PK analyses. Of these, one patient had no measurable tumor region at baseline. This patient was excluded from the efficacy analysis. At the time of data analysis, all patients discontinued the study treatment: three patients because of disease progression, two because of adverse events (Grade 2 sudden hearing loss and Grade 1 interstitial pneumonia) and one according to the protocol (Grade 4 neutropenia that did not resolve within the prespecified period). The mean number of treatment cycles was 3 (range, 2–5). The mean relative dose intensity (=[total dose received/total dose expected per initial dose] $\times$ 100) was 91% (range, 57–100%) for ganitumab and 90% (range, 68–100%) for gemcitabine.

Table 1 shows the demographic and baseline characteristics of the study patients. The median age was 62 (range, 43–69) years. Three patients (50%) had ECOG performance status of zero. All patients had Stage IV PC. No patients received prior radiotherapy or other medication for PC.

Table 1. Demographic and baseline characteristics of the study patients

	Number of patients ($n = 6$)
Median age, years (range)	62.0 (43–69)
Sex, *n* (%)	
Male	5 (83.3)
Female	1 (16.7)
Median weight, kg (range)	58.05 (49.0–75.4)
ECOG performance status, *n* (%)	
0	3 (50.0)
1	3 (50.0)
Medical and surgical history, *n* (%)	
Yes	6 (100.0)
Disease stage, *n* (%)	
IV	6 (100.0)
Prior radiotherapy, *n* (%)	
No	6 (100.0)
Prior other medication for cancer, *n* (%)	
No	6 (100.0)

ECOG, Eastern Cooperative Oncology Group.

Safety

Table 2 summarizes the common adverse events. All patients had thrombocytopenia and leukopenia. Other most common adverse events were neutropenia and nausea. Most adverse events were mild to moderate in severity. One patient had a DLT defined as Grade 3 neutropenia with fever. This patient experienced pyrexia (38.9°C) on Day 3 followed by Grade 3 neutropenia on Day 4.

Serious adverse events were reported in two patients: Grade 2 constipation in one; and Grade 3 decreased appetite and Grade 3 nausea in one. Of these, decreased appetite and nausea were considered to be related to ganitumab and gemcitabine by the investigator. The patient who had treatment-related serious adverse events was hospitalized and recovered with medication.

Three patients discontinued the study treatment owing to adverse events mentioned above. These events were considered to be related to ganitumab. Of these, neutropenia and sudden hearing loss resolved with treatment discontinuation and standard medication (prednisolone, adenosine triphosphate disodium hydrate and mecobalamin for sudden hearing loss; and filgrastim for neutropenia). Interstitial pneumonia did not resolve during the study.

One patient had Grade 2 hyperglycemia. This patient had a history of diabetes, and the blood glucose level was high (7.3 mmol/l) at screening. Hyperglycemia did not resolve during the study despite the medication, and the event was considered to be related to ganitumab and gemcitabine.

All patients were tested for anti-ganitumab antibodies and no one was positive for anti-ganitumab binding antibodies. No neutralizing antibodies were detected.

Table 2. Adverse events occurring in at least two patients or categorized into Grade 3 or 4

Preferred term	Number of patients by adverse event grade ($n = 6$)				Percentage of Grade 3/4 events
	Grade 1	Grade 2	Grade 3	Grade 4	
Hematologic					
Thrombocytopenia	0	4	2	0	33
Leukopenia	1	4	1	0	17
Neutropenia	0	1	2	2	67
Lymphopenia	0	3	1	0	17
Non-hematologic					
Nausea	3	1	1	0	17
Constipation	1	3	0	0	0
Decreased appetite	1	1	1	0	17
Vomiting	2	1	0	0	0
Weight decreased	1	2	0	0	0
Angiopathy	2	0	0	0	0
Cancer pain	1	1	0	0	0
Fatigue	1	1	0	0	0
Infusion-related reaction	0	2	0	0	0
Pyrexia	2	0	0	0	0
Rash	2	0	0	0	0
Laboratory changes of interest					
ALT increased	3	1	0	0	0
AST increased	3	0	0	0	0
Hemoglobin decreased	1	3	0	0	0
Blood sodium decreased	0	0	1	0	17

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

PHARMACOKINETICS

Figure 1 shows the individual values of area under the serum concentration–time curve (AUC) of ganitumab in this study and previous studies. The distribution of AUC values after the first infusion of ganitumab 20 mg/kg in this study was similar to that in the Phase 1 study in Japanese patients with advanced solid tumors (9). Furthermore, individual AUC values in this study were higher than any value after the first infusion of ganitumab 12 mg/kg in the Phase 2 study in patients with mPC (10).

Figure 2 shows the individual values of dose-normalized AUC and maximum observed concentration (C_{max}) of gemcitabine on Days 1 and 8. Both of the individual AUC and C_{max} fluctuated and did not show meaningful changes between before (i.e. Day 1) and after (i.e. Day 8) administration of ganitumab. The mean (SD) C_{max} of gemcitabine was 12 990 (3727) ng/ml on Day 1 and 13 380 (6239) ng/ml on Day 8. The mean (SD) AUC_{0-last} of gemcitabine was 7740 (2173) and 6957 (3260) h·ng/ml, respectively.

Antitumor Activity

In the analysis of tumor response, four patients (80%) had a best response of stable disease and one had progressive disease. The mean percent change of maximum tumor reduction from baseline was 6.6% (SD, 28.9%). The median time to progression was 58.0 (range, 37–113) days. Three patients had a time to progression longer than 100 days (113, 113 and 106 days).

DISCUSSION

This is the first study which evaluated the tolerability of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2, and the results show that this regimen was tolerable for patients with previously untreated mPC. Although three of six patients discontinued the study treatment owing to adverse events, these adverse events were generally manageable with treatment discontinuation and standard therapy. One event, interstitial pneumonia, did not resolve during the study, but its severity was mild.

The safety profile of this regimen was consistent with those in the previous studies. In our study, the most common adverse events were thrombocytopenia, leukopenia, neutropenia and nausea. These events were frequently reported in the previous single-agent studies of ganitumab (8,9). In these studies, patients with advanced solid tumors refractory to standard treatment received up to 20 mg/kg of ganitumab every 2 weeks, and the most common toxicities included fatigue and thrombocytopenia (8), as well as neutropenia and leukopenia (9). Neutropenia and thrombocytopenia were also frequently reported in the patients who received ganitumab 12 mg/kg in combination with gemcitabine 1000 mg/m^2 (10). Furthermore, leukopenia and neutropenia are the most common severe toxicities of gemcitabine (13). These results suggest that the safety profile of ganitumab does not differ whether it is administered as monotherapy or in combination with gemcitabine, even though its dose is increased to 20 mg/kg. They also suggest that ganitumab and gemcitabine may be combined without synergistic increase of toxicity.

In our study, Grade 2 hyperglycemia was reported in one patient. Although this patient had a history of diabetes, hyperglycemia was noted in 5 of 50 patients without diabetes in the previous single-agent study (8). Ganitumab did not bind to the insulin receptor in non-clinical experiments (7), but hyperglycemia is one of the major toxicities of IGF-1R inhibitors and mild increases in blood glucose levels occur in ~25% of patients treated with anti-IGF-1R antibodies (14). Thus, careful monitoring for hyperglycemia is considered to be necessary. It should also be noted that sudden hearing loss occurred in one patient. A previous study in patients with

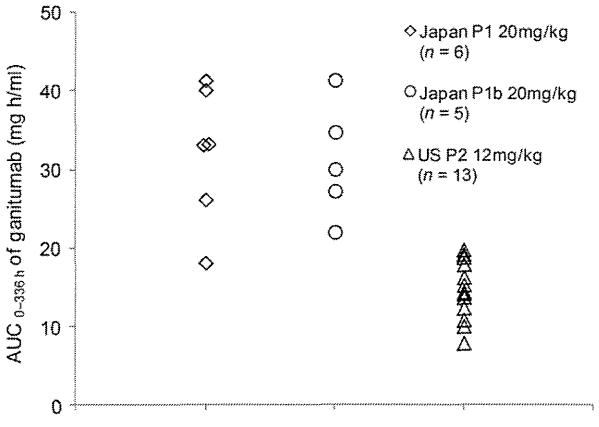

Figure 1. Individual AUC values of ganitumab at the first infusion. $AUC_{0-336\ h}$, the area under the concentration–time curve from time 0–336 h. Phase 1 study in Japan includes patients with non-pancreatic cancer who received ganitumab alone. Phase 1b study in Japan and Phase 2 study in the USA include patients with pancreatic cancer who received ganitumab after gemcitabine infusion. In the Japanese Phase 1b study, one patient was excluded from the pharmacokinetic analysis, because the serum concentration data were not available.

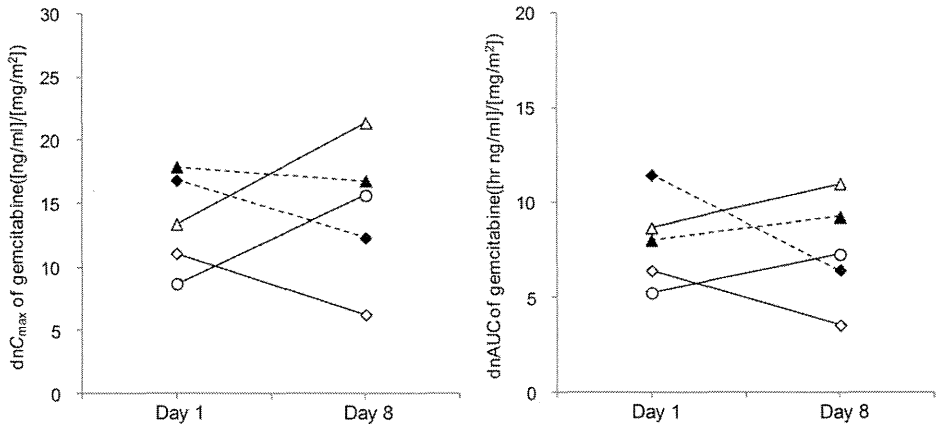

Figure 2. Individual values of dose-normalized C_{max} and AUC of gemcitabine on Days 1 and 8. dnC_{max}, dose-normalized maximum observed concentration; dnAUC, dose-normalized area under the concentration–time curve; Day 1, after completing gemcitabine infusion, and before ganitumab infusion; Day 8, after completing gemcitabine infusion, and 7 days after ganitumab infusion.

Turner's syndrome has shown that sensorineural hearing loss was negatively correlated with the serum concentration of IGF-1 (15), which suggests that hearing loss may be associated with the use of IGF-1R inhibitors.

In the PK analysis, no apparent drug–drug interaction between ganitumab and gemcitabine was observed. Similar AUC values of ganitumab between our study and a Japanese Phase 1 study in patients with advanced solid tumors (9) indicated that exposure to ganitumab 20 mg/kg would not be affected by the administration of gemcitabine. The mean C_{max} and AUC of gemcitabine in our study did not show any meaningful change between before and after administration of ganitumab. Gemcitabine is a small-molecule drug that is mainly eliminated by cytidine deaminase, whereas ganitumab is an immunoglobulin G1 monoclonal antibody considered to be mainly eliminated via catabolism. Therefore, a mechanism-based drug–drug interaction is not expected. The results on PK parameters in our study supported this expectation.

According to the exposure–response analysis, increased exposure to ganitumab was associated with prolonged progression-free survival and overall survival in patients with mPC (11). Since the ganitumab exposure at 20 mg/kg in our study appeared to be increased in a dose-dependent manner, when compared with that at 12 mg/kg in the Phase 2 study (10), further evaluation on the efficacy outcome at a ganitumab 20 mg/kg dose in patients with mPC is warranted.

No anti-ganitumab binding antibodies were detected in our study. In the previous single-agent study, anti-ganitumab binding antibodies were detected in one patient at Week 9, but no neutralizing antibodies were detected (8). In addition, the AUC values of ganitumab in this patient were similar after the first and third doses. Thus, we consider that the anti-ganitumab binding antibodies had no apparent effect on serum ganitumab concentrations.

Although assessment of efficacy was not a primary objective of our study, the combination of ganitumab and gemcitabine showed potential activity. Four patients (80%) achieved a best response of stable disease, and three (60%) had a time to progression longer than 100 days.

In conclusion, ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2 was tolerable and showed an acceptable safety profile in Japanese patients with untreated mPC. Exposure to ganitumab at 20 mg/kg in our study was higher than that at 12 mg/kg in the previous Phase 2 study. Appropriateness of using the dose level of ganitumab 20 mg/kg for patients with mPC was confirmed by these findings, and the efficacy and safety of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m^2 were evaluated in the randomized Phase 3 study (GAMMA [Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas], Clinical Trials gov. NCT01231347). However, this Phase 3 study was stopped because of futility. Currently, the other clinical data on efficacy, safety and PK are under analysis.

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Conflict of interest statement

Y.K., K.S. and T.T. are employees of Takeda Bio Development Center Ltd. J.G. is employed in a leadership position and owns stock of Amgen Inc. M.I. has no conflict of interest to disclose.

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Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic 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^2 oxaliplatin, 180 mg/m^2 irinotecan, and 200 mg/m^2 *l*-leucovorin, followed by a bolus of 400 mg/m^2 fluorouracil and a 46-h continuous infusion of 2400 mg/m^2 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.[1] In Japan, approximately 30 000 people die of pancreatic cancer annually, accounting for 8.3% of all malignant neoplasm-related deaths.[2] 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.[3]

In a randomized study, GEM monotherapy showed significant improvements in OS and clinical benefit response compared to 5-FU.[4] 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,[5] 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.*[6] 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 ≥9.0 g/dL, white blood cell count ≤10 000/mm^3, neutrophil count ≥2000/mm^3, platelet count ≥100 000/mm^3, total bilirubin ≤ 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: 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^2 and 2-h i.v. infusion of *l*-leucovorin at 200 mg/m^2 (during which irinotecan was also i.v. infused over 90 min at 180 mg/m^2), followed by an i.v. bolus of 5-FU at 400 mg/m^2 and continuous i.v. infusion of 5-FU over 46 h at 2400 mg/m^2. This regimen was repeated every 2 weeks. Prior to the study treatment, a 5-HT$_3$ 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^3, platelet count <75 000/mm^3, 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^2 and 120 mg/m^2 for irinotecan, 65 mg/m^2 and 50 mg/m^2 for oxaliplatin, and 1800 mg/m^2 and 1200 mg/m^2 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.*[6] 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^2)		
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.

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
l-Leucovorin	82.71	62.2–100.0

Dose reductions	Per patient		Per cycle	
	n	%	*n*	%
Total	32	88.9	88	27.1
Main reason for reduction				
Neutropenia	27	75.0	77	23.7
Febrile neutropenia	5	13.9	5	1.5
Thrombocytopenia	6	16.7	7	2.2
Diarrhea with fever (≥38°C)	3	8.3	3	0.9
Mucositis (≥Grade 3)	1	2.8	1	0.3
Anaphylaxis	1	2.8	1	0.3
Peripheral sensory neuropathy	2	5.6	3	0.9
Investigator decision	7	19.4	8	2.5

Delayed cycles	Per patient		Per cycle†	
	n	%	*n*	%
Total	32	88.9	115	39.8
Main reason for delay				
Neutropenia	27	75.0	80	27.7
Thrombocytopenia	5	13.9	6	2.1
Diarrhea (≥Grade 2 or watery stool)	2	5.6	2	0.7
Total bilirubin (>1.5 mg/dL)	1	2.8	2	0.7
Peripheral sensory neuropathy	1	2.8	1	0.3
Investigator decision	12	33.3	26	9.0
Patient conveniences	7	19.4	10	3.5
Other	5	13.9	5	1.7

†After two cycles.

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 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.

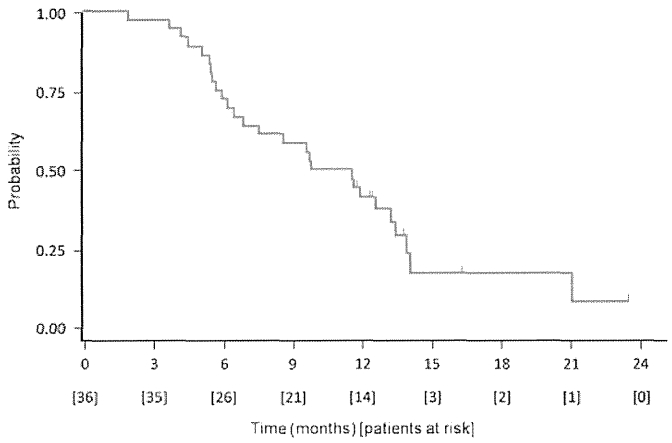

Fig. 1. Kaplan–Meier analysis of overall survival in a phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. The median survival was 10.7 months (95% confidence interval, 6.9–13.2). One-year overall survival was 41.5% (95% confidence interval, 25.4–56.8). 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.*[6] 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. However, 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),[6] 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

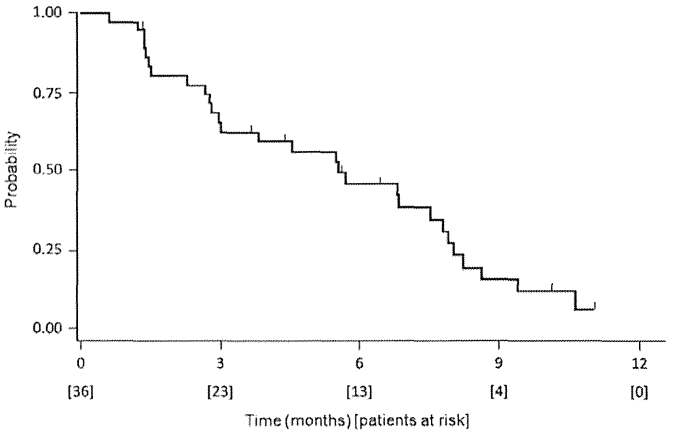

Fig. 2. Kaplan–Meier analysis of progression-free survival in a phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. The median progression-free survival was 5.6 months (95% confidence interval, 3.0–7.8). Data on eight patients were censored.

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

	Any grade		≥Grade 3	
	n	%	*n*	%
Hematological toxicities				
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
Non-hematological toxicities				
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.