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

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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 CHRYSLIS 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, $\leq 80$ 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.

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. CHRYSLIS study design and patient disposition for amivantamab monotherapy. The CHRYSLIS study consisted of a dose-escalation and dose-expansion phase. (A) Patients with advanced (continued on following page)
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 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 discontinued, had disease progression, or died and were defined as the pivotal efficacy population.

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 81 patients enrolled (four from dose expansion cohorts only). Monitoring for CNS disease was not mandatory and performed in accordance with local practice.

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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.
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 mg/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 acniform) 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 1. Demographic and Baseline Disease Characteristics

| Characteristic | Dose Escalation (n = 77) | Efficacy Population (n = 81)* |
|---------------|-------------------------|-------------------------------|
| 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, 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. (%) | | |
| Platinum-based chemotherapy | 63 (82) | 81 (100) |
| Immuno-oncology therapy | 29 (38) | 37 (46) |
| EGFR TKI, No. (%) | | |
| 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.

$^f$Pozotinib and mobocertinib.
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 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*   | 40 (35)                             | 88 (34)                                       |

#### Most Common AE (≥ 10%)

| Event                              | Safety Population (n = 114), No. (%) | Patients Treated at the RP2D (n = 258), No. (%) |
|------------------------------------|-------------------------------------|-----------------------------------------------|
| Rashb                             | Total 98 (86)                        | Total 202 (78)                                 |
| Infusion-related reaction         | Grade 1 43 (38)                     | Grade 1 101 (39)                               |
| Paronychia                        | Grade 2 51 (45)                     | Grade 2 94 (36)                                |
| Hypoalbuminemia                   | Grade 3 4 (4)                       | Grade 3 7 (3)                                  |
| Constipation                      | Total 27 (24)                       | Total 58 (23)                                  |
| Nausea                            | Grade 1 17 (15)                     | Grade 1 36 (14)                                |
| Dyspnea                           | Grade 2 5 (4)                       | Grade 2 22 (9)                                 |
| Stomatitis                        | Grade 3 0                           | Grade 3 0                                      |
| Peripheral edema                  | Total 21 (18)                       | Total 55 (21)                                  |
| Pruritus                           | Grade 1 17 (15)                     | Grade 1 40 (16)                                |
| Fatigue                           | Grade 2 5 (4)                       | Grade 2 14 (5)                                 |
| Cough                             | Grade 3 0                           | Grade 3 1 (0.4)                                |
| Decreased appetite                | Total 16 (14)                       | Total 39 (15)                                  |
| Dry skin                          | Grade 1 7 (6)                       | Grade 1 23 (9)                                 |
| Increased alanine aminotransferase| Grade 2 9 (8)                       | Grade 2 16 (6)                                 |
| Vomiting                          | Grade 3 0                           | Grade 3 0                                      |
| Myalgia                           | Total 14 (12)                       | Total 30 (12)                                  |
| Dizziness                         | Grade 1 11 (10)                     | Grade 1 22 (9)                                 |
| Headache                          | Grade 2 5 (4)                       | Grade 2 6 (2)                                  |
| Increased blood alkaline phosphatase| Grade 3 1 (1)                   | Grade 3 1 (0.4)                                |
| Diarrhea                          | Total 10 (9)                        | Total 28 (11)                                  |
| Back pain                         | Grade 1 8 (7)                       | Grade 1 23 (9)                                 |
| Pyrexia                           | Grade 2 2 (2)                       | Grade 2 5 (2)                                  |
| Hypokalemia                       | Grade 3 0                           | Grade 3 0                                      |

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

*Excludes infusion-related reactions.

*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.
TABLE 3. Response as Assessed by Blinded Independent Central Review

| Response per RECIST | Efficacy Population (n = 81) |
|---------------------|-----------------------------|
| ORR, % (95% CI)     | 40 (29 to 51)               |
| CBR, % (95% CI)     | 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.

*Proportion of total patients in the efficacy population who had partial and complete response.

*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).

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. Using a similar real-world data set, a median OS of 12.5 months was reported in the relapsed or refractory setting. 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. 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.

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)
The bispecific nature of amivantamab may affect the safety profile, potentially through altered target cell selectivity (eg, tumor cells).

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%.

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**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. *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. *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.
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.

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Amivantamab in EGFR Exon20ins NSCLC Postplatinum Chemotherapy

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.

REFERENCES
1. 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
2. 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
3. Pao W, Miller V, Zakowski M, et al: EGFR 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
4. Arriola 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. Wu YJ, 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
12. 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:e830-e836, 2015
13. 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:W628, 2019
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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.

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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 14:5681, 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. 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

24. 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

25. Le X, Goldman JW, Clarke JM, et al: Pozotinib shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients. J Clin Oncol 38, 2020 (abstr 9514)

26. 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 VIII542)

27. Park K, Ahn M-J, Lee S-H, et al: A first-in-human phase 1 trial of the EGFR-c Met bispecific antibody JNJ-61186372 in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 37, 2019 (abstr 9512)

28. Cho BC, Lee K, 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
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/fwc or ascopubs.org/loc/authors/author-center.

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### APPENDIX

| 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                        |
| K 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)
| Principal Investigator | Clinical Site                                                                 | No. of Patients Enrolled |
|------------------------|--------------------------------------------------------------------------------|--------------------------|
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| 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 Diaz, Madrid, Spain                  | 1                        |
| Makoto Nishio           | The Cancer Institute 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                        |