



Universiteit
Leiden
The Netherlands

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

Riely, G.J.; Ahn, M.J.; Clarke, J.M.; Dagogo-Jack, I.; Esper, R.; Felip, E.; ... ; Johnson, B.E.

Citation

Riely, G. J., Ahn, M. J., Clarke, J. M., Dagogo-Jack, I., Esper, R., Felip, E., ... Johnson, B. E. (2025). 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. *Journal Of Thoracic Oncology*, 20(10), 1538-1547. doi:10.1016/j.jtho.2025.05.023

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/4295349>

Note: To cite this publication please use the final published version (if applicable).



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

Gregory J. Riely, MD, PhD,^{a,*} Myung-Ju Ahn, MD, PhD,^b Jeffrey M. Clarke, MD,^c Ibiayi Dagogo-Jack, MD,^d Raymond Esper, MD, PhD,^e Enriqueta Felip, MD, PhD,^f Francesco Gelsomino, MD, PhD,^g Jonathan W. Goldman, MD,^h Maen Hussein, MD,^e Melissa Johnson, MD,ⁱ Kristen A. Marrone, MD,^j Daniel Morgensztern, MD,^k Ernest Nadal, MD, PhD,^l Marcelo V. Negrao, MD,^m Michael Offin, MD,^a Mariano Provencio, MD, PhD,ⁿ Suresh S. Ramalingam, MD,^o Logan Roof, MD, MS,^p Rachel E. Sanborn, MD,^q Egbert F. Smit, MD, PhD,^r Anne Tsao, MD,^m Tiziana Usari, BSc,^s Ann Alcasid, BA,^t Keith Wilner, PhD,^u Svitlana Tonkovyd, MD,^v Xiaosong Zhang, MD, PhD,^w Bruce E. Johnson, MD^x

^aMemorial Sloan Kettering Cancer Center, New York, New York

^bSamsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

^cDuke Cancer Center, Durham, North Carolina

^dMassachusetts General Hospital, Boston, Massachusetts

^eFlorida Cancer Specialists, Fort Myers, Florida

^fVall d'Hebron Institute of Oncology, Barcelona, Spain

^gMedical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

^hDavid Geffen School of Medicine at UCLA, Los Angeles, California

ⁱTennessee Oncology, Sarah Cannon Research Institute, Nashville, Tennessee

^jJohns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland

^kWashington University School of Medicine, St. Louis, Missouri

^lMedical Oncology, Catalan Institute of Oncology, IDIBELL, Barcelona, Spain

^mThe University of Texas MD Anderson Cancer Center, Houston, Texas

ⁿHospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

^oWinship Cancer Institute of Emory University, Atlanta, Georgia

^pThe Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute, Columbus, Ohio

^qEarle A. Chiles Research Institute, Providence Cancer Institute, Portland, Oregon

^rDepartment of Pulmonary Diseases, Leiden University Medical Center, Leiden, The Netherlands

^sPfizer Italia S.r.l., Milano, Italy

^tPfizer, Collegeville, Pennsylvania

^uPfizer, La Jolla, California

^vPfizer, Warsaw, Poland

^wPfizer, South San Francisco, California

^xDana-Farber Cancer Institute, Boston, Massachusetts

Received 20 December 2024; revised 16 April 2025; accepted 26 May 2025

Available online - 4 June 2025

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

*Corresponding author.

Address for correspondence: Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, 530 E 74th Street, New York 10021, New York. E-mail: rielyg@mskcc.org

Cite this article as: Riely GJ, Ahn MJ, Clarke JM, et al. 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. *J Thorac Oncol.* 2025;20:1538-1547.

© 2025 The Authors. Published by Elsevier Inc. on behalf of International Association for the Study of Lung Cancer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2025.05.023>

(59 treatment-naïve 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-naïve and 5.5 months in previously treated patients; minimum follow-up was approximately 32 and 22 months, respectively. In treatment-naïve 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-naïve patients, with a manageable safety profile in patients with BRAF V600E-mutant mNSCLC.

Clinical Trial Information: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03915951) Identifier: NCT03915951

© 2025 The Authors. Published by Elsevier Inc. on behalf of International Association for the Study of Lung Cancer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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-naïve 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-naïve 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-naïve and previously treated patients; safety was assessed in all patients. Post hoc analyses included efficacy and safety end points assessed separately in treatment-naïve 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-naïve, n = 59; previously treated, n = 39) received encorafenib plus binimetinib. At data cutoff (April 1, 2024), treatment was ongoing in 11 (19%) treatment-naïve patients and four (10%) previously treated patients ([Supplementary Fig. 1](#)). Minimum follow-up was approximately 32 months in treatment-naïve 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-naïve 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-Naïve Patients. In treatment-naïve 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. 1A](#)), 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. 2A](#)). 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. 2B](#)).

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. 1B](#)), 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. 2C](#)). Median OS was 22.7 months (95% CI: 14.1–32.2) ([Fig. 2D](#)).

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 ($\geq 30\%$) 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-naïve 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-naïve 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 ($\geq 15\%$) 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-naïve 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-naïve 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.

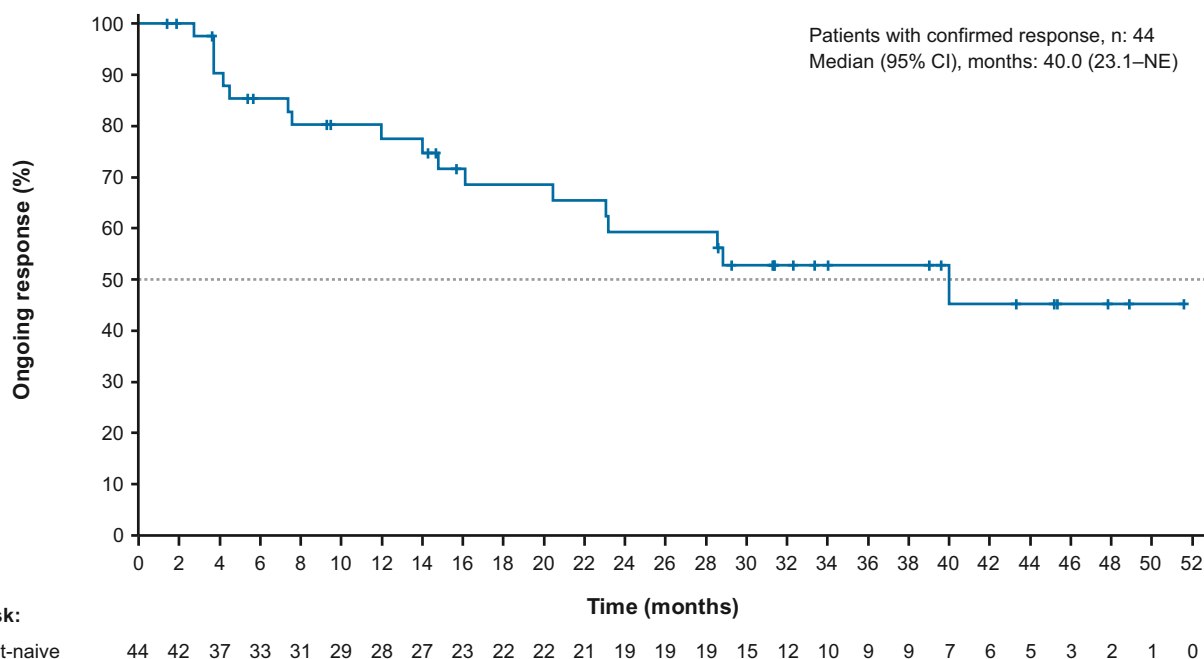
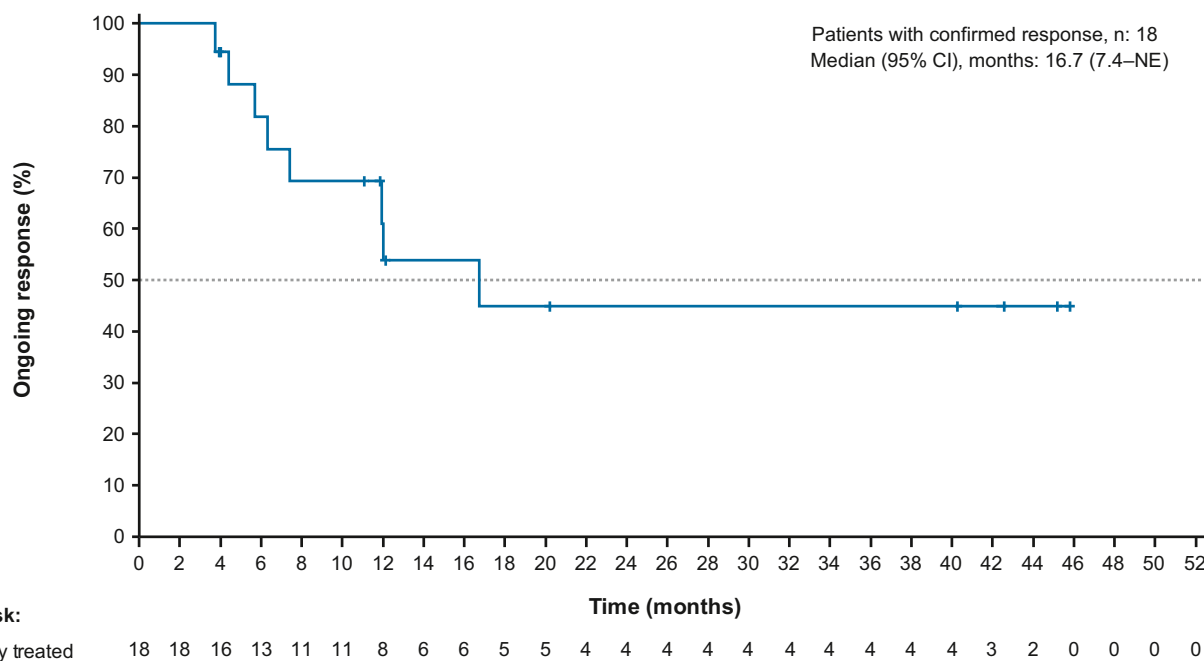
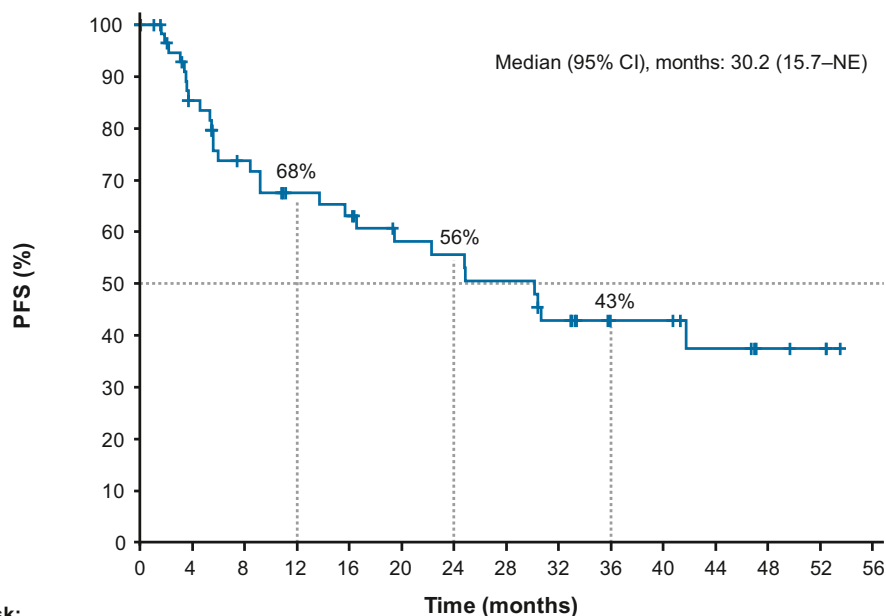
A**B**

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

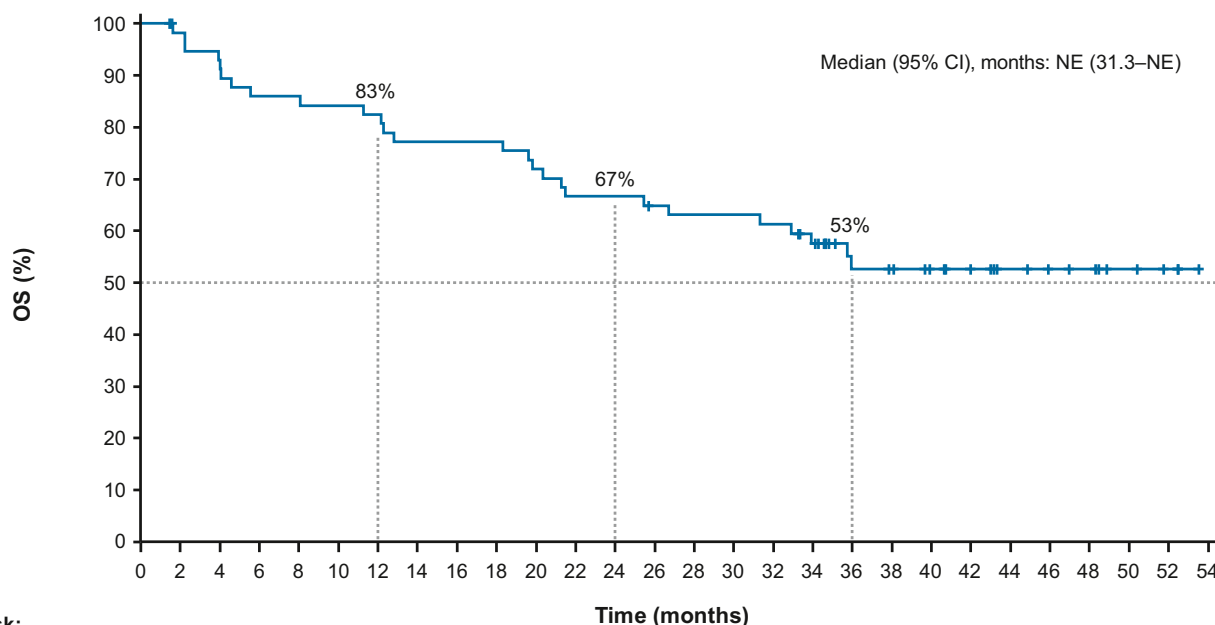
Given the response durability of encorafenib plus binimetinib, it is essential to proactively identify and manage AEs with supportive care and dose modifications; previously described therapy management

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

A**No. at risk:**

Treatment-naïve

59 45 36 30 28 23 22 20 16 10 10 7 4 3 0

B**No. at risk:**

Treatment-naïve

59 56 53 49 49 48 47 44 44 44 41 38 38 36 35 35 34 30 21 20 17 14 11 9 8 5 3 0

Figure 2. Kaplan-Meier estimate 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. 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

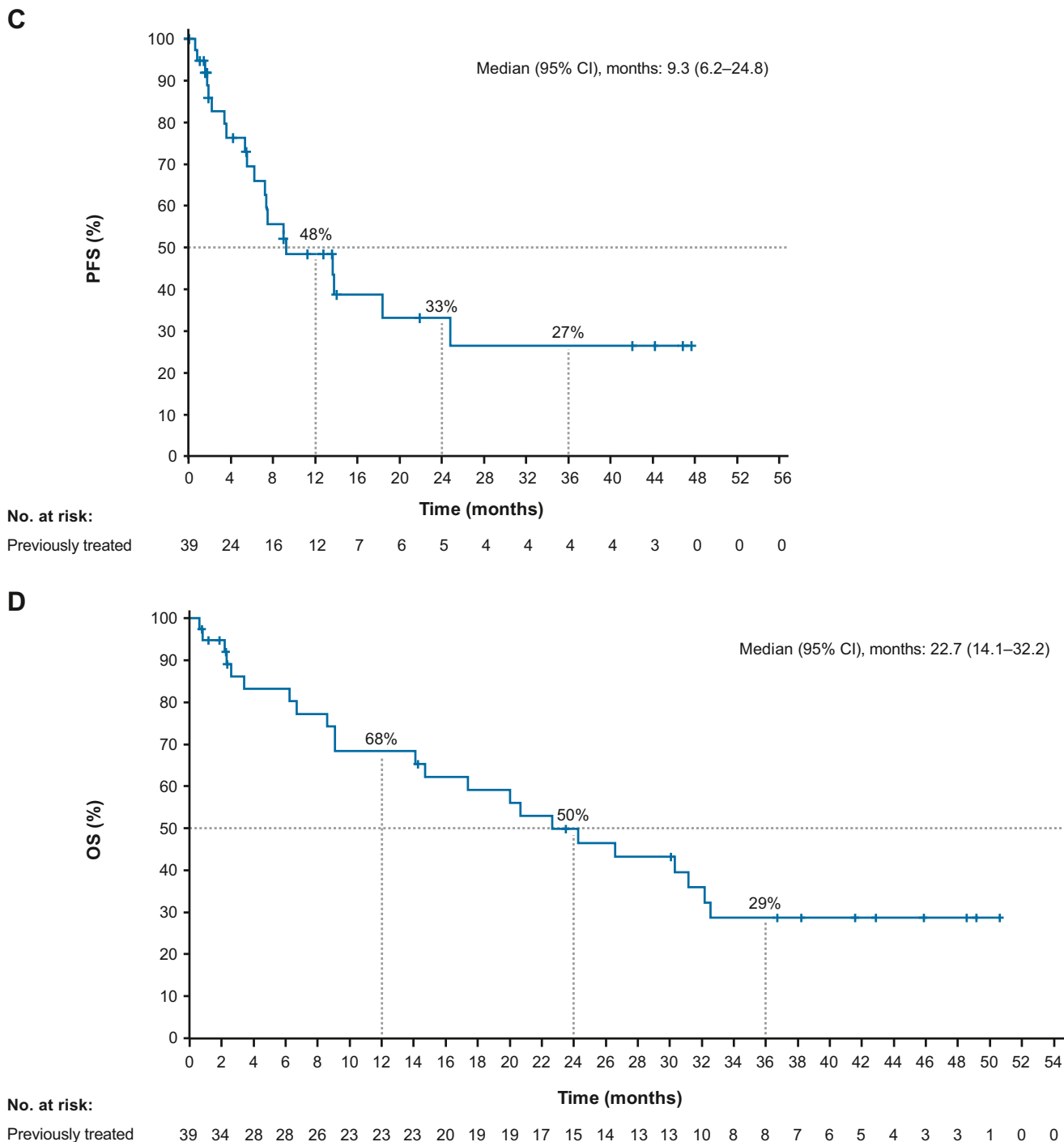


Figure 2. (continued).

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-naïve patients correspond to the longest DOR and PFS compared with

Table 1. TRAEs in Treatment-Naïve and Previously Treated Patients ($\geq 10\%$ Any Grade in Either Cohort)

Preferred Term	Treatment-Naïve (n = 59)		Previously Treated (n = 39)	
	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)

^aThere 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-naïve 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.

Myung-Ju Ahn: Investigation, Writing - original draft, Writing - review and editing.

Jeffrey M. Clarke: Investigation, Writing - original draft, Writing - review and editing.

Ibiayi Dagogo-Jack: Investigation, Writing - original draft, Writing - review and editing.

Raymond Esper: Investigation, Writing - original draft, Writing - review and editing.

Enriqueta Felip: Investigation, Writing - original draft, Writing - review and editing.

Francesco Gelsomino: Investigation, Writing - original draft, Writing - review and editing.

Jonathan W. Goldman: Investigation, Writing - original draft, Writing - review and editing.

Maen Hussein: Investigation, Writing - original draft, Writing - review and editing.

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

Kristen A. Marrone: Investigation, Writing - original draft, Writing - review and editing.

Daniel Morgensztern: Investigation, Writing - original draft, Writing - review and editing.

Ernest Nadal: Investigation, Writing - original draft, Writing - review and editing.

Marcelo V. Negrao: Investigation, Writing - original draft, Writing - review and editing.

Michael Offin: Investigation, Writing - original draft, Writing - review and editing.

Mariano Provencio: Investigation, Writing - original draft, Writing - review and editing.

Suresh S. Ramalingam: Investigation, Writing - original draft, Writing - review and editing.

Logan Roof: Investigation, Writing - original draft, Writing - review and editing.

Rachel E. Sanborn: Investigation, Writing - original draft, Writing - review and editing.

Egbert F. Smit: Investigation, Writing - original draft, Writing - review and editing.

Anne Tsao: Investigation, Writing - original draft, Writing - review and editing.

Tiziana Usari: Investigation, Writing - original draft, Writing - review and editing.

Ann Alcasid: Investigation, Writing - original draft, Writing - review and editing.

Keith Wilner: Investigation, Writing - original draft, Writing - review and editing.

Svitlana Tonkovyd: Investigation, Writing - original draft, Writing - review and editing.

Xiaosong Zhang: Investigation, Writing - original draft, Writing - review and editing.

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. Filip 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

Therapeutics, Normunity, Novocure, Pfizer, Seagen, Synthekine, and Zai Lab; and has received research funding from EMD Serono, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Novartis, Array BioPharma, Regeneron, Merck, Hengrui Pharmaceutical, BeiGene, Loxo, AbbVie, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, CytomX Therapeutics, Corvus Pharmaceuticals, Incyte, Genocera Biosciences, Gritstone Bio, Amgen, Genentech/Roche, Adaptimmune, Syndax, Neovia Oncology, Takeda, Shattuck Labs, GSK, Immunocore, TCR2 Therapeutics, Arcus Biosciences, Ribon Therapeutics, BerGenBio, Calithera Biosciences, Tmunity Therapeutics Inc., Seven and Eight Biopharmaceuticals, Rubius Therapeutics, Curis, Silicon Therapeutics, Dracen, PMV Pharma, Artios, BioAtla, Elicio Therapeutics, Erasca Inc., Harpoon, Helsinn Healthcare, Hutchison MediPharma, IDEAYA Biosciences, IGM Biosciences, Memorial Sloan Kettering Cancer Center, NeoImmuneTech, Numab, Relay Therapeutics, Revolution Medicines, Tempest Therapeutics, Tizona Therapeutics Inc., Turning Point Therapeutics, Vyriad, Y-mAbs Therapeutics, Exelixis, Fate Therapeutics, Merus, Black Diamond Therapeutics, Kartos Therapeutics, Carisma Therapeutics, Rain Therapeutics, Nuvalent, Palleon Pharmaceuticals, EQRx, Immunitas, ArriVent BioPharma, Bayer, Bristol Myers Squibb, City of Hope, Conjupro Biotherapeutics, Immuneering Corporation, Impact Therapeutics, LockBody, Mythic Therapeutics, Neovia Oncology, NextPoint Therapeutics, OncoC4, Rascal Therapeutics, Systimmune, Taiho Oncology, Theras, and Vividion. Dr. Marrone has had a consulting or advisory role with AstraZeneca, Amgen, Bristol Myers Squibb, Janssen, Daiichi Sankyo, Regeneron, and Merus; and has received research funding from Bristol Myers Squibb. Dr. Morgensztern has had a consulting or advisory role with AbbVie, G1 Therapeutics, Lilly Medical, Mirati Therapeutics, Arcus Biosciences, Bayer, Boehringer Ingelheim, Tubulis, Johnson & Johnson, and Natera; and has received research funding from Heat Biologics, Merck, Celgene, AstraZeneca, Baxter, Incyte, AbbVie, Bristol Myers Squibb, EpicentRx, Pfizer, Roche, Lilly, Altum Pharmaceuticals, Array BioPharma, Surface Oncology, Arcus Biosciences, Boehringer Ingelheim, and Y-mAbs Therapeutics. 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. Dr. Offin has received honoraria from OncLive, American Society for Radiation Oncology, Pfizer, and Targeted Oncology; has had a consulting or advisory role with Novartis, Jazz Pharmaceuticals, the U.S. Department of Defense, and Pfizer; has received travel accommodations and expenses from DAVA Oncology and the International Association for the Study of Lung Cancer; has received research funding from the Druckenmiller Foundation, LUNgevity Foundation, and the U.S. Department of Defense; and has had a role with Mesothelioma Applied Research Foundation. Dr. Provencio has had a consulting or advisory role with Bristol Myers Squibb, Roche, MSD, AstraZeneca, Takeda, Lilly, Janssen Oncology, Pfizer, and Merck; has had a speakers' bureau role for Bristol Myers Squibb, Roche, AstraZeneca, MSD, and Takeda; has received research funding from Pierre Fabre, Roche, Boehringer Ingelheim, and Bristol Myers Squibb (institution); and has received other expenses from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Roche, Pierre Fabre, Takeda, and MSD. Dr. Ramalingam has received research funding from Pfizer. Dr. Sanborn has received honoraria from AstraZeneca, GameOn!, Illumina, OncLive, and Targeted Oncology; has had a consulting or advisory role with Amgen, AstraZeneca, EMD Serono, Daiichi Sankyo, G1 Therapeutics, GE HealthCare, Gilead, GSK, Janssen Oncology, Regeneron, and Sanofi Aventis; and has received research funding from Bristol Myers Squibb, Merck, and AstraZeneca. Dr. Smit has received honoraria from Daiichi Sankyo and Boehringer Ingelheim; and has had a consulting or advisory role with Eli Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol Myers Squibb, Merck, MSD Oncology, Takeda, Daiichi Sankyo, Janssen, Sanofi, Pfizer, DSI DSMB, Taiho DSMB, and Mythic DSMB. Dr. Tsao has had a consulting or advisory role with Novartis, Boehringer Ingelheim, Genentech/Roche, Lilly, Bristol Myers Squibb, Epizyme, AstraZeneca/MedImmune, ARIAD, EMD Serono, Takeda, and Heron; and has received research funding from Merck, Genentech/Roche, Seagen, Millennium, Bristol Myers Squibb, Boehringer Ingelheim, Polaris, EMD Serono, and Takeda. Dr. B.E. Johnson has had a consulting or advisory role with Novartis, Daiichi Sankyo, Checkpoint Therapeutics, G1 Therapeutics, Jazz Pharmaceuticals, GSK, Genentech, AstraZeneca, Hummingbird Diagnostics, BlueDot, Merus NV, Abdera Therapeutics, and Simcere. Usari, Alcasid, Dr. Wilner, Dr. Tonkovyd, and Dr. Zhang are employees of

and own stock in Pfizer. The remaining authors declare no conflict of interest.

Acknowledgments

This study was sponsored by Pfizer. This study was designed by the sponsor (Pfizer), study investigators, and members of the steering committee. Data were collected by investigators and analyzed by the sponsor. The funder of the study contributed to the study design, data collection, data analysis, and data interpretation in collaboration with the authors, and provided financial support for editorial and writing assistance. The authors thank the participating patients and their families, investigators, subinvestigators, research nurses, study coordinators, and operations staff. Editorial and medical writing support was provided by Robyn Roth, PhD, of Nucleus Global, and was funded by Pfizer. We acknowledge funding from Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (grant number: P30 CA008748).

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>.

References

1. Riely GJ, Smit EF, Ahn MJ, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with BRAF^{V600}-mutant metastatic non-small-cell lung cancer. *J Clin Oncol*. 2023;41:3700-3711.
2. Planchard D, Sanborn RE, Negrao MV, Vaishnavi A, Smit EF. BRAF^{V600E}-mutant metastatic NSCLC: disease overview and treatment landscape. *NPJ Precis Oncol*. 2024;8:90.
3. U.S. Food and Drug Administration. FDA approves encorafenib with binimetinib for metastatic non-small cell lung cancer with a BRAF V600E mutation. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-binimetinib-metastatic-non-small-cell-lung-cancer-braf-v600e-mutation>. Accessed November 21, 2024.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Non-Small Cell Lung Cancer v3.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed February 28, 2025. To view the most recent complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. NCCN, National Comprehensive Cancer Network[®] (NCCN[®]).
5. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:339-357.
6. Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol*. 2022;17:103-115.
7. Di Federico A, Chen MF, Pagliaro A, et al. 1299P First-line immunotherapy versus BRAF and MEK inhibitors for patients with BRAF V600E mutant metastatic non-small cell lung cancer. *Ann Oncol*. 2024;35:S826-S827.
8. Wiesweg M, Alaffas A, Rasokat A, et al. 1300P Treatment sequences in BRAF-V600-mutant non-small cell lung cancer: first-line targeted therapy versus first-line (chemo-) immunotherapy. *Ann Oncol*. 2024;35:S827-S828.
9. Russo A, Sini C, Cortinovis DL, et al. 1301P BRAF-mutant metastatic non-small cell lung cancer: real-world data from the Italian biomarker ATLAS database. *Ann Oncol*. 2024;35:S828.
10. Wang H, Cheng L, Zhao C, et al. Efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer harboring BRAF mutations. *Transl Lung Cancer Res*. 2023;12:219-229.
11. Li H, Zhang Y, Xu Y, et al. Tumor immune microenvironment and immunotherapy efficacy in BRAF mutation non-small-cell lung cancer. *Cell Death Dis*. 2022;13:1064.
12. Goodwin K, Orbaugh K, Duncan K, Stumpf E. Optimizing treatment of BRAFV600E-mutant metastatic NSCLC with encorafenib and binimetinib: a practical resource for advanced practice providers. *J Adv Pract Oncol*. 2024;12:1-17.
13. Baik C, Cheng ML, Dietrich M, Gray JE, Karim NA. A practical review of encorafenib and binimetinib therapy management in patients with BRAF V600E-mutant metastatic non-small cell lung cancer. *Adv Ther*. 2024;41:2586-2605.
14. Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol*. 2019;30:839-844.
15. Lin JJ, Chin E, Yeap BY, et al. Increased hepatotoxicity associated with sequential immune checkpoint inhibitor and crizotinib therapy in patients with non-small cell lung cancer. *J Thorac Oncol*. 2019;14:135-140.