Original Article

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

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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 chemonaive 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 (1–16). 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), 38.1% 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.
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 event 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 sequel 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 10.8; Fig. 2b). (86–101 days). Subgroup analysis, as shown in Table 5, demonstrated that patients without additional affected organs had longer median physician-assessed median PFS (125 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.

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, 8.5% of patients, all cases were grade ≥ 1 rash had a sequel 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 10.8; Fig. 2b). (86–101 days). Subgroup analysis, as shown in Table 5, demonstrated that patients without additional affected organs had longer median physician-assessed median PFS (125 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 (4.1%), 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 metastatic foci                     |                 |
| 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 primary tumor                       |                 |
| Liver                                       | 448 (63.6)      |
| Peritoneal                                   | 163 (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)         |
| ECOC PS                                     |                 |
| 0                                           | 583 (69.2)      |
| 1                                           | 251 (29.8)      |
| 2                                           | 7 (0.8)         |
| Unknown                                     | 2 (0.2)         |

COPD, chronic obstructive pulmonary disease; ECOC 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 and previous/concurrent 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 (tors 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
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

| 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 (20).
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.

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

| Exploratory variable | Total number of patients | Incidence of ILD, % | Univariate analysis\(^a\) | Multivariate analysis\(^b\) |
|----------------------|--------------------------|---------------------|--------------------------|--------------------------|
| Gender               |                          |                     |                          |                          |
| Female               | 346                      | 5.5                 | 1.3                      | 0.7–2.2                 | 0.4033                  |
| Male                 | 483                      | 6.8                 |                          |                          |                         |
| Age, years           |                          |                     |                          |                          |
| <75                  | 722                      | 5.7                 | 1.8                      | 0.9–3.6                 | 0.0719                  |
| ≥75                  | 107                      | 10.3                |                          |                          |                         |
| Previous or concurrent lung disease | | | | | |
| No                   | 746                      | 5.8                 | 1.9                      | 0.9–3.9                 | 0.0849                  |
| Yes                  | 83                       | 10.8                | 2.2                      | 1.0–4.5                 | 0.0365                  |
| Smoking history      |                          |                     |                          |                          |
| No                   | 460                      | 4.6                 | 1.8                      | 1.1–3.2                 | 0.0298                  |
| Yes                  | 369                      | 8.4                 |                          |                          |                         |
| ECOG PS              |                          |                     |                          |                          |
| 0                    | 572                      | 6.1                 | 1.5                      | 0.9–2.7                 | 0.1495                  |
| ≥1                   | 257                      | 6.6                 |                          |                          |                         |
| 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                |

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.

Table 5. Physician-assessed median PFS by subgroup


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**Conflict of interest statement**

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