Received: 24 May 2022 | Revised: 29 August 2022 | Accepted: 7 October 2022

DOI: 10.1002/cncr.34553

ORIGINAL ARTICLE

A randomized Phase 2 study to compare erlotinib with or without bevacizumab in previously untreated patients with advanced non–small cell lung cancer with *EGFR* mutation

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Abstract

Background: This study evaluated whether an addition of bevacizumab to erlotinib improves clinical outcomes in patients with advanced *EGFR*-mutated non–small cell lung cancer (NSCLC).

Methods: This is an open-label, multicenter, randomized Phase 2 study in South Korea. Chemonaïve patients with Stage IIIB/IV NSCLC with *EGFR* 19 deletion or L858R mutation were eligible. Asymptomatic brain metastasis (BM) was enrolled without local treatment. Patients received either erlotinib plus bevacizumab or erlotinib.

Results: Between December 2016 and March 2019, 127 patients were randomly assigned to receive erlotinib plus bevacizumab (n = 64) or erlotinib (n = 63). Fifty-nine (46.5%) patients had baseline BM. Fewer patients in the erlotinib plus bevacizumab arm received radiotherapy for BM than in the erlotinib arm (10.3% vs. 40.0%). A trend toward longer progression-free survival (PFS) was observed in the erlotinib plus bevacizumab arm compared with the erlotinib alone arm; however, it was not statistically significant (median PFS, 17.5 months vs. 12.4 months; hazard ratio [HR], 0.74; 95% CI, 0.51–1.08; p = .119). The unplanned subgroup analysis showed a longer PFS with erlotinib plus bevacizumab in patients with BM (median PFS, 18.6 months vs. 10.3 months; HR, 0.54; 95% CI, 0.31–0.95; p = .032). Grade 3 or worse adverse events occurred in 56.6% of the erlotinib plus bevacizumab arm and 20.6% of the erlotinib arm.

Conclusions: Although it was not statistically significant, a trend to improvement in PFS was observed in patients with erlotinib plus bevacizumab compared to erlotinib alone.

The first two authors contributed equally to this work.

This study was presented in part at the 2022 American Society for Clinical Oncology, June 4–8, 2022, Chicago, Illinois.

Funding information
National Cancer Center Research Grant, Grant/Award Number: 2210551-1

Plain Language Summary

A randomized Phase 2 study compared erlotinib with or without bevacizumab in previously untreated patients with advanced non–small cell lung cancer with *EGFR* mutation. The erlotinib plus bevacizumab failed to improve median progression-free survival compared with the erlotinib alone. However, the progression-free survival benefit from erlotinib plus bevacizumab was found in patients with brain metastasis with no severe hemorrhagic adverse effects.

KEYWORDS
anti-angiogenesis, brain metastasis, *EGFR* mutation, nonsmall cell lung cancer, targeted therapy

INTRODUCTION

Molecularly targeted drugs blocking the activity of epidermal growth factor receptor (EGFR) were developed and marketed in the early 2000s.[1] Multiple clinical and translational studies revealed these drugs demonstrated dramatic and durable response in tumors harboring the mutations in the *EGFR* gene including exon 19 deletion and exon 21 L858R.[2–6] Thus, the use of an EGFR tyrosine kinase inhibitor (TKI) has been the standard first-line treatment for patients with advanced non–small cell lung cancer (NSCLC) with *EGFR* mutations. However, most patients who exhibit an initial good response to EGFR-TKI develop drug resistance and experience disease progression, with median response duration of no longer than 2 years, regardless of drug type.[7] Moreover, after discontinuation of the drug, no promising strategy to overcome the resistance to EGFR-TKIs has been developed. Efforts to extend the treatment duration of first-line EGFR-TKI treatments have been actively ongoing. The addition of different therapeutics to the EGFR-TKI treatment has been the main approach to improve the efficacy of EGFR-TKI.

The vascular endothelial growth factor receptor (VEGFR) pathway is a key mediator of angiogenesis in cancer cells, which is essential for rapid cell development and growth.[8] Preclinical studies reported that *EGFR*-mutant cancer cells have higher levels of VEGF and VEGFR expression compared with *EGFR* wild-type cancer cells and that this VEGF/VEGFR signaling pathway itself activates the PI3K/AKT and MAPK pathways.[9,10] Moreover, this phenomenon was enhanced when the *EGFR*-mutant cancer cells became resistant to EGFR inhibition after treatment with an EGFR inhibitor.[11] These studies provided evidence that blocking both EGFR and VEGFR in cancer cells with *EGFR* mutations would prolong the treatment efficacy and delay drug resistance. Recently, several randomized Phase 2 and 3 clinical studies evaluated first-line combination treatments using EGFR and VEGFR inhibitors in patients with advanced NSCLC and *EGFR* mutations.[12–18] Some studies showed significant progression-free survival (PFS) benefit from the concurrent blockade of EGFR and VEGFR,[12–15] whereas other studies failed to demonstrate any PFS benefit.[16–18] Thus, this study aimed to investigate the effect of combining the anti-VEGF monoclonal antibody, bevacizumab, with the EGFR-TKI, erlotinib, in improving clinical outcomes in previously untreated Korean patients with advanced *EGFR*-mutated NSCLC.

PATIENTS AND METHODS

Patients

This study is a multicenter, prospective, open-label, randomized, Phase 2 study that was conducted at four medical centers in South Korea (ClinicalTrials.gov, no. NCT03126799). Eligibility criteria were age 19 years or older; cytologically or histologically confirmed NSCLC; chemonaïve Stage IIIB or IV lung cancer, as defined by the 8th American Joint Committee on Cancer Staging criteria for lung cancer; the presence of either *EGFR* exon 19 deletion or exon 21 L858R mutation in the tumor, which was tested at each institution using approved methods; performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale; adequate organ function and normal hematologic function; and measurable tumor lesions according to Response Evaluation Criteria in Solid Tumors, version 1.1. Patients with symptomatic brain metastases (BM) were eligible if they had received local treatment for BM before the study enrollment. Patients with asymptomatic BM were enrolled regardless of previous local treatment. All patients provided written informed consent. This study was approved by the institutional review board of the National Cancer Center (no. NCC2016-0107).

Study design and treatment

Eligible patients were randomized 1:1 to one of two arms: erlotinib alone or erlotinib plus bevacizumab. The patients were stratified by *EGFR* mutation type (19 deletion vs. L858R). The erlotinib alone arm received 150 mg/day erlotinib orally, whereas the erlotinib plus bevacizumab arm received 150 mg/day erlotinib orally plus 15 mg/kg bevacizumab intravenously on day 1 every 3 weeks until disease progression or development of intolerable severe toxicity.

Tumor assessment

Tumors were assessed by computed tomography or magnetic resonance imaging every 6 weeks until disease progression. The overall response rate was defined as the number of patients who had a

complete response or partial response according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

The primary end point was PFS after treatment. The expected median PFS of the erlotinib-alone treatment was 10 months.[6] This study was designed to detect a 30% reduction in hazard ratio (HR) after the erlotinib plus bevacizumab treatment with a one-sided type I error rate of 10%. A total of 92 progression events were required to ensure 80% power to detect an HR less than 0.7. With a 5% dropout rate expected, the study sample size was set at 128 patients. All patients were followed up for 12 months after the last patient was enrolled.

All efficacy analyses were conducted for the intent-to-treat population. Adverse effects were analyzed only in patients who received treatment. Pearson χ^2 test and Fisher exact test were used to determine relationships between categorical variables, where appropriate. The relationships between categorical variables and continuous variables were tested using the Mann-Whitney *U* test. PFS was calculated from the beginning of study treatment to the first documentation of disease progression, death, or last follow-up visit. Overall survival (OS) was calculated from the beginning of study treatment to death or final follow-up visit. Central nervous system (CNS) PFS was calculated from the beginning of study treatment to the first documentation of progression to the CNS, death, or last follow-up visit. Survival rate was estimated using the Kaplan–Meier method and the difference in survival between groups was assessed via the log-rank test. Cox proportional hazards models were used to calculate the HRs of survival. A two-sided *p* value less than .05 was considered significant.

RESULTS

Patient characteristics

Between December 16, 2016, and March 8, 2019, 127 patients were randomly assigned to receive either erlotinib plus bevacizumab ($n = 64$) or erlotinib alone ($n = 63$) (Figure 1). Patient characteristics were well balanced between both treatment arms (Table 1). The median age of all patients was 63 years (range, 31–84 years). Females (66.1%), never smokers (64.6%), and those with adenocarcinoma histology (91.3%) predominated the patient characteristics. The tumors carried either *EGFR* exon 19 deletion mutation (58.3%) or exon 21 L858R mutation (41.7%). Fifty-nine (46.5%) patients had BM at baseline. The prevalence of initial BM was similar between the erlotinib alone (47.6%) and erlotinib plus bevacizumab arms (45.3%). However, more patients in the erlotinib alone arm received local treatment such as radiotherapy for BM before the study enrollment, compared with the erlotinib plus bevacizumab arm (40.0% vs. 10.3%).

Safety

All 127 patients were included for safety evaluation. The most common adverse effects were skin rash (76.4%), diarrhea (63.0%), and paronychia (53.5%) (Table 2). Grade 3 or worse adverse effects reported in more than 5% of patients included skin rash (11.0%), diarrhea (5.5%), increase in aspartate transaminase (AST) level (7.9%), increase in alanine transaminase (ALT) level (6.3%), and

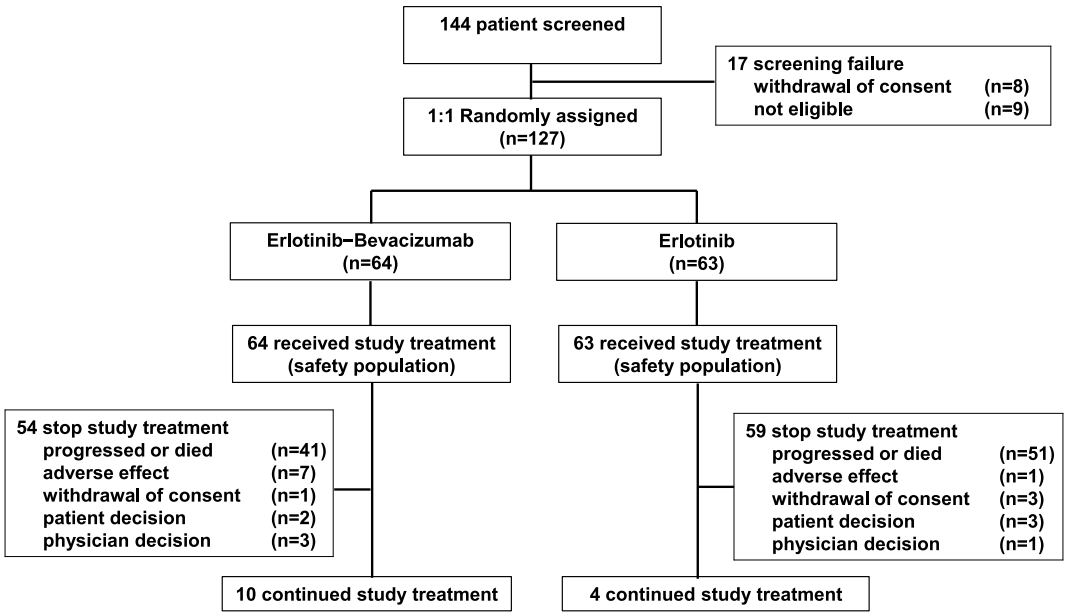

FIGURE 1 CONSORT study diagram.

TABLE 1 Patient characteristics

Characteristics		Erlotinib plus bevacizumab No. (%)	Erlotinib No. (%)	p^*
Age	<65 years	33 (51.6)	39 (61.9)	.240
	≥65 years	31 (48.4)	24 (38.1)	
Sex	Male	20 (31.2)	23 (36.5)	.531
	Female	44 (68.8)	40 (63.5)	
Smoking	Never	41 (64.1)	42 (66.1)	.808
	Ever	23 (35.9)	21 (33.9)	
ECOG	0	33 (51.6)	28 (44.4)	.422
	1	31 (48.4)	35 (55.6)	
Stage[a]	IIIB	3 (4.7)	3 (4.8)	.984
	IV	61 (95.3)	60 (95.2)	
Histology	Adenocarcinoma	60 (93.8)	56 (88.9)	.330
	Nonadenocarcinoma	4 (6.2)	7 (11.1)	
EGFR mutation	Exon 19 deletion	37 (57.8)	37 (58.7)	.916
	Exon 21 L858R	27 (42.2)	26 (41.3)	
Brain metastasis	Yes	29 (45.3)	30 (47.6)	.794
	No	35 (54.7)	33 (52.4)	
Local treatment on brain metastasis	No	26 (89.7)	18 (60.0)	.005
	Yes	3 (10.3)	12 (40.0)	
	Gamma knife surgery	3 (10.3)	4 (13.3)	
	WBRT	0 (0.0)	8 (26.7)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; WBRT, whole brain radiotherapy.

[a]Staging according to the 8th edition of the American Joint Commission on Cancer Staging System.

*Tested with Pearson χ^2 test or Fisher exact test.

hypertension (7.1%). No treatment-related deaths occurred. Grade 3 or worse adverse events occurred in 56.6% of patients in the erlotinib plus bevacizumab arm and in 20.6% of the erlotinib arm ($p < .001$). Skin rash with Grade 3 or more were higher in the erlotinib plus bevacizumab arm than the erlotinib arm (17.2% vs. 4.8%; $p = .025$). Hypertension with Grade 3 or more was more highly observed in the erlotinib plus bevacizumab arm (14.1% vs. 0.0%; $p = .003$). The addition of bevacizumab tended to increase the incidence or severity of certain erlotinib-related adverse effects including paronychia (60.9% vs. 46.0%), oral mucositis (51.6% vs. 33.3%), increased AST level (45.3% vs. 25.4%), increased ALT level (43.8% vs. 22.2%), increased bilirubin level (18.8% vs. 4.8%), and grade 3 skin rash (17.2% vs. 4.8%), respectively. However, the incidence or severity of pneumonitis did not differ between the two arms. Anti-VEGF–mediated events predominantly occurred in the erlotinib plus bevacizumab arm, including proteinuria (45.3% vs. 0.0%), hypertension (42.2% vs. 1.6%), hemorrhagic event (18.8% vs. 3.2%), grade 3 proteinuria (7.8% vs. 0.0%), and grade 3 hypertension (14.1% vs. 0.0%), respectively. Three patients in the erlotinib plus bevacizumab arm had grade 3 or worse cardiovascular adverse events including grade 4 acute myocardial infarction ($n = 1$), grade 3 congestive heart failure ($n = 1$), and grade 3 pulmonary embolism ($n = 1$). The number of patients who discontinued the treatment because of adverse effects was higher in the erlotinib plus bevacizumab arm (total $n = 7$, 10.9%; abnormal liver function, $n = 3$; colon perforation, $n = 1$; myocardial infarction, $n = 1$; skin rash, $n = 1$; and fatigue, $n = 1$) than in the erlotinib alone arm (oral mucositis, $n = 1$; 1.6%) ($p = .062$).

Progression-free survival

As of the data cutoff on August 30 2021, the median follow-up duration was 38.9 months (37.2–40.6 months), and 107 (84.3%) patients had experienced disease progression or death. Ten (15.6%) patients in the erlotinib plus bevacizumab arm and four (6.4%) in the erlotinib arm were still receiving the study treatment (Figure 1). The erlotinib plus bevacizumab treatment did not significantly prolong PFS compared with treatment with erlotinib alone (median PFS, 17.5 months [95% CI, 12.5–22.5] vs. 12.4 months [95% CI, 9.1–15.7]; HR, 0.74 [95% CI, 0.51–1.08], $p = .119$) (Figure 2A). The overall response rate was similar between the two treatment arms (erlotinib

TABLE 2 Summary of adverse effects

	Any grade, No (%)			≥ Grade 3, No. (%)		
Adverse effects	**Erlotinib/bevacizumab**	**Erlotinib**	***p****	**Erlotinib/bevacizumab**	**Erlotinib**	***p****
Fatigue	14 (21.9)	10 (15.9)	.388	0 (0.0)	1 (1.6)	.496
Anorexia	23 (35.9)	19 (30.2)	.489	1 (1.6)	1 (1.6)	1.000
Skin rash	50 (78.1)	47 (74.6)	.640	11 (17.2)	3 (4.8)	.025
Pruritus	25 (39.1)	26 (41.3)	.800	1 (1.6)	0 (0.0)	1.000
Dryness	10 (15.6)	17 (27.0)	.118	0 (0.0)	1 (1.6)	.496
Paronychia	39 (60.9)	29 (46.0)	.092	1 (1.6)	0 (0.0)	1.000
Oral mucositis	33 (51.6)	21 (33.3)	.038	2 (3.1)	1 (1.6)	1.000
Diarrhea	42 (65.6)	38 (60.3)	.584	4 (6.3)	3 (4.8)	1.000
AST increased	29 (45.3)	16 (25.4)	.019	7 (10.9)	3 (4.8)	.324
ALT increased	28 (43.8)	14 (22.2)	.010	6 (9.4)	2 (3.2)	.273
Bilirubin increased	12 (18.8)	3 (4.8)	.015	3 (4.7)	0 (0.0)	.244
Pneumonitis	2 (3.1)	2 (3.2)	1.000	2 (3.1)	1 (1.6)	1.000
Proteinuria	29 (45.3)	0 (0.0)	<.001	5 (7.8)	0 (0.0)	.058
Hypertension	27 (42.2)	1 (1.6)	<.001	9 (14.1)	0 (0.0)	.003
Hemorrhagic events	12 (18.8)	2 (3.2)	.005	0 (0.0)	0 (0.0)	-
Cardiovascular disease	7 (10.9)	2 (3.2)	.164	3[a] (4.7)	0 (0.0)	.244

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

[a]Acute myocardial infarction (n = 1), congestive heart failure (n = 1), pulmonary embolism (n = 1).

*Tested with Pearson χ^2 test or Fisher exact test.

plus bevacizumab 55/64 [85.9%] vs. erlotinib 52/62 [83.9%]; p = .746). There was no difference in the extent of tumor shrinkage between the two arms (erlotinib plus bevacizumab [45.5%] vs. erlotinib [45.9%]; p = .909) (Figure S1).

Brain metastasis

The subgroup analysis of PFS was performed according to risk factors including age, sex, ECOG status, smoking history, *EGFR* mutation type, BM, and bone metastasis (Figure S2). Although this analysis was exploratory, the PFS improvement with the erlotinib plus bevacizumab treatment was found in the subgroup of patients with BM (erlotinib plus bevacizumab vs. erlotinib; median PFS, 18.6 months [95% CI, 15.2–22.0] vs. 10.3 months [95% CI, 6.5–14.0]; HR, 0.54 [95% CI, 0.31–0.95], p = .032) (Figure 2C).

As the disease progressed, any progression in the CNS was less frequently found in the erlotinib plus bevacizumab arm, compared with the erlotinib arm (5/51 [9.8%] vs. 12/52 [23.1%]; p = .070) (Table S1). This finding was more significant in patients with baseline BM (erlotinib plus bevacizumab 3/23 [13.0%] vs. erlotinib 9/23 [39.1%]; p = .044) (Table S2). The cumulative incidence of CNS progression at 12 and 24 months was 4.4% and 6.8%, respectively, in the erlotinib plus bevacizumab arm, and 15.1% and 32.5%, respectively, in the erlotinib alone arm. A lower rate of CNS progression in the erlotinib plus bevacizumab arm compared with the erlotinib arm was more prominent among the patients with baseline BM (erlotinib plus bevacizumab vs. erlotinib: 4.8% vs. 23.1% at 12 months and 18.4% vs. 63.7% at 24 months). Thus, the erlotinib plus bevacizumab treatment significantly reduced the risk of CNS progression compared with the erlotinib treatment alone (HR, 0.33 [95% CI, 0.11–0.93], p = .035) (Figure 3A). A similar result was observed in patients with baseline BM (HR, 0.18 [95% CI, 0.05–0.67], p = .011) (Figure 3B).

Subsequent therapy and overall survival

OS data, composed of 43 death events (33.8%), were immature and median OS was not reached for both arms. At the data cutoff time, there was no significant difference in OS between the erlotinib plus bevacizumab and erlotinib alone arms (HR, 1.24 [95% CI, 0.68–2.26], p = .484) (Figure 2B).

After discontinuing the study treatment, the poststudy evaluation and further treatment were determined at the treating physician's discretion. Among 113 patients who discontinued the study treatment, 96 (85.0%) patients underwent sequencing tests to assess their T790M mutation status (45 [83.3%] of 54 in the erlotinib plus bevacizumab arm and 51 [86.4%] of 59 in the erlotinib arm). Tissue-based testing was less frequently performed in the erlotinib plus bevacizumab arm than the erlotinib arm (64.4% vs. 82.4%, p = .046) (Table 3). Overall, tissue-based testing showed higher T790M positivity than plasma-based testing (56.3% vs. 40.0%, p = .160)

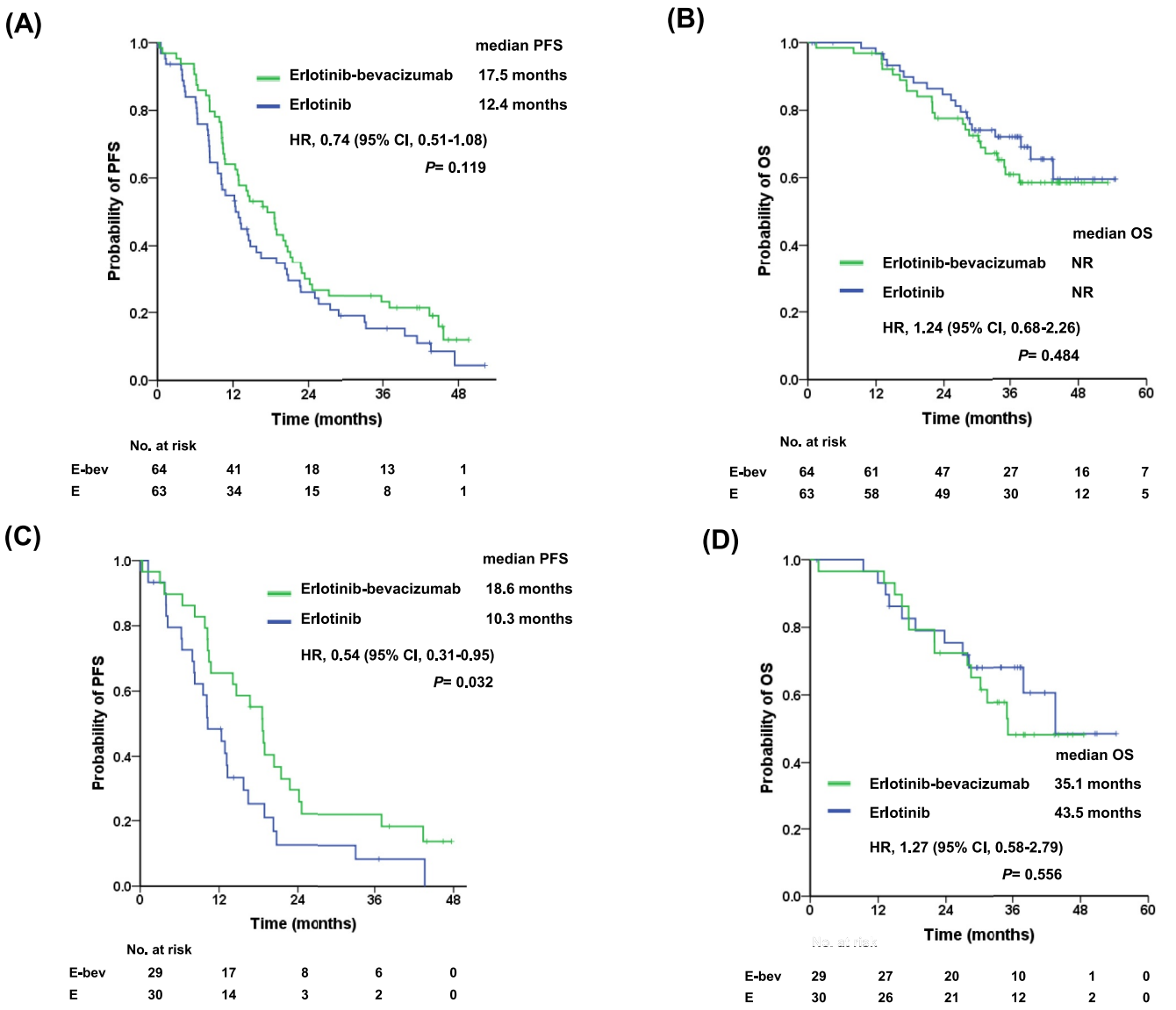

FIGURE 2 Kaplan–Meier curves of PFS and OS. (A-B) All patients and (C-D) patients with baseline brain metastasis. Abbreviations: E indicates erlotinib alone arm; E-bev, erlotinib plus bevacizumab arm; OS, overall survival; PFS, progression-free survival.

(Table S3). Thus, the T790M positivity rate in the erlotinib plus bevacizumab arm was lower than in the erlotinib arm (42.2% vs. 60.8%, $p = .062$) (Table 3). Consequently, fewer patients in the erlotinib plus bevacizumab arm were treated with a third-generation EGFR-TKI as subsequent therapy after tumor progression than in the erlotinib arm (35.3% vs. 61.5%, $p = .001$). However, no difference in OS between the two arms was observed even when the analysis was restricted to patients who received a third-generation EGFR-TKI as a second-line treatment (HR, 1.19 [95% CI, 0.54–2.63], $p = .668$] (Figure S3).

Resistance mechanisms

We explored an acquired resistance mechanisms for the erlotinib plus bevacizumab treatment using the FoundationOne liquid assay. Paired next-generation sequencing data from plasma circulating tumor DNA (ctDNA), which was collected at both baseline and disease progression, were available for analysis in 20 (31%) patients of the erlotinib plus bevacizumab arm. Acquired resistance mechanism to the erlotinib plus bevacizumab treatment was identified in 13 (65%) patients. *EGFR* T790M mutation ($n = 8$, 40%), *ATM* mutation ($n = 3$, 15%), *KRAS* mutation ($n = 1$, 5%), and *NF1* deletion ($n = 1$, 5%) were newly detected in the posttreatment plasma samples (Figure S4 and Table S4).

ctDNA clearance

We checked out the presence of plasma *EGFR* mutation at 6 weeks after starting the treatment in 72 of 127 (56.7%) patients. Droplet digital polymerase chain reaction test was performed to detect *EGFR*

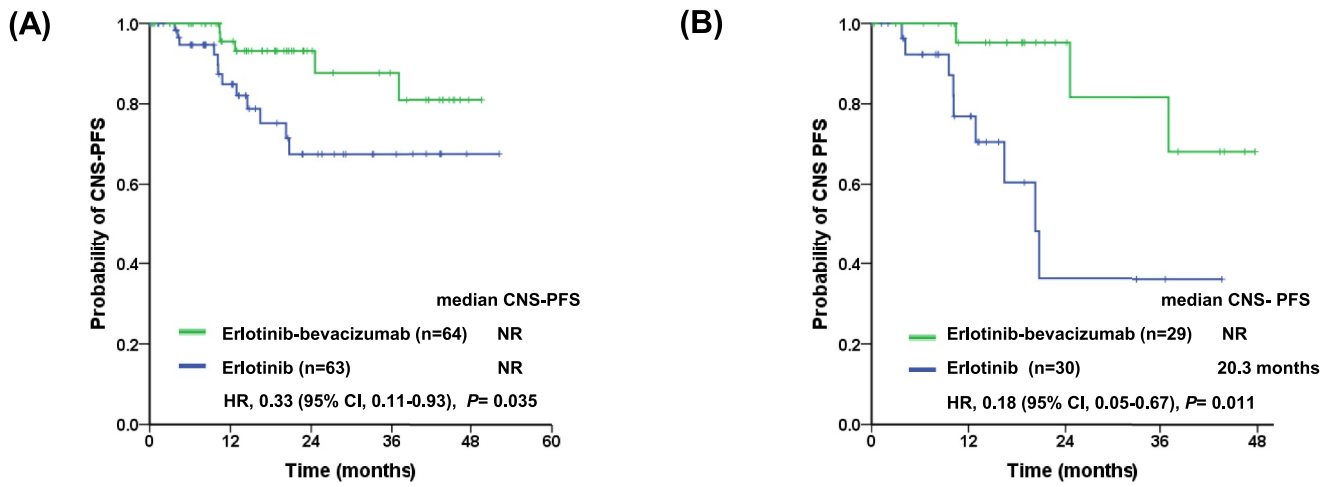

FIGURE 3 Kaplan–Meier curves of CNS-PFS. (A) All patients and (B) patients with baseline brain metastasis. Abbreviations: CNS indicates central nervous system; NR, not reached; PFS, progression-free survival.

TABLE 3 Subsequent evaluation and treatment after tumor progression

Category	Erlotinib plus bevacizumab No. (%)	Erlotinib No. (%)	*p**
EGFR sequencing method			.046
Tissue ± plasma ctDNA	29/45 (64.4)	42/51 (82.4)	
Plasma ctDNA only	16/45 (35.6)	9/51 (17.6)	
EGFR test results[a]			.107
Sensitive mutation + T790M	19/45 (42.2)	31/51 (60.8)	
Sensitive mutation	17/45 (37.8)	16/51 (31.4)	
Not detected	9/45 (20.0)	4/51 (7.8)	
Second-line treatment			.002
Third-generation EGFR-TKI	18/51 (35.3)	32/52 (61.5)	
First-generation EGFR-TKI	10/51 (19.6)	7/52 (13.5)	
Platinum	14/51 (27.5)	9/52 (17.3)	
Immunotherapy	0/51 (0.0)	3/52 (5.8)	
Resection	0/51 (0.0)	1/52 (1.9)	
None	8/51 (15.7)	0/52 (0.0)	

Abbreviations: ctDNA, circulating tumor DNA; TKI, tyrosine kinase inhibitor.

[a]In the cases with both tissue and plasma test, the results from the tissue test were chosen.

*tested with Pearson χ^2 test or Fisher exact test.

mutation in plasma ctDNA. Early clearance of the *EGFR* mutation in plasma predicted longer PFS (no detection vs. detection at 6 weeks; median PFS, 17.5 months [95% CI, 10.2–24.7] vs. 10.6 months [95% CI, 3.5–17.7]; $p = .052$) (Figure S5). There was no significant difference in the 6-week ctDNA clearance rate between the two treatment arms (erlotinib plus bevacizumab [86.5%] vs. erlotinib [85.7%]; $p = 1.000$).

DISCUSSION

We conducted this randomized Phase 2 study to evaluate the efficacy and toxicity of the combination erlotinib and bevacizumab treatment in Korean patients with chemonaïve advanced *EGFR*-mutant NSCLC. Although this study failed to meet the primary end point, it demonstrated that patients receiving the combination treatment had

promising outcomes with a median PFS of 17.5 months, comparable to those receiving osimertinib treatment in the FLAURA China randomized study.[19] Some adverse effects were more common in the combination treatment arm but were not severe and were manageable.

One third of all study patients had asymptomatic BM before they started treatment. Thus, our study population characteristics seemed similar to real-world characteristics of a population with advanced *EGFR*-mutant NSCLC. Interestingly, the PFS benefit from the addition of bevacizumab to erlotinib was greater in the subgroup with baseline BM, even though more patients with previously untreated BM were included in the erlotinib plus bevacizumab arm. In patients with BM, the combination treatment showed a longer PFS compared with the erlotinib alone treatment (18.6 months vs. 10.3 months, $p = .030$). However, in patients without BM, there was no difference in median PFS between the two treatment arms (14.4 months vs. 14.5 months, $p = .678$). The erlotinib plus bevacizumab treatment significantly reduced the risk of CNS progression compared with the erlotinib alone treatment. This effect of bevacizumab on decreasing the risk of CNS progression was more significant in patients with baseline BM. Although our subgroup analysis was not preplanned and underpowered because of the small number of patients, these findings are consistent with the results from a recent study, ARTEMIS-CTONG1509, which was a randomized Phase 3 study to evaluate the efficacy of bevacizumab plus erlotinib in 311 Chinese patients with chemonaïve, *EGFR*-mutated, and advanced NSCLC.[14] That study also showed that a subgroup with baseline BM treated with bevacizumab plus erlotinib had significantly longer PFS (HR, 0.48; 95% CI, 0.27–0.84; $p = .008$).[14] Although multiple clinical studies have found that bevacizumab plus cytotoxic chemotherapy is beneficial and safe for patients with NSCLC and BM, the practical utility of bevacizumab in patients with untreated BM has been restricted because of safety concerns such as hemorrhagic events.[20–23] However, in this study, no bevacizumab-related hemorrhagic events in the CNS were observed, including patients with BM. Collectively, both our study and the ARTEMIS-CTONG1509 study suggest that the concurrent treatment with bevacizumab and erlotinib might be more effective and even tolerated in patients with *EGFR*-mutant NSCLC who have BM. Thus, we suggest that further confirmative randomized clinical trials are needed in patients with baseline BM. Currently, a randomized Phase 2 study to compare osimertinib plus bevacizumab with osimertinib alone in *EGFR*-mutant NSCLC with BM is ongoing in the United States (ClinicalTrials.gov, no. NCT02971501), which may answer the questions about beneficial effects of bevacizumab in patients with BM. Previous clinical trials evaluating the combination of EGFR-TKI and an antiangiogenesis drug have reported that certain subgroups experience more benefits from the combination treatment than from a single treatment alone. The BOOSTER trial recently reported that osimertinib plus bevacizumab showed a significant PFS improvement in the smoker group rather than in the never-smoker group (a HR of PFS; 0.52 for smokers vs. 1.47 for never smokers).[18] However, our subgroup analysis suggests that the addition of bevacizumab to erlotinib had no increased PFS benefit for smokers compared with never smokers. On the other hand, three Phase 3 studies (NET026, RELAY, and ARTEMIS-CTONG1509) showed that patients with exon 21 L858R mutation had greater a reduction in the risk of disease progression than those with exon 19 deletions in the bevacizumab plus erlotinib treatment.[12–14] The present study also showed the same trend of more favorable efficacy for the combination treatment in the subgroup harboring exon 21 L858R mutation. Patients with tumors harboring *EGFR* L858R mutation are known to have poorer clinical outcomes after treatment with a single-agent EGFR-TKI compared with those with tumors harboring *EGFR* 19 deletion. Based on those clinical trials and our study, a mutation-specific treatment strategy should be strongly considered.[24]

In this study, more patients received a third-generation EGFR-TKI as a second-line treatment in the erlotinib alone arm compared with those in the erlotinib plus bevacizumab arm (61.5% vs. 35.3%). Naturally, this finding is related to the higher detection rate of *EGFR* T790M mutation in the erlotinib arm than in the combination treatment arm (60.8% vs. 42.2%). However, no other clinical trial reported significant difference in the acquired resistance mechanism profiles between groups receiving erlotinib alone or in combination with bevacizumab.[13] The lower T790M positivity in the combination treatment arm may reflect that fewer patients were tested using the tissue-based sequencing method, which had a higher T790M detection rate than the plasma-based sequencing method. The reason why fewer patients in the combination group were tested using tissue-based sequencing remains unclear. There was no difference in the extent of tumor shrinkage, which might affect the feasibility of tissue biopsy after disease progression between the two treatment arms. On the other hand, the ARTEMIS-CTONG1509 study also presented the similar results of lower T790M positivity in the bevacizumab combination arm (33% vs. 45% for erlotinib alone). A further study is required to determine whether this finding has an underlying biological cause.

We also explored the mechanisms of acquired resistance to bevacizumab plus erlotinib treatment. In this study, the frequency of the *EGFR* T790M mutation was 40%, which is lower than the frequencies reported in other studies (50%–60% using plasma ctDNA tests).[25–27] This might result from a small number of tissue tests.

The number of patients who discontinued the EGFR-TKI treatment was higher in the combination group than in EGFR-TKI alone group. The main cause of terminating the EGFR-TKI treatment was acute hepatitis in the bevacizumab plus erlotinib arm. The combination treatment tended to increase some EGFR TKI-specific toxicities such skin rash, paronychia, oral mucositis, AST, or ALT elevation as well as the toxicities related to antiangiogenesis effect. However, these additive adverse effects were generally manageable. In particular, severe hemorrhagic events of grade 3 or higher did not develop in the bevacizumab combination group. Overall, the safety profiles of this study were comparable to those of previous studies using EGFR-TKIs plus antiangiogenesis drugs.

In conclusion, the addition of bevacizumab to erlotinib did not show a significant improvement in PFS as a first-line treatment in patients with advanced *EGFR*-mutant NSCLC.

AUTHOR CONTRIBUTIONS

Youngjoo Lee: Methodology development; data acquisition; data analysis and interpretation; and manuscript writing, review, and/or revision. **Hye Ryun Kim:** Methodology development; data acquisition; and manuscript writing, review, and/or revision. **Min Hee Hong:** Data acquisition. **Ki Hyeong Lee:** Data acquisition. **Keon Uk Park:** Data acquisition. **Geon Kook Lee:** Data acquisition. **Hyae Young Kim:** Data acquisition. **Soo-Hyun Lee:** Data acquisition. **Kun Young Lim:** Data acquisition. **Sung Jin Yoon:** Administrative, technical, or material support. **Byoung Chul Cho:** Conception and design; data acquisition; manuscript writing, review, and/or revision; and study supervision. **Ji-Youn Han:** conception and design; data acquisition; data analysis and interpretation; manuscript writing, review, and/or revision; and study supervision.

ACKNOWLEDGMENTS

We thank the patients and their families who participated in the study. The study was supported partly by a National Cancer Center Research Grant (2210551-1) and Roche Korea Inc.

CONFLICT OF INTEREST

Youngjoo Lee reports consulting fees from Roche, Merck, Yuhan, and Bayer. Byoung Chul Cho reports research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD, AbbVie, Medpacto, GIInnovation, Eli Lilly, Blueprint medicines, Interpark Bio Convergence Corp; consulting fees from Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, Janssen, Medpacto, Blueprint medicines; stock ownership with TheraCanVac Inc, Gencurix Inc, Bridgebio therapeutics, KANAPH Therapeutic Inc, Cyrus therapeutics, and Interpark Bio Convergence Corp; scientific advisory board with KANAPH Therapeutic Inc, Brigebio therapeutics, Cyrus therapeutics, Guardant Health, and Joseah BIO; board of director with Gencurix Inc and Interpark Bio Convergence Corp; royalty from Champions Oncology; and founder of DAAN Biotherapeutics. Ki Hyeong Lee reports honoraria for an advisory role with BMS, MSD, AstraZeneca, Pfizer, Eli_Lilly, and Yuhan. Ji-Youn Han reports research grants from Roche, ONO, Pfizer, and Takeda; consulting fees from Astra Zeneca, BMS, Eli Lilly, Merck, Novartis, Pfizer, Abion, and Jints Bio; and honoraria for lectures from Astra Zeneca, BMS, Merck, Takeda, and Novartis. The other authors made no disclosures.

DATA AVAILABILITY

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee Y, Kim HR, Hong MH, et al. A randomized Phase 2 study to compare erlotinib with or without bevacizumab in previously untreated patients with advanced non–small cell lung cancer with *EGFR* mutation. *Cancer*. 2023;129(3):405-414. doi:10.1002/cncr.34553