ORIGINAL ARTICLE

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

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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 $\geq$ 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.

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 $\geq$ 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 alterative 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.
[a]Patients could be counted in more than one category.
[b]Included patients who had a history of brain or CNS metastases or had brain or CNS lesions as target or non-target lesions at baseline.
[c]Study 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 ≥ 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 (≥ 10%) by Preferred Term, n (%)	**N = 162 All Grades**	**Grade ≥ 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

[a]Excludes infusion-related reactions.
[b]Includes 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.
[c]The 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)

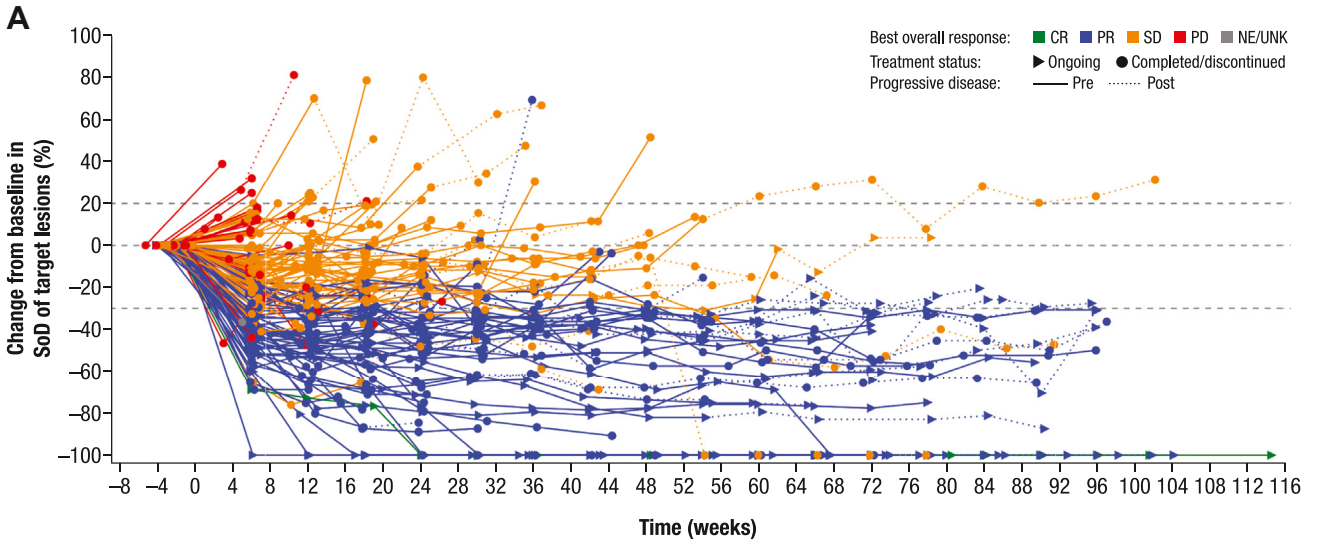
[a]Percentage of patients with confirmed response or durable stable disease (duration of ≥ 11 wk).
BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; INV, investigator; ORR, overall response rate.

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. 1*A* 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 prespecified subpopulations (Fig. 1*B*). ORRs in the previous therapy subgroup, as assessed by BICR, were relatively similar regardless of the previous treatment category (Fig. 1*B* 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).



B

Parameter	ORR (%)	No./Total No.	ORR (95% CI), %
Overall		56/162	34.6 (27.3–42.4)
Age, years			
<65		32/97	33.0 (23.8–43.3)
≥65		24/65	36.9 (25.3–49.8)
Sex			
Male		13/57	22.8 (12.7–35.8)
Female		43/105	41.0 (31.5–51.0)
Race			
Asian		34/100	34.0 (24.8–44.2)
Non-Asian		22/62	35.5 (23.7–48.7)
Baseline ECOG PS score			
0		18/49	36.7 (23.4–51.7)
≥1		38/113	33.6 (25.0–43.1)
History of smoking			
Yes		13/49	26.5 (14.9–41.1)
No		43/111	38.7 (29.6–48.5)
Prior line of therapy			
First-line osimertinib→platinum-based chemotherapy		9/39	23.1 (11.1–39.3)
1st- or 2nd-gen TKI→osimertinib→platinum-based chemotherapy		25/67	37.3 (25.8–50.0)
Heavily pre-treated or out of sequence		22/56	39.3 (26.5–53.2)
***EGFR* mutation**			
Ex19del		38/112	33.9 (25.3–43.5)
L858R		18/50	36.0 (22.9–50.8)

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

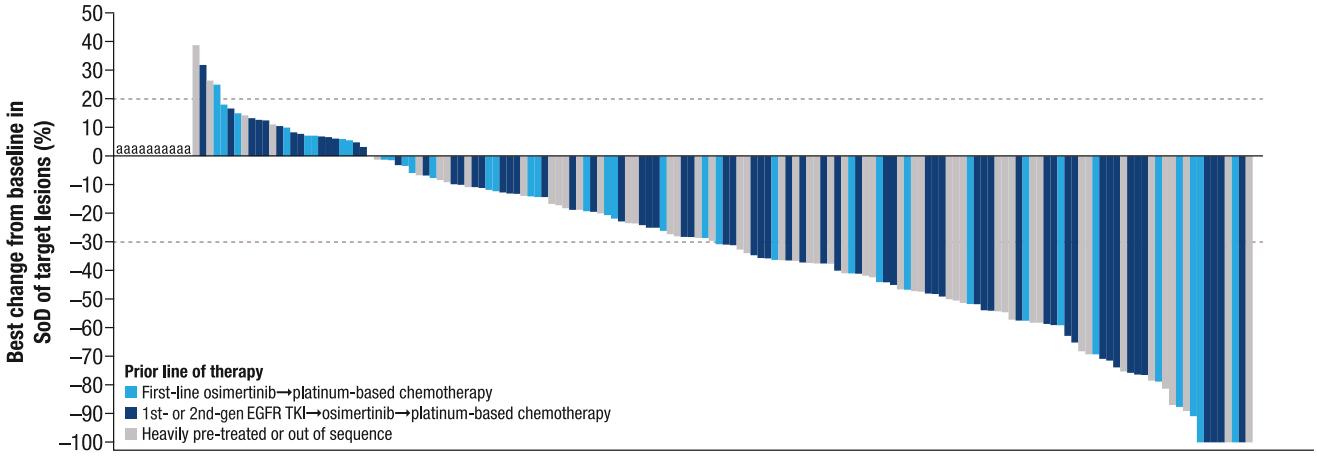


Figure 2. Best percent change from baseline in SoD of target lesions by previous therapy group as assessed by BICR. [a]Efficacy-evaluable patients who did not have any assessable target lesion measurements in any post-baseline disease assessment. BICR, blinded independent central review; SoD, sum of 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]
EGFR or *MET* dependent[b]	30	8	27%
EGFR or *MET* independent	33	10	30%
Unknown	52	22	42%
Patients with detectable ctDNA	115	40	35%
Patients without detectable ctDNA	47	16	34%

[a]Responses were assessed by a blinded independent central review according to the Response Evaluation Criteria in Solid Tumors version 1.1.
[b]Includes 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.

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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.

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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.

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