ORIGINAL ARTICLE

Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions

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ABSTRACT

BACKGROUND

Amivantamab has been approved for the treatment of patients with advanced non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertions who have had disease progression during or after platinum-based chemotherapy. Phase 1 data showed the safety and antitumor activity of amivantamab plus carboplatin–pemetrexed (chemotherapy). Additional data on this combination therapy are needed.

METHODS

In this phase 3, international, randomized trial, we assigned in a 1:1 ratio patients with advanced NSCLC with *EGFR* exon 20 insertions who had not received previous systemic therapy to receive intravenous amivantamab plus chemotherapy (amivantamab–chemotherapy) or chemotherapy alone. The primary outcome was progression-free survival according to blinded independent central review. Patients in the chemotherapy group who had disease progression were allowed to cross over to receive amivantamab monotherapy.

RESULTS

A total of 308 patients underwent randomization (153 to receive amivantamab–chemotherapy and 155 to receive chemotherapy alone). Progression-free survival was significantly longer in the amivantamab–chemotherapy group than in the chemotherapy group (median, 11.4 months and 6.7 months, respectively; hazard ratio for disease progression or death, 0.40; 95% confidence interval [CI], 0.30 to 0.53; P<0.001). At 18 months, progression-free survival was reported in 31% of the patients in the amivantamab–chemotherapy group and in 3% in the chemotherapy group; a complete or partial response at data cutoff was reported in 73% and 47%, respectively (rate ratio, 1.50; 95% CI, 1.32 to 1.68; P<0.001). In the interim overall survival analysis (33% maturity), the hazard ratio for death for amivantamab–chemotherapy as compared with chemotherapy was 0.67 (95% CI, 0.42 to 1.09; P=0.11). The predominant adverse events associated with amivantamab–chemotherapy were reversible hematologic and EGFR-related toxic effects; 7% of patients discontinued amivantamab owing to adverse reactions.

CONCLUSIONS

The use of amivantamab–chemotherapy resulted in superior efficacy as compared with chemotherapy alone as first-line treatment of patients with advanced NSCLC with *EGFR* exon 20 insertions. (Funded by Janssen Research and Development; PAPILLON ClinicalTrials.gov number, NCT04538664.)

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*A complete list of the investigators in the PAPILLON trial is provided in the Supplementary Appendix, available at NEJM.org.

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Alterations in the gene encoding epidermal growth factor receptor (*EGFR*) are among the most frequent activating mutations in non–small-cell lung cancer (NSCLC).[1,2] Insertions in exon 20 are the third most common type of *EGFR* mutation, representing up to 12% of all *EGFR*-mutated NSCLCs.[3-6] Because of an altered conformation at the kinase-active site that limits the binding of tyrosine kinase inhibitors, NSCLC with insertions in *EGFR* exon 20 is largely insensitive to tyrosine kinase inhibitors that have been approved for the treatment of patients with common *EGFR*-mutated NSCLC.[7,8]

The first-line standard therapy for locally advanced or metastatic NSCLC with *EGFR* exon 20 insertions remains platinum-based chemotherapy, owing to the lack of targeted therapies and no demonstrated benefit from immunotherapies.[9-11] In such cases, platinum-based chemotherapy is associated with an objective response of 23 to 29% and a median progression-free survival of 3.4 to 6.9 months.[12] Although patients with common *EGFR*-mutated NSCLC have a median overall survival of up to 38.6 months,[13] recent analyses of real-world data obtained from patients with advanced NSCLC with *EGFR* exon 20 insertions showed a median overall survival ranging from 16.2 to 24.3 months,[14-16] with a 5-year overall survival of 8%.[14]

Amivantamab is an EGFR mesenchymal–epithelial transition factor (MET) bispecific antibody with immune cell–directing activity that has multiple mechanisms of action as defined in preclinical models. These mechanisms include the inhibition of ligand binding, endocytosis and degradation of receptors, and the engagement of macrophages, monocytes, and natural killer cells through its Fc domain.[17-20] Collectively, these mechanisms can bypass the ligand-site resistance against tyrosine kinase inhibitors in patients who have NSCLC with *EGFR* exon 20 insertions, address MET as a bypass resistance mechanism, and recruit effector cells to exert an anticancer effect. On the basis of the results of the phase 1 CHRYSALIS trial, amivantamab was approved for the treatment of patients with advanced NSCLC with *EGFR* exon 20 insertions,[21] with results that included an objective response of 40% and a median response duration of 11.1 months on blinded independent central review. In this trial, patients had a median progression-free survival of 8.3 months and a median overall survival of 22.8 months.[22] Indirect comparisons with the use of real-world data showed that the use of amivantamab resulted in better outcomes than other real-world therapies.[23]

Amivantamab plus carboplatin–pemetrexed (amivantamab–chemotherapy) was previously studied in 20 patients with NSCLC who were enrolled in the CHRYSALIS trial.[24] The safety profile was consistent with that of each individual agent, and amivantamab exposure was not adversely affected in combination with chemotherapy. In addition, among 5 patients who had not received previous treatment for NSCLC with *EGFR* exon 20 insertions, 4 had a partial response to amivantamab–chemotherapy. These findings, coupled with the aforementioned immune-cell engagement of amivantamab, suggested the potential for synergy with chemotherapy.

We conducted the phase 3, international, randomized PAPILLON trial to assess the efficacy and safety of amivantamab–chemotherapy as compared with standard chemotherapy alone as first-line treatment in patients with advanced NSCLC with *EGFR* exon 20 insertions.

METHODS

PATIENTS

Eligible patients were 18 years of age or older and had received no previous treatment for locally advanced or metastatic NSCLC with insertions in *EGFR* exon 20. Brief monotherapy with an approved EGFR tyrosine kinase inhibitor (i.e., gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib) was allowed if a lack of response had been documented. Patients with treated brain metastases were eligible if they were asymptomatic, if their condition was clinically stable, and if they had received no glucocorticoid treatment for at least 2 weeks before randomization. For additional inclusion and exclusion criteria, see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

OVERSIGHT

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, Janssen Research and Development. The

trial was designed by representatives of the sponsor, who were responsible for the collection and analysis of the data and for the interpretation of the trial data in collaboration with the authors. The first draft of the manuscript was written by the authors, with medical writing assistance funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, which is available at NEJM.org.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive amivantamab–chemotherapy or chemotherapy alone in 21-day cycles (Fig. S1 in the Supplementary Appendix). Intravenous amivantamab at a dose of 1400 mg (1750 mg for a body weight of ≥80 kg) was administered weekly for the first 4 weeks, with the first infusion split over 2 days (at a dose of 350 mg on cycle 1, day 1, and the remainder on cycle 1, day 2). Starting at cycle 3 (week 7), the dose of amivantamab was increased to 1750 mg (2100 mg for a body weight of ≥80 kg) administered every 3 weeks until disease progression. Carboplatin was administered at an area under the concentration-time curve of 5 mg per milliliter per minute (AUC 5) for up to 4 cycles. Pemetrexed was administered at a dose of 500 mg per square meter of body-surface area until disease progression.

Treatment blinding was not feasible because of differences in administration, premedication requirements, and safety profiles of the regimens. Patients in the chemotherapy-only group could cross over to receive amivantamab monotherapy (on an every-3-week regimen) after documented disease progression according to blinded independent central review. Randomization was stratified according to the performance-status score (0 or 1) on the Eastern Cooperative Oncology Group (ECOG) scale (a 5-point scale with higher numbers reflecting greater disability), history of brain metastases (yes or no), and previous receipt of an EGFR tyrosine kinase inhibitor (yes or no).

OUTCOMES

The primary outcome was progression-free survival as determined by blinded independent central review according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.[25] Key secondary outcomes were objective response, overall survival, response duration, time to subsequent therapy, progression-free survival after first subsequent therapy, symptomatic progression-free survival, and safety. A complete list of secondary outcomes is available in the protocol.

Progression-free survival was defined as the time from randomization until the date of objective disease progression or death, whichever came first. An objective response was defined as a complete or partial response according to the RECIST definition. Overall survival was defined as the time from randomization until death from any cause.

ASSESSMENTS

Disease assessments (computed tomography or magnetic resonance imaging) were performed within 28 days after randomization, then at 6 weeks (maximum, 7 weeks) after randomization and subsequently every 6 weeks (within a 1-week window) for the first 18 months and every 12 weeks (also within a 1-week window) thereafter until disease progression. All assessments were performed by blinded independent central review according to RECIST definitions. Survival, subsequent treatment, and disease status were assessed approximately every 12 weeks after disease progression. All the patients were required to undergo brain imaging at baseline; however, subsequent imaging was performed according to local standards. Adverse events, vital signs, and laboratory tests were assessed at each visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Electrocardiograms were assessed at baseline and at cycle 3, day 1.

STATISTICAL ANALYSIS

The efficacy analysis included all the patients who had undergone randomization; the safety analysis included all the patients who were included in the efficacy analysis and who had received at least one dose of any trial treatment. For the calculation of progression-free survival (the primary outcome), we estimated that a sample of at least 300 patients with 200 events of disease progression or death would provide the trial with 90% power to detect a hazard ratio of 0.625 at a two-sided alpha level of 0.05. This estimation corresponded to an extension of at least 3 months in median progression-free survival, which was estimated at 8 months in the amivantamab–chemo-

therapy group and 5 months in the chemotherapy-only group.

We evaluated the treatment effect of amivantamab–chemotherapy as compared with chemotherapy alone using a log-rank test that was stratified according to the ECOG performance-status score and history of brain metastases. Previous use of an EGFR tyrosine kinase inhibitor was removed from the stratification analysis because only 4 patients met this criterion. The P value that was generated from the stratified log-rank test was used for primary hypothesis testing. We estimated the hazard ratio and its 95% confidence interval using a stratified Cox regression model with treatment as the sole explanatory variable. A hierarchical testing approach was used according to the following sequence: progression-free survival, then objective response, and followed by overall survival. An interim overall survival analysis was planned at the time of the primary analysis for progression-free survival. Additional statistical and crossover details are described in the Supplementary Appendix.

The analyses of the additional secondary or other outcomes including the subgroup analyses were not part of the hypothesis testing in the trial. Therefore, the results are reported as point estimates and 95% confidence intervals without adjustment for multiplicity. All the data that are reported here are based on the primary analysis and were reported before the data-cutoff date of May 3, 2023.

RESULTS

PATIENTS AND TREATMENT

From December 2020 to November 2022, a total of 542 patients were screened, and 308 patients underwent randomization (153 to receive amivantamab–chemotherapy and 155 to receive chemotherapy alone). A total of 306 patients received at least one dose of a trial treatment (2 patients in the amivantamab–chemotherapy group discontinued before receiving treatment) (Fig. S2). The demographic characteristics of the patients were well balanced between the two groups (Table 1). The percentages of female patients, Asian patients, and patients who had never smoked were representative of the population with NSCLC with *EGFR* exon 20 insertions (Table S1). The patients' mutational status was determined by local testing of tissue samples (in 92% of cases) or plasma samples (in 8% of cases).

At a median follow-up of 14.9 months, the median treatment duration was 9.7 months (range, 0.1 to 26.9) with amivantamab–chemotherapy and 6.7 months (range, 0 to 25.3) with chemotherapy; the number of cycles of individual drugs is shown in Table S2. At the data cutoff, the assigned treatment was still being administered in 70 patients (46%) in the amivantamab–chemotherapy group and in 24 patients (15%) in the chemotherapy group. The most common reason for treatment discontinuation was progressive disease, which occurred in 50 of 151 patients (33%) in the amivantamab–chemotherapy group and in 107 of 155 patients (69%) in the chemotherapy group. A total of 65 patients crossed over from the chemotherapy group as part of the trial, and 6 additional patients received amivantamab monotherapy as their first subsequent therapy off protocol (Table S3), representing 66% (71 of 107) of patients in the chemotherapy group with disease progression. The results of the efficacy and safety analyses among the crossover patients are provided in Table S4 and Table S5, respectively.

EFFICACY

The median progression-free survival by blinded independent central review was 11.4 months (95% CI, 9.8 to 13.7) in the amivantamab–chemotherapy group and 6.7 months (95% confidence interval [CI], 5.6 to 7.3) in the chemotherapy group (Fig. 1A). Progression-free survival was significantly longer in the amivantamab–chemotherapy group than in the chemotherapy group (hazard ratio for disease progression or death, 0.40; 95% CI, 0.30 to 0.53; P<0.001). At 18 months, progression-free survival was reported in 31% of the patients in the amivantamab–chemotherapy group and in 3% of those in the chemotherapy group. The progression-free survival estimates for all prespecified subgroups are shown in Figure 1C.

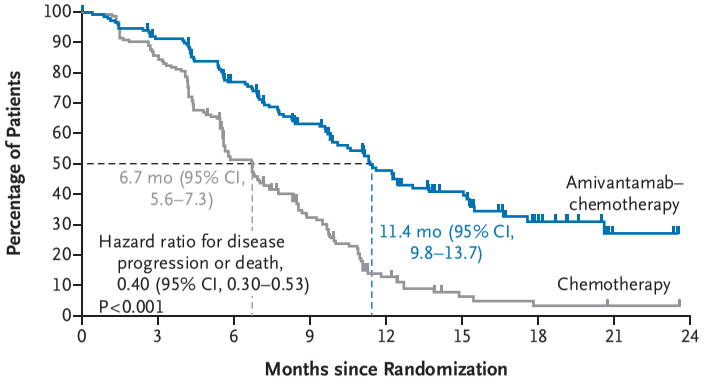
The investigator-assessed progression-free survival was 12.9 months (95% CI, 11.4 to 16.7) with amivantamab–chemotherapy and 6.9 months (95% CI, 6.2 to 8.3) with chemotherapy (hazard ratio for disease progression or death, 0.38; 95% CI, 0.29 to 0.51) (Fig. 1B); the results of the subgroup analysis that are shown in Figure 1D were consistent with the findings of the blinded independent central review (Table S6).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Amivantamab–Chemotherapy (N=153)	Chemotherapy (N=155)
Age		
Median (range) — yr	61 (27–86)	62 (30–92)
Distribution — no. (%)		
<65 yr	97 (63)	92 (59)
65 to <75 yr	44 (29)	48 (31)
≥75 yr	12 (8)	15 (10)
Sex — no. (%)		
Female	85 (56)	93 (60)
Male	68 (44)	62 (40)
Race or ethnic group — no./total no. (%)†		
Asian	97/151 (64)	89/152 (59)
White	49/151 (32)	60/152 (39)
Black	2/151 (1)	0
American Indian or Alaska Native	1/151 (1)	2/152 (1)
Multiple	1/151 (1)	0
Unknown	1/151 (1)	1/152 (1)
Region of enrollment — no. (%)‡		
North America	14 (9)	13 (8)
South America	6 (4)	5 (3)
Europe	35 (23)	36 (23)
Asia	96 (63)	97 (63)
Oceania	2 (1)	4 (3)
Body weight		
Median (range) — kg	61.8 (39–127)	66.5 (37–112)
Distribution — no. (%)		
<80 kg	132 (86)	128 (83)
≥80 kg	21 (14)	27 (17)
ECOG performance-status score — no. (%)		
0	54 (35)	55 (35)
1	99 (65)	100 (65)
History of smoking — no. (%)		
No	88 (58)	91 (59)
Yes	65 (42)	64 (41)
Median time from initial diagnosis (range) — mo	1.8 (0.5–80.8)	1.8 (0.6–95.9)
Median time from metastatic diagnosis (range) — mo	1.5 (0.2–40.0)	1.6 (0.3–30.7)
Histologic type — no. (%)		
Adenocarcinoma	151 (99)	153 (99)
Large-cell carcinoma	0	1 (1)
Other§	2 (1)	1 (1)
History of brain metastases — no. (%)	35 (23)	36 (23)

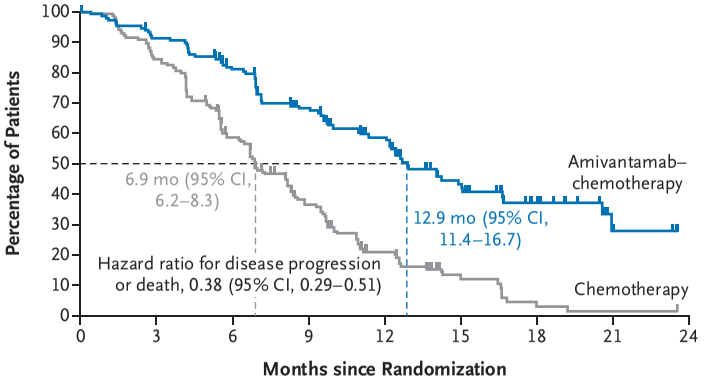
* ECOG denotes Eastern Cooperative Oncology Group.
† Race or ethnic group was reported by the patients. In some regions, reporting of race was not required. One patient reported being of multiple races.
‡ Russia was counted as part of Europe, and Turkey was counted as part of Asia.
§ Other histologic types included bronchoalveolar carcinoma, non–squamous-cell non–small-cell lung cancer, and non–small-cell carcinoma.

A Progression-free Survival, Blinded Independent Central Review



No. at Risk									
Amivantamab–chemotherapy	153	135	105	74	50	33	15	3	0
Chemotherapy	155	131	74	41	14	4	2	1	0

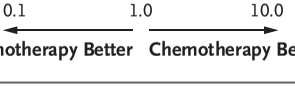
B Progression-free Survival, Investigator Assessment



No. at Risk									
Amivantamab–chemotherapy	153	136	111	83	60	34	17	4	0
Chemotherapy	155	130	84	46	22	9	3	1	0

C Subgroup Analysis for Progression-free Survival, Blinded Independent Central Review

Subgroup	Amivantamab–Chemotherapy (no. of events/total no.)	Chemotherapy (no. of events/total no.)	Hazard Ratio for Disease Progression or Death (95% CI)
All patients	84/153	132/155	0.40 (0.30–0.53)
Age			
<65 yr	56/97	77/92	0.37 (0.26–0.53)
≥65 yr	28/56	55/63	0.44 (0.27–0.70)
Sex			
Female	41/85	81/93	0.31 (0.21–0.46)
Male	43/68	51/62	0.51 (0.34–0.78)
Race			
Asian	55/97	77/89	0.36 (0.25–0.52)
Non-Asian	27/53	51/62	0.41 (0.26–0.67)
Weight			
<80 kg	74/132	108/128	0.41 (0.31–0.56)
≥80 kg	10/21	24/27	0.26 (0.12–0.57)
ECOG score			
0	31/59	51/58	0.35 (0.22–0.55)
1	53/94	81/97	0.42 (0.29–0.61)
History of smoking			
Yes	37/65	57/64	0.45 (0.29–0.68)
No	47/88	75/91	0.37 (0.25–0.53)
History of brain metastases			
Yes	28/36	34/38	0.63 (0.38–1.06)
No	56/117	98/117	0.33 (0.23–0.46)



D Subgroup Analysis for Progression-free Survival, Investigator Assessment

Subgroup	Amivantamab–Chemotherapy (no. of events/total no.)	Chemotherapy (no. of events/total no.)	Hazard Ratio for Disease Progression or Death (95% CI)
All patients	76/153	127/155	0.38 (0.29–0.51)
Age			
<65 yr	51/97	74/92	0.34 (0.24–0.50)
≥65 yr	25/56	53/63	0.41 (0.25–0.67)
Sex			
Female	38/85	77/93	0.31 (0.21–0.46)
Male	38/68	50/62	0.47 (0.30–0.72)
Race			
Asian	45/97	76/89	0.31 (0.21–0.45)
Non-Asian	28/53	48/62	0.45 (0.28–0.72)
Weight			
<80 kg	66/132	106/128	0.38 (0.28–0.52)
≥80 kg	10/21	21/27	0.32 (0.14–0.71)
ECOG score			
0	31/59	47/58	0.37 (0.23–0.58)
1	45/94	80/97	0.39 (0.27–0.57)
History of smoking			
Yes	32/65	55/64	0.38 (0.24–0.59)
No	44/88	72/91	0.37 (0.25–0.54)
History of brain metastases			
Yes	26/36	34/38	0.47 (0.28–0.80)
No	50/117	93/117	0.34 (0.24–0.48)

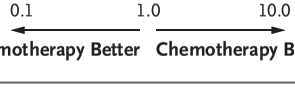


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Figure 1 (facing page). Progression-free Survival by Blinded Independent Central Review (Primary Outcome) and by Investigator Assessment.

Shown are Kaplan–Meier estimates of progression-free survival as assessed by blinded independent central review in the efficacy population (Panel A) and in a forest plot of patient subgroups (Panel C) along with the results of corresponding analyses performed according to investigator assessment (Panels B and D). The efficacy population included all the patients who had undergone randomization. In Panels A and B, the dashed lines indicate the median progression-free survival in the two groups, and the tick marks indicate censoring of data. The shaded areas in Panels C and D indicate 95% confidence intervals for the overall hazard ratio in all the patients. Except for the primary outcome, 95% confidence intervals in this figure were not adjusted for multiplicity and should not be used in place of hypothesis testing. ECOG denotes Eastern Cooperative Oncology Group.

An objective response (complete or partial response) was reported in 73% of the patients (95% CI, 65 to 80) in the amivantamab–chemotherapy group and in 47% (95% CI, 39 to 56) of those in the chemotherapy group (rate ratio, 1.50; 95% CI, 1.32 to 1.68; P<0.001) (Table 2 and Fig. 2A and 2B). The mean percent decrease in tumor size was 53% with amivantamab–chemotherapy and 34% with chemotherapy. The median duration of objective response was 9.7 months (95% CI, 8.2 to 13.5) with amivantamab–chemotherapy and 4.4 months (95% CI, 4.1 to 5.6) with chemotherapy (Fig. S3). At the time of the primary analysis, treatment was ongoing in 49% of the patients with a response in the amivantamab–chemotherapy group and in 17% of those in the chemotherapy group. The median time until response was 6.7 weeks (range, 5.1 to 72.5) with amivantamab–chemotherapy and 11.4 weeks (range, 5.1 to 60.2) with chemotherapy. Investigator-assessed objective response and duration of responses are presented in Table S6.

At the time of the interim survival analysis, 70 deaths had been reported at a calculated 33% data maturity, with 210 deaths anticipated during the trial period (hazard ratio for death for amivantamab–chemotherapy vs. chemotherapy, 0.67; 95% CI, 0.42 to 1.09; P=0.11) (Table 2 and Fig. 2C). This increased risk of death in the chemotherapy group persisted even though 66% of the patients in the chemotherapy group who had

Table 2. Key Efficacy Outcomes.*

Outcome	Amivantamab–Chemotherapy (N=153)	Chemotherapy (N=155)	Treatment Effect (95% CI)	P Value
Progression-free survival†				
Median (95% CI) — mo	11.4 (9.8–13.7)	6.7 (5.6–7.3)	Hazard ratio, 0.40 (0.30–0.53)	<0.001
Patients (95% CI) — %				
At 6 mo	77 (69–83)	51 (43–59)		
At 12 mo	48 (39–56)	13 (8–19)		
At 18 mo	31 (22–40)	3 (1–9)		
Objective response‡				
Patients (95% CI) — %	73 (65–80)	47 (39–56)	Rate ratio, 1.50 (1.32–1.68)	<0.001
Overall survival				
Median (95% CI) — mo	NE	24.4 (22.1–NE)	Hazard ratio, 0.67 (0.42–1.09)	0.11
Patients (95% CI) — %				
At 12 mo	86 (79–91)	82 (74–87)		
At 18 mo	74 (64–82)	68 (58–76)		
At 24 mo	72 (61–81)	54 (37–68)		

* The efficacy population included all the patients who had undergone randomization. NE denotes not estimable.
† Progression-free survival (the primary outcome) was assessed by blinded independent central review.
‡ The objective response (complete or partial response) was assessed by blinded independent central review. Included in the analysis were 152 patients with measurable disease at baseline in each group.

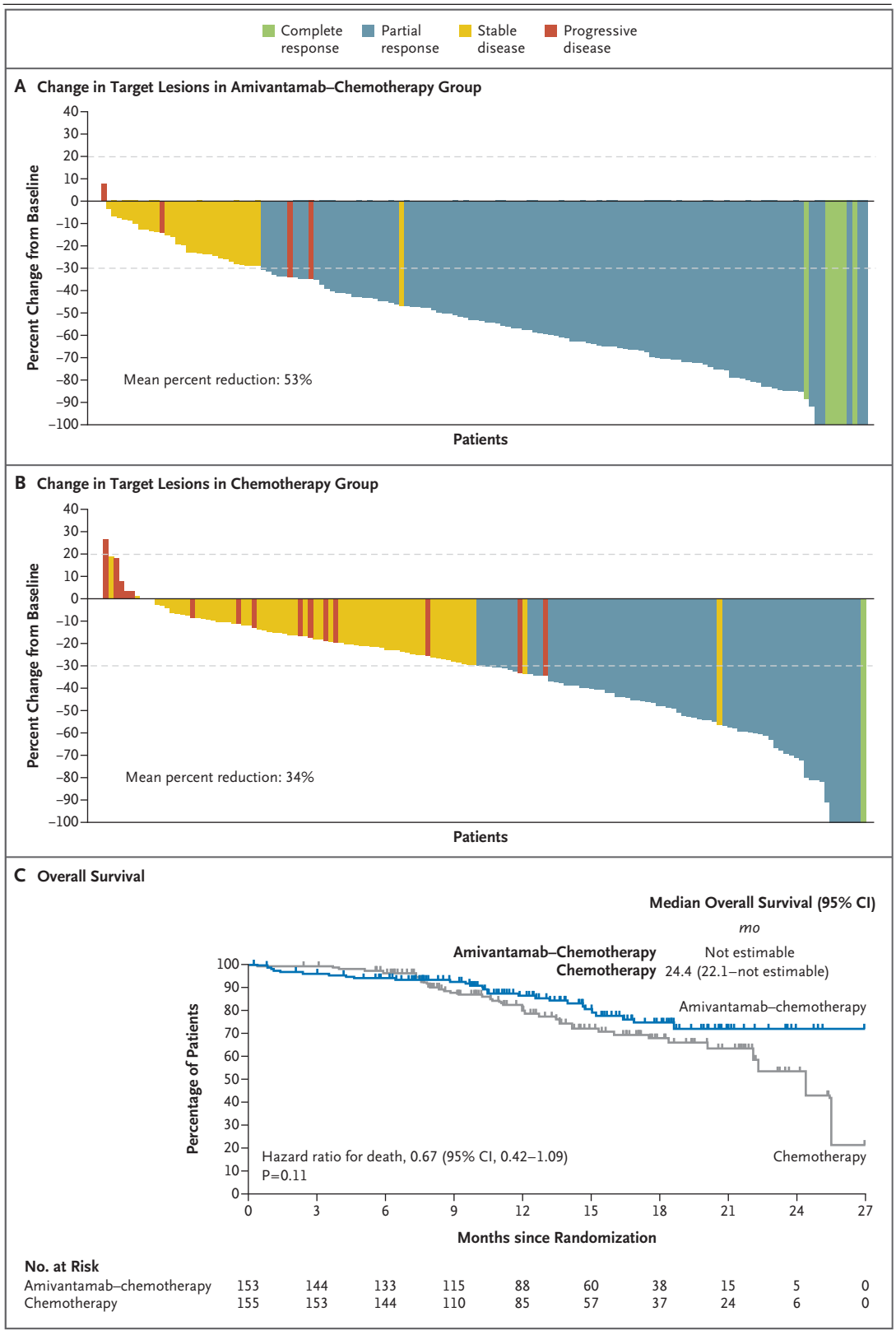

Figure 2 (facing page). Best Response and Interim Overall Survival.

Shown are waterfall plots of the best percent change from baseline in target lesions in the amivantamab–chemotherapy group (Panel A) and in the chemotherapy group (Panel B). Target lesions were measured as the sum of the longest diameters. Also shown is a Kaplan–Meier estimate of interim overall survival (Panel C). The number of patients with measurable disease at baseline in each group was 152, as determined by blinded independent central review. In Panel C, because of the small number of events, the hazard ratio for death in the interim analysis of overall survival was obtained by unstratified analysis; tick marks indicate censoring of data.

disease progression received amivantamab monotherapy. Data regarding progression-free survival after the first subsequent therapy and types of first subsequent therapies are presented in Figure S4 and Table S3, respectively.

SAFETY

The majority of patients in the trial had at least one adverse event (Table 3 and Table S7). The most common adverse events that were reported in at least 15% of the patients in either group were neutropenia (in 59% of the patients), paronychia (in 56%), and rash (in 54%) in the amivantamab–chemotherapy group and anemia (in 55%), neutropenia (in 45%), and nausea (in 42%) in the chemotherapy group. The incidence of infusion-related reactions was 42% in the amivantamab–chemotherapy group and 1% in the chemotherapy group. Additional information regarding adverse events of special interest is available in Table S8.

The incidence of febrile neutropenia was 3% with amivantamab–chemotherapy and 2% with chemotherapy. The most common grade 3 or higher adverse events were neutropenia (in 33%), leukopenia (in 11%), and rash (in 11%) with amivantamab–chemotherapy and neutropenia (in 23%), anemia (in 12%), and thrombocytopenia (in 10%) with chemotherapy. Serious adverse events were reported in 37% of the patients in the amivantamab–chemotherapy group and in 31% of those in the chemotherapy group (Table S9).

In the amivantamab–chemotherapy group, adverse events leading to dose interruptions of any trial agent were reported in 104 patients (69%), dose reductions in 73 patients (48%), and dose discontinuations in 36 patients (24%); the numbers in the chemotherapy group were 56 (36%), 35 (23%), and 16 (10%), respectively (Table 3 and Table S10). Discontinuations of amivantamab because of adverse reactions were reported in 7% of the patients.

Death occurred in 28 patients (18%) in the amivantamab–chemotherapy group and in 42 patients (27%) in the chemotherapy group, with 20 and 30 deaths, respectively, caused by progressive disease (Table S11). Death within 30 days after the last dose of a trial medication occurred in 7 patients (5%) in the amivantamab–chemotherapy group and in 4 patients (3%) in the chemotherapy group. Of the 7 deaths in this category in the amivantamab–chemotherapy group, no clear pattern of toxic events was detected, with 1 death considered by investigators to be related to amivantamab. All grade 5 adverse events are listed in Table S12.

DISCUSSION

In our trial, we found that the receipt of amivantamab–chemotherapy treatment significantly prolonged progression-free survival as compared with chemotherapy alone according to blinded independent central review (hazard ratio for disease progression or death, 0.40; 95% CI, 0.30 to 0.53; P<0.001). Similar progression-free survival benefit was observed according to investigator assessment. Moreover, the progression-free survival benefit was observed across all prespecified subgroups according to race, age, sex, history of smoking, ECOG performance-status score, and history of brain metastases.

In addition, treatment with amivantamab–chemotherapy was associated with deeper and more durable responses, which led to a higher frequency of objective response and a longer duration of response than with chemotherapy. Furthermore, progression-free survival curves showed a clear, early separation indicating rapid disease control that improved with longer follow-up, as reflected in the 18-month progression-free survival of 31% in the amivantamab–chemotherapy group as compared with 3% in the chemotherapy group. Additional studies are needed to confirm whether the potential immune cell–directing activity of amivantamab contributed to this prolonged benefit.

Although the number of deaths in our trial was too few to provide robust conclusions, the interim overall survival analysis (at 33% data maturity) showed evidence of improved survival with first-line amivantamab–chemotherapy despite a high frequency of crossover to second-line amivantamab monotherapy in the chemotherapy group. A final overall survival analysis is planned at approximately 48 months after the first patient underwent randomization.

Our results support the value of testing patients with NSCLC for insertions in the *EGFR* exon 20 at the time of metastatic diagnosis. Polymerase-chain-reaction assays miss 50% of such mutations because of the inability of the assay to capture the full variability of insertion-mutated subtypes.[26] Next-generation sequencing is more sensitive and cost-effective[27] for detecting such mutations. The efficacy results of our trial further support recommendations to identify all oncogenic driver mutations to help select the appropriate first-line therapy before the initiation of chemotherapy–immunotherapy treatments, which do not improve clinical outcomes as compared with chemotherapy alone in patients with *EGFR*-mutated NSCLC.[28,29]

The majority of grade 3 or higher adverse events were driven by skin-related EGFR toxic effects observed with amivantamab, such as rash, paronychia, and dermatitis acneiform,[22,24] and reversible hematologic effects, such as neutropenia, associated with chemotherapy.[30,31] Most of the hematologic effects with amivantamab–chemotherapy were not high grade, and discontinuations because of these events were uncommon. The majority of rashes were managed on an outpatient basis, and no severe (grade 4 or 5) rash was reported. The overall incidence of serious adverse events and deaths was similar in the two groups. During the pandemic period, there were 2 deaths from coronavirus disease 2019 in the amivantamab–chemotherapy group and none in the chemotherapy group.

In our trial, the incidence of infusion-related reactions was lower among patients who received amivantamab–chemotherapy than among those who received amivantamab monotherapy in previous studies (42% and 67%, respective-

Table 3. Adverse Events.*

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any event	151 (100)	114 (75)	152 (98)	83 (54)
Any serious event	56 (37)		48 (31)	
Any event resulting in death	7 (5)		4 (3)	
Any event leading to interruption of any agent	104 (69)		56 (36)	
Interruption in dose of amivantamab				
Any	97 (64)			
Related to amivantamab†	63 (42)			
Any event leading to reduction of any agent	73 (48)		35 (23)	
Reduction in dose of amivantamab				
Any	54 (36)			
Related to amivantamab†	54 (36)			
Any event leading to discontinuation of any agent	36 (24)		16 (10)	
Discontinuation of amivantamab				
Any	17 (11)			
Related to amivantamab†	10 (7)			
Discontinuation of all agents because of adverse events‡	12 (8)		12 (8)	

Table 3. (Continued.)

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Adverse events reported in ≥15% of patients in either group§				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Increased alanine aminotransferase	50 (33)	6 (4)	56 (36)	2 (1)
Increased aspartate aminotransferase	47 (31)	1 (1)	51 (33)	1 (1)
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Covid-19	36 (24)	3 (2)	21 (14)	1 (1)
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)
Asthenia	30 (20)	8 (5)	29 (19)	4 (3)
Pyrexia	24 (16)	0	9 (6)	0
Fatigue	23 (15)	1 (1)	32 (21)	2 (1)
Increased γ-glutamyltransferase	21 (14)	4 (3)	26 (17)	6 (4)
Cough	21 (14)	0	24 (15)	0

* The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. Adverse events that are graded 1, 2, and 3 or higher are shown in Table S13 in the Supplementary Appendix. Covid-19 denotes coronavirus disease 2019.
† The determination of whether an event was related to amivantamab was made by the investigator.
‡ In the amivantamab–chemotherapy group, this category included patients who discontinued amivantamab, carboplatin, and pemetrexed at any time and those who discontinued amivantamab and pemetrexed after the completion of carboplatin. In the chemotherapy group, this category included patients who discontinued carboplatin and pemetrexed at any time and those who discontinued pemetrexed after the completion of carboplatin.
§ Events in this category are listed according to decreasing incidence in the amivantamab–chemotherapy group.

ly).[32] One explanation could be the increased use of preinfusion glucocorticoids for the management of adverse events associated with pemetrexed, which may have blunted the effect of amivantamab-associated infusion-related reactions. Prophylaxis with preinfusion glucocorticoids is being prospectively evaluated in the phase 2 SKIPPirr trial (ClinicalTrials.gov number, NCT05663866). In addition, a subcutaneous formulation of amivantamab, which is associated

with low rates of infusion-related reactions,[33] is under development in the PALOMA studies (NCT04606381, NCT05498428, and NCT05388669).

The data from the CHRYSALIS trial that led to the accelerated approval of amivantamab were corroborated in the crossover group in the PAPILLON trial. In addition, the efficacy and safety results were consistent with initial and long-term data from the CHRYSALIS trial and showed similar antitumor activity and safety profiles with every-2-week administration (CHRYSALIS schedule) and every-3-week administration (PAPILLON schedule).[22,34]

In our trial, we found that patients with previously untreated, advanced NSCLC with *EGFR* exon 20 insertions who received amivantamab–chemotherapy had significantly longer progression-free survival than those who received chemotherapy alone. Safety results were consistent with previous adverse-event reports with respect to the individual agents in each treatment. Our results indicate that amivantamab–chemotherapy was an effective first-line treatment in patients with advanced NSCLC with *EGFR* exon 20 insertions.

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APPENDIX

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