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Original Article

Real-world use of osimertinib for epidermal growth factor receptor T790M-positive non-small cell lung cancer in Japan

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Abstract

Objective: Adverse drug reactions (ADRs) during real-world osimertinib use were investigated in Japan.

Methods: Patients with epidermal growth factor receptor (EGFR) T790M-positive non-small cell lung cancer treated with second-line or later oral osimertinib per the Japanese package insert (80 mg once daily) were included. Data were collected between 28 March 2016 and 31 August 2018.

Results: The median observation period in the safety analysis population ($n = 3578$) was 343.0 days. ADRs (defined as adverse events whose causality to osimertinib could not be denied by the attending physicians or manufacturer) were reported in 58.1% (2079/3578) of patients. ADRs of interstitial lung disease events were reported in 6.8% (245/3578; Grade $\geq$ 3, 2.9% [104/3578]) of patients, of whom 29 (11.8%) died (0.8% of patients overall). ADRs of QT interval prolonged, liver disorder and haematotoxicity were reported in 1.3% (45/3578; Grade $\geq$ 3, 0.1% [5/3578]), 5.9% (212/3578; Grade $\geq$ 3, 1.0% [35/3578]) and 11.4% (409/3578; Grade $\geq$ 3, 2.9% [104/3578]) of patients, respectively. In the efficacy analysis population ($n = 3563$), 119 (3.3%) patients had complete

responses, 2373 (66.6%) had partial responses and 598 (16.8%) had stable disease. The objective response rate was 69.9%; disease control rate was 86.7%; and median progression-free survival (PFS) was 12.3 months. At 6 and 12 months, PFS rates were 77.4% (95% confidence interval [CI], 75.9–78.9) and 53.2% (95% CI, 51.3–55.1) and overall survival rates were 88.3% (95% CI, 87.2–89.4) and 75.4% (95% CI, 73.8–77.0), respectively.

Conclusions: These data support the currently established benefit-risk assessment of osimertinib in this patient population.

Key words: non-small cell lung cancer, epidermal growth factor receptor, osimertinib, safety, treatment outcome

Introduction

Lung cancer is the most commonly diagnosed form of cancer worldwide and is the leading cause of cancer mortality (1). The incidence and prevalence are particularly high in Asian countries (1,2). Agents targeting the epidermal growth factor receptor (EGFR) are the current mainstay of treatment for non-small cell lung cancer (NSCLC); however, resistance eventually develops to these EGFR-tyrosine kinase inhibitors (TKIs) due to the development of acquired mutations, with T790M observed in ~50% of cases (3,4).

Osimertinib is a third-generation, irreversible, oral EGFR-TKI (5) that inhibits EGFR-TKI sensitizing (EGFRm) and T790M resistance mutations (6–11). Results from the randomized, open-label, phase III AURA3 study in patients with NSCLC who had progressed during first-line EGFR-TKI therapy showed that osimertinib provided significantly greater efficacy in terms of progression-free survival (PFS) (10.1 vs. 4.4 months in median PFS; hazard ratio [HR] after adjustment for Asian or non-Asian race, 0.30; 95% confidence interval [CI], 0.23–0.41; $P < 0.001$) (7). A statistically significant improvement in overall survival (OS) between treatment with osimertinib vs. platinum therapy plus pemetrexed was not observed (26.8 vs. 22.5 months, respectively; HR, 0.87; 95% CI, 0.67–1.12; $P = 0.277$) (12). PFS results were consistent within the Japanese subpopulation (13). In the multicentre, double-blind, phase III FLAURA study in treatment-naive patients, globally, osimertinib significantly improved OS (11) and PFS (8) compared with the standard-of-care, gefitinib or erlotinib (OS 38.6 vs. 31.8 months, respectively; HR, 0.80; 95.05% CI, 0.64–1.00; $P = 0.046$; median PFS 18.9 vs. 10.2 months; HR, 0.46; 95% CI, 0.37–0.57; $P < 0.001$). The first-line PFS results were also recently confirmed in the Japanese subpopulation of the FLAURA study (median PFS with osimertinib 19.1 months vs. gefitinib 13.8 months; HR, 0.61; 95% CI, 0.38–0.99) (14) and were consistent with data from a treatment-naive cohort of the AURA study (median PFS with osimertinib 22.1 months) (15).

Osimertinib was approved in Japan on 28 March 2016 for the second- or later-line treatment of patients with EGFR T790M mutation-positive NSCLC, who had progressed on prior EGFR-TKIs (16). Osimertinib was subsequently approved as first-line therapy in 2018 (17).

The Japan-local all-patient Clinical Experience Investigation (CEI) was initiated as part of the post-marketing activities in patients receiving treatment in the second-line or later setting, as required by pharmaceutical regulatory rules. The objectives of the CEI were to collect information regarding the development of adverse drug reactions (ADRs) during the real-world use of osimertinib; to investigate factors that may affect the safety and efficacy outcomes resulting from the use of osimertinib; to investigate the occurrence of interstitial lung diseases (ILDs); and to record any unexpected ADRs or new safety concerns associated with osimertinib treatment that are not already included in the Japanese package insert (16).

Materials and methods

Study design and patients

This was a post-marketing investigation (ClinicalTrials.gov Identifier: NCT02756039) conducted at 718 hospitals in Japan between 28 March 2016 (date of Japanese regulatory approval) and 31 August 2018 (data cutoff date). An early access program (EAP) was conducted at 37 sites between the approval date and 24 May 2016 (launch date); patients who participated in the EAP were retrospectively enrolled into the CEI after launch. The remaining patients were all those enrolled after launch. The planned study observation period was 12 months, with formal data collection using case report forms (CRFs). The planned sample size was 3000 patients who received treatment with osimertinib second-line or later according to the approved indication at the start of the investigation, namely, EGFR T790M mutation-positive inoperable or recurrent NSCLC resistant to EGFR-TKIs. Of note, this differs from the current indication in Japan, which is 'inoperable or recurrent EGFR gene mutation-positive NSCLC' (16).

All patients were enrolled by a central registration system, and there were no inclusion or exclusion criteria (as the name suggests, all-patient investigations must include all patients registered, regardless of indication; patients with the approved indication and with evaluable data are then selected for safety and efficacy analyses). As this was a post-marketing study, it was not necessary to obtain approval from an ethical review board or patient informed consent, based on Japanese regulatory guidelines for Good Post-marketing Surveillance Practice (18). Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at http://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Treatment

Patients were treated with oral osimertinib according to the Japanese package insert (16), which states that the usual adult dosage is 80 mg once daily (QD); the dosage should be adjusted, where necessary, according to the patient's condition.

Outcome measures

Adverse events (AEs) were recorded using preferred terms (PTs) from the Japanese Medical Dictionary for Regulatory Activities (MedDRA/J) version 21.0. AEs whose causality to osimertinib could not be denied by the attending physicians or the manufacturer (AstraZeneca, Cambridge, United Kingdom) were reported as ADRs for this CEI; thus, ADRs in this report included those in which the causal relationship may be unclear due to insufficient information. Similarly, ADRs with the outcome of death included events for which a relationship to osimertinib could not be ruled out or events not attributable to ADRs but which nonetheless resulted in death.

Table 1. Patient demographic data and disease characteristics (safety analysis population)

Characteristic	Patients n = 3578, n (%)
Age, years	
<65	1005 (28.1)
≥65	2573 (71.9)
Sex	
Male	1207 (33.7)
Female	2371 (66.3)
BMI, kg/m^2	
<18.5	883 (24.7)
≥18.5–<25	2023 (56.5)
≥25–<30	355 (9.9)
≥30	45 (1.3)
No data	272 (7.6)
Smoker	
No	2513 (70.2)
Yes	1063 (29.7)
No data	2 (0.1)
WHO PS	
≤1	2904 (81.2)
≥2	674 (18.8)
Treatment line	
≤3	1794 (50.1)
≥4	1760 (49.2)
Unknown	24 (0.7)
EGFR mutation test performed	
No	5 (0.1)
Yes	3564 (99.6)
Specimen for EGFR mutation test[a]	
Lung (histology sample)	1487 (41.6)
Lung (cytology sample)	365 (10.2)
Organ other than lung	733 (20.5)
Plasma	335 (9.4)
Other liquid sample	759 (21.2)
EGFR mutation status[a]	
T790M[b]	3466 (96.9)
Exon 19 deletion	1761 (49.2)
L858R	1243 (34.7)
Others	88 (2.5)
Unknown	9 (0.3)
Clinical stage	
IIIB	142 (4.0)
IV	3086 (86.2)
Other	350 (9.8)
Histology at the time of diagnosis[a]	
Adenocarcinoma	3524 (98.5)
Squamous cell carcinoma	29 (0.8)
Large cell carcinoma	5 (0.1)
Others	26 (0.7)
Prior anticancer drug treatment	
No	38 (1.1)
Yes[a]	3540 (98.9)
EGFR-TKI	3492 (97.6)
Gefitinib	2471 (69.1)
Erlotinib hydrochloride	1750 (48.9)
Afatinib maleate	1138 (31.8)
Chemotherapy	2271 (63.5)
Immuno-checkpoint inhibitor	288 (8.0)
Others	1204 (33.7)
History of lung surgery	
No	2458 (68.7)
Yes	1120 (31.3)
History of lung radiotherapy	
No	3325 (92.9)
Yes	253 (7.1)

Abbreviations: BMI, body mass index; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

[a]Patients can be counted multiple times if applicable to multiple categories.

[b]In this post-marketing investigation, the registration form was used as the primary source for evaluating patient eligibility for treatment with osimertinib per the Japanese package insert for second- or later-line treatment settings. However, the data collected from the case report forms included additional data to that obtained from the registration form. There remain some inconsistencies in the data between the registration form and case report forms. The data reported in this table are consistent with that collected from the case report forms.

As per the Japan-local risk management plan of osimertinib, important identified risks included ADRs of ILD-related events, QT interval prolonged, liver disorder and haematotoxicity; important potential risks included ADRs of cardiac disorders (excluding QT interval prolonged), infection, thromboembolism and corneal disorders. Time to first onset of the important identified risks was also evaluated.

As this was an observational investigation of real-world clinical experience, the timing of computed tomography (CT) image evaluation could not be stipulated. The efficacy outcomes of this analysis were adjudicated by the attending physician referring to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. These included best overall response (complete response [CR], partial response [PR] or stable disease [SD]), objective response rate (ORR; CR + PR) and disease control rate (DCR; CR + PR + SD). PFS and OS were also evaluated.

Statistical methods

The planned sample size of 3000 was determined to ensure that sufficient patients were included in the CEI for evaluating factors potentially associated with the incidence of ILD in the real-world clinical use setting, rather than for overall safety or efficacy. However, no ILD data directly relevant to the sample size rationale were included in this report. There were several statistical considerations for the sample size calculation. These included a 3:1 ratio of subjects at high and low risk, respectively, of developing ILD; an ILD incidence rate of 4% in the low-risk group; and an odds ratio of developing ILD for the high-risk:low-risk groups of 2.0. Using these assumptions, ∼2200 patients were needed to achieve 90% power to detect the difference between groups, with a two-sided significance level of 5%. To allow for variability in the ratio of patients in the low- and high-risk groups with respect to some risk factors of ILD, the target sample size was set at 3000 patients.

The analysis sets were defined based on pre-specified case-handling criteria. The safety population comprised all enrolled

patients who received osimertinib administration, completed at least one clinic visit after treatment initiation and had CRF data (with a safety evaluation) available, with the exception of patients violating the contract or registration to the CEI, duplicated patients and patients who had previously been treated with osimertinib. The efficacy population was the same as the safety population, with the exception of patients who did not use the drug for the approved indication (for the indication at the time of study initiation, see section 'Study design and patients') which was subject to re-examination by the Japanese regulatory agency, those who used the drug outside of the approved dosage or administration method and those without an efficacy evaluation, all of whom were not included in the efficacy analyses.

Patient demographic data, safety data and efficacy data were reported descriptively. When multiple ADRs of the same kind developed in one patient, the events were counted once for each patient. Efficacy outcomes were evaluated according to background patient factors, including age, the World Health Organization performance status (WHO PS), EGFR mutation status, central nervous system (CNS) metastasis and pleural effusion. The Clopper–Pearson exact method was used to calculate the 95% CI for ORR and DCR. PFS and OS were analysed using Kaplan–Meier methodology. Subgroup analyses of ORR, DCR and PFS were conducted for selected patient demographic and disease characteristics. No imputation was made for missing data. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

The patient disposition is shown in Fig. 1. Data were collected from a total of 3629 patients between 28 March 2016 and 31 August 2018, of whom 3578 were included in the safety analysis population and 3563 were included in the efficacy analysis population. The majority of patients (n = 43) excluded from the safety analysis population had previously received osimertinib. The majority of patients (n = 10) excluded from the efficacy analysis population had used osimertinib outside of the approved indication at the time of study initiation (see section 'Study design and patients').

Table 1 summarizes patient demographic data and disease characteristics. Two-thirds of patients were female (66.3%), and 71.9% were aged ≥65 years. More than two-thirds of patients were non-smokers (70.2%), and the majority had WHO PS ≤ 1 (81.2%) and stage IV disease (86.2%). Around half of patients were receiving osimertinib as second- or third-line therapy and half as fourth- or later-line.

The median observation period for patients in the safety analysis set was 343.0 days (range: 1–764).

ADRs

ADRs were reported in 58.1% (2079/3578) of patients (Table 2). Thirty percent (624/2079) of patients with an ADR were reported to have recovered, and 39.7% (825/2079) were reported to be improving. The outcome for 52 patients with ADRs was death (2.5% [52/2079]), corresponding to 1.5% of the 3578 patients in the safety analysis population. The outcomes were unknown for 22 patients (1.1% [22/2079]).

Table 3 shows details of key ADRs reported in this analysis. The most frequently reported ADRs were diarrhoea (10.9% [390/3578]) and paronychia (10.3% [370/3578]). ILD events were reported in 6.8% (245/3578) of patients, of which 2.9% (104/3578) were Grade ≥ 3. Of the 245 patients who developed ILD, 29 (11.8%) died. This corresponds to 0.8% of the 3578 patients in the safety analysis population. ADRs of QT interval prolonged, liver disorder and haematotoxicity were reported in 1.3% (45/3578; Grade ≥ 3, 0.1% [5/3578]), 5.9% (212/3578; Grade ≥ 3, 1.0% [35/3578]) and 11.4% (409/3578; Grade ≥ 3, 2.9% [104/3578]) of patients, respectively.

Table 2. ADRs and outcomes (safety analysis population)

ADR[a]	Patients n = 3578
Number of patients (%)	2079 (58.1)
Number of events[b]	4255
Outcome[c], n (%)	(Percentage based on patients with ADRs, n = 2079)
Recovered	624 (30.0)
Improving	825 (39.7)
Still present	547 (26.3)
Recovered with sequelae	9 (0.4)
Death	52 (2.5)[d]
Unknown	22 (1.1)

Abbreviation: ADR, adverse drug reaction.
The number of patients (%) with ADR was calculated based on the safety analysis population. Outcome data were calculated based on the number of patients reporting an ADR.
[a]ADRs include adverse events for which causality to osimertinib could not be denied by the attending physician or drug manufacturer (AstraZeneca, Cambridge, United Kingdom).
[b]If multiple events of the same kind (at preferred term level) were observed within a patient, they were counted as one event in the table.
[c]When multiple ADRs were observed within a patient, outcome was chosen based on the following priority: death > recovered with sequelae > still present > improving > recovered. When the outcome of an event was unknown, the event was not included in the priority judgement. Only when the outcomes of all events were unknown for a given patient, the patient was reported as 'unknown'.
[d]The percentage of patients with ADRs with fatal outcome in the overall safety analysis population was 1.5% (52/3578).

The time to onset of key ADRs is illustrated in Fig. 2. The median onset of haematotoxicity following osimertinib initiation was 14.0 days from the first dose, whereas ILD and QT interval prolonged were reported at ~2 months after the first dose.

Additional key safety results are shown in Table 3. Grade ≥ 3 events of diarrhoea, skin disorder or paronychia each occurred in <1% of patients.

Efficacy outcomes

Of the 3563 patients in the efficacy analysis population, 119 (3.3%) had CR, 2373 (66.6%) had PR and 598 (16.8%) had SD. The ORR was 69.9% (2492/3563; 95% CI, 68.4–71.4). The DCR was 86.7% (3090/3563; 95% CI, 85.6–87.8).

Efficacy outcomes according to background patient factors are shown in Table 4. The ORR and DCR were higher in patients with WHO PS 0–1 (compared with PS 2–4) and in patients without CNS metastasis or with asymptomatic CNS metastasis (compared with patients with symptomatic CNS metastasis). The ORR and DCR were slightly higher in patients without pleural effusion. No notable differences were observed according to age or EGFR mutation.

PFS and OS Kaplan–Meier curves are shown in Figs 3 and 4. In the overall population, median PFS was 12.3 months (95% CI,

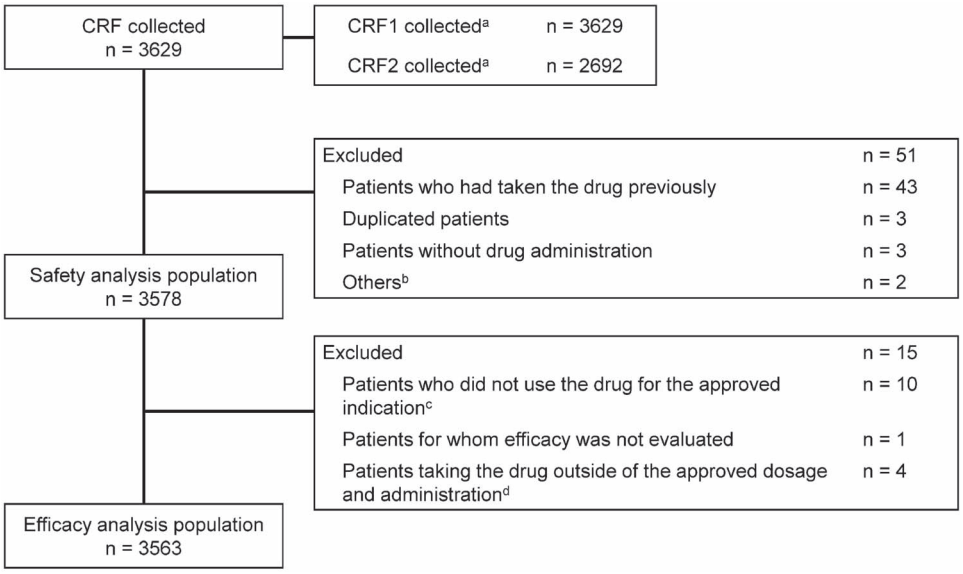

Figure 1. Patient disposition. Abbreviations: CRF, case report form; EGFR, epidermal growth factor receptor. [a]The observation period was 12 months. The data up to 3 months after osimertinib was started were entered in CRF1. Any additional data after 3 months of osimertinib treatment were entered in CRF2. [b]Included patients who started treatment prior to study registration. [c]The indication in the osimertinib package insert at the start of the investigation was EGFR T790M mutation-positive inoperable or recurrent non-small cell lung cancer resistant to EGFR-tyrosine kinase inhibitors. [d]The dosage and administration in the osimertinib package insert were 'Normally, orally administer 80 mg of osimertinib once daily in adults. Lower the dose as appropriate according to the patient's condition' (16).

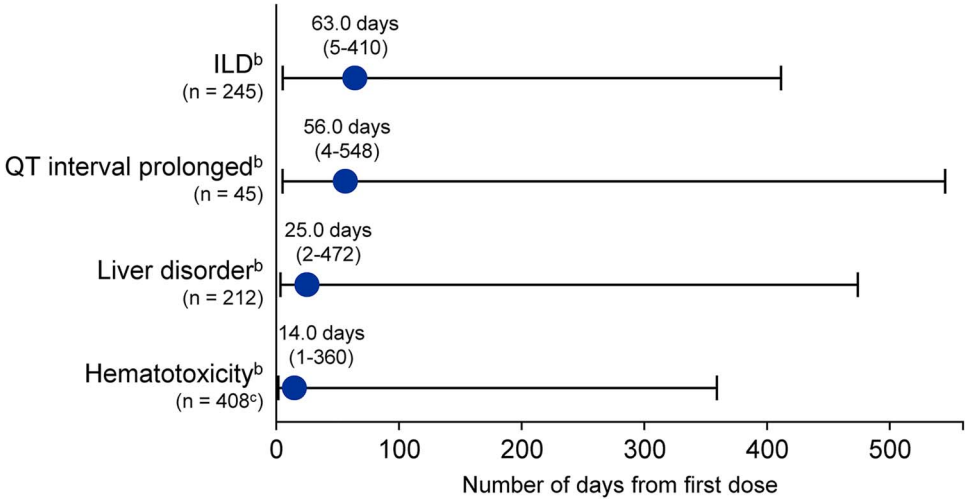

Figure 2. Median (range) time to onset of key ADRs[a] (safety analysis population). Abbreviations: ADR, adverse drug reaction; AE, adverse event; ECG, electrocardiogram; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term. [a]AEs whose causality to osimertinib could not be denied by the attending physicians or drug manufacturer (AstraZeneca, Cambridge, United Kingdom). [b]Grouped term based on investigator-reported AEs (not including laboratory/ECG abnormalities that were not reported by investigator). ILD (investigator assessment) includes the following PTs (per MedDRA/J version 21.0): alveolitis, idiopathic pulmonary fibrosis, interstitial lung disease, lung disorder, pneumonitis, pulmonary fibrosis, diffuse alveolar damage, pulmonary toxicity, acute interstitial pneumonitis, acute respiratory distress syndrome, organizing pneumonia and acute lung injury. [c]Data for the number of days from first dose were missing for one patient with haematotoxicity.

12.2–12.6), and PFS rates at 6 and 12 months were 77.4% (95% CI, 75.9–78.9) and 53.2% (95% CI, 51.3–55.1), respectively (Fig. 3A). When PFS rates were stratified by different patient demographics and disease characteristics (Fig. 3B–F), median PFS was longer in patients aged ≥75 years than in younger patients (Fig. 3B), in those with WHO PS 0–1 than in those with PS 2–4 (Fig. 3C), and in patients with no or asymptomatic CNS metastasis than in those with symptomatic CNS metastasis (Fig. 3E). OS rates at 6 and 12 months were 88.3% (95% CI, 87.2–89.4) and 75.4% (95% CI, 73.8–77.0), respectively (Fig. 4).

Discussion

Although the introduction of EGFR-TKIs into the treatment paradigm for NSCLC improved clinical outcomes for patients (4,19), these agents are associated with several kinds of ADRs, particularly

Table 3. Summary of safety outcomes (safety analysis population)

Event	Patients n = 3578, n (%)
Patients with ADR[a]	2079 (58.1)
Most frequently reported ADRs (≥5% of patients)[b]	
Diarrhoea	390 (10.9)
Paronychia	370 (10.3)
Rash	304 (8.5)
Platelet count decreased	221 (6.2)
Decreased appetite	207 (5.8)
Interstitial lung disease	197 (5.5)
Important identified risks[c,d]	
ILD[e] (grouped term)	245 (6.8)[f]
QT interval prolonged[g]	45 (1.3)
Liver disorder[h]	212 (5.9)
Haematotoxicity[i]	409 (11.4)
Important potential risks[c,d]	
Cardiac disorder (excluding QT interval prolonged)[j]	101 (2.8)
Infection[k]	79 (2.2)
Thromboembolism[l]	45 (1.3)
Corneal disorder[m]	20 (0.6)
Other priority surveillance items	
Grade ≥ 3 diarrhoea	25 (0.7)
Grade ≥ 3 skin disorder[d,n]	26 (0.7)
Grade ≥ 3 paronychia[d,o]	16 (0.4)

Abbreviations: ADR, adverse drug reaction; ILD, interstitial lung disease; MedDRA/J, Japanese Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; SMQ, standardized MedDRA query.

[a]Adverse events for which causality to osimertinib could not be denied by attending physicians or drug manufacturer (AstraZeneca, Cambridge, United Kingdom).

[b]MedDRA/J version.21.0 preferred term.

[c]Safety specification based on the Japanese risk management plan.

[d]Grouped term based on investigator-reported adverse events (not including laboratory/electrocardiogram abnormalities which were not reported by the investigator).

[e]ILD (grouped term) includes the following PTs (per MedDRA/J version 21.0): alveolitis, idiopathic pulmonary fibrosis, interstitial lung disease, lung disorder, pneumonitis, pulmonary fibrosis, diffuse alveolar damage, pulmonary toxicity, acute interstitial pneumonitis, acute respiratory distress syndrome, organizing pneumonia and acute lung injury.

[f]Out of 245 patients with ILD (grouped term), 29 patients (11.8%) died.

[g]QT interval prolonged includes the PTs reported among the following terms: electrocardiogram QT interval abnormal, long QT syndrome congenital, long QT syndrome and electrocardiogram QT prolonged.

[h]Liver disorder includes the PTs reported among the following terms: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic function abnormal, liver disorder, drug-induced liver injury and hyperbilirubinaemia.

[i]Haematotoxicity includes the PTs reported among the following terms: anaemia, leukopenia, neutropenia, neutrophil count decreased, platelet count decreased, thrombocytopenia and white blood cell count decreased.

[j]Cardiac disorder (excluding QT interval prolonged) includes PTs reported among the following terms: cardiac disorders (SOC), cardiac failure (SMQ) and cardiomyopathy (SMQ) excluding grouped term of QT interval prolonged.

[k]Infection includes PTs reported among the following terms: infections and infestations (SOC) excluding PTs of paronychia, nail bed infection, nail infection, folliculitis and rash pustular.

[l]Thromboembolism includes PTs reported among the following terms: embolic and thrombotic events, arterial (SMQ); embolic and thrombotic events, venous (SMQ); embolic and thrombotic events, vessel type unspecified; and mixed arterial and venous (SMQ) and thrombophlebitis (SMQ).

[m]Corneal disorder includes PTs reported among the following terms: eye disorders (SOC).

[n]Skin disorder includes the following terms: eczema, dry skin, skin fissures, xeroderma, xerosis, pruritus, eyelids pruritus, pruritus generalized, rash, rash generalized, rash macular, rash maculopapular, rash maculovesicular, rash vesicular, rash follicular, acne pustular, rash pustular, folliculitis, eyelid folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, rash erythematous, rash papular, rash pruritic, skin erosion, erythema and eyelid rash.

[o]Paronychia includes the following terms: paronychia, nail bed infection, nail infection, nail bed inflammation, nail bed disorder, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail pigmentation, nail ridging, onycholysis, onychomadesis, onychomalacia and nail toxicity.

diarrhoea and rash (20–22). However, a recent network meta-analysis suggested that osimertinib provided an improved benefit-risk profile compared with other EGFR-TKIs (23).

The current analysis was a CEI initiated at the time of marketing approval in Japan for second- or later-line patients who progressed on or after EGFR-TKI treatment. The CEI aimed to evaluate ADRs during real-world use of osimertinib and to examine the factors affecting safety and efficacy outcomes associated with osimertinib. During a median observation period of ∼1 year, the incidence of ADRs in this CEI was 58.1%. This was lower than the incidence reported from the Japanese subpopulation in the phase III AURA3 study after a median duration of osimertinib treatment of

Table 4. Efficacy according to background patient factors (efficacy analysis population)

Factor	*n*	ORR % (95% CI)	DCR % (95% CI)
All patients	3563	69.9 (68.4–71.4)	86.7 (85.6–87.8)
Age, years			
<75	2458	69.4 (67.6–71.3)	86.2 (84.7–87.5)
≥75	1105	71.0 (68.3–73.7)	88.0 (85.9–89.8)
WHO PS			
0–1	2895	73.6 (71.9–75.2)	90.0 (88.8–91.1)
2–4	668	54.2 (50.3–58.0)	72.6 (69.1–76.0)
EGFR mutation status			
Exon 19 deletion	1757	72.5 (70.4–74.6)	87.8 (86.2–89.3)
L858R	1233	67.1 (64.4–69.7)	85.5 (83.4–87.4)
CNS metastasis			
Symptomatic	233	58.4 (51.8–64.8)	78.5 (72.7–83.6)
Asymptomatic	601	69.7 (65.9–73.4)	86.9 (83.9–89.5)
Absent	2729	71.0 (69.2–72.7)	87.4 (86.1–88.6)
Pleural effusion			
Present	940	62.2 (59.0–65.3)	83.4 (80.9–85.7)
Absent	2623	72.7 (71.0–74.4)	87.9 (86.6–89.1)

Abbreviations: CI, confidence interval; CNS, central nervous system; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, overall response rate; WHO PS, World Health Organization performance status.

9.95 months, in which 39 patients (95.1%) treated with osimertinib and 22 patients (100%) treated with platinum-pemetrexed reported at least 1 AE considered at least possibly related to treatment (13). However, the patient numbers in the AURA3 sub-study were small (n = 41 and 22, respectively) (13). The incidences of important identified risks defined for this CEI per the requirements of the Japanese regulatory authority were similar to, or slightly lower than, those reported in AURA3. In this CEI, the incidences of haematotoxicity, ILD, liver disorder and QT prolongation were 11.4, 6.8, 5.9 and 1.3%, respectively. In AURA3, the incidences of haematotoxicity, ILD, liver disorder and QT prolongation were 4.9–12.2, 7.3, 12.2 and 2.4%, respectively (13).

Again, it must be remembered that our study was a large, real-world study and not a controlled clinical trial. However, when compared with the safety outcomes observed in ASTRIS, a global, real-world safety study of osimertinib in >3000 patients with NSCLC, the CEI tolerability profile was also similar, with no new safety signals observed (24). The incidence of ADRs resulting in death was 1.5% in this CEI, whereas the incidence of AEs resulting in death was 4.9% in ASTRIS. ADRs of ILD and QT interval prolonged were reported in 6.8 and 1.3% of the CEI patients, respectively. In ASTRIS, AEs of ILD and QT interval prolonged were reported in 0.9 and 2.5% of patients, respectively.

The development of EGFR-TKI-associated ILD is a common clinical problem with the use of first-generation agents (25, 26), with a higher susceptibility reported among Japanese patients (27). The ILD rate associated with osimertinib in this analysis was 6.8%, and fatal outcomes resulting from ILD occurred in 0.8% (11.8% of the ILD population). In post-marketing studies of gefitinib, erlotinib or afatinib, ILD rates ranging from 4.3 to 15.2% have been reported (28–30). In terms of ILD mortality rate, among the latter studies, the death rate from ILD was 1.5% (153/9909) (i.e. 35.7% of the ILD population who received erlotinib) (29) and 0.7% (12/1602) (i.e. 17.1% of the ILD population who received afatinib) (30). By comparison, ILD rates of 5.0–5.8% have been reported among Japanese patients treated with gefitinib or erlotinib in two clinical trials, both of which reported an ILD death rate of 1.0% (31,32). In light of potential alternative causes or contributory factors in all the fatal outcomes of patients with ILD (including progression of the underlying lung cancer or rapid deterioration of the patient's medical condition, or other concomitant diseases, at the time of diagnosis of ILD), it is difficult to assess the extent to which ILD may contribute towards a fatal outcome, because the lack of autopsy reports precludes confirmation of the true causes of death in a majority of the fatal case reports. Individual case reports did not identify specific risk factors for fatal ILD.

The use of osimertinib in the CEI resulted in positive efficacy outcomes for patients with NSCLC. In reference to RECIST v1.1, the overall response rate was 69.9%, and the DCR was 86.7%; these results are comparable with those reported in the phase III AURA3 clinical trial in Japanese patients, in which the response rate was 70.7% and the DCR was 95.1% with osimertinib (13). They are also in line with those observed for patients globally; patients from the phase II AURA extension study had a response rate of 62% and a DCR of 90%, those from the phase II AURA2 trial had a 70% response rate and a 92% DCR and the AURA3 trial (all patients) reported a response rate and DCR of 71 and 93%, respectively (7,33,34). Furthermore, the data also support the levels of clinical activity observed in real-world treatment studies of osimertinib, such as ASTRIS (investigator-assessed response rate 57.1%) (24). Subgroup analysis in our study showed that ORR and DCR were similar between age groups and EGFR mutation status, whereas differences in ORR and DCR were observed in patients based on WHO PS and pleural effusion status. Moreover, patients without CNS metastasis or with asymptomatic CNS metastasis had similar ORRs and DCRs, while those with symptomatic CNS metastasis had lower respective ORR and DCR rates.

We observed an overall PFS of 12.3 months which is similar to that observed in both the global (10.1 months) and Japanese (12.5 months) populations in AURA3, the global phase II AURA2 trial (12.3 months) and global real-world study, ASTRIS (11.1 months) (7,13,24,33). The subgroup analysis of PFS according to patient factors also supported the clinical benefit of osimertinib in hard-to-treat populations. Elderly patients (≥75 years of age)

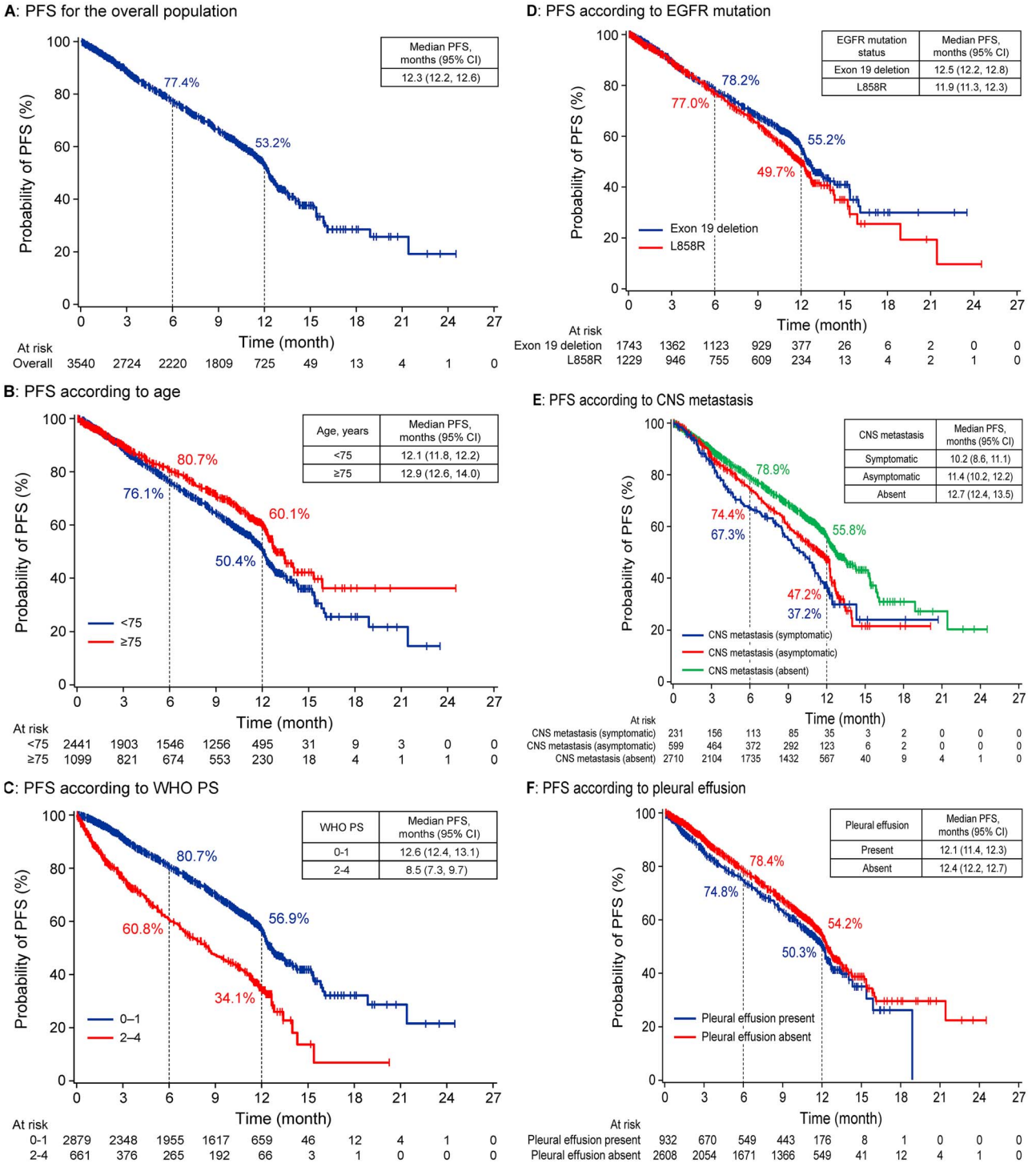

Figure 3. Progression-free survival rates[a] (efficacy analysis population). (A) PFS for the overall population. (B) PFS according to age. (C) PFS according to WHO PS. (D) PFS according to EGFR mutation. (E) PFS according to CNS metastasis. (F) PFS according to pleural effusion. Abbreviations: CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; PFS, progression-free survival; WHO PS, World Health Organization performance status. [a]Evaluated by attending physicians in the real-world setting.

had a PFS of 12.9 months, demonstrating that osimertinib was effective regardless of age. The PFS of patients with WHO PS 0–1 was comparable with that reported for the Japanese patients in the AURA3 trial, in which all patients had a WHO PS 0–1 (12.6 and 12.5, respectively) (13). In patients with a poor PS (WHO PS 2–4), osimertinib did provide clinical benefit in this patient subgroup (PFS: 8.5 months). This is slightly better than the PFS of 6.5 months reported for first-line gefitinib in patients with a poor performance status (as assessed by European Cooperative Oncology Group criteria) (35). Subgroup analysis in our study demonstrated

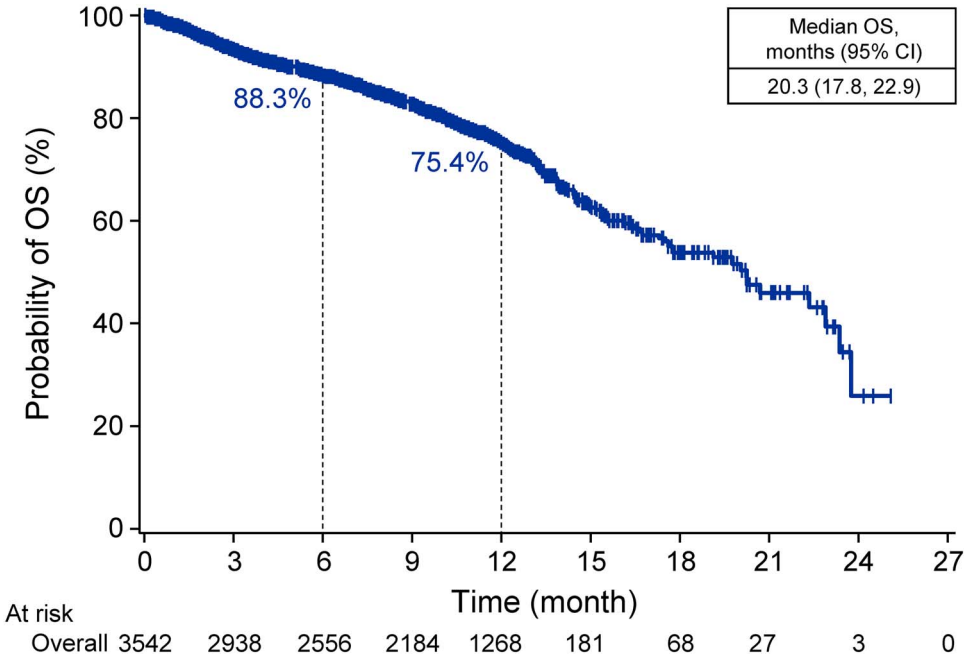

Figure 4. Overall survival (efficacy analysis population). Abbreviations: CI, confidence interval; OS, overall survival.

that patients with both symptomatic and asymptomatic CNS metastasis experienced clinical benefit (symptomatic, 10.2 months; asymptomatic, 11.4 months), in agreement with that reported for patients with asymptomatic CNS metastasis in the AURA3 trial (PFS, 8.5 months) (7). Osimertinib was effective regardless of EGFR mutation status or pleural effusion status. The data for elderly patients and those with poor PS have been lacking, as they have historically been excluded from clinical trials due to poor outcomes (36) and there is a clear need for new treatment options with proven clinical activity to improve the prognosis for these patients.

The results of this CEI confirm and expand the currently established benefit-risk assessment of osimertinib in patients with EGFR T790M-positive NSCLC and are expected to inform future therapeutic decision-making for patients who have traditionally had few available treatment options. However, this study has some limitations, including its single-arm, uncontrolled, observational design and that the lack of pre-specified patient selection criteria allowed enrolment of a heterogeneous population. Of the 3578 patients in the safety analysis population, a high proportion of them were female (2371 [66.3%]) or ≥65 years of age (2573 [71.9%]). Furthermore, there were no stringent schedules for visits or chest CT (e.g. every 6 weeks with confirmation of response as in a clinical trial), and there was a short observation period (pre-defined to be 1 year) for time-to-event analyses. This means that the PFS would be biased to be longer due to delays in the detection of progressive disease. Limitations related to safety were that, in this study, ADRs were reported, whereas AEs are the primary safety items reported in other studies; furthermore, the ADR definition used was unique to this CEI and may differ from other analyses, making it difficult to draw comparisons. In addition, important identified and potential risks defined for this CEI were specific to Japan-local situations per the requirement by the regulatory agency and may not hold true for osimertinib use globally. Finally, as described earlier, the events of ILD with a fatal outcome must be evaluated in the context of the patient's overall condition and the presence of other potential mortality-contributory factors. However, this is the largest reported study to date of osimertinib in patients with T790M-positive NSCLC, and the study population is likely more representative of the Japanese NSCLC population than in a highly selected clinical trial, allowing the data to be extrapolated to the general clinical population. Furthermore, the results from this CEI are in line with previous clinical trial data, suggesting a robust evidence base for this agent overall.

In conclusion, in this large post-marketing investigation in >3500 Japanese patients with EGFR T790M-positive NSCLC, osimertinib 80 mg QD provided clinical benefit to patients with no new safety concerns. These results were comparable with clinical trial data and other real-world analyses of osimertinib in this patient population and support the currently established benefit-risk assessment of this important therapeutic agent.

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Conflict of interest statement

Yuichiro Ohe received fees from AstraZeneca, Chugai, Eli Lilly, Ono and Kyorin and research funds from AstraZeneca, Ono, Taiho, Chugai, Bristol-Myers Squibb, Kyorin, Sumitomo Dainippon, Kissei, Janssen, Loxo Oncology, Takeda and MSD. Terufumi Kato received

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Contributor statements

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