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Randomized Trial of Afatinib Plus Cetuximab Versus Afatinib Alone for First-Line Treatment of *EGFR*-Mutant Non–Small-Cell Lung Cancer: Final Results From SWOG S1403

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abstract

PURPOSE The irreversible ErbB family tyrosine kinase inhibitor (TKI) afatinib plus the EGFR monoclonal antibody cetuximab was previously shown to overcome resistance to EGFR TKIs. We studied whether the combination of afatinib plus cetuximab compared with afatinib alone would improve progression-free survival (PFS) in patients with treatment-naive *EGFR*-mutant non–small-cell lung cancer (NSCLC) by preventing or delaying resistance.

METHODS Patients with *EGFR*-mutant NSCLC without prior treatment of advanced disease were enrolled in this phase II, multicenter trial and randomly assigned to receive afatinib 40 mg orally daily plus cetuximab 500 mg/m^2 intravenously every 2 weeks or afatinib alone. The primary end point was PFS.

RESULTS Between March 25, 2015 and April 23, 2018, 174 patients were randomly assigned, and 168 (83 on afatinib + cetuximab and 85 on afatinib) were eligible. There was no improvement in PFS in patients receiving afatinib plus cetuximab compared with afatinib alone (hazard ratio [HR], 1.01; 95% CI, 0.72 to 1.43; $P = .94$; median, 11.9 months *v* 13.4 months). Similarly, there was no difference in response rate (67% *v* 74%; $P = .38$) or overall survival (HR, 0.82; 95% CI, 0.50 to 1.36; $P = .44$). Toxicity was greater with the combination: grade ≥ 3 adverse events related to treatment occurred in 72% of patients receiving afatinib plus cetuximab compared with 40% of those receiving afatinib alone, most commonly rash and diarrhea. Dose reductions were more common in patients receiving the combination, and 30% of patients in this arm discontinued cetuximab due to toxicity. At interim analysis, there was insufficient evidence to support continued accrual, and the trial was closed.

CONCLUSIONS The addition of cetuximab to afatinib did not improve outcomes in previously untreated *EGFR*-mutant NSCLC, despite recognized activity in the acquired resistance setting.

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INTRODUCTION

Activating *EGFR* mutations are present in approximately 15% of patients with lung adenocarcinomas in Western populations and confer increased sensitivity to EGFR tyrosine kinase inhibitors (TKIs).[1] Several clinical trials have clearly demonstrated the benefit of treating patients with *EGFR*-mutant non–small-cell lung cancer (NSCLC) with an EGFR TKI compared with chemotherapy.[2-4] However, despite the improvement in clinical outcomes, quality of life, and toxicity profile compared with chemotherapy, EGFR TKIs are not curative, and the median progression-free survival (PFS) observed with first- and second-generation EGFR TKIs ranges from 10 to 12 months.[2-4] Recently, a phase III trial demonstrated superior outcomes with the third-generation TKI osimertinib compared with first-generation TKIs, with a median PFS of 19 months.[5]

Many strategies have been tested to overcome acquired resistance to first-generation EGFR TKIs, which is most commonly mediated by the secondary *EGFR* mutation T790M.[6] Based on the superior outcomes with the third-generation EGFR TKI osimertinib compared with chemotherapy, osimertinib is now the standard treatment for patients with T790M-mediated resistance, yet it is not effective in TKI-resistant T790M-negative disease.[7] The second-generation, irreversible, ErbB family TKI afatinib cannot overcome resistance when used alone[8]; however, a phase Ib trial of patients with *EGFR*-mutated NSCLC with acquired resistance found that the combination of afatinib with the EGFR antibody cetuximab resulted in a response rate of 29%, with comparable activity in patients with T790M-postive or T790M-negative tumors.[9] Other combinations of EGFR TKIs with EGFR antibodies are

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Single-agent EGFR tyrosine kinase inhibitor (TKI) therapy is the standard first-line treatment of patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC). We aimed to determine whether adding cetuximab to afatinib improves progression-free survival in this treatment setting.

Knowledge Generated

This randomized trial found that afatinib plus cetuximab did not improve clinical outcomes compared with afatinib alone. The combination resulted in increased toxicity and more frequent dose reduction and treatment discontinuation.

Relevance

There is currently no role for the combination of afatinib and cetuximab in patients with treatment-naïve *EGFR*-mutated NSCLC; however, further investigation into more tolerable combinations of EGFR TKIs with EGFR antibodies is warranted.

ineffective,[10] indicating that afatinib plus cetuximab has a unique capability of overcoming resistance to first-generation agents regardless of the presence of a T790M resistance mutation.

Preclinical studies have demonstrated the benefit of afatinib plus cetuximab compared with afatinib or erlotinib alone at delaying resistance when used as initial therapy in *EGFR*-mutant lung cancer mouse models.[11] We hypothesized that the combination of afatinib and cetuximab would be superior to afatinib alone as first-line treatment of patients with *EGFR*-mutant NSCLC.

METHODS

Participants and Study Design

The full protocol is available in the Data Supplement (online only). Patients had stage IV or recurrent NSCLC with a common sensitizing *EGFR* mutation (exon 19 deletion or L858R point mutation). Uncommon mutations were not allowed, as afatinib was not yet US Food and Drug Administration approved for these mutations at the time of study initiation. Eligible patients had not received prior systemic anticancer therapy for advanced or metastatic disease or any prior EGFR TKI and had a performance status (PS) of 0-2 on the Zubrod scale. Given the potential for CNS penetration of both afatinib and cetuximab,[12,13] untreated brain metastases were allowed if they were asymptomatic, they did not require corticosteroids, and there was no evidence of leptomeningeal carcinomatosis. Tumor tissue for correlative analysis was required for study entry. Measurable disease per RECIST[14] was not mandatory.

The trial was initially designed as a randomized phase II/III study, with the primary end point of the phase II component being PFS and the primary end point of the phase III component being overall survival (OS). During the conduct of the study, the design was modified due to slow accrual and the changing treatment landscape of *EGFR*-mutant NSCLC. The revised design was a randomized phase II trial with a primary end point of PFS. PFS was defined as the date of randomization to the date of first documentation of progression, symptomatic deterioration, or death due to any cause. PFS for patients last known to be alive, progression free, and free of symptomatic deterioration was censored at the date of last contact.

Secondary end points included overall response rate (ORR, defined as confirmed and unconfirmed complete and partial responses among patients with measurable disease at baseline), time to treatment discontinuation (TTD, defined as the date of registration to the date of discontinuation of treatment or death), OS, and toxicity as graded by the National Cancer Institute Common Toxicity Criteria version 4.0. Post hoc analysis of site of disease progression (brain or systemic) was performed for all randomly assigned patients, regardless of whether routine brain imaging was performed. Exploratory translational end points were included and will be presented in a future report.

This trial was open to accrual through SWOG and supported by Alliance and Eastern Cooperative Oncology Group–American College of Radiology Imaging Network. It was approved by the institutional review boards of each institution, and patients provided written informed consent before any study activities.

Procedures

Patients were randomly assigned with equal probability to receive afatinib 40 mg orally daily plus cetuximab intravenously (IV) 500 mg/m^2 every 2 weeks or afatinib alone using a dynamic balancing algorithm.[15] Randomization was stratified based on performance status (0-1 *v* 2) and *EGFR* mutation type (exon 19 deletion *v* L858R mutation). Sites registered patients through the Oncology Patient Enrollment Network portal, located within the Cancer Trials Support Unit website, which is used by all National Clinical Trial Network group studies. Sites received randomized arm assignment for the patient being registered immediately at the time of registration to the study.

Diphenhydramine 50 mg IV was administered before the first dose of cetuximab to prevent hypersensitivity reaction and recommended before subsequent doses. Treatment was continued until disease progression, symptomatic deterioration, unacceptable toxicity, pregnancy, treatment delay > 28 days, or patient decision. Treatment could be continued after radiographic progression per RECIST if the patient was still deriving clinical benefit in the opinion of the treating physician. Local therapy (ie, radiotherapy or surgery) could be administered for palliative treatment while patients were in the study.

Dose reduction was required for most treatment-related grade 3-4 adverse events (AEs), and reductions were allowed for medically concerning, prolonged, or poorly tolerated grade 2 AEs. Once a reduction was applied, the reduced dose was maintained unless further dose reduction was needed. An aggressive dose-reduction schema was used, given the known toxicity profile of afatinib + cetuximab[9] (Appendix Table A1, online only).

All patients underwent disease assessment with computed tomography (CT) of the chest and abdomen as well as magnetic resonance imaging or CT of the brain within 42 days of study registration. Systemic disease assessment was repeated every 8 weeks, along with brain imaging for patients who had brain metastases at baseline, or as clinically indicated. The study was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02438722).

Statistical Analysis

The initial design required 605 patients to achieve 90% power to rule out the null of no difference in OS between the arms, at the one-sided 0.025 level using a stratified log-rank test, if the true hazard ratio (HR) for OS was 0.69. This design had an interim analysis evaluating early stopping for futility based on a comparison of PFS between the arms, on the observation of 64 PFS events, testing the alternative hypothesis (HR, 0.69) at the one-sided 10% level using a modified log-rank test statistic for testing hypotheses with HR not equal to 1, which resulted in an adjusted power of 81% (90% × 90%).[16,17] This analysis was estimated to take place when approximately 212 patients had been enrolled.

The analysis plan was revised when the primary end point of the trial was changed to PFS. The revised design required 212 eligible patients to rule out the null hypothesis of no difference in PFS between the arms, at the one-sided 0.025 level with 90% power (unadjusted), if the true PFS HR was 0.57. The design retained the interim analysis for futility when at least 64 PFS events occurred, testing the alternative hypothesis at the one-sided 10% level and recommended stopping for futility if the *P* value from a stratified log-rank test, modified for testing the non-null hypothesis, was < 10%.

The distributions for time-to-event outcomes (PFS, OS, and TTD) were estimated using the Kaplan-Meier method, and comparison of distributions was done using a stratified log-rank test and summarized with HRs estimated from Cox proportional hazards regression. Binary outcomes (response, toxicity) were summarized as proportions with associated 95% CIs, and comparisons between the arms were done using a Fisher's exact test.

Comparisons were performed using a modified intention-to-treat principle by including all eligible randomly assigned patients (excluding those who were found to be ineligible centrally after random assignment). Toxicity rates included all patients who received at least one dose of study treatment.

RESULTS

Patient Characteristics and Study Treatment

Between March 26, 2015 and April 23, 2018, 174 treatment-naïve patients with *EGFR*-mutant NSCLC were enrolled and randomly assigned to receive afatinib + cetuximab (n = 89) or afatinib alone (n = 85); of these patients, 168 were determined to be eligible (afatinib + cetuximab n = 83, afatinib alone n = 85; Fig 1). On April 23, 2018, the SWOG data safety and monitoring committee, on review of the interim analysis, determined that there was insufficient evidence to support continued accrual, and the trial was closed to further accrual.

The median age was 66 years (range, 27-93 years), 66% were female, 12% were Asian, and 53% were never-smokers (Table 1). A total of 91% of patients had a PS of 0-1. Most patients (96%) had adenocarcinoma histology, with an *EGFR* exon 19 deletion mutation detected in 64% of patients and an L858R point mutation in 36%.

As of October 18, 2019, 29 patients remained on treatment—15 in the afatinib + cetuximab arm and 14 in the afatinib arm. Reasons for trial discontinuation are included in Fig 1. During this time, a total of 138 PFS events were observed—70 in patients randomly assigned to afatinib + cetuximab and 68 in patients randomly assigned to afatinib. Among patients randomly assigned to afatinib + cetuximab, 15 continued treatment after disease progression, and 19 patients randomly assigned to afatinib alone continued treatment beyond progression.

Efficacy

There was no improvement in the primary end point of PFS in patients receiving afatinib plus cetuximab compared with afatinib alone (HR, 1.01; 95% CI, 0.72 to 1.43; $P = .94$; median, 11.9 months *v* 13.4 months; Fig 2A). Analysis of various subsets demonstrated no difference in PFS between the two arms regardless of clinical or tumor characteristic (Fig 2B).

Because patients could remain on study treatment beyond progression, TTD could differ from progression time. The duration on treatment within each arm was not different (HR, 0.90; 95% CI, 0.64 to 1.26; $P = .54$), and the median was 12.7 months (95% CI, 10.8 to 17.6 months) in the

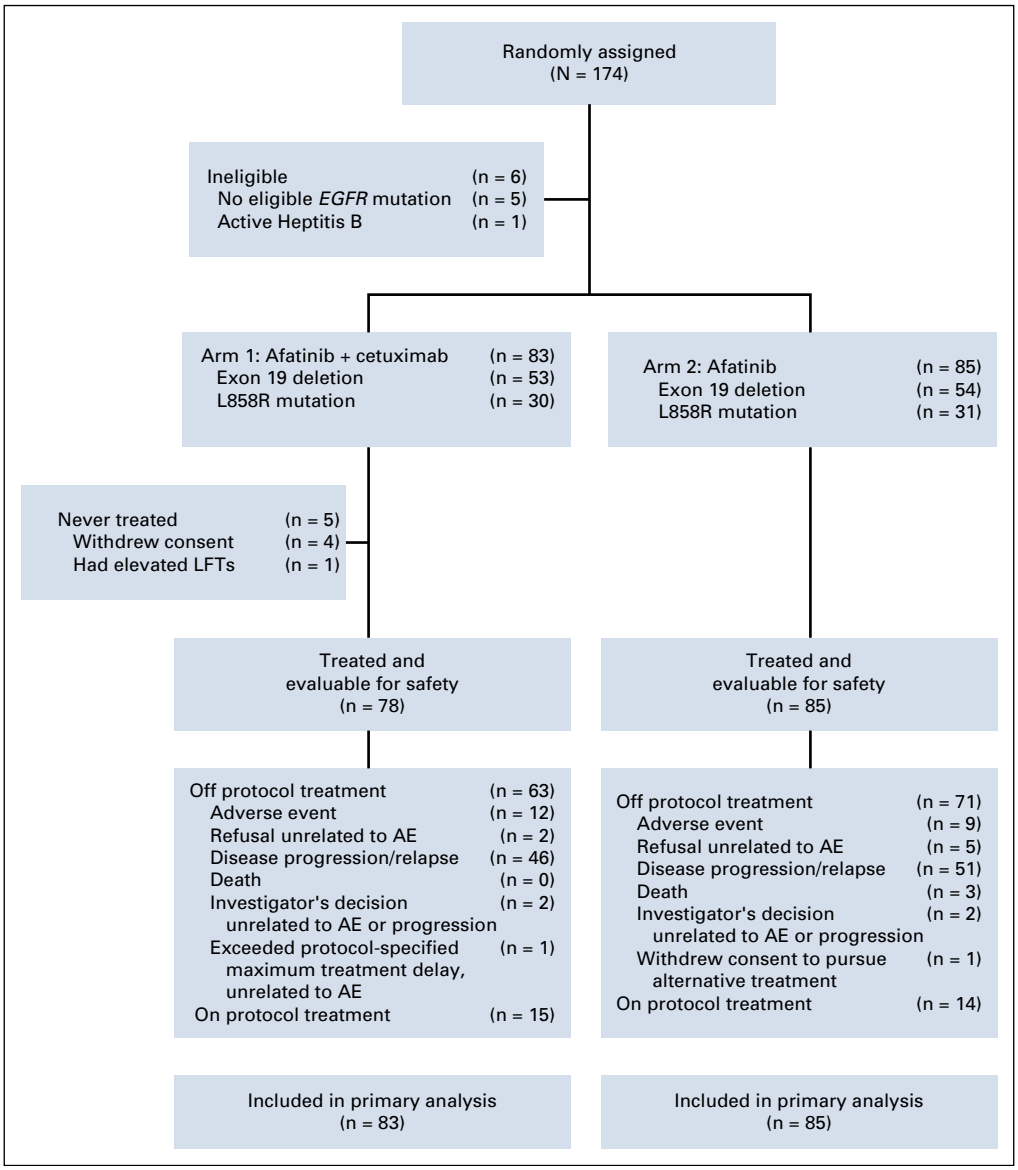

FIG 1. CONSORT diagram. AE, adverse event; LFTs, liver function tests.

cetuximab + afatinib arm and 12.2 months (95% CI, 9.3 to 15.1 months) in the afatinib arm. The median duration on treatment post progression was 5.0 months (95% CI, 2.1 to 7.2 months) for patients in the afatinib + cetuximab arm and 3.3 months (95% CI, 1.9 to 4.2) for patients in the afatinib arm.

We examined the pattern of disease progression including CNS and systemic sites (Appendix Fig A1, online only). The 1-year incidence of progression in the brain was 8% (95% CI, 3% to 15%) for patients in the afatinib + cetuximab arm and 14% (95% CI, 8% to 23%) for those in the afatinib arm, and the 1-year systemic progression rate was 46% (95% CI, 35% to 57%) and 34% (95% CI, 24% to 44%), respectively.

Of the 153 patients who had baseline measurable disease and were evaluable for response assessment, 67% in the afatinib + cetuximab arm and 74% in the afatinib arm achieved a confirmed or unconfirmed response ($P = .38$). The time to response was similar between the arms, with a median of 2.0 months (95% CI, 1.94 to 3.81 months) with afatinib + cetuximab and 1.94 months (95% CI, 1.87 to 2.04 months) with afatinib. The median duration of response was 9.4 months (95% CI, 6.6 to 16.6 months) with afatinib + cetuximab and 11.3 months (95% CI, 5.7 to 13.0 months) with afatinib. There was no difference in OS between patients receiving afatinib plus cetuximab and those receiving afatinib alone in the overall population (HR, 0.82; 95% CI, 0.50 to 1.36; $P = .44$; 2-year OS rates, 67% *v* 70%; Fig 3A) or in any subgroup (Fig 3B).

Patients with tumors harboring exon 19 deletion mutations had a longer PFS and OS compared with those with L858R mutations (Appendix Fig A2, online only). There was no difference in PFS or OS between the two treatment arms regardless of the mutation subtype (Appendix Figs A3 and A4, online only).

TABLE 1. Baseline Patient Characteristics

Characteristic	Afatinib + Cetuximab (n = 83)	Afatinib (n = 85)
Median age, years (range)	65.5 (27.9-90.5)	66.3 (39.3-93)
Female sex	59 (71)	53 (62)
Race/ethnicity		
White	59 (71)	63 (74)
Black	3 (4)	8 (9)
Asian	11 (13)	10 (12)
Pacific Islander		1 (1)
Native American	2 (2)	
Multiracial	1 (1)	
Unknown	7 (8)	3 (4)
Hispanic	9 (11)	8 (9)
Performance status		
0	38 (46)	32 (38)
1	36 (43)	47 (55)
2	9 (11)	6 (7)
EGFR mutation type		
Exon 19 deletion	53 (64)	54 (64)
L858R mutation	30 (36)	31 (36)
Histology		
Adenocarcinoma	80 (96)	81 (95)
Large cell		1 (1)
Squamous	3 (4)	
Mixed (≥ 50% squamous)		1 (1)
Mixed (< 50% squamous)		1 (1)
Other non–small cell		1 (1)
Smoking history		
Current smoker	8 (10)	6 (7)
Former smoker	32 (39)	32 (38)
Never smoker	43 (52)	47 (55)
Weight loss in the last 6 months, %		
< 5	57 (69)	57 (67)
5%-10	13 (16)	15 (18)
10-20	12 (14)	9 (11)
≥ 20	0 (0)	1 (1)
Brain metastases	27 (33)	21 (25)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Toxicity

Five patients did not receive protocol treatment and therefore were not evaluable for AEs. Grade ≥ 3 AEs related to treatment occurred in more patients who received afatinib + cetuximab compared with afatinib alone (72% *v* 40%; $P < .0001$). The most common grade ≥ 3 AEs related to treatment were acneiform rash (27% in the afatinib + cetuximab arm and 2% in the afatinib arm), maculopapular rash (13% in the afatinib + cetuximab arm and 0 in the afatinib arm), and diarrhea (15% in the afatinib + cetuximab arm and 20% in the afatinib arm). AEs related to treatment are summarized in Table 2. Treatment-related deaths occurred in one patient on afatinib + cetuximab and none on afatinib.

Dose reductions of afatinib to 30 mg were more frequent in patients receiving afatinib + cetuximab than afatinib alone (56.7% *v* 26.2%), although a similar number of patients required reduction of dose to 20 mg (13.6% *v* 16.7%). Twenty-five patients in the afatinib + cetuximab arm (30%) discontinued cetuximab because of toxicity, with a median of nine cycles containing at least one dose of cetuximab (range, 0-51). Trial discontinuation due to an AE occurred in 12 (14%) patients in the afatinib + cetuximab arm and 9 (11%) patients in the afatinib arm (Fig 1).

DISCUSSION

On the basis of the preclinical and clinical activity of the afatinib-cetuximab combination in the acquired resistance setting along with preclinical data in the TKI-naïve setting, we performed this randomized multicenter trial in treatment-naïve patients with *EGFR*-mutated NSCLC, hypothesizing that a delay in acquired resistance would occur. Unfortunately, the combination did not improve PFS. Other clinical end points, including OS, TTD, and ORR, were also not superior in patients receiving afatinib plus cetuximab compared with afatinib alone.

Treatment with a single-agent EGFR TKI remains the standard of care for patients with *EGFR*-mutant NSCLC. Although erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib are all potential options for patients, the improvement in PFS and OS of osimertinib compared with erlotinib or gefitinib[5,18] has resulted in frequent use of this agent as first-line therapy. However, even with osimertinib, almost all patients eventually develop acquired resistance, with limited treatment options available at progression. Thus, improving first-line treatment strategies for *EGFR*-mutated NSCLC remains a high research priority.

Why this combination, which is active in the resistance setting, failed in the first-line setting is unclear. Toxicity was greater in those receiving the combination, as was the frequency of afatinib dose reduction. However, these factors alone were unlikely to have accounted for the results, as prior studies have demonstrated that reduction in the dose of afatinib to 30 mg daily does not impact PFS.[19] Although trial discontinuation was similar in the two arms, many patients in the combination arm discontinued cetuximab due to adverse events, which could have diluted any biologic benefit that might have been attained with the combination. Given that afatinib + cetuximab is active in a subset of patients after progressive disease from EGFR

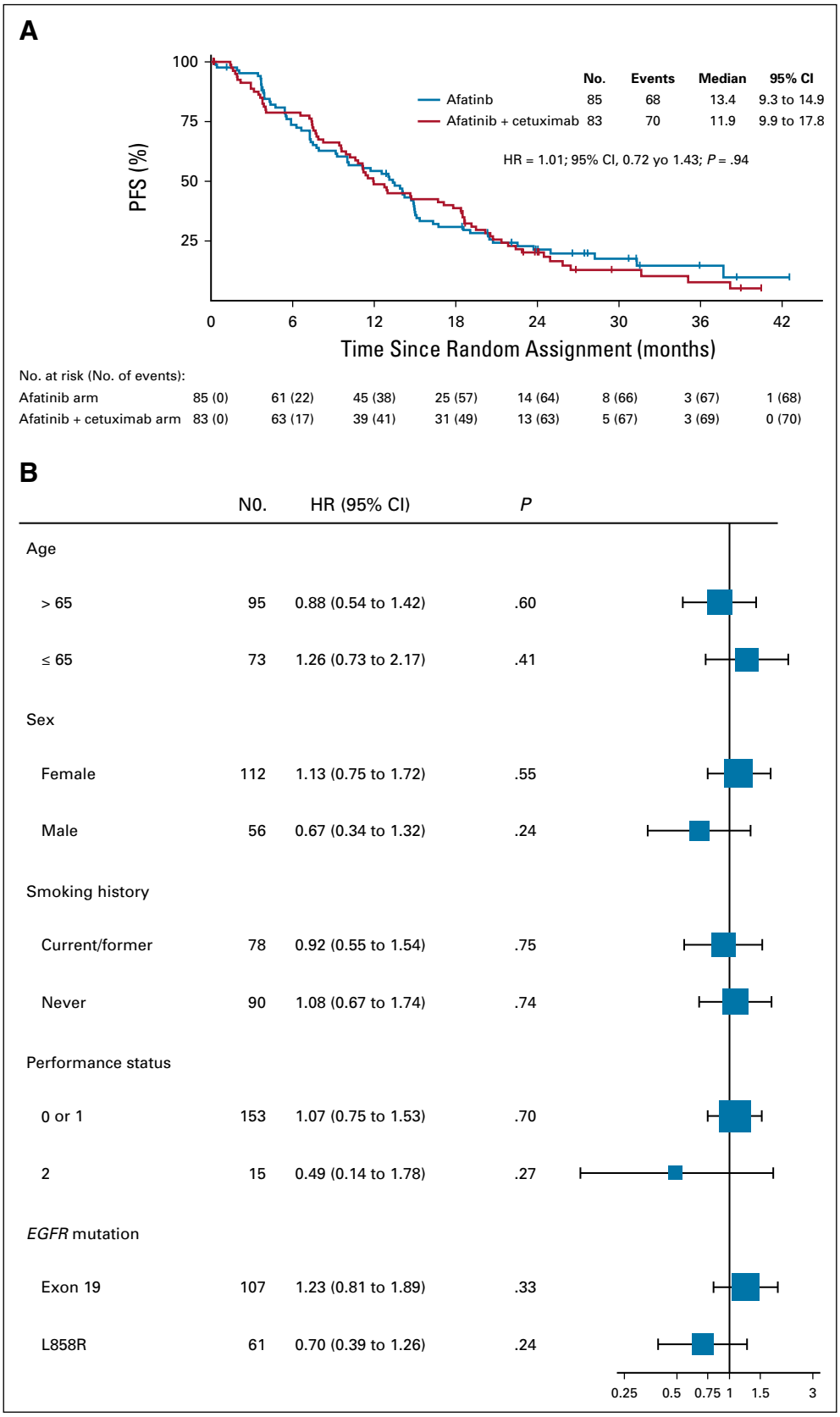

FIG 2. Progression-free survival (PFS). (A) Kaplan-Meier estimate of PFS. (B) Subgroup analysis of PFS. HR, hazard ratio.

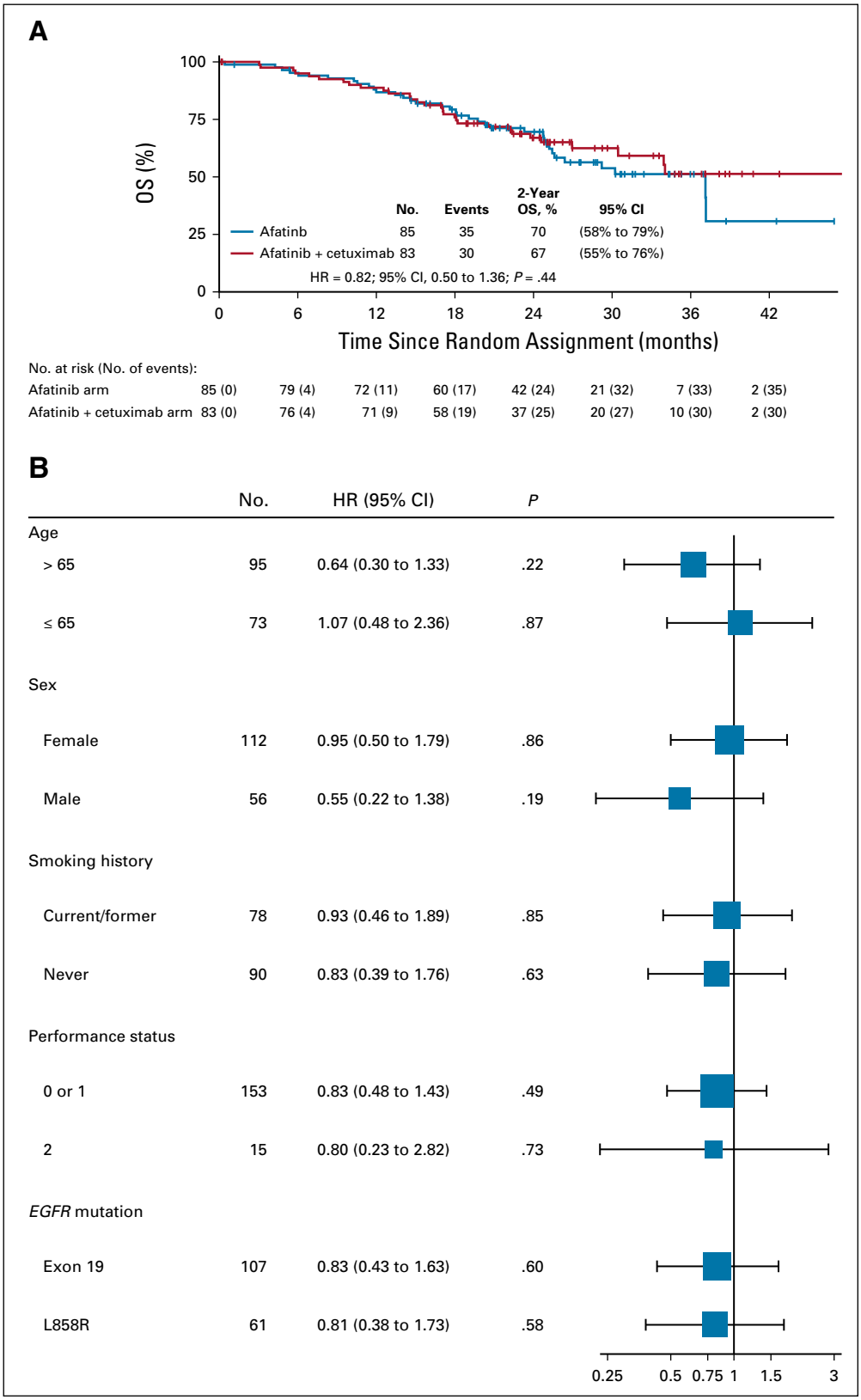

FIG 3. Overall survival (OS). (A) Kaplan-Meier estimate of OS. (B) Subgroup analysis of OS. HR, hazard ratio.

TKIs,[9] it appears likely that failure of the combination as initial therapy in our trial reflects differences in the biology of treatment-naïve disease compared with that of acquired resistance.

Since the time our study was initiated, additional preclinical data in support of EGFR TKI–monoclonal antibody combinations targeting HER-family members have emerged. Of particular interest are observations regarding *HER2*

TABLE 2. Adverse Events

	Afatinib + Cetuximab (n = 78)					Afatinib (n = 85)				
	Grade					Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Acute kidney injury		1 (1)		1 (1)				1 (1)		
Allergic reaction		1 (1)	1 (1)	1 (1)						
ALT increased	15 (19)	2 (3)		1 (1)		13 (15)	5 (6)	1 (1)		
Anemia	14 (18)	5 (6)	1 (1)			16 (19)	2 (2)		1 (1)	
AST increased	20 (26)			1 (1)		14 (16)	3 (4)			
Atrial fibrillation									1 (1)	
Creatinine increased	4 (5)	1 (1)				11 (13)	1 (1)	1 (1)	1 (1)	
Diarrhea	34 (44)	24 (31)	12 (15)			36 (42)	22 (26)	17 (20)		
Dry skin	23 (29)	21 (27)	3 (4)			28 (33)	7 (8)			
Fatigue	31 (40)	22 (28)	1 (1)			28 (33)	10 (12)	1 (1)		
Hypokalemia	16 (21)	5 (6)	4 (5)			6 (7)	2 (2)	4 (5)	1 (1)	
Lymphocyte count decreased	4 (5)	6 (8)		1 (1)		4 (5)	4 (5)	2 (2)		
Mucositis, oral	23 (29)	8 (10)	6 (8)			25 (29)	10 (12)	4 (5)		
Nausea	30 (38)	4 (5)	2 (3)			18 (21)	7 (8)	3 (4)		
Paronychia	15 (19)	19 (24)	4 (5)			19 (22)	14 (16)			
Pneumonitis			2 (3)		1 (1)					
Pruritus	17 (22)	10 (13)	3 (4)			18 (21)	5 (6)	1 (1)		
Rash, acneiform	12 (15)	29 (37)	21 (27)			33 (39)	15 (18)	2 (2)		
Rash, maculopapular	11 (14)	15 (19)	10 (13)			25 (29)	7 (8)			
Sepsis									1 (1)	
Maximum grade of any adverse event	2 (3)	20 (26)	52 (67)	3 (4)	1 (1)	9 (11)	41 (48)	31 (36)	3 (4)	

NOTE: Data are presented as No. (%). Adverse events listed include those attributed to treatment and either grade ≥ 4 or that had at least one patient with grade 3 and at least 20% with ≥ grade 1 in either arm.

Abbreviation: ALT, alanine aminotransferase.

amplification/overexpression as a resistance mechanism to EGFR-TKIs.[20] Recent studies have demonstrated that HER2 monoclonal antibody–mediated inhibition together with cetuximab and osimertinib prevent the onset of resistance to EGFR TKIs through enhanced degradation of EGFR and HER2, enhanced apoptosis, inhibition of ERK activation, and reduced levels of bypass proteins including MET, AXL, and HER3.[21] Furthermore, combinations of EGFR- and HER family–directed antibodies (targeting HER2 and ERBB3) together with EGFR TKIs have been observed to effectively overcome TKI resistance by impairing activation of bypass signaling pathways.[22,23]

Although the results of our trial do not support the use of afatinib plus cetuximab in the broad population of patients with *EGFR*-mutant lung cancer, additional investigation combining an EGFR TKI with an EGFR antibody should focus on optimizing the appropriate dose and schedule of treatment to improve tolerability and ability to deliver adequate treatment. In addition, there may be subsets of patients in whom this combination is worthy of further study. Afatinib is a pan-HER inhibitor that binds to the intracellular domain of the receptor, whereas cetuximab binds extracellularly; dual inhibition of EGFR may be more useful in tumors that are particularly dependent on signaling through the receptor. Supporting this possibility are initial data from the study of osimertinib plus necitumumab in *EGFR*-mutant tumors resistant to osimertinib that demonstrate promising activity in tumors harboring the *EGFR* C797S resistance mutation and are therefore still dependent on mutant *EGFR*.[24] Whether this combination is effective at preventing the emergence of osimertinib resistance in TKI-naïve tumors remains to be determined. In addition, preclinical studies have shown that other *EGFR* mutations that are typically resistant to EGFR TKIs may respond well to the combination of a TKI plus cetuximab, including the EGFR exon 20 insertion mutations,[25] which were not included in this trial. Finally, emerging evidence suggests that cetuximab sensitivity may vary between different types of *EGFR* mutations with reduced sensitivity of *EGFR* exon 19 deletion mutations.[26] Identifying biomarkers predictive of benefit from the addition of an EGFR antibody to a TKI is of

utmost importance, given the lack of benefit in the overall population of patients with *EGFR*-mutated lung cancer.

An important unanswered question is whether the mechanisms of resistance differ when using dual EGFR inhibition compared with treatment with a TKI alone. Resistance mechanisms vary based on the drug used, with the *EGFR* T790M mutation emerging as the dominant mechanism in patients treated with both first- and second-generation TKIs but not with third-generation agents. Whether this remains true when combining a TKI with cetuximab remains unknown, although preclinical data suggest that T790M will remain an important mechanism of resistance[11] and that third-generation TKIs such as osimertinib are likely to have activity in these cases after treatment with afatinib + cetuximab.[27] In our study, tissue- and blood-based circulating tumor DNA testing will provide insight into resistance mechanisms with combination therapy.

In summary, the addition of cetuximab to afatinib did not improve clinical outcomes and resulted in an increase in toxicity. Additional investigation into combinations of agents will be necessary to delay resistance and improve survival for patients with *EGFR*-mutant lung cancer.

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DISCLAIMER

The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. Boehringer Ingelheim Pharmaceuticals (BIPI) had no role in the design, analysis or interpretation of the results in this study; BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to BIPI substances, as well as intellectual property considerations. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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CLINICAL TRIAL INFORMATION

NCT02438722 (SWOG S1403)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.01149.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available in the Supplement tab of this article at DOI https://doi.org/10.1200/JCO.20.01149.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Trial of Afatinib Plus Cetuximab Versus Afatinib Alone for First-Line Treatment of *EGFR*-Mutant Non–Small-Cell Lung Cancer: Final Results From SWOG S1403

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APPENDIX

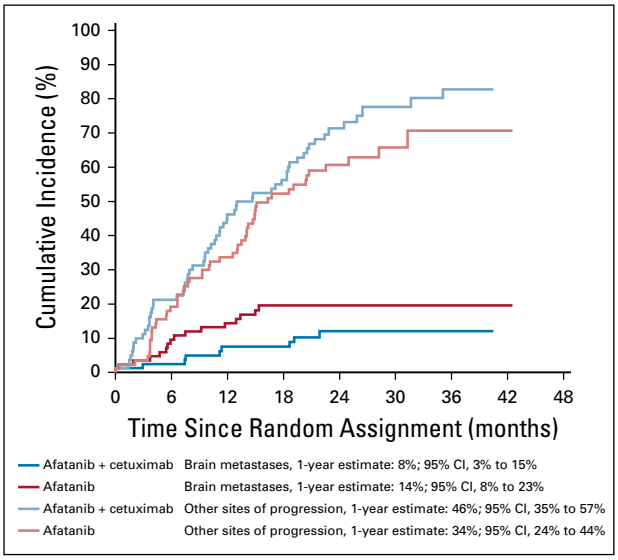

FIG A1. Cumulative incidence of disease progression in the brain or other sites.

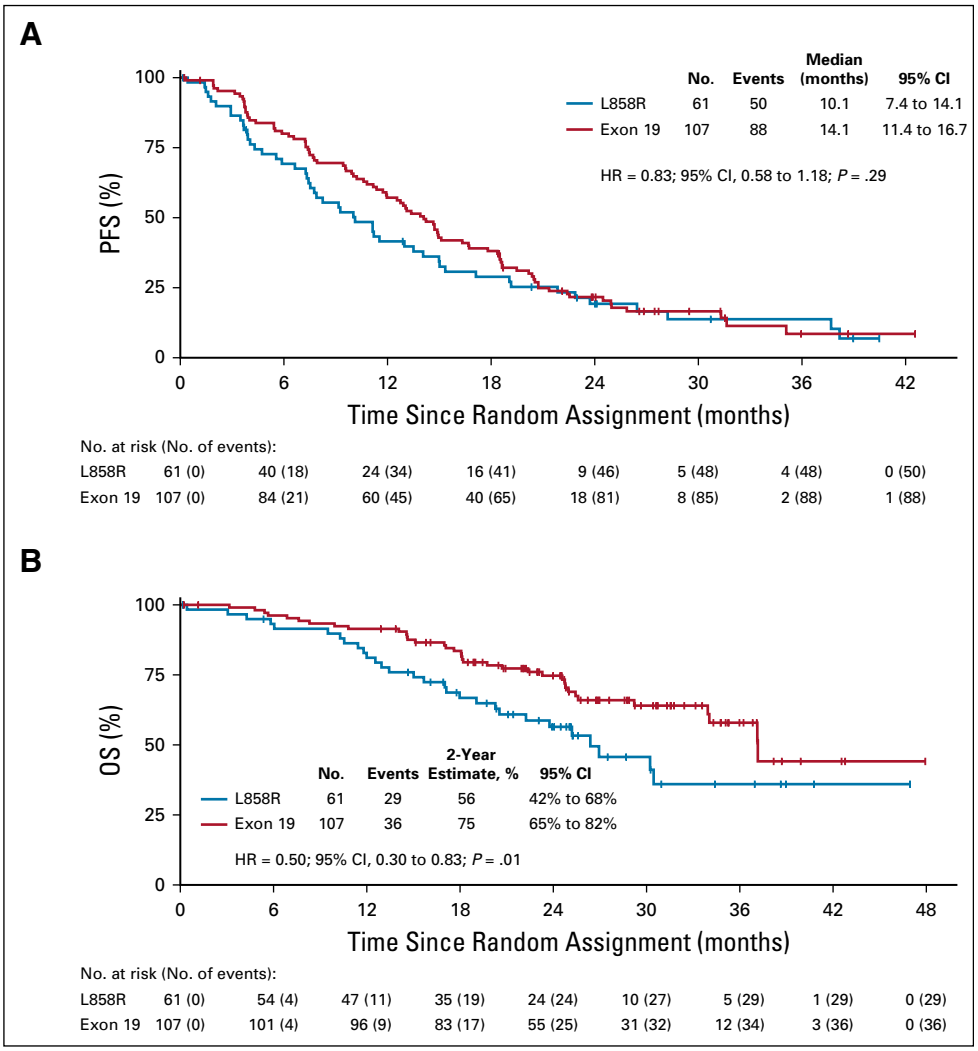

FIG A2. (A) Progression-free survival (PFS), and (B) overall survival (OS) of the different *EGFR* mutation subtypes. HR, hazard ratio.

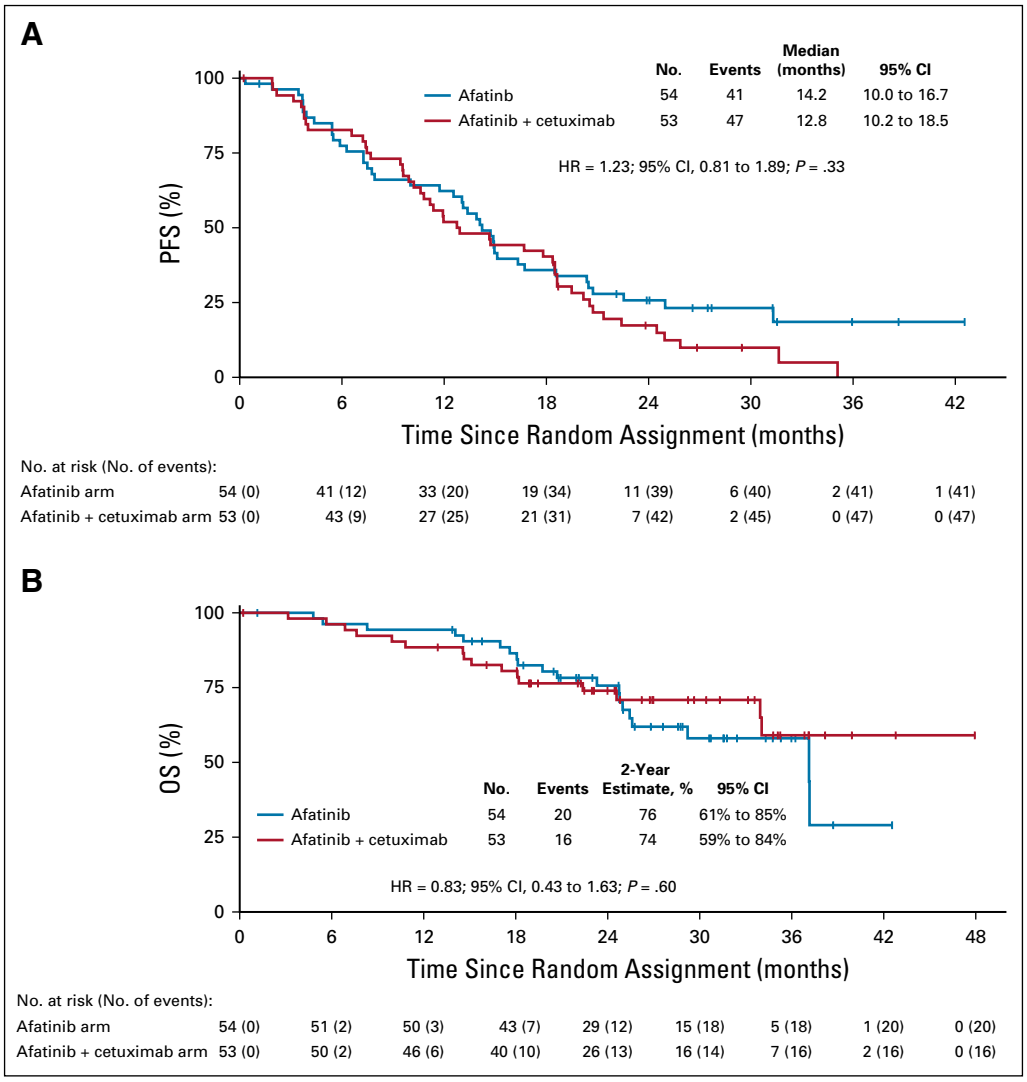

FIG A3. (A) Progression-free survival (PFS), and (B) overall survival (OS) of afatinib + cetuximab versus afatinib alone in patients with *EGFR* exon 19 deletion mutations. HR, hazard ratio.

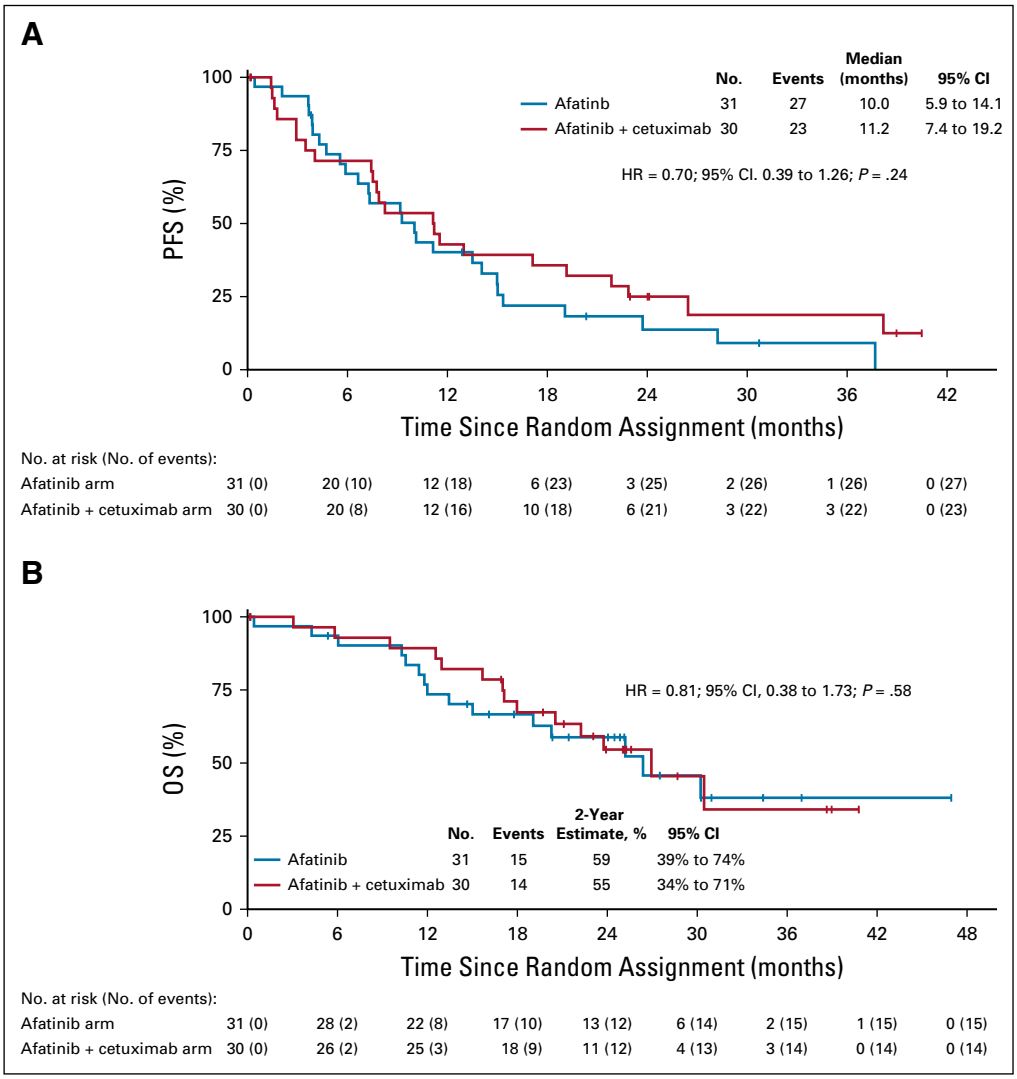

FIG A4. (A) Progression-free survival (PFS), and (B) overall survival (OS) of afatinib + cetuximab versus afatinib alone in patients with *EGFR* L858R mutations.

TABLE A1. Dose Reduction Schema

Drug	Level 0	Level 1	Level 2	Level 3	Level 4
Afatinib + cetuximab arm					
Afatinib	40 mg	30 mg	30 mg	30 mg	20 mg
Cetuximab	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue	—
Afatinib arm					
Afatinib	40 mg	30 mg	20 mg	Discontinue	—