



Amivantamab Plus Lazertinib in Patients With *EGFR*-Mutant NSCLC After Progression on Osimertinib and Platinum-Based Chemotherapy: Results From CHRYSALIS-2 Cohort A

Benjamin Besse, MD, PhD,^a Koichi Goto, MD, PhD,^b Yongsheng Wang, MD,^c Se-Hoon Lee, MD, PhD,^d Melina E. Marmarelis, MD,^e Yuichiro Ohe, MD, PhD,^f Reyes Bernabe Caro, MD,^g Dong-Wan Kim, MD, PhD,^h Jong-Seok Lee, MD, PhD,^h Sophie Cousin, MD, MSc,ⁱ Eiki Ichihara, MD, PhD,^j Yongsheng Li, MD, PhD,^k Luis Paz-Ares, MD, PhD,^l Akira Ono, MD, PhD,^m Rachel E. Sanborn, MD,ⁿ Naohiro Watanabe, MD,^o Maria Jose de Miguel, MD, PhD,^p Carole Helissey, MD, PhD,^q Catherine A. Shu, MD,^r Alexander I. Spira, MD, PhD,^s Pascale Tomasini, MD, MSc,^t James Chih-Hsin Yang, MD, PhD,^u Yiping Zhang, MD,^v Enriqueta Felip, MD, PhD,^w Frank Griesinger, MD, PhD,^x Saama N. Waqar, MD,^y Antonio Calles, MD,^z Joel W. Neal, MD, PhD,^{aa} Christina S. Baik, MD, MPH,^{bb} Pasi A. Jänne, MD, PhD,^{cc} S. Martin Shreeve, MD, PhD,^{dd} Joshua C. Curtin, PhD,^{ee} Bharvin Patel, PhD,^{ee} Michael Gormley, PhD,^{ee} Xuesong Lyu, PhD,^{ff} Jun Chen, MD, MSc,^{ee} Pei-Ling Chu, PhD,^{gg} Janine Mahoney, BSN, RN,^{ee} Leonardo Trani, MD,^{ee} Joshua M. Bauml, MD,^{ee} Meena Thayu, MD, MSCE,^{ee} Roland E. Knoblauch, MD, PhD,^{ee} Byoung Chul Cho, MD, PhD^{hh,*}

^aParis-Saclay University, Institut Gustave Roussy, Villejuif, France

^bNational Cancer Center Hospital East, Kashiwa, Japan

^cInstitute of Clinical Trial Center and Cancer Center, West China Hospital, Sichuan University, Chengdu, People's Republic of China

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

^eUniversity of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania

^fNational Cancer Center Hospital, Tokyo, Japan

^gHospital Universitario Virgen Del Rocío, Seville, Spain

^hSeoul National University College of Medicine and Seoul National University Hospital, Seoul, Republic of Korea

ⁱInstitut Bergonié, Bordeaux, France

^jCenter for Clinical Oncology, Okayama University Hospital, Okayama, Japan

^kChongqing University Cancer Hospital, Chongqing, People's Republic of China

^lHospital Universitario 12 de Octubre, Madrid, Spain

^mShizuoka Cancer Center, Shizuoka, Japan

ⁿEarle A. Chiles Research Institute, Providence Cancer Institute, Portland, Oregon

^oDepartment of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

^pSTART Madrid-CIOCC, Hospital HM Sanchinarro, Madrid, Spain

^qClinical Research unit, Military Hospital Begin, Saint-Mandé, France

^rColumbia University Medical Center, New York, New York

*Corresponding author.

Previous presentations: CHRYSALIS-2 Cohort A clinical data were presented at the European Society for Medical Oncology Annual Meeting; September 16-21, 2021; virtual. Updated data were presented at the American Society for Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL, USA. NGS/biomarker analyses were presented at the American Association for Cancer Research Annual Meeting; April 14-19, 2023; Orlando, FL, USA.

Address for correspondence: Byoung Chul Cho, MD, PhD, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea. E-mail: CBC1971@yuhs.ac

Cite this article as: Besse B, Goto K, Wang Y, et al. Amivantamab plus lazertinib in patients with *EGFR*-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy: results from CHRYSALIS-2 cohort A. *J Thorac Oncol*. 2025;20:651-664.

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

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2024.12.029>

^sVirginia Cancer Specialists, Fairfax, Virginia

^tAix Marseille University - CNRS, INSERM, CRCM; CEPCM - AP-HM Hopital de La Timone, Marseille, France

^uNational Taiwan University Cancer Center, Taipei, Taiwan

^vZhejiang Cancer Hospital, Hangzhou, People's Republic of China

^wMedical Oncology Service, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain

^xPius-Hospital, University Medicine of Oldenburg, Oldenburg, Germany

^yDivision of Oncology, Washington University School of Medicine, St. Louis, Missouri

^zHospital General Universitario Gregorio Marañón, Madrid, Spain

^{aa}Stanford University Medical Center, Stanford, California

^{bb}University of Washington, Fred Hutchinson Cancer Center, Seattle, Washington

^{cc}Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Boston, Massachusetts

^{dd}Johnson & Johnson, San Diego, California

^{ee}Johnson & Johnson, Spring House, Pennsylvania

^{ff}Johnson & Johnson, Shanghai, People's Republic of China

^{gg}Johnson & Johnson, Raritan, New Jersey

^{hh}Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Received 10 October 2024; revised 20 December 2024; accepted 28 December 2024

Available online - 2 January 2025

ABSTRACT

Introduction: Treatment options for patients with *EGFR*-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy are limited.

Methods: CHRYSALIS-2 cohort A evaluated amivantamab plus lazertinib in patients with *EGFR* exon 19 deletion- or L858R-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy. Primary end point was investigator-assessed objective response rate (ORR). The patients received 1050 mg of intravenous amivantamab (1400 mg if ≥ 80 kg) plus 240 mg of oral lazertinib.

Results: In cohort A ($N = 162$), the investigator-assessed ORR was 28% (95% confidence interval [CI]: 22–36). The blinded independent central review-assessed ORR was 35% (95% CI: 27–42), with a median duration of response of 8.3 months (95% CI: 6.7–10.9) and a clinical benefit rate of 58% (95% CI: 50–66). At a median follow-up of 12 months, 32 of 56 responders (57%) achieved a duration of response of more than or equal to 6 months. Median progression-free survival by blinded independent central review was 4.5 months (95% CI: 4.1–5.8); median overall survival was 14.8 months (95% CI: 12.2–18.0). Preliminary evidence of central nervous system antitumor activity was reported in seven patients with baseline brain lesions and no previous brain radiation or surgery. Exploratory biomarker analyses using next-generation sequencing of circulating tumor DNA revealed responses in patients with and without *EGFR*- or *MET*-dependent resistance. The most frequent adverse events were rash (grouped term; 81%), infusion-related reaction (68%), and paronychia (52%). The most common grade greater than or equal to 3 treatment-related adverse events were rash (grouped term; 10%), infusion-related reaction (9%), and hypoalbuminemia (6%).

Conclusions: For patients with limited treatment options, amivantamab plus lazertinib demonstrated an antitumor activity with a safety profile characterized by *EGFR*- or

MET-related adverse events, which were generally manageable.

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

Keywords: Amivantamab; Biomarker analyses; Lazertinib; NSCLC

Introduction

Activating *EGFR* mutations are the most common actionable alteration observed in NSCLC. Exon 19 deletion (Ex19del) and exon 21 L858R (L858R) substitution mutations comprise up to 90% of activating *EGFR* mutations.¹ A recommended first-line therapy for patients with advanced NSCLC harboring these mutations is osimertinib, a third-generation *EGFR* tyrosine kinase inhibitor (TKI).^{2,3} Nevertheless, nearly all patients eventually develop resistance to osimertinib and have disease progression.⁴ Osimertinib-based resistance is diverse and often associated with multiple co-existing resistance mechanisms. The two most frequently identified resistance mechanisms involve *EGFR*-related co-mutations (e.g., C797S mutation) and *MET* alterations (e.g., amplification or exon 14 skipping mutations); however, approximately 50% of cases have no identified genetic resistance mechanism.^{4–6} Amivantamab in combination with carboplatin and pemetrexed or chemotherapy alone is a recommended treatment option for patients with disease progression on or after osimertinib.² Chemotherapy alone has limited efficacy after disease progression on osimertinib with an objective response rate (ORR) of 25%, median progression-free survival (PFS) of 2.8 months, and median overall survival (OS) of as little as

10.5 months.^{7,8} After disease progression on or after platinum-based chemotherapy, treatment options are even more limited; single-agent chemotherapy with docetaxel has an ORR of 11.2% and median PFS of 3.5 months.⁹ Ramucirumab plus docetaxel is another approved treatment option in this patient population, but it is associated with a 1.4-month improvement in OS compared with docetaxel monotherapy.¹⁰ Retrospective analyses of real-world databases found that patients with disease progression after osimertinib and platinum-based chemotherapy had poorer clinical outcomes compared with patients who were receiving first-line treatment.^{11,12}

Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that binds to the extracellular domains of EGFR and MET, which may help address resistance to EGFR TKIs.^{13–16} In global, phase 3 studies, amivantamab plus chemotherapy demonstrated superior PFS versus chemotherapy alone in the first-line treatment of patients with *EGFR* exon 20 insertions (PAPILLON) and in the post-osimertinib setting for patients with *EGFR* mutations (e.g., Ex19del, L858R; MARIPOSA-2), resulting in regulatory approvals in multiple countries.^{17–20}

Lazertinib is a highly selective, brain-penetrant, third-generation EGFR TKI with efficacy in activating *EGFR* mutations and T790M-resistance mutations.^{21,22} In a phase 3 study evaluating 393 patients with *EGFR*-mutated advanced NSCLC in the first-line setting, lazertinib resulted in significantly longer PFS (20.6 versus 9.7 mo, hazard ratio [HR] = 0.45, 95% confidence interval [CI]: 0.34–0.58, $p < 0.001$) than gefitinib. At an early interim analysis, there was a trend in OS favoring lazertinib over gefitinib (HR = 0.74, 95% CI: 0.51–1.08, $p = 0.116$). In addition, lazertinib demonstrates low rates of cardiotoxicity, such as QTc prolongation or cardiomyopathy.²³

The combination of amivantamab plus lazertinib was initially evaluated in the CHRYSALIS study, which focused on patients with *EGFR* Ex19del- or L858R-mutated metastatic NSCLC with disease progression on osimertinib who were chemotherapy naive.²⁴ Treatment with the combination of amivantamab plus lazertinib in this patient population resulted in an ORR of 36%. Additional descriptive cross-cohort analyses of the combination of amivantamab plus lazertinib (cohort E) versus amivantamab monotherapy (pooled from other CHRYSALIS cohorts) suggested that the combination therapy was associated with a numerically higher ORR (36% versus 19%) and longer duration of response (DoR; 9.6 versus 5.9 mo) in the post-osimertinib setting.²⁵ With this promising activity in the treatment-refractory setting, MARIPOSA evaluated amivantamab plus lazertinib in the first-line setting, where it demonstrated superior PFS versus osimertinib (HR = 0.70, 95% CI: 0.58–0.85, $p < 0.001$) at a median follow-up of 22 months,²⁶ leading to

the approval of this combination by the Food and Drug Administration after priority review.¹⁹

CHRYSALIS-2 cohort A was designed to evaluate treatment with a combination of amivantamab plus lazertinib in patients with *EGFR* Ex19del- or L858R-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy.

Materials and Methods

Study Design

CHRYSALIS-2 is an open-label, two-part, phase 1/1b study of lazertinib as monotherapy or in combination with amivantamab in patients with advanced NSCLC (Supplementary Fig. 1). This analysis presented the results of cohort A, which evaluated the combination of amivantamab and lazertinib in patients with *EGFR* Ex19del- or L858R-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy.

The primary objective of cohort A was to evaluate the safety, tolerability, and preliminary antitumor activity of the combination of amivantamab plus lazertinib. The primary end point was the ORR, as assessed by the investigator and confirmed by a blinded independent central review (BICR). Secondary end points included DoR, clinical benefit rate (CBR), PFS, OS, time to treatment failure, and adverse events (AEs).

An exploratory objective of cohort A was to identify biomarkers that were predictive of response to therapy. Circulating tumor DNA (ctDNA) and plasma samples were collected to evaluate the pretreatment mutational status of key oncogenes using next-generation sequencing (NGS).

Patients in cohort A received oral lazertinib 240 mg daily in 28-day cycles with intravenous (IV) amivantamab 1050 mg (or 1400 mg for patients with body weight ≥ 80 kg). Amivantamab was administered weekly in cycle 1 (the first dose was split between cycle 1 day 1 [350 mg] and cycle 1 day 2 [either 700 mg or 1050 mg depending on body weight]) and then every 2 weeks in subsequent cycles, starting at week 5. Treatment was continued until disease progression, unacceptable toxicity, noncompliance, withdrawal of consent, or discontinuation per the investigator's discretion. Treatment after Response Evaluation Criteria in Solid Tumors (RECIST; version [v.] 1.1)-defined disease progression was allowed at the investigator's discretion.

The CHRYSALIS-2 trial was approved by an independent ethics committee, and all patients provided written informed consent.

Patients

Patients in cohort A had advanced or metastatic NSCLC with *EGFR* Ex19del or L858R mutations, an

Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1, and measurable disease according to RECIST v.1.1. The eligibility criteria for cohort A included disease progression on or after previous treatment with osimertinib and platinum-based chemotherapy. Patients in cohort A were either treated with first- or second-line osimertinib followed by platinum-based chemotherapy as the most recent line of therapy before enrollment or more heavily pretreated or treated out of sequence (platinum-based chemotherapy followed by osimertinib). Previous use of a first- or second-generation EGFR TKI was allowed if it was administered before osimertinib treatment. The study initially included patients with stable or asymptomatic treated or untreated brain metastases (BM) at baseline, but it was later amended to include only patients who had completed definitive therapy for BM. This was amended to ensure uniform central nervous system (CNS) baseline status for all enrolled patients.

Study Assessments

Response was assessed by the investigator, according to RECIST v.1.1, and confirmed using BICR. Disease was assessed at baseline and then every 6 weeks after cycle 1 day 1 of treatment until disease progression by imaging, initiation of new anticancer therapy, or withdrawal of consent. For a response to qualify as stable disease, follow-up measurements after the initial stable disease assessment must have met the stable disease criteria at least once.

Baseline brain imaging was performed for all patients at screening. Subsequent brain imaging was not mandatory for patients without baseline BM, and follow-up was performed as per the local surveillance practice. However, if a brain lesion was identified as a target or non-target lesion (brain lesion < 10 mm or not amenable to accurate and reproducible measurement) at baseline, subsequent brain assessments were required, with each disease assessment in accordance with RECIST v.1.1. The severity of AEs was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0.

Statistical Analysis

The clinical cutoff date for the final analysis of cohort A was November 15, 2022. The full- or all-treatment analysis set included all patients who received at least one dose of any study treatment. This population was considered as the primary efficacy analysis and used for all analyses, unless otherwise specified.

Assuming a non-evaluable rate of 15%, approximately 100 patients were enrolled in cohort A, although additional patients could be included to

further characterize the activity of the subpopulations within the cohort. The sample size consideration was based on the null hypothesis that the ORR is less than or equal to 12% and the alternative hypothesis that the ORR is more than or equal to 25%. With a one-sided alpha of 2.5% and power of 87.5%, the total number of response-evaluable patients needed for cohort A was approximately 86.

ORR was defined as the proportion of patients who achieved either complete response (CR) or partial response (PR), as defined by the investigator or BICR through RECIST v.1.1. CBR was calculated as the percentage of patients who achieved CR, PR, or durable stable disease (duration $\geq$ 11 wk). Time-to-event end points (PFS, DoR, and OS) were estimated using the Kaplan-Meier method.

Exploratory Biomarker Analysis

For patients in cohort A, plasma samples were collected before treatment, on cycle 3 day 1, on cycle 5 day 1, and at the end of the treatment. NGS of plasma ctDNA was performed and analyzed with Guardant360 (Guardant Health, Redwood City, CA).²⁷

Patients with detectable ctDNA at baseline and clinical response data were categorized as *EGFR* or *MET* dependent (alterations in *EGFR* [e.g., C797S] or *MET* [e.g., amplification]) or *EGFR* or *MET* independent (alterations in *RAS*, *RAF*, *MEK*, *PI3K*, cell-cycle genes, and fusion events) based on previously reported osimertinib resistance mechanisms.⁴ Patients who did not have any of the currently known *EGFR*- or *MET*-dependent or *EGFR*- or *MET*-independent mechanisms were classified as unknown, whereas those with both dependent and independent mechanisms were classified as *EGFR* or *MET* dependent. All analyses were descriptive.²⁷

Results

Patients

As of the clinical cutoff, cohort A was fully enrolled at 162 patients (Table 1). The median follow-up was 12.3 months (range, 0.3–27.2), and the median treatment duration of amivantamab plus lazertinib was 4.6 months (range, 0.03–26.7). Of the 162 patients, the median age was 61.5 years (range, 31–83), 105 were women (65%), 100 were Asian (62%), and the median number of previous lines of therapy was three (range, 2–14). A total of 88 patients had a history of brain or CNS metastases or had brain or CNS lesions at baseline.

Among the 162 enrolled patients, 39 (24%) had previously received first-line osimertinib followed by platinum-based chemotherapy and 67 (41%) had received osimertinib as a second-line treatment (after

Table 1. Patient Demographic and Baseline Disease Characteristics

Characteristic, n (%)	N = 162
Median age (range), y	61.5 (31–83)
Female or male	105 (65) or 57 (35)
Race	
White	53 (33)
Asian	100 (62)
Black	3 (2)
Not reported	6 (4)
ECOG PS score of 0 or 1	49 (30) or 113 (70)
Smoking history	
Nonsmoker	111 (69)
History of inhaled tobacco use	49 (30)
Unknown	2 (1)
Median time from initial diagnosis (range), mo	38 (5–201)
NSCLC subtype	
Adenocarcinoma	158 (98)
Squamous cell carcinoma	1 (1)
Large cell carcinoma	1 (1)
Others	2 (1)
Location of metastases ^a	
Lung	89 (55)
Bone	87 (54)
Lymph node	82 (51)
Brain	65 (40)
Liver	43 (27)
Adrenal gland	18 (11)
Others	54 (33)
History of brain metastases at baseline ^b	88 (54)
Brain metastases by imaging at baseline ^c	66 (41)
Untreated	29 (18)
Treated	37 (23)
Median number of previous lines of therapy (range)	3 (2–14)
Prior therapy regimens	
First-line osimertinib → platinum-based chemotherapy	39 (24)
1st- or 2nd-generation EGFR TKI → osimertinib → platinum-based chemotherapy	67 (41)
Heavily pretreated or out of sequence	56 (35)

Note: Percentages may not sum to 100 due to rounding.

^aPatients could be counted in more than one category.

^bIncluded patients who had a history of brain or CNS metastases or had brain or CNS lesions as target or non-target lesions at baseline.

^cStudy initially allowed stable or asymptomatic treated or untreated brain metastases and was later amended to allow for treated brain metastases only; it included only patients who had brain or CNS lesions as target or non-target lesions on imaging at baseline.

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.

a previous first- or second-generation EGFR TKI) followed by platinum-based chemotherapy. A total of 56 patients (35%) were heavily pretreated or had their previous therapy out of sequence. Of the 56 patients, 32 (20%) were treated out of sequence (with platinum-based chemotherapy followed by osimertinib).

Safety

The safety profile of amivantamab plus lazertinib was consistent with that reported previously (Table 2). Treatment-emergent AEs (TEAEs) were mostly grades 1 and 2. The most frequent AEs according to the preferred terms were rash (grouped term; 81%), infusion-related reaction (IRR; 68%), paronychia (52%), and hypoalbuminemia (47%). Grade greater than or equal to 3 TEAEs were reported in 120 patients (74%). Grade greater than or equal to 3 treatment-related AEs were reported in 81 patients (50%). The most frequent treatment-related grade greater than or equal to 3 AEs were rash (grouped term; 10%), IRR (9%), and hypoalbuminemia (6%; Supplementary Table 1). Treatment-related serious AEs were reported in 34 patients (21%); all individual serious AEs had an incidence of less than 5% (Supplementary Table 2).

Dose interruptions, dose reductions, and discontinuations of any study agent due to treatment-related AEs were observed in 90 (56%), 47 (29%), and 25 (15%) patients, respectively (Table 2). Discontinuation of all study agents due to treatment-related AEs occurred in 11 patients (7%), with IRRs (7 [4%]) being the most frequently reported event leading to discontinuation. The most common AEs leading to dose reduction were rash (8%), paronychia (8%), and dermatitis acneiform (4%). There were no treatment-related grade 5 AEs.

IRRs (110 [68%]) occurred mostly on cycle 1 day 1 (64%) and cycle 1 day 2 (7%). The median time to the first onset of IRR was 53 minutes after infusion initiation, and most IRRs were grades 1 and 2 (Supplementary Table 3 and Supplementary Fig. 2). Venous thromboembolism (VTE) was reported in 30 patients (19%), including deep vein thrombosis (DVT) in 10 patients (6%) and pulmonary embolism (PE) in 12 patients (7%). Grade greater than or equal to 3 VTE was observed in 3 patients (2%), with PE in 2 patients (1%) and no DVTs (Supplementary Table 3). Furthermore, 18 patients (11%) were on anticoagulants for prophylaxis (n = 6) or due to a medical history of VTE (n = 12) at study enrollment. Among the total population, three patients who were on anticoagulation therapy at study enrollment experienced four VTE events, including superficial vein thrombosis, DVT, jugular vein thrombosis, and PE. Additional details (e.g., timing of AE) for selected AEs of interest (i.e., rash, paronychia, hypoalbuminemia, stomatitis, peripheral edema, diarrhea, pruritus, VTE, and interstitial lung disease) are presented in the Supplement (Supplementary Table 3 and Supplementary Fig. 3).

Efficacy

The investigator-assessed ORR was 28% (95% CI: 22–36), with one CR and 45 PRs observed (Table 3). The

Table 2. Summary of TEAEs

Event, n (%)	N = 162	
Any TEAE	162 (100)	
Grade $\geq$ 3 TEAEs	120 (74)	
Serious TEAEs	88 (54)	
Treatment-related dose interruption of any study agent ^a	90 (56)	
Treatment-related dose reduction of any study agent	47 (29)	
Treatment-related discontinuation of any study agent	25 (15)	
TEAEs ($\geq$ 10%) by Preferred Term, n (%)	N = 162	
	All Grades	Grade $\geq$ 3
Associated with EGFR inhibition		
Rash ^b	131 (81)	17 (10)
Paronychia	84 (52)	8 (5)
Stomatitis	64 (40)	3 (2)
Diarrhea	38 (23)	1 (1)
Pruritus	30 (19)	1 (1)
Associated with MET inhibition		
Hypoalbuminemia	76 (47)	16 (10)
Peripheral edema	47 (29)	2 (1)
Other		
Infusion-related reaction	110 (68)	15 (9)
Increased ALT	51 (31)	6 (4)
Paresthesia ^c	40 (25)	0
Nausea	44 (27)	3 (2)
Constipation	43 (27)	0
Increased AST	42 (26)	3 (2)
Decreased appetite	41 (25)	3 (2)
Dry skin	39 (24)	0
Asthenia	38 (23)	7 (4)
Vomiting	37 (23)	1 (1)
Thrombocytopenia	36 (22)	2 (1)
Dyspnea	34 (21)	13 (8)
Fatigue	32 (20)	4 (2)
Headache	30 (19)	2 (1)
Anemia	31 (19)	5 (3)
Hypocalcemia	26 (16)	1 (1)
Back pain	23 (14)	4 (2)
Dizziness	22 (14)	0
Arthralgia	19 (12)	0
Hypomagnesemia	19 (12)	1 (1)
Skin fissures	19 (12)	0
Hypokalemia	18 (11)	1 (1)
Pneumonia	18 (11)	11 (7)
Increased blood creatine phosphokinase	18 (11)	4 (2)
Myalgia	17 (10)	0
Pyrexia	17 (10)	0
Cough	17 (10)	0
Muscle spasms	17 (10)	0

^aExcludes infusion-related reactions.^bIncludes dermatitis, dermatitis acneiform, acne, erythema, folliculitis, rash, maculopapular rash, pustular rash, erythematous rash, macular rash, papular rash, pruritic rash, skin exfoliation, skin lesions, pustules, and papules.^cThe preferred terms paresthesia and peripheral sensory neuropathy were combined.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Table 3. Response as Assessed by the Investigator and BICR

	INV	BICR
Response	N = 162	N = 162
ORR, % (95% CI)	28 (22–36)	35 (27–42)
CBR, ^a % (95% CI)	58 (50–66)	58 (50–66)
Best response, n (%)		
Complete response	1 (1)	1 (1)
Partial response	45 (28)	55 (34)
Stable disease	79 (49)	67 (41)
Progressive disease	34 (21)	30 (19)
Not evaluable or unknown	3 (2)	9 (6)
DoR, median (95% CI), mo	8.4 (5.4–15.2)	8.3 (6.7–10.9)

^aPercentage of patients with confirmed response or durable stable disease (duration of $\geq$ 11 wk).

BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; INV, investigator; ORR, overall response rate.

corresponding median DoR was 8.4 months (95% CI: 5.4–15.2), and CBR was 58% (95% CI: 50–66), which included an additional 48 patients (30%) with stable disease at 11 or more weeks (Supplementary Fig. 4).

The BICR-assessed ORR, CBR, and median DoR were 35% (95% CI: 27–42), 58% (95% CI: 50–66), and 8.3 months (95% CI: 6.7–10.9), respectively (Table 3). Among 56 responders, 32 responders (57%) had a response duration of more than or equal to 6 months and 19 responders (34%) remained on treatment at the time of the clinical cutoff (Fig. 1A and Supplementary Fig. 5). The median time to response was 6.4 weeks (range, 5.4–54.0). For 67 patients with a best response of stable disease, 15 had a stable disease duration of more than or equal to 6 months and one remained on treatment at the time of the clinical cutoff. Furthermore, 35 patients were treated beyond investigator-assessed progression, with a median treatment duration after progression of 2.3 months (range, 0.5–16.5).

The antitumor response was consistent across pre-specified subpopulations (Fig. 1B). ORRs in the previous therapy subgroup, as assessed by BICR, were relatively similar regardless of the previous treatment category (Fig. 1B and Fig. 2). The ORRs were similar in patients with and without BM at baseline (including patients with a history of BM and those with brain lesions as target or non-target lesions at baseline; Supplementary Table 4).

The median PFS was 4.5 months (95% CI: 4.1–5.8) in the BICR assessment (Supplementary Table 5). The median PFS was comparable between patients who received osimertinib before platinum-based chemotherapy and those who were heavily pretreated or treated out of sequence (Supplementary Table 5). The most common sites of initial progression were the lung or pleura (57%), lymph nodes (23%), brain (20%), and liver (18%; Supplementary Fig. 6). The median OS was 14.8 months (95% CI: 12.2–18.0).

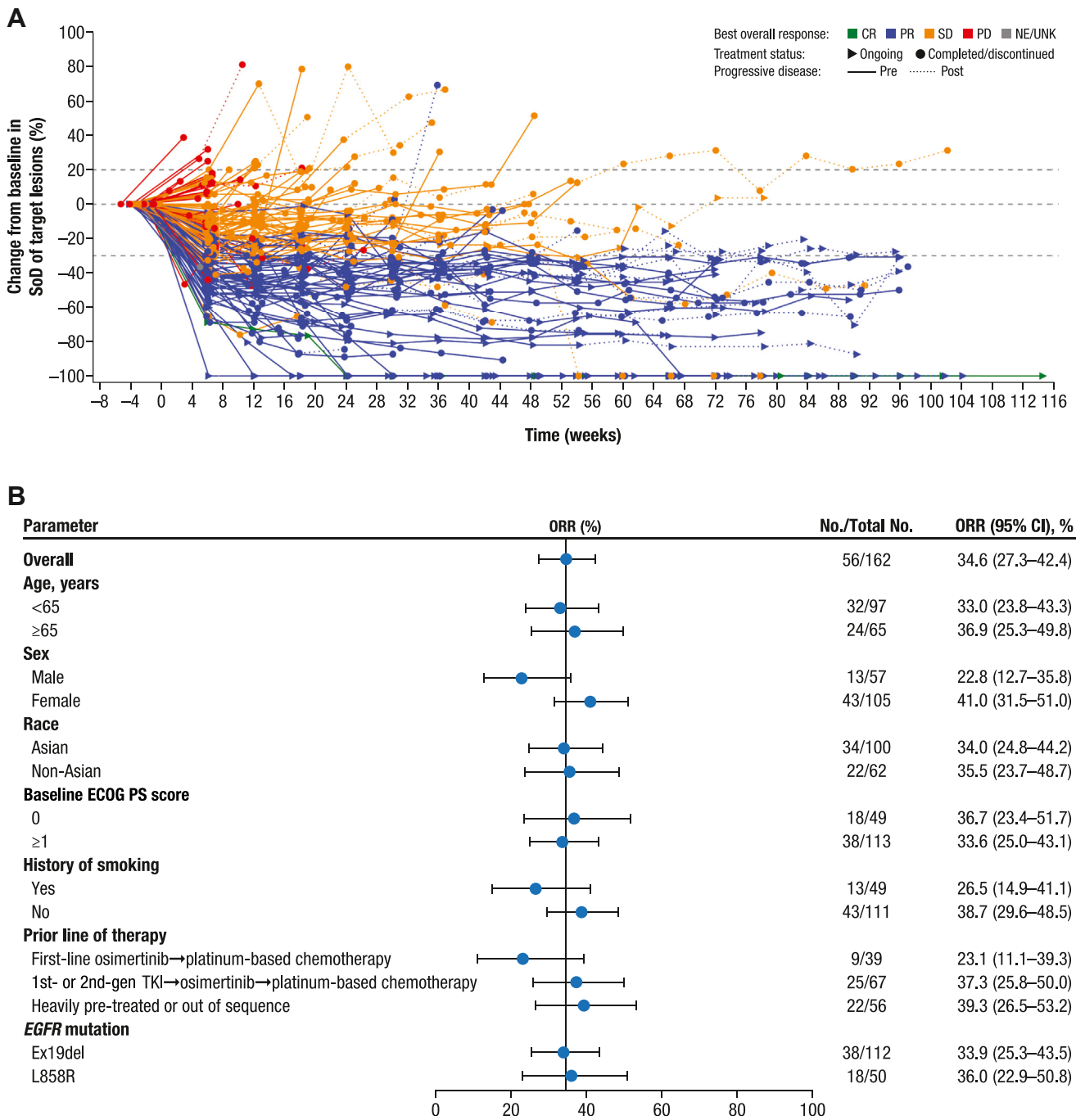


Figure 1. Tumor response over time and ORR by subgroup. (A) Percent change from baseline in SoD of target lesions over time as assessed by BICR and (B) ORR by subgroup as assessed by BICR. Note: Ten efficacy-evaluable patients did not have any assessable post-baseline target lesion measurements. Dotted lines at 20% and –30% indicate thresholds for PD and PR, respectively, as per Response Evaluation Criteria in Solid Tumors version 1.1. BICR, blinded independent central review; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; Ex19del, exon 19 deletion; gen, generation; L858R, exon 21 L858R; NE/UNK, not evaluable or unknown; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameter; TKI, tyrosine kinase inhibitor.

Biomarker Analysis

Given the heterogeneous nature of osimertinib resistance and the fact that both amivantamab and lazertinib are targeted therapies, an exploratory analysis was performed to assess whether *EGFR*- or *MET*-

dependent osimertinib resistance mechanisms were correlated with the response to amivantamab plus lazertinib in patients with *EGFR*-mutated NSCLC whose disease progressed after osimertinib and platinum-based chemotherapy. Detectable ctDNA data

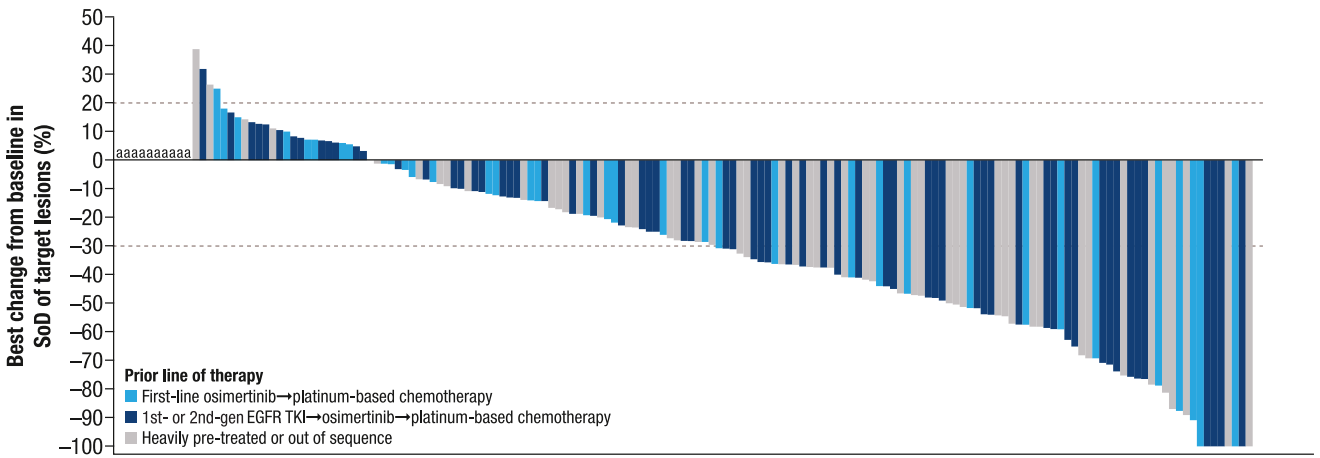


Figure 2. Best percent change from baseline in SoD of target lesions by previous therapy group as assessed by BICR. ^aEfficacy-evaluable patients who did not have any assessable target lesion measurements in any post-baseline disease assessment. BICR, blinded independent central review; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

were available for 115 of 162 patients (71%). Of the 115 patients with detectable ctDNA, genetic testing identified 30 patients (26%) with *EGFR*- or *MET*-dependent osimertinib resistance mechanisms, 33 patients (29%) with *EGFR*- or *MET*-independent resistance mechanisms, and 52 patients (45%) with unknown resistance mechanisms (Supplementary Fig. 7). The most common resistance mutation was *EGFR* C797S (17%).

The ORR was 27% for patients with *EGFR*- or *MET*-dependent resistance and 30% for those with *EGFR*- or *MET*-independent mechanisms of resistance (Table 4). Among the patients with unknown resistance mechanisms identified by ctDNA NGS, the ORR was 42%. Similar ORRs were observed in patients with and without detectable baseline ctDNA levels (35% and 34%, respectively). The corresponding baseline genomic profiles categorized by general osimertinib resistance patterns are presented in Supplementary Figure 8.

Table 4. ORR by Type of Resistance Mechanism			
Resistance Mechanism	n	No. of Responders	ORR ^a
<i>EGFR</i> or <i>MET</i> dependent ^b	30	8	27%
<i>EGFR</i> or <i>MET</i> independent	33	10	30%
Unknown	52	22	42%
Patients with detectable ctDNA	115	40	35%
Patients without detectable ctDNA	47	16	34%

^aResponses were assessed by a blinded independent central review according to the Response Evaluation Criteria in Solid Tumors version 1.1.
^bIncludes co-occurring independent resistance mechanisms.
ctDNA, circulating tumor DNA; ORR, overall response rate.

Retrospective, Exploratory CNS Analysis

A total of 66 patients underwent BM by imaging at screening. Among the 60 (of 66) patients with at least one post-baseline scan, an intracranial response was observed in 17 patients (28%). Of note, 26 patients had untreated BM (no previous brain radiation or surgery), and an investigator-assessed intracranial response was observed in seven patients (27%). Brain magnetic resonance images from a patient with an untreated CNS lesion who had an intracranial response to amivantamab plus lazertinib at week 6, which was maintained until week 54, are presented in Supplementary Figure 9.

Discussion

In the CHRYSALIS-2 cohort A, the combination of amivantamab and lazertinib demonstrated durable antitumor activity in patients with *EGFR*-mutated NSCLC after disease progression on or after both osimertinib and platinum-based chemotherapy. The patient population evaluated in this study, including a higher percentage of Asian patients (62%), was reflective of the patient population with *EGFR*-mutant NSCLC.²⁸ The antitumor activity of the combination of amivantamab plus lazertinib in this patient population (as assessed by BICR, ORR = 35%) was comparable to that previously reported in post-osimertinib patients who were chemotherapy naive (ORR = 36%),²⁴ suggesting that intervening chemotherapy does not affect the clinical activity of the regimen.

The combination of amivantamab and lazertinib was hypothesized to provide key benefits in this setting based on their complementary mechanisms of action. By targeting the extracellular domain of *EGFR* while blocking *MET* signaling,^{13,14,16} amivantamab has been hypothesized to target a wide range of resistance mechanisms and

improve responses. In addition, although both lazertinib and osimertinib are third-generation TKIs found to have efficacy in activating *EGFR* mutations and CNS disease,^{21,22,29} lazertinib is structurally different and has advantages in CNS penetration, target specificity, and dose-limiting toxicity in preclinical studies.^{30,31} In this study, all patients with measurable brain metastases, regardless of previous brain treatment, who had a systemic RECIST response also had an intracranial RECIST response, which is consistent with a regimen with intracranial activity.

Patients with *EGFR*-mutated NSCLC with disease progression on or after both osimertinib and platinum-based chemotherapy have poor outcomes and limited treatment options.^{11,12} The current recommended treatment options after disease progression on osimertinib and platinum-based chemotherapy include single-agent chemotherapy, such as docetaxel and docetaxel in combination with ramucirumab.² Antibody-drug conjugates, such as datopotamab deruxtecan and patritumab deruxtecan, are also being investigated in this population.^{32,33} In the TROPION-Lung01 (NCT04656652) and HERTHENA-Lung01 (NCT04619004) studies, datopotamab deruxtecan and patritumab deruxtecan demonstrated an ORR of 26% and 29%, median DoR of 7.1 months and 6.4 months, and median PFS of 4.4 months and 5.5 months, respectively.

The safety profile of the combination of amivantamab and lazertinib was consistent with that of previous reports. The most frequently reported TEAEs were associated with the inhibition of *EGFR* (e.g., rash, dermatitis acneiform, and paronychia) or *MET* (e.g., hypoalbuminemia and peripheral edema). IRRs were mostly grades 1 and 2 and primarily occurred during the first infusion cycle. Of the patients who reported VTE, 27 of 30 patients (90%) were not receiving anticoagulation therapy at study entry, highlighting the benefit of prophylactic anticoagulation in patients receiving amivantamab plus lazertinib.

Since the CHRYSALIS-2 study, additional trials have been conducted to evaluate proactive approaches to improve the safety and tolerability profile of amivantamab plus lazertinib. In the phase 3 PALOMA-3 study (NCT05388669), subcutaneous amivantamab plus lazertinib demonstrated noninferiority to intravenous amivantamab plus lazertinib, offering reduced rates of IRRs, increased convenience, and prolonged survival.³⁴ The SKIPPirr study (NCT05663866) revealed an approximately three-fold reduction in the rate of IRRs at first amivantamab infusion (cycle 1 day 1) with the addition of an oral dexamethasone 8-mg twice-daily regimen compared with historical intravenous amivantamab data with standard IRR prophylaxis (22.5% versus 67.4%).³⁵ In addition, enhanced management of

dermatologic AEs with prophylactic antibiotics, paronychia prophylaxis, and skin moisturization is being investigated in the COCOON study (NCT06120140).³⁶ These studies highlight the ongoing efforts to address the most common AEs associated with amivantamab plus lazertinib.

Although serial molecular testing to identify targetable mechanisms of resistance to personalized subsequent therapy in patients with disease progression on or after osimertinib treatment is a promising strategy, this approach is limited because of the complex and heterogeneous resistance mechanisms to osimertinib. In addition, approximately 50% of the patients did not have a clear resistance mechanism identified by molecular testing.⁶ NGS of ctDNA samples from patients in this study found that responses to the combination of amivantamab and lazertinib were observed among patients with and without identified *EGFR*- or *MET*-dependent resistance. These findings are consistent with the CHRYSALIS cohort E exploratory analysis, which found that NGS of ctDNA and tumor biopsy were not strong predictors of response in patients who were post-osimertinib and chemotherapy naive because of the complexity of the disease landscape. However, amivantamab plus lazertinib has efficacy, even in patients without a known resistance mechanism.

Among the patients with *EGFR*-mutated NSCLC with disease progression on or after osimertinib and platinum-based chemotherapy, the combination of amivantamab plus lazertinib demonstrated clinically significant and durable antitumor activity.

CRediT Authorship Contribution Statement

Benjamin Besse: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Koichi Goto: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Yongsheng Wang: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Se-Hoon Lee: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Melina E. Marmarelis: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Yuichiro Ohe: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Reyes Bernabe Caro: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Dong-Wan Kim: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Jong-Seok Lee: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Sophie Cousin: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Eiki Ichihara: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Yongsheng Li: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Luis Paz-Ares: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Akira Ono: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Rachel E. Sanborn: Data curation, Investigation, Validation, Writing - original draft, Writing - review & editing.

Naohiro Watanabe: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Maria Jose de Miguel: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Carole Helissey: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Catherine A. Shu: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Alexander I. Spira: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Pascale Tomasini: Data curation, Investigation, Writing - original draft, Writing - review & editing.

James Chih-Hsin Yang: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Yiping Zhang: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Enriqueta Felip: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Frank Griesinger: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Saiama N. Waqar: Data curation, Investigation, Supervision, Writing - original draft, Writing - review & editing.

Antonia Calles: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Joel W. Neal: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Christina S. Baik: Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing.

Pasi A. Jänne: Data curation, Investigation, Resources, Writing - original draft, Writing - review & editing.

S. Martin Shreeve: Writing - original draft, Writing - review & editing.

Joshua C. Curtin: Writing - original draft, Writing - review & editing.

Bharvin Patel: Writing - original draft, Writing - review & editing.

Michael Gormley: Writing - original draft, Writing - review & editing.

Xuesong Lyu: Formal analysis, Writing - original draft, Writing - review & editing.

Jun Chen: Formal analysis, Writing - original draft, Writing - review & editing.

Pei-Ling Chu: Formal analysis, Validation, Writing - original draft, Writing - review & editing.

Janine Mahoney: Writing - original draft, Writing - review & editing.

Leonardo Trani: Writing - original draft, Writing - review & editing.

Joshua M. Bauml: Writing - original draft, Writing - review & editing.

Meena Thayu: Writing - original draft, Writing - review & editing.

Roland E. Knoblauch: Writing - original draft, Writing - review & editing.

Byoung Chul Cho: Data curation, Investigation, Writing - original draft, Writing - review & editing.

Data Availability Statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at <https://www.janssen.com/clinical-trials/transparency>. As noted on this website, requests for access to study data can be submitted through the Yale University Open Data Access (YODA) Project website at <http://yoda.yale.edu>.

Disclosure

Dr. Besse reports receiving research funding (institution) from AstraZeneca, Pfizer, Eli Lilly, Onxeo, Bristol Myers Squibb, Inivata, AbbVie, Amgen, Blueprint Medicines, Celgene, GlaxoSmithKline, Sanofi, Takeda, Cristal Therapeutics, Daiichi Sankyo, Janssen, Ose Immunotherapeutics, BeiGene, Boehringer Ingelheim, Genentech/Roche, Tolero Pharmaceuticals, 4D Pharma, Aptitude Health, and Cergentis, outside of the current work. Dr. Goto reports serving in a consulting or advisory role for Takeda, Bayer US, Eli Lilly Japan, Amgen, Medpace Japan K.K., and Janssen; receiving honoraria from Guardant Health, Janssen, Daiichi Sankyo, Amgen, Eisai, AstraZeneca Japan, Chugai Pharmaceutical Co., Eli Lilly Japan, Boehringer Ingelheim, Takeda, Otsuka, Amoy Diagnostics, Bayer US, and Merck; and receiving research funding from Medical & Biological Laboratories, Kyowa Kirin, Kissei Pharmaceutical, Merck, Merus, Spectrum Pharmaceuticals, Shanghai HaiHe Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical Co., Boehringer Ingelheim, Ono Pharmaceutical, Sumitomo Dainippon Pharma, Takeda, Eisai, Eli Lilly Japan, Pfizer, Bristol Myers Squibb, Ignyta, Janssen, Loxo, Sysmex, Amgen, Thermo Fisher Scientific, Daiichi Sankyo, NEC Corporation, and Turning Point Therapeutics, outside of the current work. Dr. Lee reports serving in a consulting or advisory role for AstraZeneca, Bristol Myers Squibb, and

Roche; receiving travel, accommodations, or expenses from Novartis; receiving honoraria from AstraZeneca/MedImmune, Bristol Myers Squibb, and Merck; and receiving research funding from Merck, outside of the current work. Dr. Marmarelis reports serving in a consulting or advisory role for AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Ikena, Janssen, Novocure, Takeda, and Regeneron; holding stock in Janssen; and receiving research funding (institution) from AstraZeneca, Eli Lilly, Janssen, Takeda, and Genentech, outside of the current work. Dr. Ohe reports serving in a consulting or advisory role for AstraZeneca, Chugai Pharmaceutical Co., Eli Lilly Japan, Ono Pharmaceutical, Novartis, Kyorin, Takeda, Celltrion, and Amgen; receiving honoraria from AstraZeneca, Chugai Pharmaceutical Co., Eli Lilly Japan, Ono Pharmaceutical, Bristol Myers Squibb Japan, Boehringer Ingelheim, Bayer, Pfizer, Merck Sharp & Dohme, Taiho Pharmaceutical, Kyorin, Kyowa Kirin, Takeda, Celltrion, Amgen, Novartis, and Nippon Kayaku; and receiving research funding (institution) from AstraZeneca, Chugai Pharmaceutical Co., Eli Lilly Japan, Ono Pharmaceutical, Bristol Myers Squibb Japan, Kyorin, Pfizer, Taiho Pharmaceutical, Novartis, Takeda, Ignyta, Janssen, Loxo, and Kissei Pharmaceutical, outside of the current work. Dr. Kim reports receiving research funding (institution) from Alpha Biopharma, Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, Bristol Myers Squibb, Bridge BioTherapeutics, Chong Keun Dang, Daiichi Sankyo, GlaxoSmithKline, Hanmi, inno.N, Janssen, Merck, Merus, Mirati Therapeutics, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan; and receiving medical writing assistance from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chong Keun Dang, Daiichi Sankyo, GlaxoSmithKline, Pfizer, Merck Sharp & Dohme, Merck, Novartis, Roche, Takeda, and Yuhan, outside of the current work. Dr. Cousin reports receiving honoraria from AstraZeneca, Janssen, Takeda, Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Roche, and AbbVie, outside of the current work. Dr. Ichihara reports receiving research funding from Janssen, Bristol Myers Squibb, Takeda, Pfizer, and Ono Pharmaceutical; receiving honoraria from AstraZeneca, Janssen, Eli Lilly Japan K.K., Bristol Myers Squibb, Takeda, Novartis, Chugai Pharmaceutical Co., Pfizer, Ono Pharmaceutical Co., and Boehringer Ingelheim; and receiving equipment, materials, drugs, medical writing, gifts, or other services from Astellas Pharma, Janssen, and Eli Lilly Japan K.K., outside of the current work. Dr. Paz-Ares reports receiving grants or contracts from Merck Sharp & Dohme, AstraZeneca, Pfizer, and Bristol Myers Squibb; receiving consulting fees from Eli Lilly, Merck Sharp &

Dohme, Roche, PharmaMar, Merck, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Sanofi, Bayer, Bristol Myers Squibb, Mirati Therapeutics, GlaxoSmithKline, Janssen, and Takeda; receiving honoraria from AstraZeneca, Janssen, Merck, and Mirati Therapeutics; participating on a data safety monitoring board or advisory board for Altum Sequencing and Genomica; and serving in a leadership or fiduciary role for Alkermes, Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, IO Biotech, Janssen-Cilag, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Takeda, and Tesaro, outside of the current work. Dr. Ono reports receiving research funding (institution) from AstraZeneca K.K., Chugai Pharmaceutical Co., and Janssen Pharmaceutical K.K.; and receiving honoraria from AstraZeneca K.K., Chugai Pharmaceutical Co., Ono Pharmaceutical, and Indica Labs, outside of the current work. Dr. Sanborn reports serving in a consulting or advisory role for Amgen, AstraZeneca, BeiGene, GE Healthcare, Gilead, G1 Therapeutics, GlaxoSmithKline, EMD Serono, Daiichi Sankyo, Eli Lilly Oncology, Janssen Oncology, MacroGenics, Sanofi/Aventis, and Regeneron; receiving honoraria from Targeted Oncology, Illumina, and OncLive; and receiving research funding from AstraZeneca (self), Bristol Myers Squibb (institution), and Merck (self), outside of the current work. Dr. Watanabe reports receiving grants or contracts from Janssen Oncology, Ono Pharmaceutical, Pfizer, and Dizal Pharma, outside of the current work. Dr. Jose de Miguel reports receiving research funding from Merck Sharp & Dohme, PharmaMar, Roche, Novartis, AbbVie, Array BioPharma, Eisai, Faron, and Sanofi; and serving on a speakers bureau for Merck Sharp & Dohme, Janssen, and Roche, outside of the current work. Dr. Helissey reports receiving honoraria from Janssen, Astellas Pharma, Sanofi, AstraZeneca, Bayer, Ipsen, and Roche; and receiving travel, accommodations, or expenses from Janssen, outside of the current work. Dr. Shu reports serving as a consulting or advisory role for AstraZeneca, Genentech/Roche, Janssen, Mirati Therapeutics, Arcus Biosciences, Gilead, and Takeda; and receiving research funding (institution) from AstraZeneca, Genentech/Roche, and Janssen, outside of the current work. Dr. Spira reports serving in a leadership role at NEXT Oncology Virginia; holding stock in Eli Lilly; receiving honoraria from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Bayer; serving in a consulting or advisory role for Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Regeneron, Array BioPharma, AstraZeneca/MedImmune, Merck, Bristol Myers Squibb, and Blueprint Medicines; and receiving research funding

from LAM Therapeutics, Regeneron, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, NewLink Genetics, Incyte, AbbVie, Ignyta, Trovogene, Takeda, MacroGenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone Bio, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Alkermes, and Revolution Medicines, outside of the current work. Dr. Tomasini reports receiving honoraria from Takeda, Bristol Myers Squibb, Roche, Janssen, Amgen, and AstraZeneca; and receiving travel, accommodations, or expenses from Takeda, Bristol Myers Squibb, and AstraZeneca, outside of the current work. Dr. Yang reports serving in a consulting or advisory role for Boehringer Ingelheim, Novartis, AstraZeneca, Clovis Oncology, Eli Lilly, Merck Sharp & Dohme, Merck Serono, Celgene, Bayer, Pfizer, Ono Pharmaceutical, Bristol Myers Squibb, Yuhon, Hansoh, Blueprint Medicines, Daiichi Sankyo, G1 Therapeutics, AbbVie, Takeda, Amgen, and Incyte; receiving travel, accommodations, or expenses from Pfizer; receiving honoraria from Boehringer Ingelheim, Roche, Merck Sharp & Dohme, AstraZeneca, Novartis, Bristol Myers Squibb, Ono Pharmaceutical, Takeda, Eli Lilly, and Pfizer; and receiving research funding (institution) from Boehringer Ingelheim, Merck Serono, Janssen, GlaxoSmithKline, Amgen, Takeda, Daiichi Sankyo, AstraZeneca, Novartis, and Merck Sharp & Dohme, outside of the current work. Dr. Felipe reports serving in a consulting or advisory role for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, Takeda, and Peptomyc; receiving speakers bureau fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Medscape, Merck Sharp & Dohme, PeerVoice, Pfizer, Roche, Takeda, and CME Outfitters; having other relationships with Grifols; and receiving research funding (institution) from Merck and Merck KGaA, outside of the current work. Dr. Griesinger reports serving in a consulting or advisory role for AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Takeda, and Regeneron; receiving honoraria from AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Takeda, Regeneron, and Sanofi; receiving speakers bureau fees from AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Ipsen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre,

Roche, Sanofi, and Takeda; providing expert testimony for AbbVie, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Janssen, Merck, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda; and receiving grants or funding from AbbVie, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Takeda, and Regeneron, outside of the current work. Dr. Waqar reports serving in a consulting or advisory role for AstraZeneca, Daiichi Sankyo, Gilead, Pfizer, Boehringer Ingelheim, and Janssen; receiving grants or funding from SWOG–Clinical Trials Partnership and American Society of Hematology (institution); receiving honoraria from American Society for Clinical Oncology for Editorial Board Role for ASCO–SEP; and receiving research funding (institution) from Nuvalent, AbbVie, Genentech, Immunomedics, Roche, Astellas Pharma, Daiichi Sankyo, Cullinan Pearl, Verastem, GlaxoSmithKline, Janssen, Elevation Oncology, Loxo Oncology, Takeda, Ribon Therapeutics, AstraZeneca, and Advenchen, outside of the current work. Dr. Calles reports serving in a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Pfizer, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Takeda, Eli Lilly, Roche, Sanofi, and Bayer, outside of the current work. Dr. Neal reports serving in a consulting or advisory role for AstraZeneca, Genentech/Roche, Exelixis, Jounce Therapeutics, Takeda, Eli Lilly, Calithera Biosciences, Amgen, Iovance Biotherapeutics, Blueprint Medicines, Regeneron, Natera, Sanofi, D2G Oncology, Surface Oncology, Turning Point Therapeutics, Mirati Therapeutics, and Gilead; receiving honoraria from CME Matters and Clinical Care Options CME; and receiving research funding from Genentech/Roche, Exelixis, Takeda, Merck, Novartis, Boehringer Ingelheim, and Nektar Therapeutics, outside of the current work. Dr. Baik reports serving in a consulting or advisory role for Daiichi Sankyo, AstraZeneca, Pfizer, Janssen, Boehringer Ingelheim, Genentech, and Bristol Myers Squibb; and receiving research funding from Daiichi Sankyo, AbbVie, AstraZeneca, Pfizer, Eli Lilly, Turning Point Therapeutics, Janssen, Blueprint Medicines, Nuvalent, Black Diamond Therapeutics, Bristol Myers Squibb, Boehringer Ingelheim, and Ellipses, outside of the current work. Dr. Jänne reports serving in a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Genentech, Eli Lilly, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Biocartis, Novartis, Sanofi Oncology, Transcenta, Mirati Therapeutics, Nuvalent, Bayer, Allorion Therapeutics, Accutar Biotech, Monte Rosa, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotechnology, Duality Biologics, Blueprint Medicines, and Dizal

Pharma; receiving travel, accommodations, or expenses from AstraZeneca and Voronoi; receiving research funding from AstraZeneca, Eli Lilly, Revolution Medicines, Takeda, and Transcenta; and holding patents, royalties, or other intellectual property at Labcorp, outside of the current work. Dr. Shreeve, Dr. Curtin, Dr. Patel, Dr. Gormley, Dr. Lyu, Dr. Chen, Dr. Chu, Janine Mahoney, Dr. Trani, Dr. Bauml, Dr. Thayu, and Dr. Knoblauch report being employed by Janssen Research & Development (or were employed at the time of the study) and may be holding stock in Johnson & Johnson, outside of the current work. Dr. Cho reports serving in a consulting or advisory role for AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, BridgeBio, Bristol Myers Squibb, Cyrus Therapeutics, Guardant Health, Janssen, J Ints Bio, Kanaph Therapeutics, Eli Lilly, Medpacto, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, Takeda, and Yuhan; serving in a leadership role for Interpark Bio and J Ints Bio; holding patents, royalties, or other intellectual property at Champions Oncology; having other relationships with DAAN Biotherapeutics; holding stock in Theravance, Gencurix, BridgeBio, Kanaph Therapeutics, Cyrus Therapeutics, and Interpark Bio; and receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Biotechnology Research Institute, Dong-A ST, Champions Oncology, Janssen, and Yuhan, outside of the current work. The remaining authors declare no conflict of interest.

Acknowledgments

The authors thank all patients who participated in this study and their families and caregivers. The authors also thank the physicians and nurses who cared for the patients and the staff at the clinical sites.

This study (NCT04077463) was funded by Janssen Research and Development, LLC, a Johnson & Johnson Company. Medical writing and editorial support were provided by David Le, PharmD, of Lumanity Communications Inc., and funded by Johnson & Johnson.

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.2024.12.029>.

References

1. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene*. 2009;28:S24-S31.
2. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2024;22:249-274.
3. ESMO. Clinical practice guidelines: metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. <https://www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf>. Accessed October 17, 2022.
4. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725-737.
5. Le X, Puri S, Negrao MV, et al. Landscape of EGFR-dependent and -independent resistance mechanisms to osimertinib and continuation therapy beyond progression in EGFR-mutant NSCLC. *Clin Cancer Res*. 2018;24:6195-6203.
6. Bertoli E, De Carlo E, Del Conte A, et al. Acquired resistance to osimertinib in EGFR-mutated non-small cell lung cancer: how do we overcome it? *Int J Mol Sci*. 2022;23:6936.
7. Long Y, Xiong Q, Song Q, et al. Immunotherapy plus chemotherapy showed superior clinical benefit to chemotherapy alone in advanced NSCLC patients after progression on osimertinib. *Thorac Cancer*. 2022;13:394-403.
8. Di Noia V, D'Aveni A, D'Argento E, et al. Treating disease progression with osimertinib in EGFR-mutated non-small-cell lung cancer: novel targeted agents and combination strategies. *ESMO Open*. 2021;6:100280.
9. Borghaei H, Gettinger S, Vokes EE, et al. Five-year outcomes from the randomized, phase III trials CheckMate 017 and 057: nivolumab versus docetaxel in previously treated non-small-cell lung cancer. *J Clin Oncol*. 2021;39:723-733.
10. Larkins E, Scepura B, Blumenthal GM, et al. U.S. Food and Drug Administration approval summary: ramucirumab for the treatment of metastatic non-small cell lung cancer following disease progression on or after platinum-based chemotherapy. *Oncologist*. 2015;20:1320-1325.
11. Girard N, Besse B, Bernabé Caro R, et al. EP08.02-016 Frontline and post-osimertinib therapy for EGFR-mutant advanced NSCLC: treatment patterns, outcomes, healthcare use and costs. *J Thorac Oncol*. 2022;17:S404-S405.
12. Sabari J, Pisano S, Gemmler K, et al. EP08.02-173 treatment patterns and outcomes among patients with EGFR-mutant advanced NSCLC in the frontline and post-osimertinib settings. *J Thorac Oncol*. 2022;17:S488-S489.
13. Moores SL, Chiu ML, Bushey BS, et al. A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. *Cancer Res*. 2016;76:3942-3953.
14. Vijayaraghavan S, Lipfert L, Chevalier K, et al. Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis. *Mol Cancer Ther*. 2020;19:2044-2056.

15. Cho BC, Simi A, Sabari J, Vijayaraghavan S, Moores S, Spira A. Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer*. 2023;24:89-97.
16. Yun J, Lee SH, Kim SY, et al. Antitumor activity of amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in diverse models of EGFR exon 20 insertion-driven NSCLC. *Cancer Discov*. 2020;10:1194-1209.
17. Zhou C, Tang KJ, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR Exon 20 insertions. *N Engl J Med*. 2023;389:2039-2051.
18. Passaro A, Wang J, Wang Y, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol*. 2024;35:77-90.
19. Rybrevant. RYBREVANT (amivantamab-vmjw) Injection, for Intravenous Use [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc; 2024.
20. Rybrevant. Rybrevant 350 mg Concentrate for Solution for Infusion, [Product Information]. Leiden, The Netherlands: Janssen Biologics B.V; 2024.
21. Ahn MJ, Han JY, Lee KH, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1-2 study. *Lancet Oncol*. 2019;20:1681-1690.
22. Cho BC, Han JY, Kim SW, et al. A phase 1/2 study of lazertinib 240 mg in patients with advanced EGFR T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors. *J Thorac Oncol*. 2022;17:558-567.
23. Cho BC, Ahn MJ, Kang JH, et al. Lazertinib versus gefitinib as first-line treatment in patients with EGFR-mutated advanced non-small-cell lung cancer: results from LASER301. *J Clin Oncol*. 2023;41:4208-4217.
24. Bauml J, Cho BC, Park K, et al. Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response. *J Clin Oncol*. 2021;39(suppl 15):9006.
25. Leighl NB, Shu CA, Minchom A, et al. 1192MO Amivantamab monotherapy and in combination with lazertinib in post-osimertinib EGFR-mutant NSCLC: analysis from the CHRYSALIS study. *Ann Oncol*. 2021;32:S951-S952.
26. Cho BC, Lu S, Felip E, et al. Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med*. 2024;391:1486-1498.
27. Sanborn RE, Waqar SN, Cho BC, et al. Abstract 2166: Analysis of ctDNA next generation sequencing (NGS) for predicting response to amivantamab and lazertinib among patients with EGFR-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy (CHRYSALIS-2 Cohort A). *Cancer Res*. 2023;83(suppl 7):2166.
28. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7:78985-78993.
29. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41-50.
30. Yun J, Hong MH, Kim SY, et al. YH25448, an irreversible EGFR-TKI with potent intracranial activity in EGFR mutant non-small cell lung cancer. *Clin Cancer Res*. 2019;25:2575-2587.
31. Heppner DE, Wittlinger F, Beyett TS, et al. Structural basis for inhibition of mutant EGFR with lazertinib (YH25448). *ACS Med Chem Lett*. 2022;13:1856-1863.
32. Yu HA, Goto Y, Hayashi H, et al. HERTHENA-Lung01, a Phase II trial of patritumab deruxtecan (HER3-DXd) in epidermal growth factor receptor-mutated non-small-cell lung cancer after epidermal growth factor receptor tyrosine kinase inhibitor therapy and platinum-based chemotherapy. *J Clin Oncol*. 2023;41:5363-5375.
33. Ahn MJ, Lisberg A, Paz-Ares L, et al. LBA12 Datopitamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): results of the randomized phase III study TROPION-Lung01. *Ann Oncol*. 2023;34:S1305-S1306.
34. Leighl NB, Akamatsu H, Lim SM, et al. Subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in refractory epidermal growth factor receptor-mutated non-small cell lung cancer: primary results from the phase III PALOMA-3 study. *J Clin Oncol*. 2024;42:3593-3605.
35. Lopes G, Spira AI, Han JY, et al. MA12.08 Preventing infusion-related reactions with intravenous amivantamab: primary results from SKIPPirr, a phase 2 study. *J Clin Oncol*. 2024;19:S104-S105.
36. Cho BC, Girard N, Sauder MB, et al. P3.12D.04 Enhanced vs standard dermatologic management with amivantamab-lazertinib in advanced NSCLC: phase 2 COCOON study. *J Thorac Oncol*. 2024;19:S347.