



Sequencing of therapy following first-line afatinib in patients with *EGFR* mutation-positive non-small cell lung cancer

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ABSTRACT

Objectives: With the availability of several epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), sequential therapy could potentially render *EGFR* mutation-positive non-small cell lung cancer a chronic disease in some patients. In this retrospective analysis of *EGFR* mutation-positive (Del19/L858R) patients receiving first-line afatinib in LUX-Lung 3, 6, and 7, we assessed uptake of, and outcomes following, subsequent therapies including the third-generation EGFR TKI, osimertinib.

Methods: Post-progression therapy data were prospectively collected during follow-up. Molecular testing of tumours at progression/discontinuation of afatinib was not mandatory. Duration of subsequent therapies, and

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survival following osimertinib, were calculated with Kaplan–Meier estimates.

Results: Among 553 patients who discontinued first-line afatinib, second-, third- and fourth-line therapy was administered in 394 (71%), 265 (48%), and 156 (28%) patients. The most common post-progression therapy was platinum-based chemotherapy (46%). Thirty-seven patients received subsequent osimertinib, 10 as second-line treatment. Median progression-free survival on afatinib in these 37 patients was 21.9 months. Median duration of osimertinib therapy was 20.2 months; median overall survival was not reached after a median follow-up of 4.7 years.

Conclusions: Most patients treated with first-line afatinib received subsequent therapy. Although limited by sample size, enrichment, and a retrospective nature, data from patients who received sequential afatinib and osimertinib are encouraging, warranting further investigation.

1. Introduction

The development of several highly effective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), along with expanding knowledge about mechanisms of acquired resistance and tumour evolution offers the possibility of sequential therapy in patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC). Currently, the optimal sequence of therapy is unknown. Five EGFR TKIs are available: the first-generation reversible TKIs, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation *EGFR*-wild-type sparing, irreversible TKI, osimertinib. Recent head-to-head prospective trials have demonstrated that first-line afatinib [1], dacomitinib [2], and osimertinib [3] are associated with improved progression-free survival (PFS) versus first-generation TKIs. Moreover, exploratory analysis of the ARCHER 1050 trial demonstrated a significant improvement in overall survival (OS) with dacomitinib versus gefitinib (HR: 0.76; 95% CI: 0.58–0.99) [4]. In the LUX-Lung 7 trial, there was a non-significant trend towards improved OS with afatinib versus gefitinib (HR: 0.86; 95% CI: 0.66–1.12) [5]; OS data from the FLAURA trial (osimertinib versus gefitinib/erlotinib) are currently immature [3]. No prospective data are available that have compared second- and third-generation EGFR TKIs in a first-line setting, so it is unknown which treatment regimen is likely to provide the longest overall survival (OS).

The likely availability and uptake of subsequent treatment options is an important factor when considering first-line therapy for *EGFR* mutation-positive NSCLC. Regardless of which EGFR TKI is used as first-line treatment, it seems inevitable that tumours acquire resistance to therapy. The most common resistance mechanism, identified in ~50–70% of tumours treated with gefitinib, erlotinib, and afatinib, is the emergence of the ‘gatekeeper’ T790 M mutation in exon 20 of *EGFR* [6]. Osimertinib was initially developed to target T790M-positive tumours and has demonstrated striking efficacy as a second-line option in this setting [7]. However, mechanisms of resistance to osimertinib appear to be very heterogeneous [8], so targeted treatment options beyond osimertinib are uncertain at this time.

In this study, we have undertaken a retrospective analysis of patients with *EGFR* mutation-positive NSCLC who were treated with first-line afatinib in the randomised LUX-Lung 3, 6, and 7 trials. The aim of the study was to assess the uptake of, and clinical outcomes following, subsequent lines of therapy in these patients, with a particular focus on those who received subsequent osimertinib.

2. Patients and methods

2.1. Study design and patients

Detailed study designs, patient inclusion/exclusion criteria, and methods of the primary analyses of LUX-Lung 3, 6, and 7 have been published [1,9,10]. In brief, LUX-Lung 3 and 6 were randomised, open-label, phase III studies; LUX-Lung 7 was a randomised, open-label, phase IIb study. Eligible patients had previously untreated stage IIIB/IV lung adenocarcinoma harbouring centrally confirmed EGFR mutations

(common mutations only [Del19 or L858R] in LUX-Lung 7) based on analysis of biopsy tissue using a validated test kit (Therascreen EGFR 29; Qiagen, Manchester, UK). Patients had Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1. In all three studies, patients with clinically asymptomatic and controlled brain metastases (stable for ≥ 4 weeks and/or asymptomatic and/or not requiring treatment with anticonvulsants or steroids and/or no leptomeningeal disease) were permitted.

2.2. Study treatment

In LUX-Lung 3 and 6, eligible patients were randomised 2:1 to oral afatinib 40 mg once daily (QD) or up to 6 cycles of intravenous platinum-based chemotherapy (LUX-Lung 3: cisplatin 75 mg/m² and pemetrexed 500 mg/m² once every 21 days; LUX-Lung 6: gemcitabine 1000 mg/m² on day 1 and day 8 plus cisplatin 75 mg/m² on day 1 of a 21-day cycle). Randomisation was stratified by EGFR mutation type (Del19, L858R, or other) and race (Asian or non-Asian for LUX-Lung 3 only; all patients in LUX-Lung 6 were Asian). In LUX-Lung 7, patients were randomised 1:1 to afatinib 40 mg QD or gefitinib 250 mg QD stratified by EGFR mutation type (Del19, L858R) and baseline brain metastases (presence vs. absence). In all studies, treatment with afatinib continued until investigator-assessed disease progression or intolerable adverse events (AEs). The primary endpoint of LUX-Lung 3 and 6 was progression-free survival (PFS) by independent central review; OS was a key secondary endpoint. LUX-Lung 7 had three co-primary endpoints: PFS (independent central review), time-to-treatment failure and OS.

2.3. Analysis of post-progression therapy

Subsequent therapy after discontinuation of study medication was the decision of the treating physician. Data regarding subsequent therapy were prospectively collected as study follow-up information. Follow-up visits occurred every 21 $\pm$ 7 days after the end of treatment visit until progression or start of subsequent anticancer treatment. After the last follow-up visit, patients entered an observation period; data regarding progression and subsequent therapy was collected every 60 $\pm$ 15 days, based on patient notes or by telephone contact with the patient, until death or 5 years after the last follow-up visit, whichever occurred first. Time on treatment with subsequent therapies was collected, but response to treatment, duration of response, and PFS were not collected. Molecular testing of tumour samples at progression/discontinuation was not mandatory and was not documented. Duration of any subsequent treatments, median OS, 3-year survival rates and PFS-2, defined as time from initiation of afatinib to the last day of osimertinib therapy, were calculated using Kaplan–Meier estimates. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs). All statistical analyses were exploratory; there was no formal statistical analysis plan.

3. Results

3.1. Analysis of subsequent therapies following discontinuation of afatinib

Across LUX-Lung 3, 6, and 7, 579 patients with common mutations received first-line afatinib (Supplementary Fig. 1). At the time of data cut-off (LUX-Lung 3 and 6: March 2016; LUX-Lung 7: December 2016), 553 of these patients had discontinued afatinib. The uptake of subsequent therapy was high; second-, third-, and fourth-lines of therapy were administered in 71%, 48%, and 28% of patients, respectively (Table 1). The most common post-progression therapy was platinum-based doublet chemotherapy (50% of patients), which was predominantly received as second-line treatment (46% of patients). Single-agent chemotherapy was administered to 33% of patients and was predominantly received as third-line treatment (19% of patients). First-generation EGFR TKIs were received in 34% of patients following discontinuation of afatinib. Other types of subsequent therapy, received in a total of 22% of patients, included chemotherapy plus EGFR TKI combinations, osimertinib, rociletinib, olmutinib, or afatinib re-challenge. Uptake of subsequent therapy varied depending on country/region and was higher in countries with optimised comprehensive cancer care such as Japan, South Korea, Singapore, Taiwan, Hong Kong, Western Europe, Canada, North America, and Australia (80%; Supplementary Table 1). Uptake was lower in Latin America (56%), Eastern Europe (36%), and other Asian countries such as China, Malaysia, Thailand, and the Philippines (65%).

3.2. Analysis of clinical outcomes in patients who received chemotherapy or first-generation TKIs following discontinuation of afatinib

The median duration of therapy with platinum-based doublet chemotherapy, single-agent chemotherapy and first-generation EGFR TKIs in any treatment line was 3.5, 2.3, and 3.9 months, respectively (Supplementary Fig. 2). The median duration of first-generation EGFR TKIs as second-line treatment was 5.7 months. Median PFS on first-line afatinib in these patients was 13.6 months. Most patients who received first-generation EGFR TKIs in the second line had previously achieved a deep response to afatinib, with subsequent tumour regrowth from the nadir classified as progressive disease (Supplementary Fig. 3). There was no clear difference in treatment duration with subsequent therapies following discontinuation of afatinib across Del19 and L858R EGFR mutational subgroups (Supplementary Fig. 4).

3.3. Analysis of clinical outcomes in patients who received osimertinib following discontinuation of afatinib or gefitinib

Given its limited availability at the time of the LUX-Lung trials, which recruited globally from August 2009 to August 2013, only 37 patients across LUX-Lung 7 ($n = 27$) and LUX-Lung 3/6 ($n = 10$) received osimertinib at any point following discontinuation of afatinib (27 of these patients received osimertinib in $\geq$ third-line setting;

updated data cut-off for LUX-Lung 7, August 2017). In LUX-Lung 7, 23 patients received sequential gefitinib followed by osimertinib. There were no notable differences in the baseline characteristics of patients who received sequential therapy compared with the overall LUX-Lung 7 population (Table 2). Exposure to first-line therapy was longer in patients who received sequential therapy than in the overall LUX-Lung 7 population (median of 17.5 months for afatinib and 18.0 months for gefitinib in LUX-Lung 7; median of 21.9 months in LUX-Lung 3, 6, and 7 combined).

After a median follow-up of 4.7 years, median OS in patients treated with sequential afatinib and osimertinib has not yet been reached (Fig. 1A). The median time from initiation of afatinib therapy to initiation of osimertinib therapy was 3.6 years. Median time on osimertinib was 20.2 months (95% CI 12.8–31.5; Fig. 1B) in any treatment line, 20.2 months if received as second-line treatment, and 17.5 months if received as third- or higher-line treatment. In the 10 patients who received consecutive afatinib and osimertinib, median PFS-2 was 53.3 months (95% CI 36.9–not reached).

Analysis of OS was also undertaken in patients who received afatinib/osimertinib ($n = 27$) or gefitinib/osimertinib ($n = 23$) specifically within LUX-Lung 7. Most patients (18/27 in the afatinib arm and 18/23 in the gefitinib arm) received osimertinib as third-line treatment or later. After a median follow-up of 52.8 and 56.0 months, respectively, median OS was not reached in either the afatinib or gefitinib group (Fig. 2).

4. Discussion

In this pooled analysis of patients with common EGFR mutations in LUX-Lung 3, 6, and 7, we observed high rates of subsequent therapy (71%) following first-line afatinib, with similar rates across EGFR mutation subtypes. The most common subsequent therapy was platinum-based chemotherapy. Only a minority of patients received osimertinib following afatinib, reflecting its restricted availability at the time the studies were undertaken and the fact that testing for T790 M was not mandated or documented. However, as osimertinib is now widely available, we hypothesise that, in principle, ~50% of all patients with EGFR mutation-positive NSCLC could be eligible for, and fit enough to receive, sequential afatinib and osimertinib, given our observation of ~70% uptake of subsequent therapy (88% in countries with a universal reimbursement policy) and recent observations that T790 M is present in ~50–70% of patients following failure of afatinib [11,12]. However, attainment of this level of uptake of sequential treatment in the ‘real-world’ clinical setting would probably require improvements in testing strategies for T790 M, given the invasive nature of tissue rebiopsy, and will be dependent on country-specific reimbursement policies. Nevertheless, improvements in liquid biopsy techniques should facilitate identification of T790 M in some patients when rebiopsy is not feasible.

Notwithstanding the retrospective nature of this study, the small sample size, lack of data on the mechanisms of resistance to afatinib and enrichment for patients who received several lines of therapy,

Table 1

Rates of subsequent therapy in patients who discontinued afatinib in the LUX-Lung 3, 6, and 7^a studies.

	Any subsequent systemic treatment	Platinum-based chemotherapy	Single-agent chemotherapy	First-generation TKI monotherapy ^b	Other ^c
Any-line, n (%)	394 (71)	277 (50)	181 (33)	186 (34)	121 (22)
Second-line, n (%)	394 (71)	252 (46)	39 (7)	49 (9)	54 (10)
Third-line, n (%)	265 (48)	48 (9)	104 (19)	75 (14)	38 (7)
Fourth-line, n (%)	156 (28)	27 (5)	50 (9)	49 (9)	30 (5)

Percentages are of the total number of patients who had discontinued afatinib at the time of analysis ($N = 553$).

Abbreviation: TKI = tyrosine kinase inhibitor.

^a Data cut-off for LUX-Lung 7: December 2016.

^b Erlotinib, gefitinib and icotinib.

^c Includes: platinum-based, single-agent, and other chemotherapy combination therapies; osimertinib, afatinib, HM61713, and rociletinib monotherapies; erlotinib-, gefitinib-, icotinib-, and afatinib-containing combinations; immune checkpoint inhibitors; and ‘other’ therapies.

Table 2
Baseline characteristics of patients who received subsequent osimertinib.

Characteristic	LUX-Lung 3, 6, and 7	LUX-Lung 7			
		Afatinib		Gefitinib	
		Received sequential afatinib-osimertinib ^a (n = 37)	Received subsequent osimertinib (n = 27)	ITT (n = 160)	Received subsequent osimertinib (n = 23)
Female, n (%)	25 (67.6)	18 (66.7)	91 (56.9)	20 (87.0)	106 (66.7)
Median age, years (range)	59 (35–78)	61 (37–78)	63 (30–86)	67 (44–81)	63 (32–89)
Asian, n (%)	20 (54.1)	12 (44.4)	94 (58.8)	10 (43.5)	88 (55.3)
Never smoked, n (%)	29 (78.4)	20 (74.1)	106 (66.3)	19 (82.6)	106 (66.7)
ECOG PS 0, n (%)	15 (40.5)	10 (37.0)	51 (31.9)	8 (34.8)	47 (29.6)
<i>EGFR</i> Del19 mutation, n (%)	23 (62.2)	15 (55.6)	93 (58.1) ^b	17 (73.9)	93 (58.5)
Brain metastases at screening, n (%)	2 (5.4)	2 (7.4)	26 (16.3)	3 (13.0)	24 (15.1)
Median exposure to study drug, months	21.9	17.5	13.7	17.9	11.5
Osimertinib					
Second-line, n (%)	10 (27.0)	9 (33.3)	–	5 (21.7)	–
≥ Third-line, n (%)	27 (73.0)	18 (66.7)	–	18 (78.3)	–

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; ITT = intent-to-treat.

^a Patients with common *EGFR* mutations only.

^b One patient in the afatinib group with wild-type *EGFR* was erroneously included in the trial and was reported as exon 19 deletion at the time of randomisation by the investigator.

exploratory analysis in patients who received sequential afatinib and osimertinib were noteworthy. After a median follow-up of 4.7 years, median OS was not reached. This, together with the findings from a recent pooled analysis of the AURA extension and AURA2 trials (n = 411), in which median OS with second- or later-line osimertinib was 26.8 months [13], is encouraging for EGFR TKI-pretreated patients who receive subsequent osimertinib. Patients previously treated with afatinib were able to remain on osimertinib therapy for more than 1.5 years (median duration: 20.2 months). Median duration of osimertinib therapy was higher in the 10 patients who received it as second-line treatment than in the 27 patients who received it in a third-line setting or later. Moreover, median PFS-2 in these patients was over 4 years. It must be noted that the fact that most patients who received osimertinib received it late in the disease course; the median time between initiation of afatinib and osimertinib being 3.6 years. Thus, the prolonged OS may reflect the fact that these patients already had a favorable prognosis rather than their response to sequential therapy. Nevertheless, these observations support other recent studies that suggest a sequential approach of first-/second-generation EGFR TKIs followed by osimertinib could be a promising therapeutic strategy in patients with *EGFR* mutation-positive NSCLC and T790M-driven acquired resistance after first-line therapy, to potentially maximise the duration of chemotherapy-free treatment. For example, in a multicentre observational study of 204 patients who received second-line osimertinib after first-line afatinib, overall median time to treatment failure was 27.6 months [14]. Furthermore, in patients who received a subsequent third-generation TKI in the ARCHER 1050 trial, median OS was 36.7 months (95% CI 30.1–not reached) in the dacomitinib arm (n = 22) and not reached in the gefitinib arm (n = 25) [4]. Although it is not clear which first-line EGFR TKI would provide the best foundation for sequential treatment, a more pronounced benefit of osimertinib after second-generation TKIs than after first-generation TKIs might be expected due to a higher allelic frequency of T790 M following first-line treatment [15]. Indeed, in a recent phase II trial of 111 T790M-positive patients, PFS and response rate were significantly better in patients treated with sequential afatinib and osimertinib versus sequential erlotinib/gefitinib and osimertinib [16].

In summary, this retrospective study indicates that most patients treated with first-line afatinib were sufficiently fit to receive at least one subsequent line of therapy. Analysis of outcomes in patients who received osimertinib after afatinib are of interest. Although limited by sample size, lack of genomic data, enrichment, and a retrospective

nature, these data are encouraging and warrant further investigation.

Author contributions

All authors contributed to the study design and, with the exception of Angela Märten and Wenbo Tang, data acquisition. Data analysis and interpretation, and manuscript preparation was undertaken by Keunchil Park and Angela Märten. Statistical analysis was undertaken by Wenbo Tang. All authors were involved in manuscript editing and review, and were involved at all stages of manuscript development. The authors were fully responsible for all content and editorial decisions, and have approved the final version.

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Conflict of interests

KP has received personal fees from Boehringer Ingelheim, Clovis, Eli Lilly, Hanmi, Kyowa Hakko Kirin, Ono, Novartis, and Roche; and research funding from AstraZeneca. JB has received personal fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, and Roche. MB has received payment for study-related activities from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharpe and Dohme, Pfizer, and Roche. TH has received research grants from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharpe and Dohme, Ono, Chugai, Eli Lilly, Novartis, Taiho, Pfizer, Clovis, Kissel, Ignyta, Eirai, Takeda, Dainippon Sumitomo, Abbvie, Merck Serono, Kyowa Hakko Kirin, Daiichi Sankyo, Astellas, and Servier; and personal fees from Chugai, Eli Lilly, Novartis, Taiho, Pfizer, Clovis, Kissel, Ignyta, Merck Sharpe and Dohme, and Bristol Myers Squibb. TK has received research grants and personal fees from Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Eli Lilly, Kyowa Hakko Kirin, Merck Sharpe and Dohme, No Ono, Pfizer, Quintiles, Taiho, and Sumitomo Dainippon; personal fees from Novartis, Roche, and Sumitomo Dainippon; and a research grant from Parexel. TM has received personal fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Serono,

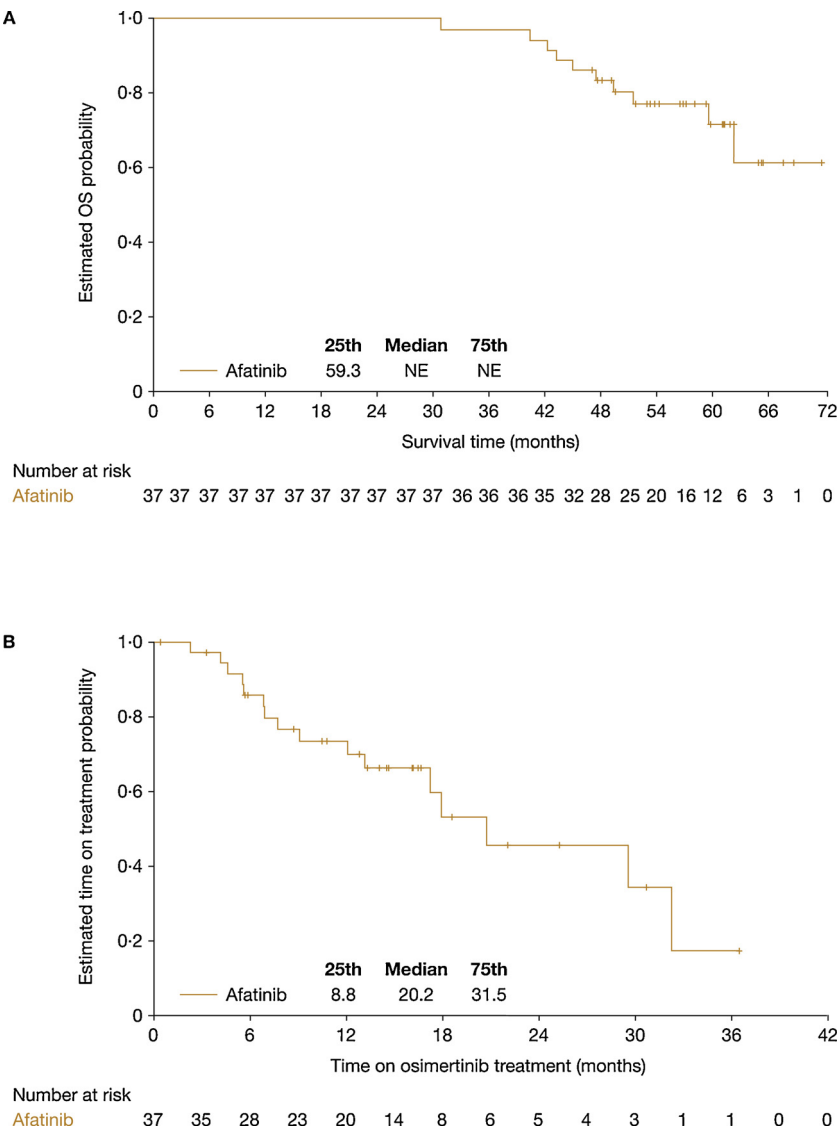


Fig. 1. (A) Overall survival and (B) exposure to osimertinib treatment in patients who received osimertinib in any line following afatinib in LUX-Lung 3, 6, and 7. Data cut-off for LUX-Lung 7: August 2017. Abbreviations: NE not estimable; OS overall survival.

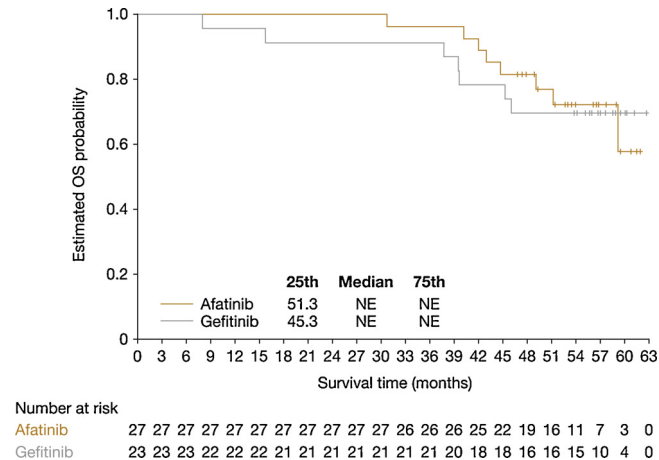


Fig. 2. Overall survival in patients who received osimertinib in any line following afatinib or gefitinib in LUX-Lung 7. Data cut-off for LUX-Lung 7: August 2017. Abbreviations: NE = not estimable; OS = overall survival.

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Ethical considerations

Studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines on Good Clinical Practice, and the protocols were approved by local ethics committees at each participating centre. All patients provided written informed consent for trial participation.

Availability of data and materials

The datasets generated and analysed during the study are available from Keunchil Park on reasonable request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.04.014>.

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