ORIGINAL ARTICLE

Final Analysis Data and Exploratory Biomarker Analysis of a Randomized Phase 2 Study of Osimertinib Plus Bevacizumab Versus Osimertinib Monotherapy for Untreated Patients With Nonsquamous NSCLC Harboring EGFR Mutations: The WJOG9717L Study

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ABSTRACT

Introduction: EGFR tyrosine kinase inhibitors have been the standard treatment for patients with NSCLC who have sensitive *EGFR* mutations. This study revealed final analysis survival data, biomarkers, and resistance mechanisms of osimertinib plus bevacizumab or osimertinib monotherapy in previously untreated patients with advanced *EGFR*-positive nonsquamous NSCLC.

Methods: We previously reported the primary results of a randomized, open-label, phase 2 study comparing osimertinib plus bevacizumab with osimertinib monotherapy for this population. In this exploratory analysis using tissue

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and plasma samples, we evaluated gene profiles at baseline and disease progression or the last dose using targeted deep sequencing.

Results: The median progression-free survival (PFS) by the blinded independent central reviewer was 22.1 months for the osimertinib plus bevacizumab arm and 20.2 months for the osimertinib arm (hazard ratio [HR] = 0.864, 95% confidence interval [CI]: 0.549–1.359). The 3-year overall survival was not different between the two arms (osimertinib plus bevacizumab: 57.1%; osimertinib monotherapy: 65.0%; HR 1.271, 95% CI: 0.727–2.223). A total of 94 patients had assessable plasma samples at baseline, and 40 had assessable pretreatment tissue samples. *EGFR* mutations (76.6%) and *TP53* mutations (44.7%) were detected in plasma samples at baseline. In patients with plasma *TP53* mutations (n = 42), the median PFS by blinded independent central reviewer was 19.8 months for the osimertinib plus bevacizumab arm and 20.2 months for the osimertinib arm (HR = 1.107, 95% CI: 0.534–2.297).

Conclusions: There was also no significant difference in the PFS between the two arms, even in patients with *TP53* mutations.

Keywords: Non–small cell lung cancer; *EGFR* mutation; Osimertinib; Bevacizumab; *TP53* mutation

Introduction

NSCLC is the most common prevalent lung cancer subtype, and a clinically considerable proportion of patients with NSCLC have sensitive mutations in *EGFR*.[1] Several phase 3 studies have revealed that EGFR tyrosine kinase inhibitors (TKIs) significantly prolong progression-free survival (PFS) compared with platinum-based chemotherapy in patients with NSCLC harboring *EGFR* mutations.[2–7] The FLAURA study, a phase 3 study comparing osimertinib with gefitinib or erlotinib as an initial treatment, revealed the superiority of osimertinib in terms of PFS in patients with advanced NSCLC harboring *EGFR* mutations.[8]

In preclinical studies, the antivascular endothelial growth factor monoclonal antibody bevacizumab has been reported to inhibit the vascular permeability of tumors, thereby improving drug delivery in the tumor.[9–12] A randomized phase 2 study comparing erlotinib plus bevacizumab with erlotinib monotherapy for treatment-naive patients with advanced NSCLC harboring *EGFR* mutations (JO25567) revealed that erlotinib plus bevacizumab have statistically superior PFS.[13,14] In addition, phase 3 study confirmed the efficacies of the combination of erlotinib and bevacizumab in PFS for patients with *EGFR*-positive NSCLC.[15,16]

We previously reported the primary results of a multicenter randomized controlled trial (WJOG9717L) aimed at evaluating the efficacy of osimertinib plus bevacizumab in previously untreated patients with advanced nonsquamous NSCLC harboring *EGFR*-sensitizing mutations.[17] In the subgroup analysis of smoking history, patients in the osimertinib plus bevacizumab arm with a smoking history had better PFS trends compared with those in the osimertinib monotherapy arm. *TP53* mutations were more frequently observed in smokers with lung cancer, and patients with a smoking history may have had coexisting *TP53* mutations that affect sensitivity to osimertinib.[18] Therefore, we conducted an exploratory biomarker study to elucidate predictive biomarkers or resistance mechanisms in this population.

Materials and Methods

Study Design and Patients

The WJOG9717L study is a multicenter, open-label, randomized phase 2 trial conducted at 21 study sites in Japan. The study protocol was approved by the institutional review board of each participating institution and conducted in accordance with the principles of the Declaration of Helsinki. This study, including the biomarker analysis, was registered in the University Hospital Medical Information Network database (UMIN000030206). All patients provided written informed consent for this biomarker analysis before registration.

This study included treatment-naive patients with advanced nonsquamous NSCLC harboring *EGFR*-sensitizing mutations (exon 19 deletion or the L858R mutation in exon 21). The patients received either oral osimertinib 80 mg once daily and bevacizumab 15 mg/kg on day 1 through intravenous infusion every 3 weeks or oral osimertinib 80 mg once daily. These treatments were continued until disease progression, unacceptable toxicities, or termination of the study in July 2021.

Sample Collection

Tissue samples were obtained before treatment, including archived tissues, and at disease progression, if possible. Plasma samples were obtained for this study at baseline, cycles 2 and 9, and disease progression or the last dose of the study treatment. These samples were obtained from patients who provided written informed consent for this biomarker analysis, and assessable tissue and plasma samples were evaluated.

Tumor tissue specimens were subjected to histologic review, and only those containing sufficient tumor cells,

as determined using hematoxylin-eosin staining, were subjected to DNA extraction. Genomic DNA was extracted from tumor tissues using the GeneRead DNA FFPE kit (Qiagen, Valencia, CA). Cell-free DNA (cfDNA) was extracted from 4 mL of the plasma using an AVENIO cfDNA isolation kit (Roche Sequencing Solutions, Pleasanton, CA). DNA quality and quantity were verified using a NanoDrop 2000 device and PicoGreen dsDNA Reagent (all from Thermo Scientific, Wilmington, DE).

DNA Sequencing and Data Analysis

Tumor DNA was sequenced using the AVENIO tumor tissue surveillance kit (Roche Sequencing Solutions), and cfDNA was sequenced using the AVENIO cfDNA surveillance kit (Roche Sequencing Solutions), according to the manufacturer's instructions. Purified libraries were pooled and sequenced on an Illumina NextSeq 500 system (Illumina, San Diego, CA) using a 300-cycle high-output kit. Variants were called using the AVENIO oncology analysis software (version 2.0; Roche Sequencing Solutions).

All variants were manually inspected, and gene variants present in more than 0.1% of the population databases (EXAC, dbSNP, 1000 Genomes) were excluded as germline mutations. Variants were selected from variants designated as loci of interest in the AVENIO oncology analysis software, and variants were annotated as pathogenic or likely pathogenic by submitting the target variants to the COSMIC disease association database.

Procedures

Radiologic assessments were performed within 28 days before randomization, every 6 weeks until 6 months, and every 9 weeks thereafter until disease progression. Brain magnetic resonance imaging or computed tomography was performed at baseline for all patients to evaluate the presence of brain metastases, and brain metastasis was evaluated until disease progression in patients with brain metastasis at baseline. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Radiologic assessment of the tumor was continued following the protocol for patients who discontinued the study treatment because of unacceptable toxicities.

Outcomes

The primary end point, PFS, was defined as the time from randomization to disease progression or death, whichever occurred first. It was assessed according to Response Evaluation Criteria in Solid Tumor version 1.1 by a blinded independent central reviewer (BICR). The secondary end points included PFS, which was evaluated by investigators, overall survival (OS), and safety.

Statistical Analysis

The final efficacy analysis was performed in the intention-to-treat (ITT) population, and biomarker analysis was conducted in the population with assessable samples, at 2 years after the day of the last patient enrollment. PFS and OS were estimated by using the Kaplan–Meier method, and hazard ratios (HRs) and their confidence intervals (CIs) were estimated using the Cox proportional hazards models. *p* values of the log-rank test were denoted as one sided in the biomarker analysis. Subsequent subgroup analyses were performed for PFS stratified on the basis of the *TP53* mutation status in cfDNA at baseline. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Between January 19, 2018, and September 11, 2018, 122 patients were enrolled in this study from 21 participating institutions (Supplementary Data 1). Among them, 61 were assigned to the osimertinib monotherapy arm and 61 to the osimertinib plus bevacizumab arm (ITT population). At the data cutoff (July 31, 2021), 13 patients (21.3%) in the osimertinib monotherapy arm and 14 patients (23.0%) in the osimertinib plus bevacizumab arm completed the study treatment without disease progression. One patient in the osimertinib monotherapy arm did not start the assigned treatment but was included in the ITT analysis. Two patients in the osimertinib monotherapy arm were considered unassessable by BICR. Therefore, three patients were excluded from the per-protocol analysis, including the evaluation of response.

Final PFS and OS Analysis

With a median follow-up time of 36.5 months (interquartile range [IQR]: 11.7–38.7 mo), disease progression or death was reported in 38 patients (62.3%) in the osimertinib monotherapy arm and 37 patients (60.7%) in the osimertinib plus bevacizumab arm. There was no significant difference in the PFS assessed by the BICR between the treatment arms (median PFS, osimertinib monotherapy arm: 20.2 mo [95% CI: 12.5–32.9] and osimertinib plus bevacizumab arm: 22.1 mo [95% CI: 19.8–34.0]), with an HR for combination therapy of 0.864 (60% CI: 0.711–1.049; 95% CI: 0.549–1.359) (Fig. 1*A*). The PFS rates assessed by the BICR at 24 and 36 months were 45.4% and 33.1% in the osimertinib monotherapy arm and 49.8% and 31.9% in the osimertinib plus bevacizumab arm, respectively. The

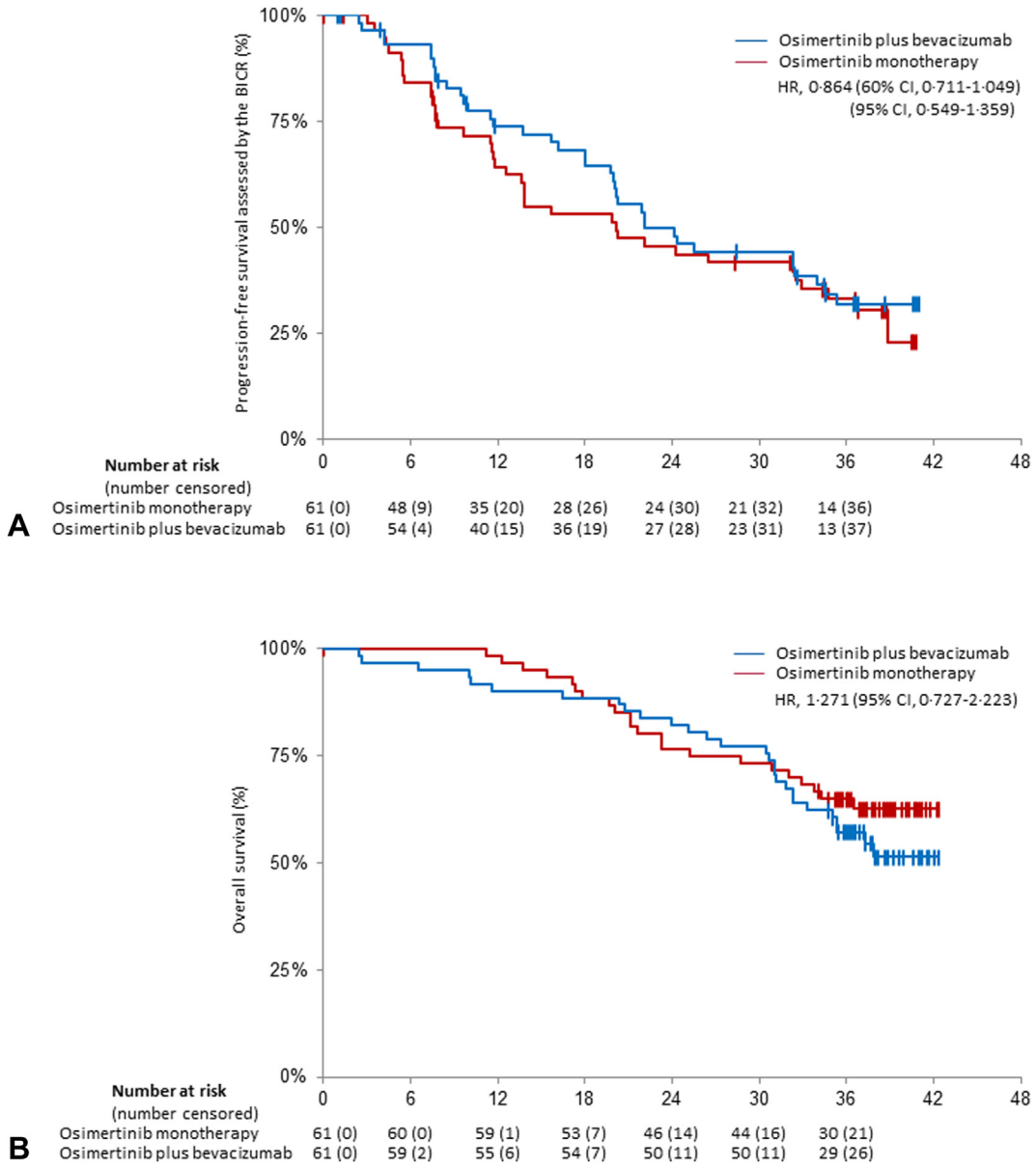

Figure 1. (*A*) The progression-free survival assessed by the blinded independent central radiologic reviewer (n = 122). (*B*) Overall survival (n = 122). BICR, blinded independent central radiologic reviewer; CI, confidence interval; HR, hazard ratio.

post hoc exploratory subgroup analysis of the PFS by the BICR revealed rates similar to those of the previous analysis, with a trend of better PFS in the osimertinib plus bevacizumab arm among patients with a smoking history and deletions in exon 19 (Supplementary Data 2).[17]

At the data cutoff, 22 events (36.1%) in the osimertinib monotherapy arm and 28 events (45.9%) in the osimertinib plus bevacizumab arm were observed in the OS analysis. With a median follow-up of 37.8 months (IQR: 36.2–40.0 mo), there was no significant difference in the OS between the two arms (3-y OS, osimertinib monotherapy arm: 65.0% [95% CI: 51.5–75.6] and osimertinib plus bevacizumab arm: 57.1% [95% CI: 43.8–68.5]), with an HR for the combination therapy of 1.271 (95% CI: 0.727–2.223) (Fig. 1*B*).

Treatment Exposure and Safety

Among the 121 patients receiving at least one dose of assigned treatment, the median duration of exposure to osimertinib was 57.6 weeks (IQR: 23.6–151.1 wk) in the osimertinib monotherapy arm (n = 60) and 94.0 weeks (IQR: 37.0–148.9 wk) in the osimertinib plus bevacizumab arm (n = 61). The median duration of exposure to bevacizumab was 33.4 weeks (IQR: 20.9–56.9 wk), and there was a median of 11 cycles (IQR: 7–19) of bevacizumab administered in the osimertinib plus

bevacizumab arm. Adverse events of grade 3 or 4 occurred in 29 patients (48%) in the osimertinib monotherapy arm and 35 patients (57%) in the osimertinib plus bevacizumab arm. One treatment-related death due to pneumonitis was observed in the osimertinib plus bevacizumab arm.

Biomarker Analysis

Tissue (n = 40) and plasma (n = 94) samples at baseline were assessed, and 197 genes were evaluated using targeted deep sequencing. The median depth of coverage was 9630 (range: 5269–15,469) and 13,084 (range: 6835–30,879) in tissue and baseline plasma analyses, respectively.

Of the 40 tissue samples at baseline, *EGFR* mutations were observed in 38 (95.0%) and *TP53* mutations in 20 (50.0%) (Supplementary Data 3). The incidences of copy number variants (CNVs) in *EGFR* and *ERBB2* were 20.0% (eight of 40) and 7.5% (three of 40), respectively. Among 94 patients with plasma samples at baseline, 72 (76.6%) had *EGFR* mutations in the plasma and 42 (44.7%) had *TP53* mutations (Table 1). In patients with assessable plasma samples at baseline (n = 94), patients harboring *TP53* mutations had a tendency of worse PFS assessed by the BICR compared with patients not harboring *TP53* mutations (median PFS, 19.8 mo versus 32.3 mo), with an HR for *TP53* mutation of 1.510 (95% CI: 0.900–2.533, $p = 0.1143$) (Fig. 2*A*). There were no significant differences in patient characteristics, including smoking status, between patients with and without *TP53* mutations (Table 2).

There was no difference in PFS assessed by the BICR between the two arms among patients with *TP53* mutations in the baseline plasma samples (n = 42) (median

Table 1. Gene Profile of Plasma Sample at Baseline

	All Cases (N = 94)		Osimertinib Monotherapy (n = 46)		Osimertinib Plus Bevacizumab (n = 48)		
Gene Alterations	N	%	n	%	n	%	*p* Value
EGFR	72	76.6	39	84.8	33	68.8	0.1115
TP53	42	44.7	23	50.0	19	39.6	0.1115
APC	11	11.7	4	8.7	7	14.6	0.4191
MET	9	9.6	4	8.7	5	10.4	0.5709
ERBB2	6	6.4	2	4.3	4	8.3	1
ALK	5	5.3	4	8.7	1	2.1	0.7128
BRAF	5	5.3	2	4.3	3	6.3	0.3329
CTNNB1	5	5.3	3	6.5	2	4.2	1
PIK3CA	5	5.3	3	6.5	2	4.2	0.9610
BRCA1	4	4.3	2	4.3	2	4.2	0.9610
ASTN1	2	2.1	1	2.2	1	2.1	1
BRCA2	2	2.1	1	2.2	1	2.1	1
KRAS	2	2.1	1	2.2	1	2.1	1
LRFN5	2	2.1	1	2.2	1	2.1	1
LRRTM4	2	2.1	2	4.3	0	0.0	1
ROS1	2	2.1	2	4.3	0	0.0	0.4561
TRPS1	2	2.1	2	4.3	0	0.0	0.4561
BRINP3	1	1.1	1	2.2	0	0.0	0.4561
CNTNAP2	1	1.1	1	2.2	0	0.0	0.9829
CSMD3	1	1.1	1	2.2	0	0.0	0.9829
FBXL7	1	1.1	0	0.0	1	2.1	0.9829
GRIN2B	1	1.1	0	0.0	1	2.1	1
KIT	1	1.1	1	2.2	0	0.0	1
MYH7	1	1.1	1	2.2	0	0.0	0.9829
RET	1	1.1	1	2.2	0	0.0	0.9829
ROBO2	1	1.1	1	2.2	0	0.0	0.9829
SLITRK1	1	1.1	0	0.0	1	2.1	0.9829
SV2A	1	1.1	0	0.0	1	2.1	1
TNR	1	1.1	0	0.0	1	2.1	1
ZNF521	1	1.1	0	0.0	1	2.1	1
EGFR CNV	51	54.3	28	60.9	23	47.9	1
ERBB2 CNV	2	2.1	2	4.3	0	0.0	0.2923
MET CNV	18	19.1	10	21.7	8	16.7	0.4561

CNV, copy number variant.

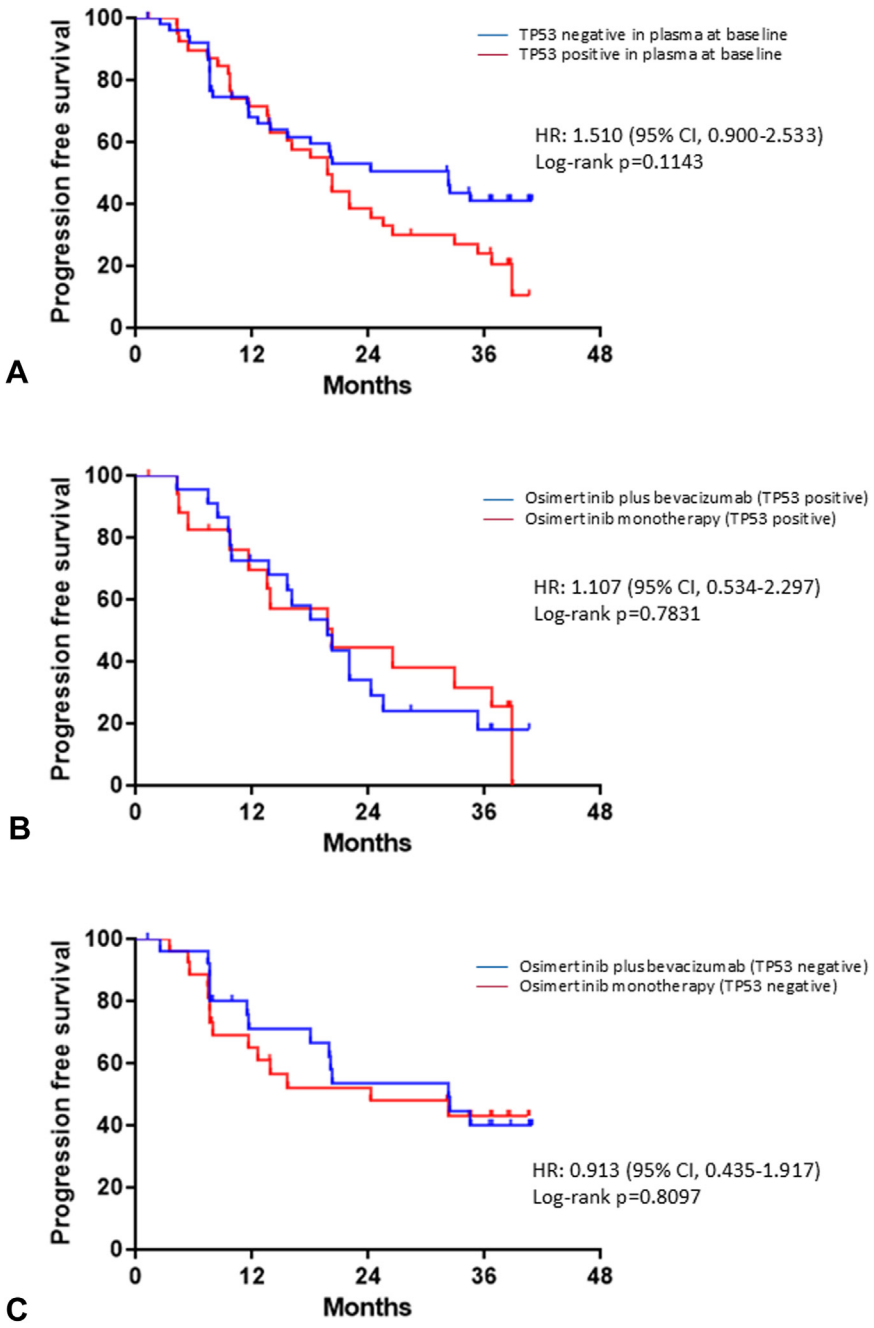

Figure 2. Progression-free survival assessed by the blinded independent central radiologic reviewer (*A*) in patients with plasma samples at baseline (n = 94), (*B*) in patients with plasma *TP53* co-mutation at baseline (n = 42), and (*C*) in patients without plasma *TP53* co-mutation at baseline (n = 52). BICR, blinded independent central radiologic reviewer; CI, confidence interval; HR, hazard ratio.

PFS, osimertinib monotherapy arm: 20.2 mo and osimertinib plus bevacizumab arm: 19.8 mo), with an HR for combination therapy of 1.107 (95% CI: 0.534–2.297, $p = 0.7831$) (Fig. 2*B*). In patients without *TP53* mutation in baseline plasma samples (n = 52), there was no difference in PFS assessed by the BICR between the two arms (median PFS, osimertinib monotherapy arm: 24.2 mo and osimertinib plus bevacizumab arm: 32.3 mo), with an HR for combination therapy of 0.913 (95% CI: 0.435–1.917, $p = 0.8097$) (Fig. 2*C*).

Among 91 patients with plasma samples at disease progression or the last dose of osimertinib, C797S in exon 20 was newly observed in two patients (2.2%), both of whom received osimertinib monotherapy (Supplementary Data 4). One patient (2.2%) receiving osimertinib monotherapy had a *MET* CNV at disease

Table 2. Characteristics of Patients With *TP53* Mutation in Plasma at Baseline

Variables		*TP53* Mutation Positive (n = 42)		*TP53* Mutation Negative (n = 52)		*p* Value
		n	%	n	%	
Age	<65 y	19	45.2	17	32.7	0.2862
	≥65 y	23	54.8	35	67.3	
Sex	Male	19	45.2	20	38.5	0.5342
	Female	23	54.8	32	61.5	
Stage	IIIB	1	2.4	0	0.0	0.4367
	IIIC	1	2.4	0	0.0	
	IV	33	78.6	41	78.8	
	Postoperative recurrence	7	16.7	11	21.2	
Smoking	Ever	16	38.1	25	48.1	0.4044
	Never	26	61.9	27	51.9	
ECOG performance status	0	22	52.4	29	55.8	0.8358
	1	20	47.6	23	44.2	
Brain metastases	Yes	16	38.1	14	26.9	0.2730
	No	26	61.9	38	73.1	
Liver metastasis	Yes	8	19.0	6	11.5	0.3868
	No	34	81.0	46	88.5	

ECOG, Eastern Cooperative Oncology Group.

progression or the last dose, as did two (4.4%) patients who received osimertinib plus bevacizumab (Fig. 3*A*–*C*).

Discussion

The final analysis results of the WJOG9717L study indicated no significant difference in PFS between osimertinib plus bevacizumab and osimertinib monotherapy in untreated patients with nonsquamous NSCLC harboring *EGFR* mutations. To the best of our knowledge, this is the first randomized phase 2 study to compare the efficacy and safety of osimertinib plus bevacizumab with those of osimertinib monotherapy as a first-line treatment. Previous randomized phase 2 trials comparing osimertinib plus bevacizumab with osimertinib monotherapy in patients with EGFR T790M-mutated NSCLC also found no differences in PFS between the two arms.[19,20] For untreated patients with NSCLC harboring *EGFR* mutations, a single-arm phase 1-2 study revealed a 12-month PFS rate of 76% and a median PFS of 19 months, similar to our study results.[21] Therefore, consistent with our study results, these results indicate that the impact of bevacizumab on the efficacy of osimertinib may be limited in patients with *EGFR*-positive NSCLC.

In the subgroup analysis of the PFS assessed by the BICR, patients in the osimertinib plus bevacizumab arm with a smoking history had better trends in PFS than those in the osimertinib monotherapy arm (HR of combination therapy, 0.565), which is consistent with the results of previous studies evaluating EGFR TKIs plus antiangiogenesis inhibitors.[13,14,22–24] Smoking-related malignancies have high mutation burdens, including *TP53* mutations, and *TP53* mutations are more frequently observed in smokers with lung cancer.[18,25] In the RELAY study, patients receiving erlotinib plus ramucirumab had better PFS than those receiving erlotinib plus placebo among patients with *TP53* co-mutations.[26] In this study, *TP53* co-mutations were associated with worse PFS; however, there was no difference in PFS between the two arms in patients with *TP53* co-mutations in the baseline plasma samples. In addition, no association between *TP53* co-mutations and smoking history was observed. Therefore, it was still unclear why patients in the osimertinib plus bevacizumab arm with a smoking history had better trends compared with those in the osimertinib monotherapy arm (HR = 0.565).

Gene profiles at disease progression or the last dose were similar between the two arms. The C797S mutation in exon 20 was observed in 2.2% of plasma samples at disease progression or the last dose of osimertinib, and *MET* CNV was observed in 3.3%. In the FLAURA study, the most common resistance mechanisms in patients receiving osimertinib as first-line treatment were the C797S mutation (7%) and *MET* amplification (15%).[27] There are limited data available on the mechanism of resistance to first-line osimertinib. In preclinical studies, EGFR and vascular endothelial growth factor receptors induce activation of signal transduction pathways to regulate cellular growth and proliferation at the acquired resistance of EGFR TKI treatment, and the vascular endothelial growth factor pathway may

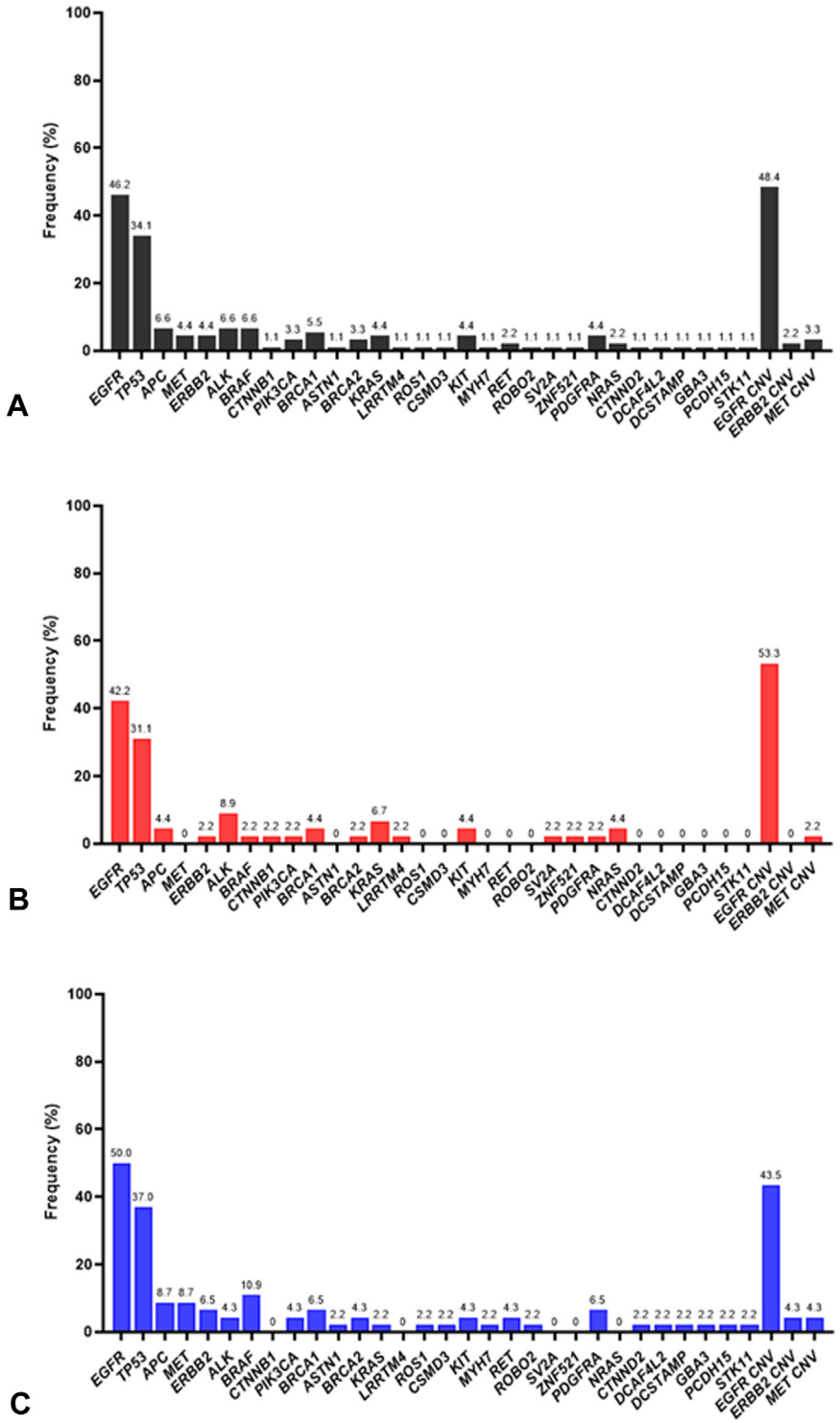

Figure 3. Gene profiles of plasma samples at disease progression or the last dose of osimertinib in (*A*) the entire population (n = 91), (*B*) patients receiving osimertinib monotherapy (n = 45), and (*C*) patients receiving osimertinib plus bevacizumab (n = 46). CNV, copy number variant.

function exclusively for EGFR signaling to maintain tumor growth.[12] Nevertheless, we did not identify an effect of bevacizumab on osimertinib resistance.

Our study has several limitations. First, there were insufficient OS events to compare OS between the two arms. Previous randomized studies have revealed that the combination of erlotinib and bevacizumab improved PFS compared with erlotinib monotherapy among patients with *EGFR*-positive NSCLC; however, no OS benefit was observed.[14,16] We also identified no difference in OS

between the two arms. Second, tissue and plasma samples at baseline were available in only 33% and 78% of the entire cohort, respectively. Nevertheless, a relatively high number of patients were included in the biomarker analysis of the clinical trial.

In conclusion, these final analysis results indicate no superiority of osimertinib plus bevacizumab compared with osimertinib monotherapy in improving PFS and OS in patients with nonsquamous NSCLC harboring *EGFR* mutations. Regardless of *TP53* co-mutation in the plasma samples at baseline, there was no significant difference in the PFS between the two arms.

CRediT Authorship Contribution Statement

Hirotsugu Kenmotsu: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing—original draft preparation.

Kazuko Sakai: Methodology, Investigation, Resources, Analysis and interpretation of data, Writing—review & editing.

Keita Mori: Conceptualization, Methodology, Data curation, Analysis and interpretation of data.

Terufumi Kato: Investigation, Resources, Writing—review & editing.

Shunichi Sugawara: Investigation, Resources, Writing—review & editing.

Keisuke Kirita: Investigation, Resources, Writing—review & editing.

Yasuto Yoneshima: Investigation, Resources, Writing—review & editing.

Koichi Azuma: Investigation, Resources, Writing—review & editing.

Kazumi Nishino: Investigation, Resources, Writing—review & editing.

Shunsuke Teraoka: Investigation, Resources, Writing—review & editing.

Ryo Koyama: Investigation, Resources, Writing—review & editing.

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Hidetoshi Hayashi: Investigation, Resources, Writing—review & editing.

Ryo Toyozawa: Investigation, Resources, Writing—review & editing.

Satoru Miura: Investigation, Resources, Writing—review & editing.

Yuki Sato: Investigation, Resources, Writing—review & editing.

Kazuhiko Nakagawa: Investigation, Resources, Writing—review & editing, Project administration.

Nobuyuki Yamamoto: Investigation, Resources, Writing—review & editing, Project administration.

Kazuto Nishio: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing—review & editing.

Toshiaki Takahashi: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing—review & editing, Project administration.

Data Sharing Statement

Beginning 6 months and ending 5 years after article publication. The individual participant data underlying the results will be shared after deidentification to investigators whose proposed data use has been approved by investigators of the WJOG thoracic group identified for that purpose. The proposal should be directed to h.kenmotsu@scchr.jp.

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100716.

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