Afatinib as First-line Treatment of Older Patients With *EGFR* Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 Trials

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Abstract

There are limited data on the efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in older patients. In these subanalyses of the LUX-Lung 3, 6, and 7 trials, the efficacy of first-line afatinib in older patients with *EGFR* mutation-positive non-small-cell lung cancer was consistent with the overall study populations, with no unexpected safety signals. Progression-free survival was improved versus platinum-doublet chemotherapy (LUX-Lung 3/6) or gefitinib (LUX-Lung 7).

Background: Afatinib is approved in the US, Europe, and several other regions for first-line treatment for epidermal growth factor receptor mutation-positive (*EGFR*m$^+$) non-small-cell lung cancer (NSCLC). **Patients and Methods:** Treatment-naive patients with advanced *EGFR*m$^+$ NSCLC were randomized to afatinib (40 mg/d) versus cisplatin/pemetrexed (LUX-Lung 3 [LL3]) or cisplatin/gemcitabine (LUX-Lung 6 [LL6]), or versus gefitinib (250 mg/d; LUX-Lung 7 [LL7]). We report subgroup analyses according to age, including 65 years or older versus younger than 65 years (preplanned; LL3/LL6) and additional cutoffs up to 75 years and older (exploratory; LL7). Progression-free survival

Presented, in part, at the European Society of Medical Oncology (ESMO) Asia 2015 Congress, Singapore, December 18-21, 2015 (abstract 446P); the 2016 International Association for the Study of Lung Cancer (IASLC) Asia Pacific Lung Cancer Conference, Chiang Mai, Thailand, May 13-15, 2016 (poster PB21); and the 2016 IASLC World Conference on Lung Cancer, Vienna, Austria, December 4-7, 2016 (poster P3.02b-044)

The LUX-Lung trials 3, 6, and 7 are registered at ClinicalTrials.gov: NCT00949650, NCT01121393, NCT01466660, respectively

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Submitted: Nov 8, 2017; Revised: Feb 20, 2018; Accepted: Mar 10, 2018; Epub: Mar 17, 2018

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https://doi.org/10.1016/j.cllc.2018.03.009

(PFS), overall survival (OS), and adverse events (AEs) were evaluated. **Results:** Among the 134 of 345 (39%) and 86 of 364 (24%) patients aged 65 years and older in LL3 and LL6, median PFS was improved with afatinib versus chemotherapy (LL3: hazard ratio [HR], 0.64 [95% confidence interval (CI), 0.39-1.03]; LL6: HR, 0.16 [95% CI, 0.07-0.39]). Afatinib significantly improved OS versus chemotherapy in elderly patients with Del19$^+$ NSCLC in LL3 (HR, 0.39 [95% CI, 0.19-0.80]). Among the 40 of 319 patients (13%) aged 75 years or older in LL7, median PFS (HR, 0.69 [95% CI, 0.33-1.44]) favored afatinib, consistent with the overall population. Afatinib-associated AEs in older patients were consistent with the overall populations. **Conclusions:** Subgroup analyses of the LL3, LL6, and LL7 trials show that afatinib is an effective and tolerable treatment for patients with *EGFR*m$^+$ NSCLC, independent of age.

Clinical Lung Cancer, Vol. 19, No. 4, e465-79

Keywords: EGFR blocker, Elderly, Gefitinib, NSCLC, Tyrosine kinase inhibitor

Introduction

Lung cancer remains the most common malignancy worldwide, most frequently diagnosed in patients aged 65 to 74 years.[1,2] Of the > 1.8 million lung cancer cases diagnosed in 2012, 60% and 32% were patients aged 65 years and older and 75 years and older, respectively.[2] With an ever-increasing population of older lung cancer patients, clinicians are faced with important age-related factors, such as poor functional status, high comorbidity burden, and polypharmacy, which affect treatment decisions.[3-6] Intensive therapy options are often limited in elderly patients with non-small-cell lung cancer (NSCLC). For example, although clinical outcomes with platinum-doublet chemotherapy appear to be comparable in elderly (70 years of age and older) and younger patients who are eligible for treatment,[7] physicians are reluctant to consider such treatment in elderly patients because of toxicity concerns.[6] In the case of epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC, age-related factors might be less of an issue because first-line treatment generally comprises monotherapy with EGFR tyrosine kinase inhibitors (TKIs). However, although these agents are generally associated with manageable tolerability profiles, there are currently no specific recommendations for the use of EGFR TKIs on the basis of patient age.[6,8]

In phase III trials, the first-generation reversible EGFR TKIs, erlotinib[9-11] and gefitinib,[12-14] and the second-generation ErbB family blocker, afatinib,[9,10] have shown superior progression-free survival (PFS) versus platinum-doublet chemotherapy in patients with *EGFR* mutation-positive (*EGFR*m$^+$) NSCLC and is approved in the US, Europe and subsequently other regions. In prespecified analyses of the LUX-Lung 3 (LL3) and LUX-Lung 6 (LL6) trials, afatinib also showed superior overall survival (OS) versus chemotherapy in patients with tumors harboring *EGFR* Del19 mutations.[11] The recent head-to-head randomized trials, LUX-Lung 7 (LL7),[12] ARCHER-1050,[15] and FLAURA[16] have shown that afatinib, dacomitinib, and osimertinib are more active than first-generation EGFR TKIs in a first-line setting. Although data from small early-phase studies, retrospective analyses, and subgroup analyses suggest that all approved, and emerging, EGFR TKIs might be similarly effective and well tolerated in older and younger populations,[17,18] there have been no prospective phase III trials specifically conducted in elderly patients (ie, 65 years or older) in this setting to help drive therapeutic decisions in this subset of patients.[5,19]

To evaluate the effect of advancing age on clinical outcomes and tolerability with first-line afatinib in patients with *EGFR*m$^+$ NSCLC, preplanned subgroup analyses of patients aged years and older and younger than 65 years in LL3 and LL6 were conducted. Additional exploratory analyses on the basis of age cutoffs up to 75 years and older in LL7 were also performed, with a primary focus on the older age subgroup.

Patients and Methods

Patients and Study Designs

Study design and eligibility criteria for the phase III LL3 (NCT00949650) and LL6 (NCT01121393), and phase IIb LL7 (NCT01466660), studies have been published.[20-22] Each study enrolled treatment-naive patients with confirmed *EGFR*m$^+$ (Del19 or L858R in all 3 trials; uncommon *EGFR* mutations were also included in LL3/LL6), stage IIIB/IV NSCLC. In LL3/LL6, patients were randomized (2:1) to oral afatinib (40 mg/d) or up to 6 cycles of chemotherapy (LL3: cisplatin/pemetrexed; LL6: cisplatin/gemcitabine; full dosing and schedules previously reported), stratified according to *EGFR* mutation type (Del19 vs. L858R vs. other "uncommon" mutations) and race (LL3 only; Asian vs. non-Asian). In LL7, patients were randomized (1:1) to afatinib (40 mg/d) or gefitinib (250 mg/d), stratified according to *EGFR* mutation type (Del19 vs. L858R) and baseline brain metastases (presence vs. absence).

The primary end point of LL3/LL6 was PFS (independent central review); OS was a key secondary end point. LL7 had 3 co-primary end points: PFS (independent central review), time to treatment failure, and OS. The primary analyses for each of these end points have been published.[20-24]

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

Subgroup Analyses

All treated patients were included in the analyses. In LL3/LL6, analyses on the basis of an age cutoff of younger than 65 years and 65 years of age and older were prespecified; analyses according to age within mutation subgroups were post hoc. Prespecified analyses on the basis of a 65-year old age cutoff were also conducted in LL7 and have been reported.[21,23] Additional exploratory analyses using age cutoffs of younger than 60, younger than 70, 75 years and older, and younger than 75 years were conducted in LL7 and are reported herein, with a focus on the 75 years of age and older subgroup,

representing the largest cohort of afatinib-treated patients in any LUX-Lung trial in this older age group (Figure 1). Because of different comparators and randomization schemes for LL3, LL6, and LL7 (Figure 1), combined study analyses for age groups were not conducted; findings from each study are reported separately.

Data cutoffs for PFS were at the time of primary PFS analysis for each study (LL3: January 11, 2012; LL6: October 29, 2012; LL7: August 21, 2015)[20-22]; data cutoffs for OS and safety analyses were at the time of primary OS analysis for each study (LL3: November 14, 2013; LL6: December 27, 2013; LL7: April 8, 2016).[23,24] Kaplan–Meier estimates were used to construct survival curves and calculate median PFS and OS. A Cox proportional hazards model was used to derive hazard ratios (HRs) and 95% confidence intervals (CIs); treatment groups were compared using a log rank test. Statistical analyses were performed with SAS (version 9.2 or later; SAS Institute Inc).

Results

Patients

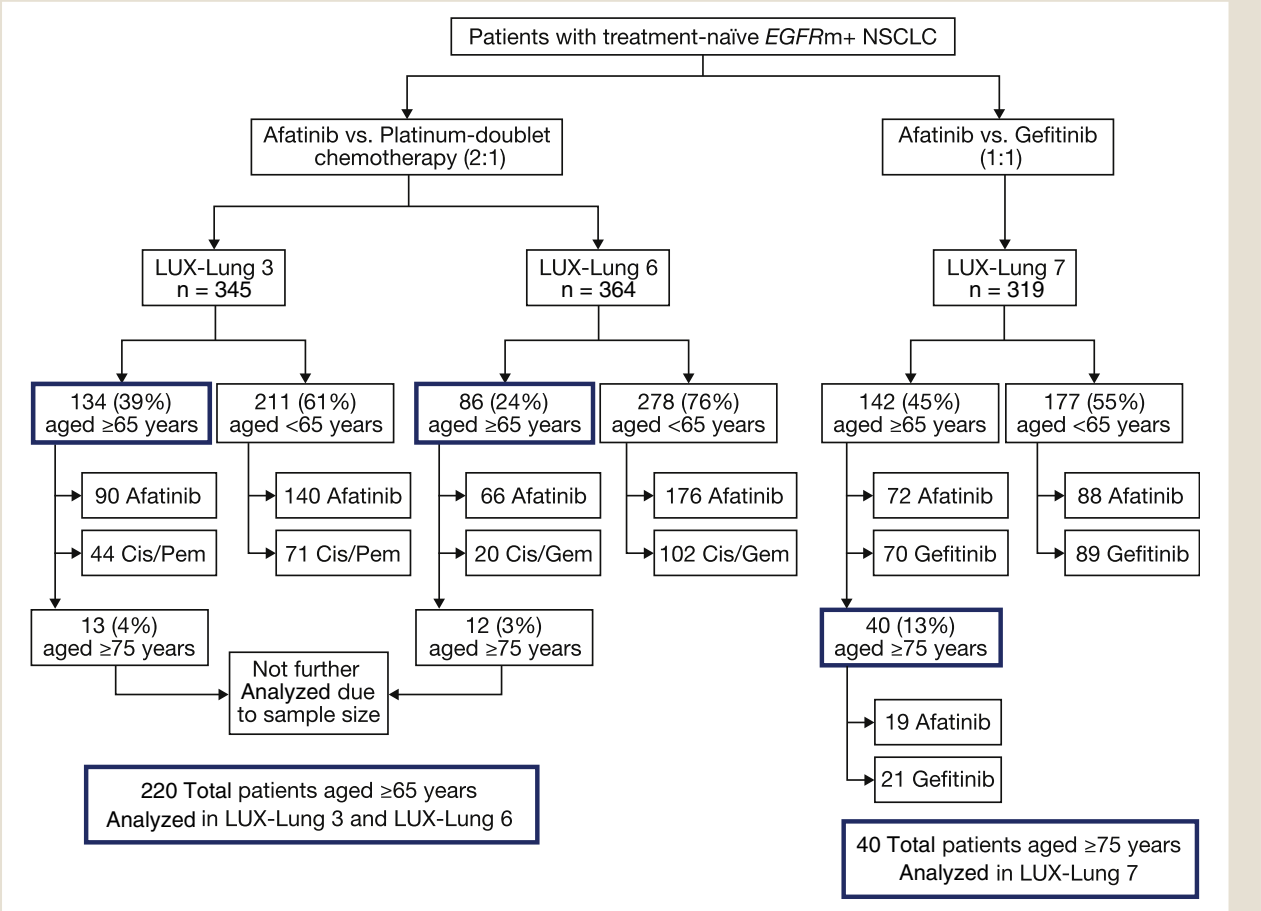
Of the 345 and 364 patients randomized in LL3 and LL6, 134 (39%) and 86 (24%), respectively, were aged 65 years or older (Figure 1; see Supplemental Figure 1 in the online version), hereafter described as the "elderly" subgroup. Whereas only 3% to 4% (13 and 12 patients, respectively) in LL3/LL6 were aged 75 years or older, LL7 enrolled the largest cohort of afatinib-treated patients within this age group (13% [n = 40] of the study population; Figure 1; see Supplemental Figure 1 in the online version). Thus, additional exploratory analyses with a focus on this "older" subgroup of LL7 were conducted.

In each study, baseline demographic and disease characteristics were generally well balanced between treatments within each age subgroup (Table 1). Of note, frequencies of *EGFR* Del19 versus L858R mutations were similar in the elderly subgroups of LL3 and LL6, whereas a higher frequency of L858R versus Del19 mutation was observed in afatinib-treated patients aged 75 years or older in LL7 (63% vs. 37%, compared with similar frequencies observed in gefitinib-treated patients [52% vs. 48%]). A higher frequency of Del19 versus L858R mutations was observed for the younger subgroup in each study.

Treatment Exposure

In LL3 and LL6, median treatment exposure was longer with afatinib than chemotherapy in elderly (65 years or older; LL3: 9.4

Figure 1 Patient Disposition by Age Subgroup in the LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7 Trials[a]



Abbreviations: Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed; EGFR = epidermal growth factor receptor; NSCLC = non-small-cell lung cancer. [a]Patient data from the LL3, LL6, and LL7 trials could not be combined in 1 analysis due to different comparators and randomization schemes.

Table 1 Baseline Demographic and Disease Characteristics

Characteristic	LUX-Lung 3				LUX-Lung 6				LUX-Lung 7			
	≥65 Years		<65 Years		≥65 Years		<65 Years		≥75 years		<75 years	
	Afatinib (n = 90)	Cis/Pem (n = 44)	Afatinib (n = 140)	Cis/Pem (n = 71)	Afatinib (n = 66)	Cis/Gem (n = 20)	Afatinib (n = 176)	Cis/Gem (n = 102)	Afatinib (n = 19)	Gefitinib (n = 21)	Afatinib (n = 141)	Gefitinib (n = 138)
Sex, n (%)												
Female	56 (62)	29 (66)	91 (65)	48 (68)	46 (70)	13 (65)	109 (62)	70 (69)	14 (74)	14 (67)	77 (55)	92 (67)
Male	34 (38)	15 (34)	49 (35)	23 (32)	20 (30)	7 (35)	67 (38)	32 (31)	5 (26)	7 (33)	64 (45)	46 (33)
Median Age (Range), Years	70 (65-86)	69 (65-83)	56 (28-64)	56 (31-64)	69 (65-79)	68 (65-76)	53 (29-64)	56 (27-64)	79 (75-86)	79 (75-89)	61 (30-74)	62 (32-74)
Age Category, n (%)												
<75 years	81 (90)	40 (91)	140 (100)	71 (100)	56 (85)	18 (90)	176 (100)	102 (100)	0 (0)	0 (0)	141 (100)	138 (100)
≥75 years	9 (10)	4 (9)	0 (0)	0 (0)	10 (15)	2 (10)	0 (0)	0 (0)	19 (100)	21 (100)	0 (0)	0 (0)
Race/Ethnicity, n (%)												
Asian	61 (68)	31 (70)	105 (75)	52 (73)	66 (100)	20 (100)	176 (100)	102 (100)	9 (47)	9 (43)	85 (60)	79 (57)
Non-Asian[a]	29 (32)	13 (30)	35 (25)	19 (27)	0 (0)	0 (0)	0 (0)	0 (0)	7 (37)	9 (43)	42 (30)	45 (33)
Missing[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (16)	3 (14)	14 (10)	14 (10)
ECOG PS, n (%)												
0	42 (47)	16 (36)	50 (36)	25 (35)	10 (15)	4 (20)	38 (22)	37 (36)	3 (16)	4 (19)	48 (34)	43 (31)
1	48 (53)	28 (64)	90 (64)	46 (65)[c]	56 (85)	16 (80)	138 (78)	65 (64)	16 (84)	17 (81)	93 (66)	95 (69)
Smoking Status, n (%)												
Never	56 (62)	33 (75)	99 (71)	48 (68)	48 (73)	18 (90)	133 (76)	81 (79)	13 (68)	14 (67)	93 (66)	92 (67)
Former	34 (38)	10 (23)	36 (26)	22 (31)	14 (21)	2 (10)	30 (17)	11 (11)	6 (32)	6 (29)	42 (30)	44 (32)
Current	0 (0)	1 (2)	5 (4)	1 (1)	4 (6)	0 (0)	13 (7)	10 (10)	0 (0)	1 (5)	6 (4)	2 (1)
Adenocarcinoma Stage, n (%)												
IIIB	11 (12)	8 (18)	9 (6)	9 (13)	3 (5)	0 (0)	13 (7)	6 (6)	1 (5)	2 (10)	7 (5)	1 (1)
IV	79 (88)	36 (82)	131 (94)	62 (87)	63 (95)	20 (100)	163 (93)	96 (94)	18 (95)	19 (90)	134 (95)	137 (99)
Number of Metastatic Sites, n (%)												
0	3 (3)	1 (2)	2 (1)	1 (1)	2 (3)	0 (0)	3 (2)	1 (1)	1 (5)	2 (10)	4 (3)	2 (1)
1	30 (33)	11 (25)	30 (21)	23 (32)	21 (32)	7 (35)	51 (29)	45 (44)	7 (37)	5 (24)	32 (23)	31 (22)
2	18 (20)	12 (27)	41 (29)	18 (25)	24 (36)	7 (35)	67 (38)	29 (28)	3 (16)	7 (33)	47 (33)	45 (33)
≥3	39 (43)	20 (45)	67 (48)	29 (41)	19 (29)	6 (30)	55 (31)	27 (26)	8 (42)	7 (33)	58 (41)	60 (43)

Table 1 Continued

Characteristic	LUX-Lung 3				LUX-Lung 6				LUX-Lung 7			
	≥65 Years		<65 Years		≥65 Years		<65 Years		≥75 years		<75 years	
	Afatinib (n = 90)	Cis/Pem (n = 44)	Afatinib (n = 140)	Cis/Pem (n = 71)	Afatinib (n = 66)	Cis/Gem (n = 20)	Afatinib (n = 176)	Cis/Gem (n = 102)	Afatinib (n = 19)	Gefitinib (n = 21)	Afatinib (n = 141)	Gefitinib (n = 138)
EGFR Mutation, n (%)												
Common mutations	81 (90)	37 (84)	122 (87)	67 (94)	59 (89)	19 (95)	157 (89)	89 (87)	19 (100)	21 (100)	140 (99)	138 (100)
Del19	40 (44)	21 (48)	72 (51)	36 (51)	27 (41)	12 (60)	97 (55)	50 (49)	7 (37)	10 (48)	85 (60)	83 (60)
L858R	41 (46)	16 (36)	50 (36)	31 (44)	32 (48)	7 (35)	60 (34)	39 (38)	12 (63)	11 (52)	55 (39)	55 (40)[f]
Uncommon mutations[d,e]	9 (10)	7 (16)	18 (13)	4 (6)	7 (11)	1 (5)	19 (11)	13 (13)	0 (0)	0 (0)	1 (1)	0 (0)

Abbreviations: Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor.
[a]Including American Indian/Alaska Native, Black/African American, Hawaiian/Pacific Islander and White.
[b]Patients recruited at French sites did not have their race/ethnicity reported.
[c]Includes 1 patient with an ECOG PS of 2.
[d]Including T790M, exon 20 insertions, G719X, S768I and L861Q, alone or as complex mutations in 2 or more exons.
[e]Including 1 patient in LL3 and 1 patient in LL7 with wild-type EGFR who were randomly assigned in error. For LL7 analyses, the patient reported with wild-type EGFR was included in the Del19 stratum (as randomized).
[f]Including 1 patient with both L858R and Del19 mutation.

vs. 3.0 months; LL6: 13.9 vs. 2.0 months) and younger patients (LL3: 11.4 vs. 3.4 months; LL6: 12.5 vs. 3.0 months). In LL7, median treatment durations with afatinib versus gefitinib were generally similar in older (75 years and older; 11.9 vs. 12.0 months) and younger patients (14.4 vs. 11.3 months).

Survival Outcomes

Progression-free survival and OS outcomes according to age subgroup for the overall study populations and according to *EGFR* mutation type in LL3 and LL6 are shown in Supplemental Table 1 in the online version. Median PFS was improved with afatinib versus chemotherapy in elderly patients (LL3: 11.3 vs. 8.2 months, HR, 0.64 [95% CI, 0.39-1.03]; LL6: 13.7 vs. 4.1 months, HR, 0.16 [95% CI, 0.07-0.39]) and younger patients (11.0 vs. 5.8 months, HR, 0.53 [95% CI, 0.36-0.76]; LL6: 11.0 vs. 5.6 months, HR, 0.30 [95% CI, 0.21-0.43]) in the overall *EGFR*m$^+$ population, as well as those with tumors harboring common *EGFR* mutations (Figure 2A). Analysis of patients from LL7 using the 65-year cutoff were in line with LL3/LL6 analyses, showing a median PFS of 11.0 months with afatinib in each age subgroup (younger than 65 years and 65 years and over).[21]

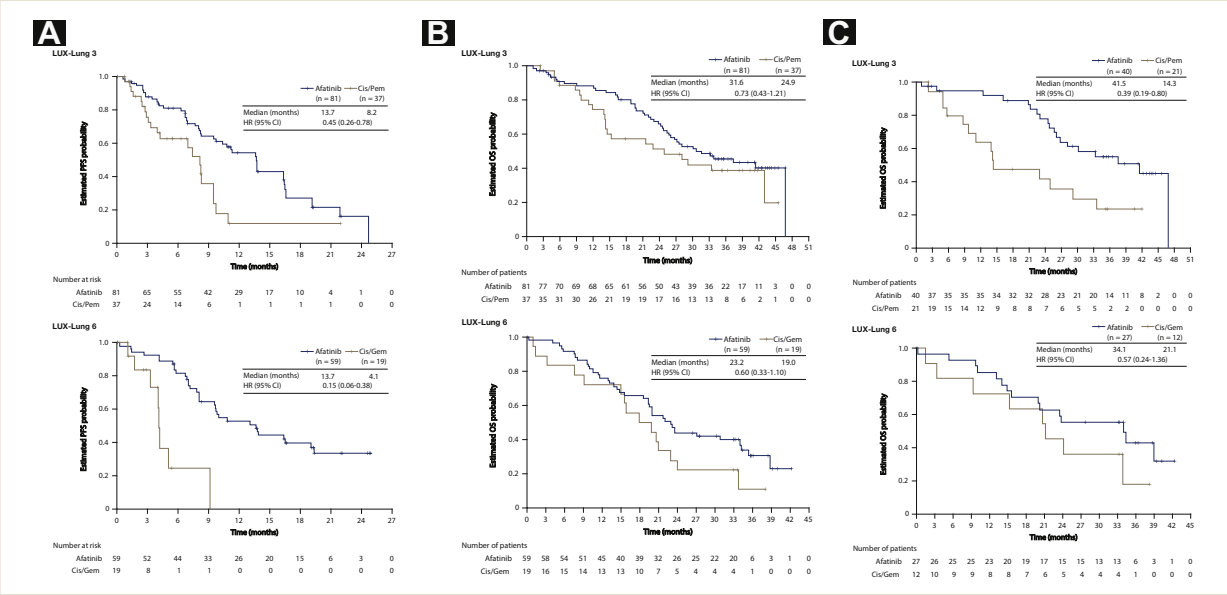
A trend toward improved OS with afatinib was observed in elderly patients in the overall study population of LL6 (22.7 vs. 18.0 months, HR, 0.59 [95% CI, 0.33-1.05]), and those with tumors harboring common *EGFR* mutations in LL3 (31.6 vs. 24.9 months, HR, 0.73 [95% CI, 0.43-1.21]) as well as LL6 (23.2 vs. 19.0 months, HR, 0.60 [95% CI, 0.33-1.10]; Figure 2B). In elderly patients with Del19$^+$ NSCLC, OS was significantly improved with afatinib versus chemotherapy in LL3 (41.5 vs. 14.3 months, HR, 0.39 [95% CI, 0.19-0.80]), with a trend toward improved OS in LL6 (34.1 vs. 21.1 months, HR, 0.57 [95% CI, 0.24-1.36]; Figure 2C). A trend toward OS improvement with afatinib was also observed in elderly patients with L858R$^+$ NSCLC in LL6 (19.8 vs. 16.0 months, HR, 0.43 [95% CI, 0.18-1.04]).

In exploratory analyses of patients aged 75 years or older in LL7, a trend toward improved median PFS was observed with afatinib versus gefitinib (14.7 vs. 10.8 months, HR, 0.69 [95% CI, 0.33-1.44]; Figure 3A), consistent with the overall population and younger subgroup. Median OS with afatinib versus gefitinib was 27.9 versus 19.7 months (HR, 1.05 [95% CI, 0.50-2.21]) in patients aged 75 years or older, and 28.9 versus 25.2 months (HR, 0.85 [95% CI, 0.64-1.12]) in patients aged younger than 75 years (Figure 4A). PFS and OS with afatinib were generally consistent across other exploratory age cutoffs in LL7, with notable improvements versus gefitinib observed in patients aged younger than 70 years (Figures 3B and 4B).

Safety

The overall safety profiles of afatinib and chemotherapy were similar in the elderly and younger subgroups of LL3/LL6, with slightly greater incidences of Grade 3/4 treatment-related adverse events (AEs) observed in elderly patients irrespective of treatment (Table 2; see Supplemental Tables 2 and 3 in the online version). The most frequent treatment-related AEs with afatinib, irrespective of age, were diarrhea, rash/acne, stomatitis, and nail effects. The most frequent treatment-related AEs with chemotherapy were nausea, vomiting, fatigue, decreased appetite, and hematological

Figure 2 PFS (A) and OS (B) in Patients Aged 65 Years or Older With NSCLC Harboring Common *EGFR* Mutations (Del19/L858R), and OS (C) in Patients Aged 65 Years and Older With Del19+ Disease in LUX-Lung 3 and LUX-Lung 6



Abbreviations: Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed; *EGFR* = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

AEs (eg, anemia, neutropenia, and leukopenia). Afatinib was associated with a higher incidence of treatment-related AEs leading to dose reduction compared with chemotherapy in elderly (LL3: 64% vs. 20%; LL6: 42% vs. 17%) as well as younger patients (LL3: 53% vs. 12%; LL6: 29% vs. 28%; see Supplemental Table 2 in the online version). However, fewer discontinuations due to treatment-related AEs were observed with afatinib versus chemotherapy irrespective of age (elderly LL3: 14% vs. 16%; LL6: 9% vs. 72%; younger LL3: 4% vs. 9%; LL6: 5% vs. 34%). The incidence of treatment-related serious AEs was similar across treatment groups in LL3/LL6, and slightly higher in elderly patients, with few deaths, independent of treatment.

No new or unexpected AEs with afatinib were observed in patients aged 75 years or older in LL7 (Table 2; see Supplemental Tables 2 and 3 in the online version). The incidence of treatment-related Grade 3/4 AEs was slightly higher with afatinib and gefitinib in older (42% and 29%) versus younger patients (30% and 17%). Discontinuation rates due to treatment-related AEs were also similar between afatinib and gefitinib, and higher in older (16% and 14%) versus younger patients (5% each). Most treatment-related serious AEs with afatinib in the older subgroup were due to diarrhea (5 of 6 patients); interstitial lung disease was the most common treatment-related serious AE with gefitinib (2 of 3 patients). No treatment-related deaths occurred with afatinib in LL7; 1 patient died from treatment-related hepatic and renal failure with gefitinib.

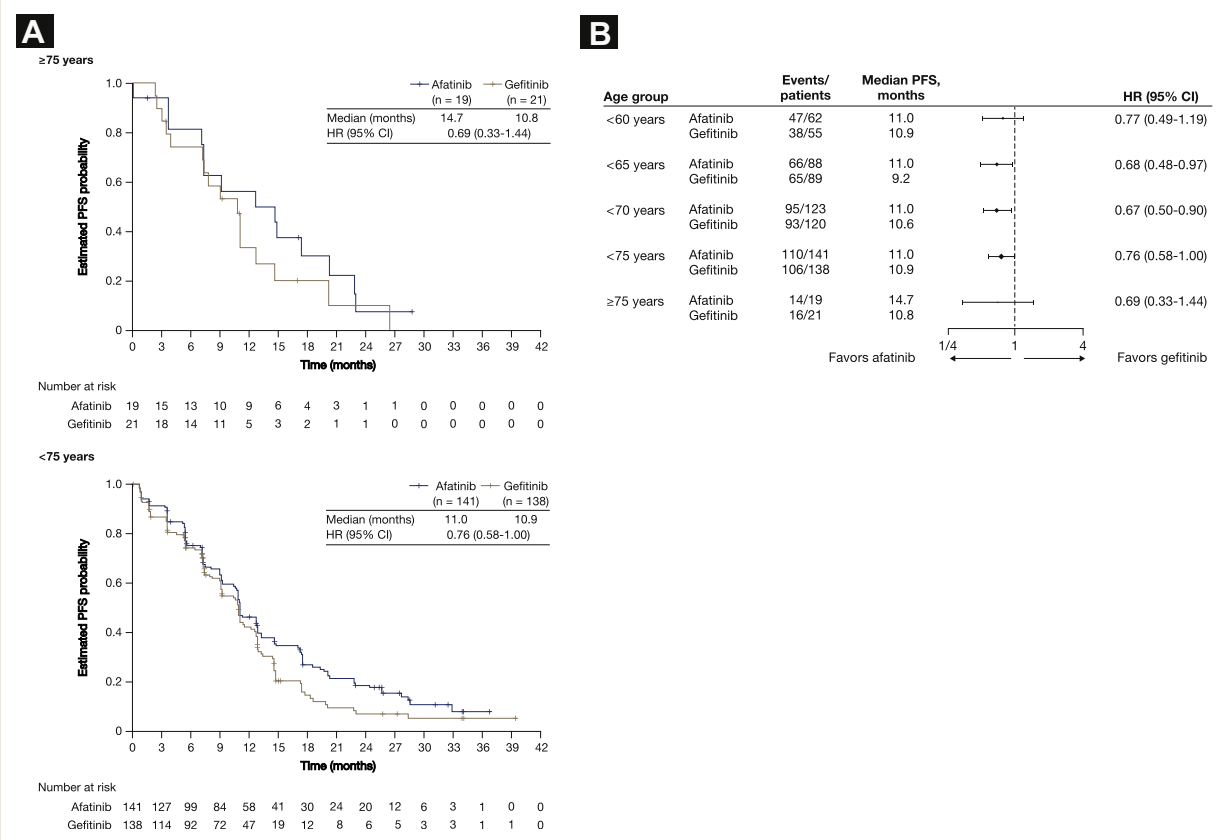
Discussion

Consistent with the overall populations of LL3 and LL6,[20,22,24] afatinib conferred substantial clinical benefit versus chemotherapy in subgroup analyses of patients aged 65 years or older. PFS was improved with afatinib in elderly *EGFR*m$^+$ NSCLC patients harboring common *EGFR* mutations in both trials, with a trend toward improved OS observed in the overall population of elderly *EGFR*m$^+$ NSCLC patients, as well as those harboring common *EGFR* mutations. OS was significantly improved with afatinib in patients with *EGFR* Del19$^+$ NSCLC in LL3, with a trend toward improved OS observed in patients with Del19$^+$ or L858R$^+$ NSCLC in LL6. Further, in exploratory analyses of patients across different age subgroups in LL7, including the older subgroup (75 years or older), PFS and OS findings were consistent with the overall study population,[21,23] indicating that afatinib is an effective treatment for older patients with *EGFR*m$^+$ NSCLC.

The incidence of treatment-related AEs, including serious AEs, and discontinuations due to AEs was slightly higher in the older versus younger subgroups in all 3 studies, independent of treatment. However, the overall safety profile observed with afatinib in older patients was as expected and consistent with the younger subgroup, with diarrhea, rash/acne, stomatitis, and nail effects as the most common treatment-related AEs. Dose reductions due to treatment-related AEs were common with afatinib irrespective of age, reflecting afatinib's well defined dose optimization protocol,[25] and ultimately resulting in few treatment discontinuations. Overall, these findings suggest that afatinib is associated with a predictable and manageable safety profile irrespective of patient age.

Most phase III trials evaluating EGFR-targeted agents in NSCLC included patient subgroup analyses on the basis of a 65 years of age or older cutoff, whereas smaller phase II trials and retrospective analyses have explored cutoffs of 70 years or older and younger than 75 years,[5,19] reflecting the variable definition of "older" cancer patients. The current literature describes 65 years and older as "older," with

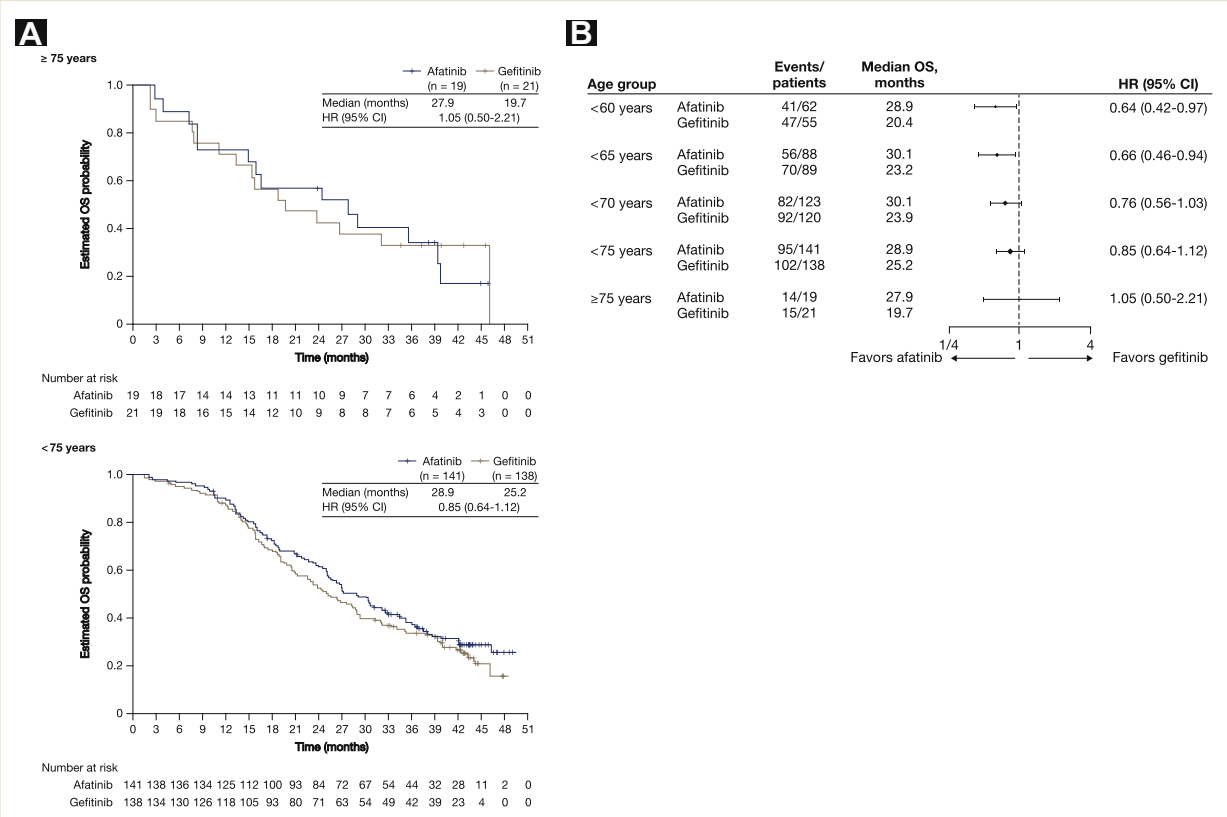
Figure 3 PFS Based on the 75 Years of Age and Older Versus Participants Younger Than 75-Years (A) and Across Additional Age Cut-offs (B) in Patients With NSCLC Harbouring Common *EGFR* Mutations (Del19/L858R) in LUX-Lung 7



Abbreviations: *EGFR* = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival.

subcategories of 65 to 75 years ("young old"), 76 to 85 years ("old"), and older than 85 years ("oldest old").[4] In the context of lung cancer treatment, 75 years and older has been identified as a relevant cutoff when considering chemotherapy and the age at which more effective therapies with improved tolerability are needed.[19] Similar to other phase III trials in this setting, LL3 and LL6 included prespecified subgroup analyses on the basis of a 65 years or older cutoff, including 39% and 24% of the study populations, respectively. Although these proportions are relatively small and represent a limitation to the analysis, they are consistent with most oncology trials (25%-30% of patients aged 65 years or older),[5] reflecting routine trial eligibility criteria, which often limits inclusion of older patients (eg, Eastern Cooperative Oncology Group performance status [ECOG PS] < 2; no significant comorbidities). Although the small number of patients aged 75 years or older in LL3/LL6 prevented further analysis of this older population, a larger cohort of patients aged 75 years or older was enrolled in LL7, allowing for a more meaningful analysis of this older age group. LL7 provided the best available comparison of afatinib with gefitinib in older patients; a head-to-head assessment of EGFR-targeted agents has not been previously reported. Experts agree that chronological age alone should not determine treatment choice in older patients, and that biological age, which takes into account age-related factors such as functional status and comorbidity burden, provides the most relevant information for predicting treatment outcomes and tolerability.[3,5,6] The older subgroups of the LUX-Lung studies might be considered relatively "fit," because of eligibility criteria that excluded patients with poor functional status (ie, ECOG PS ≥ 2) and significant comorbidities (eg, cardiovascular abnormalities). However, previously published subgroup analyses in LL3, LL6, and LL7 have shown significant improvements in PFS, and a trend toward improved OS, with afatinib versus comparators in patients with an ECOG PS of 1, similar to the overall study populations.[20-24] One advantage of afatinib treatment for patients who are receiving multiple medications for comorbidities (as is often observed in elderly patients) is the low occurrence of drug−drug interactions. This is aided by the fact that only a small fraction of afatinib is exposed to hepatic metabolism and excretion, compared with other EGFR TKIs that undergo extensive hepatic metabolism by cytochrome P450-dependent enzymes.[26] Further analyses to determine the effect of poorer functional status and other key factors associated with advancing biological age, such as comorbidities and polypharmacy, on clinical outcomes with afatinib are warranted. Of note, there are some ongoing studies in advanced NSCLC patients currently evaluating the utility of standardized Comprehensive Geriatric Assessment in guiding treatment decisions in older cancer patients[27]; however, to the best of our knowledge, there are no such trials including EGFR-

Figure 4 Estimated OS Probability in (A) Participants 75 Years of Age and Older Versus Participants Younger Than 75 Years and Across Additional Age Cut-offs (B) in Patients With NSCLC Harboring Common *EGFR* Mutations (Del19/L858R) in LUX-Lung 7



Abbreviations: *EGFR* = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival.

targeted agents, and these types of assessments are not routinely used in the clinic.

Conclusion

In summary, subgroup analyses of treatment-naive patients with *EGFR*m$^+$ advanced NSCLC in the LUX-Lung trials showed that advancing age alone did not adversely affect the clinical benefits observed with afatinib versus chemotherapy (LL3/LL6) or gefitinib (LL7). Of note, exploratory analyses across different age cutoffs in LL7 showed that efficacy outcomes with afatinib were consistent independent of age, with notable improvements over gefitinib in patients aged younger than 70 years. Further, afatinib was associated with a predictable and manageable safety profile irrespective of age in all studies. Taken together, these findings show that afatinib can provide an effective and tolerable treatment for older patients with *EGFR*m$^+$ NSCLC.

Clinical Practice Points

- There are limited data on the efficacy of EGFR TKIs in older patients.
- These subanalyses show that first-line afatinib can provide effective and tolerable treatment for patients with EGFRm$^+$ NSCLC, and is superior to platinum-doublet chemotherapy or gefitinib in this clinical setting; therefore, afatinib is an appropriate treatment choice to consider in older patients.
- These data are relevant to day-to-day clinical practice because of the aging population and increased incidence of *EGFR*m$^+$ NSCLC in older patients.
- However, chronological age alone should not determine treatment choice; clinicians should consider physiological age and take into account age-related factors such as functional status and comorbidity burden when considering treatment choice. These provide more information for predicting treatment outcomes and tolerability.
- Afatinib might be an advantageous treatment choice for elderly patients who are receiving multiple medications for comorbidities because drug–drug interactions are less likely than with other EGFR TKIs.
- Clinicians should exercise judgement when prescribing afatinib in all older patients and decisions should be made on a case-by-case basis.

Acknowledgments

The conduct of this research, study design, data collection, and analysis was financially supported by Boehringer Ingelheim. Medical

Table 2 Frequent Treatment-Related AEs in Patients Aged ≥ 65 Years in LUX-Lung 3 and LUX-Lung 6, and ≥ 75 Years in LUX-Lung 7 (≥ 20% All Grade in Any Treatment Group)

	LUX-Lung 3 (≥65 Years)				LUX-Lung 6 (≥65 Years)				LUX-Lung 7 (≥75 Years)			
	Afatinib (n = 90)		Cis/Pem (n = 44)		Afatinib (n = 64)		Cis/Gem (n = 18)		Afatinib (n = 19)		Gefitinib (n = 21)	
	All	G3/4[a]	All	G3/4	All	G3/4[a]	All	G3/4[a]	All	G3/4	All	G3/4
Any AE	90 (100)	53 (59)	43 (98)	25 (57)	64 (100)	27 (42)	18 (100)	12 (67)	17 (89)	8 (42)	20 (95)	6 (29)
Diarrhea	85 (94)	19 (21)	7 (16)	0 (0)	59 (92)	5 (8)	2 (11)	0 (0)	17 (89)	4 (21)	12 (57)	2 (10)
Rash/Acne[b]	79 (88)	17 (19)	3 (7)	0 (0)	50 (78)	6 (9)	1 (6)	0 (0)	15 (79)	1 (5)	13 (62)	0 (0)
Stomatitis[b]	63 (70)	9 (10)	9 (20)	0 (0)	37 (58)	2 (3)	1 (6)	0 (0)	8 (42)	2 (11)	5 (24)	0 (0)
Nail Effect/Paronychia[b]	55 (61)	14 (16)	0 (0)	0 (0)	23 (36)	0 (0)	0 (0)	0 (0)	5 (26)	0 (0)	5 (24)	1 (5)
Dry Skin	34 (38)	0 (0)	2 (5)	0 (0)	6 (9)	0 (0)	1 (6)	0 (0)	7 (37)	0 (0)	9 (43)	0 (0)
Decreased Appetite	26 (29)	5 (6)	24 (55)	2 (5)	13 (20)	2 (3)	7 (39)	0 (0)	6 (32)	0 (0)	6 (29)	0 (0)
Pruritus	18 (20)	1 (1)	1 (2)	0 (0)	10 (16)	1 (2)	0 (0)	0 (0)	5 (26)	0 (0)	2 (10)	0 (0)
Vomiting	16 (18)	3 (3)	16 (36)	2 (5)	9 (14)	1 (2)	16 (89)	6 (33)	2 (11)	0 (0)	3 (14)	1 (5)
Nausea	15 (17)	0 (0)	28 (64)	3 (7)	7 (11)	0 (0)	13 (72)	3 (17)	4 (21)	0 (0)	4 (19)	0 (0)
Fatigue[b]	13 (14)	1 (1)	21 (48)	8 (18)	11 (17)	0 (0)	4 (22)	0 (0)	6 (32)	2 (11)	4 (19)	0 (0)
Anemia	4 (4)	0 (0)	15 (34)	1 (2)	4 (6)	1 (2)	5 (28)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	4 (4)	0 (0)	13 (30)	0 (0)	2 (3)	0 (0)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	3 (3)	1 (1)	11 (25)	4 (9)	3 (5)	1 (2)	5 (28)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Neutropenia	1 (1)	1 (1)	17 (39)	8 (18)	3 (5)	1 (2)	8 (44)	5 (28)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)	5 (11)	2 (5)	2 (3)	1 (2)	4 (22)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Neutrophil Count Decreased	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	4 (22)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data are presented as n (%).
Abbreviations: AE = adverse event; Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed.
[a]In patients aged ≥ 65 years, Grade 5 AEs considered potentially related to treatment by the investigators were reported in 3 patients treated with afatinib (dyspnoea, sepsis and unknown) in LL3, and in 1 patient each treated with afatinib (sudden death) or cis/gem (cardiac failure) in LL6. In LL 7, no patients aged ≥ 75 years experienced a treatment-related Grade 5 AE.
[b]Grouped term. Note that the names and definitions of some grouped terms may have changed based on the MedDRA versions used for the different LUX-Lung trials.

writing assistance, supported financially by Boehringer Ingelheim, was provided by Katie Dean, PhD, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the preparation of this manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

We thank the patients, their families, and all of the investigators who participated in these studies.

Disclosure

Dr Wu reports receiving honoraria from AstraZeneca, Roche, Eli Lilly, Pfizer, and Sanofi. Dr Sequist has received advisory board fees from AstraZeneca, Genentech, Bristol-Myers Squibb (BMS), and Ariad, and has provided unpaid consulting for Clovis, Boehringer Ingelheim (BI), and Merrimack. Dr Geater has participated on boards for Novartis and BI, and has conducted corporate-sponsored research for AstraZeneca, Novartis, BI, and Roche. Dr Zhang is on the board of directors for the Multinational Association of Supportive Care in Cancer, and has conducted corporate-sponsored research for BMS and Pfizer. Dr Kato has received honoraria and conducted corporate-sponsored research for BI. Dr Barrios reports conducting corporate-sponsored research for Pfizer, Novartis, Amgen, AstraZeneca, BI, GlaxoSmithKline, Roche/Genentech, Lilly, Sanofi, Taiho Pharmaceutical, Mylan, Merrimack, Merck, AbbVie, Astellas Pharma, BioMarin, BMS, Abraxis BioScience, AB Science, Asana Biosciences, Medivation, Daiichi Sankyo, Exelixis, ImClone Systems, LEO Pharma, and Millennium, participating on advisory boards for BI, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and Eisai, and has received honoraria from BI, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and Eisai. Dr Schuler reports participating on advisory boards for AstraZeneca, BI, BMS, Celgene, Eli Lilly, Novartis, and Roche, conducting corporate-sponsored research for BI, BMS, and Novartis, receiving honoraria from Alexion, BI, BMS, Celgene, Eli Lilly, MSD, Novartis, AstraZeneca, and Roche; and holds patents with University Duisburg-Essen. Dr Hirsh has received honoraria and participated on advisory boards for BI, AstraZeneca, Roche, Amgen, Pfizer, Eli Lilly, and BMS. Dr Yamamoto has received honoraria and participated on advisory boards for AstraZeneca, BI, Chugai, Eli Lilly, MSD, Novartis, Ono Pharmaceutical Co. Ltd, and Taiho, and has conducted corporate-sponsored research for BI, Chugai, Eli Lilly, and MSD. Dr O'Byrne has received honoraria and participated on advisory boards for MSD, BMS, BI, Roche, Lilly, Novartis, AstraZeneca, and Pfizer, and is a shareholder in CARP Pharmaceuticals. Dr Boyer has participated on advisory boards for Pfizer, AstraZeneca, Merck and BMS, and has conducted corporate-sponsored research for Pfizer, AstraZeneca, Merck, BMS, Amgen, BI, and Roche/Genentech. Dr Mok has participated on advisory boards for AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, BI, Clovis Oncology, Merck Serono, MSD, Novartis, SFJ Pharmaceuticals Group, and BMS, received lecture fees from AstraZeneca, Roche/Genentech, Pfizer, Eli Lilly, BI, MSD, Novartis, BMS, and Taiho, and owns stock in Sanomics Ltd. Dr Peil is an employee of BI. Dr Märten is an employee of BI. Dr Yang has received honoraria and participated on advisory boards for BI, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceutical Co. Ltd, Daiichi Sankyo, and AstraZeneca. Dr Park has participated on advisory boards for Astellas, AstraZeneca, BI, Clovis, Eli Lilly, Hanmi, Loxo Oncology, MSD, Novartis, Ono Pharmaceutical Co. Ltd, and Roche. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.03.009.

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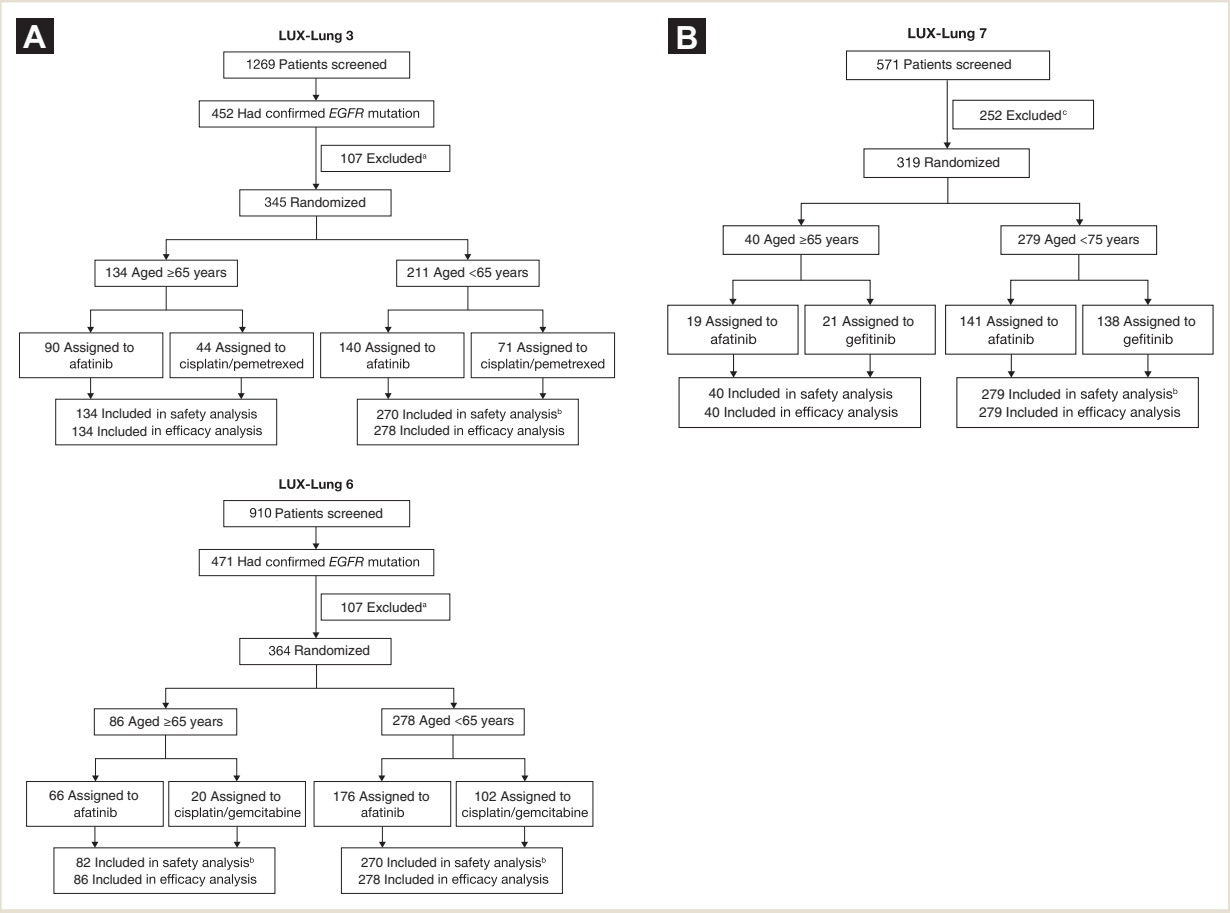
Supplemental Figure 1 Patient Disposition by Age Subgroup in LUX-Lung 3, LUX-Lung 6 (A) and LUX-Lung 7 (B)



Abbreviations: Cis/Pem = cisplatin/pemetrexed; *EGFR* = epidermal growth factor receptor. [a]Reasons for exclusion prior to randomization included did not meet inclusion criteria (n = 58), withdrew consent (n = 24), AEs (n = 5), lost to follow-up (n = 5) and other reason (n = 15) in LL3, and did not meet inclusion criteria (n = 51), withdrew consent (n = 38), AEs (n = 1) and other reason (n = 17) in LL6. [b]Safety analyses included randomized patients who received at least 1 dose of study drug. Following randomization in LL3, 1 patient did not receive afatinib and 4 patients did not receive chemotherapy. In LL6, 3 patients did not receive afatinib and 9 patients did not receive chemotherapy. All patients randomized in LL7 received treatment. [c]Reasons for exclusion prior to randomization included did not meet inclusion criteria (n = 233), withdrew consent (n = 12), AEs (n = 3) and other reason (n = 4).

Supplemental Table 1 Survival Outcomes by Age Subgroup in LUX-Lung 3 and LUX-Lung 6

	LUX-Lung 3				LUX-Lung 6			
	≥ 65 years		<65 years		≥ 65 years		<65 years	
Outcome	**Afatinib**	**Cis/Pem**	**Afatinib**	**Cis/Pem**	**Afatinib**	**Cis/Gem**	**Afatinib**	**Cis/Gem**
Overall Population, n	90	44	140	71	66	20	176	102
Median PFS, Months	11.3	8.2	11	5.8	13.7	4.1	11	5.6
HR (95% CI)	0.64 (0.39-1.03)	0.53 (0.36-0.76)	0.16 (0.07-0.39)	0.30 (0.21-0.43)				
P	.0636	.0006	<.0001	<.0001				
Median OS, Months	27.6	29.1	29.4	26.2	22.7	18	23.1	24.7
HR (95% CI)	0.94 (0.58-1.51)	0.84 (0.59-1.19)	0.59 (0.33-1.05)	0.95 (0.70-1.28)				
P	.7861	.3206	.0676	.7251				
Common EGFR Mutations, n	81	37	122	67	59	19	157	89
Median PFS, months	13.7	8.2	11.8	5.8	13.7	4.1	11	5.6
HR (95% CI)	0.45 (0.26-0.78)	0.48 (0.32-0.71)	0.15 (0.06-0.38)	0.27 (0.19-0.40)				
Median OS, months	31.6	24.9	31.5	28.6	23.2	19	24.2	24.5
HR (95% CI)	0.73 (0.43-1.21)	0.82 (0.57-1.19)	0.60 (0.33-1.10)	0.87 (0.64-1.20)				
Del19	40	21	72	36	27	12	97	50
Median OS, months	41.5	14.3	31.6	25.6	34.1	21.1	30.4	17.5
HR (95% CI)	0.39 (0.19-0.80)	0.64 (0.40-1.03)	0.57 (0.24-1.36)	0.65 (0.42-0.99)				
L858R	41	16	50	31	32	7	60	39
Median OS, months	27.2	43.2	31	29.5	19.8	16	19.3	25.4
HR (95% CI)	1.40 (0.63-3.12)	1.25 (0.67-2.31)	0.43 (0.18-1.04)	1.50 (0.94-2.40)				

Abbreviations: Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Supplemental Table 2 Overall Safety Summary by Age Subgroup in LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7

	LUX-Lung 3				LUX-Lung 6				LUX-Lung 7			
	≥65 Years		<65 Years		≥65 Years		<65 Years		≥75 Years		<75 Years	
	Afatinib (n = 90)	Cis/Pem (n = 44)	Afatinib (n = 139)	Cis/Pem (n = 67)	Afatinib (n = 64)	Cis/Gem (n = 18)	Afatinib (n = 175)	Cis/Gem (n = 95)	Afatinib (n = 19)	Gefitinib (n = 21)	Afatinib (n = 141)	Gefitinib (n = 138)
Any AE	90 (100)	44 (100)	139 (100)	65 (97)	64 (100)	18 (100)	175 (100)	94 (99)	18 (95)	21 (100)	140 (99)	138 (100)
Treatment-Related AEs	90 (100)	43 (98)	138 (99)	63 (94)	64 (100)	18 (100)	172 (98)	94 (99)	17 (89)	20 (95)	139 (99)	133 (96)
Leading to Dose Reduction	58 (64)	9 (20)	74 (53)	8 (12)	27 (42)	3 (17)	51 (29)	27 (28)	10 (53)	1 (5)	56 (40)	2 (1)
Leading to Discontinuation	13 (14)	7 (16)	6 (4)	6 (9)	6 (9)	13 (72)	9 (5)	32 (34)	3 (16)	3 (14)	7 (5)	7 (5)
Treatment-Related Serious AEs	17 (19)	8 (18)	16 (12)	7 (10)	7 (11)	2 (11)	8 (5)	7 (7)	6 (32)	3 (14)	11 (8)	6 (4)
Treatment-Related Deaths	3 (3)[a]	0 (0)	1 (1)[b]	0 (0)	1 (2)[c]	1 (6)[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)[e]

Data are presented as n (%).
Abbreviation: AE = adverse event.
[a]Death, dyspnea and sepsis.
[b]Acute respiratory distress syndrome.
[c]Sudden death.
[d]Cardiac failure.
[e]Hepatic failure and renal failure.

Supplemental Table 3 Frequent Treatment-Related AEs in Patients Younger Than 65 Years in LUX-Lung 3 and LUX-Lung 6, and Younger Than 75 Years in LUX-Lung 7 (Occurrence of 20% or More Across All Grade in Any Treatment Group)

	LUX-Lung 3 (<65 years)				LUX-Lung 6 (<65 years)				LUX-Lung 7 (<75 years)			
	Afatinib (n = 139)		Cis/Pem (n = 67)		Afatinib (n = 175)		Cis/Gem (n = 95)		Afatinib (n = 141)		Gefitinib (n = 138)	
	All	G3/4[a]	All	G3/4	All	G3/4[a]	All	G3/4[a]	All	G3/4	All	G3/4[a]
Any AE	138 (99)	57 (41)	63 (94)	27 (40)	172 (98)	59 (34)	94 (99)	55 (58)	139 (99)	42 (30)	133 (96)	24 (17)
Diarrhea	133 (96)	15 (11)	10 (15)	0 (0)	153 (87)	8 (5)	10 (11)	0 (0)	127 (90)	17 (12)	85 (62)	0 (0)
Rash/Acne[b]	126 (91)	20 (14)	4 (6)	0 (0)	144 (82)	30 (17)	9 (9)	0 (0)	127 (90)	14 (10)	116 (84)	5 (4)
Stomatitis[b]	104 (75)	11 (8)	8 (12)	1 (1)	88 (50)	11 (6)	5 (5)	0 (0)	95 (67)	5 (4)	33 (24)	0 (0)
Nail Effect/Paronychia[b]	88 (63)	15 (11)	0 (0)	0 (0)	60 (34)	0 (0)	0 (0)	0 (0)	85 (60)	3 (2)	23 (17)	0 (0)
Dry Skin	35 (25)	1 (1)	0 (0)	0 (0)	8 (5)	0 (0)	0 (0)	0 (0)	45 (32)	0 (0)	50 (36)	0 (0)
Ocular Effect/Conjunctivitis[b]	29 (21)	0 (0)	0 (0)	0 (0)	10 (6)	0 (0)	0 (0)	0 (0)	8 (6)	0 (0)	10 (7)	1 (1)
Fatigue[b]	28 (20)	2 (1)	31 (46)	6 (9)	14 (8)	1 (1)	37 (39)	1 (1)	27 (19)	7 (5)	19 (14)	0 (0)
Nausea	28 (20)	2 (1)	45 (67)	1 (1)	11 (6)	0 (0)	72 (76)	6 (6)	22 (16)	2 (1)	18 (13)	0 (0)
Pruritus	28 (20)	0 (0)	0 (0)	0 (0)	16 (9)	0 (0)	0 (0)	0 (0)	32 (23)	0 (0)	34 (25)	0 (0)
Vomiting	26 (19)	4 (3)	31 (46)	1 (1)	14 (8)	1 (1)	75 (79)	16 (17)	15 (11)	0 (0)	3 (2)	0 (0)
Decreased Appetite	23 (17)	2 (1)	35 (52)	1 (1)	11 (6)	1 (1)	39 (41)	2 (2)	20 (14)	1 (1)	13 (9)	0 (0)
ALT Increased	17 (12)	1 (1)	2 (3)	0 (0)	39 (22)	2 (1)	16 (17)	3 (3)	15 (11)	0 (0)	36 (26)	11 (8)
AST Increased	13 (9)	0 (0)	2 (3)	1 (1)	32 (18)	1 (1)	10 (11)	2 (2)	10 (7)	0 (0)	31 (22)	3 (2)
Anemia	5 (4)	1 (1)	16 (24)	6 (9)	9 (5)	0 (0)	26 (27)	9 (9)	3 (2)	0 (0)	1 (1)	0 (0)
Neutropenia	1 (1)	0 (0)	18 (27)	12 (18)	3 (2)	0 (0)	53 (56)	25 (26)	3 (2)	1 (1)	1 (1)	0 (0)
Leukopenia	1 (1)	0 (0)	10 (15)	5 (7)	5 (3)	0 (0)	53 (56)	15 (16)	1 (1)	0 (0)	0 (0)	0 (0)
Neutrophil Count Decreased	1 (1)	1 (1)	7 (10)	3 (4)	2 (1)	0 (0)	25 (26)	11 (12)	0 (0)	0 (0)	0 (0)	0 (0)
WBC Count Decreased	0 (0)	0 (0)	2 (3)	0 (0)	1 (1)	0 (0)	24 (25)	7 (7)	0 (0)	0 (0)	0 (0)	0 (0)

Data are presented as n (%).

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; Cis/Gem = cisplatin/gemcitabine; Cis/Pem = cisplatin/pemetrexed; G3/4 = Grade 3 or 4; WBC = white blood cell.

[a]In patients aged < 65 years, Grade 5 AEs considered potentially related to treatment by the investigators were reported in 1 patient treated with afatinib (acute respiratory distress syndrome) in LL3, and no patients in LL6. In patients aged < 75 years in LL7, 1 patient treated with gefitinib had a treatment-related Grade 5 AE (hepatic and renal failure).

[b]Grouped term. Note that the names and definitions of some grouped terms may have changed based on the MedDRA versions used for the different LUX-Lung trials.