ORIGINAL ARTICLE

Addition of Bevacizumab to Erlotinib as First-Line Treatment of Patients With *EGFR*-Mutated Advanced Nonsquamous NSCLC: The BEVERLY Multicenter Randomized Phase 3 Trial

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ABSTRACT

Introduction: Adding bevacizumab to erlotinib prolonged progression-free survival (PFS) of patients with *EGFR*-mutated advanced NSCLC in the Japanese JO25567 trial, but limited data were available in non-Asian patients. BEVERLY is an Italian, multicenter, randomized, phase 3 investigating the addition of bevacizumab to erlotinib as first-line treatment of advanced *EGFR*-mutated NSCLC.

Methods: Eligible patients were randomized 1:1 to erlotinib plus bevacizumab or erlotinib alone. Investigator-assessed PFS and blinded independent centrally reviewed PFS were coprimary end points. With 80% power in detecting a 0.60 hazard ratio and two-sided α error of 0.05, 126 events of 160 patients were needed. The trial was registered as NCT02633189 and EudraCT 2015-002235-17.

Results: From April 11, 2016, to February 27, 2019, a total of 160 patients were randomized to erlotinib plus bevacizumab (80) or erlotinib alone (80). At a median follow-up of 36.3 months, median investigator-assessed PFS was 15.4 months (95% confidence interval [CI]: 12.2–18.6) with erlotinib plus bevacizumab and 9.6 months (95% CI: 8.2–10.6) with erlotinib alone (hazard ratio = 0.66, 95% CI: 0.47–0.92). Blinded independent centrally reviewed PFS analysis confirmed this result. A statistically significant interaction with treatment effect was found for smoking habit ($p = 0.0323$), with PFS prolongation being clinically significant only among current or previous smokers. Hypertension (grade $\geq$3: 24% versus 5%), skin rash (grade $\geq$ 3: 31% versus 14%), thromboembolic events (any grade: 11% versus 4%), and proteinuria (any grade: 23% versus 6%) were more frequent with the combination.

Conclusions: The addition of bevacizumab to first-line erlotinib prolonged PFS in Italian patients with *EGFR*-mutated NSCLC; toxicity was increased with the combination but without unexpected safety issues.

Keywords: NSCLC; EGFR; Bevacizumab; Randomized clinical trial

Introduction

EGFR tyrosine kinase inhibitors (TKIs) are recommended first-line therapy for patients with NSCLC carrying *EGFR* mutations. Nevertheless, not all patients equally benefit from this treatment, suggesting features other than *EGFR* mutation may affect response to *EGFR* TKIs. Preclinical models suggested that vascular epithelial growth factor signaling might play a role in resistance to anti-*EGFR* therapies,[1,2] providing the rationale for combining anti-*EGFR* and anti-*vascular epithelial growth factor* agents. The Japanese phase 2 JO25567 trial provided the first evidence of progression-free survival (PFS) improvement with the addition of bevacizumab to erlotinib as first-line therapy in *EGFR*-mutated NSCLC.[3] In 2015, two phase 2 trials studying the same combination, one single arm (BELIEF)[4] and one randomized (ACCRU-RC1126),[5] were ongoing and results were awaited. In such scenario, we designed the BEVacizumab plus ERLotinib studY (BEVERLY), with the aim to test whether the addition of bevacizumab to first-line erlotinib prolonged PFS of patients with NSCLC with activating *EGFR* mutation.[6]

Material and Methods

Study Design

BEVERLY is a multicenter, randomized, phase 3 trial promoted by the Istituto Nazionale Tumori of Naples, Italy, and involved 43 national centers. The protocol was

approved by Ethics Committees at each participating institutions and is available online in the Supplementary Materials. The study was performed in accordance with the Declaration of Helsinki. All the patients provided informed consent before the initiation of any trial procedure. The trial was registered as NCT02633189 and EudraCT 2015-002235-17.

Patients aged at least 18 years with metastatic or locally advanced nonsquamous NSCLC harboring an activating *EGFR* mutation were eligible (see the protocol for the full list of inclusion criteria).

Main exclusion criteria were previous medical treatment for advanced NSCLC (previous adjuvant or neoadjuvant chemotherapy was allowed if ended >6 mo before randomization); mixed adenosquamous histotype with a predominant squamous component; *EGFR* T790M mutation or exon 20 insertions as unique mutations; brain metastases; concomitant pathologies or laboratory alterations or concomitant medication use that prevents or contraindicates the use of erlotinib or bevacizumab.

To recognize a 0.60 hazard ratio (HR) of progression or death, with 80% power and 0.05 two-tailed α, 126 PFS events were needed and 200 patients, to be randomized in 20 months, were the initially estimated sample size. On October 2017, owing to slow enrolment, the sample size was amended at 160 patients, without changing the study hypothesis and two interim analyses were added.

Procedures

Registration, randomization, and data collection were web based at Clinical Trials Unit of Istituto Nazionale Tumori, Istituto di Ricovero e Cura a Carattere Scientifico, Fondazione G. Pascale (Naples, Italy). The participants were randomly assigned (1:1) to receive erlotinib plus bevacizumab (experimental arm) or erlotinib alone (standard arm). Randomization procedure included a minimization to ensure balance within center, performance status (0–1 versus 2) and type of mutation (exon 19 deletion versus exon 21 L858R mutation versus others) stratification variables. The trial was open label; however, central radiologic revision and statistical analyses were conducted with blinded arms.

Erlotinib dose was 150 mg orally once daily in both arms; bevacizumab, 15 mg/kg intravenously, was given every 21 days. In both arms, each subsequent 3-week interval was defined as a cycle. No dose reduction of bevacizumab was planned, but the drug could be temporarily or permanently suspended in case of hypertension, proteinuria, thrombosis/embolism, hemorrhage, cardiac heart failure, or wound healing complications in addition to any other serious (grade 3 or 4) bevacizumab-related toxicity. Dose reduction for adverse events was allowed for erlotinib. Patients in both arms were treated until disease progression or unacceptable toxicity or patient's or physician's motivated decision.

Computed tomography scans of the brain, chest, and abdomen, 12-lead electrocardiogram, and bone scan were required at baseline. Restaging was performed by computed tomography scan at the end of cycles 3, 6, and every further four cycles. Response was reported according to Response Evaluation Criteria in Solid Tumors version 1.1.

Quality of life (QoL) was assessed with the European Organisation for Research and Treatment of Cancer C30 and LC13 questionnaires, at baseline, at the end of cycles 1 to 6, and every 12 weeks thereafter, until progression. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.03.

Outcomes

Investigator-assessed (IA) PFS and blinded independent centrally reviewed (BICR) PFS, defined as the time from randomization to either the first occurrence of disease progression or death from any cause, were co-primary end points. Secondary outcomes were overall survival (OS), QoL, IA, and BICR objective response rate (ORR), and safety.

Statistical Analysis

Efficacy analyses were performed on an intention-to-treat (ITT) basis. Analyses end date was July 31, 2021.

IA-PFS and BICR-PFS were co-primary end points, the latter used to validate possible statistically significant results of the former one; therefore, both IA-PFS and BICR-PFS had to be statistically significant at the $p = 0.05$ threshold, for declaring the study result as positive and no adjustment for multiple comparison was planned. Treatment groups were compared by unstratified log-rank test. The HR of PFS was estimated by a Cox model with performance status (1 versus 0 and 2 versus 0), type of mutation (exon 19 deletion versus 21 L858R mutation versus others), and center (3 categories according to tertiles of the distribution by number of patients enrolled). Schoenfeld residual test was used to judge the proportional hazards assumption.

Two-sided 95% confidence interval (CI) of the HR was provided, and an exploratory subgroup analysis for PFS was performed to test whether any interaction exists between treatment arm and stratifying or clinically relevant covariates. First-order interactions were tested by likelihood ratio test of the two nested models, with and without interaction. Heterogeneity of treatment effect across major subgroups was described in a forest plot. OS was analyzed by applying the same methods described for PFS.

The rate of missing baseline European Organisation for Research and Treatment of Cancer questionnaires was described in the ITT population; missing rates of subsequent questionnaires were described by arm in the modified ITT (mITT) population including patients completing the baseline questionnaire.

Two types of analysis were performed in the mITT population, defining a change of at least 10 points from baseline as clinically relevant.[7] Patients were defined as responders if they reported a score more than or equal to 10 points better than baseline at any time; remaining patients (either not improved or missing all questionnaires after the baseline one) were defined as non-responders. Chi-square test was applied to test statistical significance.

Time-to-deterioration was the time from randomization to QoL worsening of more than or equal to 10 points from baseline, using progression/death as competing event which prevented QoL assessment. In the competing risk approach, different types of events are not considered independent, and subjects who progress/die before documented QoL worsening are not censored at the time of progression/death. The probability for each domain of deteriorating over time was compared between the two arms with the Fine and Gray regression model.[8]

ORR was defined as the ratio of patients who experienced a complete or partial response (according to the Response Evaluation Criteria in Solid Tumors version 1.1) in the ITT population. ORRs in the two arms were described with their 95% confidence limits and compared with the chi-square test. ORR was analyzed both with IA and BICR response categorization.

Patients with at least one administration known were eligible for safety assessment. For each patient and for each type of toxicity, the worst degree according to the Common Terminology Criteria for Adverse Events ever suffered during treatment was used for the analysis. The proportion of patients experiencing severe toxicities and the ordered categorical responses of the worst grades suffered by patients were compared between the two groups using chi-square or Fisher's exact test as appropriate.

Results

Between April 11, 2016, and February 27, 2019, a total of 160 patients were randomized, 80 to receive erlotinib plus bevacizumab and 80 erlotinib alone (Fig. 1). Baseline characteristics of patients are reported in Table 1. Of note, former/current smokers were more represented in the erlotinib (43 patients, 53.8%) than in the erlotinib plus bevacizumab arm (34, 42.5%).

An interim analysis, performed by the Independent Data Monitoring Committee on October 2019, when the enrolment had been completed and 58% of planned events had been reported, did not reveal futility; no further interim analyses were performed (due to problems caused by the SARS-CoV-2 pandemic) and final analysis is reported here.

At a median follow-up of 36.3 months (95% CI: 30.7–40.9), 140 PFS events (87.5%) were reported, 72 (90.0%) with erlotinib and 68 (85.0%) with erlotinib

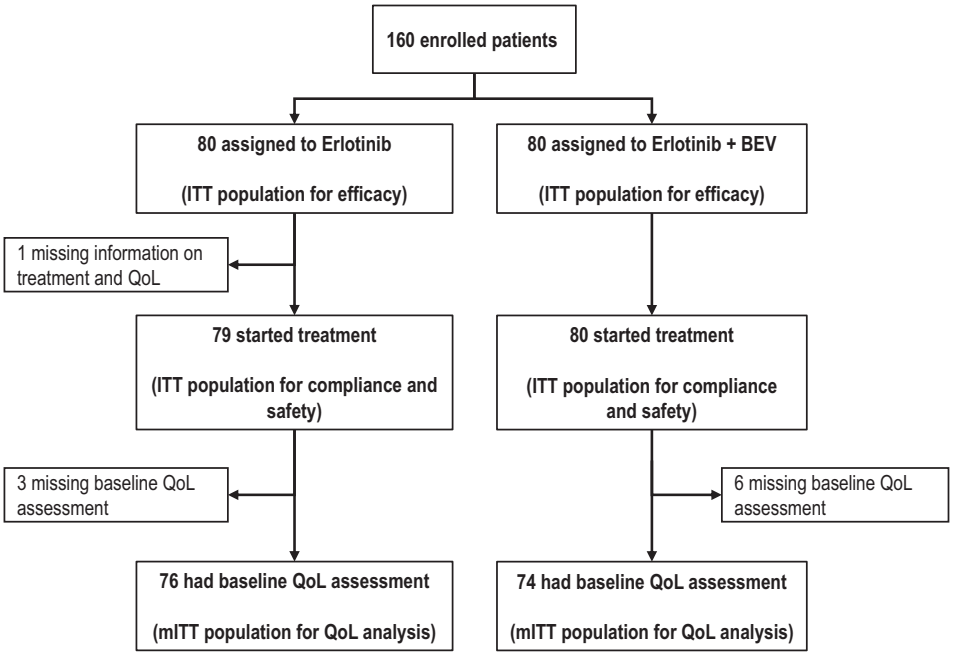

Figure 1. Study flow. BEV, bevacizumab; ITT, intention-to-treat; mITT, modified intention-to-treat; QoL, quality of life.

Table 1. Baseline Characteristics by Assigned Treatment Arm

Characteristic	Erlotinib (n = 80)		Erlotinib + BEV (n = 80)	
Age, median (IQR)	67.7	(60.7-73.6)	65.9	(57.9-71.8)
Age elderly, n (%)				
≤65	31	(38.8)	38	(47.5)
>65	49	(61.3)	42	(52.5)
Sex, n (%)				
Female	50	(62.5)	52	(65.0)
Male	30	(37.5)	28	(35.0)
Smoking status, n (%)				
Never	37	(46.3)	46	(57.5)
Former/current	43	(53.8)	34	(42.5)
Performance status, n (%)				
0	47	(58.8)	52	(65.0)
1	29	(36.3)	26	(32.5)
2	4	(5.0)	2	(2.5)
EGFR mutation, n (%)				
Exon 19 deletion	44	(55.0)	44	(55.0)
Exon 21 L858R mutation	32	(40.0)	34	(42.5)
Other	4	(5.0)	2	(2.5)
Stage, n (%)				
IIIB	5	(6.3)	3	(3.8)
IV	75	(93.8)	77	(96.3)

BEV, bevacizumab; IQR, interquartile range.

plus bevacizumab. Median IA-PFS was 9.6 months (95% CI: 8.2–10.6) with erlotinib and 15.4 months (95% CI: 12.2–18.6) with erlotinib plus bevacizumab (Fig. 2*A*). At multivariable analysis, a statistically significant advantage for erlotinib plus bevacizumab in IA-PFS was confirmed (HR = 0.66 [95% CI: 0.47–0.92], $p = 0.015$; Supplementary Table 1). Proportional hazard assumption was met. BICR-PFS analysis confirmed the results (Fig. 2*B* and Table 1).

Overall, 90 deaths (56.3%) were reported, 49 (61.3%) with erlotinib and 41 (51.3%) with erlotinib plus bevacizumab. Median OS was 22.8 months (95% CI: 18.3–33.0) with erlotinib and 33.3 months (95 CI: 24.3–45.1) with erlotinib plus bevacizumab (Fig. 2*C*). No statistically significant difference in OS was found at multivariable analysis (HR = 0.72 [95% CI: 0.47–1.10], $p = 0.132$; Supplementary Table 1).

PFS and OS according to subgroups are reported in Figure 3. A statistically significant interaction with treatment effect was found for smoking habit for both IA-PFS ($p = 0.0323$) and OS ($p = 0.0077$). Former or current smokers who received erlotinib plus bevacizumab had a longer IA-PFS (16.9 mo [95% CI: 10.2–21.8] versus 8.8 mo [95% CI: 5.6–9.6]) (Fig. 4*B*) and OS (35.3 mo [95% CI: 25.6–not estimated] versus 19.7 mo [95% CI: 12.5–23.4]) (Fig. 4*D*) than those receiving erlotinib alone, whereas there was no apparent treatment effect among never smokers (Fig. 4*A* and *C*). Subgroup analysis for BICR-PFS confirmed these results (Supplementary Fig. 1). No statistically significant interaction with treatment effect was found for type of *EGFR* mutation (Supplementary Fig. 2).

Baseline QoL questionnaires were completed by 76 patients (95.0%) in erlotinib arm versus 74 patients (92.5%) in erlotinib plus bevacizumab arm representing the mITT population. The rate of missing questionnaires was similar in the two arms up to the 10th cycle, and the timing of QoL assessment was similar up to 2 years (Supplementary Figs. 3 and 4). For all QoL items, the rate of responders was not statistically significantly different between the two arms (Supplementary Table 2). Time-to-deterioration of functional (Supplementary Fig. 5) and symptom's scales (Supplementary Fig. 6) was similar in the two arms, whereas a statistically significant difference favoring the standard arm was found in coughing ($p = 0.02$) and sore mouth ($p = 0.04$) (Supplementary Fig. 7).

Furthermore, 40 patients (50.0%, 95% CI: 39.0%–60.9%) with erlotinib and 56 patients (70.0%, 95% CI: 60.0%–80.0%) with erlotinib plus bevacizumab achieved a complete or partial response per investigator assessment ($p = 0.010$). BICR-ORR analysis confirmed the result (Supplementary Table 3).

One patient assigned to erlotinib alone, with missing information on treatment, was excluded from compliance analysis. Median duration of erlotinib was 9.3 (interquartile range [IQR]: 4.6–14.7) months in the standard arm and 14.4 (IQR: 8.8–24.2) months in the

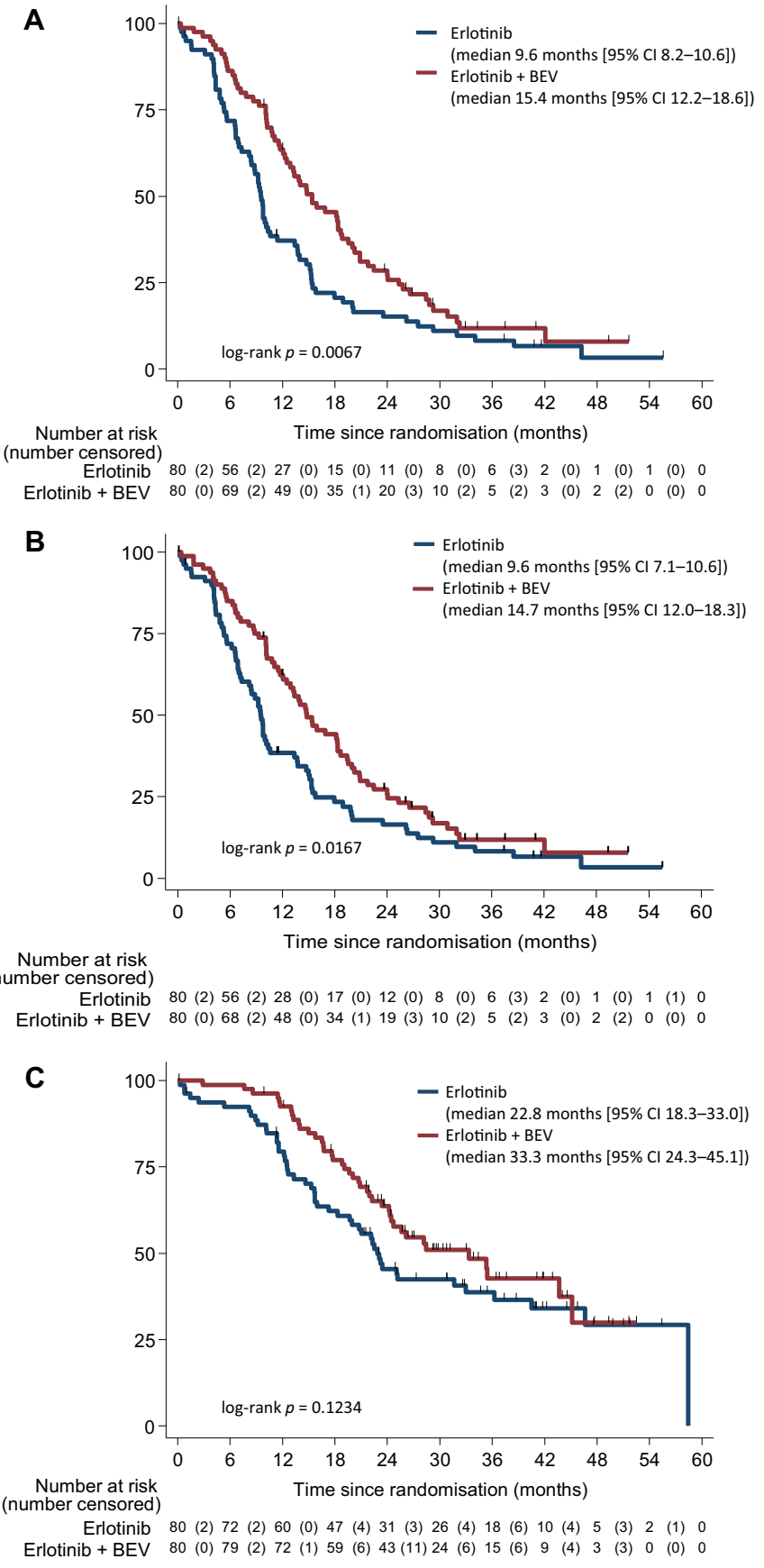

Figure 2. (*A*) Investigator-assessed and (*B*) BICR progression-free survival and (*C*) overall survival by treatment arm. Vertical black line represents censoring. BEV, bevacizumab; BICR, blinded independent central review; CI, confidence interval.

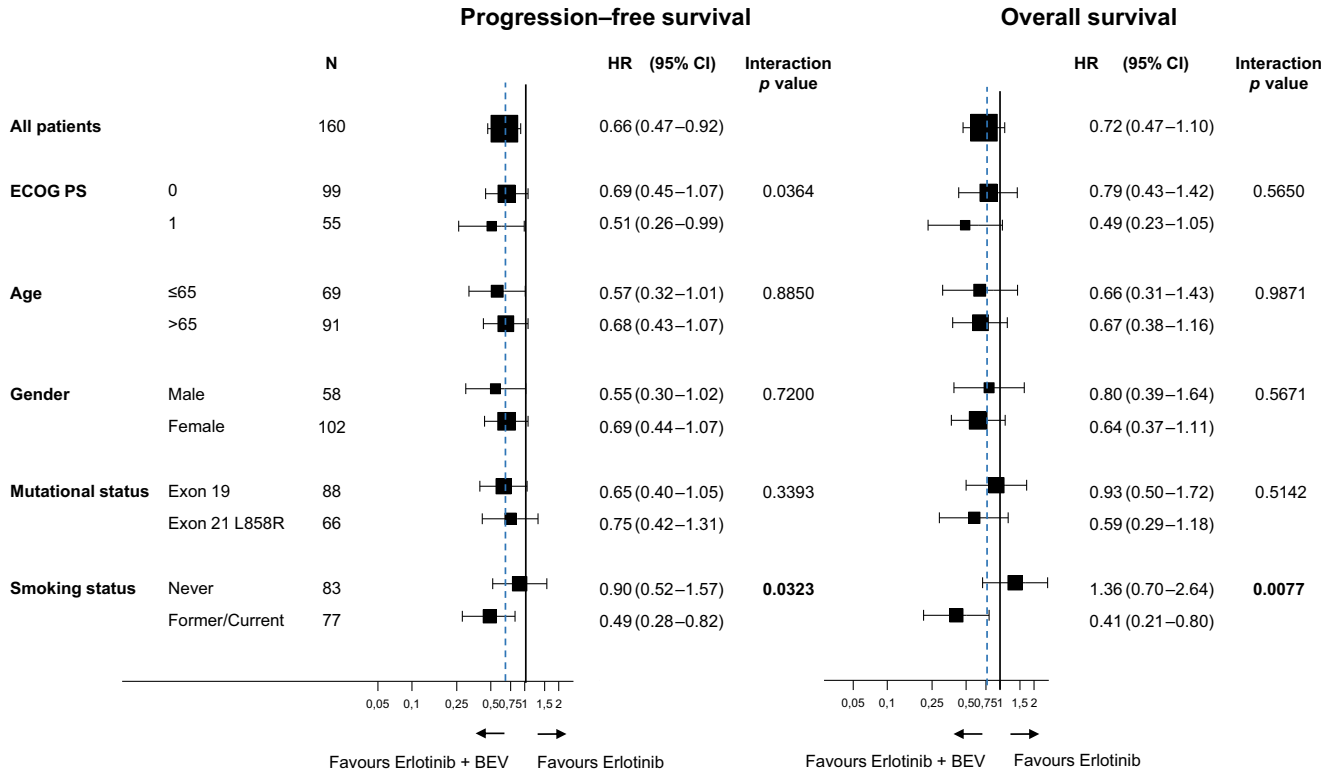

Figure 3. Forest plot for subgroup analyses of investigator-assessed progression-free survival and overall survival. BEV, bevacizumab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.

experimental arm; median duration of bevacizumab in the experimental arm was 14.2 (IQR: 5.8–22.3) months. Number of patients experiencing at least one dose reduction or delay of treatment was comparable between arms (Supplementary Table 4). Ten patients were still on treatment (1 [1.3%] with erlotinib and 9 [11.3%] with erlotinib + bevacizumab). Main reason of erlotinib discontinuation was radiologic or clinical progression; toxicity led to discontinuation of erlotinib in 13 patients (16.5%) in the standard arm and 11 patients (13.8%) in the experimental one; bevacizumab was discontinued for toxicity in 24 (30.0%) patients (Supplementary Table 4).

After study discontinuation, 56 patients (71.8%) in the standard arm and 49 patients (69.0%) in the experimental arm received second-line treatment (Supplementary Table 5), prevalently osimertinib (32 [57.1%] in standard arm and 24 [49.0%] in experimental arm).

One patient assigned to erlotinib alone, with missing information on treatment, was excluded from safety analysis (Fig. 1); all remaining patients received the assigned treatment. Serious adverse events (45 versus 30 events) and the rate of serious adverse events certainly or likely related to the study drugs were higher in the experimental arm (9 of 45 events [20.0%] versus 1 of 30 events [3.3%]) (Supplementary Table 6). Eight fatal adverse events (four [5.0%] in erlotinib arm and four [5.0%] in erlotinib + bevacizumab arm) were registered, but only one death due to intracranial hemorrhage was reported as related to the study treatment in erlotinib plus bevacizumab arm. Furthermore, 39 patients (49%) in the erlotinib arm and 45 patients (56%) in the erlotinib plus bevacizumab arm experienced an adverse event grade more than or equal to 3. The most frequent adverse events in both arms were rash (73 patients [92%] in the standard arm and 70 patients [88%] in the experimental arm) and diarrhea (47 patients [59%] versus 56 [70%]); whereas dyspepsia, weight loss, gamma-glutamyltransferase increase, and pruritus were more frequent in the experimental arm (Table 2). Proteinuria, epistaxis, and hypertension were more frequent and more severe in the erlotinib plus bevacizumab arm (Supplementary Table 7).

Discussion

In the BEVERLY study, the addition of bevacizumab to first-line erlotinib improved the outcome of patients with *EGFR*-mutated NSCLC; that is, PFS was statistically significantly longer and response rate was higher both at IA and BICR analyses; OS was longer but the difference did not reach statistical significance; QoL was similar; and as expected, typical side effects were more frequent and severe with the combined treatment.

To the best of our knowledge, BEVERLY is the first trial in Western countries with positive results, which

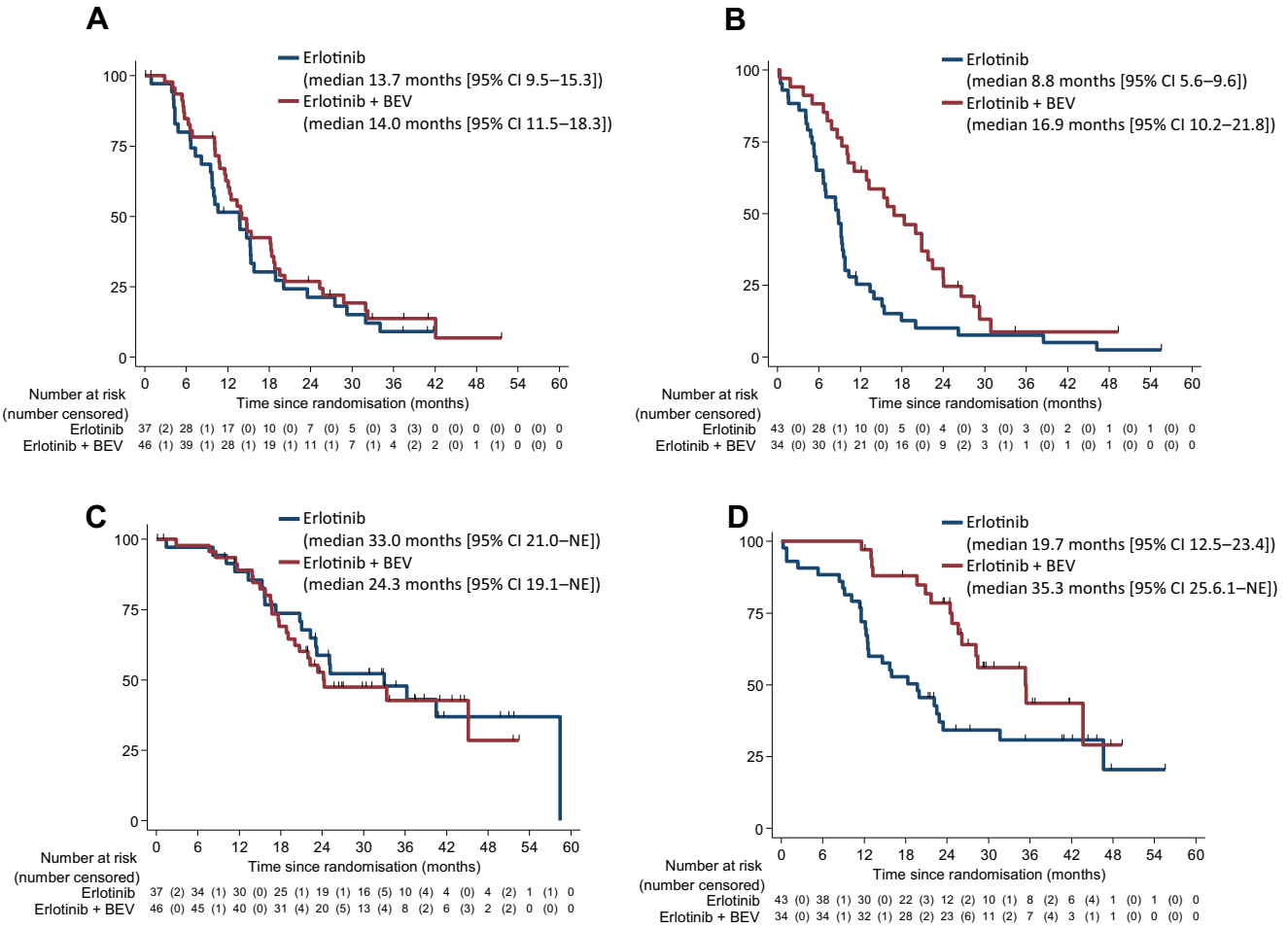

Figure 4. Progression-free survival (*A*: never, *B*: former/current) and overall survival (*C*: never, *D*: former/current) by smoking status. BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; NE, not estimated.

are consistent with data from trials dedicated to Eastern patients.[3,9] BEVERLY results are also consistent with the benefit reported with the addition of ramucirumab in the same setting, in a trial where 75% of patients had East Asian origin.[10] In contrary, the American ACCRU-RC1126 trial, with a small sample size (n = 88), did not find any advantage for the addition of bevacizumab to erlotinib.[5] It is important to add that all the trials assessing the addition of bevacizumab to osimertinib reported negative findings, both in second-line[11,12] and in first-line treatments.[13]

Interesting findings come from BEVERLY subgroup analyses. First, no statistically significant interaction with treatment effect was found for the type of *EGFR* mutation, a result that does not support the hypothesis (generated in the ARTEMIS-CTONG1509 and JO25567 trials) that patients with *EGFR* L858R mutation derived more benefit from the addition of bevacizumab to erlotinib than those with *EGFR* exon 19 deletion.[3,14] Second, the statistically significant interaction with smoking habit in BEVERLY generates the hypothesis that the addition of bevacizumab to erlotinib might be exclusively important among previous or current smoking patients. We acknowledge that, as smoking status was not a stratification factor, the distribution was slightly unbalanced (but not statistically significantly different) with more smokers in the erlotinib arm, therefore potentially unfavoring the experimental arm. Among the trials with erlotinib as control arm, the interaction of bevacizumab addition with smoking habit was tested in two,[3,9] and no differential effect of the experimental treatment was found; similarly, there was no interaction in the trial testing the addition of ramucirumab to erlotinib.[10] In contrary, an interaction was found in all the trials testing the addition of bevacizumab to osimertinib, always in the same direction reported in the BEVERLY analysis[11–13]; it is of note that all these trials had negative results at the primary analyses in the overall populations.

EGFR mutations are relatively rare in ever smokers, and the genomic landscape of lung cancer is different between ever and never smokers.[15,16] Cigarette smoke is a powerful carcinogen and together a mutagen that

Table 2. Adverse Events in the Safety Population

	Erlotinib (n = 79)								Erlotinib + BEV (n = 80)							
	Grades 1–2		Grade 3		Grade 4		Grade 5		Grades 1–2		Grade 3		Grade 4		Grade 5	
Adverse Event	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Anemia	10	(13)	–		–		–		14	(18)	1	(1)	–		–	
Cardiac arrest	–		–		–		–		–		–		–		1	(1)
Pericardial effusion	–		–		1	(1)	–		–		–		–		–	
Pericardial tamponade	–		–		1	(1)	–		–		–		–		–	
Other cardiac events	1	(1)	–		1	(1)	–		–		–		–		–	
Conjunctivitis	22	(28)	–		–		–		19	(24)	–		–		–	
Corneal ulcer	–		–		–		–		–		1	(1)	–		–	
Abdominal pain	3	(4)	1	(1)	–		–		5	(6)	–		–		–	
Diarrhea	44	(56)	3	(4)	–		–		52	(65)	4	(5)	–		–	
Mucositis oral	21	(27)	2	(3)	–		–		25	(32)	3	(4)	–		–	
Nausea	13	(16)	1	(1)	–		–		17	(21)	1	(1)	–		–	
Vomiting	6	(8)	1	(1)	–		–		6	(8)	1	(1)	–		–	
Other GI events	1	(1)	–		–		–		2	(3)	1	(1)	–		–	
Death NOS	–		–		–		2	(3)							1	(1)
Fatigue	38	(48)	–		–		–		41	(51)	5	(6)	–		–	
Fever	12	(15)	–		–		–		18	(23)	–		–		–	
Pain	3	(4)	1	(1)	–		–		4	(6)	–		–		–	
Other general conditions	–		–		–		1[a]	(1)							–	
Biliary tract infection	–		1	(1)	–		–		–		–		–		–	
Gum infection	–		1	(1)	–		–		–		–		–		–	
Lung infection	–		1	(1)	–		–		2	(3)	–		–		–	
Pancreas infection	–		–		–		–		–		1	(1)	–		–	
Paronychia	4	(5)	–		–		–		9	(11)	–		–		–	
Sepsis	–		–		1	(1)	–		–		–		–		–	
Other infections	–		–		–		–		2	(3)	1	(1)	–		–	
ALT increased	14	(18)	2	(3)	–		–		18	(23)	2	(3)	–		–	
ALP increased	1	(1)	1	(1)	–		–		2	(3)	–		–		–	
AST increased	12	(15)	4	(5)	–		–		14	(17)	1	(1)	–		–	
Blood bilirubin increased	14	(18)	2	(3)	–		–		18	(22)	2	(3)	1	(1)	–	
Creatinine increased	5	(6)	–		–		–		5	(6)	1	(1)	–		–	
INR increased	–		–		–		–		–		1	(1)	–		–	
Lipase increased	1	(1)	1	(1)	1	(1)	–		–		–		–		–	
Neutropenia	2	(3)	1	(1)	–		–		1	(1)	–		–		–	
Serum amylase increased	3	(4)	1	(1)	–		–		–		–		–		–	
Weight gain	–		1	(1)	–		–		–		–		–		–	
Weight loss	1	(1)	–		–		–		8	(10)	1	(1)	–		–	
Other investigations	2	(3)	–		–		–		3	(4)	1	(1)	–		–	
Anorexia	10	(13)	–		–		–		18	(23)	1	(1)	–		–	
Hypokalemia	–		–		–		–		3	(4)	1	(1)	–		–	
Hyponatremia	–		–		–		–		–		1	(1)	–		–	
Avascular necrosis	–		–		–		–		–		1	(1)	–		–	
Chest wall pain	4	(5)	–		–		–		3	(4)	1	(1)	–		–	
Intracranial hemorrhage	–		–		–		–		–		–		–		1	(1)
Headache	–		1	(1)	–		–		4	(5)	–		–		–	

(continued)

Table 2. Continued

	Erlotinib (n = 79)								Erlotinib + BEV (n = 80)							
	Grades 1-2		Grade 3		Grade 4		Grade 5		Grades 1-2		Grade 3		Grade 4		Grade 5	
Adverse Event	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Seizure	–		2	(3)	–		–		1	(1)	–		–		–	
Stroke	1	(1)	–		1	(1)	–		1	(1)	–		–		–	
Syncope	–		–		–		–		–		1	(1)	–		–	
Other neurologic events	–		–		–		–		1	(1)	1	(1)	–		–	
Confusion	1	(1)	1	(1)	–		–		–		–		–		–	
Hematuria	–		1	(1)	–		–		2	(3)	–		–		–	
Proteinuria	4	(5)	1	(1)	–		–		13	(16)	5	(6)	–		–	
Pulmonary hemorrhage	–		–		–		–		2	(2)	1	(1)	–		–	
Cough	14	(18)	–		–		–		16	(20)	–		–		–	
Dyspnea	15	(19)	1	(1)	–		–		14	(17)	1	(1)	–		–	
Epistaxis	2	(3)	–		–		–		12	(16)	–		–		–	
Pleural effusion	1	(1)	1	(1)	–		–		–		1	(1)	–		–	
Pulmonary hypertension	–		–		–		–		–		1	(1)	–		–	
Respiratory failure	–		–		–		1	(1)	–		–		–		1	(1)
Other respiratory events	2	(3)	–		–		–		–		2	(3)	–		–	
Dry skin	22	(28)	–		–		–		21	(27)	1	(1)	–		–	
Erythema multiforme	1	(1)	2	(3)	–		–		1	(1)	1	(1)	–		–	
Nail ridging	18	(23)	–		–		–		19	(24)	–		–		–	
Pruritus	12	(15)	–		–		–		22	(27)	1	(1)	–		–	
Rash[b]	60	(76)	13	(16)	–		–		43	(54)	26	(33)	1	(1)	–	
Vascular disorders	15	(19)	5	(6)	–		–		21	(26)	22	(28)	1	(1)	–	
Hypertension	10	(13)	4	(5)	–		–		21	(26)	19	(24)	–		–	
Thromboembolic event	3	(4)	1	(1)	–		–		5	(6)	3	(4)	1	(1)	–	

Note: The table reveals adverse events that were severe (grade ≥3) in at least one case or mild/moderate (grades 1-2) in at least 10% of patients in either group.

[a]Worsening of general conditions.

[b]*Rash* includes the following: papulopustular rash (infection and infestations), rash pustular (infection and infestations), rash acneiform (skin and subcutaneous tissue disorders), and rash maculopapular (skin and subcutaneous tissue disorders).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BEV, bevacizumab; GI, gastrointestinal; INR, international normalized ratio; NOS, not otherwise specified.

determines specific and peculiar genetic alterations.[17] Among these alterations, TP53 mutations are frequent, occurring in approximately 15% of NSCLC from never smokers but in more than 30% of NSCLC from smokers.[18] Interestingly, the presence of specific TP53 variants has been associated with resistance to *EGFR* TKIs in several reports,[19,20] although it was not confirmed by our group in a retrospective analysis.[21] Recently, it has been reported that changes in TP53 status can affect primary sensitivity and acquired resistance to *EGFR* TKIs depending on the genetic background of the target cell type.[22] Taken together, these data suggest a possible link between smoke, TP53 mutations, and resistance to *EGFR* TKIs, although other molecular determinants are likely to play a role in this phenomenon. Therefore, the combination with an anti-angiogenic might be especially effective in the presence of co-mutations, as in the case of smokers.

BEVERLY has some limitations. The first refers to the exclusion of patients with brain metastasis. This should be considered in the interpretation of the results because it could affect the prognosis of the overall population. The second one derives from the long time (34 mo) we spent for completing planned accrual; this was not unexpected because the enrolment time in trials dedicated to *EGFR*-mutated NSCLC tends to be longer in Western countries due to the lower prevalence of *EGFR* mutations. Finally, the fact that erlotinib is no longer considered a standard

in countries where osimertinib is available, following the results of the FLAURA study, might represent a limitation in terms of generalizability.[23]

Nevertheless, we believe that BEVERLY results may be relevant within future scenarios for at least two aspects. First, affordability of the combination of a first-generation TKI, such as erlotinib, and bevacizumab is going to be high, also in lower-middle income countries, thanks to the low cost of generic and biosimilar products, but, in contrary, cost-effectiveness of osimertinib is highly controversial.[24–26] In an international, cross-sectional survey distributed to a network of oncologists in 89 countries, asking for the 10 cancer medicines that would provide the greatest public health benefit to their country, osimertinib was not considered at all among the group of physicians from low and lower-middle income countries and was associated to a risk of catastrophic expenditure for 41% of responding physicians from upper-middle income countries.[27]

Second, in developed countries, osimertinib is going to migrate to the adjuvant setting for patients with an operable NSCLC, after the results of the ADAURA study.[28] Nevertheless, even if uncertainty still exists on real-world efficacy, it is reasonable to think that approximately one-fourth of patients will have recurrence after an adjuvant treatment with osimertinib. For these patients, chemotherapy will be a reasonable choice at the presentation of metastasis, but the hypothesis of a combination of an antiangiogenic drug with a TKI different from osimertinib might be an option, eventually worthy of being prospectively tested in clinical trials, particularly for smoker patients.

In conclusion, bevacizumab plus erlotinib might be considered among the first-line therapeutic option in patients who cannot receive osimertinib and the strategy of combining an antiangiogenic drug with a TKI is worth of further investigation.

CRediT Authorship Contribution Statement

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Maria Carmela Piccirillo, Laura Arenare, Ciro Gallo, and Francesco Perrone: Methodology and formal analysis.

Maria Carmela Piccirillo, Raimondo Di Liello, Laura Arenare, Nicola Normanno, Ciro Gallo, and Francesco Perrone: Writing.

Maria Carmela Piccirillo, Laura Bonanno, Marina Chiara Garassino, Giovanna Esposito, Claudio Dazzi, Luigi Cavanna, Marco Angelo Burgio, Francesco Rosetti, Simona Rizzato, Floriana Morgillo, Saverio Cinieri, Antonello Veccia, Maximilan Papi, Giuseppe Tonini, Vittorio Gebbia, Serena Ricciardi, Daniele Pozzessere, Alessandra Ferro, Claudia Proto, Raffaele Costanzo, Manolo D'Arcangelo, Manuela Proietto, Piera Gargiulo, Raimondo Di Liello, Laura Arenare, Filippo De Marinis, Lucio Crinò, Fortunato Ciardiello, Nicola Normanno, Ciro Gallo, Francesco Perrone, Cesare Gridelli, Alessandro Morabito: Final approval of manuscript and accountable for all aspects of the work.

Data sharing statement

A core data set of this study is available in a public repository (URL: DOI 10.5281/zenodo.6142888). Full data of this study will be shared with publication on motivated request to the corresponding author (f.perrone@istitutotumori.na.it). The following deidentified IPD will be available for sharing: baseline characteristics of patients, treatment data, safety data, and follow-up data. There will be no time limit for data sharing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.05.008.

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