Real-world osimertinib for *EGFR* mutation-positive non-small-cell lung cancer with acquired T790M mutation

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Aim: Osimertinib is a key drug for *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). As the hazards ratio of overall survival in comparison with first-generation *EGFR*-tyrosine kinase inhibitors was almost similar between FLAURA and ARCHER 1050, salvage use of osimertinib is still a treatment option.

Patients & methods: We retrospectively analyzed the clinical courses of *EGFR* mutation-positive NSCLC patients who were potential candidates for salvage osimertinib. **Results:** Among 524 patients enrolled from five hospitals, 302 patients underwent biopsy, with 52.6% detection rate of T790M. Osimertinib was administered in 93.6% of the T790M-positive patients. The overall response rate and median progression-free survival time of osimertinib were calculated with 147 patients, to be 55.6% and 17.2 months, respectively. **Conclusion:** Osimertinib is active for T790M-driven acquired resistance in *EGFR*-mutant NSCLC, but the detection of T790M was unsatisfactory.

Clinical Trial Registration: UMIN000028989 (UMIN Clinical Trials Registry)

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EGFR-tyrosine kinase inhibitors (*EGFR*-TKIs) are key drugs for treating *EGFR*-mutant non-small-cell lung cancer (NSCLC). Starting with gefitinib, several first-, second- and third-generation (1st-, 2nd- and 3rd-G, respectively) *EGFR*-TKIs have been developed. The toxicity and efficacy of these three generations of *EGFR*-TKIs were compared in three randomized trials, LUX-Lung 7, ARCHER 1050 and FLAURA [1–3]. All three trials showed clinical benefits of 2nd- or 3rd-G *EGFR*-TKIs compared with 1st-G *EGFR*-TKIs. Whereas all studies have shown improvement in progression-free survival (PFS) by 2nd- or 3rd-G *EGFR*-TKIs, statistically significant improvement of overall survival (OS) was attained only with osimertinib in FLAURA. OS improvement was also observed with dacomitinib in ARCHER1050, but statistical analysis was not performed because of the adoption of the gatekeeping method.

Osimertinib is a 3rd-G *EGFR*-TKI that yields a durable response in patients with NSCLC harboring common *EGFR* mutations [3,4]. It is also effective for T790M-mediated acquired resistance (AR) to 1st- or 2nd-G *EGFR*-TKIs [5]. It was first approved as a salvage drug for T790M-mediated AR and was made available in Japan from 25 May 2016. Its frontline application became popular worldwide since the FLAURA study showed that frontline therapy using osimertinib improved PFS compared with 1st-G *EGFR*-TKIs. When PFS is compared between LUX-Lung 7, ARCHER 1050 and FLAURA, osimertinib appears to provide the longest PFS and is therefore one of the key drugs. It also has excellent penetrative capacity to the central nervous system. On the other hand, OS improvement is similar in frontline use between 2nd- and 3rd-G *EGFR*-TKIs, with hazard ratios of 0.760 in ARCHER1050 and 0.788 in FLAURA. Additionally, salvage osimertinib is a reasonable choice for the appreciable number of *EGFR*-mutant patients who started the treatment with 1st- or 2nd-G *EGFR*-TKIs but have not yet received a 3rd-G *EGFR*-TKI therapy. Therefore, there are two main first-line strategies for advanced *EGFR*-mutant

NSCLC at present, one being frontline osimertinib and the other salvage osimertinib for T790M-positive AR preceded by frontline 1st- or 2nd-G EGFR-TKI therapy. A key future strategy using EGFR-TKIs would involve regulating the development of AR. Importantly, the mechanisms of AR to osimertinib differ between frontline and salvage therapy [6,7]. It must be said that the optimal usage of EGFR-TKIs is still under consideration.

Salvage osimertinib is presently applicable only for T790M-positive NSCLC. T790M is detected by rebiopsy of cancer tissue or by liquid biopsy of plasma. The reported rates of T790M in AR to 1st- or 2nd-G EGFR-TKIs have a wide distribution depending on the patient population examined and the platform for analysis adopted [8–11]. Pooled analysis revealed that T790M was detected in approximately 50–60% of NSCLC cases with common *EGFR* mutations exhibiting AR to 1st- or 2nd-G EGFR-TKIs [12]. Because tissue biopsy is invasive and the sensitivity of liquid biopsy is not satisfactory, biopsy still presents a challenge especially in the real-world setting [13–15]. Therefore, it is important to know how frequently salvage osimertinib is applicable and how effective it is in a real-world setting. In the present study, patients from five Japanese institutes who had *EGFR*-mutant NSCLC and were potential candidates for salvage osimertinib were registered for retrospective analysis of their clinical courses.

Patients

Inclusion & exclusion criteria

Eligible patients were required to be histologically or cytologically confirmed NSCLC harboring an activated *EGFR* mutation. Patients with disease recurrence after treatments with curative intent such as surgery or radiation therapy were included. In Japan, osimertinib in salvage use was approved on 25 May 2016. In order to accumulate the candidates for salvage osimertinib efficiently, eligible patients were required to meet one of the following two criteria:

- They were on any systemic treatment on 25 May 2016 and were considered to be in good conditions on 25 May 2016 enough to receive the next line of systemic treatment if the disease recurs in the future;
- They started first-line systemic treatment after 25 May 2016. Patients who had received a 3rd-G EGFR-TKI including osimertinib as the 1st EGFR-TKI or those with insufficient clinical records were excluded from the analysis.

Patient subsets

As mentioned above, osimertinib in salvage use was approved on 25 May 2016 in Japan. This means that the patients who had started the treatment with EGFR-TKIs before and after 25 May 2016 had different accessibility to osimertinib. Therefore, the patients in this study were divided into two groups, group 1 and group 2, consisting of patients who started any systemic treatments for *EGFR*-mutant NSCLC before and after 25 May 2016, respectively.

Methods

This is a protocol-based retrospective study. The study protocol (UMIN000028989) was approved by the ethics committee of each of the five participating institutes. The clinical data of patients with advanced NSCLC who met the eligibility criteria were retrospectively collected from each institute from 1 March 2017 to 31 October 2018 by an independent site-monitoring organization (EP-SOGO Co., Tokyo, Japan). Treatment responses were evaluated according to RECIST criteria version 1.1 [16]. A statistical analysis of response data was performed using the χ^2 test. PFS of the patients who received osimertinib was calculated: PFS was defined as the time interval from the start of osimertinib to patient death or the detection of progressive disease (PD) to osimertinib. Kaplan–Meyer analysis and Cox proportional hazards tests were performed using SPSS statistics software, version 17.0. Patient accrual stopped on 31 October 2018 and the first data cut-off time was 31 October 2018. *EGFR* mutations in rebiopsy and liquid biopsy were examined by the tests which are reimbursed by insurance in Japan such as the clamp and covas method, not next-generation sequencing (NGS)-based methods.

Results

In total, 542 patients were enrolled between 25 January 2018 and 11 September 2018. Among these, 17 were excluded from the analysis because 1st- or 2nd-G EGFR-TKIs were switched to osimertinib without PD mainly due to toxicity. Patient characteristics of the 525 patients included are shown in Table 1. All patients except five with adenosquamous carcinoma carried adenocarcinoma; 0.8% patients had an ECOG performance status (PS) of 3; 95.4% had common *EGFR* mutations; 35.2% had undergone treatment with curative intent such as surgery or

Table 1. Patient characteristics.

Patients	Total enrolled	Osimertinib treated
Number of patients	525	147
Age (years), mean (range)	67.0 (35–89)	66.7 (38–87)
Sex:		
– Women	351	97
– Men	174	50
PS:		
– 0	229	33
– 1	258	91
– 2	31	17
– 3	4	4
– Unknown	3	2
<i>EGFR</i> [†] :		
– Exon19 del	266	89
– L858R	235	58
– Minor mutation	24	–
Stage:		
– Recurrence [‡]	185	45
– Stage I–III [§]	39	8
– Stage IV	301	94
Group [¶] :		
– 1	299	101
– 2	226	46

Data at the start of any systemic treatment for *EGFR*-mutant NSCLC for the total enrolled patients and at the start of osimertinib for the osimertinib-treated patients.

[†]Performed by commercial test such as clamp and covas method.

[‡]Recurrence after the treatments with curative intent.

[§]One, three and thirty-five patients with stage IB, II and III, respectively. All patients with stage I–II were refused or contraindicated for local therapy. All patients with stage III were not fit for standard chemoradiation.

[¶]Group 1 and 2 consist of the patients who started any systemic treatments for *EGFR*-mutant NSCLC before and after 25 May 2016, respectively.

NSCLC: Non-small-cell lung cancer; PS: Performance status.

radiation. The consort diagram of the 525 patients is shown in Figure 1. Because the treatments prior to osimertinib were still effective in 132 (25.1% of 525) patients at the time of the data cut-off and these patients were therefore not administered osimertinib, the analysis of salvage osimertinib was performed on the remaining 393 patients.

Biopsy to detect T790M was performed using tissue (rebiopsy) or plasma (liquid biopsy) in 302 (76.8%) of 393 patients. The repetition of biopsy and T790M positivity rates in rebiopsy and liquid biopsy are shown in Table 2. Target lesions in the first to the third rebiopsy were intrathoracic 60%, pleural effusion 19% and metastatic site 21%, respectively. The cumulative positive rate of T790M was 52.6% (159 out of 302 patients). T790M was detected in 112 (37.1%) patients in the first biopsy, indicating that repetition of biopsy is useful in detecting the mutation. A total of 462 biopsies was performed and the detection rate of T790M was 34.4% per biopsy (159 out of 462). The first three biopsies occupied approximately 96.3% of total biopsies, which in turn detected 98.1% of T790M-positive cases. Liquid biopsy was approved in December 2016 in Japan and was applied to 24.5% of all biopsies, with a T790M detection rate of 28.8%.

Excluding two patients with uncommon *EGFEventR* mutations, 147 (37.4%) out of 393 patients (93.6% of 157 T790M-positive patients) received salvage osimertinib. On the other hand, the treatments for the patients for whom T790M was not detected were different depending on various conditions including treatment lines, age and PS of the patients. For example, second-line therapy for the patients who had undergone first-line therapy with an *EGFR*-TKI and developed T790M-unrelated AR were cytotoxic monotherapy (15.5%), platinum doublets (46.5%) and *EGR*-TKI-based therapy (38.0%).

The adverse events (AEs) of osimertinib are summarized in Table 3. Discontinuation and grade ≥ 3 AEs of osimertinib were observed in 8.2 and 10.2% of patients, respectively. Interstitial pneumonitis occurred in 2.0%, leading to one treatment-related death. Responses were evaluable in 147 patients (101 in group 1 and 46 in group 2). The objective response rate (ORR), disease control rate (DCR) and median PFS of osimertinib were 55.6%,

Figure 1. Consort diagram. Treatments for the patients whose non-small-cell lung cancer carried T790M but was not treated with osimertinib were as follows: 4, continuation of the most recent treatment; 6, no treatments; 1, not specified.
†Osimertinib was not yet administered because the preceding treatments were still active at the data cut-off time.
PD: Progressive disease.

Table 2. Rebiopsy and liquid biopsy.						
Biopsy to detect T790M (%)‡	Total biopsy		Rebiopsy§		Liquid biopsy	
	n	T790M+ (%)	n (%)†	T790M+ (%)‡	n (%)†	T790M+ (%)
1st	302	112 (37.1)	215 (71.2)	88 (40.9)	87 (28.8)	24 (27.6)
2nd	110	33 (30.0)	82 (74.5)	23 (28.0)	28 (25.5)	10 (35.7)
3rd	33	10 (30.3)	22 (66.7)	8 (36.4)	11 (33.3)	2 (18.2)
4th–7th	17	4 (23.5)	11 (64.7)	2 (18.2)	6 (35.3)	2 (33.3)
Overall:	302	159 (52.6)				
– Group 1	203	111 (54.7)				
– Group 2	99	48 (48.5)				
Total biopsy:	461	159 (34.5)				
– Rebiopsy	329	121 (36.8)				
– Liquid biopsy	132	38 (28.8)				

Biopsy includes rebiopsy with tissue and liquid biopsy with plasma.
†Numbers of rebiopsy or liquid biopsy/number of total biopsy.
‡Positive rates of T790M in rebiopsy or liquid biopsy.
§Target lesions in 1st–3rd rebiopsy were intrathoracic 60%, pleural effusion 19% and metastatic site 21%, respectively.

88.9% and 17.2 months, respectively (Table 4). No significant difference in PFS was observed with respect to age (<75 vs ≥75), sex, treatment line (2nd vs 3rd–4th vs ≥5th) or method of biopsy (rebiopsy vs liquid biopsy) in univariate analysis (Table 5; Figures 2 & 3). On the other hand, significant prolongation of PFS was observed in patients with good PS (0 vs 1 vs ≥2; Figure 2D). Patients with stage IV NSCLC and those in group 2 showed a tendency of shorter PFS. Multivariate analysis was performed adjusted with sex, type of *EGFR* mutations, age (<75 vs ≥75), PS (0 vs 1 vs ≥2), stage (IV vs others), line of osimertinib treatment (2th vs 3th–4th vs ≥5th), time of start of any systemic treatment (group 1 vs group 2). The analysis revealed that PS was the only factor that significantly correlated with longer PFS of salvage osimertinib (PS: 0 vs 1; p = 0.002; PS: ≥2 vs 0; p = 0.512; overall; p = 0.003).

Table 3. Adverse events.

Event	n (%)
Leading to discontinuation	12 (8.2)
Leading to death	1 (0.7)
Toxicities of grade ≥ 3	15 (10.2)
Neutropenia	1
Anemia	1
Bacterial pneumonia	2
Hepatic	2
ILD	3 (2.0) [†]
Musculoskeletal	2
Cardiac	1
Renal	1
Skin	1
Paronychia	1

[†]Including one treatment-related death.
ILD: Interstitial lung disease.

Table 4. Responses to osimertinib.

Group	1	2	Total
CR	2	1	3
PR	52	16	68
SD	27	14	41
PD	7	7	14
NE	13	8	21
ORR [†]	61.4%	44.7%	56.3%
DCR	91.0%	81.6%	88.9%

[†] $p = 0.076$ by χ^2 test.

CR: Complete response; DCR: Disease control rate; NE: Nonevaluable; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

Discussion

This is one of the most comprehensive real-world studies to report the results of salvage osimertinib strategy for *EGFR*-mutant NSCLC. The detection of T790M mutation is a prerequisite for salvage osimertinib, thus resulting in limited application of the drug. At the time of the first data cut-off, 76.8% of our patients who had a history of AR to 1st- or 2nd-G *EGFR*-TKIs underwent at least one rebiopsy or liquid biopsy and T790M was detected in 52.6% of these. These biopsy results are comparable with those of a preceding Japanese report of 395 *EGFR*-mutated NSCLC patients from 28 centers, in which rebiopsy and T790M detection were successful in 79.5 and 46.8% cases, respectively [13]. Because T790M was detected in 50–60% of patients with AR to 1st- or 2nd-G *EGFR*-TKIs in a pooled analysis, these studies indicate that there may be little room for improvement of T790M detection in the real-world setting. Our data also suggest that liquid biopsy has a certain, but limited role in detecting T790M, which is consistent with previous reports [17,18].

Reflecting real-world nature of this study, *EGFR* mutations in rebiopsy and liquid biopsy were examined by PCR-based tests which are reimbursed by insurance in Japan, not NGS-based methods. Therefore, information on changes of the genes other than *EGFR* were not available. In addition, because only one test which proved the presence of T790M mutation was necessary and sufficient for salvage osimertinib use, rebiopsy and liquid biopsy were performed as independent examinations. We have no data on concordance or discordance of the results of rebiopsy and liquid biopsy.

The toxicity of osimertinib was generally mild. As shown in Table 3, the frequency of grade ≥ 3 AEs was 10.2%, which is similar to the 12.2% reported in the Japanese subset of the AURA3 study [19,20]. When compared with 1st-G *EGFR*-TKI, osimertinib was reported to exhibit decreased severity in skin toxicity and transaminase elevation. On the contrary, a tendency of increased frequency was reported in the ejection fraction decrement and QT interval prolongation on electrocardiography [4]. ORR, DCR and PFS for osimertinib were reported to be 70.7,

Table 5. Progression-free survival.

Factors	n	Median (95% CI)	HR	p-value
Overall	147	17.2 (11.9–22.5)		
Sex				
Men [†]	50	17.2 (9.5–25.2)		0.88
Women	97	18.7 (12.2–25.2)		0.36
EGFR				
L858R [†]	59	14.7 (9.1–20.3)		0.89
T790M	88	18.9 (9.9–27.9)		0.65
Age (years)				
<75 [†]	78	15.5 (7.6–23.3)		0.87
≥75	69	19.7 (12.8–26.7)		0.28
PS				
0	32	NR [‡]	0.36	<0.01
1 [†]	93	10.9 (8.1–15.7)		
≥2	22	18.7 (3.3–34.1)		1.47
Stage				
IV [†]	94	13.6 (6.9–20.4)		0.77
Others	53	26.4 (12.5–40.4)		0.06
Line				
2 [†]	55	15.5 (9.2–21.7)		0.27
3–4	55	26.4 (13.6–39.3)		0.83
≥5	37	10.9 (6.8–15.1)		1.10
Group of patients				
Group 1 [†]	101	18.9 (13.4–24.4)		1.32
Group 2	46	10.6 (7.5–13.8)		0.06
T790M detection with liquid biopsy or tissue biopsy				
Tissue biopsy [†]	111	17.2 (9.9–15.8)		1.06
Liquid biopsy	36	19.4 (9.2–28.2)		0.74

†Control.

‡Not reached.

HR: Hazard ratio; PS: Performance status.

95.1% and 12.5 M, respectively, in the Japanese subset. In our study, the results of efficacy depended on the group of patients, as shown in Tables 4 and 5 and Figure 3B. The worse results in group-2 patients may be ascribed to the inclusion of patients with poor conditions due to the real-world setting, while the better results in group-1 patients appear to reflect a selection bias. In fact, the median PFS was 11.5 months (95% CI: 9.3–13.7 months) when group 2 patients with a PS of 0–1, who had received osimertinib as the second or third line of therapy (n = 32), was analyzed. Group-1 patients had longer histories of the treatment with a preceding EGFR-TKI than group-2 patients and hence possibly included patients with relatively less-aggressive NSCLC or NSCLC controlled well by the preceding treatments. Prolonged PFS was consistently observed in patients with good PS both in univariate and multivariate analysis. Univariate analysis showed a tendency of longer PFS in patients with stage I–III NSCLC or with NSCLC that recurred after curative treatments. Notably, PFS was similar between the patients whose T790M was detected with rebiopsy and liquid biopsy.

Whereas prospective clinical trials are undoubtedly important to determine treatment strategies, they are limited in the extrapolation of results. In this sense, retrospective analysis has certain contribution. For example, Mu *et al.* reported real-world data of their recent experiences of salvage osimertinib in 91 patients [21]. DCR and PFS were reported to be 91.9% and 8.6 months for patients with detectable T790M mutation, respectively. The results mean that the data in AURA3 study can be almost reproduced in real-world setting. On the other hand, clinical practice for EGFR-mutant NSCLC involves many aspects, including first exposure to an EGFR-TKI, development of AR to it, rebiopsy or liquid biopsy, determination of the possible mechanism of AR such as T790M and treatment of the disease with AR. Even if osimertinib is highly effective against NSCLC with T790M-mediated AR, its low

Figure 2. Progression-free survival. (A) Overall, **(B)** stage of disease at the start of osimertinib (recurrence after treatment with curative intent vs I–III vs IV), **(C)** sex (women vs men), **(D)** performance status at the start of osimertinib (0 vs 1 vs ≥ 2). PFS: Performance free survival.

accessibility to osimertinib via poor detection of T790M, for example, must hamper its clinical utility. Thus, what is important is not only the efficacy of osimertinib, but also the frequency of success at each clinical step above, which we intended to evaluate in this study.

A comprehensive analysis of entire clinical processes is necessary to develop effective strategies for *EGFR*-mutant NSCLC. Recently, Zhou *et al.* comprehensively reported their experiences of 632 patients with *EGFR*-mutant NSCLC from a single institution [22]. According to their report, biopsy was performed in 55.5% of 555 patients who had experienced PD and T790M was detected in 43.5% of the biopsied patients (24.1% of 555 patients). 3rd-G *EGFR*-TKIs were administered in 80 patients with T790M-positive NSCLC (14.4% of 555 patients) and

Figure 3. Progression-free survival (2). (A) Line of osimertinib (2nd vs 3rd–4th vs ≥5th), (B) start of any systemic treatment (before vs after 25 May 2016), (C) EGFR mutation type (exon 19 deletion vs L858R), (D) method of biopsy (rebiopsy vs liquid biopsy).

the PFS with 3rd-G EGFR-TKIs was 8.2 months. These results are fairly different from ours. Undoubtedly, these outcomes depend on the spread of rebiopsy and liquid biopsy, methods of T790M detection, characteristics of patients enrolled into studies and availability of 3rd-G EGFR-TKIs during study periods, among others. Their results, together with ours, indicate that salvage osimertinib has several problems to be solved.

Our study is limited by its retrospective nature and the fact that only Asian patients were included. However, it conveys the important message that the excellent performance of salvage osimertinib observed in the AURA3 study appears to be reproducible in a real-world setting. On the other hand, it also revealed that only 37.4% of the patients could receive osimertinib. Together with longer PFS, excellent CNS penetration and lower toxicity of osimertinib, these results indicate the advantage of frontline osimertinib. On the contrary, recent publication of the FLAURA study suggested that OS was comparable between 1st-G EGFR-TKIs and osimertinib in an Asian population and in patients with L858R-positive NSCLC. More effective strategies might appear in the future by combining different EGFR-TKIs or combining osimertinib with other categories of drugs.

Future perspective

Molecular-targeted therapy has opened a new era of treatment for cancer, with EGFR-TKIs for NSCLC with activating *EGFR* mutations to be a representative. A notable feature of treatments for *EGFR* mutation-positive NSCLC is the availability of multiple TKIs. Although each EGFR-TKI has achieved remarkable success, there still exist challenges how to use these drugs over time. Our study showed that several clinically essential gates exist to deliver each regimen to a patient at the appropriate timing. This means that OS depends on the sequence of regimens and the ratio of passing through these gates. Therefore, not only the efficacy of each regimen but evaluation of entire treatment processes is essential in the future. Real-world studies are becoming increasingly important in the treatment for cancer with driver mutations.

Summary points

- Osimertinib, a third-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI), is a key drug in the treatment of advanced non-small-cell lung cancer (NSCLC) harboring activated *EGFR* mutations and has attained the best hazard ratio of progression-free survival in comparison with first-generation EGFR-TKIs.
- At present, two strategies, frontline osimertinib and salvage osimertinib for the T790M-mediated progression to a first or second-generation EGFR-TKI, are popular in the treatment with EGFR-TKIs.
- Because hazard ratio of overall survival in comparison with first-generation EGFR-TKIs was almost similar between FLAURA study with osimertinib and ARCHER 1050 study with dacomitinib, salvage osimertinib may be a treatment option for certain subsets of the patients.
- Among 524 NSCLC patients with activated *EGFR* mutations in Japanese five hospitals, 393 patients experienced disease progression to a first- or second generation EGFR-TKI and 302 patients underwent rebiopsy or liquid biopsy.
- Rebiopsy and liquid biopsy detected T790M in 52.6% of the patients tested; osimertinib was administered in 93.6% of the T790M-positive patients; overall response rate (ORR) and median progression-free survival time of osimertinib were 55.6% and 17.2 months, respectively.
- Activity of osimertinib for T790M-driven acquired resistance in *EGFR*-mutant NSCLC was confirmed in real world setting, but the probability of losing the opportunity to use osimertinib is quite high when salvage use of osimertinib is adopted.

Author contributions

F Imamura performed planning of research, data analysis and preparation of manuscript. M Kimura performed data collection and data analysis. Y Yano, H Suzuki, S Ihara and T Shiroyama performed data collection. M Mori, T Hirashima, I Nagatomo, K Komuta and T Kumagai performed planning of research and critical review of data.

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Ethical conduct of research

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