



# A Prospective Observational Study of Osimertinib for Chemo-Naive Elderly Patients with *EGFR* Mutation-Positive Non-Small Cell Lung Cancer

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**Background:** The clinical outcomes of elderly patients with *EGFR*-mutated non-small cell lung cancer (NSCLC) who are treated with osimertinib have not been sufficiently evaluated. This study aimed to assess the efficacy and safety of osimertinib in elderly chemotherapy-naïve patients with NSCLC harboring sensitive *EGFR* mutations.

**Patients and Methods:** We assessed the clinical effects of osimertinib as a first-line treatment for elderly NSCLC patients ( $\geq 75$  years of age) with an exon 19 deletion or exon 21 L858R mutation in *EGFR*. All patients were administered 80 mg/day osimertinib as initial treatment.

**Results:** Forty-three patients (24 women and 19 men) with adenocarcinoma who were treated between August 2018 and July 2021 were included in this study; their median age was 79 years (range, 75–90 years). The overall objective response rate was 60.5%. The median progression-free survival (PFS) and time to treatment failure (TTF) of the entire patient population were 22.1 months and 14.6 months, respectively. The most common adverse event was rash acneiform (42%), followed by diarrhea (33%) and paronychia (28%); none of these were grades  $\geq 3$ . Interstitial lung disease developed in 8 patients (18.6%); however, no treatment-related deaths occurred. Multivariate analysis identified performance status and disease stage as predictors of PFS and TTF.

**Conclusion:** Considering the findings of this study and despite an observed discordance between PFS and TTF, osimertinib appears to be an effective and safe treatment option in elderly patients with advanced NSCLC harboring sensitive *EGFR* mutations. To obtain conclusive results, further studies in a larger elderly population are warranted.

**Keywords:** non-small cell lung carcinoma, chemotherapy-naïve patients, efficacy

## Introduction

Lung cancer is a major cause of cancer-related deaths, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all such malignancies.<sup>1</sup> In recent years, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have markedly improved the prognoses of patients with NSCLC harboring *EGFR*-activating mutations. Based on positive results from Phase III trials,<sup>1–8</sup> EGFR-TKIs have become standard regimens for such patients, and several EGFR-TKIs are currently approved as first-line treatments for *EGFR* mutation-positive NSCLC in Japan. These include the first-generation TKIs erlotinib and gefitinib, second-generation TKIs afatinib and dacomitinib, and third-generation TKI osimertinib. Osimertinib is a mono-anilino-pyrimidine compound that

irreversibly and selectively targets EGFR-TKI-sensitizing and T790M-resistant forms of mutated *EGFR* while sparing the wild-type gene.

Two-thirds of all new lung cancer diagnoses are in patients aged >65 years, with this rate anticipated to increase owing to the growing proportion of the elderly population.<sup>9,10</sup> Accordingly, greater attention is being paid to improving treatment strategies for elderly patients with lung cancer. It has been reported that such patients showed very high response rates to first-line gefitinib and erlotinib, with prolonged survival times achieved.<sup>11–18</sup> Additionally, Japanese Phase II studies have indicated the efficacy and safety of first-line afatinib in elderly *EGFR* mutation-positive patients with NSCLC.<sup>19,20</sup> The FLAURA trial included patients of all ages and demonstrated that the safety profile of osimertinib was similar to that of gefitinib and erlotinib,<sup>8</sup> indicating that osimertinib may be a feasible intervention for elderly patients. However, existing data remain insufficient to determine the efficacy of osimertinib in elderly patients with NSCLC who harbor *EGFR*-activating mutations.

Hence, the aim of this prospective observational study was to evaluate the efficacy and safety of first-line osimertinib for patients with advanced NSCLC harboring sensitive *EGFR* mutations.

## Patients and Methods

### Patient Selection

We conducted a prospective observational cohort study at Kitasato University Hospital between August 2018 and July 2021 to evaluate the efficacy and safety of osimertinib in patients with *EGFR* mutation-positive advanced NSCLC who were 75 years of age or older. The eligibility criteria for this study were as follows: histologically or cytologically confirmed NSCLC harboring either an exon 19 deletion or exon 21 L858R mutation in *EGFR*, stage IIIB–IV disease with postoperative recurrence according to the new Union for International Cancer Control criteria (version 8), having at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1,<sup>21</sup> and the ability to receive oral treatment. Patient characteristics including age at diagnosis, sex, Eastern Cooperative Oncology Group performance status (PS) at the start of osimertinib treatment, smoking status, clinical stage, tumor histology, and brain metastasis status were identified via chart review. The Institutional Ethics Review Board of Kitasato University Hospital approved

this prospective observational study, which was conducted in accordance with the tenets of the Declaration of Helsinki. All patients provided written informed consent before enrollment, after which they were treated with 80 mg of osimertinib daily until disease progression or the development of unacceptable adverse events.

### Analysis of EGFR Mutations

Initial testing for *EGFR* mutation status was performed using a sample of the primary tumor, a metastatic lesion, or pleural effusion fluid via the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method or Oncomine Dx Target Test.

### Response Assessment

After the initiation of osimertinib treatment, computed tomography of the chest and abdomen was performed every 2 to 3 months or at more frequent intervals if necessary. Positron emission tomography or bone scintigraphy as well as computed tomography or magnetic resonance imaging of the cranium were performed at 6-month intervals or whenever patients had significant symptoms associated with tumor lesions. The response to treatment was re-evaluated by two investigators (S.I. and M.S.).

### Toxicity Assessment and Dose Modification

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 5). Physical conditions, symptoms, blood tests, and chest X-rays of all patients were evaluated at an interval based on the discretion of the physician in charge throughout osimertinib treatment. Any interruption, discontinuation, or dose reduction of osimertinib caused by toxicities was at the discretion of the physician in charge.

### Statistical Analysis

Progression-free survival (PFS) was defined as the interval between the date of osimertinib therapy initiation and that of disease progression or death; if neither occurred, the patient was censored on the date of the last follow-up examination. Time to treatment failure (TTF) was measured from the start of osimertinib therapy to either death, documentation of disease progression, or cessation of osimertinib therapy owing to the development of unacceptable toxicity. Survival curves were plotted using the Kaplan–Meier method, and differences according to PS status were

analyzed using the Log rank test. Sex, smoking status, PS, stage, brain metastasis status, and *EGFR* genotype were used as variables analyzed via Cox proportional hazards models to predict the hazard ratios for PFS and TTF. A *P*-value <0.05 denoted statistical significance. All statistical analyses were performed using the SPSS software program, version 28.0 for Windows (IBM Corp., Armonk, NY, USA).

## Results

### Patient Characteristics

Forty-three patients with NSCLC who were treated with osimertinib between August 2018 and January 2021 were included in the final analysis. As shown in Table 1, the median patient age was 79 years; 65% were women and 77% had a good PS score (0 or 1). All patients had adenocarcinomas; 56% had an *EGFR* exon 19 deletion while 44% had an L858R point mutation. Moreover, 21% of the patients had brain metastasis.

### Response and Survival Analysis

Table 2 shows the objective tumor responses. An objective response was obtained in 26 of the 43 patients, indicating an objective response rate (ORR) of 60.5% (95% confidence interval [CI]: 44.9–76.0%). A partial response was observed in 4 of the 10 patients with poor PS (ie, a score

**Table 2** Response to Osimertinib Therapy

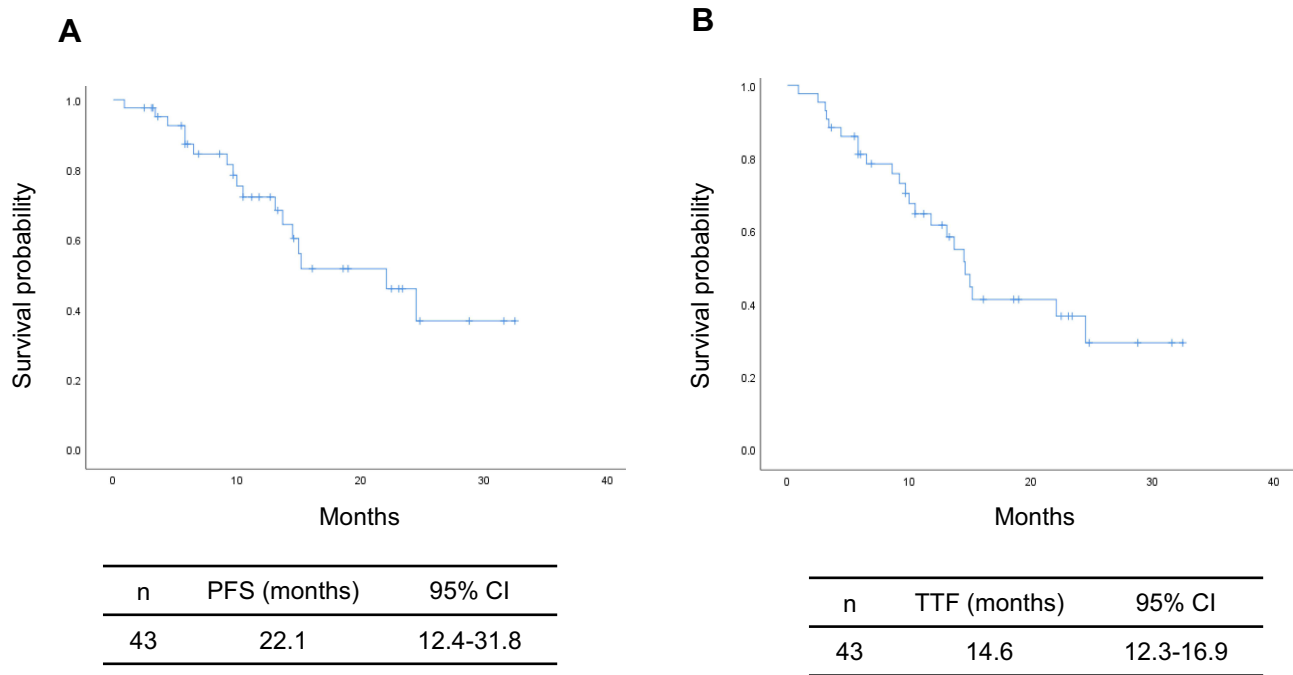
|                     | n=43      |
|---------------------|-----------|
| Complete response   | 0         |
| Partial response    | 26        |
| Stable disease      | 14        |
| Progressive disease | 3         |
| Response rate       | 60.5%     |
| 95% CI              | 44.9–76.0 |

of 2), indicating a response rate of 40.0% (95% CI: 19.0–61.0%); patients with favorable PS (scores of 0 or 1) had a higher response rate of 66.7% (95% CI: 46.5–86.8%), although the difference was not significant (*P* = 0.17). Of the 9 patients pre-existing brain metastasis, an objective response was achieved in 4, indicating an ORR of 44.4%. No disease progression owing to the exacerbation of brain metastatic lesions was observed among the 9 patients.

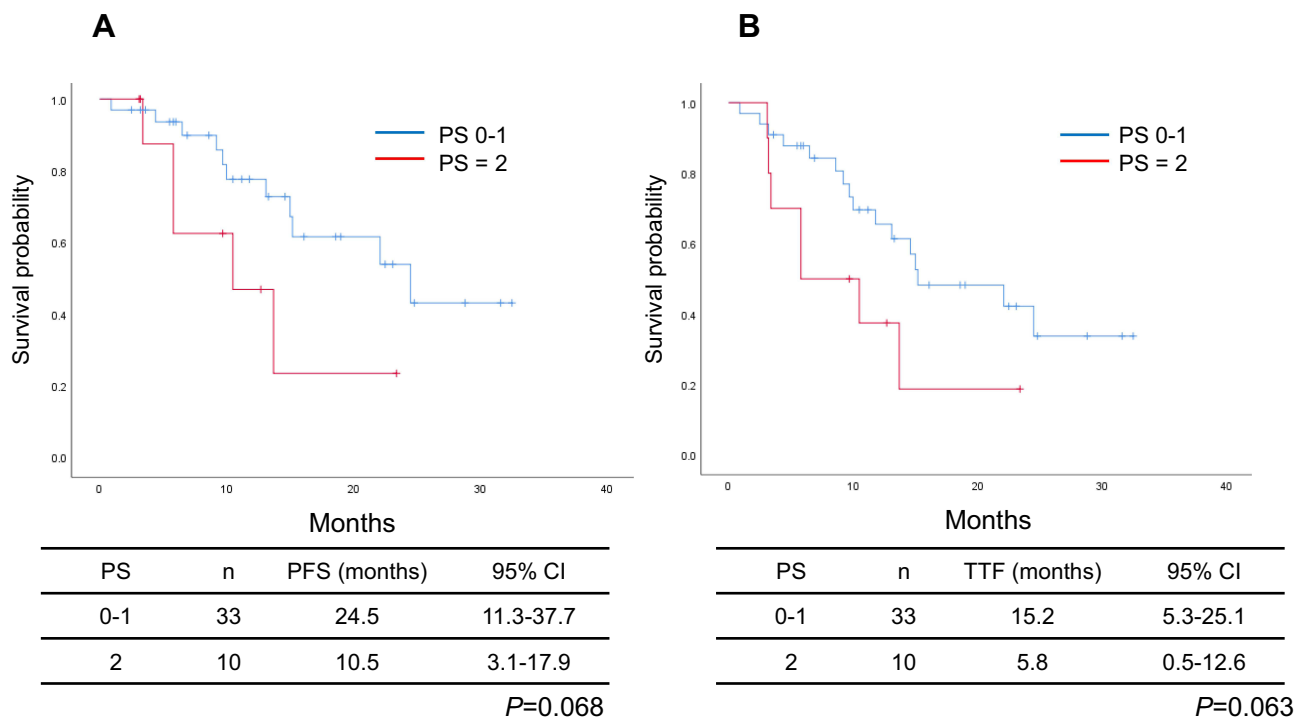
The cut-off date for survival analysis was July 2021, and the median follow-up period by that date was 17.2 months. The median PFS and TTF of the entire patient population were 22.1 months (95% CI: 12.4–31.8 months; Figure 1A) and 14.6 months (95% CI: 12.3–16.9 months; Figure 1B), respectively. The median PFS in the favorable and poor PS groups were 24.5 months (95% CI: 11.3–37.7 months) and 10.5 months (95% CI: 3.1–17.9 months), respectively, with the difference just outside the threshold for significance (*P* = 0.068; Figure 2A). The median TTF in the favorable and poor PS groups were 15.2 months (95% CI: 5.3–25.1 months) and 5.8 months (95% CI: 0.5–12.6 months), respectively; the difference was also just outside the threshold for significance (*P* = 0.063; Figure 2B). The median PFS in patients without versus with brain metastasis was 24.5 months (95% CI: 19.5–29.6 months) and 13.7 months (95% CI: 6.1–23.1 months), respectively, although the difference was not significant (*P* = 0.14). The median TTF in patients without versus with brain metastasis were 15.0 months (95% CI: 3.6–26.4 months) and 10.0 months (95% CI: 0.5–22.3 months), respectively; the difference was not significant (*P* = 0.17). The median PFS in patients with the exon 19 deletion versus those with the L858R mutation were 24.5 months (95% CI: 9.7–39.2 months) and 22.1 months (95% CI: 6.5–37.7 months), respectively, with no significant difference (*P* = 0.94). The median TTF in the exon 19 deletion versus L858R mutation groups were 13.7 months (95% CI: 8.4–19.0 months) and 15.0 months (95% CI:

**Table 1** Patient Characteristics

|  | n=43 (%)           |
|--|--------------------|
| Age (years), median, range                                       | 79 (75–90)         |
| Gender<br>Female/Male  | 24 (56)/19 (44)    |
| Performance status<br>0–1/2                                      | 33 (77)/10 (23)    |
| <i>EGFR</i> genotype<br>Del 19/L858R                             | 24 (56)/19 (44)    |
| Histology<br>Adenocarcinoma                                      | 43 (100)           |
| Stage<br>IV/Recurrence   | 30 (70)/13 (30)    |
| Smoking status<br>Current smoker<br>Never or former light smoker | 18 (42)<br>25 (58) |
| Brain metastasis<br>Negative/Positive                            | 34 (79)/9 (21)     |



**Figure 1** Kaplan–Meier curves showing (A) progression free survival (PFS) and (B) time to treatment failure (TTF) to osimertinib therapy.



**Figure 2** Kaplan–Meier curves showing (A) PFS and (B) TTF in patients receiving osimertinib therapy according to their Eastern Cooperative Oncology Group performance status score.

4.3–25.7 months), respectively, also with no significant difference ( $P = 0.70$ ). Multivariate analysis identified PS and disease stage as independent predictors of PFS and TTF (Tables 3 and 4).

### Toxicities

The toxicity of osimertinib was evaluated in all patients; the main adverse events observed during treatment are presented in Table 5. The most common was rash

**Table 3** Univariate and Multivariate Analyses for Factors That May Influence Progression-Free Survival

| Variable              | Univariate Analysis   |         | Multivariate Analysis |         |
|-----------------------|-----------------------|---------|-----------------------|---------|
|                       | Hazard Ratio (95% CI) | P-value | Hazard Ratio (95% CI) | P-value |
| Sex                   |                       |         |                       |         |
| Female                | I (Ref.)              | 0.68    |                       |         |
| Male                  | 1.22 (0.47–3.19)      |         |                       |         |
| Performance status    |                       |         |                       |         |
| 0–I                   | I (Ref.)              | 0.08    | I (Ref.)              | 0.021   |
| 2                     | 2.62 (0.89–7.69)      |         | 3.94 (1.23–12.7)      |         |
| Smoking status        |                       |         |                       |         |
| Never                 | I (Ref.)              | 0.19    | Excluded              |         |
| Smoker                | 1.91 (0.73–4.98)      |         |                       |         |
| Stage                 |                       |         |                       |         |
| Stage IV              | I (Ref.)              | 0.018   | I (Ref.)              | 0.006   |
| Recurrence            | 0.31 (0.12–0.82)      |         | 0.24 (0.08–0.66)      |         |
| Brain metastasis      |                       |         |                       |         |
| Negative              | I (Ref.)              | 0.19    | Excluded              |         |
| Positive              | 2.00 (0.70–5.71)      |         |                       |         |
| Type of EGFR mutation |                       |         |                       |         |
| L858R                 | I (Ref.)              | 0.86    |                       |         |
| Del. 19               | 0.91 (0.35–2.40)      |         |                       |         |

**Abbreviations:** CI, confidence interval; Del 19, exon 19 deletion; L858R, exon 21 point mutation.

**Table 4** Univariate and Multivariate Analyses for Factors That May Influence Time to Treatment Failure

| Variable              | Univariate Analysis   |         | Multivariate Analysis |         |
|-----------------------|-----------------------|---------|-----------------------|---------|
|                       | Hazard Ratio (95% CI) | P-value | Hazard Ratio (95% CI) | P-value |
| Sex                   |                       |         |                       |         |
| Female                | I (Ref.)              | 0.65    |                       |         |
| Male                  | 1.21 (0.53–2.75)      |         |                       |         |
| Performance status    |                       |         |                       |         |
| 0–I                   | I (Ref.)              | 0.047   | I (Ref.)              | 0.015   |
| 2                     | 2.53 (1.01–6.33)      |         | 3.35 (1.27–8.86)      |         |
| Smoking status        |                       |         |                       |         |
| Never                 | I (Ref.)              | 0.31    |                       |         |
| Smoker                | 1.53 (0.67–3.49)      |         |                       |         |
| Stage                 |                       |         |                       |         |
| Stage IV              | I (Ref.)              | 0.023   | I (Ref.)              | 0.008   |
| Recurrence            | 0.38 (0.17–0.88)      |         | 0.31 (0.13–0.74)      |         |
| Brain metastasis      |                       |         |                       |         |
| Negative              | I (Ref.)              | 0.11    | Excluded              |         |
| Positive              | 2.05 (0.84–4.99)      |         |                       |         |
| Type of EGFR mutation |                       |         |                       |         |
| L858R                 | I (Ref.)              | 0.87    |                       |         |
| Del. 19               | 0.91 (0.40–2.08)      |         |                       |         |

**Table 5** Toxicities

| Adverse Event             | Any Grade (%) | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---------------------------|---------------|-------------|-------------|-------------|-------------|
| Rash acneiform            | 18 (42)       | 13 (30)     | 5 (12)      | 0           | 0           |
| Diarrhea                  | 14 (33)       | 14 (33)     | 0           | 0           | 0           |
| Paronychia                | 12 (27)       | 9 (21)      | 3 (6)       | 0           | 0           |
| Oral mucositis            | 7 (16)        | 7 (16)      | 0           | 0           | 0           |
| Anorexia                  | 6 (13)        | 5 (11)      | 1 (2)       | 0           | 0           |
| Dry skin                  | 3 (6)         | 3 (6)       | 0           | 0           | 0           |
| Fatigue                   | 3 (6)         | 2 (4)       | 1 (2)       | 0           | 0           |
| Nausea                    | 2 (4)         | 2 (4)       | 0           | 0           | 0           |
| Dysgeusia                 | 2 (4)         | 2 (4)       | 0           | 0           | 0           |
| Neutropenia               | 7 (16)        | 4 (10)      | 2 (4)       | 1 (2)       | 0           |
| Leukopenia                | 6 (13)        | 5 (11)      | 1 (2)       | 0           | 0           |
| Anemia                    | 6 (13)        | 2 (4)       | 1 (2)       | 3 (7)       | 0           |
| Thrombocytopenia          | 5 (11)        | 3 (7)       | 2 (4)       | 0           | 0           |
| Creatinine increased      | 5 (11)        | 3 (7)       | 1 (2)       | 1 (2)       | 0           |
| AST/ALT increased         | 4 (10)        | 4 (10)      | 0           | 0           | 0           |
| QTc prolongation          | 2 (4)         | 0           | 2 (4)       | 0           | 0           |
| Interstitial lung disease | 8 (18)        | 4 (10)      | 3 (6)       | 1 (2)       | 0           |

acneiform (18 patients [42%], none with grade  $\geq 3$ ) followed by diarrhea (14 patients [33%], none with grade  $\geq 3$ ) and paronychia (12 patients [28%], none with grade  $\geq 3$ ). Interstitial lung disease (ILD) was detected in 8 patients (18.6%), 1 of whom had grade 3. The ILD occurred in the 8 patients were all manageable. Furthermore, 1 patient developed grade 3 neutropenia, while none developed febrile neutropenia. No treatment-related deaths occurred.

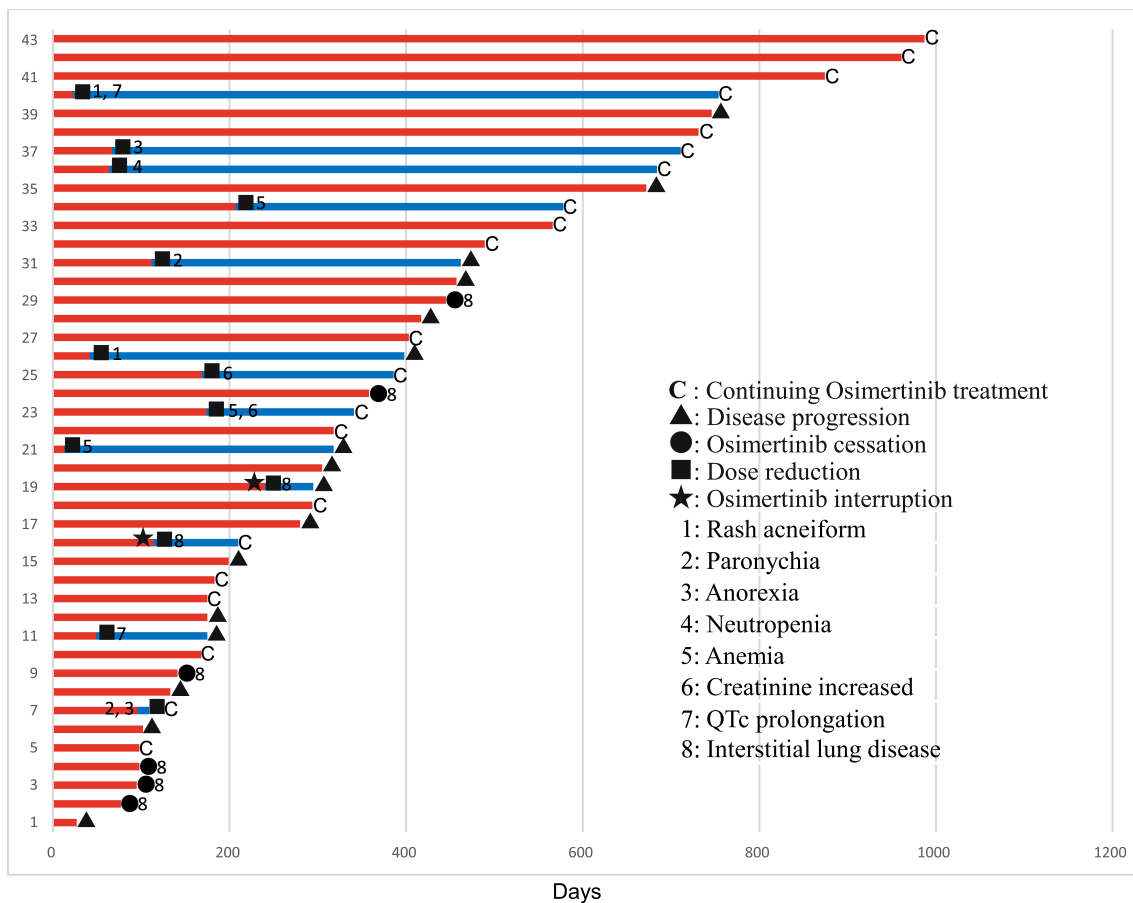
Thirteen patients (30.2%) required osimertinib dose reduction owing to adverse events, while its administration was ceased in 6 patients (14.0%) owing to ILD (from which they recovered after corticosteroid therapy). None of the patients discontinued osimertinib therapy because of other adverse events. Osimertinib administration was interrupted in 2 other patients with ILD until their conditions improved; subsequently, 40 mg of osimertinib was administered per the physician's discretion. As a result, no recrudescence of drug-induced ILD was observed.

Twenty-two patients discontinued osimertinib treatment because of disease progression or ILD, among whom 11 received second-line treatments (other EGFR-TKIs [n = 5], platinum plus pemetrexed [n = 5], and atezolizumab [n = 1]). Six patients with disease progression continued osimertinib despite progression; 3 of them were still receiving this agent by the data cut-off date. Twenty-one patients remained on osimertinib without disease progression. The osimertinib treatment durations until disease progression or cessation owing to adverse events in individual patients are summarized in Figure 3.

## Discussion

The advent of targeted therapy has revolutionized treatments for a subset of patients with NSCLC, and testing newly diagnosed subjects for the presence of an *EGFR* mutation is now considered the standard of care. Our study found that first-line treatment with osimertinib provided a response rate of 60.5% and a median PFS of 22.1 months in elderly patients with NSCLC who harbor *EGFR* mutations. In the double-blind, phase III FLAURA study, osimertinib was found to significantly prolong PFS in comparison to gefitinib or erlotinib among patients with NSCLC who harbor sensitive *EGFR* mutations.<sup>8</sup> Analysis of the Japanese subset of the FLAURA study revealed a PFS of 19.1 months in the osimertinib group, indicating the efficacy of first-line therapy with this agent in the Japanese population.<sup>22</sup> Regarding osimertinib administration to the elderly population, the FLAURA study was notable in that it revealed the benefit of osimertinib over gefitinib and erlotinib with respect to PFS across different subgroups, including those categorized by age (<65 vs  $\geq 65$  years).<sup>8</sup> However, while that study compared PFS according to the predefined subgroups of race (Asian vs non-Asian) and type of *EGFR* alteration (exon 19 deletion vs L858R mutation), age was not predefined for PFS analysis. Therefore, we concluded that none of the preexisting prospective studies had satisfactorily evaluated the efficacy and safety of osimertinib among elderly patients with NSCLC harboring sensitive *EGFR* mutations; to





**Figure 3** Durations of treatment with osimertinib before disease progression or cessation owing to adverse events in individual patients.

the best of our knowledge, ours is the first study to do so.

Notably, the PFS of 22.1 months owing to osimertinib therapy among the elderly population in our study was comparable to that derived from the analysis of the Japanese subset of FLAURA study.<sup>22</sup> Previous studies have found that first-line EGFR-TKIs such as gefitinib, erlotinib, and afatinib are feasible and effective in elderly patients with NSCLC harboring *EGFR* mutations.<sup>11–20</sup> Table 6 provides a summary of 4 prospective and 2 retrospective studies on patients  $\geq 75$  years of age who were treated with EGFR-TKIs. The response rate in our present study was identical to that found in previous studies of first-line EGFR-TKI treatment in elderly patients with NSCLC harboring sensitive *EGFR* mutations; however, our patients’ PFS appeared to be longer than that of patients who were treated with other EGFR-TKIs.

The PFS and TTF in our study were 22.1 and 14.6 months, respectively, indicating a lack of congruence between these parameters; this was attributed to treatment

failure in the 6 patients who discontinued osimertinib owing to drug-induced ILD. Meanwhile, the 14.6-month TTF observed in our study was comparable to the PFS observed in previously reported elderly patients aged  $\geq 75$  years who were administered other EGFR-TKIs, demonstrating the efficacy of osimertinib in this population. With respect to drug-induced ILD, its incidence in the Japanese subgroup of the FLAURA study was approximately 1.8% in those administered gefitinib but was 12.3% in those administered osimertinib.<sup>22</sup> The findings of both our study and the FLAURA trial<sup>22</sup> indicate that the incidence of osimertinib-induced ILD may be high among Japanese patients. Meanwhile, a previous study demonstrated that 80% of patients with ILD complicated by osimertinib recovered, and that mortality from drug-induced ILD was lower in those administered osimertinib (11.8%) than in those treated with gefitinib (38.9%) and erlotinib (35.6%);<sup>23</sup> these data suggested that recovery from ILD can be expected in many patients receiving osimertinib.

**Table 6** Clinical Studies on Patients  $\geq 75$  Years of Age Who Were Treated with EGFR-TKIs

|                | Drug | No of Pts. | Study Design  | EGFR Mutation Type (Del. 19/L858R) | Age (Years) | Median Age (Range) | Response Rate (%) | Median PFS (Months) |
|----------------|------|------------|---------------|------------------------------------|-------------|--------------------|-------------------|---------------------|
| Maemondo (11)  | GEF  | 31         | Prospective   | Not reported                       | $\geq 75$   | 80 (75–89)         | 74.0              | 12.3                |
| Takeishi (15)  | GEF  | 55         | Retrospective | 31/24                              | $\geq 75$   | 81 (75–94)         | 72.7              | 13.8                |
| Kuwako (16)    | GEF  | 62         | Retrospective | 24/38                              | $\geq 75$   | 80 (75–89)         | 61.3              | 13.2                |
| Inoue (18)     | ERL  | 32         | Prospective   | 12/20                              | $\geq 75$   | 80 (85–87)         | 56.3              | 15.5                |
| Minegishi (20) | AFA  | 40         | Prospective   | 23/15                              | $\geq 75$   | 78 (75–91)         | 75.7              | 14.2                |
| Present report | OSIM | 43         | Prospective   | 24/19                              | $\geq 75$   | 79 (75–90)         | 60.5              | 22.1                |

**Abbreviations:** Pts, patients; PFS, progression-free survival; GEF, gefitinib; ERL, erlotinib; AFA, afatinib; OSIM, Osimertinib.

We identified poor PS as an independent predictor of unfavorable PFS and TTF among patients undergoing osimertinib therapy. Additionally, the response rate tended to be lower in patients with poor PS than in those with favorable PS, although the difference was not significant (40.0% vs 66.7%,  $P = 0.17$ ). Meanwhile, previous studies that comprised patients of all ages found that the PFS of those with poor PS who were treated with gefitinib and afatinib were 6.6 and 8.8 months, respectively.<sup>24,25</sup> However, the PFS of patients with poor PS who were treated with osimertinib was significantly shorter than that of patients with favorable PS (10.5 vs 24.5 months); as such, the PFS of patients with poor PS treated with osimertinib appears to be comparable to that of counterparts administered other EGFR-TKIs.<sup>24,25</sup>

We also identified postoperative recurrence as a significant predictor of favorable PFS and TTF. Likewise, the phase III WJTOG3405 trial revealed that postoperative recurrence was independently associated with a longer PFS in patients receiving gefitinib.<sup>26</sup> Moreover, we previously identified postoperative recurrence as a significant predictor of favorable PFS in patients with advanced NSCLC receiving the EGFR-TKIs gefitinib and erlotinib.<sup>27</sup> With respect to osimertinib, the present study is the first to prospectively identify postoperative recurrence as a significant favorable predictor of PFS. While the reasons for this remain unclear, we propose the following hypotheses. First, regular follow-up with imaging after curative surgery can detect early recurrence in the absence of symptoms; accordingly, the tumor burden of patients with recurrence is usually lower than that of those with stage IV NSCLC at diagnosis. Second, there is a higher possibility of tumor heterogeneity in patients with a large tumor burden; hence, anticancer drugs are less likely to be effective.<sup>28,29</sup> The differences in tumor burden and heterogeneity between patients with stage IV disease and those who experience postoperative recurrence may therefore explain the more favorable PFS and overall survival in the latter group, particularly if they also harbor *EGFR* mutations.<sup>30–33</sup>

Regarding the type of *EGFR* mutations, no significant difference in either PFS or TTF was observed between patients with an exon 19 deletion and those with an L858R point mutation in the present study. The FLAURA study revealed a consistent PFS benefit for osimertinib treatment over first-generation EGFR-TKIs across all predefined subgroups that were assessed, including race (Asian vs non-Asian) and sensitive *EGFR* mutation type.<sup>8</sup>



Additionally, other previously conducted studies found no significant differences in PFS according to the type of sensitive *EGFR* mutation.<sup>34–36</sup> This indicated that our findings with respect to the lack of PFS differences between patients with different *EGFR* genotype were consistent with those of previous studies. As for brain metastases, the FLAURA study<sup>8</sup> showed that central nervous system progression was less frequent in patients receiving osimertinib than in those receiving first-generation EGFR-TKIs (15% vs 6%). Other studies have also shown that osimertinib is effective against both systemic and brain metastatic lesions in patients with pre-existing brain metastases.<sup>37,38</sup> In the present study, no statistically significant difference was observed in either PFS or TTF according to the presence or absence of brain metastases; as such, our findings were consistent with those of previous studies.

There were several limitations to our study. First, the sample size may not have been sufficiently large; moreover, the study was performed at a single institution. Second, although the individuals included in this study were elderly, data regarding their quality of life were not evaluated.

## Conclusion

Osimertinib appears to be an effective and safe treatment option for elderly patients with advanced NSCLC harboring *EGFR* mutations. However, it is important to note the frequency of drug-induced ILD, which highlights the importance of a careful follow-up in this population. To obtain more conclusive results, additional studies in a larger elderly population are warranted.

## Research Involving Human Participants and/or Animals

This study does not include human participants and animals.

## Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Ethics Review Board of Kitasato University Hospital. All patients gave informed consent for study participation.

## Informed Consent

Informed consent was obtained from all individual participants included in the study.

## Consent for Publication

All authors the study gave consent to publication of this study.

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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