First-line Osimertinib for Poor Performance Status Patients With EGFR Mutation-positive Non-small Cell Lung Cancer: A Prospective Observational Study

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Abstract

***Objective**:* The clinical outcomes of poor performance status (PS) patients with *epidermal growth factor receptor* (*EGFR*)-mutated non-small cell lung cancer (NSCLC) who are treated with osimertinib as a first-line treatment have not been sufficiently evaluated. This study aimed to assess the efficacy and safety of osimertinib in chemotherapy-naive and poor PS (2 or more) patients with NSCLC harboring sensitive *EGFR* mutations.

***Materials and Methods**:* We assessed the clinical effects of osimertinib as a first-line treatment for patients with poor PS NSCLC with an exon 19 deletion or exon 21 L858R mutation in *EGFR*. All patients were administered osimertinib (80 mg/day) as the initial treatment.

***Results**:* Sixteen patients (nine women and seven men) who were treated between August 2018 and July 2021 were included in this study; their median age was 78 years. The overall objective response rate was 56.3%. The median progression-free survival (PFS) of the entire patient population was 10.5 months and the PS score improved in 8 of 16 patients (50%). The most common adverse event was acneiform rash (42%), followed by diarrhea (36%) and paronychia (36%); none of these were of grade ≥ 3. Interstitial lung disease occurred in 2 patients (12.5%); however, no treatment-related deaths occurred.

***Conclusion**:* Considering the findings of this study, osimertinib appears to be an effective and safe treatment option for patients with poor PS and advanced NSCLC harboring sensitive *EGFR* mutations. To obtain conclusive results, further studies with larger cohorts are warranted.

Introduction

Lung cancer is one of the main causes of cancer-related deaths, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [1]. Recently, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have markedly improved the prognosis of patients with NSCLC harboring *EGFR*-activating mutations. Approximately 70% of NSCLC patients are diagnosed at advanced stages, and NSCLC is a common cause of cancer-related mortality [2]. *EGFR* gene mutations are detected in approximately 30% of East Asian patients with NSCLC [3, 4]. Based on the positive results from phase III trials [5–12], EGFR-TKIs have been administered to such patients, and several EGFR-TKIs are currently approved as first-line treatments for *EGFR* mutation-positive NSCLC in Japan. These include the first-, second-, and third-generation TKIs: erlotinib and gefitinib, afatinib and dacomitinib, and osimertinib, respectively. We have previously reported real-world data, indicating the efficacy of first- and second-generation TKIs for patients with *EGFR* mutation-positive NSCLC [13–15]. It was reported that osimertinib had survival benefits compared to first-generation EGFR-TKIs, with not only a significantly superior survival time, but also a less toxic profile in the FLAURA trial [12]. This resulted in its approval as a standard first-line treatment for *EGFR*-mutated NSCLC, indicating that its administration may be a feasible intervention for patients with poor performance status (PS). PS is an important prognostic and predictive factor in most cancer treatments. Previous studies have supported the use of first-and second-

generation EGFR-TKIs, such as gefitinib and afatinib, as a first-line treatment for patients with NSCLC and poor PS harboring sensitive *EGFR* mutations [16–18]. Several studies have indicated that osimertinib could be beneficial in poor PS patients with *EGFR* T790M mutation-positive NSCLC whose disease has progressed following first-line EGFR-TKI treatment [19–21]. However, existing data are insufficient to determine the efficacy of osimertinib in chemo-naïve patients with NSCLC and poor PS.

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

Materials 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 with a poor PS score (2 or more). The eligibility criteria 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 one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [22], and the ability to receive oral treatment. Patient characteristics, including age at diagnosis, sex, Eastern Cooperative Oncology Group PS at the start of the osimertinib treatment, smoking status, clinical stage, tumor histology, and brain metastasis status, were identified via chart review. The PS score of each patient was assessed by two investigators (S.I. and M.K.). All patients provided written informed consent prior to enrollment.

Treatment and Response assessment

All patients received a single daily dose (80 mg) of osimertinib. Treatment was continued until disease progression or the occurrence of unacceptable adverse events. After initiating the osimertinib treatment, computed tomography of the chest and abdomen was performed every 2 to 3 months or more frequently, if necessary. Positron emission tomography, bone scintigraphy, 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.), and the treatment efficacy was assessed using the RECIST. The best overall response and maximum tumor control were recorded as tumor responses. Radiation therapy for patients with pre-existing brain metastasis prior to osimertinib treatment was performed at the discretion of the physician in charge. Among the patients with pre-existing brain metastasis, computed tomography or magnetic resonance imaging of the head was performed every 6 months or more frequently, if necessary.

Toxicity assessment and dose modification

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 5). The physical conditions, symptoms, blood tests, and chest X-rays of patients were evaluated throughout the osimertinib treatment at the discretion of the physician in charge. Any interruption, discontinuation, or dose reduction of osimertinib caused by toxicity was done 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. Survival curves were plotted using the Kaplan-Meier method, and differences according to brain metastasis status were analyzed using the log-rank test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 28.0 for Windows (IBM Corp., Armonk NY, USA).

Results

Patient characteristics

Sixteen 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 78 years, and 56% were men. Fourteen and two patients had a PS score of 2 and 3, respectively. Fourteen patients had adenocarcinomas, two had adeno-squamous carcinomas, 63% had an *EGFR* exon 19 deletion, and 38% had an L858R point mutation. Four patients with postoperative recurrence were included in the entire patient population. Nine patients (56%) had brain metastasis before osimertinib treatment, including two patients who received radiotherapy for brain metastasis prior to osimertinib treatment.

Overall efficacy

Table 2 presents the objective tumor responses. An objective response was obtained in 9 of the 16 patients, indicating an objective response rate of 56.3% (95% confidence interval [CI]: 47.1%–78.0%). The cut-off date for survival analysis was September 2021, and the median follow-up period by that date was 18.7 months. The median PFS of the entire patient population was 10.5 months (95% CI: 2.8–18.2 months; Figure 1). The median PFS in patients with versus without pre-existing brain metastasis was 13.7 months (95% CI: 4.4–23.0 months) and 10.5 months (95% CI: 5.6–15.4 months), respectively; the difference was not significant ($P = 0.77$, Figure 2). Among the nine patients with pre-existing brain metastasis prior to osimertinib treatment, disease progression following osimertinib treatment owing to the progression of intracranial lesion was observed in 2 patients (22.2%), as follows; aprogression of pre-existing brain metastasis in one patient and leptomeningeal carcinomatosis in another patient. In the two patients who received radiotherapy for brain metastasis prior to osimertinib treatment, partial responses were observed and they remained on osimertinib without disease progression at the cut-off date for survival analysis. Among the seven patients who did not have pre-existing intracranial lesions before osimertinib treatment, disease progression due to the occurrence of a new brain metastasis was observed

in one patient (14.3%). Eleven patients discontinued osimertinib treatment because of disease progression, among whom six patients received second-line treatments (carboplatin plus pemetrexed [n = 3], other EGFR-TKIs [n = 2], and pembrolizumab [n = 1]). No patient continued osimertinib treatment beyond disease progression.

The overall changes in PS scores during osimertinib treatment in all patients are shown in Figure 3. The PS score improved to a score of 1 in 8 out of 16 patients (50%), including the improvement of the PS score to a score of 1 from a score of 3 in two patients who had a partial response to osimertinib treatment.

Toxicities

The toxicity of osimertinib was evaluated in all patients. The main adverse events observed during treatment are presented in Table 3. The most common ones were rash acneiform (7 patients [44%], none with a grade ≥ 3), diarrhea (6 patients [38%], none with a grade ≥ 3), and paronychia (6 patients [36%], none with a grade ≥ 3). Interstitial lung disease (ILD) was detected in two patients (12.5%), one of whom had grade 3 ILD. Furthermore, one patient developed grade 3 fatigue, and another developed grade 3 anemia. Six patients (37.5%) required an osimertinib dose reduction due to adverse events. Osimertinib administration was discontinued in two patients (12.5%) owing to ILD (from which they recovered after corticosteroid therapy and no recrudescence was observed). None of the patients discontinued osimertinib therapy because of other adverse events.

The duration of osimertinib treatment until disease progression or cessation owing to adverse events in individual patients is summarized in Figure 4.

Discussion

In a phase III study (FLAURA), osimertinib was found to significantly prolong the PFS compared with gefitinib or erlotinib in NSCLC patients harboring sensitive *EGFR* mutations [12]. Moreover, the osimertinib group of the Japanese subset of the FLAURA study had a PFS of 19.1 months, indicating the efficacy of osimertinib as first-line therapy in the Japanese population [23]. However, the poor PS population was not included in the FLAURA study, and existing data remain insufficient to determine the efficacy of osimertinib as first-line treatment in patients with poor PS. We found, for the first time, that first-line treatment with osimertinib provided a response rate of 56.3% and a median PFS of 10.5 months in this patient population.

Osimertinib treatment for patients with poor PS could be beneficial and clinically meaningful, considering that cytotoxic chemotherapy provides limited benefits to NSCLC patients with a PS score of 2 and that, currently, the only option for patients with PS scores of 3–4 is best supportive care. Regarding the changes in PS scores during osimertinib treatment, the PS scores were improved in 8 of 16 patients (50%), including notable improvements to a score of 1 from a score of 3 in two patients who had a partial response to osimertinib. In general, the preservation of the PS is indispensable for connecting patients to

post-treatment with sequential chemotherapy, which prolongs patient survival. Of the 11 patients with disease progression on osimertinib, 6 patients (55%) received second-line chemotherapy based on the preservation of PS with the osimertinib treatment. Notably, three of these patients received carboplatin plus pemetrexed, suggesting the clinical usefulness of osimertinib in patients with poor PS.

The incidence of drug-induced ILD in the Japanese subgroup of the FLAURA study was approximately 1.8% in those administered gefitinib but was 12.3% in those administered osimertinib [23]. Inoue et al. reported the safety of gefitinib for EGFR-TKI-naive patients with poor PS [16], showing that the incidence of ILD was 3.3%. A phase II study reported that the incidence of ILD induced by osimertinib was observed in 17% of patients with poor PS with *EGFR* T790M mutation-positive advanced NSCLC who were pretreated with other EGFR-TKIs [21]. Additionally, ILD due to osimertinib was observed in two patients (12%), indicating that ILD incidence may be high in poor PS patients treated with osimertinib.Meanwhile, the patients with drug-induced ILD recovered after corticosteroid therapy, and no mortality due to drug-induced ILD was observed in our study. A previous study demonstrated that 80% of patients with ILD complicated by osimertinib recovered, and that the 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%) [24], suggesting that recovery from ILD is mostly expected in patients receiving osimertinib.

The proportion of patients with brain metastases was 56% here, and most patients initially received systemic chemotherapy with osimertinib, except for two patients who received radiotherapy for brain metastasis prior to osimertinib treatment. As for patients with pre-existing brain metastases prior to osimertinib treatment, the FLAURA study [12] showed that central nervous system progression was less frequent in patients receiving osimertinib than in those receiving first-generation EGFR-TKIs, such as gefitinib and erlotinib (6% vs. 15%). Other studies have shown that osimertinib is effective for both systemic and brain metastatic lesions in patients with pre-existing brain metastases [25, 26]. Here, no statistically significant difference was observed in PFS according to the presence or absence of pre-existing brain metastases; as such, our findings were consistent with those of the above studies. Therefore, it may be reasonable to mention that osimertinib is expected to be effective for brain metastatic lesions in both poor and good PS populations.

Table 4 provides a summary of previous studies on patients with poor PS who were treated with first-line EGFR-TKIs, showing that the response rate found here was identical to that found in previous studies of other EGFR-TKIs; however, the PFS of our patients appeared to be longer than that of patients who were treated with other EGFR-TKIs.

This study has several limitations. First, the cohort size is very small, and the study was performed at a single institution. Second, we did not include patients with a PS score of 4, for which the clinical efficacy and safety of osimertinib remains unclear. Third, the evaluation of the PS is very difficult. While the PS score of each patient was assessed by two investigators in our study, bias arising from the subjectivity of investigators might not be completely excluded. Fourth, while the individuals included in this study had poor PS, their quality of life was not evaluated.

Considering our findings, osimertinib appears to be an effective and safe treatment option for patients with poor PS and advanced NSCLC harboring sensitive *EGFR* mutations. To obtain conclusive results, further studies with larger cohorts are warranted.

Declarations

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 provided written informed consent prior to enrollment.

Consent for publication: All authors the study gave consent to publication of this study.

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

Competing interests

There was no competing interest to declare.

Author contributions: All authors contributed to the study conception and design. Data collection was performed by all authors, and analysis was performed by SI and MK. The first draft of the manuscript was written by SI and KN. All authors commented on versions of the manuscript. All authors read and approved the final version of the manuscript.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Not applicable.

Informed consent

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

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Tables

Table 1.

	n = 16 (%)
Age (years), median, range	78 (54–89)
Gender	
Male/Female	9 (56)/7 (44)
Performance status	
2/3	14 (88)/2(12)
EGFR genotype	
Del 19/L858R	10 (62)/6 (38)
Histology	
Adenocarcinoma/Adeno-squamous	14 (88)/2 (12)
Stage	
IV/Recurrence	12 (75)/4 (25)
Smoking status	
Smoker/Never smoker	9 (56)/7 (44)
Brain metastasis	
Positive/Negative	9 (56)/7 (44)

Table 2.

	n = 16
Complete response	0
Partial response	9
Stable disease	4
Progressive disease	3
Response rate	56.3%
95% CI	47.1–78.0

Table 3.

Adverse event	Any Grade (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Rash acneiform	7 (44)	5 (31)	2 (13)	0	0
Diarrhea	6 (38)	5 (31)	1 (6)	0	0
Paronychia	6 (38)	6 (38)	0	0	
Oral mucositis	4 (24)	4 (24)	0	0	0
Anorexia	4 (24)	2 (18)	2 (12)	0	0
Fatigue	4 (24)	2 (18)	1 (6)	1 (6)	
Nausea	3 (18)	2 (12)	1 (6)	0	
Dry skin	2 (12)	2 (12)	0	0	
Constipation	2 (12)	2 (12)	0	0	
Tinnitus	1 (6)	1 (6)	0	0	
Neutropenia	7 (44)	6 (38)	1 (6)	0	0
Leukopenia	7 (44)	5 (31)	2 (12)	0	0
Anemia	4 (24)	2 (12)	1 (6)	1 (6)	0
Thrombocytopenia	3 (18)	3 (18)	0	0	0
Creatinine increased	3 (18)	2 (18)	1 (6)	0	0
AST/ALT increased	3 (18)	2 (12)	1 (6)	0	0
QTc prolongation	1 (6)	1 (6)	0	0	0
Interstitial lung disease	2 (12)	0	1 (6)	1 (6)	0

Table 4.

	Drug	No. of Pts.[a]	Study design	Response rate (%)	Median PFS[b] (months)
Inoue (16)	GEF	31	Prospective	66.0	6.5
Okuma (17)	GEF[c]	52	Retrospective	65.4	6.6
Wu (18)	AFA[d]	62	Retrospective	58.1	8.8
Present study	OSIM[e]	16	Prospective	56.3	10.5

[a]Pts, patients; [b]PFS, progression-free survival; [c]GEF, gefitinib; [d]AFA, afatinib; [e]OSIM, osimertinib

Figures

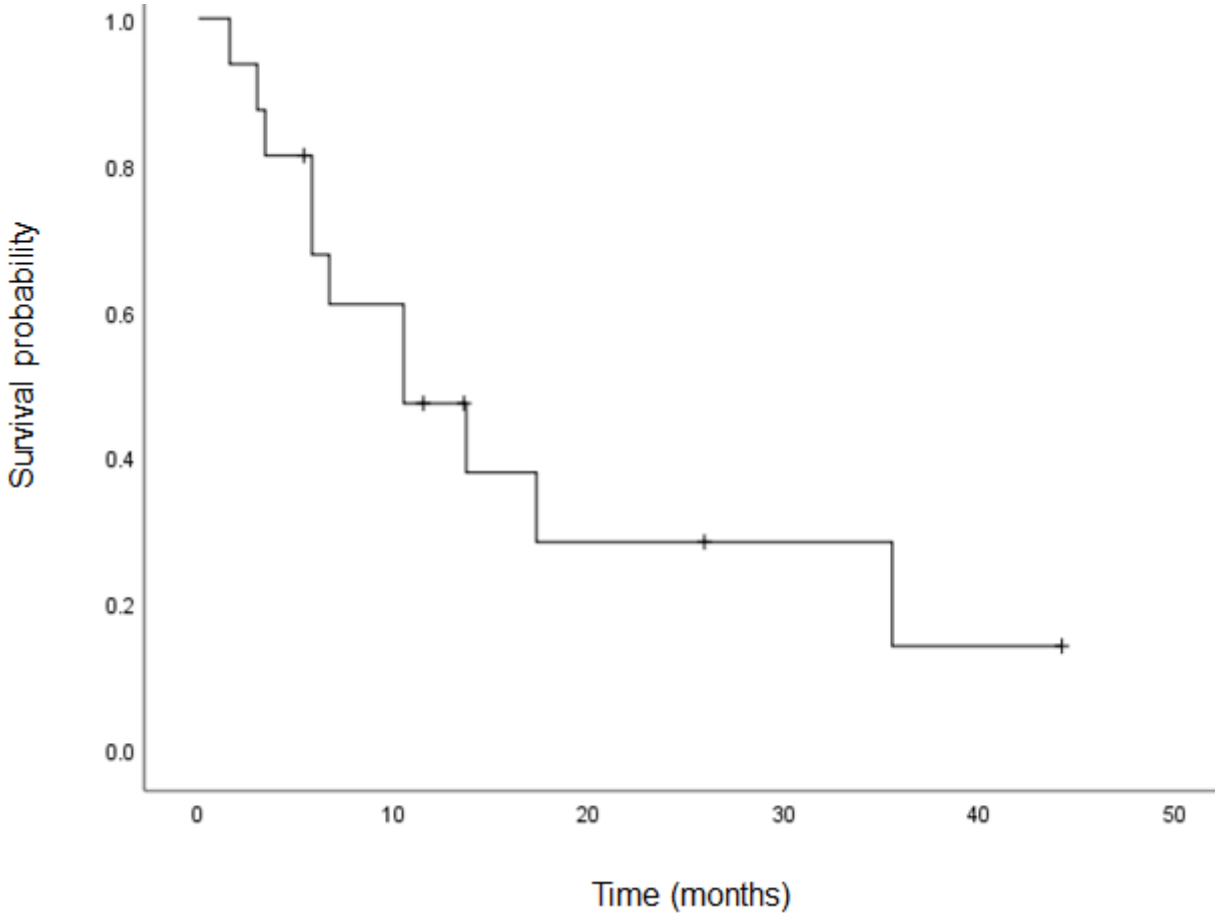

Figure 1

Kaplan-Meier curves showing the progression-free survival to osimertinib therapy

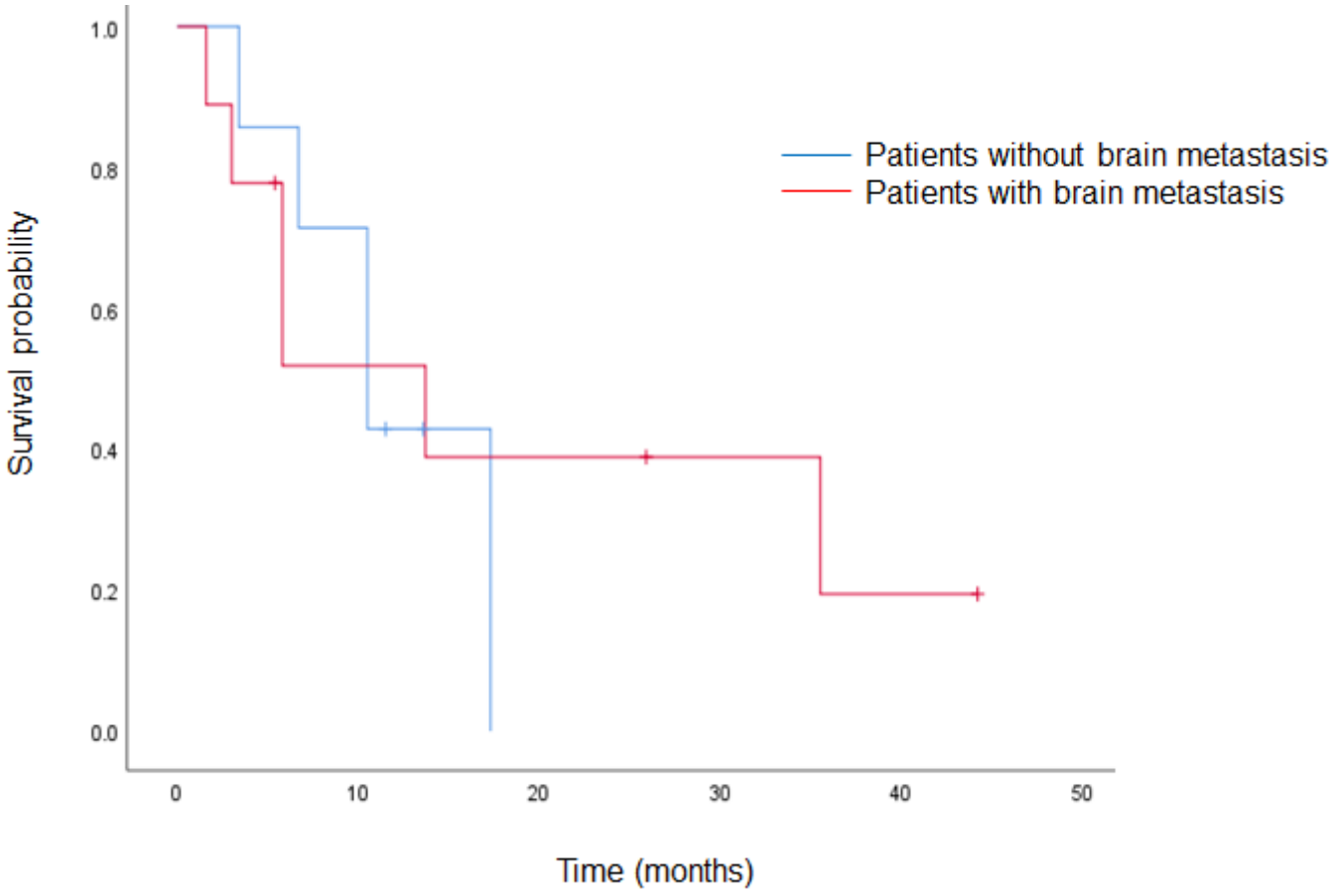

Figure 2

Kaplan-Meier curves showing the progression-free survival of patients with versus without pre-existing brain metastasis

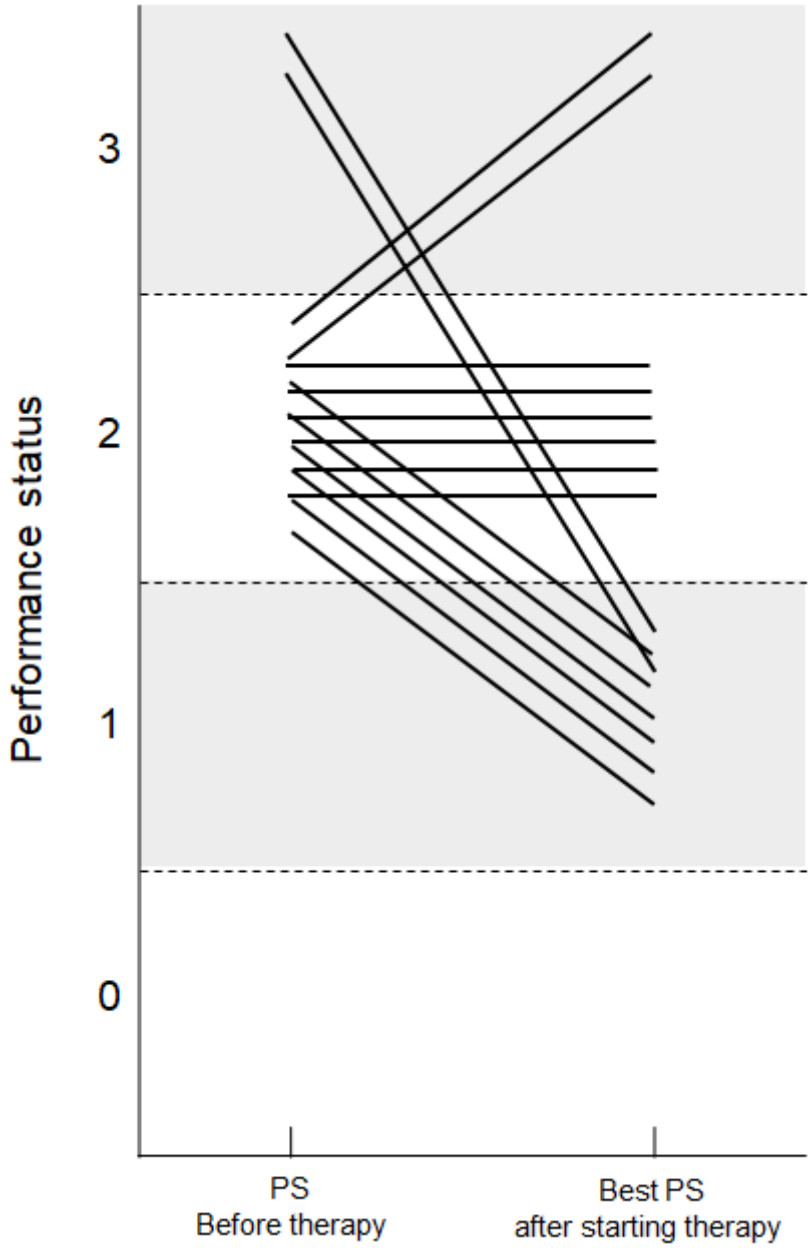

Figure 3

The overall changes in the PS scores of all patients during osimertinib treatment

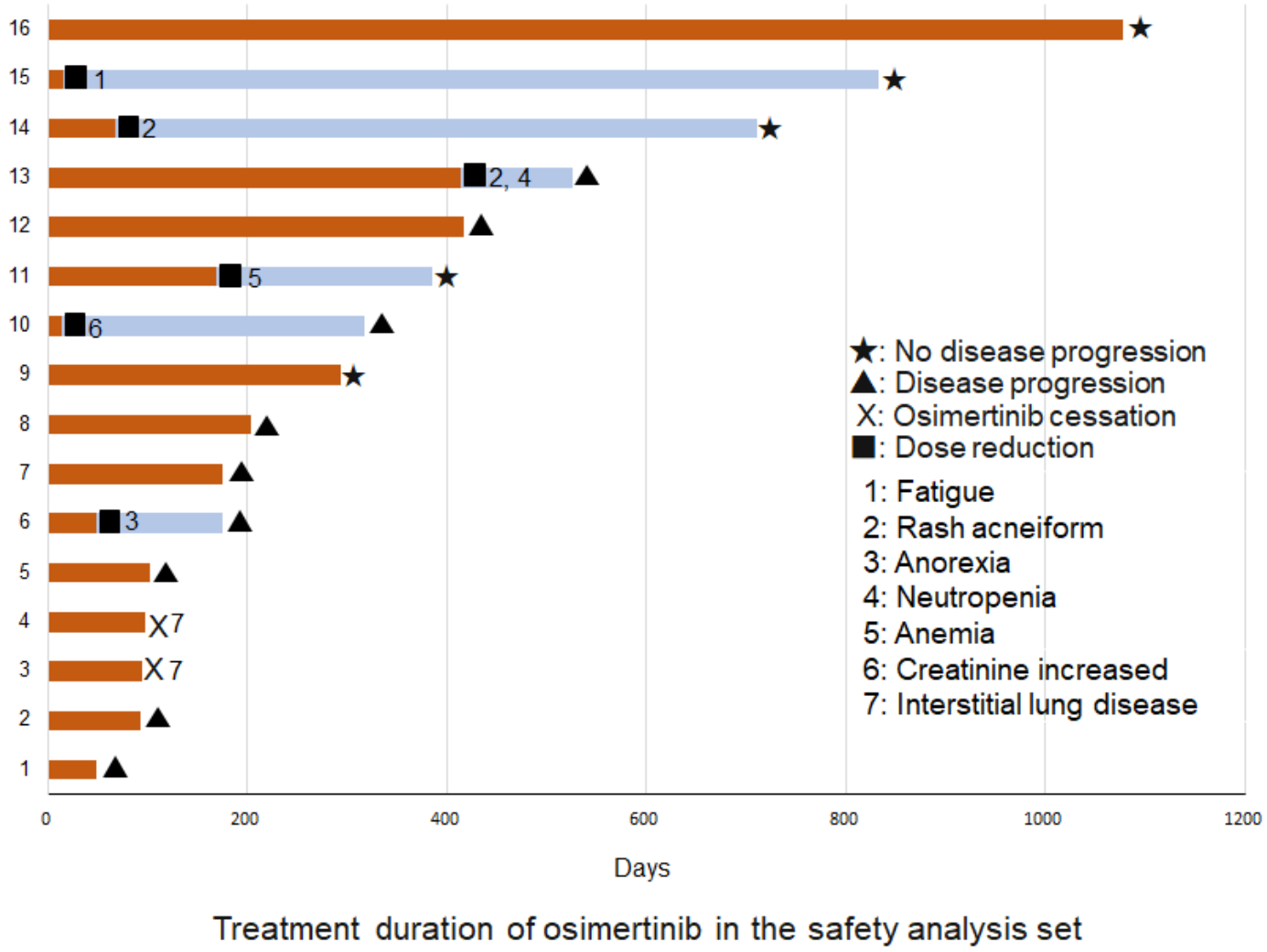

Figure 4

Duration of osimertinib treatment before disease progression or cessation owing to adverse events in individual patients