BRIEF REPORT

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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.

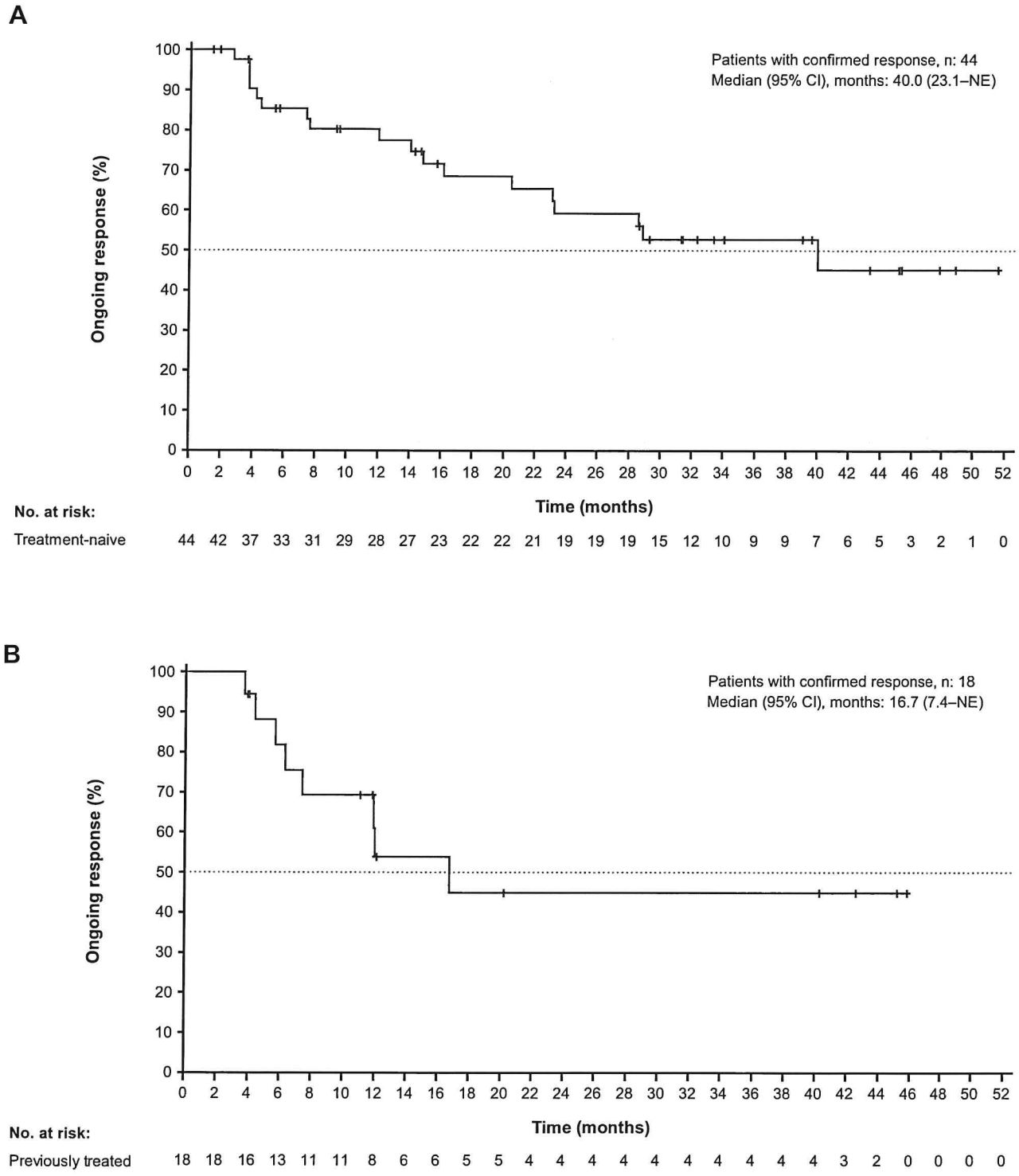

Figure 1. Kaplan-Meier estimate of DOR by IRR for (*A*) treatment-naive and (*B*) previously treated patients. CI, confidence interval; DOR, duration of response; IRR, independent radiology review; NE, not estimable.

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

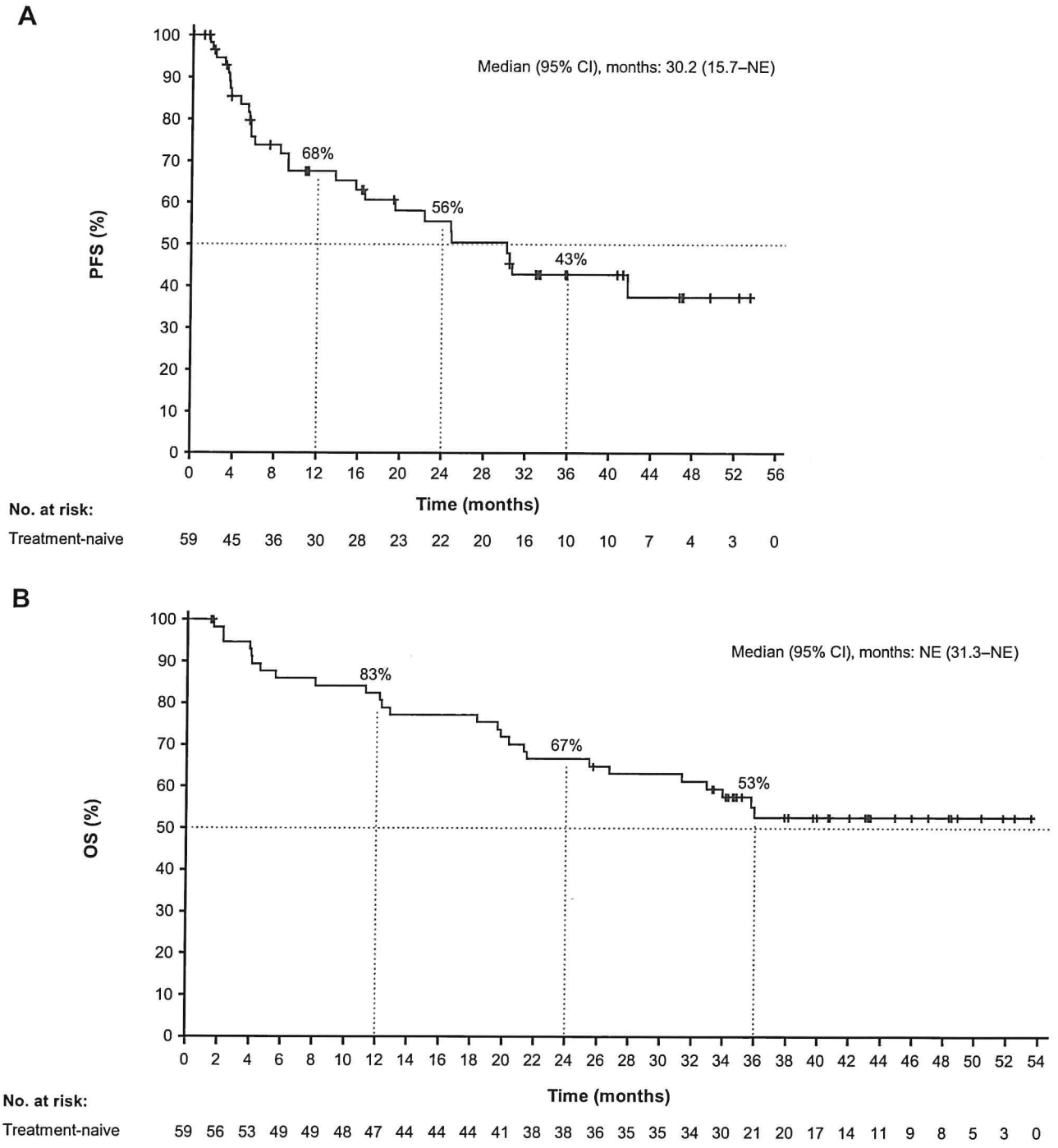

Figure 2. Kaplan-Meier estimate of (*A*) PFS by IRR in treatment-naive patients, (*B*) OS in treatment-naive patients, (*C*) PFS by IRR in previously treated patients, and (*D*) OS in previously treated patients. CI, confidence interval; IRR, independent radiology review; OS, overall survival; NE, not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

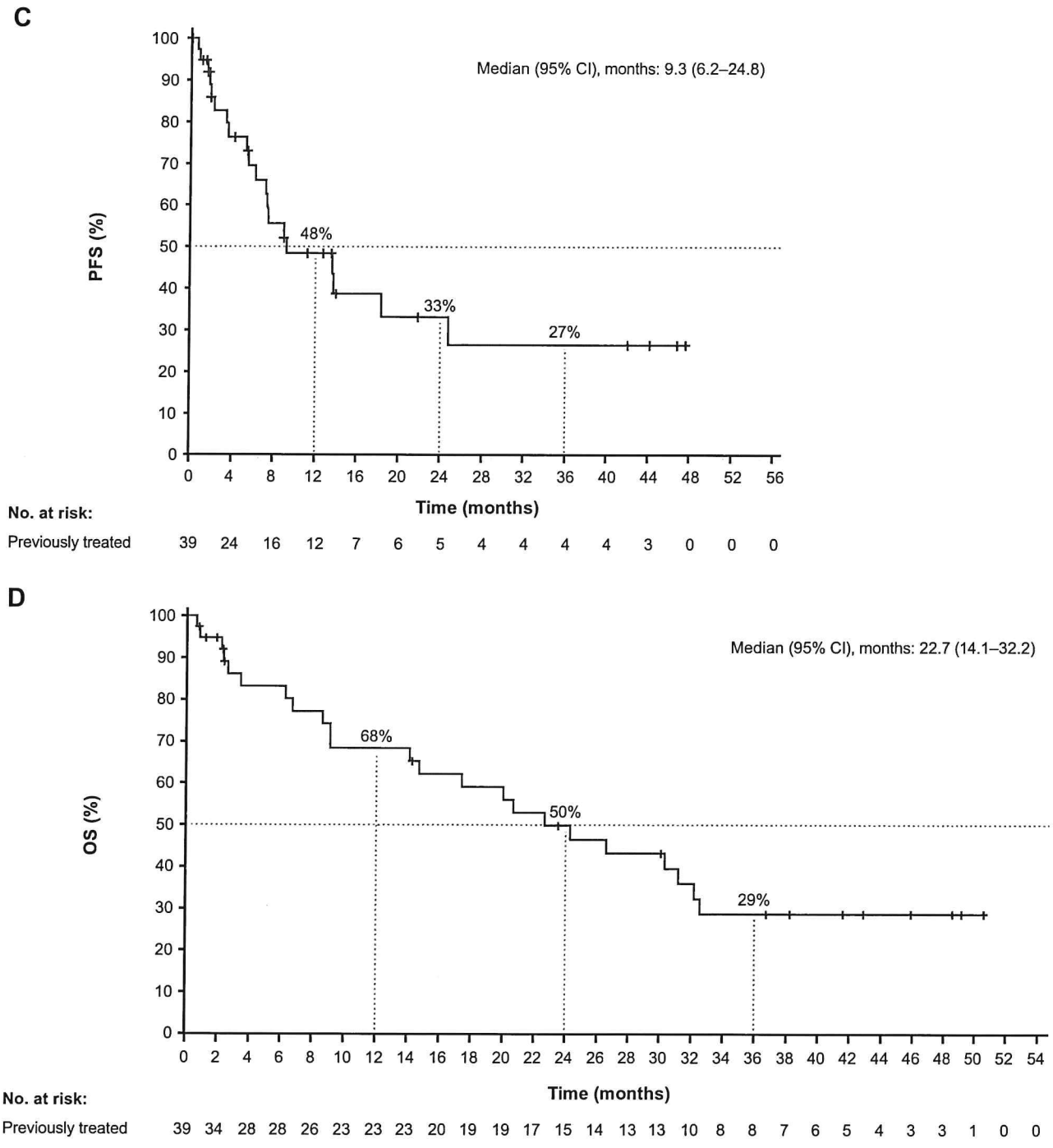

Figure 2. (*continued*).

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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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. 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 a 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. 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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.

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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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Division of Hematology & Oncology

B-RAF Mutations in NSCLC: Current State of the Art
Encorafenib and Binimetinib

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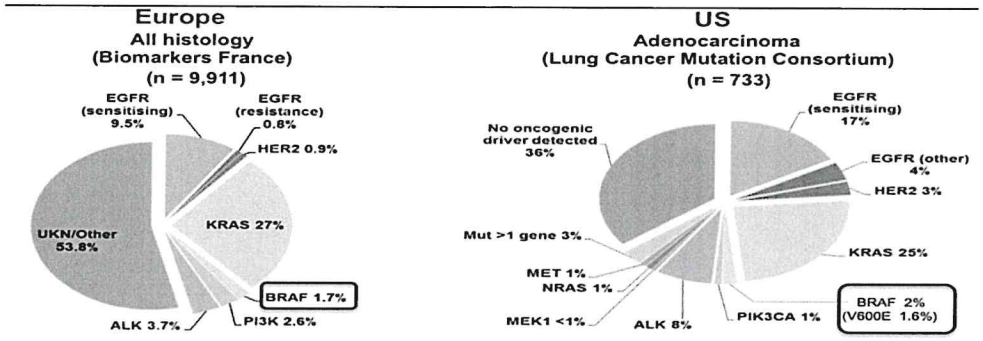
- **Scientific Advisor:**
  - Lilly, Pfizer, Synta, Boehringer-Ingelheim, AstraZeneca, Novartis, Abbott, Genentech/Roche, Bayer/Onyx, Celgene, Clarient, Clovis, Guardant, Merck, Gilead, Regeneron
- **Data Safety Monitoring Committees:**
  - Lilly, Incyte, SWOG, Oncocyte, VALOR, SUMMIT Oncology

2

BRAF Mutations in NSCLC



- BRAF Mutations are usually missense, across exons 11 or 15
- About 50% of NSCLC BRAF Mutations are non-V600E (G6469A, D594G)
- V600E Mutations may be related to non-smoking history
- V600E MT are more likely to occur in females, and independently assoc w/ short DFS and OS

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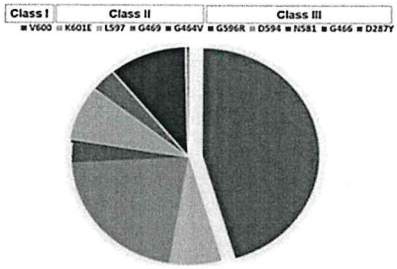
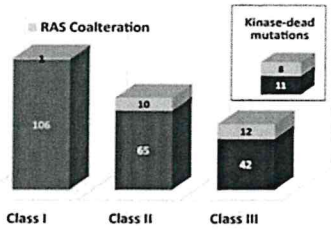
B-RAF Mutant NSCLC

- Characterization of 236 BRAF-mutant NSCLC
  - 107 class I (45%), 75 class II (32%), 54 class III (23%)
  - Never smokers- Class I- 22%, Class II- 3%, Class III- 6%
  - Class II/III more likely to have KRAS co-mutation, brain mets, worse clinical outcomes (PFS, OS) and shorter PFS with platinum based chemotherapy





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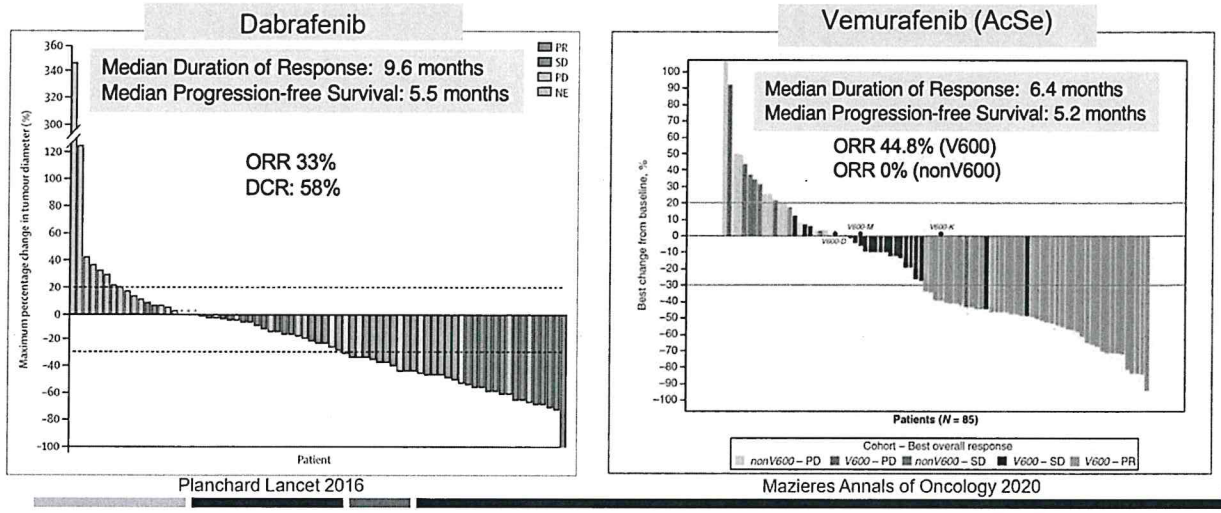
BRAF Inhibitor Monotherapy in V600^{mut} NSCLC



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B-RAF Inhibition in NSCLC SOC
Dabrafenib and Trametinib

Stage IV NSCLC
BRAF V600E
ECOG 0-2
Line of Tx ≥ 2

Cohort A
Dabrafenib 150mg BID
N = 84

ORR 33%; mPFS: 5.5 mo; Lancet Oncol 2016
Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

Cohort B
Dabrafenib 150mg BID+
Trametinib 2mg QD
N = 59

ORR 63%; mPFS: 9.7 mo; Lancet Oncol 2016
Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

Stage IV NSCLC
BRAF V600E
ECOG 0-2
No prior Tx

Cohort C
Dabrafenib 150mg BID+
Trametinib 2mg QD
N = 36

ORR 64%; mPFS: 10.9 mo; Lancet Oncol 2017
Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

Planchard D, et al. *Lancet Oncol.* 2016;17(7):984-993. Mazieres J, et al. *Ann Oncol.* 2020;31(2):289-294.

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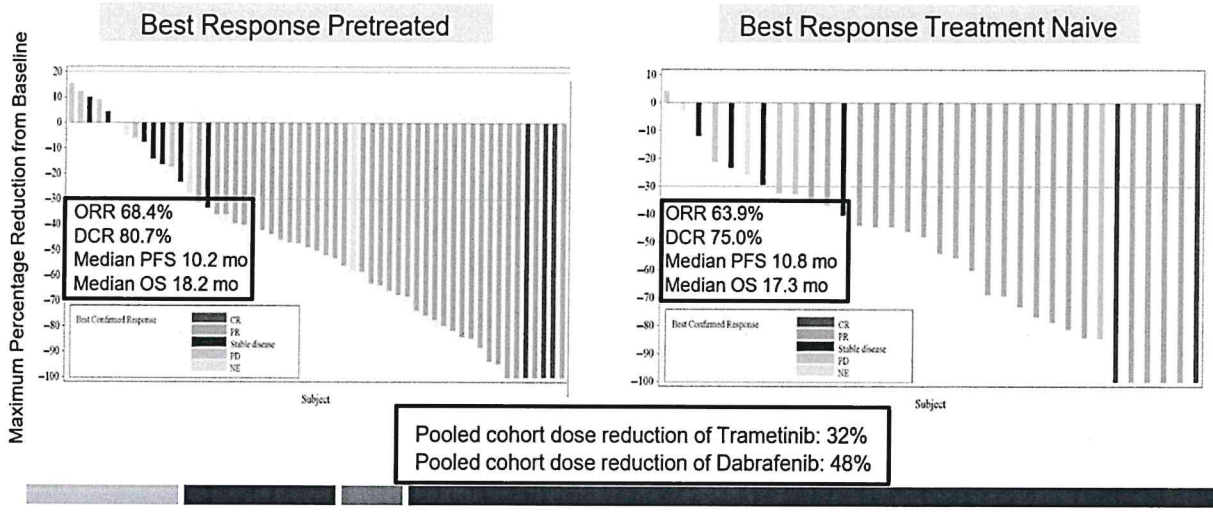
B-RAF + MEK Combination Therapy in V600^{mut} NSCLC



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Abstract 9018

Efficacy and safety of encorafenib plus binimetinib in patients with *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study

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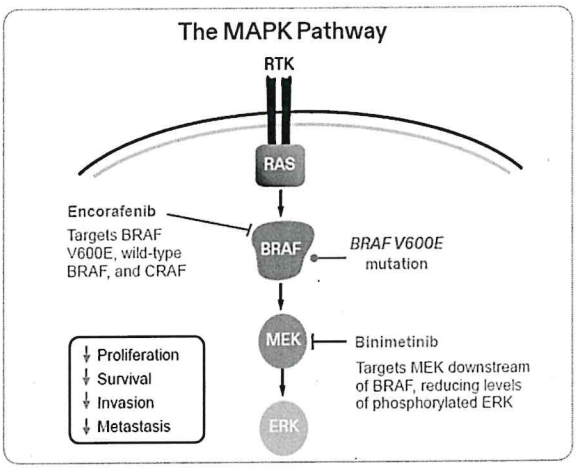
Encorafenib and Binimetinib Mechanism of Action

- Encorafenib is a selective, reversible small molecule inhibitor with a long dissociation half-life of >30 hours[1]
- Binimetinib is an ATP-uncompetitive, reversible inhibitor of MEK1 and MEK2[1]
- Activating *BRAF* mutations drive aberrant cell growth and proliferation through constitutive MAPK pathway activation[2]
- The encorafenib + binimetinib combination targets two kinases in the MAPK pathway, inhibiting deregulated growth and proliferation caused by *BRAF* driver mutations[2]
- Co-administration of encorafenib + binimetinib leads to greater anti-proliferative activity than either drug alone[3,4]



Correspondence: Gregory Riely, rielyg@MSKCC.ORG

PHAROS is a Single-arm, Open-label, Multicenter Phase II Study[1–5]

Key Eligibility Criteria

- *BRAF V600E*–mutant metastatic NSCLC
- ECOG performance status 0 or 1
- No EGFR mutation, ALK fusion, or ROS1 rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

Enrollment*†

- Treatment-naïve (N=59)
- Previously treated (N=39) Post first-line platinum-based CT or post first-line PD-1/L-1 therapy (alone or in combination)

Treatment period

- Encorafenib: 450 mg PO QD
- Binimetinib: 45 mg PO BID
- 28-day cycles‡

Radiographic disease assessments every 8 weeks until PD§

Endpoints

Primary Endpoint
Confirmed ORR by IRC per RECIST v1.1

Secondary Endpoints
Confirmed ORR by investigator assessment; DOR, TTR, DCR, and PFS by IRC and investigator assessment; OS; and safety

Exploratory Endpoints
- PK
- Genomic analysis of ctDNA in blood samples

Encorafenib plus binimetinib in BRAF V600E-mutant metastatic NSCLC

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Baseline Characteristics in the Efficacy Population (n=98)[1,2,*]

Characteristic	N=98
Line of treatment, n	
Treatment naïve	59
Previously treated	39
Median age at screening, years (range)	70 (47–86)
Female sex, %	53
Ethnicity†, %	
White	88
Asian	7
Black or African American	3
American Indian or Alaska Native	1
ECOG performance status, %	
1	73
Smoking status, %	
Current	13
Former	57
Never[3]	30

Characteristic	N=98
Specimen used for *BRAF* testing, %	
Tissue	78
Blood	22
Tumor histology, %	
Adenocarcinoma	97
Brain metastases, %	
Yes	8
Prior radiotherapy[3], %	
Yes	27
No	73
Prior systemic therapy[3], %	40
Immunotherapy	24
Monotherapy PD-(L)1	12
Combination PD-(L)1	12
Chemotherapy	18

*Data on file. Not reported in the primary publication.[1]
1. Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain. 2. Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

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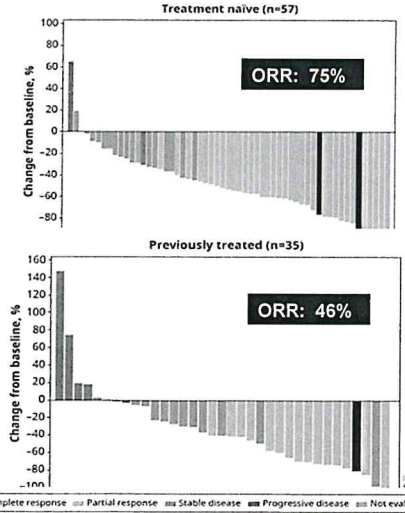
Antitumor activity of encorafenib plus binimetinib in NSCLC

- Deep and durable response with combination of encorafenib plus binimetinib

Table 2: Efficacy endpoints by IRR

	Treatment naive n=59	Previously treated n=39
Objective response rate, n/N (%)* (95% CI), %	44/59 (75) (62, 85)	18/39 (46) (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)

*Response of 3 patients were not evaluable in the treatment-naive group, and 5 were not evaluable in the previously treated group.



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*Data on file. Not reported in the primary publication.[1]
1. Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain. 2. Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

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Treatment Ongoing and Duration of Treatment[1]

	Primary Analysis (Data Cutoff: Sep 22, 2022)[2]		Current Analysis (Data Cutoff: Apr 1, 2024)	
	Treatment Naïve	Previously Treated	Treatment Naïve	Previously Treated
Treatment ongoing, n (%)	25 (42)	8 (21)	11 (19)	4 (10)
Treatment duration, median (range), months				
Encorafenib	15.1 (0–35.1)	5.4 (0.1–31.2)	16.3 (0–54.0)	5.5 (0.1–49.5)
Binimetinib	14.4 (0–35.1)	5.4 (0.1–31.2)	16.3 (0–54.0)	5.5 (0.1–49.5)
>2 years of treatment, n (%)				
Encorafenib	14 (24)*	3 (8)*	24 (41)	4 (10)
Binimetinib	13 (22)*	3 (8)*	24 (41)	4 (10)

*Data on file. Not reported in the primary publication.[1]
1. Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain. 2. Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

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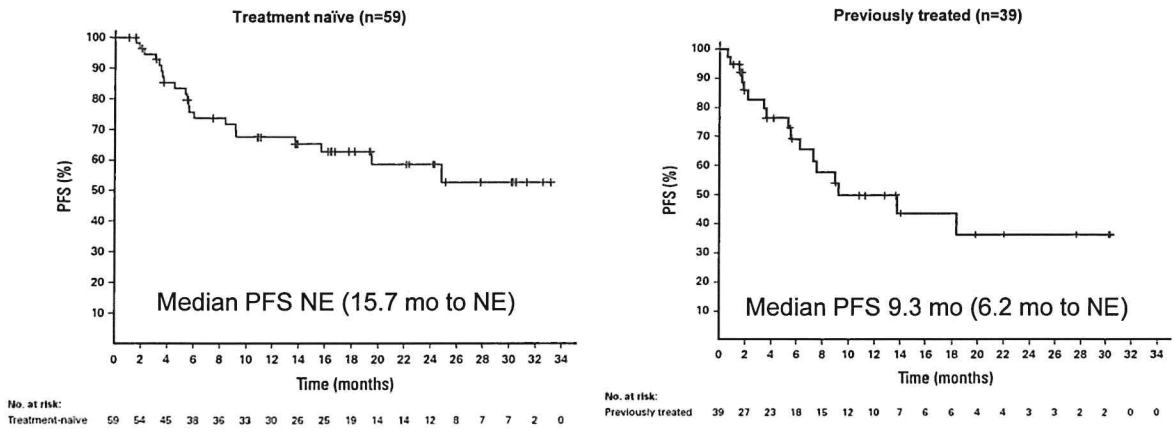
Encorafenib plus binimetinib in BRAF V600E-mutant metastatic NSCLC
Progression-free survival by IRR



- **The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients**

Riely et al, J Clin Onc 2023

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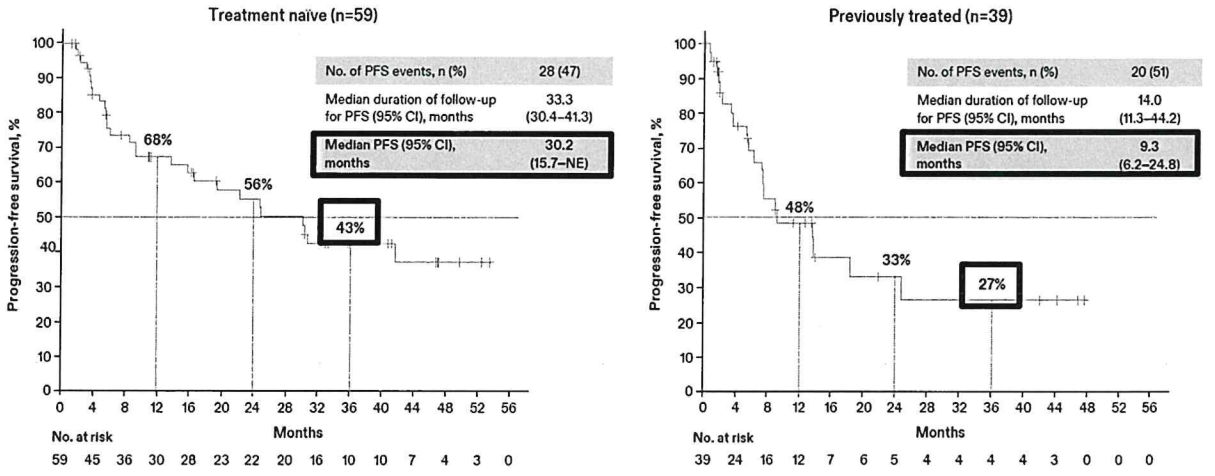
Progression-Free Survival by IRR (Data Cutoff: Apr 1, 2024)



IRR, independent radiology review; NE, not estimable; PFS, progression-free survival.
Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain.

*Data on file. Not reported in the primary publication.[1]
1. Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain. 2. Riely GJ, et al. *J Clin Oncol*. 2023;41(21):3700-3711.

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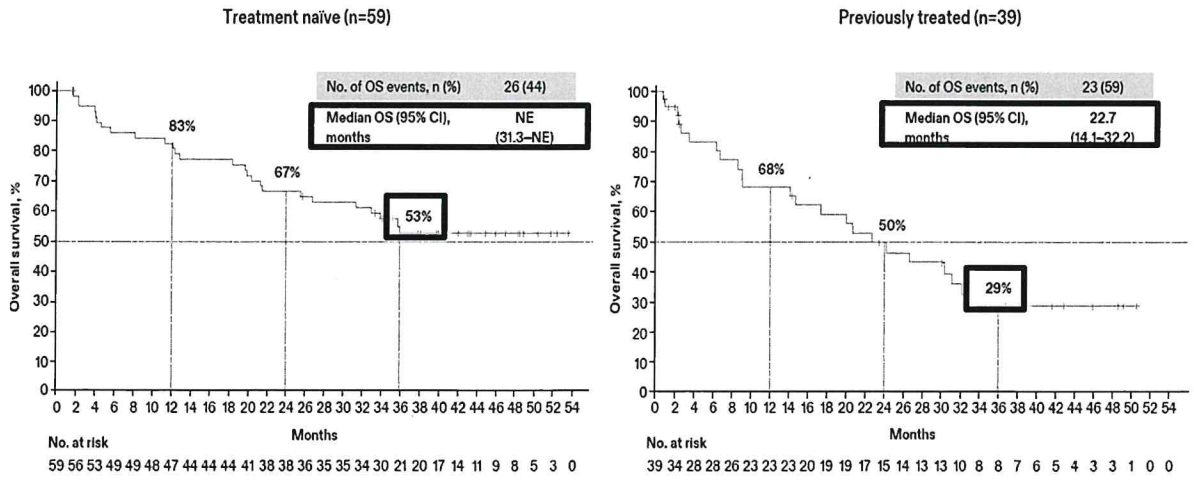
Overall Survival (Data Cutoff: Apr 1, 2024)



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Dabrafenib + Trametinib vs Encorafenib + Binimetinib: $BRAF^{V600E}$ NSCLC Efficacy

	Dabrafenib/Trametinib		Encorafenib/Binimetinib	
Study	Single Arm Phase II		Single Arm Phase II	
Pts	Tx-Naïve	Previously Tx'd	Tx-Naive	Previously Tx'd
No of Pts	36	57	59	39
Med Age	67	64	68	71
Never Smoker	28%	28%	31%	28%
Evaluation	Investigator-Assessed		Blinded Independent Review (BICR)	
TRAE Gr 3/4	68%	69%	54%	33%
Med F/U	60 m	60 m	36.2 m	30.8 m
ORR	64%	68%	75%	46%
DOR	10.2 m	9.8 m	40 m	16.7 m
mPFS	10.8 m	10.2 m	30.2 m	9.3 m
mOS	17.3 m	18.2 m	47.6	22.7 m

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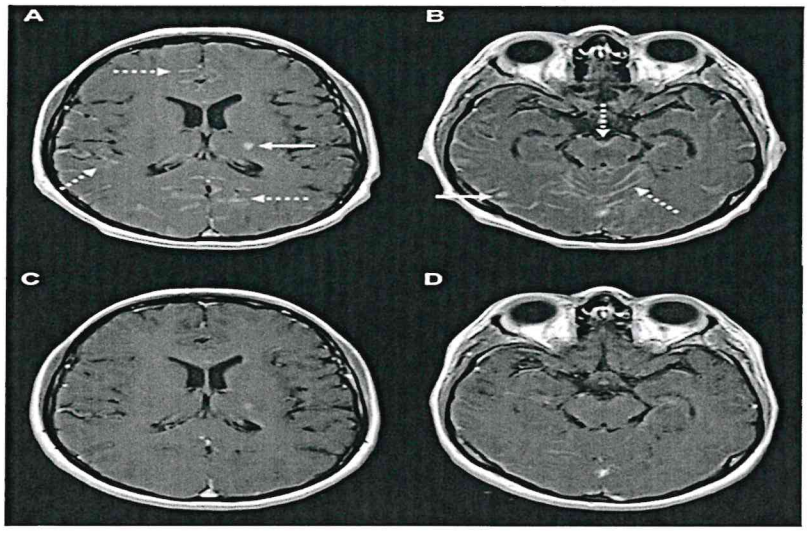
Encorafenib and Binimetinib CNS activity



CNS = central nervous system.
McLoughlin EM, et al. *J Thorac Oncol*. 2019;12(4):e269-e271.

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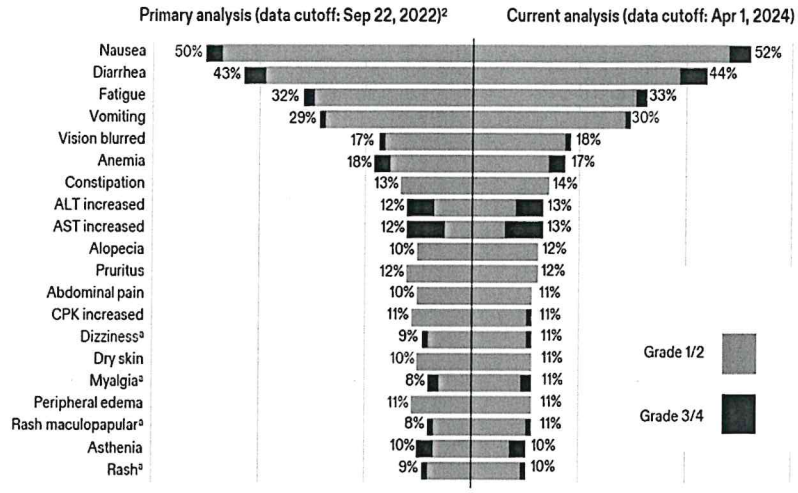
Treatment-Related AEs (≥10%) in Overall Population (N=98)[1]



- With additional follow-up, safety profile was consistent with the primary analysis
- **Similar to the primary analysis, any-grade treatment-related pyrexia occurred in 8% of patients; all were grade 1/2**
- Treatment-related AEs leading to dose reduction and permanent discontinuation of encorafenib plus binimetinib were consistent with those in the primary analysis

[a]Data on file. These treatment-related AEs were not reported in the primary publication[2] as they were not above the 10% threshold.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
1. Riely GJ, et al. Presented at: ESMO Congress; September 13-17th, 2024; Barcelona, Spain. 2. Riely GJ, et al. J Clin Oncol. 2023;41(21):3700-3711.

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Dabrafenib plus trametinib *vs* encorafenib plus binimetinib in *BRAF*^{V600E} NSCLC: Adverse events

Dabrafenib plus trametinib

	Maximum Grade							
Preferred Term	1	2	3	4	3+4	5	Unknown	Total
Any event	6 (6%)	17 (18%)	52 (56%)	9 (10%)	61 (66%)	8 (9%)	0	92 (99%)
Pyrexia	22 (24%)	24 (26%)	6 (6%)	0	6 (6%)	0	0	52 (56%)
Nausea	25 (27%)	22 (24%)	0	0	0	0	0	47 (51%)
Vomiting	25 (27%)	9 (10%)	3 (3%)	0	3 (3%)	0	1 (1%)	38 (41%)
Dry skin	32 (34%)	3 (3%)	1 (1%)	0	1 (1%)	0	0	36 (39%)
Oedema peripheral	32 (34%)	3 (3%)	0	0	0	0	0	35 (38%)
Diarrhoea	24 (26%)	8 (9%)	2 (2%)	0	2 (2%)	0	0	34 (37%)
Decreased appetite	18 (19%)	13 (14%)	0	0	0	0	0	31 (33%)
Cough	23 (25%)	6 (6%)	0	0	0	0	0	29 (31%)
Asthenia	13 (14%)	10 (11%)	4 (4%)	0	4 (4%)	0	0	27 (29%)
Fatigue	12 (13%)	12 (13%)	3 (3%)	0	3 (3%)	0	0	27 (29%)
Rash	22 (24%)	3 (3%)	2 (2%)	0	2 (2%)	0	0	27 (29%)
Dyspnoea	14 (15%)	5 (5%)	7 (8%)	0	7 (8%)	0	0	26 (28%)
Arthralgia	20 (22%)	4 (4%)	1 (1%)	0	1 (1%)	0	0	25 (27%)
Chills	17 (18%)	8 (9%)	0	0	0	0	0	25 (27%)
Headache	16 (17%)	2 (2%)	1 (1%)	0	1 (1%)	0	0	19 (20%)

Dose reduction : 48% for D; 32% for T
Dose interruption or delay: 77% for D; 71% for T
Permanent discontinuation due to TRAEs: 22%

Encorafenib plus binimetinib

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Pyrexia (treatment-related) was the cause of dose interruption of encorafenib plus binimetinib in one patient but did not result in dose reduction or permanent treatment discontinuation

Dose reduction : 25%
Dose interruption : 44%
Permanent discontinuation due to TRAEs: 15% (nausea, vomiting, diarrhea)

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Planchard et al JTO 2022 *Reily et al ASCO 2023* ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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Dabrafenib plus trametinib *vs* encorafenib plus binimetinib in *BRAF*^{V600E} NSCLC: Adverse events

Dabrafenib plus trametinib

Preferred Term	Maximum Grade: 1	2	3	4	3+4	5	Unknown	Total
Any event	6 (6%)	17 (18%)	52 (56%)	9 (10%)	61 (66%)	8 (9%)	0	92 (99%)
Pyrexia	22 (24%)	24 (26%)	6 (6%)	0	6 (6%)	0	0	52 (56%)
Nausea	25 (27%)	22 (24%)	0	0	0	0	0	47 (51%)
Vomiting	25 (27%)	9 (10%)	3 (3%)	0	3 (3%)	0	1 (1%)	38 (41%)
Dry skin	32 (34%)	3 (3%)	1 (1%)	0	1 (1%)	0	0	36 (39%)
Oedema peripheral	32 (34%)	3 (3%)	0	0	0	0	0	35 (38%)
Diarrhoea	24 (26%)	8 (9%)	2 (2%)	0	2 (2%)	0	0	34 (37%)
Decreased appetite	18 (19%)	13 (14%)	0	0	0	0	0	31 (33%)
Cough	23 (25%)	6 (6%)	0	0	0	0	0	29 (31%)
Asthenia	13 (14%)	10 (11%)	4 (4%)	0	4 (4%)	0	0	27 (29%)
Fatigue	12 (13%)	12 (13%)	3 (3%)	0	3 (3%)	0	0	27 (29%)
Rash	22 (24%)	3 (3%)	2 (2%)	0	2 (2%)	0	0	27 (29%)
Dyspnoea	14 (15%)	5 (5%)	7 (8%)	0	7 (8%)	0	0	26 (28%)
Arthralgia	20 (22%)	4 (4%)	1 (1%)	0	1 (1%)	0	0	25 (27%)
Chills	17 (18%)	8 (9%)	0	0	0	0	0	25 (27%)
Headache	16 (17%)	2 (2%)	1 (1%)	0	1 (1%)	0	0	19 (20%)

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Encorafenib plus binimetinib

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)*	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Pyrexia (treatment-related) was the cause of dose interruption of encorafenib plus binimetinib in one patient but did not result in dose reduction or permanent treatment discontinuation

Dose reduction : 25%
Dose interruption : 44%
Permanent discontinuation due to TRAEs: 15% (nausea, vomiting, diarrhea)

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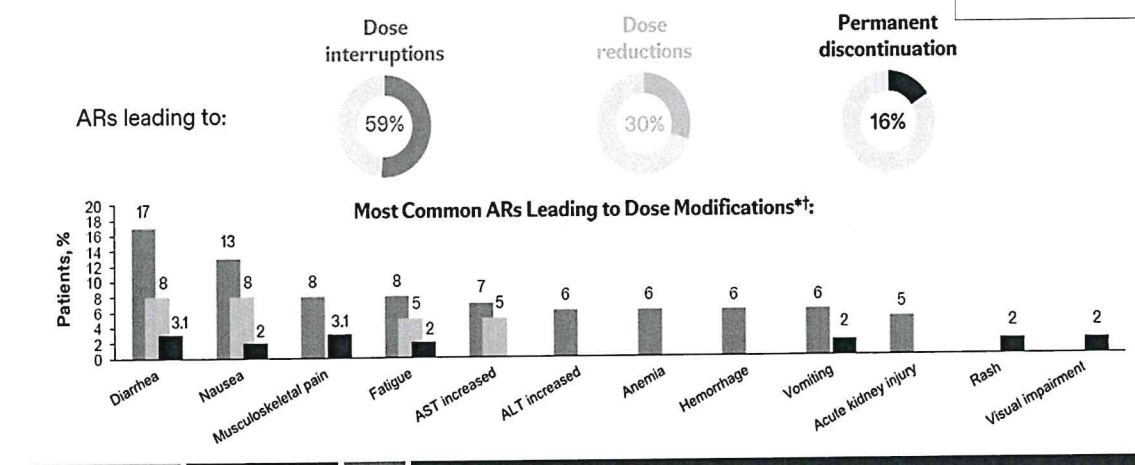
Encorafenib Dose Modifications: 2024 Update



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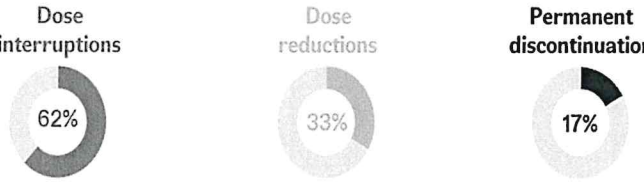
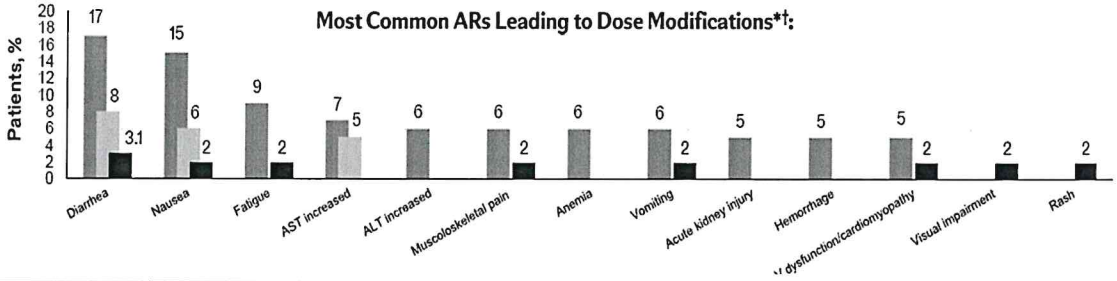
Binimetnib Dose Modifications: 2024 Update

ARs leading to...





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Encorafenib and Binimetnib: BRAF V600 mt (+) NSCLC: Data Summary

Study Design[1]

- PHAROS is a single-arm, open-label, multicenter Phase II study investigating the efficacy, safety, and tolerability of encorafenib + binimetinib in treatment-naïve and previously treated patients with *BRAF V600E*-mutated mNSCLC

PHAROS TRAEs

- The most common TRAEs (≥25%) were nausea (50%), diarrhea (43%), fatigue (32%), and vomiting (29%)[1]
- With additional follow-up, safety profile in current analysis (data cutoff: April 1, 2024) was consistent with the primary analysis[4]
- Similar to the primary analysis, any-grade treatment-related pyrexia occurred in 8% of patients; all were grade 1/2[4]
- TRAEs leading to dose reduction and permanent discontinuation of encorafenib plus binimetinib were consistent with those in the primary analysis[4]

Efficacy: Treatment-naïve[1-4]

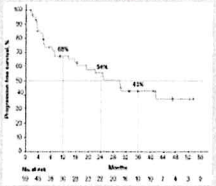
Primary analysis (data cutoff: Sep 22, 2022)

- ORR by IRC was 75%
- Responses were durable (≥12 months); mDOR by IRC was NE (95% CI, 23.1–NE)
- Median PFS by IRC was not estimable (95% CI, 15.7–NE)

Updated analysis (data cutoff: Apr 1, 2024)

- ORR by IRC was 75%
- mDOR by IRC was 40.0 (95% CI, 23.1–NE)
- mPFS by IRC was 30.2 (95% CI, 15.7–NE)
- mOS was not estimable

PFS - Treatment-naïve (N=59)



Efficacy: Previously Treated[1-4]

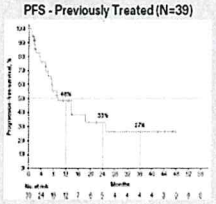
Primary analysis (data cutoff: Sep 22, 2022)

- ORR by IRC was 46%
- Responses were durable (≥12 months); mDOR was 16.7 months (95% CI, 7.4–NE)
- Median PFS by IRC was 9.3 months (6.2–NE)

Updated analysis (data cutoff: Apr 1, 2024)

- ORR by IRC was 46%
- mDOR by IRC was 16.7 (95% CI, 7.4–NE)
- mPFS by IRC was 9.3 (95% CI, 6.2–24.8)
- mOS was 22.7 months (95% CI, 14.1–32.2)

PFS - Previously Treated (N=39)



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Conclusions: TKIs in B-RAF mutation (+) NSCLC

- Dabrafenib and Trametinib: erstwhile standard of care (SOC) with activity both 1L and 2L in Class I BRAF mutation
- Encorafenib and Binimetinib current SOC
  - Similar ORR% to Dab/Tram
  - Superior PFS and OS data, particularly 1L
  - Improved toxicity profile (far less fever, fewer gr 3 and 4 events, lower Tx discontinuations)
  - Clear cut CNS penetrance
- Neither combination yields activity outside BRAF V600 mutations.
- Whether to proceed first with CPIs or TKIs is a point of controversy
- Need to explore means to prevent or overcome resistance

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Thank you for your attention

Perelman Center for Advanced Medicine
University of Pennsylvania, Philadelphia, PA

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Backup Slides

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Recommended Dosage and Administration[1,2]

Confirm the presence of a *BRAF V600E* mutation in tumor or plasma specimens prior to initiating encorafenib or binimetinib

Encorafenib

450 mg QD

Each capsule: 75 mg

+

Binimetinib

First dose 45 mg

Each tablet: 15 mg

Approximately 12 hours later

Second dose 45 mg

Each tablet: 15 mg

Continue treatment until disease progression or unacceptable toxicity

- Encorafenib and binimetinib may be taken with or without food
- Instruct patients to not take a missed dose of encorafenib within 12 hours the next dose, or binimetinib within 6 hours of the next dose
- Instruct patients to not take an additional dose if vomiting occurs after administration of encorafenib or binimetinib but continue with the next scheduled dose
- Hemodialysis is likely to be ineffective in the treatment of overdose, as encorafenib and binimetinib are 86% and 97% bound to plasma proteins, respectively
- Patients with moderate or severe hepatic impairment: the recommended dose of binimetinib is 30 mg orally BID

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Recommended Dose Reductions for Adverse Reactions

- If binimetinib is withheld, reduce encorafenib to a maximum dose of 300 mg QD until binimetinib is resumed[1]
- If encorafenib is permanently discontinued, discontinue binimetinib[2]

	Recommended Dose[1,2]	
	Encorafenib	**Binimetinib**
Starting dose	450 mg orally QD	45 mg orally BID
First dose reduction	300 mg orally QD	30 mg orally BID
Second dose reduction	225 mg orally QD	Permanently discontinue If unable to tolerate 30 mg orally BID
Subsequent modification	Permanently discontinue If unable to tolerate 225 mg orally QD	N/A

AE = adverse event; BID = twice daily; N/A = not available; QD = once daily.
1. Braftovi® (encorafenib) Prescribing Information. New York, NY: Pfizer Inc.; 2025; 2. Mektovi® (binimetinib) Prescribing Information. New York, NY: Pfizer Inc.; 2025.

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Summary and Overview of Management Guidelines for *BRAF V600E*-mutant mNSCLC

	NCCN Guidelines 2025[1]	
Latest update	January 2025	
1L	Mutation discovered **prior to 1L** • **Preferred:** Dabrafenib + trametinib* or **encorafenib + binimetinib*** • **Useful in certain circumstances:** Vemurafenib*† or dabrafenib*† • **Other recommended:** Systemic therapy for adenocarcinoma or squamous cell carcinoma	Mutation discovered **during 1L** • Complete planned systemic therapy, including maintenance therapy, or interrupt current therapy, followed by dabrafenib + trametinib* or **encorafenib + binimetinib**
Subsequent therapy	• Post-dabrafenib + trametinib, **encorafenib + binimetinib**, or single-agent dabrafenib/vemurafenib: CT +/- IO +/- anti-VEGF • Post-CT +/- IO +/- anti-VEGF: Dabrafenib + trametinib† or **encorafenib + binimetinib** – Following progression: subsequent CT and/or IO	

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