ORIGINAL ARTICLE

First-Line Sunvozertinib in NSCLC with *EGFR* Exon 20 Insertion Mutations

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ABSTRACT

BACKGROUND

Sunvozertinib received accelerated approval for use in later lines of therapy for patients with advanced non–small-cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations. Data are needed on the efficacy and safety of sunvozertinib as a first-line treatment for NSCLC.

METHODS

In this phase 3, international trial, we randomly assigned, in a 1:1 ratio, patients with advanced nonsquamous NSCLC with *EGFR* exon 20 insertions to receive sunvozertinib or chemotherapy (carboplatin–pemetrexed). The primary end point was progression-free survival as assessed by blinded independent central review. Crossover to the sunvozertinib group was allowed after disease progression was confirmed. Secondary end points included overall survival, investigator-assessed progression-free survival, objective response (complete or partial response), change in tumor size, and duration of response.

RESULTS

A total of 324 patients were randomly assigned to receive sunvozertinib (163 patients) or chemotherapy (161 patients). Treatment with sunvozertinib led to significantly longer median progression-free survival than chemotherapy (10.3 vs. 7.5 months; hazard ratio for disease progression or death, 0.65; 95% confidence interval, 0.50 to 0.85; P<0.001). At 12 months, progression-free survival was reported in 46.1% of the patients in the sunvozertinib group and in 26.7% of those in the chemotherapy group; the data for overall survival were immature (38.9% maturity). The percentage of patients with an objective response was 58.9% in the sunvozertinib group and 31.1% in the chemotherapy group; the median best percentage change in tumor size was –42.1% and –24.7% respectively, and the median duration of response was 11.2 and 7.1 months. Grade 3 or higher adverse events were reported in 75.5% of the patients in the sunvozertinib group and in 56.7% of those in the chemotherapy group. In the sunvozertinib group, the most common adverse events of grade 3 or higher included increased serum creatine kinase levels, diarrhea, and anemia. No deaths were attributed to adverse events considered by the investigators to be related to sunvozertinib.

CONCLUSIONS

The efficacy of sunvozertinib was superior to that of chemotherapy as first-line treatment for advanced NSCLC with *EGFR* exon 20 insertions. (Funded by Dizal Pharmaceuticals; WU-KONG28 ClinicalTrials.gov number, NCT05668988.)

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*A complete list of the WU-KONG28 investigators is provided in the Supplementary appendix, available at NEJM.org.

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Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations occur in 2 to 3% of cases of non–small-cell lung cancer (NSCLC) and in up to 12% of cases of *EGFR*-mutated NSCLC.[1-4] *EGFR* exon 20 insertions are highly heterogeneous, with over 100 subtypes, clustered in near-loop, far-loop, and helical regions.[5-7] The insertional mutations at *EGFR* exon 20 induce a rigid conformation of the kinase-active site and form steric hindrance, an effect that results in a smaller drug-binding pocket and limits effective binding of conventional first- to third-generation EGFR tyrosine kinase inhibitors (TKIs).[6]

Platinum-based chemotherapy is a commonly used first-line treatment for advanced NSCLC in patients with *EGFR* exon 20 insertions. However, its clinical efficacy leaves room for improvement, with an objective response of 19 to 47%, a median progression-free survival of 4.5 to 9.6 months, and a median overall survival of 17 to 25 months.[8-15] The addition of immunotherapy to a platinum-based chemotherapy regimen has failed to improve efficacy.[16] Aside from platinum-based chemotherapy, another treatment option is amivantamab, an EGFR mesenchymal–epithelial transition factor (MET) bispecific antibody. After the approval of amivantamab as a monotherapy for later-line treatment on the basis of findings that included an objective response of 40% and a median response duration of 11.1 months,[17] it was approved for use in combination with platinum-based chemotherapy as first-line treatment. Although progression-free survival was shown to be significantly longer with amivantamab plus chemotherapy than with chemotherapy alone (median, 11.4 months vs. 6.7 months),[14] it remains a chemotherapy-based, intravenous regimen. An effective oral, chemotherapy-free therapy could provide patients with a more convenient treatment option with an acceptable safety profile.

A few EGFR-TKIs have progressed into clinical development to assess the possibility of their use as first-line treatment of advanced NSCLC with *EGFR* exon 20 insertions.[6,15,18] Mobocertinib was granted accelerated approval by the Food and Drug Administration as a later-line treatment, but it was withdrawn from the market after the phase 3 trial failed to show superiority for the primary end point in the first-line setting.[15] Recently, furmonertinib, a third-generation EGFR-TKI, was approved in China as a later-line treatment at a dose triple that approved for advanced NSCLC with an *EGFR* sensitizing mutation. This approval was based on results of a nonrandomized study of furmonertinib, which showed an objective response of 44.3% and a median response duration of 8.3 months.[18] A phase 3 study of furmonertinib as first-line treatment is ongoing.

Sunvozertinib is specifically designed to target *EGFR* exon 20 insertions, as well as sensitizing and uncommon mutations, and it has shown antitumor activity across a broad spectrum of *EGFR* exon 20 insertion subtypes to overcome the heterogeneous effects of these mutations.[19] Sunvozertinib was approved in the United States and China as a later line of treatment for NSCLC with *EGFR* exon 20 insertions on the basis of the results of the WU-KONG1B trial and the WU-KONG6 trial, respectively. Both trials showed substantially higher responses (46% in the WU-KONG1B trial and 61% in the WU-KONG6 trial),[20,21] than the range seen in historical data for chemotherapy (3.1 to 16.1%).[11-13] In addition, the antitumor efficacy of sunvozertinib was durable in both trials, with a response duration of 11.1 months in the WU-KONG1B trial and 8.3 months in the WU-KONG6 trial. In early-phase studies, sunvozertinib also showed promising antitumor efficacy as first-line treatment, with a response of 73.1 to 78.6% and a median progression-free survival of 10.1 to 12.4 months.[22,23] These findings suggested that sunvozertinib might benefit patients in the first-line setting.

We conducted the phase 3, international, randomized WU-KONG28 trial to evaluate the antitumor efficacy and safety of sunvozertinib as compared with platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC with *EGFR* exon 20 insertions. Here, we report the primary results of the trial.

METHODS

PATIENTS

Eligible patients were 18 years of age or older, had a diagnosis of histologically or cytologically confirmed nonsquamous NSCLC, and had received no previous systemic anticancer therapy (e.g., chemotherapy or EGFR-TKIs) for locally advanced (stage IIIB or IIIC according to the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer) or metastatic (stage IV) NSCLC with *EGFR* exon 20 insertions. Other key

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eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (range, 0 to 5 with higher scores indicating greater disability) and adequate organ function. Patients with brain metastases were allowed to participate if the metastases were stable after local therapy. Details of the inclusion and exclusion criteria are provided in 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) and applicable regulatory requirements. The trial protocol (available at NEJM.org) was approved by the institutional review board or ethics committee at each site. All the patients provided written informed consent before participating in the trial.

The trial was designed by the sponsor, with input from the investigators. The sponsor was responsible for data collection and analysis and for data interpretation in collaboration with the authors. The first draft of the manuscript was written by the authors and by employees of the sponsor. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

TRIAL DESIGN AND TREATMENT

Eligible patients were randomly assigned in a 1:1 ratio to receive sunvozertinib or chemotherapy in 3-week cycles, stratified according to brain metastasis status at baseline (yes or no).

In the sunvozertinib group, patients received treatment until disease progression or other discontinuation criteria were met as defined in the protocol. The dose of oral sunvozertinib was 300 mg once daily. In the chemotherapy group, patients received carboplatin–pemetrexed for up to 4 or 6 cycles, at the discretion of the investigator, followed by pemetrexed maintenance therapy until disease progression or other discontinuation criteria were met. Carboplatin was administered at a target area under the plasma concentration-time curve of 5, and pemetrexed at a dose of 500 mg per square meter of body-surface area, by intravenous infusion every 3 weeks, along with adequate supplementation with folic acid and vitamin B12.

Patients in the chemotherapy group were allowed to cross over to receive sunvozertinib treatment after confirmed disease progression as assessed by blinded independent central review. Treatment was allowed after disease progression if the patient was still deriving clinical benefit from the treatment, which was determined by the investigator.

END POINTS

The primary end point was progression-free survival, defined as the time from randomization until disease progression (as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause. The key secondary end point was overall survival, defined as the time from randomization until death from any cause. Other secondary end points included investigator-assessed progression-free survival; objective response, defined as the best overall response of complete or partial response (as assessed by both blinded independent central review and investigators according to RECIST, version 1.1); and duration of response, defined as the time from the date of the first documented confirmed response until the date of disease progression or death from any cause. A confirmed response was defined as complete or partial response on two consecutive assessments performed at least 4 weeks apart. The change in tumor size was calculated as the postbaseline tumor size minus the baseline tumor size, divided by the baseline tumor size, and multiplied by 100.

Exploratory end points, including second progression-free survival and health-related quality of life, were also evaluated. Additional details about the trial end points are provided in the protocol.

ASSESSMENTS

Tumor response was assessed at 6 weeks after randomization, followed by every 6 weeks for the first 12 months, and every 12 weeks thereafter until the occurrence of disease progression. All assessments were performed by blinded independent central review and investigators, according to RECIST, version 1.1. All the patients were required to undergo brain imaging at baseline; however, subsequent imaging was performed as clinically indicated. The preferred imaging method was magnetic resonance imaging. Health-related

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quality of life was measured every 6 weeks until treatment discontinuation by means of the EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire. Data with regard to survival status were obtained approximately every 12 weeks. Adverse events were assessed at each visit and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

STATISTICAL ANALYSIS

The sample size in this trial was estimated on the basis of the primary end point, under the assumption of a median duration of progression-free survival of 9.5 months in the sunvozertinib group and 6.5 months in the chemotherapy group. For the calculation of progression-free survival, we estimated that a sample of 320 patients with 219 events of disease progression or death would provide the trial with 80% power to detect a hazard ratio of 0.684 at a one-sided alpha level of 0.025.

The efficacy analysis included all the patients who had undergone randomization. The safety analysis included all the patients who received at least one dose of any trial treatment. The crossover analysis included all the patients initially assigned to the chemotherapy group and whose treatment was subsequently switched to sunvozertinib; patients had to have received at least one dose of each treatment. The one-sided type I error was controlled for the primary end point and the key secondary end point (overall survival) with a hierarchical testing procedure, as described in the protocol. For all other end points, the confidence intervals were not adjusted for multiplicity and should not be interpreted as hypothesis tests.

A stratified log-rank test was used to compare time-to-event end points between treatment groups, with the hazard ratio estimated with the use of a stratified Cox regression model, with baseline brain metastasis (yes or no) as the stratification factor. An interim analysis of overall survival was planned to be performed at the primary analysis of progression-free survival. Analyses of other secondary end points are provided in the statistical analysis plan in the Supplementary Appendix. The data-cutoff date for the primary analysis was January 16, 2026.

RESULTS

PATIENTS AND TREATMENT

From December 2022 through May 2025, a total of 449 patients were screened at 154 sites across 15 countries, and 324 patients were randomly assigned to receive sunvozertinib (163 patients) or chemotherapy (161 patients) (Fig. S1 and Table S1 in the Supplementary Appendix). The demographic and clinical characteristics of the patients at baseline were generally well balanced between the two groups, with the exception of sex and the number of organs involved at baseline. The sunvozertinib group had a higher percentage of men than the chemotherapy group, as well as a higher percentage of patients with more than three organs involved at baseline (Table 1). Of the patients who underwent randomization, more than 50% were women, had never smoked, and had an ECOG performance-status score of 1. Roughly two thirds of the patients were Asian; Black patients were underrepresented. Approximately 31% of the patients were from North America (the United States and Canada) or European countries and 13% had brain metastases at baseline. The percentages of patients who were women, Asian, and had never smoked were representative of the population with NSCLC with *EGFR* exon 20 insertions (Table S2). The status of *EGFR* exon 20 insertions was determined by testing tumor tissue samples (311 patients [96.0%]) or plasma samples (13 patients [4.0%]). Tests were performed at local laboratories (314 patients [96.9%]) and at the sponsor-designated central laboratory (10 patients [3.1%]). At least 54 distinct *EGFR* exon 20 insertion subtypes were detected (Table S3).

At the data-cutoff date, the median duration of treatment was 9.9 months (range, 0.7 to 34.6) with sunvozertinib and 7.6 months (range, 0.7 to 32.6) with chemotherapy. The number of chemotherapy cycles and the overall duration of exposure to each treatment are shown in Table S4. A total of 244 patients discontinued treatment (119 patients in the sunvozertinib group and 125 in the chemotherapy group). Among the 313 patients who received at least one dose of sunvozertinib or chemotherapy, the most common reasons for discontinuation of treatment were disease progression (in 193 patients [61.7%]), adverse event (in

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

Characteristic	Sunvozertinib (N=163)	Chemotherapy (N=161)
Age		
Median (range) — yr	62 (27–87)	62 (28–85)
Distribution — no. (%)		
<65 yr	89 (54.6)	93 (57.8)
≥65 yr	74 (45.4)	68 (42.2)
Sex — no. (%)		
Male	76 (46.6)	56 (34.8)
Female	87 (53.4)	105 (65.2)
Race — no. (%)†		
Asian	102 (62.6)	102 (63.4)
Non-Asian	61 (37.4)	59 (36.6)
Geographic region — no. (%)		
North America or European Union‡	50 (30.7)	52 (32.3)
Other§	113 (69.3)	109 (67.7)
History of smoking — no. (%)		
Yes	62 (38)	54 (33.5)
No	101 (62)	107 (66.5)
ECOG performance-status score — no. (%)¶		
0	46 (28.2)	43 (26.7)
≥1	117 (71.8)	118 (73.3)
Baseline brain metastasis — no. (%)		
Yes	21 (12.9)	20 (12.4)
No	142 (87.1)	141 (87.6)
Number of organs involved — no. (%)		
1 to 3	92 (56.4)	106 (65.8)
>3	71 (43.6)	55 (34.2)
EGFR exon 20 insertion subtype — no. (%)		
769_ASV	51 (31.3)	52 (32.3)
770_SVD	21 (12.9)	32 (19.9)
Other‖	83 (50.9)	69 (42.9)
Unknown	8 (4.9)	8 (5.0)
EGFR exon 20 insertion region — no. (%)		
Near loop	111 (68.1)	109 (67.7)
Far loop	41 (25.2)	43 (26.7)
C-helix	3 (1.8)	1 (0.6)
Unknown	8 (4.9)	8 (5.0)
Histologic type — no. (%)		
Adenocarcinoma subtype	160 (98.2)	158 (98.1)
Other	3 (1.8)	3 (1.9)

* ECOG denotes Eastern Cooperative Oncology Group, and *EGFR* epidermal growth factor receptor.
† Race was reported by the patients. Non-Asian included White, Black or African American, and other.
‡ North America and European Union included Austria, Belgium, Canada, the Czech Republic, France, Germany, Italy, Poland, Spain, and the United States.
§ Other geographic regions included Argentina, Australia, Brazil, China, and Turkey.
¶ The latest assessment result relative to receipt of the first dose was selected as the baseline value. Two patients had an ECOG score of 1 at screening that was changed to 2 after randomization. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‖ A list of other *EGFR* exon 20 insertion subtypes is provided in Table S2 in the Supplementary Appendix.

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25 patients [8.0%]), and patient decision (in 20 patients [6.4%]). A total of 101 of 112 patients (90.2%) in the chemotherapy group crossed over to receive sunvozertinib after disease progression had been confirmed on blinded independent central review. The results of the efficacy and safety analyses among the crossover patients are summarized in Table S5 and Table S6, respectively.

EFFICACY

With a median follow-up of 24.0 months (95% confidence interval [CI], 20.8 to 26.5) in the sunvozertinib group and 18.0 months (95% CI, 13.1 to 26.0) in the chemotherapy group, the median progression-free survival was 10.3 months (95% CI, 8.3 to 14.0) and 7.5 months (95% CI, 6.7 to 8.5), respectively (hazard ratio for disease progression or death, 0.65; 95% CI, 0.50 to 0.85; P< 0.001) (Fig. 1). At 12 months, progression-free survival was observed in 46.1% of the patients in the sunvozertinib group and in 26.7% of those in the chemotherapy group; at 18 months, progression-free survival was observed in 33.2% and 17.1% of the patients, respectively. The progression-free survival results for the predefined subgroups are shown in Figure S2.

The percentage of patients with an objective response, as assessed by blinded independent central review, was 58.9% (95% CI, 50.9 to 66.5) in the sunvozertinib group and 31.1% (95% CI, 24.0 to 38.8) in the chemotherapy group (Table 2). The median best percentage change from baseline in tumor size was −42.1% (range, −88.6 to 21.3) in the sunvozertinib group and −24.7% (range, −85.6 to 362.2) in the chemotherapy group (Fig. 2A and 2B). The median duration of response was 11.2 months (95% CI, 8.2 to 13.9) and 7.1 months (95% CI, 6.9 to 11.1), respectively (Table 2, and Fig. 2C).

At the time of the primary analysis of progression-free survival, the data for overall survival were immature (38.9% maturity). At a median follow-up for overall survival of 26.1 months (95% CI, 25.0 to 27.0) in the sunvozertinib group and 26.7 months (95% CI, 25.2 to 28.9) in the chemotherapy, 62 patients in the sunvozertinib group and 64 patients in the chemotherapy group had died (Fig. S3). An early intersection of the overall survival curves for sunvozertinib and chemotherapy was observed during the trial, which resulted from a small number of early deaths that were unrelated to the trial treatment and were associated with disease progression or underlying disease with heavy tumor burden (Table S7).

Further details regarding the use of subsequent anticancer therapies and treatment beyond disease progression are summarized in Table S8 and Table S9, respectively. The minimal changes

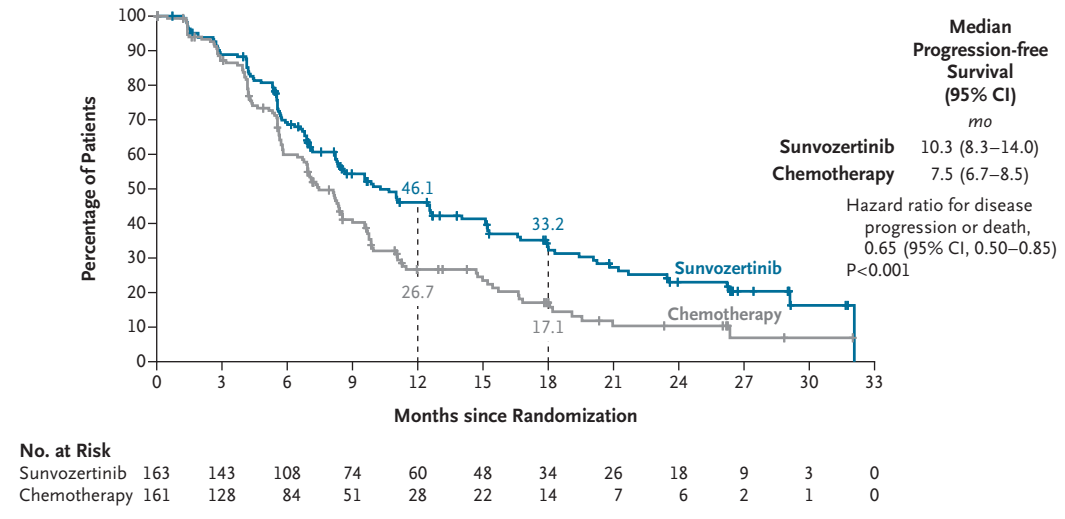

Figure 1. Progression-free Survival.

Shown are Kaplan–Meier estimates of progression-free survival as assessed by blinded independent central review in the efficacy population, which included all the patients who had undergone randomization. The tick marks indicate censoring of data.

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Table 2. Key Efficacy End Points.*

End Point	Sunvozertinib (N=163)	Chemotherapy (N=161)	Treatment Effect (95% CI)†	P Value
Progression-free survival‡				
Median (95% CI) — mo	10.3 (8.3–14.0)	7.5 (6.7–8.5)	0.65 (0.50–0.85)	<0.001
Percentage of patients (95% CI)				
At 12 mo	46.1 (37.9–53.9)	26.7 (19.3–34.6)	NA	NA
At 18 mo	33.2 (25.3–41.3)	17.1 (10.7–24.7)	NA	NA
At 24 mo	23.0 (15.8–31.0)	10.3 (5.1–17.6)	NA	NA
Objective response‡				
Percentage of patients (95% CI)	58.9 (50.9–66.5)	31.1 (24.0–38.8)	3.2 (2.0–5.0)	NA
Duration of response				
Median (95% CI) — mo	11.2 (8.2–13.9)	7.1 (6.9–11.1)	NA	NA
Overall survival				
Median (95% CI) — mo	29.8 (21.8–NE)	28.8 (20.7–NE)	0.99 (0.70–1.40)	0.48
Percentage of patients (95% CI)				
At 18 mo	65.5 (56.9–72.9)	67.2 (58.4–74.5)	NA	NA
At 24 mo	57.4 (48.3–65.4)	56.2 (46.9–64.5)	NA	NA
At 30 mo	50.0 (39.4–59.6)	49.1 (39.4–58.1)	NA	NA

* The efficacy population included all the patients who had undergone randomization. NA denotes not applicable, and NE could not be estimated.
† The treatment effect is shown as a hazard ratio for progression-free survival and overall survival and as an odds ratio for objective response.
‡ Progression-free survival and objective response were assessed by blinded independent central review.

seen in the score on the EQ-5D-5L visual analogue scale and weighted health state index indicated that there were no substantial differences between the two groups with respect to health-related quality of life (Table S10).

SAFETY

Overall, 313 patients who received at least one dose of trial treatment (163 patients in the sunvozertinib group and 150 patients in the chemotherapy group) were included in the safety analysis. The majority of patients had at least one adverse event that emerged during treatment (Table 3). Among the adverse events that emerged during treatment and were reported in at least 20% of the patients in either group, the most common grade 3 or higher adverse events were increased serum creatine kinase level (in 20.9% of the patients), diarrhea (in 14.1%), and anemia (in 9.2%) in the sunvozertinib group, and decreased neutrophil count (in 18.7%), anemia (in 11.3%), decreased white-cell count (in 6.7%), and decreased platelet count (in 6.7%) in the chemotherapy group (before crossover to sunvozertinib) (Table 3). The most common adverse events that emerged during treatment and were reported in at least 10% of the patients in either group are listed in Table S11. Serious adverse events that emerged during treatment were reported in 45.4% of the patients in the sunvozertinib group and in 26.7% of those in the chemotherapy group (Table S12).

Adverse events leading to drug interruption, dose reduction, or drug discontinuation were reported in 58.3%, 41.7%, and 11.7% of the patients in the sunvozertinib group, respectively, and in 37.3%, 26.7%, and 12.0% of the patients in the chemotherapy group, respectively (Table 3). Adverse events that emerged during treatment and led to dose reduction included increased serum creatine kinase level (in 12.9% of the patients), diarrhea (in 8.6%), rash (in 2.5%), vomiting (in 2.5%), nausea (in 1.8%), paronychia (in 1.8%), and increased serum creatinine level (in 1.8%) in the sunvozertinib group, and decreased platelet count (in 5.3% of the patients), fatigue (in 4.7%), decreased white-cell count (in 4.0%), decreased neutrophil count (in 3.3%), anemia (in

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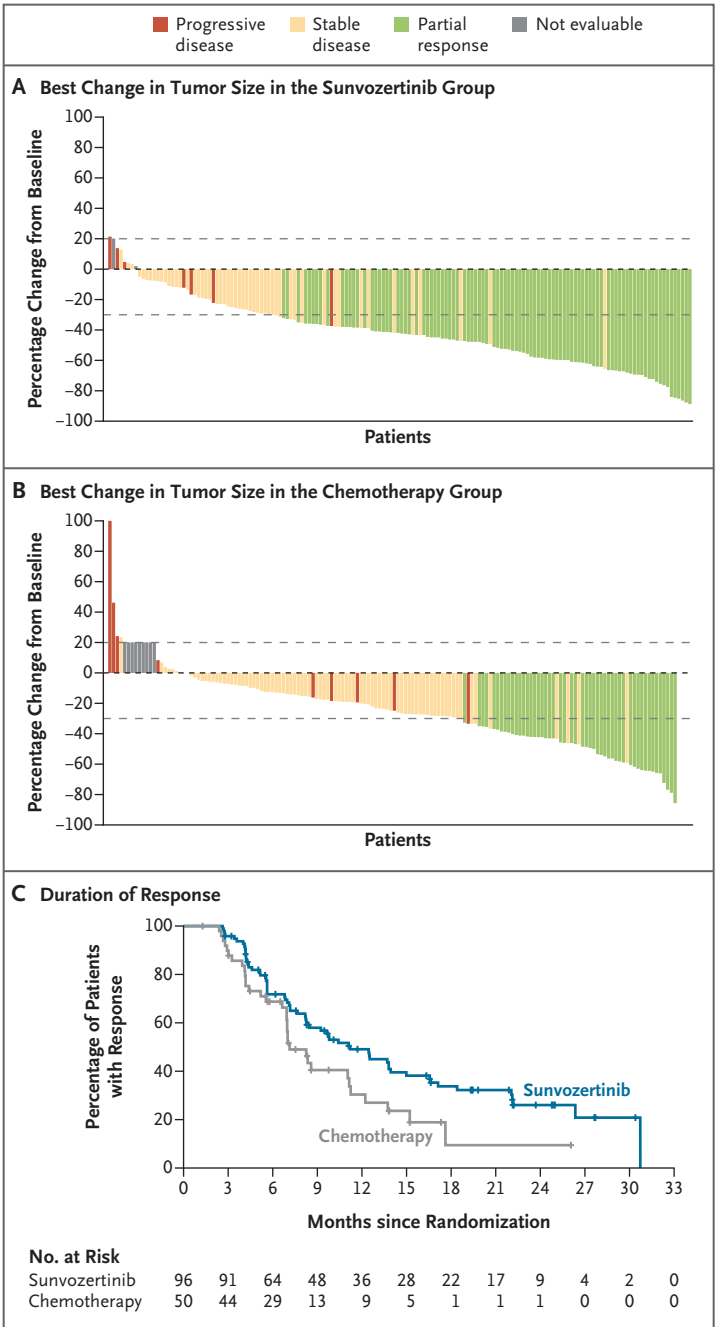

Figure 2. Best Response and Duration of Response.

Shown are waterfall plots of the best percentage change from baseline in tumor size as assessed by blinded independent central review among patients in the sunvozertinib group (Panel A) and among those in the chemotherapy group (Panel B). A total of 158 patients with measurable target lesions (determined by blinded independent central review) were included in the sunvozertinib group, and 154 were included in the chemotherapy group. Also shown are Kaplan–Meier estimates of duration of response as assessed by blinded independent central review (Panel C) in the efficacy population.

3.3%), asthenia (in 2.7%), nausea (in 2.0%), and increased serum creatinine level (in 2.0%) in the chemotherapy group. In the sunvozertinib group, the adverse events that emerged during treatment and led to treatment discontinuation in at least 2 patients were interstitial lung disease (in 1.8% of the patients) and pneumonitis (in 1.2%); in the chemotherapy group, these events included anemia (in 2.0% of the patients), asthenia (in 1.3%), fatigue (in 1.3%), infusion-related reaction (in 1.3%), nausea (in 1.3%), and pneumonia (in 1.3%). Additional details are provided in Table S13. Adverse events that resulted in death are summarized in Table S14. No treatment-related adverse events were associated with a fatal outcome in the sunvozertinib group; one case of treatment-related pneumonia with a fatal outcome was reported in the chemotherapy group.

A prolongation of the corrected QT interval, calculated with the use of Fridericia's formula (QTcF), of greater than 500 msec and an increase from baseline in the QTcF of more than 60 msec was reported in 1.8% of the patients in the sunvozertinib group (Table S15). No patient had dose modification or drug discontinuation owing to QTcF prolongation, a finding that indicates a low cardiac risk associated with sunvozertinib.

DISCUSSION

In this trial, sunvozertinib showed significantly longer progression-free survival than platinum-based chemotherapy as assessed by blinded independent central review when used as first-line treatment among patients with *EGFR*-mutated advanced NSCLC (10.3 vs. 7.5 months; hazard ratio for disease progression or death from any cause, 0.65; P<0.001). The early and clear separation of the progression-free survival curves suggests rapid disease control in the sunvozertinib group. Moreover, treatment with sunvozertinib appeared to be associated with deeper tumor response, higher objective response, and longer remission duration than chemotherapy.

Results of this study also echoed findings in early-phase studies of sunvozertinib.[22,23] In the PAPILLON study,[14] the median progression-free survival with amivantamab in combination with platinum-based chemotherapy was 11.4 months, and the percentage of patients with progression-

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Table 3. Adverse Events.*

Event	Sunvozertinib (N=163)		Chemotherapy (N=150)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	163 (100.0)	123 (75.5)	149 (99.3)	85 (56.7)
Any treatment-related adverse event	163 (100.0)	100 (61.3)	146 (97.3)	74 (49.3)
Any serious adverse event	74 (45.4)	NA	40 (26.7)	NA
Any treatment-related serious adverse event	30 (18.4)	NA	19 (12.7)	NA
Any adverse event leading to drug interruption	95 (58.3)	NA	56 (37.3)	NA
Any treatment-related adverse event leading to drug interruption	74 (45.4)	NA	41 (27.3)	NA
Any adverse event leading to dose reduction	68 (41.7)	NA	40 (26.7)	NA
Any treatment-related adverse event leading to dose reduction	66 (40.5)	NA	36 (24.0)	NA
Any adverse event leading to drug discontinuation	19 (11.7)	NA	18 (12.0)	NA
Any treatment-related adverse event leading to drug discontinuation	12 (7.4)	NA	17 (11.3)	NA
Any adverse event with fatal outcome	7 (4.3)	NA	2 (1.3)	NA
Any treatment-related adverse event with fatal outcome	0	NA	1 (0.7)	NA
Adverse events that emerged during treatment and were reported in ≥20% of patients in either group				
Diarrhea	142 (87.1)	23 (14.1)	25 (16.7)	0
Serum creatine kinase increased	95 (58.3)	34 (20.9)	6 (4.0)	1 (0.7)
Anemia	93 (57.1)	15 (9.2)	94 (62.7)	17 (11.3)
Rash	86 (52.8)	1 (0.6)	10 (6.7)	0
Paronychia	79 (48.5)	6 (3.7)	1 (0.7)	0
Weight decreased	71 (43.6)	6 (3.7)	17 (11.3)	1 (0.7)
Decreased appetite	63 (38.7)	3 (1.8)	42 (28.0)	2 (1.3)
Serum creatinine increased	55 (33.7)	1 (0.6)	14 (9.3)	0
Nausea	46 (28.2)	3 (1.8)	69 (46.0)	2 (1.3)
Vomiting	46 (28.2)	3 (1.8)	36 (24.0)	3 (2.0)
Hypokalemia	41 (25.2)	6 (3.7)	11 (7.3)	1 (0.7)
Amylase increased	38 (23.3)	2 (1.2)	17 (11.3)	0
Lipase increased	38 (23.3)	9 (5.5)	11 (7.3)	2 (1.3)
Aspartate aminotransferase increased	36 (22.1)	4 (2.5)	56 (37.3)	1 (0.7)
Mouth ulceration	33 (20.2)	2 (1.2)	5 (3.3)	0
Alanine aminotransferase increased	29 (17.8)	3 (1.8)	52 (34.7)	2 (1.3)
Fatigue	25 (15.3)	2 (1.2)	30 (20.0)	4 (2.7)
Neutrophil count decreased	24 (14.7)	4 (2.5)	68 (45.3)	28 (18.7)
White-cell count decreased	20 (12.3)	1 (0.6)	59 (39.3)	10 (6.7)
Constipation	18 (11.0)	1 (0.6)	38 (25.3)	0
Platelet count decreased	15 (9.2)	4 (2.5)	33 (22.0)	10 (6.7)

* The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. Adverse events were assessed at each visit and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

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free survival at 12 and 18 months was approximately 48% and 31%, respectively. In this trial, the median progression-free survival with sunvozertinib was 10.3 months, and the percentage of patients with progression-free survival at 12 and 18 months was approximately 46% and 33%, respectively. Furthermore, patients receiving sunvozertinib were candidates for subsequent platinum-based chemotherapy after disease progression.

A less profound progression-free survival benefit was observed among non-Asian patients as compared with Asian patients, a finding that could be a result of the high heterogeneity of the disease and imbalanced disease characteristics (i.e., exon 20 insertion subtypes) (Table S16). The data for overall survival were immature (data maturity, 38.9%) and require further follow-up. Of note, the interpretation of overall survival was possibly confounded by the crossover design of the trial. The safety profile of sunvozertinib as first-line treatment was similar to what has been reported for the agent as later-line treatment, even with the longer duration of treatment in this trial. The median relative dose intensity of sunvozertinib was 95%. Adverse events of grade 3 or higher were more common with sunvozertinib than with chemotherapy (75.5% vs. 56.7%). The most common adverse events of grade 3 or higher that emerged during treatment included increased serum creatine kinase levels and diarrhea, which are considered to be related to inhibition of wild-type *EGFR* and underlying disease status. In the sunvozertinib group, 8.6% and 12.9% of the patients had a dose reduction owing to diarrhea or increased serum creatine kinase levels, respectively; only a small percentage these patients discontinued treatment (0.6% with diarrhea and none with increased serum creatine kinase levels), a finding that suggests that these common adverse events had a minimal effect on maintaining sunvozertinib treatment. The safety profile of chemotherapy in this trial was similar to what has been previously reported in other studies.[14,15] The incidence of treatment discontinuation owing to treatment-related adverse events was lower in sunvozertinib group than in the chemotherapy group. The baseline characteristics of enrolled patients were similar to what has been previously reported in patients with advanced NSCLC with *EGFR* exon 20 insertions,[14,15,24,25] and were considered to be representative of the target patient population.

One limitation of this trial was the inability to directly measure the central nervous system activity of sunvozertinib owing to the relatively small number of patients with brain metastases at baseline, and all the brain lesions in these patients had been irradiated. In addition, the marginal benefit observed with sunvozertinib treatment as compared with chemotherapy could have resulted from the imbalanced disease burden between the two groups among patients with baseline brain metastasis (Table S17).

In this trial, patients with previously untreated, advanced NSCLC with *EGFR* exon 20 insertions who received oral sunvozertinib had significantly longer progression-free survival than those who received intravenous chemotherapy. Safety results showed high-grade adverse events in 75% of patients, most of which were gastrointestinal events (e.g., diarrhea and nausea) and elevated serum creatine kinase levels. Our results indicate that sunvozertinib was an effective first-line treatment in patients with advanced NSCLC with *EGFR* exon 20 insertions.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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