Received: 5 April 2022 | Accepted: 28 May 2022

DOI: 10.1111/1759-7714.14541

ORIGINAL ARTICLE

WILEY

Erlotinib with or without bevacizumab as a first-line therapy for patients with advanced nonsquamous epidermal growth factor receptor-positive non-small cell lung cancer: Exploratory subgroup analyses from the phase II JO25567 study

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Funding information
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Abstract

Background: In the phase II JO25567 study (JapicCTI-111390), erlotinib plus bevacizumab demonstrated a significant clinical benefit in Japanese patients with epidermal growth factor receptor mutation-positive (*EGFR*+) non-small cell lung cancer (NSCLC). Here, we present an exploratory analysis investigating the impact of baseline pleural/pericardial effusion (PPE) on patient outcomes.

Methods: Patients with stage IIIB/IV or postoperative recurrent *EGFR*+ NSCLC were randomized 1:1 to receive erlotinib (150 mg/day) plus bevacizumab (15 mg/kg every 3 weeks) or erlotinib monotherapy. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and safety were evaluated according to the presence or absence of baseline PPE.

Results: The population comprised 152 patients, 66 with baseline PPE and 86 without. Median PFS was longer with erlotinib plus bevacizumab than with erlotinib alone, with (hazard ratio [HR] 0.45; 95% confidence interval [CI]: 0.25–0.82) or without (HR 0.62; 95% CI: 0.37–1.04) baseline PPE. Median OS was also prolonged with erlotinib plus bevacizumab relative to erlotinib regardless of the presence (HR 0.82; 95% CI: 0.46–1.47) or absence (HR 0.84; 95% CI: 0.46–1.55) of baseline PPE. ORR was higher with erlotinib plus bevacizumab (70.0%) than with erlotinib (55.6%) in patients with baseline PPE, but similar (68.9% vs. 70.7%) in patients without. Most common grade ≥3 adverse events were hypertension and rash in the erlotinib plus bevacizumab arm, and rash in the erlotinib arm, regardless of baseline PPE status.

Conclusions: Erlotinib plus bevacizumab may be a beneficial treatment strategy in patients with *EGFR*+ NSCLC, especially for those with baseline PPE.

KEYWORDS
bevacizumab, *EGFR*, erlotinib, NSCLC, pleural/pericardial effusion

INTRODUCTION

Activating epidermal growth factor receptor (*EGFR*+) mutations are found in a substantial proportion of patients with non-small cell lung cancer (NSCLC), accounting for approximately 30% of cases among Asian patients and 10% of cases among non-Asian patients.[1] EGFR tyrosine kinase inhibitors (TKIs) are the standard first-line therapy for patients with advanced *EGFR*+ NSCLC.[2–4] Erlotinib is an orally active, potent EGFR TKI that demonstrated a survival benefit over standard chemotherapy as first-line treatment in phase III trials,[5–7] and is approved for the treatment of

patients with metastatic NSCLC harboring *EGFR* exon 19 deletions or exon 21 *L858R* substitutions.[8] Several EGFR TKIs have now been approved for the treatment of *EGFR*+ NSCLC.[2,3] The third-generation EGFR TKI osimertinib was approved for use in this setting based on results of the phase III FLAURA trial.[9,10]

Despite the promising efficacy demonstrated by EGFR TKI monotherapy, not all patients derive equal benefit. Resistance and relapse remain major problems for patients with *EGFR*+ NSCLC, as almost all patients develop acquired resistance to erlotinib, gefitinib, or osimertinib treatment, typically within 10–14 months;[5,6,9,11–16] resistance mechanisms include secondary *EGFR* mutations, *MET* gene amplification, and hepatocyte growth factor overexpression.[17,18] Developing rational, synergistic therapeutic combinations that address this unmet need, and improve outcomes for patients with *EGFR*+ NSCLC who develop resistance, is therefore a prominent goal in oncology research.

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF); it is currently approved for use in combination with carboplatin and paclitaxel for first-line treatment of locally advanced, recurrent, or metastatic nonsquamous NSCLC, as well as several other indications in patients with solid tumors.[19] The combination of erlotinib and bevacizumab was investigated as a first-line treatment in Japanese patients with stage IIIB/IV or recurrent *EGFR*+ NSCLC in the phase II JO25567 (JapicCTI-111390) study.[20] In the primary analysis (data cutoff June 30, 2013), a clinically meaningful and statistically significant improvement in median progression-free survival (PFS) was seen in patients treated with erlotinib plus bevacizumab (16.0 months; 95% confidence interval [CI]: 13.9–18.1) compared with erlotinib monotherapy (9.7 months; 95% CI: 5.7–11.1; hazard ratio [HR] 0.54; 95% CI: 0.36–0.79; $p = 0.0015$).[20]

Among patients with NSCLC, a number of clinical factors have been associated with poorer survival, including pleural/pericardial effusion (PPE).[21,22] As VEGF, the main target of bevacizumab, has been shown to be associated with the formation of pleural effusion,[23] it is important to understand the efficacy and safety of erlotinib plus bevacizumab in patients with *EGFR*+ NSCLC and PPE at baseline. Here, we report exploratory subgroup analyses from the JO25567 study investigating the impact of baseline PPE on patient outcomes.

METHODS

Study design

Full details of the study design have been previously published.[20] In brief, JO25567 was an open-label, multicenter, randomized phase II study examining the addition of bevacizumab to erlotinib as a first-line therapy in patients with histologically and/or cytologically confirmed stage IIIB/IV or postoperative, recurrent nonsquamous *EGFR*+ (either exon 19 deletion or exon 21 *L858R* mutation) NSCLC. Enrolled patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients with pleural effusion, ascites, or pericardial effusion requiring treatment were excluded from this study, although patients could be enrolled if at least 2 weeks had elapsed since pleurodesis and continuous drainage at the time of enrollment. Patients were randomized 1:1 to receive erlotinib 150 mg once daily plus bevacizumab 15 mg/kg every 3 weeks, or erlotinib 150 mg once daily, until disease progression or unacceptable toxicity. Patients were enrolled from 30 centers across Japan. The study was performed 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, and written informed consent was obtained from all patients. The study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-111390.

Study endpoints

For this exploratory analysis, PFS, objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety were analyzed according to the presence or absence of PPE as nontarget lesion at baseline by independent review committee (IRC; blinded review).

Study assessments

In this exploratory analysis, tumor assessments were performed by IRC according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. PFS was defined as the time from randomization to the date of confirmed disease progression or death from any cause (within study period), whichever occurred first. ORR was defined as the proportion of patients achieving an objective response (complete response [CR] or partial response [PR]), based on RECIST v1.1; confirmed objective responses were those determined on two consecutive occasions 28 days apart. Patients who did not achieve a CR or PR and those without a post-baseline tumor assessment were regarded as non-responders. DCR was defined as the proportion of patients with at least one post-baseline assessment as CR, PR, or stable disease (SD). OS was defined as the time from randomization to death from any cause. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (v14.0) preferred terms and tabulated by grade.

Statistical analysis

Median PFS and OS for each treatment arm were estimated by the Kaplan–Meier method. Greenwood's formula was used to calculate 95% CIs for the median PFS and OS for

TABLE 1 Baseline demographics and clinical characteristics according to treatment arm and baseline PPE status

	Erlotinib plus bevacizumab		Erlotinib		Total	
Characteristic, n (%)	**PPE ($n = 30$)**	**No PPE ($n = 45$)**	**PPE ($n = 36$)**	**No PPE ($n = 41$)**	**PPE ($n = 66$)**	**No PPE ($n = 86$)**
Age, years						
<75	24 (80.0)	39 (86.7)	30 (83.3)	32 (78.0)	54 (81.8)	71 (82.6)
≥75	6 (20.0)	6 (13.3)	6 (16.7)	9 (22.0)	12 (18.2)	15 (17.4)
Median (range)	67.0 (40–83)	68.0 (38–81)	65.5 (36–81)	68.0 (36–84)	66.5 (36–83)	68.0 (36–84)
Sex						
Male	12 (40.0)	18 (40.0)	10 (27.8)	16 (39.0)	22 (33.3)	34 (39.5)
Female	18 (60.0)	27 (60.0)	26 (72.2)	25 (61.0)	44 (66.7)	52 (60.5)
Smoking history						
Nonsmoker	17 (56.7)	25 (55.6)	23 (63.9)	22 (53.7)	40 (60.6)	47 (54.7)
Other	13 (43.3)	20 (44.4)	13 (36.1)	19 (46.3)	26 (39.4)	39 (45.3)
ECOG PS						
0	15 (50.0)	28 (62.2)	15 (41.7)	26 (63.4)	30 (45.5)	54 (62.8)
1	15 (50.0)	17 (37.8)	21 (58.3)	15 (36.6)	36 (54.5)	32 (37.2)
Clinical stage						
IIIB	—	1 (2.2)	—	—	—	1 (1.2)
IV	28 (93.3)	32 (71.1)	34 (94.4)	28 (68.3)	62 (93.9)	60 (69.8)
Recurrent	2 (6.7)	12 (26.7)	2 (5.6)	13 (31.7)	4 (6.1)	25 (29.1)
EGFR mutation type						
Exon 19 deletion	16 (53.3)	24 (53.3)	19 (52.8)	21 (51.2)	35 (53.0)	45 (52.3)
Exon 21 *L858R* mutation	14 (46.7)	21 (46.7)	17 (47.2)	20 (48.8)	31 (47.0)	41 (47.7)
SLD of target lesions						
≥37.5 mm	20 (66.7)	19 (42.2)	19 (52.8)	18 (43.9)	39 (59.1)	37 (43.0)
<37.5 mm	10 (33.3)	26 (57.8)	17 (47.2)	23 (56.1)	27 (40.9)	49 (57.0)
Number of affected organs						
≥3	26 (86.7)	15 (33.3)	31 (86.1)	14 (34.1)	57 (86.4)	29 (33.7)
<3	4 (13.3)	30 (66.7)	5 (13.9)	27 (65.9)	9 (13.6)	57 (66.3)
Histopathological classification						
Adenocarcinoma	30 (100.0)	44 (97.8)	35 (97.2)	41 (100.0)	65 (98.5)	85 (98.8)
Large cell carcinoma	—	—	1 (2.8)	—	1 (1.5)	—
Other	—	1 (2.2)	—	—	—	1 (1.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PPE, pleural/pericardial effusion; SLD, sum of longest diameter.

each treatment. HRs were calculated by unstratified Cox proportional hazard methodology. ORR and DCR were estimated based on IRC assessments and 95% CIs were calculated using the Clopper–Pearson method. The date of data cutoff was June 30, 2013 for PFS, ORR, and DCR; and October 31, 2017 for OS.

RESULTS

Patients

Among the 152 patients with *EGFR*+ NSCLC who were randomized to receive erlotinib plus bevacizumab ($n = 75$) or erlotinib ($n = 77$), 66 had PPE at baseline and 86 did not. Baseline patient demographics and clinical characteristics were generally balanced between subgroups (Table 1). However, a slightly higher proportion of patients had PPE at baseline in the erlotinib arm (46.8%) compared with the erlotinib plus bevacizumab arm (40.0%). The number of patients who had at least three affected organs was higher among patients with PPE at baseline, but the percentages were similar between treatment arms in this subgroup (erlotinib, 86.1%; erlotinib plus bevacizumab, 86.7%; Table 1).

Efficacy

Kaplan–Meier analysis showed that median PFS was numerically longer with erlotinib plus bevacizumab compared with erlotinib monotherapy, irrespective of the presence

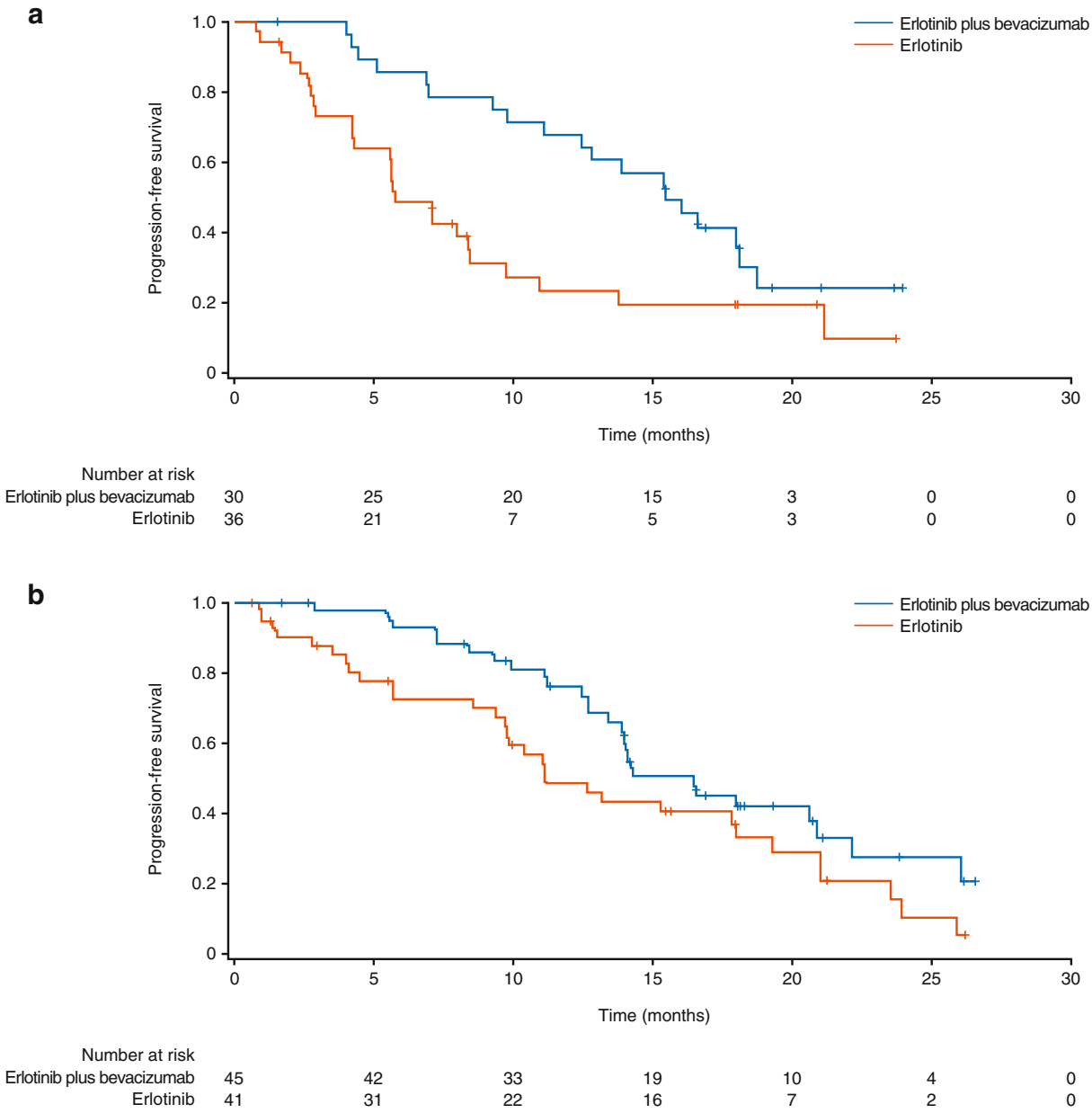

FIGURE 1 Kaplan–Meier analysis of progression-free survival (PFS) according to treatment arm. (a) Patients with baseline pleural/pericardial effusion (PPE). (b) Patients without baseline PPE per independent review committee assessment

(HR 0.45; 95% CI: 0.25–0.82) or absence (HR 0.62; 95% CI: 0.37–1.04) of PPE at baseline (Figure 1(a),(b)); in patients with baseline PPE, median PFS was 15.4 months (95% CI: 11.1–18.1) versus 5.7 months (95% CI: 4.2–8.4; Figure 1(a)) and in patients without baseline PPE, median PFS was 16.4 months (95% CI: 13.4–20.9) versus 11.1 months (95% CI: 9.7–18.0; Figure 1(b)), respectively.

Median OS was also numerically longer in patients who received erlotinib plus bevacizumab than erlotinib monotherapy, regardless of the presence (HR 0.82; 95% CI: 0.46–1.47) or absence (HR 0.84; 95% CI: 0.46–1.55) of PPE at baseline (Figure 2(a),(b)). Among patients with baseline PPE, median OS was 35.3 months (95% CI: 25.1–47.0) in patients treated with erlotinib plus bevacizumab (20/30 patients had events, all disease progression) and 30.1 months (95% CI: 17.9–48.7) in patients treated with erlotinib monotherapy (27/36 patients had events: 26 disease progression, 1 other; Figure 2(a)). Among patients without baseline PPE, median OS was 67.9 months (95% CI: 36.6–not estimable) in patients treated with erlotinib plus bevacizumab (20/45 patients had events: 19 disease progression, 1 other) and 60.8 months (95% CI: 44.2–73.4) in patients treated with erlotinib (22/41 patients had events: 21 disease progression, 1 other; Figure 2(b)).

ORR was determined according to treatment arm and PPE status at baseline (Table 2). In patients with baseline

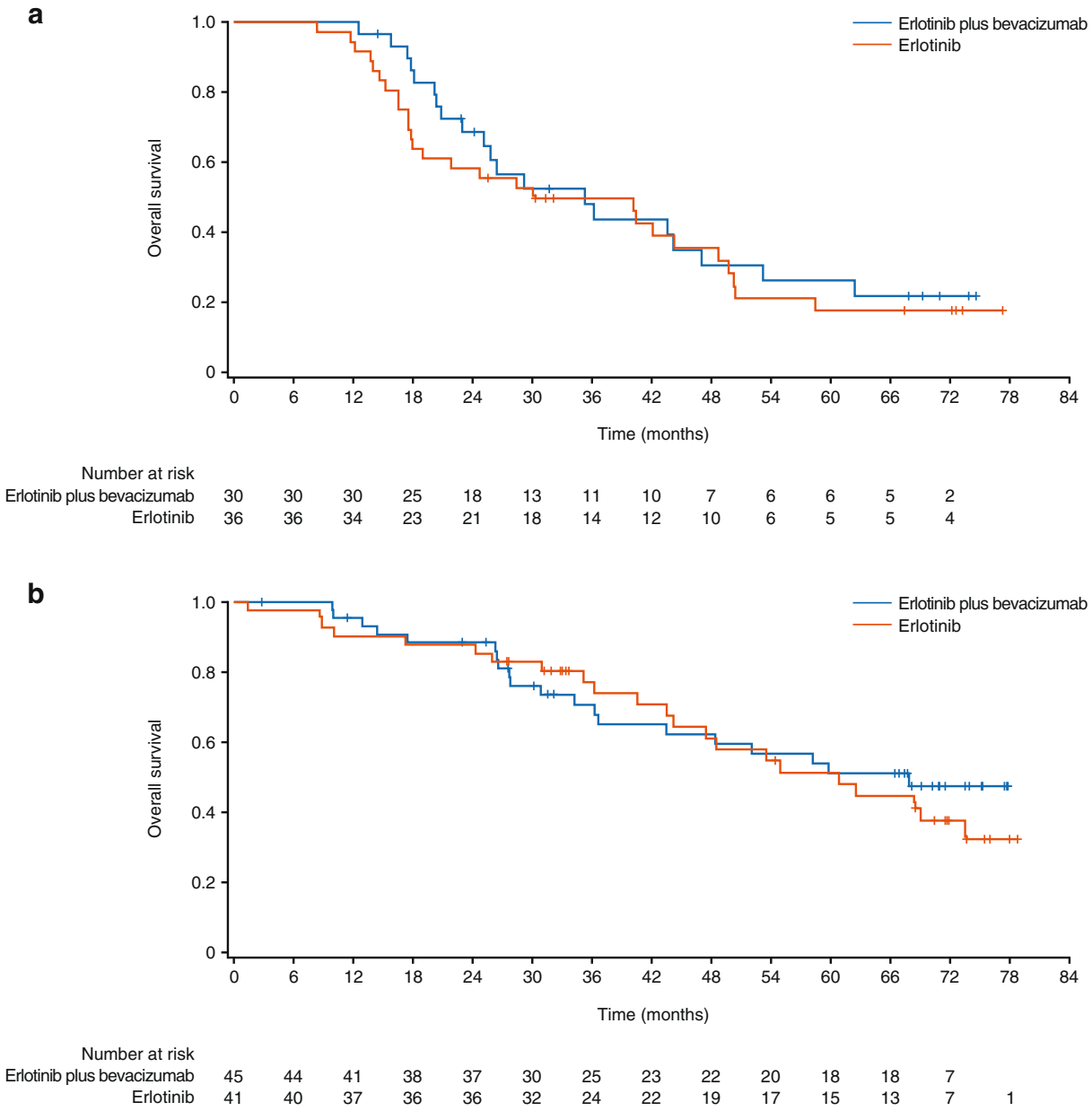

FIGURE 2 Kaplan–Meier analysis of overall survival (OS) according to treatment arm. (a) Patients with baseline pleural/pericardial effusion (PPE). (b) Patients without baseline PPE

TABLE 2 Patient response by treatment arm and baseline PPE status per independent review committee assessment

	Erlotinib plus bevacizumab		Erlotinib	
Response, n (%); 95% CI	**PPE ($n = 30$)**	**No PPE ($n = 45$)**	**PPE ($n = 36$)**	**No PPE ($n = 41$)**
ORR	21 (70.0); 50.6–85.3	31 (68.9); 53.4–81.8	20 (55.6); 38.1–72.1	29 (70.7); 54.5–83.9
CR	0 (0); 0.0–11.6	3 (6.7); 1.4–18.3	0 (0); 0.0–9.7	1 (2.4); 0.1–12.9
PR	21 (70.0); 50.6–85.3	28 (62.2); 46.5–76.2	20 (55.6); 38.1–72.1	28 (68.3); 51.9–81.9
SD	9 (30.0); 14.7–49.4	13 (28.9); 16.4–44.3	11 (30.6); 16.3–48.1	8 (19.5); 8.8–34.9
PD	0 (0); 0.0–11.6	0 (0); 0.0–7.9	3 (8.3); 1.8–22.5	3 (7.3); 1.5–19.9
Missing	0 (0)	1 (2.2)	2 (5.6)	1 (2.4)
DCR	30 (100); 88.4–100.0	44 (97.8); 88.2–99.9	31 (86.1); 70.5–95.3	37 (90.2); 76.9–97.3

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PPE, pleural/pericardial effusion; PR, partial response; SD, stable disease.

PPE, ORR was numerically higher in patients receiving erlotinib plus bevacizumab (70.0%; 95% CI: 50.6–85.3) compared with those receiving erlotinib monotherapy (55.6%; 95% CI: 38.1–72.1). By contrast, in patients without baseline PPE, ORR was similar in patients treated with erlotinib plus bevacizumab (68.9%; 95% CI: 53.4–81.8) or erlotinib monotherapy (70.7%; 95% CI: 54.5–83.9). DCR was higher in patients who received erlotinib plus bevacizumab than in patients who received erlotinib monotherapy, regardless of the presence or absence of PPE at baseline; in patients with PPE at baseline, DCR was 100% (95% CI: 88.4–100.0) versus 86.1% (95% CI: 70.5–95.3) and in patients without PPE at baseline, DCR was 97.8% (95% CI: 88.2–99.9) versus 90.2% (95% CI: 76.9–97.3), respectively. Fewer patients experienced worsening of their PPE while receiving erlotinib plus bevacizumab (16.7%) compared with those patients who received erlotinib monotherapy (30.6%; Table 3). However, the proportion of patients who developed PPE during treatment did not differ between the treatment arms (1.3%; Table 3).

Safety

In patients with baseline PPE, grade ≥3 AEs occurred in 90.0% of patients ($n = 27$) treated with erlotinib plus bevacizumab compared with 47.2% of patients ($n = 17$) treated with erlotinib alone (Table 4). In patients without baseline PPE, grade≥3 AEs occurred in 91.1% of patients ($n = 41$) receiving erlotinib plus bevacizumab and 58.5% of patients ($n = 24$) receiving erlotinib monotherapy (Table 4). The most common grade ≥3 AEs were hypertension and rash in the erlotinib plus bevacizumab arm, and rash and liver function disorder or abnormal hepatic function in the erlotinib arm, regardless of PPE status at baseline (Table 4).

TABLE 3 Pattern of PPE progression according to treatment arm

Progression pattern, n (%)	Erlotinib plus bevacizumab	Erlotinib
Worsening of baseline PPE[a]	5 (16.7)	11 (30.6)
Newly developed PPE[b]	1 (1.3)	1 (1.3)

Abbreviations: PPE, pleural/pericardial effusion.
[a]Denominator is the number of patients with PPE at baseline.
[b]Denominator is the total number of patients.

DISCUSSION

The combination of erlotinib plus bevacizumab demonstrated clinical benefit in Japanese patients with stage IIIB/IV or postoperative, recurrent *EGFR*+ NSCLC in the phase II JO25567 study,[20] with a median PFS of 16.0 months for erlotinib plus bevacizumab and 9.7 months for erlotinib monotherapy (HR 0.54; 95% CI: 0.36–0.79, $p = 0.0015$).[20] Follow-up survival analyses showed that median OS was similar between the erlotinib plus bevacizumab and erlotinib monotherapy treatment arms (47.0 vs 47.4 months, respectively; HR 0.81; 95% CI: 0.53–1.23).[24] The exploratory analyses from JO25567 reported here demonstrate that, consistent with the primary analysis,[20] erlotinib plus bevacizumab shows clinical benefit in terms of PFS compared with erlotinib monotherapy across all patient subgroups defined according to baseline characteristics and, in particular, in patients with baseline PPE. However, patients with pleural effusion, ascites, or peripheral effusion requiring treatment were excluded from this study, which should be noted.

Few studies have investigated the efficacy and safety of targeted therapy in patients with *EGFR*+ NSCLC and PPE at baseline. However, a combined analysis of data from JO22903, a single-arm study of erlotinib monotherapy for *EGFR*+ NSCLC (JapicCTI-101085), and JO25567 found that treatment with erlotinib monotherapy resulted in a shorter median PFS in patients with baseline PPE compared with patients without baseline PPE (8.0 vs. 15.3 months, respectively; HR 0.38; 95% CI: 0.25–0.58).[25] In the randomized, open-label, phase III NEJ026 study, erlotinib plus bevacizumab also demonstrated improved PFS versus erlotinib monotherapy (median 16.9 vs. 13.3 months, respectively; HR 0.61; 95% CI: 0.42–0.88), with numerically longer median PFS observed in both patients with baseline PPE (16.9 vs. 12.6 months; HR 0.58; 95% CI: 0.34–1.02) and without baseline PPE (16.6 vs. 14.2 months; HR 0.67; 95%

TABLE 4 Grade ≥3 adverse events occurring in >5% of patients according to treatment arm and baseline PPE status

	Erlotinib plus bevacizumab		Erlotinib	
Adverse event, n (%)	PPE ($n = 30$)	No PPE ($n = 45$)	PPE ($n = 36$)	No PPE ($n = 41$)
Total	27 (90.0)	41 (91.1)	17 (47.2)	24 (58.5)
Hypertension	18 (60.0)	26 (57.8)	3 (8.3)	5 (12.2)
Rash	5 (16.7)	14 (31.1)	8 (22.2)	7 (17.1)
Liver function disorder or abnormal hepatic function	3 (10.0)	3 (6.7)	5 (13.9)	9 (22.0)
Proteinuria	3 (10.0)	2 (4.4)	—	—
Paronychia	2 (6.7)	—	1 (2.8)	2 (4.9)
Periodontal disease	2 (6.7)	—	—	—

Abbreviations: PPE, pleural/pericardial effusion.

CI: 0.41–1.10).[26] The findings presented here add to these results, demonstrating that median PFS was longer in patients with *EGFR*+ NSCLC who received erlotinib plus bevacizumab compared with erlotinib monotherapy, regardless of PPE status at baseline. In addition to the PFS benefit observed with combination therapy, fewer patients experienced worsening of their PPE during treatment with erlotinib plus bevacizumab compared with erlotinib monotherapy. It is worth noting that these findings are based on a Japanese study population and may not be indicative of the global population. The small populations within each subgroup and the exploratory nature of the analyses should also be noted.

The safety profile of erlotinib plus bevacizumab demonstrated in this study was consistent with previous literature, with no new safety signals identified.[20,25–27] These cumulative data suggest that the combination of erlotinib plus bevacizumab could be a beneficial treatment strategy in patients with *EGFR*+ NSCLC, regardless of baseline PPE.

Several other treatment strategies for *EGFR*+ NSCLC are currently under investigation to overcome the ongoing challenge of acquired resistance to first-line treatment with EGFR TKIs. The combinations of gefitinib plus platinum chemotherapy and erlotinib plus ramucirumab have demonstrated promising efficacy in patients with *EGFR*+ NSCLC.[28,29] In addition, combinations with second- and third-generation EGFR TKIs are now being evaluated in the first-line setting. The dual EGFR TKI combination of osimertinib plus gefitinib is being investigated for first-line treatment of *EGFR*+ NSCLC.[30] Furthermore, the combination of an EGFR TKI and VEGF inhibitor is being assessed in the phase II WJOG9717L study, which will investigate the combination of osimertinib plus bevacizumab,[31] and in the TORG1833 study, which will evaluate the combination of osimertinib plus ramucirumab.[32] The triple combination of osimertinib, pemetrexed, and platinum-based chemotherapy is being investigated in the phase III trial FLAURA2[33] and the phase II OPAL trial.[34] Although the optimal strategy for patients with *EGFR*+ NSCLC with PPE is currently unclear, it is possible that the combined use of EGFR and VEGF inhibitors may achieve further improvement in efficacy outcomes in this setting. As such, the efficacy of osimertinib and bevacizumab in patients with *EGFR*+ NSCLC and PPE is currently being investigated.[35]

In conclusion, the phase II JO25567 study of erlotinib plus bevacizumab demonstrated clinical benefit in Japanese patients with stage IIIB/IV or postoperative, recurrent *EGFR*+ NSCLC. The data reported here add to the existing literature supporting the use of the combination of erlotinib plus bevacizumab as a beneficial treatment strategy in patients with *EGFR*+ NSCLC, in particular for those with baseline PPE.

ACKNOWLEDGMENTS

We thank the investigators, the patients, and their families for their contribution to this clinical study; and Misa Tanaka for supporting with data analysis. Third-party medical writing assistance, under the direction of the authors, was provided by Ben Castle, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by Chugai Pharmaceutical Co., Ltd.

CONFLICT OF INTEREST

Yukio Hosomi has received payment/honoraria from Chugai Pharmaceutical, AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Bristol-Myers Squibb, Kyowa Kirin, and Ono Pharmaceutical. Takashi Seto has received funding from Chugai Pharmaceutical (institution); and grants or contracts from Daiichi-Sankyo, Eli Lilly Japan, MSD, Novartis Pharma, Pfizer Japan, Takeda Pharmaceutical, AbbVie, Kissei Pharmaceutical, Loxo Oncology, and Merck Biopharma. Makoto Nishio has received grants and personal fees from AstraZeneca, Amgen, MSD, Taiho Pharmaceutical, Takeda Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Novartis, Pfizer, Bristol-Myers Squibb, and Merck Biopharma; personal fees from Ono Pharmaceutical, Boehringer Ingelheim, and Janssen Pharmaceutical; and grants from Daiichi-Sankyo. Koichi Goto has received research grants from Amgen Astellas BioPharma, Astellas Pharma, Amgen, AstraZeneca, Boehringer Ingelheim Japan, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Eli Lilly Japan, Ignyta, Janssen Pharmaceutical, Kissei Pharmaceutical, Kyowa Kirin, Loxo Oncology, Medical and Biological Laboratories, Merck Biopharma, Merus, MSD, NEC Corporation, Novartis Pharma Ono Pharmaceutical, Pfizer Japan, Sumitomo Dainippon Pharma, Spectrum Pharmaceuticals, Sysmex Corporation, Haihe Biopharma, Taiho Pharmaceutical, and Takeda Pharmaceutical; honoraria from Amgen Astellas BioPharma, Amgen, Amoy Diagnosties, AstraZeneca, Boehringer Ingelheim Japan, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi-Sankyo, Eisai, Eli Lilly Japan, Guardant Health, Janssen Pharmaceutical, Kyowa Kirin, Life Technologies Japan, MSD, Novartis Pharma, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer Japan, Taiho Pharmaceutical, and Takeda Pharmaceutical. Noboru Yamamoto has received research grants from Chugai Pharmaceutical, Taiho Pharmaceutical, Eisai, Eli Lilly, Quintiles, GlaxoSmithKline, Sumitomo Dainippon, Chiome Bioscience, Otsuka, Janssen Pharma, MSD, Merck, Astellas Pharma, Bristol-Myers Squibb, Novartis Pharma, Daiichi-Sankyo, Pfizer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Bayer, Ono Pharmaceutical, and Takeda; honoraria from Chugai Pharmaceutical, AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Ono Pharmaceutical, Sysmex, and Pfizer; and consulting fees from Eisai, Otsuka, Takeda, Boehringer Ingelheim, and Cimic. Isamu Okamoto has received payment/honoraria from Chugai Pharmaceutical. Kosei Tajima and Yusuke Kajihara are employees of Chugai Pharmaceutical. Nobuyuki Yamamoto has received honoraria from MSD, AstraZeneca, Ono Pharmaceutical, Thermo Fisher Scientific, Daiichi-Sankyo, Takeda, Chugai Pharmaceutical, Eli Lilly Japan, Boehringer Ingelheim, Novartis, Pfizer, Bristol-Myers Squibb, Nippon Kayaku, GlaxoSmithKline, Sanofi,

Hisamitsu Pharmaceutical, and Merck Biopharma; participated on a data safety monitoring board/advisory board for MSD, AstraZeneca, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Chugai Pharmaceutical, Eli Lilly Japan, Boehringer Ingelheim, Novartis, Pfizer, Bristol-Myers Squibb, Life Technologies Japan, Nippon Kayaku, Amgen, Guardant Health Japan, and Janssen Pharmaceutical; and performed in a leadership role for The Japan Lung Cancer Society, Japanese Association of Supportive Care in Cancer, and West Japan Oncology Group.

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How to cite this article: Hosomi Y, Seto T, Nishio M, Goto K, Yamamoto N, Okamoto I, et al. Erlotinib with or without bevacizumab as a first-line therapy for patients with advanced nonsquamous epidermal growth factor receptor-positive non-small cell lung cancer: Exploratory subgroup analyses from the phase II JO25567 study. Thorac Cancer. 2022;13(15): 2192–200. https://doi.org/10.1111/1759-7714.14541