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BRIEF REPORT

Updated Efficacy and Safety From the Phase 2 PHAROS Study of Encorafenib Plus Binimetinib in Patients With BRAF V600E-Mutant Metastatic NSCLC—A Brief Report

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ABSTRACT

Introduction: The PHAROS primary analysis revealed robust antitumor activity and acceptable safety with encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC). We report results after 18 months of additional follow-up.

Methods: In this ongoing open-label, single-arm, phase 2 study, patients with BRAF V600E-mutant mNSCLC

(59 treatment-naive and 39 previously treated) received encorafenib 450 mg once daily and binimetinib 45 mg twice daily. Primary end point was objective response rate (ORR). Secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: At this data cutoff, median treatment duration with encorafenib plus binimetinib was 16.3 months in treatment-naive and 5.5 months in previously treated patients; minimum follow-up was approximately 32 and 22 months, respectively. In treatment-naive patients, the ORR was 75%, median DOR was 40.0 months, median PFS was 30.2 months, median OS was not estimable (95% confidence interval: 31.3–not estimable), and the 3-year OS probability was 53%. In previously treated patients, the ORR was 46%, median DOR was 16.7 months, median PFS was 9.3 months, median OS was 22.7 months, and the 3-year OS probability was 29%. Overall, the most frequent treatment-related adverse events were nausea (52%), diarrhea (44%), fatigue (33%), and vomiting (30%). Treatment-related adverse events led to dose reductions and permanent treatment discontinuations in 25 (26%) and 16 (16%) patients, respectively.

Conclusions: With longer follow-up, encorafenib plus binimetinib showed durable and clinically meaningful antitumor activity, especially in treatment-naive patients, with a manageable safety profile in patients with BRAF V600E-mutant mNSCLC.

Clinical Trial Information: ClinicalTrials.gov Identifier: NCT03915951

Keywords: Non–small cell lung cancer; BRAF; Encorafenib; Binimetinib

Introduction

The *BRAF* V600E mutation occurs in approximately 1% to 2% of NSCLC cases and is sensitive to BRAF and MEK inhibition.[1,2] Encorafenib is an oral, selective, reversible BRAF kinase inhibitor, and binimetinib is an oral, ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2. The combination of encorafenib and binimetinib is approved for patients with BRAF V600E-mutant metastatic NSCLC (mNSCLC) based on the primary analysis results of the phase 2 PHAROS study.[3] In treatment-naive patients (n = 59), the objective response rate (ORR) by independent radiology review (IRR) was 75%; the median duration of response (DOR) and median progression-free survival (PFS) were not estimable (NE). In previously treated patients (n = 39), the ORR by IRR was 46%, the median DOR was 16.7 months, and median PFS was 9.3 months. Median overall survival (OS) was not reached in either group.[1] We report updated efficacy (including DOR, PFS, and OS) and safety results after 18 months of additional follow-up.

Materials and Methods

Study Design, End Points, and Statistical Analyses

Full study design, methods, oversight, and statistical analyses were published previously.[1] Briefly, PHAROS (NCT03915951) is an ongoing, single-arm, open-label, multicenter, phase 2 study evaluating antitumor activity and safety of encorafenib plus binimetinib in treatment-naive or previously treated adult patients with BRAF V600E-mutant mNSCLC. Patients received oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily in 28-day cycles.

The study was performed in accordance with requirements of applicable local regulatory authorities and International Conference on Harmonisation Good Clinical Practice Guidelines. The protocol and all amendments were approved by an ethics committee. All patients provided written informed consent.

The primary end point was confirmed ORR, assessed per Response Evaluation Criteria in Solid Tumors version 1.1 by IRR. Efficacy end points were assessed separately in treatment-naive and previously treated patients; safety was assessed in all patients. Post hoc analyses included efficacy and safety end points assessed separately in treatment-naive and previously treated patients and in previously treated patients who had received previous immunotherapy and those who had not.

Results

Patient Disposition

Overall, 98 patients (treatment-naive, n = 59; previously treated, n = 39) received encorafenib plus binimetinib. At data cutoff (April 1, 2024), treatment was ongoing in 11 (19%) treatment-naive patients and four (10%) previously treated patients (Supplementary Fig. 1). Minimum follow-up was approximately 32 months in treatment-naive patients and approximately 22 months in previously treated patients.

Patient Characteristics

Baseline characteristics were previously reported (Supplementary Table 1).[1] The median duration of treatment for both encorafenib and binimetinib was 16.3 (range, 0–54.0) months in treatment-naive patients and 5.5 (range 0.1–49.5) months in previously treated patients; 41% and 10% of patients, respectively, received the combination for at least 2 years (Supplementary

Fig. 2). For patients with baseline brain metastases, previous intracranial treatment and study treatment duration are found in Supplementary Table 2.

Efficacy

Treatment-Naive Patients. In treatment-naive patients, the ORR by IRR was 75% (95% CI: 62–85) (Supplementary Table 3). The median DOR was 40.0 months (95% CI: 23.1–NE) (Fig. 1*A*), with responses lasting at least 24 months in 19 patients (43%). The median follow-up duration for PFS by IRR was 33.3 months (95% CI: 30.4–41.3); median PFS by IRR was 30.2 months (95% CI: 15.7–NE) (Fig. 2*A*). Median OS was NE (95% CI: 31.3–NE), and OS probabilities at 2 and 3 years were 67% (95% CI: 53–77) and 53% (95% CI: 38–65), respectively, based on the survival curves (Fig. 2*B*).

Previously Treated Patients. In previously treated patients, the ORR by IRR was 46% (95% CI: 30–63) (Supplementary Table 3). The median DOR was 16.7 months (95% CI: 7.4–NE) (Fig. 1*B*), with responses lasting at least 24 months in four patients (22%). The median follow-up duration for PFS by IRR was 14.0 months (95% CI: 11.3–44.2), and median PFS by IRR was 9.3 months (95% CI: 6.2–24.8) (Fig. 2*C*). Median OS was 22.7 months (95% CI: 14.1–32.2) (Fig. 2*D*).

Safety

All-causality adverse events (AEs) of any grade and grade 3/4 occurred in 97 patients (99%) and 61 patients (62%), respectively (Supplementary Table 4). Any-grade and grade 3/4 treatment-related AEs (TRAEs) occurred in 92 patients (94%) and 45 patients (46%), respectively. The most frequently reported (≥30%) any-grade TRAEs were nausea (52%), diarrhea (44%), fatigue (33%), and vomiting (30%), with median times to onset of 9.0, 16.0, 15.0, and 7.0 days, respectively (Supplementary Table 5). All-causality and treatment-related pyrexia of any grade occurred in 22% and 8% of patients, respectively, with no grade 3 or higher events. One grade 5 AE, an intracranial hemorrhage, occurred in the treatment-naive group and was considered treatment-related by the investigator. This patient had no reported brain metastases.

In a post hoc analysis, safety was considered comparable when encorafenib plus binimetinib was administered in treatment-naive and previously treated patients (Table 1). Another post hoc analysis explored the potential impact of previous immunotherapy on safety in previously treated patients (Supplementary Table 6). Although overall TRAE profiles were comparable, occurrences of fatigue (54% versus 7%), pruritus (25% versus 0%), and maculopapular rash (17% versus 0%) were higher (≥15%) in patients who received previous immunotherapy than in those who had not. The incidence of immune-related TRAEs was low; acute pancreatitis and pneumonitis each occurred in one patient (4%) who had received previous immunotherapy and were not observed in patients who did not receive previous immunotherapy.

Overall, TRAEs led to dose reduction of both encorafenib and binimetinib in 25 patients (26%) and permanent discontinuation of both encorafenib and binimetinib in 16 patients (16%); rates were similar across lines of therapy (Supplementary Table 7). Many patients remained on treatment after dose reduction of encorafenib or binimetinib (Supplementary Fig. 2).

Discussion

In this updated analysis of the PHAROS study, encorafenib plus binimetinib showed substantial clinically meaningful benefit, with durable responses and prolonged survival in patients with BRAF V600E-mutant mNSCLC. In treatment-naive patients, median DOR by IRR was 40.0 months; median PFS by IRR was reached at 30.2 months, and median OS was NE, with the lower limit of the 95% CI being 31.3 months. In previously treated patients, median OS was reached at 22.7 months.

The NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines) and ESMO guidelines recommend targeted therapy, such as encorafenib and binimetinib, as the preferred first-line treatment for BRAF V600E-mutant mNSCLC.[4,5] Dabrafenib plus trametinib, another recommended regimen for this indication, showed an investigator-assessed ORR of 64% and 68%, investigator-assessed median PFS of 10.8 and 10.2 months, and median OS of 17.3 and 18.2 months in treatment-naive and previously treated patients, respectively.[6]

Recent retrospective studies have focused on determining the optimal sequencing of targeted therapies and immunotherapy-based approaches for patients with BRAF-mutant mNSCLC.[7–11] These studies reported conflicting results on whether targeted therapy or an immunotherapy-based approach provided better outcomes in the first-line setting and were limited by their retrospective nature, small patient numbers, and predominant use of dabrafenib and trametinib as the targeted therapy regimen.

In PHAROS, in previously treated patients, the ORR in the first-line setting was 24% with immunotherapy (n = 21) and 22% with chemotherapy monotherapy (n = 18).[1] Although the patient numbers in these post hoc analyses were small, response to first-line immunotherapy- or chemotherapy-based regimens was low. Given that only approximately 50% of patients with mNSCLC receive a second-line therapy,[2] it is important to use the most effective therapy in the frontline setting.

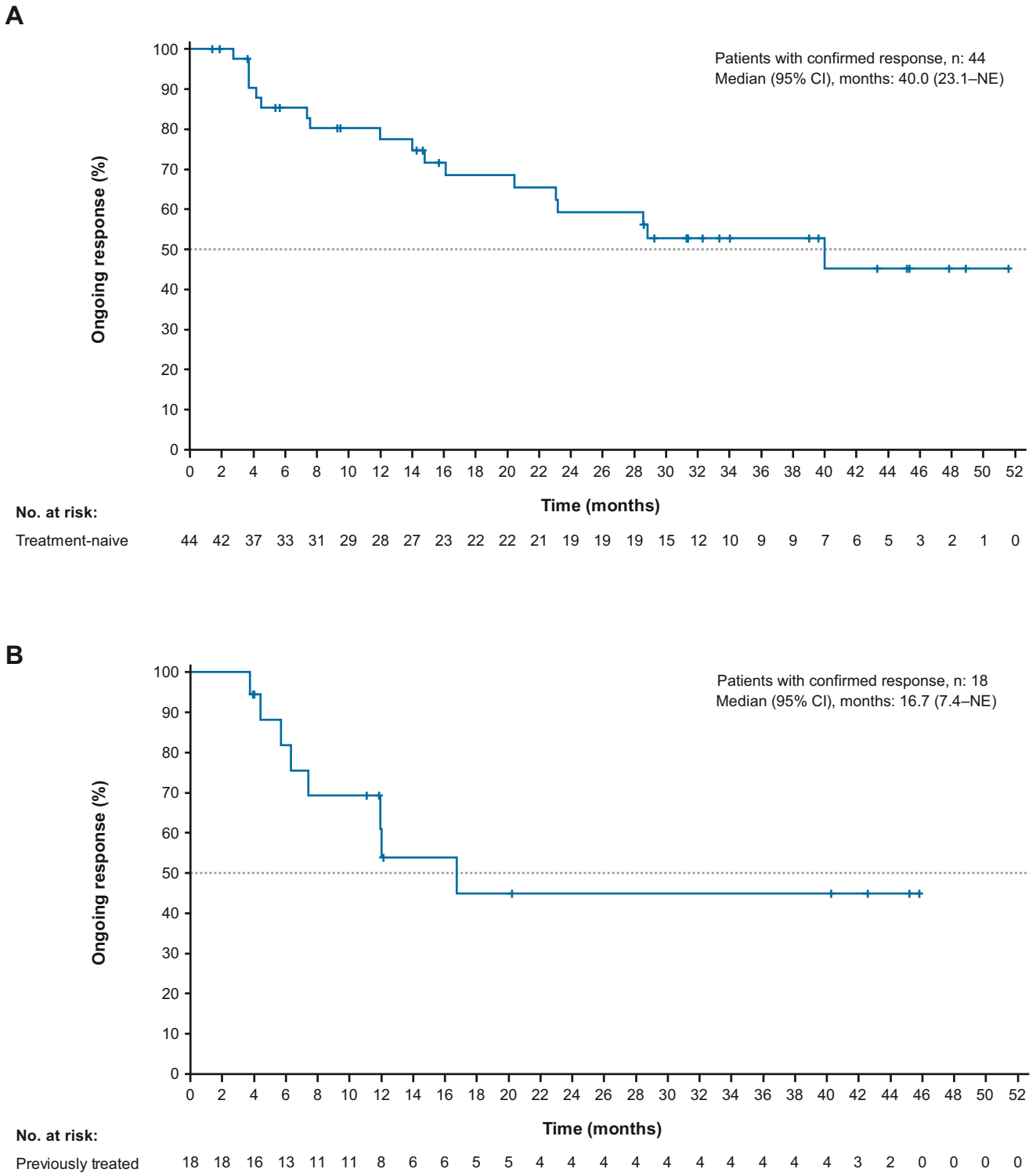

Figure 1. Kaplan-Meier estimate of DOR by IRR for (*A*) treatment-naive and (*B*) previously treated patients. CI, confidence interval; DOR, duration of response; IRR, independent radiology review; NE, not estimable.

Given the response durability of encorafenib plus binimetinib, it is essential to proactively identify and manage AEs with supportive care and dose modifications; previously described therapy management principles may allow patients who derive clinical benefit to safely remain on therapy.[12,13] The overall safety profile in this updated analysis was consistent with that found in the primary analysis,[1] with no new safety

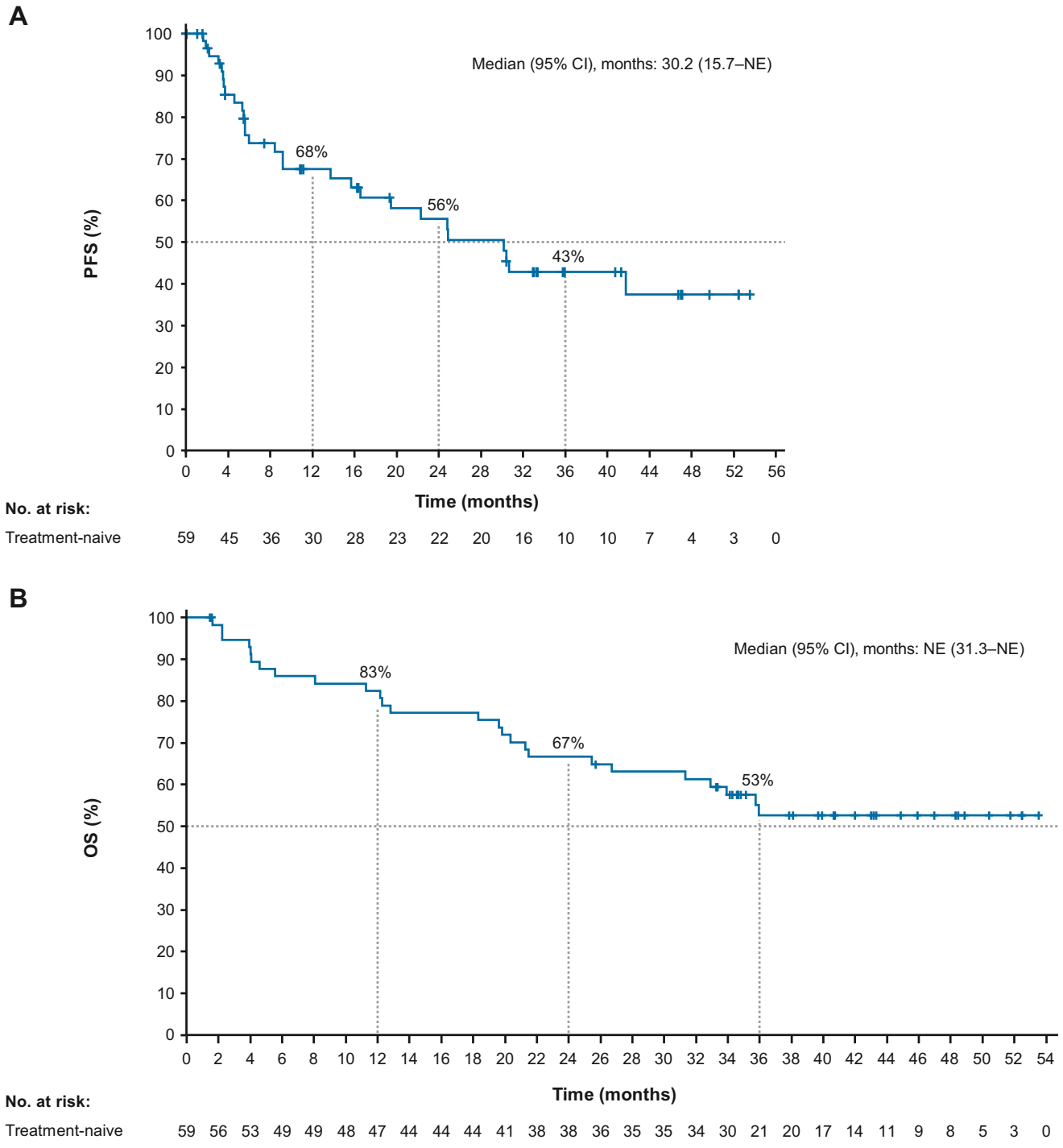

Figure 2. Kaplan-Meier estimate of (*A*) PFS by IRR in treatment-naive patients, (*B*) OS in treatment-naive patients, (*C*) PFS by IRR in previously treated patients, and (*D*) OS in previously treated patients. CI, confidence interval; IRR, independent radiology review; OS, overall survival; NE, not estimable; PFS, progression-free survival.

signals identified. In addition, the safety profile was generally similar across lines of therapy. Treatment-related and all-causality pyrexia of any grade occurred in 8% and 22% of patients, respectively, were all grade 1/2, and did not result in any dose reductions or permanent discontinuations of encorafenib plus binimetinib. In comparison, pyrexia has been a treatment-limiting factor with dabrafenib plus trametinib, which is associated with a higher frequency of all-causality pyrexia (any grade, 56%; grade 3/4, 6%).[6]

A few retrospective studies investigating the safety of sequential immunotherapy followed by targeted therapy

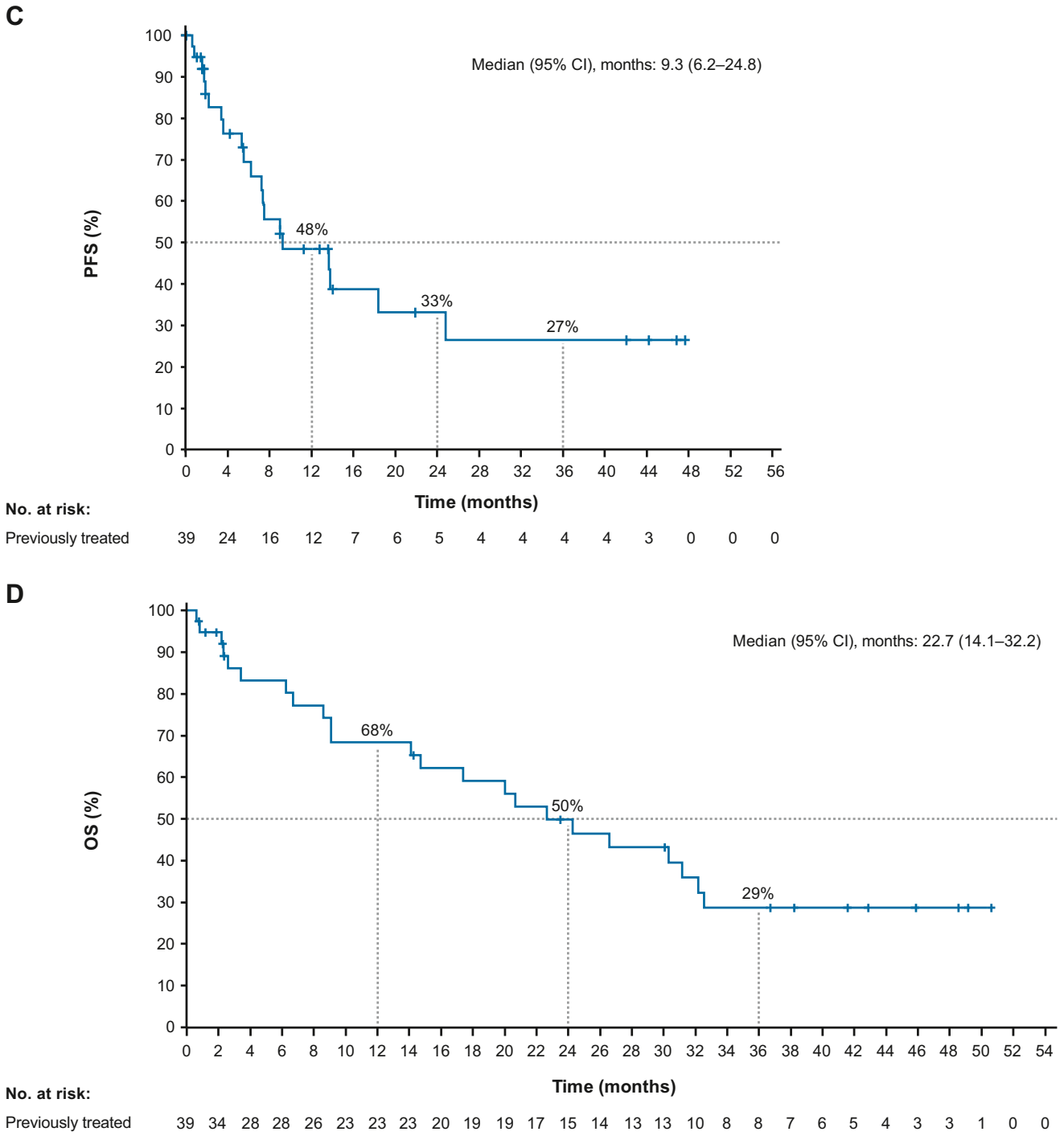

Figure 2. (*continued*).

for oncogene-driven NSCLC reported higher incidences of immune-related AEs (e.g., pneumonitis, colitis, hepatitis) than for the reverse treatment order or targeted therapy without previous immunotherapy.[14,15] In PHAROS, the incidence of immune-related AEs in patients with previous immunotherapy was low, with pancreatitis and pneumonitis each occurring in one patient (4%). Although it is unclear whether the immune-related AEs can be attributed to prior immunotherapy, it may provide further support to use targeted therapy in frontline as recommended by guidelines.[4,5]

In this updated analysis, encorafenib plus binimetinib continued to show durable antitumor activity with a consistent safety profile over a longer treatment duration. The outcomes in treatment-naive patients correspond to the longest DOR and PFS compared with

Table 1. TRAEs in Treatment-Naive and Previously Treated Patients (≥10% Any Grade in Either Cohort)

	Treatment-Naive (n = 59)		Previously Treated (n = 39)	
Preferred Term	Any Grade	Grade 3/4[a]	Any Grade	Grade 3/4
Any TRAE, n (%)	58 (98)	32 (54)	34 (87)	13 (33)
Nausea	35 (59)	3 (5)	16 (41)	1 (3)
Diarrhea	24 (41)	3 (5)	19 (49)	2 (5)
Fatigue	18 (31)	0	14 (36)	2 (5)
Vomiting	18 (31)	1 (2)	11 (28)	0
Vision blurred	12 (20)	1 (2)	6 (15)	0
ALT increased	11 (19)	4 (7)	2 (5)	1 (3)
AST increased	11 (19)	6 (10)	2 (5)	1 (3)
Anemia	10 (17)	2 (3)	7 (18)	1 (3)
Alopecia	9 (15)	0	3 (8)	0
Constipation	9 (15)	0	5 (13)	0
Abdominal pain	8 (14)	0	3 (8)	0
Blood alkaline phosphatase increased	8 (14)	2 (3)	0	0
Blood creatine phosphokinase increased	8 (14)	1 (2)	3 (8)	0
Dry skin	8 (14)	0	3 (8)	0
Lipase increased	8 (14)	7 (12)	1 (3)	0
Decreased appetite	7 (12)	0	2 (5)	1 (3)
Pyrexia	7 (12)	0	1 (3)	0
Rash	7 (12)	0	3 (8)	1 (3)
Rash maculopapular	7 (12)	1 (2)	4 (10)	0
Dizziness	6 (10)	0	5 (13)	1 (3)
Myalgia	6 (10)	2 (3)	5 (13)	0
Peripheral edema	6 (10)	0	5 (13)	0
Pruritus	6 (10)	0	6 (15)	0
Dysgeusia	5 (9)	0	4 (10)	0
Ejection fraction decreased	5 (9)	2 (3)	4 (10)	1 (3)
Asthenia	3 (5)	1 (2)	7 (18)	2 (5)

[a]There was one grade 5 AE (intracranial hemorrhage) determined by investigator to be treatment related.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

historical outcomes in patients with BRAF V600E-mutant mNSCLC.[2] After a minimum follow-up of almost 3 years, median OS in treatment-naive patients was still not reached. These data continue to support encorafenib and binimetinib as a first-line treatment option for patients with BRAF V600E-mutant mNSCLC.

CRediT Authorship Contribution Statement

Gregory J. Riely: Investigation, Writing - original draft, Writing - review and editing.

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Bruce E. Johnson: Investigation, Writing - original draft, Writing - review and editing.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Pfizer Medical AI Assistant (MAIA) to generate the first manuscript draft. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Disclosure

Dr. Riely has received research funding from Amgen, Novartis, Roche/Genentech, Mirati Therapeutics, Merck, Takeda, Lilly, and Pfizer; has had a consulting or advisory role with Novartis; and has received honoraria from MJH Life Sciences and DAVA Oncology. Dr. Ahn has received honoraria from AstraZeneca, MSD, Takeda, Amgen, Merck Serono, Daiichi Sankyo, Roche/Genentech, Ono Pharmaceutical, and Genexine; has had a consulting or advisory role with AstraZeneca, MSD, Takeda, Alpha Pharmaceuticals, Amgen, Merck Serono, Pfizer, Yuhan, Daiichi Sankyo, Roche/Genentech, Ono Pharmaceutical, Genexine, and BioNTech; and has received research funding from Yuhan. Dr. Clarke has had a consulting or advisory role with AstraZeneca, Bristol Myers Squibb, Coherus BioSciences, CDR-Life, Black Diamond Therapeutics, AbbVie, Amgen, Sanofi, Corbus, Janssen, Omega, G1 Therapeutics, and Bio-Thera; has received honoraria from Amgen and AstraZeneca; has received research funding from Bristol Myers Squibb, Adaptimmune, AbbVie, Moderna Therapeutics, GSK, Array BioPharma, AstraZeneca, Grid Therapeutics, Achilles Therapeutics, Genentech, CBMG, and Pfizer; and has received travel accommodations and expenses from Amgen and Bristol Myers Squibb. Dr. Dagogo-Jack has received honoraria from Foundation Medicine, Aptitude Health, Creative Educational Concepts, OncLive, American Society of Clinical Oncology, DAVA Oncology, Medscape, Total Health, Research to Practice, American Lung Association, PeerView, and Curio; has had a consulting or advisory role with Boehringer Ingelheim, AstraZeneca, Xcovery, Catalyst Pharmaceuticals, Pfizer, Syros Pharmaceuticals, BostonGene, Bayer, Genentech, Sanofi, Janssen, Bristol Myers Squibb Foundation, and Novocure; and has received research funding from Pfizer, Array BioPharma, Novartis, Genentech, Calithera Biosciences, Vivace Therapeutics, Guardant Health, BostonGene, and Tango Therapeutics. Dr. Felip has received personal honoraria for advisory board participation from AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Genmab, Gilead, GSK, Janssen, Merck Serono, MSD, Novartis, Peptomyc, Pierre Fabre, Pfizer, Regeneron, Sanofi, Takeda, Turning Point, and Daiichi Sankyo; has received personal speaker honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffmann-La Roche, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, MSD, PeerVoice, Pfizer, Sanofi, Takeda, and Touch Oncology; has had a board of director role for Grifols; and has received financial support for meeting attendance and/or travel from AstraZeneca, Janssen, and Roche. Dr. Gelsomino has had a consulting or advisory role with Novartis, Eli Lilly, Pfizer, Bristol Myers Squibb, AstraZeneca, and Regeneron. Dr. Goldman has had a consulting or advisory role with AstraZeneca, Bristol Myers Squibb, Lilly, Pfizer, AbbVie, Genentech, Regeneron, Jazz Pharmaceuticals, Gritstone Bio, Turning Point Therapeutics, Puma Biotechnology, and Janssen; and has received research funding from Lilly, Genentech/Roche, Bristol Myers Squibb, AstraZeneca/MedImmune, AbbVie, Spectrum Pharmaceuticals, Advaxis, and Pfizer. Dr. Hussein has had a consulting or advisory role with AbbVie, Genentech/Roche, CLL Consulting, Tecentriq, Coherus BioSciences, Athenex, Karyopharm Therapeutics, Bristol Myers Squibb, AstraZeneca, Mirati Therapeutics, Exelixis, Ipsen, BeiGene, Aveo, and National Community Oncology Dispensing Association (NCODA); and is president of Florida Society of Clinical Oncology. Dr. M. Johnson has had a consulting or advisory role with Genentech/Roche, AstraZeneca, Merck, Sanofi, Mirati Therapeutics, AbbVie, GSK, Gritstone Bio, Janssen Oncology, Lilly, Amgen, Daiichi Sankyo, Regeneron, Revolution Medicines, Takeda, Alentis Therapeutics, Arcus Biosciences, Biohaven, Boehringer Ingelheim, Bristol Myers Squibb, D3 Bio, Fate Therapeutics, Gilead, Hookipa, Immunocore, Jazz, ModeX

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Dr. Nadal has had a consulting or advisory role with MSD, Bristol Myers Squibb, Roche, Boehringer Ingelheim, Pfizer, Takeda, AstraZeneca, Lilly, Amgen, Sanofi, Merck Serono, Janssen Oncology, Qiagen, Daiichi Sankyo, Genmab, Apollomics, and Pierre Fabre; has received research funding from Roche, Pfizer, Bristol Myers Squibb, and Merck Serono; and has received other expenses from MSD, Bristol Myers Squibb, Pfizer, Roche, and Lilly. Dr. Negrao has received research funding to institution from Lilly, Mirati, Bristol Myers Squibb, Novartis, Checkmate, Alaunos, AstraZeneca, Pfizer, Genentech, and Navire; has had a consultant or advisory role with Genentech, Mirati, Merck/MSD, Novartis, Sanofi, Pfizer, Lilly, and AstraZeneca; has had a speakers' bureau role for OncLive, Ideology, BIO Brasil, Medscape, DAVA Oncology, and Targeted Oncology; has received travel expenses from Ideology, DAVA Oncology, and Targeted Oncology; and has received writing support from ApotheCom and Ashfield Healthcare. 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Data Sharing Statement

On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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.2025.05.023.

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