Amivantamab Plus Lazertinib in Atypical *EGFR*-Mutated Advanced Non–Small Cell Lung Cancer: Results From CHRYSALIS-2

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ABSTRACT

PURPOSE For patients with advanced non–small cell lung cancer (NSCLC) harboring atypical epidermal growth factor receptor (*EGFR*) mutations (eg, S768I, L861Q, G719X), efficacy of current treatment options is limited.

PATIENTS AND METHODS CHRYSALIS-2 Cohort C enrolled participants with NSCLC harboring atypical *EGFR* mutations (G719X, S768I, L861Q, etc) and ≤2 previous lines of therapy. Participants were treatment-naïve or previously received first- or second-generation EGFR tyrosine kinase inhibitors. Coexisting exon 20 insertions, exon 19 deletions, or exon 21 L858R mutations were exclusionary. Participants received 1,050 mg (1,400 mg if ≥80 kg) intravenous amivantamab once weekly for the first 4 weeks and then once every 2 weeks plus 240 mg oral lazertinib once daily. The primary end point was investigator-assessed objective response rate (ORR).

RESULTS As of January 12, 2024, 105 participants received amivantamab-lazertinib. Most common atypical mutations were G719X (56%), L861X (26%), and S768I (23%), including single and compound mutations. In the overall population (median follow-up: 16.1 months), the ORR was 52% (95% CI, 42 to 62). The median duration of response (mDoR) was 14.1 months (95% CI, 9.5 to 26.2). The median progression-free survival (mPFS) was 11.1 months (95% CI, 7.8 to 17.8); median overall survival (mOS) was not estimable (NE; 95% CI, 22.8 to NE). Adverse events were consistent with previous studies and primarily grade 1 and 2. Among treatment-naïve participants, the ORR was 57% (95% CI, 42 to 71). The mPFS was 19.5 months (95% CI, 11.2 to NE), the mDoR was 20.7 months (95% CI, 9.9 to NE), and mOS was NE (95% CI, 26.3 to NE). Solitary or compound *EGFR* mutations had no major impact on ORR. The ORR in participants with P-loop and αC-helix compressing, classical-like, and T790M-like mutations was 45% (n = 38), 64% (n = 14), and 67% (n = 3), respectively.

CONCLUSION In participants with atypical *EGFR*-mutated advanced NSCLC, amivantamab-lazertinib demonstrated clinically meaningful antitumor activity with no new safety signals.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

Non–small cell lung cancer (NSCLC) is a complex and heterogeneous disease that accounts for approximately 80%-85% of all lung cancer cases.[1,2] Activating mutations in the epidermal growth factor receptor (*EGFR*) gene are commonly observed in NSCLC, with exon 19 deletions (Ex19del) and exon 21 L858R (L858R) substitutions being the most common (85%-90%).[2-4] Exon 20 insertions (Ex20ins) and atypical *EGFR* mutations each account for approximately 5%-10% of all *EGFR* mutations in NSCLC.[3-8] The most common atypical mutations are G719X in exon 18, S768I in

CONTEXT

Key Objective

Does amivantamab plus lazertinib (amivantamab-lazertinib) exert clinically meaningful and durable antitumor activity in participants with advanced non–small cell lung cancer (NSCLC) harboring atypical epidermal growth factor receptor (*EGFR*) mutations?

Knowledge Generated

Amivantamab-lazertinib demonstrated durable antitumor activity in participants with atypical *EGFR*-mutated advanced NSCLC (objective response rate [ORR], 52%), including in those who were treatment-naïve (ORR, 57%) and those with previous treatment (ORR, 48%). No new safety signals were identified. At a median follow-up of 17.3 months, participants who received first-line amivantamab-lazertinib had a median progression-free survival of 19.5 months and a median response duration of 20.7 months, and median overall survival was not estimable.

Relevance *(T.E. Stinchcombe)*

This combination is another treatment option for patients with NSCLC harboring these rare *EGFR* mutations.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

exon 20, and L861Q in exon 21, but can include others.[9,10] These can present in patients as single or compound mutations.[11]

Patients with atypical *EGFR*-mutated advanced NSCLC have significantly worse outcomes compared with those with common *EGFR* mutations when receiving EGFR-targeted therapies.[12] Consequently, overall survival (OS) is substantially shorter among patients whose tumors harbor atypical versus common mutations.[12] Patients with NSCLC harboring compound atypical *EGFR* mutations exhibit even poorer survival compared with those with single atypical mutations.[13,14]

In a post hoc analysis of prospectively collected data from three trials including 38 patients with tumors harboring atypical *EGFR* mutations, the second-generation EGFR-tyrosine kinase inhibitor (TKI) afatinib demonstrated a median progression-free survival (PFS) of 10.7 months,[15] resulting in afatinib's US Food and Drug Administration (FDA) approval for first-line treatment of patients with nonresistant *EGFR* mutations (S768I, L861Q, and G719X) other than Ex19del or exon 21 L858R substitutions and European Medicines Agency (EMA) approval for EGFR-TKI-naïve patients with advanced/metastatic NSCLC harboring uncommon *EGFR* mutations.[16,17] However, this study included participants with tumors harboring atypical mutations with or without compound common *EGFR* mutations (Ex19del or L858R substitutions), which could influence the benefit observed. Patients with tumors harboring atypical mutations alongside common mutations experience more favorable outcomes with EGFR-targeted therapies compared with those with only atypical compound mutations.[11,18-21] While not currently indicated for this population, the third-generation EGFR-TKI osimertinib is used globally for first-line treatment of patients with atypical *EGFR*-mutated advanced NSCLC.[22-26]

Amivantamab is an EGFR-MET bispecific antibody that exerts antitumor activity through multiple mechanisms of action, including inhibition of ligand binding, endocytosis and degradation of receptors, and immune cell–directing activity.[27-30] It is approved for use in several indications for patients with both common mutations and Ex20ins, alone or in combination with other agents. Lazertinib, a highly selective, CNS-penetrant, third-generation EGFR-TKI, has demonstrated activity in patients with atypical *EGFR*-mutated advanced NSCLC.[31,32] In the LASER301 study, among patients harboring common *EGFR* mutations, alone or in combination with other *EGFR* mutations, lazertinib markedly improved efficacy over gefitinib for first-line treatment of *EGFR*-mutated advanced NSCLC and is approved as a monotherapy in the Republic of Korea.[33,34] Combining these two agents results in synergistic *EGFR* inhibition, with amivantamab targeting the extracellular domains of *EGFR* and MET, thereby being unaffected by intracellular resistance mechanisms, whereas lazertinib binds to the EGFR receptor intracellularly.[30,35] Amivantamab-lazertinib has shown potent clinical activity across a wide range of *EGFR* alterations.[36-39] In the phase III MARIPOSA trial, amivantamab-lazertinib improved the median PFS by 7.1 months versus osimertinib in patients with treatment-naïve, common *EGFR*-mutated advanced NSCLC (hazard ratio [HR], 0.70 [95% CI, 0.58 to 0.85]; $P < .001$). In addition, in the protocol-specified final OS analysis of MARIPOSA (median follow-up of 37.8 months), amivantamab-lazertinib showed a statistically significant and clinically meaningful improvement in OS versus osimertinib (HR, 0.75; $P < .005$), with the median OS benefit projected to exceed 1 year.[40] Amivantamab-lazertinib is

FDA-approved as first-line treatment for patients with advanced NSCLC with *EGFR* Ex19del or L858R substitutions.[41]

In Cohort C of the CHRYSALIS-2 study (ClinicalTrials.gov Identifier: NCT04077463), we prospectively evaluated the efficacy and safety of amivantamab-lazertinib in participants with advanced NSCLC harboring atypical *EGFR* mutations, excluding those with compound common mutations.

PATIENTS AND METHODS

Participants

Eligible participants for CHRYSALIS-2 Cohort C were 18 years and older and had advanced or metastatic NSCLC. Participants with tumors harboring any atypical activating *EGFR* mutations, including but not limited to S768I, L861Q, and G719X, were eligible. Those with solitary Ex20ins or coexisting Ex20ins or Ex19del/L858R *EGFR* mutations were excluded. Participants had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1. Participants were treatment-naïve or had received ≤2 previous lines of treatment with chemotherapy and/or first- or second-generation EGFR-TKIs as the most recent line of therapy; the receipt of third-generation EGFR-TKIs was exclusionary. Participants with stable, treated CNS metastases were eligible.

Study Design and Treatment

CHRYSALIS-2 is an open-label, 2-part, phase I/Ib, multicenter study of lazertinib, alone or in combination with amivantamab, in participants with advanced *EGFR*-mutated NSCLC (Data Supplement, Fig S1, online only). This analysis presents the results from Cohort C, which evaluated amivantamab-lazertinib in participants with tumors harboring atypical *EGFR* mutations. Subgroup analyses based on the line of treatment (first-line *v* later-line treatment with amivantamab-lazertinib) were performed. Participants in Cohort C received amivantamab-lazertinib in 28-day cycles until disease progression, unacceptable toxicity, noncompliance, withdrawal of consent, or discontinuation at the investigator discretion. Lazertinib was dosed at 240 mg orally once daily. Amivantamab was administered intravenously once every week during Cycle (C) 1 at a dose of 1,050 mg (1,400 mg for ≥80 kg weight), with the first dose split between 2 days (350 mg once daily on C1 Day [D] 1, and the remainder on C1D2) and then every 2 weeks in subsequent cycles.

End Points and Assessments

The primary end point was objective response rate (ORR) per RECIST v1.1, as determined by the investigator. Secondary end points included duration of response (DoR), clinical benefit rate (CBR; defined as a complete response [CR], partial response [PR], or stable disease [SD] for ≥11 weeks), PFS, OS, time to treatment discontinuation, and adverse events (AEs). Biomarkers were analyzed as exploratory end points.

Disease was assessed at baseline and every 6 weeks (±1 week) via contrast-enhanced computed tomography (CT; noncontrast CT was acceptable if contrast administration was contraindicated), magnetic resonance imaging, and other imaging/examination scans per RECIST v1.1.

AEs were recorded from consent until 30 days after the last treatment dose or start of subsequent anticancer therapy and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v5.0. Testing for atypical mutations, including solitary versus compound *EGFR* analyses, was based on local testing. Blood samples were collected at baseline for circulating tumor DNA (ctDNA) analyses and tested centrally. Next-generation sequencing of plasma ctDNA was performed and analyzed using Guardant360 (Guardant Health, Redwood City, CA), excluding participants from China.

Trial Oversight

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), and applicable regulatory and country-/territory-specific requirements. The protocol was approved by the local institutional review boards and independent ethics committees of the participating centers. Participants provided written informed consent.

Statistical Analysis

The sample size for Cohort C was based on the null hypothesis that the ORR is ≤50% and the alternative hypothesis that the ORR is ≥68%. With a one-sided alpha of 2.5% and a power of 90%, 92 response-evaluable participants were needed for expansion Cohort C. Assuming a nonevaluable rate of 15%, approximately 108 participants were planned to be enrolled in Cohort C.

Data were summarized using descriptive statistics. Time-to-event end points were summarized using Kaplan-Meier estimates. The medians and 95% CIs were provided. No data imputation was applied for missing safety and efficacy evaluations. All data used for this interim analysis were reported before January 12, 2024.

RESULTS

Participants

As of January 12, 2024, 105 participants received amivantamab-lazertinib in Cohort C. Among the 105 participants, 49 participants were treatment-naïve, whereas

TABLE 1. Demographic and Clinical Characteristics of Participants at Baseline

Characteristic	Overall Population (N = 105)	Treatment-Naïve Subgroup (n = 49)	Previous Treatment Subgroup (n = 56)
Age, years, median (range)	64 (30-85)	60 (30-80)	67 (32-85)
Male, No. (%)	53 (50)	27 (55)	26 (46)
Race, No. (%)			
Asian	71 (68)	28 (57)	43 (77)
White	31 (30)	19 (39)	12 (21)
Black or African American	1 (1)	1 (2)	0
Not reported	2 (2)	1 (2)	1 (2)
Brain metastases at baseline, No. (%)	33 (31)[a]	13 (27)	20 (36)
Previous therapies in the metastatic setting, No. (%)			
Treatment-naïve	49 (47)	49 (100)	0
Previous afatinib	34 (32)	0	34 (61)
Previous first-/second-generation EGFR-TKI (other than afatinib)[b]	9 (9)	0	9 (16)
Previous platinum chemotherapy	7 (7)	0	7 (13)
Previous afatinib + previous platinum chemotherapy	6 (6)	0	6 (11)
ECOG PS, No. (%)			
0	33 (31)	18 (37)	15 (27)
1	72 (69)	31 (63)	41 (73)
Type of *EGFR* mutation,[c] No. (%)			
Exon 18 G719X[d]	59 (56)	27 (55)	32 (57)
Exon 21 L861X[e]	27 (26)	12 (24)	15 (27)
Exon 20 S768X[f]	24 (23)	13 (27)	11 (20)
Exon 18 E709K	2 (2)	2 (4)	0
Exon 18 E709A	2 (2)	1 (2)	1 (2)
L833V	2 (2)	2 (4)	0
R776C	2 (2)	2 (4)	0
R776H	1 (1)	1 (2)	0
R831H	1 (1)	1 (2)	0
V744M	1 (1)	1 (2)	0
V769L	1 (1)	0	1 (2)
V774M	1 (1)	0	1 (2)
Other	10 (10)	5 (10)	5 (9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

[a]Brain metastases were confirmed by imaging in 37 (35%) participants.

[b]First-/second-generation EGFR-TKIs, other than afatinib, included gefitinib, dacomitinib, erlotinib, and icotinib.

[c]Participants may be counted in ≥1 category.

[d]G719X included G719A, G719S, and G719C. Compound mutations were observed in 24 participants in the overall population, with 14 participants in the treatment-naïve subgroup and 10 participants in the previous treatment subgroup.

[e]L861X included L861Q, L861R, and L861G. Compound mutations were observed in seven participants in the overall population, with four participants in the treatment-naïve subgroup and three participants in the previous treatment subgroup.

[f]S768X included S768I and S768L. Compound mutations were observed in 18 participants in the overall population, with 11 participants in the treatment-naïve subgroup and seven participants in the previous treatment subgroup.

56 participants had received a previous treatment. The most common treatments among those who received previous therapy were EGFR-TKIs (88%).

Baseline demographic and disease characteristics are shown in Table 1. The median age was 64 years (range, 30-85); 50% was male, and 68% was Asian. The most common types of atypical *EGFR* mutations, including both single and compound mutations, were G719X (56%), L861X (26%), and S768X (23%); 29 (28%) participants had compound mutations. A total of 37 (35%) participants had brain/CNS metastasis confirmed by imaging at baseline.

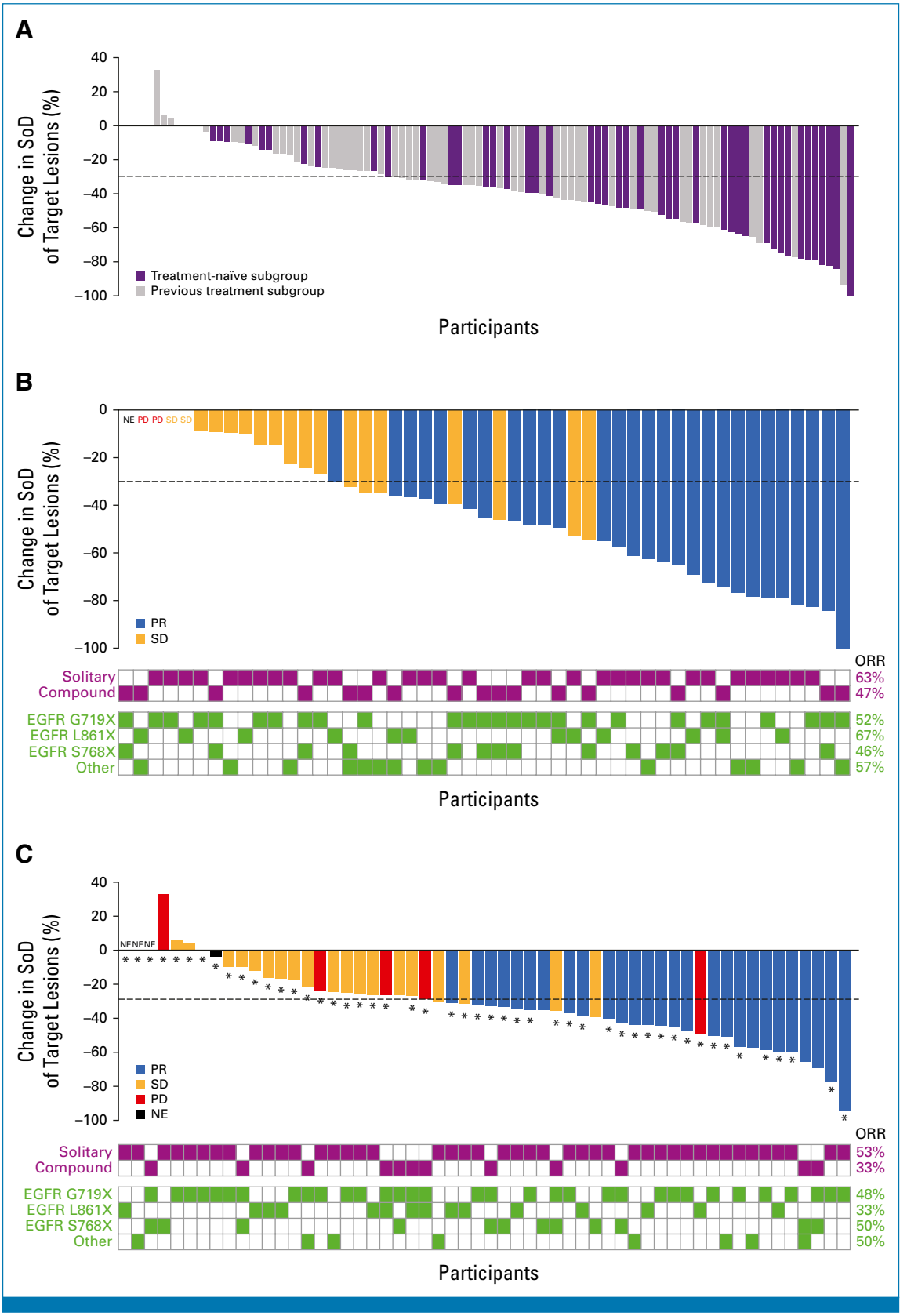

FIG 1. Best percentage change from baseline in target lesions and ORR by mutation type. Best response in the (A) overall population, (B) treatment-naïve subgroup, and (C) previous treatment subgroup. EGFR, epidermal growth factor receptor; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

TABLE 2. Summary of Efficacy Outcomes in Cohort C

Investigator-Assessed Response	Overall Population (N = 105)	Treatment-Naïve Subgroup (n = 49)	Previous Treatment Subgroup (n = 56)
Follow-up, months, median (range)	16.1 (0.1-31.5)	17.3 (0.1-31.5)	15.4 (0.3-30.8)
ORR, % (95% CI)	52 (42 to 62)	57 (42 to 71)	48 (35 to 62)
Best response, No. (%)			
CR	0	0	0
PR	55 (52)	28 (57)	27 (48)
SD	37 (35)	18 (37)	19 (34)
PD	8 (8)	2 (4)	6 (11)
NE/unknown	5 (5)	1 (2)	4 (7)
Median DoR, months (95% CI)	14.1 (9.5 to 26.2)	20.7 (9.9 to NE)	11.0 (4.5 to NE)
DoR ≥6 months, No. (%)[a]	38 (69)	21 (75)	17 (63)
CBR, % (95% CI)[b]	79 (70 to 86)	84 (70 to 93)	75 (62 to 86)
Median PFS, months (95% CI)	11.1 (7.8 to 17.8)	19.5 (11.2 to NE)	7.8 (5.4 to 11.1)
Median OS, months (95% CI)	NE (22.8 to NE)	NE (26.3 to NE)	22.8 (16.9 to NE)
24-month rate, % (95% CI)	58 (43 to 70)	77 (56 to 89)	34 (12 to 58)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]Among responders.
[b]CBR is defined as the percentage of participants achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

Efficacy

Overall Population

At a median follow-up of 16.1 months (range, 0.1-31.5), the median duration of treatment in the overall population was 11.1 months (range, 0.03-31.5). The investigator-assessed ORR was 52% (95% CI, 42 to 62). All responses observed were PRs (52%; Fig 1 and Table 2). The median DoR was 14.1 months (95% CI, 9.5 to 26.2), and the CBR was 79% (95% CI, 70 to 86). The median PFS was 11.1 months (95% CI, 7.8 to 17.8; Fig 2A), and the median OS was not estimable (NE; 95% CI, 22.8 to NE; Fig 2B).

Treatment-Naïve Subgroup

At a median follow-up of 17.3 months (range, 0.1-31.5), the median duration of treatment with first-line amivantamab-lazertinib was 12.7 months (range, 0.03-31.5). The investigator-assessed ORR was 57% (95% CI, 42 to 71; Fig 1 and Table 2). The median DoR was 20.7 months (95% CI, 9.9 to NE), and the CBR was 84% (95% CI, 70 to 93). The median PFS was 19.5 months (95% CI, 11.2 to NE), and median OS was NE (95% CI, 26.3 to NE), with 77% of participants still alive at 24 months. To provide context for this single-arm trial, a trial-matched real-world analysis was conducted on existing therapies from the Flatiron Health NSCLC database, which are described in the Data Supplement.

Previous Treatment Subgroup

At a median follow-up of 15.4 months (range, 0.3-30.8), the median duration of treatment with later-line amivantamab-lazertinib was 8.9 months (range, 0.2-29.9). The investigator-assessed ORR was 48% (95% CI, 35 to 62). PR was observed in 27 (48%) participants, SD in 19 (34%) participants, and PD in six (11%) participants (Fig 1 and Table 2). The median DoR was 11.0 months (95% CI, 4.5 to NE), and the CBR was 75% (95% CI, 62 to 86). The median PFS was 7.8 months (95% CI, 5.4 to 11.1), and the median OS was 22.8 months (95% CI, 16.9 to NE).

Safety

In the overall population, the safety profile of amivantamab-lazertinib was consistent with that previously reported (Table 3).[37-39] Individual treatment-emergent AEs (TEAEs; by preferred term) most commonly reported by participants were rash (67%), paronychia (67%), hypoalbuminemia (59%), and infusion-related reactions (IRRs; 56%) and were mostly grade 1 and 2. The majority (95%) of IRRs occurred during the first infusion and were grade 1 and 2. Overall, grade ≥3 TEAEs were reported in 73 (70%) participants. Fifty (48%) participants experienced grade ≥3 treatment-related AEs. The most frequent grade ≥3 treatment-related AEs reported by participants were rash (13%) and hypoalbuminemia (8%). Serious TEAEs were reported for 53 (50%) participants, 22 (21%) of which were considered related to treatment. Dose interruptions, reductions, and discontinuations of any study agent because of TEAEs were seen in 73 (70%), 52 (50%), and 29 (28%) participants, respectively. Discontinuation of all study agents because of treatment-related AEs occurred in seven (7%) participants. Death occurred in 12 (11%) participants, one (1%) of which was considered related to treatment.

Venous thromboembolism (VTE) was reported in 31 (30%) participants; most events occurred in the first 4 months of

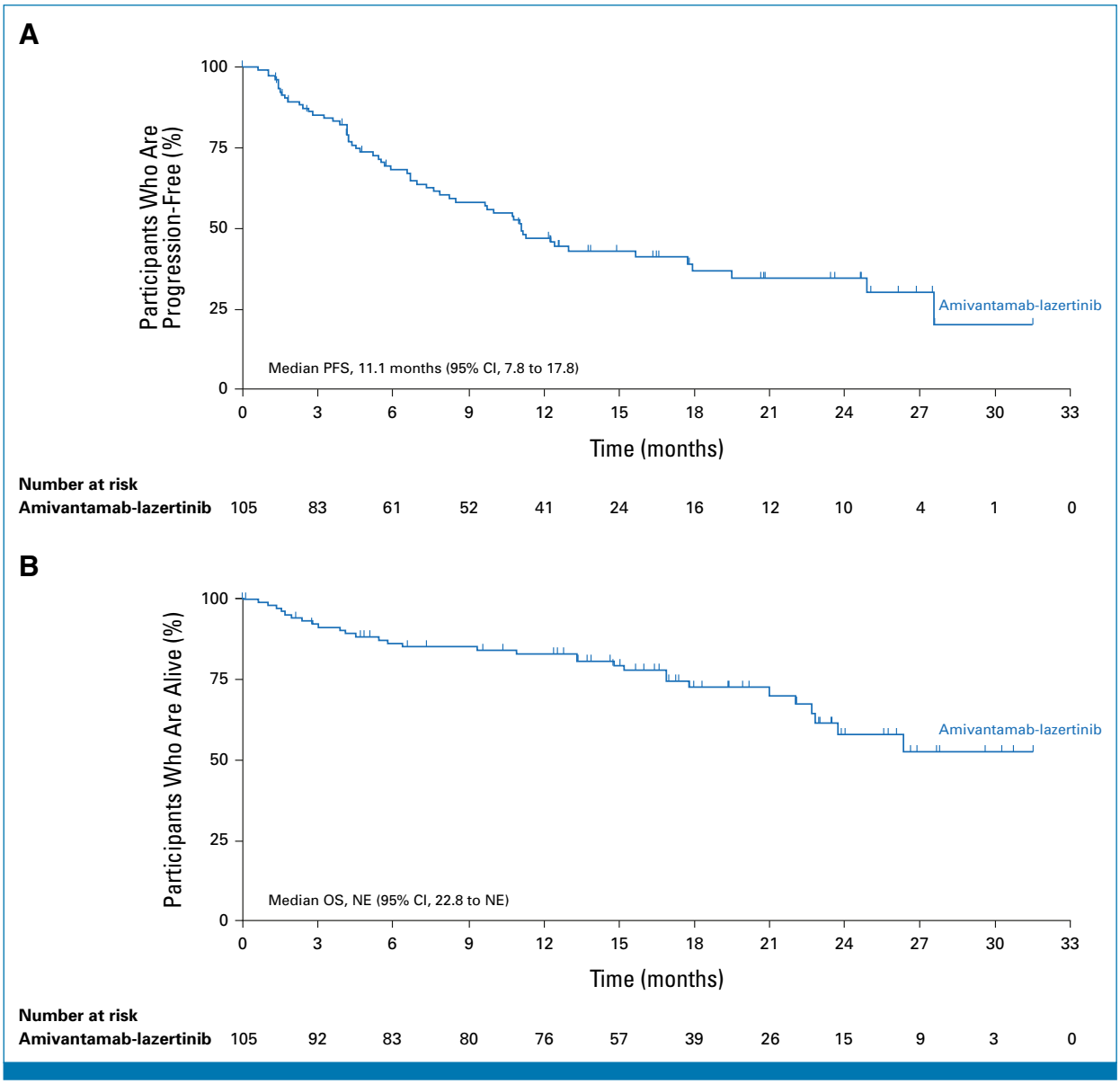

FIG 2. PFS and OS in the overall population. Kaplan-Meier curves for (A) PFS and (b) OS for participants treated with amivantamab-lazertinib in the overall population. NE, not estimable; OS, overall survival; PFS, progression-free survival.

treatment (71% [22 of 31]). Grade 3 VTE was observed in 10 (10%) participants; no grade 4 and 5 events occurred. At baseline, 16% (17 of 105) of all participants received anticoagulation for prophylaxis or based on the medical history of VTE. Most participants (94% [29 of 31]) were not on anticoagulation at the time of first VTE.

Exploratory Analyses

Biomarker Analysis

Among participants treated with first-line amivantamab-lazertinib and among those treated with later-line amivantamab-lazertinib, most participants had solitary *EGFR* mutations. Among participants treated with first-line amivantamab-lazertinib, the confirmed ORR was 63% (95% CI, 44 to 79) for those with solitary mutations and 47% (95% CI, 23 to 72) for those with compound mutations (nominal $P = .299$). The corresponding values among those treated with later-line amivantamab-lazertinib were 52% (95% CI, 37 to 67.5) and 33% (95% CI, 10 to 65), respectively (nominal $P = .244$). The presence of solitary or compound *EGFR* mutations had no major impact on ORR, as indicated by the 95% CIs (Fig 1).

Of the 73 participants who had analyzable baseline ctDNA data, 65 (89%) participants had detectable ctDNA and 59 (81%) participants had any detectable pathogenic alterations. Of these participants, *TP53* comutations were detected in 37 (63%) participants. The ORR was 54% (95% CI, 37 to 71) among participants with *TP53* mutations and 46% (95% CI, 28 to 66) among those without *TP53* mutations.

TABLE 3. Summary of TEAEs

Event	N = 105, No. (%)
Any TEAE	105 (100)
Grade ≥3 TEAE	73 (70)
Serious TEAE	53 (50)
Dose interruption of any study agent[a]	73 (70)
Dose reduction of any study agent	52 (50)
Discontinuation of any study agent	29 (28)

TEAE (≥10%) by Preferred Term	All Grades, No. (%)	Grade ≥3, No. (%)
Associated with EGFR inhibition		
Rash	70 (67)	14 (13)
Paronychia	70 (67)	5 (5)
Stomatitis	31 (30)	2 (2)
Diarrhea	24 (23)	0
Pruritus	24 (23)	0
Dermatitis acneiform	23 (22)	4 (4)
Associated with MET inhibition		
Hypoalbuminemia	62 (59)	8 (8)
Peripheral edema	38 (36)	3 (3)
Other		
IRR	59 (56)	4 (4)
ALT increased	43 (41)	2 (2)
Constipation	34 (32)	0
Hypocalcemia	33 (31)	1 (1)
AST increased	32 (30)	1 (1)
COVID-19 disease	31 (30)	2 (2)
Anemia	28 (27)	3 (3)
Decreased appetite	28 (27)	2 (2)
Nausea	27 (26)	2 (2)
Asthenia	26 (25)	7 (7)
Blood lactate dehydrogenase increased	24 (23)	7 (7)
Hypokalemia	20 (19)	4 (4)
Thrombocytopenia	19 (18)	2 (2)
Muscle spasms	19 (18)	0
Gamma-glutamyl transferase increased	18 (17)	1 (1)
Cough	18 (17)	0
Lymphopenia	17 (16)	2 (2)
Fatigue	17 (16)	0
Pulmonary embolism	16 (15)	8 (8)
Peripheral sensory neuropathy	16 (15)	0
Vomiting	16 (15)	0
Pneumonia	15 (14)	10 (10)
Dizziness	15 (14)	3 (3)
Blood creatine phosphokinase increased	15 (14)	2 (2)
Hypomagnesemia	15 (14)	0
Hypophosphatasemia	15 (14)	0
Myalgia	15 (14)	0
Paresthesia	15 (14)	0
Neutropenia	14 (13)	1 (1)
Dry skin	14 (13)	0
Hyponatremia	14 (13)	1 (1)
Dyspnea	13 (12)	6 (6)
Headache	13 (12)	0
Pyrexia	13 (12)	0
Blood creatinine increased	12 (11)	0
Hyperglycemia	12 (11)	0
Back pain	11 (11)	1 (1)
Blood alkaline phosphatase increased	11 (11)	0
Insomnia	11 (11)	0
Leukopenia	11 (11)	0

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.
[a]Excludes IRRs.

Participants were further classified using the structure-based approach described by Robichaux et al.[42] In the overall population, P-loop and αC-helix compressing (PACC) mutations were observed in 38 participants, classical-like mutations in 14 participants, and T790M-like mutations in three participants. The ORRs in these groups were 45% (95% CI, 29 to 62), 64% (95% CI, 35 to 87), and 67% (95% CI, 9 to 99), respectively (Fig 3).

DISCUSSION

In Cohort C of the CHRYSALIS-2 study, after a median follow-up of 16.1 months, amivantamab-lazertinib demonstrated clinically meaningful and durable antitumor activity in participants with atypical *EGFR*-mutated advanced NSCLC; OS was NE at the time of analysis. Among participants who were treatment-naïve, the ORR by investigator review was 57%, with a median PFS of 19.5 months, which is substantially longer than the <1-year PFS reported for participants receiving EGFR-TKI monotherapy.[10,15] Participants from CHRYSALIS-2 Cohort C had a 24-month OS rate of 77%. Amivantamab-lazertinib also showed benefits among participants who received previous treatments in Cohort C, with an ORR rate of 48% and a median PFS of 7.8 months. These results suggest that amivantamab-lazertinib could be a treatment option for patients with atypical *EGFR*-mutated advanced NSCLC.

Afatinib, the only approved agent in this setting, demonstrated a median PFS of 10.7 months and an ORR of 71% in a post hoc analysis of data from three trials involving 38 participants with atypical *EGFR* mutations.[15] In a prospective study of 40 participants with atypical *EGFR*-mutated NSCLC, osimertinib demonstrated a median PFS of 9.4 months and an ORR of 55%. Although osimertinib demonstrated an ORR

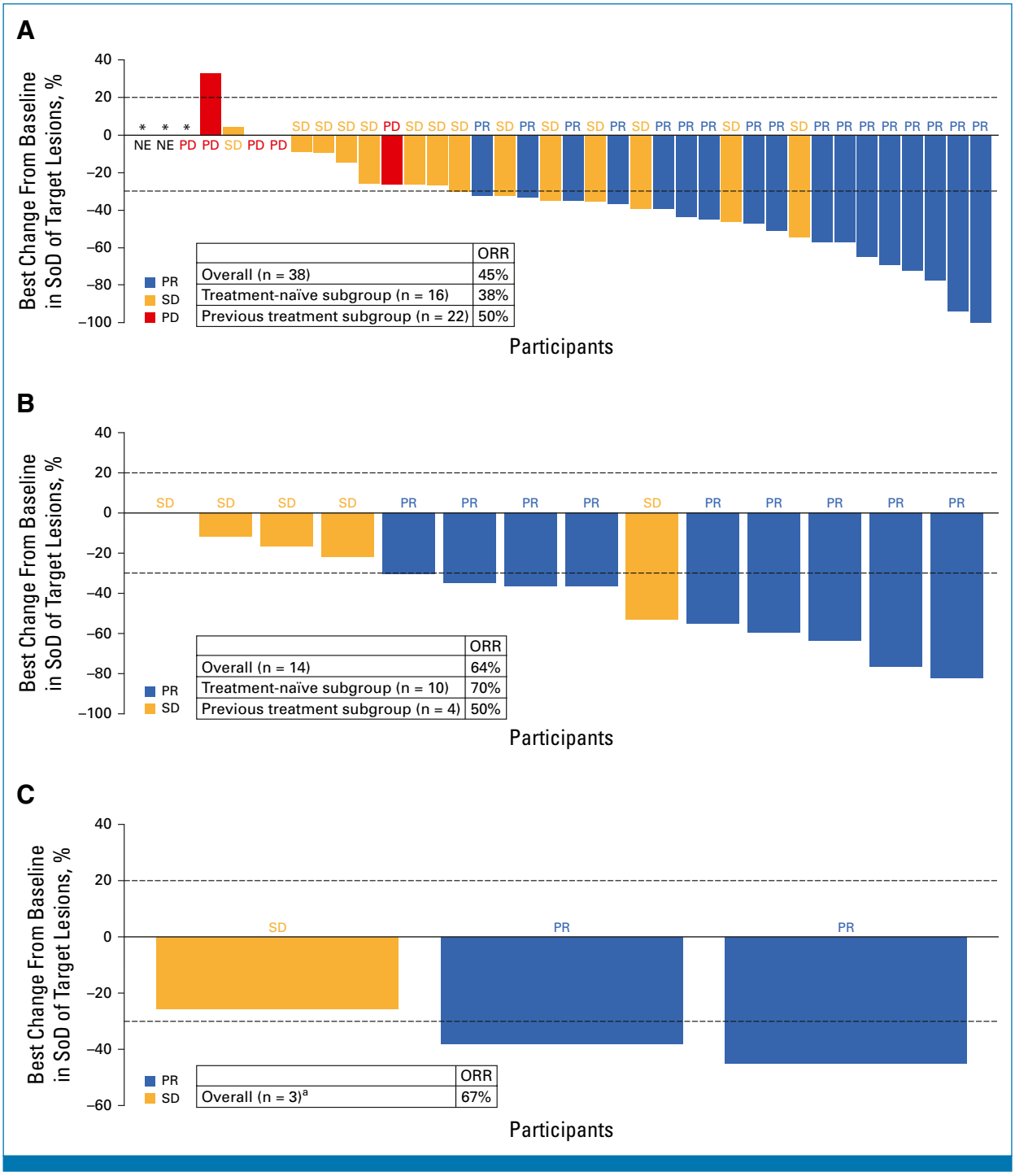

FIG 3. Best percentage change from baseline in target lesions by the location of mutations in different structural entities of *EGFR*. Best response for participants with (A) PACC mutations, (B) classical-like mutations, and (C) T790M-like mutations. EGFR, epidermal growth factor receptor; NE, not evaluable; ORR, objective response rate; PACC, P-loop and αC-helix compressing; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

of 86% among participants who harbored solitary L861Q mutations (n = 7), the ORR among those who harbored G719X solitary mutations (n = 10) was only 30%.[10] In a retrospective, multicenter study of participants with atypical *EGFR*-mutated NSCLC in Germany, afatinib and osimertinib demonstrated a median PFS of 12.0 and 5.0 months, respectively (independent of the treatment line).[43] However, these studies also included participants with tumors harboring atypical mutations with common compound *EGFR* mutations (Ex19del or L858R), potentially influencing the observed benefits. In another phase II study conducted in participants with tumors harboring *EGFR* mutations other

than Ex19del, L858R, T790M, and Ex20ins in Korea, osimertinib demonstrated an ORR of 50% (n = 36) and a PFS of 8.2 months.[44]

Although atypical mutations vary from other common *EGFR* mutations and structure-based classifications suggest that a structure-function–based approach could predict drug sensitivity to targeted therapies,[42] the sensitivity of each mutation to EGFR-TKIs is still not fully understood. Nonetheless, data from CHRYSALIS-2 Cohort C showed that amivantamab-lazertinib is effective against all atypical mutations, including single and compound atypical mutations, irrespective of the structural implication of the mutation locus in the *EGFR* gene. Among all participants with PACC mutations, amivantamab-lazertinib demonstrated an ORR of 45%, regardless of previous treatment. Firmonertinib is another EGFR-TKI that has demonstrated efficacy in TKI-naïve participants with PACC mutations, with an investigator-assessed ORR of 52% for the 160 mg once daily dose and 82% for the 240 mg once daily dose. Amivantamab-lazertinib has also demonstrated efficacy irrespective of the presence of high-risk features including baseline liver metastases, *TP53* comutations, and detectable baseline circulating tumor DNA.[45]

The complementary mechanisms of action of amivantamab and lazertinib[30,32] expand coverage against additional *EGFR* (eg, C797S) and MET (eg, amplification) TKI resistance mutations,[38] potentially delaying disease resistance and prolonging disease control beyond that observed with other EGFR-TKIs alone. These mechanisms may explain the improved efficacy of amivantamab-lazertinib in this setting. In addition, next-generation sequencing of ctDNA samples at baseline showed that the presence of *TP53* mutations was not associated with a lower response rate with amivantamab-lazertinib.

The safety profile of amivantamab-lazertinib was consistent with previous reports, with no new safety signals.[37-39] IRRs were mostly grade 1 and 2 and primarily occurred during the first infusion cycle. IRRs can be further reduced with prophylactic oral dexamethasone 8 mg twice daily plus standard prophylaxis before first intravenous amivantamab infusion.[46] VTE was reported in 30% of participants; none were grade 4 and 5, and most events occurred in the first 4 months of treatment. The majority of participants were not receiving anticoagulation at the time of first VTE. Prophylactic anticoagulation is now recommended for the first 4 months of treatment with amivantamab-lazertinib in all ongoing trials and in the prescribing information.[37,41,47,48] In the PALOMA-3 study, prophylactic anticoagulation was safely implemented and effective in reducing the risk for VTE. Among all participants in PALOMA-3, VTE rates for those who received prophylactic anticoagulation was 10% versus 21% for those who did not receive anticoagulation. The subcutaneous formulation of amivantamab may further reduce overall VTE rates.[47]

There are some limitations in our study. This was a phase I proof-of-concept study conducted in a limited population, and ORR was not analyzed by blinded independent central review. However, the totality of the efficacy data presented, including ORR, DoR, PFS, and OS, demonstrates that amivantamab-lazertinib can be used as a clinically meaningful treatment in a patient population with very few available options. As shown in our real-world analyses (Data Supplement, Methods and Results), most participants treated with first-line physician-selected EGFR-TKI monotherapy do not receive second-line treatment. Furthermore, amivantamab-lazertinib demonstrates improved survival outcomes compared with physician-selected EGFR-TKIs, including afatinib and osimertinib, in the real-world setting after applying key trial eligibility criteria and adjusting for confounding differences. Of note, the real-world analyses may be subject to potential selection biases, variability in treatment approaches, and confounding effects of subsequent therapies. However, rigorous statistical methods were used, such as propensity score methods, to ensure that the comparative analyses were robust and reflective of true clinical scenarios. Key eligibility criteria from the trial were used to identify the target population, and an e-value analysis was performed to measure the impact of unmeasured confounding.

In conclusion, amivantamab-lazertinib demonstrated clinically meaningful and durable antitumor activity while maintaining safety in participants with atypical *EGFR*-mutated advanced NSCLC. To our knowledge, this is the largest, single-cohort, prospective study of atypical *EGFR*-mutated advanced NSCLC. Our results contribute to findings of other studies that demonstrated the efficacy and safety of amivantamab-based regimens in participants with advanced NSCLC harboring common *EGFR* mutations,[49] *EGFR* Ex20ins,[50] and now atypical *EGFR* mutations.

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Pharmaceutical (Inst), Takeda (Inst), Eisai (Inst), Lilly Japan (Inst), Bristol Myers Squibb K.K (Inst), Ignyta (Inst), Janssen (Inst), Loxo (Inst), Daiichi SankyO Co, Ltd (Inst), Turning Point Therapeutics (Inst), Novartis (Inst), Blueprint Medicines (Inst), Bayer Yakuhin (Inst), Amgen (Inst), HaiHe Biopharma Co, Ltd (Inst), Sumitomo Pharma Co, Ltd (Inst), Pfizer (Inst), CRAIF Inc (Inst), Riken Genesis Co, Ltd (Inst), AnHeart Therapeutics Inc (Inst), Guardant Health Asia, Middle East & Africa, Inc (Inst), Lunit (Inst), AbbVie Inc, (Inst), ArriVent Biopharma, Inc (Inst), AccuraGen Inc (Inst), BillionToOne, Inc (Inst), Nippon Kayaku (Inst), Nippon Kayaku (Inst)

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Consulting or Advisory Role: AstraZeneca, Pfizer, Janssen, Boehringer Ingelheim, Daiichi Sankyo/UCB Japan, Genentech/Roche, Bristol Myers Squibb Foundation, Natera, Takeda, Regeneron
Research Funding: AstraZeneca (Inst), Pfizer (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), AbbVie (Inst), TP Therapeutics (Inst), Lilly (Inst), Janssen (Inst), Nuvalent, Inc (Inst), Boehringer Ingelheim (Inst), Black Diamond Therapeutics (Inst), Bristol Myers Squibb Foundation (Inst), Ellipses Pharma (Inst)

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Stock and Other Ownership Interests: Merck, Johnson & Johnson
Honoraria: Janssen Oncology, Takeda
Consulting or Advisory Role: AstraZeneca, Bristol Myers Squibb/Celgene, AstraZeneca, Janssen Oncology, Daiichi Sankyo/Astra Zeneca, Boehringer Ingelheim, NEUVOGEN, Bayer
Research Funding: Lilly (Inst), AstraZeneca (Inst), Janssen Oncology (Inst), Ikena Oncology (Inst), Genentech (Inst), Merck (Inst)
Travel, Accommodations, Expenses: Regeneron
Open Payments Link: https://openpaymentsdata.cms.gov/physician/856967

Eiki Ichihara
Honoraria: AstraZeneca, Takeda, Pfizer, Novartis, Chugai Pharma, Merck, Janssen, Kyowa Kirin International, Daiichi Sankyo/UCB Japan
Research Funding: Janssen

Se-Hoon Lee
Honoraria: AstraZeneca/MedImmune, Roche, Lilly, Amgen, Yuhan, Merck Sharp & Dohme, Bristol Myers Squibb Foundation
Consulting or Advisory Role: AstraZeneca, Roche, Pfizer, Lilly, BMS/Ono, Takeda, Janssen, IMBdx, Abion, BeiGene, Daiichi Sankyo, ImmuneOncia, Merck (German), Merck Sharp & Dohme, Novartis
Speakers' Bureau: Abion
Research Funding: AstraZeneca (Inst), Lunit (Inst), Merck Sharp & Dohme (Inst), Daiichi Sankyo

James Chih-Hsin Yang
Honoraria: Boehringer Ingelheim (Inst), Takeda (Inst), Pfizer (Inst), Amgen (Inst), AstraZeneca/MedImmune (Inst), Roche/Genentech (Inst), Daiichi Sankyo/Astra Zeneca (Inst), MSD Oncology (Inst)
Consulting or Advisory Role: AstraZeneca (Inst), Lilly (Inst), MSD Oncology (Inst), Daiichi Sankyo (Inst), Amgen (Inst), Takeda (Inst), MSD Oncology (Inst), Janssen Oncology (Inst), Daiichi Sankyo/Astra Zeneca (Inst), AbbVie (Inst), ArriVent Biopharma (Inst)
Research Funding: AstraZeneca (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Dizal Pharma, Takeda

Sebastian Michels
Honoraria: AstraZeneca, Janssen Oncology, Takeda, BeiGene, Bristol Myers Squibb
Consulting or Advisory Role: AstraZeneca, Janssen Oncology, Takeda, BeiGene, Bristol Myers Squibb
Research Funding: Pfizer (Inst), Novartis (Inst), Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Janssen Oncology, Lilly, BeiGene, Takeda

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Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen

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Employment: Janssen Research & Development
Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Xuesong Lyu
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Stock and Other Ownership Interests: Johnson & Johnson/Janssen

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Leadership: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Research Funding: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Levon Demirdjian
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Stock and Other Ownership Interests: Johnson & Johnson
Research Funding: Johnson & Johnson
Travel, Accommodations, Expenses: Johnson & Johnson

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Stock and Other Ownership Interests: Johnson & Johnson/Janssen

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Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Patricia Lorenzini
Employment: Janssen Pharmaceuticals of Johnson & Johnson

Roland E. Knoblauch
Employment: Johnson & Johnson
Stock and Other Ownership Interests: Johnson & Johnson
Research Funding: Johnson & Johnson Interventional Oncology
Travel, Accommodations, Expenses: Johnson & Johnson

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Stock and Other Ownership Interests: JnJ

Mahadi Baig
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Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Joshua M. Bauml
Employment: Janssen Research & Development
Stock and Other Ownership Interests: Janssen Research & Development

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Employment: Yonsei University Health System
Leadership: J INTS BIO
Stock and Other Ownership Interests: Theravance, Gencurix, Bridgebio, Kanaph Therapeutics, Cyrus therapeutics, Interpark Bio, J INTS BIO
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Roche, Yuhan, Pfizer, Janssen, Takeda, MSD, Lilly, Novartis, CJ bioscience, BeiGene, BMS, Ono Pharmaceutical, Cyrus therapeutics, Gilead Sciences, Amgen, Daiichi Sankyo, Regeneron, Sanofi, AnHeart Therapeutics, Seagen, Harpoon Therapeutics, GlaxoSmithKline, ArriVent Biopharma, Bridgebio, Kanaph Therapeutics, Cyrus therapeutics, Guardant Health, J INTS Bio, Therapex Co, Ltd
Research Funding: AstraZeneca, Dong-A ST, Champions Oncology, Janssen, Yuhan, MSD, GI Innovation, CJ bioscience, Cyrus Therapeutics, ImmuneOncia, Therapex, J Ints Bio, Vertical Bio AG
Patents, Royalties, Other Intellectual Property: Champions Oncology, Crown Bioscience, Imagen, PearlRiver Bio GmbH
Other Relationship: DAAN Biotherapeutics

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of CHRYSALIS-2 Cohort C Investigators

Principal Investigator	Clinical Site
Gee-Chen Chang	Chung Shan Medical University Hospital
Byoung Chul Cho	Yonsei Cancer Center
Sophie Cousin	Institut Bergonié
Jiuwei Cui	The First Bethune Hospital of Jilin University
Giuseppe Curigliano	IRCCS Istituto Europeo di Oncologia
Gianluca Del Conte	IRCCS Ospedale San Raffaele
Xiaorong Dong	Union Hospital Tongji Medical College of Huazhong University of Science and Technology
Enriqueta Felip	Vall d'Hebron Institute of Oncology (VIHO)
Pilar Garrido	University Hospital Ramón y Cajal
Nicolas Girard	Paris-Saclay University, Université de Versailles Saint-Quentin-en-Yvelines
Adriano Gravina	Istituto Nazionale Tumori Fondazione G. Pascale
Frank Griesinger	Pius-Hospital Oldenburg
Matthew Gubens	UCSF Helen Diller Comprehensive
Eric Haura	Houston Lee Moffitt Cancer Center & Research Institute
Eiki Ichihara	Okayama University Hospital
Dong-Wan Kim	Seoul National University College of Medicine and Seoul National University Hospital
Se Hyun Kim	Seoul National University Bundang Hospital
Se-Hoon Lee	Samsung Medical Center
Yongsheng Li	Chongqing University Cancer Hospital
Shun Lu	Shanghai Chest Hospital, Affiliated Chest Hospital of Shanghai Jiao Tong University School of Medicine
Melina Marmarelis	Perelman School of Medicine, University of Pennsylvania
Sebastian Michels	Uniklinik Koeln
Joel Neal	Stanford University Medical Center
Jorge Nieva	USC Norris Comprehensive Cancer Center
Luis Paz-Ares	Hospital Universitario 12 de Octubre
Niels Reinmuth	Asklepios Klinik Gauting GmbH—Asklepios Fachkliniken Munchen-Gauting
Yuki Sato	Kobe City Medical Center General Hospital
Alexander Spira	Virginia Cancer Specialists
Meili Sun	Central Hospital of Jinan
Pascale Tomasini	Aix-Marseille University
Yongsheng Wang	West China Hospital of Sichuan University
Marcel Wiesweg	Universitaetsklinikum Essen
Lin Wu	Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University
James Chih-Hsin Yang	National Taiwan University Cancer Center
Yu Yao	The First Affiliated Hospital of Xi'an Jiaotong University
Yiping Zhang	Zhejiang Cancer Hospital
Minglei Zhuo	Beijing Cancer Hospital