Original Article

Postmarketing surveillance study of erlotinib plus gemcitabine for pancreatic cancer in Japan: POLARIS final analysis

Junji Furuse[1,2,*], Akihiko Gemma[2,3], Wataru Ichikawa[2,4], Takuji Okusaka[2,5], Akihiro Seki[6], and Tadashi Ishii[6]

[1]Department of Medical Oncology, Kyorin University School of Medicine, Tokyo, [2]Independent Advisory Board for Erlotinib, Tokyo, [3]Department of Respiratory Medicine and Oncology, Nippon Medical School Graduate School of Medicine, Tokyo, [4]Department of Medical Oncology, Showa University Fujigaoka Hospital, Tokyo, [5]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, and [6]Chugai Pharmaceuticals Ltd, Tokyo, Japan

*For reprints and all correspondence: Junji Furuse, Department of Medical Oncology, Kyorin University School of Medicine, Shinkawa 6-20-2, Mitaka-city, Tokyo 1818611, Japan. E-mail: jfuruse@ks.kyorin-u.ac.jp

Abstract

Objective: Erlotinib plus gemcitabine is approved in Japan for the treatment of metastatic pancreatic cancer. The POLARIS surveillance study investigated safety (focusing on interstitial lung disease [ILD]) and efficacy of erlotinib plus gemcitabine in Japanese pancreatic cancer patients.

Methods: Patients receiving erlotinib plus gemcitabine for pancreatic cancer in Japan between July 2011 and August 2012 were enrolled. ILD-like events were independently confirmed by a review committee. Overall survival (OS) and progression-free survival (PFS) were assessed, and risk factors for ILD occurrence were analyzed by multivariate Cox regression analysis.

Results: Safety data were available for 843 patients and efficacy data for 841. Adverse drug reactions were reported in 83.5% of patients, no new safety signals were identified. ILD events were confirmed by the review committee in 52 patients (6.2%), with two fatal cases (0.2%). Median time from initial erlotinib treatment to ILD events was 70.5 days. Of the 52 patients with ILD events, 86.5% improved or fully recovered from ILD (median time 24 days). Multivariate analysis identified previous or concurrent lung disease (hazard ratio [HR], 2.2; 95% confidence interval [CI], 1.0–4.5; $P = 0.0365$) and ≥3 organs with metastases (HR, 4.2; 95% CI, 2.2–8.2; $P < 0.0001$) as potential ILD risk factors. Accumulated OS rate at 28 weeks was 68.2%, and median PFS was 92 days (95% CI, 86–101).

Conclusions: Erlotinib plus gemcitabine has an acceptable safety and efficacy profile in pancreatic cancer; however, patients should be assessed for previous/concurrent lung disease and metastatic burden, before and during treatment.

Key words: erlotinib, gemcitabine, pancreatic cancer, Japanese, surveillance

Introduction

Over 300 000 individuals were diagnosed with pancreatic cancer worldwide in 2012 (1). A total of 31 046 patients in Japan died from pancreatic cancer in 2012, making it the fourth leading cause of cancer death in Japan (1). Current recommended treatments for

pancreatic cancer are gemcitabine regimens. A median overall survival (OS) of 5.7 months has been reported with single-agent gemcitabine in chemonaïve patients with pancreatic cancer (2). Several combinations of gemcitabine with cytotoxic agents and biological agents have been investigated; however, most have not significantly improved survival

versus gemcitabine alone (3–16). Current recommended treatments for metastatic pancreatic cancer in Japan are FOLFIRINOX therapy (leucovorin, fluorouracil, irinotecan and oxaliplatin) and gemcitabine plus nab-paclitaxel therapy. However, in cases where treatment with FOLFIRINOX or gemcitabine plus nab-paclitaxel is not suitable, gemcitabine monotherapy, concomitant gemcitabine with erlotinib or S-1 chemotherapy are recommended (17–20).

Erlotinib is an epidermal growth factor receptor tyrosine-kinase inhibitor approved as primarily first-line therapy in combination with gemcitabine (GE) for unresectable pancreatic cancer (21–24). GE was well tolerated in a Japanese phase II pancreatic cancer trial (22), and in the pivotal international phase III PA.3 trial, with mild-to-moderate rash and diarrhea being the most common adverse events (AEs) (21). In the Japanese pancreatic cancer study, interstitial lung disease (ILD), a heterogeneous group of parenchymal lung diseases, was reported in 8.5% of patients (9/106) and was highlighted as an adverse drug reaction (ADR) of particular concern (22). Consequently, a prospective observational study investigated erlotinib safety (focusing on ILD) and efficacy in Japanese patients with pancreatic cancer. A similar Japanese postmarketing surveillance study in non-small-cell lung cancer (NSCLC) patients treated with erlotinib, which evaluated ILD, has also been completed (25). The POLARIS (POst-Launch All-patient-RegIstration Surveillance in erlotinib-treated pancreatic cancer patients) study investigated the occurrence of ILD and risk factors for onset of ILD, and evaluated other ADRs in all Japanese patients with pancreatic cancer treated with GE in Japan.

Methods

Surveillance study design and treatment

All Japanese patients with advanced pancreatic cancer treated with GE (gemcitabine 1000 mg/m² weekly for 3 weeks, followed by a 1-week rest; erlotinib 100 mg orally, once daily) were enrolled from 1 July 2011 to 31 August 2012. A 28-week observation period was used, based on a median duration of erlotinib treatment of 102.5 days and peak ILD incidence at 187 days in the phase II trial (22). The surveillance period was 1 July 2011 to 31 December 2013, on which date case report forms were collected. The planned sample size was 800 patients, with planned surveillance duration of 42 months from the date of erlotinib approval in pancreatic cancer in Japan (1 July 2011). All patients provided informed consent and all appropriate ethical guidelines were followed during the study.

Safety assessments

Demographic and baseline data including gender, age, body mass index, tumor histology, disease stage, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, treatment status, metastases, medical history (including lung disorders, e.g. emphysema, chronic obstructive pulmonary disease [COPD], lung infection and ILD), concomitant medications and history of chemotherapy were collected. Safety and efficacy data were collected at 8, 16 and 28 weeks after treatment initiation. AEs were graded using the National Cancer Institute Common Terminology Criteria for AEs version 4.0 (Japanese version JCOG/JSCO edition, May 2009). Any AE possibly related to erlotinib was termed an ADR, with ADRs of particular interest for erlotinib also being identified (ILD, skin disorders, hepatic dysfunction, diarrhea, eye disorders, hemorrhage, microangiopathy, myocardial infarction/ischemic heart disease and cerebrovascular disorders). Patients with previous or current history of ILD were excluded as much as possible for safety

measures. Patients with confirmed ILD events were treated, if required, using treatments such as steroid pulse therapy. ILD-like events were reported through Case Report Forms by a physician, based on periodic evaluation of chest imaging or CT scans. All reported ILD-like events were assessed by an independent review committee (IRC) of pulmonologists, chest radiologists, pancreatic oncologists and pathologists based on medical and pathologic findings, periodic evaluation of chest imaging or CT scans.

Efficacy assessments

Efficacy was evaluated by OS and physician-assessed progression-free survival (PFS), using Kaplan–Meier methodology. Disease progression was assessed according to treating physicians' standard practices, without centralized independent assessment.

Statistical analyses

Assuming an ILD incidence of 8.5% (9/106 patients) (22), a planned sample size of 800 patients was established. This would detect background factors, with a risk ratio of the occurrence of ILD of ≥2 among patients with risk factors, and statistical difference with a *P*-value of <0.05.

The primary endpoint was the pattern of occurrence of ILD and risk factors for ILD. The outcome of ILD and time to ILD onset from the first erlotinib dose were also analyzed. The incidences of ILD and fatal ILD were expressed per 100 patient-weeks. Secondary endpoints included the pattern of other ADRs, and the overall safety and efficacy of erlotinib.

Multivariate Cox regression analysis with a stepwise model with forward selection method was conducted to determine ILD risk factors. Occurrence/nonoccurrence of ILD was the dependent variable. Exploratory variables included: gender, age, number of organs with metastases (<3 vs. ≥3), previous/concurrent lung disease, smoking history, ECOG PS and previous chemotherapy regimens. These baseline demographics were selected as ILD risk factors because they were previously reported as risk factors in Japan (26), or had a *P*-value of <0.05 in the univariate analyses. Additional multivariate analyses were conducted on risk factors identified to investigate two-factor interactions (statistical significance: *P* < 0.05). Statistical analyses used Statistical Analysis Software (version 9.1 and 9.3; SAS Institute, Cary, NC).

The safety population comprised all GE-treated patients with case report form data available. The efficacy population comprised the safety population, except those where gemcitabine therapy was not prescribed concomitantly at the time of this study.

Results

Patient population

A total of 901 patients received enrollment forms between 1 July 2011 and 31 August 2012. Data from 848 patients with locked case report forms were obtained by the data cut-off of 31 December 2013. Safety data were available for 843 patients (5 patients were excluded because their data were duplicated due to hospital transfers). Efficacy data were available for 841 patients (2 more patients were excluded due to not receiving concomitant gemcitabine; Fig. 1). Regarding baseline characteristics (Table 1), 58.1% of patients enrolled were male, 44.1% had any smoking history, 70.5% had stage IVb cancer and 69.2% had an ECOG PS of 0. At the start of treatment, 50.7% were 65 years or older and 83.5% had metastases.
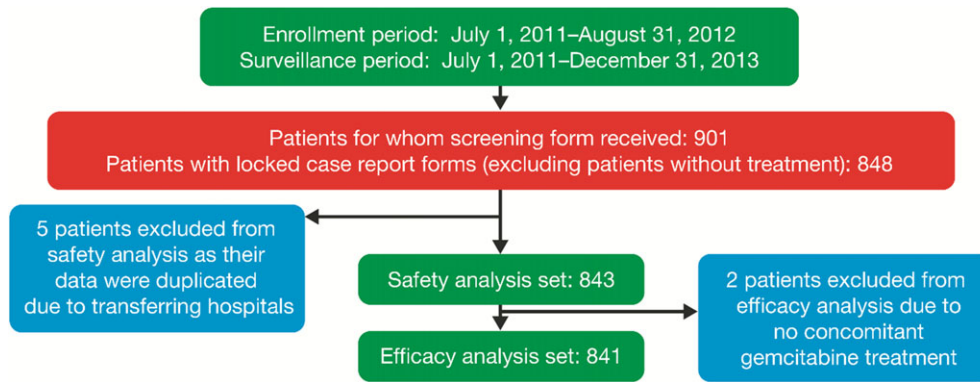
Figure 1. Patient population distribution.

Safety

Incidence of ADRs

ADRs were reported in 83.5% of patients (704/843), the most common were skin disorders (69.9%), including rash (63.6%) and diarrhea (17.6%; Table 2). No new safety signals were identified. Most ADRs were mild in severity (grades 1–2; Table 3). Median time from initial erlotinib treatment to onset of an ADR was 8.5 days for rash, 10 days for liver disorders and 14 days for diarrhea. Most patients with these ADRs improved or recovered, and the majority were able to continue erlotinib treatment (data not shown).

Interstitial lung disease

Reported ILD-like events ($n = 57$) included ILD ($n = 50$) and pneumonitis ($n = 7$). ILD events were confirmed by an independent review committee in 52 patients (6.2%), with two fatal (grade 5) ILD events (0.2% of the overall population, 3.8% of patients with a confirmed ILD event). Grade ≥ 3 ILD events were confirmed in 20 patients (2.4% of the safety population). In the 52 patients with confirmed ILD events, the median time from initial erlotinib treatment to the onset of ILD events was 70.5 days (range 13.0–212.0). Outcomes of ILD events were: 23 patients (44.2%) recovered; 22 (42.3%) improved; 3 (5.7%) did not recover; 1 patient (1.9%) had a sequela and the outcome was unknown for 1 patient (1.9%). Of these patients, 86.5% improved or fully recovered from ILD in a median time of 24 days. A total of 92.3% of patients with confirmed ILD events discontinued erlotinib treatment. The highest incidence rate per 100 patient-weeks for ILD event onset was 10–12 weeks after starting treatment, with an incidence per 100 patient-weeks of 1.4 (Fig. 2a).

Risk factors for ILD onset

In the univariate analysis, smoking history ($P = 0.0298$) and ≥ 3 organs with metastases ($P < 0.0001$) were identified as significant risk factors for developing ILD (Table 4). In the multivariate analysis, previous or concurrent lung disease (hazard ratio [HR], 2.2, 95% confidence interval [CI], 1.0–4.5; $P = 0.0365$) and ≥ 3 organs with metastases (HR, 4.2, 95% CI, 2.2–8.2; $P < 0.0001$) were identified as significant risk factors for onset of ILD (Table 4).

Efficacy

Accumulated survival rates at 8, 16 and 28 weeks were 95.3%, 85.0% and 68.2%, respectively. Physician-assessed median PFS, as evaluated by each site physician, was 92 days (3.0 months; 95% CI, 86–101 days). Subgroup analysis, as shown in Table 5, demonstrated that patients without additional affected organs had longer median physician-assessed PFS (176 days) than those with 1–2 organs affected (87 days) or ≥ 3 organs affected (63 days), and patients with grade 2 rash had longer physician-assessed median PFS (125 days) than those with grade 0–1 rash (85 days). Accumulated PFS rates at 8, 16 and 28 weeks were 70.9%, 42.7% and 23.4%, respectively.

Discussion

Final data from the POLARIS surveillance study confirm that the GE regimen has an acceptable safety and efficacy profile in Japanese patients with pancreatic cancer. Compared with a previous Japanese phase II pancreatic cancer study, no new risk information for ILD onset was identified here (22). In the phase II study, rash was the most common ADR, seen in 93.4% of patients; ILD occurred in 8.5% of patients, all cases were grade ≤ 3 and all patients improved or fully recovered (22).

In POLARIS, the ILD incidence was 6.2%, with an overall mortality rate of 0.2% ($n = 2$), which was 3.8% among patients with confirmed ILD. This incidence rate of ILD events was similar to that in the Japanese phase II pancreatic cancer study, reporting an incidence of 8.5% with no fatal cases (22). This is similar to all grades of ILD events reported in 429 patients (4.3%), grade ≥ 3 ILD events reported in 257 patients (2.6%), and grade 5 ILD events experienced by 153 patients (1.5%) in the Japanese postmarketing POLARSTAR surveillance study in 9 909 NSCLC patients (25). A surveillance study in Japanese patients with pancreatic cancer treated with gemcitabine alone ($n = 855$) demonstrated an incidence of ILD of 0.7% ($n = 6$), suggesting that the combination with erlotinib may result in a higher incidence of ILD (27). Occurrence of ILD in patients with pancreatic cancer was most common at 10–12 weeks following the start of GE treatment in POLARIS. This was in contrast to data from NSCLC POLARSTAR patients, where ILD was most commonly seen within 2 weeks of commencing erlotinib (incidence rate per 100 patient-weeks of 0.8; Fig. 2b) (25). This difference concerning ILD incidence rate between NSCLC and pancreatic cancer may be due to a cytotoxic reaction associated with combination therapy in a dose-dependent manner or due to drug induced activation of certain immune cells linked with development of pulmonary disorders (28–30). Alternatively, this difference in time of onset of ILD may be due to differences in tumor characteristics.

In the NSCLC POLARSTAR study, of the confirmed cases of ILD, 75 (17.5%) patients fully recovered, 154 (35.9%) patients

Table 1. Baseline characteristics (*n* = 843)

Characteristic	Patients, *n* (%)
Gender	
Male	490 (58.1)
Female	353 (41.9)
Age at start of erlotinib treatment	
<65 years	416 (49.3)
≥65 years	427 (50.7)
Histological type	
Adenocarcinoma	631 (74.9)
Other	12 (1.4)
Unknown	200 (23.7)
Stage of pancreatic cancer	
Postoperative recurrence	83 (9.8)
IVa	154 (18.3)
IVb	594 (70.5)
Other	5 (0.6)
Unknown	7 (0.8)
Site of primary tumor	
Head of pancreas	348 (41.3)
Body of pancreas	329 (39.0)
Tail of pancreas	200 (23.7)
Other	7 (0.8)
Metastases	
No	137 (16.3)
Yes	704 (83.5)
Unknown	2 (0.2)
Site of metastatic foci	
Liver	448 (63.6)
Peritoneal	165 (23.4)
Lymph node	263 (37.4)
Lung	118 (16.8)
Bone	28 (4.0)
Brain	2 (0.3)
Other	37 (5.3)
Previous or concurrent lung disease	
Lung infection: No	805 (95.5)
Lung infection: Yes	31 (3.7)
Unknown	7 (0.8)
ILD: No	833 (98.8)
ILD: Yes	3 (0.4)
Unknown	7 (0.8)
Lung emphysema or COPD: No	816 (96.8)
Lung emphysema or COPD: Yes	20 (2.4)
Unknown	7 (0.8)
Asthma: No	819 (97.2)
Asthma: Yes	18 (2.1)
Unknown	6 (0.7)
Tuberculosis: No	826 (98.0)
Tuberculosis: Yes	10 (1.2)
Unknown	7 (0.8)
Smoking history	
No	467 (55.4)
Yes	372 (44.1)
Current smoker	56 (15.0)
Past smoker	313 (84.1)
Unknown	3 (0.8)
Unknown	4 (0.5)
ECOG PS	
0	583 (69.2)
1	251 (29.8)
2	7 (0.8)
Unknown	2 (0.2)

COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease.

Table 2. Incidence of ADRs (*n* = 843)

ADR, *n* (%)	All grades	Grade ≥3
ILD (IRC confirmed)	52 (6.1)	20 (2.4)
Rash	536 (63.6)	34 (4.0)
Dry skin	51 (6.0)	1 (0.1)
Pruritus	25 (3.0)	0 (0.0)
Paronychia	90 (10.7)	7 (0.8)
Liver disorders	107 (12.7)	33 (3.9)
Diarrhea	148 (17.6)	14 (1.7)
Eye disorders	15 (1.8)	0 (0.0)
Hemorrhage	42 (5.0)	15 (1.8)
Cerebrovascular disorder	5 (0.6)	3 (0.4)
Myocardial infarction	0 (0.0)	0 (0.0)
Thrombotic microangiopathy	0 (0.0)	0 (0.0)
Gastrointestinal perforation	2 (0.2)	1 (0.1)
Gastrointestinal ulcer	9 (1.1)	4 (0.5)
Acute renal failure	1 (0.1)	1 (0.1)

ADR, adverse drug reaction; IRC, independent review committee.

improved, 32 (7.5%) patients did not recover, 5 (1.2%) patients had sequelae, 153 (35.7%) patients died and 10 (2.3%) patients had unknown outcomes (25). Although the ILD incidence rate in POLARIS exceeded that in the final POLARSTAR analysis, the ILD mortality rate was lower in patients with pancreatic cancer, perhaps reflecting the lower incidence of confounding lung disease or reduced normal lung area on computed tomography scan in patients with pancreatic cancer. In POLARIS, 86.5% of patients with an ILD event improved or fully recovered from ILD, compared with 53.4% of patients with ILD from POLARSTAR. This again may be due to differences in tumor characteristics or confounding lung disease that may affect the severity of ILD.

The two risk factors for ILD onset identified by the Cox regression multivariate analysis in POLARIS were previous or concurrent lung disease and ≥3 organs with metastases. However, previous/concurrent ILD and previous/concurrent emphysema/COPD, which were included in the exploratory variables for the NSCLC POLARSTAR study, were excluded from the exploratory variables in POLARIS and tabulated as 'lung disease' because few patients with those variables received erlotinib on the basis of erlotinib safety measures. Therefore, the authors suggest administering erlotinib to patients with the following risk factors only after careful consideration and with thorough observation of patient status: concurrent or previous ILD, concurrent or previous emphysema or COPD and concurrent or previous pulmonary infection.

In a study reviewing records of patients with NSCLC or pancreatic cancer treated with gemcitabine alone, pre-existing pulmonary fibrosis and prior thoracic radiotherapy were identified as risk factors for developing ILD, suggesting prior lung conditions may be a risk factor independent of erlotinib treatment (26). After reviewing the POLARIS data, the ILD review committee recommended that patients with pancreatic cancer should be evaluated for the risk factors identified here prior to beginning GE treatment. During GE treatment, it is necessary to continually monitor for early symptoms of ILD (dry cough, dyspnea, pyrexia) and perform regular chest computed tomography scans, as ILD onset can occur throughout the treatment course. If ILD symptoms occur, discontinuation of GE is recommended.

Erlotinib was generally well tolerated in POLARIS, with rash and diarrhea being the most frequently observed ADRs, which is consistent with phase III trials of GE for pancreatic cancer. These

Table 3. Incidence of prespecified ADRs by grade (_n_ = 843)

ADR, _n_ (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
ILD (IRC confirmed)	19 (2.3)	13 (1.5)	17 (2.0)	1 (0.1)	2 (0.2)	52 (6.2)
Skin disorders	309 (36.7)	234 (27.8)	44 (5.2)	1 (0.1)	0 (0.0)	589 (69.9)
Rash	304 (36.1)	197 (23.4)	34 (4.0)	0 (0.0)	0 (0.0)	536 (63.6)
Dry skin	38 (4.5)	12 (1.4)	1 (0.1)	0 (0.0)	0 (0.0)	51 (6.0)
Pruritus	20 (2.4)	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	25 (2.9)
Paronychia	38 (4.5)	45 (5.3)	7 (0.8)	0 (0.0)	0 (0.0)	90 (10.7)
Liver disorder	41 (4.9)	33 (3.9)	31 (3.7)	2 (0.2)	0 (0.0)	107 (12.7)
Diarrhea	85 (10.8)	49 (5.8)	13 (1.5)	2 (0.2)	0 (0.0)	148 (17.6)
Eye disorders	12 (1.4)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (1.8)
Hemorrhage	23 (2.7)	4 (0.5)	9 (1.1)	2 (0.2)	4 (0.5)	42 (5.0)
Thrombotic microangiopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral disorders	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	5 (0.6)
Gastrointestinal perforation	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)
Gastrointestinal ulcer	1 (0.1)	4 (0.5)	4 (0.5)	0 (0.0)	0 (0.0)	9 (1.1)
Renal failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
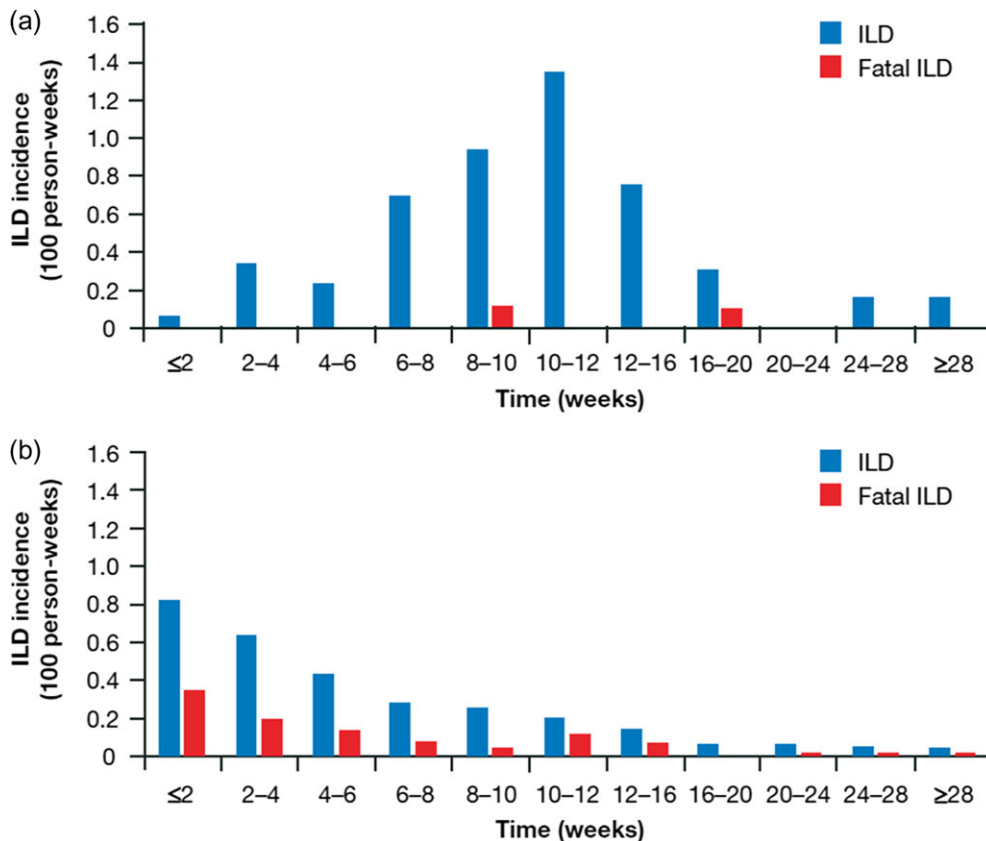
Figure 2. (a) Time to onset and outcome of ILD in the pancreatic POLARIS study. (b) Time to onset and outcome of ILD in the non-small-cell lung cancer (NSCLC) POLARSTAR study (25).

events were predominantly grades 1–2, manageable and their frequency was comparable to that reported in the Japanese phase II pancreatic cancer clinical trial of erlotinib (22).

Efficacy in terms of physician-assessed median PFS in POLARIS (3.0 months) was similar to previously reported studies of GE in pancreatic cancer. The PA.3 study reported median PFS of 3.8 months with GE versus 3.6 months with gemcitabine plus placebo, while the AViTA study reported median PFS of 3.6 months with GE (21,23). In a Japanese population, a phase II pancreatic cancer study demonstrated a median PFS of 3.5 months with GE (22). Subgroup analysis in POLARIS suggested that patients with higher grade of rash may benefit more in terms of physician-assessed median PFS than those who do not experience rash. This is consistent with results from the global studies AViTA and PA.3, and the Japanese

Table 4. Univariate and multivariate analysis of risk factors for developing ILD

Exploratory variables Criterion variable Evaluation variable	Total number of patients	Incidence of ILD, %	Univariate analysis[a]			Multivariate analysis[b]		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Overall	829	6.3						
Gender								
Female	346	5.5						
Male	483	6.8	1.3	0.7–2.2	0.4033			
Age, years								
<75	722	5.7						
≥75	107	10.3	1.8	0.9–3.6	0.0719			
Previous or concurrent lung disease								
No	746	5.8						
Yes	83	10.8	1.9	0.9–3.9	0.0849	2.2	1.0–4.5	0.0365
Smoking history								
No	460	4.6						
Yes	369	8.4	1.8	1.1–3.2	0.0298			
ECOG PS								
0	572	6.1						
≥1	257	6.6	1.5	0.9–2.7	0.1495			
Number of chemotherapy regimens for primary disease: two categories								
≥1	162	2.5						
0	667	7.2	2.6	0.9–7.2	0.0667			
Number of affected organs: two categories								
0 or ≤2	748	5.3						
≥3	81	14.8	3.9	2.1–7.5	<0.0001	4.2	2.2–8.2	<0.0001

CI, confidence interval; HR, hazard ratio.

[a]Fourteen patients for whom not all exploratory variable data were obtained were excluded from the univariate and multivariate analyses.

[b]Exploratory variables included: gender, age, number of organs affected by metastases (categorical variable <3 vs. ≥3), previous/concurrent lung disease, smoking history, ECOG PS and previous chemotherapy regimens. These baseline demographics were selected as ILD risk factors because they were previously reported as ILD risk factors in Japan (26) or were statistically different with a *P*-value of <0.05 in univariate analyses. 75 years was selected as the exploratory variable for age because it had a higher univariate HR compared with 65 years.

Table 5. Physician-assessed median PFS by subgroup

Subgroup	Median PFS (95% CI), days
Overall	92 (86–101)
Gender	
Male	87 (79–99)
Female	100 (90–115)
Age, years	
<65	97 (87–113)
≥65	89 (80–100)
Metastatic sites[a]	
Liver	69 (63–79)
Peritoneum	99 (78–114)
Lymph nodes	92 (79–106)
Lung	91 (69–105)
Number of additional affected organs	
0	176 (148–213)
<2	87 (79–94)
≥3	63 (53–89)
Smoking history	
Yes	91 (85–97)
No	92 (84–105)
Rash	
Grade 0–1	85 (76–91)
Grade 2	125 (110–152)

PFS, progression-free survival.

[a]Patients may have multiple metastases.

phase II pancreatic cancer study, showing that rash correlates with improved efficacy outcomes with GE (21–23).

Limitations to consider include the single-arm nature of this observational trial without a control group. Unlike a clinical trial, this analysis was regulated to have a maximum observation period of 28 weeks and could not estimate median OS despite the existence of accumulated survival rate. Additionally, there was a lack of specific patient selection criteria for enrollment, including no specification regarding history of ILD, which could potentially affect the ILD risk factor analysis.

The POLARIS postmarketing surveillance study showed that GE has an acceptable safety and efficacy profile in Japanese patients with pancreatic cancer. No new safety signals were detected and the risk/benefit balance of GE was considered favorable, suggesting that GE is a generally well tolerated treatment option for Japanese patients with pancreatic cancer. However, patients should be carefully monitored for the risk factors identified in this surveillance study, both before and during treatment.

Funding

Conflict of interest statement

References

1. World Health Organization, GLOBOCAN 2012 (http: //globocan.iarc.fr/). Last accessed 15 February 2017.
2. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
3. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270–5.
4. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002;94:902–10.
5. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776–83.
6. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509–16.
7. Oettle H, Richards D, Ramanathan RK, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 2005;16:1639–45.
8. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006;24:4441–7.
9. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946–52.
10. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587–92.
11. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007;25:2212–17.
12. Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004;22:1430–38.
13. Bramhall SR, Rosemurgy A, Brown PD, et al. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol* 2001;19:3447–55.
14. Moore M, Hamm J, Dancey J, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2003;21:3296–302.
15. Philip PA, Benedetti J, Fenoglio-Preiser C, et al. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [Pca]: SWOG S0205 study. *J Clin Oncol* 2007;25:199s Abstract LBA4509.
16. Kindler HL, Niedzwiecki D, Hollis E, et al. A double-blind, placebo controlled, randomized phase III trial of gemcitabine (G) plus bevacizumab (B) versus gemcitabine plus placebo (P) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis of Cancer and Leukemia Group B (CALGB). *J Clin Oncol* 2007;25:199s Abstract 4508.
17. Conroy T, Destine F, Chou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
18. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–703.
19. Burris HA, Moore MJ, Anderson J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;16:2403–13.
20. Ueno H, Ioka T, Ikeda M, et al. Randomised phase III study of gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 2013;31:1640–48.
21. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada. *J Clin Oncol* 2007;25:1960–6.
22. Okusaka T, Furuse J, Funakoshi A, et al. Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer. *Cancer Sci* 2011;102:425–31.
23. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 2009;27:2231–7.
24. Nakai Y, Isayama H, Sasaki T, et al. A multicentre randomised phase II trial of gemcitabine alone vs gemcitabine and S-1 combination therapy in advanced pancreatic cancer: GEMSAP study. *Br J Cancer* 2012;106:1934–9.
25. Gemma A, Kudoh A, Ando M, et al. Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10708 Japanese patients with non-small-cell lung cancer. *Cancer Sci* 2014;105:1584–90.
26. Umemura S, Yamane H, Suwaki T, et al. Interstitial lung disease associated with gemcitabine treatment in patients with non-small-cell lung cancer and pancreatic cancer. *J Cancer Res Clin Oncol* 2011;137:1469–75.

27. Ioka T, Katayama K, Tanaka S, et al. Safety and effectiveness of gemcitabine in 855 patients with pancreatic cancer under Japanese clinical practice based on post-marketing surveillance in Japan. *Jpn J Clin Oncol* 2013;43:139–45.

28. Limer AH, Rosenow EC. Drug-induced pulmonary disease. In: Murray J, Nadel J, Mason R, Boushey A, editors. *Textbook of Respiratory Medicine*. Philadelphia: Saunders, 2000;1971–94.

29. Naba T, Tanaka K, Hoshino T, et al. Suppression of expression of heat shock protein 70 by gefitinib and its contribution to pulmonary fibrosis. *PLoS One* 2011;6:e27296.

30. Tanaka K, Tanaka Y, Namba T, et al. Heat shock protein 70 protects against bleomycin-induced pulmonary fibrosis in mice. *Biochem Pharmacol* 2010;80:920–31.