ORIGINAL ARTICLE

Zongertinib in Previously Treated *HER2*-Mutant Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Innovative oral targeted therapies are warranted for patients with human epidermal growth factor receptor 2 (*HER2*)–mutant non–small-cell lung cancer (NSCLC). Zongertinib is an oral, irreversible, HER2-selective tyrosine kinase inhibitor that has been shown to have efficacy in persons with advanced or metastatic solid tumors with HER2 alterations in a phase 1 study.

METHODS

We evaluated zongertinib in a multicohort, phase 1a–1b trial involving patients with advanced or metastatic *HER2*-mutant NSCLC. Here we report the primary analysis of zongertinib in previously treated patients: those with tumors harboring a mutation in the tyrosine kinase domain (cohort 1), those with tumors harboring a mutation in the tyrosine kinase domain previously treated with a HER2-directed antibody–drug conjugate (cohort 5), and those with tumors harboring a non–tyrosine kinase domain mutation (cohort 3). In cohort 1, patients were initially randomly assigned to receive zongertinib at a dose of 120 mg or 240 mg once daily. Patients in cohorts 5 and 3 initially received 240 mg daily. After an interim analysis of data from cohort 1, subsequently recruited patients across all cohorts received zongertinib at a dose of 120 mg. The primary end point was an objective response assessed by blinded independent central review (cohorts 1 and 5) or by investigator review (cohort 3). Secondary end points included the duration of response and progression-free survival.

RESULTS

In cohort 1, a total of 75 patients received zongertinib at a dose of 120 mg. At the data cutoff (November 29, 2024), 71% of these patients (95% confidence interval [CI], 60 to 80; $P<0.001$ against a ≤30% benchmark) had a confirmed objective response; the median duration of response was 14.1 months (95% CI, 6.9 to not evaluable), and the median progression-free survival was 12.4 months (95% CI, 8.2 to not evaluable). Grade 3 or higher drug-related adverse events occurred in 13 patients (17%). In cohort 5 (31 patients), 48% of the patients (95% CI, 32 to 65) had a confirmed objective response. Grade 3 or higher drug-related adverse events occurred in 1 patient (3%). In cohort 3 (20 patients), 30% of the patients (95% CI, 15 to 52) had a confirmed objective response. Grade 3 or higher drug-related adverse events occurred in 5 patients (25%). Across all three cohorts, no cases of drug-related interstitial lung disease occurred.

CONCLUSIONS

Zongertinib showed clinical benefit with mainly low-grade adverse events in patients with previously treated *HER2*-mutant NSCLC. (Funded by Boehringer Ingelheim; Beamion LUNG-1 ClinicalTrials.gov number, NCT04886804.)

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This article was published on April 28, 2025, at NEJM.org.

N Engl J Med 2025;392:2321-33.
DOI: 10.1056/NEJMoa2503704
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According to recent real-world studies involving patient registries, mutations in human epidermal growth factor receptor 2 (*HER2*; also known as ErbB-2 receptor tyrosine kinase 2 [*ERBB2*]) are present in approximately 2 to 4% of non–small-cell lung cancers (NSCLCs).[1-3] *HER2* mutations are most common within the active site of the tyrosine kinase domain (approximately 53% occur in exons 18 to 21), particularly exon 20, and are mostly insertion mutations.[4] Other *HER2* mutations are highly heterogeneous and occur predominantly in the extracellular domain (approximately 25%) and the transmembrane domain (approximately 10%) of the receptor.[4]

Currently, the only Food and Drug Administration (FDA)–approved HER2-directed treatment for *HER2*-mutant NSCLC is the intravenous antibody–drug conjugate trastuzumab deruxtecan, which gained accelerated approval for patients who had received a previous systemic therapy.[5] Trastuzumab deruxtecan has shown durable anticancer activity and is recommended as the standard of care in *HER2*-mutant NSCLC[6] but can be associated with potentially serious adverse events, including interstitial lung disease.[7] Although pan-HER tyrosine kinase inhibitors (TKIs) have been successful in other treatment contexts, they have only shown marginal benefit in *HER2*-mutant NSCLC.[8] Some pan-HER TKIs, including poziotinib and pyrotinib, have shown activity in patients with *HER2*-mutant NSCLC. However, these agents are associated with a high incidence of epidermal growth factor receptor (EGFR)–related toxic effects, including diarrhea and rash.[9-14] Therefore, an effective, oral, HER2-targeted treatment option with improved safety is needed.

Zongertinib (BI 1810631) is an oral, irreversible TKI that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxic effects.[15] Beamion LUNG-1 is an ongoing, first-in-human, phase 1a–1b trial assessing zongertinib in patients with HER2-altered advanced or metastatic solid tumors (phase 1a) and those with *HER2*-mutant advanced or metastatic NSCLC (phase 1b). In the phase 1a dose-escalation trial, zongertinib was associated with a low incidence of grade 3 or higher toxic effects and showed encouraging preliminary activity at the recommended expansion doses of 120 mg and 240 mg once daily.[16] Here, we report the primary data from three cohorts from the phase 1b dose-expansion trial, which assessed the efficacy and safety of zongertinib in patients with previously treated *HER2*-mutant advanced or metastatic NSCLC. Three distinct clinical scenarios were addressed in the three cohorts. In cohort 1, zongertinib was assessed in patients with tumors harboring mutations in the tyrosine kinase domain, the most common category of *HER2* mutation encountered in the clinic. In cohort 5, zongertinib was assessed for activity in patients who had previously received antibody–drug conjugates, predominantly trastuzumab deruxtecan. Cohort 3 included patients with tumors harboring non–tyrosine kinase domain mutations, who are often poorly represented in clinical studies.

METHODS

STUDY DESIGN AND PATIENTS

Phase 1b of the trial assessed the efficacy and safety of zongertinib in patients with previously treated *HER2*-mutant advanced or metastatic NSCLC: those with nonsquamous NSCLC with a mutation in the tyrosine kinase domain (cohort 1), those with nonsquamous NSCLC with a mutation in the tyrosine kinase domain who had been previously treated with a HER2-directed antibody–drug conjugate (cohort 5), and those with nonsquamous NSCLC with a non–tyrosine kinase domain mutation or with squamous NSCLC with a mutation in the tyrosine kinase domain (exploratory cohort 3). Two additional global cohorts are ongoing (patients with nonsquamous NSCLC with a mutation in the tyrosine kinase domain who had not previously received treatment [cohort 2], and patients with NSCLC with a mutation in the tyrosine kinase domain and with active brain metastases [cohort 4]). Here, we report the primary data for previously treated patients (cohorts 1, 5, and 3 [non–tyrosine kinase domain mutations only]) (Fig. 1).

Eligible patients were at least 18 years of age with a histologically or cytologically confirmed diagnosis of *HER2*-mutant advanced or metastatic NSCLC according to local laboratory assessment; at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability); and had received at least one line of systemic therapy for advanced

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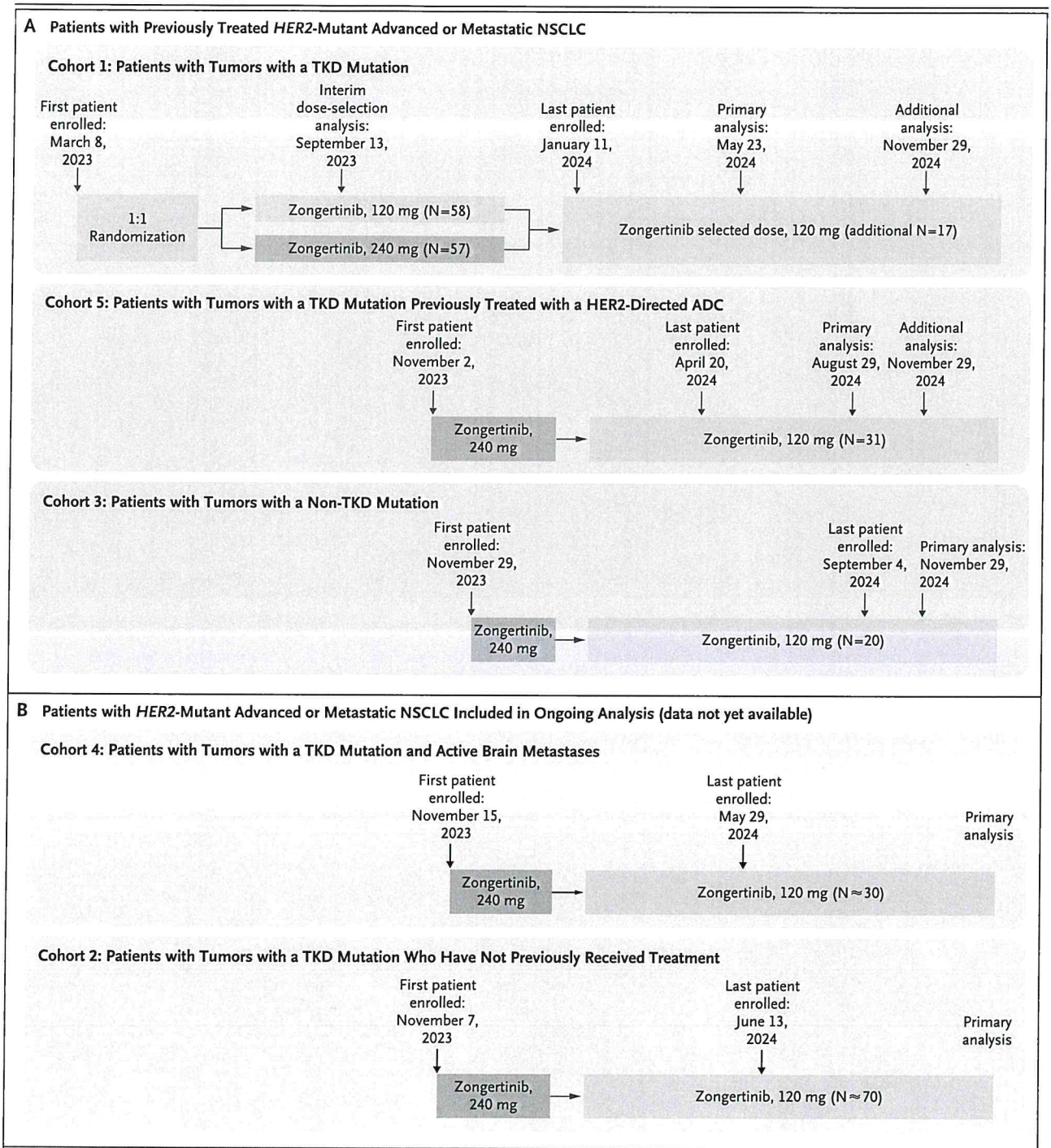

Figure 1. **Phase 1b Trial Cohorts.**

Shown are all five global cohorts in phase 1b of the trial. Panel A shows global cohorts 1, 5, and 3, which comprised patients with previously treated human epidermal growth factor receptor 2 (*HER2*)–mutant advanced or metastatic non–small-cell lung cancer (NSCLC). The median follow-up at the data-cutoff date (November 29, 2024) was 11.3 months in cohort 1, 6.8 months in cohort 5, and 8.3 months in cohort 3. The interim dose-selection analysis of cohort 1 was performed once 20 patients per dose group had completed one postbaseline tumor assessment or had discontinued treatment. Randomization continued while the interim dose-selection analysis was conducted. Primary analyses of data from cohorts 1, 5, and 3 were undertaken once all patients treated with the selected dose had completed two postbaseline tumor assessments or had discontinued treatment. Panel B shows global cohorts 4 and 2 (data not yet available). ADC denotes antibody–drug conjugate, and TKD tyrosine kinase domain.

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or metastatic disease that included a platinum-based combination chemotherapy. Patients with stable or asymptomatic brain metastasis were eligible. An archival or fresh tumor sample was required for central retrospective confirmatory testing for *HER2* mutations with the use of the Oncomine Dx Target Test (Thermo Fisher Scientific). Patients who had previously received any HER2-directed treatment were ineligible for participation in cohorts 1 and 3. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available with the full text of this article at NEJM.org).

In cohort 1, two doses from phase 1a were assessed to determine which dose was more effective, in agreement with the FDA as part of Project Optimus. Initially, patients in cohort 1 were randomly assigned in a 1:1 ratio to receive zongertinib at a dose of either 120 mg or 240 mg once daily in 21-day cycles until the dose of 120 mg once daily was selected during an interim dose-selection analysis; randomization was stratified according to the presence of A775_G776insYVMA, P780_Y781insGSP, or other mutations. In cohorts 5 and 3, patients initially received zongertinib at a dose of 240 mg once daily in 21-day cycles. After the dose-selection analysis in cohort 1, newly enrolled patients in cohorts 5 and 3 received 120 mg once daily. Treatment continued until the occurrence of progressive disease, withdrawal of consent, or the occurrence of unacceptable toxic effects.

STUDY OVERSIGHT

The conduct of the trial was overseen by the investigators and Boehringer Ingelheim (the sponsor), which also funded the trial. The trial was approved by the institutional review board at each site and was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant local regulations. Patients provided written informed consent before participation. Data were gathered, analyzed, and interpreted by the funder and the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available at NEJM.org). The authors agreed to maintain data confidentiality and contributed to the development of the manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version. Editorial assistance with an earlier draft of the manuscript was provided by a medical writer and funded by Boehringer Ingelheim.

END POINTS

The primary end point was an objective response (a best overall complete or partial response) as assessed by blinded independent central review (cohorts 1 and 5) or investigator review (cohort 3) according to RECIST, version 1.1.[17] Secondary end points included duration of response (time from the first complete or partial response until disease progression or death); progression-free survival according to RECIST, version 1.1; and an objective response according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria for patients with central nervous system lesions at baseline.

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Details of tumor and safety assessments are included in the Supplementary Appendix.

STATISTICAL ANALYSIS

We planned to perform an interim dose-selection analysis in cohort 1 once 20 patients per dose group had completed one postbaseline tumor assessment or had discontinued treatment (Fig. 1). Randomization continued while the interim dose-selection analysis was conducted. Overall, a sample size of approximately 60 patients per dose group was planned, with approximately 70 patients treated with the selected final dose to ensure sufficient power to reject the null hypothesis (an objective response of ≤30%, which was derived by benchmarking against the percentage of patients with an objective response with docetaxel as previously described[7]).

For cohort 5, we calculated that a sample size of 30 patients treated with the selected dose would provide sufficient power to reject the null hypothesis (an objective response of ≤25%). For exploratory cohort 3, we calculated that a sample size of 30 patients would provide sufficient power for signal detection (an objective response of ≥40%). In cohort 3, no confirmatory testing was performed and no hypotheses were defined.

The primary analyses of cohorts 1, 5, and 3 were undertaken once all patients treated with

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the selected dose had completed two postbaseline tumor assessments or had discontinued treatment. In cohorts 1 and 5, the null hypotheses were analyzed with the use of one-sided z-tests at an overall alpha level of 0.025 (no adjustment for type 1 error was carried out in cohorts 1 and 5). In cohort 1, the alpha level was split with the use of a Bonferroni correction to account for the two doses being investigated, resulting in an alpha level of 0.0125. Further analyses with longer follow-up were performed to allow for the assessment of time-to-event outcomes.

Kaplan–Meier estimates were used to analyze time-to-event end points with 95% confidence intervals with the use of Greenwood's variance estimate. Safety data were analyzed descriptively.

RESULTS

PATIENTS AND TREATMENT

Between March 8, 2023, and November 29, 2024, a total of 132 patients with previously treated NSCLC with a mutation in the tyrosine kinase domain (cohort 1), 39 patients with NSCLC with a mutation in the tyrosine kinase domain who had been previously treated with a HER2-directed antibody–drug conjugate (cohort 5), and 25 patients with previously treated NSCLC with a non–tyrosine kinase domain mutation (cohort 3) were treated at 74 sites in Australia, Europe, Asia, and the United States. At the interim dose-selection analysis in cohort 1, a total of 24 and 28 patients had been randomly assigned to receive zongertinib at a dose of 120 mg and a dose of 240 mg, respectively. The 120-mg dose was selected on the basis of the benefit–risk profile and exposure–response analyses. Although the efficacy was similar across both doses, patients who received 240 mg had an increased incidence of serious adverse events, which led to more dose interruptions and dose reductions.

The overall representativeness of the trial population is described in Table S1. As of November 29, 2024, a total of 75 patients in cohort 1 had received zongertinib at a dose of 120 mg (Fig. S1 in the Supplementary Appendix), of whom treatment was ongoing in 44%. Baseline demographic and disease characteristics of these patients are shown in Table 1. More than one third (37%) of these patients had brain metastases at baseline. The patients had been heavily pretreated; 39% had received at least two previous systemic therapies. The median duration of treatment with zongertinib from the first dose until the data cutoff was 11.0 months (range, 1.0 to 19.0) in cohort 1. In total, 57 patients in cohort 1 received zongertinib at a dose of 240 mg (Table S2). The baseline characteristics of patients treated with zongertinib at a dose of 120 mg in cohort 5 (31 patients) and cohort 3 (20 patients) are shown in Table S3.

EFFICACY

In the primary analysis of cohort 1 (May 23, 2024), a confirmed objective response was observed in 50 of 75 patients (67%; 97.5% confidence interval [CI], 54 to 78; $P<0.001$ against the ≤30% benchmark). The median duration of response and progression-free survival data were not yet mature.

At the data-cutoff date that was used for the analysis of time-to-event outcomes (November 29, 2024), the median follow-up was 11.3 months (95% CI, 10.2 to 12.3). At this time, 53 patients (71%; 95% CI, 60 to 80; $P<0.001$ against the ≤30% benchmark) had a confirmed objective response: 5 patients (7%) had a complete response, and 48 patients (64%) had a partial response (Table 2). Of the 53 patients who had a response, 21 (40%) had an ongoing response at the data-cutoff date (Fig. 2A). The median duration of response was 14.1 months (95% CI, 6.9 to not evaluable) (Fig. 3A). The median progression-free survival was 12.4 months (95% CI, 8.2 to not evaluable) (Fig. 3B). Responses in patient subgroups are shown in Figure 2B. A total of 28 patients had brain metastases at screening, of whom 18 (64%; 95% CI, 46 to 79) had a confirmed systemic objective response according to RECIST, version 1.1; of these 28 patients, 1 (4%) had a complete response and 17 (61%) had a partial response. Among the 27 patients who were eligible for assessment according to RANO-BM criteria, the confirmed intracranial objective response was 41% (95% CI, 25 to 59) (Table S4).

Among all 75 patients in cohort 1, the median best percentage change from baseline in the sum of the diameters of target lesions was −43% (range, −100 to 22) (Fig. S2). Of the 75 patients, 42 had disease progression: 8 (11%) had isolated central nervous system progression, 26 (35%) had isolated non–central nervous system progression, 4 (5%) had simultaneous central nervous system and non–central nervous system progression (according to investigator assessment), and

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Table 1. **Baseline Demographic and Disease Characteristics of Patients in Cohort 1 Treated with Zongertinib at a Dose of 120 mg.***

Characteristic	Cohort 1 (N=75)
Median age (range) — yr	62 (30–80)
Sex — no. (%)	
Female	51 (68)
Male	24 (32)
Race — no. (%)†	
Asian	40 (53)
White	24 (32)
Missing‡	11 (15)
ECOG performance-status score — no. (%)§	
0	28 (37)
1	47 (63)
Tobacco use — no. (%)	
Never	49 (65)
Current	2 (3)
Former	24 (32)
No. of previous lines of systemic anticancer treatment — no. (%)	
0	3 (4)¶
1	43 (57)
2	12 (16)
3 or 4	13 (17)
5 or 6	2 (3)
≥7	2 (3)
Previous systemic therapy — no. (%)	
Chemotherapy	71 (95)
Antibody therapy	18 (24)
Immunotherapy	52 (69)
Tyrosine kinase inhibitor therapy	2 (3)
Previous HER2-targeted therapy — no. (%)‖	7 (9)
Previous immune checkpoint inhibitor therapy — no. (%)	57 (76)
Previous brain radiotherapy — no. (%)	13 (17)
Site of metastases at screening — no. (%)	
Brain	28 (37)
Liver	17 (23)
Method used for *HER2* sequencing — no. (%)	
Next-generation sequencing	70 (93)
Polymerase chain reaction	3 (4)
Other	1 (1)
Missing	1 (1)

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Table 1. **(Continued.)**

Characteristic	Cohort 1 (N=75)
HER2 tyrosine kinase domain mutation — no. (%)	
A775_G776insYVMA	43 (57)
P780_Y781insGSP	8 (11)
A775_G776insYVMA, other	5 (7)
G776>VC	3 (4)
L755P	2 (3)
G776V	2 (3)
Other	12 (16)

* The date of data cutoff was November 29, 2024. HER2 denotes human epidermal growth factor receptor 2.
† Race was reported by the investigators at screening.
‡ Data on race were missing because of legal requirements.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ Patients had received previous treatment in an adjuvant context only but within 6 months before initiating zongertinib; therefore, these patients were considered as having been previously treated in the context of advanced or metastatic disease in accordance with the protocol.
‖ The exclusion criterion regarding previous HER2 therapy was added during a protocol amendment after initiation of recruitment.

4 (5%) had an unknown site of progression. Among the 55 patients in cohort 1 who received zongertinib at a dose of 240 mg during the randomization phase (2 patients were recruited before randomization and were not included in the analysis), the confirmed objective response was 84% (95% CI, 72 to 91) (Table S5 and Fig. S3), the median duration of response was 9.7 months (95% CI, 8.3 to 11.0), and the median progression-free survival was 10.9 months (95% CI, 9.6 to 12.4). Among the 24 patients who were eligible for assessment according to RANO-BM criteria and received zongertinib at a dose of 240 mg during the randomization phase, the confirmed intracranial objective response was 42% (95% CI, 25 to 61).

In the primary analysis of cohort 5 (August 29, 2024), the confirmed objective response among patients with NSCLC with a mutation in the tyrosine kinase domain who had been previously treated with a HER2-directed antibody–drug conjugate was 42% (95% CI, 26 to 59; P=0.01 against the ≤25% benchmark). The data on median duration of response and progression-free survival were not yet mature. By November 29, 2024, the median duration of follow-up was 6.8 months (95% CI, 5.5 to 8.5). At this time, 15 patients (48%; 95% CI, 32 to 65) had a confirmed objective response (Table S6). Of the 22 patients who had previously received trastuzumab deruxtecan, 9 had an objective response (41%; 95% CI, 23 to 61). Overall, the median duration of response was 5.3 months (95% CI, 2.8 to not evaluable). The

Table 2. **Response to Zongertinib at a Dose of 120 mg in Cohort 1.***

Response	Cohort 1 (N=75)
Objective response	
Total no. of patients	53
Percent (95% CI)	71 (60–80)
P value	<0.001
Complete response — no. (%)	5 (7)
Partial response — no. (%)	48 (64)
Disease control	
Total no. of patients	72
Percent (95% CI)	96 (89–99)
Stable disease — no. (%)	19 (25)
Progressive disease — no. (%)	3 (4)

* Response was assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The date of data cutoff was November 29, 2024.

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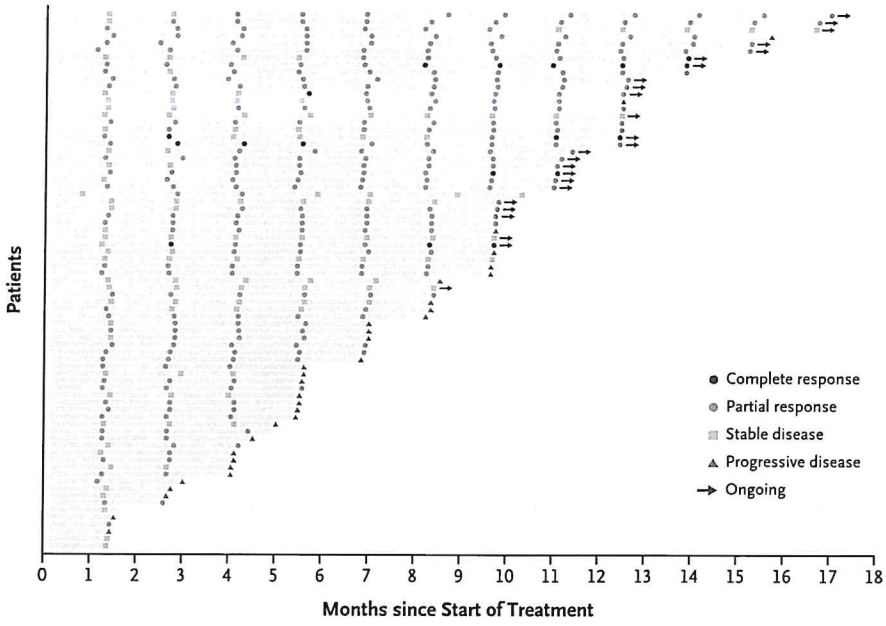
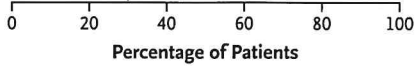
A Response Assessments and Duration of Treatment in Cohort 1



B Response in Patient Subgroups in Cohort 1

Subgroup	No. of Patients (%)	Objective Response (95% CI)
Overall	75 (100)	71 (60–80)
Sex		
Male	24 (32)	63 (43–79)
Female	51 (68)	75 (61–85)
Race		
Asian	40 (53)	75 (60–86)
Non-Asian	24 (32)	63 (43–79)
Age		
<65 yr	43 (57)	65 (50–78)
≥65 yr	32 (43)	78 (61–89)
ECOG performance-status score		
0	28 (37)	71 (53–85)
1	47 (63)	70 (56–81)
Brain metastases at screening		
No	47 (63)	74 (61–85)
Yes	28 (37)	64 (46–79)
Tumor mutation status		
A775_G776insYVMA	48 (64)	81 (68–90)
P780_Y781insGSP	8 (11)	75 (41–93)
Other	19 (25)	42 (23–64)
Previous immune checkpoint inhibitor		
No	18 (24)	72 (49–88)
≤90 days	35 (47)	69 (52–81)
>90 days	21 (28)	71 (50–86)
Tobacco use		
Never	49 (65)	76 (62–85)
Current or former	26 (35)	62 (43–78)
Weight		
<60 kg	38 (51)	74 (58–85)
≥60 kg	37 (49)	68 (52–80)



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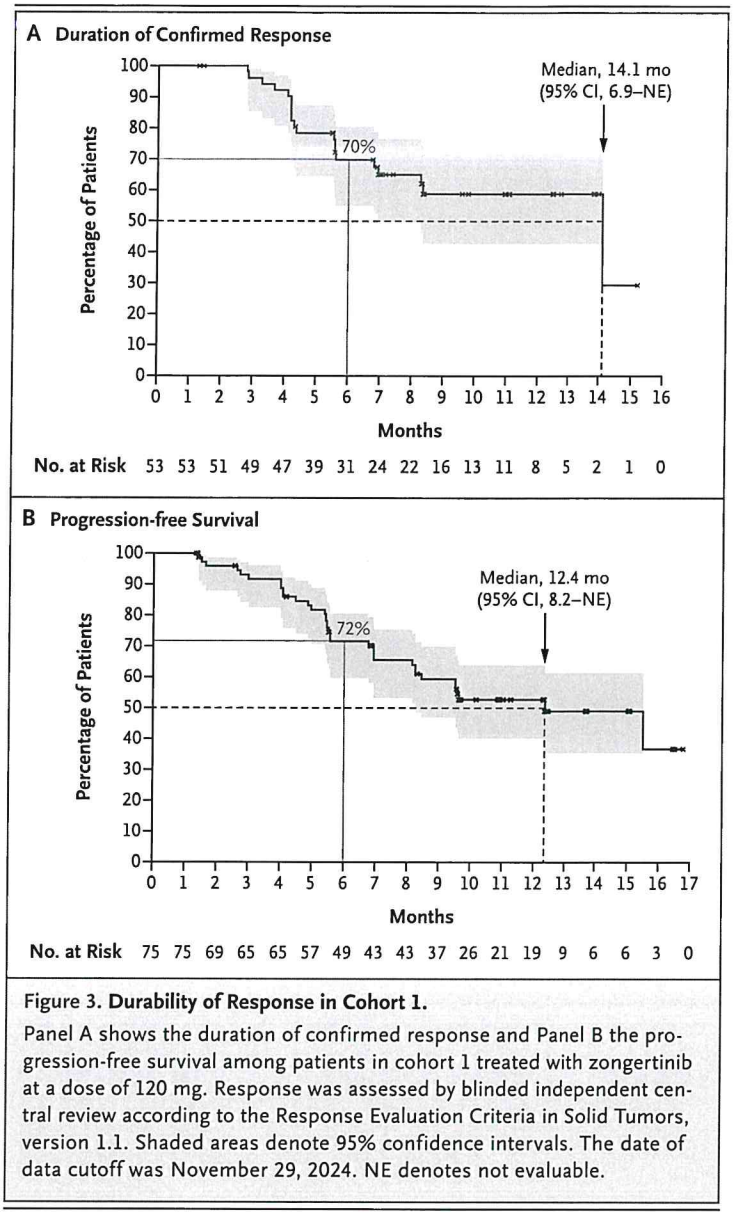

Figure 2 (facing page). **Tumor Response in Cohort 1.**
Panel A shows the tumor response among patients in cohort 1 with previously treated *HER2*-mutant NSCLC with mutations in the tyrosine kinase domain who received zongertinib at a dose of 120 mg. Panel B shows the tumor response among patients in cohort 1 with stratification according to subgroups. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Data on whether an immune checkpoint inhibitor had been received previously were not available for one patient. Response was assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The 95% confidence intervals were not adjusted for multiplicity, and no formal testing was defined. The date of data cutoff was November 29, 2024.

Figure 3. **Durability of Response in Cohort 1.**
Panel A shows the duration of confirmed response and Panel B the progression-free survival among patients in cohort 1 treated with zongertinib at a dose of 120 mg. Response was assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Shaded areas denote 95% confidence intervals. The date of data cutoff was November 29, 2024. NE denotes not evaluable.

median progression-free survival was 6.8 months (95% CI, 5.4 to not evaluable).

In the exploratory cohort 3, a total of 6 patients with NSCLC with non–tyrosine kinase domain mutations (30%; 95% CI, 15 to 52) had a confirmed objective response. Responses were observed across non–tyrosine kinase domain mutation types (Table S7). The median duration of response and progression-free survival were not yet mature at the data-cutoff date.

SAFETY

In cohort 1, adverse events that occurred during the treatment period were reported in all patients who received zongertinib at a dose of 120 mg (Table S8). Drug-related adverse events were reported in 73 patients (97%) (Table 3), and grade 3 or higher drug-related adverse events were reported in 13 patients (17%), the most common being an increased alanine aminotransferase level (8%) and increased aspartate aminotransferase level (5%). One patient (1%) had grade 4 drug-related adverse events (increased alanine aminotransferase level, transaminitis, and suspected drug-induced liver injury). A total of 7 patients (9%) had fatal adverse events; none were considered by the investigators to be related to zongertinib (malignant neoplasm progression in 5 patients, disease progression in 1 patient, and acute respiratory failure in 1 patient). No cases of drug-related interstitial lung disease or toxic effects related to interstitial lung disease were reported. Overall, 42 patients (56%) had drug-related diarrhea: 48% had grade 1, 7% had grade 2, and 1 (1%) had grade 3. All cases of drug-related rash (33%) were grade 1 (24%) or grade 2 (9%). Adverse events leading to dose reduction of zongertinib were reported in 5 patients (7%), and adverse events leading to discontinuation of zongertinib were reported in 2 patients (3%). In cohort 1, the incidence of grade 3 or higher drug-related adverse events was slightly higher among patients treated with zongertinib at a dose of 240 mg than those treated at a dose of 120 mg during the randomization phase (25% vs. 22%), as was the incidence of grade 3 or higher drug-related diarrhea (5% vs. 2%) and the incidence of adverse events of any grade leading to dose reduction (22% vs. 7%) (Table S9). The safety profile of

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Table 3. **Safety Summary and the Most Common Drug-Related Adverse Events among the 75 Patients in Cohort 1 Treated with Zongertinib at a Dose of 120 mg.**

Event	All	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Adverse events that occurred during the treatment period						
Any	75 (100)	11 (15)	29 (39)	26 (35)	2 (3)	7 (9)
Led to dose reduction*	5 (7)	1 (1)	0	3 (4)	1 (1)	0
Led to treatment discontinuation†	2 (3)	1 (1)	0	1 (1)	0	0
Serious drug-related adverse events‡	3 (4)	0	0	2 (3)	1 (1)	0
Any drug-related adverse event§	73 (97)	27 (36)	33 (44)	12 (16)	1 (1)	0
Diarrhea¶	42 (56)	36 (48)	5 (7)	1 (1)	0	0
Rash‖	25 (33)	18 (24)	7 (9)	0	0	0
Increased aspartate aminotransferase	18 (24)	11 (15)	3 (4)	4 (5)	0	0
Increased alanine aminotransferase	16 (21)	9 (12)	1 (1)	5 (7)	1 (1)	0
Nausea	11 (15)	10 (13)	1 (1)	0	0	0
Dry skin	11 (15)	11 (15)	0	0	0	0
Pruritus	10 (13)	9 (12)	1 (1)	0	0	0
Decreased white-cell count	10 (13)	5 (7)	5 (7)	0	0	0
Anemia	9 (12)	6 (8)	3 (4)	0	0	0
Decreased neutrophil count	9 (12)	3 (4)	5 (7)	1 (1)	0	0
Nail disorder	8 (11)	8 (11)	0	0	0	0

* Adverse events included increased aspartate aminotransferase (2 patients), increased alanine aminotransferase (2 patients), decreased neutrophil count (1 patient), transaminitis (1 patient), suspected drug-induced liver injury (1 patient), increased blood creatine kinase (1 patient), and increased γ-glutamyltransferase (1 patient).
† Adverse events included increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased γ-glutamyltransferase, and pyrexia (1 patient each).
‡ Events included increased alanine aminotransferase (3 patients), increased aspartate aminotransferase (2 patients), transaminitis (1 patient), and suspected drug-induced liver injury (1 patient).
§ Drug-related adverse events were assessed by the investigator; those reported in more than 10% of patients are included.
¶ The grouped term diarrhea includes the preferred terms diarrhea and intestinal transit time decreased.
‖ The grouped term rash includes the preferred terms dermatitis, dermatitis acneiform, dermatitis allergic, rash, rash erythematous, rash maculopapular, and rash pustular.

zongertinib in cohorts 5 and 3 is shown in Table S10. Grade 3 or higher drug-related adverse events were reported in 1 patient (3%) in cohort 5 and in 5 patients (25%) in cohort 3.

DISCUSSION

In this phase 1b trial involving patients with previously treated *HER2*-mutant nonsquamous advanced or metastatic NSCLC, zongertinib showed durable clinical activity, had a manageable safety profile, and resulted in notably low levels of grade 3 or higher drug-related adverse events, including those associated with EGFR inhibitors (e.g., diarrhea and rash). Among patients with *HER2*-mutant NSCLC with a mutation in the tyrosine kinase domain (cohort 1), only 2 patients (3%) discontinued treatment because of adverse events. No cases of drug-related interstitial lung disease were noted in any cohort.

At the data-cutoff date (November 29, 2024), 71% of patients with previously treated *HER2*-mutant NSCLC with a mutation in the tyrosine kinase domain (cohort 1) treated with zongertinib at a dose of 120 mg had a confirmed objective response. Responses with zongertinib were durable; the median duration of response and the median progression-free survival were both over 1 year (14.1 months and 12.4 months, respectively). Responses were observed across patient subgroups regardless of sex, age, previous treatment, race, mutation type, and presence of brain metastases. Of note, the systemic objective response according to RECIST, version 1.1, was similar in the

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subgroup of patients in cohort 1 with brain metastases at screening who were treated with zongertinib at a dose of 120 mg (64%) and the overall cohort 1 population treated at the same dose (71%), which suggests that zongertinib may be a promising treatment option in patients with brain metastases. Zongertinib was active across mutation subtypes in the tyrosine kinase domain, with a promising confirmed objective response observed in patients with A775_G776insYVMA (81%) and P780_Y781insGSP (75%) insertions.

Zongertinib also showed activity in patients with *HER2*-mutant NSCLC with non–tyrosine kinase domain mutations (exploratory cohort 3), including known activating mutations in the extracellular (S310X) and transmembrane (V659E) domains. However, this cohort was highly heterogeneous and included some mutations that are not considered to be activating (i.e., S113F and P1199S), so further research is required.[18] Overall, our findings show that zongertinib has clinical activity against activating *HER2* mutations both within and outside the tyrosine kinase domain in patients with previously treated *HER2*-mutant NSCLC.

Zongertinib showed clinical activity in patients who had been previously treated with a HER2-directed antibody–drug conjugate (cohort 5; confirmed objective response, 48%), including those who had received previous trastuzumab deruxtecan (confirmed objective response, 41%). Although the mechanisms of resistance to trastuzumab deruxtecan have not been fully elucidated,[19] our findings indicate that, in many cases, these resistance mechanisms may not confer cross-resistance to zongertinib.

The safety profile of zongertinib was consistent with its mechanism of action and previous clinical experience. Among patients in cohort 1 treated with zongertinib at a dose of 120 mg, the most common grade 3 or higher drug-related adverse events were laboratory findings (i.e., elevated levels of liver enzymes). Adverse events, including cases of hepatotoxic effects, were generally reversible, and the percentages of patients with adverse events that led to treatment discontinuation or dose reduction were low. The low incidence of grade 3 or higher EGFR-related toxic effects was expected because zongertinib spares EGFR. The most common drug-related adverse event was diarrhea (56%), which was grade 1 in 48% of patients, grade 2 in 7%, and grade 3 in 1%. These cases were generally managed with supportive care and conventional antidiarrheal medication. Drug-related rash was reported in 33% of the patients; all cases were grade 1 (24%) or grade 2 (9%). Furthermore, no drug-related interstitial lung disease events were reported.

Notwithstanding the inherent difficulties with cross-study comparisons, our results indicate that the efficacy and safety profile of zongertinib compare favorably with those of trastuzumab deruxtecan and HER2-targeted therapies in development for patients with previously treated *HER2*-mutant NSCLC. In the phase 2 DESTINY-Lung01 study, trastuzumab deruxtecan at a dose of 6.4 mg per kilogram of body weight conferred a centrally confirmed objective response of 55% among 91 patients with previously treated *HER2*-mutant NSCLC; the median duration of response was 9.3 months, and the median progression-free survival was 8.2 months. Overall, 46% of patients had grade 3 or higher drug-related adverse events, including interstitial lung disease in 26% of patients.[7] In the subsequent phase 2 dose-optimization study DESTINY-Lung02, the centrally confirmed objective response with trastuzumab deruxtecan was 49% at the recommended approved dose of 5.4 mg per kilogram; the median progression-free survival was 9.9 months. Grade 3 or higher drug-related adverse events were reported in 39% of the patients and drug-related interstitial lung disease was reported in 13%, including one fatal case.[20] These findings led to the approval of trastuzumab deruxtecan for previously treated NSCLC with metastatic or unresectable HER2 mutations.[21] The ongoing DESTINY-Lung04 study is assessing trastuzumab deruxtecan as a first-line treatment.[22]

In a recent phase 2 study of 94 patients with *HER2*-mutant NSCLC, the HER2-directed antibody–drug conjugate trastuzumab rezetecan (SHR-A1811) showed an objective response rate of 73% and a median progression-free survival of 11.5 months.[23] A total of 62% of patients had grade 3 or higher drug-related adverse events, and 7% had drug-related interstitial lung disease. The pan-HER TKIs pyrotinib and poziotinib have resulted in objective responses of 19 to 30% and 27 to 28%, respectively, but are associated with a high incidence of grade 3 or higher EGFR-related toxic effects, particularly diarrhea (17 to 26%) and, in the case of poziotinib, rash (47 to 49%).[10,11,13,14] New TKIs, such as BAY 2927088, were designed

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to have lower affinity for wild-type EGFR.[24] In the phase 1–2 SOHO-01 study, BAY 2927088 conferred an objective response of 72% (assessed by investigator review) and a median progression-free survival of 7.5 months, and 25% of patients had grade 3 drug-related diarrhea.[25] These observations highlight the need for HER2-selective TKIs for patients with *HER2*-mutant NSCLC that are effective and have manageable safety profiles.

Our trial has several limitations, including the open-label design and the lack of a standard-of-care comparator group. The ongoing phase 3 Beamion LUNG-2 trial (ClinicalTrials.gov number, NCT06151574) is evaluating the efficacy and safety of first-line zongertinib as compared with the standard of care in patients with unresectable, locally advanced or metastatic *HER2*-mutant nonsquamous NSCLC.

The data in the current trial show the antitumor activity of zongertinib at a dose of 120 mg in patients with previously treated *HER2*-mutant advanced or metastatic NSCLC.

Supported by Boehringer Ingelheim. The authors did not receive payment related to the development of the manuscript.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the patients and their families; the investigators and staff at the participating sites; Lukas Schröter, of Boehringer Ingelheim, for contributions to the data generation and analysis; Kristie Fernamberg, of Boehringer Ingelheim, for contributions toward the development of the manuscript; and Hannah Simmons, M.Sc., of Ashfield MedComms (an Inizio company) for providing medical writing support during the development of this manuscript under the direction of the authors.

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ORIGINAL ARTICLE

Sevabertinib in Advanced *HER2*-Mutant Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

HER2 gene mutations occur in 2 to 4% of patients with non–small-cell lung cancer (NSCLC). Sevabertinib is an oral, reversible tyrosine kinase inhibitor that has shown anti-HER2 activity in preclinical models.

METHODS

We conducted an open-label, multicenter, multicohort, phase 1–2 study to evaluate sevabertinib at a twice-daily dose of 20 mg in patients with locally advanced or metastatic *HER2*-mutant NSCLC. Three cohorts were defined according to previous therapy: cohort D comprised previously treated patients who had not received HER2-targeted therapy; cohort E, patients who had previously received HER2-directed antibody–drug conjugates; and cohort F, patients who had not previously received treatment. The primary end point was an objective response, as assessed by blinded independent central review. Secondary end points were duration of response and progression-free survival.

RESULTS

A total of 209 patients received sevabertinib (as of June 27, 2025, the data-cutoff date); the median duration of follow-up was 13.8 months in cohort D, 11.7 months in cohort E, and 9.9 months in cohort F. Among 81 patients in cohort D, an objective response was observed in 64% (95% confidence interval [CI], 53 to 75); the median duration of response was 9.2 months (95% CI, 6.3 to 13.5), and the median progression-free survival was 8.3 months (95% CI, 6.9 to 12.3). Among 55 patients in cohort E, an objective response was observed in 38% (95% CI, 25 to 52); the median duration of response was 8.5 months, and the median progression-free survival was 5.5 months. Among 73 patients in cohort F, an objective response was observed in 71% (95% CI, 59 to 81), and the median duration of response was 11.0 months; data on progression-free survival were immature. Grade 3 or higher drug-related adverse events occurred in 31% of the patients. The most common adverse event was diarrhea (in 84 to 91%), with diarrhea of grade 3 or higher occurring in 5 to 23%. Treatment was discontinued by 3% of the patients owing to drug-related adverse events.

CONCLUSIONS

Sevabertinib showed antitumor activity in patients with locally advanced or metastatic *HER2*-mutant NSCLC. Diarrhea was the most common adverse event. (Funded by Bayer; SOHO-01 ClinicalTrials.gov number, NCT05099172.)

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*The SOHO-01 investigators are listed in the Supplementary Appendix, available at NEJM.org.

Xiuning Le and Tae Min Kim contributed equally to this article.

This article was published on October 17, 2025, at NEJM.org.

N Engl J Med 2025;393:1819-32.
DOI: 10.1056/NEJMoa2511065
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Lung cancer is the leading cause of cancer-related death worldwide.[1,2] Alterations in the ErbB receptor tyrosine kinase family, including epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), are implicated in the pathogenesis of non–small-cell lung cancer (NSCLC) and disease progression.[3,4] Activating oncogenic mutations in *HER2* are observed in approximately 2 to 4% of patients with NSCLC.[4,5]

Platinum-based chemotherapy with or without immunotherapy is the first-line standard of care; however, precision-oncology therapeutics for advanced *HER2*-mutant NSCLC are needed.[6-8] The HER2-targeted antibody–drug conjugate trastuzumab deruxtecan received accelerated approval from the Food and Drug Administration (FDA) for previously treated patients with *HER2*-mutant NSCLC; however, adjudicated drug-related interstitial lung disease is a notable adverse event.[8-10] Although pan-HER tyrosine kinase inhibitors show limited clinical efficacy in this patient population,[11-13] with 0 to 19% having a response, the new oral, irreversible HER2 tyrosine kinase inhibitor zongertinib, which spares wild-type EGFR, showed promising efficacy in 75 patients who had not previously received HER2-targeted treatment, inducing a response in 71% and leading to a median progression-free survival of 12.4 months.[14] Zongertinib received FDA accelerated approval for previously treated patients.[15]

Sevabertinib (BAY 2927088, Bayer) is an oral, reversible tyrosine kinase inhibitor that potently inhibits tumors with *EGFR* and *HER2* mutations, including exon 20 insertions (ex20ins), while sparing wild-type EGFR.[16,17] The ongoing phase 1–2 SOHO-01 trial is evaluating sevabertinib in patients with advanced *EGFR*- or *HER2*-mutant NSCLC in dose-escalation and dose-expansion phases. Here, we report the results from the dose-expansion and dose-extension phases in patients with *HER2*-mutant NSCLC.

METHODS

STUDY DESIGN AND PATIENTS

SOHO-01 is an open-label, single-group, multicenter, international study. The dose-escalation phase evaluated sevabertinib at a once-daily dose of 10 mg and increasing doses up to the maximum tolerated dose (i.e., the maximum daily dose with ≤30% of patients having a dose-limiting toxic effect during the first 21 days), with at least 3 patients at each dose level. Treatment in concurrent backfill cohorts (≤24 patients in each) was initiated at doses that have been shown to be safe and reach efficacious exposure or induce a response. Analyses with respect to safety and efficacy of sevabertinib across the clinically evaluated total daily dose range of 10 to 80 mg indicated the potential for improved efficacy and an increased incidence of adverse events with increasing doses. After a risk–benefit assessment in a dose-escalation study with backfill[18] and integrative analyses, sevabertinib at a dose of 20 mg twice daily was considered to achieve a balance between the highest predicted benefit and an acceptable safety profile and was administered as the recommended dose in the dose-expansion and dose-extension phases until the occurrence of disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; unacceptable toxic effects; or other events meeting withdrawal criteria.

Eligible patients were 18 years of age or older with histologically or cytologically confirmed, locally advanced, recurrent or metastatic NSCLC, with a documented *EGFR*- or *HER2*-activating mutation according to local assessment; at least one measurable lesion according to RECIST, version 1.1; and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). Full inclusion, exclusion, and withdrawal criteria are provided in the Supplementary Appendix and protocol, both available with the full text of this article at NEJM.org.

The dose-escalation phase included patients with any *EGFR* or *HER2* mutation. The dose-expansion phase included four cohorts of patients with *EGFR* mutations (Fig. S1 in the Supplementary Appendix) and another four cohorts of patients with *HER2*-activating mutations who received the recommended expansion dose of sevabertinib (20 mg twice daily). These latter four cohorts were cohort D, comprising patients who had not previously received *HER2* ex20ins-targeted therapy; cohort E, patients who had previously received HER2-targeted antibody–drug conjugates; cohort F, patients who had not previously received systemic anticancer therapy for locally advanced or metastatic disease; and cohort G, patients

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with active, clinically stable brain metastases who had not previously received *HER2* ex20ins-targeted tyrosine kinase inhibitors. Sevabertinib at a dose of 10 mg twice daily was explored alongside the dose of 20 mg twice daily in patients who had not previously received *HER2* ex20ins-targeted therapy (cohort D1). The dose-extension phase included patients who received the recommended phase 2 dose and met the eligibility criteria for expansion (cohorts D, E, and F). Patients with previously treated brain metastases who were asymptomatic at screening were eligible for inclusion in the expansion and extension cohorts, with the exception of cohort G. Here, we present data for the expansion cohort D1 and the expansion and extension cohorts D, E, and F. Details on the methods used for determining *HER2* mutation status and coalterations and for circulating tumor DNA (ctDNA) profiling are provided in the Supplementary Appendix.

STUDY OVERSIGHT

This study was sponsored and designed by Bayer and conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, the principles of the Declaration of Helsinki, the international ethical guidelines of the Council for International Organizations of Medical Sciences, and applicable laws and regulations. An institutional review board or independent ethics committee at each site approved the protocol. All the patients provided written, informed consent before enrollment. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. Caudex, an IPG Health company, provided medical writing assistance, including the development of the first draft of the manuscript (funded by Bayer).

END POINTS

The primary end points of the dose-escalation-with-backfill and dose-expansion phases were adverse events, serious adverse events, maximum tolerated and maximum administered dose, and pharmacokinetic measures. Secondary end points included a response according to RECIST, version 1.1, as assessed by an investigator, and overall survival. The primary end point of the extension phase was an objective response (a complete or partial response) according to RECIST, version 1.1, as assessed by blinded independent central review.[19] Secondary end points included duration of response; progression-free survival according to RECIST, version 1.1, as assessed by the investigator and by blinded independent central review; and safety and side-effect profile. Adverse events were categorized and graded by an investigator according to the *Medical Dictionary for Regulatory Activities*, version 28.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, respectively. Additional details regarding the end points, including guidance for dose reductions and interruptions for the management of drug-related adverse events, are provided in Table S1.

STATISTICAL ANALYSIS

Safety and efficacy analyses were performed in the safety population (patients who received at least one dose of sevabertinib). Data from patients in the dose-escalation-with-backfill and dose-expansion phases who received the same dose in each phase and met the eligibility criteria for an extension cohort were combined for analysis. In cohort D, we hypothesized that at least 50% of the patients would have a response, and a sample of approximately 70 patients, with at least 30 who would have a response, was estimated to provide sufficient power to detect a lower boundary of a two-sided 95% confidence interval exceeding the 30% response threshold. The response threshold was estimated on the basis of the response to standard-care therapy that is considered to be promising in this population. In cohort E, we hypothesized that at least 40% of the patients would have a response, and a sample of approximately 51 patients, with at least 17 who would have a response, was estimated for a 20% response threshold. In cohort F, we hypothesized that at least 60% of the patients would have a response, and a sample of approximately 72 patients, with at least 38 who would have a response, was estimated for a 40% response threshold.

Responses were summarized as frequencies and percentages with 95% exact binomial confidence intervals. Time-to-event end points were summarized as Kaplan–Meier estimates. The widths of the confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. Analyses were performed with SAS statistical software, version 9.4 (SAS Institute).

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Table 1. **Demographic and Disease Characteristics of the Patients Who Received Sevabertinib, 20 mg Twice Daily, at Baseline.***

Characteristic	Cohort D (N=81)	Cohort E (N=55)	Cohort F (N=73)
Median age (range) — yr	60 (29–82)	65 (35–91)	65 (31–82)
Female sex — no. (%)	50 (62)	36 (65)	46 (63)
Race — no. (%)†			
Asian	57 (70)	32 (58)	51 (70)
White	18 (22)	15 (27)	19 (26)
Black or African American	1 (1)	4 (7)	0
Not reported	5 (6)	4 (7)	3 (4)
Region — no. (%)			
Asia	57 (70)	32 (58)	49 (67)
Western Europe and Israel	23 (28)	13 (24)	24 (33)
North America	1 (1)	10 (18)	0
ECOG performance-status score — no. (%)‡			
0	31 (38)	15 (27)	18 (25)
1	50 (62)	40 (73)	54 (74)
2	0	0	1 (1)
Smoking history — no. (%)			
Never	50 (62)	35 (64)	57 (78)
Former	27 (33)	19 (35)	15 (21)
Current	4 (5)	1 (2)	1 (1)
NSCLC histology — no. (%)			
Adenocarcinoma§	77 (95)	55 (100)	71 (97)
Squamous-cell carcinoma¶	4 (5)	0	2 (3)
HER2 TKD mutation — no. (%)			
Yes	73 (90)	52 (95)	71 (97)
No	7 (9)	3 (5)	2 (3)
Not applicable‖	1 (1)	0	0
Activating *HER2* mutation — no. (%)			
Y772_A775dupYVMA	49 (60)	40 (73)	58 (79)
Other *HER2* ex20ins	19 (23)	9 (16)	11 (15)
HER2 point mutation	12 (15)	5 (9)	1 (1)
Not applicable**	1 (1)	1 (2)	3 (4)
Brain metastases — no. (%)††	18 (22)	15 (27)	9 (12)
Median time since initial diagnosis (range) — mo	13 (2–110)	22 (2–103)	2 (0–76)
No. of previous lines of systemic anticancer therapy — no. (%)			
0	0	0	67 (92)
1	46 (57)	12 (22)	4 (5)‡‡
2	16 (20)	17 (31)	1 (1)‡‡
≥3	19 (23)	26 (47)	1 (1)‡‡

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Table 1. **(Continued.)**

Characteristic	Cohort D (N=81)	Cohort E (N=55)	Cohort F (N=73)
Previous anticancer therapy — no. (%)			
Chemotherapy	78 (96)	44 (80)	6 (8)
Platinum-based and no immunotherapy	20 (25)	12 (22)	3 (4)
Platinum-based and immunotherapy	56 (69)	31 (56)	3 (4)
Anti–PD-1/PD-L1	58 (72)	31 (56)	3 (4)
HER2-targeted therapy			
Trastuzumab deruxtecan	2 (2)§§	41 (75)	0
Other HER2-targeted ADCs	0	14 (25)	0
HER2 ex20ins-targeted TKIs	0	2 (4)§§	0

* Percentages may not total 100 because of rounding. ADC denotes antibody–drug conjugate, ex20ins exon 20 insertion, HER2 human epidermal growth factor receptor 2, NSCLC non–small-cell lung cancer, PD-1 programmed cell death protein 1, PD-L1 programmed death ligand 1, TKD tyrosine kinase domain, and TKI tyrosine kinase inhibitor.
† Race was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability. One patient had an ECOG performance-status score of 1 at screening, but at the start of treatment (baseline), the score had changed to 2.
§ Adenocarcinoma was defined by acinar adenocarcinoma, acinar-cell carcinoma, adenocarcinoma with mixed subtypes, adenocarcinoma (not otherwise specified [NOS]), bronchiolar adenocarcinoma, papillary adenocarcinoma (NOS), or solid adenocarcinoma with mucin formation per medical review.
¶ Squamous-cell carcinoma was defined by squamous-cell carcinoma (NOS), squamous carcinoma, or small-cell nonkeratinizing squamous-cell carcinoma.
‖ "Not applicable" indicates that a TKD variant and a non-TKD *HER2* variant were detected.
** "Not applicable" indicates that a specific variant was not an ex20ins or point mutation or that an unspecified *HER2* driver could not be classified as Y772_A775dupYVMA or other *HER2* ex20ins according to local *HER2* assessment.
†† Brain metastases at baseline included any target or nontarget lesion (or both) with an anatomical location in the brain according to investigator assessment, including previously treated and asymptomatic brain metastases at baseline.
‡‡ Five patients in cohort F had received and completed adjuvant or neoadjuvant therapy for stage I to III disease at least 12 months before the first dose of study treatment and were included in the study, as allowed by the protocol; one patient had received and completed adjuvant therapy less than 12 months before the first dose of study treatment, which was recorded as a protocol deviation.
§§ According to the protocol, patients who had previously received *HER2* ex20ins-targeted therapy for 2 months or less and had stopped treatment because of reasons other than progressive disease were eligible for the study if the treatment had led to unacceptable side effects.

RESULTS

PATIENTS AND TREATMENT

Patients were enrolled between October 25, 2021, and December 24, 2024. A total of 209 patients with *HER2*-mutant NSCLC received sevabertinib at a dose of 20 mg twice daily across the following cohorts: cohort D, 81 previously treated patients who had not received HER2-targeted therapy; cohort E, 55 patients who had previously received HER2-targeted antibody–drug conjugates; and cohort F, 73 patients who had not previously received systemic therapy for locally advanced or metastatic disease (Table 1 and Fig. S2). In cohort D1, 36 patients received sevabertinib at a dose of 10 mg twice daily (Table S2). Patients were representative of the Chinese population with locally advanced or metastatic *HER2*-mutant NSCLC (Table S3); therefore, White patients and Black patients were underrepresented. Most patients were women and had never smoked (Table 1).

A *HER2* tyrosine kinase domain (TKD) mutation was present in 90% of patients in cohort D, in 95% in cohort E, and in 97% in cohort F, and Y772_A775dupYVMA (also denoted as A775_G776insYVMA) was observed in 60%, 73%, and 79%, respectively (Table 1 and Table S4). In cohorts D and E, 43% and 78% of patients, respec-

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Table 2. **Response in Patients Treated with Sevabertinib, 20 mg Twice Daily.***

Response	Cohort D (N=81)	Cohort E (N=55)	Cohort F (N=73)
Best overall response — no. (%)			
Complete response	2 (2)	3 (5)	3 (4)
Partial response	50 (62)	18 (33)	49 (67)
Stable disease	20 (25)	23 (42)	16 (22)
Progressive disease	6 (7)	7 (13)	2 (3)
Not evaluable†	3 (4)	4 (7)	1 (1)
Not available‡	0	0	2 (3)
Objective response			
No. of patients	52	21	52
Percent (95% CI)	64 (53–75)	38 (25–52)	71 (59–81)
Disease control§			
No. of patients	66	39	65
Percent (95% CI)	81 (71–89)	71 (57–82)	89 (80–95)
Median duration of response (95% CI) — mo	9.2 (6.3–13.5)	8.5 (5.6–16.4)	11.0 (8.1–NE)
Median progression-free survival (95% CI) — mo	8.3 (6.9–12.3)	5.5 (4.3–8.3)	NE (9.6–NE)

* The data-cutoff date for the analyses was June 27, 2025. Response was assessed by blinded independent central review according to the Response Evaluation Criteria for Solid Tumors, version 1.1. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. NE denotes not estimable.

† Not evaluable indicates that the requirement of having a complete response, a partial response, stable disease, or progressive disease was not met.

‡ Shown are data from patients who had no postbaseline tumor assessment but who discontinued treatment because of a drug-related toxic effect, death, or disease progression (as determined by clinical judgment before disease was re-evaluated) and were therefore considered to be evaluable as not having a response.

§ Disease control refers to a confirmed complete response, a confirmed partial response, or stable disease for at least 12 weeks.

tively, had previously received at least two lines of systemic anticancer therapy, and 96% and 80%, respectively, had previously received chemotherapy. Previous platinum-based chemotherapy and immunotherapy was reported in 69% of the patients in cohort D, 56% in cohort E, and 4% in cohort F.

EFFICACY

The data-cutoff date was June 27, 2025. A confirmed objective response was observed in 64% (95% confidence interval [CI], 53 to 75) of the patients in cohort D, in 38% (95% CI, 25 to 52) of the patients in cohort E, in 71% (95% CI, 59 to 81) of the patients in cohort F, and in 36% (95% CI, 21 to 54) of the patients in cohort D1 (Table 2 and Table S5). Data on the best overall responses, as assessed in a blinded manner, and the clinical features of the patients in cohorts D, E, and F are provided in Figure 1A. In cohort D, 57% of the patients who had previously received at least two lines of systemic therapy had a response (Fig. S3). Among the patients with brain metastases at baseline, a response was observed in 61% of those in cohort D, in 27% in cohort E, and in 78% in cohort F (Table S6). Among the patients without brain metastases at baseline, the initial site of progression was the central nervous system in 5% (8 of 167 patients) (Table S7). Among the 55 patients in cohort E (those who had previously received HER2-targeted antibody–drug conjugates), 41 had received trastuzumab deruxtecan, of whom 14 (34%; 95% CI, 20 to 51) had a response to sevabertinib.

The median duration of follow-up was 13.8 months (range, 1 to 32) in cohort D, 11.6 months (range, 2 to 22) in cohort E, and 9.9 months (range, <1 to 15) in cohort F. At the time of the analysis, treatment was ongoing in 30% of the patients in cohort D, in 25% in cohort E, and in 66% in cohort F (Fig. S4).

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On blinded independent central review, the median duration of response was 9.2 months (95% CI, 6.3 to 13.5) and the median progression-free survival 8.3 months (95% CI, 6.9 to 12.3) in cohort D and 8.5 months (95% CI, 5.6 to 16.4) and 5.5 months (95% CI, 4.3 to 8.3), respectively, in cohort E (Fig. 1B and 1C). In cohort F, the median duration of response was 11.0 months (95% CI, 8.1 to not estimable); data on progression-free survival were immature (Fig. 1B and 1C). Responses were typically observed early. Among the patients in cohort D1, the median duration of response was 6.9 months (95% CI, 4.1 to 15.0) and the median progression-free survival was 5.6 months (95% CI, 4.1 to 12.3) according to investigator assessment. Among the patients in cohort D who had dose reductions or interruptions, the benefit of sevabertinib was durable (Fig. S5).

SAFETY

Adverse events were reported in all the patients; the most common adverse events are shown in Tables S8 and S9. Drug-related adverse events were reported in 78 patients (96%) in cohort D, in 55 patients (100%) in cohort E, and in 71 patients (97%) in cohort F; adverse events of grade 3 or greater were reported in 31 (38%), 17 (31%), and 17 (23%), respectively (Table 3; the results for cohort D1 are provided in Table S10). Drug-related high-grade adverse events across cohorts included 1 patient (1%) each with dyspnea, hypokalemia, and elevated alanine aminotransferase level (all grade 4) and 1 patient with cardiorespiratory arrest (grade 5).

Diarrhea was the most common drug-related adverse event and was reported in 70 patients (86%) in cohort D, in 50 patients (91%) in cohort E, in 61 patients (84%) in cohort F, and in 21 patients (58%) in cohort D1 (Table 3); grade 3 diarrhea was reported in 19 (23%), 6 (11%), 4 (5%), and 1 (3%), respectively. Diarrhea led to a dose reduction in 10 patients (12%) in cohort D, in 6 (11%) in cohort E, and in 5 (7%) in cohort F. Grade 4 diarrhea and treatment discontinuations due to diarrhea were not reported. Rash was reported in 47 to 51% of the patients, including grade 3 rash in 3 patients. Paronychia was reported in 22 to 29% of the patients.

Drug-related adverse events led to dose reductions in 21 patients (26%) in cohort D, in 19 patients (35%) in cohort E, and in 18 patients (25%) in cohort F (Table S11) and to treatment discontinuation in 4 (5%), 2 (4%), and 1 (1%), respectively; serious drug-related adverse events were reported in 12 (15%), 5 (9%), and 6 (8%), respectively. Interstitial lung disease or pneumonitis was not reported. Additional details on patients who reported dyspnea of grade 3 or higher are shown in Table S12.

BIOMARKERS IN COHORT D

Detailed exploratory biomarker analyses were performed in cohort D, because that was the largest group and had the most mature follow-up data. Among the 73 patients with *HER2* TKD mutations, the percentage of those who had an objective response appeared to be higher than that among the 7 patients with non-TKD mutations (70% [95% CI, 58 to 80] vs. 14% [95% CI, <1 to 58]), and the median progression-free survival appeared to be longer (9.6 months [95% CI, 6.9 to 12.3] vs. 6.9 months [2.5 to not estimable]) (Fig. 2A and Fig. S6A). Among the 70 patients with nonsquamous NSCLC and *HER2* TKD mutations, 71% (95% CI, 59 to 82) had an objective response; the median duration of response was 9.2 months (95% CI, 6.3 to 13.5), and the median progression-free survival was 9.6 months (95% CI, 6.9 to 14.7) (Fig. S7). Among the 49 patients with Y772_A775dupYVMA, the most prevalent *HER2* ex20ins in NSCLC,[20] the percentage of those who had an objective response appeared to be higher than that among the patients with other *HER2* TKD alterations (78% [95% CI, 63 to 88] vs. 57% [95% CI, 35 to 77]) and the median progression-free survival appeared to be longer (12.2 months [95% CI, 6.9 to 16.4] vs. 7.0 months [95% CI, 4.0 to not estimable]) (Fig. 2B and 2C).

Among the 73 patients (90%) in whom the baseline ctDNA level was analyzed, 61 (84%) had detectable *HER2* alterations (Table S13). Higher variant allele frequency was associated with increased metastatic organ involvement (Fig. S8). *TP53* mutations were the most frequently observed coalterations (present in 17 of 61 patients [28%] with detectable *HER2* ctDNA); other coalterations were rare, with PIK3CA-pathway variants present in 2 patients (3%) and MAPK-pathway variants in 1 patient (2%). It is notable that the presence of *TP53* coalterations was associated

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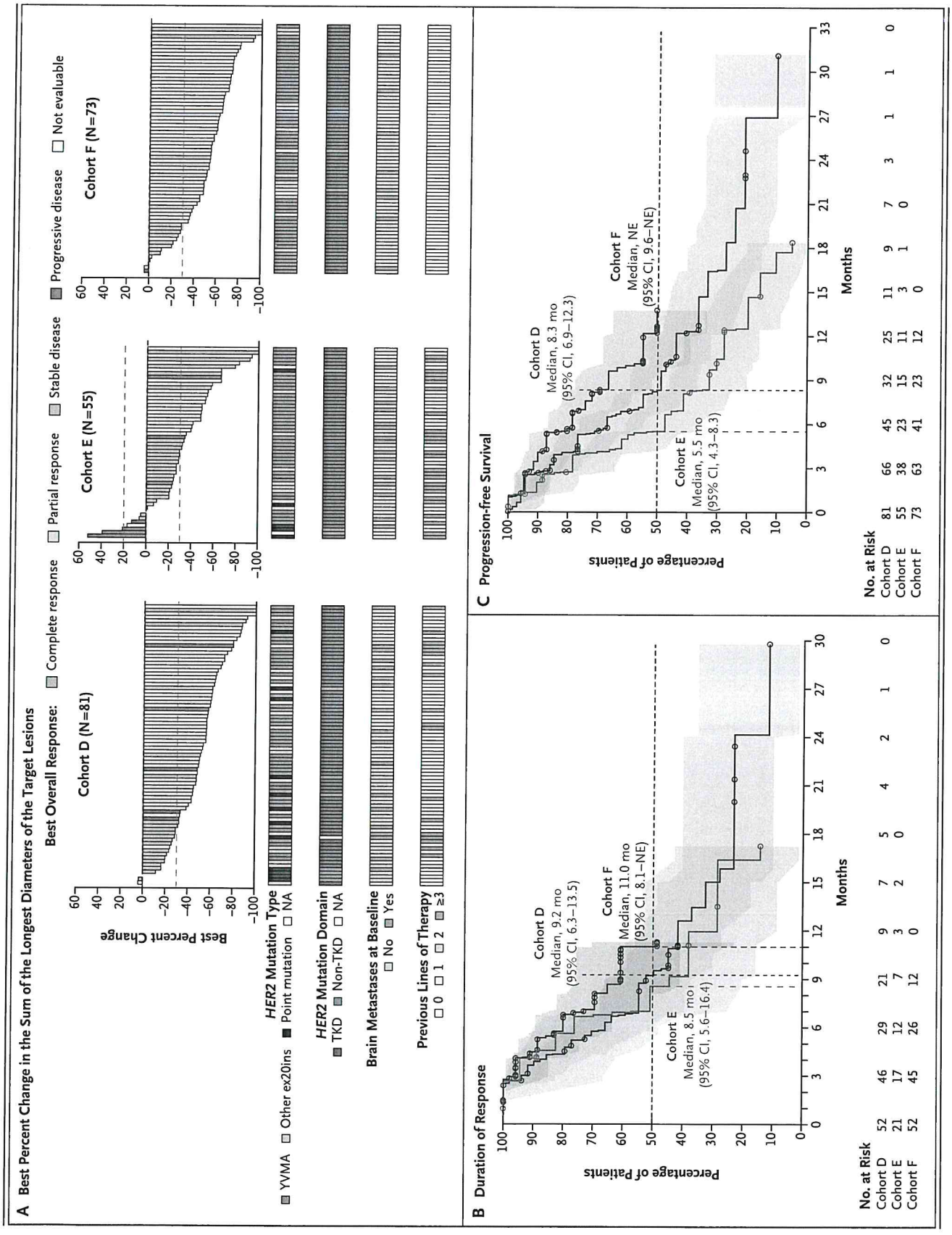

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Figure 1 (facing page). **Clinical Efficacy Outcomes in Patients Who Received Sevabertinib, 20 mg Twice Daily.**

Panel A shows the best overall response and clinical features of the patients in cohort D (previously treated patients who had not received *HER2* exon 20 insertion [ex20ins]–targeted therapy), cohort E (patients who had previously received HER2-directed antibody–drug conjugates), and cohort F (patients who had not previously received systemic anticancer therapy for locally advanced or metastatic disease). Panel B shows the duration of response in the three cohorts. Panel C shows progression-free survival in the three cohorts. Best overall response, duration of response, and progression-free survival were assessed on the basis of blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The date-cutoff date for the analyses was June 27, 2025. Patients who did not have a postbaseline target lesion measurement are not shown (two patients in cohort D, one patient in cohort E, and three patients in cohort F). Shaded areas denote 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. HER2 denotes human epidermal growth factor receptor 2, NA not applicable, NE not estimable, TKD tyrosine kinase domain, and YVMA Y772_A775dupYVMA.

with shorter progression-free survival than no detected *TP53* coalterations (5.3 months [95% CI, 2.7 to 8.1] vs. 12.3 months [95% CI, 6.7 to 18.4]) (Fig. 2D).

Early ctDNA dynamics were assessed with the use of baseline and on-treatment samples (2 to 6 weeks); 65 patients had paired successful sequencing at baseline and at least one on-treatment result. The ctDNA subgroups "never detected" (12 patients [18%]) and "clearance" (28 patients [43%]) had prolonged progression-free survival (12.3 months [95% CI, 2.5 to not estimable] and 14.7 months [95% CI, 6.9 to not estimable], respectively), as compared with the "persistent detection" subgroup (25 patients [38%]), in which the median progression-free survival was 7.0 months (95% CI, 3.9 to 16.4) (Fig. 2E). These data are supported by a sensitivity analysis involving patients with ctDNA assessments at 6 weeks (Fig. S9). No association was observed between early clinical response (at the first RECIST-based assessment at 6 weeks) and progression-free survival (Fig. S6B) in this population. The ctDNA subgroups remained distinct after adjustment for the first RECIST-based assessment (Table S14).

DISCUSSION

Among patients with advanced *HER2*-mutant NSCLC, sevabertinib showed durable antitumor activity, and toxic effects were mainly below grade 3. In a blinded assessment of outcomes, an objective response was observed in 64% of the patients in cohort D and in 71% of those in cohort F (each of which comprised patients who had not previously received HER2-targeted antibody–drug conjugates). Among the patients in cohort E (those who had previously received HER2-directed antibody–drug conjugates), an objective response was observed in 38%. In cohort D, sevabertinib led to a median duration of response of 9.2 months and a progression-free survival of 8.3 months — findings that indicate a clinical benefit in patients who had received previous systemic treatment for *HER2*-mutant NSCLC. The percentages of patients with a response were similar across subgroups, regardless of previous treatment and brain metastases at baseline.

As an *ERBB* family member, *HER2* kinase domain mutations share similarities with *EGFR* mutations.[21] Given the success of EGFR tyrosine kinase inhibitors in *EGFR*-mutant lung cancer, long-standing efforts have aimed to develop HER2 tyrosine kinase inhibitors; however, with the pan-ERBB tyrosine kinase inhibitors afatinib and dacomitinib, a response was reported in only 8% of patients or less.[22,23] Although poziotinib (response in 28%[24] and 39%[25]) and pyrotinib (response in 30%)[26] showed improved efficacy, toxic effects were frequent and included high-grade adverse events. Newer tyrosine kinase inhibitors were developed with higher anti-HER2 potency while sparing wild-type EGFR, which increased efficacy. In patients with *HER2* TKD mutations who had not previously received HER2-targeted antibody–drug conjugates, zongertinib induced a response in 71%, with a median duration of response of 14.1 months and a median progression-free survival of 12.4 months.[14] Thus, both sevabertinib and zongertinib showed impressive response outcomes in patients with *HER2*-mutant NSCLC, which approached the 70 to 80% response outcomes reported with osimertinib, lazertinib, and furmonertinib in patients with *EGFR*-mutant NSCLC.[27-29] Although it is not possible to directly compare results across trials, the median progression-free survival with sevabertinib (9.6 months) appeared to be similar to

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Table 3. **Drug-Related Adverse Events among Patients Treated with Sevabertinib, 20 mg Twice Daily.***

Event	Cohort D (N=81)	Cohort E (N=55)	Cohort F (N=73)
	number of patients (percent)		
Drug-related adverse event†			
Any grade	78 (96)	55 (100)	71 (97)
Grade 1	13 (16)	9 (16)	14 (19)
Grade 2	34 (42)	29 (53)	40 (55)
Grade 3	29 (36)	17 (31)	15 (21)
Grade 4	2 (2)‡	0	1 (1)§
Grade 5	0	0	1 (1)¶
Leading to dose reduction	21 (26)	19 (35)	18 (25)
Leading to dose interruption or delay	25 (31)	27 (49)	21 (29)
Leading to treatment discontinuation	4 (5)	2 (4)	1 (1)
Serious drug-related adverse event	12 (15)	5 (9)	6 (8)
Most common drug-related adverse events of any grade‖			
Diarrhea	70 (86)	50 (91)	61 (84)
Rash	41 (51)	26 (47)	37 (51)
Paronychia	22 (27)	16 (29)	16 (22)
Stomatitis	15 (19)	6 (11)	19 (26)
Anemia	13 (16)	8 (15)	16 (22)
Hypokalemia	14 (17)	16 (29)	13 (18)
Vomiting	14 (17)	5 (9)	13 (18)
Pruritus	16 (20)	5 (9)	9 (12)
Nausea	17 (21)	12 (22)	8 (11)
Increased AST level	14 (17)	6 (11)	10 (14)
Increased ALT level	13 (16)	6 (11)	11 (15)
Increased lipase level	10 (12)	11 (20)	13 (18)
Decreased weight	14 (17)	6 (11)	9 (12)
Dry skin	14 (17)	8 (15)	7 (10)
Decreased appetite	12 (15)	11 (20)	9 (12)
Increased amylase level	12 (15)	11 (20)	8 (11)
Increased blood creatinine level	9 (11)	2 (4)	8 (11)
Dermatitis acneiform	11 (14)	6 (11)	3 (4)
Mouth ulceration	5 (6)	3 (5)	12 (16)
Alopecia	4 (5)	0	8 (11)

* The data-cutoff date for the analyses was June 27, 2025. Drug-related adverse events were categorized and graded by the investigator with the use of the *Medical Dictionary for Regulatory Activities*, version 28.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, respectively. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† An adverse event was determined to be related to the study drug by an investigator.

‡ Dyspnea and hypokalemia occurred in one patient each.

§ An increased ALT level occurred in one patient.

¶ Cardiorespiratory arrest occurred in a 69-year-old man with advanced lung cancer, emphysema, coronary-artery calcification, sinus tachycardia, and left anterior fascicular block. Multiple adverse events developed in the patient during the treatment period, including grade 3 kidney failure with diffuse bilateral renal lesions leading to the discontinuation of sevabertinib, followed by clinical deterioration and death. The role of sevabertinib and kidney failure in this outcome remains unclear and was reported by the investigator to be "possibly related" to the study drug.

‖ Shown are the adverse events of any grade that occurred in more than 10% of patients from cohorts D, E, and F. Grade 1 or 2 and grade 3 adverse events that occurred in more than 10% of patients are shown in Table S8.

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that observed with zongertinib in a similar population of patients with a TKD mutation and nonsquamous-cell histology in cohort D.

In addition to small-molecule inhibitors, antibody–drug conjugates have shown clinical efficacy in *HER2*-altered lung cancers. Ado-trastuzumab emtansine induced a response in 44% of patients,[30] and among 91 patients, trastuzumab deruxtecan induced a response in 55%.[11] Among 94 patients, trastuzumab rezetecan induced a response in 73% and the median progression-free survival was 11.5 months.[31] In our study, 38% of patients who had previously received treatment with HER2-targeted antibody–drug conjugates had a response to sevabertinib, with a median duration of response of 8.5 months — findings that are similar to those in patients who had not previously received HER2-targeted antibody–drug conjugates and consistent with the clinical responses observed among similar patients who received zongertinib.[14] Therefore, HER2-targeted tyrosine kinase inhibitors, including sevabertinib, may represent a valuable addition to the anti-HER2 therapeutic landscape for NSCLC, for both patients who had not previously received HER2-targeted antibody–drug conjugates and those who did but subsequently had disease progression, as well as for patients who have not previously received any treatment.

The safety profile of sevabertinib was consistent with the profiles of other targeted HER2 inhibitors. Drug-related adverse events of grade 3 or higher were reported in 23 to 38% of patients across cohorts. The most common drug-related adverse event was diarrhea (in 84 to 91% of patients), with grade 3 diarrhea more commonly reported in cohort D (in 23%), as compared with cohort E (in 11%) and cohort F (in 5%). In comparison, drug-related diarrhea was reported in 32% of patients with *HER2*-mutant NSCLC who received trastuzumab deruxtecan (with grade 3 or 4 diarrhea in 3%),[11] in 12% of those who received trastuzumab rezetecan (with grade 3 diarrhea in 1%),[31] and in 56% of those who received zongertinib at a dose of 120 mg (with grade 3 diarrhea in 1%).[14] Although the incidence of diarrhea differed, discontinuation due to drug-related adverse events occurred in 1 to 5% of patients who received sevabertinib, which is similar to the percentage of patients who discontinued zongertinib because of adverse events (3%)[14] and suggests that active management of adverse events was effective for the continuation of sevabertinib therapy.

Sevabertinib had limited activity in patients with non-TKD alterations in cohort D (in one of seven patients who had a response). In cohort E, one of three patients with a non-TKD alteration had a response, whereas in cohort F, both patients with non-TKD alterations had a response. With sevabertinib therapy, *HER2* Y772_A775dupYVMA was associated with a greater response and a longer progression-free survival than other *HER2* TKD mutations — findings that are consistent with the greater response outcome reported for the *HER2* Y772_A775dupYVMA subgroup among patients who received zongertinib.[14] In contrast, inferior outcomes were reported for the Y772_A775dupYVMA subgroup among patients who received poziotinib or pyrotinib.[24-26] Although preclinical studies have shown no significant differences in responses across *HER2* alterations,[16,17] the observed differences in our study, which were potentially driven by higher oncogenic potential increasing HER2 pathway dependence in the Y772_A775dupYVMA subgroup, remain speculative and warrant further exploration.

The findings from our ctDNA biomarker analysis, as well as from aggregated analyses,[32] support previous evidence that ctDNA dynamics are prognostic in patients receiving tyrosine kinase inhibitors, including anti-EGFR,[33,34] anti-ALK,[35] and anti-MET therapies.[36] In our study, three ctDNA subgroups were associated with distinct outcomes: patients in whom ctDNA was never detected and those with ctDNA clearance appeared to have prolonged progression-free survival, as compared with patients with persistent detection of ctDNA. The ctDNA dynamics data inform prognostic understanding and future trial designs, with potential for dynamic assessment and adjustment of treatment intensity over time.

Study limitations included the underrepresentation of some racial groups, the open-label design and lack of a standard-care comparison group, and the short follow-up time for cohort F. The ongoing phase 3, randomized SOHO-02 trial (ClinicalTrials.gov number, NCT06452277) of sevabertinib as first-line therapy in patients with locally advanced or metastatic *HER2*-mutant NSCLC aims to address these gaps. Future studies are

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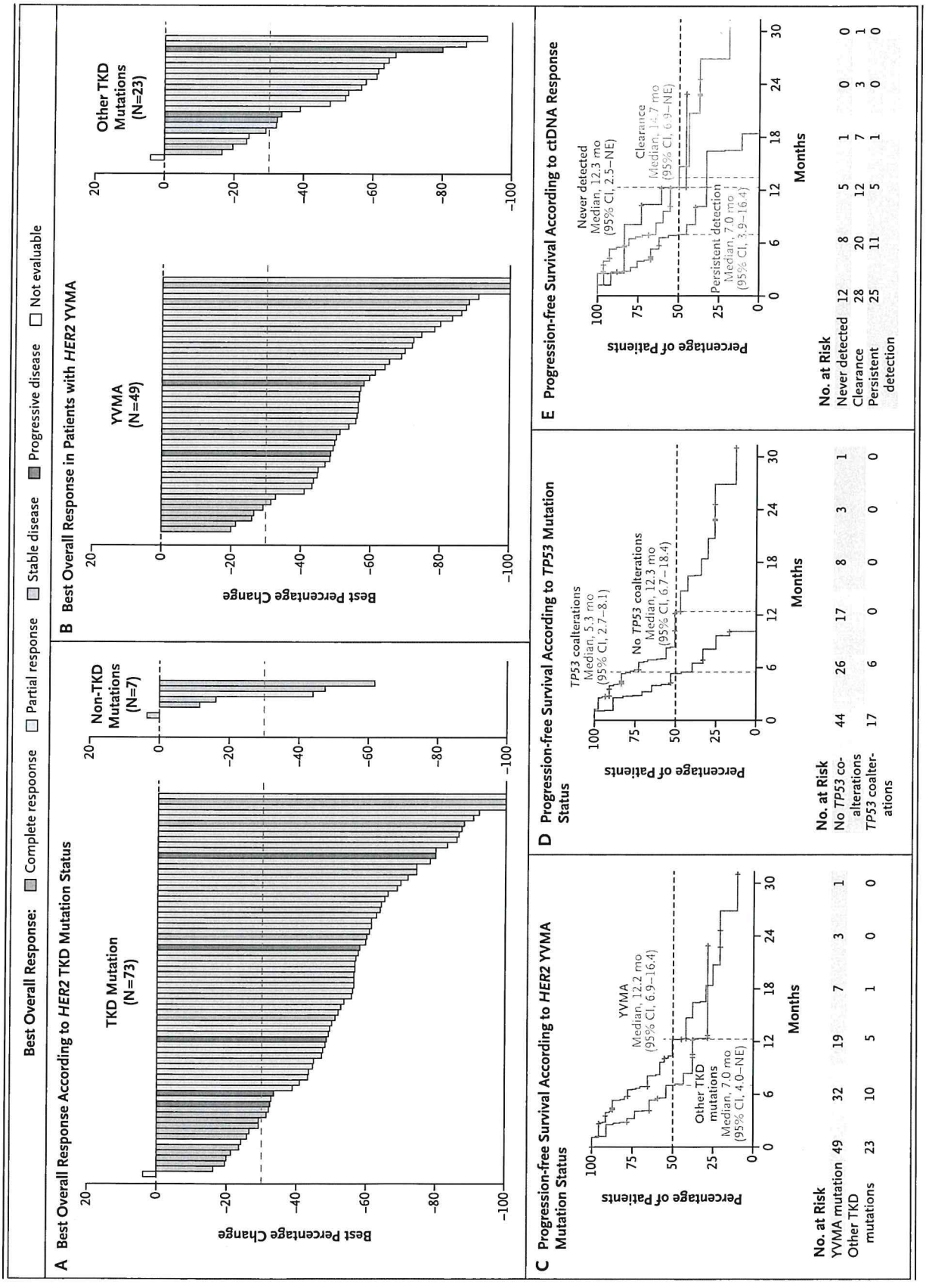

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Figure 2 (facing page). **Progression-free Survival in Cohort D According to Mutation Status, Response Status, and ctDNA Level.**

Panel A shows the best overall response according to *HER2* TKD mutation status (assessed on the basis of blinded independent central review according to RECIST, version 1.1). The percentage of patients with *HER2* TKD mutations who had a response was higher than that among those with non-TKD mutations (70% [95% CI, 58 to 80] vs. 14% [95% CI, <1 to 58]). Panel B shows the best overall response in patients with *HER2* YVMA (assessed on the basis of blinded independent central review according to RECIST, version 1.1). The percentage of patients with *HER2* YVMA who had a response was higher than that among those with other *HER2* TKD mutations (78% [95% CI, 63 to 88] vs. 57% [95% CI, 35 to 77]). Panel C shows progression-free survival according to *HER2* YVMA mutation status (assessed on the basis of blinded independent central review according to RECIST, version 1.1). Panel D shows progression-free survival according to *TP53* mutation status (assessed on the basis of blinded independent central review according to RECIST, version 1.1). The median progression-free survival was higher among patients without *TP53* coalterations than among those with *TP53* coalterations. Panel E shows progression-free survival according to circulating tumor DNA (ctDNA) response. The results of a sensitivity analysis in patients with ctDNA assessments at baseline and 6 weeks are provided in Figure S9 in the Supplementary Appendix. The data-cutoff date for the analyses was June 27, 2025. Patients who did not have a postbaseline target lesion measurement are not shown (two patients). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

warranted to provide further insights into sevabertinib in patients with non-TKD *HER2* mutations or brain metastases, assessment of ctDNA dynamics at later time points, and potential resistance mechanisms. Data from patients with active, clinically stable brain metastases (cohort G) will help to elucidate the activity of sevabertinib in the central nervous system.

In our study, sevabertinib showed antitumor activity in patients with *HER2*-mutant NSCLC who had not received and in those who had received previous treatment, including treatment with HER2-directed antibody–drug conjugates. Diarrhea was a common adverse event. No interstitial lung disease was reported as a sevabertinib-related side effect in this study.

Supported by Bayer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

We thank the patients and their families for participating in the SOHO-01 study; the members of the investigators' teams for their support in executing the study; Michel Theron (Bayer Consumer Care) and Andreas Schlicker (Bayer) for their support with biomarker data generation and analyses; and Su-Fen Pu (Bayer HealthCare Pharmaceuticals), Barbara J. Brennan (Bayer HealthCare Pharmaceuticals), Stefanie Reif (Bayer), Bart Ploeger (Bayer), and the SOHO-01 team for their work on the study. Medical writing and editorial support with an earlier version of the manuscript was provided by Alice Xue, Karishma Smart, Erica Sedgwick, and Rachel Fairbanks at Caudex, an IPG Health company.

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