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Regular Article

Upfront Use of First-/Second-Generation EGFR-TKI Followed by Osimertinib Shows Better Prognosis than Upfront Osimertinib Therapy in Japanese Patients with Non-small-cell Lung Cancer with Exon 19 Deletion: A Single-Center Retrospective Study

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Clinical evidence on the increased efficacy of sequential epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) therapy in patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC) is limited. This study aimed to compare the efficacy of upfront use of first-/second-generation TKI followed by osimertinib with upfront osimertinib therapy for each representative *EGFR* mutation in Japanese patients with NSCLC. Patients with *EGFR*-mutated NSCLC were classified into two groups: first-/second-generation TKI followed by osimertinib (sequential TKI group) and upfront osimertinib groups. The total time to treatment failure (TTF) of TKI therapies, progression-free survival (PFS), and overall survival (OS) were retrospectively evaluated. Of the 74 patients included in the analysis, 38 and 34 patients had exon 19 deletion and L858R, respectively, and other two patients had minor mutations. The sequential TKI group had a significantly longer TTF than the upfront osimertinib group in overall patients (33.2 *vs.* 11.2 months; $p = 0.007$) and in the subgroup of exon 19 deletion (36.7 *vs.* 10.0 months; $p = 0.004$), but not in the subgroup of L858R (22.6 *vs.* 15.6 months; $p = 0.37$). The similar tendency was observed in PFS. OS of the sequential TKI group was significantly longer compared with the upfront osimertinib group in overall patients, the subgroup of exon 19 deletion, and the subgroup of L858R. The upfront use of first-/second-generation TKI followed by osimertinib is one of the feasible and effective strategies in Japanese patients with *EGFR*-mutated NSCLC, especially in patients with exon 19 deletion.

Key words non-small cell lung cancer, epidermal growth factor receptor–tyrosine kinase inhibitor, osimertinib, exon 19 deletion, T790M

INTRODUCTION

Epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors (TKIs) are the standard of care for the first-line treatment for patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC). Recently, according to the results of multiple clinical trials,[1–5] five EGFR-TKIs, namely, erlotinib and gefitinib (first-generation reversible TKIs), afatinib and dacomitinib (second-generation irreversible ErbB family blockers), and osimertinib (third-generation irreversible EGFR/T790M inhibitor) are suggested as the first-line EGFR-TKI therapy for *EGFR*-mutated NSCLC in the practical guidelines.[6]

A phase III randomized, open-label, multicenter, international study (AURA3 study) reported that osimertinib had a significantly greater efficacy than platinum plus pemetrexed in patients with T790M-positive NSCLC who had experienced progression during first-line EGFR-TKI therapy.[7] In a phase III randomized, double-blind, multicenter, international study (FLAURA study),[5] osimertinib significantly improved progression-free survival (PFS) compared with gefitinib/erlotinib. Additionally, osimertinib is commonly used as a first-line EGFR-TKI therapy in patients with a performance status of 0 or 1.[8] However, in an Asian subset of FLAURA study, the first-generation EGFR-TKI group tended to have a more prolonged overall survival (OS) than the osimertinib group; therefore, Asian patients may not benefit from upfront osimertinib therapy in terms of OS.[9] This might be partly due to the large impact of osimertinib which was used as a later-treatment in the first-generation EGFR-TKI group.

The most common predictor of acquired resistance to EGFR-TKI therapy is T790M mutation in *EGFR* exon 20.[10,11] This mutation exists in approximately 50–79% of tumors at the time of acquired resistance[12,13] and is known to be more likely to occur in patients with exon 19 deletion mutation.[14–17] A retrospective study using the real-world data of 203 patients treated with afatinib followed by osimertinib (Gio-Tag study) suggested that the sequential TKI therapy was associated with encouraging outcomes in patients with *EGFR*-mutated NSCLC, especially in patients with exon 19 deletion and in Asian population.[14] Exon 19 deletion and L858R are known as the major *EGFR* mutations in Japanese patients with NSCLC.[15] Exon 19 deletion removes several residues from the loop of the ATP-binding site of EGFR, while L858R lies away from the ATP-binding site.[16] The difference in location site between the two mutations was reported to associate with the response to EGFR-TKI.[17] Hence, the efficacy of sequential TKI therapy may depend on the *EGFR* mutation type, and

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identifying a highly effective population is important to maximize the EGFR-TKI therapeutic period.[18)]

Given the lack of established and available options for target therapy after osimertinib failure, researchers argue for reserving osimertinib for second- or later-line therapy after the failure of first-/second-generation EGFR-TKI for patients with clinical factors predicting T790M mutation before the first-line EGFR-TKI therapy.[19)] Predictive clinical factors for T790M mutation include exon 19 deletion, postsurgery recurrence, and longer total duration of EGFR-TKI therapy before rebiopsy.[20–26)] However, the therapeutic effect of sequential EGFR-TKI administration according to the individual factors has not yet been evaluated.

Hence, this study aimed to evaluate the efficacy of first-/second-generation EGFR-TKI followed by osimertinib in comparison with the upfront osimertinib therapy focusing on each major *EGFR* mutation, exon19 deletion and L858R, in Japanese patients with NSCLC.

PATIENTS AND METHODS

Study Participants We retrospectively enrolled patients with pathologically confirmed advanced or postsurgery recurrent *EGFR*-mutated NSCLC whose therapy was started with EGFR-TKI as a first line at the Nara Prefecture General Medical Center (Nara, Japan) between May 2016 and August 2020. The exclusion criteria were as follows: (1) participated in clinical studies involving drug therapy-related interventions, (2) concomitantly used CYP3A inducers (phenytoin, rifampicin, and carbamazepine) in TKI therapeutic duration, (3) did not use osimertinib as a first-line therapy or after the treatment with first-/second-generation TKI, (4) used anticancer agents other than TKI between TKI sequences, (5) had an unknown number of TKI therapeutic days, (6) received radiation therapy between TKI sequences, and (7) judged of inappropriateness for the enrollment of this study by the researcher. This study conformed to the provisions of the Declaration of Helsinki. The Institutional Review Board of Nara Prefecture General Medical Center approved the study protocol (Approval No.577) and each patient can opt-out of the study at any time.

Grouping According to the TKI Therapy According to the therapy, the overall population was classified into two groups, namely, upfront first-/second-generation TKI followed by osimertinib (sequential TKI group) and upfront osimertinib groups, respectively. The dose of each EGFR-TKI was as follows: gefitinib was 250 mg/d (reduced dose was 250 mg/every other day), erlotinib was 150 mg/d (reduced doses were 100, 75, 50, and 25 mg/d, or 150 mg/every other day), afatinib was 40 mg/d (reduced doses were 30 and 20 mg/d, or 20 mg/every other day), and osimertinib was 80 mg/d (reduced doses were 40 mg/d or 40 mg/every other day).

Outcome Measures The primary outcome was time to treatment failure (TTF), which was defined in this study as the time from the date of induction therapy with EGFR-TKI to the last day of TKI use in a series of EGFR-TKI therapies or to the date of death (Supplementary Fig. 1). The TTF excluded the suspension period. In the sequential therapy of TKIs, the TTF of each TKI was added up.[14)] According to the last recorded date when the patient received the final dose, data for those who had not completed EGFR-TKI therapy at the cutoff date were censored.

As the secondary outcome, OS was defined as the time from the date of induction therapy with EGFR-TKI to the date of death for any cause. Data for patients who had not died at the cutoff day were censored according to the last recorded date on which the patient was alive. Another secondary outcome PFS was defined as the duration from the initiation date of EGFR-TKI therapy to the date of disease progression or death on the treatment of osimertinib. TTF, PFS, and OS were compared with the sequential TKI group and the upfront osimertinib group in overall patients, as well as the subgroup of exon 19 deletion and L858R mutations, respectively. Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1. The observation period was 48 months and the data cut-off was November 30, 2022. Adverse events leading to treatment interruption or withdrawal of TKI were collected.

Statistical Analysis Patient characteristics were compared using Fisher's exact test and Mann–Whitney *U* test. TTF, PFS, and OS were estimated using the Kaplan–Meier method, and statistical differences were determined using the log-rank test. A p-value of less than 0.05 was considered statistically significant. All statistical data were analyzed using IBM SPSS Statistics Version 28.0 (IBM, Armonk, NY, U.S.A.).

RESULTS

Patient Characteristics We recruited 120 patients with NSCLC showing advanced *EGFR* mutation or recurring after surgery whose therapy was started with EGFR-TKI as a first line, while 46 patients were excluded (patients who did not use osimertinib after the treatment with first-/second-generation TKI ($n = 25$), patients using anti-cancer agents other than TKI between TKI sequences ($n = 15$), patients with the unknown number of TKI therapeutic days ($n = 5$), and patients with radiation therapy between TKI sequences ($n = 1$)). Ultimately, we analyzed 74 patients, including patients detected with exon19 deletion ($n = 38$), with L858R ($n = 34$), and with minor mutations ($n = 2$). Histologically, all enrolled patients had adenocarcinoma. Seventeen patients received the sequential TKI therapy, and 57 patients received the upfront osimertinib therapy in the overall population. Patient characteristics were shown in Table 1. No significant differences in patient backgrounds were observed between two groups. In the patient characteristics of the upfront osimertinib group, no significant differences were observed between the subgroups of exon 19 deletion and L858R in the stage (advanced: 83% (24/29) *vs.* 73% (19/26)) and programmed death ligand 1 tumor proportion score (PD-L1 TPS) (≥1%: 61.9% (13/21) *vs.* 64.3% (9/14)).

Contents of EGFR-TKI Therapy and T790M Mutation in the Sequential TKI Group Over 70% of patients received one or two TKI therapies before osimertinib (Table 2). Among 17 patients in the sequential TKI group, T790M mutation was examined in only 10 patients. The T790M mutation was observed in 85.7% of patients in the subgroup of exon19 deletion (6/7) and 33.3% in the subgroup of L858R (1/3), respectively.

TTF Figure 1 illustrates the Kaplan–Meier curves of TTF in the overall patients and the subgroups of exon19 deletion or L858R. In the overall patients, TTF was significantly different between the sequential TKI group and the upfront osimertinib

Table 1. Patient Characteristics

Variables		1st–2nd TKI followed by osimertinib ($n = 17$)	Upfront osimertinib ($n = 57$)	p-Value
Age, median (range), years		74 (46–91)	75 (46–90)	0.57[b]
Age, *n* (%)	≥75 years	5 (29)	30 (53)	0.11[a]
Sex, *n* (%)	Female	9 (53)	39 (68)	0.26[a]
Pathology, *n* (%)	Adenocarcinoma	17 (100)	57 (100)	—
Stage, *n* (%)	Advanced (II, III or IV)	14 (82)	45 (79)	1[a]
	Postsurgery recurence	3 (18)	12 (21)	
Surgical history, *n* (%)	Yes	4 (24)	11 (19)	0.74[a]
Smoking status, *n* (%)	Never	13 (76)	43 (75)	1[a]
	Current or former	4 (24)	14 (25)	
CNS metastasis, *n* (%)	Yes	6 (35)	19 (33)	1[a,c]
	No	10 (59)	33 (58)	
	Unknown	1 (6)	5 (9)	
Liver metastasis, *n* (%)	Yes	3 (18)	6 (11)	0.42[a]
	No	14 (82)	51 (89)	
Bone metastasis, *n* (%)	Yes	7 (41)	24 (42)	1[a]
	No	10 (59)	33 (58)	
EGFR mutation, *n* (%)	Exon 19 deletion	9 (53)	29 (51)	1[a]
	Exon 21 L858R	8 (47)	26 (46)	
	Minor mutation	0 (0)	2 (4)	
PD-L1 TPS, *n* (%)	≥50%	1 (6)	10 (17)	1[a,c]
	49–1%	2 (12)	13 (23)	
	<1%	2 (12)	14 (25)	
	Unknown	12 (70)	20 (35)	
BSA (DuBois Method), *n* (%)	≥1.5 m^2	12 (71)	30 (53)	0.27[a]
	<1.5 m^2	5 (29)	27 (47)	
Hypoalbuminemia (CTCAE version 5.0), *n* (%)	Grade 0	2 (12)	16 (28)	0.89[a,c]
	Grade 1	7 (41)	33 (58)	
	Grade 2	1 (6)	8 (14)	
	Unknown	7 (41)	0 (0)	
ALT increased (CTCAE version 5.0), *n* (%)	Grade 0	15 (88)	52 (91)	1[a,c]
	Grade 1	1 (6)	5 (9)	
	Unknown	1 (6)	0 (0)	
Blood bilirubin increased (CTCAE version 5.0), *n* (%)	Grade 0	15 (88)	57 (100)	0.22[a,c]
	Grade 1	1 (6)	0 (0)	
	Unknown	1 (6)	0 (0)	
Acid suppressant co-administration, *n* (%)	Yes	6 (35)	15 (26)	0.18[a]

All p-values were calculated with following test: *a*) Fisher's exact test, *b*) Mann–Whitney U test. *c*) Fisher exact test was performed except for unknown cases. ALT, alanine aminotransferase; BSA, body surface area; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; PD-L1 TPS, programmed death ligand 1 tumor proportion score; TKI, tyrosine kinase inhibitor.

Table 2. Contents of EGFR-TKI Therapy and T790M Mutation in Patients Treated with First-/Second-Generation TKI Followed by Osimertinib

Variables		1st–2nd TKI followed by osimertinib ($n = 17$)
Number of previous TKI regimens before osimertinib, *n* (%)	1	11 (65)
	2	2 (12)
	3	4 (24)
Received TKI before osimertinib, *n* (%)	Gefitinib	9 (53)
	Erlotinib	11 (65)
	Afatinib	7 (41)
T790M mutation, *n* (Exon 19 deletion/Exon 21 L858R)	Yes	7 (6/1)
	No	3 (1/2)
	Unknown	7 (2/5)

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

group (median TTF: 33.2 *vs.* 11.2 months; $p = 0.007$) (Fig. 1A). In the subgroup of exon 19 deletion, TTF was significantly longer in the sequential TKI group than in the upfront osimertinib group (median TTF: 36.7 *vs.* 10.0 months; $p = 0.004$) (Fig. 1B). In the subgroup of L858R, TTF was not significantly different between the two groups (median TTF: 22.6 *vs.* 15.6 months; $p = 0.37$) (Fig. 1C). In the upfront osimertinib group, treatment discontinuation occurred in 25 patients (86.2%) in the subgroup of exon 19 deletion and 21 patients (80.8%) in the subgroup of L858R, respectively. The swimmer plots show the treatment duration and reason for change or termination of TKI therapy in the subgroup of exon 19 deletion (Fig. 2).

PFS and OS Figure 3 illustrates the Kaplan–Meier curves of PFS and OS in the overall patients and in the subgroups of exon 19 deletion and L858R, respectively. In the overall patients, PFS significantly differed between the groups of the sequential TKI and the upfront osimertinib (median PFS: 37.7 months *vs.* 20.0 months, $p = 0.017$; Fig. 3A). In the subgroup of

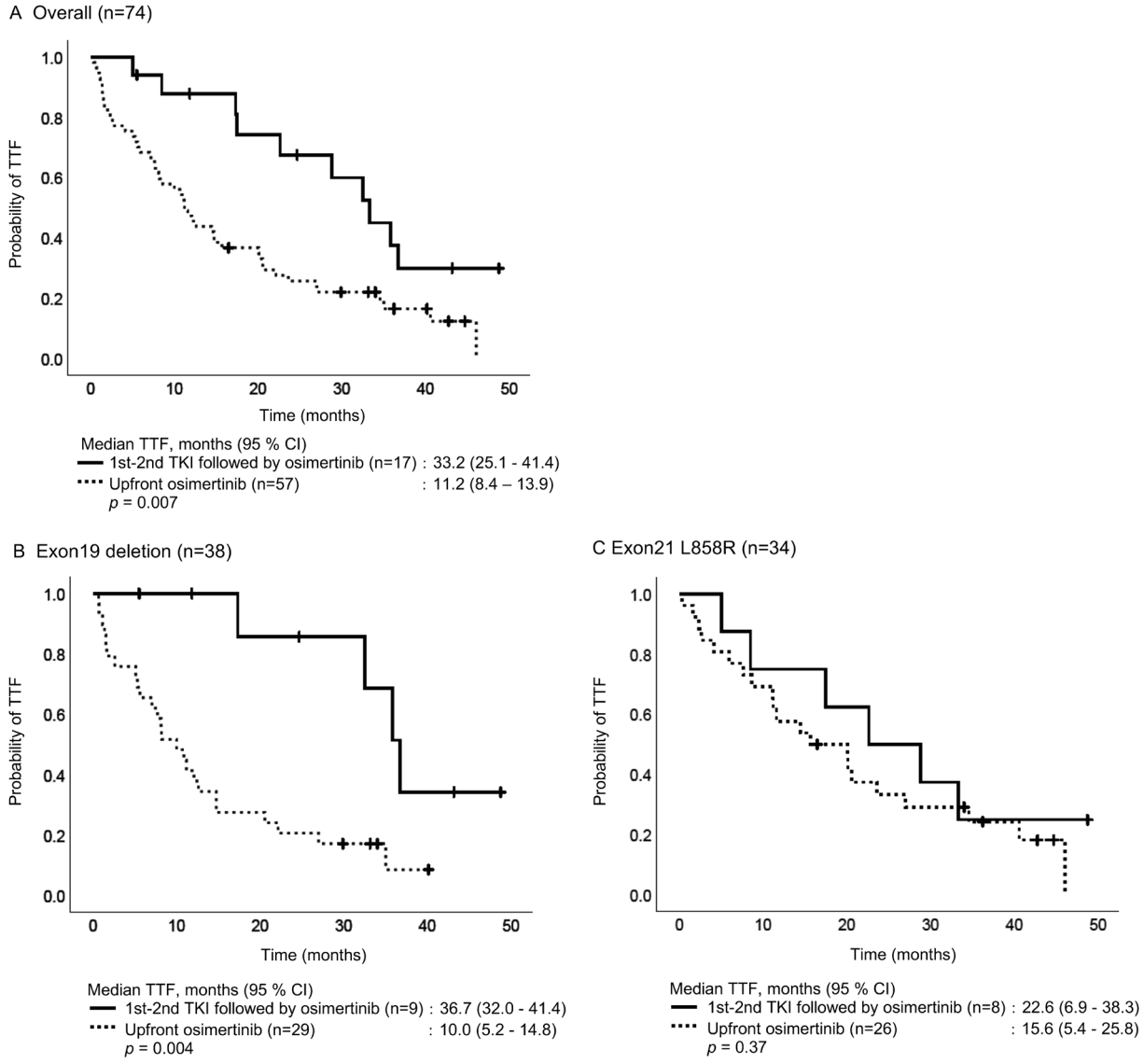

Fig. 1. Kaplan–Meier Curves for Time to Treatment Failure (TTF)

A: Overall patients ($n = 74$), B: Subgroup of exon 19 deletion ($n = 38$) and C: Subgroup of exon 21 L858R ($n = 34$). AE, adverse event, CI, confidence interval; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.

exon 19 deletion, PFS was significantly longer in the sequential TKI group than in the upfront osimertinib group (median PFS: 37.7 *vs.* 14.7 months, $p = 0.048$; Fig. 3B). In the subgroup of L858R, PFS was not significantly differed between the two groups (median PFS: 34.5 *vs.* 20.5 months, $p = 0.25$; Fig. 3C).

In the overall patients, the OS was significantly longer in the sequential TKI group than in the upfront osimertinib group (not calculable (NC) *vs.* 35.6 months, $p < 0.001$; Fig. 3D). In addition, the OS was significantly longer in the sequential TKI group than in the upfront osimertinib group in the subgroup of exon 19 deletion (NC *vs.* 32.9 months, $p = 0.003$; Fig. 3E) and with L858R (NC *vs.* 44.6 months, $p = 0.03$; Fig. 3F).

DISCUSSION

NSCLC requires an optimal therapeutic strategy for EGFR-TKIs. To our knowledge, this is the first study to demonstrate the superiority of first-/second-generation TKI followed by osimertinib therapy in comparison with the upfront osimertinib therapy in Japanese patients with NSCLC. In addition, the advantage of first-/second-generation TKI followed by osimertinib therapy is observed especially in patients with exon 19 deletion.

The TTF in the sequential TKI group was significantly prolonged than that in the upfront osimertinib group in overall patients and in the subgroup of exon 19 deletion (Figs. 1A, B). The median TTF of the sequential TKI group (33.2 months) and the upfront osimertinib group (11.2 months) in our overall population were similar to that observed in the sequential afatinib and osimertinib in an Asian population of the GioTag study (37.1 months) and the first-line osimertinib therapy group in Japanese subset of FLAURA study (15.3 months), respectively.[14,27] In our subgroup analyses, the TTF of the sequential TKI group was significantly prolonged than that of the upfront osimertinib group in the subgroup of exon 19 deletion, but not in the subgroup of L858R. According to the previous reports that patients with exon19 deletion mutation were more likely to occur T790M mutation,[20,21,24,25] we hypothesized that patients with exon 19 deletion would be

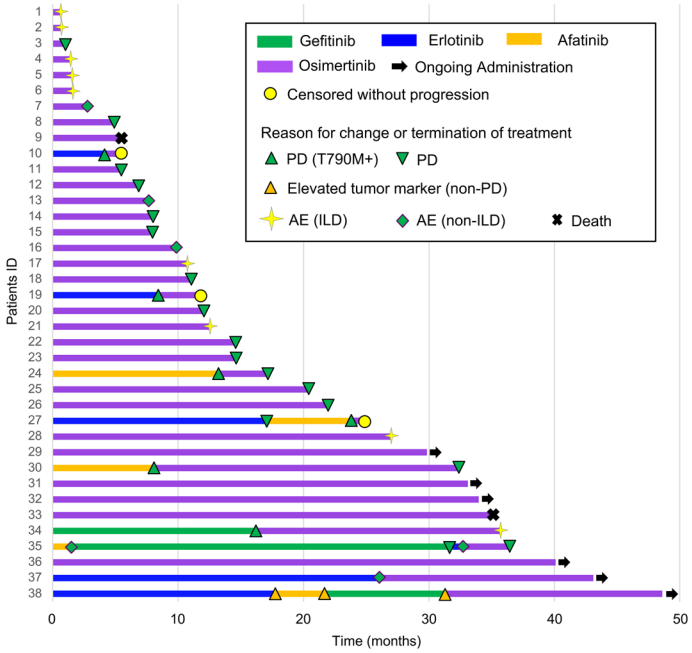

Fig. 2. Swimmer Plot in the Subgroup of Exon 19 Deletion

Treatment duration and reason for change or termination of TKI therapy were summarized in individual patients with first-/second-generation TKI followed by osimertinib ($n = 9$) and upfront of osimertinib ($n = 29$). AE, adverse event; ILD, interstitial lung disease; PD, progressive disease; TKI, tyrosine kinase inhibitor.

more likely to receive the benefit of the upfront first-/second-generation EGFR-TKI followed by osimertinib therapy. Our study showed that in the sequential TKI group, excluding cases without T790M information, the ratio of T790M mutation positive was 85.7% (6/7) in the subgroup of exon 19 deletion and 33.3% (1/3) in the subgroup of L858R. Although the implementation of T790M mutation test was limited and the number of study patients was small, a longer TTF of the sequential TKI group in the subgroup of exon 19 deletion may be attributed to a higher ratio of T790M mutation.

At present, it is difficult to accurately predict the occurrence of T790M mutation at the initiation of the therapy. Further studies are needed to evaluate whether exon 19 deletion mutation is a valid predictor of the T790M mutation during first-/second-generation EGFR-TKI therapy. Exon 19 deletion and L858R mutations map to the vicinity of the active site cleft of the kinase.[16] Exon 19 deletion removes three to eight residues from the loop leading into the αC-helix, whereas the L858R mutation lies in the activation loop of the kinase.[16] Furthermore, gefitinib inhibits EGFR, Akt, and Erk phosphorylation and causes G1 arrest to greater degrees in exon 19 deletion cells than in L858R cells.[28] These previous reports showed that these two genetic abnormalities were different in molecular structure. However, possible mechanisms responsible for the differences in T790M mutation prevalence between exon 19 deletion and L858R remain unknown.

In another aspect, the upfront osimertinib group showed a shorter TTF in overall patients (11.2 months) and the subgroup of exon 19 deletion (10.0 months) in our study than those in the global FLAURA study (20.8 months).[5] A higher treatment discontinuation rate due to interstitial lung disease (ILD) (21.1%, 12/57, data not shown) may influence the shortness of the median TTF in the upfront osimertinib group in our study. This rate was about twofold higher than that in the FLAURA study (12.3%)[27] and the OSI-FACT study (12.8%).[8] Japanese patients were more likely to develop osimertinib-induced adverse events, especially ILD.[5,27] Moreover, it is known that 70% of osimertinib-induced ILD was developed within 16 weeks in Japanese patients.[29] The upfront osimertinib group in the subgroup of exon 19 deletion in our study discontinued the therapy due to the early onset of ILD (Fig. 2). As mentioned above, TTF of the upfront osimetinib in FLAURA study including multiple races was 20.8 months, although TTF of the Japanese subset of this study was 15.3 months.[5,27] Therefore, shortened TTF of the upfront osimertinib group in our study due to the early development of adverse events might also contribute to the difference between the sequential TKI group and the upfront osimertinib group. In our study, PFS and OS showed almost similar trends to TTF except for OS in the subgroup of L858R. OS in the sequential TKI group was significantly longer than that in osimertinib group in the subgroup of L858R, which might be partly due to the small patient number. Further studies including a large number of patients are needed to examine superiority of the sequential therapy in OS. In general, osimertinib is prioritized as first-line treatment if patients have brain metastases. This is because it can greatly penetrate the blood–brain barrier and has a reduced risk for central nervous system progression compared with first-generation EGFR-TKIs such as gefitinib and erlotinib.[30,31] Although there were no differences in the patient characteristics of brain metastasis rate between these groups in this study (Table 1), the prognosis of the sequential TKI group was better than the upfront osimertinib group in the overall patients and the subgroup of exon 19 deletion. In the sequential TKI group, osimertinib was used in all patients in later-line, even if brain metastases were present at the start of treatment, the impact of the osimertinib therapy on the central nervous system progression would have been limited. Therefore, we considered that brain metastasis may not weaken the therapeutic effect of sequential TKI therapy. This finding

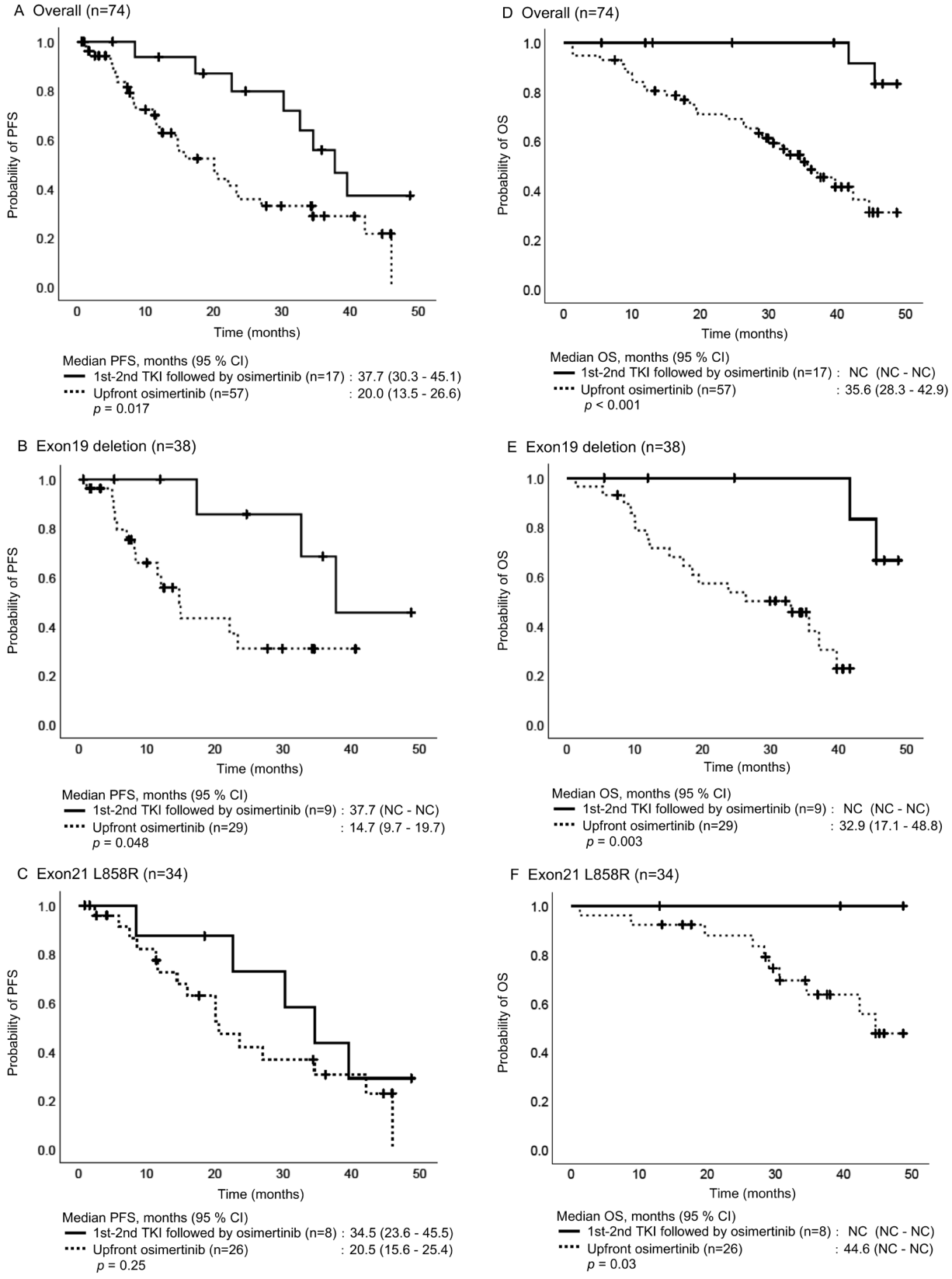

Fig. 3. Kaplan–Meier Curves for Progression-Free Survival (PFS) (A, B, C) and Overall Survival (OS) (D, E, F)

A, D: Overall patients ($n = 74$), B, E: Subgroup of exon 19 deletion ($n = 38$) and C, F: Subgroup of exon 21 L858R ($n = 34$). CI, confidence interval; NC, not calculable; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor.

should be verified in a future confirmatory study.

This study has a lot of limitations. This study is a single-center retrospective analysis with a small sample size. Because sequential TKI therapy and upfront osimertinib therapy were performed at different times and the number of patients included in the two therapies were unbalanced, a large pro-

spective randomized study is needed to validate the results of this study. In addition, since this was a retrospective analysis using the electronic medical record, the performance status (PS), which is a factor that significantly impacts the choice of EGFR-TKI and prognosis, could not be obtained. Therefore, the multivariate analysis considering PS and other prognostic factors could not be performed due to incomplete data. However, since there were no significant differences in patient characteristics in terms of age, stage and metastasis, which can relate to PS, we considered that the lack of PS data had a limited effect on our conclusion. The 41.2% of 17 patients of the sequential TKI group could not receive a re-biopsy examination for T790M mutation due to various reasons; hence, the T790M mutation status was unknown in many patients. Most reasons for not undergoing re-biopsy were worsening of the patient's condition, discontinuation due to adverse events except for ILD occurred by the first-/second-generation TKI, and inability to change to osimertinib due to the onset of ILD. The low execution rate of the T790M mutation test may lead to a decreased rate of change to TKI sequential therapies followed by osimertinib. Prospective studies are needed to determine optimal therapeutic approaches in patients with *EGFR*-mutated NSCLC.

In conclusion, TTF was significantly prolonged in the sequential use of EGFR-TKI including osimertinib compared with that in upfront osimertinib as first-line treatment in Japanese patients with NSCLC, especially with exon 19 deletion mutation. The upfront use of first-/second-generation TKI expecting the emergence of T790M resistance mutations could be one of the feasible and effective strategies in managing patients with *EGFR* exon 19 deletion-mutated NSCLC.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.

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