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Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With *EGFR* Mutations

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ABSTRACT

Purpose
The LUX-Lung 3 study investigated the efficacy of chemotherapy compared with afatinib, a selective, orally bioavailable ErbB family blocker that irreversibly blocks signaling from epidermal growth factor receptor (EGFR/ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), and ErbB4 and has wide-spectrum preclinical activity against *EGFR* mutations. A phase II study of afatinib in *EGFR* mutation–positive lung adenocarcinoma demonstrated high response rates and progression-free survival (PFS).

Patients and Methods
In this phase III study, eligible patients with stage IIIB/IV lung adenocarcinoma were screened for *EGFR* mutations. Mutation-positive patients were stratified by mutation type (exon 19 deletion, L858R, or other) and race (Asian or non-Asian) before two-to-one random assignment to 40 mg afatinib per day or up to six cycles of cisplatin plus pemetrexed chemotherapy at standard doses every 21 days. The primary end point was PFS by independent review. Secondary end points included tumor response, overall survival, adverse events, and patient-reported outcomes (PROs).

Results
A total of 1,269 patients were screened, and 345 were randomly assigned to treatment. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; $P = .001$). Median PFS among those with exon 19 deletions and L858R *EGFR* mutations (n = 308) was 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; $P = .001$). The most common treatment-related adverse events were diarrhea, rash/acne, and stomatitis for afatinib and nausea, fatigue, and decreased appetite for chemotherapy. PROs favored afatinib, with better control of cough, dyspnea, and pain.

Conclusion
Afatinib is associated with prolongation of PFS when compared with standard doublet chemotherapy in patients with advanced lung adenocarcinoma and *EGFR* mutations.

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INTRODUCTION

Driver mutations in the *EGFR* gene are found in a subset of lung adenocarcinomas and define cancers in which tumor cell survival is exquisitely dependent on epidermal growth factor receptor (EGFR) pathway signaling.[1] The addiction to EGFR signaling leaves the cancers uniquely susceptible to selective oral EGFR tyrosine kinase inhibitors (TKIs),[1] and patients with advanced *EGFR*-mutant non–small-cell lung cancer (NSCLC) may experience dramatic tumor shrinkage and durable responses with the reversible EGFR TKIs gefitinib and erlotinib. Randomized phase III clinical trials have demonstrated that personalizing first-line treatment by *EGFR* mutation status with these EGFR TKIs leads to improvement in progression-free survival (PFS) compared with chemotherapy.[2-6] The trials have all used platinum doublet chemotherapy combinations with a taxane or gemcitabine as the second

drug in the regimen. Recently, pemetrexed has become a preferential drug for patients with lung adenocarcinoma; randomized trials have shown it yields favorable responses and survival with better tolerability compared with taxanes and gemcitabine in those with non-squamous NSCLC.[7-9] First-line, genotype-directed EGFR inhibition has yet to be compared against pemetrexed-containing chemotherapy.

Afatinib is an orally available, irreversibly binding ErbB family blocker with the ability to block signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), ErbB4, and all relevant ErbB family dimers.[10,10a] In vitro, the median inhibitory concentration is lower than those of currently available EGFR TKIs.[10] In a large phase II study of *EGFR*-mutant NSCLC, the response rate to afatinib was 61% (independent review), with median PFS of 12 months for treatment-naive patients and 8 months for EGFR TKI–naive patients after first-line chemotherapy.[11] To determine if *EGFR* genotype–directed therapy with afatinib is superior to pemetrexed-based chemotherapy, we embarked on the LUX-Lung 3 randomized phase III trial.

PATIENTS AND METHODS

Study Design and Patients

LUX-Lung 3 was a global, randomized, open-label phase III study comparing first-line afatinib with cisplatin plus pemetrexed chemotherapy in patients with advanced lung adenocarcinoma and proven *EGFR* mutations. The primary end point was PFS, defined as time from random assignment to progression (as determined by independent blinded review) or death.

To qualify for enrollment, a patient's tumor had to harbor an activating mutation in *EGFR* when tested at one of three central laboratories employing a standardized allele-specific quantitative real-time polymerase chain reaction kit (Therascreen EGFR 29; Qiagen, Manchester, United Kingdom). In addition, eligible patients had treatment-naive advanced lung adenocarcinoma; good performance status, defined as 0 or 1 on the Eastern Cooperative Oncology Group scale[12]; adequate end-organ function; and measurable disease using RECIST version 1.1.[13] A list of the *EGFR* mutations detectable by Therascreen and the full eligibility criteria are provided in the protocol.

Secondary end points included objective response (complete response [CR] and partial response [PR]) and disease control (CR/PR + stable disease [SD]) and their duration, overall survival (OS), patient-reported outcomes (PROs), treatment safety, adverse event (AE) profiles, and pharmacokinetics of afatinib.

Treatment

Patients were randomly assigned in a two-to-one fashion to oral afatinib 40 mg once per day or intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 once every 21 days up to a maximum of six cycles. Randomization was stratified by type of *EGFR* mutation (L858R, exon 19 deletion, or other) and race (Asian or non-Asian). Patients randomly assigned to afatinib were permitted to dose escalate to 50 mg daily after the first 21-day cycle if they did not experience rash, diarrhea, mucositis, or any other drug-related AE $>$ grade 1 in severity. Patients randomly assigned to chemotherapy received folic acid, vitamin B12, and dexamethasone, as per package recommendations for pemetrexed. No maintenance chemotherapy was permitted. Treatment continued until investigator-assessed progression. Recommendations for management of AEs and dose reductions were provided to all investigators, including reduction of afatinib by 10-mg decrements down to 20 mg per day for treatment-related grade 3 or selected prolonged grade 2 AEs according to the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events).

Assessments

Tumor assessments were performed by computed tomography or magnetic resonance imaging every 6 weeks for the first 48 weeks and then every 12 weeks thereafter until disease progression or start of new anticancer therapy. Scans were reviewed by an independent central imaging group incorporating both radiologist and oncologist reviewers blinded to treatment assignments. PROs were assessed every 21 days until disease progression or start of new anticancer therapy using the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire)[14] and EORTC QLQ-LC13 (lung cancer–specific module)[15] questionnaires. PROs were assessed per standard published EORTC algorithms, including time to deterioration of symptoms calculated as the time from random assignment to the first 10-point worsening from the baseline score (considered clinically meaningful).[16,17] Analyses reported here focused on three common lung cancer–related symptoms: cough (Q1 of LC13), dyspnea (Q3 and Q5 of LC13), and pain (Q9 and Q19 of C30). Detailed analyses of these outcomes have been reported elsewhere.[17a]

AEs were categorized and graded using NCI-CTCAE version 3.0.[18] An independent data safety monitoring board conducted ongoing assessments of efficacy and safety data. Afatinib plasma concentrations were analyzed by validated high-performance liquid chromatography tandem mass spectrometry.

Statistical and Regulatory Considerations

The trial sponsor collected and analyzed the data; the lead investigators had full access to the data. The sample size was specified assuming a hazard ratio (HR) of 0.64, equating to an increase in median PFS from an expected 7 months for chemotherapy to 11 months for afatinib. To provide 90% power at a two-sided 5% significance level, 217 progression or death events were required. The samples size was calculated to be 330 patients and the estimated time of primary analysis to be approximately 2 years after study initiation. No interim analyses to compare treatment arms were planned. All efficacy analyses were performed in an intent-to-treat manner and included all randomly assigned patients. The comparison of PFS between arms was calculated by a stratified log-rank test, using the same stratification factors used in randomization. Cox proportional hazard models were used to compare PFS between arms, and Kaplan-Meier estimates were calculated. PFS analysis in patients with common *EGFR* mutations (L858R and exon 19 deletions) was prespecified. Median follow-up time was calculated with the reverse Kaplan-Meier method. Response rate was defined for each arm as the proportion of patients with best overall RECIST response of CR or PR, divided by the total number of patients randomly assigned to that arm; logistic regression models were used to compare arms.

Safety analyses included all patients receiving at least one dose of trial medication. Descriptive statistics were used for all other secondary and exploratory analyses. The primary analysis for OS is scheduled to occur when approximately 209 deaths are observed.

RESULTS

Patients

This study was performed at 133 centers in 25 countries in Asia, Europe, North America, South America, and Australia. Between August 2009 and February 2011, 1,269 patients were screened to identify and randomly assign 345 eligible patients with *EGFR* mutations (Fig 1). Median laboratory turnaround time for *EGFR* mutation analysis was 5 days (range, 1 to 15 days). Five randomly assigned patients withdrew before receiving any study medication.

Treatment arms were balanced in terms of patient demographics and clinical characteristics (Table 1). As expected for a population selected by virtue of *EGFR* mutations, 72% of patients were East Asian, 68% were never-smokers, and 65% were women. *EGFR* mutations were predominantly exon 19 deletions (49%) and L858R point mutations (40%).

Treatment Delivery and Efficacy

Afatinib was administered for a median of 11.0 months (16 cycles). Mean overall compliance with afatinib assessed per patient was 98%. Dose reduction to less than 40 mg per day was required for 120 patients (52%),

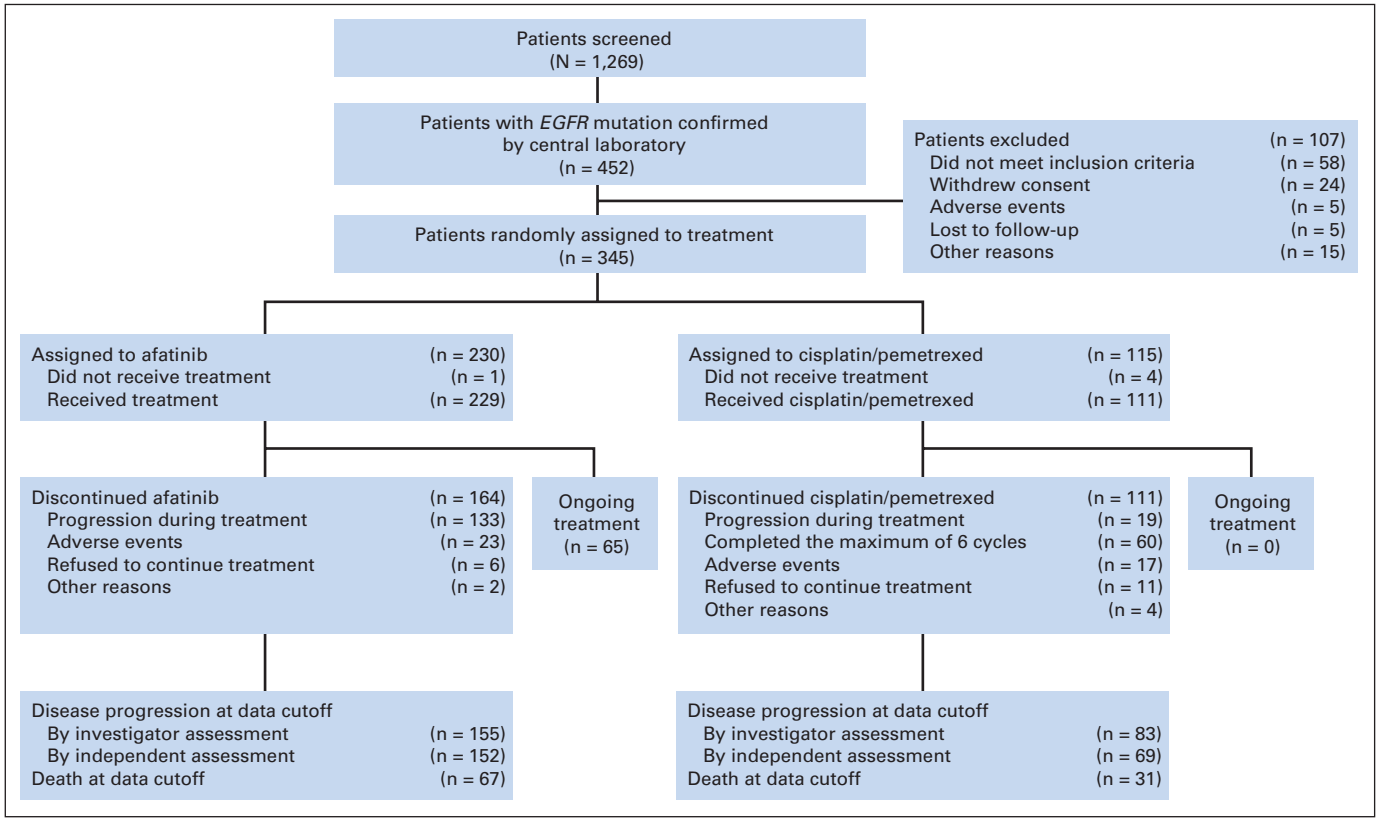

Fig 1. Patient disposition.

with 43 (19%) having more than one dose reduction. Five patients erroneously began afatinib at 50 mg per day, and 16 (7%) exercised the option to increase from 40 to 50 mg per day after the first cycle. Median number of chemotherapy cycles was six; 83 patients (75%) received ≥ four cycles, and 61 (55%) received all six cycles. Eighteen patients (16%) had a chemotherapy dose reduction for AEs, and treatment administration was delayed by ≥ 6 days in 41 patients (40%).

At the time of data cutoff for the primary analysis, median follow-up time was 16.4 months, and 221 progression or death events, as assessed by independent review, had occurred. The primary end point—PFS assessed by independent review—was significantly prolonged for patients receiving afatinib compared with cisplatin plus pemetrexed; median PFS was 11.1 and 6.9 months, respectively (HR, 0.58; 95% CI, 0.43 to 0.78; $P = .001$; Fig 2A). Investigator-reviewed PFS yielded similar results (Fig 3A). At the time of data cutoff, investigators had observed 238 PFS events, with a median PFS of 11.1 months for afatinib and 6.7 months for chemotherapy (HR, 0.49; 95% CI, 0.37 to 0.65; $P = .001$).

Several previous phase III studies included only common sensitizing *EGFR* mutations (L858R and exon 19 deletions).[3,5,6] In our study, the preplanned analysis of those with common *EGFR* mutations (n = 308) showed the magnitude of PFS benefit was even larger, with a median PFS (by independent review) of 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; $P = .001$; Fig 2B). By investigator assessment, HR was 0.41 (95% CI, 0.31 to 0.55; $P = .001$). Subgroup analyses showed the PFS benefit for afatinib persisted among most clinically relevant subgroups examined (age, sex, race, Eastern Cooperative Oncology Group status), although many subgroups were underpowered for meaningful conclusions (Fig 2C). Subgroup analyses using investigator-determined PFS yielded similar results (Fig 3B). Exploratory subgroup analyses for common mutations are shown in Appendix Figure A1 (online only). The numbers of uncommon mutations were too small (26 in afatinib arm; 11 in chemotherapy arm) for further analysis, although outcomes for those receiving afatinib will be analyzed together with those for patients with uncommon mutations from other afatinib studies.

Significantly higher response rates were observed with afatinib compared with chemotherapy according to both independent (56% and 23%, respectively) and investigator (69% and 44%, respectively) assessments (both $P = .001$). Both treatment arms had a high proportion of patients achieve disease control (90% in afatinib arm; 81% in chemotherapy arm, by independent review). Median duration of response was independently assessed as 11.1 and 5.5 months for afatinib and chemotherapy, respectively, whereas median duration of disease control was 13.6 and 8.1 months, respectively. At the time of data cutoff, only 98 patients (28%) had died; hence, the OS data are considered preliminary. OS did not differ between afatinib and chemotherapy in the overall study population (HR, 1.12; 95% CI, 0.73 to 1.73; $P = .60$; 25th percentile, 16.6 *v* 14.8 months). Median OS has not yet been reached for any group. A high degree of postprogression crossover to EGFR TKIs among patients receiving chemotherapy (65%) and to chemotherapy among those receiving afatinib (62%) was observed.

For PROs, prespecified analyses of time to deterioration of symptoms and clinically meaningful worsening of cough (HR, 0.60; 95% CI, 0.41 to 0.87; $P = .007$) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; $P = .01$) showed significant delay with afatinib compared with

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Afatinib (n = 230) No.	Afatinib (n = 230) %	Cisplatin Plus Pemetrexed (n = 115) No.	Cisplatin Plus Pemetrexed (n = 115) %
Sex				
Male	83	36.1	38	33.0
Female	147	63.9	77	67.0
Age, years				
Median	61.5		61.0	
Range	28-86		31-83	
Race				
White	61	26.5	30	26.1
East Asian	165	71.7	83	72.2
Other	4	1.7	2	1.7
Smoking status				
Never	155	67.4	81	70.4
Former	70	30.4	32	27.8
Current	5	2.2	2	1.7
ECOG PS				
0	92	40.0	41	35.7
1	138	60.0	73	63.5
2	0	0.0	1	0.9
Adenocarcinoma stage*				
IIIB with pleural effusion	20	8.7	17	14.8
IV	210	91.3	98	85.2
EGFR mutation				
Exon 19 deletion	113	49.1	57	49.6
L858R	91	39.6	47	40.9
Other	26	11.3	11	9.6

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*By American Joint Committee on Cancer, sixth edition.

chemotherapy. Time to deterioration of pain was also longer with afatinib, but it was not statistically significant (HR, 0.83; 95% CI, 0.62 to 1.10; $P = .19$).

Treatment-Related AEs

Both treatments were well tolerated, and AEs were manageable with dose reductions and delays. Treatment-related AEs grade ≥ 3 occurred in 112 patients (49%) receiving afatinib and 53 patients (48%) receiving chemotherapy. Diarrhea, rash, and dryness or irritation of the skin, mucosa, and nails were the most common treatment-related AEs with afatinib, whereas decreased appetite, fatigue, nausea/vomiting, and myelosuppression were most common with chemotherapy (Table 2). Therapy was discontinued because of treatment-related AEs in 8% of those receiving afatinib and 12% of those receiving chemotherapy. Of the most common AEs associated with afatinib, only diarrhea (1.3%) and paronychia (0.9%) resulted in treatment discontinuation. There were three cases (1%) of potentially related interstitial lung disease–like events, and four deaths among those receiving afatinib were considered potentially treatment related by the investigator (two respiratory decompensations, one sepsis, and one unknown). There were no treatment-related fatal toxicities in the chemotherapy arm.

Pharmacokinetics

To obtain a comprehensive picture of exposure, predose plasma samples were taken on days 1 and 8 of cycle two and day 1 of cycle three. Afatinib plasma levels showed high interpatient variability. Dose modifications, which were based on individual tolerability, reduced excessive afatinib levels and thus the variability observed in the 40-mg dose group from 85.0% (day 1 of cycle two) to 66.5% (day 1 of cycle three; Appendix Fig A2A, online only). Ranges and geometric mean values of trough plasma concentrations were comparable for all dose groups at the last pharmacokinetic visit on day 1 of cycle three (Appendix Fig A2B, online only).

DISCUSSION

To our knowledge, LUX-Lung 3 is the largest prospective, randomized trial reported to date in patients with advanced stage *EGFR* mutation–positive NSCLC and the first study to compare first-line EGFR-targeted TKI therapy with the best-in-class chemotherapy regimen of cisplatin plus pemetrexed. The study showed a significant PFS benefit for personalized, genotype-directed therapy with the ErbB family blocker afatinib compared with cisplatin plus pemetrexed chemotherapy. In addition, patients treated with afatinib had statistically significant and clinically meaningful improvements in response rate and lung cancer symptoms. Afatinib treatment was associated with manageable AEs, and hence, discontinuation because of drug-related AEs was low. At the time of analysis, no difference in OS between treatment arms was apparent.

The perception of optimal EGFR TKI placement in the treatment algorithms for NSCLC has evolved over the last decade. Gefitinib and erlotinib were initially considered salvage therapies, with low response rates but marginal improvement in survival compared with placebo in unselected patients.[19,20] Once the qualitative difference in response to EGFR TKIs among *EGFR*-mutant patients was appreciated, randomized studies were performed in Asian patients comparing gefitinib or erlotinib with taxane- and gemcitabine-based chemotherapy.[2-5] These showed remarkable PFS improvement, but questions as to whether benefit was restricted to Asian patients arose. The recent EURTAC (European Tarceva versus Chemotherapy) study using erlotinib in European patients[6] and our study using afatinib in patients from around the world clearly support initial EGFR TKI treatment in patients with *EGFR* mutation–positive NSCLC, regardless of race. *EGFR* testing should be tightly woven into lung cancer diagnostic workup algorithms worldwide.

Key strengths of this study were central *EGFR* mutation testing and central review of radiographs. Molecular testing methods are essential components of biomarker-directed therapy. The sensitivity and specificity of *EGFR* mutation screening methods vary,[21] and calculated PFS statistics for *EGFR* mutation–positive patients may vary within the same overall cohort of gefitinib-treated patients when different *EGFR* mutation detection methods are used.[22] Therefore, standardization of the testing assay and methodology is crucial to define the population to be treated and assure reproducibility of results. Central radiology interpretation is important to reduce bias in the interpretation of PFS. In our study, disease progression was recorded by investigators more often than by independent reviewers, particularly among patients randomly assigned to chemotherapy (chemotherapy arm: 83 progression events by investigators *v* 69 by independent review; afatinib arm: 155 by investigators *v* 152 by central review). It is possible that investigators were more likely to stop chemotherapy than afatinib in patients known to harbor *EGFR* mutations. In the primary

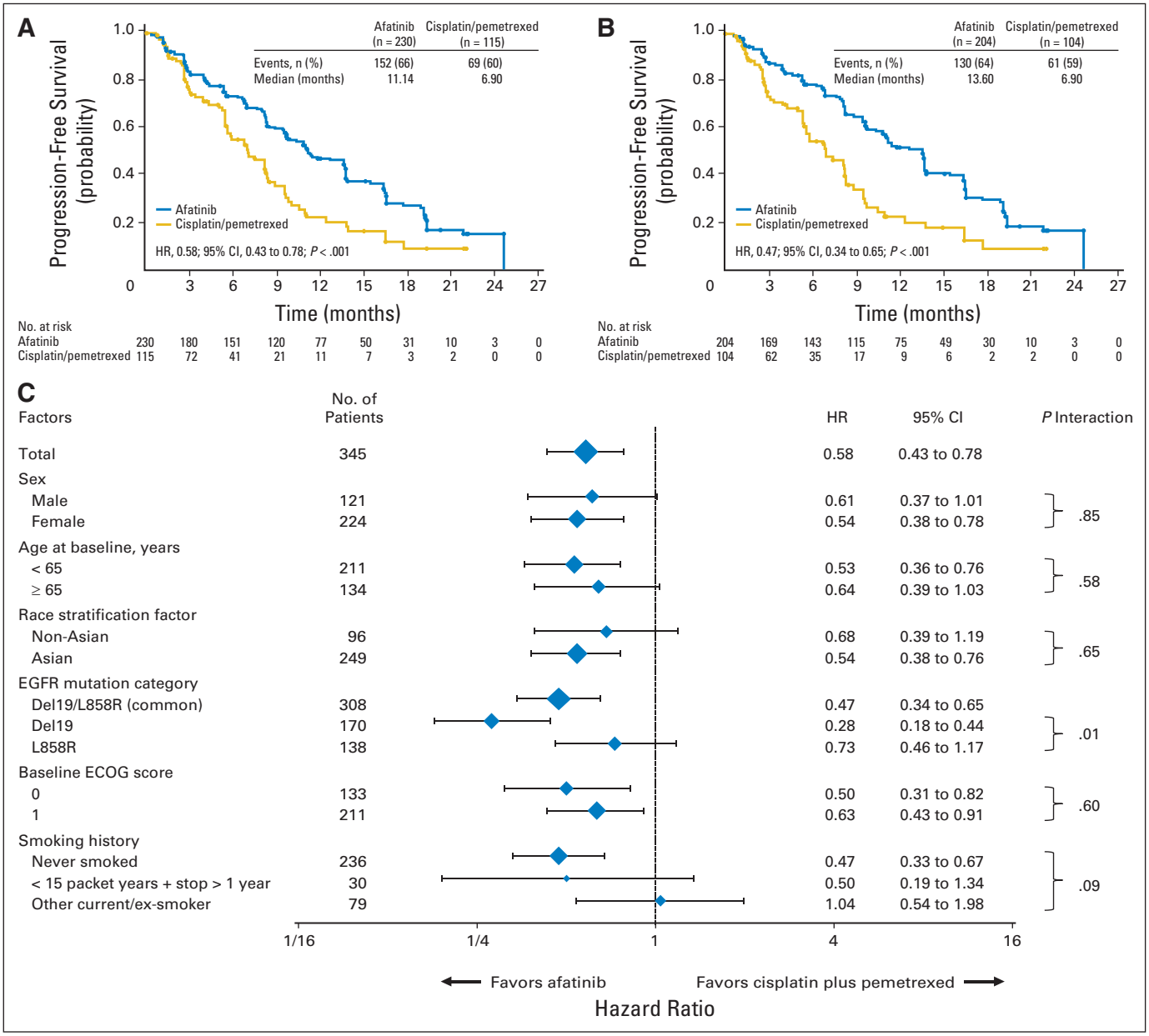

Fig 2. Primary analysis. (A) Progression-free survival (PFS) by independent review for all randomly assigned patients. At the time of data cutoff for primary analysis of PFS, 45 patients (20%) in the afatinib arm and three patients (3%) in the chemotherapy arm were known to be alive and progression free. (B) PFS by independent review in patients with common mutations (del19/L858R; n = 308). (C) Forest plot of subgroups of patients showing PFS by independent review. HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

analysis, any events reported by investigators that were nonevents by independent review were censored at the time of discrepancy; therefore, the true treatment effect could have been underestimated, as was shown in several preplanned sensitivity and subgroup analyses using investigator-generated progression events.

Despite the high response rate and prolonged PFS of patients with *EGFR* mutations treated with gefitinib or erlotinib, there are still major clinical obstacles. Approximately half of those with *EGFR* mutations will develop the T790M resistance mutation when their tumors are rebiopsied after treatment with erlotinib or gefitinib.[23-25] T790M mutations may already be present in EGFR TKI treatment–naive patients,[26,27] and the presence of a detectable de novo T790M mutation predicts for shorter PFS with EGFR TKIs.[26,28,29] Afatinib had in vitro activity against the T790M variant[10] and improved PFS compared with placebo in a randomized phase III trial in an NSCLC population clinically enriched for the presence of such mutations.[30] Therefore, afatinib may inhibit the selective expansion of T790M clones and prolong PFS. Afatinib-treated patients with exon 19 deletion and L858R mutations had a prolonged PFS of 13.6 months.

An important accompaniment to PFS gains with a genotype-directed therapeutic strategy is improvement in PROs.[31] We demonstrated clinically meaningful delays in worsening of lung cancer–related symptoms in afatinib-treated patients compared with those treated with chemotherapy. The AE profile of afatinib was manageable

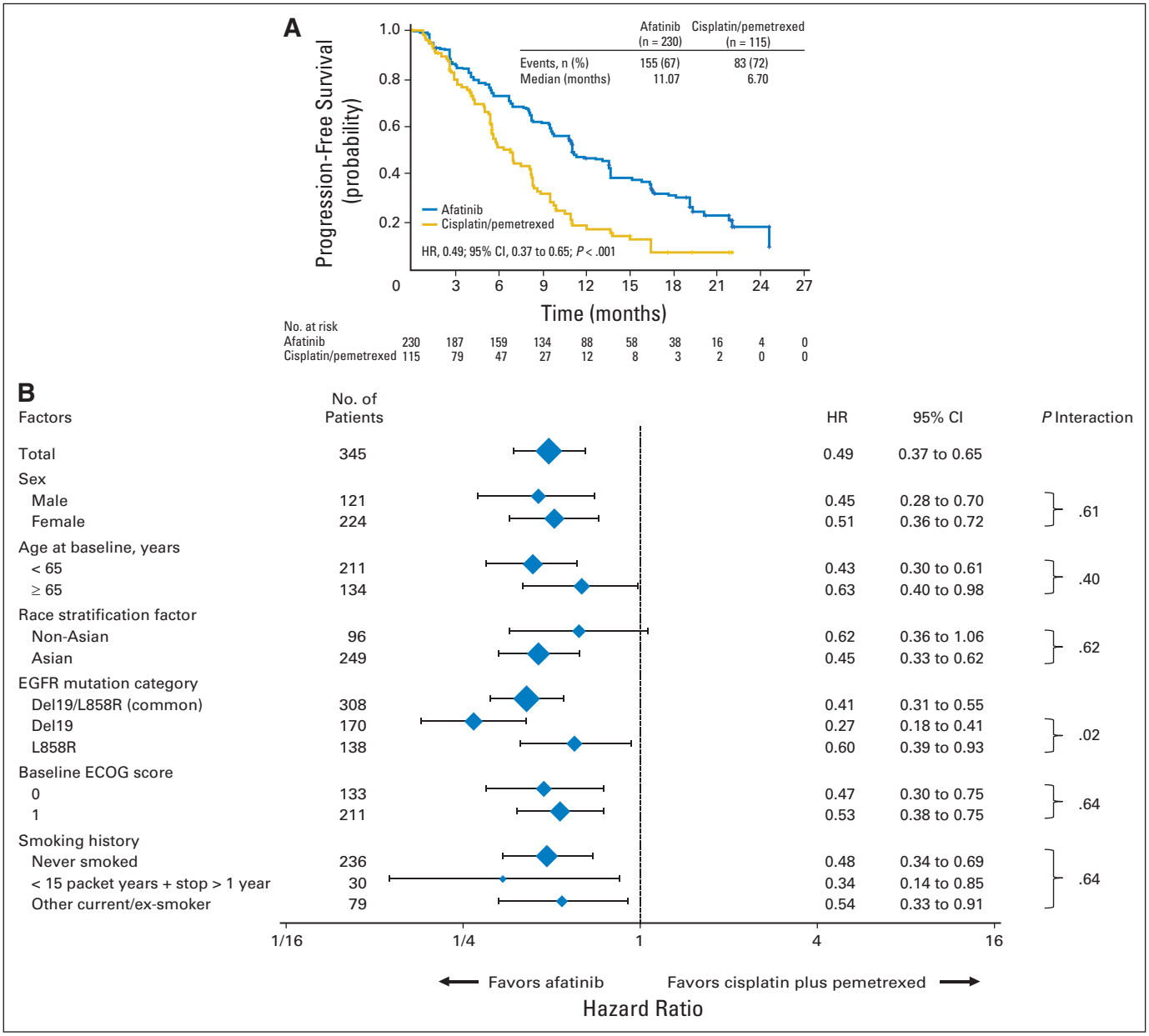

Fig 3. (A) Progression-free survival (PFS) by investigator review for all randomly assigned patients. (B) Forest plot of subgroups of patients showing PFS by investigator review. HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

and consisted primarily of rash, diarrhea, stomatitis, and paronychia, as expected from EGFR inhibition.[2-6] Despite higher frequencies of such AEs in our trial, these AEs rarely led to drug discontinuation, indicating that proactive supportive treatment and dose modification were an adequate strategy to properly manage the expected class effects associated with EGFR inhibition. In addition, the results of the pharmacokinetic analysis indicate that afatinib dose modification based on individual tolerability optimized the exposure to afatinib and maintained efficacious plasma levels.

Cisplatin plus pemetrexed is widely considered the optimal chemotherapy doublet for patients with nonsquamous NSCLC. The efficacy of this regimen is supported by the PFS observed in our control arm, which exceeded the results observed in other studies comparing EGFR TKIs with first-line chemotherapy.[2-6] One of the limitations of our study is that the chemotherapy arm was devoid of maintenance pemetrexed and/or bevacizumab. However, at the time of study design, cisplatin plus pemetrexed without maintenance was considered an efficacious treatment choice for patients with adenocarcinoma.[31a] The prevailing treatment standard changed after LUX-Lung 3 accrual was completed, when the results of a trial of maintenance pemetrexed after cisplatin plus pemetrexed showed significant improvement compared with placebo, with a median PFS of 6.9 months.[32] Another limitation is that bevacizumab treatment was not included in the comparator arm of this study. There were two reasons for this: first, although addition of bevacizumab to paclitaxel plus carboplatin is

Table 2. Treatment-Related AEs*

	Afatinib (n = 229)				Cisplatin Plus Pemetrexed (n = 111)			
	All Grades		≥ Grade 3		All Grades		≥ Grade 3	
AE	No.	%	No.	%	No.	%	No.	%
Diarrhea	218	95.2	33	14.4	17	15.3	0	0.0
Rash/acne†	204	89.1	37	16.2	7	6.3	0	0.0
Stomatitis/mucositis†	165	72.1	20	8.7	17	15.3	1	0.9
Paronychia	130	56.8	26	11.4	0	0.0	0	0.0
Dry skin	67	29.3	1	0.4	2	1.8	0	0.0
Decreased appetite	47	20.5	7	3.1	59	53.2	3	2.7
Pruritus	43	18.8	1	0.4	1	0.9	0	0.0
Nausea	41	17.9	2	0.9	73	65.8	4	3.6
Fatigue†	40	17.5	3	1.3	52	46.8	14	12.6
Vomiting	39	17.0	7	3.1	47	42.3	3	2.7
Epistaxis	30	13.1	0	0.0	1	0.9	1	0.9
Cheilitis	28	12.2	0	0.0	1	0.9	0	0.0
Anemia‡	7	3.1	1	0.4	31	27.9	7	6.3
Constipation	6	2.6	0	0.0	21	18.9	0	0.0
Leukopenia‡	4	1.7	1	0.4	21	18.9	9	8.1
Neutropenia‡	2	0.9	1	0.4	35	31.5	20	18.0

Abbreviation: AE, adverse event.
*Events were included if reported in > 10% of patients in either treatment group and if there was ≥ 10% difference between the groups. Events are listed according to incidence in the afatinib group.
†Group term.
‡Numbers are based on AEs reported by the investigator, not derived from laboratory data.

a standard regimen in the United States,[33] bevacizumab use is not standard around the world; similarly, the addition of bevacizumab to cisplatin and pemetrexed is not a current standard regimen.

In conclusion, patients with lung adenocarcinoma with *EGFR* mutations have significant PFS, tumor response, and lung cancer–related symptom benefits when treated with first-line afatinib compared with cisplatin plus pemetrexed. Afatinib could be considered a standard option for such patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

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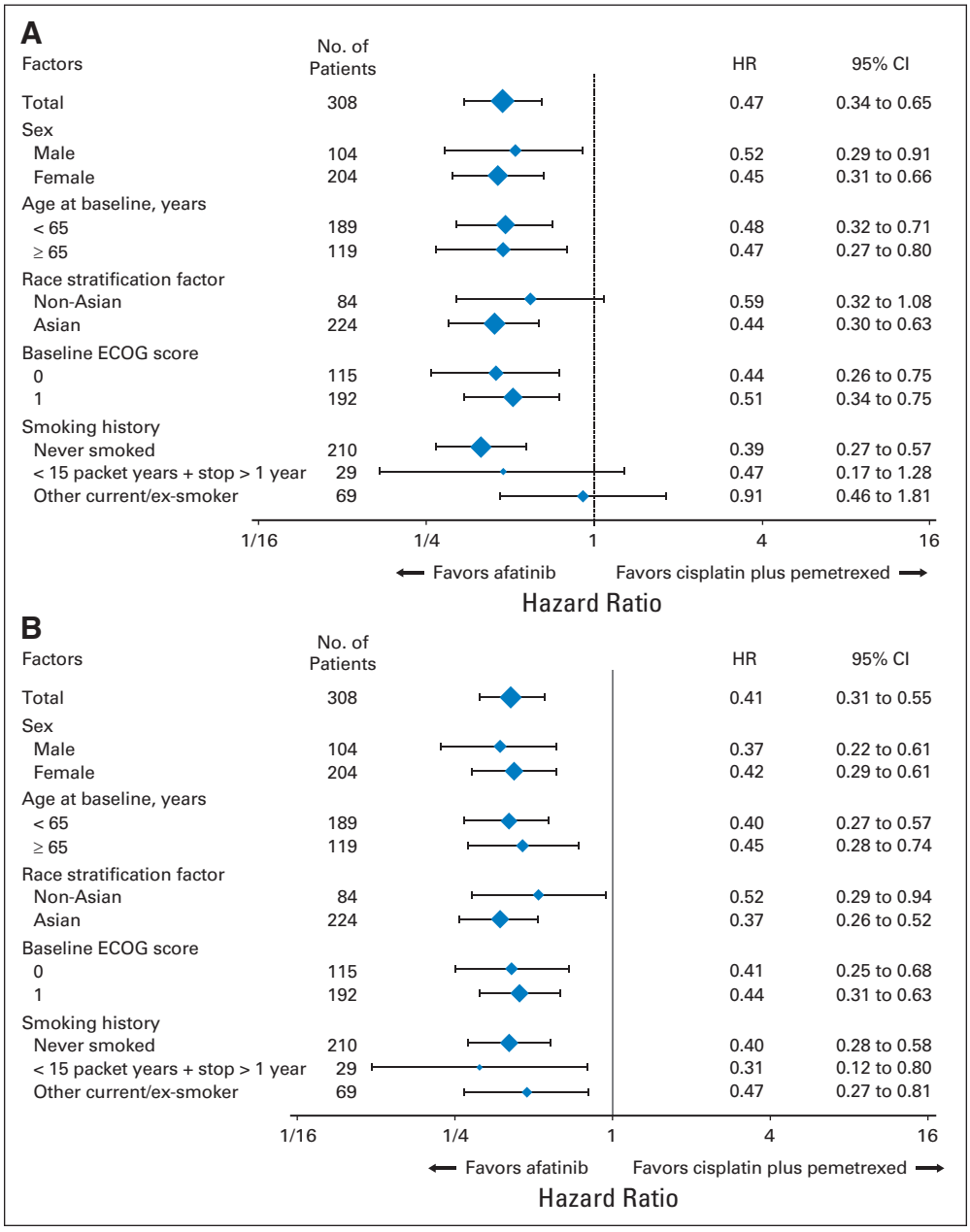

Fig A1. Forest plot for subgroups of patients among those with common mutations, showing progression-free survival by (A) independent and (B) investigator review (exploratory analyses). HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group.

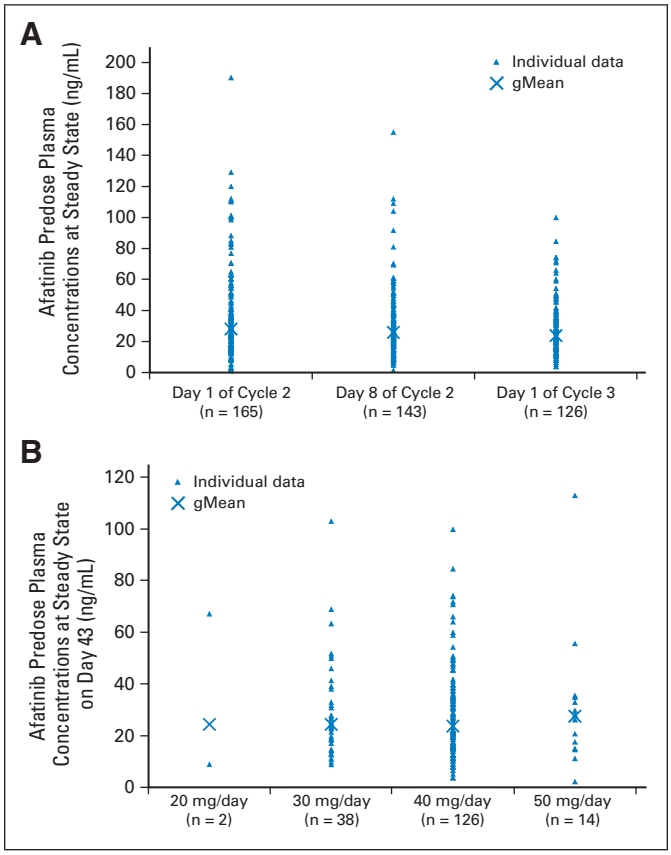

Fig A2. Comparison of individual and geometric mean (gMean) predose plasma concentrations of afatinib at steady state (A) after multiple oral administrations of afatinib 40 mg per day and (B) on day 1 of cycle three after multiple oral administrations of 20, 30, 40, or 50 mg of afatinib per day.