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

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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, ≥ 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.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

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

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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 (≤ 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]

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

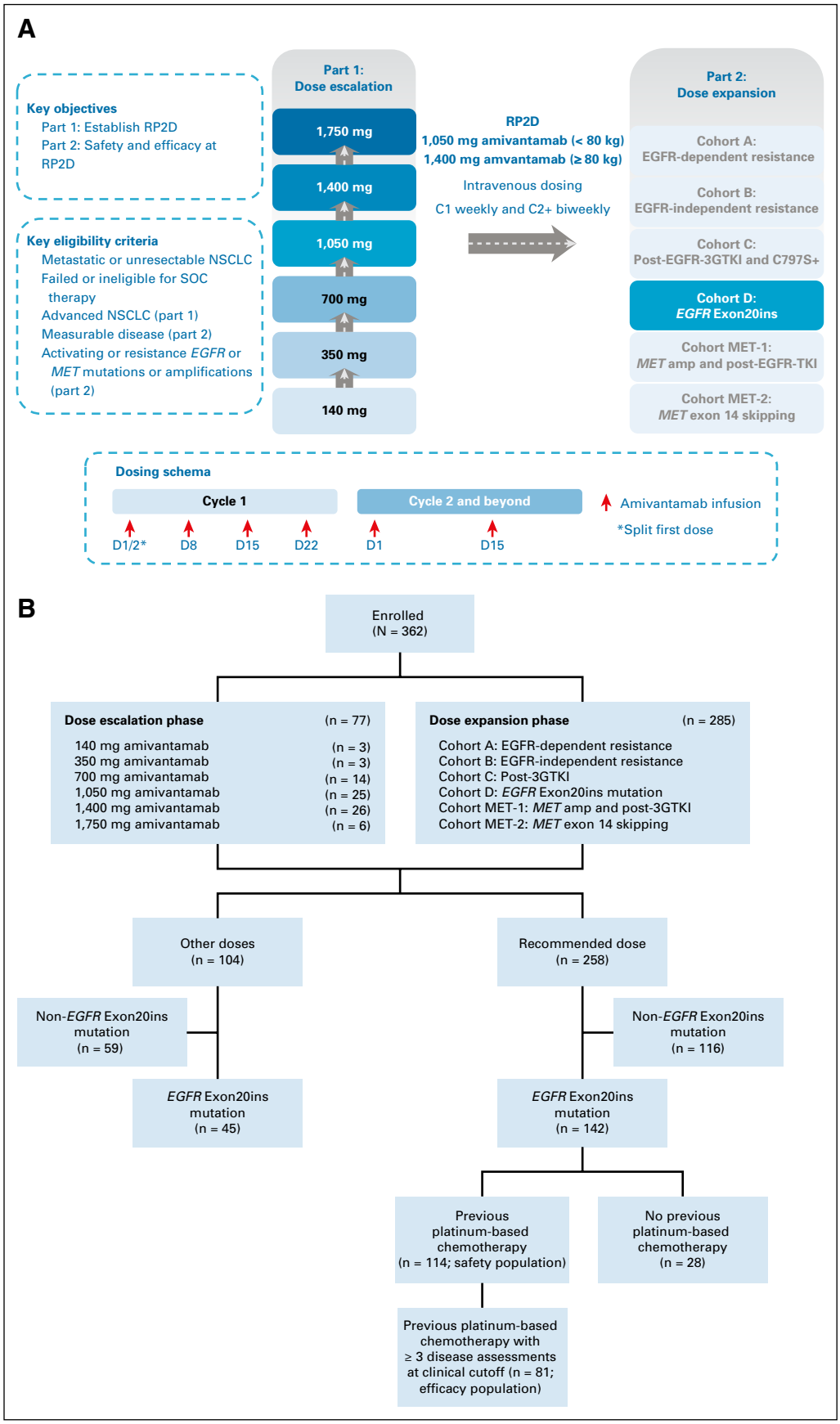

FIG 1. CHRYSALIS study design and patient disposition for amivantamab monotherapy. The CHRYSALIS study consisted of a dose-escalation and dose-expansion phase. (A) Patients with advanced (continued on following page)

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 Oncomine 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 ≥ 35%, an enrollment of ≥ 60 patients was estimated to achieve a lower bound of 95% CI ≥ 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, years (range)	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, months (range)	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.

[a]The efficacy population includes four patients from the dose-escalation phase.

[b]Patients could be counted in more than one category.

[c]Erlotinib and gefitinib.

[d]Afatinib.

[e]Osimertinib, ASP8273, and nintedanib.

[f]Poziotinib 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 ≥ 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 μg/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 ≥ 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 ≥ 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%).

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 ≥ 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)

	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
Most Common AE (≥ 10%)	Total	Grade 1	Grade 2	Grade ≥ 3	Total	Grade 1	Grade 2	Grade ≥ 3
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.

[a]Excludes infusion-related reactions.

[b]Rash 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.

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

[a]Proportion of total patients in the efficacy population who had partial and complete response.

[b]Proportion 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 the 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

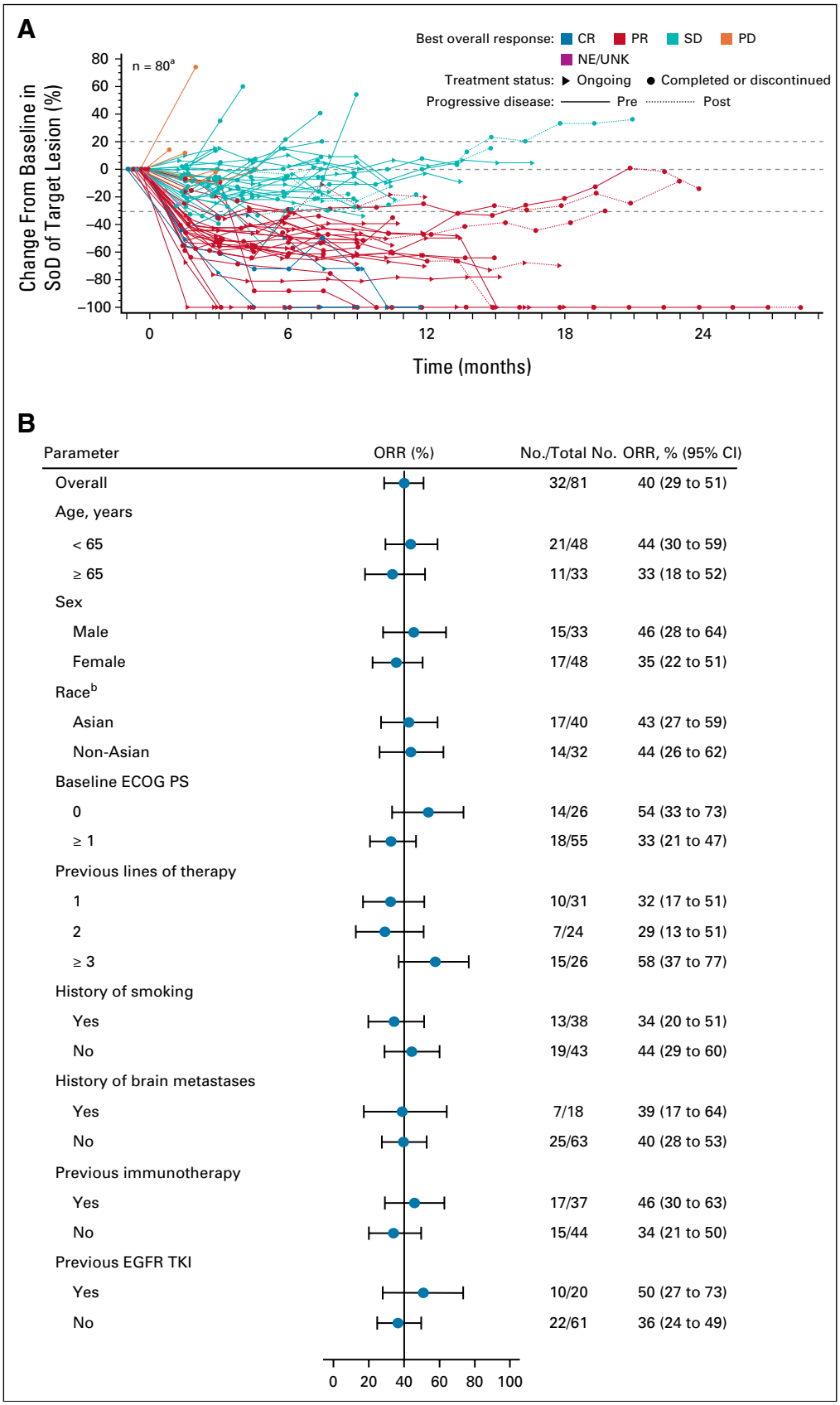

FIG 2. Tumor response over time and ORR by subgroups. (A) Spider plot of percent change from baseline in sum of target lesion diameters over time in the efficacy population (n = 81) as assessed (continued on following page)

FIG 2. (Continued). by BICR. [a]One 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. [b]Does 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

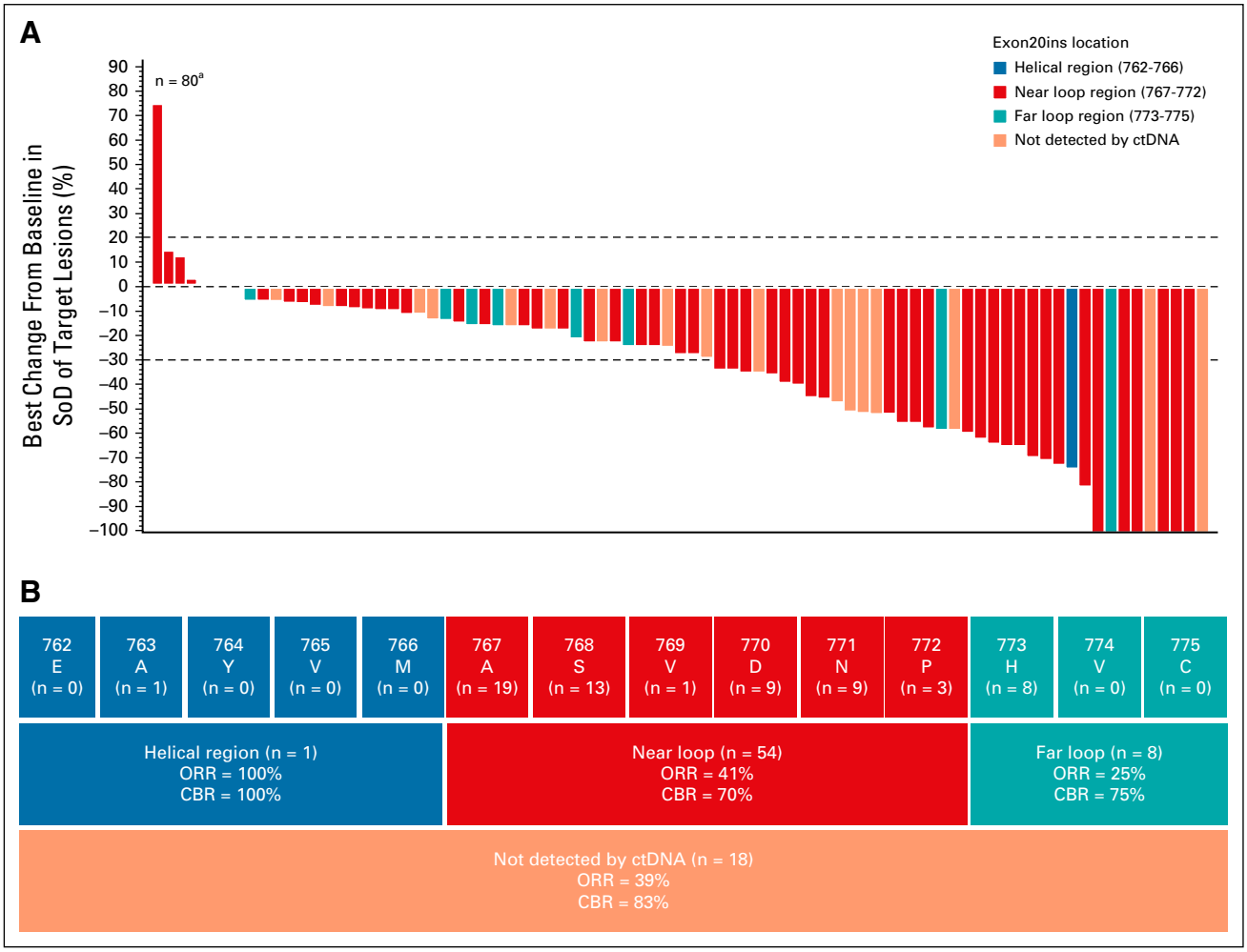

FIG 3. Tumor reduction and responses in the efficacy population. (A) Waterfall plot displaying best percent change from baseline in sum of target lesion diameters by location of *EGFR* Exon20ins (determined by Guardant360 testing) for patients in the efficacy population (n = 81) as assessed by BICR. [a]One 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 study[35] 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.

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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.

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

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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, Dizal Pharma, MSD, AbbVie, Medpacto, GIInnovation, 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

TABLE. 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
Tsung-Ying Yang	Taichung Veterans General Hospital, Taiwan, China	3

(continued on following page)

TABLE. List of Investigators (continued)

Principal Investigator	Clinical Site	No. of Patients Enrolled
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