



original reports

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Keunchil Park, MD, PhD¹; Eric B. Haura, MD²; Natasha B. Leighl, MD³; Paul Mitchell, MD⁴; Catherine A. Shu, MD⁵; Nicolas Girard, MD, PhD⁶; Santiago Viteri, MD⁷; Ji-Youn Han, MD, PhD⁸; Sang-We Kim, MD, PhD⁹; Chee Khoon Lee, MD¹⁰; Joshua K. Sabari, MD¹¹; Alexander I. Spira, MD, PhD¹²; Tsung-Ying Yang, MD, PhD¹³; Dong-Wan Kim, MD, PhD¹⁴; Ki Hyeong Lee, MD, PhD¹⁵; Rachel E. Sanborn, MD¹⁶; José Trigo, MD¹⁷; Koichi Goto, MD, PhD¹⁸; Jong-Seok Lee, MD, PhD¹⁹; James Chih-Hsin Yang, MD, PhD²⁰; Ramaswamy Govindan, MD²¹; Joshua M. Bauml, MD²²; Pilar Garrido, MD, PhD²³; Matthew G. Krebs, MD, PhD²⁴; Karen L. Reckamp, MD²⁵; John Xie, PhD²⁶; Joshua C. Curtin, PhD²⁶; Nahor Haddish-Berhane, PhD²⁶; Amy Roshak, BS²⁶; Dawn Millington, MS²⁶; Patricia Lorenzini, MS²⁶; Meena Thayu, MD²⁶; Roland E. Knoblauch, MD, PhD²⁶; and Byoung Chul Cho, MD, PhD²⁷

abstract

PURPOSE Non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertion (Exon20ins) mutations exhibits inherent resistance to approved tyrosine kinase inhibitors. Amivantamab, an *EGFR*-MET bispecific antibody with immune cell–directing activity, binds to each receptor’s extracellular domain, bypassing resistance at the tyrosine kinase inhibitor binding site.

METHODS CHRYSALIS is a phase I, open-label, dose-escalation, and dose-expansion study, which included a population with *EGFR* Exon20ins NSCLC. The primary end points were dose-limiting toxicity and overall response rate. We report findings from the postplatinum *EGFR* Exon20ins NSCLC population treated at the recommended phase II dose of 1,050 mg amivantamab (1,400 mg, \geq 80 kg) given once weekly for the first 4 weeks and then once every 2 weeks starting at week 5.

RESULTS In the efficacy population (n = 81), the median age was 62 years (range, 42–84 years); 40 patients (49%) were Asian, and the median number of previous lines of therapy was two (range, 1–7). The overall response rate was 40% (95% CI, 29 to 51), including three complete responses, with a median duration of response of 11.1 months (95% CI, 6.9 to not reached). The median progression-free survival was 8.3 months (95% CI, 6.5 to 10.9). In the safety population (n = 114), the most common adverse events were rash in 98 patients (86%), infusion-related reactions in 75 (66%), and paronychia in 51 (45%). The most common grade 3–4 adverse events were hypokalemia in six patients (5%) and rash, pulmonary embolism, diarrhea, and neutropenia in four (4%) each. Treatment-related dose reductions and discontinuations were reported in 13% and 4% of patients, respectively.

CONCLUSION Amivantamab, via its novel mechanism of action, yielded robust and durable responses with tolerable safety in patients with *EGFR* Exon20ins mutations after progression on platinum-based chemotherapy.

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

INTRODUCTION

Activating mutations in the epidermal growth factor receptor (*EGFR*) are a major oncogenic driver in non–small-cell lung cancer (NSCLC), with 85% of cases arising from an exon 19 deletion or exon 21 L858R point substitution.^{1–3} The third most frequently occurring mutations (\leq 12% of cases) are exon 20 insertion (Exon20ins) mutations, which are characterized by in-frame insertions and duplications near the C-helix of the *EGFR* kinase domain.^{4,8} Collectively, *EGFR* Exon20ins mutations are molecularly

heterogeneous, with > 100 variants identified by next-generation sequencing (NGS).⁹

While similar to other *EGFR* mutations in biology and epidemiology,^{4,5} *EGFR* Exon20ins mutations are defined by an altered active site that sterically hinders tyrosine kinase inhibitor (TKI) binding, resulting in low response rates (0%–9%) with approved *EGFR* TKIs.^{10–14} As a result, the standard of care remains platinum-based chemotherapy, with an associated reduced median overall survival (OS) of 16 months, compared with 39 months in *EGFR* TKI–sensitive disease.^{12,15–20}

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 28, 2021 and published at ascopubs.org/journal/jco on August 2, 2021; DOI <https://doi.org/10.1200/JCO.21.00662>

CONTEXT

Key Objective

To determine the recommended phase II dose of amivantamab, a novel epidermal growth factor receptor (EGFR)-MET bispecific antibody, and its antitumor activity in patients with *EGFR* exon 20 insertion (Exon20ins)-mutated non-small-cell lung cancer whose disease had progressed on platinum-based chemotherapy.

Knowledge Generated

To our knowledge, amivantamab is the first biologic therapy to demonstrate efficacy in patients with *EGFR* Exon20ins non-small-cell lung cancer after progression on standard-of-care platinum-based chemotherapy. Amivantamab exhibited a tolerable safety profile consistent with on-target inhibition of EGFR and MET pathways.

Relevance

We provide proof of concept that the EGFR can be effectively targeted through the extracellular domain for mutations that are resistant to EGFR tyrosine kinase inhibitors, including *EGFR* Exon20ins mutations, for which there are no approved therapies.

Amivantamab (JNJ-61186372) is a fully human EGFR-MET bispecific antibody with immune cell-directing activity designed to engage two distinct driver pathways in NSCLC.²¹⁻²³ By binding to each receptor's extracellular domain, amivantamab can inhibit ligand binding, promote receptor-antibody complex endocytosis and degradation, and induce Fc-dependent trogocytosis by macrophages and antibody-dependent cellular cytotoxicity by natural killer cells.²¹⁻²³

CHRYSALIS, a first-in-human, phase I dose-escalation, and dose-expansion study (NCT02609776), evaluates the efficacy, safety, and pharmacokinetics of amivantamab in patients with advanced NSCLC. During the conduct of the study, amivantamab received Breakthrough Therapy Designation on the basis of the preliminary efficacy within the *EGFR* Exon20ins population, who had previous treatment with platinum-based chemotherapy and for whom limited treatment options were available. Here, we report the updated results from the postplatinum *EGFR* Exon20ins population.

METHODS

Patients

Eligible patients had confirmed metastatic or unresectable NSCLC and an Eastern Cooperative Oncology Group performance status ≤ 1 and had progressed on, were ineligible for, or declined standard-of-care therapy. Patients in dose expansion had measurable disease per RECIST version 1.1 and qualifying *EGFR* mutations or *MET* mutations or amplifications, as assessed by local testing or central NGS testing of circulating tumor DNA (ctDNA) or tumor tissue. Previous treatment with investigational EGFR Exon20ins-targeted TKIs was prohibited in the *EGFR* Exon20ins expansion cohort. Patients with untreated or active brain metastases were excluded; however, patients whose brain metastases were previously treated and asymptomatic at

screening were eligible. Additional criteria are detailed in the Protocol (online only) and Data Supplement (online only).

Study Design

CHRYSALIS is an ongoing, first-in-human, open-label, multicenter, two-part phase I study of amivantamab as monotherapy (Fig 1A) and in combination with other therapies in patients with advanced NSCLC. The current analysis presents the results of amivantamab monotherapy after platinum-based chemotherapy, in patients who harbored *EGFR* Exon20ins mutations. The results from the other populations are ongoing and will be reported separately (Fig 1B).

The primary objective of dose escalation was to determine the maximum tolerated dose and recommended phase II dose (RP2D), and that of dose expansion was to evaluate the safety, tolerability, and antitumor activity of amivantamab at the RP2D. Primary end points for dose escalation and expansion were incidence of dose-limiting toxicity and overall response rate (ORR), respectively. Key secondary end points included duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), and OS.

A dose-escalation 3 + 3 design was used to assess amivantamab doses administered intravenously once weekly in the first 28-day cycle and every other week for subsequent cycles (Fig 1A). Additional enrollment (≤ 20 patients) in dose cohorts that were declared safe was allowed. For dose expansion, the RP2D was administered to cohorts assigned on the basis of qualifying *EGFR* and/or *MET* mutations or amplifications, and previous therapy.

Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Treatment beyond RECIST-defined disease progression was allowed in cases of continuous clinical benefit. To mitigate infusion-related reactions (IRRs), the first dose was split over two days and prophylactic premedication was required (Data Supplement). Management of rash was recommended per

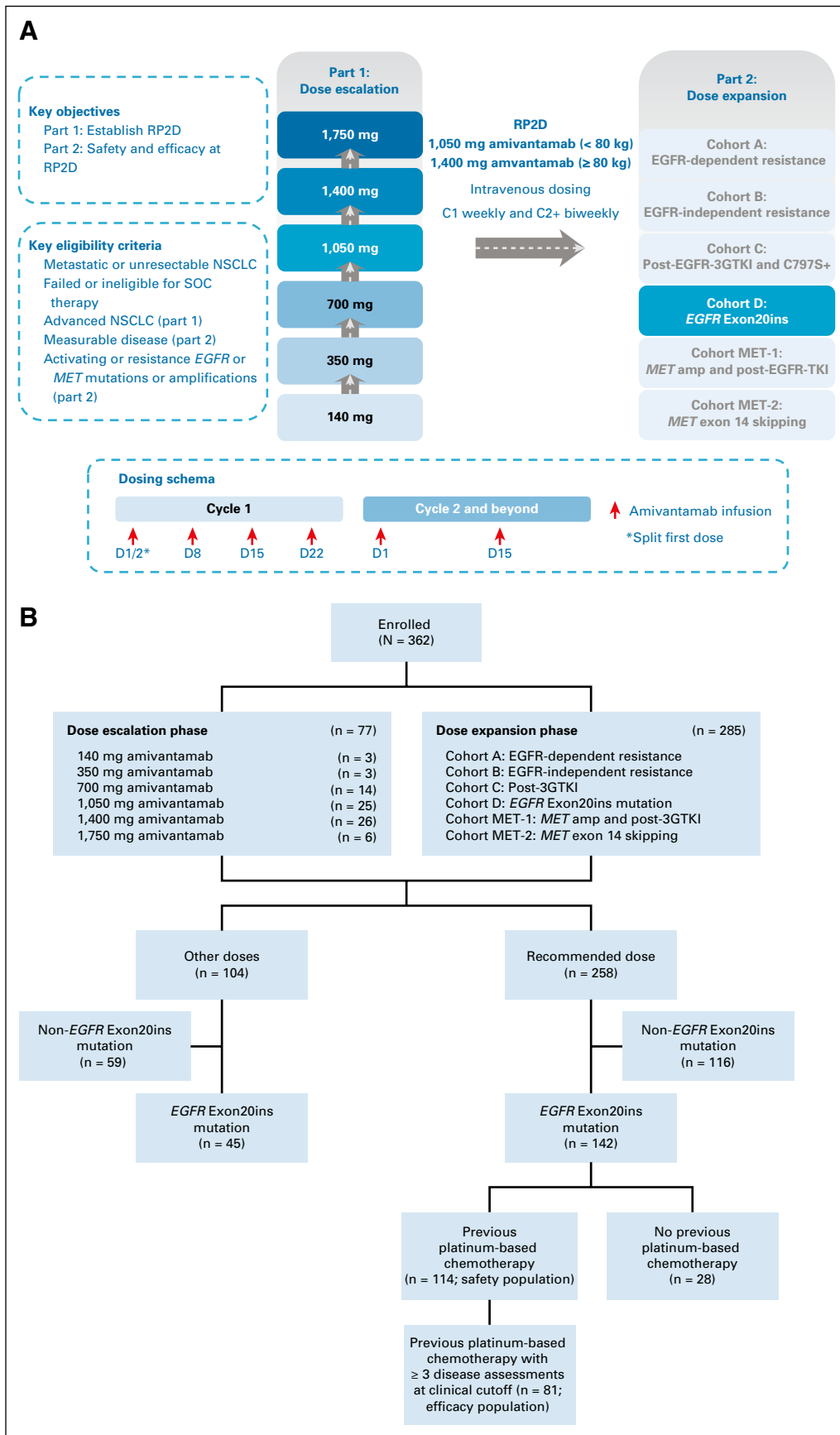


FIG 1. CHRYSALIS study design and patient disposition for amivantamab monotherapy. The CHRYSALIS study consisted of a dose-escalation and dose-expansion phase. (A) Patients with advanced (continued on following page)

FIG 1. (Continued). NSCLC were enrolled in dose-escalation cohorts and patients were assigned to dose-expansion cohorts on the basis of *EGFR* and *MET* mutation status and previous therapy. (B) Patients were allocated to six different dose cohorts in the dose-escalation portion of the study. The safety population included all patients with *EGFR* Exon20ins NSCLC who had progressed on previous platinum-based chemotherapy and were treated at the RP2D (n = 114) by the data cutoff of June 8, 2020. At this clinical cutoff, the first 81 patients (four from dose escalation cohort, four from cohort A, and 73 from cohort D) met the criteria of having at least three scheduled disease assessments or discontinued, had disease progression, or died and were defined as the pivotal efficacy population. 3GTKI, third-generation tyrosine kinase inhibitor; amp, amplification; C, cycle; *EGFR*, epidermal growth factor receptor; Exon20ins, exon 20 insertion; NSCLC, non-small-cell lung cancer; RP2D, recommended phase II dose; SOC, standard of care; TKI, tyrosine kinase inhibitor.

Protocol or in accordance with institutional guidelines (Data Supplement). The study was approved by an Independent Ethics Committee, and all patients provided written informed consent.

Study Assessments

Baseline imaging of thorax, abdomen, and pelvis was performed by computed tomography during screening. Response was assessed according to RECIST by the investigator at least every 6 weeks after the first amivantamab administration and confirmed by blinded independent central review (BICR). Baseline brain imaging by magnetic resonance imaging was performed for dose-expansion cohorts only. Monitoring for CNS disease was not mandatory and performed in accordance with local practice.

Patients with *EGFR* Exon20ins mutations were enrolled on the basis of local testing (tissue or ctDNA). Serum, plasma, and biopsy tissue were collected for pharmacokinetic, immunogenicity, or biomarker analyses. Guardant360 CDx (Guardant Health, Redwood City, CA) and OncoPrint Dx Target Test (Thermo Fisher, Waltham, MA) companion diagnostics are being developed.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

An interim analysis was planned after dose-expansion cohorts enrolled ≥ 30 patients and had sufficient data to evaluate response (Data Supplement). For full expansion, assuming an ORR $\geq 35\%$, an enrollment of ≥ 60 patients was estimated to achieve a lower bound of 95% CI $\geq 12\%$ (single-agent chemotherapy as the benchmark)²⁴ with a one-sided alpha of .025. After receiving Breakthrough Therapy Designation for the population with previous platinum-based chemotherapy, in consultation with Health Authorities, a minimum of 80 patients was identified as a potential threshold, using similar assumptions, for a postplatinum-based chemotherapy comparison ORR of 23%.²⁵

The safety population included patients with *EGFR* Exon20ins NSCLC who had progressed on platinum-based chemotherapy and were treated at the RP2D (n = 114) by the data cutoff of June 8, 2020. The pivotal efficacy population

included the first 81 patients enrolled with *EGFR* Exon20ins NSCLC, after previous platinum-based chemotherapy (four patients from dose escalation and 77 from dose expansion [four from cohort A and 73 from cohort D]), who had at least three scheduled disease assessments or had discontinued, progressed, or died by the data cutoff of June 8, 2020 (Fig 1B). The efficacy data presented here reflect follow-up of this population through October 8, 2020, at which time all active responders in the efficacy population had ≥ 6 months of follow-up from the time of their first response.

ORR was calculated as the proportion of patients who achieved complete response (CR) or partial response (PR) as assessed by the investigator or BICR using RECIST. CBR was calculated as the proportion of patients achieving CR or PR or stable disease ≥ 11 weeks, corresponding to two disease assessments.

Data were summarized using descriptive statistics. Time-to-event end points were summarized using Kaplan-Meier estimates. No data imputation was applied for missing safety and efficacy evaluations. Additional statistical methods are provided in the Protocol.

RESULTS

Patients

Between May 27, 2016, and June 8, 2020, 362 patients were enrolled in the study. The initial dose escalation enrolled patients at two sites in South Korea and subsequently enrolled patients from sites in Japan and the United States to confirm the safety and pharmacokinetics of amivantamab, leading to a total enrollment of 77 patients. Across dose escalation and expansion, 258 patients were treated at the RP2D of 1,050 mg amivantamab (1,400 mg for patients ≥ 80 kg) given once weekly for the first 4 weeks and then once every 2 weeks starting at week 5. At the safety data cutoff of June 8, 2020, the median follow-up was 5.1 months (range, 0.2-29.3 months).

In the efficacy population, the median age was 62 years (range, 42-84), 48 patients (59%) were women, 40 (49%) were Asian, and all had received previous platinum-based chemotherapy (Table 1). Eighteen patients (22%) had a history of treated brain lesions before receiving the first dose.

TABLE 1. Demographic and Baseline Disease Characteristics

Characteristic	Dose Escalation (n = 77)	Efficacy Population (n = 81) ^a
Median age (range), years	63 (32-86)	62 (42-84)
Sex, No. (%)		
Female	49 (64)	48 (59)
Male	28 (36)	33 (41)
Race, No. (%)		
Asian	48 (62)	40 (49)
White	26 (34)	30 (37)
Black	3 (4)	2 (2)
Not reported	0	9 (11)
ECOG PS, No. (%)		
0	22 (29)	26 (32)
1	55 (71)	54 (67)
2	0	1 (1)
Smoking history, No. (%)		
Nonsmoker	46 (60)	43 (53)
Smoker	31 (40)	38 (47)
Median time from initial diagnosis (range), months	37 (2-173)	17 (1-130)
NSCLC subtype, No. (%)		
Adenocarcinoma	73 (95)	77 (95)
Squamous cell carcinoma	3 (4)	3 (4)
Others	1 (1)	1 (1)
Location of metastases, ^b No. (%)		
Lymph node	34 (44)	43 (53)
Bone	26 (34)	34 (42)
Brain	15 (20)	18 (22)
Liver	14 (18)	7 (9)
Adrenal gland	8 (10)	3 (4)
Others	44 (57)	45 (56)
Median previous lines of therapy (range)	3 (0-10)	2 (1-7)
Previous systemic therapy, No. (%)	75 (97)	81 (100)
Platinum-based chemotherapy	63 (82)	81 (100)
Immuno-oncology therapy	29 (38)	37 (46)
EGFR TKI, No. (%)	59 (77)	20 (25)
First-generation ^c	45 (58)	7 (9)
Second-generation ^d	15 (20)	6 (7)
Third-generation ^e	37 (48)	6 (7)
Exon20ins-targeted ^f	5 (7)	1 (1)
No previous therapy, No. (%)	2 (3)	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Exon20ins, exon 20 insertion; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor.

^aThe efficacy population includes four patients from the dose-escalation phase.

^bPatients could be counted in more than one category.

^cErlotinib and gefitinib.

^dAfatinib.

^eOsimertinib, ASP8273, and nintedanib.

^fPozotinib and mobocertinib.

The median number of previous lines of therapy was two (range, 1-7); 20 (25%) had previous treatment with EGFR TKIs, and 37 (46%) had previous immuno-oncology therapies. At the efficacy data cutoff of October 8, 2020, the median follow-up was 9.7 months (range, 1.1-29.3 months).

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

No maximum tolerated dose had been identified through the maximum assessed dose of 1,750 mg; therefore, selection of the RP2D of 1,050 mg (1,400 mg for patients \geq 80 kg) was based on safety, pharmacokinetic, and pharmacodynamic data. Amivantamab exhibited linear pharmacokinetics at 350-1,750 mg and nonlinear pharmacokinetics below 350 mg (Data Supplement). The mean nonspecific linear clearance of amivantamab was 0.36 L/d, with a mean half-life of 11.3 days, associated with linear elimination. The RP2D of 1,050 mg provided saturation of circulating serum EGFR and MET targets and coverage of the preclinically established target concentration of 168 μ g/mL. Saturation of circulating targets started at 350 mg for EGFR and 140 mg for MET after a single dose, consistent with manifestation of on-target EGFR (rash) and MET (hypoalbuminemia and peripheral edema) toxicities (Data Supplement). Complete saturation of EGFR and MET circulating targets throughout the dosing period was achieved at \geq 700 mg (Data Supplement). To reduce pharmacokinetic variability and exposure differences, two-tiered weight-based dosing was established using population pharmacokinetic analysis. The RP2D of 1,400 mg for patients \geq 80 kg provided similar exposure to those $<$ 80 kg at 1,050 mg (Data Supplement).

The incidence of antibodies to amivantamab was low. No evident impact of antibody titer levels on pharmacokinetic parameters, clinical activity, or safety of amivantamab was observed (Data Supplement).

Safety

The safety profile of the EGFR Exon20ins safety population and patients treated at the RP2D was consistent with on-target anti-EGFR and anti-MET activity (Table 2). The median treatment duration was 3.7 months for the safety population (range, 0.03-23.9 months) and patients treated at the RP2D (range, 0.03-29.7 months). Safety in the dose-escalation cohorts is presented in the Data Supplement.

AEs associated with EGFR inhibition included rash (including dermatitis acneiform) in 98 patients (86%), paronychia in 51 (45%), stomatitis in 24 (21%), pruritus in 19 (17%), and diarrhea in 14 (12%). AEs associated with MET inhibition included hypoalbuminemia and peripheral edema in 31 (27%) and 21 (18%) patients, respectively. Interstitial lung disease (including pneumonitis) was reported in five patients (4%).

IRRs were commonly observed (75 [66%]), occurred almost exclusively on cycle 1, day 1 (93%) or day 2 (4%; first

TABLE 2. Summary of AEs

Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade \geq 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption ^a	40 (35)	88 (34)

Most Common AE (\geq 10%)	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
	Total, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade \geq 3, No. (%)	Total, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade \geq 3, No. (%)
Rash ^b	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)
Pruritus	19 (17)	11 (10)	8 (7)	0	49 (19)	40 (16)	9 (4)	0
Fatigue	21 (18)	15 (13)	4 (4)	2 (2)	47 (18)	29 (11)	16 (6)	2 (1)
Cough	16 (14)	11 (10)	5 (4)	0	40 (16)	25 (10)	15 (6)	0
Decreased appetite	16 (14)	7 (6)	9 (8)	0	39 (15)	23 (9)	16 (6)	0
Dry skin	18 (16)	18 (16)	0	0	33 (13)	32 (12)	1 (0.4)	0
Increased alanine aminotransferase	17 (15)	15 (13)	1 (1)	1 (1)	30 (12)	22 (9)	5 (2)	3 (1)
Vomiting	12 (11)	10 (9)	2 (2)	0	29 (11)	22 (9)	6 (2)	1 (0.4)
Myalgia	14 (12)	12 (11)	2 (2)	0	28 (11)	23 (9)	5 (2)	0
Dizziness	9 (8)	8 (7)	0	1 (1)	28 (11)	24 (9)	3 (1)	1 (0.4)
Headache	8 (7)	4 (4)	3 (3)	1 (1)	28 (11)	17 (7)	8 (3)	3 (1)
Increased blood alkaline phosphatase	10 (9)	8 (7)	1 (1)	1 (1)	28 (11)	22 (9)	4 (2)	2 (1)
Diarrhea	14 (12)	8 (7)	2 (2)	4 (4)	27 (11)	16 (6)	6 (2)	5 (2)
Back pain	12 (11)	6 (5)	6 (5)	0	26 (10)	13 (5)	11 (4)	2 (1)
Pyrexia	15 (13)	12 (11)	3 (3)	0	26 (10)	21 (8)	5 (2)	0
Hypokalemia	12 (11)	5 (4)	1 (1)	6 (5)	21 (8)	11 (4)	3 (1)	7 (3)

Abbreviations: AE, adverse event; RP2D, recommended phase II dose.

^aExcludes infusion-related reactions.

^bRash is defined by acne, dermatitis, dermatitis acneiform, erythema, erythema multiform, folliculitis, macule, perineal rash, pustule, rash, rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion, and toxic epidermal necrolysis.

dose is split over two days), and rarely recurred with subsequent dosing (one event was reported after cycle 2 [0.09% of doses administered]; Data Supplement). Given the observed risk with the first exposure, amivantamab was initially administered at a reduced rate of 25 mL/h in the first

2 hours and increased to 50 mL/h for the remainder of the day 1 infusion of 350 mg. With this administration, the median time to first onset of IRR was 45 minutes and the majority of IRRs were grade 1-2; predisposing factors were not identified.

TABLE 3. Response as Assessed by Blinded Independent Central Review

Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI) ^a	40 (29 to 51)
CBR, % (95% CI) ^b	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

Abbreviations: CBR, clinical benefit rate; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

^aProportion of total patients in the efficacy population who had partial and complete response.

^bProportion of total patients in the efficacy population who had partial and complete response or stable disease for at least 11 weeks (corresponding to two disease assessments).

Grade ≥ 3 AEs were observed in 40 patients (35%; Table 2), with most frequent being hypokalemia in six (5%) and rash, pulmonary embolism, diarrhea, and neutropenia in four (4%) each. Treatment-related grade ≥ 3 AEs were reported in 18 patients (16%); most common included rash in four (4%) and IRR and neutropenia in three (3%) each. Serious AEs occurred in 34 patients (30%); pulmonary embolism and back pain were most frequently reported (3% each; Data Supplement). Treatment-related serious AEs were reported in 10 patients (9%) and included IRR and diarrhea (two patients each; 2%) and single reports each of cellulitis, infected dermal cyst, interstitial lung disease, pneumonitis, atrial flutter, rash, and toxic epidermal necrolysis.

Treatment-related dose reductions occurred in 15 patients (13%), with rash (11 [10%]) being most frequently reported. Five patients (4%) had treatment-related discontinuation: rash and IRR in two (1.8%) each and paronychia in one (1%). There were no treatment-related grade 5 events.

Efficacy

Tumor response. In the efficacy population, three confirmed CRs and 29 PRs were observed, for an ORR of 40% (95% CI, 29 to 51) as assessed by BICR (Table 3). With 15 responders remaining on treatment at the data cutoff, the median DOR was 11.1 months (95% CI, 6.9 to not reached), with 75% of responses observed at the first disease assessment (Fig 2A and Data Supplement). The CBR, which included an additional 28 patients with stable disease ≥ 11 weeks, was 74% (95% CI, 63 to 83). The investigator-assessed ORR of 36% (95% CI, 25 to 47) was consistent with the BICR (Data Supplement). Antitumor

activity was observed across all prespecified and post hoc subpopulations (Fig 2B).

All 81 patients in the efficacy population had ctDNA or tumor samples submitted for central testing, of which 63 had detectable ctDNA, identifying 25 distinct Exon20ins variants. Antitumor responses were observed in patients who harbored insertions within the helical, near-loop, and far-loop regions of exon 20 (Figs 3A and 3B). Through central NGS testing, one patient was identified with *MET* amplification (copy number of 8); this patient had a PR.

PFS and OS. Progression or death occurred in 47 patients (58%); the median PFS was 8.3 months (95% CI, 6.5 to 10.9) by BICR and investigator (95% CI, 5.5 to 10.6) assessments. The median OS was 22.8 months (95% CI, 14.6 to not reached), although with 23 deaths, this end point remains immature.

DISCUSSION

Patients with *EGFR* Exon20ins NSCLC have among the poorest prognoses of patients with NSCLC. A recent real-world analysis demonstrated a 13% ORR across second-line treatments, with a median PFS of 3.5 months.²⁶ Using a similar real-world data set, a median OS of 12.5 months was reported in the relapsed or refractory setting.¹⁵ Given amivantamab's unique mechanism of action and the unmet medical need associated with *EGFR* Exon20ins NSCLC, this population was among the initial populations selected for exploration of amivantamab activity.

The therapeutic challenge with *EGFR* Exon20ins-directed TKI therapy has been overcoming steric hindrance at the active site, while maintaining selectivity against the wild-type receptor to minimize toxicity. Two *EGFR* Exon20ins-directed TKIs, poziotinib and mobocertinib, have recently reported results. Among 115 patients with *EGFR* Exon20ins NSCLC, poziotinib demonstrated a 14.8% ORR. Rates of treatment-related grade ≥ 3 rash and diarrhea were 28% and 26%, respectively.²⁷ Mobocertinib showed a 28% ORR in 114 patients with *EGFR* Exon20ins NSCLC who progressed on platinum-based chemotherapy. Grade ≥ 3 treatment-related AEs were reported in 46%. Treatment-related AEs of diarrhea in 90% of patients (21% grade 3-4) and rash in 45% were reported.²⁸

The safety profile of amivantamab was consistent with expected on-target toxicities associated with inhibition of *EGFR* and *MET*. IRRs were frequently observed but were low grade, primarily limited to the first infusion, and rarely occurred with further dosing. The risk of IRR was mitigated by splitting the first dose over two days and through administration of prophylactic premedication (Data Supplement) and reduced initial infusion rates using diluent priming of tubing to ensure slow initial exposure to amivantamab. The incidence of severe toxicity and toxicity-related discontinuations were low despite a lack of selectivity against the wild-type *EGFR*, suggesting that the

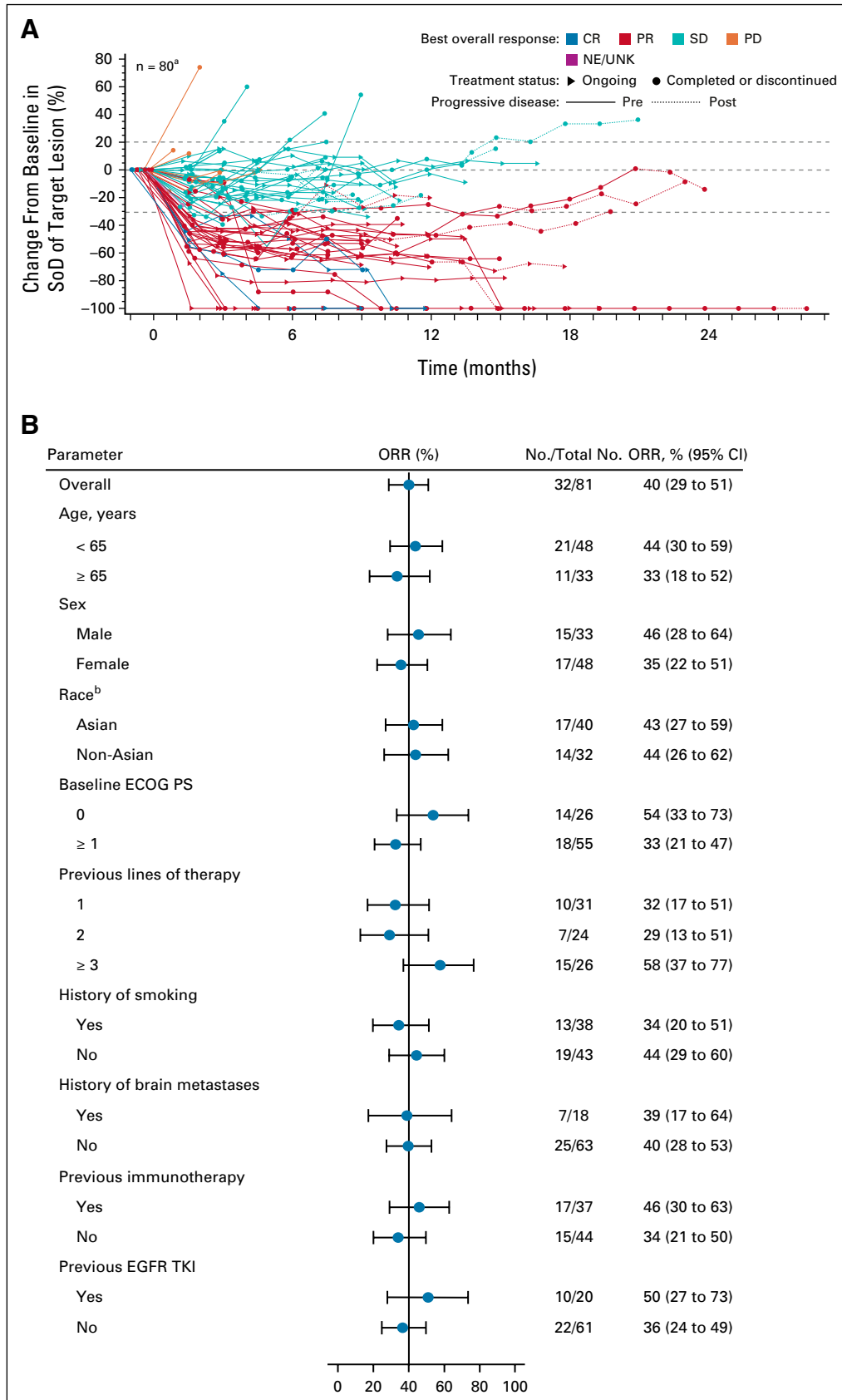


FIG 2. Tumor response over time and ORR by subgroups. (A) Spider plot of percent change from baseline in sum of target lesion diameters over time in the efficacy population ($n = 81$) as assessed (continued on following page)

FIG 2. (Continued). by BICR. ^aOne patient discontinued before any disease assessment and is not included in the plot. Dotted lines at 20% and -30% indicate thresholds for PD and PR, respectively, as per RECIST, v1.1. (B) Results of prespecified (age, sex, race, baseline ECOG PS, history of smoking, and previous immunotherapy) and post hoc (history of brain metastases, previous lines of therapy, and previous EGFR TKI) subgroup analysis of ORR in the efficacy population on the basis of BICR. ^bDoes not include nine patients with race not reported and multiple race. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of lesion diameters; TKI, tyrosine kinase inhibitor; UNK, unknown.

bispecific nature of amivantamab may affect the safety profile, potentially through altered target cell selectivity (eg, tumor cells).^{21,29,30}

Early efficacy in this study identified clinically significant monotherapy activity of amivantamab in *EGFR* Exon20ins NSCLC in the chemotherapy-naive (n = 10) and chemotherapy-relapsed setting (n = 29). This experience

led to Breakthrough Therapy Designation in both the United States and China for the latter population on the basis of the investigator-assessed ORR of 41%, the median DOR of 7 months, and the CBR of 72%.³¹ These preliminary data were confirmed in the current expanded population of 81 patients with increased follow-up, demonstrating a BICR-assessed ORR of 40%, a median

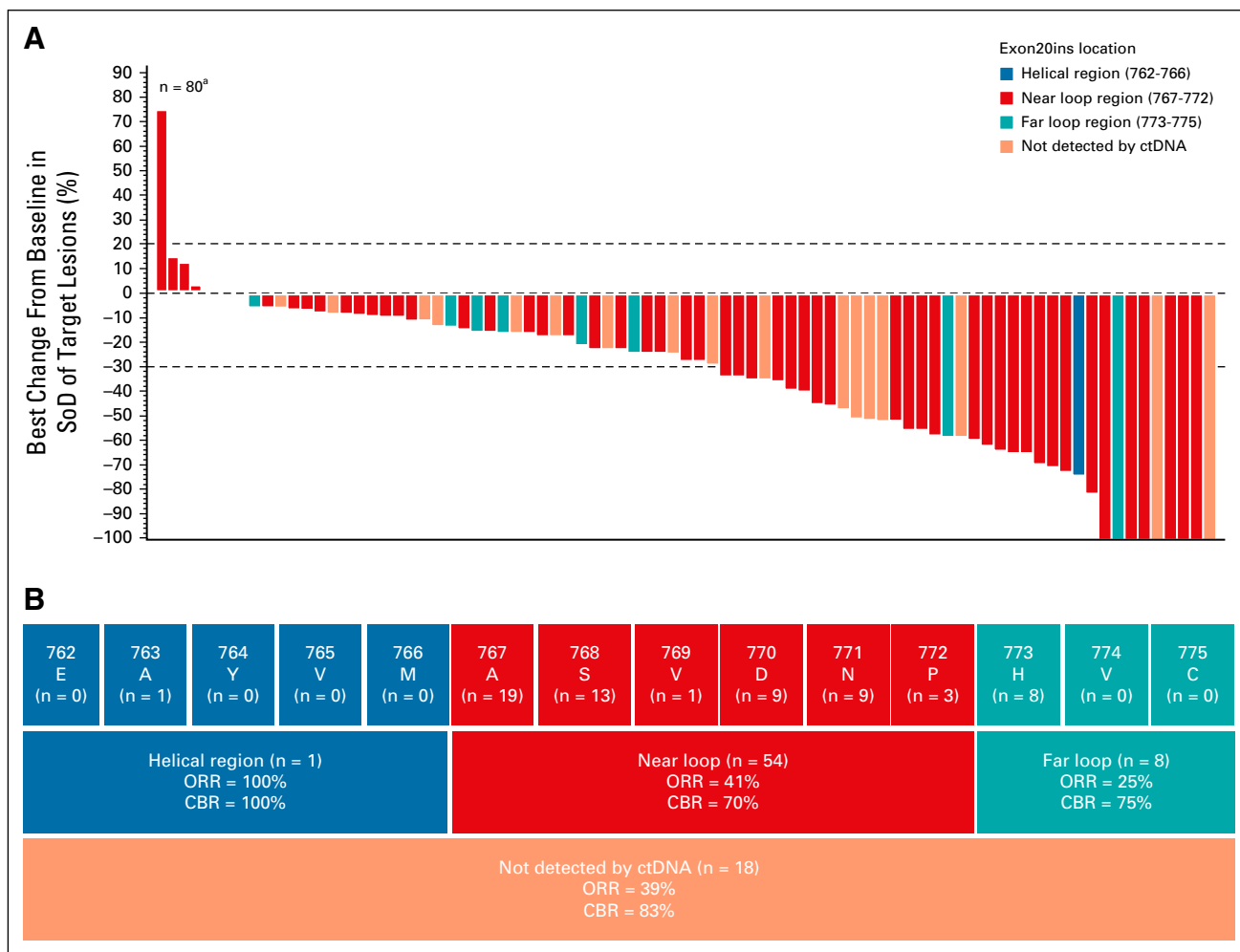


FIG 3. Tumor reduction and responses in the efficacy population. (A) Waterfall plot displaying best percent change from baseline in sum of target lesion diameters by location of *EGFR* Exon20ins (determined by Guardant360 testing) for patients in the efficacy population (n = 81) as assessed by BICR. ^aOne patient discontinued before any disease assessment and is not included in the plot. Dotted lines at 20% and -30% indicate thresholds for progressive disease and partial response, respectively, as per RECIST, v1.1. (B) Insertion regions of *EGFR* Exon20ins identified in the efficacy population and ORR as assessed by BICR for each key region of exon 20 (blue, red, and teal boxes). Site of *EGFR* Exon20in could not be identified by ctDNA analysis for 18 patients (dark orange). BICR, blinded independent central review; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; Exon20ins, exon 20 insertion; ORR, overall response rate; SoD, sum of lesion diameters.

DOR of 11.1 months, and a CBR of 74%. On the basis of these data, amivantamab is approved in the United States for the treatment of patients with *EGFR* Exon20ins NSCLC whose disease progressed on or after platinum-based chemotherapy.

The role of MET expression and/or activation is not well-defined in *EGFR* Exon20ins disease; therefore, the anti-MET activity of amivantamab may not play a large role in initial response in this population. Only one patient was identified with baseline MET amplification, and this patient achieved a confirmed PR, suggesting that when both driver pathways are active, amivantamab retains antitumor activity.³² Furthermore, it is possible that the anti-MET activity of amivantamab may contribute to response duration, by preventing emergence of tumor resistance through MET activation.

Amivantamab has demonstrated preliminary activity in *EGFR* TKI-resistant tumors driven by *EGFR* secondary mutations (T790M and/or C797S) or new MET amplification.³²⁻³⁴ Similarly, one patient from the present study, previously treated with poziotinib and with T790M resistance mutation, had a PR to amivantamab. The ability to inhibit *EGFR*-based and/or MET-based resistance mechanisms to *EGFR* TKIs was the basis for the bispecific strategy underlying amivantamab development, and this study suggests that both pathways need not be activated for initial amivantamab response.^{32,34}

Limitations of this study were related to both the early phase of the study and the patient population under study. The analysis presented here does not include the full enrollment of the *EGFR* Exon20ins population, but represents a subset of patients without standard of care and with sufficient follow-up to support regulatory review. As such, it includes

all postplatinum patients with *EGFR* Exon20ins enrolled on the CHRYSALIS study, through the clinical cutoff. An analysis of the entire *EGFR* Exon20ins population, including those without previous chemotherapy treatment, will be conducted after sufficient follow-up. As an exploratory phase I study that was not randomized and did not include a control arm, interpretation of the data must be made by historical comparison within the literature, or through the use of real-world evidence, to inform clinical outcomes in a population that has been excluded from most phase III *EGFR*-mutated NSCLC studies. Additionally, not all Exon20ins mutations were detectable by ctDNA analysis and tumor tissues were often not of sufficient quality or quantity, limiting genomic data available for central analysis. Finally, as patients with active or untreated brain metastases were excluded from the study, the activity of amivantamab in CNS disease will need to be explored in future studies.

In conclusion, amivantamab is the first bispecific antibody to demonstrate clinically meaningful efficacy in patients with *EGFR* Exon20ins NSCLC. Amivantamab has the potential to target other *EGFR*-driven and/or MET-driven tumors, as monotherapy or in combination, given its favorable safety profile.³²⁻³⁵ These combined approaches are under investigation in the CHRYSALIS study³⁵ and in frontline and relapsed *EGFR*-mutated NSCLC ([NCT04487080](#), [NCT04538664](#), and [NCT04077463](#)). These early data suggest that specificity of an antibody-based strategy can be successfully broadened through a bispecific approach, while maintaining clinically significant activity in a population thought to be dependent on only one of the targeted driver proteins.

AFFILIATIONS

¹Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

²H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

³Princess Margaret Cancer Centre, Toronto, Canada

⁴Olivia Newton-John Cancer Wellness and Research Centre, Austin Hospital, Heidelberg, Australia

⁵Columbia University Medical Center, New York, NY

⁶Institut Curie, Paris, France

⁷Instituto Oncológico Dr Rosell, Hospital Universitari Dexeus, Grupo QuironSalud, Barcelona, Spain

⁸National Cancer Center, Gyeonggi-do, South Korea

⁹Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

¹⁰St George Hospital, Kogarah, Australia

¹¹New York University School of Medicine, New York, NY

¹²Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA

¹³Taichung Veterans General Hospital, Taiwan, China

¹⁴Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea

¹⁵Chungbuk National University Hospital, Cheongju, South Korea

¹⁶Earle A. Childs Research Institute, Providence Cancer Institute, Portland, OR

¹⁷Hospital Universitario Virgen de la Victoria y Regional, IBIMA, Malaga, Spain

¹⁸National Cancer Center Hospital East, Kashiwa, Japan

¹⁹Seoul National University Bundang Hospital, Seongnam, South Korea

²⁰National Taiwan University Cancer Center, Taiwan, China

²¹Washington University School of Medicine, St Louis, MO

²²Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

²³Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain

²⁴Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester and The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

²⁵City of Hope Comprehensive Cancer Center, Duarte, CA

²⁶Janssen R&D, Spring House, PA

²⁷Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

CORRESPONDING AUTHOR

Byoung Chul Cho, MD, PhD, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; e-mail: cbc1971@yuhs.ac.

PRIOR PRESENTATION

Presented at the ASCO 2020 Annual Meeting, virtual, May 29-31, 2020, and updated data were presented at the International Association for the Study of Lung Cancer World Conference on Lung Cancer (WCLC) 2020 Annual Meeting, virtual, January 28-31, 2021.

SUPPORT

This study was funded by Janssen R&D LLC. M.G.K. acknowledges support from National Institute for Health Research (NIHR) Manchester Biomedical Research Centre and NIHR Manchester Clinical Research Facility at The Christie and Manchester Experimental Cancer Medicine Centre (Manchester, United Kingdom). Medical writing assistance was funded by Janssen Global Services LLC and provided by Tracy T. Cao, PhD (Janssen Global Services LLC).

CLINICAL TRIAL INFORMATION

NCT02609776 (CHRYSALIS)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.21.00662>.

DATA SHARING 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 site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at <http://yoda.yale.edu>.

AUTHOR CONTRIBUTIONS

Conception and design: Keunchil Park, Nicolas Girard, Santiago Viteri, Joshua K. Sabari, José Trigo, Jong-Seok Lee, John Xie, Roland E. Knoblauch, Byoung Chul Cho

Provision of study materials or patients: Keunchil Park, Natasha B. Leighl, Paul Mitchell, Santiago Viteri, Ji-Youn Han, Sang-We Kim, Alexander I. Spira, Dong-Wan Kim, Ki Hyeong Lee, Rachel E. Sanborn, José Trigo, Koichi Goto, James Chih-Hsin Yang, Ramaswamy Govindan, Joshua M. Bauml, Pilar Garrido, Matthew G. Krebs, Karen L. Reckamp, John Xie

Collection and assembly of data: Keunchil Park, Eric B. Haura, Natasha B. Leighl, Catherine A. Shu, Nicolas Girard, Santiago Viteri, Ji-Youn Han, Sang-We Kim, Chee Khoon Lee, Joshua K. Sabari, Alexander I. Spira, Tsung-Ying Yang, Ki Hyeong Lee, Rachel E. Sanborn, José Trigo, Koichi Goto, Jong-Seok Lee, James Chih-Hsin Yang, Ramaswamy Govindan, Joshua M. Bauml, Matthew G. Krebs, Karen L. Reckamp, John Xie, Dawn Millington, Patricia Lorenzini, Meena Thayu, Roland E. Knoblauch, Byoung Chul Cho

Data analysis and interpretation: Keunchil Park, Eric B. Haura, Natasha B. Leighl, Paul Mitchell, Catherine A. Shu, Nicolas Girard, Santiago Viteri, Ji-Youn Han, Sang-We Kim, Chee Khoon Lee, Joshua K. Sabari, Alexander I. Spira, Tsung-Ying Yang, Dong-Wan Kim, Ki Hyeong Lee, Rachel E. Sanborn, José Trigo, Koichi Goto, James Chih-Hsin Yang, Ramaswamy Govindan, Joshua M. Bauml, Pilar Garrido, Matthew G. Krebs, Karen L. Reckamp, John Xie, Joshua C. Curtin, Nahor Haddish-Berhane, Amy Roshak, Dawn Millington, Patricia Lorenzini, Meena Thayu, Roland E. Knoblauch, Byoung Chul Cho

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

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

K.L.R. is currently at Cedars-Sinai Medical Center, Los Angeles, CA.

REFERENCES

- Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350:2129-2139, 2004
- Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 304:1497-1500, 2004
- Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 101:13306-13311, 2004
- Arcila ME, Nafa K, Chaft JE, et al: EGFR exon 20 insertion mutations in lung adenocarcinomas: Prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther* 12:220-229, 2013
- Oxnard GR, Lo PC, Nishino M, et al: Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol* 8:179-184, 2013
- Riess JW, Gandara DR, Frampton GM, et al: Diverse EGFR exon 20 insertions and co-occurring molecular alterations identified by comprehensive genomic profiling of NSCLC. *J Thorac Oncol* 13:1560-1568, 2018
- Kumar A, Petri ET, Halmos B, et al: Structure and clinical relevance of the epidermal growth factor receptor in human cancer. *J Clin Oncol* 26:1742-1751, 2008
- Shigematsu H, Lin L, Takahashi T, et al: Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 97:339-346, 2005
- Bauml JM, Viteri S, Minchom A, et al: FP07.12 underdiagnosis of EGFR exon 20 insertion mutation variants: Estimates from NGS-based real-world datasets. *J Thorac Oncol* 16:S208-S209, 2021
- Kate S, Chougule A, Joshi A, et al: Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: A single center retrospective analysis. *Lung Cancer (Auckl)* 10:1-10, 2019
- Wu JY, Yu CJ, Shih JY: Effectiveness of treatments for advanced non-small-cell lung cancer with exon 20 insertion epidermal growth factor receptor mutations. *Clin Lung Cancer* 20:e620-e630, 2019
- Yang JC, Sequist LV, Geater SL, et al: Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: A combined post-hoc analysis of LUX-lung 2, LUX-lung 3, and LUX-lung 6. *Lancet Oncol* 16:830-838, 2015
- Kim TM, Ock C-Y, Kim M, et al: Phase II study of osimertinib in NSCLC patients with EGFR exon 20 insertion mutation: A multicenter trial of the Korean Cancer Study Group (LU17-19). *Ann Oncol* 30:V628, 2019
- Robichaux JP, Elamin YY, Tan Z, et al: Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med* 24:638-646, 2018

15. Dersarkissian M, Bhak R, Lin H, et al: Real-world treatment patterns and survival in non-small cell lung cancer patients with EGFR exon 20 insertion mutations. *J Thorac Oncol* 14:S681, 2019
16. Ramalingam SS, Vansteenkiste J, Planchard D, et al: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 382:41-50, 2020
17. Beau-Faller M, Prim N, Ruppert AM, et al: Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: A multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol* 25:126-131, 2014
18. Naidoo J, Sima CS, Rodriguez K, et al: Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. *Cancer* 121:3212-3220, 2015
19. Yasuda H, Park E, Yun CH, et al: Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med* 5:216ra177, 2013
20. Lee CK, Davies L, Wu YL, et al: Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: Individual patient data meta-analysis of overall survival. *J Natl Cancer Inst* 109, 2017
21. 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* 76:3942-3953, 2016
22. Vijayaraghavan S, Lipfert L, Chevalier K, et al: Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor down-modulation and antitumor activity by monocyte/macrophage trogocytosis. *Mol Cancer Ther* 19:2044-2056, 2020
23. 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* 10:1194-1209, 2020
24. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 22:1589-1597, 2004
25. Garon EB, Ciuleanu TE, Arrieta O, et al: Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. *Lancet* 384:665-673, 2014
26. Horn L, Lin HM, Padda SK, et al: Indirect comparison of TAK-788 vs real-world data outcomes in refractory non-small cell lung cancer (NSCLC) with EGFR exon 20 insertions. *J Clin Oncol* 38:9580, 2020
27. Le X, Goldman JW, Clarke JM, et al: Poziotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. *J Clin Oncol* 38, 2020 (abstr 9514)
28. Zhou C, Ramalingam S, Li B, et al: OA04.03 mobocertinib in NSCLC with *EGFR* exon 20 insertions: Results from EXCLAIM and pooled platinum-pretreated patient populations. *J Thorac Oncol* 16:S108, 2021
29. Huang S, van Duijnhoven SMJ, Sijts A, et al: Bispecific antibodies targeting dual tumor-associated antigens in cancer therapy. *J Cancer Res Clin Oncol* 146:3111-3122, 2020
30. Jarantow SW, Bushey BS, Pardinas JR, et al: Impact of cell-surface antigen expression on target engagement and function of an epidermal growth factor receptor x c-MET bispecific antibody. *J Biol Chem* 290:24689-24704, 2015
31. Park K, John T, Kim S-W, et al: Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). *J Clin Oncol* 38, 2020 (abstr 9512)
32. Haura EB, Cho BC, Lee JS, et al: JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 37, 2019 (abstr 9009)
33. Cho BC, Lee J-S, Han J-Y, et al: JNJ-61186372 (JNJ-372), an EGFR-cMET bispecific antibody, in advanced non-small cell lung cancer (NSCLC): An update on phase 1 results. *Ann Oncol* 29, 2018 (abstr VIII542)
34. Park K, Ahn M-J, Lee S-H, et al: A first-in-human phase 1 trial of the EGFR-cMET bispecific antibody JNJ-61186372 in patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol* 13:S344-S345, 2018
35. Cho BC, Lee KH, Cho EK, et al: 12580 Amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in combination with lazertinib, a 3rd-generation tyrosine kinase inhibitor (TKI), in advanced EGFR NSCLC. *Ann Oncol* 31:S813, 2020



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

Keunchil Park

Consulting or Advisory Role: AstraZeneca, Lilly, Ono Pharmaceutical, Bristol Myers Squibb, MSD, Blueprint Medicines, Amgen, Merck KGaA, LOXO, AbbVie, Daiichi Sankyo, Boehringer Ingelheim, JNJ, Eisai, Puma Biotechnology

Speakers' Bureau: Boehringer Ingelheim

Research Funding: AstraZeneca, MSD Oncology

Eric B. Haura

Consulting or Advisory Role: Janssen Oncology, Revolution Medicines, Ellipse Pharma, Janssen Research & Development, Amgen

Research Funding: Janssen, Novartis, Revolution Medicines, AstraZeneca, Incyte, Genentech, Spectrum Pharmaceuticals

Patents, Royalties, Other Intellectual Property: Protein-Protein Interactions as Biomarkers Patent

Natasha Leigh

Honoraria: Boehringer Ingelheim

Consulting or Advisory Role: Xcovery

Research Funding: Novartis, Roche Canada, Guardant Health, MSD, EMD Serono, Lilly

Travel, Accommodations, Expenses: Merck Sharp & Dohme, Bristol Myers Squibb, Nektar, GlaxoSmithKline, Roche, AstraZeneca

Paul Mitchell

Honoraria: MSD, AstraZeneca, Roche

Consulting or Advisory Role: Roche, Specialised Therapeutics, PUMA Biotechnology, AstraZeneca, Boehringer Ingelheim, BMS, MSD, Amgen

Catherine A. Shu

Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Genentech/Roche

Research Funding: Celgene, Genentech/Roche, Janssen, MedImmune

Travel, Accommodations, Expenses: Genentech/Roche

Nicolas Girard

Employment: AstraZeneca

Consulting or Advisory Role: Roche, Lilly, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Bristol Myers Squibb, MSD, Takeda, GlaxoSmithKline, AbbVie, Pharmamar, Janssen, Sanofi

Research Funding: Roche, AstraZeneca, Boehringer Ingelheim

Travel, Accommodations, Expenses: Roche, AstraZeneca, Bristol Myers Squibb, MSD Oncology

Santiago Viteri

Consulting or Advisory Role: Roche, Bristol Myers Squibb, Janssen, Takeda, Reddy Pharma Iberia, Merck KGaA

Speakers' Bureau: Bristol Myers Squibb, Roche

Travel, Accommodations, Expenses: Roche, MSD, Merck KGaA

Ji-Youn Han

Honoraria: Roche, AstraZeneca, Bristol Myers Squibb, Takeda

Consulting or Advisory Role: MSD Oncology, AstraZeneca, Bristol Myers Squibb, Lilly, Novartis, Takeda, Pfizer

Research Funding: Roche, Pfizer, Ono Pharmaceutical, Takeda

Chee Khoon Lee

Honoraria: AstraZeneca, Pfizer, Amgen, Takeda, Yuhan, Boehringer Ingelheim

Consulting or Advisory Role: Novartis, Boehringer Ingelheim, Takeda, AstraZeneca, Yuhan, Amgen

Research Funding: AstraZeneca, Roche, Merck KGaA

Joshua K. Sabari

Consulting or Advisory Role: AstraZeneca, Janssen Oncology, Navire, Pfizer, Regeneron, Medscape, Takeda

Alexander I. Spira

Stock and Other Ownership Interests: Lilly

Honoraria: CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol Myers Squibb, Bayer

Consulting or Advisory Role: Array BioPharma, Incyte, Amgen, Novartis, AstraZeneca/MedImmune, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Merck, Bristol Myers Squibb

Research Funding: Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, NewLink Genetics, Incyte, AbbVie, Ignyta, LAM Therapeutics, Trovogene, Takeda, MacroGenics, CytomX Therapeutics, LAM Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone Oncology, Plexikon, Amgen, Loxo, Daiichi Sankyo, ADC Therapeutics, Janssen Oncology, Mirati Therapeutics, Rubius Therapeutics

Dong-Wan Kim

Research Funding: Alpha Biopharma, AstraZeneca/MedImmune, Hanmi, Janssen, Merus, Mirati Therapeutics, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, Yuhan, Boehringer Ingelheim, Amgen, Daiichi Sankyo, Chong Kun Dang Pharmaceutical, BridgeBio Pharma, GlaxoSmithKline

Travel, Accommodations, Expenses: Daiichi Sankyo, Amgen

Ki Hyeong Lee

Consulting or Advisory Role: Bristol Myers Squibb, MSD, AstraZeneca, Pfizer, Lilly

Rachel E. Sanborn

Honoraria: AstraZeneca, Amgen

Consulting or Advisory Role: Genentech/Roche, AstraZeneca, EMD Serono, Blueprint Medicines, Daiichi Sankyo/Lilly, Janssen Oncology, MacroGenics

Research Funding: Bristol Myers Squibb, MedImmune, Merck, AstraZeneca

Travel, Accommodations, Expenses: AstraZeneca

José Trigo

Consulting or Advisory Role: Takeda, Boehringer Ingelheim, Bristol Myers Squibb, Merck Serono

Speakers' Bureau: MSD Oncology, AstraZeneca, Merck Serono, Roche

Travel, Accommodations, Expenses: MSD Oncology, Bristol Myers Squibb, AstraZeneca

Koichi Goto

Honoraria: Guardant Health, Janssen, Daiichi Sankyo Co Ltd, Amgen, Eisai, Kyowa Kirin Co Ltd, Bristol Myers Squibb, AstraZeneca Japan, Pfizer, Chugai Pharma, Taiho Pharmaceutical, Ono Pharmaceutical, Novartis, Lilly Japan, Boehringer Ingelheim, Life Technologies, MSD K.K., Nippon Kayaku, Takeda, Otsuka

Consulting or Advisory Role: Otsuka

Research Funding: Medical & Biological Laboratories Co Ltd, Kyowa Kirin Co Ltd, Amgen Astellas BioPharma, Kissei Pharmaceutical, Merck, Merus, NEC Corporation, Spectrum Pharmaceuticals, Shanghai HaiHe Pharmaceutical, MSD K.K., AstraZeneca Japan, Taiho Pharmaceutical, Chugai Pharma, Boehringer Ingelheim, Ono Pharmaceutical, Sumitomo Dainippon Pharma Co Ltd, Takeda, Astellas Pharma, Eisai, Lilly Japan, Pfizer, Bristol Myers Squibb, Ignyta, Life Technologies, Janssen, Xcoo, Loxo, Sysmex, Amgen

James Chih-Hsin Yang

Honoraria: Boehringer Ingelheim, Roche, MSD, AstraZeneca, Novartis, Bristol Myers Squibb, Ono Pharmaceutical, Takeda, Lilly, Pfizer

Consulting or Advisory Role: Boehringer Ingelheim, Novartis, AstraZeneca, Clovis Oncology, Lilly, MSD Oncology, Merck Serono, Celgene, Bayer, Pfizer, Ono Pharmaceutical, Bristol Myers Squibb, Yuhan, Hansoh, Blueprint Medicines, Daiichi Sankyo, G1 Therapeutics, AbbVie, Takeda Oncology, Amgen, Incyte, Merck Serono, Janssen, GSK, Takeda, Daiichi Sankyo, Novartis

Travel, Accommodations, Expenses: Pfizer

Ramaswamy Govindan

Honoraria: Genentech/AbbVie, AbbVie, Genepus-Beijing Institute

Consulting or Advisory Role: Genentech/Roche, AbbVie, AstraZeneca/MedImmune, Pfizer, Bristol Myers Squibb, Nektar, Jounce Therapeutics, F. Hoffmann La Roche AG, Janssen, Amgen, Achilles Therapeutics

Joshua M. Bauml

Consulting or Advisory Role: Bristol Myers Squibb, Merck, AstraZeneca, Genentech, Celgene, Boehringer Ingelheim, Guardant Health, Takeda, Novartis, Janssen, Ayala Pharmaceuticals, Regeneron, Inivata, Novartis, Foundation Medicine

Research Funding: Merck, Carevive Systems, Novartis, Incyte, Bayer, Janssen, AstraZeneca, Takeda, Amgen, Pfizer, Mirati Therapeutics

Pilar Garrido

Consulting or Advisory Role: Roche Pharma AG, AstraZeneca, MSD Oncology, Bristol Myers Squibb, Takeda, Lilly, Pfizer, Novartis/Pfizer, Boehringer Ingelheim, AbbVie, Amgen, Bayer, Gebro Pharma, Nordic Group, Boehringer Ingelheim, Janssen Biotech, Janssen Oncology, GlaxoSmithKline

Speakers' Bureau: Roche Pharma AG, Takeda, AstraZeneca, MSD Oncology, BMS, Pfizer, Novartis, Boehringer Ingelheim, Nordic Group, Janssen, Boehringer Ingelheim, Janssen Oncology

Travel, Accommodations, Expenses: AstraZeneca, Roche, Bristol Myers Squibb
Other Relationship: Janssen Oncology, Novartis

Matthew G. Krebs

Honoraria: Roche

Consulting or Advisory Role: Roche, Achilles Therapeutics, Janssen, Seattle Genetics, OM Pharma, Bayer

Speakers' Bureau: Roche, Janssen

Research Funding: Roche

Travel, Accommodations, Expenses: AstraZeneca, BerGenBio, Immunetp

Karen L. Reckamp

Consulting or Advisory Role: Amgen, Tesaro, Boehringer Ingelheim, Takeda, AstraZeneca, Seattle Genetics, Calithera Biosciences, Genentech, Blueprint Medicines, Daiichi Sankyo/Lilly, EMD Serono, Janssen Oncology, Lilly, Merck KGaA

Research Funding: Bristol Myers Squibb, Pfizer, ARIAD, Xcovery, Adaptimmune, Genentech/Roche, Boehringer Ingelheim, AbbVie, ACEA Biosciences, Loxo, GlaxoSmithKline, Guardant Health, Janssen Oncology, Seattle Genetics, Zeno Pharmaceuticals, Calithera Biosciences, Elevation Oncology, Daiichi Sankyo/Astra Zeneca

John Xie

Employment: JNJ

Stock and Other Ownership Interests: JNJ

Joshua C. Curtin

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Nahor Haddish-Berhane

Employment: Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Amy Roshak

Employment: Janssen Pharmaceutical Company of Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Dawn Millington

Employment: Janssen Research & Development

Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Travel, Accommodations, Expenses: Janssen Research & Development

Patricia Lorenzini

Employment: Janssen Pharmaceuticals of Johnson & Johnson

Meena Thayu

Employment: Janssen Oncology

Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Other Relationship: Janssen Oncology

Roland E. Knoblauch

Employment: Johnson & Johnson

Stock and Other Ownership Interests: Johnson & Johnson

Travel, Accommodations, Expenses: Johnson & Johnson

Byoung Chul Cho

Leadership: Gencurix Inc, Interpark Bio Convergence Corp

Stock and Other Ownership Interests: TheraCanVac Inc, Gencurix Inc, Bridgebio Therapeutics, KANAPH Therapeutic Inc, Cyrus Therapeutics, Interpark Bio Convergence Corp

Consulting or Advisory Role: Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol Myers Squibb, Yuhan, Pfizer, Janssen, Takeda, MSD, Ono Pharmaceutical, Eli Lilly, Medpacto, Blueprint Medicines, KANAPH Therapeutic Inc, Brigebio Therapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc

Research Funding: Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dival Pharma, MSD, AbbVie, Medpacto, GInnovation, Eli Lilly, Blueprint Medicines, Interpark Bio Convergence Corp

Patents, Royalties, Other Intellectual Property: Champions Oncology

Other Relationship: DAAN Biotherapeutics

No other potential conflicts of interest were reported.

APPENDIX 1. List of Investigators

Principal Investigator	Clinical Site	No. of Patients Enrolled
Byoung Chul Cho	Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea	54
Keunchil Park	Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea	45
Eric Haura	H. Lee Moffitt Cancer and Research Institute, Tampa, FL	15
Jong-Seok Lee	Seoul National University Bundang Hospital, Seongnam, South Korea	14
Joshua Sabari	NYU School of Medicine, New York, NY	14
Joshua Bauml	Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA	12
Catherine Shu	Columbia University Medical Center, New York, NY	12
Koichi Goto	National Cancer Center Hospital East, Kashiwa, Japan	11
Ji-Youn Han	National Cancer Center, Goyang-si, South Korea	10
Natasha Leighl	University Health Network, Toronto, Canada	10
Dong Wan Kim	Seoul National University Hospital, Seoul, South Korea	9
Karen Reckamp; Ravi Salgia	City of Hope, Duarte, CA	9
Ramaswamy Govindan	Washington University School of Medicine, St Louis, MO	8
Ki Hyeong Lee	Chungbuk National University Hospital, Cheongju, South Korea	8
Rachel Sanborn	Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR	8
Alexander Spira	Virginia Cancer Specialists, Fairfax, VA	8
Nicolas Girard	Institut Curie, Paris, France	6
Chee Lee	St George Hospital, Kogarah, Australia	6
Pascale Tomasini	Hopital de la Timone, Marseille, France	6
James Chih-Hsin Yang	National Taiwan University Cancer Center, Taiwan, China	6
Benjamin Besse	Institut Gustave Roussy, Villejuif, France	5
Enriqueta Felip	Vall d'Hebron University Hospital, Barcelona, Spain	5
Pasi Janne	Dana Farber Cancer Institute, Boston, MA	5
Sang-We Kim	Asan Medical Center, Seoul, South Korea	5
Aaron Mansfield	Mayo Clinic, Rochester, NY	5
Paul Mitchell	Olivia Newton-John Cancer Wellness and Research Centre, Austin Hospital, Heidelberg, Australia	5
Santiago Viteri	Instituto Oncológico Dr Rosell, Centro Médico Teknon, Grupo QuironSalud, Barcelona, Spain	5
Eun Kyung Cho	Gachon University Gil Medical Center, Incheon, South Korea	4
Jorge Gomez	Icahn School of Medicine at Mt Sinai, New York, NY	4
Yuichiro Ohe	National Cancer Center Hospital, Tokyo, Japan	4
Jose Trigo	Hospital Universitario Virgen de la Victoria y Regional, IBIMA, Malaga, Spain	4
Rosa Álvarez	Hospital General Universitario Gregorio Marañón, Madrid, Spain	3
Pilar Garrido	Hospital Ramón y Cajal, Madrid, Spain	3
Anna Minchom	Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, United Kingdom	3
Hiroshi Tanaka	Niigata Cancer Center Hospital, Niigata, Japan	3

(continued on following page)

(continued)

Principal Investigator	Clinical Site	No. of Patients Enrolled
Tsung-Ying Yang	Taichung Veterans General Hospital, Taiwan, China	3
Qing Zhou	Guangdong Provincial People's Hospital, Guangzhou, China	3
Michael Boyer	Chris O'Brien Lifehouse, Camperdown, Australia	2
Philippe Cassier	Centre Leon Bérard, Lyon, France	2
Chao-Hua Chiu	Taipei Veterans General Hospital, Taipei City, China	2
Yoshihiro Hattori	Hyogo Cancer Center, Akashi, Japan	2
Toyoaki Hida	Aichi Cancer Center Hospital, Nagoya-Shi, Japan	2
Te-Chun Hsia	China Medical University Hospital, Taichung, China	2
Sophie Cousin	Institut Bergonié, Bordeaux, France	1
Maria Jose De Miguel	HM University Sanchinarro Hospital, Madrid, Spain	1
Jonathan Goldman	University of California Los Angeles, Los Angeles, CA	1
Alastair Greystoke	Sir Bobby Robson Unit, Northern Centre for Cancer Care, Newcastle upon Tyne, United Kingdom	1
Matthew Krebs	The Christie NHS Foundation Trust, Manchester, United Kingdom	1
Victor Moreno	Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain	1
Makoto Nishio	The Cancer Institute Hospital of JFCR, Tokyo, Japan	1
Sai-Hong Ignatius Ou	Chao Family Comprehensive Cancer Center, Orange, CA	1
Yuichi Ozawa	Wakayama Medical University Hospital, Wakayama, Japan	1
Tomohiro Sakamoto	Tottori University Hospital, Yonago, Japan	1