Table 2 AEs (all-causality) reported in >2 patients in the monotherapy and combination therapy parts overall (safety population)

	Number of patients, n (%)				
	AZD8931 monotherapy part			AZD8931 combination part	
Adverse event	40 mg bid (*n*=3)	60 mg bid (*n*=4)	80 mg bid (*n*=4)	40 mg bid + paclitaxel (*n*=6)	Total (*n*=17)
Any AE	3 (100)	4 (100)	4 (100)	6 (100)	17 (100)
Diarrhea	1 (33)	3 (75)	4 (100)	4 (67)	12 (71)
Paronychia	2 (67)	3 (75)	3 (75)	3 (50)	11 (65)
Dry skin	2 (67)	3 (75)	3 (75)	3 (50)	11 (65)
Pustular rash	3 (100)	2 (50)	3 (75)	2 (33)	10 (59)
Stomatitis	3 (100)	1 (25)	1 (25)	4 (67)	9 (53)
Epistaxis	2 (67)	1 (25)	0	4 (67)	7 (41)
Nausea	0	3 (75)	0	3 (50)	6 (35)
Rash	0	1 (25)	1 (25)	4 (67)	6 (35)
Dysgeusia	1 (33)	1 (25)	0	3 (50)	5 (29)
Constipation	1 (33)	1 (25)	1 (25)	2 (33)	5 (29)
Eczema	1 (33)	1 (25)	1 (25)	1 (17)	4 (24)
Vomiting	0	2 (50)	0	2 (33)	4 (24)
Pyrexia	0	1 (25)	1 (25)	2 (33)	4 (24)
Alopecia	0	0	0	4 (67)	4 (24)
Fatigue	0	1 (25)	0	3 (50)	4 (24)
Neutropenia	0	0	0	4 (67)	4 (24)
Increased ALT	2 (67)	0	0	1 (17)	3 (18)
Hypertension	0	2 (50)	1 (25)	0	3 (18)
Decreased hemoglobin	0	0	1 (25)	2 (33)	3 (18)
Peripheral sensory neuropathy	0	0	0	3 (50)	3 (18)
Leucopenia	0	0	0	3 (50)	3 (18)

Patients with multiple occurrences of the same event were counted only once per event. Includes AEs with onset from the first dose to 30 days following the last dose of AZD8931

Pharmacokinetic evaluation

In the monotherapy part following single oral dosing, quantifiable plasma concentrations of AZD8931 (Fig. 1) were present up to 72 h post-dose at all dose levels investigated, indicating that the drug was bioavailable following oral administration. AZD8931 exposure increased approximately dose proportionally after single and multiple dosing. AZD8931 was rapidly absorbed with maximum plasma concentrations (C_{max}) being achieved at a median of 1–2 h across doses (Table 3). Following C_{max}, the elimination was biphasic with a mean terminal elimination half-life of approximately 11.4–12.8 h, which appeared to be independent of dose. Plasma clearance of AZD8931 remained approximately constant across the dose range. The geometric mean steady-state (pre-dose) plasma concentration was achieved by day 3 of continuous dosing (R3). Consistent with single-dose data, the mean accumulation ratio observed for AZD8931 40–80 mg ranged from 1.62–to 1.83-fold. The formation of *O*-desmethyl AZD8931 was achieved with a median t_{max} of 36–60 h post-dose; its elimination was slow, resulting in increased plasma accumulation compared with AZD8931 following bid dosing. Area under the concentration–time curve from zero to last quantifiable concentration and C_{max} ratios of *O*-desmethyl AZD8931 to AZD8931 were 25.8–53.7 and 4.0–6.6 % after single dosing, and 57.8–69.7 and 33.4–42.5 % after multiple dosing, respectively. In the combination part, there was no apparent PK interaction between paclitaxel and AZD8931 (Tables 4 and 5).

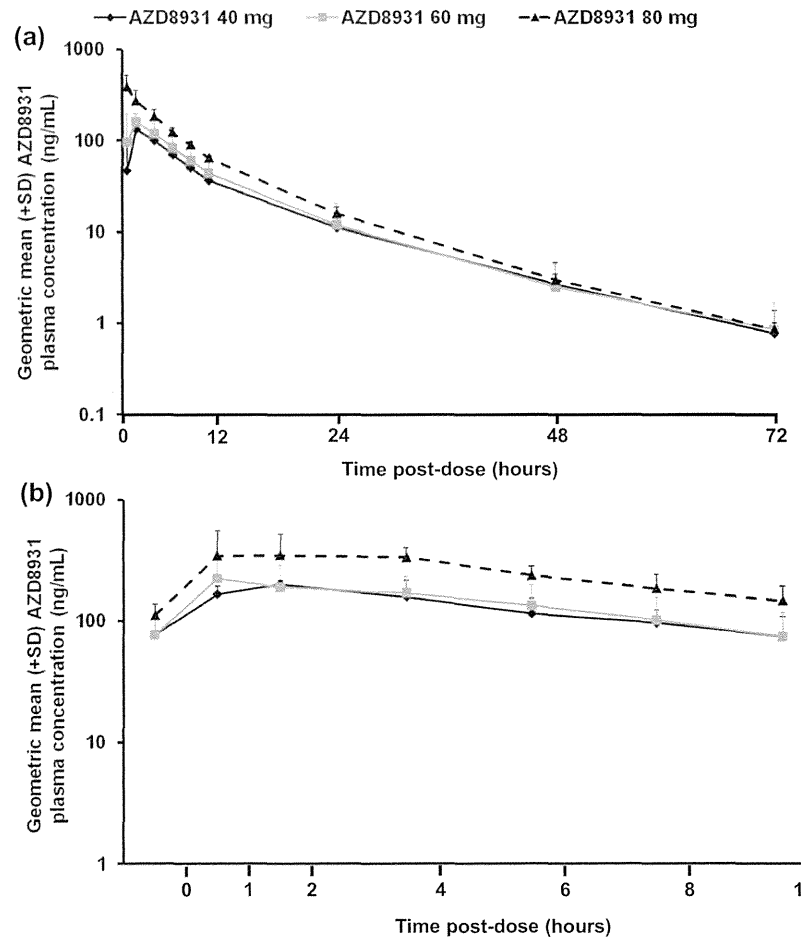

Fig. 1 Geometric mean plasma concentration of AZD8931 following (**a**) single and (**b**) multiple doses in the monotherapy part (PK population)

Table 3 Pharmacokinetic parameters of AZD8931 after single and multiple dosing in the monotherapy part (PK population)

PK parameter	AZD8931 single dosing			AZD8931 multiple dosing		
	40 mg bid (n=3)	60 mg bid (n=4)	80 mg bid (n=4)	40 mg bid (n=3)	60 mg bid (n=4)	80 mg bid (n=4)
AUC, ng.h/mL	1,322 (18)	1,620 (41)	2,519 (16)	–	–	–
$AUC_{0-12,}$[a] ng.h/mL	812 (3)	1,035 (29)	1,780 (21)	1,466 (22)	1,645 (41)	2,953 (18)
AUC_{0-t}, ng.h/mL	1,307 (17.2)	1,599 (40)	2,502 (15.8)	–	–	–
CL/F,[a,b] L/h	30.6 (5.4)	39.2 (15.5)	32.1 (5.2)	27.7 (5.5)	38.5 (14.7)	27.4 (4.7)
$C_{max,}$[a] ng/mL	132 (14)	189 (24)	388 (36)	207 (12)	278 (41)	474 (16)
$t_{½,}$[b] h	12.6 (1.4)	12.8 (1.7)	11.4 (1.0)	–	–	–
$t_{max,}$[a,c] h	2 (2–2)	1.5 (1–2)	1 (1–1)	2 (2–4)	1.5 (1–4)	1 (1–4)
V_{ss}/F,[b] L	375 (34)	428 (109)	303 (72)	–	–	–
Linearity factor[b]	–	–	–	1.1 (0.1)	1.0 (0.1)	1.2 (0.5)
R_{AC}[b]	–	–	–	1.8 (0.4)	1.6 (0.3)	1.7 (0.8)

Values are presented as geometric mean (% coefficient of variation) unless otherwise stated; [a] at steady state for multiple dosing; [b] arithmetic mean (standard deviation); [c] median (range); AUC, area under the plasma concentration–time curve; AUC_{0-12}, area under the plasma concentration–time curve from time zero to 12 h; AUC_{0-t}, area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; CL/F, total apparent drug clearance; C_{max}, maximum plasma concentration; $t_{½}$, terminal elimination half-life; t_{max}, time to reach maximum plasma concentration; V_{ss}/F, apparent volume of distribution at steady state; R_{AC}, accumulation ratio

Table 4 Pharmacokinetic parameters of AZD8931 monotherapy and in combination with paclitaxel (PK population)

PK parameter	AZD8931 (n=6)	AZD8931 + paclitaxel (n=6)
AUC_{0-10}, ng.h/mL	1,047 (47)	1,220 (58)
C_{max}, ng/mL	202 (30)	211 (60)
t_{max},[a] h	1 (1–2)	2 (1–4)

Values are presented as geometric mean (% coefficient of variation) unless otherwise stated; [a] median (range)

Efficacy assessment

One patient receiving AZD8931 80 mg bid monotherapy had an unconfirmed partial response (PR); this 63-year-old male patient with metastatic gastric carcinoma had no prior surgery for gastric cancer and had received two previous chemotherapy regimens (plus prior radiotherapy for brain metastases). This patient had a HER2-negative tumor (IHC 1+); the retrospective use of this information, which was not part of the study protocol, was approved by the Institutional Review Board of Kinki University. At day 50, the patient had a 30.3 % reduction in target lesion size; by day 92, the target lesion size had increased by 52.2 % compared with the prior lowest size, and the overall response was therefore classified as progressive disease. A 49-year-old female patient with HER2-negative (IHC 0; information obtained as above) advanced breast cancer receiving AZD8931 plus paclitaxel had a confirmed PR with duration of response of 172 days. This patient had prior surgery for breast cancer and had received adjuvant radiotherapy followed by one chemotherapy (endoxan and farmorubicin) and two hormone therapy regimens. The patient had target lesions of skin/soft tissue and liver. A 48.7 % reduction in target lesion size was recorded at day 55, which reached a maximum reduction of 79.5 % at day 114; the patient was recorded as having progressive disease at day 255 with a 20 % increase in target lesion size.

Table 5 Pharmacokinetic parameters of paclitaxel monotherapy and in combination with AZD8931 (PK population)

PK parameters	Paclitaxel (n=6)	Paclitaxel + AZD8931 (n=6)
AUC_{0-10}, ng.h/mL	7,022 (26)	7,116 (25)
C_{max}, ng/mL	6,367 (33)	5,758 (44)
t_{max},[a] h	1 (1–1)	1 (1–1)

Values are presented as geometric mean (% coefficient of variation) unless otherwise stated; [a] median (range)

Seven patients had stable disease (≥6 weeks): one, two and four patients in the 40 mg bid (maxillary sinus cancer), 60 mg bid (colorectal cancer; stomach cancer) and combination therapy (all breast cancer) cohorts, respectively.

Discussion

This two-part, single-center, Phase I, open-label study demonstrated that AZD8931, both alone and in combination with paclitaxel, was generally well tolerated in Japanese patients with advanced solid tumors and advanced breast cancer, respectively. The MTD of AZD8931 could not be confirmed in this study, in either the monotherapy or the combination part, since no DLTs were observed up to the highest studied dose (80 mg bid). However, based on the overall incidence of rash and diarrhea AEs in the AZD8931 80 mg bid group, AZD8931 doses up to 60 mg bid in monotherapy and 40 mg bid in combination with paclitaxel were considered to be the highest tolerable doses. In a recently published Phase I study of Caucasian patients, AZD8931 monotherapy was generally well tolerated at doses up to and including 240 mg bid over a 21-day period in patients with advanced solid tumors [23]. Due to two DLTs in the 300 mg bid cohort, AZD8931 240 mg bid was declared the MTD. However, this was a small dose-escalation study of relatively short duration and the authors concluded that more long-term data are needed to confirm a dose suitable for chronic treatment. A lower MTD of 40 mg bid, which is comparable to that defined in Japanese patients, was determined for AZD8931 in combination with paclitaxel in a recent Phase I dose-finding study in Caucasian patients with refractory tumors who were exposed to AZD8931 for a longer duration (median 52 days) [25].

The safety profile of AZD8931 observed in this study of Japanese patients is consistent with that previously reported in the Caucasian population [25–28]. In both parts of the study, skin/subcutaneous and gastrointestinal disorders were amongst the most common AEs; this is consistent with the mechanisms and known safety profiles of agents that target HER signaling [26–28] and therefore suggests that relevant target inhibition is being achieved at the AZD8931 doses investigated in this study. Most observed AEs were mild or moderate in nature (CTCAE grade ≤2) and only one AE classified as CTCAE grade ≥3, which was observed in the combination therapy cohort, was considered to be related to AZD8931 treatment. Only two patients experienced severe AEs during the study, neither of which were considered to be related to AZD8931 treatment. There were some differences in the most commonly reported AEs between the monotherapy and combination therapy cohorts, although these differences

generally included a greater proportion of AEs known to be associated with paclitaxel treatment, such as neutropenia, leucopenia and alopecia [29]. It is interesting to note that around 50 % of Caucasian patients enrolled in the Phase I study experienced ophthalmic AEs that were considered to be related to treatment with AZD8931 [23]. In contrast, only two ophthalmic AEs related to AZD8931 treatment were reported in the present study. Furthermore, the rate of grade ≥3 AEs (41 % [*n*=7/17] versus 64 % [*n*=18/28]) and the discontinuation rate due to AEs (6 % [*n*=1/17] versus 21 % [*n*=6/28]) was lower in Japanese patients compared with the Caucasian study. These differences may reflect the relatively low dose ranges evaluated in the present study and suggest that a more conservative AZD8931 dosing regimen may lead to a better risk:benefit profile.

The steady-state PK profile of AZD8931 was supportive of bid oral dosing. Absorption was rapid after single and bid doses of AZD8931, with a median t_{max} of between 1 and 2 h across the dose levels. Pre-dose plasma concentrations of AZD8931 achieved steady state by day R3 following bid dosing, and exposure increased in an approximately dose-proportional manner. This PK profile is consistent with that reported in the Caucasian population [23]. Importantly, co-administration with paclitaxel had no apparent effect on the PK of AZD8931, suggesting that the combination of these agents is feasible from a PK perspective.

AZD8931 is an equipotent inhibitor of EGFR, HER2 and HER3 signaling; amplification of HER2 is observed in ~20 % of patients with gastric cancer and ~25 % of patients with breast cancer [30, 31]. Unconfirmed and confirmed PRs were reported following AZD8931 80 mg bid monotherapy (in a patient with gastric cancer) and combination therapy (in a patient with breast cancer). Of interest, neither of these patients had HER2-amplified tumors. The PR in the monotherapy part suggests preliminary efficacy of AZD8931 treatment in gastric cancer, likely based on the inhibition of HER-family signaling by AZD8931. The PR in the patient with breast cancer in the combination part may have been attributable to the presence of paclitaxel. These PRs were reported on days 50 and 55, respectively, suggesting that the efficacy of AZD8931 is best observed over longer-term treatment. This is in line with the conclusions of the Phase I study in Caucasian patients, which suggested that the lack of objective tumor responses at day R21 may have been due to the short evaluation time frame and that a longer study period is necessary to observe responses beyond stable disease. However, further investigation is needed to establish the efficacy of AZD8931.

In conclusion, although no DLTs were observed, the safety profile of patients who received AZD8931 ≥60 mg bid suggests that AZD8931 doses up to 60 mg bid as monotherapy, and 40 mg bid combined with paclitaxel, are the feasible doses for evaluation in Japanese patients. AZD8931, is no longer in AstraZeneca-sponsored development following data from two Phase IIb trials in breast cancer that showed no evidence of a therapeutic benefit in patients receiving AZD8931 [32, 33]. Investigator-sponsored studies are continuing in other indications.

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Ethical standards All patients provided written informed consent. The study was approved by the Institutional Review Board of Kinki University, Osakasayama, Japan, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on bioethics [22]. The experiments comply with the current laws of the country in which they were performed.

Conflict of interest Takayasu Kurata has received lecturer's fees from AstraZeneca. Yasuhito Fujisaka has received research fees for clinical studies from AstraZeneca. Kazuhiko Nakagawa has received lecturer's fees and research fees for clinical studies from AstraZeneca. Eisei Shin and Nobuya Hayashi are employees of AstraZeneca. Junji Tsurutani, Wataru Okamoto, Hidetoshi Hayashi and Hisato Kawakami have no conflicts of interest to disclose.

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Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring *EGFR* mutations (JO25567): an open-label, randomised, multicentre, phase 2 study

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Summary

Background With use of EGFR tyrosine-kinase inhibitor monotherapy for patients with activating *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), median progression-free survival has been extended to about 12 months. Nevertheless, new strategies are needed to further extend progression-free survival and overall survival with acceptable toxicity and tolerability for this population. We aimed to compare the efficacy and safety of the combination of erlotinib and bevacizumab compared with erlotinib alone in patients with non-squamous NSCLC with activating *EGFR* mutation-positive disease.

Methods In this open-label, randomised, multicentre, phase 2 study, patients from 30 centres across Japan with stage IIIB/IV or recurrent non-squamous NSCLC with activating *EGFR* mutations, Eastern Cooperative Oncology Group performance status 0 or 1, and no previous chemotherapy for advanced disease received erlotinib 150 mg/day plus bevacizumab 15 mg/kg every 3 weeks or erlotinib 150 mg/day monotherapy as a first-line therapy until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival, as determined by an independent review committee. Randomisation was done with a dynamic allocation method, and the analysis used a modified intention-to-treat approach, including all patients who received at least one dose of study treatment and had tumour assessment at least once after randomisation. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-111390.

Findings Between Feb 21, 2011, and March 5, 2012, 154 patients were enrolled. 77 were randomly assigned to receive erlotinib and bevacizumab and 77 to erlotinib alone, of whom 75 patients in the erlotinib plus bevacizumab group and 77 in the erlotinib alone group were included in the efficacy analyses. Median progression-free survival was 16·0 months (95% CI 13·9–18·1) with erlotinib plus bevacizumab and 9·7 months (5·7–11·1) with erlotinib alone (hazard ratio 0·54, 95% CI 0·36–0·79; log-rank test p=0·0015). The most common grade 3 or worse adverse events were rash (19 [25%] patients in the erlotinib plus bevacizumab group *vs* 15 [19%] patients in the erlotinib alone group), hypertension (45 [60%] *vs* eight [10%]), and proteinuria (six [8%] *vs* none). Serious adverse events occurred at a similar frequency in both groups (18 [24%] patients in the erlotinib plus bevacizumab group and 19 [25%] patients in the erlotinib alone group).

Interpretation Erlotinib plus bevacizumab combination could be a new first-line regimen in *EGFR* mutation-positive NSCLC. Further investigation of the regimen is warranted.

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Introduction

Lung cancer is a leading cause of death worldwide; it is the primary cause of cancer deaths in men and the secondary cause in women.[1] Most patients with lung cancer have non-small-cell lung cancer (NSCLC) and a clinically significant proportion of patients have activating mutations of *EGFR*.[2] In this subgroup of patients, EGFR tyrosine-kinase inhibitors have consistently led to better outcomes than has standard chemotherapy.[3–6] Erlotinib and gefitinib have been shown to prolong progression-free survival compared with chemotherapy in several phase 3 trials.[7–10] Unfortunately, most patients with NSCLC with activating *EGFR* mutations who are given EGFR tyrosine-kinase inhibitors eventually develop resistance and relapse within about 1 year of initiation of treatment.[5,7–11] To improve outcomes, the foundation treatment of EGFR tyrosine-kinase inhibitors should be built on through investigation of biologically synergistic combinations.

The anti-angiogenic monoclonal antibody bevacizumab targets the VEGF signalling pathway and has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC.[12–14] The combination of erlotinib and bevacizumab has the potential to prolong progression-free survival in unselected populations of patients with NSCLC.[15,16] In a subgroup analysis of *EGFR*

mutation-positive participants in the phase 3 BeTa study of second-line treatment of NSCLC (12 patients treated with erlotinib and bevacizumab and 18 with erlotinib alone), median progression-free survival with erlotinib plus bevacizumab in patients with *EGFR* mutation-positive disease was substantially higher than with erlotinib alone (17·1 months *vs* 9·7 months).[16,17] However, this analysis was post-hoc and *EGFR* mutation status was not a prespecified stratification factor in this trial. Because of this limitation, we undertook this phase 2 trial to examine the combination of erlotinib and bevacizumab in patients with *EGFR* mutation-positive NSCLC.

Methods

Study design and patients

JO25567 was a randomised, open-label, multicentre, phase 2 study in patients with stage IIIB/IV (according to the 7th edition of the General Rule for Clinical and Pathological Record of Lung Cancer[18]) or recurrent NSCLC with activating *EGFR* mutations. Patients were enrolled from 30 centres across Japan.

Eligible patients had histologically or cytologically (excluding sputum cytology) confirmed stage IIIB/IV or postoperative recurrent non-squamous NSCLC with activating *EGFR* mutation (either exon 19 deletion or Leu858Arg mutation). Tumour samples were screened for *EGFR* mutation by PCR-based hypersensitive *EGFR* mutation testing in local laboratories, according to standard testing practices. Other criteria included age 20 years or older when giving informed consent; Eastern Cooperative Oncology Group performance status 0 or 1; adequate haematological, hepatic, and renal function; and life expectancy 3 months or more at the time of registration. No previous chemotherapy for advanced disease was allowed, but postoperative adjuvant or neoadjuvant therapy of 6 months or more previously was allowed. Previous radiotherapy was also allowed, but only for non-lung lesions. Patients had to have one or more measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Major exclusion criteria included confirmation of Thr790Met mutation, presence of brain metastases, history or presence of haemoptysis or bloody sputum, any coagulation disorder, tumour invading or abutting major blood vessels, coexistence or history of interstitial lung disease, and previous receipt of EGFR inhibitors or VEGF receptor inhibitors.

This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review boards of the participating institutions (appendix p 10), and written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either erlotinib plus bevacizumab or erlotinib alone with a dynamic allocation method. Central randomisation was done by a clinical research organisation (EPS Corporation, Tokyo, Japan). Patients were stratified according to sex (men *vs* women), disease stage (stage IIIB *vs* stage IV *vs* postoperative relapse), smoking history (never smokers or former light smokers *vs* others), and type of *EGFR* mutation (exon 19 deletion *vs* Leu858Arg mutation). All patients and investigators were unmasked to treatment allocation.

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Procedures

Patients assigned to the erlotinib plus bevacizumab group received bevacizumab 15 mg/kg by intravenous infusion on day 1 of a 21-day cycle and erlotinib orally once daily at 150 mg/day, starting from day 1 of cycle 1. Patients in the erlotinib alone group received erlotinib orally once a day at 150 mg/day. Patients remained on treatment until disease progression or unacceptable toxicity. Changes to dose of erlotinib or bevacizumab because of adverse events were allowed, as per the protocol. The dose of bevacizumab was not to be reduced except when dose adjustment was needed because of change in bodyweight. Dose reduction of erlotinib was allowed for up to two doses (100 mg/day and 50 mg/day) in a stepwise decrease. After two steps of dose reduction, erlotinib was discontinued. Patients who required suspension of erlotinib for more than 3 weeks consecutively, or of bevacizumab for more than 6 weeks from the date of previous administration, were discontinued from study treatment. In the erlotinib plus bevacizumab group, if either drug was discontinued, the other could be

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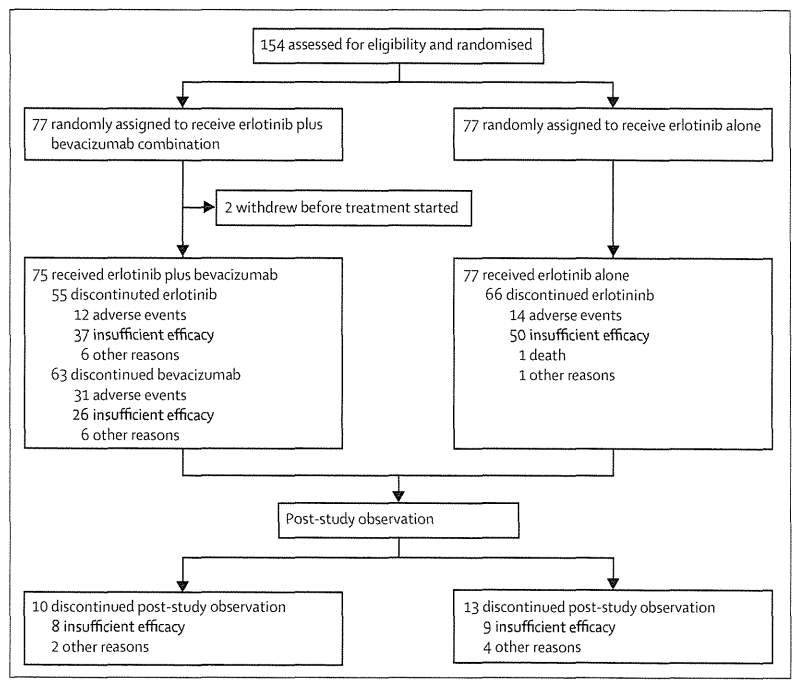

Figure 1: **Trial profile**

continued. Tumour lesions were assessed radiologically at baseline, week 4, week 7, every 6 weeks from week 7 to 18 months, and every 12 weeks thereafter until disease progression according to RECIST 1.1.

	Erlotinib plus bevacizumab group (n=75)	Erlotinib alone group (n=77)
Age (years)		
Median	67·0 (59-73)	67·0 (60-73)
<75	63 (84%)	62 (81%)
≥75	12 (16%)	15 (19%)
Sex		
Male	30 (40%)	26 (34%)
Female	45 (60%)	51 (66%)
Smoking status		
Never smoker	42 (56%)	45 (58%)
Former light smoker	9 (12%)	6 (8%)
Other	24 (32%)	26 (34%)
ECOG performance status		
0	43 (57%)	41 (53%)
1	32 (43%)	36 (47%)
Histopathological classification		
Adenocarcinoma	74 (99%)	76 (99%)
Large-cell carcinoma	0	1 (1%)
Adenosquamous carcinoma	1 (1%)	0
Clinical stage at screening		
IIIB	1 (1%)	0
IV	60 (80%)	62 (81%)
Postoperative recurrence	14 (19%)	15 (19%)
***EGFR* mutation type**		
Exon 19 deletion	40 (53%)	40 (52%)
Exon 21 Leu858Arg mutation	35 (47%)	37 (48%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline demographics and clinical characteristics**

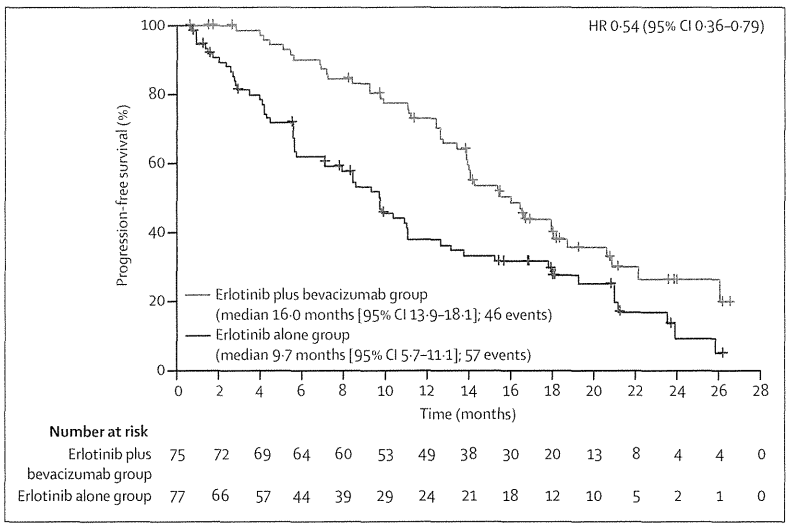

Figure 2: **Progression-free survival, as determined by independent review committee, in the modified intention-to-treat population**
HR=hazard ratio.

Patient-reported outcomes were assessed with the Functional Assessment of Cancer Therapy for patients with Lung cancer (FACT-L) scale until disease progression. An independent review committee of clinicians and radiologists masked to treatment assignment reviewed all tumour images and determined tumour response and progression status. Laboratory studies including blood and urine tests were done at days 1, 8, and 15 in cycles 1 and 2, and day 1 in cycle 3 and thereafter. Adverse events were monitored throughout the study period and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 4.03.

Outcomes

The primary endpoint was progression-free survival, as determined by an independent review committee. Secondary endpoints were overall survival, tumour response (the proportion of patients with an objective response and disease control, and duration of response) according to RECIST 1.1, quality of life, symptom improvement measured by the FACT-L scale, and safety profile.

Statistical analysis

A median progression-free survival of 13 months was estimated for the erlotinib alone group, and 89 events were deemed necessary to detect a hazard ratio (HR) of 0·7 in favour of erlotinib plus bevacizumab, with a one-sided significance level of 0·2 and a power of 0·8. The target sample size was set at 150 patients (75 patients in both groups), allowing for dropouts. Median progression-free survival was estimated by the Kaplan-Meier method and compared between groups with an unstratified log-rank test. Greenwood's formula was used to calculate 95% CIs. HRs were calculated by unstratified Cox proportional hazard methodology.

In the safety analysis, adverse events were converted to Medical Dictionary for Regulatory Activities (version 14.0) preferred terms, and tabulated by grade. Changes in laboratory test data with time were summarised in tables and graphs.

All patients who received at least one dose of the study treatment were included in the safety analysis population. The modified intention-to-treat population for the efficacy analysis included all patients who received at least one dose of study treatment and had tumour assessment at least once after randomisation. Statistical analyses were done with SAS version 9.2.

The study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-111390.

Role of the funding source

The study was designed and funded by Chugai Pharmaceutical Co Ltd and monitored by a clinical research organisation (Niphix Corp, Tokyo, Japan) who obtained all data and did all initial data analyses; further analysis and interpretation was done by the funder, with

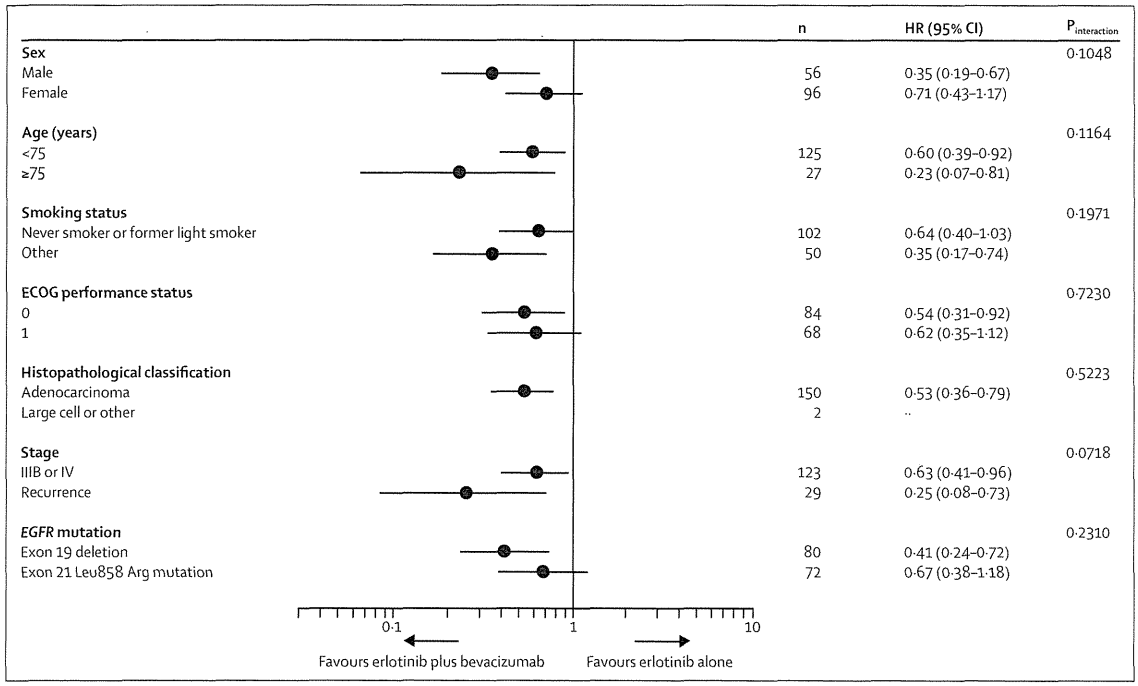

Figure 3: **Forest plot of hazard ratios for progression-free survival by baseline characteristics**
HR=hazard ratio.

	Erlotinib plus bevacizumab group (n=75)	Erlotinib alone group (n=77)
Complete response	3 (4%)	1 (1%)
Partial response	49 (65%)	48 (62%)
Stable disease	22 (29%)	19 (25%)
Progressive disease	0	6 (8%)
Non-evaluable	1 (1%)	3 (4%)

RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: **Best RECIST response, as determined by independent review committee**

input from the authors and investigators. The initial draft of the report was reviewed and commented on by all authors and by employees of Chugai Pharmaceutical Co Ltd. NobuY had full access to all data, and had final responsibility for the decision to submit the results for publication.

Results

Between Feb 21, 2011, and March 5, 2012, 154 patients were enrolled, of whom 77 were randomly assigned to receive erlotinib plus bevacizumab and 77 to erlotinib alone. Two patients withdrew before treatment started and were excluded (one had multiple thrombosis and the other had increased pleural effusion). Thus, data from 152 patients (75 patients in the erlotinib plus bevacizumab group and 77 in the erlotinib alone group) were included in the analysis population (figure 1). The cutoff date for the primary analysis was June 30, 2013, when 103 progression events had occurred; median follow-up was 20·4 months (IQR 17·4–24·1).

The baseline characteristics of patients were well balanced between the groups (table 1). Median age was 67 years (IQR 60–73), and 27 (18%) patients were aged 75 years or older. *EGFR* mutation subtypes were balanced between the two groups.

Progression-free survival was significantly prolonged with erlotinib plus bevacizumab compared with erlotinib alone (log-rank test p=0·0015; figure 2). When subgroup analyses were done by baseline clinical characteristics, most patient subgroups seemed to have greater benefit from erlotinib plus bevacizumab compared with erlotinib alone. No significant difference was noted between any of the subgroups ($p_{interaction}$>0·05 for all subgroups; figure 3).

Analysis of progression-free survival by mutation subtype showed that in patients whose tumours had an exon 19 deletion (40 [53%] of 75 patients in the erlotinib plus bevacizumab group and 40 [52%] of 77 patients in the erlotinib alone group), median progression-free survival was significantly longer with erlotinib plus bevacizumab than with erlotinib alone (18·0 months [95% CI 14·1–20·6] *vs* 10·3 months [95% CI 8·0–13·1]; HR 0·41 [95% CI 0·24–0·72]; p=0·0011; appendix p 1). In patients whose tumours harboured the Leu858Arg mutation (35 [47%] patients in the erlotinib plus bevacizumab group; 37 [48%] patients in the erlotinib alone group), median progression-free survival was numerically longer with erlotinib plus bevacizumab than with erlotinib alone, but

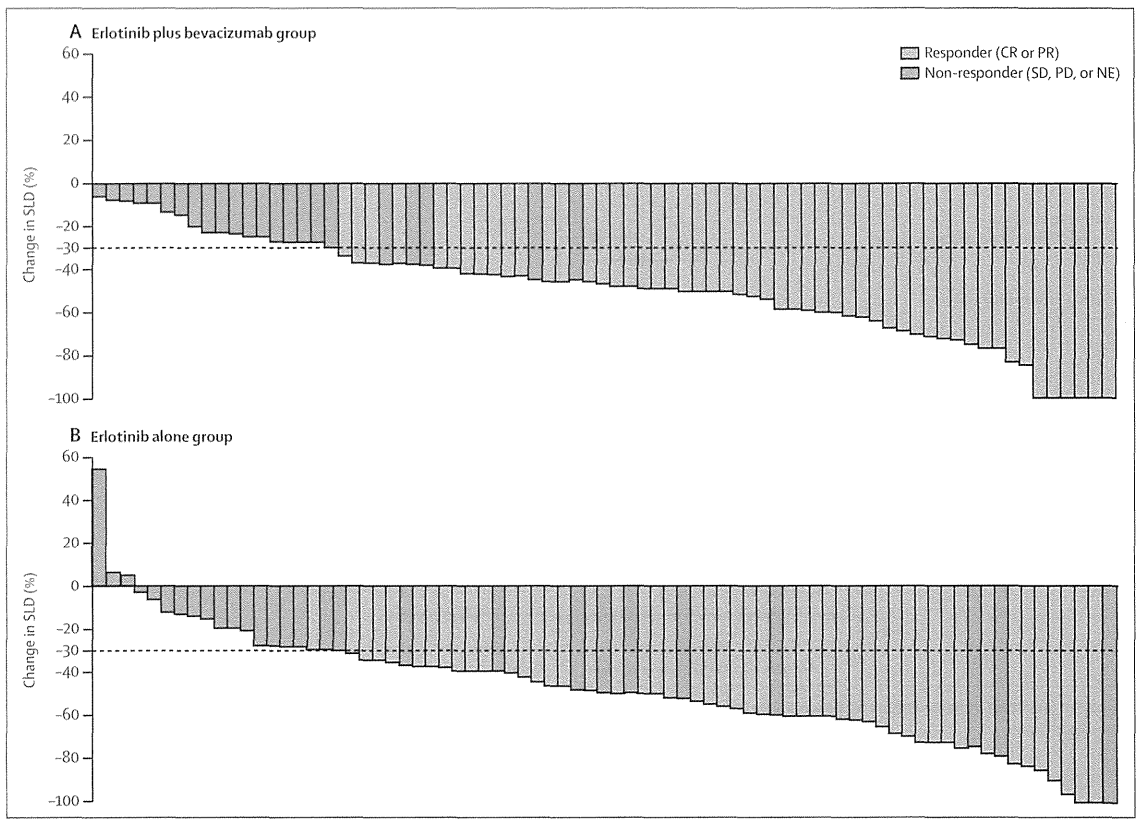

Figure 4: **Waterfall plot of best percentage change from baseline in the sum of longest tumour diameters**
Responders were confirmed by Response Evaluation Criteria in Solid Tumors. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. NE=non-evaluable. SLD=sum of longest diameters.

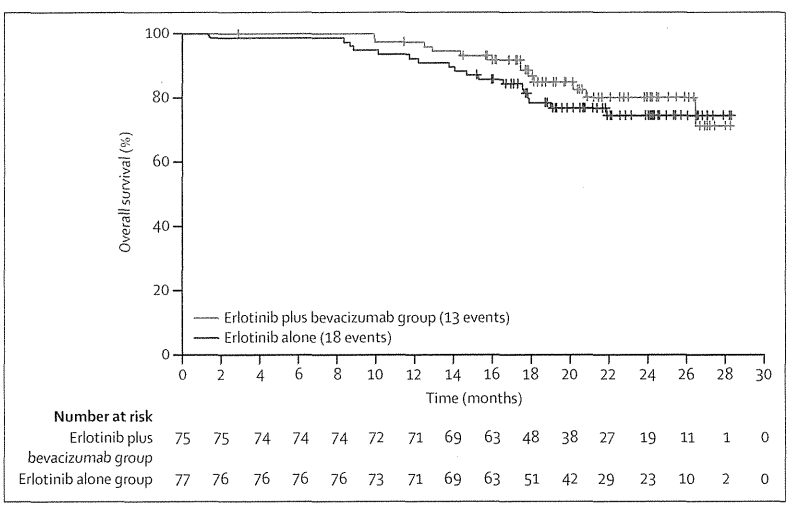

Figure 5: **Overall survival, as determined by independent review committee, in the modified intention-to-treat population**

the difference was not significant (13·9 months [95% CI 11·2–20·9] *vs* 7·1 months [95% CI 4·3–15·2], respectively; HR 0·67 [95% CI 0·38–1·18]; p=0·1653; appendix p 2).

52 (69% [95% CI 58–80]) patients in the erlotinib plus bevacizumab group had an objective response, as did 49 (64% [52–74]) patients in the erlotinib alone group (p=0·4951), although median duration of response was not significantly longer with erlotinib plus bevacizumab than with erlotinib alone (13·3 months [95% CI 11·6–16·5] *vs* 9·3 months [6·9–13·8]; p=0·1118). A greater proportion of patients achieved disease control with erlotinib plus bevacizumab (74 [99%] *vs* 68 [88%]; p=0·0177). Best responses to treatment are shown in table 2.

Figure 4 shows change in tumour size from baseline in the two groups. All patients in the erlotinib plus bevacizumab achieved tumour reduction, but three patients in the erlotinib alone group did not. Of patients who had a 30% or greater reduction in tumour size during treatment, six (8%) patients in the erlotinib plus bevacizumab group and 12 (16%) patients in the erlotinib alone group did not meet the criteria for complete or partial response according to RECIST.

Overall survival data are immature at present and so we cannot present any statistical analyses. At data cutoff, only 13 events (17%) had occurred in the erlotinib plus bevacizumab group and 18 events (23%) in the erlotinib alone group (figure 5).

	Erlotinib plus bevacizumab group (n=75)					Erlotinib alone group (n=77)				
	All	Grade 1–2	Grade 3	Grade 4	Grade 5	All	Grade 1–2	Grade 3	Grade 4	Grade 5
Rash	74 (99%)	55 (73%)	19 (25%)	0	0	76 (99%)	61 (79%)	15 (19%)	0	0
Diarrhoea	61 (81%)	60 (80%)	1 (1%)	0	0	60 (78%)	59 (77%)	1 (1%)	0	0
Paronychia	57 (76%)	55 (73%)	2 (3%)	0	0	50 (65%)	47 (61%)	3 (4%)	0	0
Dry skin	56 (75%)	54 (72%)	2 (3%)	0	0	45 (58%)	45 (58%)	0	0	0
Stomatitis	47 (63%)	46 (61%)	1 (1%)	0	0	46 (60%)	44 (57%)	2 (3%)	0	0
Haemorrhagic event	54 (72%)	52 (69%)	2 (3%)	0	0	22 (29%)	22 (29%)	0	0	0
Liver function disorder or abnormal hepatic function	33 (44%)	27 (36%)	5 (7%)	1 (1%)	0	39 (51%)	25 (32%)	7 (9%)	7 (9%)	0
Hypertension	57 (76%)	12 (16%)	45 (60%)	0	0	10 (13%)	2 (3%)	8 (10%)	0	0
Pruritus	34 (45%)	33 (44%)	1 (1%)	0	0	32 (42%)	32 (42%)	0	0	0
Weight decreased	33 (44%)	33 (44%)	0	0	0	19 (25%)	19 (25%)	0	0	0
Decreased appetite	26 (35%)	25 (33%)	1 (1%)	0	0	26 (34%)	25 (32%)	1 (1%)	0	0
Proteinuria	39 (52%)	33 (44%)	6 (8%)	0	0	3 (4%)	3 (4%)	0	0	0
Dysgeusia	20 (27%)	20 (27%)	0	0	0	17 (22%)	17 (22%)	0	0	0
Nasopharyngitis	20 (27%)	20 (27%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Constipation	17 (23%)	17 (23%)	0	0	0	15 (19%)	14 (18%)	1 (1%)	0	0
Alopecia	13 (17%)	13 (17%)	0	0	0	14 (18%)	14 (18%)	0	0	0
Nausea	12 (16%)	12 (16%)	0	0	0	15 (19%)	15 (19%)	0	0	0
Vomiting	14 (19%)	14 (19%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Malaise	10 (13%)	10 (13%)	0	0	0	10 (13%)	10 (13%)	0	0	0
Insomnia	8 (11%)	8 (11%)	0	0	0	8 (10%)	8 (10%)	0	0	0
Pyrexia	7 (9%)	7 (9%)	0	0	0	9 (12%)	9 (12%)	0	0	0
Upper respiratory tract infection	9 (12%)	9 (12%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Conjunctivitis	8 (11%)	8 (11%)	0	0	0	7 (9%)	7 (9%)	0	0	0
Peripheral oedema	8 (11%)	8 (11%)	0	0	0	6 (8%)	6 (8%)	0	0	0
Fatigue	10 (13%)	9 (12%)	1 (1%)	0	0	3 (4%)	3 (4%)	0	0	0
Nail disorder	9 (12%)	9 (12%)	0	0	0	4 (5%)	4 (5%)	0	0	0
Dry eye	8 (11%)	8 (11%)	0	0	0	3 (4%)	3 (4%)	0	0	0
Dysphonia	8 (11%)	8 (11%)	0	0	0	1 (1%)	1 (1%)	0	0	0

Data are n (%).

Table 3: **Adverse events reported by 10% or more patients for grades 1 and 2 and all adverse events for grades 3–5 (safety population)**

68 (91%) patients in the erlotinib plus bevacizumab group and 41 (53%) patients in the erlotinib group had grade 3 or 4 adverse events. The most common adverse events of any grade in the erlotinib plus bevacizumab group were rash, diarrhoea, hypertension, and paronychia, and in the erlotininb alone group were rash, diarrhoea, and paronychia (table 3). The most common grade 3 or worse adverse events in the erlotinib plus bevacizumab group were hypertension, rash, proteinuria, and liver function disorder or abnormal hepatic function, and in the erlotinib group were rash, liver function disorder or abnormal hepatic function, and hypertension (table 3). Substantially higher (>40%) incidences of hypertension, haemorrhagic events, and proteinuria were noted in the erlotinib plus bevacizumab group compared with the erlotinib alone group (table 3). Serious adverse events were reported by 18 (24%) patients in the erlotinib plus bevacizumab group and 19 (25%) patients in the erlotinib group.

12 (16%) patients in the erlotinib plus bevacizumab group and 14 (18%) patients in the erlotinib group discontinued erlotinib because of adverse events. 31 (41%) patients discontinued bevacizumab because of adverse events (figure 1). Ten patients discontinued both erlotinib and bevacizumab because of adverse events in the erlotinib plus bevacizumab group. Of these patients, seven discontinued erlotinib and bevacizumab simultaneously because of adverse events (liver function disorder or abnormal hepatic function in two patients, and infection, pancreatic cancer, rash, interstitial lung disease, and cerebral infarction in one patient each). In the remaining three patients, bevacizumab was initially discontinued, and patients continued on erlotinib monotherapy, although this was also subsequently discontinued. The dose of erlotinib was reduced to 100 mg for 34 (45%) of 75 patients in the erlotinib plus bevacizumab group and 33 (43%) of 77 patients in the erlotinib alone group; and to 50 mg for 17 (23%) of patients in the erlotinib plus bevacizumab group and eight (10%) patients in the erlotinib alone group.

The major adverse events leading to discontinuation of erlotinib in both groups were liver function disorder or abnormal hepatic function (two [3%] patients in the erlotinib plus bevacizumab group, eight [10%] in the

Panel: Research in context

Systematic review

We searched PubMed for articles published in English until Feb 1, 2014 (with no restrictions for the starting date), using the search terms "bevacizumab", "erlotinib", "NSCLC", and "EGFR". We identified two studies that had assessed the efficacy of erlotinib plus bevacizumab in the first-line setting.[19,20] However, no previous study had assessed the efficacy of the combination of erlotinib and bevacizumab as first-line therapy for patients with activating *EGFR* mutation-positive NSCLC.

Interpretation

To our knowledge, this study is the first to show that the combination of erlotinib and bevacizumab can significantly prolong progression-free survival compared with erlotinib alone in patients with non-squamous *EGFR* mutation-positive NSCLC. Some degree of increased toxicity, particularly hypertension, proteinuria, and haemorrhagic events, was noted with the addition of bevacizumab. Our findings suggest that the combination of erlotinib and bevacizumab could be a new first-line regimen in *EGFR* mutation-positive NSCLC. Two clinical trials, BELIEF (NCT01562028) and ACCRU RC1126 (NCT01532089) are ongoing and the results are awaited to confirm the efficacy and safety shown in our study.

erlotinib alone group), interstitial lung disease (two [3%], three [4%]), and rash (two [3%], none). Major adverse events leading to discontinuation of bevacizumab were proteinuria (11 [15%] patients), haemorrhagic events (nine [12%]), and hypertension (two [3%]). Most haemorrhagic events were low-grade epistaxis or haemorrhoidal bleeding. All of the 11 patients who discontinued bevacizumab because of proteinuria had grade 3 or lower events, and five of these patients recovered during the study period. All of the nine patients who discontinued because of haemorrhagic events had grade 3 or lower events; eight patients improved or recovered during the study period.

The median duration of erlotinib treatment was 431 days (range 21–837) in the erlotinib plus bevacizumab group and 254 days (18–829) in the erlotinib group, whereas median duration of bevacizumab was 325 days (1–815). The median duration of bevacizumab in patients who discontinued treatment because of proteinuria was 329 days (113–639) and because of haemorrhagic events was 128 days (23–357).

The relative dose intensity of erlotinib (calculated as [totally administered dose / total treatment duration] / 150 × 100) was similar in both groups (95·3% [range 34·7–100·0] in the erlotinib plus bevacizumab group and 98·7% [33·3–100·0] in the erlotinib alone group), whereas that of bevacizumab (calculated as totally administered dose/planned dose × 100) was 93·9% (72·4–99·7).

Haemoptysis was reported in six (8%) patients in the erlotinib plus bevacizumab group (five [7%] patients had grade 1 events and one [1%] had a grade 2 event); one patient (1%) had a grade 1 event in the erlotinib alone group. Interstitial lung disease was reported for five (3%) of all patients. One patient in the erlotinib alone group had grade 3 interstitial lung disease, but all other cases were grade 1 or 2, and all patients recovered. During the study period, one patient in the erlotinib group died by drowning, and a potential association with the study drug was confirmed.

No significant difference was noted between the two groups in terms of quality of life, including total FACT-L score, trial outcome index score, and all other subscores, since the standard deviations at each time point overlapped (appendix pp 3–9).

Discussion

In this study, the addition of bevacizumab to erlotinib significantly prolonged progression-free survival in patients with NSCLC with activating *EGFR* mutation-positive disease compared with erlotinib alone. To our knowledge, this is the first randomised study to show a clinically significant treatment effect of combining an EGFR tyrosine-kinase inhibitor with another biological drug in patients with activating *EGFR* mutation-positive NSCLC (panel). We noted clear separation of the Kaplan-Meier survival curves from the start of treatment, despite the use of erlotinib in both groups.

Multivariate analysis according to baseline patient characteristics showed a consistent treatment benefit, with longer progression-free survival noted with erlotinib plus bevacizumab across most subgroups of patients. Previous studies have reported that erlotinib tends to be more effective in tumours with *EGFR* exon 19 deletions versus those with Leu858Arg mutations,[7,8,21] which is consistent with our results.

No new safety signals were identified and the incidence of adverse events (any grade) and serious adverse events was similar between the two groups. There were more grade 3 or worse adverse events in the erlotinib plus bevacizumab group. Discontinuation of bevacizumab because of adverse events was more common than that reported in previous studies.[13,14] One possible reason for this discrepancy could be the longer duration of treatment than in previous studies: the median treatment duration of bevacizumab was 325 days (16 cycles), which is substantially longer than that in previous studies. Furthermore, proteinuria was one of the major adverse events that led to discontinuation of bevacizumab, and the time to onset of bevacizumab discontinuation because of proteinuria tended to be in the later treatment phase (median 329 days [range 113–639]). Nevertheless, despite the high incidence of bevacizumab discontinuation because of adverse events, most of these events (mainly proteinuria and haemorrhagic events) were deemed non-serious and reversible.

The incidence of grade 3 or greater hypertension and proteinuria were higher than those in previous studies, again possibly related to the prolonged duration of treatment. Another potential factor that could explain the difference in the incidence of hypertension is in the definition of grading used; we used CTC-AE version 4.03, whereas previous studies[14,16] used CTC-AE version 3. Akhtar and colleagues[22] showed that the change in CTC-AE version from 3 to 4 could lead to a significant

shift in the severity of adverse events in clinical trials. Furthermore, despite the somewhat higher incidence of hypertension observed in this study, only two (3%) of 75 patients discontinued bevacizumab administration because of hypertension.

Although we noted no significant difference in the proportion of patients achieving an objective response between the erlotinib plus bevacizumab group and erlotinib alone groups, all patients in the erlotinib plus bevacizumab group had a reduction in tumour size. Of those patients who had a greater than 30% reduction in the sum of longest diameter of their target lesions from baseline, more patients in the erlotinib alone group failed to meet the criteria for complete or partial response. These findings suggest that the addition of bevacizumab to erlotinib might help to maintain the tumour-suppressing effect after reduction in tumour size, which might explain the difference in progression-free survival between the two groups.

One possible mechanism to explain this effect could be improved drug delivery. Bevacizumab changes tumour vessel physiology, resulting in increased intratumoral uptake of drugs.[23,24] The results of a preclinical study suggested that patients on lower doses of EGFR tyrosine-kinase inhibitors tend to develop treatment resistance earlier than those who receive higher doses.[25,26] Therefore, achieving a higher intratumoral concentration of erlotinib could delay the appearance of resistant cells. Another possible mechanism that could explain these findings is the effective blocking of angiogenesis signalling via the VEGF receptor and EGFR signalling pathways, which is thought to promote tumour growth.[27,28] In addition to synergistic inhibition of tumour growth signalling, VEGF signal inhibition is still effective for tumours harbouring EGFR tyrosine-kinase inhibitor resistance mutations. In preclinical studies, blocking the VEGF receptor signalling pathway overcame resistance for EGFR signalling blockage by Thr790Met EGFR mutation in vivo.[29,30]

Another treatment strategy that has been recently investigated is the combination of an EGFR tyrosine-kinase inhibitor with chemotherapy. Wu and colleagues[31] reported that platinum doublet chemotherapy with intercalated erlotinib increased progression-free survival compared with platinum doublet chemotherapy alone. In a subset analysis of the *EGFR* mutation-positive population in this study, progression-free survival was 16·8 months. In our study, median progression-free survival with erlotinib and bevacizumab was 16·0 months. The first-line use of erlotinib and bevacizumab could allow chemotherapy to be reserved for subsequent lines of treatment, which might further improve survival outcomes in these patients.

Our study has several limitations. First, the analysis of *EGFR* mutations was not done at a central laboratory and various methods were used, including the peptide nucleic acid, locked nucleic acid PCR clamp method, the PCR invader method, and the cycleave method. However, on the basis of previous evidence, these methods are generally judged to provide consistent results.[32] Second, because some patients are still receiving the first-line treatment and overall survival data are still immature, assessment of subsequent treatment effects after progression is not possible. Data relating to post-study treatment will be reported in due course with updated overall survival results. Third, we did not use the EQ-5D questionnaire developed by the EuroQol group for quality-of-life assessment. Therefore, we could not formally estimate quality-adjusted life-years for a cost-effectiveness analysis. The health economics related to the combined use of erlotinib and bevacizumab remains unclear and should be discussed in future studies. Additionally, follow-up for overall survival is still ongoing and these results are needed before the clinical value of this combination can be determined.

In summary, our study provides, to the best of our knowledge, the first evidence that the addition of bevacizumab to erlotinib confers a significant improvement in progression-free survival when used as first-line treatment for patients with non-squamous NSCLC with activating *EGFR* mutation-positive disease. Some degree of increased toxicity, particularly hypertension, proteinuria, and haemorrhagic events, seems to be associated with the addition of bevacizumab. Our findings suggest that the combination of erlotinib and bevacizumab could be a new first-line regimen in *EGFR* mutation-positive NSCLC, and that further investigation of the regimen is warranted. Two clinical trials, BELIEF (NCT01562028) and ACCRU RC1126 (NCT01532089), are ongoing and the results are awaited to confirm the efficacy and safety shown in our study.

Contributors

NobuY was the principal investigator. TS, TK, MN, KG, NoboY, IO, TY, KT, RH, MF, and NobuY contributed to the study design and data analysis and data interpretation. TS, TK, MN, KG, SA, YH, NoboY, TH, MM, KN, SN, IO, and NobuY contributed to patient recruitment and data collection. NobuY, TS, KT, and RH prepared the initial draft of the report input from other authors. All authors approved the final version of the report.

Declaration of interests

TS received research grants and honoraria from Chugai Pharmaceutical. TK received research grants and honoraria from Chugai Pharmaceutical; honoraria from Eli Lilly, Ono Pharmaceutical, Novartis Pharma, Taiho Pharmaceutical, and AstraZeneca; and research grants from Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Pfizer, and Shionogi. MN received research grants and honoraria from Chugai Pharmaceutical, Pfizer, Novartis Pharma, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, and AstraZeneca; research grants from MSD and Bristol-Myers Squibb. KG received research grants and honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical and Nippon Boehringer Ingelheim; honoraria from AstraZeneca, Sanofi, Novartis Pharma, Pfizer, Yakult Honsha, Ono Pharmaceutical and Eli Lilly. SA received honoraria from Chugai Pharmaceutical, Eli Lilly, Taiho Pharmaceutical, Sawai Pharmaceutical, and Novartis Pharma. YH received research grants and honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, and Taiho Pharmaceutical; honoraria from AstraZeneca, Eli Lilly, Novartis Pharma, and Takeda Pharmaceutical; research grants form Yakult Honsha, MSD, Kyowa Hakko Kirin, and Daiichi Sankyo. NoboY received research grants form Chugai Pharmaceutical, Pfizer, Takeda Bio, Astellas Pharma, Taiho Pharmaceutical, and Bristol-Myers Squibb. TH received research grants form Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, Pfizer, Eli Lilly, Takeda Bio, Novartis Pharma, Ono Pharmaceutical, Daiichi Sankyo, Merck Serono, Kyowa Hakko Kirin, Dainippon Sumitomo Pharma, Bristol-Myers Squibb, and Esai.

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Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer

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Interstitial lung disease (ILD) occurrence and risk factors were investigated in the Japanese non-small-cell lung cancer, post-marketing, large-scale surveillance study, POLARSTAR. All patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Primary endpoints were patterns of ILD and risk factors for onset of ILD and ILD-related death. Overall survival, progression-free survival, and occurrence of adverse drug reactions were secondary endpoints. Interstitial lung disease was confirmed in 429 (4.3%) patients. Concurrent/previous ILD (hazard ratio, 3.19), emphysema or chronic obstructive pulmonary disease (hazard ratio, 1.86), lung infection (hazard ratio, 1.55), smoking history (hazard ratio, 2.23), and period from initial cancer diagnosis to the start of treatment (<360 days; hazard ratio, 0.58) were identified as significant risk factors for developing ILD by Cox multivariate analysis. Logistic regression analysis identified Eastern Cooperative Oncology Group performance status 2–4 (odds ratio, 2.45 [95% confidence interval, 1.41–4.27]; $P = 0.0016$), ≤50% remaining normal lung area (odds ratio, 3.12 [1.48–6.58]; $P = 0.0029$), and concomitant honeycombing with interstitial pneumonia (odds ratio, 6.67 [1.35–32.94]; $P = 0.02$) as poor prognostic factors for ILD death. Median overall survival was 277 days; median progression-free survival was 67 days. These data confirm the well-characterized safety profile of erlotinib. Interstitial lung disease is still an adverse drug reaction of interest in this population, and these results, including ILD risk factors, give helpful information for treatment selection and monitoring. Erlotinib efficacy was additionally confirmed in this population. (POLARSTAR trial ML21590.)

Erlotinib is an orally administered EGFR TKI that has demonstrated survival benefits over placebo (median OS 6.7 *vs* 4.7 months, respectively; $P = 0.002$) with acceptable tolerability in previously treated patients with NSCLC.[1] Promising survival data were also reported in two Japanese phase 2 trials of erlotinib in patients with advanced NSCLC (median OS 13.5–14.7 months).[2,3] This led to the approval of erlotinib in Japan for the treatment of patients with recurrent/advanced NSCLC after failure on at least one prior chemotherapy regimen.

Interstitial lung disease has been reported as an AE of special interest in erlotinib-treated Japanese patients with NSCLC in 4.9% (6/123) of patients with a mortality rate of 2.4% (3/123 patients).[2–4] Similar incidences of ILD have been reported in Japanese patients with NSCLC treated with the EGFR TKI gefitinib, suggesting this may be a class-related AE.[5,6]

Risk factors for developing ILD have been previously reported primarily in gefitinib-treated patients. Kudoh *et al.*[6] reported old age, smoking history, pre-existing ILD, poor ECOG PS, short duration since NSCLC diagnosis, and ≤50% normal lung area as ILD risk factors, with all of the factors, except ECOG PS and short duration since NSCLC diagnosis, also being associated with poor ILD prognosis (fatal ILD).

Hotta *et al.*[7] reported existing pulmonary fibrosis, poor ECOG PS, and prior irradiation as risk factors for ILD. Pre-existing pulmonary fibrosis and poor ECOG PS have also been shown to be associated risk factors for ILD in patients treated with either gefitinib or erlotinib.[8]

POLARSTAR was a large-scale surveillance study including all Japanese patients with NSCLC treated with erlotinib,[9] undertaken as a post-approval commitment in Japan to monitor safety and efficacy. The objectives were to obtain decisive information on the incidence of ILD, risk factors for developing ILD, and the efficacy of erlotinib. Here, we report the final analysis of the POLARSTAR surveillance study investigating the safety and efficacy of erlotinib treatment in Japanese patients with NSCLC.

Methods

Study design. All patients with unresectable, recurrent /advanced NSCLC who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Eligible patients receiving erlotinib (150 mg orally, once daily), from the 1027 institutions that could prescribe erlotinib, were monitored until erlotinib therapy termination or completion of 12 months of treatment. The study was approved by the relevant ethics committees and patients gave informed consent to participate in the analysis.

Assessments. Demographic and baseline data were collected for each patient, including age, gender, body mass index, tumor histology, ECOG PS, smoking history, and medical history (including hepatic dysfunction, renal dysfunction, cardiovascular disease, and lung disorders). Safety data were collected at 1, 6, and 12 months after the start of erlotinib therapy. All AE reports were collected and graded using the National Cancer Institute Common Terminology Criteria for AEs version 3.0 and coded using the Medical Dictionary for Regulatory Activities version 14.1 thesaurus terms.

Outcome measures. Primary endpoints were patterns of occurrence of ILD and risk factors for onset of ILD. Overall survival and PFS were secondary endpoints and were assessed according to the treating physician's standard clinical practice. The pattern of ADRs, excluding ILD, was an additional secondary endpoint.

Statistical analyses. The sample size determination is previously described.[9] Briefly, 3000 patients were to be enrolled to detect an AE in one case out of 3000 patients with at least a power of 95%; however, during enrolment, target accrual was increased to 10 000 patients by the Japanese Health Authority to further evaluate the safety and efficacy of erlotinib. The increased patient number allows high sensitivity regarding low-frequency ADRs. The safety population comprised all patients who received erlotinib and had case report form data available. The efficacy population comprised all patients included in the safety population, except those where erlotinib therapy was prescribed off-label (i.e. in the first-line setting) at the time of this study, or where a patient's therapeutic history was unknown.

Median PFS and OS were estimated using Kaplan–Meier methodology. Patients without data for the duration of the observation period or from the time of treatment initiation were excluded from the PFS analyses.

Statistical analyses were carried out using Statistical Analysis Software version 9.1 and 9.2 (SAS Institute, Cary, NC). Multivariate Cox regression analysis using a stepwise model was carried out to determine risk factors for ILD; occurrence of ILD was used as the dependent variable. Exploratory variables with $P > 0.05$ were not included in the final model. In the final step, additional multivariate analyses were carried out to investigate two-factor interactions; statistical significance was set at $P < 0.05$. This method is described in more detail in the interim analysis publication.[9]

To examine factors affecting poor prognosis in ILD, a stepwise, 5% significance level, multivariate logistic regression analysis was carried out with an analysis set of 310 patients in whom an ILD diagnosis was confirmed by the ILD Review Committee. The target variable was fatal ILD; exploratory variables included gender, age, primary lesion, histological type, smoking history, ECOG PS, honeycomb lung, non-metastatic lesions, and remaining normal lung. The exploratory variables were chosen by the results of a univariate analysis using ILD death as the target variable, with baseline characteristics and characteristics previously reported to affect poor ILD prognosis as the univariate exploratory variables.

Results

A total of 10 708 patients were enrolled in this study. Of these, 9909 patients were evaluated for the final safety analysis and 9663 patients were evaluated for the final efficacy analysis (Fig. 1). Baseline characteristics are shown in Table 1. Of note, more males than females were enrolled; the majority of patients had adenocarcinoma histology (80.9%) and most had ECOG PS 0–1 (74.0%).

Safety analysis. Adverse drug reactions were reported in 79.1% (7835/9909) of patients, the most common being skin disorders (67.4%), including rash (60.9%), diarrhea (21.5%), hepatitis, hepatic failure and hepatic function disorder (9.8%), eye disorders (3.3%) and hemorrhage (1.6%; Table 2). Median time to onset of ADRs was 9 days for rash, 8 days for diarrhea, 13 days for hepatitis, hepatic failure, and hepatic function

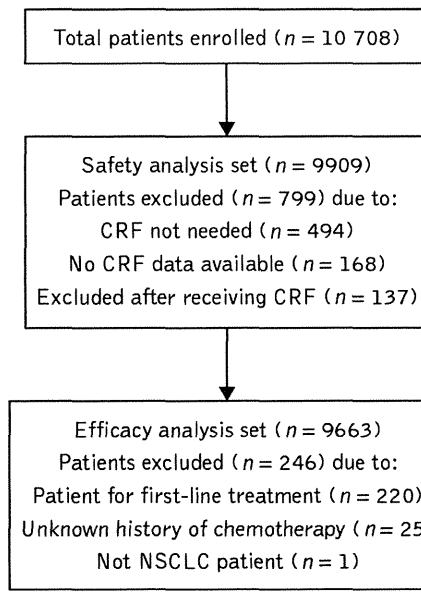

Fig. 1. Disposition of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 and who were included in the final analysis. CRF, case report form; NSCLC, non-small-cell lung cancer.

Table 1. Baseline characteristics of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

Characteristic	Patients, *n* (%) (*n* = 9909)
Gender	
Male	5300 (53.5)
Female	4609 (46.5)
Age	
<65 years	4466 (45.1)
65–74 years	3382 (34.1)
≥75 years	2059 (20.8)
Histology	
Adenocarcinoma	7950 (80.9)
Squamous cell	1285 (13.1)
Large cell	155 (1.6)
Other	438 (4.5)
ECOG PS	
0–1	7315 (74.0)
2–4	2576 (26.0)
Smoking history	
No	4366 (44.9)
Yes	5367 (55.1)
Number of previous treatment lines	
0	220 (2.2)
1	2481 (25.1)
2	2646 (26.8)
3	1993 (20.2)
4	1546 (15.6)
≥5	998 (10.1)
Previous gefitinib treatment	
Yes	4396 (44.7)
No	5446 (55.3)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Incidence of the most common adverse drug reactions (ADRs) in patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

ADR	All grades		Grade ≥3	
	Patients		Patients	
	n	%	*n*	%
ILD	429	4.3	257	2.6
Skin disorder				
Rash	6032	60.9	673	6.8
Dry skin	738	7.4	30	0.3
Pruritus	351	3.5	13	0.1
Paronychia	654	6.6	77	0.8
Hepatitis, hepatic failure, hepatic function disorder	976	9.8	183	1.8
Diarrhea	2133	21.5	137	1.4
Eye disorders	331	3.3	19	0.2
Corneal disorders	186	1.9	11	0.1
Hemorrhage	158	1.6	46	0.5
Gastrointestinal hemorrhage	39	0.4	20	0.2

ILD, interstitial lung disease.

disorder, 15 days for eye disorders, and 16 days for hemorrhage.

Interstitial lung disease. *Incidence.* Of the patients analyzed, 491 patients had 497 ILD-like events, of which 62 events were deemed non-ILD by the independent ILD Review Committee. In total, 429 (4.3%) patients were classified as having ILD (310 confirmed and reported by the ILD Review Committee, 119 patients not confirmed by the ILD Review Committee due to not having an evaluated image [*n* = 93], too difficult to distinguish from tumor progression [*n* = 4], and too difficult to distinguish from pneumonia due to insufficient evaluable images or clinical findings [*n* = 22] were still classified as ILD), with an overall mortality rate of 1.5% and a mortality rate of 35.7% in patients with ILD.

The majority of ILD cases (58.5%) were reported within 4 weeks of receiving erlotinib. The incidence of ILD (per 100 patient-weeks) was 0.63–0.81 within 4 weeks of the start of erlotinib treatment and 0.09–0.27 from 6 weeks after the start of erlotinib treatment (Fig. 2). Univariate analysis identified patients who were female, patients with non-adenocarcinoma histology, those with a period of treatment from initial NSCLC diagnosis to the start of treatment <360 days, concomitant or previous emphysema or COPD, concomitant or previous ILD, concomitant or previous lung infections, concomitant hepatic disorders, concomitant renal disorders, history of allergies, smoking history, ECOG PS 2–4, prior chest radiotherapy, pretreatment lactate dehydrogenase, and no previous treatment with gefitinib as risk factors for ILD development (Table 3). Age at start of treatment, body mass index, concurrent cardiovascular disorders, number of chemotherapy regimens and previous treatment with gemcitabine were variables that were not identified as risk factors from the univariate analysis. Multivariate analysis showed that concurrent/previous ILD (HR, 3.19), concurrent/previous emphysema or COPD (HR, 1.86), concurrent/previous lung infection (HR, 1.55), smoking history (HR, 2.25), and period from initial NSCLC diagnosis to the start of treatment (<360 days; HR, 0.58) were identified as significant risk factors for developing ILD by multivariate analysis (Table 3).

Outcomes of ILD. Of the confirmed cases of ILD, 75 (17.5%) patients fully recovered, 154 (35.9%) patients improved their condition, 32 (7.5%) patients did not recover, five (1.2%) patients had sequelae, 153 (35.7%) patients died, and 10 (2.3%) patients had unknown outcomes.

The outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. Diffuse alveolar damage-like pattern on CT was defined as abnormalities that showed non-segmental ground-glass attenuation or airspace consolidation with traction bronchiectasis and loss of volume. In the 63 patients with CT-DAD-like pattern, six (9.5%) patients recovered, 12 (19.1%) patients improved, three (4.8%) patients did not recover, one (1.6%) patient had residual ILD sequelae, and 41 (65.1%) patients died. In the 220 patients with a CT-non-DAD-like pattern, 37 (16.8%) patients recovered, 95 (43.2%) patients improved, 13 (5.9%) patients did not recover, one (0.5%) patient had residual ILD sequelae, 71 (32.3%) patients died, and three (1.4%) patients had unknown outcomes.

Fatal outcome of ILD. The multivariate logistic analysis identified ECOG PS 2–4 (OR, 2.45), ≤50% remaining normal lung area (OR, 3.12), and concomitant honeycombing with

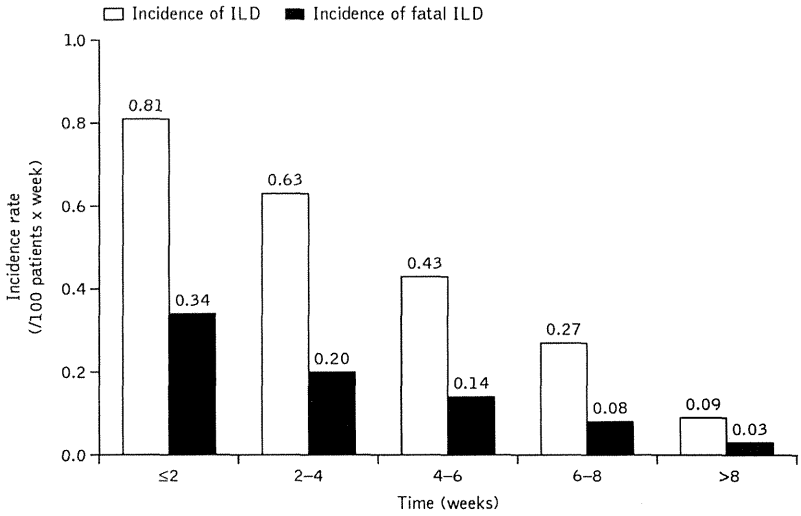

Fig. 2. Incidence rate of interstitial lung disease (ILD) stratified by time from start of erlotinib treatment to onset of ILD. The 34 patients without data for either the duration of observation or the time from the start of erlotinib treatment to the onset of ILD were excluded from the analysis. Value determined by dividing the number of patients developing ILD during the specified duration of observation by the patient-days during the observation period (total duration [number of days] of observation of all patients receiving erlotinib during the specified duration of observation).

Table 3. Cox regression univariate and multivariate analysis of factors affecting the incidence of interstitial lung disease (ILD) in patients with unresectable, recurrent/advanced non-small-cell lung cancer (NSCLC) who were treated with erlotinib in Japan between December 2007 and October 2009

Variables	Criterion variable	Evaluation variable	X^2 value	*P*-value	HR	95% CI
Univariate analysis						
Gender	Male	Female	76.3424	<0.0001	0.390	0.315–0.481
Age (years)	<55	≥55	2.257	0.133	1.256	0.933–1.692
Body mass index (kg/m^2)	<25	≥25	2.4468	0.1178	0.788	0.585–1.062
Histology	Adenocarcinoma	Non-adenocarcinoma	32.0958	<0.0001	1.847	1.494–2.283
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	20.1885	<0.0001	0.638	0.525–0.776
Concurrent/previous emphysema or COPD	No	Yes	85.1118	<0.0001	3.071	2.420–3.898
Concurrent/previous ILD	No	Yes	88.7072	<0.0001	3.862	2.915–5.116
Concurrent/previous lung infection	No	Yes	18.7152	<0.0001	1.979	1.453–2.697
Concurrent hepatic disorder	No	Yes	4.9716	0.0258	1.426	1.044–1.949
Concurrent renal disorder	No	Yes	9.1417	0.0025	1.611	1.183–2.195
Concurrent cardiovascular disorder	No	Yes	2.8576	0.0909	1.191	0.973–1.459
History of allergies	No	Yes	5.2846	0.0215	1.358	1.046–1.764
Smoking history	No	Yes	87.4412	<0.0001	2.896	2.318–3.620
ECOG PS	0–1	2–4	20.0203	<0.0001	1.620	1.311–2.001
Prior chest radiation therapy	No	Yes	11.9016	0.0006	1.431	1.167–1.753
Baseline lactate dehydrogenase†	–	–†	7.0077	0.0081	1	1–1
Number of chemotheraphy regimens for the primary diseases	–	–†	1.2809	0.2577	1.033	0.977–1.092
History of gemcitabine treatment	No	Yes	0.1141	0.7355	0.967	0.797–1.174
History of gefitinib treatment	No	Yes	38.7111	<0.0001	0.517	0.420–0.636
Multivariate analysis						
Concurrent/previous ILD	No	Yes	55.3796	<0.0001	3.187	2.349–4.325
Smoking history	No	Yes	34.1327	<0.0001	2.246	1.712–2.946
Concurrent/previous emphysema or COPD	No	Yes	20.704	<0.0001	1.860	1.424–2.431
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	19.3818	<0.0001	0.581	0.456–0.740
Concurrent/previous lung infection	No	Yes	6.5905	0.0103	1.550	1.109–2.165
ECOG PS	0–1	2–4	8.9467	0.0028	1.431	1.131–1.809
History of gefitinib treatment	No	Yes	5.3133	0.0212	0.729	0.557–0.954
Number of chemotherapy regimens†	–	–†	10.4136	0.0013	1.121	1.046–1.201

Objective variable: occurrence or non-occurrence of ILD. Explanatory variables: gender, age, body mass index, histological type, concurrent/previous emphysema or chronic obstructive pulmonary disease (COPD), concurrent/previous ILD, concurrent/previous lung infection, concomitant hepatic disorder, concomitant renal disorder, period from initial NSCLC diagnosis to the start of treatment, concomitant cardiovascular disease, history of allergies, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), radiotherapy (chest), pretreatment lactate dehydrogenase, number of chemotherapy regimens for the primary disease, history of gemcitabine treatment, history of gefitinib treatment. †Analyzed as a continuous quantity. NSCLC, non-small-cell lung cancer; ILD, interstitial lung disease.; CI, confidence interval; HR, hazard ratio.

Table 4. Interstitial lung disease (ILD) poor prognosis risk factors from the final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Risk factors for ILD-related death	Criterion variable	Evaluation variable	X^2 value	*P*-value	OR	95% CI
ECOG PS 2–4	0–1	2–4	9.974	0.0016	2.45	1.41–4.27
≤50% normal lung area	>50	≤50	8.896	0.0029	3.12	1.48–6.58
Concomitant honeycombing	No	Yes	5.414	0.02	6.67	1.35–32.94

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

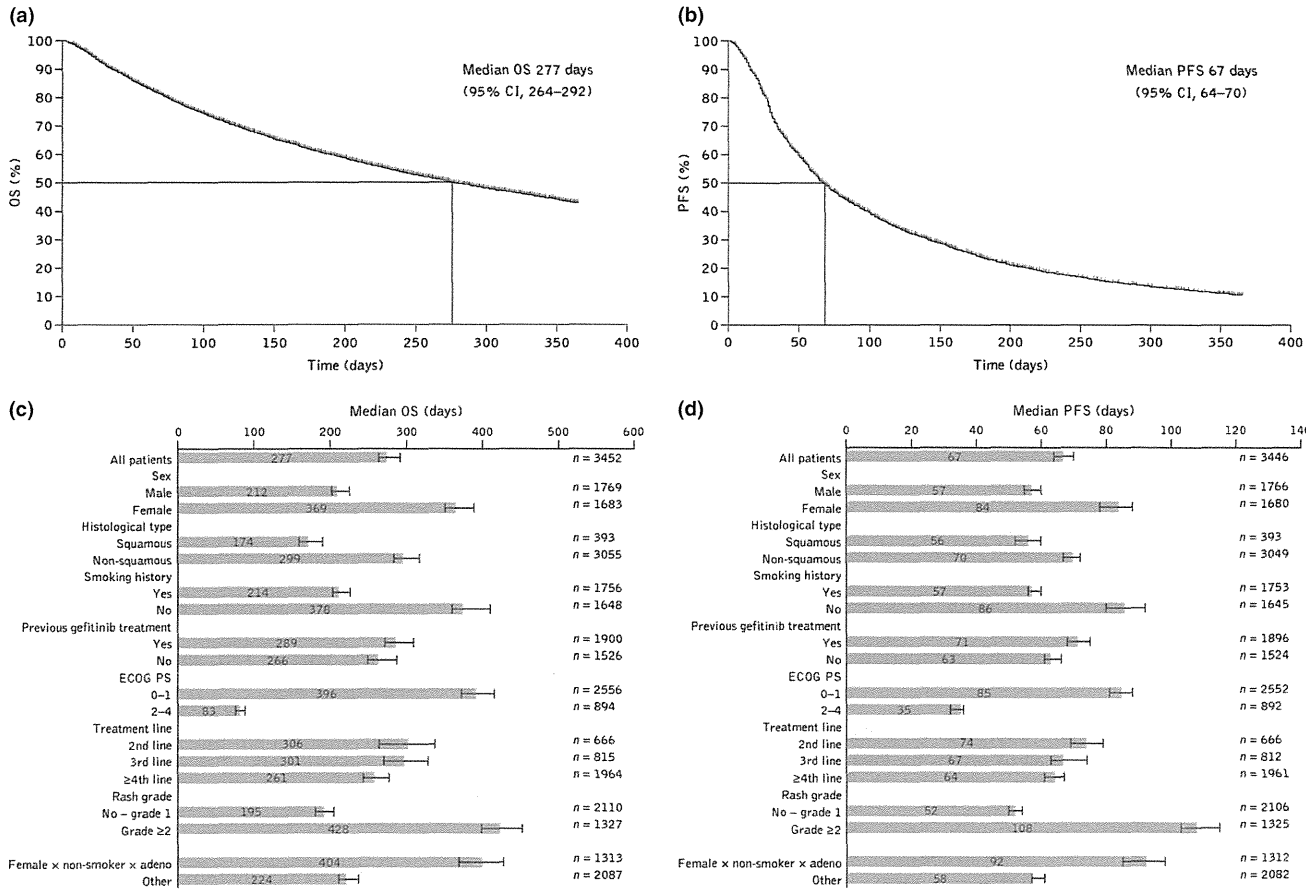

Fig. 3. (a) Overall survival (OS) and (b) progression-free survival (PFS) assessed by Kaplan–Meier methodology in the overall population of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009; (c) median OS and (d) PFS in patient subpopulations. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

interstitial pneumonia (OR, 6.67) as poor prognostic factors for ILD death (Table 4).

A total of 12 patients reported concomitant honeycombing and interstitial pneumonia; of these patients, nine patients died of ILD, two patients improved their condition, and one patient did not recover. Of those who died, eight were determined as having CT-non-DAD-like pattern on CT scan and the remaining patient was determined as having CT-DAD-like pattern.

Efficacy. Median OS was 277 days (95% CI, 264–292), with a 6-month survival rate of 62.6% and a 12-month survival rate of 42.8% (Fig. 3a). Median PFS was 67 days (95% CI, 64–70), with a 6-month progression-free rate of 25.8% and a 12-month progression-free rate of 10.6% (Fig. 3b). Compared with the overall population, median OS and PFS appeared to be longer in female patients, non-smokers, patients with ECOG PS 0–1, and patients with grade ≥2 rash (Fig. 3c,d).

Discussion

The development of drug-induced acute pulmonary disorders or interstitial pneumonia caused by EGFR TKIs is a common problem; this has particular importance in Japan, because a variety of evidence has suggested that Japanese populations are more vulnerable to these disorders. This large-scale POLARSTAR study provides further decisive information on this issue. Final data from the POLARSTAR study confirm that erlotinib has a well-characterized safety profile with proven efficacy in Japanese patients in routine clinical practice.

In the final analysis from POLARSTAR, the rates of ILD development and mortality in patients with ILD (4.3% and 35.7%, respectively) were comparable with the ILD-associated incidence rates of 3–5% and mortality rates of 27.9–50.0% previously reported among Japanese patients with NSCLC and ILD treated with gefitinib or erlotinib.[2,3,5,6,9] In the POLARSTAR analysis, it was shown that ILD onset was typically soon after initiation of erlotinib, with the highest incidence occurring during the first 4 weeks. Physicians should therefore monitor patients for the symptoms of ILD, which usually occur within 8 weeks of treatment initiation. These findings are further supported by those reported in Japanese NSCLC studies with gefitinib.[5,6]

The risk factors identified as significant primary risk factors (HR, ≥1.5) for ILD occurrence or exacerbation using a Cox proportional hazards multivariate analysis were concurrent/previous ILD, concurrent/previous lung infection, concurrent/previous emphysema or COPD, and smoking history. Cox proportional hazards multivariate analysis was selected for this assessment as the authors considered that a time-dependent analysis was needed, as there was no information regarding the ILD development point in the initial analysis. Concurrent /previous emphysema or COPD was newly identified as a significant primary risk factor for ILD occurrence when analyzed in 9909 patients compared with the result of the interim analysis of 3488 patients (Table 5).[9,10] As ILD is a collective term for a variety of different lung conditions, it is important to be careful not to misdiagnose conditions as ILD, as this will affect the risk factor analysis.

The period from initial NSCLC diagnosis to the start of treatment (<360 days) was not considered as a risk factor for ILD that needed to be highlighted at this time (HR, 0.58), as the clinical grounds for this factor were not clear. Stage of progression of primary disease or bias of observational period from initial NSCLC diagnosis to termination of treatment were speculated to be the reason; however, details of these reasons are uncertain. In contrast to this analysis, risk factors for ILD associated with gefitinib have been reported as ECOG PS ≥2, smoking history, concomitant interstitial pneumonia, and prior chemotherapy.[5,7,8]

The multivariate analysis identified ECOG PS 2–4, ≤50% remaining normal lung area and concomitant honeycombing with interstitial pneumonia as poor prognostic factors for ILD death in POLARSTAR. Many patients with idiopathic interstitial pneumonias have idiopathic pulmonary fibrosis or non-specific interstitial pneumonia, which have a heterogeneous natural progression, with some patients remaining stable for extended periods, while others show steady worsening of the condition.[11] Some patients with chronic idiopathic interstitial pneumonias, such as idiopathic pulmonary fibrosis and non-specific interstitial pneumonia, experience acute exacerbations characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of DAD.[12] It should be noted that there are racial differences between Mongolians (including the Japanese) and Caucasians in the frequency of acute exacerbations.[13] In the POLARSTAR study, the outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. The mortality rate for ILD among patients who were deemed to have CT-DAD-like pattern was higher than that seen among patients who were deemed as having CT-non-DAD-like pattern (65.1% *vs* 32.2%, respectively). Those patients with honeycombing and interstitial pneumonia (n = 12) had a high risk of poor prognosis, regardless of their CT pattern. Therefore, physicians should be actively aware of the symptoms of ILD and it is suggested to carefully monitor for these symptoms by CT image or X-ray throughout the disease course. Once physicians recognize ILD, they should immediately discontinue the EGFR TKI and should take the necessary steps to manage the ILD.

The final efficacy results from POLARSTAR are in line with the results of our interim analysis of the study (Table 6).[9] The final efficacy results (median OS, 277 days; median PFS, 67 days) were also comparable with efficacy reported in previous clinical trials of erlotinib treatment. The BR.21 study reported median PFS of 2.2 months (67 days) versus 1.8 months (55 days) and OS of 6.7 months (203 days) versus 4.7 months (143 days) for erlotinib and placebo, respectively, in the second- or third-line setting.[1] Kubota *et al.* investigated second-line erlotinib in Japanese patients, resulting in a median PFS of 77 days and OS of 14.7 months (447 days).[2] In a sec-

Table 5. Comparison of the interstitial lung disease (ILD) analysis from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, n = 3488) (efficacy, n = 3453)	Final analysis (safety, n = 9909) (efficacy, n = 9663)
ILD analysis		
Patients with confirmed ILD, n (%)	158 (4.5)	429 (4.3)
ILD-related mortality rate, %	1.6	1.5
ILD-related mortality rate in ILD patients	34.8	35.7
Risk factors for ILD development, HR		
Previous/concurrent ILD	4.1	3.2
Previous/concurrent Emphysema or COPD	–	1.9
Previous/concurrent lung infection	2.0	1.6
Smoking history	3.0	2.2
ECOG PS 2–4	1.6	1.4
<360 days from diagnosis to treatment	–	0.58

COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Table 6. Comparison of the efficacy endpoints from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, n = 3488) (efficacy, n = 3453)	Final analysis (safety, n = 9909) (efficacy, n = 9663)
Efficacy endpoints		
Median OS, days	260	277
6-month OS rate, %	62.2	62.6
12-month OS rate, %	40.9	42.8
Median PFS, days	64	67
6-month PFS rate, %	23.7	25.8
12-month PFS rate, %	9.6	10.6

OS, overall survival; PFS, progression-free survival.