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ORIGINAL ARTICLE

Lazertinib with stereotactic body radiotherapy in oligometastatic *EGFR*-mutant non-small-cell lung cancer

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Available online 27 January 2026

Background: Lazertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that demonstrated progression-free survival (PFS) benefit in treatment-naive, *EGFR*-mutant advanced non-small-cell lung cancer (NSCLC) as a single agent and in combination with amivantamab. Here, we report the clinical efficacy and safety profile of lazertinib plus stereotactic body radiotherapy (SBRT) in treatment-naive, *EGFR*-mutant oligometastatic NSCLC.

Patients and methods: ABLATE is a phase II, multicenter, randomized, non-comparative study that included patients harboring activating *EGFR* mutations (ex19del or L858R) with synchronous oligometastatic disease (metastatic lesion $\leq$5). Patients received oral lazertinib 240 mg as monotherapy or in combination with SBRT, which was given immediately or 8 weeks after initiation of lazertinib. The primary endpoint was investigator-assessed PFS of lazertinib plus SBRT.

Results: A total of 67 patients were enrolled in the study ($n = 34$, lazertinib; $n = 33$, lazertinib plus SBRT). At a median follow-up duration of 23.1 months (range 7.1-34.1 months), the median PFS was 34.0 months [90% confidence interval (CI) 19.2 months-not reached (NR)] and objective response rate (ORR) was 58% (95% CI 40.7% to 74.4%) for the lazertinib plus SBRT group. In lazertinib monotherapy, the median duration of follow-up was 22.4 months (range 3.7-33.5 months), the median PFS was 24.8 months (90% CI 15.7 months-NR), and ORR was 68% (95% CI 51.9% to 83.4%). SBRT led to local treatment effect with 92% ($n = 12/14$) progressing to new sites at progression. No new safety signals were seen with the addition of SBRT, and no grade $\geq$3 radiation pneumonitis was seen. Whole-exome sequencing of baseline tumor samples revealed that *TP53* (64%), *CRLF2* (43%), and *P2RY9* (43%) were the most common mutations in patients treated with lazertinib plus SBRT.

Conclusion: In treatment-naive, *EGFR*-mutant oligometastatic NSCLC, adding upfront SBRT to lazertinib is a viable therapeutic option with a manageable safety profile.

Key words: *EGFR* mutation, NSCLC, oligometastasis, lazertinib, SBRT

INTRODUCTION

In non-small-cell lung cancer (NSCLC), epidermal growth factor receptor (*EGFR*) represents one of the most frequently observed mutations accounting for 15%-50% of oncogenic driver alterations.[1] Previously, the standard of care for advanced NSCLC harboring *EGFR* mutation was EGFR tyrosine kinase inhibitor (TKI) as monotherapy, preferably osimertinib, a third-generation EGFR TKI with its intracranial efficacy and manageable safety profile.[2] Despite treatment, however, patients inevitably experience relapse,[3] with a predilection for brain metastasis in 20%-40% of the patients.[4] Furthermore, treatment with *EGFR* L858R has shown suboptimal response to EGFR TKIs in contrast to exon 19 deletion (ex19del).[2,5]

Recently, the treatment landscape for treatment-naive, *EGFR*-mutant advanced NSCLC has evolved to include two pivotal studies of osimertinib plus platinum-based chemotherapy[6] and lazertinib plus amivantamab[7] as combination

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approaches to maximize treatment outcomes. Despite promising outcomes with statistically significant and clinically meaningful PFS benefit in both regimens, and overall survival (OS) benefit in the lazertinib plus amivantamab combination, concerns remain regarding toxicity over prolonged treatment duration and over-treatment in patients who are amenable to EGFR TKI monotherapy.[8] Furthermore, subgroup analysis of patients treated with amivantamab plus lazertinib demonstrated that those with high-risk features, defined as a history of brain metastasis, baseline liver metastasis, concurrent *TP53* mutation, circulating tumor DNA (ctDNA) detected at baseline, and ctDNA persistence during treatment, derive greater clinical benefit compared with those treated with lazertinib monotherapy.[9] Identifying patients who will clinically benefit from monotherapy or combination treatment is paramount to the treatment landscape of *EGFR*-mutant advanced NSCLC. Moreover, there is still debate on whether all patients are candidates for combination treatment.

Currently, EGFR TKI remains the cornerstone of *EGFR*-mutant NSCLC, but there is an unmet need for the subset of patients with oligometastatic disease (OMD) who may benefit from the addition of local control. Although OMD can be categorized further into *de novo*, repeat, or induced OMD, the definition of *de novo* OMD is heterogeneous and arbitrary ranging from three to five metastatic lesions.[10,11] Several phase II and phase III studies have reported the antitumor efficacy of local radiotherapy plus EGFR TKI.[3,12-14] The addition of stereotactic body radiotherapy (SBRT) to EGFR TKI results in local control and improved PFS with relatively minimal treatment-related toxicity.[15,16] However, the trials that have investigated the efficacy of SBRT in addition to TKI were based on first-generation TKIs, and the efficacy of SBRT in the context of third-generation EGFR TKI remains to be elucidated.[3,17]

Lazertinib is a third-generation EGFR TKI designed to selectively target sensitizing mutations while sparing wild-type EGFR, which demonstrated improved PFS and intracranial efficacy in the LASER301 trial.[5] Here, we report the findings of ABLATE trial (KCSG-LU21-11, ClinicalTrials.gov identifier: NCT05167851), which assessed the clinical efficacy and safety profile of lazertinib plus SBRT in treatment-naive, *EGFR*-mutant, synchronous oligometastatic NSCLC.

PATIENTS AND METHODS

Study design

This study was a multicenter, non-comparative, randomized controlled phase II study designed to evaluate the efficacy of first-line lazertinib with locally ablative radiotherapy in patients with synchronous oligometastatic *EGFR*-mutant NSCLC.[18] Although both lazertinib monotherapy and lazertinib plus SBRT were included in the study, the non-comparative trial intentionally does not include a formal, pre-specified statistical comparison between arms for the primary outcome. The study was approved by the institutional review board of all participating sites and all the patients provided written informed consent (approval number: 4-2021-1227).

Patients

Key eligibility criteria included: (i) patient's age $\geq$18 years; (ii) histologically confirmed, treatment-naive *EGFR*-mutant (ex19del or L858R) advanced NSCLC with or without T790M resistance mutation; (iii) synchronous OMD defined as five or fewer metastatic lesions; (iv) all lesions amenable to SBRT, including brain lesions; (v) an Eastern Cooperative Oncology Group performance status of 0-2; (vi) measurable disease according to RECIST v1.1; (vii) adequate hematological, renal, and liver function.

Exclusion criteria included prior chemotherapy, immunotherapy, or radiotherapy or therapeutic surgery for advanced NSCLC. Patients with leptomeningeal seeding or symptomatic spinal cord compression were not included. Patients who were receiving medications or herbal supplements known to be potent CYP3A4 inducers were excluded. Patients who were unable to swallow or received bowel resection that would preclude adequate absorption of lazertinib were not included. Patients with underlying interstitial lung disease and idiopathic pulmonary fibrosis were also excluded from the study.

Eligible patients were assessed by screening evaluations to determine eligibility within 28 days before randomization. Initial staging methods included computed tomography (CT), positron emission tomography—CT, and magnetic resonance imaging (MRI) of the brain. All patients were enrolled only after the radiologist reviewed the imaging scans and confirmed as oligometastatic. All patients were randomly assigned using permuted block randomization, which was concealed and stratified by *EGFR* mutation type (ex19del versus L858R) using the Interactive Web Response System, to receive lazertinib monotherapy or lazertinib plus SBRT to all metastatic sites.

Treatment with lazertinib

All patients were given oral lazertinib 240 mg once daily until disease progression or unacceptable toxicity. Lazertinib can be interrupted or reduced to 160 mg upon toxicity in alignment with the LASER301 study.[5]

Radiotherapy

SBRT was given either (i) within 4 weeks or (ii) 8 weeks after initiation of lazertinib. For SBRT given within 4 weeks, (i) the primary lung lesion was $<$5 cm without mediastinal lymph node metastasis, (ii) $<$5 cm without abutting the gastrointestinal tract, and (iii) fewer than two metastatic lesions in the lung.

Radiotherapy was given once daily or every alternative day. Each lesion was treated with either one, three, or five fractions at the discretion of the radiologist. The preferred doses were 20 Gy in one fraction, 30 Gy in three fractions, and 35 Gy in five fractions. A prescription of 45 Gy in 15 fractions was also allowed for the treatment of primary

tumors and metastatic mediastinal lymph nodes. Target volumes did not cover elective volumes and dose constraints for organs at risk may not be exceeded. Palliative radiotherapy (e.g. 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions) was allowed in the lazertinib arm upon progression to palliate symptoms.

Assessments

The primary endpoint was investigator-assessed PFS of lazertinib plus SBRT using RECIST v1.1. Secondary endpoints included PFS of lazertinib monotherapy, in addition to OS, objective response rate (ORR), duration of response (DoR), and safety by Common Terminology Criteria for Adverse Events criteria of both treatment arms. CT and MRI scans were carried out at baseline and every 12 weeks until investigator-assessed disease progression. After treatment discontinuation, patients were followed up for disease progression and survival every 12 weeks until loss to follow-up, consent withdrawal, or death. Patients were monitored for 6 weeks after the last dose for adverse events (AEs).

Statistical analysis

A randomized, non-comparative, parallel, two-arm design was used for sample size calculation. We chose PFS as the primary endpoint and calculated the sample size based on appropriate calibration for the null hypothesis formulation. Patients with brain metastasis treated with first-line osimertinib or lazertinib demonstrated an mPFS of 15.2[19] and 16.4[5] months, respectively. However, the efficacy of lazertinib for patients with brain metastasis was not published at the time of study design. Hence, we based the null hypothesis on a PFS of 14 months, which was considered non-compelling from historical data. Assuming a power of 80%, a two-sided alpha of 0.1, a hazard ratio of 0.58, and a 10% dropout rate, we calculated that each arm requires 34 patients. Patients treated with lazertinib monotherapy were enrolled to ensure appropriate calibration for the null hypothesis formulated for lazertinib plus SBRT. No formal statistical comparison between the two groups was carried out.

PFS was analyzed according to the intention-to-treat population stratified by *EGFR* mutation type (ex19del or exon 21 L858R) and was shown using the Kaplan−Meier survival curve by treatment group. All analysis was carried out using R (R Development Core Team, 2022, Vienna, Austria) v4.3.3 and SAS (SAS Institute Inc, Cary, NC) v9, and 90% and 95% confidence intervals (CIs) were reported for the primary and secondary endpoints, respectively.

Exploratory analysis

As an exploratory objective, we also examined whole-exome sequencing (WES) and bulk RNA sequencing (RNA-seq) at baseline and at progression (optional) of biopsied tissue samples.

Library preparation and sequencing

Genomic DNA purity and concentration were assessed using the PicoGreen dsDNA assay (Invitrogen, Waltham, MA; RRID: SCR_008410) and agarose gel electrophoresis method. Genomic fragment library was constructed from 57 tumor and matched normal blood samples using the SureSelect V6-Post kit (Agilent Technologies, Santa Clara, CA; RRID: SCR_013575) and sequenced on a NovaSeq 6000 (Illumina, San Diego, CA; RRID: SCR_010233). RNA was isolated using TRizol (Invitrogen; RRID: SCR_008410). RNA libraries were generated from 59 tumor samples using the TruSeq RNA Access Library Prep Kit (Illumina; RRID: SCR_010233) and sequenced on a NovaSeq 6000.

Whole-exome sequencing analysis

The sequenced reads were aligned to the human genome reference (GRCh38) using Burrows-Wheeler Alignment (BWA-0.7.17; RRID: SCR_010910). Then, they were analyzed with the genome analysis toolkit. Matched normal and tumor data were used for mutation calling. Somatic mutations were called using GATK (version 4.1.4.1; RRID: SCR_001876) and MuTect2 (Broad Institute, MA; RRID: SCR_007073) within the docker system and annotated with Funcotator (FUNCtional annOTATOR). Nonsynonymous mutations included in the Cancer Gene Census (CGC, GRCh38 v102) (COSMIC; RRID: SCR_002260) with a mutant allele frequency >0.01 and a tumor read depth >10 were extracted. Copy number (CN) variation analysis was carried out using etal/cnvkit (version 0.9.5; RRID: SCR_021917) on the docker system, with CN >5 indicating amplification and CN <1 indicating biallelic inactivation. The 30 most frequent genes were selected and visualized using the ComplexHeatmap package (RRID: SCR_017270) in R.

Bulk RNA sequencing analysis

The sequenced raw reads were obtained in FASTQ format, and adapter sequences as well as low-quality bases were removed using Trimmomatic (version 0.39; RRID: SCR_011848). Cleaned reads were aligned to GRCh38 using HISAT2 (version 2.2.1; RRID: SCR_015530) with default parameters. Transcript assembly and gene-level quantification were carried out using StringTie (version 2.2.1; RRID: SCR_016323) in reference-guided mode (-G and -e options), with a GTF annotation file based on RefSeq (RRID: SCR_003496). For strand-specific libraries, expression from sense and antisense strands was quantified separately. Expression values were obtained as raw read counts and normalized to fragments per kilobase of transcript per million mapped reads (FPKM) and transcripts per million (TPM).

Functional class scoring analyses, including gene set enrichment analysis (GSEA; RRID: SCR_003199) and gene set variation analysis (GSVA; RRID: SCR_021058), were carried out in the R programming environment. Gene ontology biological process terms from the Molecular Signatures Database (MSigDB) were used as the reference

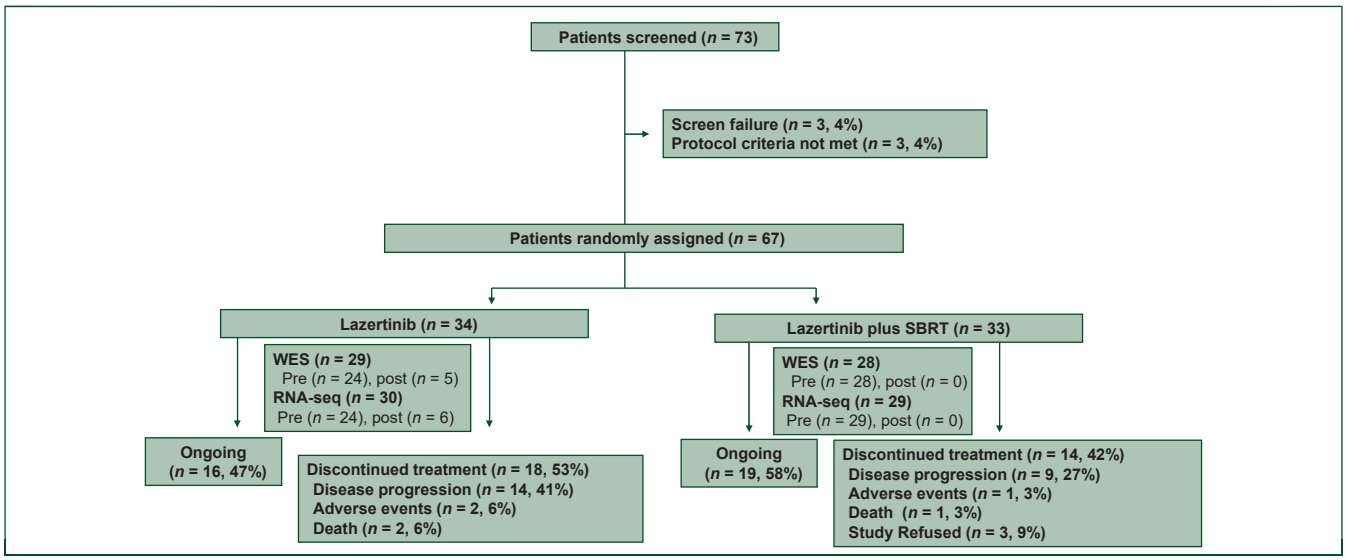

Figure 1. CONSORT diagram of patients treated with lazertinib ($n = 34$) and lazertinib plus SBRT ($n = 33$).
CONSORT, Consolidated Standards of Reporting Trials; RNA-seq, RNA-sequencing; SBRT, stereotactic ablative radiotherapy; WES, whole-exome sequencing.

gene sets. To reduce statistical noise from genes with extremely low expression, only genes with a median TPM >0 across all samples were retained. Functional gene sets containing more than five genes were included in the analysis. GSEA was conducted using the R clusterProfiler package (version 4.14.6; RRID: SCR_016884) with default parameters. GSVA was carried out using the R GSVA package (version 2.1.11) with Poisson kernel.

Visualization of swimmer plot

The swimmer plot was visualized using dplyr (RRID: SCR_016708) and ggplot2 (RRID: SCR_014601) in R.

RESULTS

Patient population

Between 31 January 2022 and 8 May 2023, a total of 73 patients were screened and provided informed consent across four treatment centers. At the data cut-off of 31 December 2024, the study was fully enrolled and 67 patients were randomly assigned (Figure 1). Thirty-four patients were allocated to the lazertinib group, and 33 patients were allocated to the lazertinib plus SBRT group. Most of the patients had three or more metastatic sites, which accounted for 79% ($n = 27/34$) and 73% ($n = 24/33$) in the lazertinib monotherapy and lazertinib plus SBRT groups, respectively (Table 1). Brain metastasis accounted for 41% ($n = 14/34$) in the lazertinib monotherapy group and 58% ($n = 19/33$) in the lazertinib plus SBRT group. Before treatment, 47% ($n = 16$) and 42% ($n = 14$) had one metastatic organ in the lazertinib monotherapy and lazertinib plus SBRT groups, respectively. Asymptomatic brain metastasis accounted for 41% ($n = 14$) in the lazertinib monotherapy group and 58% ($n = 19$) in the lazertinib plus SBRT group.

All enrolled patients in the lazertinib plus SBRT group completed full doses of planned radiotherapy. Seven (21%) and 26 (79%) patients received SBRT within 4 and 8 weeks, respectively. The median fraction dose was 7 Gy (range 3-10 Gy) and median fraction number was 5 (3-15) for primary tumor and regional lymph node (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.106057). Three patients did not receive radiotherapy in the primary lung lesion. For metastatic lesions, the median fraction dose was 8 Gy (5-20 Gy) and median fraction number was 3 (1-5). The most common dose schedule was 30 Gy delivered in five fractions. Eight patients received palliative radiotherapy in the lazertinib monotherapy arm. In the lazertinib plus SBRT group, subsequent SBRT was carried out for recurred lesions in five patients.

At the time of data analysis, 47% ($n = 16$) in the lazertinib monotherapy group and 58% ($n = 19$) in the lazertinib plus SBRT group were continuing treatment with lazertinib (Figure 2A). The most common cause of treatment discontinuation was disease progression for both treatment arms (lazertinib, 41%; lazertinib plus SBRT, 27%).

Efficacy

The median duration of follow-up was 22.4 months (range 3.7-33.5 months) and 23.1 months (range 7.1-34.1 months) for the lazertinib monotherapy and lazertinib plus SBRT groups, respectively. The ORR was 68% (95% CI 51.9% to 83.4%) and 58% (95% CI 40.7% to 74.4%) for the lazertinib monotherapy and lazertinib plus SBRT groups, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.106057). Median DoR was 24.1 months [95% CI 13.8 months-not reached (NR)] for the lazertinib monotherapy group and 25.8 months (95% CI 16.6 months-NR) for the lazertinib plus SBRT group, respectively.

The median PFS was 24.8 months (90% CI 15.7 months-NR) for the lazertinib monotherapy group and 34.0 months (90% CI 19.2 months-NR) for the lazertinib plus SBRT group (Figure 2B).

Table 1. Baseline characteristics of the lazertinib monotherapy and lazertinib plus SBRT groups

Characteristics	Lazertinib (n = 34) n (%)	Lazertinib + SBRT (n = 33) n (%)
Sex		
Female	20 (59)	20 (61)
Male	14 (41)	13 (39)
Age (years)		
<60	10 (29)	12 (36)
≥60	24 (71)	21 (64)
ECOG		
0	10 (29)	16 (48)
1	24 (71)	17 (52)
Number of metastatic sites		
1-2	7 (21)	9 (27)
3-5	27 (79)	24 (73)
Number of metastatic organs		
1	16 (47)	14 (43)
2	7 (21)	7 (21)
3	7 (21)	8 (24)
4	4 (11)	4 (12)
Brain metastasis		
Yes	14 (41)	19 (58)
No	20 (59)	14 (42)
EGFR mutation		
Ex19del	16 (44)	17 (52)
L858R	18 (50)	16 (48)
Smoking status		
Never (all tobacco)	22 (65)	22 (67)
Former	9 (26)	11 (33)
Current (all tobacco)	3 (9)	0 (0)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; SBRT, stereotactic ablative radiotherapy.

The PFS rate at 12, 18, and 24 months was 71%, 65%, and 50% for the lazertinib group and 88%, 72%, and 65% for the lazertinib plus SBRT group, respectively. Among patients with *EGFR* ex19del, the median PFS was 24.8 months (90% CI 14.5 months-NR) for the lazertinib group (n = 16) and NR (90% CI 15.7 months-NR) for the lazertinib plus SBRT group (n = 17). In patients with *EGFR* L858R, the median PFS was 20.3 months (90% CI 10.8-25.7 months) and 27.6 months (90% CI 18.2 months-NR) for the lazertinib monotherapy (n = 18) and lazertinib plus SBRT groups (n = 16), respectively (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.106057). Among patients with brain metastasis, the median PFS was 25.7 months (90% CI 15.7 months-NR) for the lazertinib monotherapy group (n = 14) and NR (90% CI 14.5 months-NR) for the lazertinib plus SBRT group (n = 19) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.106057). For patients without brain metastasis, the median PFS was 18.9 months (90% CI 10.8 months-NR) and 27.6 months (90% CI 19.1 months-NR) for the lazertinib (n = 20) and lazertinib plus SBRT groups (n = 14), respectively. There were no statistically significant differences in PFS in terms of *TP53* mutation with lazertinib (P = 0.45) or lazertinib plus SBRT (P = 0.76) although a trend toward longer PFS for *TP53* wild type was observed (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.106057). The median PFS was 25.7 months and 19.3 months for *TP53* mutant (n = 14) and *TP53* wild type (n = 10) in patients treated with lazertinib, and 15.7 months and 26.6 months for *TP53* mutant (n = 18) and *TP53* wild type (n = 10) in those treated with lazertinib plus SBRT. At the time of data cut-off, the OS data remained immature with three death events. The median OS was 31.4 months (95% CI 25.0 months-NR) for lazertinib monotherapy, and it was NR in the lazertinib plus SBRT group (95% CI 30.4 months-NR) (Figure 2D).

Subgroup analysis

Further, we analyzed the patterns of recurrence in each group (Figure 2E, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.106057). In the lazertinib group, 41% (n = 14/34) presented with relapse during treatment. These patients showed relapse to original site (58%, n = 8), followed by new site of metastasis (21%, n = 3) or both (21%, n = 3). In patients who were treated with lazertinib plus SBRT, 39% (n = 13/33) relapsed, with 85% (n = 11) identified as new site of metastasis. Only one patient experienced progression to primary lung lesion along with new metastatic lesions.

Safety

Overall, lazertinib was well tolerated as monotherapy and in combination with SBRT (Table 2). The most common treatment-related AEs in the lazertinib monotherapy and lazertinib plus SBRT groups, respectively, were paresthesia (94%, 79%), rash (65%, 46%), urticaria (32%, 24%), paronychia (24%, 24%), and stomatitis (35%, 12%) of any grade. Abnormal laboratory findings such as increases in aspartate aminotransferase, alanine aminotransferase, amylase, and lipase of any grade accounted for 18%, 9%, 12%, and 12% in the lazertinib group and 6%, 9%, 12%, and 15% in the lazertinib plus SBRT group. Four patients (12%) in the lazertinib plus SBRT group experienced grade 1-2 radiation pneumonitis, which was resolved after the use of oral steroids. Grade ≥3 AEs occurred rarely in both treatment groups. Paresthesia (3%), rash (3%), and increase in creatinine phosphokinase (3%) were observed in the lazertinib monotherapy group, whereas paresthesia (12%) and increase in lipase (6%) and amylase (3%) occurred in the lazertinib plus SBRT group. No grade 5 treatment-related AEs were observed.

Treatment-related dose reductions were comparable in both groups and accounted for 35% and 39% in the lazertinib and lazertinib plus SBRT groups, respectively. Permanent discontinuation was reported in 3% in the lazertinib group and 6% in the lazertinib plus SBRT group. During treatment, there was no dose interruption in both groups.

Exploratory analysis

A total of 57 and 59 samples were evaluated for WES and bulk RNA-seq, respectively. WES of baseline biopsy samples for lazertinib plus SBRT (n = 28) revealed that the most common mutations were *TP53* (64%), followed by *CRLF2* (43%) and *P2RY9* (43%) mutations (Figure 3A). Rebiopsy at progression was not mandatory and no tumor samples were collected for the lazertinib plus SBRT group. *TP53* mutation was also present at baseline (58%) (Figure 3A) and at progression with lazertinib monotherapy (n = 5) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.106057). Matched

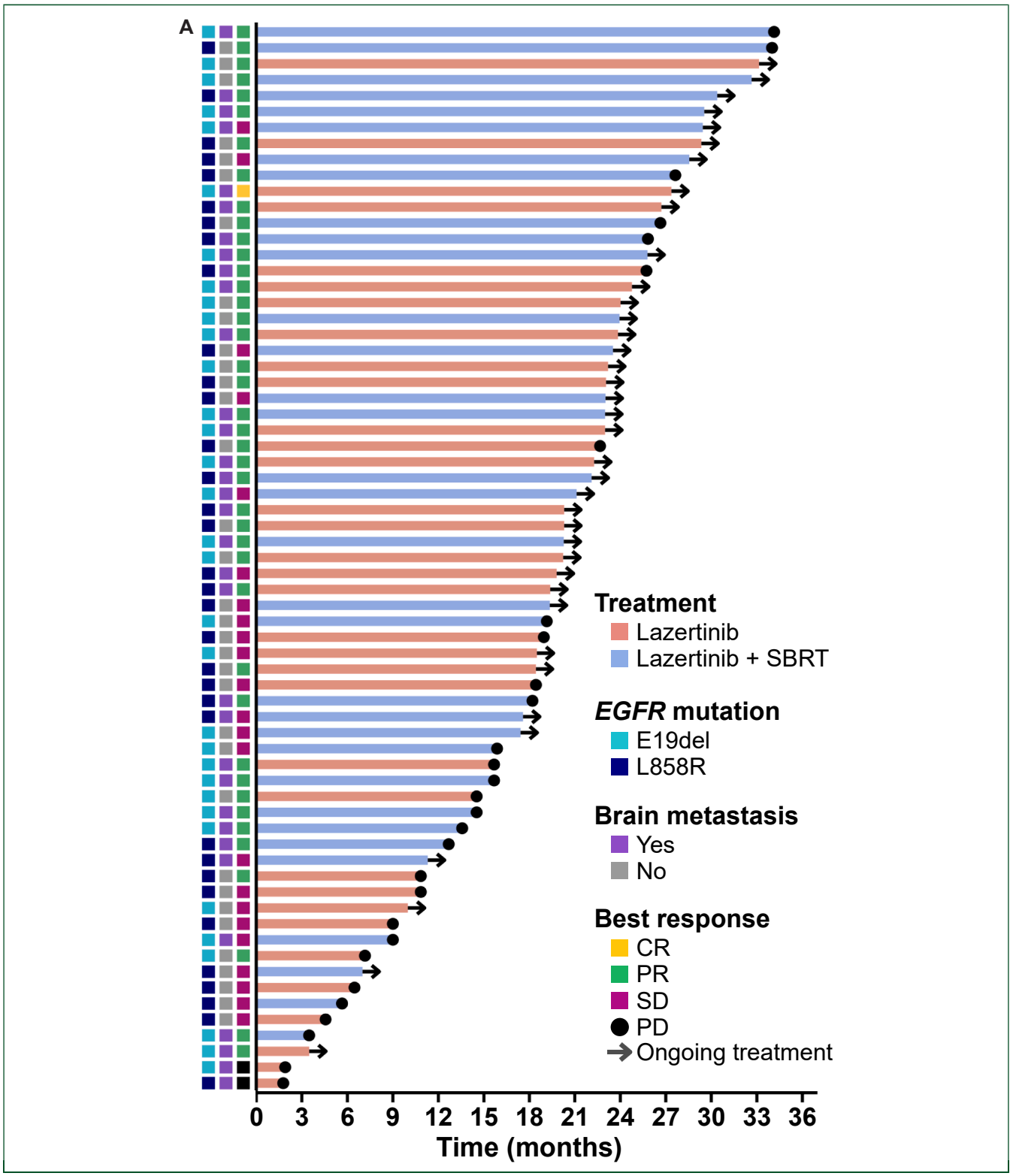

Figure 2. Efficacy outcomes. (A) Swimmer plot, (B) PFS of the lazertinib and lazertinib plus SBRT groups, (C) PFS of the patient subgroup, (D) OS of the lazertinib and lazertinib plus SBRT groups, and (E) patterns of disease progression by treatment group and disease site.
CI, confidence interval; HR, hazard ratio; Laz, lazertinib; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic ablative radiotherapy; WES, whole-exome sequencing.

baseline and progression samples of lazertinib ($n = 2$) showed heterogeneity in genomic alterations (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.106057).

Functional characteristics associated with treatment response were explored using transcriptome of baseline biopsy samples from bulk RNA-seq for lazertinib plus SBRT ($n = 29$) and lazertinib monotherapy ($n = 24$). GSEA and

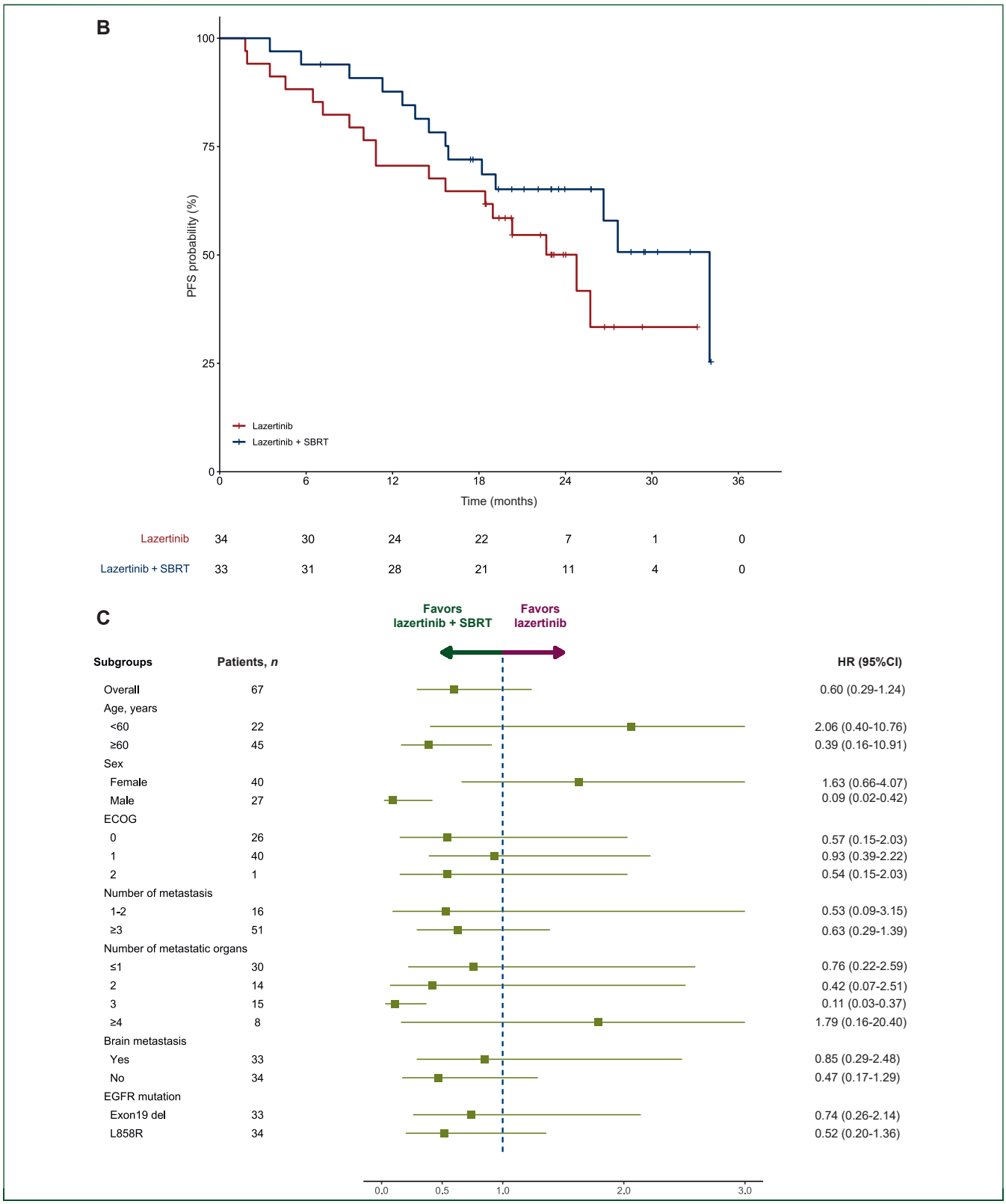

Figure 2. **Continued.**

GSVA were applied to derive functional class scores, which were subsequently evaluated in univariate survival analyses of PFS (Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2025.106057). In the lazertinib plus SBRT group, functional analysis revealed that pathways including negative regulation of DNA repair, cell division, and sister chromatid cohesion were significantly associated with PFS (Figure 3B, Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.106057). Moreover, this combination of functional scores was significantly

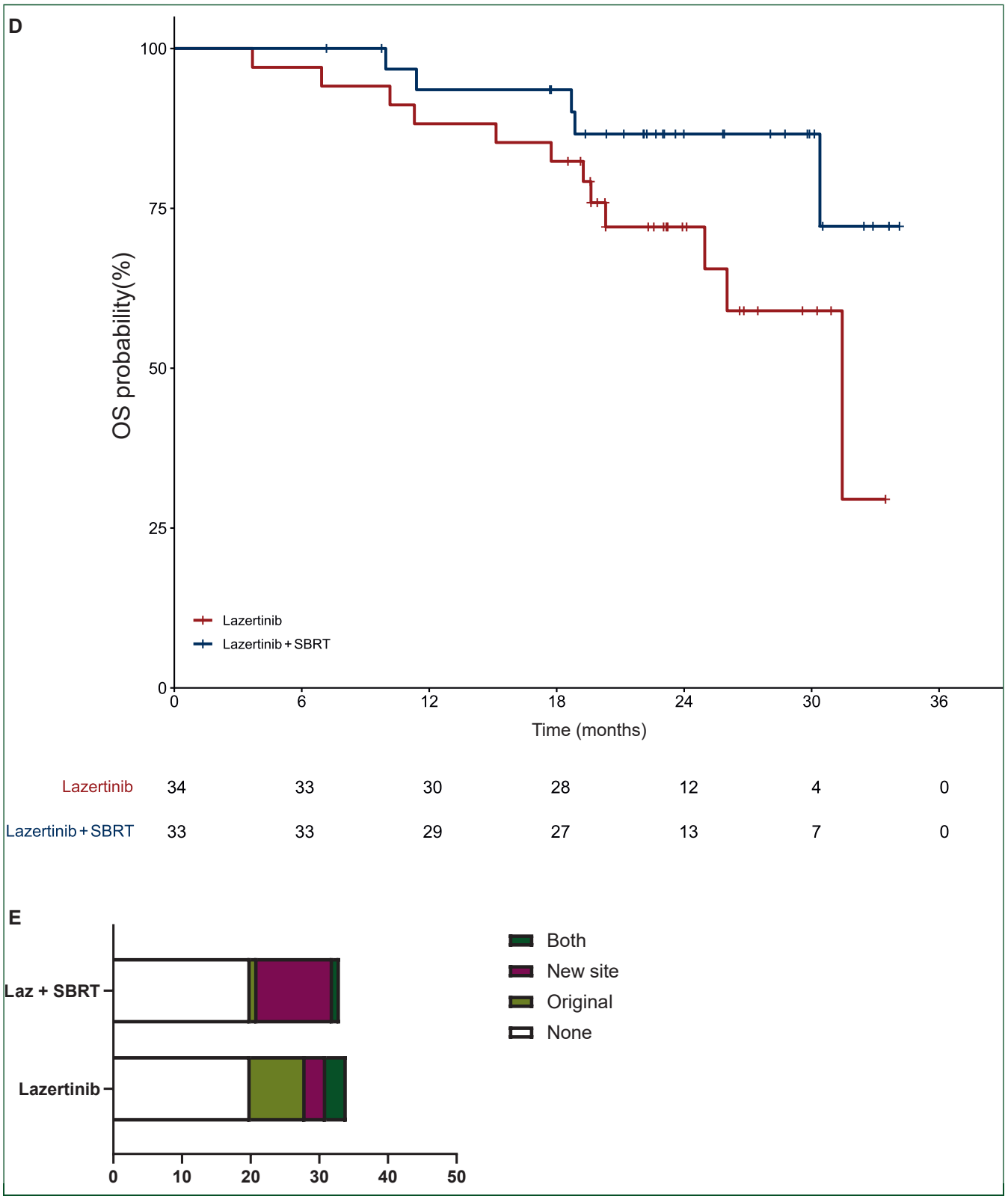

Figure 2. **Continued.**

associated with worse PFS in the lazertinib plus SBRT group ($P = 0.005$, 15.8 months in the high group versus NR in the low group) (Figure 3C and D).

DISCUSSION

This is the first trial to report the clinical results of adding SBRT to lazertinib across all oligometastatic sites in patients

Table 2. Treatment-related adverse events of the lazertinib monotherapy and lazertinib plus SBRT groups

Characteristics	Lazertinib (n = 34), n (%)			Lazertinib + SBRT (n = 33), n (%)		
	Any grade	Grade 1/2	Grade 3/4	Any grade	Grade 1/2	Grade 3/4
Paresthesia	32 (94)	32 (94)	1 (3)	26 (79)	26 (79)	4 (12)
Rash	22 (65)	21 (62)	1 (3)	15 (46)	15 (46)	0
Urticaria	11 (32)	11 (32)	0	8 (24)	8 (24)	0
Paronychia	8 (24)	8 (24)	0	8 (24)	8 (24)	0
Stomatitis	12 (35)	12 (35)	0	4 (12)	4 (12)	0
Diarrhea	4 (12)	4 (12)	0	7 (21)	7 (21)	0
Lipase increased	4 (12)	4 (12)	0	5 (15)	4 (12)	2 (6)
Amylase increased	4 (12)	4 (12)	0	4 (12)	3 (9)	1 (3)
AST increased	6 (18)	6 (18)	0	2 (6)	2 (6)	0
Dermatitis acneiform	3 (9)	3 (9)	0	4 (12)	4 (12)	0
ALT increased	3 (9)	3 (9)	0	3 (9)	3 (9)	0
CPK increased	4 (12)	4 (12)	1 (3)	2 (6)	2 (6)	0
Constipation	2 (6)	2 (6)	0	3 (9)	3 (9)	0
Radiation pneumonitis	0	0	0	4 (12)	4 (12)	0
Decreased appetite	2 (6)	2 (6)	0	1 (3)	1 (3)	0
Creatinine increased	1 (3)	1 (3)	0	1 (3)	1 (3)	0
Dysphonia	1 (3)	1 (3)	0	1 (3)	1 (3)	0
Gastritis	0	0	0	2 (6)	2 (6)	0
Hypophagia	1 (3)	1 (3)	0	1 (3)	1 (3)	0
Nausea	0	0	0	2 (6)	2 (6)	0
Peripheral edema	1 (2.9)	1 (3)	0	1 (3)	1 (3)	0
Palmar-plantar erythrodysesthesia syndrome	0	0	0	2 (6)	2 (6)	0
Total	33 (97)	33 (97)	3 (9)	31 (94)	31 (94)	6 (18)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; SBRT, stereotactic body radiotherapy.

with advanced, metastatic *EGFR*-mutant NSCLC. This multicenter, randomized, controlled phase II study was designed in a non-comparative manner. Hence, our study indicated that the addition of SBRT demonstrated a clinically meaningful benefit of prolonged PFS (34 months) compared with the historical control. Moreover, the addition of SBRT demonstrated a trend toward prolonging OS. Our study also showed that the addition of SBRT did not show any grade 3 pneumonitis or any grade 4 or 5 AEs related to lazertinib plus SBRT.

In this study, patients were diagnosed with *EGFR* mutation via EGFR droplet digital PCR identified in tissue samples. Hence, liquid or tissue next-generation sequencing was not mandatory. Baseline *EGFR* mutation in ctDNA or concurrent mutations such as *TP53* were not assessed in tissue or liquid biopsy before treatment. Although these parameters are not actively utilized in the clinical setting, these are distinct biomarkers of high-risk disease, and this subset of patients has shown to benefit from combination treatments such as lazertinib plus amivantamab.[9] In our study, *TP53* co-mutation was the most common concurrent alteration at baseline. However, no statistically significant differences in PFS were observed in lazertinib plus SBRT in terms of *TP53* co-mutation. Furthermore, patients with relatively intact DNA repair system with low combination score of DNA repair, cell division, and sister chromatid cohesion in the lazertinib plus SBRT group responded favorably with longer median PFS (NR versus 15.8 months). This finding is in alignment with radioresistance in patients with intact DNA repair pathways.[20]

Patterns of relapse after failure with EGFR TKIs in *EGFR*-mutant metastatic NSCLC have been comparable across agents.[21,22] The most common site of relapse is the originally involved site, which was observed in ∼50% of patients, followed by both original and new metastatic sites (28%) and new metastasis (22%) in patients treated with first-line osimertinib.[22] In the present trial, despite the reduction in progression at original sites, the most common site of progression observed was at new sites in the lazertinib plus SBRT group. This pattern is in line with the CURB trial that evaluated the efficacy of SBRT in oligoprogressive NSCLC, which showed significant PFS benefit.[13] Although this discrepancy remains difficult to explain, recent studies suggest that radiation may promote tumor metastasis.[23,24] These findings underscore the need for additional strategies to modulate and harness this radiation-induced biological response.

In the LASER301[5] trial, 25% of patients with asymptomatic central nervous system metastases were enrolled to compare the efficacy of lazertinib with gefitinib.[5] In our study, 58% of patients with asymptomatic brain metastases were enrolled and demonstrated a median PFS of 24.8 months which was longer than the median PFS of 20.6 months in the LASER301 trial. The durable benefit of lazertinib as monotherapy may be attributable to the patients enrolled in this study since only oligometastatic lesions were included.

Synchronous oligometastatic NSCLC accounts for one-third of metastatic disease at diagnosis.[25] *De novo* oligometastatic NSCLC harboring *EGFR* mutation represents a distinct entity with different biology that necessitates tailored treatment.[26] The definition of oligometastasis in NSCLC remains heterogeneous, with oligometastasis defined as up to three metastases in the European Society for Medical Oncology (ESMO) guideline, three to five metastases in the National Comprehensive Cancer Network (NCCN) guideline, and up to five metastases in up to three organs in the International Association for the Study of Lung Cancer (IASLC) guideline.[26]

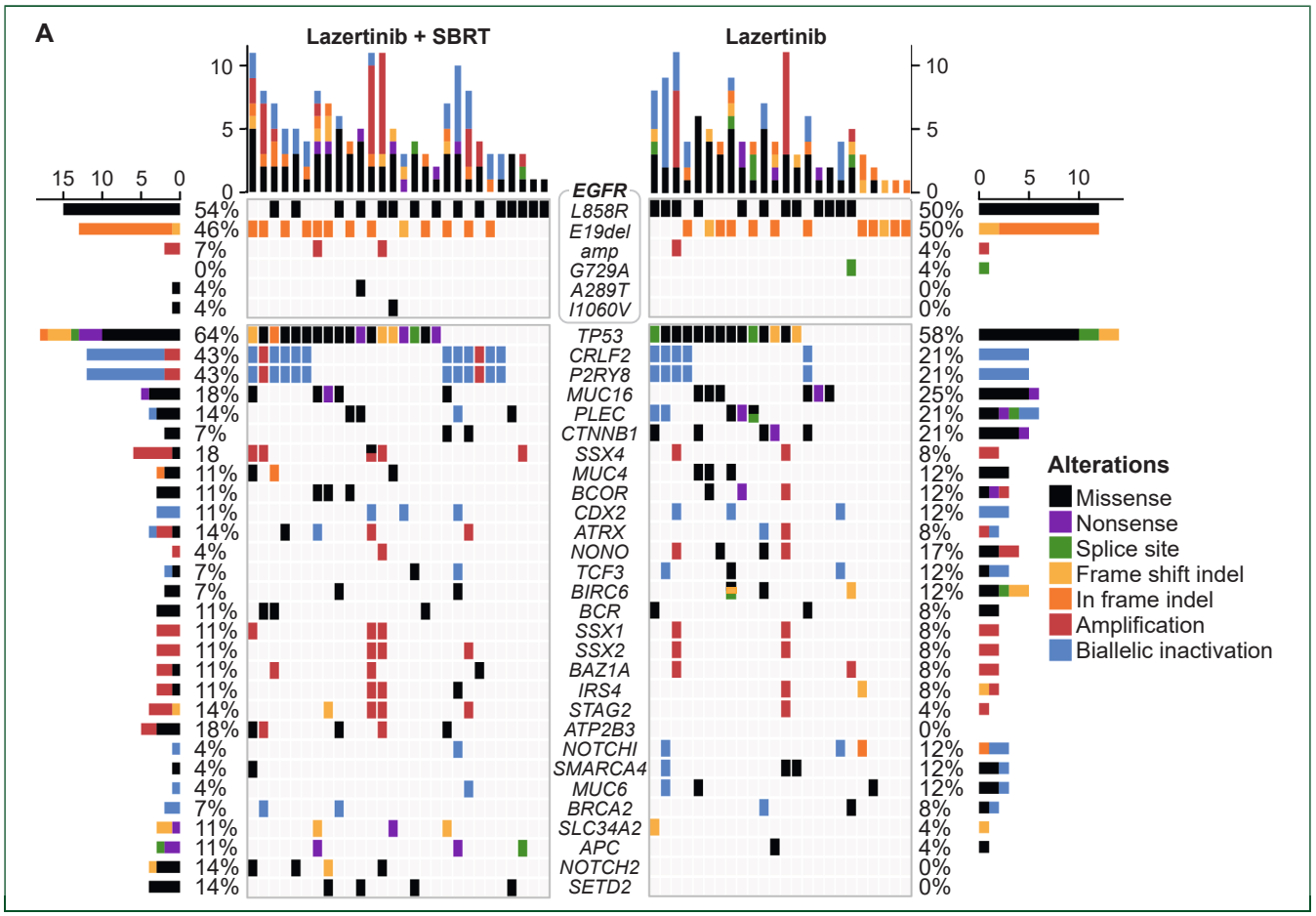

Figure 3. Biomarker analyses. (A) WES of the lazertinib and lazertinib plus SBRT groups, (B) heat map of significant GSVA scores of the lazertinib and lazertinib plus SBRT groups, (C) forest plots of presented HRs for PFS obtained from significant GSVA scores, (D) PFS of high- and low-functional score groups associated with negative regulation of DNA repair (GO: 0045738).
GSVA, gene set variation analysis; HR, hazard ratio; PFS, progression-free survival; SBRT, stereotactic ablative radiotherapy; WES, whole-exome sequencing.

Current treatment guideline recommends third-generation EGFR TKI monotherapy or combination with chemotherapy or amivantamab. However, the risk of toxicity at the cost of clinical benefit calls for tailored treatment based on patient's condition and preference.[27] Furthermore, treatment outcomes in oligometastatic, *EGFR*-mutant NSCLC have been scarce, and use of SBRT to oligometastatic sites is heterogeneous. Osimertinib given with consolidative SBRT demonstrated a median PFS of 35.7 months and OS of 45.7 months, respectively, in a single-arm phase II study.[28] Of note, patients included in this study received SBRT to oligo-persistent lesion after 8 weeks of osimertinib, and SBRT was not restricted by number, size, and site of metastasis. Hence, the addition of SBRT upfront to EGFR TKI in *EGFR*-mutant NSCLC has been an unmet need especially in patients with low disease burden. For this subset of patients, local control may be a feasible approach rather than the addition of chemotherapy or targeted agents.[29]

Our study shows that lazertinib plus SBRT in oligometastatic, *EGFR*-mutant NSCLC resulted in longer PFS than EGFR TKI monotherapy or combination approach (osimertinib plus chemotherapy or lazertinib plus amivantamab), respectively, potentially due to low tumor burden that was amenable to local therapy.

The ABLATE study has a few limitations. Firstly, it is a phase II study with a relatively small sample size in both arms, and the sample size was calculated in a non-comparative manner. As a result, this study is not a head-to-head comparison and is not intended to directly compare the clinical efficacy of lazertinib monotherapy versus lazertinib plus SBRT. Thus, a larger prospective trial comparing third-generation EGFR TKI as monotherapy and in combination with SBRT is warranted in *EGFR*-mutant NSCLC with oligometastasis. Considering that combination approaches, such as lazertinib plus amivantamab, are associated with increased toxicity at the cost of durable response and improved survival outcomes, patients with oligometastatic lesion amenable to SBRT may consider lazertinib monotherapy with the addition of local radiotherapy. Secondly, the protocol specified that all patients receive radiotherapy to all sites. However, three patients did not receive radiotherapy to the primary lung lesion, and subsequently experienced relapse. These patients received radiotherapy to all other metastatic lesions and were included in the analysis. However, considering that this study was primarily driven by investigators across multiple centers, and the dataset was meticulously analyzed by the Korean Cancer Study Group (KCSG), this study unveils the

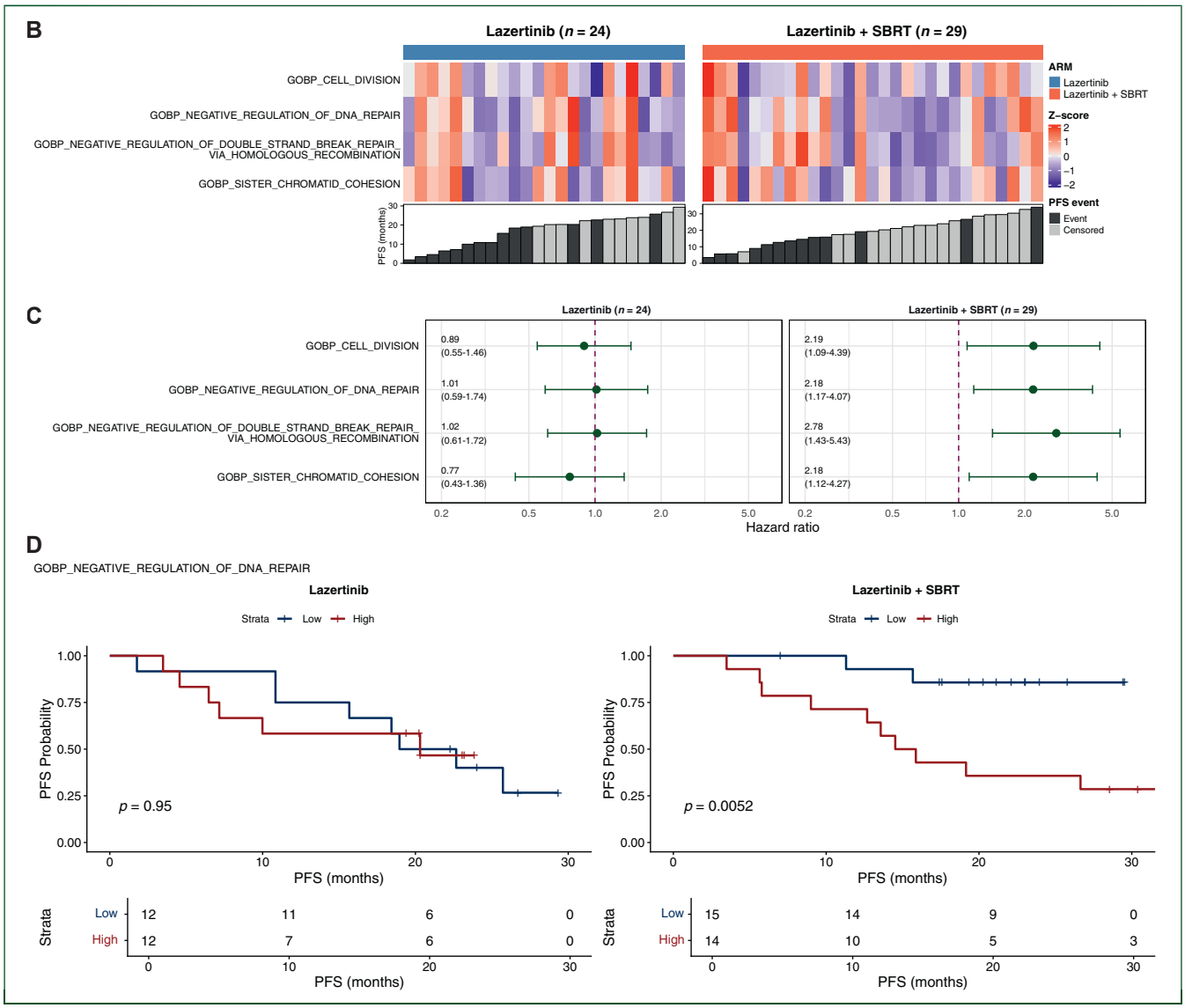

Figure 3. Continued.

robust clinical activity of lazertinib plus SBRT, demonstrating clinically meaningful PFS. No grade ≥3 AEs, such as pneumonitis, were observed in *EGFR*-mutant NSCLC with oligometastasis treated with lazertinib plus SBRT.

In conclusion, lazertinib plus SBRT demonstrated clinical efficacy and manageable safety profile in treatment-naive, *EGFR*-mutant oligometastatic NSCLC. Further analysis including a randomized phase III trial is warranted to validate our findings.

FUNDING

This work was supported in part by the Korean Cancer Study Group (KCSG) and Yuhan Corporation (no grant number).

DISCLOSURE

JBL reports research grants from Yuhan.

MHH reports grants from AstraZeneca, Merck Sharp & Dohme, Novartis, and Yuhan; personal fees from AstraZeneca, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Ono Pharmaceutical, Takeda, Roche, Pfizer, and Yuhan; and participating in clinical trials funded by AbbVie, IMPACT, Ignyta, Loxo Oncology, Novartis, Merck Sereno, ORIC, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Pfizer, and Yuhan outside the submitted work. BCC reports the following: invited speaker: ASCO, AstraZeneca, Guardant, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, Pfizer; advisory board: KANAPH Therapeutics Inc, BridgeBio Therapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc. (financial interests); member of the board of directors: Interpark Bio Convergence Corp., J INTS BIO (financial interests); stocks/shares: TheraCanVac Inc, Gencurix Inc, BridgeBio Therapeutics, KANAPH Therapeutics Inc., Cyrus Therapeutics, Interpark Bio Convergence Corp., J INTS BIO (financial interests); royalties: Champions Oncology (financial interests); research grants:

MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GIInnovation, GI-Cell, Abion, Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ Bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, BridgeBio Therapeutics, Yuhan, ImmuneOncia, Illumina, KANAPH Therapeutics, Therapex, JINTSbio, Hanmi (financial interests); advisory role: Abion, BeiGene, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, CJ, CureLogen, Cyrus therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI-Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc., Janssen, Takeda, MSD, Janssen, Medpacto, Blueprint medicines, RandBio, Hanmi (financial interests); other: DAAN Biotherapeutics (founder). SML reports grants from Yuhan, Beigene, Boehringer Ingelheim, BridgeBio Therapeutics, Roche, GSK, Jiangsu Hengrui, AstraZeneca, Lily, Takeda, Daiichi Sankyo, and J Ints Bio. All other authors have declared no conflicts of interest.

DISCLAIMER

The funding source did not partake in the study design, data collection, data analysis, data interpretation, and writing of the report.

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