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ABSTRACT

The phase II PHAROS study previously showed that encorafenib plus binimetinib has antitumor activity in patients with BRAF V600E-mutant metastatic non–small cell lung cancer (mNSCLC). In PHAROS, 98 patients (59 treatment-naïve; 39 previously treated) received encorafenib 450 mg once daily and binimetinib 45 mg twice daily. We report updated results from data cutoff of March 14, 2025. The median duration of treatment with both encorafenib and binimetinib was 16.3 months in treatment-naïve and 5.5 months in previously treated patients. After median follow-up for overall survival (OS) of 52.3 months in treatment-naïve patients, mOS was 47.6 months (95% CI, 31.3 to not estimable); 4-year OS probability was 49% (95% CI, 35 to 62). After median follow-up for OS of 48.2 months in previously treated patients, mOS was 22.7 months (95% CI, 14.1 to 32.6); 4-year OS probability was 31% (95% CI, 16 to 47). In treatment-naïve and previously treated groups, 58% and 26% received ≥1 subsequent systemic anticancer treatment, respectively. Safety profile remained consistent with that in previous analyses. Although comparisons across trials should be done cautiously, to our knowledge, encorafenib plus binimetinib was associated with the longest mOS reported to date with targeted treatment in patients with treatment-naïve BRAF V600E-mutant mNSCLC.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Data Supplement
Protocol

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INTRODUCTION

BRAF V600E–mutant non–small cell lung cancer (NSCLC) accounts for 1%-2% of NSCLC cases.[1-3] For BRAF V600E–mutant metastatic NSCLC (mNSCLC), two BRAF plus MEK inhibitor combinations, encorafenib plus binimetinib and dabrafenib plus trametinib, have received regulatory approval and are recommended by current guidelines as the preferred first-line treatment or as subsequent treatment when not prescribed in the first line.[4-7] Other first-line options include immunotherapy, chemotherapy, or a combination of the two.[4,5]

The combination of encorafenib, an oral, selective, reversible BRAF kinase inhibitor, and binimetinib, an oral, ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2, received regulatory approval for BRAF V600E-mutant mNSCLC on the basis of the phase II PHAROS study.[7-11] In the primary analysis (September 22, 2022),[7] the primary end point of objective response rate (ORR) by independent radiology review (IRR) was met in both treatment-naïve (n = 59; 75%) and previously treated (n = 39; 46%) patients.[12] In an updated analysis (April 1, 2024), the ORR was unchanged in both groups.[13] The median duration of response (mDOR) and median progression-free survival (mPFS) by IRR were 40.0 and 30.2 months in treatment-naïve patients, respectively, and 16.7 and 9.3 months in previously treated patients, respectively. For the prespecified secondary end point of overall survival, median overall survival (mOS) was 22.7 months in previously treated patients and still not reached in treatment-naïve patients. We report updated results, including OS, at a data cutoff of March 14, 2025.

METHODS

Full study design details for the ongoing single-arm, open-label, multicenter, phase II PHAROS study (ClinicalTrials.gov identifier: NCT03915951) were previously published.[9,12,13] Patients with treatment-naïve or previously treated BRAF V600E-mutant mNSCLC received oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily in 28-day cycles. This study was performed in accordance with and with approval from institutional ethics review boards, and all patients provided informed consent before study enrollment.

RESULTS

Patient Disposition and Characteristics

Overall, 98 patients (treatment-naïve, n = 59; previously treated, n = 39) received encorafenib plus binimetinib. Baseline characteristics are reported in Table 1.[12] At data cutoff, treatment was ongoing in five (8%) treatment-naïve patients and three (8%) previously treated patients. In treatment-naïve patients, the median duration of treatment with both encorafenib and binimetinib was 16.3 months (range, 0-63.9); 41% received both treatments for >2 years, with 31% and 29% having received encorafenib and binimetinib, respectively, for ≥3 years. In previously treated patients, the median duration of treatment with both encorafenib and binimetinib was 5.5 months (range, 0.1-60.9); 13% received both treatments for >2 years and 8% for ≥3 years.

Antitumor Activity

In treatment-naïve patients, the ORR by IRR was 75% (95% CI, 62 to 85); mDOR was 40.0 months (95% CI, 23.2 to not estimable [NE]; Appendix Table A1, online only). Median PFS by IRR was 30.4 months (95% CI, 15.7 to NE; Fig 1A). After median follow-up for OS of 52.3 months (95% CI, 46.8 to 58.3), 30 deaths (51%) occurred; mOS was 47.6 months (95% CI, 31.3 to NE; Fig 1B). Given the median follow-up, we are describing a 4-year OS probability of 49% (95% CI, 35 to 62) on the basis of the Kaplan-Meier estimate.

In previously treated patients, the ORR by IRR was 49% (95% CI, 32 to 65); mDOR was 16.7 months (95% CI, 7.4 to NE; Appendix Table A1). Median PFS by IRR was 9.3 months (95% CI, 6.2 to 24.8; Fig 1C). After median follow-up for OS of 48.2 months (95% CI, 41.6 to 57.4), 23 deaths (59%) occurred; mOS was 22.7 months (95% CI, 14.1 to 32.6; Fig 1D). Four-year OS probability was 31% (95% CI, 16 to 47) on the basis of the Kaplan-Meier estimate.

A post hoc analysis showed similar antitumor activity across subgroups on the basis of baseline characteristics (Table 2). Among both treatment-naïve and previously treated patients, PFS and OS were numerically longer in patients without versus with a smoking history.

In the treatment-naïve and previously treated groups, 34 (58%) and 10 (26%) received ≥1 subsequent systemic anticancer treatment, respectively (Appendix Table A2). Of those patients, 19 (56%) and four (40%) received immunotherapy as their first subsequent therapy, respectively.

Safety

Overall, all-causality adverse events (AEs) of any grade and grade 3/4 occurred in 97 (99%) and 63 (64%) patients, respectively (Appendix Table A3). Treatment-related AEs (TRAEs) of any grade and grade 3/4 occurred in 92 (94%) and 45 (46%) patients, respectively (Appendix Table A4). The most common (≥30%) any-grade TRAEs were nausea (52%), diarrhea (44%), fatigue (33%), and vomiting (30%). Treatment-related pyrexia occurred in 8% of patients. Overall, TRAEs led to dose reduction of encorafenib and binimetinib in 32 patients (33%) each and permanent discontinuation in 20 patients (20%; Appendix Table A5). Although one grade 5 TRAE of intracranial hemorrhage occurred in the treatment-naïve cohort, safety was considered comparable across treatment lines (Appendix Table A6).

DISCUSSION

In this updated analysis of PHAROS, encorafenib plus binimetinib showed sustained long-term survival in patients with BRAF V600E-mutant mNSCLC. Although comparisons across trials should be done cautiously, the current findings suggest that encorafenib plus binimetinib may be associated with, to our knowledge, the longest mOS reported to date with targeted treatment in treatment-naïve BRAF V600E-mutant mNSCLC (Data Supplement, online only).

Current guidelines recommend BRAF plus MEK inhibitors as preferred first-line treatment of BRAF V600E-mutant mNSCLC; immunotherapy, chemotherapy, or a combination of the two are listed as other recommended options.[4,5] Dabrafenib plus trametinib was the first approved BRAF plus MEK inhibitor combination for BRAF V600E-mutant mNSCLC; approval was based on results of a single-arm phase II study.[6,14,15] At a 5-year follow-up analysis, in treatment-naïve (n = 36) and previously treated (n = 57) patients, ORR by investigator was 64% and 68%, mPFS by investigator was 10.8 and 10.2 months, and mOS was 17.3 and 18.2 months, respectively.[16] Immunotherapy and chemotherapy, although approved for mNSCLC, are not specifically approved for BRAF V600E-mutant mNSCLC.[17,18]

The optimal sequencing of therapeutic options for patients with BRAF V600E-mutant mNSCLC continues to be evaluated. In addition, programmed death-ligand 1 expression levels (ie, tumor proportion score) were not available in the PHAROS study, limiting the ability to draw interpretations regarding treatment sequencing. Retrospective studies reported conflicting results on whether targeted therapies

TABLE 1. Patient Characteristics

Characteristic	Treatment-Naïve (n = 59)	Previously Treated (n = 39)	Overall (N = 98)
Age, years, median (range)	68 (47-83)	71 (53-86)	70 (47-86)
Sex, No. (%)			
Female	33 (56)	19 (49)	52 (53)
Male	26 (44)	20 (51)	46 (47)
Race and ethnicity, No. (%)			
White	53 (90)	33 (85)	86 (88)
Asian	3 (5)	4 (10)	7 (7)
Black	1 (2)	2 (5)	3 (3)
American Indian	1 (2)	0	1 (1)
Unknown	1 (2)	0	1 (1)
ECOG PS, No. (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72 (73)
Smoking status, No. (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
BRAF V600 status, No. (%)			
V600E	59 (100)	39 (100)	98 (100)
V600D[a]	0	1 (3)	1 (1)
Method of local *BRAF* testing, No. (%)			
PCR	15 (25)	11 (28)	26 (26)
Tissue NGS	44 (75)	27 (69)	71 (72)
Plasma NGS	0	1 (3)	1 (1)
Tumor histology, No. (%)			
Adenocarcinoma	57 (97)	38 (97)	95 (97)
Squamous cell carcinoma	1 (2)	1 (3)	2 (2)
Other	1 (2)	0	1 (1)
Brain metastases, No. (%)			
No	55 (93)	35 (90)	90 (92)
Yes	4 (7)	4 (10)	8 (8)
Previous systemic treatment for metastatic disease, No. (%)	0	39 (100)	39 (40)
Immunotherapy	NA	24 (62)[b]	24 (24)[b]
Monotherapy PD-(L)1	NA	12 (31)	12 (12)
Combination PD-(L)1[c]	NA	12 (31)	12 (12)
Chemotherapy	NA	18 (46)	18 (18)
Previous radiotherapy, No. (%)			
No	50 (85)	22 (56)	72 (73)
Yes	9 (15)	17 (44)	26 (27)

NOTE. Borrowed with permission from Riely et al.[12]

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction.

[a]Comutation with V600E.

[b]Three patients were also included in the immunotherapy group as they had first-line chemotherapy followed by immunotherapy.

[c]With chemotherapy or non-PD-(L)1 immunotherapy.

or immunotherapy-based approaches had better outcomes in the first-line setting.[19-23] Additionally, as encorafenib plus binimetinib received regulatory approval in October 2023, these studies mostly included dabrafenib and trametinib as the targeted therapy regimen.[7,19-21] There are currently no published retrospective studies on immunotherapy versus encorafenib and binimetinib, which may be important to analyze as more real-world data become

available. As approximately half of the patients may not receive a second-line therapy,[24,25] it is important to use the most effective therapy in the first-line setting to maximize survival.

Safety of treatment sequencing is another consideration. Although studies of treatment sequencing for BRAF V600E-mutant NSCLC are limited, retrospective studies investigating immunotherapy with subsequent targeted therapy for

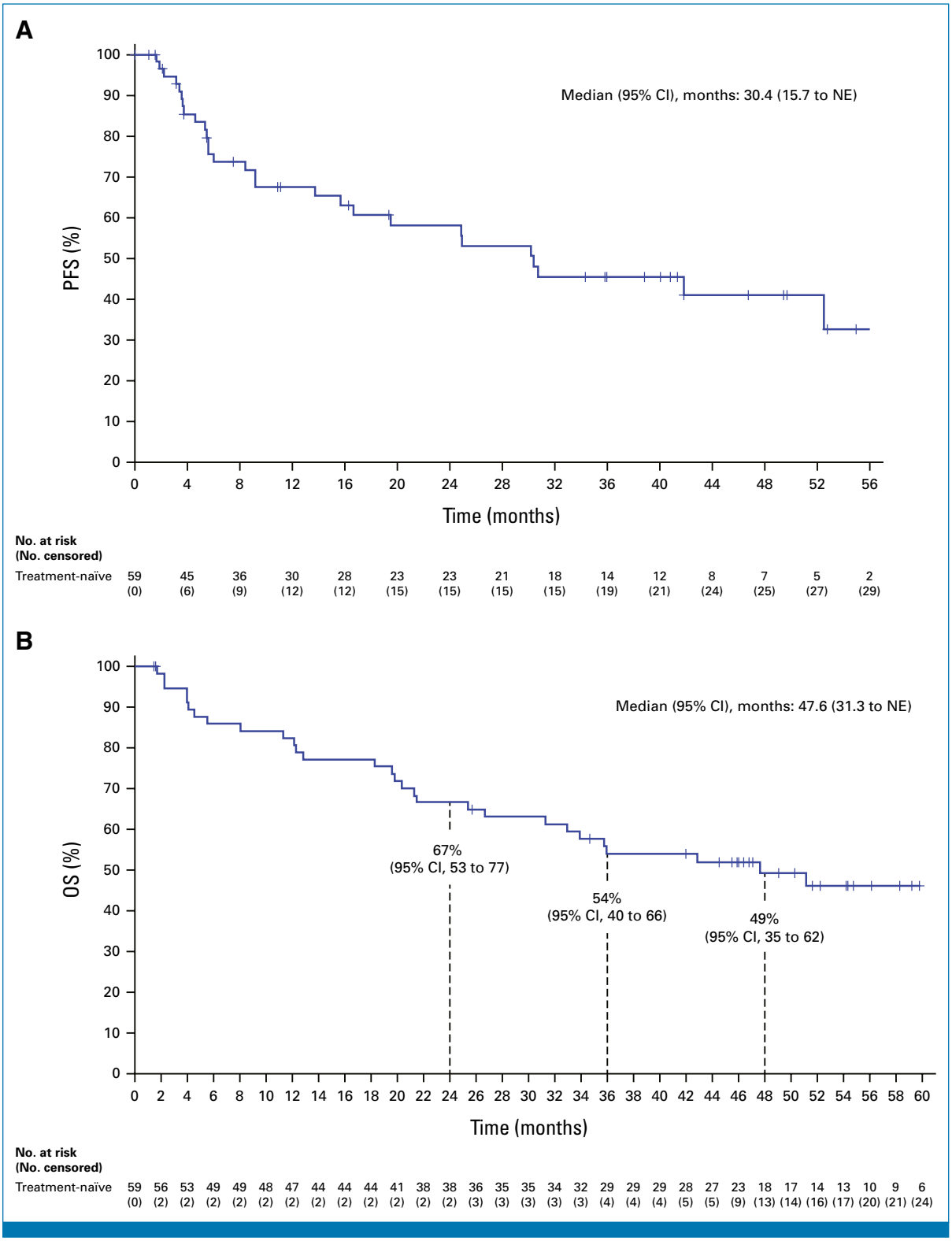

FIG 1. Kaplan-Meier estimates of (A) PFS by IRR in treatment-naïve patients, (B) OS in treatment-naïve patients, (C) PFS by IRR in previously treated patients, and (D) OS in previously treated patients. IRR, independent radiology review; NE, not estimable; OS, overall survival; PFS, progression-free survival. (continued on following page)

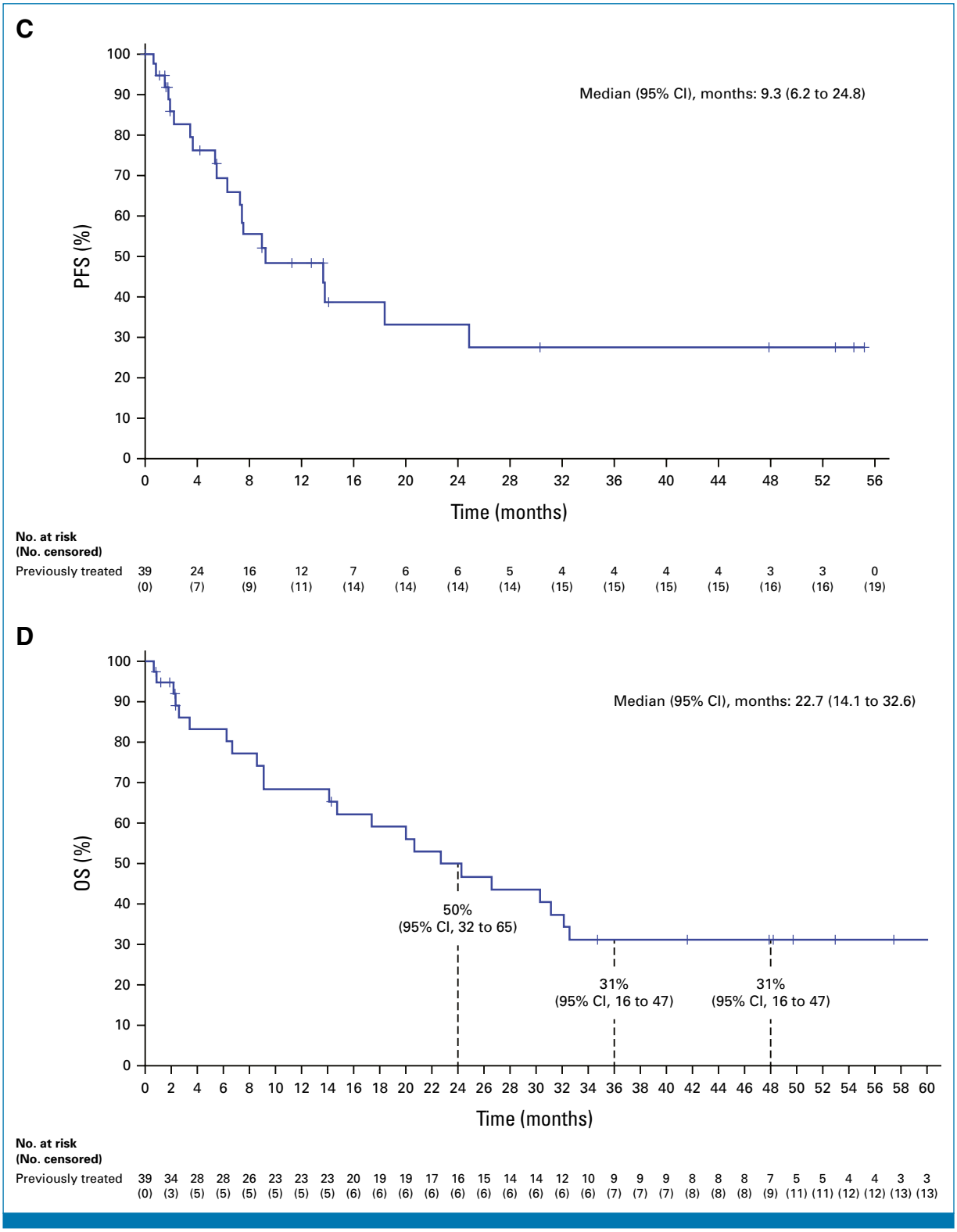

FIG 1. (Continued).

oncogene-driven NSCLC reported a high incidence of immune-related AEs, such as pneumonitis, colitis, and hepatitis.[26,27] In the previous analysis of the PHAROS study, although there were differences in the safety profile for previously treated patients who did or did not receive previous immunotherapy (low-grade fatigue: 54% *v* 7%; pruritus: 25% *v* 0%; maculopapular rash: 17% *v* 0%), the incidence of immune-related AEs was low, with pancreatitis and pneumonitis each occurring in one patient (4%) each who received previous immunotherapy.[13] This analysis

TABLE 2. Antitumor Activity in Subgroups

Characteristic	Treatment-Naïve				Previously Treated			
	No.	ORR,[a] % (95% CI)	mPFS,[a] Months (95% CI)	mOS, Months (95% CI)	No.	ORR,[a] % (95% CI)	mPFS, Months[a] (95% CI)	mOS, Months (95% CI)
Age group								
<65 years	23	74 (52 to 90)	24.9 (5.6 to NE)	51.2 (19.8 to NE)	13	38 (14 to 68)	9.0 (1.9 to NE)	32.6 (3.4 to NE)
≥65 years	36	75 (58 to 88)	30.4 (15.7 to NE)	39.3 (25.4 to NE)	26	54 (33 to 73)	9.3 (6.2 to 24.8)	22.7 (14.1 to 31.1)
Sex								
Female	33	70 (51 to 84)	30.7 (15.7 to NE)	47.6 (21.5 to NE)	19	53 (29 to 76)	9.3 (7.4 to 24.8)	30.3 (20.7 to NE)
Male	26	81 (61 to 93)	30.2 (9.2 to NE)	51.2 (19.6 to NE)	20	45 (23 to 69)	7.3 (3.6 to NE)	14.7 (6.7 to NE)
ECOG PS								
0	19	74 (49 to 91)	30.7 (15.7 to NE)	NE (35.7 to NE)	7	86 (42 to 100)	18.4 (7.4 to NE)	32.2 (22.7 to NE)
1	40	75 (59 to 87)	30.4 (9.2 to NE)	32.9 (20.3 to 61.4)	32	41 (24 to 59)	7.5 (5.4 to 24.8)	20.0 (9.1 to 32.6)
Smoking status								
Current/former	41	71 (55 to 84)	24.8 (9.2 to NE)	35.7 (20.3 to NE)	28	46 (28 to 66)	9.0 (6.2 to NE)	20.0 (9.1 to 32.6)
Never	18	83 (59 to 96)	41.8 (16.6 to NE)	61.4 (61.4 to NE)	11	55 (23 to 83)	18.4 (3.6 to NE)	32.2 (8.6 to NE)
Previously treated with IO								
No			NA		15	33 (12 to 62)	9.0 (3.6 to 18.4)	20.7 (8.6 to NE)
Yes			NA		24	58 (37 to 78)	13.8 (6.2 to NE)	26.6 (14.1 to NE)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immunotherapy; IRR, independent radiology review; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; NE, not estimable; ORR, objective response rate.
[a]ORR and mPFS were assessed by IRR.

was limited by small patient numbers, and it cannot be determined whether immune-related AEs seen in patients who received treatment with encorafenib plus binimetinib after immunotherapy are associated with this previous exposure. Overall, the efficacy and safety of treatment sequencing with immunotherapy and targeted therapy should be tested in a prospective study with balanced baseline characteristics.

Although patient numbers were small in this study, mPFS and mOS appeared to be shorter in patients with versus without smoking history. In treatment-naïve patients, mPFS was 24.8 versus 41.8 months, and mOS was 35.7 versus 61.4 months. This trend is consistent with the PHAROS primary analysis and may be explained by smoking inducing CYP1A2 isoform, which lowers exposure to binimetinib.[12,28,29]

In summary, encorafenib plus binimetinib showed prolonged survival, with a mOS of 47.6 months in patients with treatment-naïve BRAF V600E-mutant mNSCLC. The safety profile was consistent with previous analyses, with no new safety signals observed with this longer follow-up. These data continue to support encorafenib and binimetinib as a first-line treatment option for BRAF V600E-mutant mNSCLC.

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DATA SHARING STATEMENT

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Upon request, and subject to review, Pfizer will provide the data supporting 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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Updated Overall Survival Analysis From the Phase II PHAROS Study of Encorafenib Plus Binimetinib in Patients With BRAF V600E-Mutant Metastatic Non–Small Cell Lung Cancer

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APPENDIX

TABLE A1. Antitumor Activity by IRR

End Point	Treatment-Naïve (n = 59)	Previously Treated (n = 39)
Objective response rate, % (95% CI)	75 (62 to 85)	49 (32 to 65)
Best overall response, No. (%)		
Complete response	12 (20)	5 (13)
Partial response	32 (54)	14 (36)
Stable disease	10 (17)	12 (31)
Progressive disease	2 (3)	3 (8)
Not evaluable	3 (5)	5 (13)
DOR, months, median (95% CI)[a]	40.0 (23.2 to NE)	16.7 (7.4 to NE)
DOR ≥6 months, No. (%)[a]	33 (75)	14 (74)
DOR ≥12 months, No. (%)[a]	28 (64)	8 (42)
DOR ≥24 months, No. (%)[a]	20 (45)	5 (26)
Time to response, months, median (range)[a]	1.9 (1.1-5.6)	1.7 (1.2-16.5)

NOTE. Adapted from Riely et al.[13] Copyright © 2025 The Authors. Published by Elsevier Inc on behalf of International Association for the Study of Lung Cancer.
Abbreviations: DOR, duration of response; IRR, independent radiology review; NE, not estimable.
[a]Calculated only for patients with responses (treatment-naïve, n = 44; previously treated, n = 19).

TABLE A2. Subsequent Treatments

Patient	Treatment-Naïve (n = 59), No. (%)	Previously Treated (n = 39), No. (%)
Received ≥1 subsequent treatment	34 (58)	10 (26)
First subsequent therapy[a]		
Immunotherapy-based regimen	19 (56)	4 (40)
Monotherapy	7 (21)	2 (20)
Combination with chemotherapy or other immunotherapy	12 (35)	2 (20)
Chemotherapy-based regimen without immunotherapy	5 (15)	3 (30)
BRAF ± MEK inhibitor	10 (29)	3 (30)
Received ≥1 subsequent BRAF ± MEK inhibitor[a]	13 (38)	3 (30)
Received ≥1 subsequent anticancer radiotherapy course	9 (15)	4 (10)

[a]Calculated only for patients who received ≥1 subsequent treatment.

TABLE A3. Incidence of All-Causality AEs of Any Grade in ≥15% of the Overall Population (N = 98)

Preferred Term	Any Grade, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)[a]
Any AE	97 (99)	2 (2)	20 (20)	51 (52)	12 (12)
Nausea	57 (58)	27 (28)	26 (27)	4 (4)	0
Diarrhea	51 (52)	25 (26)	19 (19)	7 (7)	0
Fatigue	45 (46)	15 (15)	26 (27)	4 (4)	0
Vomiting	41 (42)	29 (30)	11 (11)	1 (1)	0
Anemia	34 (35)	7 (7)	13 (13)	14 (14)	0
Constipation	29 (30)	21 (21)	8 (8)	0	0
Dyspnea	27 (28)	8 (8)	10 (10)	6 (6)	3 (3)
Pyrexia	22 (22)	20 (20)	2 (2)	0	0
Back pain	21 (21)	12 (12)	8 (8)	1 (1)	0
Vision blurred	21 (21)	18 (18)	2 (2)	1 (1)	0
Abdominal pain	20 (20)	11 (11)	9 (9)	0	0
Dizziness	20 (20)	16 (16)	3 (3)	1 (1)	0
Peripheral edema	20 (20)	14 (14)	6 (6)	0	0
Arthralgia	19 (19)	16 (16)	2 (2)	1 (1)	0
AST increased	19 (19)	8 (8)	3 (3)	8 (8)	0
Asthenia	18 (18)	9 (9)	5 (5)	4 (4)	0
Blood creatinine increased	18 (18)	9 (9)	9 (9)	0	0
Cough	18 (18)	12 (12)	6 (6)	0	0
ALT increased	17 (17)	4 (4)	7 (7)	6 (6)	0
Lipase increased	17 (17)	4 (4)	2 (2)	9 (9)	2 (2)
Decreased appetite	16 (16)	8 (8)	7 (7)	1 (1)	0
Myalgia	16 (16)	10 (10)	4 (4)	2 (2)	0
Pruritus	16 (16)	11 (11)	5 (5)	0	0
Blood creatine phosphokinase increased	15 (15)	7 (7)	5 (5)	2 (2)	1 (1)

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Abbreviation: AE, adverse event.

[a]Based on MedDRA by investigator, grade 5 all-causality AEs include disease progression/neoplasm progression (10%), myocardial infarction (1%), and intracranial hemorrhage (1%).

TABLE A4. Incidence of TRAEs of Any Grade in ≥10% of the Overall Population (N = 98)

Preferred Term	Any Grade, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)[b]
Any TRAE[a]	92 (94)	9 (9)	37 (38)	41 (42)	4 (4)
Nausea	51 (52)	25 (26)	22 (22)	4 (4)	0
Diarrhea	43 (44)	20 (20)	18 (18)	5 (5)	0
Fatigue	32 (33)	13 (13)	17 (17)	2 (2)	0
Vomiting	29 (30)	19 (19)	9 (9)	1 (1)	0
Vision blurred	18 (18)	15 (15)	2 (2)	1 (1)	0
Anemia	17 (17)	3 (3)	10 (10)	4 (4)	0
Constipation	14 (14)	10 (10)	4 (4)	0	0
ALT increased	13 (13)	3 (3)	5 (5)	5 (5)	0
AST increased	13 (13)	6 (6)	0	7 (7)	0
Alopecia	12 (12)	12 (12)	0	0	0
Pruritus	12 (12)	10 (10)	2 (2)	0	0
Abdominal pain	11 (11)	5 (5)	6 (6)	0	0
Blood creatine phosphokinase increased	11 (11)	5 (5)	5 (5)	0	1 (1)
Dizziness	11 (11)	8 (8)	2 (2)	1 (1)	0
Dry skin	11 (11)	11 (11)	0	0	0
Myalgia	11 (11)	6 (6)	3 (3)	2 (2)	0
Peripheral edema	11 (11)	7 (7)	4 (4)	0	0
Rash maculopapular	11 (11)	6 (6)	4 (4)	1 (1)	0
Asthenia	10 (10)	5 (5)	2 (2)	3 (3)	0
Rash	10 (10)	8 (8)	1 (1)	1 (1)	0

NOTE. Adapted from Riely et al.[13]

Abbreviations: AE, adverse event; TRAE, treatment-related adverse event.

[a]Any-grade pyrexia occurred in 8% of patients, with only grade 1 (7%) and grade 2 (1%) events.

[b]There was one grade 5 AE (intracranial hemorrhage), which was determined by the investigator to be treatment-related.

TABLE A5. Summary of AEs Leading to Dose Reduction or Permanent Discontinuation of Encorafenib and Binimetinib

Category	Overall (N = 98), No. (%)	Treatment-Naïve (n = 59), No. (%)	Previously Treated (n = 39), No. (%)
Patients with all-causality AEs			
Leading to dose reduction of encorafenib	33 (34)	20 (34)	13 (33)
Leading to dose reduction of binimetinib	33 (34)	21 (36)	12 (31)
Leading to dose discontinuation of encorafenib	20 (20)	14 (24)	6 (15)
Leading to dose discontinuation of binimetinib	20 (20)	14 (24)	6 (15)
Patients with TRAEs			
Leading to dose reduction of encorafenib	32 (33)	20 (34)	12 (31)
Leading to dose reduction of binimetinib	32 (33)	21 (36)	11 (28)
Leading to dose discontinuation of encorafenib	20 (20)	14 (24)	6 (15)
Leading to dose discontinuation of binimetinib	20 (20)	14 (24)	6 (15)

Abbreviations: AE, adverse event; TRAE, treatment-related AE.

TABLE A6. Incidence of TRAEs of Any Grade in Treatment-Naïve and Previously Treated Patients (in ≥10% of either arm)

	Treatment-Naïve (n = 59), No. (%)		Previously Treated (n = 39), No. (%)	
Preferred Term	Any Grade	Grade 3/4[a]	Any Grade	Grade 3/4
Any TRAE	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)	3 (5)	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 (8)	0	4 (10)	0
Ejection fraction decreased	5 (8)	2 (3)	4 (10)	1 (3)
Asthenia	3 (5)	1 (2)	7 (18)	2 (5)

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Abbreviations: AE, adverse event; TRAE, treatment-related adverse event.

[a]There was 1 grade 5 AE (intracranial hemorrhage), which was determined by the investigator to be treatment-related.