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ORIGINAL REPORT

Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial

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See accompanying editorial on page 3985

A B S T R A C T

Purpose

Epidermal growth factor receptor (EGFR) –tyrosine kinase inhibitors have proven efficacy in advanced non–small-cell lung cancer (NSCLC). We hypothesized that erlotinib would be efficacious in the adjuvant setting.

Patients and Methods

An international randomized, double-blind, placebo-controlled study was conducted in patients with completely resected IB to IIIA NSCLC whose tumors expressed *EGFR* protein by immunohistochemistry or *EGFR* amplification by fluorescence in situ hybridization. Patients were assigned 2:1 to erlotinib 150 mg once per day or placebo for 2 years. Stratification factors were stage, histology, previous adjuvant chemotherapy, smoking status, *EGFR* amplification status, and country. The primary end point was disease-free survival (DFS); key secondary end points were overall survival (OS) and DFS and OS in patients whose tumors had *EGFR*-activating mutations (*EGFR*m-positive).

Results

A total of 973 patients were randomly assigned (November 26, 2007, to July 7, 2010). There was no statistically significant difference in DFS (median, 50.5 months for erlotinib and 48.2 months for placebo; hazard ratio, 0.90; 95% CI, 0.74 to 1.10; $P = .324$). Among the 161 patients (16.5%) in the *EGFR*m-positive subgroup, DFS favored erlotinib (median, 46.4 *v* 28.5 months; hazard ratio, 0.61; 95% CI, 0.38 to 0.98; $P = .039$), but this was not statistically significant because of the hierarchical testing procedure. OS data are immature. Rash and diarrhea were common adverse events occurring in 528 (86.4%) and 319 (52.2%) patients treated with erlotinib, respectively, versus 110 (32.1%) and 54 (15.7%) patients receiving placebo. The most common grade 3 adverse events in patients treated with erlotinib were rash (22.3%) and diarrhea (6.2%).

Conclusion

Adjuvant erlotinib did not prolong DFS in patients with *EGFR*-expressing NSCLC or in the *EGFR*m-positive subgroup. Further evaluation of erlotinib is warranted in the *EGFR*m-positive subgroup.

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INTRODUCTION

Resectable non–small-cell lung cancer (NSCLC) accounts for 20% to 25% of lung cancer cases diagnosed annually; however, only 60% of patients survive 5 years after surgery.[1] The first trial to demonstrate a significant survival benefit with adjuvant cisplatin-based chemotherapy was reported a decade ago.[2] Subsequently, additional randomized trials confirmed the role of adjuvant chemotherapy in patients with pathologic stage II and III NSCLC, and subset analyses suggested a benefit in patients with large IB tumors.[3-5] A meta-analysis provided further support for adjuvant chemotherapy.[1] Although a cisplatin-based regimen is the treatment of choice, its significant toxicity may limit its use.

Erlotinib, an oral, small-molecule tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), has proven efficacy in the treatment of advanced stage NSCLC in three distinct

settings: in an unselected and previously treated patient population (BR.21)[6]; as maintenance therapy in nonprogressing patients who had received a platinum doublet (Sequential Tarceva in Unresectable NSCLC; SATURN)[7]; and as first-line therapy in patients whose tumors have *EGFR* exon 19 deletion/exon 21 L858R-activating mutations (European Randomized Trial of Tarceva *v* Chemotherapy; EURTAC).[8]

Efforts have been made to identify patients most likely to respond to EGFR-TKIs. An exploratory analysis of the BR.21 study revealed that patients whose tumor expressed *EGFR* protein by immunohistochemistry (IHC), high polysomy, or amplification of *EGFR* by fluorescence in situ hybridization (FISH) had prolonged survival with erlotinib treatment.[9] Similarly, patients with *EGFR* IHC-positive or *EGFR* FISH-positive tumors had superior survival with gefitinib compared with placebo.[10] Collectively, these results suggested, at the time of protocol design, that *EGFR* expression by IHC or *EGFR* gene copy number may predict EGFR-TKI benefit. This hypothesis was not supported by a subsequent maintenance trial in the metastatic setting.[11]

The signal of activity observed with erlotinib in patients with *EGFR*-expressing tumors combined with its oral availability and mild nonhematologic toxicity profile led to its evaluation in earlier stages of lung cancer. The Randomized Double-Blind Trial in Adjuvant NSCLC With Tarceva (RADIANT) study evaluated whether erlotinib would increase disease-free survival (DFS) in patients with completely resected stage IB to IIIA NSCLC whose tumors express *EGFR*.

PATIENTS AND METHODS

Study Design and Patients

RADIANT was a randomized, double-blind, placebo-controlled phase III trial conducted in 204 centers across 19 countries. Adult patients with completely resected, early-stage NSCLC were eligible if they had pathologically confirmed stage IB to IIIA (microscopic N2 only) disease by the American Joint Committee on Cancer 6th edition staging system.[12] Primary tumor tissue must have been analyzed by the central laboratory and determined to be EGFR-positive by IHC ($\geq$ 1% staining) and/or FISH (*EGFR* amplification [*EGFR* gene-to-chromosome ratio of $\geq$ 2 or $\geq$ 15 *EGFR* gene copies in $\geq$ 10% of tumor cells] or high polysomy [$\geq$ 4 *EGFR* gene copies in $\geq$ 40% of tumor cells]). *EGFR* and *KRAS* mutation status was also determined by the central laboratory using WAVE HS (Transgenomic, Omaha, NE) and confirmed by Sanger sequencing. Patients must have started treatment within 3 months from surgery or if they received adjuvant chemotherapy within 6 months from surgery. Patients had to have an Eastern Oncology Cooperative Group performance status of 0 to 2 and adequate organ function. Neoadjuvant systemic therapy or adjuvant radiotherapy was not allowed. All patients provided written informed consent. Institutional review boards/ethics committees approved the protocol at all participating institutions. The study was conducted in accordance with the protocol, International Conference on Harmonization guidelines, including Good Clinical Practice, and the ethical principles that have their origin in the Declaration of Helsinki. An independent data and safety monitoring committee reviewed safety and efficacy data.

Random Assignment and Masking

Patients were randomly assigned in a 2:1 ratio to receive oral erlotinib (150 mg) or placebo once per day for 2 years. Patients were stratified according to stage, histology, previous adjuvant chemotherapy, smoking status, *EGFR* FISH status, and country. An adaptive random assignment method by Pocock and Simon[13] was used with a minimization probability parameter of 0.80. For patients receiving adjuvant chemotherapy, random assignment occurred at least 21 days from day 1 of last cycle. Baseline radiologic assessments were to be performed after surgery and within 42 days before random assignment.

Study Assessment

Patients underwent a baseline history and physical examination, postoperative computed tomography (CT) of the chest and upper abdomen, a chest radiograph, complete blood cell count, and metabolic panel. During the treatment period, CT scans were repeated at months 6, 12, 18, and 24 and chest radiographs at months 3, 9, 15, and 21. Laboratory and toxicity assessments were performed at months 1 and 3 and every 3 months thereafter during the treatment period. During the long-term follow-up period, CT scans were performed yearly and patients were observed every 6 months until year 5 and yearly thereafter. Adverse event (AE) grading was conducted according to the Common Terminology Criteria for Adverse Events, version 3.0.[14] Two dose reductions were allowed. Patients were discontinued from study treatment for unacceptable toxicity, patient or physician request, or disease relapse.

Outcomes

The primary end point was DFS in the intent-to-treat (ITT) population, defined as the time from random assignment to relapse or until death in the absence of relapse. Key secondary end points included overall survival (OS) in the ITT population, DFS, OS in the *EGFR*-activating mutations (*EGFR*m-positive) subgroup, and safety.

Statistical Analysis

The study was designed to have 80% power to detect a 33% improvement in median DFS (hazard ratio [HR], 0.75) with erlotinib (two-sided log-rank test with 5% significance) for all randomly assigned patients. The final DFS analysis would occur at 410 DFS events. The sample size calculation was based on a two-look group sequential design. One interim analysis for efficacy was planned when 75% (308 events) of the required 410 DFS events occurred. A Lan-DeMets α spending function with an O'Brien-Fleming boundary was used at the interim analysis to maintain an overall α of .05.

The null hypothesis was that DFS of the two arms was equivalent. The alternative hypothesis was that DFS was longer in either arm. The interim analysis occurred at 304 DFS events with an α of .0185; the primary DFS analysis was performed at 410 events with an α of .0445. If the primary DFS analysis was statistically significant favoring erlotinib, the null hypothesis for key secondary efficacy variables would be tested hierarchically in the following order: OS in the ITT population, DFS, and then OS in the *EGFR*m-positive subgroup.

RESULTS

The study was activated in 2006. A total of 2,500 patients were screened; 2,395 patients had results for both *EGFR* IHC and FISH. Among these patients, 92.1%, 67.9%, and 64.6% were positive for *EGFR* by IHC, FISH, or both, respectively; only 3.3% were negative for *EGFR* by both IHC and FISH. Approximately 50% of patients proceeded to random assignment. After 278 patients were randomly assigned, a drug-labeling error was discovered and enrollment was restarted. Data from the breached patient cohort are not included herein. From November 2007 through July 2010, 973 patients were randomly assigned (Fig 1; data on one additional patient were removed from the database because of inadequate Health Insurance Portability and Accountability Act documentation), with 623 and 350 patients in the erlotinib and placebo arms, respectively. A total of 11 patients (1.8%) assigned to erlotinib and 8 patients (2.3%) assigned to placebo did not receive treatment. The study groups were well balanced with respect to demographics and clinical characteristics (Table 1). Most patients were white, male, younger than 65 years, had a smoking history, and had stage IB adenocarcinoma. More than one

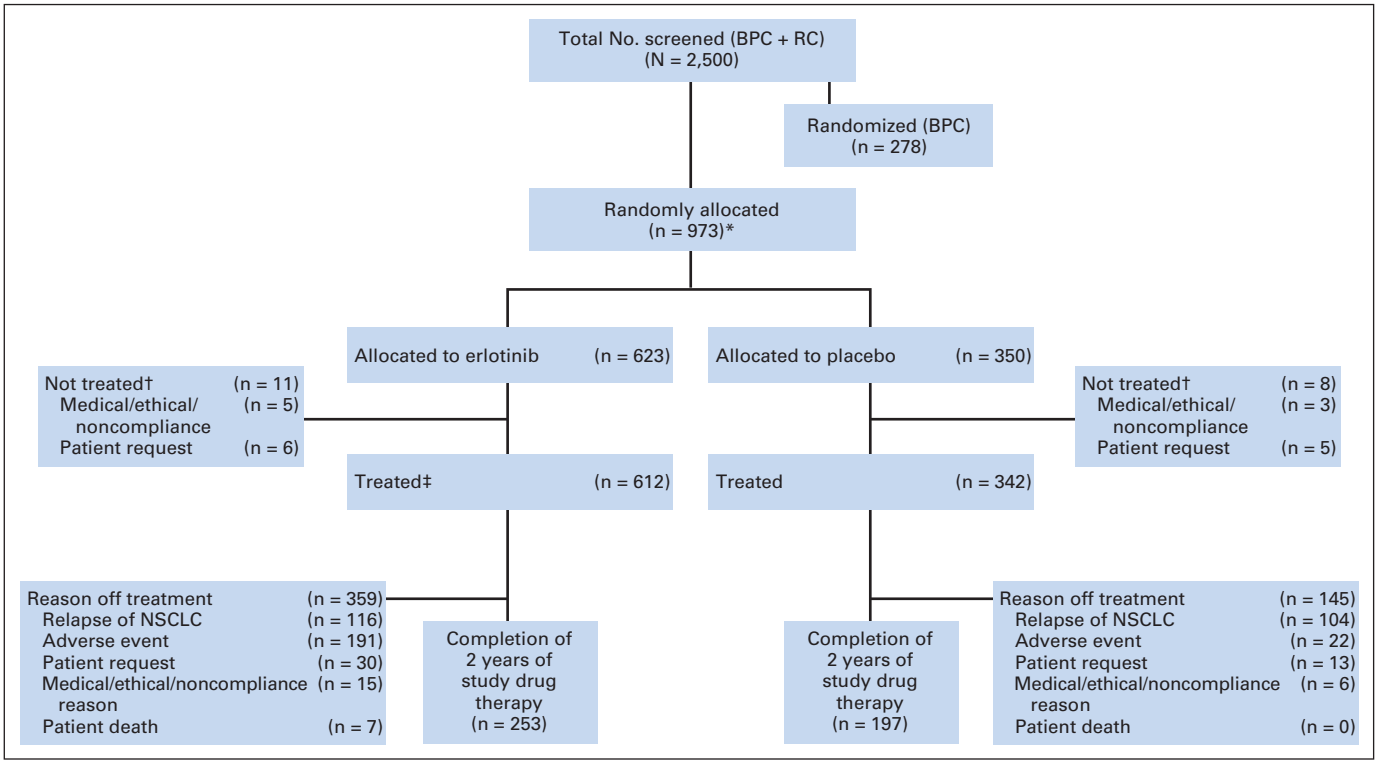

Fig 1. CONSORT diagram. (*) One additional patient was randomly assigned and received study drug but did not have appropriate Health Insurance Portability and Accountability Act documentation at the site; consequently, data for this patient were removed from the database per institutional review board request. (†) The primary reason for discontinuing treatment was reported on the case report form. (‡) The values reported represent the assigned treatment. One patient was assigned to the erlotinib arm but received placebo instead because of a dispensing error. BPC, breached patient cohort; NSCLC, non–small-cell lung cancer; RC, randomly assigned cohort.

half of the patients received adjuvant chemotherapy. The *EGFR*m-positive subgroup accounted for 16.5% (n = 161) of the total patient population. Of those patients, 55.3% (n = 89) and 44.7% (n = 72) had del19 and L858R mutations, respectively. In contrast to the ITT population, these patients were more likely to be female, never smokers, and Asian (Table 1).

At the April 2013 cutoff, there were 410 (42%) DFS events and 277 (15%) deaths. The median follow-up time was 47 months. There was no significant between-arm difference in DFS (HR, 0.90; 95% CI, 0.741 to 1.104; $P = .324$; Fig 2A). The median DFS was 50.5 months for erlotinib and 48.2 months for placebo. For subgroup analyses, refer to Table 2. The OS data are immature, with death occurring in 28% of patients (Appendix Table A1, online only). No survival difference in OS was observed (HR, 1.13; 95% CI, 0.881 to 1.448; $P = .335$; Appendix Fig A1A, online only). The stratified DFS analyses yielded consistent results.

In the *EGFR*m-positive subgroup, 102 patients were randomly assigned to erlotinib and 59 patients to placebo. Some imbalances were observed, with more patients in the erlotinib arm having stage IB and more patients in the placebo arm having stage IIIA disease. A smaller proportion of patients receiving erlotinib had lobectomies and received adjuvant chemotherapy (Table 1). Prolonged DFS was not seen in the *EGFR*m-positive subgroup for patients treated with erlotinib (HR, 0.61; 95% CI, 0.384 to 0.981; Fig 2B). The median DFS was 46.4 and 28.5 months, with 2-year DFS rates of 75% and 54% for erlotinib and placebo, respectively. This result was not statistically significant because of hierarchical testing. The median DFS in the placebo arm in the *EGFR*m-positive subgroup was shorter than that in the ITT population (28.5 and 48.2 months, respectively). In a post hoc exploratory analysis of *EGFR*m-positive patients, correcting for other variables (stage, previous chemotherapy, age, sex, smoking status, *EGFR* mutation type, and tumor size), the treatment effect on DFS (HR, 0.60; 95% CI, 0.362 to 0.978; $P = .041$) was consistent with the unadjusted analysis. Analysis by *EGFR* mutation type showed similar results between del19 and L858R subgroups (HR, 0.68 [95% CI, 0.36 to 1.28] and HR, 0.55 [95% CI, 0.27 to 1.12], respectively). The OS data are immature, with 35 deaths (22%) reported (Appendix Table A1). There was no between-arm difference in OS (HR, 1.09; 95% CI, 0.545 to 2.161; $P = .815$; Appendix Fig A1B, online only).

KRAS testing was performed on 828 patient samples. Seventeen percent (n = 143; 96 and 47 in the erlotinib and placebo groups, respectively) of the samples had a mutation. *KRAS* mutations were found in 120 (21%) of 578 patients with adenocarcinoma. *KRAS* mutational status was not prognostic nor was it predictive of a benefit to erlotinib.[14]

The most common site of relapse was lung in the ITT population and *EGFR*m+ subgroup (Appendix Table A2, online only). Among the 66 patients with *EGFR*m+ tumors who experienced a relapse, a higher rate of brain relapse was reported with erlotinib (n = 13; 37.1%) versus placebo (n = 4; 1.9%), and a lower rate of bone relapse with erlotinib (n = 5; 14.3%) versus placebo (n = 9; 29.0%).

The safety analysis was conducted on 954 (98%) of patients who received treatment. An AE was reported in 98.0% of patients receiving erlotinib and 89.5% of patients receiving placebo. Rash (defined as a

Table 1. Summary of Demographic and Baseline Characteristics (ITT population and *EGFR*m+ subgroup)

Characteristic	Patients in the ITT Population			Patients With *EGFR*m+ Tumors		
	Erlotinib (n = 623)	Placebo (n = 350)	Total (n = 973)	Erlotinib (n = 102)	Placebo (n = 59)	Total (n = 161)
Sex, No. (%)						
Female	257 (41.3)	141 (40.3)	398 (40.9)	66 (64.7)	39 (66.1)	105 (65.2)
Male	366 (58.7)	209 (59.7)	575 (59.1)	36 (35.3)	20 (33.9)	56 (34.8)
Age, years						
Mean (SD)	62.0 (9.28)	61.8 (9.34)	61.9 (9.30)	60.3 (10.15)	60.4 (9.50)	60.3 (9.89)
Median	62.0	62.0	62.0	62.0	60.0	61.0
Range	20-84	23-86	20-86	38-84	42-86	38-86
Race, No. (%)						
White	500 (80.3)	279 (79.7)	779 (80.1)	51 (50.0)	33 (55.9)	84 (52.2)
Black	14 (2.2)	11 (3.1)	25 (2.6)	0	1 (1.7)	1 (0.6)
Asian	107 (17.2)	60 (17.1)	167 (17.2)	51 (50.0)	25 (42.4)	76 (47.2)
Far East	89 (14.3)	48 (13.7)	137 (14.1)	40 (39.2)	19 (32.2)	59 (36.6)
Southeast Asia	17 (2.7)	12 (3.4)	29 (3.0)	11 (10.8)	6 (10.2)	17 (10.6)
Indian subcontinent	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian/Alaska Native	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
ECOG performance status, No. (%)						
0	385 (61.8)	211 (60.3)	596 (61.3)	61 (59.8)	38 (64.4)	99 (61.5)
1	230 (36.9)	134 (38.3)	364 (37.4)	40 (39.2)	21 (35.6)	61 (37.9)
2	6 (1.0)	5 (1.4)	11 (1.1)	1 (1.0)	0 (0.0)	1 (0.6)
Not done	2 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cigarette smoking history, No. (%)						
Never smoked or ≤ 100 cigarettes in lifetime	129 (20.7)	70 (20.0)	199 (20.5)	66 (64.7)	35 (59.3)	101 (62.7)
Former smoker	423 (67.9)	240 (68.6)	663 (68.1)	36 (35.3)	20 (33.9)	56 (34.8)
Current smoker	71 (11.4)	40 (11.4)	111 (11.4)	0 (0.0)	4 (6.8)	4 (2.5)
Region, No. (%)						
Asia Pacific	107 (17.2)	58 (16.6)	165 (17.0)	46 (45.1)	22 (37.3)	68 (42.2)
Western Europe*	167 (26.8)	89 (25.4)	256 (26.3)	12 (11.8)	10 (16.9)	22 (13.7)
Eastern Europe†	151 (24.2)	96 (27.4)	247 (25.4)	18 (17.6)	12 (20.3)	30 (18.6)
Latin America	6 (1.0)	2 (0.6)	8 (0.8)	1 (1.0)	0 (0.0)	1 (0.6)
North America	192 (30.8)	105 (30.0)	297 (30.5)	25 (24.5)	15 (25.4)	40 (24.8)
Histology, No. (%)						
Adenocarcinoma	367 (58.9)	211 (60.3)	578 (59.4)	91 (89.2)	55 (93.2)	146 (90.7)
Squamous cell carcinoma	196 (31.5)	111 (31.7)	307 (31.6)	7 (6.9)	3 (5.1)	10 (6.2)
Undifferentiated large cell	22 (3.5)	8 (2.3)	30 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed NSCLC	29 (4.7)	18 (5.1)	47 (4.8)	4 (3.9)	1 (1.7)	5 (3.1)
Other	9 (1.4)	2 (0.6)	11 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Extent of disease at diagnosis, No. (%)						
Stage IA	1 (0.2)	2 (0.6)	3 (0.3)	1 (1.0)	1 (1.7)	2 (1.2)
Stage IB	329 (52.8)	167 (47.7)	496 (51.0)	52 (51.0)	23 (39.0)	75 (46.6)
Stage IIA	42 (6.7)	24 (6.9)	66 (6.8)	9 (8.8)	0 (0.0)	9 (5.6)
Stage IIB	155 (24.9)	99 (28.3)	254 (26.1)	21 (20.6)	17 (28.8)	38 (23.6)
Stage IIIA	93 (14.9)	58 (16.6)	151 (15.5)	18 (17.6)	18 (30.5)	36 (22.4)
Stage IIIB	2 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Stage IV	1 (0.2)	0 (0.0)	1 (0.1)	1 (1.0)	0 (0.0)	1 (0.6)
Primary surgical procedure, No. (%)						
Pneumonectomy	83 (13.3)	38 (10.9)	121 (12.4)	8 (7.8)	1 (1.7)	9 (5.6)
Lobectomy	491 (78.8)	286 (81.7)	777 (79.9)	86 (84.3)	57 (96.6)	143 (88.8)
Bilobectomy	41 (6.6)	20 (5.7)	61 (6.3)	8 (7.8)	1 (1.7)	9 (5.6)
Sleeve lobectomy	6 (1.0)	3 (0.9)	9 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (0.3)	3 (0.9)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Adjuvant chemotherapy, No. (%)						
Yes	315 (50.6)	200 (57.1)	515 (52.9)	46 (45.1)	33 (55.9)	79 (49.1)
No	308 (49.4)	150 (42.9)	458 (47.1)	56 (54.9)	26 (44.1)	82 (50.9)
EGFR mutation status, No. (%)‡						
Activating mutation positive	102 (16.4)	59 (16.9)	161 (16.5)	102 (100.0)	59 (100.0)	161 (100.0)
Wild type	458 (73.5)	245 (70.0)	703 (72.3)	0 (0.0)	0 (0.0)	0 (0.0)
Undetermined	29 (4.7)	16 (4.6)	45 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)

(continued on following page)

Table 1. Summary of Demographics and Baseline Characteristics (ITT population and *EGFR*m+ subgroup) (continued)

Parameter	Patients in the ITT Population			Patients With *EGFR*m+ Tumors		
	Erlotinib (n = 623)	Placebo (n = 350)	Total (n = 973)	Erlotinib (n = 102)	Placebo (n = 59)	Total (n = 161)
Activating mutation not positive	30 (4.8)	27 (7.7)	57 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)
Other mutation positive	19 (3.0)	18 (5.1)	37 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Other mutation status undetermined	11 (1.8)	9 (2.6)	20 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Data not available	4 (0.6)	3 (0.9)	7 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor size, mm						
Mean (SD)	42.94 (22.794)	40.36 (20.235)	42.01 (21.931)	36.19 (16.034)	32.86 (11.701)	34.97 (14.646)
Median	38.00	35.00	37.00	32.00	33.00	32.00
Range	9.0-180.0	10.0-140.0	9.0-180.0	13.0-90.0	10.0-70.0	10.0-90.0

NOTE. All randomly assigned patients (ITT population).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*m+, epidermal growth factor receptor–activating mutation; ITT, intent to treat; NSCLC, non–small-cell lung cancer; SD, standard deviation.
*Western Europe included Austria, Belgium, France, Germany, Greece, Italy, Spain, and the United Kingdom.
†Eastern Europe included the Czech Republic, Hungary, Poland, Romania, and Russia.
‡The categories for *EGFR* mutation status were defined as follows: activating mutation positive, exon 19 deletion or exon 21 L858R (or both) was detected; wild type, neither exon 19 deletion nor exon 21 L858R was detected (and neither had undetermined status) and no other mutation (exons 18, 19, 20, and 21) was detected (and none had undetermined status); undetermined, exon 19 deletion or exon 21 L858R (or both) mutation status was undetermined; activating mutation not positive–other mutation positive, neither exon 19 deletion nor exon 21 L858R was detected (and neither had undetermined status), but another mutation (exon 18, 19, 20, or 21) was detected; and activating mutation not positive–other mutation status undetermined, neither exon 19 deletion nor exon 21 L858R was detected (and neither had undetermined status) and no other mutation (exon 18, 19, 20, or 21) was detected but the mutation status was undetermined for at least one.

grouped term) was the most common AE, occurring in 86.4% and 32.1% of patients, respectively (Table 3). Diarrhea was more frequent with erlotinib (52.2% versus 15.7% for placebo). Grade 3 or greater AEs that occurred in the erlotinib arm with a 1% or greater absolute difference between arms were rash (22.3%), diarrhea (6.2%), and pruritus (1.3%). Drug-related serious AEs occurred in 2.5% of patients receiving erlotinib and 1.5% of patients receiving placebo. Deaths on treatment or within 30 days of last dose of study drug occurred in 2.0% of patients receiving erlotinib and 0.9% of patients receiving placebo (Appendix Table A1). No treatment-related deaths occurred. AEs leading to permanent discontinuation occurred in 33.6% of patients receiving erlotinib and 8.5% of patients receiving placebo. An AE led to dose reduction, temporary interruption, or both in 24.5%, 18.5%, and 25.5% of patients receiving erlotinib and in 2.6%, 6.7%, and 1.5% of patients receiving placebo.

The median treatment duration in the ITT population was 11.9 and 21.9 months for erlotinib and placebo, respectively. Dose reductions occurred in 44.4% of patients receiving erlotinib versus 3.8% of patients receiving placebo. Completion of planned treatment was reported as the reason for discontinuing treatment in 40.6% and 56.3% of randomly assigned patients in the erlotinib and placebo arms, respectively (41.3% and 57.6% of treated patients in the erlotinib and placebo arms, respectively).

The safety profile for the 159 treated patients in the *EGFR*m-positive subgroup was similar to the overall population (Table 3). Rash and diarrhea were more frequent for erlotinib, at 93.0% and 62.0%, respectively, versus 40.7% and 18.6% for placebo, respectively. Grade 3 or greater AEs occurring in more than 2% of patients were experienced in patients receiving erlotinib only (rash, 19%; and diarrhea, 5%). An AE leading to permanent discontinuation occurred in 30.0% of patients receiving erlotinib and in 5.1% of patients receiving placebo. AEs led to dose reduction, interruption, or both in 22.0%, 22.0%, and 34.0% of patients receiving erlotinib versus 1.7%, 6.8%, and 1.7% of patients receiving placebo.

The median treatment duration in the *EGFR*m-positive subgroup was 21.2 and 21.9 months for erlotinib and placebo, respectively. Dose reductions occurred in 46.0% of patients receiving erlotinib versus 3.4% of patients receiving placebo. Most erlotinib dose reductions were 100 mg. Completion of planned treatment was reported as the reason treatment was discontinued in 52.9% of erlotinib-treated patients and 54.2% of placebo-treated patients.

DISCUSSION

Adjuvant erlotinib did not improve DFS in patients with *EGFR* IHC- or FISH-positive tumor in this trial. Our hypothesis that this subset of patients might benefit from adjuvant erlotinib was based on data from retrospective exploratory biomarker analyses of two trials in advanced NSCLC (BR.21[15] and ISEL [Iressa Survival Evaluation in Lung Cancer][10]), which suggested that IHC and FISH might be predictive of EGFR-TKI efficacy. Subsequent to activation of RADIANT, results from two phase III studies failed to show that *EGFR* expression by IHC or FISH was predictive of EGFR-TKI responsiveness in the metastatic setting. The INTEREST (Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere) trial, a noninferiority trial of gefitinib versus docetaxel in previously treated patients, did not meet its coprimary end point for *EGFR* FISH positivity to predict improved survival with gefitinib.[16] *EGFR* protein expression also was not shown to predict improved survival with gefitinib.[16] The SATURN trial, which evaluated erlotinib or placebo as maintenance therapy after a first-line doublet in unselected patients, met its coprimary end point of prolonging progression-free survival in patients with 10% or greater *EGFR* IHC expression; however, the prospective molecular marker analysis did not demonstrate that *EGFR* expression by IHC or FISH was predictive of erlotinib responsiveness.[11]

During the years, emerging data have demonstrated that *EGFR*m-positive del19 and L858R are the strongest predictors of EGFR-TKI sensitivity in advanced disease. Our study, the largest prospective data set of resected *EGFR*m-positive NSCLC treated with an EGFR-TKI, is limited because patients were not stratified by *EGFR* mutation status. Stratification by *EGFR*m-positive status was not

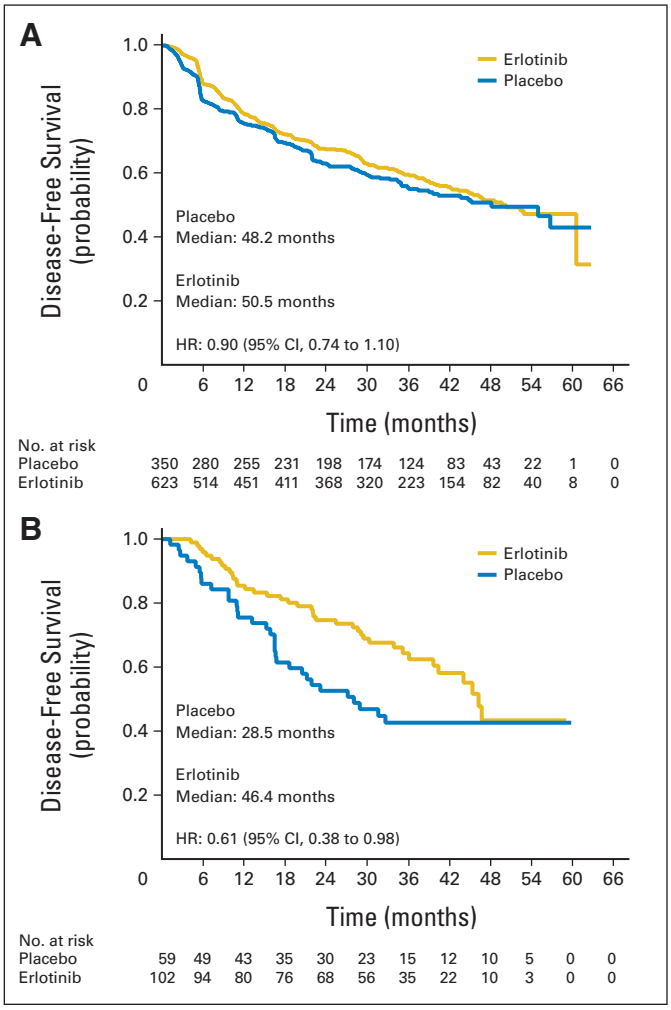

Fig 2. Disease-free survival in (A) the intent-to-treat population, and (B) the subgroup with epidermal growth factor receptor–activating mutations. HR, hazard ratio.

Table 2. Subgroup Analysis of DFS by Stratification Factor (excluding country)

Category	Subgroup	No.	Hazard Ratio	95% CI
All	All*	973	0.90	0.741 to 1.104
Disease stage†				
Stage IB		496	0.98	0.710 to 1.352
Stage II		320	0.82	0.594 to 1.138
Stage IIIA		151	1.08	0.712 to 1.631
Adjuvant chemotherapy				
Yes		515	0.87	0.672 to 1.130
No		458	0.98	0.716 to 1.337
Cigarette smoking history				
Never		199	0.91	0.596 to 1.387
Current		111	0.79	0.446 to 1.406
Former		663	0.93	0.724 to 1.185

NOTE. Data included are subject to a cutoff date of April 6, 2013.
Abbreviation: DFS, disease-free survival.
*Cox model without stratification.
†Six patients had stage other than IB to IIIA: IA (n = 1), IIIB (n = 2), and IV (n = 1) patients in the erlotinib arm and IA (n = 2) patients in the placebo arm.

feasible, because a substantial proportion of patients were already enrolled by the time definitive evidence emerged in the literature. There were between-arm imbalances in some disease characteristics, and the placebo arm in the *EGFR*m-positive subgroup had substantially worse DFS than the ITT population. Thus, interpretation of the near doubling of the median DFS with erlotinib in the *EGFR*m-positive subgroup is limited.

A possible benefit for adjuvant EGFR-TKI was suggested in a retrospective analysis of 167 patients with resected stage I to IIIA NSCLC with *EGFR*-mutated tumors.[17] Fifty-six patients (33%) received an EGFR-TKI. In a multivariable analysis, the 2-year DFS rate was 89% for the EGFR-TKI group versus 72% for the untreated group (HR, 0.53; 95% CI, 0.28 to 1.03; $P = .06$). These data led to a single-arm, multi-institutional, prospective phase II study known as the SELECT trial, in which 100 patients with resected stage IA to IIIA NSCLC and an *EGFR*-mutated tumor received adjuvant erlotinib for 2 years after standard-of-care treatment.[18] With a median follow-up of 3.4 years, the 2-year DFS rate was encouraging at 89%.[18] These results must be viewed cautiously and cannot be compared directly with our results because of the differences in patient characteristics, especially the inclusion of patients with stage IA disease, the shorter follow-up time, and the lack of an untreated control arm.

We undertook an exploratory analysis to determine if *KRAS* mutation status could have influenced our results. We did not observe a prognostic or predictive role for *KRAS* mutational status, but our analysis is limited by small patient numbers.

No new safety signals were observed in the overall population or in the *EGFR*m-positive subgroup. Although a slight imbalance of deaths was observed during the treatment period, there were no treatment-related deaths. Erlotinib treatment duration was substantially longer in the *EGFR*m-positive subgroup than in the overall group, despite a similar rate of AEs, perhaps because patients with clinical characteristics associated with an increased frequency of having an *EGFR*m-positive tumor were encouraged to remain on treatment (results of centralized EGFR mutation testing were not provided to investigators unless requested, which rarely occurred). Slightly more than half of the patients in the mutant subgroup completed the planned treatment period.

It is not known if a longer treatment duration would have provided a different result. Two years of therapy was selected to be consistent with the BR.19 study and the SWOG 0023 trial, which evaluated postoperative adjuvant and maintenance gefitinib in patients with locally advanced lung cancer, respectively.[19,20] Data supporting evaluation of a longer duration of adjuvant EGFR-TKI come from the SELECT trial, in which only four patients experienced relapse while still receiving erlotinib.[18] A treatment duration longer than that studied in this trial may be needed to achieve the goal of increasing the cure rate of early-stage NSCLC in an *EGFR*m-positive population. We observed that early-stage patients are often unwilling to tolerate even modest toxicity, and so a starting dose of lower than 150 mg once per day may be needed for future adjuvant studies to minimize toxicity and improve compliance. The efficacy of a lower dose of erlotinib has not been studied prospectively in a randomized trial in patients with NSCLC. There have been reports of responses in patients with *EGFR*m-positive advanced NSCLC receiving 25 mg once per day[21]; however, a single-arm phase II study[22] and a retrospective series[23] suggest that response rate and progression-free survival observed with a reduced erlotinib dose may not be equivalent to that of the standard dose.

Table 3. AEs ≥ 5% in Either Arm or Grade 3 or Greater AEs in ≥ 1% in Either Arm (treated population and *EGFR*m+ subgroup)

	All Treated				*EGFR*m+ Subgroup			
	Erlotinib (n = 611)		Placebo (n = 343)		Erlotinib (n = 100)		Placebo (n = 59)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
AEs, No. (%)								
Rash*	528 (86.4)	136 (22.3)	110 (32.1)	1 (0.3)	93 (93.0)	19 (19.0)	24 (40.7)	0 (0.0)
Diarrhea	319 (52.2)	38 (6.2)	54 (15.7)	1 (0.3)	62 (62.0)	5 (5.0)	11 (18.6)	0 (0.0)
Pruritus	161 (26.4)	8 (1.3)	51 (14.9)	0 (0.0)	44 (44.0)	0 (0.0)	9 (15.3)	0 (0.0)
Dry skin	127 (2.8)	2 (0.3)	50 (14.6)	0 (0.0)	23 (23.0)	0 (0.0)	12 (20.3)	0 (0.0)
Cough	121 (19.8)	1 (0.2)	69 (20.1)	1 (0.3)	27 (27.0)	0 (0.0)	17 (28.8)	0 (0.0)
Fatigue	119 (19.5)	5 (0.8)	49 (14.3)	3 (0.9)	19 (19.0)	1 (1.0)	13 (22.0)	0 (0.0)
Dyspnea	89 (14.6)	7 (1.1)	62 (18.1)	5 (1.5)	15 (15.0)	0 (0.0)	7 (11.9)	0 (0.0)
Nausea	84 (13.7)	2 (0.3)	45 (13.1)	1 (0.3)	13 (13.0)	0 (0.0)	10 (16.9)	0 (0.0)
Anorexia	80 (13.1)	4 (0.7)	24 (7.0)	2 (0.6)	14 (14.0)	1 (1.0)	8 (13.6)	0 (0.0)
Alopecia	67 (11.0)	1 (0.2)	11 (3.2)	0 (0.0)	11 (11.0)	0 (0.0)	4 (6.8)	0 (0.0)
Stomatitis	61 (10.0)	3 (0.5)	4 (1.2)	0 (0.0)	17 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased weight	56 (9.2)	2 (0.3)	20 (5.8)	1 (0.3)	9 (9.0)	0 (0.0)	3 (5.1)	0 (0.0)
Vomiting	55 (9.0)	4 (0.7)	24 (7.0)	1 (0.3)	6 (6.0)	0 (0.0)	5 (8.5)	0 (0.0)
Epistaxis	48 (7.9)	0 (0.0)	5 (1.5)	2 (0.6)	10 (10.0)	0 (0.0)	1 (1.7)	0 (0.0)
Headache	42 (6.9)	3 (0.5)	41 (12.0)	4 (1.2)	8 (8.0)	0 (0.0)	10 (16.9)	0 (0.0)
Back pain	40 (6.5)	4 (0.7)	25 (7.3)	2 (0.6)	8 (8.0)	1 (1.0)	6 (10.2)	0 (0.0)
Insomnia	40 (6.5)	2 (0.3)	21 (6.1)	0 (0.0)	11 (11.0)	0 (0.0)	7 (11.9)	0 (0.0)
Asthenia	39 (6.4)	5 (0.8)	21 (6.1)	1 (0.3)	6 (6.0)	1 (1.0)	2 (3.4)	0 (0.0)
Paronychia	39 (6.4)	6 (1.0)	2 (0.6)	0 (0.0)	13 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasms	36 (5.9)	1 (0.2)	7 (2.0)	0 (0.0)	4 (4.0)	0 (0.0)	3 (5.1)	0 (0.0)
Abdominal pain	35 (5.7)	3 (0.5)	14 (4.1)	4 (1.2)	8 (8.0)	0 (0.0)	2 (3.4)	0 (0.0)
Constipation	35 (5.7)	0 (0.0)	23 (6.7)	0 (0.0)	10 (10.0)	0 (0.0)	2 (3.4)	0 (0.0)
Conjunctivitis	34 (5.6)	3 (0.5)	0 (0.0)	0 (0.0)	7 (7.0)	1 (1.0)	0 (0.0)	0 (0.0)
Depression	33 (5.4)	2 (0.3)	12 (3.5)	0 (0.0)	4 (4.0)	0 (0.0)	3 (5.1)	0 (0.0)
Dry eye	31 (5.1)	1 (0.2)	3 (0.9)	0 (0.0)	8 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	31 (5.1)	1 (0.2)	15 (4.4)	0 (0.0)	3 (3.0)	0 (0.0)	2 (3.4)	0 (0.0)
Nasopharyngitis	29 (4.7)	0 (0.0)	30 (8.7)	0 (0.0)	6 (6.0)	0 (0.0)	9 (15.3)	0 (0.0)
Upper abdominal pain	28 (4.6)	0 (0.0)	20 (5.8)	1 (0.3)	7 (7.0)	0 (0.0)	4 (6.8)	0 (0.0)
Dizziness	26 (4.3)	1 (0.2)	22 (6.4)	0 (0.0)	7 (7.0)	1 (1.0)	5 (8.5)	0 (0.0)
Arthralgia	23 (3.8)	1 (0.2)	25 (7.3)	1 (0.3)	7 (7.0)	0 (0.0)	3 (5.1)	0 (0.0)
Musculoskeletal pain	20 (3.3)	0 (0.0)	24 (7.0)	1 (0.3)	4 (4.0)	0 (0.0)	5 (8.5)	0 (0.0)
Pneumonia	22 (3.6)	8 (1.3)	7 (2.0)	2 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increased weight	16 (2.6)	5 (0.8)	20 (5.8)	14 (4.1)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	3 (0.5)	3 (0.5)	5 (1.5)	4 (1.2)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)
AE of interest								
ILD-like events†	11 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. All treated patients. One patient was assigned to the erlotinib arm but received placebo instead because of a dispensing error. The safety analyses using all randomly assigned patients who received at least one dose of study drug were based on the actual treatment the patient received; therefore, n = 611 for the erlotinib arm, and n = 343 for the placebo arm.
Abbreviations: AE, adverse event; *EGFR*m+, epidermal growth factor receptor–activating mutation; ILD, interstitial lung disease.
*Grouped term.
†Broad standardized *Medical Dictionary for Regulatory Activities* query.

In conclusion, this study did not show a DFS benefit for erlotinib in patients with IHC- or FISH-positive NSCLC. Similarly, the study failed to demonstrate a DFS benefit for erlotinib in the *EGFR*m-positive subgroup. The trend toward improvement in DFS with erlotinib in the *EGFR*m-positive subgroup warrants further evaluation. A phase III US intergroup trial of adjuvant erlotinib in *EGFR*m-positive NSCLC is actively enrolling patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial

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Appendix

Table A1. Summary of Deaths (all treated population and *EGFR*m+ subgroup)

Variable	All Treated Population		*EGFR*m+ Subgroup	
	Erlotinib (n = 611)	Placebo (n = 343)	Erlotinib (n = 100)	Placebo (n = 59)
All deaths				
Died, No. (%)	179 (29.3)	93 (27.1)	21 (21.0)	13 (22.0)
Primary cause of death, No. (%)				
NSCLC relapse	120 (19.6)	69 (20.1)	12 (12.0)	11 (18.6)
Intercurrent illness	13 (2.1)	7 (2.0)	0	0
Other	15 (2.5)	6 (1.7)	4 (4.0)	1 (1.7)
Unknown	31 (5.1)	11 (3.2)	5 (5.0)	1 (1.7)
Deaths during treatment or within 30 days from last dose				
Died, No. (%)	12 (2.0)	3 (0.9)	2 (2.0)	0
Primary cause of death, No. (%)				
NSCLC relapse	3 (0.5)	2 (0.6)	—	—
Intercurrent illness	5 (0.8)	1 (0.3)	—	—
Cardiac failure	1 (0.2)	0	0	0
Cardiorespiratory arrest	1 (0.2)	0	0	0
Cardiovascular insufficiency	1 (0.2)	0	0	0
Cerebrovascular accident	1 (0.2)	0	0	0
Pulmonary embolism	1 (0.2)	1 (0.2)	0	0
Other	3 (0.5)	0	2	—
Cerebrovascular accident	1 (0.2)	0	0	0
Multiorgan failure	1 (0.2)	0	1 (1.0)	0
Respiratory failure	1 (0.2)	0	1 (1.0)	0
Unknown	1 (0.2)	0	—	—

Abbreviations: *EGFR*m+, epidermal growth factor receptor–activating mutation; NSCLC, non–small-cell lung cancer.

Table A2. Site of Disease Relapse for the ITT Population and *EGFR*m+ Subgroup

Site of Relapse*	ITT Population		*EGFR*m+ Subgroup	
	Erlotinib (n = 623)	Placebo (n = 350)	Erlotinib (n = 102)	Placebo (n = 59)
Patients experiencing relapse, No. (%)	230 (36.9)	152 (43.4)	35 (34.3)	31 (52.5)
Disease site, No. (%)				
Lung	105 (45.7)	66 (43.4)	15 (42.9)	17 (54.8)
Brain	48 (20.9)	26 (17.1)	13 (37.1)	4 (12.9)
Mediastinum	34 (14.8)	21 (13.8)	2 (5.7)	2 (6.5)
Bone	32 (13.9)	27 (17.8)	5 (14.3)	9 (29.0)
Liver	24 (10.4)	14 (9.2)	2 (5.7)	2 (6.5)
Adrenal	13 (5.7)	14 (9.2)	1 (2.9)	0 (0.0)
Pleura	10 (4.3)	10 (6.6)	4 (11.4)	2 (6.5)
Peripheral lymph node	6 (2.6)	7 (4.6)	1 (2.9)	2 (6.5)
Pleural effusion	6 (2.6)	2 (1.3)	1 (2.9)	2 (6.5)
Kidney	5 (2.2)	2 (1.3)	0 (0.0)	0 (0.0)
Pelvic	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Central nervous system/spinal	2 (0.9)	2 (1.3)	1 (2.9)	0 (0.0)
Head and neck	2 (0.9)	3 (2.0)	0 (0.0)	0 (0.0)

NOTE. All randomly assigned patients (ITT population). Includes all sites of relapse reported within 30 days of the first relapse date. More than one site of relapse may have been reported for a patient.
Abbreviations: *EGFR*m+, epidermal growth factor receptor–activating mutation; ITT, intent to treat.
*Occurring in 1% or greater of patients in either arm in the ITT population.

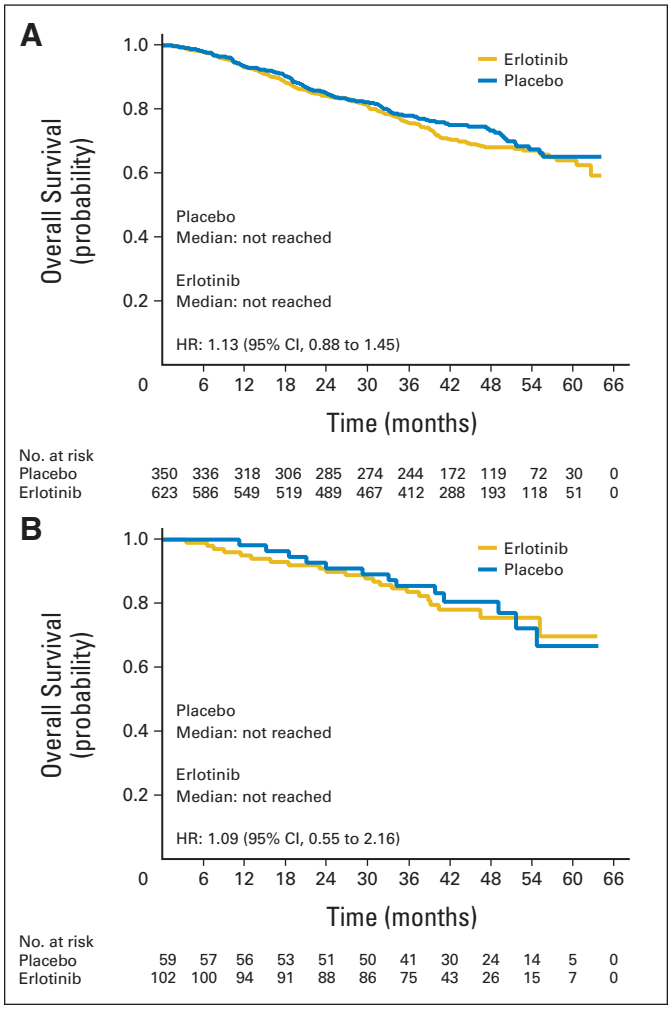

Fig A1. Overall survival in (A) the intent-to-treat population, and (B) the subgroup with epidermal growth factor receptor–activating mutations. HR, hazard ratio.