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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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

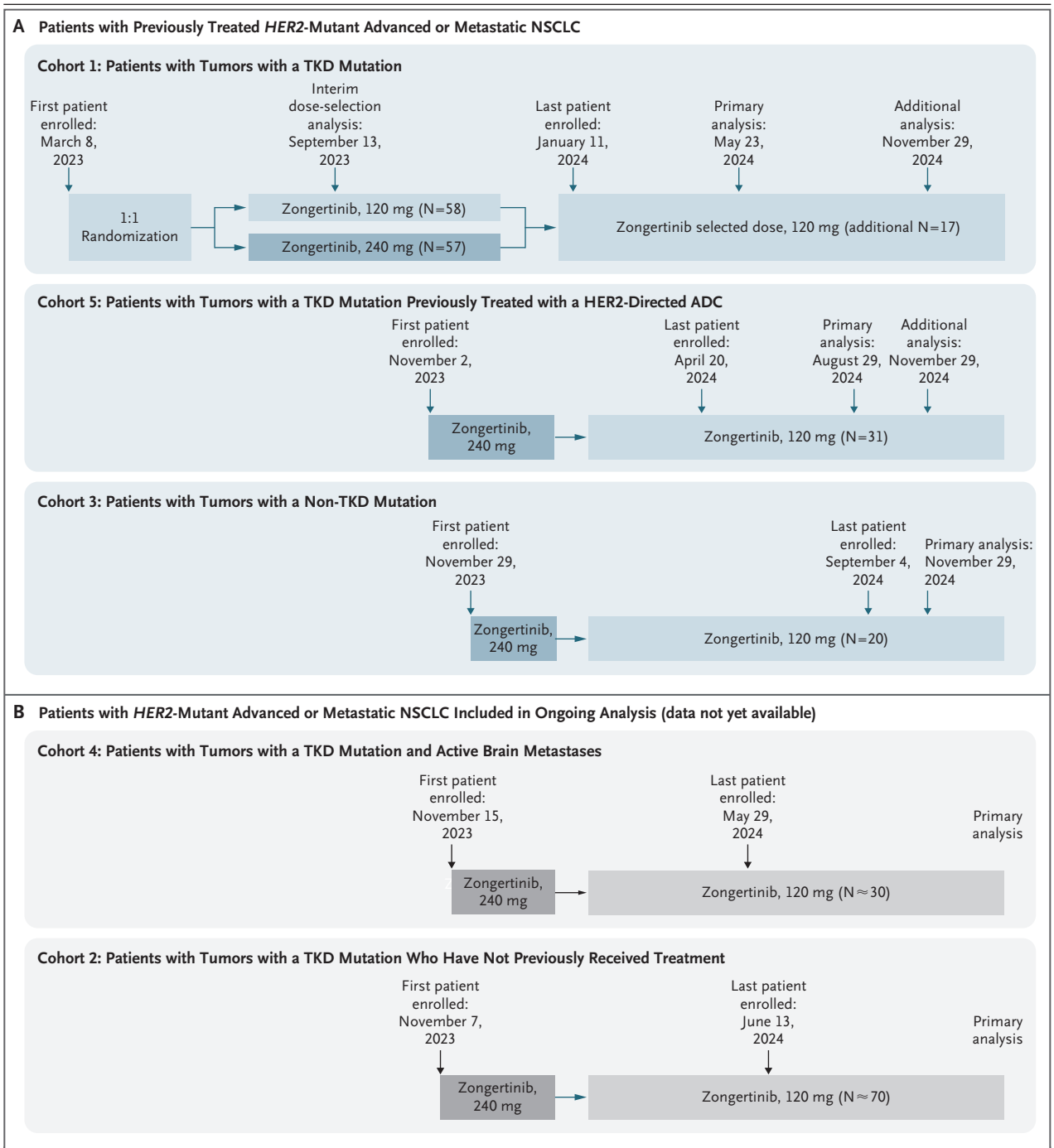


Figure 1. Phase 1b Trial Cohorts.

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.

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

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

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)

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).

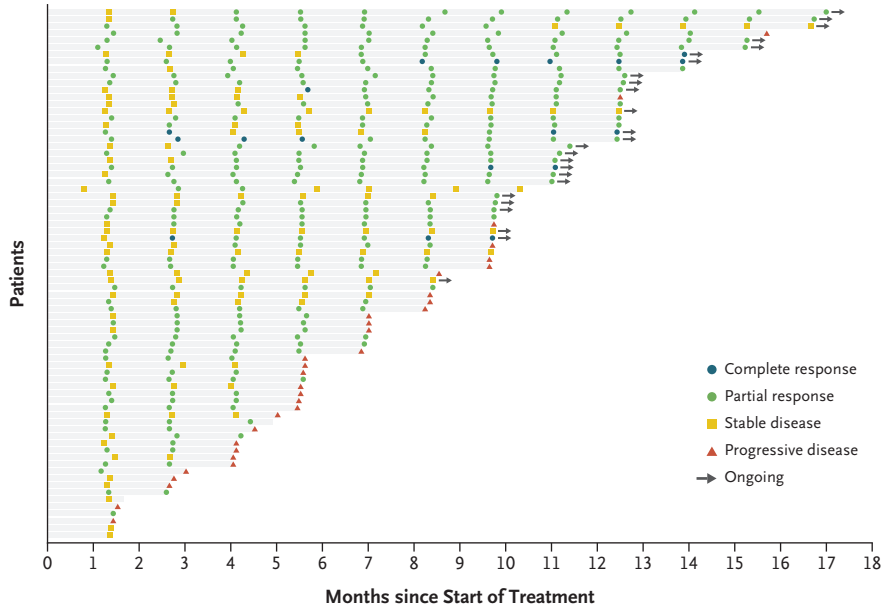
In the primary analysis of cohort 5 (August 29, 2024), the confirmed objective response among patients with NSCLC with a mutation in the tyrosine kinase domain who had been previously treated with a HER2-directed antibody–drug conjugate was 42% (95% CI, 26 to 59; P=0.01 against the ≤25% benchmark). The 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.

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)

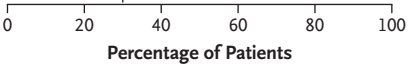
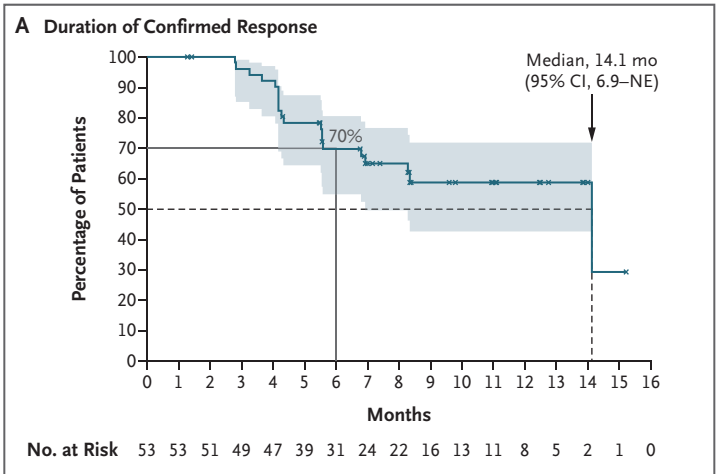


Figure 2 (facing page). Tumor Response in Cohort 1.
Panel A shows the tumor response among patients in cohort 1 with previously treated *HER2*-mutant NSCLC with mutations in the tyrosine kinase domain who received zongertinib at a dose of 120 mg. Panel B shows the tumor response among patients in cohort 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.



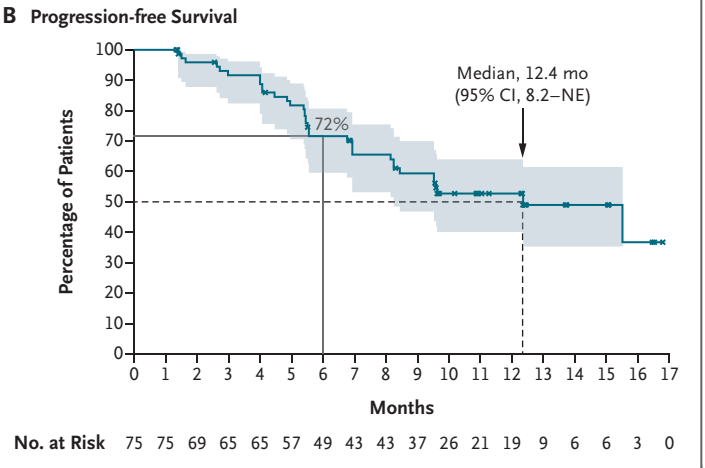


Figure 3. Durability of Response in Cohort 1.
Panel A shows the duration of confirmed response and Panel B the progression-free survival among patients in cohort 1 treated with zongertinib at a dose of 120 mg. Response was assessed by blinded independent central review according to the Response Evaluation 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

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

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

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.

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