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First-line afatinib for advanced *EGFR*m + NSCLC: Analysis of long-term responders in the LUX-Lung 3, 6, and 7 trials

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ABSTRACT

Objectives: In patients with advanced epidermal growth factor receptor mutation-positive (*EGFR*m +) non-small cell lung cancer (NSCLC), first-line afatinib significantly improved progression-free survival (PFS) and objective response vs. platinum-doublet chemotherapy in the phase III LUX-Lung 3 and LUX-Lung 6 trials, and significantly improved PFS, time to treatment failure and objective response vs. gefitinib in the phase IIb LUX-Lung 7 trial. We report post-hoc analyses of efficacy, safety and patient-reported outcomes (PROs) in afatinib long-term responders (LTRs) in these trials.

Methods: Treatment-naïve patients with stage IIIB/IV *EGFR*m + NSCLC randomized to afatinib in LUX-Lung 3/LUX-Lung 6/LUX-Lung 7 were included in the analysis. Patients treated with afatinib for ≥ 3 years were defined as LTRs.

Results: In LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, 24/229 (10%), 23/239 (10%) and 19/160 (12%) afatinib-treated patients were LTRs. Baseline characteristics were similar to the study populations, except for the proportions of women (LUX-Lung 3/LUX-Lung 6 only; 92/78% vs. 64% overall) and Del19-positive patients (63–79% vs. 49–58% overall). Median treatment duration among LTRs was 50, 56 and 42 months, and median PFS was 49.5, 55.5, and 42.2 months in LUX-Lung 3/LUX-Lung 6/LUX-Lung 7, respectively. Median overall survival could not be estimated. Frequency of afatinib dose reduction was consistent with the LUX-Lung 3/LUX-

*Abbreviations: EGFR*m + , epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; PFS, progression-free survival; LTR, long-term responder; PRO, patient-reported outcome; OS, overall survival; TKIs, tyrosine kinase inhibitors; QoL, quality of life; AE, adverse event; Del19, exon 19 deletion; TTF, time to treatment failure; RECIST, Response Evaluation Criteria in Solid Tumors; EORTC, European Organization for Research and Treatment of Cancer; GH, global health; PF, Performance Functioning; EQ, EuroQol; VAS, Visual Analogue Scale; OR, objective response; CR, complete response; PR, partial response; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; SD, stable disease

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Lung 6/LUX-Lung 7 overall populations. PROs were stable in LTRs, with slight improvements after 3 years of afatinib treatment vs. baseline scores.
Conclusions: In the LUX-Lung 3/LUX-Lung 6/LUX-Lung 7 trials, 10–12% of afatinib-treated patients were LTRs. Long-term afatinib treatment was independent of tolerability-guided dose adjustment and had no detrimental impact on safety or PROs.

1. Introduction

Targeted therapeutics have resulted in improved responses in patients with different tumors, with a subset of these patients remaining on such therapies for prolonged periods and achieving long-term progression-free survival (PFS) and overall survival (OS) [1]. These patients, termed 'super-responders' or 'long-term responders' (LTRs), may be heterogeneous in terms of their baseline characteristics [2], spurring interest in determining patient or tumor characteristics that may help identify those individuals most likely to achieve long-term responses.

Among patients with non-small cell lung cancer (NSCLC), the epidermal growth factor receptor (EGFR) represents the most established target for therapy, with mutations in *EGFR* occurring in approximately 50% of Asian patients and 10–15% of Caucasian patients with lung adenocarcinoma [3]. As such, patients with *EGFR* mutation-positive (*EGFR*m +) NSCLC are highly sensitive to EGFR-targeted therapy. While most patients treated with EGFR tyrosine kinase inhibitors (TKIs) eventually experience disease progression within 8–19 months after starting treatment [4], some patients can remain on treatment and achieve very durable responses, remaining on treatment for years. Currently, data on clinical outcomes in patients with long-term responses to EGFR TKIs are limited, and this is further complicated by the varying definitions of a long-term response in different studies [5–7]. Importantly, identifying demographic and/or clinical characteristics that may predict long-term response to therapy could be instrumental in determining optimal treatment strategies for individual patients.

Several EGFR TKIs provide marked efficacy benefits as first-line therapy in patients with *EGFR*m + NSCLC, with long-term responses occurring in some patients. These agents include the first-generation reversible TKIs, erlotinib and gefitinib; the irreversible second-generation ErbB family blockers, afatinib and dacomitinib; and the third-generation EGFR-wild-type sparing, irreversible EGFR/T790 M inhibitor, osimertinib [8–18]. Recent data from the phase III LUX-Lung 3 and LUX-Lung 6 trials showed that treatment with afatinib resulted in significantly improved OS compared to platinum-based chemotherapy in patients with exon 19 deletion (Del19) mutations [19]. In addition, the LUX-Lung 7, ARCHER-1050 and FLAURA trials have demonstrated that second- and third-generation TKIs provide superior outcomes to first-generation TKIs [16–18]. Treatment with dacomitinib improved OS compared to gefitinib in the first-line setting in the ARCHER 1050 trial [20]. In contrast to the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials [14–16], the ARCHER 1050 trial excluded patients with brain metastases [17], limiting the generalizability of the OS data in a patient population where brain metastases are common [21].

We conducted this post-hoc analysis of LTRs in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials who have been treated with afatinib for at least 3 years to identify baseline characteristics associated with long-term treatment with afatinib, and to assess efficacy outcomes, long-term tolerability of afatinib treatment and its impact on quality of life (QoL), and patient-reported outcomes (PROs). In addition, we aimed to evaluate the impact of long-term afatinib treatment on use of subsequent therapies.

2. Methods

2.1. Study designs and patients

Details of the study designs, patient eligibility criteria and primary analyses for LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 have been published previously [14–16]. Briefly, treatment-naïve patients with stage IIIB/IV adenocarcinoma of the lung and confirmed *EGFR* mutations were enrolled in LUX-Lung 3 (NCT00949650; n = 345; global; any *EGFR* mutations), LUX-Lung 6 (NCT01121393; n = 364; China, Korea and Thailand; any *EGFR* mutations) and LUX-Lung 7 (NCT01466660; n = 319; global; only Del19 or L858R *EGFR* mutations). Patients with clinically asymptomatic and controlled brain metastases (defined as stable for at least 4 weeks and/or asymptomatic and/or not requiring treatment with anticonvulsants or steroids and/or no leptomeningeal disease) were included. Stratification factors included *EGFR* mutation type (Del19 vs. L858R [and vs. other 'uncommon' mutations in LUX-Lung 3 and LUX-Lung 6]), race (Asian vs. non-Asian; LUX-Lung 3 only), and brain metastases (presence vs. absence; LUX-Lung 7 only).

2.2. Study treatment

Patients were randomized (LUX-Lung 3/LUX-Lung 6 2:1; LUX-Lung 7 1:1) to receive oral afatinib (starting dose 40 mg/day) or intravenous pemetrexed/cisplatin (LUX-Lung 3), gemcitabine/cisplatin (LUX-Lung 6), or oral gefitinib (LUX-Lung 7) at standard doses. Treatment with afatinib continued until investigator-assessed disease progression, intolerable adverse events (AEs), or other reasons. In LUX-Lung 7 only, treatment beyond radiological progressive disease was allowed if deemed beneficial by the treating physician.

Dose escalation to 50 mg was allowed during the first treatment cycle, in the absence of grade > 1 treatment-related AEs. In case of grade ≥ 3 or selected, prolonged grade 2 treatment-related AEs, the afatinib dose was interrupted for up to 14 days. Upon recovery to grade 1 or baseline severity, afatinib was re-instated at a reduced dose (10 mg decrements to a minimum of 20 mg/day).

2.3. Endpoints and assessments

The primary endpoint in LUX-Lung 3 and LUX-Lung 6 was PFS by independent review, whereas LUX-Lung 7 included three co-primary endpoints: PFS, time to treatment failure (TTF), and OS. Other key endpoints and assessments included overall response rate, disease control rate, PROs and safety. Tumor responses were assessed according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1); AEs were categorized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. PROs were measured using the European Organization for Research and Treatment of Cancer (EORTC) Global Health Status/QoL (GH) scale and the EORTC Performance Functioning (PF) scale in LUX-Lung 3 and LUX-Lung 6, and the EuroQol (EQ) Visual Analogue Scale (VAS) and EQ5D UK utility score (EQ UK utility) self-assessment questionnaire in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7. For LUX-Lung 3 and LUX-Lung 6, PROs were completed at random assignment and every 3 weeks until treatment termination. For LUX-Lung 7, PROs were completed at random assignments and every 8 weeks until week 64 and then every 12 weeks until treatment termination.

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

2.4. Analysis of LTRs

All patients randomized to afatinib 40 mg/day in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 were included in the analysis; treatment in LUX-Lung 3 and LUX-Lung 6 was maintained until disease progression, while in LUX-Lung 7, treatment continued until disease progression, or beyond if deemed beneficial by the investigator. LTRs were defined as patients who received afatinib treatment for at least 3 years; this time period was selected because PFS (LUX-Lung 3 and LUX-Lung 6) and TTF (LUX-Lung 7) curves reached a plateau at around 36 months (Supplementary Fig.1). Data cut-offs were March 25 2016 for LUX-Lung 3 and LUX-Lung 6, and July 26 2016 for LUX-Lung 7 (March 25 2016 for AE data).

To identify possible factors predictive of long-term exposure to afatinib, a post-hoc analysis of LTRs to afatinib was conducted; the following factors were assessed: baseline demographics/disease characteristics, total treatment duration, survival outcomes (PFS and OS), best overall tumor responses, and duration of response. Incidence, intensity, and onset of selected AEs (diarrhea, rash/acne, and stomatitis; all grouped terms) among LTRs were analyzed; these AEs were chosen because they were the most common treatment-related AEs with afatinib in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials [14–16]. Afatinib dose reductions and final treatment doses, and subsequent anticancer therapies were also evaluated. Changes in PROs over time were analyzed using mixed-effects growth curve models. The estimated mean profile over time for each PRO endpoint was described using a piecewise linear model. For LUX-Lung 3 and LUX-Lung 6, the PRO data were pooled, and the models allowed the slope to change at 48 and 105 weeks; a term indicating the study (LUX-Lung 3 or LUX-Lung 6) the PRO data came from was included in the model. For LUX-Lung 7, the models allowed the slope to change at 48 and 100 weeks. The plotted mean profiles were examined for evidence of long-term treatment having any adverse effect on patients' QoL.

Descriptive statistics were calculated, with quantitative variables expressed as medians and ranges.

3. Results

3.1. Patients and treatment duration

The recruitment periods were August 2009 to February 2011 for LUX-Lung 3, April 2010 to November 2011 for LUX-Lung 6, and December 2011 to August 2013 for LUX-Lung 7 [14–16]. Twenty-four of 229 afatinib-treated patients (10%) in LUX-Lung 3, 23 of 239 patients (10%) in LUX-Lung 6, and 19 of 160 patients (12%) in LUX-Lung 7 were LTRs (Supplementary Fig. 1). At the time of data analysis (49.5, 40.9, and 35.6 months after the data cut-offs from the primary study analysis for LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively) [14–16], the median duration of afatinib treatment in LTRs was 50 (range 41–73), 56 (37–68), and 42 months (37–50) in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively. Eight LTRs in LUX-Lung 7 received afatinib beyond radiological progression, according to the judgement of the investigator; per protocol, no patients received afatinib beyond progression in the LUX-Lung 3 and LUX-Lung 6 studies. In LUX-Lung 7, 4% of gefitinib-treated patients were LTRs; the median treatment duration in these patients was 46.7 months (range 37.0–52.5). Further analysis demonstrated that, in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively, 47/46/45 patients (21%/19%/28%) received afatinib for at least 2 years, and 34/32/25 patients (15%/13%/16%) for at least 2.5 years. At data cut-off, 29 of 66 afatinib-treated LTRs (44%) were still receiving treatment (6 [25%], 9 [39%], and 14 [74%] from LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively). This included 6 of 8 LTRs from LUX-Lung 7 who received afatinib beyond progression. A total of 37 LTRs had discontinued afatinib.

Baseline characteristics of LTRs to afatinib were generally consistent with those of the overall study populations (Table 1). In each study, the proportion of patients with Del19 mutations was slightly higher among the LTRs (63–79%) than in the overall population (49–58%). In LUX-Lung 3 and LUX-Lung 6 only, the proportion of women was slightly higher among the LTRs (92%/78%) than in the overall population (64%/64%). Baseline brain metastases were present in 4–11% of LTRs compared with 11–16% in the overall populations. Eight percent of LTRs in LUX-Lung 3, and 4% in LUX-Lung 6, had tumors harboring uncommon *EGFR* mutations (LUX-Lung 3: S768I [2 patients]; LUX-Lung 6: G719X [1 patient]), compared with 11% in the overall populations in either study.

3.2. Efficacy outcomes

Median PFS (by investigator assessment) in LTRs to afatinib was 49.5, 55.5, and 42.2 months, in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively. Median follow-up time for the analysis of OS for afatinib-treated LTRs was 64.6, 57.0, and 42.1 months in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7; median OS could not be estimated due to the small numbers of deaths in these subgroups. PFS, OS and treatment duration for individual LTRs are shown in Fig. 1.

Best objective response (OR) and maximum tumor shrinkage in LTRs are shown in Fig. 2. Across all three trials, 5 (8%) LTRs had a complete response (CR), 47 (71%) had a partial response (PR) and 9 (14%) had stable disease. Response was not evaluable in 5 (8%) LTRs. Median duration of OR was 34.5 months (range 15.0–42.8) in LUX-Lung 3, 28.3 months (4.2–37.3) in LUX-Lung 6, and 19.4 months (7.4–33.0) in LUX-Lung 7. Supplementary Table 1 shows treatment outcomes according to different baseline demographic and clinical characteristics. No major differences in efficacy outcomes were identified across patient subgroups with respect to gender (except for PFS in LUX-Lung 6: male: 41.3 months; female: 54.3 months), age (except for PFS in LUX-Lung 3: 65 years: 57.4 months; < 65 years: 46.3 months), race (Asian vs. non-Asian), Eastern Cooperative Oncology Group performance status (ECOG PS), *EGFR* mutation status (Del19 vs. L858R vs. other). While the number of LTRs with brain metastases was low in all three studies, there were no apparent differences in median PFS, OS, or duration of response according to the presence or absence of brain metastases (data not shown).

3.3. Safety and dose adjustment

Among afatinib-treated LTRs in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, the frequencies of treatment-related grade 3 diarrhea, rash/acne, and stomatitis were 25%/13%/37%, 21%/13%/16%, and 17%/0%/5%, respectively. Treatment-related AEs generally occurred soon after treatment onset (median 4.5–7 days for diarrhea, 17.5–24 days for rash/acne and 7–31.5 days for stomatitis; Table 2). There were no treatment-related discontinuations due to these AEs.

Dose modifications and duration on each dose for each LTR are shown in Fig. 3. The frequency of tolerability-guided afatinib dose reduction was broadly consistent with that in the overall populations in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 (LTRs: 75%/39%/53%; overall population: 52%/28%/42%, in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, respectively). In most patients, the dose was adjusted within 6 months of starting treatment. Final afatinib doses of 20/30/

Table 1
Baseline characteristics in LTRs and the overall LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 populations.

Characteristic	LUX-Lung 3		LUX-Lung 6		LUX-Lung 7	
	LTRs (n = 24)	Overall population [14] (n = 230)	LTRs (n = 23)	Overall population [15] (n = 242)	LTRs (n = 19)	Overall population [16] (n = 160)
Median age, years (range)	64 (42–74)	62 (28–86)	64 (38–77)	58 (49–65)	65 (42–79)	63 (30–86)
≥ 65 years, n (%)	11 (46)	90 (40) [34]	11 (48)	66 (27) [34]	10 (53)	72 (45) [35]
Gender, n (%)						
Male	2 (8)	83 (36)	5 (22)	87 (36)	9 (47)	69 (43)
Female	22 (92)	147 (64)	18 (78)	155 (64)	10 (53)	91 (57)
Race, n (%)						
Asian	16 (67)	165 (72)	23 (100)	242 (100)	8 (42)[a]	94 (59)[a]
Non-Asian	8 (33)	65 (29)	0 (0)	0 (0)	10 (53)[a]	49 (31)[a]
Smoking status, n (%)						
Never smoked	20 (83)	155 (67)	20 (87)	181 (75)	12 (63)	106 (66)
Current/ex-smoker	4 (17)	75 (33)	3 (13)	61 (25)	7 (37)	53 (34)
Baseline ECOG PS, n (%)						
0	18 (75)	92 (40)	8 (35)	48 (20)	7 (37)	51 (32)
1	6 (25)	138 (60)	15 (65)	194 (80)	12 (63)	109 (68)
NSCLC stage, n (%)						
IIIB	1 (4)	20 (9)	3 (13)	16 (7)	1 (5)	8 (5)
IV	23 (96)	210 (91)	20 (87)	226 (93)	18 (95)	152 (95)
Brain metastases[b], n (%)						
Present	1 (4)[b]	20 (11)[b]	2 (9)[b]	28 (13)[b]	2 (11)	26 (16)
Absent	22 (92)[b]	166 (89)[b] [36]	20 (87)[b]	185 (87)[b] [36]	17 (89)	134 (84)
EGFR mutation, n (%)						
Del19	15 (63)	113 (49)	15 (65)	124 (51)	15 (79)	93 (58)[c]
L858R	7 (29)[d]	91 (40)	7 (30)	92 (38)	4 (21)	67 (42)
Uncommon	2 (8)[d]	26 (11)	1 (4)	26 (11)	–	–

Del19: exon 19 deletion, ECOG PS: Eastern Cooperative Oncology Group performance status, *EGFR*: epidermal growth factor receptor, LTRs: long-term responders, NSCLC: non-small cell lung cancer.
[a] Missing for 17 patients in LUX-Lung 7, including one LTR (patients recruited in French sites did not have their ethnic origin recorded).
[b] Unknown for 21 patients (including one LTR) in LUX-Lung 3, and 3 patients (including one LTR) in LUX-Lung 6.
[c] One patient in the afatinib group with wild-type *EGFR* was included in the trial in error and was reported as exon 19 deletion at the time of randomization.
[d] One patient had L858R and uncommon mutations.

40/50 mg were received by 50%/25%/21%/4% of LTRs in LUX-Lung 3, 13%/22%/61%/4% in LUX-Lung 6, and 32%/21%/47%/0% in LUX-Lung 7.

3.4. PROs

PRO questionnaire completion was high in all three studies (97% for LUX-Lung 3, 92% for LUX-Lung 6, 88% for LUX-Lung 7). The longitudinal analysis of the PROs for the afatinib-treated LTRs in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 produced estimated mean profiles over time which are shown in Fig. 4. Among LTRs, the estimated mean profiles of QoL measured by EORTC GH, EORTC PF, EQ VAS and EQ5D UK utility index appears to be stable from about 48 weeks to about 156 weeks, with slight improvements observed after approximately 3 years of afatinib treatment vs. the start of treatment.

3.5. Subsequent therapy

Thirty-seven patients discontinued afatinib, the majority of whom (86%) discontinued due to disease progression according to RECIST; other reasons for discontinuation included 1 patient in LUX-Lung 3 who discontinued due to AE (non-treatment related), 1 patient in LUX-Lung 6 refused medication, 1 patient in LUX-Lung 6 died due to disease progression, and 1 patient in LUX-Lung 7 had worsening of their underlying tumor. Among LTRs with baseline brain metastases, 2 patients discontinued due to disease progression; at the time of analysis, treatment was ongoing in the remaining 3 patients.

Of the 37 LTRs who had discontinued afatinib, 14/18 (78%) in LUX-Lung 3, 4/14 (29%) in LUX-Lung 6, and 4/5 (80%) in LUX-Lung 7 received subsequent anticancer therapy; of these, 55%, 27%, and 18% had received 1, 2 or at least 3 lines of subsequent therapy. Details of subsequent use of systemic anticancer therapies by afatinib LTRs are shown in Supplementary Table 2.

4. Discussion

In this post-hoc analysis, we identified a subgroup of patients who received prolonged treatment (≥ 3 years) with first-line afatinib. These LTRs benefited from long-term clinical activity with median PFS in excess of 3.5 years; over three quarters of these patients had an OR, the duration of which was impressive (19.4–34.5 months). Importantly, long-term treatment with afatinib was tolerable and manageable; most grade ≥ 3 AEs occurred during early treatment cycles and were managed on-treatment by utilizing a tolerability-guided dose reduction protocol. None of the LTRs had to discontinue treatment due to treatment-related AEs, and the frequency of dose reductions was consistent with the overall patient populations. Also, long-term treatment did not have any adverse effect on patients' QoL. Finally, LTRs were generally sufficiently fit to be eligible for at least one further line of treatment following afatinib. Overall, these findings suggest that a substantial proportion of patients can achieve a favorable and sustained long-term benefit with afatinib. In the absence of head-to-head data comparing afatinib with third-generation EGFR TKIs, these data suggest that the sequential use of long-term afatinib followed by a third-generation TKI may be feasible in patients with *EGFR*m + NSCLC.

There are limited data assessing long-term response to second-/third-generation EGFR TKIs in *EGFR*m + NSCLC. Moreover, differing definitions of long-term response have been used to generate

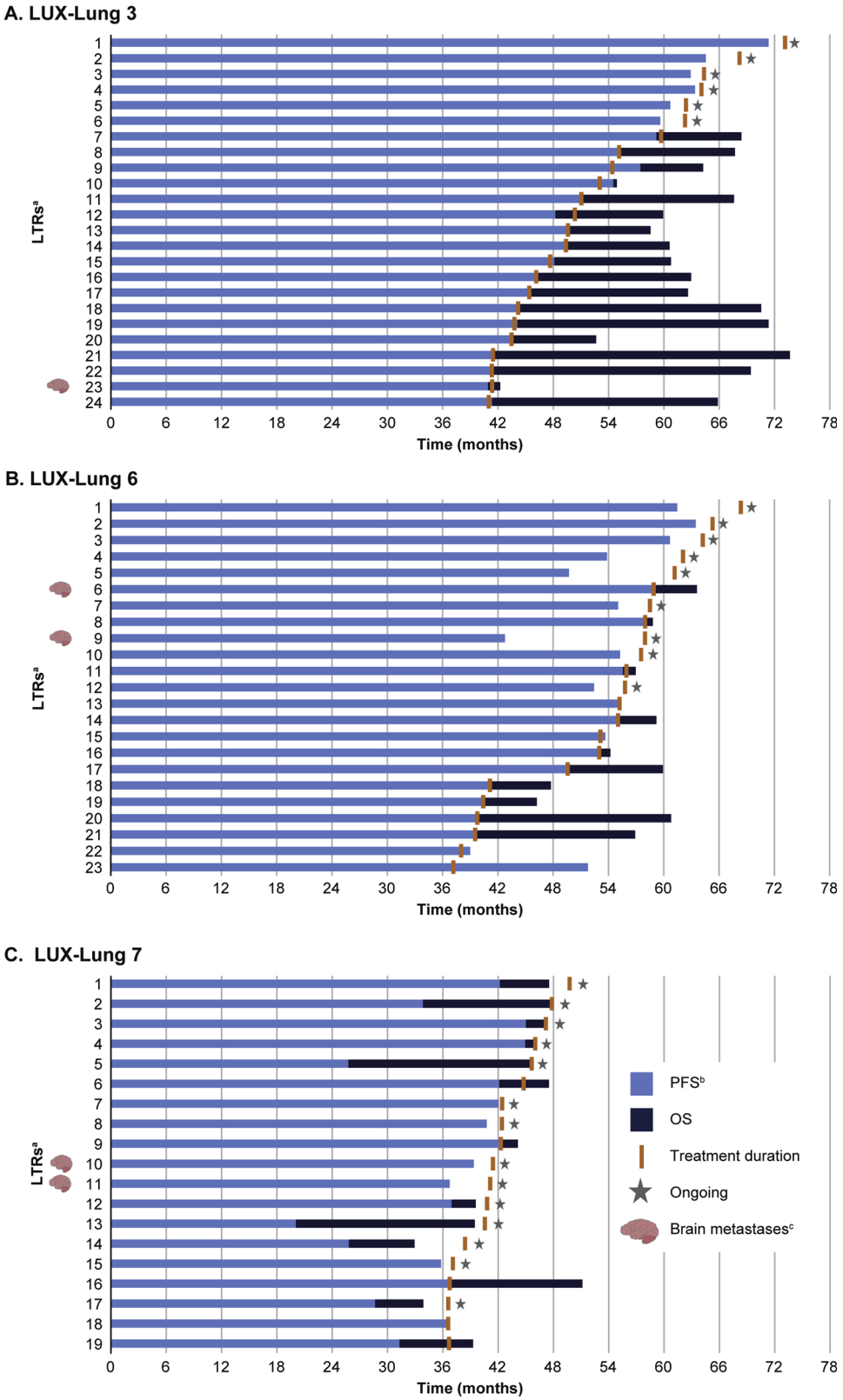

Fig. 1. Total afatinib treatment duration, OS and PFS in afatinib-treated LTRs from LUX-Lung 3 (A), LUX-Lung 6 (B) and LUX-Lung 7 (C).
LTRs: long-term responders, OS: overall survival, PFS: progression-free survival.
[a]Patients were ordered and numbered by treatment duration, with Patient 1 being on treatment longest.
[b]Investigator assessment.
[c]At the time of enrolment.

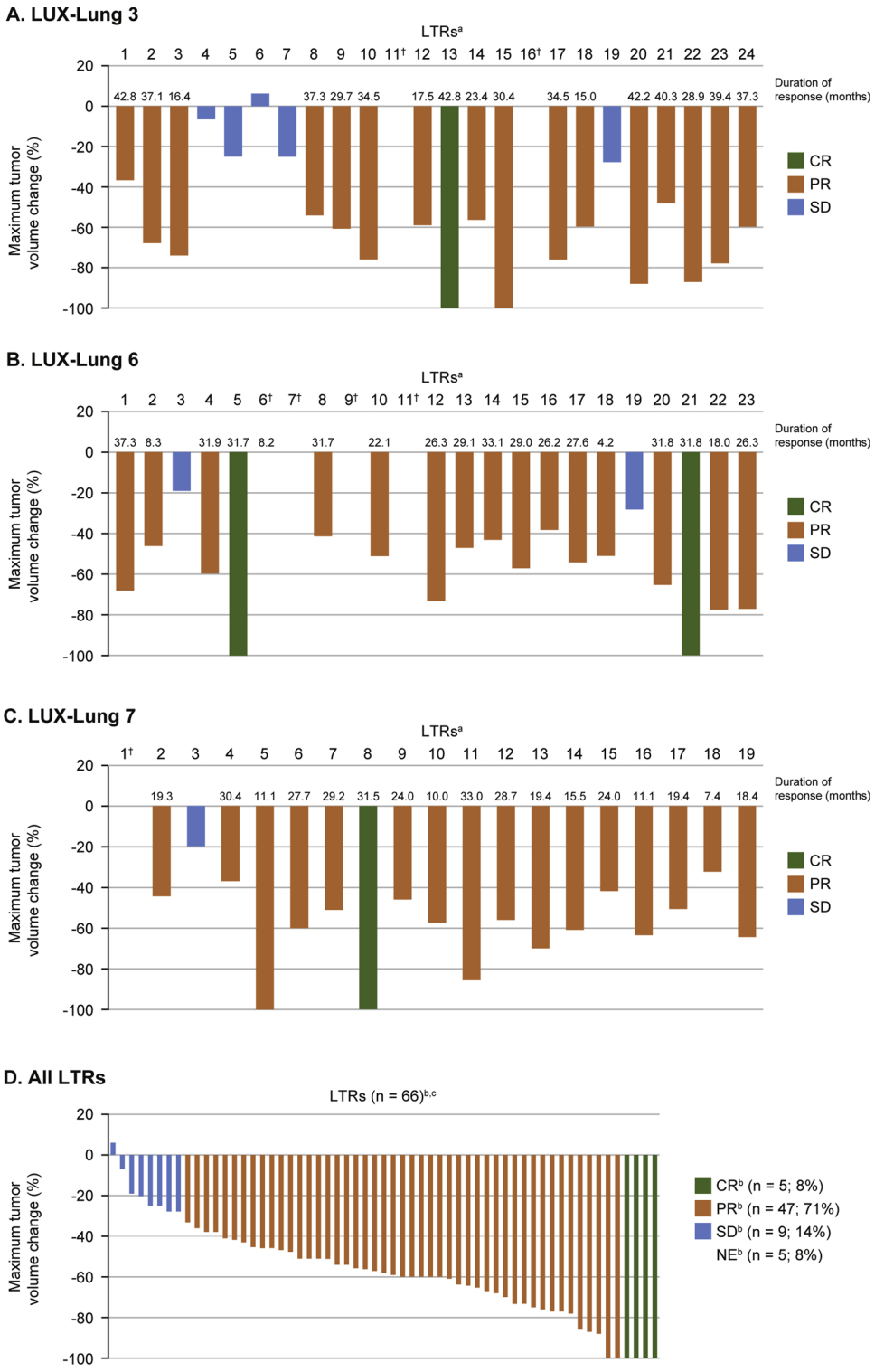

Fig. 2. Outcomes in LTRs to afatinib. Maximum tumor shrinkage, best overall response, and duration of response in LTRs from LUX-Lung 3 (A), LUX-Lung 6 (B), LUX-Lung 7 (C) and all three trials (D). CR: complete response, LTRs: long-term responders, NE: not evaluable, PR partial response, SD: stable disease.

[a]Patients ordered and numbered by treatment duration, with Patient 1 being on treatment longest.

[b]Change in tumor volume not available for 7 patients (LUX-Lung 3: Patients 11 and 16 were NE; LUX-Lung 6: Patient 6 had a CR and Patients 7, 9, and 11 were NE; LUX-Lung 7: Patient 1 had SD).

[c]Patients ordered by maximum percentage decrease in the sum of target lesion diameters from baseline.

the available data for first-generation TKIs. For example, some investigators defined LTRs as patients who achieved at least stable disease for > 6 months following treatment with gefitinib or erlotinib [5,6]. Conversely, in a recent expanded access program (EAP) study of 430 patients treated with gefitinib, 4% were considered LTRs because they received a minimum duration of 2 years of therapy [7]. Two other EAP studies found that 6.3% and 1.0% of patients were LTRs, respectively, when this group was defined in both studies as those treated with gefitinib for more than, or at least, 3 years [22,23]. In our analysis of LUX-Lung 7, 4% of gefitinib-treated patients received treatment for ≥ 3 years and were regarded as LTRs. Regardless of differences in the definition of LTRs, these studies indicate that LTRs to first-generation EGFR TKIs appear to be relatively rare. This may explain the perception that while targeted therapies are often associated with immediate

Table 2
Summary of overall safety in LTRs in the LUX-Lung trials.

Patients, n (%)	Diarrhea			Rash/acne			Stomatitis		
	LUX-Lung 3 (n = 24)	LUX-Lung 6 (n = 23)	LUX-Lung 7 (n = 19)	LUX-Lung 3 (n = 24)	LUX-Lung 6 (n = 23)	LUX-Lung 7 (n = 19)	LUX-Lung 3 (n = 24)	LUX-Lung 6 (n = 23)	LUX-Lung 7 (n = 19)
Treatment-related AEs	24 (100)	20 (87)	19 (100)	24 (100)	22 (96)	18 (95)	24 (100)	12 (52)	14 (74)
Treatment-related grade 3 AEs	6 (25)	3 (13)	7 (37)	5 (21)	3 (13)	3 (16)	4 (17)	0 (0)	1 (5)
Dose reduction due to AEs	6 (25)	3 (13)	8 (42)	8 (33)	3 (13)	5 (26)	6 (25)	0 (0)	1 (5)
Median time to onset, days (range)	5 (1–1405)	4.5 (1–625)	7 (1–193)	23 (1–1652)	24 (3–787)	17.5 (2–703)	7 (4–727)	31.5 (4–979)	15 (3–549)

AE: adverse event, LTRs: long-term responders.

responses, these are not considered durable. Nevertheless, a recent analysis of long-term (> 10 years) safety and survival data from the IRESSA Clinical Access Program found that a subset of 75 patients continuing long-term gefitinib treatment (median duration 11.1 years) experienced excellent long-term safety, with 10- and 15-year survival rates of 86% and 59%, respectively [24]. This, together with the findings of the current analysis, suggests that outcomes can be favorable with both first- and second-generation EGFR TKIs for patients classed as LTRs. Of note, the immuno-oncology agents that have been introduced in the treatment of several cancers (including lung cancer, albeit they are not recommended for TKI-naïve *EGFR*m + NSCLC) are associated with long-term survival in less than 20% of NSCLC patients when used as monotherapy in unselected patients [25–28]. Our analysis suggests that afatinib results in around 10% of patients achieving long-term clinical benefit (≥ 3 year PFS and OS), which is greater than that observed with first-generation EGFR-TKIs but slightly lower than the long-term survival rate observed with immuno-oncology agents for second/higher line treatment of patients without actionable mutations.

While this study indicates that approximately 10% of patients treated with afatinib are likely to be LTRs, we were unable to identify any baseline clinical or tumor characteristics that could potentially identify patients most likely to achieve long-term benefit. The baseline characteristics of afatinib LTRs were generally comparable with those of the overall afatinib-treated groups in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 studies. The frequency of Del19 mutation-positive NSCLC was slightly higher among LTRs, presumably reflecting its known status as an indicator of improved outcomes with EGFR TKIs vs. other mutation types [29,30]. Importantly, other factors, such as presence of brain metastases or uncommon mutations, did not preclude long-term response to afatinib. These findings are consistent with previous analyses of LUX-Lung 3 and 6 that showed that afatinib can provide clinical benefit in advanced NSCLC patients with brain metastases or uncommon mutations [31,32]. In our analysis, the proportion of LTRs with brain metastases at enrolment was slightly less than in the overall study populations. Nevertheless, some patients with brain metastases at baseline (across all 3 trials) were able to obtain long-term clinical benefit with afatinib. Furthermore, previous analyses of patients with tumors harboring uncommon mutations in LUX-Lung 3 and 6 showed that afatinib demonstrated activity in certain uncommon mutation types [32]. We also noted that LTRs in LUX-Lung 3 and 6 included patients with NSCLC harboring uncommon mutations (specifically, S768I, or G719X mutations). Our analysis of molecular factors predictive of long-term response is limited because tumor tissue or plasma samples were not collected at baseline or at the time of progression. As such, it was not possible to identify potential molecular biomarkers indicative of long-term response to afatinib.

Safety analysis in this post-hoc analysis focused on AEs that were most frequently reported in afatinib-treated patients in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials (diarrhea, rash/acne, and stomatitis). The incidence and onset of these AEs among LTRs was consistent with previously reported findings for the overall afatinib treatment groups in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 [14–16]. Since only selected AEs were evaluated, we cannot conclude from this analysis whether other safety signals were more or less frequent in LTRs. Afatinib-related AEs have previously been shown to be effectively managed with supportive care and tolerability-guided dose adjustment [33]. The frequency of dose reductions with afatinib due to treatment-related AEs was similar between the LTRs and the overall afatinib treatment groups in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 [14–16]. Among the LTRs to afatinib, dose reductions tended to occur early in the treatment course (most within 6 months of initiating treatment). Previous analyses have shown that tolerability-guided dose adjustment of afatinib does not impact efficacy [33] and our analysis indicates that tolerability-guided dose adjustment does not prevent a patient from having a long-term response. Indeed, some LTRs had their dose reduced to 20 mg shortly after initiation of treatment but obtained long-term clinical benefit with afatinib. This highlights the importance of determining a tolerable dose for each patient on a case-by-case basis. The long-term tolerability of afatinib was further substantiated by assessment of PROs in afatinib LTRs. PRO scores in afatinib-treated LTRs remained stable, and were slightly improved after approximately 3 years of treatment compared with the scores at treatment initiation. Again, this is consistent with data from the overall populations of LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, which showed that afatinib was associated with clinically relevant improvements in QoL and lung cancer symptoms [14–16].

In the current analysis of LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, long-term treatment with afatinib had no detrimental impact on the use of subsequent treatments. As in the overall populations of LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7, patients were able to receive a variety of subsequent treatment options, including chemotherapy and/or other EGFR TKIs. The rates of subsequent therapy uptake were lowest in LUX-Lung 6 (29%), which may be due to reimbursement and availability of specific drugs in the countries involved in the study. Duration of subsequent treatment also appeared similar to the overall LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 populations. When looking at subsequent treatments in the individual trials, it is of note that most afatinib LTRs in LUX-Lung 7 (74%) were still on afatinib treatment at the time of analysis, so have not yet received any subsequent treatment. Following recent progress in our understanding of resistance mechanisms to afatinib, it is now clear that the emergence of the *T790M* mutation is as common in afatinib-treated patients (50–70%) as it is in those receiving erlotinib or gefitinib [4]. In principal, therefore, the majority of LTRs to first-line afatinib would be fit enough, and eligible for, subsequent

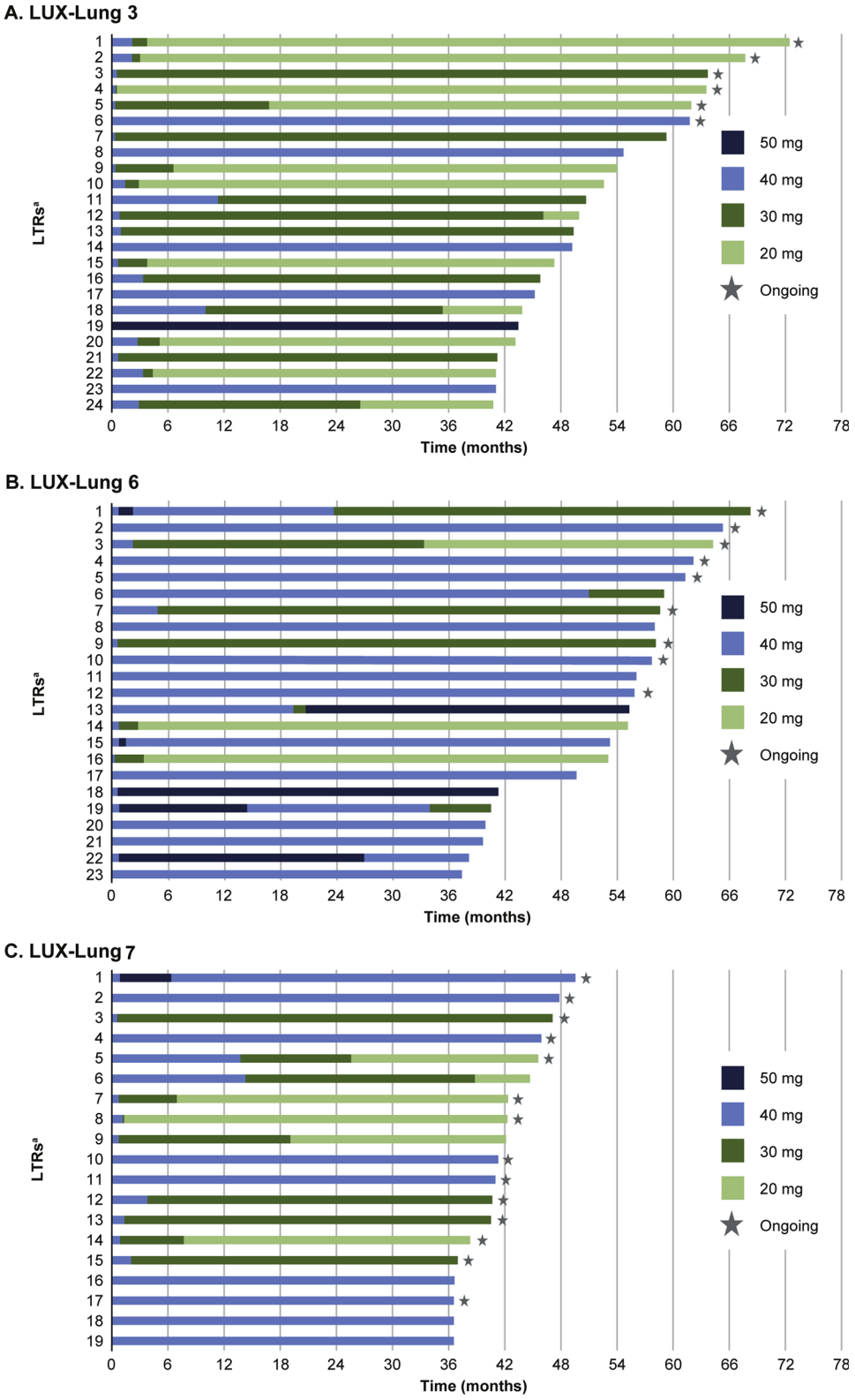

Fig. 3. Treatment duration and tolerability-guided dose adjustments in LTRs. LTRs: long-term responders.
[a]Patients were ordered and numbered by treatment duration, with Patient 1 being on treatment longest.

treatment with osimertinib. In this study, few LTRs had received osimertinib. This reflects the fact it has only recently been approved in this indication, based on the AURA and AURA3 trials [34,35].

Overall, the results of this analysis suggest that around 10% of patients with *EGFR*m + advanced NSCLC who receive first-line afatinib can achieve long-term clinical benefit, defined by the authors as continuous afatinib treatment for a period ≥ 3 years. We were unable to identify any patient or tumor characteristics that appeared to predict

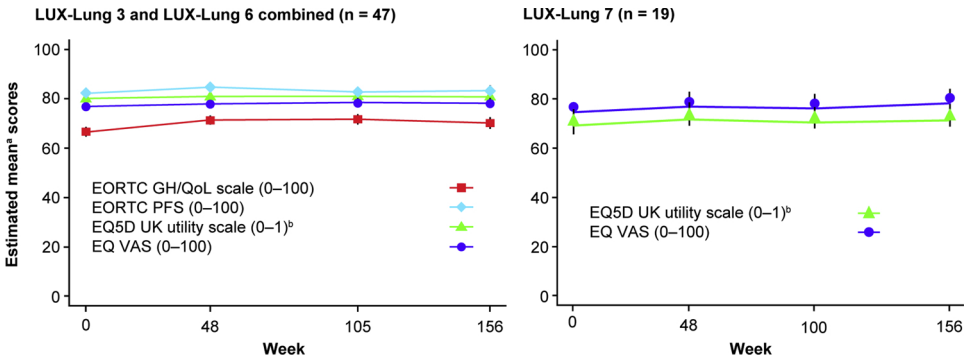

Fig. 4. Patient-reported outcomes in LTRs. EORTC: European Organization for Research and Treatment of Cancer, EQ: EuroQol, GH, global health, LTRs: long-term responders, PF: Performance Functioning, QoL: quality of life, VAS: Visual Analogue Scale.
[a]Estimated mean (± standard error) from a longitudinal model.
[b]EQ5D utility scores were scaled from (0–1) to (0–100).

long-term response. Nevertheless, known indicators of poor prognosis, including presence of brain metastases at baseline or uncommon *EGFR* mutations, did not appear to preclude prolonged treatment. Long-term clinical benefit with afatinib was independent of tolerability-guided dose adjustment and was achieved without negatively impacting safety or PROs. Further studies to identify markers/characteristics that can predict long-term response to afatinib are warranted.

Author contribution statement

MS and AM: contributed towards study conception and design. All authors contributed towards data collection, analysis, and interpretation. All authors contributed towards writing and revision of the manuscript, are fully responsible for all content and editorial decisions, and have approved the final version.

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Data sharing statement

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

Conflict(s) of interest

MS reports being a compensated consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, and Roche; honoraria for CME presentations from Abbvie, Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, MSD, Novartis, and Pierre Fabre; research funding to the institution from AstraZeneca, Boehringer Ingelheim, Bristol Myers-Squibb, and Novartis.

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WT reports employment from Boehringer Ingelheim.

AM reports employment from Boehringer Ingelheim.

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JC-HY reports personal fees from Boehringer Ingelheim, Eli Lilly, Roche/Genentech, Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, Bristol-Myers Squibb, Ono Pharmaceuticals, Daiichi Sankyo, AstraZeneca, Hansoh Pharmaceuticals, and Takeda Pharmaceuticals.

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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.2019.04.006.

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