RESEARCH ARTICLE

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Erlotinib for Japanese patients with activating *EGFR* mutation-positive non-small-cell lung cancer: combined analyses from two Phase II studies

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Aims: We evaluated the efficacy and safety of erlotinib, and patient characteristics affecting progression-free survival (PFS), by analyzing data from two Phase II studies of first-line erlotinib in activating *EGFR* mutation-positive non-small-cell lung cancer. **Methods:** Data were combined from patients who received first-line erlotinib monotherapy in JO22903 (single-arm study; JapicCTI-101085) and JO25567 (randomized study; JapicCTI-111390). **Results:** Median PFS was 10.9 months in efficacy-evaluable patients (n = 177). Major adverse events were dermatologic; no new safety signals were observed. Baseline pleural/cardiac effusion notably affected PFS (yes median 8.0 months vs no median 15.3 months) as confirmed in multivariate analysis (hazard ratio: 0.38; 95% CI: 0.25–0.58). **Conclusion:** Efficacy and safety of erlotinib monotherapy were consistent with previous studies. Baseline pleural/pericardial effusion was associated with shorter PFS.

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Lung cancer is the most common cause of cancer-related deaths worldwide [1]. In Japan, an estimated 94,855 cases of lung cancer were reported in 2012, with an estimated 75,120 deaths due to the disease [2]. Recent advances in molecular translational research have led to breakthroughs in the treatment and diagnosis of lung cancer. One of the most researched genetic alterations in non-small-cell lung cancer (NSCLC) has been mutations of the *EGFR* gene. The *EGFR* family receptor tyrosine kinases are responsible for the regulation of developmental, metabolic and physiologic processes. *EGFR*-activating mutations occur more frequently in Asian-Pacific patients than in European patients, with observed mutation rates of 20–76% versus 6–41%, respectively [3]. The development of *EGFR* tyrosine kinase inhibitors (TKIs) to target these mutations has led to significant progress in the treatment of NSCLC.

Current clinical guidelines recommend *EGFR* TKIs for the treatment of *EGFR* mutation-positive NSCLC [4,5]. Three *EGFR* TKIs, erlotinib, gefitinib and afatinib, are approved in the USA, EU and Japan for the first-line treatment of patients with this distinct subset of NSCLC. In seven randomized Phase III trials, these *EGFR* TKIs consistently showed significant progression-free survival (PFS) benefits compared with standard chemotherapy in patients with advanced NSCLC whose tumors harbored activating *EGFR* mutations [6]. In Asian patients with activating *EGFR*

KEYWORDS

- combined analyses • *EGFR* mutations • erlotinib • first line • Japanese patients
- non-small-cell lung cancer

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mutation-positive NSCLC, first-line erlotinib, gefitinib and afatinib also showed improved clinical outcomes compared with chemotherapy [7–9]. Furthermore, in the Phase II, single-arm, JO22903 study (JapicCTI-101085) in Japanese patients whose tumors harbored activating *EGFR* mutations, erlotinib monotherapy provided a median PFS (primary end point) of 11.8 months (95% CI: 9.7–15.3) [10]. Similarly, the Phase II, JO25567 (JapicCTI-111390) randomized study demonstrated a median PFS (primary end point) of 16.0 months (95% CI: 13.9–18.1) versus 9.7 months (95% CI:

5.7–11.1), respectively, for erlotinib plus bevacizumab versus erlotinib alone; hazard ratio (HR): 0.54; 95% CI: 0.36–0.79; $p = 0.0015$ [11].

Although *EGFR* TKI monotherapy has demonstrated good clinical efficacy in the first-line treatment of *EGFR* mutation-positive NSCLC, not all patients benefit to the same extent. The association between poor efficacy with *EGFR* TKIs and baseline characteristics of patients with activating *EGFR* mutation-positive NSCLC is still not well known. Identifying this link could be valuable for the development of more effective *EGFR* TKI treatment strategies

Table 1. Baseline characteristics.

Characteristic	JO25567 (n = 77), n (%)	JO22903 (n = 100 [†]), n (%)	Combined population (n = 177), n (%)
Gender:			
– Male:female	26 (34):51 (66)	33 (33):67 (67)	59 (33):118 (67)
Age (years):			
– Median (range)	67 (36–84)	65 (36–86)	66 (36–86)
– ≥75 years	15 (20)	14 (14)	29 (16)
– <75 years	62 (81)	86 (86)	148 (84)
ECOG PS:			
– 0	41 (53)	47 (47)	88 (50)
– 1	36 (47)	53 (53)	89 (50)
Stage:			
– Recurrence	15 (20)	24 (24)	39 (22)
– Stage IIIB/IV	62 (81)	76 (76)	138 (78)
Smoking status:			
– Nonsmoker	45 (58)	57 (57)	102 (58)
– Current/former smoker	32 (42)	43 (43)	75 (42)
<i>EGFR</i> mutation:			
– L858R mutation	37 (48)	50 (50)	87 (49)
– Exon 19 deletion	40 (52)	50 (50)	90 (51)
Sum of baseline longest diameter of tumor (mm):			
– ≥41	35 (45)	54 (54)	89 (50)
– <41	42 (55)	46 (46)	88 (50)
– ≥67	19 (25)	27 (27)	46 (26)
– <67–41	16 (21)	27 (27)	43 (24)
– <41–26	20 (26)	24 (24)	44 (25)
– <26	22 (29)	22 (22)	44 (25)
Number of affected organs:			
– ≥3	45 (58)	81 (81)	126 (71)
– <3	32 (42)	19 (19)	51 (29)
PPE:			
– Yes	36 (47)	33 (33)	69 (39)
– No	41 (53)	67 (67)	108 (61)
Brain metastases:			
– Yes	NA	20 (20)	20 (11)
– No	77 (100)	80 (80)	157 (89)

[†]Two patients with T790M mutation and one patient with a major protocol violation were excluded.

ECOG PS: Eastern Cooperative Oncology Group performance status; NA: Not applicable; PPE: Pleural/pericardial effusion.

Figure 1. Progression-free survival with first-line erlotinib in JO22903, JO25567 and combined populations.

PFS: Progression-free survival.

and for designing future clinical trials in activating *EGFR* mutation-positive NSCLC. In addition, the pattern of tumor progression and metastasis, especially in the brain, could affect available treatment options and patient prognosis. Data from prospective studies on the pattern of disease progression following first-line *EGFR* TKI treatment are limited. For these reasons, we sought to evaluate the efficacy and safety of erlotinib more precisely by performing a combined analysis of the JO22903 and JO25567 study data, with particular focus on the sites of progression following first-line erlotinib monotherapy and on potential factors that could affect erlotinib efficacy.

Methods

• Study design & patients

This combined analysis only included patients who were receiving first-line erlotinib monotherapy in study JO22903 or JO25567.

JO22903 (single arm [10]) and JO25567 (randomized [11]) were Phase II, multicenter, open-label studies conducted at 25 and 30 centers in Japan, respectively. Eligible patients were aged ≥ 20 years, had not received prior chemotherapy, and had advanced, untreated, metastatic stage IIIB/IV or recurrent NSCLC with Eastern

Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Patients with tumors harboring confirmed activating mutations of *EGFR* (exon 19 deletion or L858R point mutation in exon 21) with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST; v.1.0 for JO22903 or v.1.1 for JO25567) were enrolled. Patients were excluded in JO25567 if they had *EGFR* T790M mutation, squamous cell carcinoma or brain metastases. Patients enrolled in JO22903 whose tumors harbored T790M mutations were excluded from this combined analysis in order to align the patient groups between the two studies.

In total, 103 patients were enrolled in JO22903 between April 2010 and October 2010, and 77 patients were enrolled in the erlotinib monotherapy arm of JO25567 between February 2011 and March 2012. In the combined analysis, 178 patients were included in the safety population, 101 from JO22903 and 77 from JO25567 (two patients from JO22903 who had *EGFR* T790M mutations were excluded). One patient from JO22903 was excluded from the efficacy population due to a major protocol violation, leaving 177 efficacy-evaluable patients. Both studies were carried out in accordance with the Declaration of Helsinki and Good Clinical

Practice guidelines. The protocol for each study was approved by the appropriate ethics committees and all patients gave informed consent for study participation.

• Procedures

Eligible patients received oral erlotinib 150 mg/day until disease progression (PD) or unacceptable toxicity in JO22903 and the erlotinib monotherapy arm of JO25567. In JO25567, patients were randomly allocated in a 1:1 ratio to receive erlotinib (150 mg/day) plus bevacizumab (15 mg/kg) or erlotinib alone (150 mg/day) using a dynamic allocation method. Patients were screened for *EGFR* mutations in a local or central laboratory according to standard testing practice. Further study details have been reported in the primary manuscripts [10,11].

• Assessments

Tumor response was assessed by an independent review committee using RECIST. Tumor response evaluation was scheduled every 6 weeks. Adverse events (AEs) were graded according to the National Cancer Institute Common

Terminology Criteria for Adverse Events (NCI-CTC AE) v. 4.0. Safety was assessed according to the Medical Dictionary for Regulatory Activities (MedDRA; v.13.0 for JO22903 and v.14.0 for JO25567) preferred terms and tabulated by grade. At baseline, mandatory lung and abdominal scans (computerized tomography [CT]/MRI), brain scans (CT/MRI) and bone scans (bone scintigraphy, PET, CT or MRI) were performed.

• Study end points

The primary end point in both studies was independent review committee-assessed PFS according to RECIST. Secondary end points included overall response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

• Statistical analyses

Kaplan–Meier methodology was used to assess median PFS; 95% CI limit was calculated using the Greenwood method; HRs were estimated by Cox model. Individual patient data from JO22903 and the erlotinib monotherapy arm of JO25567 were combined. Univariate Cox

Figure 2. Univariate Cox regression analysis of progression-free survival. ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio; PFS: Progression-free survival.

Table 2. Multivariate Cox regression[†] for progression-free survival.

Covariate	HR [‡]	95% CI	p-value
Age:			
– ≥75 vs <75 years	1.31	0.78–2.18	0.303
<i>EGFR</i> mutation:			
– Exon 19 deletion vs L858R	0.74	0.49–1.12	0.148
Stage:			
– Recurrence vs stage IIIB/IV	0.93	0.54–1.60	0.780
Gender:			
– Female vs male	0.69	0.43–1.11	0.129
Smoking status:			
– Nonsmoker vs current/former smoker	1.15	0.72–1.85	0.559
ECOG PS:			
– 0 vs 1	0.67	0.45–0.99	0.046
Sum of baseline longest diameter of tumor (mm):			
– <26 vs ≥67	0.56	0.30–1.07	0.078
– <41–26 vs ≥67	0.69	0.39–1.20	0.190
– <67–41 vs ≥67	1.06	0.64–1.77	0.820
Number of affected organs:			
– ≥3 vs <3	1.15	0.71–1.86	0.578
PPE:			
– No vs yes	0.38	0.25–0.58	<0.0001

[†]All variables included in the analysis are described in the table.
[‡]HR <1.0 means that PFS was better in the left group compared with the right group.
ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio; PPE: Pleural/pericardial effusion.

regression analysis of PFS was conducted by baseline characteristics; age, *EGFR* mutation type, stage, gender, smoking status, ECOG PS, sum of the longest diameter of target lesions, number of affected organs and pleural/pericardial effusions (PPE). Multivariate Cox regression was used to estimate HRs for risk of PD associated with each baseline characteristic. All patients with activating *EGFR* mutations who received at least one dose of study treatment (excluding two patients with *EGFR* T790M mutations) were included in the safety population. Patients with major protocol violations were excluded from the efficacy population. Statistical analyses were performed using SAS v. 9.2.

Results

• Patient population

Baseline characteristics for the combined population are shown in **Table 1**. There were some differences between the two populations in terms of the proportion of patients with ≥3 or <3 affected organs and the proportion of patients with PPE at baseline. The majority of patients were female (n = 118; 67%), aged <75 years (n = 148; 84%) and were nonsmokers (n = 102; 58%). Median age was 66 years (range: 36–86), 87 patients (49%) had an *EGFR* L858R mutation and 90

patients (51%) had an *EGFR* exon 19 deletion. A total of 69 patients (39%) had PPE and 20 patients (11%) had brain metastases at baseline.

• Efficacy

Median PFS with first-line erlotinib monotherapy was 10.9 months (95% CI: 9.7–12.5) for the combined analysis compared with 12.3 months (95% CI: 9.7–15.3) and 9.7 months (95% CI: 5.7–11.1) for the individual JO22903 and JO25567 study populations, respectively (**Figure 1**). ORR was 73% (95% CI: 66–79) and DCR was 92% (95% CI: 87–96). Univariate Cox regression analysis for PFS is shown in **Figure 2**. Despite many patient characteristics showing improvements in PFS, only ECOG PS (HR: 0.67; 95% CI: 0.45–0.99; p = 0.046) and PPE at baseline (HR: 0.38; 95% CI: 0.25–0.58; p < 0.0001) were significant risk factors for PFS in multivariate analysis (**Table 2 & Figure 3**). Specific *EGFR* mutations, being female, having smaller tumor diameter and fewer affected organs appeared to be associated with improved PFS in the multivariate analysis, but these associations were not statistically significant.

ORR and DCR in patients with PPE were 61 and 86%, respectively, versus 81 and 96%, respectively, in patients without PPE.

Common sites of progression are shown in [Table 3](#). The majority of patients had PD in the lung (n = 101; 81%), lymph nodes (n = 31; 25%) and bone (n = 20; 16%). Progression of brain metastases was observed in six patients (4.8%) who had PD. Of these six patients, three had brain metastases at baseline and three patients did not ([Table 4](#)); two of the patients had carcinomatous meningitis at PD.

• Safety

AEs reported in >20% of patients in the safety population, or AEs considered to be of special interest, are presented in [Table 5](#). The most common AEs were rash (99% of patients at any grade, 19% at grade ≥3), and diarrhea (79% of patients at any grade, 1% at grade ≥3). Interstitial lung disease was reported in 5% (any grade) and 2% (grade ≥3) of patients.

Discussion

EGFR TKIs are the standard of care for the treatment of *EGFR* mutation-positive NSCLC and are recommended in clinical guidelines [4,5]. Erlotinib has shown significantly improved clinical outcomes compared with standard chemotherapy in the first-line treatment setting for *EGFR* mutation-positive NSCLC [7,12–13]. The

Phase II JO22903 and JO25567 studies were prospectively designed to investigate erlotinib for the first-line treatment of Japanese patients with *EGFR* mutation-positive NSCLC [10,11].

In this combined analysis of JO22903 and JO25567, first-line erlotinib monotherapy had a favorable efficacy and safety profile in Japanese patients with *EGFR* mutation-positive NSCLC. This analysis revealed a median PFS of 10.9 months, which is in line with Phase III studies of first-line erlotinib in *EGFR* mutation-positive NSCLC; a median PFS of 13.1 and 11.0 months, respectively, was reported in the OPTIMAL trial [7] and in the ENSURE trial [13], both enrolling Chinese patients, compared with 10.4 months in the EURTAC trial [12], which enrolled European patients. Also, first-line erlotinib monotherapy was well tolerated with an acceptable safety profile in patients with *EGFR* mutation-positive NSCLC. The safety profile of erlotinib was as expected, with rash and diarrhea being the most common AEs in this combined analysis, which were in line with previous Phase III studies of erlotinib [6].

An advantage of this combined analysis is that both of the studies were conducted during the same time period, solely in Japanese patients, such that all patients were treated under almost

Figure 3. Combined analysis of progression-free survival according to pleural/pericardial effusions at baseline.
HR: Hazard ratio; PFS: Progression-free survival.

identical medical conditions. As combined analyses are useful in terms of increased precision, due to a larger sample size, the results of this study provide further support for erlotinib monotherapy as an effective treatment option for first-line *EGFR* mutation-positive NSCLC.

It is well known that certain patient groups respond better to *EGFR* TKIs. These include female patients, nonsmokers and patients who have tumors with *EGFR*-activating mutations [14]. However, the clinical factors that could affect the efficacy of *EGFR* TKIs are still unclear. In multivariate Cox regression analysis, PPE status was identified as an independent risk factor for PFS. Although there has been a wealth of data on *EGFR* TKIs in patients whose tumors harbor *EGFR*-activating mutations, few studies have reported data in patients with pleural effusions [15]. In a study of 150 patients from Taiwan with pleural effusion, mean age 68.2 years (± 13.7 years), who received *EGFR* TKIs as first-line treatment, median PFS was 9.6 months in 59 patients with L858R mutation or *EGFR* exon 19 deletion [16]. Pleural effusion was associated with decreased survival in patients with distant metastases [17]. Furthermore, in a retrospective study of 283 patients with lung adenocarcinoma from China, median age 59 years (range: 30–81), there was positive association between activating *EGFR* mutations and pleural effusion [18]. A number of preclinical findings also support these clinical observations. VEGF expression contributes to *EGFR* TKI efficacy [19] and has also been implicated as a critical cytokine in pleural effusion pathogenesis [20]. Furthermore, mutant *EGFR* tumor has itself been shown to promote malignant pleural effusion formation via activation of the C-X-C motif chemokine ligand pathway [21]. To our knowledge, the results of this combined analysis are the first to suggest that the absence of PPE may be a predictive factor of improved efficacy with erlotinib. These data suggest that

Table 3. Sites of progression in patients who had disease progression following *EGFR* tyrosine kinase inhibitor treatment (n = 125).

Progression site	Patients (n)
Lung	101
Lymph nodes	31
Bone	20
Pleura	18
PPE	18
Liver	11
Brain [†]	6
Adrenal gland	3
Kidney	2
Pericardial effusion	2
Peritoneum	1
Ovary	1
Ascites	1
Other	3

[†]Two patients had carcinomatous meningitis at disease progression.
PPE: Pleural/pericardial effusion.

more efficacious treatment strategies with *EGFR* TKIs are desired in patients with PPE who have activating *EGFR* mutations. It should be noted that due to the absence of a control arm in this combined analysis, any predictive factors could not be statistically evaluated against placebo. Therefore, as similar studies looking at erlotinib monotherapy for patients with PPE are limited, these findings should be examined more closely in prospective studies.

Although the pattern of tumor progression, particularly in the brain, following *EGFR* TKI treatment could affect subsequent treatment options and patient prognosis, data are still limited. In a retrospective Japanese study of 92 patients, the development of CNS metastases after acquired resistance to *EGFR* TKIs in patients with activating *EGFR* mutations was associated with poor prognosis, which suggested that controlling CNS metastases is important

Table 4. Patient characteristics of six patients who had CNS progression.

Number	Age (years)	ECOG PS	<i>EGFR</i> mutation	Baseline CNS metastases	Erlotinib dose at PD (mg)	PFS (days)	Simultaneous progression site	Subsequent treatment after PD
1	50	1	19 del	No	100	106	None	Yes
2	55	1	19 del	Yes	150	335	Lung	Yes
3	55	0	L858R	No	150	168	Lung	Yes
4	73	1	L858R	Yes	150	80	Lung	Yes
5	60	0	L858R	No	150	188	None	None
6	54	0	L858R	Yes	100	377	Lung	Yes

del: deletion; ECOG PS: Eastern Cooperative Oncology Group performance status; PD: Progressive disease; PFS: Progression-free survival.

Table 5. Adverse events with an incidence of >20% or considered adverse events of special interest.

Adverse event	All grades, n (%)	Grade ≥3, n (%)
Rash†	176 (99)	34 (19)
Diarrhea	141 (79)	2 (1)
Dry skin	125 (70)	5 (3)
Paronychia	118 (66)	4 (2)
Stomatitis	111 (62)	3 (2)
Pruritus	99 (56)	3 (2)
Hepatic dysfunction†	93 (52)	28 (16)
Anorexia	61 (34)	4 (2)
Nasopharyngitis	53 (30)	0 (0)
Alopecia	43 (24)	0 (0)
Decreased weight	40 (23)	1 (1)
Nausea	38 (21)	1 (1)
Constipation	38 (21)	1 (1)
Dysgeusia	38 (21)	0 (0)
Interstitial lung disease‡	9 (5)	3 (2)*

†Group term.

‡Two of the three cases of grade ≥3 interstitial lung disease were grade 5.

to improve OS [22]. In previous reports, brain or leptomeningeal metastases as the initial PD site were present in >30% of patients who had an objective response to gefitinib (median age: 64 years [range: 38–87 years]) [23]. Other studies have reported that brain metastases were present in 8% of patients as the initial site of PD following EGFR TKI therapy (gefitinib: n = 11; erlotinib: n = 90) [24]. In our combined analysis, brain lesions were well controlled by erlotinib, with progression in the brain observed in only 4.8% of patients who had PD, which is consistent with previous reports [24]. However, a limitation of these analyses is that the status of metastases at baseline may differ between studies, which could affect the pattern of progression. These results should be validated further in prospective studies.

Conclusion

Combined analyses of the Phase II JO22903 and JO25567 studies revealed that first-line erlotinib monotherapy demonstrates favorable efficacy and safety in Japanese patients with EGFR mutation-positive NSCLC. Exploratory analysis showed that erlotinib controls brain lesions well and that the absence of PPE was associated with a better PFS; these findings suggest that the efficacy of EGFR TKIs will be affected by disease status and some patients, such as those with PPE, may require more intensive therapy.

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been obtained from the participants involved. The protocol for each study was approved by the appropriate ethics committees and all patients gave informed consent for study participation.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has

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EXECUTIVE SUMMARY

- Erlotinib is a standard of care for the treatment of *EGFR* mutation-positive non-small-cell lung cancer (NSCLC) with significantly improved clinical outcomes compared with chemotherapy in the first-line treatment setting.
- The Phase II JO22903 and JO25567 studies demonstrated that first-line erlotinib monotherapy is both effective and tolerable in Japanese patients with *EGFR* mutation-positive NSCLC.
- A median progression-free survival of 10.9 months with erlotinib monotherapy was reported in this combined analysis of the JO22903 and JO25567 studies and was in line with previous Phase III studies of first-line erlotinib for *EGFR* mutation-positive NSCLC.
- The absence of pleural/pericardial effusions was associated with a better progression-free survival.
- Brain lesions were well controlled by erlotinib with progression in the brain observed in only 4.8% of patients who had progressive disease.
- Erlotinib monotherapy had a tolerable and manageable safety profile.

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