Thoracic Cancer

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Real-World Study of EGFR-TKI Rechallenge With Another TKI After First-Line Osimertinib Discontinuation in Patients With EGFR-Mutated Non-Small Cell Lung Cancer: A Subset Analysis of the Reiwa Study

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ABSTRACT

Introduction: First-line osimertinib is widely used to treat patients with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancers (NSCLC). In clinical practice, rechallenge therapy with another EGFR-tyrosine kinase inhibitor (TKI) is often performed after first-line TKI discontinuation owing to resistance or toxicity; however, the efficacy and toxicity of EGFR-TKI rechallenge after first-line osimertinib have not been adequately investigated. This study aimed to examine the efficacy and safety of EGFR-TKI rechallenge with another TKI.

Methods: This multicenter prospective observational study enrolled patients with EGFR-mutated NSCLC who received first-line osimertinib and another EGFR-TKI as second- or third-line treatment between September 2018 and August 2020.

Results: Fifty-three patients received rechallenge with another EGFR-TKI in the second-line ($n = 38$, 71.7%) or third-line ($n = 15$, 28.3%) setting. The primary reason for first-line osimertinib discontinuation was toxicity in 32 (60.4%, 17 patients with pneumonitis) and disease progression in 20 (37.7%) patients. The most common rechallenge EGFR-TKI was afatinib ($n = 24$, 45.3%), followed by gefitinib ($n = 16$, 30.2%) and erlotinib ($n = 8$, 15.1%). The real-world time to treatment failure (rwTTF) was 7.3 months. The rwTTF for the toxicity discontinuation and progressive disease discontinuation groups was 9.3 months and 5.1 months, respectively, (HR 1.61, $p = 0.119$). EGFR-TKI rechallenge was discontinued due to toxicity in nine patients (17.0%), but no patient developed pneumonitis.

Conclusion: EGFR-TKI rechallenge with another TKI is well tolerated in patients with EGFR-mutated NSCLC. Thus, it may be a useful treatment option after first-line osimertinib failure, especially after osimertinib discontinuation due to toxicity.

1 | Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. However, the prognosis of advanced and recurrent non-small cell lung cancer (NSCLC) has recently improved significantly with the introduction of targeted tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors, in addition to cytotoxic anticancer drugs. In Asia, the most common driver gene mutation of lung cancer is the epidermal growth factor receptor (EGFR) mutation [2]. In the FLAURA trial, the third-generation EGFR-TKI osimertinib was associated with both significantly higher progression-free survival (PFS) and overall survival (OS) than was first-generation EGFR-TKIs. Thus, osimertinib has been established as the standard first-line treatment for untreated EGFR-mutated NSCLC patients [3]. However, subsequent treatment after osimertinib discontinuation due to resistance or toxicity has not yet been established. Although platinum-based chemotherapy is the most commonly used subsequent treatment after first-line osimertinib resistance, evidence on its efficacy is insufficient. Several phase III trials have verified the efficacy of chemoimmunotherapy for EGFR-mutated NSCLC, but superior survival with chemoimmunotherapy compared with chemotherapy has not been observed [4, 5].

In addition to chemotherapy and chemoimmunotherapy, EGFR-TKI rechallenge with another TKI is commonly used as subsequent treatment after first-line osimertinib treatment failure. In the FLAURA trial, 21% and 32% of patients in the osimertinib arm received EGFR-TKI as first- and second-line treatment, respectively [3]. It is unclear whether rechallenge with another EGFR-TKI after first-line osimertinib has a reasonable survival benefit. However, the efficacy of EGFR-TKI rechallenge after first-generation TKI treatment has been verified in several retrospective studies in Japan, with objective response rates (ORRs) of 17%–25% and a median PFS of 3.4–8.0 months [6–8]. In a phase II study examining the efficacy of gefitinib rechallenge (third-line) after first-line gefitinib in EGFR-mutated NSCLC, the ORR was 4.9%, and the median PFS was 2.8 months. Another Phase II study examining the efficacy of afatinib after first- or second-generation TKI in EGFR-mutated NSCLC reported an ORR of 17% and a median PFS of 4.2 months [9, 10].

As mentioned above, limited studies have examined the efficacy of EGFR-TKI rechallenge; particularly, no studies have been conducted on another rechallenge with EGFR-TKI after osimertinib administration. A Phase II trial is currently ongoing to assess the efficacy of afatinib after first-line osimertinib for EGFR-mutated NSCLC in Japan [11]. The toxicity that requires the most attention in first-line osimertinib is pneumonitis. In a Japanese subset of the FLAURA trial, the incidence of any-grade pneumonitis was 12.3% (Grade > 3: 1.5%) [12]. In OSI-FACT, a real-world multicenter retrospective analysis of osimertinib in Japan, the incidence of any grade pneumonitis was 12.8% [13]. The most common subsequent treatment after osimertinib-induced pneumonitis was platinum-based chemotherapy (46.9%), followed by rechallenge with another EGFR-TKI (37.5%) [13]. In clinical practice, rechallenge with another EGFR-TKI is commonly used after first-line osimertinib-induced pneumonitis, but its efficacy and safety have not been extensively studied. Another EGFR-TKI rechallenge following first-line osimertinib is widely used in clinical practice; however, only some studies exist on the efficacy and safety of this. Even fewer reports exist based on patient classification into discontinuation due to toxicity and discontinuation due to progressive disease (PD) groups. The Reiwa study was a large-scale multicenter prospective observational study that examined the efficacy, safety, progression patterns, and subsequent treatment for first-line osimertinib in the real world [14]. The purpose of the current study was to analyze the characteristics of patients who receive rechallenge with another EGFR-TKI after first-line osimertinib failure and to examine the efficacy and safety of this strategy using data from the Reiwa study.

2 | Methods

2.1 | Study Design, Patients, and Data Collection

This multicenter, prospective, observational study was approved by the Institutional Review Board of the Japanese Red Cross Medical Center (April 26, 2019, Order No. 976) and the relevant committees at each institution. The study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects. Written informed consent was obtained from all the patients.

Patients aged ≥ 20 years who were diagnosed with advanced or recurrent EGFR-mutated NSCLC and scheduled for EGFR-TKI treatment from 30 centers in Japan were enrolled from September 2018 to August 2020. This study used the data collection methods detailed in our previous protocol. The data of patients lost to follow-up during the observation period were censored on the date of discontinuation, whereas those of patients who did not show disease progression during the observation period were censored on the date of final confirmation. The final follow-up was conducted in August 2022. Data of patients who received first-line osimertinib and rechallenge with other EGFR-TKIs in the second- or third-line setting were obtained from the Reiwa study database.

2.2 | Variable Definition and Assessments

The real-world time to treatment failure (rwTTF) was defined as the period from the start of rechallenge with another EGFR-TKI to discontinuation due to any cause, including toxicity, disease progression, patient refusal, or death. OS was defined as the period from the start of rechallenge with another EGFR-TKI until any-cause death. PFS was defined as the period from the start of osimertinib treatment to PD or death. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1 [15]. The ORR was defined as the sum of the complete response (CR) rate plus the partial response (PR) rate, while the disease control rate (DCR) was defined as the sum of the rates of CR, PR, and stable disease (SD). The primary endpoint was rwTTF and safety of another EGFR-TKI.

2.3 | Statistical Analysis

Patients who discontinued first-line osimertinib due to toxicity and patient refusal were included in the toxicity discontinuation group, while patients who discontinued first-line osimertinib due to PD were included in the PD discontinuation groups, and statistical analysis was performed. PFS, OS, and rwTTF analyses were conducted using the Kaplan–Meier method with log–rank tests. Univariate and multivariate analyses were performed using Cox regression modeling to determine the prognostic factors associated with rwTTF. Clinically significant variables ($p < 0.10$) in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using IBM SPSS Statistics version 26.

3 | Results

3.1 | Patient Characteristics

This study included 53/583 patients who received first-line osimertinib. The patient selection flow chart is shown in Figure S1. The patient characteristics are summarized in Table 1. The median PFS with first-line osimertinib was 12.2 months (95% confidence interval [CI], 7.5–16.9). Rechallenge with another EGFR-TKI was given in the second- and third-line settings in 38 (71.7%) and 15 (28.3%) patients, respectively. The second-line regimen for patients with third-line EGFR-TKI rechallenge is summarized in Table S1. The most common drug for rechallenge with another EGFR-TKI was afatinib ($n = 24$%, 45.3%), followed by gefitinib ($n = 16$%, 30.2%), erlotinib ($n = 8$%, 15.1%), erlotinib plus bevacizumab ($n = 3$%, 5.7%), and erlotinib plus ramucirumab ($n = 2$%, 3.8%). The reasons for first-line osimertinib discontinuation were toxicity in 32 (60.4%), disease progression in 20 (37.7%), and patient refusal in 1 (1.9%) patient. The toxicities that led to discontinuation of first-line osimertinib are summarized in Table S2. The most common toxicity was pneumonitis ($n = 17$%, 53.1%), followed by skin rash ($n = 4$%, 12.5%).

TABLE 1 | Patient characteristics.

Category	All patients, *N* (%)
Patients, (*N*)	53
Age (years), median (range)	73 (45–87)
Sex, male/female	21 (39.6)/32 (60.4)
ECOG PS	
(First-line osimertinib introduction), 0/1/2/3/unknown	21 (39.6)/28 (52.8)/3 (5.7)/0 (0.0)/1 (1.9)
(Another EGFR-TKI rechallenge introduction), 0/1/2/3/unknown	12 (22.6)/35 (66.0)/2 (3.8)/3 (5.7)/1 (1.9)
Smoking history, yes/no	21 (39.6)/32 (60.4)
Histologic subtype, adeno/other	52 (98.1)/1 (1.9)
EGFR mutation, Del19/L858R/other mutation	24 (45.3)/26 (49.1)/3 (5.7)
Staging (TNM 8th), IVA/IVB/recurrence	17 (32.1)/18 (34.0)/18 (34.0)
Reason for first-line osimertinib discontinuation, PD/toxicity/patient refusal	20 (37.7)/32 (60.4)/1 (1.9)
Toxicity subtype ($N = 32$), pneumonitis/other	17 (53.1)/15 (46.9)
Line of another EGFR-TKI rechallenge, second/third	38 (71.7)/15 (28.3)
Type of second-line EGFR-TKI ($N = 38$)	
Gefitinib	16 (42.1)
Erlotinib	4 (10.5)
Afatinib	16 (42.1)
Erlotinib + bevacizumab	2 (5.3)
Erlotinib + ramucirumab	0 (0.0)
Type of third-line EGFR-TKI ($N = 15$)	
Gefitinib	0 (0.0)
Erlotinib	4 (26.7)
Afatinib	8 (53.3)
Erlotinib + bevacizumab	1 (6.7)
Erlotinib + ramucirumab	2 (13.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD, progressive disease; PS, performance status; TKI, tyrosine kinase inhibitor.

3.2 | Tumor Response and Survival

The tumor responses to first-line osimertinib and rechallenge with another EGFR-TKI are summarized in Table 2. The ORR and DCR in first-line osimertinib were 58.5% (95% CI, 45.1–71.9) and 77.4% (95% CI, 66.0–88.7), respectively. The ORR and DCR in rechallenge with another EGFR-TKI were 32.1% (95% CI, 19.4–44.8) and 73.6% (95% CI, 61.6–85.6), respectively. The ORR and DCR in rechallenge with another EGFR-TKI were 36.4% (95% CI, 19.7–53.0) and 81.8% (95% CI, 68.5–95.2), respectively, for the toxicity discontinuation group and 25.0% (95% CI, 5.5–44.5) and 60.0% (95% CI, 38.0–82.0), respectively, and for the PD discontinuation group. The median rwTTF was 7.3 months (95% CI, 3.7–10.9). The Kaplan–Meier curves of rwTTF for the toxicity discontinuation and PD discontinuation groups are presented in Figure 1. The rwTTF of the toxicity discontinuation group and the PD discontinuation group were 9.3 months (95% CI, 4.2–14.4) and 5.1 months (95% CI, 2.3–7.9), respectively (hazard ratio [HR]: 1.61, 95% CI, 0.89–2.93, $p = 0.119$). The median OS was 23.9 months (95% CI, 16.8–31.1). The Kaplan–Meier curves of OS for the toxicity discontinuation and PD discontinuation groups are presented in Figure 2. The median OS of the toxicity discontinuation group and the PD discontinuation group were 29.8 months (95% CI, 23.1–36.5) and 12.8 months (95% CI, 9.1–16.5), respectively (HR: 3.10, 95% CI, 1.39–6.95, $p = 0.006$). The Kaplan–Meier curves of rwTTF for the afatinib group and first-generation EGFR-TKIs (gefitinib and erlotinib) groups are

TABLE 2 | Efficacy of first-line osimertinib and EGFR-TKI rechallenge with another TKI treatment.

Efficacy	First-line osimertinib, *N* (%)	Another EGFR-TKI rechallenge, *N* (%)
Complete response	1 (1.9)	0 (0.0)
Partial response	30 (56.6)	17 (32.1)
Stable disease	10 (18.9)	22 (41.5)
Progressive disease	4 (7.5)	8 (15.1)
Not evaluable	8 (15.1)	6 (11.3)
ORR, % (95%. CI)	58.5 (45.1–71.9)	32.1 (19.4–44.8)
DCR, % (95%, CI)	77.4 (66.0–88.7)	73.6 (61.6–85.6)

Abbreviations: CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

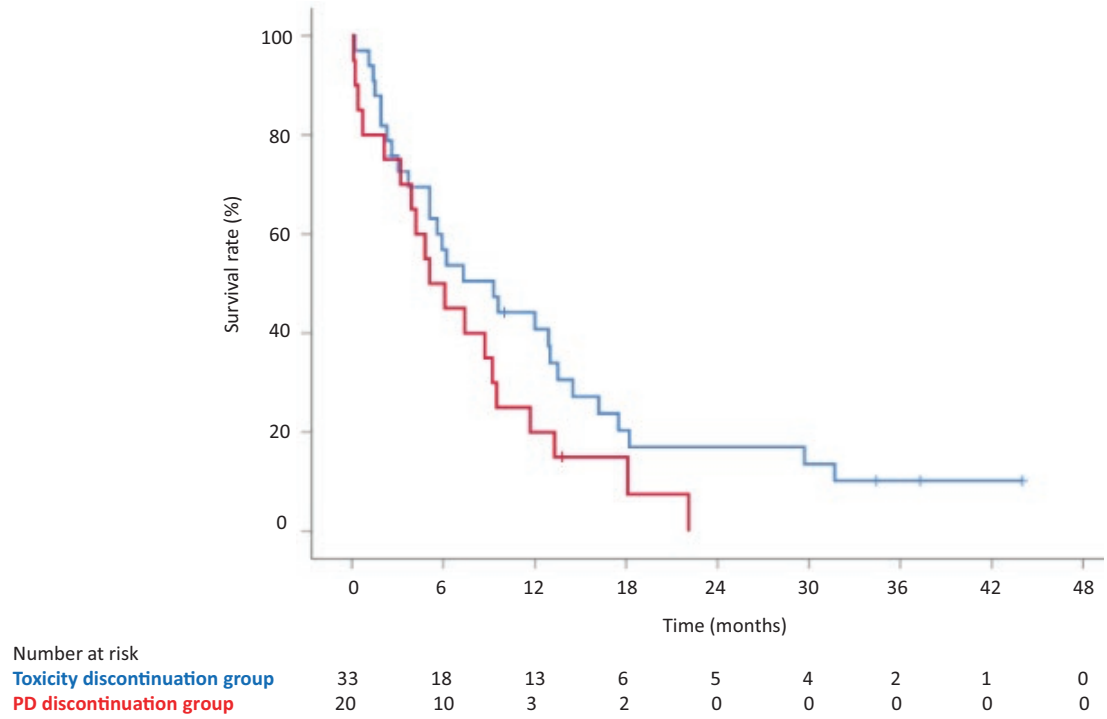

FIGURE 1 | Kaplan–Meier curves of real-world time to treatment failure (rwTTF) in patients who receive rechallenge with another EGFR-TKI after first-line osimertinib failure. The median rwTTF in the toxicity discontinuation and PD discontinuation groups is 9.3 months (95% CI, 4.2–14.4) and 5.1 months (95% CI, 2.3–7.9), respectively, with no significant difference (HR: 1.61, 95% CI, 0.89–2.93, $p = 0.119$). CI, confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; PD, progressive disease.

presented in Figure S2. The median rwTTF for the afatinib and first-generation EGFR-TKI groups were 5.1 months (95% CI, 2.2–8.0) and 9.2 months (95% CI, 6.6–11.8), respectively (HR: 0.82, 95% CI, 0.45–1.49, $p = 0.509$).

3.3 | Prognostic Factors Associated With rwTTF

The prognostic factors associated with rwTTF are summarized in Table 3. In the multivariate Cox hazard analysis, good performance status (PS) of 0–1 and Del 19 EGFR mutation type were independent prognostic factors associated with rwTTF (HR: 5.27, 95% CI, 1.47–19.0, $p = 0.011$ and HR: 2.52, 95% CI, 1.30–4.89. $p = 0.006$, respectively).

3.4 | Toxicity

The rate of toxicity-related treatment discontinuation was 17.0%. Details of the toxicity that led to the discontinuation of rechallenge with another EGFR-TKI are summarized in Table S3. Rechallenge with another EGFR-TKI was discontinued in nine patients because of toxicity; among them, eight patients discontinued first-line osimertinib because of toxicity. There was no significant difference in the rate of discontinuation of EGFR-TKI rechallenge due to toxicity between the discontinuation due to toxicity and due to PD groups (first-line osimertinib), but the incidence tended to be higher in the toxicity discontinuation group (24.2% vs. 5.0%, $p = 0.071$). Reasons for discontinuation of the EGFR-TKI rechallenge were skin disorder and liver function

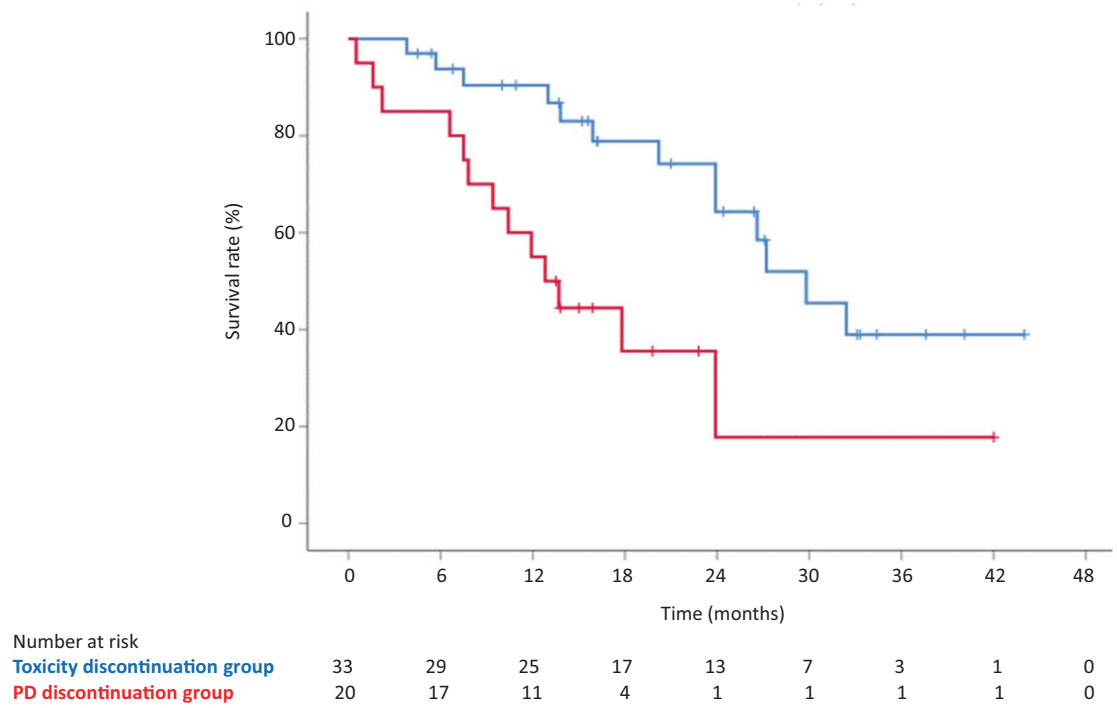

FIGURE 2 | Kaplan–Meier curves of overall survival (OS) in patients who receive rechallenge with another EGFR-TKI after first-line osimertinib failure. The median OS is significantly longer in the toxicity discontinuation group than in the PD discontinuation groups (29.8 months [95% CI, 23.1–36.5] vs. 12.8 months [95% CI, 9.1–16.5], HR: 3.10, 95% CI, 1.39–6.95, $p = 0.006$). CI, confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; PD, progressive disease.

TABLE 3 | Univariate and multivariate Cox hazard analyses of prognostic factors associated with real-world time to treatment failure.

		Univariate			Multivariate		
Category	**rwTTF (months)**	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Line of another EGFR-TKI rechallenge							
Second versus third	5.6 versus 7.4	1.04	0.54–2.00	0.900			
Age, years							
< 75 versus ≥ 75	7.3 versus 5.9	0.96	0.57–1.71	0.886			
Sex							
Male versus female	6.1 versus 7.4	0.67	0.38–1.20	0.182			
ECOG Performance status							
0–1 versus 2–3	8.7 versus 0.7	3.96	1.36–11.6	0.012	5.27	1.47–19.0	0.011
Smoking history							
Yes versus no	6.1 versus 8.7	0.60	0.34–1.08	0.089	0.57	0.31–1.05	0.071
Staging (TNM 8th)							
IV versus recurrence	NR versus 23.1	0.62	0.33–1.16	0.136			
EGFR mutation							
Del19 versus L858R	7.4 versus 5.1	1.74	0.95–3.17	0.074	2.52	1.30–4.89	0.006
Discontinuation due to toxicity							
Yes versus no	9.3 versus 5.1	1.61	0.89–2.93	0.119			

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; NR, not reached; rwTTF, real-world time to treatment failure; TKI, tyrosine kinase inhibitor.

disorder in two patients each (3.8%). None of the patients developed pneumonitis. Regarding the details of toxicity for the discontinuation of first-line osimertinib, four patients had pneumonitis and one patient each had paronychia, renal dysfunction, decreased cardiac function, and a prolonged QT interval.

3.5 | Clinical Characteristics of Patients With First-Line Osimertinib-Induced Pneumonitis

The clinical characteristics who received another EGFR-TKI rechallenge after first-line osimertinib-induced pneumonitis are summarized in Table 4. The most common drug for EGFR-TKI rechallenge was gefitinib ($n=8$, 47.1%), followed by afatinib ($n=6$, 35.3%), erlotinib ($n=2$, 11.8%), and erlotinib plus ramucirumab ($n=1$, 5.9%). The ORR and DCR in the EGFR-TKI rechallenge group were 17.6% (95% CI, 0.0–36.3) and 76.5% (95% CI, 55.7–97.3), respectively. The Kaplan–Meier curves of rwTTF and OS are presented in Figure 3. The median rwTTF was 6.2 months (95% CI, 4.1–8.3), and the median OS was 27.2 months (95% CI, 20.6–33.8). The rate of toxicity-related treatment discontinuation was 23.1%.

TABLE 4 | Patient characteristics (first-line osimertinib-induced pneumonitis).

Category	All patients, *N* (%)
Patients, (*N*)	17
Age (years), median (range)	76 (55–87)
Sex, male/female	5 (29.4)/12 (70.6)
ECOG PS	
(First-line osimertinib introduction), 0/1	8 (47.1)/9 (52.9)
(Another EGFR-TKI rechallenge introduction), 0/1	5 (29.4)/12 (70.6)
Smoking history, yes/no	8 (47.1)/9 (52.9)
Histologic subtype, adeno/other	17 (100.0)/0 (0.0)
EGFR mutation, Del19/L858R	10 (58.8)/7 (41.2)
Staging (TNM 8th), IVA/IVB/recurrence	7 (41.1)/2 (11.8)/8 (47.1)
Line of another EGFR-TKI rechallenge, second/third	13 (76.5)/4 (23.5)
Type of second-line EGFR-TKI ($N=13$)	
Gefitinib	8 (61.5)
Erlotinib	2 (15.4)
Afatinib	3 (23.1)
Type of third-line EGFR-TKI ($N=4$)	
Afatinib	3 (75.0)
Erlotinib + ramucirumab	1 (25.0)
Efficacy of another EGFR-TKI rechallenge treatment	
ORR, % (95% CI)	17.6 (0.0–36.3)
DCR, % (95% CI)	76.5 (55.7–97.3)
Toxicity	
Discontinuation of another EGFR-TKI rechallenge due to toxicity	3 (23.1)
Discontinuation of another EGFR-TKI rechallenge due to pneumonitis	0 (0.0)

Abbreviations: CI, confidence interval; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal Growth Factor Receptor; ORR, overall response rate; PS, performance status; TKI, tyrosine kinase inhibitor.

4 | Discussion

The current study demonstrates that rechallenge with another EGFR-TKI after first-line osimertinib treatment failure in patients with EGFR-mutated NSCLC is well tolerated and thus may be a useful treatment option. Osimertinib is the most commonly used regimen for first-line treatment of EGFR-mutated NSCLC, but treatment options after resistance to osimertinib remain challenging. EGFR C797S, MET amplification, and human EGFR 2 amplification mutations are the most common mechanisms underlying osimertinib resistance, but effective treatments against these mechanisms are yet to be established [16]. In clinical practice, platinum (carboplatin or cisplatin) plus pemetrexed and carboplatin plus paclitaxel plus bevacizumab plus atezolizumab are commonly used as second-line regimens after first-line osimertinib.

In this study, rechallenge with another EGFR-TKI yielded favorable ORR and rwTTF, but they might have been overestimated. This is because the first-line osimertinib was discontinued due to toxicity in 60.4% of the patients who did not develop resistance to EGFR-TKIs. The rwTTF was not significantly different between the toxicity discontinuation and PD discontinuation groups, but rechallenge with another EGFR-TKI tended to be more effective in the toxicity discontinuation group. In a previous prospective study, the ORR and PFS of 29 patients who received first- and second-generation EGFR-TKIs after developing osimertinib resistance were 6.9% and 1.9 months, respectively [17]. In another previous retrospective study, the ORR and PFS of 96 patients who received afatinib after developing resistance to first-generation EGFR-TKIs were 11.6% and 3.9 months, respectively [18]. Thus, although EGFR-TKI rechallenge may be less effective in patients in whom osimertinib is discontinued due to PD, it may still be considered a treatment option because it does not cause serious events including pneumonitis. In the present study, the OS in the toxicity discontinuation group was significantly longer than that in the PD discontinuation group, suggesting that osimertinib was discontinued before resistance was acquired. There was no significant difference in the time from the start of first-line osimertinib until any-cause death between the discontinuation due to osimertinib-induced pneumonitis and discontinuation due to other reasons groups (not reached vs. 45.0 months [95% CI, 27.0–63.0], HR: 1.27, 95% CI, 0.42–3.84, $p=0.671$). Therefore, rechallenge with another EGFR-TKI may be effective in the toxicity discontinuation group including pneumonitis.

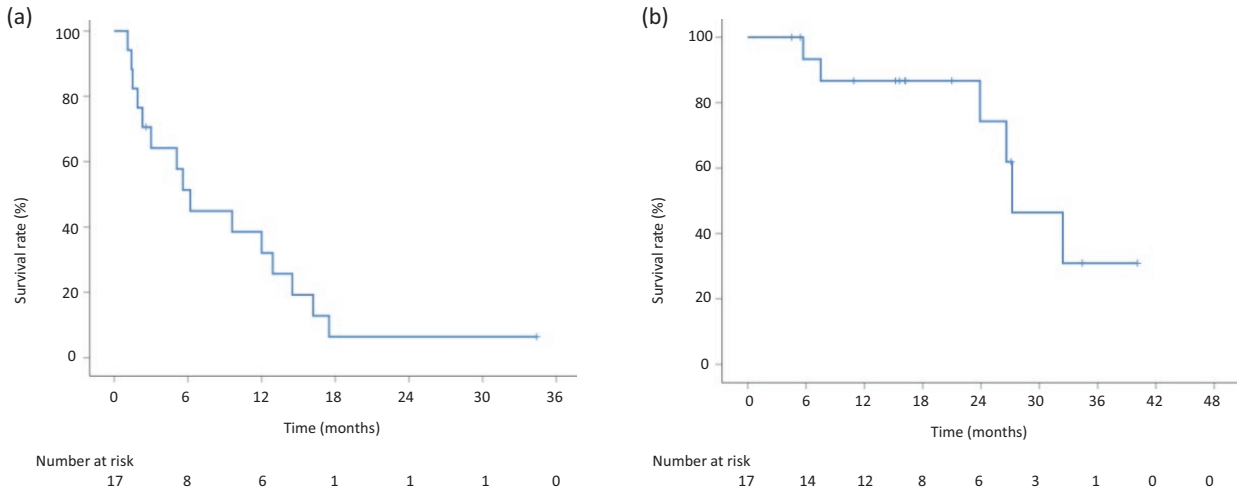

FIGURE 3 | Kaplan–Meier curves in patients who receive rechallenge with another EGFR-TKI after developing first-line osimertinib-induced pneumonitis. (a) The median real-world time to treatment failure is 6.2 months (95% CI, 4.1–8.3). (b) The median overall survival is 27.2 months (95% CI, 20.6–33.8). CI, confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

It is unclear whether a first- or second-generation EGFR-TKI is more effective in EGFR-TKI rechallenge after osimertinib treatment. In a previous meta-analysis examining the efficacy of EGFR-TKI rechallenge, the ORR of third-generation TKIs was slightly higher than that of first−/second-generation TKIs (26% vs. 14%, $p = 0.05$), but the ORR was not compared between first- and second-generation TKIs [19]. In this study, the rwTTF was not significantly different between afatinib and first-generation TKIs (gefitinib and erlotinib), but this was an analysis of a small number of patients. Further patient accumulation and investigation are required.

The current study found that Del 19 EGFR mutation was an independent favorable prognostic factor associated with rwTTF. EGFR-TKIs are more effective in patients with EGFR Del 19-mutated NSCLC than in those with EGFR L858R-mutated NSCLC . Yamaguchi et al. [7] also reported that afatinib rechallenge after previous first-generation TKIs was more effective in patients with prior EGFR-TKI rwTTF of ≥ 10 months than in those with < 10 months. Further, Cho et al. [20] reported that erlotinib improved the efficacy of EGFR-TKI treatment in patients with long-term SD from previous gefitinib treatment These results suggest that the efficacy of EGFR-TKI rechallenge may correlate with the efficacy of the initial EGFR-TKI mutation and that the efficacy may be greater in patients with Del19 EGFR-mutated NSCLC than in those with L858R EGFR-mutated NSCLC.

Regarding toxicity, the incidence rates of any-grade pneumonitis and Grade ≥ 3 pneumonitis in a real-world observation were 12.9% and 3.1%, respectively [14]. There have been recent studies on the efficacy and toxicity of EGFR-TKI rechallenge after EGFR-TKI-induced pneumonitis. In the study by Kanaji et al. [21] 13/58 (22.4%) patients who developed EGFR-TKI-induced pneumonitis developed pneumonitis recurrence during EGFR-TKI rechallenge. Nishioka et al. reported a 27% (95% CI, 17–38) incidence rate of EGFR-TKI rechallenge-induced pneumonitis after osimertinib-induced pneumonitis. Additionally, the incidence of pneumonitis was significantly higher in the osimertinib rechallenge group than in the first- or second-generation EGFR-TKI group (HR: 3.1, 95% CI, 1.3–7.5) [22]. In a multicenter retrospective study of 33 patients who received osimertinib rechallenge after first-line osimertinib-induced pneumonitis, 5 patients (15.2%) experienced pneumonitis [23]. In the present study, 17 of the patients who received rechallenge with another EGFR-TKI had first-line osimertinib-induced pneumonitis, and no pneumonitis occurred during the rechallenge. The absence of pneumonitis may not only be because of the small number of cases but also because this study excluded patients who received osimertinib rechallenge, which is associated with a high incidence of pneumonitis. Osimertinib-induced pneumonitis is characterized not only by the typical diffuse alveolar damage (DAD) reported with first- or second-generation EGFR-TKI but also by simple pulmonary eosinophilia (PEo) and transient asymptomatic pulmonary opacities (TAPO) characterized by locally and spontaneously resolving clinical course have been reported [24]. Further, patients with osimertinib-induced pneumonitis with PEo or TAPO may not develop pneumonitis even after re-challenge with a first- or second-generation EGFR-TKI.

Thus, In rechallenge with another EGFR-TKI in patients who developed osimertinib-induced pneumonitis, selecting a first- or second-generation EGFR-TKI rather than osimertinib may reduce the incidence of pneumonitis and improve prognosis. The toxicity profile differed between osimertinib and rechallenge with another EGFR-TKI in this study. However, patients who discontinue first-line osimertinib due to toxicity are more likely to discontinue second-line treatment osimertinib due to toxicity, even if it is re-administered with another EGFR-TKI.

This study has some limitations. First, the survival time after the EGFR-TKI rechallenge was evaluated using rwTTF, which may have led to an overestimation of efficacy. However, TTF was used as the endpoint because accurate evaluation of PFS after second- or third-line treatment was difficult. Second, this study did not have a control group to compare with, as it was an exploratory analysis. Third, only a small number of cases from a limited number of institutions in Japan were included. Fourth, the focus was on patients able to tolerate EGFR-TKI rechallenge; thus, the results may not be applicable to all patients treated with osimertinib (patient selection and survivor bias). Fifth, as this was a post hoc analysis, it was not possible to set thresholds for efficacy or primary endpoints.

In conclusion, this subset analysis of a multicenter prospective observational study shows that EGFR-TKI rechallenge with another TKI is well tolerated in patients with EGFR-mutated NSCLC, especially those who discontinue first-line osimertinib owing to toxicity. Thus, it may be a useful treatment option after first-line osimertinib.

Author Contributions

Kei Sonehara: conceived, designed, and coordinated the study. **Kei Sonehara** and **Hideo Kunitoh:** wrote the first draft of the manuscript. **Kazunari Tateishi**, **Kiyotaka Yoh**, **Kazuhiro Usui**, **Yukio Hosomi**, **Kazuma Kishi**, **Go Naka**, **Kageaki Watanabe**, **Shu Tamano**, and **Kohei Uemura:** critically reviewed the manuscript. **Hideo Kunitoh:** contributed to the validation and supervision. All the authors have read and approved the final manuscript.

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Ethical Statement

This multicenter, prospective, observational study protocol was reviewed and approved by the Institutional Review Board of the Japanese Red Cross Medical Center (April 26, 2019, Order No. 976) and relevant committees at each institution. Data collection and analyses were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Conflicts of Interest

K.Y. received personal fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Kyowa Kirin, Lilly, Merck Serono, Novartis, Ono, Otsuka, Taiho, and Takeda outside of the submitted work. K.Y. received consultation fees from Boehringer Ingelheim. K.Y. received grants or contracts from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Lilly, MSD, Pfizer, Taiho, and Takeda. Y.H. received personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai, Kyowa Kirin, Lilly, Eisai, Novartis, Ono, Taiho, Pfizer, Nippon Kayaku, and Takeda outside the submitted work. G.N. reported receiving personal fees from AstraZeneca, Chugai, Ono, and MSD outside the submitted work. K.W. received personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Guardant Health, Merck, MSD, Novartis, Ono, Pfizer, Riken Genesis, Sysmex, Taiho, and Takeda outside of the submitted work. K.W. received consulting fees from Bristol Myers Squibb. H.K. reported receiving personal fees from AstraZeneca, Daiichi Sankyo, MSD, Johnson and Johnson, and Taiho outside the submitted work. H.K. received consulting fees from Daiichi Sankyo.

Data Availability Statement

Data collected for the study, including individual participant data that underlie the results reported in this manuscript, after de identification, will be shared with investigators.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.