Therapies after first-line afatinib in patients with *EGFR*^{m+} NSCLC in Japan: retrospective analysis of LUX-Lung 3

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Aim: Acquired resistance to EGFR tyrosine kinase inhibitors is inevitable in non-small-cell lung cancer. To inform subsequent treatment decisions, we retrospectively assessed therapies following afatinib in Japanese patients from LUX-Lung 3. **Patients & methods:** LUX-Lung 3 was a randomized, open-label, Phase III study of afatinib versus cisplatin/pemetrexed in treatment-naïve patients with *EGFR* mutation-positive (*EGFR*^{m+}) advanced lung adenocarcinoma. **Results:** Among 47 Japanese patients who discontinued first-line afatinib, 91/81/62% received ≥one/two/three subsequent therapies. The most common second-line therapies were platinum-based chemotherapy (38%) and a first-generation EGFR tyrosine kinase inhibitor (17%). Median overall survival (afatinib vs cisplatin/pemetrexed) was 47.8 versus 35.0 months (not significant). **Conclusion:** First-line afatinib does not appear to diminish suitability for subsequent therapies in *EGFR*^{m+} non-small-cell lung cancer.

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EGFR tyrosine kinase inhibitors (TKIs) are the first-line treatment of choice for patients with *EGFR* mutation-positive (*EGFR*^{m+}) non-small-cell lung cancer (NSCLC) [1,2]. Five EGFR TKIs are available, having demonstrated robust clinical activity in this setting: the first-generation TKIs, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation EGFR wild-type sparing TKI, osimertinib [1,3–12].

Recent head-to-head trials have demonstrated that later-generation TKIs offer better efficacy outcomes than first-generation TKIs for first-line treatment of *EGFR*^{m+} NSCLC [10,11,13–16]. In the Phase IIb LUX-Lung 7 trial, afatinib significantly improved progression-free survival (PFS), time-to-treatment failure and objective response rate versus gefitinib [14,15], with a numerical, but nonsignificant difference in overall survival (OS) [15]. Dacomitinib also demonstrated significantly improved PFS versus gefitinib in the Phase III ARCHER 1050 trial, and, in exploratory analysis, OS was prolonged with dacomitinib versus gefitinib [10,13]. Furthermore, in the Phase III FLAURA trial, first-line osimertinib conferred a considerable PFS [11] and OS [16] advantage over gefitinib/erlotinib.

While these trials are clearly important in guiding first-line treatment decisions, given the inevitable acquired resistance to EGFR TKIs of any generation [17], subsequent therapy options are an important consideration in order to maximize OS. Clinical studies have shown that the most common mechanism of acquired resistance to erlotinib, gefitinib and afatinib is the emergence of the gatekeeper T790M mutation in exon 20 of the *EGFR* gene

(~50–70% of cases) [18–23]. In patients with T790M-mediated resistance, osimertinib represents a clear second-line treatment option, having demonstrated striking efficacy in this setting [23–25]. By comparison, mechanisms of resistance to osimertinib appear to be very heterogeneous [26,27], although MET-amplification and *EGFR* C797S mutation have been identified as being among the most frequent [28]. Therefore, at present, treatment options for patients who progress on first-line osimertinib are less clear and are likely to incorporate chemotherapy and potentially, immune checkpoint inhibitors [28–30]. Reflecting the uncertainty around second-line therapy for *EGFR*⁺ patients, the recent guidelines issued by the Japanese Lung Cancer Society do not provide specific recommendations for T790M-negative patients progressing after first-line *EGFR* TKI treatment. Rather, healthcare professionals, including Japanese physicians, are referred to generic treatment recommendations for all patients with driver oncogenes, which include cytotoxic chemotherapy during any line of treatment [30]. Furthermore, the Pan-Asian adapted Clinical Practice Guidelines recommend platinum-doublet chemotherapy as second-line therapy for T790M-negative *EGFR*⁺ patients [29]. Analysis of clinical outcomes in patients undergoing second-line treatment is therefore important to better inform therapeutic decision-making [28].

A retrospective analysis of the LUX-Lung 3 (afatinib vs cisplatin plus pemetrexed), LUX-Lung 6 (afatinib vs cisplatin plus gemcitabine) and LUX-Lung 7 datasets was undertaken to gain insight into postprogression therapy following first-line afatinib, and provide some insight into treatment practices and suitability for subsequent therapy [31]. This analysis demonstrated that 71% of patients with exon 19 deletion (Del19)/L858R *EGFR*⁺ NSCLC were sufficiently fit to receive at least one subsequent therapy following afatinib [31] and that uptake of subsequent therapies was particularly high in countries with optimized comprehensive cancer care (80%), including Japan (89%) [31]. Optimizing the treatment of NSCLC, which is primarily diagnosed during older age, is important particularly in Japan because the elderly population is predicted to increase at a higher rate than most Organisation for Economic Co-operation and Development (OECD) countries [31,32].

In a previous subanalysis of LUX-Lung 3 [33], PFS benefit with afatinib versus chemotherapy was similar in 77 Japanese patients with Del19/L858R *EGFR*⁺ NSCLC (13.8 vs 6.9 months; hazard ratio [HR]: 0.28; 95% CI: 0.15–0.52; *p* < 0.0001) as in all 308 patients with Del19/L858R *EGFR*⁺ NSCLC (13.6 vs 6.9 months; HR: 0.47; 95% CI: 0.34–0.65) [8]. Moreover, as with the overall dataset, afatinib conferred notable OS benefit versus chemotherapy in Japanese patients with *EGFR* Del19- or L858R-positive tumors (46.9 vs 35.0 months; HR: 0.57; 95% CI: 0.29–0.1.12; *p* = 0.10). Afatinib was similarly well tolerated in Japanese patients, with no unexpected safety signals [33]. In this prior Japanese subanalysis of LUX-Lung 3, 89.6% of patients received subsequent therapy after discontinuation of afatinib [33]; however, the number, duration, nature and impact of specific subsequent therapies has not yet been assessed. There is a relatively wide range of treatment options now available in Japan for patients with *EGFR*⁺ NSCLC, but a paucity of data relating to the sequencing of these agents. Evaluation of survival outcomes in patients who received different therapeutic modalities following first-line afatinib may therefore add to the overall clinical knowledge and assist healthcare professionals, including Japanese physicians and patients when making treatment choices.

In this retrospective analysis of LUX-Lung 3, we assessed the impact of first-line afatinib on uptake and duration of subsequent therapies, including other *EGFR* TKIs and chemotherapy, and OS, in Japanese patients with NSCLC harboring common (Del19 or L858R) *EGFR* mutations.

Methods

Study design & patients

Detailed study design, patient inclusion and exclusion criteria, and methods for the primary analysis of LUX-Lung 3 have been described previously [8]. In brief, LUX-Lung 3 was a randomized, open-label, Phase III study of afatinib versus cisplatin plus pemetrexed in patients with previously untreated stage IIIB/IV lung adenocarcinoma and centrally confirmed *EGFR* mutations. Randomization was stratified by *EGFR* mutation type (Del19, L858R or other) and race (Asian or non-Asian). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with clinically asymptomatic and controlled brain metastases (stable for ≥4 weeks, not requiring treatment with anticonvulsants or steroids, and no leptomeningeal disease) were permitted. The primary end point was PFS by independent blinded review.

LUX-Lung 3 was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines on Good Clinical Practice, and the protocol was approved by the institutional review boards at each participating center. All patients provided written informed consent.

Treatment

Eligible patients in LUX-Lung 3 were randomized 2:1 to receive oral afatinib 40 mg once daily, or up to six cycles of intravenous cisplatin 75 mg/m² and pemetrexed 500 mg/m² once every 21 days. Treatment was continued until investigator-assessed disease progression or intolerable adverse events (AEs) necessitating discontinuation of therapy.

Tumor assessment

Tumors were assessed by computed tomography or MRI every 6 weeks for the first 48 weeks, and every 12 weeks thereafter until disease progression or start of new anticancer therapy, according to RECIST version 1.1. Molecular testing of tumor samples at progression/discontinuation was neither mandatory nor documented.

Analysis of subsequent therapies

Following discontinuation of first-line afatinib or platinum-based chemotherapy in LUX-Lung 3, any further treatment decisions were made by the treating physician. Patients were followed up every 21 ± 7 days from the end-of-treatment visit until disease progression or start of a subsequent anticancer treatment, at which point patients entered an observation period. During observation, details of subsequent therapy and progression were collected from patient notes or by telephone contact with the patient every 60 ± 15 days until death or 5 years after the last follow-up visit, whichever occurred first.

Statistical analysis

Post hoc analysis of subsequent therapies was conducted in Japanese patients with NSCLC harboring common (Del19/L858R) *EGFR* mutations. Incidence, type and duration of subsequent therapy (overall and by treatment line) are reported using descriptive statistics, including descriptive medians for time on treatment. Maximum percentage tumor shrinkage and percentage growth from nadir (smallest tumor diameter), by investigator assessment, at the time of stopping first-line afatinib were also analyzed.

Cox proportional hazards models and stratified log-rank tests were used to compare OS between patients randomized to afatinib or chemotherapy, and Kaplan–Meier estimates were used to construct survival curves and calculate median OS values.

Results

Patients

The disposition of the overall study population [8] and the Japanese population enrolled in LUX-Lung 3 [33] have been described previously. In LUX-Lung 3, 54 Japanese patients were randomized to first-line afatinib and all received study treatment; 29 patients were randomized to chemotherapy and 28 were treated. Baseline characteristics were generally similar across the treatment arms, and to those of the overall study population [8,33]. 50 Japanese patients assigned to afatinib and 27 Japanese patients assigned to chemotherapy had NSCLC tumors harboring the common Del19/L858R *EGFR* mutations [33]. Of these patients, 47 (94%) and 27 (100%), respectively, had discontinued first-line therapy at the time of data cutoff (March 2016). 43 (91%) patients received subsequent therapy following afatinib (Table 1), with 81% and 62% of patients receiving third- and fourth-line therapy, respectively. Uptake of subsequent therapy following first-line afatinib was higher in the Japanese subgroup compared with the wider LUX-Lung 3 population (Table 1).

Analysis of subsequent therapies

Afatinib followed by chemotherapy

Following discontinuation of first-line afatinib, 28 (60%) patients received single-agent chemotherapy (predominantly third-line) and 21 (45%) received platinum-based chemotherapy (predominantly second-line; Tables 1 & 2). Median time on single-agent chemotherapy across all treatment lines was 3.1 months (range: 0.03–17.2 months), and on platinum-based chemotherapy was 5.3 months (range: 0.7–28.7 months; Table 2). Median time on any chemotherapy treatment across all lines was 12.6 months (range: 0.03–28.7 months; Table 2); this included patients who received bevacizumab in combination with platinum-based chemotherapy ($n = 16$), bevacizumab plus single-agent chemotherapy ($n = 1$) or other chemotherapy combinations ($n = 6$), as well as those treated with single-agent (including platinum-based) chemotherapy. Treatment sequence for patients who received first-line afatinib followed by second-line chemotherapy is shown in Figure 1.

Table 1. Rates of subsequent systemic therapy in patients with non-small-cell lung cancer harboring common *EGFR* mutations who discontinued first-line afatinib in LUX-Lung 3.

Line	All patients [†]						Japanese patients [†]							
	Any [‡]	Platinum-based CT	Single-agent CT	Any CT regimen [§]	First-generation TKI monotherapy [¶]	Any EGFR TKI [#]	Other	Any [‡]	Platinum-based CT	Single-agent CT	Any CT regimen [§]	First-generation TKI monotherapy [¶]	Any EGFR TKI [#]	Other
Any	154 (78)	106 (54)	84 (43)	137 (70)	86 (44)	100 (51)	7 (4)	43 (91)	21 (45)	28 (60)	37 (79)	26 (55)	34 (72)	2 (4)
Second	154 (78)	94 (48)	9 (5)	125 (63)	24 (12)	28 (14)	1 (<1)	43 (91)	18 (38)	2 (4)	33 (70)	8 (17)	10 (21)	0
Third	120 (61)	13 (7)	55 (28)	79 (40)	33 (17)	40 (20)	1 (<1)	38 (81)	3 (6)	25 (53)	34 (72)	3 (6)	4 (9)	0
Fourth	72 (37)	7 (4)	24 (12)	36 (18)	27 (14)	33 (17)	3 (2)	29 (62)	4 (9)	6 (13)	13 (28)	13 (28)	15 (32)	1 (2)

Data represented as n (%).

[†]Percentages are of patients who discontinued afatinib (overall: n = 197; Japanese subset: n = 47; data cutoff: March 2016).

[‡]Any subsequent systemic treatment.

[§]CT or CT-based combination.

[¶]Erlotinib or gefitinib.

[#]EGFR TKI monotherapy or EGFR TKI-containing combination.

T: Chemotherapy; TKI: Tyrosine kinase inhibitor.

Table 2. Median time on treatment of subsequent chemotherapy treatment in Japanese patients harboring common *EGFR* mutations who discontinued first-line afatinib.

Line	Platinum-based chemotherapy		Single-agent chemotherapy		Any chemotherapy regimen [†]	
	Median time on treatment, months (range)	n (%) [‡]	Median time on treatment, months (range)	n (%) [‡]	Median time on treatment, months (range)	n (%) [‡]
Any	5.3 (0.7–28.7)	21 (45)	3.1 (0.03–17.2)	28 (60)	12.6 (0–28.7)	37 (79)
Second	4.1 (0.7–15.7)	18 (38)	1.6 (0.8–2.3)	2 (4)	5.8 (0.7–24.9)	33 (70)
Third	7.5 (4.5–13.0)	3 (6)	2.3 (0.03–14.1)	25 (53)	2.4 (0–14.1)	34 (72)
Fourth	3.3 (1.0–8.0)	4 (9)	1.1 (0.03–3.4)	6 (13)	1.0 (0–8.0)	13 (28)

[†] Chemotherapy or chemotherapy-based combination.[‡] Percentages are of patients who discontinued afatinib (N = 47; data cutoff: March 2016). **Figure 1. Treatment sequence and duration for patients who received second-line platinum-based chemotherapy, single-agent chemotherapy or a third-generation EGFR TKI.**

Arrow denotes that treatment was still ongoing at data cutoff.

[†] Patients were ordered by total treatment duration, including any treatment gaps.[‡] Includes platinum-based CT plus bevacizumab.

CT: Chemotherapy; TKI: Tyrosine kinase inhibitor.

Afatinib followed by first-generation EGFR TKIs

26 (55%) patients received a first-generation EGFR TKI (erlotinib or gefitinib) after discontinuing afatinib (Table 3), predominantly as fourth-line treatment (n = 13; 28%). Median time on treatment across all lines of subsequent first-generation EGFR TKI was 4.4 months (range: 0.2–41.0 months; Table 3).

Table 3. Median time on treatment of subsequent EGFR tyrosine kinase inhibitor treatment in Japanese patients harboring common *EGFR* mutations who discontinued first-line afatinib.

Line	First-generation EGFR TKI		Any EGFR TKI [†]	
	Median time on treatment, months (range)	n (%) [‡]	Median time on treatment, months (range)	n (%) [‡]
Any	4.4 (0.2–41.0)	26 (55)	5.8 (0.2–41.0)	34 (72)
Second	4.0 (0.4–41.0)	8 (17)	4.1 (0.4–41.0)	10 (21)
Third	4.0 (3.1–21.0)	3 (6)	5.5 (3.1–21.0)	4 (9)
Fourth	2.0 (0.2–32.9)	13 (28)	3.0 (0.2–32.9)	15 (32)
Fifth	2.6 (1.1–6.6)	5 (11)	2.1 (0.9–10.2)	10 (21)

[†] EGFR TKI monotherapy or EGFR TKI-containing combination.[‡] Percentages are of patients who discontinued afatinib (N = 47; data cutoff: March 2016).

TKI: Tyrosine kinase inhibitor.

Eight (17%) patients who discontinued afatinib treatment continued ‘seamless’ EGFR TKI therapy with a first-generation EGFR TKI as second-line therapy (Figure 2A). Median time on first-generation TKI treatment in the second line was 4.0 months (range: 0.4–41.0 months) and was the same in the third line (median: 4.0 months; range: 3.1–21.0 months; Table 3). Median total time on subsequent EGFR TKI treatment across all lines was 5.8 months (range: 0.2–41.0 months; Table 3); this included afatinib (n = 8) or osimertinib (n = 1) monotherapy, and EGFR TKI-containing combination therapies (n = 3), in addition to first-generation EGFR TKI monotherapy.

All patients who received a first-generation TKI in the second-line experienced tumor shrinkage with afatinib prior to discontinuation (Figure 2B). Of these eight patients, six discontinued afatinib due to progressive disease; regrowth of target tumors was observed in four of the six tumors. Two patients discontinued afatinib due to AEs.

Afatinib followed by osimertinib

Only one patient received osimertinib following discontinuation of afatinib. Time on first-line afatinib treatment was 47.6 months, and time on second-line osimertinib treatment was 12.9 months (Figure 1); however, osimertinib treatment was still ongoing at data cutoff.

Impact of EGFR mutational subgroup on subsequent treatment

Type of subsequent therapy and median treatment duration by *EGFR* mutational status are shown in Figure 3. Some differences were observed in median treatment duration according to *EGFR* mutational status across the different lines and therapies. However, the very small-sample sizes preclude any firm conclusions.

Overall survival

At data cutoff (March 2016), median follow-up time for OS was 41.7 months. Median OS among Japanese patients with common *EGFR* mutations was 47.8 months for afatinib versus 35.0 months for cisplatin plus pemetrexed (HR: 0.75; 95% CI: 0.44–1.27; p = 0.284; Figure 4).

Discussion

In this retrospective analysis of Japanese patients from LUX-Lung 3 with NSCLC harboring common (Del19/L858R) *EGFR* mutations, patients who received first-line afatinib demonstrated a very high uptake of subsequent therapies (91%, compared with 78% in the overall study population [33]). Median OS was nearly 4 years, likely reflecting the high uptake, multiple lines (62% received ≥ four lines) and long duration of subsequent therapies. It is probable that the high uptake of subsequent therapies among Japanese patients is, at least in part, due to Japan’s public social health insurance system that provides universal health coverage for all citizens [32], and as a result, easy and timely access to approved therapies.

The most frequently received subsequent therapy was single-agent chemotherapy (received by 60% of patients in any line), although first-generation EGFR TKI monotherapy (55%) and platinum-based chemotherapy (45%) were also commonly received. Platinum-based chemotherapy was the most common second-line treatment, with a median duration of approximately 4 months. Although retrospective, these data suggest that first-line afatinib does not adversely affect suitability of subsequent therapy in Japanese patients with *EGFR*^{m+} NSCLC, and most patients were fit enough to receive further treatment. This is reassuring given that platinum-based chemotherapy is still the preferred second-line therapy in patients with T790M-negative or unknown *EGFR*^{m+} NSCLC [29,30].

Figure 2. Treatment sequence and duration, reasons for discontinuation, maximum tumor shrinkage, and percentage tumor growth from nadir for the eight Japanese patients who received a second-line, first-generation EGFR TKI. **(A)** Treatment sequence and duration; **(B)** reasons for discontinuation, maximum tumor shrinkage and percentage tumor growth from nadir (both investigator assessed) at the time of stopping afatinib treatment.

†Patients were ordered by total treatment duration, including any treatment gaps **(A)**, or by maximum percentage tumor shrinkage from baseline **(B)**.

‡Includes platinum-based CT plus bevacizumab.

AE: Adverse event; CT: Chemotherapy; PD: Progressive disease; TKI: Tyrosine kinase inhibitor.

Figure 3. Rates of subsequent systemic therapy and duration of subsequent treatment in Japanese patients who discontinued first-line afatinib, by *EGFR* mutational status. Frequencies relate to the overall number of patients with each mutation type who received one subsequent therapy. Del19: Exon 19 deletion; TKI: Tyrosine kinase inhibitor.

Figure 4. Kaplan-Meier curve of OS in Japanese patients in LUX-Lung 3 who had a common *EGFR* mutation. Cis: Cisplatin; HR: Hazard ratio; OS: Overall survival; Pem: Pemetrexed.

In another retrospective analysis of Japanese patients with *EGFR*^{m+} NSCLC (N = 1660), 97% of patients received an EGFR TKI as part of their treatment regimen in 'real-world' clinical practice [34]. Median OS among all patients in this 'real-world' population was 30.8 months. It was common for patients to receive multiple lines of EGFR TKI therapy, and to switch between different TKIs (39% of patients received ≥ 2 TKIs) [34]. Taken together with our findings of encouraging median time on EGFR TKI treatment after afatinib discontinuation (5.8 months in any line), these data suggest that EGFR TKI switching and rechallenge might further extend the survival of patients with *EGFR*^{m+} NSCLC [34,35].

Of 47 patients who had discontinued afatinib in our analysis, only one patient went on to receive subsequent treatment with osimertinib, reflecting the limited availability of osimertinib at the time the LUX-Lung 3 study was undertaken, and the fact that, in line with the study protocol, mutation testing on progression was not mandatory. Nevertheless, the time that this patient spent on second-line osimertinib (12.9 months, with treatment still ongoing at data cutoff) was comparable to that in previous reports of sequential EGFR TKI-osimertinib treatment (8–13 months) [23,24]. The potential benefit of sequential afatinib-osimertinib treatment for patients with T790M-acquired resistance has been demonstrated in a pooled analysis of LUX-Lung 3, 6 and 7 (n = 37; median OS: not reached after 4.7 years' follow-up) and the global, observational real-world GioTag study (n = 203; median OS: 41.3 months after 30.3 months' follow-up) [28,31,36]. Based on published estimates of at least 70% uptake of subsequent therapy [31] and around 45–70% of patients developing T790M-mediated resistance following failure of afatinib [21,22,37], we can estimate that almost half of patients with *EGFR*^{m+} NSCLC who receive first-line afatinib could be eligible to receive second-line osimertinib [23,24]. Although the availability, specificity and sensitivity of liquid biopsy-based PCR and next-generation sequencing analyses continue to improve worldwide, including in Japan, identification of acquired T790M mutations is still limited by tissue availability and the sensitivity of commonly used assays [38–41]. Thus, it is unclear whether the uptake of second-line osimertinib in the real-world clinical setting would be as high as estimated.

In our analysis, patient numbers were too low to make meaningful conclusions relating to subsequent treatment duration by tumor *EGFR* Del19/L858R mutational type. However, findings from the much larger pooled analysis of subsequent therapies in LUX-Lung 3, 6 and 7 [31] suggested that uptake rates of EGFR TKI therapy or chemotherapy after discontinuation of afatinib were similar regardless of whether a tumor harbors an *EGFR* Del19 or L858R mutation.

We acknowledge that the data presented herein are based on only a small number of Japanese patients, with no formal statistical analysis plan, and a relatively short follow-up duration, which precludes any conclusions on the long-term effects of the treatments received post-afatinib. There are also clear limitations relating to the retrospective nature of the analysis. For example, because of the absence of mandatory testing, few data are available regarding mechanisms of acquired resistance to afatinib in the LUX-Lung studies; therefore, the rate of T790M accrual has been assumed based on incidences reported in the literature. Furthermore, we acknowledge that the clinical management of patients with *EGFR*^{m+} NSCLC in Japan has changed substantially since the study was conducted, with a better understanding of the molecular biology of NSCLC, more frequent follow-up and widespread access to liquid biopsy-based molecular analysis at disease progression, and a broader range of treatment options now available. Although no data are available, as yet, on the use of immune checkpoint inhibitors post-afatinib in *EGFR*^{m+} patients, a subanalysis of the Phase III IMPower150 study suggests that incorporation of the PD-L1 inhibitor, atezolizumab, into second-line chemotherapy-based regimens, can improve outcomes following failure of first-line EGFR TKIs [42]. Such combination regimens represent further potential second- or third-line options following afatinib. Although this study is unable to provide any insights into the use of these and other newly approved agents post-afatinib, we believe our data on subsequent therapy duration and survival provide a benchmark against which to measure any additional benefit conferred by the newer therapeutic modalities.

Conclusion

Despite some study limitations, most notably the small size of our dataset, this analysis suggests that afatinib does not diminish the potential for subsequent therapies, including chemotherapy and other EGFR TKIs, in Japanese patients with advanced NSCLC harboring common *EGFR* mutations. The median OS of almost 4 years from the start of afatinib treatment suggests that Japanese patients with common *EGFR* mutations can derive prolonged benefit following first-line afatinib. These data on the use of subsequent chemotherapy and/or first-generation EGFR TKIs following afatinib treatment may assist healthcare professionals, including Japanese physicians, in determining the optimal role of afatinib within treatment sequencing for newly diagnosed Japanese patients.

Data disposition

The trial is registered on ClinicalTrials.gov, identifier: NCT00949650.

Summary points

- Patients with EGFR mutation-positive (*EGFR*^{m+}) non-small-cell lung cancer inevitably develop resistance to EGFR tyrosine kinase inhibitors (TKIs), yet few data are available to guide subsequent treatment decisions.
- This retrospective study used data from LUX-Lung 3 to evaluate treatment patterns and overall survival after first-line afatinib in Japanese patients with advanced lung adenocarcinoma harboring common *EGFR* mutations.
- Analysis included 47 Japanese patients who had progressed prior to data cutoff and showed that a high proportion received at least one (91%), two (81%) or three (62%) subsequent lines of systemic therapy after afatinib was discontinued.
- The uptake of subsequent treatments was higher in the Japanese subgroup than in the overall population of LUX-Lung 3, although the general trends in uptake of specific subsequent therapies were similar.
- The most frequently received second-line treatments in Japanese patients in LUX-Lung 3 were platinum-based chemotherapy (38%) and first-generation TKI (erlotinib or gefitinib) monotherapy (17%).
- Only one patient received second-line osimertinib (due to limited availability at the time and nonmandatory mutation testing on progression), but time on osimertinib was comparable to that of previous reports of sequential EGFR TKI-osimertinib treatment.
- Results of our study suggest that afatinib does not diminish the potential for subsequent therapies, including chemotherapy and other EGFR TKIs, in Japanese patients with *EGFR*^{m+} non-small-cell lung cancer.

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Data sharing statement

The datasets generated and analyzed during the study are available from H Yoshioka on reasonable request.

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