treatment, one patient experienced a rapid symptomatic response with an increase in appetite, reduction in pain, and improvement in performance status. A computed tomography (CT) scan at the end of treatment cycle 2 (8 weeks) revealed a partial tumor response, which was confirmed at 12 weeks. Another patient also showed rapid clinical improvement, with reduced pain and improved performance status, after 1 week of crizotinib treatment. Time to progression for these two patients on crizotinib treatment was ~112 and 105 days, respectively.

Crizotinib was approved by the U.S. Food and Drug Administration for the treatment of *ALK* rearrangement-positive NSCLC in 2011, and a recent report has addressed the clinical efficacy of this agent in a clinical practice setting [59]. A male patient with stage IV squamous cell lung cancer was found to be positive for *MET* amplification (*MET/CEP7* ratio of >2.2) and negative for *ALK* rearrangement by FISH analysis. He was treated with crizotinib monotherapy at the normal dose of 250 mg twice daily. An almost complete response of tumors in the left lung and a major response of the primary tumor to therapy were demonstrated by chest CT and positron emission tomography (PET)-CT after 8 weeks of therapy.

Preliminary results of the NCT00585195 phase I study for patients with *MET* amplification-positive NSCLC were reported at the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO) [60]. Patients were categorized into three classes according to *MET* amplification status as determined by FISH analysis: low (*MET/CEP7* ratio of ≥1.8 to ≤2.2), intermediate (*MET/CEP7* ratio of >2.2 to <5.0), and high (*MET/CEP7* ratio of ≥5.0). Thirteen patients with a low (n = 1), intermediate (n = 6), or high (n = 6) *MET/CEP7* ratio received crizotinib. Of the 12 evaluable patients, four (33%) showed a partial response and were found to have an intermediate (n = 1) or high (n = 3) *MET/CEP7* ratio. These findings are thus suggestive of an association between the *MET/CEP7* ratio and the clinical benefit of crizotinib in patients with *MET* amplification-positive cancer.

The accumulating clinical evidence thus suggests that *MET* amplification as strictly defined by a *MET/CEP7* ratio of >2.2 has the potential to act as an oncogenic driver and thereby to render at least a subset of affected tumors responsive to MET-TKIs such as crizotinib. Not all *MET* amplification-positive cancer patients respond to MET-TKI treatment, however, and most such patients who do respond, even those who show an initial marked response, eventually develop resistance to MET-TKIs. Preexisting and acquired resistance to MET-TKIs is thus an important clinical problem that is shared with other targeted therapies. Several mechanisms of resistance to MET-TKIs have been identified in preclinical models, including additional mutations in the activation loop of MET [61], ligand-dependent activation of EGFR signaling [61,62], *SND1-BRAF* fusion [63], and amplification and overexpression of wild-type *KRAS* [64]. Further characterization of such mechanisms will be important to provide a basis for the development of effective therapies for patients with MET-TKI resistance.

5. Conclusions

MET amplification has been identified as a potential oncogenic driver for several neoplasms, and targeted therapy with MET-TKIs for such tumors is thus a reasonable and effective treatment. Clinical trials of such drugs are strongly warranted for patients with advanced malignancies positive for *MET* amplification as strictly defined by a *MET/CEP7* ratio of >2.2 determined by FISH.

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Conflicts of Interest

The authors declare no conflict of interest.

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Cystic Brain Metastasis in Non–Small-Cell Lung Cancer With *ALK* Rearrangement

Case Report 1

A 29-year-old female former smoker was diagnosed with stage IV signet-ring cell carcinoma of the lung and multiple pulmonary metastases. After two courses of first-line chemotherapy with cisplatin and pemetrexed, she manifested progressive disease with an increase in size of the primary tumor. Fluorescent in situ hybridization analysis of biopsied tumor tissue revealed the presence of an anaplastic lymphoma kinase gene (*ALK*) rearrangement. Crizotinib was therefore administered orally at a dose of 250 mg twice a day as a second-line treatment. The treatment was well tolerated, and computed tomography (CT) of the thorax revealed a good response. After 10 months of crizotinib therapy, however, CT revealed multiple cystic lesions in the brain (Fig 1A, arrows). Two months later, these lesions had increased in size and number (Fig 1B, arrows), suggesting that they were brain

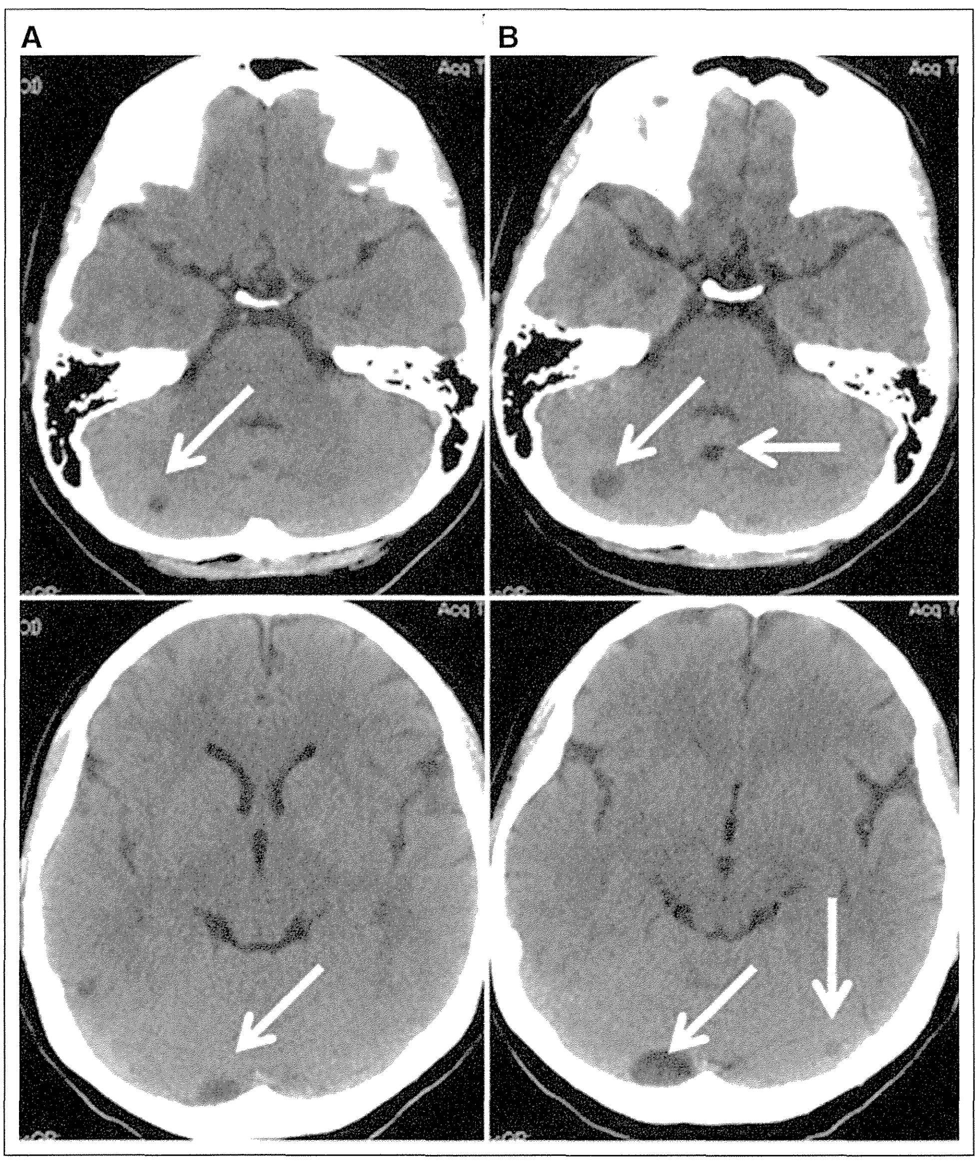

Fig 1.

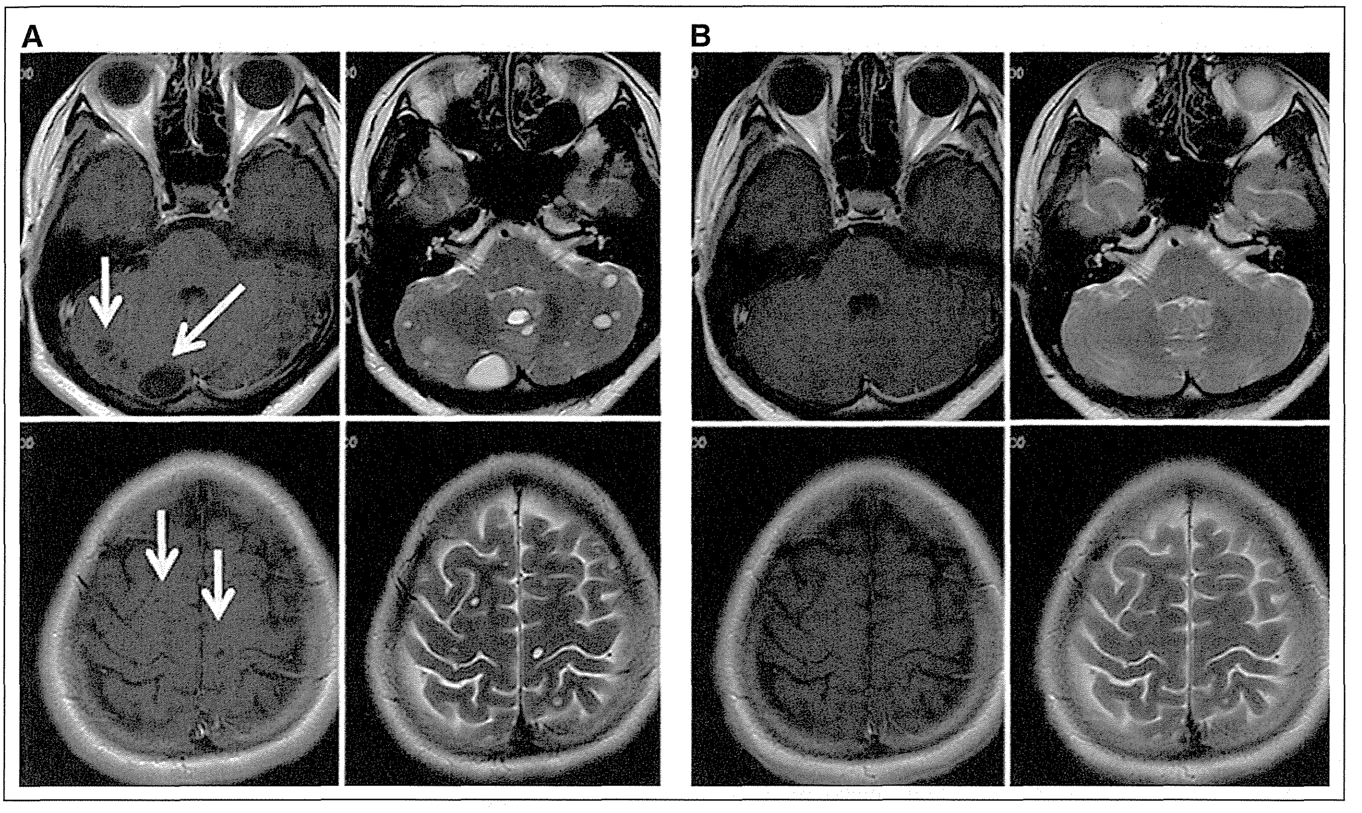

Fig 2.

metastases. Cranial magnetic resonance imaging (MRI) revealed multiple cystic masses that were predominantly centrally hypointense in T1-weighted images (Fig 2A, arrows in left panels) and hyperintense in T2-weighted images (Fig 2A, right panels) and which possessed an extremely thin cyst wall. Differential diagnoses for the cystic brain masses included abscess, tuberculosis, and parasitic infection, but such diagnoses were ruled out by the clinical course, with the patient showing no symptoms of infection such as fever or weight loss. Whole-brain radiation therapy was administered and resulted in a complete response as revealed by cranial MRI (Fig 2B). The patient has since continued with crizotinib treatment, with no evidence of extracranial tumor progression for 6 months.

Case Report 2

A 59-year-old female never-smoker presented with left-hand weakness and a poor grip. Contrast-enhanced MRI revealed a single solid tumor in the right frontal region of the brain (Fig 3A). CT of the thorax revealed a dominant lung mass in the left lower lobe, and non–small-cell lung cancer (NSCLC)—likely acinar adenocarcinoma—was confirmed by transbronchial biopsy. The patient underwent gamma knife radiosurgery for the brain tumor, resulting in prompt resolution of her neurological symptoms and tumor shrinkage (Fig 3B). After four courses of first-line chemotherapy with carboplatin and paclitaxel, she manifested progressive disease, with an increase in the size of both pulmonary and brain tumors (Fig 3C).

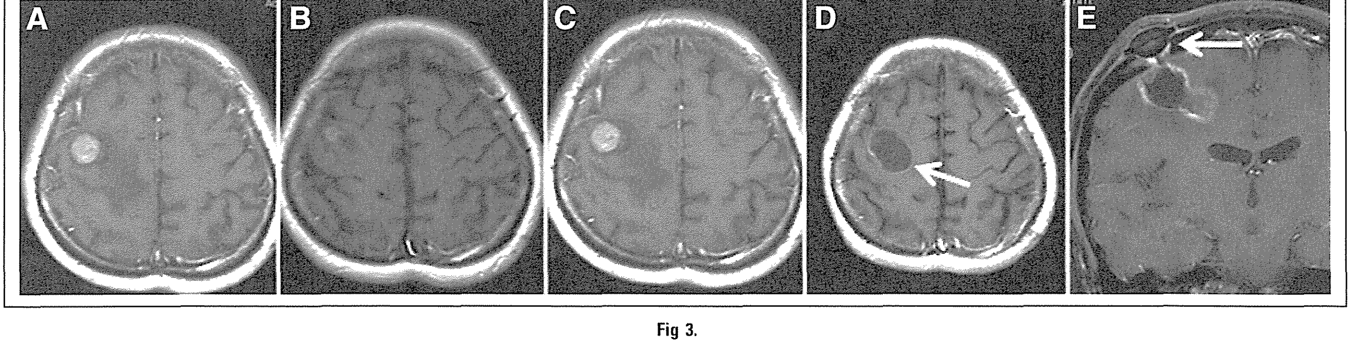

Fig 3.

Fluorescent in situ hybridization analysis with break-apart probes for *ALK* revealed the presence of an *ALK* rearrangement, and crizotinib was therefore administered orally at a dose of 250 mg twice daily. Treatment with crizotinib was well tolerated, and an interval CT scan showed a good response. At 10 months after initiation of crizotinib treatment, however, the tumor in the right frontal lobe had been replaced with a cystic tumor of increased size. MRI revealed a high internal signal intensity in T2-weighted images and a lack of gadolinium enhancement with the exception of the cyst wall in T1-weighted images (Fig 3D, arrow). An Ommaya reservoir was placed to drain the contents of the cystic mass (Fig 3E, arrow), resulting in stabilization of intracranial disease. Necrotic cells, but no malignant cells, were detected in viscous fluid obtained from the cyst. The patient has since continued crizotinib treatment for 4 months, with no evidence of extracranial disease progression.

Discussion

ALK translocation was recently identified as a targetable oncogenic driver. Crizotinib is the first ALK tyrosine kinase inhibitor to become clinically available and has shown marked and durable efficacy for the treatment of patients with NSCLC positive for *ALK* rearrangement. Despite their initial response, however, such patients treated with crizotinib eventually develop progressive disease, with the brain being the most common site for the development of new lesions.[1,2] The clinical features of brain metastasis in patients with *ALK* rearrangement–positive NSCLC remain to be fully characterized. We now describe two cases of cystic brain metastasis in such patients treated with crizotinib.

The pathogenesis of cyst formation in brain metastasis remains unclear, although several mechanisms can be considered for the present cases. Case 1 had a signet-ring cell histology, which has been described as a prominent histological type for NSCLC with *ALK* rearrangement.[3] Similar cyst formation is frequently observed in ovarian Krukenberg tumors that originate from signet-ring cell carcinoma of the stomach.[4] Given that signet-ring cells produce abundant mucus, cyst formation by such tumor cells may result from hypersecretion of mucus. In case 2, the brain tumor underwent a cystic change despite the apparent efficacy of crizotinib for treatment of extracranial disease. A case of cystic transformation of a brain metastasis after a response to gefitinib treatment was previously described for a patient with NSCLC positive for epidermal growth factor receptor gene mutation.[5] The response of the brain metastasis of case 2 to crizotinib likely resulted in the cystic change in a similar manner. It is thus possible that a good response to agents targeted to corresponding driver oncogenes may result in cystic degeneration of brain metastases.

In conclusion, as far as we are aware, the present cases are the first reported instances of cystic brain metastasis in patients with NSCLC positive for *ALK* rearrangement. Further investigation of the incidence of such metastasis in this group of patients is warranted to clarify whether *ALK* rearrangement is associated with a distinct biologic behavior of NSCLC—specifically, the formation of cystic brain metastases. Physicians should be aware of the possibility for the development of cystic brain tumors in patients with *ALK* rearrangement–positive NSCLC.

Hidetoshi Hayashi, Isamu Okamoto, Junko Tanizaki, Kaoru Tanaka, Takeshi Okuda, Amami Kato, Yasumasa Nishimura, and Kazuhiko Nakagawa
Kinki University Faculty of Medicine, Osaka, Japan

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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

Takashi Seto, Terufumi Kato, Makoto Nishio, Koichi Goto, Shinji Atagi, Yukio Hosomi, Noboru Yamamoto, Toyoaki Hida, Makoto Maemondo, Kazuhiko Nakagawa, Seisuke Nagase, Isamu Okamoto, Takeharu Yamanaka, Kosei Tajima, Ryosuke Harada, Masahiro Fukuoka, Nobuyuki Yamamoto

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National Kyushu Cancer Center, Fukuoka, Japan (T Seto MD); Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan (T Kato MD); The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan (M Nishio MD); National Cancer Center Hospital East, Chiba, Japan (K Goto MD); Kinki-chuo Chest Medical Center, Osaka, Japan (S Atagi MD); Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan (Y Hosomi MD); National Cancer Center Hospital, Tokyo, Japan (Noboru Yamamoto MD); Aichi Cancer Center, Aichi, Japan (T Hida MD); Miyagi Cancer Center, Miyagi, Japan (M Maemondo MD); Kinki University Faculty of Medicine, Osaka, Japan (Prof K Nakagawa MD); Tokyo Medical University Hospital, Tokyo, Japan (S Nagase MD); Kyushu University Hospital, Fukuoka, Japan (I Okamoto MD); National Cancer Center, Chiba, Japan (T Yamanaka PhD); Chugai Pharmaceutical Co Ltd, Tokyo, Japan (K Tajima MSc, R Harada BS); Izumi Municipal Hospital, Osaka, Japan (M Fukuoka MD); and Wakayama Medical University, Wakayama, Japan (Prof Nobuyuki Yamamoto MD)

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.

Funding Chugai Pharmaceutical Co Ltd.

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.

Correspondence to:
Prof Nobuyuki Yamamoto, Wakayama Medical University, 811-1, Kimiidera, Wakayama-shi, Wakayama 641-8509, Japan
nbyamamo@wakayama-med.ac.jp

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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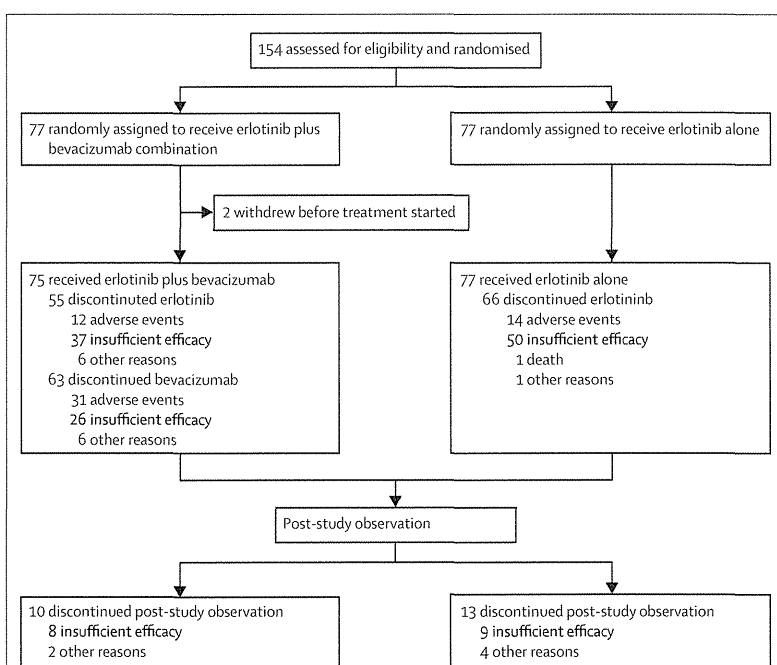

Figure 1: **Trial profile**

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**

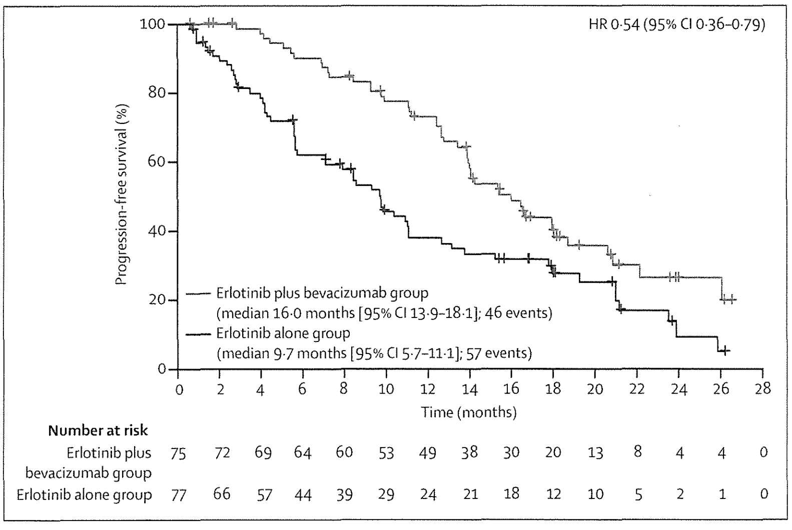

***Figure 2:* Progression-free survival, as determined by independent review committee, in the modified intention-to-treat population**
HR=hazard ratio.

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

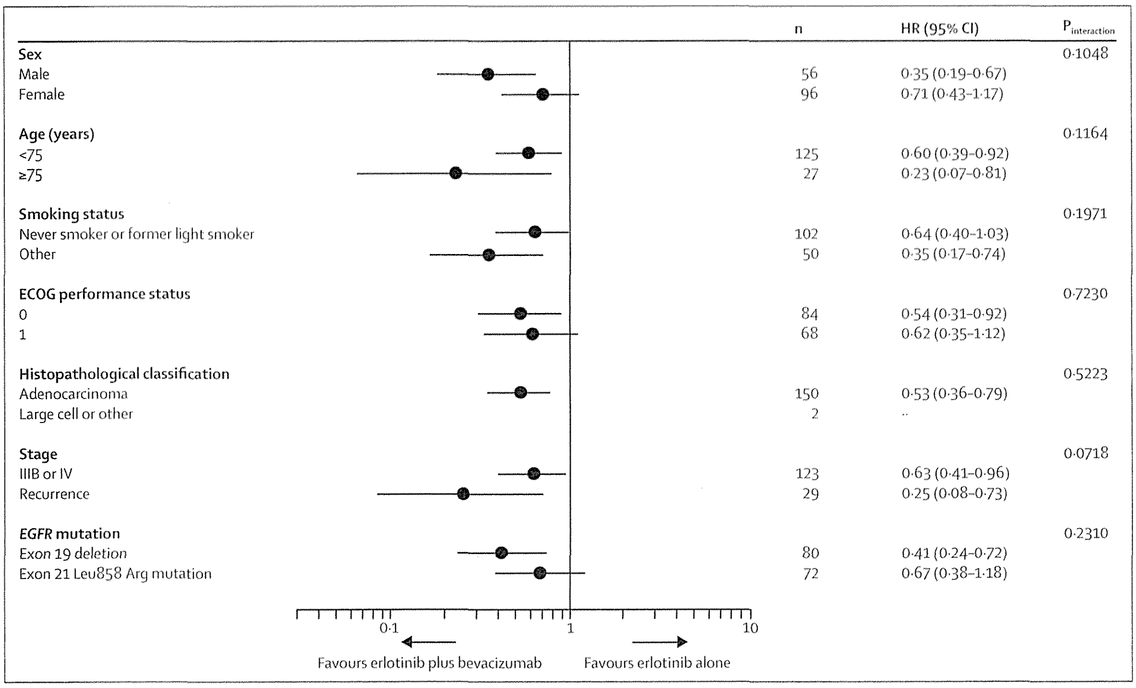

Figure 3: **Forest plot of hazard ratios for progression-free survival by baseline characteristics**
HR=hazard ratio.

	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

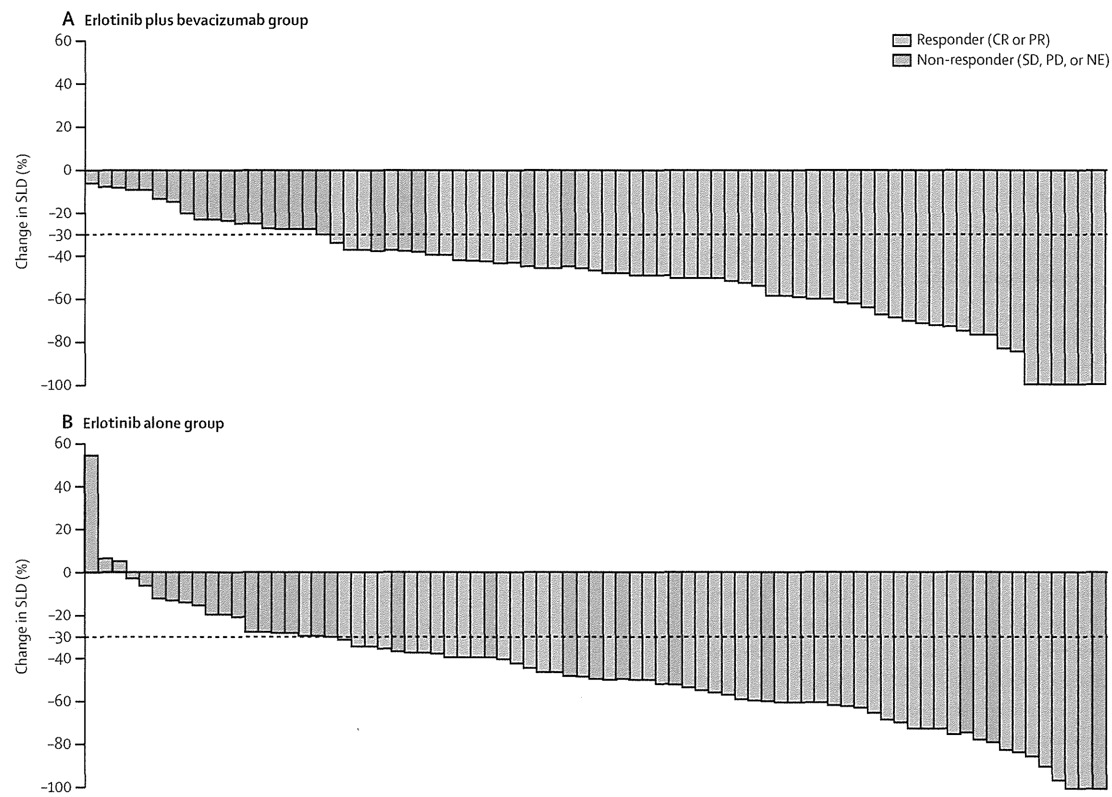

***Figure 4:* Waterfall plot of best percentage change from baseline in the sum of longest tumour diameters**

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.

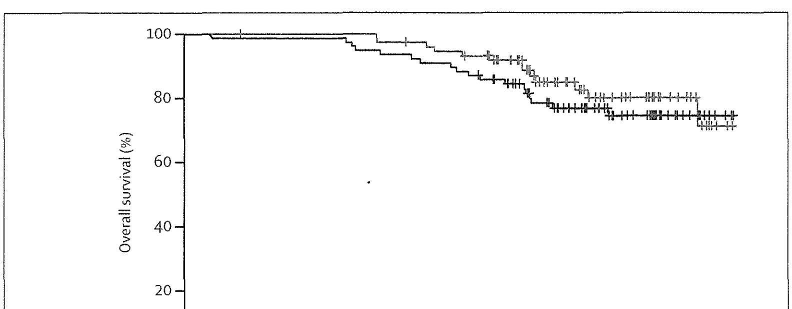

***Figure 5:* Overall survival, as determined by independent review committee, in the modified intention-to-treat population**

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

Akihiko Gemma,[1,19] Shoji Kudoh,[2,18] Masahiko Ando,[3,18] Yuichiro Ohe,[4,18] Kazuhiko Nakagawa,[5,18] Takeshi Johkoh,[6,18,19] Naoya Yamazaki,[7,18] Hiroaki Arakawa,[8,19] Yoshikazu Inoue,[9,19] Masahito Ebina,[10,19] Masahiko Kusumoto,[11,19] Kazuyoshi Kuwano,[12,19] Fumikazu Sakai,[13,19] Hiroyuki Taniguchi,[14,19] Yuh Fukuda,[15,19] Akihiro Seki,[16] Tadashi Ishii[16] and Masahiro Fukuoka[17,18]

[1]Department of Pulmonary Medicine and Oncology, Nippon Medical School, Graduate School of Medicine, Tokyo; [2]Anti-Tuberculosis Association, Double-Barred Cross Hospital, Tokyo; [3]Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine, Nagoya; [4]Department of Respiratory Medicine, National Cancer Center Hospital, Tokyo; [5]Department of Medical Oncology, Kinki University School of Medicine, Osaka; [6]Department of Radiology, Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Hyogo; [7]Department of Dermatology, National Cancer Center Hospital, Tokyo; [8]Department of Radiology, Dokkyo Medical University Hospital, Tochigi; [9]Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka; [10]Pulmonary Center, Tohoku Pharmaceutical University Hospital, Sendai; [11]Department of Diagnostic Radiology, National Cancer Center Hospital East, Chiba; [12]Division of Respiratory Medicine, Department of Internal Medicine, Jikei University School of Medicine, Tokyo; [13]Department of Diagnostic Radiology, Saitama Medical University International Medical Center, Saitama; [14]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi; [15]Division of Diagnostic Pathology, Itabashi Chuo Medical Center, Tokyo; [16]Department of Pharmacovigilance, Chugai Pharmaceutical Co. Ltd, Tokyo; [17]Izumi Municipal Hospital, Osaka, Japan

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Erlotinib, interstitial lung disease, Japanese, non-small-cell lung cancer, surveillance

correspondence
Akihiko Gemma, Department of Pulmonary Medicine and Oncology, Nippon Medical School, Graduate School of Medicine, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-860, Japan.
Tel: +81-3-3822-2131; Fax: +81-3-3823-0822;
E-mail: agemma@nms.ac.jp

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[18]Independent Advisory Board for Erlotinib

[19]Independent Interstitial Lung Disease Review Committee

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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).