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Effect of dose adjustment on the safety and efficacy of afatinib for *EGFR* mutation-positive lung adenocarcinoma: *post hoc* analyses of the randomized LUX-Lung 3 and 6 trials

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Background: Afatinib 40 mg/day is approved for first-line treatment of *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). In the case of drug-related grade ≥3 or selected prolonged grade 2 adverse events (AEs), the dose can be reduced by 10 mg decrements to a minimum of 20 mg. Here, we evaluate the influence of afatinib dose reduction on AEs, pharmacokinetics and progression-free survival (PFS) in the phase III LUX-Lung 3 and 6 (LL3/6) trials.

Patients and methods: Treatment-naïve patients with advanced *EGFR* mutation-positive NSCLC in LL3 (global) and LL6 (China, Thailand, South Korea) were randomized to afatinib or chemotherapy. All afatinib-treated patients (LL3, $n = 229$; LL6, $n = 239$) were included in the *post hoc* analyses. Incidence and severity of common AEs before and after afatinib dose reduction were assessed. Afatinib plasma concentrations were compared in patients who reduced to 30 mg versus those remaining at 40 mg. PFS was compared between patients who dose reduced within the first 6 months of treatment and those who did not.

Results: Dose reductions occurred in 53.3% (122/229) and 28.0% (67/239) of patients in LL3 and LL6, respectively; most (86.1% and 82.1%) within the first 6 months of treatment. Dose reduction led to decreases in the incidence of drug-related AEs, and was more likely in patients with higher afatinib plasma concentrations. On day 43, patients who dose reduced to 30 mg ($n = 59$) had geometric mean afatinib plasma concentrations of 23.3 ng/ml, versus 22.8 ng/ml in patients who remained on 40 mg ($n = 284$). The median PFS was similar in patients who dose reduced during the first 6 months versus those who did not {LL3: 11.3 versus 11.0 months [hazard ratio (HR) 1.25]; LL6: 12.3 versus 11.0 months (HR 1.00)}.

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Conclusions: Tolerability-guided dose adjustment is an effective measure to reduce afatinib-related AEs without affecting therapeutic efficacy.

Clinical trial registration: Clinicaltrials.gov identifiers: NCT00949650 and NCT0112393.

Key words: afatinib, NSCLC, EGFR, first-line, phase III, dose

introduction

Epidermal growth factor receptor (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC) can be treated effectively with EGFR-targeted therapy. First-line treatments include reversible EGFR tyrosine kinase inhibitors (TKI), erlotinib or gefitinib, or the irreversible ErbB family blocker afatinib [1]. Afatinib inhibits signaling from all homo/heterodimers formed by ErbB receptors (EGFR, human epidermal growth factor receptor 2, ErbB3 and ErbB4) [2].

All three agents have shown improvements in progression-free survival (PFS) and objective response rates (ORR) versus chemotherapy for first-line treatment of advanced *EGFR* mutation-positive NSCLC [3–11]. Additionally, afatinib improved overall survival (OS) in patients with *EGFR* Del19 mutation-positive disease in pre-specified analyses of the phase III LUX-Lung 3 and 6 trials (LL3/6) [12]. This OS improvement has not been observed with erlotinib or gefitinib [13]. Furthermore, in a global randomized phase IIb trial, first-line afatinib significantly improved PFS, time to treatment failure and ORR versus gefitinib in *EGFR* mutation-positive NSCLC patients [14].

These agents have well-defined adverse event (AE) profiles, which are consistent with their mode of action. Key treatment-related AEs include diarrhea, rash/acne, stomatitis and nail effects, some of which (e.g. diarrhea) appear to be more pronounced with afatinib [15]. However, these AEs are predictable and manageable with supportive care and treatment interruptions and/or dose modifications [15]. When choosing first-line treatment, it is important to consider the risk–benefit profile of individual agents, including the impact of management strategies and options to address interpatient variability. There are established protocols for dose modification of afatinib and erlotinib, and dose interruption of gefitinib, based on patient tolerability. For afatinib, the approved starting dose is 40 mg/day. Dose escalation is permitted in the absence of grade >1 treatment-related AEs in the first 21-day cycle. In the case of grade ≥3 or selected, prolonged grade 2 treatment-related AEs, the afatinib dose should be interrupted. Upon recovery to grade 1 or baseline, afatinib should be re-started at a reduced dose (10 mg decrements to a minimum of 20 mg/day) [16].

We assessed the impact of tolerability-guided afatinib dose adjustment on the incidence and severity of AEs, pharmacokinetics and PFS in *post hoc* analyses of the LL3 and LL6 trials.

methods

study design and patients

Study designs and eligibility criteria for both trials have been published [10, 11]. Briefly, LL3 (global) and LL6 (China, South Korea, Thailand) were open-label, phase III randomized trials which enrolled patients with stage IIIB/IV, *EGFR* mutation-positive NSCLC, measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1, Eastern Cooperative Oncology Group performance status of 0/1 and a life expectancy of ≥3 months.

The primary end point of both trials (previously reported) was independently assessed PFS; secondary end points included objective response and disease control and their duration, OS, patient-reported outcomes, safety and pharmacokinetics.

Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocols were approved by local ethics committees at each center. All patients provided written informed consent.

treatment

Patients were randomized (2:1) to oral afatinib 40 mg/day or up to six cycles of cisplatin-based chemotherapy (full dosing and schedule previously reported [10, 11]), stratified by *EGFR* mutation type (Del19/L858R/other) and race (Asian/non-Asian; LL3 only).

Afatinib dose escalation to 50 mg/day was permitted after the first 21-day cycle in the absence of grade >1 treatment-related AEs. In the case of the following treatment-related AEs: any grade ≥3 AE, prolonged grade 2 diarrhea, grade 2 nausea or vomiting for ≥7 days despite supportive care or grade ≥2 worsening renal function, treatment was interrupted for up to 14 days until severity reduced to grade 1 or baseline, and then resumed at a lower dose (10 mg decrements to a minimum of 20 mg).

assessments

AE grade (according to the National Cancer Institute for Common Terminology Criteria for Adverse Events version 3.0) and relation to treatment was assessed by the investigator. Tumor assessments were carried out (computed tomography or magnetic resonance imaging) every 6 weeks for the first 48 weeks and every 12 weeks thereafter until disease progression or start of new anticancer therapy. For afatinib-treated patients, blood samples were taken on day 22 (course 2, day 1), day 29 (course 2, day 8) and day 43 (course 3, day 1). Afatinib plasma concentrations were analyzed by validated high performance liquid chromatography tandem mass spectrometry.

post hoc analyses

All afatinib-treated patients in LL3 and LL6 were included in the analyses. For patients with afatinib dose reductions, frequency and severity of the most common AEs pre- and post-reduction from 40 mg were analyzed. Pharmacokinetic data (combined to increase sample size) collected at day 22 and as part of the final standard visit schedule (day 43) were used to compare plasma concentrations in patients who dose adjusted to 30 or 50 mg versus those remaining on 40 mg. PFS (at primary analysis) was compared between patients who dose reduced to <40 mg within the first 6 months of treatment (time period when most dose reductions occur) and those who remained on afatinib ≥40 mg/day. The Kaplan–Meier estimates were used to construct survival curves and calculate the median PFS; a Cox proportional-hazard model was used to derive hazard ratios (HRs) and 95% confidence intervals (CIs) comparing patients with or without dose reduction. Treatment groups were compared using a log-rank test. All other analyses were descriptive.

results

patients

Of 229 and 239 afatinib-treated patients in LL3 and LL6, respectively (supplementary Figure S1, available at *Annals of Oncology* online), dose reductions occurred in 122 (53.3%) and 67 (28.0%) patients, most occurring within the first 6 months of treatment (86.1% and 82.1%).

Dose escalations occurred in 16 of 229 (7.0%) and 38 of 239 (15.9%) patients in LL3 and LL6, respectively. Of 21 patients receiving afatinib 50 mg in LL3 (5 erroneously starting afatinib 50 mg and 16 escalated to 50 mg), 6 and 3 patients, respectively, were still on 50 mg at weeks 24 and 48. Of 38 patients receiving afatinib 50 mg in LL6, 19 and 12 were still receiving 50 mg at weeks 24 and 48.

Baseline demographics of patients with or without dose reductions within the first 6 months of treatment are shown in Table 1. Generally, dose reductions occurred more frequently in females and those with lower body weight (<50 kg) in both trials. In LL3, reduction was more frequent in older patients (≥65 years) and patients from Japanese sites.

The median body mass index (BMI) and body surface area (BSA) appeared similar between those who dose reduced and those who did not (Table 1); however, analysis of final afatinib dose by baseline BSA suggested those with lower BSA were more likely to have dose reduction. Final afatinib doses for those with baseline BSA <1.8 versus ≥1.8 m^2 in LL3 were 50 mg (2.7% versus 7.3%), 40 mg (38.3% versus 65.9%), 30 mg (40.4% versus 17.1%) and 20 mg (18.6% versus 9.8%), with a less pronounced difference observed in LL6: 50 mg (8.2% versus 9.4%), 40 mg (62.3% versus 71.9%), 30 mg (25.1% versus 15.6%) and 20 mg (4.3% versus 3.1%). Baseline BMI did not appear to be associated with substantial differences in final afatinib doses in LL3 (data not shown). In LL6, while the percentage of patients receiving afatinib 50 and 20 mg as their final dose was similar in those with BMI <25 versus ≥25 kg/m^2 (50 mg: 8.3% versus 8.7%; 20 mg: 4.1% versus 4.3%), there were differences among those receiving afatinib 40 mg (60.6% versus 76.1%) or 30 mg (26.9% versus 10.9%) as their final dose.

treatment exposure

Among patients with dose reductions from 40 mg in LL3 ($n = 122$), the median (range) total treatment time was 371.0

Table 1. Baseline demographics of patients in LUX-Lung 3 and LUX-Lung 6 based on afatinib dose level during the first 6 months of treatment

Parameter	LUX-Lung 3		LUX-Lung 6	
	<40 mg in first 6 months ($n = 105$)	≥40 mg in first 6 months ($n = 124$)	<40 mg in first 6 months ($n = 55$)	≥40 mg in first 6 months ($n = 184$)
Gender, *n* (%)				
Male	25 (23.8)	57 (46.0)	16 (29.1)	71 (38.6)
Female	80 (76.2)	67 (54.0)	39 (70.9)	113 (61.4)
Age, *n* (%)				
<65 years	55 (52.4)	84 (67.7)	39 (70.9)	136 (73.9)
≥65 years	50 (47.6)	40 (32.3)	16 (29.1)	48 (26.1)
Race, *n* (%)				
White	21 (20.0)	40 (32.3)	0	0
Asian–Japanese sites	33 (31.4)	21 (16.9)	0	0
Asian–non-Japanese sites	50 (47.6)	61 (49.2)	55 (100.0)	184 (100.0)
Other	1 (1.0)	2 (1.6)	0	0
Smoking status, *n* (%)				
Never smoked	74 (70.5)	80 (64.5)	40 (72.7)	138 (75.0)
Ex-smoker	30 (28.6)	40 (32.3)	13 (23.6)	31 (16.8)
Currently smokes	1 (1.0)	4 (3.2)	2 (3.6)	15 (8.2)
Weight category, *n* (%)				
<50 kg	29 (27.6)	16 (12.9)	12 (21.8)	20 (10.9)
≥50 kg	76 (72.4)	108 (87.1)	43 (78.2)	164 (89.1)
ECOG PS, *n* (%)				
0	40 (38.1)	52 (41.9)	13 (23.6)	35 (19.0)
1	65 (61.9)	72 (58.1)	42 (76.4)	149 (81.0)
Body mass index, kg/m^2 [median (range)]	23.5 (16.8–37.3)	23.5 (16.4–40.4)	21.8 (16.0–28.7)	23.2 (15.0–30.0)
Body surface area, m^2 [median (range)]	1.6 (1.2–2.1)	1.7 (1.1–2.3)	1.5 (1.4–2.1)	1.6 (1.3–2.0)
EGFR mutation type, *n* (%)				
Del19	55 (52.4)	57 (46.0)	30 (54.5)	94 (51.1)
L858R	44 (41.9)	47 (37.9)	20 (36.4)	69 (37.5)
Other	6 (5.7)	20 (16.1)	5 (9.1)	21 (11.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

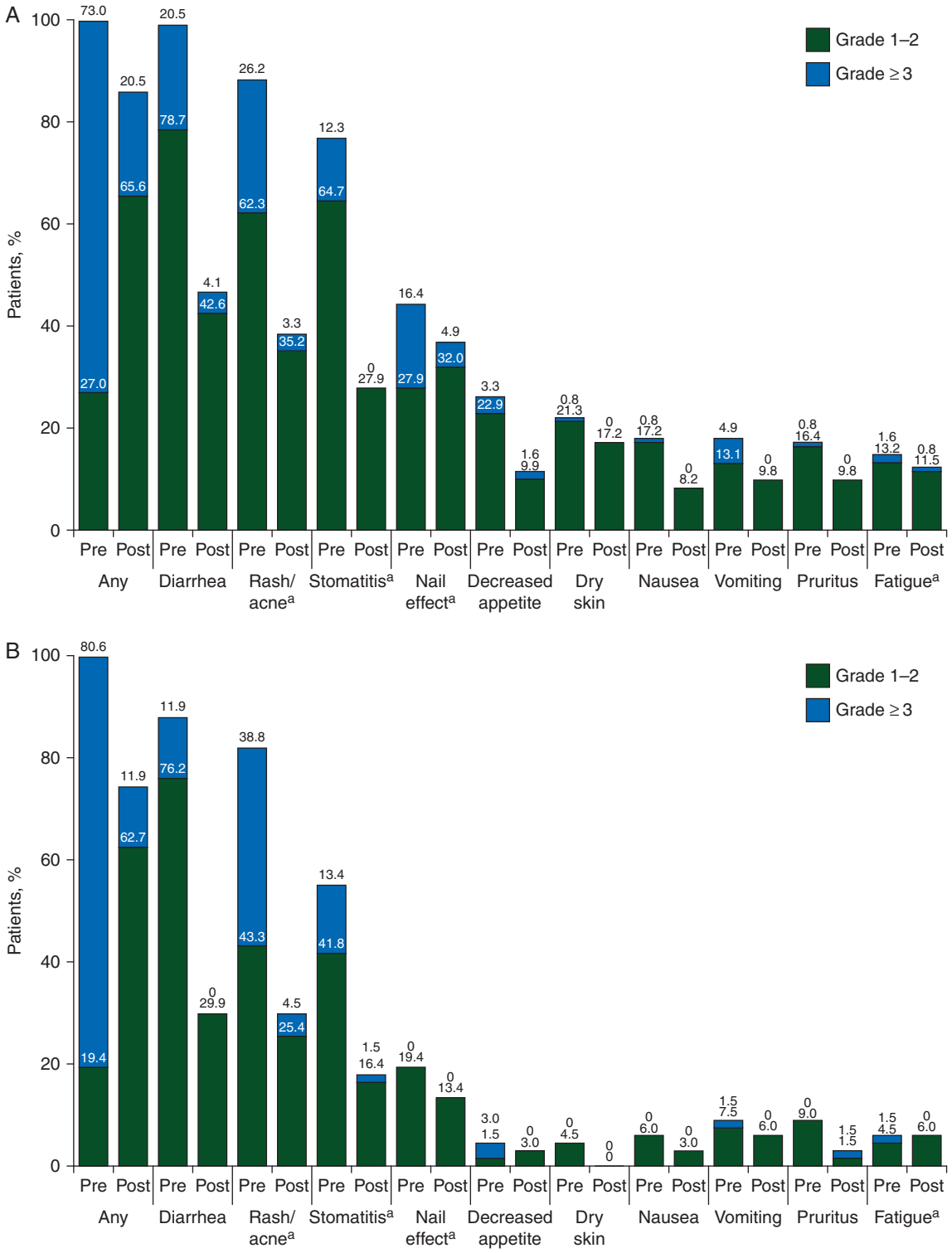

Figure 1. Most common treatment-related AEs pre- and post-afatinib dose reduction in patients in (A) LUX-Lung 3 and (B) LUX-Lung 6. [a]A grouped term; AEs, adverse events.

(28–827) days, versus 294.0 (7–827) days for those who remained on afatinib ≥40 mg ($n = 107$). In LL6, the median (range) total treatment time was 428.0 (42–832) days in patients with dose reductions ($n = 67$) versus 336.5 (3–871) days for those who remained on ≥40 mg ($n = 172$).

treatment-related AEs

Among patients who dose reduced to <40 mg in LL3, all patients (122; 100%) experienced treatment-related AEs before reduction; 89 (73.0%) experienced grade ≥3 treatment-related AEs. The most common all-grade treatment-related AEs were

diarrhea (121; 99.2%), rash/acne (108; 88.5%), stomatitis (94; 77.0%) and nail effects (54; 44.3%). Following dose reduction, treatment-related AE incidence decreased (105; 86.1%), with fewer patients experiencing grade ≥3 treatment-related AEs (25; 20.5%) (Figure 1; supplementary Table S1, available at *Annals of Oncology* online).

In LL6, all patients who dose reduced (67; 100%) experienced treatment-related AEs before reduction; 54 (80.6%) experienced grade ≥3 treatment-related AEs. The most common all-grade treatment-related AEs were diarrhea (59; 88.1%), rash/acne (55; 82.1%) and stomatitis (37; 55.2%). After dose reduction, fewer patients experienced treatment-related AEs (50; 74.6%); only 8 (11.9%) experienced grade ≥3 treatment-related AEs (Figure 1; supplementary Table S1, available at *Annals of Oncology* online).

pharmacokinetic analyses

Afatinib trough plasma concentrations with the 40 mg dose were higher at day 22 among patients who subsequently dose reduced to 30 mg versus those who remained on 40 mg [geometric mean (geometric coefficient of variation; gCV%) 45.6 (54.6) ng/ml versus 24.3 (65.0) ng/ml], with similar concentrations observed between the groups on day 43 [23.3 (60.1) ng/ml versus 22.8 (66.9) ng/ml; Figure 2]. Pharmacokinetic data were combined to increase sample size; however, these effects were observed in both individual trials (BI data on file) [17].

For those who dose escalated to 50 mg, there was some indication that initially these patients had below-average exposure with afatinib 40 mg at day 22 [20.3 ng/ml (78.3); Figure 2]. Tolerability-guided dose escalation to 50 mg after the first treatment cycle slightly increased exposure by day 43, although still within the range of patients who did not undergo dose escalations [24.2 ng/ml (63.0)].

efficacy

The median PFS was similar in patients who dose reduced during the first 6 months of afatinib treatment and those who did not: 11.3 versus 11.0 months [HR 1.25 (95% CI 0.91–1.72), $P = 0.175$; Figure 3A] in LL3, and 12.3 versus 11.0 months [HR 1.00 (0.69–1.46), $P = 0.982$; Figure 3B] in LL6.

No significant differences in PFS according to baseline BSA or BMI were observed in LL3 [BSA ≥1.8 versus <1.8 m^2: HR 1.16 (0.77–1.75); BMI ≥25 versus <25 kg/m^2: HR 0.88 (0.63–1.24)]. In LL6, PFS did not differ according to baseline BSA [HR 1.09 (0.69–1.72)]; there was a slight trend toward improved PFS among those with BMI ≥25 versus <25 kg/m^2 [13.8 versus 10.8 months; HR 0.66 (0.43–1.01)]. Of note, sample sizes were small for analyses by BSA and BMI, limiting conclusions.

discussion

Post hoc analyses from LL3 and LL6 suggest that tolerability-guided dose adjustment of afatinib is an effective measure to reduce treatment-related AEs, as well as reduce interpatient variability of afatinib exposure, without affecting treatment efficacy.

Analysis of baseline characteristics of patients who dose reduced versus those who did not suggested that reductions

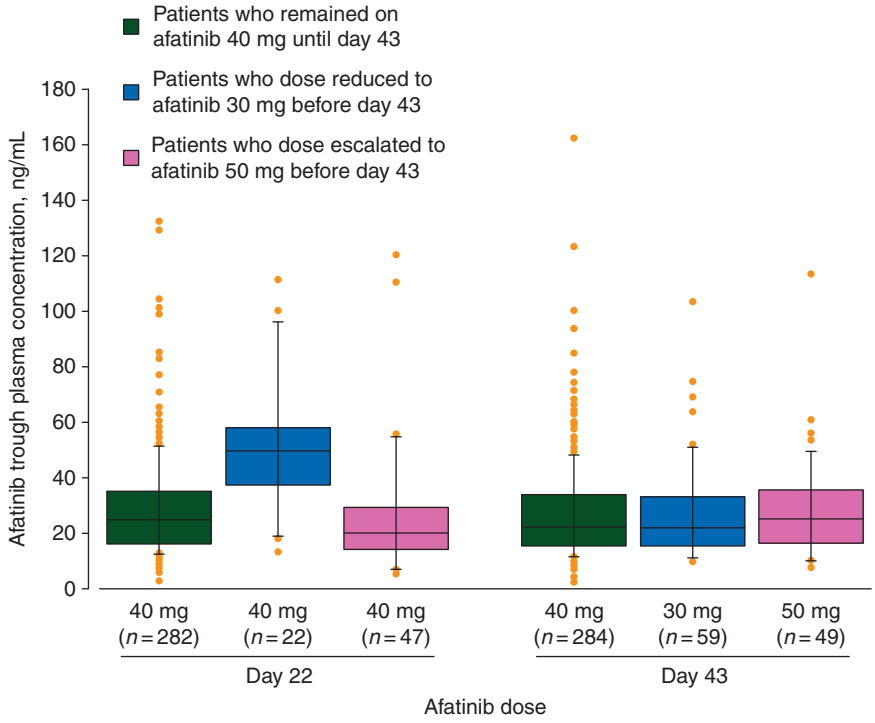

Figure 2. Comparison of trough plasma concentrations on day 22 and day 43 in patients remaining on afatinib 40 mg, dose reducing to 30 mg or dose-escalating to 50 mg in combined analyses of LUX-Lung 3 and LUX-Lung 6. Boxes represent the median and interquartile range; the whiskers represent the 10th and 90th percentiles and the dots show data points outside percentiles. For patients who dose reduced to afatinib 30 mg before day 43 ($n = 59$), only 22 had valid trough concentrations for afatinib 40 mg at day 22 [the rest had either no pharmacokinetics sampling at this time ($n = 15$), were already receiving afatinib 30 mg at day 22 ($n = 14$) or were excluded from the analysis due to invalid sampling ($n = 8$)].

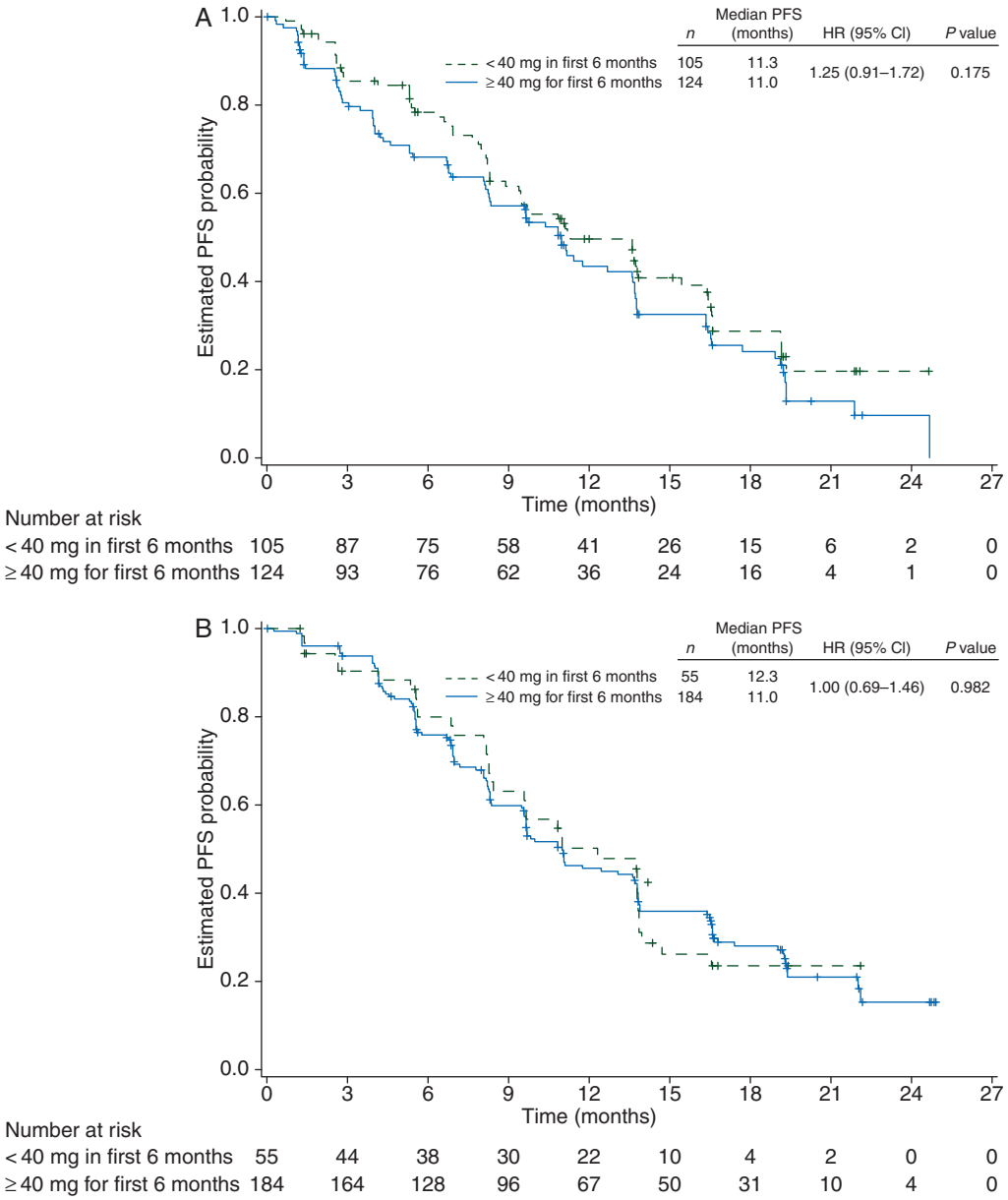

Figure 3. PFS in patients who had dose reductions within the first 6 months and those who remained on afatinib ≥40 mg once daily in (A) LUX-Lung 3 and (B) LUX-Lung 6. CI, confidence interval; PFS, progression-free survival.

occurred more frequently in females and those with lower body weight in both trials, and in older patients (≥65 years) and patients from Japanese sites in LL3. This might be partially explained by increased afatinib plasma exposure in these patients, as gender and body weight were previously identified as covariates for exposure [18]. In line with this, pharmacokinetic analyses suggested that dose reductions tended to occur in patients who had higher initial afatinib plasma concentrations, with tolerability-guided dose modification reducing excessive afatinib exposure. However, conclusions of the pharmacokinetic analysis should be treated with caution due to sparse pharmacokinetic sampling and small sample sizes. Of note, the difference in overall dose reduction frequency between the LL3 and LL6 studies may, in part, reflect the different ethnicities of the enrolled patients, as LL6 consisted of patients enrolled exclusively from Asian sites, compared with the global population enrolled in LL3. In this context, the LL3 population consisted of 24% Japanese patients, for which dose reductions occurred more frequently. It is important to note that adaptation of the approved afatinib starting dose based on clinical characteristics is not recommended as there are no data to support this. Even those who are eventually dose reduced may need the higher starting dose as an initial boost. Furthermore, under-dosing could not be excluded, even if patients were clinically selected for an adapted starting dose. As acknowledged in the current Summary of Product Characteristics, patients at higher risk of AEs, including females and those with lower body weight or underlying renal impairment, should be monitored carefully [16].

As expected, tolerability-guided dose adjustment reduced the incidence and severity of afatinib-related AEs, resulting in low

treatment discontinuation rates due to AEs in LL3 (8%) and LL6 (6%) [10, 11]. Although most dose reductions (>80%) occurred during the first 6 months of treatment, the median total time on treatment among those who dose reduced was >1 year. Furthermore, total time on treatment was numerically longer in patients with dose reductions in each trial than those who remained on ≥40 mg. Importantly, patients who dose reduced demonstrated similar PFS (>11 months) to those who did not. There were also no significant differences in PFS based on baseline BSA or BMI in either study. Similarly, a phase II study assessing the effect of malnutrition and BSA on afatinib-related AEs found that PFS was not significantly different in patients with or without dose reduction [median 9.2 versus 14.6 months ($P = 0.337$)] [19]. Overall, these findings suggest that tolerability-guided dose modification does not affect the efficacy of afatinib and, once the dose has been optimized for the individual patient, substantial clinical benefit is obtained.

Previous analyses have suggested that the severity of certain EGFR TKI-associated AEs, particularly skin rash, may be correlated with improved tumor response and survival in *EGFR* mutation-positive NSCLC patients treated with erlotinib [20]. Similar analyses have been conducted for afatinib and results were previously reported [21]. In combined analyses of patients in LL3 and LL6, no statistically significant association was observed between the severity of common treatment-related AEs observed with afatinib, namely diarrhea or rash/acne, and PFS; however, there was a trend toward longer PFS in patients experiencing grade ≥2 AEs during the first month of treatment [21].

Erlotinib and gefitinib are also administered using a fixed dose for all patients, with dose reductions or interruptions permitted in the case of AEs. However, the impact of dose reduction/interruption on safety and efficacy in erlotinib- and gefitinib-treated patients has not been investigated in prospective studies. There are some smaller, single-center studies which also suggest that age may be associated with dose reduction in these agents. For example, a study of patients aged ≥80 years ($n = 21$) receiving erlotinib or gefitinib at full starting doses showed that >70% required dose reduction due to AEs [22]. In a single-center, retrospective analysis assessing patterns of erlotinib dosing, baseline characteristics were similar between those receiving full dose ($n = 172$) versus reduced dose ($n = 34$), aside from age and performance status [23]. Of note, patients characterized as receiving reduced dose were initiated at the reduced dose rather than dose-reduced based on tolerability. The lower starting dose did not significantly affect efficacy, although PFS was numerically shorter [median 8.8 versus 11.2 months (HR 0.75; $P = 0.14$) among patients starting at a reduced versus full dose] [23]. Other retrospective analyses reported that erlotinib dose reduction or gefitinib dose interruption (e.g. dosing every other day) did not adversely affect efficacy [24–26].

Overall, our analysis provides a comprehensive assessment of the impact of tolerability-guided afatinib dose adjustment on AEs, pharmacokinetics and PFS within two prospective, randomized trials and is strengthened by the large sample size and inclusion of patients from multiple sites/countries. Limitations include the *post hoc* nature of the analysis and high number of patients from Asia included; it will be important to assess if our conclusions are generalizable across a broader population.

In conclusion, tolerability-guided dose adjustment of afatinib reduced the incidence and severity of treatment-related AEs without affecting efficacy, allowing patients to continue effective therapy while obtaining clinical benefit.

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disclosure

JC-HY has participated in advisory boards and received honoraria from Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, AstraZeneca, Astellas, Bayer, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology and Celgene. LVS has participated in advisory boards for Boehringer Ingelheim, AstraZeneca, Clovis, Novartis, Merrimack, Genentech, Ariad and Taiho. CZ has participated in advisory boards and received honoraria from Boehringer Ingelheim, AstraZeneca and Eli Lilly and has also received honoraria from Roche. MSc is employed by the University Duisberg-Essen, University Hospital Essen, Ruhrlandklinik. He has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly and Novartis and received honoraria from Alexion, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Lilly, Novartis and Pfizer. He has also conducted corporate-sponsored research for Boehringer Ingelheim, Bristol Myers-Squibb and Novartis and has patents with the Universität Duisberg-Essen. SLG is employed by Prince of Songkla University and has participated in advisory boards for Novartis and Boehringer Ingelheim. He has conducted corporate-sponsored research (with funds received by his institute) for Novartis, AstraZeneca, Boehringer Ingelheim, Eisai, Teva and Roche and has received honoraria from AstraZeneca. TM is employed by The Chinese University of Hong Kong and reports stock ownership/options in Sanomics Ltd. He has received honoraria and participated in advisory boards for AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, Boehringer Ingelheim, Merck Serono, MSD, Janssen, Clovis Oncology, BioMarin, GlaxoSmithKline, Novartis, SFJ Pharmaceutical, ACEA Biosciences, Inc., Vertex Pharmaceuticals, Bristol-Myers Squibb, AVEO and Biodesix. He has also received honoraria from Prime Oncology and Amgen and participated in advisory boards for geneDecode Co., Ltd. He has conducted corporate-sponsored research for AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, SFJ Pharmaceutical, Roche, MSD, Clovis Oncology

and Bristol-Myers Squibb. He is a member of the Board of Directors for IASLC, Chinese Lung Cancer Research Foundation Ltd, Chinese Society of Oncology and the Hong Kong Cancer Therapy Society. NY has received honoraria, participated in advisory boards and conducted corporate-sponsored research for Boehringer Ingelheim. KOB has received consultation fees from Pfizer, Roche, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Lilly Oncology and Novartis and has received honoraria for participation in a company speaker bureau from Pfizer, Roche, AstraZeneca, Lilly Oncology and Boehringer Ingelheim. He also owns stock in CARP Pharmaceuticals and Bluesky Biosciences. Through his organization of the Brisbane Cancer Conference each year he raises ~USD 100K in total from pharmaceutical and biotechnology sponsors including AstraZeneca, Roche, MSD, Bristol-Myers Squibb, Astellas, Boehringer Ingelheim, Celgene, Ipsen, Janssen, Lilly Oncology, Merck, Novartis, Pfizer, Takeda, Illumina and Thermofisher. VH has received honoraria for advisory boards from Boehringer Ingelheim, Roche, AstraZeneca, Pfizer, Merck, Amgen and Novartis. MSe has participated in advisory boards and received honoraria from Boehringer Ingelheim, Pfizer, Roche, AstraZeneca, and Novartis. IO has received honoraria from Boehringer Ingelheim. ND has received honoraria, participated in advisory boards and conducted corporate-sponsored research for Boehringer Ingelheim, Bristol-Myers Squibb, Roche, Lilly, AstraZeneca and Pfizer. RS has participated in advisory boards for Boehringer Ingelheim, Lilly, Pfizer, Pierre Fabre, AstraZeneca, MSD, Bristol-Myers Squibb, Ariad, Clovis, Novartis, Roche and Celgene. AM, DM and SW are employees of Boehringer Ingelheim. Y-LW has received speaker fees from AstraZeneca, Roche, Eli Lilly and Sanofi. All remaining authors have declared no conflicts of interest.

references

1. Sebastian M, Schmittel A, Reck M. First-line treatment of EGFR-mutated nonsmall cell lung cancer: critical review on study methodology. Eur Respir Rev 2014; 23: 92–105.
2. Solca F, Dahl G, Zoephel A et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. J Pharmacol Exp Ther 2012; 343: 342–350.
3. Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735–742.
4. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13: 239–246.
5. Wu YL, Zhou C, Liam CK et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 2015; 26: 1883–1889.
6. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947–957.
7. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380–2388.
8. Mitsudomi T, Morita S, Yatabe Y et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121–128.
9. Han JY, Park K, Kim SW et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012; 30: 1122–1128.
10. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327–3334.
11. Wu YL, Zhou C, Hu CP et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 213–222.
12. Yang JC, Wu YL, Schuler M et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16: 141–151.
13. Lee C, Davies LC, Wu YL et al. The impact on overall survival (OS) of first-line gefitinib (G) and erlotinib (E) and of clinical factors in advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor mutations (EGFR mut) based on meta-analysis of 1,231 patients (pts) enrolled in 6 major randomized trials. J Clin Oncol 2015; 33: 8072.
14. Park K, Tan EH, O'Byrne K et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016; 17: 577.
15. Califano R, Tariq N, Compton S et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. Drugs 2015; 75: 1335–1348.
16. Giotrif 40 mg film-coated tablets—Summary of Product Characteristics. 2014. http://www.giotrif.com/content/dam/internet/pm/giotrif1/com_EN/images/newone/european.pdf (29 June 2016, date last accessed).
17. Yang JC-H, Ahn M-J et al. Influence of dose adjustment on afatinib safety and efficacy in patients (pts) with advanced EGFR mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC). J Clin Oncol 2015; 33(15 Suppl): 8073.
18. Freiwald M, Schmid U, Fleury A et al. Population pharmacokinetics of afatinib, an irreversible ErbB family blocker, in patients with various solid tumors. Cancer Chemother Pharmacol 2014; 73: 759–770.
19. Arrieta O, De la Torre-Vallejo M, Lopez-Macias D et al. Nutritional status, body surface, and low lean body mass/body mass index are related to dose reduction and severe gastrointestinal toxicity induced by afatinib in patients with non-small cell lung cancer. Oncologist 2015; 20: 967–974.
20. Fiala O, Pesek M, Finek J et al. Skin rash as useful marker of erlotinib efficacy in NSCLC and its impact on clinical practice. Neoplasma 2013; 60: 26–32.
21. Yang JC, Sequist L, O'Byrne K et al. Epidermal growth factor receptor (EGFR)-mediated adverse events in patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) treated with afatinib. Eur J Cancer 2013; 49(Suppl. 2): 895.
22. Nakao M, Muramatsu H, Sone K et al. Epidermal growth factor receptor-tyrosine kinase inhibitors for non-small-cell lung cancer patients aged 80 years or older: a retrospective analysis. Mol Clin Oncol 2015; 3: 403–407.
23. Lampson B, Santos A, Janne P, Oxnard G. Reduced-dose versus full-dose erlotinib for advanced EGFR-mutant non-small cell lung carcinoma (NSCLC): a retrospective analysis. J Clin Oncol 2015; 33(Suppl. 15): 8074.
24. Sato S, Kurishima K, Miyazaki K et al. Efficacy of tyrosine kinase inhibitors in non-small-cell lung cancer patients undergoing dose reduction and those with a low body surface area. Mol Clin Oncol 2014; 2: 604–608.
25. Satoh H, Inoue A, Kobayashi K et al. Low-dose gefitinib treatment for patients with advanced non-small cell lung cancer harboring sensitive epidermal growth factor receptor mutations. J Thorac Oncol 2011; 6: 1413–1417.
26. Sim SH, Keam B, Kim DW et al. The gefitinib dose reduction on survival outcomes in epidermal growth factor receptor mutant non-small cell lung cancer. J Cancer Res Clin Oncol 2014; 140: 2135–2142.

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