Safety, tolerability, and antitumor activity of zipalertinib among patients with non-small-cell lung cancer harboring epidermal growth factor receptor exon 20 insertions

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Safety, Tolerability, and Antitumor Activity of Zipalertinib Among Patients With Non–Small-Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Exon 20 Insertions

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DOI https://doi.org/10.1200/JCO.23.00152

ABSTRACT

PURPOSE Although several agents targeting epidermal growth factor receptor (*EGFR*) exon 20 insertions (ex20ins) have recently been approved by the US Food and Drug Administration, toxicities related to the inhibition of wild-type (WT) *EGFR* are common with these agents and affect overall tolerability. Zipalertinib (CLN-081, TAS6417) is an oral EGFR tyrosine kinase inhibitor (TKI) with a novel pyrrolopyrimidine scaffold leading to enhanced selectivity for *EGFR* ex20ins-mutant versus WT *EGFR* with potent inhibition of cell growth in *EGFR* ex20ins-positive cell lines.

METHODS This phase 1/2a study of zipalertinib enrolled patients with recurrent or metastatic *EGFR* ex20ins-mutant non–small-cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy.

RESULTS Seventy-three patients were treated with zipalertinib at dose levels including 30, 45, 65, 100, and 150 mg orally twice a day. Patients were predominantly female (56%), had a median age of 64 years, and were heavily pretreated (median previous systemic therapies 2, range 1-9). Thirty six percent of patients had received previous non-ex20ins EGFR TKIs and 3/73 (4.1%) patients received previous EGFR ex20ins TKIs. The most frequently reported treatment-related adverse events of any grade included rash (80%), paronychia (32%), diarrhea (30%), and fatigue (21%). No cases of grade 3 or higher drug-related rash or diarrhea were observed at 100 mg twice a day or below. Objective responses occurred across all zipalertinib dose levels tested, with confirmed partial response (PR) observed in 28/73 (38.4%) response-evaluable patients. Confirmed PRs were seen in 16/39 (41%) response-evaluable patients at the dose of 100 mg twice a day.

CONCLUSION Zipalertinib has encouraging preliminary antitumor activity in heavily pretreated patients with *EGFR* ex20ins-mutant NSCLC, with an acceptable safety profile, including low frequency of high-grade diarrhea and rash.

ACCOMPANYING CONTENT

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Appendix

Data Sharing Statement

Protocol

Accepted May 6, 2023
Published June 29, 2023

J Clin Oncol 41:4218-4225

View Online Article

INTRODUCTION

Epidermal growth factor receptor (*EGFR*) exon 20 insertions (ex20ins), which comprise approximately 10% of *EGFR* mutations in non–small-cell lung cancer (NSCLC), are a diverse group of mutations that are structurally distinct from the more common *EGFR* exon 19 deletions and exon 21 L858R point mutations. EGFR tyrosine kinase inhibitors (TKIs) targeting the classical *EGFR* mutations have little to no efficacy in NSCLC harboring *EGFR* ex20ins.[1-3] Recently, two agents, mobocertinib and amivantamab, received accelerated US Food and Drug Administration approval for use in patients with NSCLC with *EGFR* ex20ins,[4,5] and other investigational agents are in development.[6,7] However, currently available EGFR ex20ins-specific TKIs such as mobocertinib cause frequent rash and diarrhea because of the narrow therapeutic window between inhibition of *EGFR* ex20ins and wild-type (WT) EGFR.[8] Amivantamab, a bispecific antibody targeting EGFR and mesenchymal-epithelial transition factor (MET), requires intravenous administration and causes frequent infusion reactions (IRRs).[5] Hence, despite recent progress in the development of *EGFR* ex20ins-targeting

CONTEXT

Key Objective

To evaluate the safety and preliminary efficacy of zipalertinib, a selective inhibitor of epidermal growth factor receptor (EGFR) exon 20 insertion mutations (ex20ins), in patients with EGFR ex20ins-mutant non–small-cell lung cancer.

Knowledge Generated

In this phase 1/2 study, zipalertinib showed encouraging antitumor activity among heavily pretreated patients with EGFR exon 20 insertions. Zipalertinib treatment was generally well tolerated with low rates of high-grade diarrhea or rash.

Relevance *(T.E. Stinchcombe)*

The preliminary efficacy and safety profile of zipalertinib (CLN-081, TAS6417) are promising, and further investigation is justified.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

therapies, there remains a significant need for novel agents that will maximize clinical efficacy while achieving a more favorable safety profile.

Zipalertinib (formerly CLN-081/TAS6417) is an irreversible oral EGFR TKI with a unique pyrrolopyrimidine structural scaffold distinct from other EGFR ex20ins TKIs (which use quinazoline and pyrimidine scaffolds).[9] Zipalertinib potently inhibits cell growth and EGFR signaling in *EGFR* ex20ins-mutant human cancer cell lines with improved selectivity for ex20ins-mutant versus WT EGFR.[10] Additionally, unlike many other approved and investigational ex20ins TKIs, zipalertinib does not inhibit WT or mutant HER2.[6,10] On the basis of these preclinical data, we investigated the safety, tolerability, antitumor activity, and pharmacokinetics (PK) of zipalertinib in this phase 1/2a study.

METHODS

Study Design

This international, multicenter, phase 1/2a study (ClinicalTrials.gov identifier: NCT04036682) assessed the safety, tolerability, antitumor activity, and PK of zipalertinib in patients with recurrent or metastatic NSCLC harboring *EGFR* ex20ins mutations. This study was sponsored by Cullinan Pearl Corporation, a Cullinan Oncology Inc portfolio company.

Zipalertinib was administered orally twice a day without food continuously in 21-day treatment cycles. Tumor assessments were performed at baseline, week 6, every 9 weeks until week 42, and every 12 weeks thereafter. Brain imaging was required with each restaging for patients with a history of central nervous system (CNS) metastases. Treatment was continued until disease progression, unacceptable adverse effects, withdrawal of consent, or could be discontinued at the investigator's discretion. Treatment could be continued beyond radiographic disease progression in patients with continued clinical benefit. Safety evaluations, including clinical and laboratory assessments, were conducted at baseline and at regular intervals during treatment. Adverse event (AE) severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Dose-limiting toxicities (DLTs) were defined on the basis of treatment-related AEs (TRAEs) observed during the first 21-day treatment cycle, although delayed events could be adjudicated as dose-limiting by the safety review committee (SRC).

Escalation began with a single-patient accelerated titration design with transition to a rolling six design upon the first occurrence of a grade ≥2 TRAE during cycle 1 (Appendix Fig A1 [online only]). Successive cohorts were treated with zipalertinib at 30, 45, 65, 100, and 150 mg twice a day; transition to the rolling six design occurred at the 100 mg dose level. The Protocol (online only) allowed for expanded enrollment of up to six patients in any cohort with an acceptable safety profile. For those cohorts in which at least 1/6 patients achieved a confirmed partial response (PR), enrollment could be expanded to a total of 13 patients, and for those cohorts in which 4/13 patients achieved a confirmed PR, enrollment could be expanded up to 36 total patients.

Eligibility Criteria

Eligible patients were age 18 years and older and had histologically or cytologically confirmed recurrent and/or metastatic NSCLC with an *EGFR* ex20ins mutation confirmed on local testing in a Clinical Laboratory Improvement Amendments of 1988 (CLIA)–certified or equivalent laboratory. Central confirmation of the *EGFR* ex20ins was not required. Archival tumor tissue and circulating tumor deoxyribonucleic acid for molecular profiling were collected during screening.

Previous platinum-based chemotherapy was required, unless it was contraindicated or declined by the patient, with no

restrictions on the number of previous therapies. Previous EGFR inhibitors were allowed, but previous ex20ins-specific TKIs were only allowed in the accelerated titration cohorts. Other requirements included the presence of measurable disease by Response Evaluation Criteria in Solid Tumors,[11] Eastern Cooperative Oncology Group performance status of 0-1, and adequate renal, hepatic, cardiac, and hematologic function. Patients with radiographically stable, asymptomatic brain metastases were eligible. Exclusion criteria included spinal cord compression, history of drug-induced pneumonitis, or active infection. Full inclusion/exclusion criteria are available in the Protocol.

Pharmacokinetic Analysis

Blood was collected to quantitate zipalertinib plasma concentrations after the first dose on cycle 1 day 1 (C1D1) and on cycle 1 day 15 (C1D15) in the dose-escalation cohorts. In dose-expansion, blood was collected on C1D1. PK data are included as of a PK data cutoff of November 2021. Zipalertinib concentrations were determined using a validated liquid chromatography tandem mass spectrometry assay; details of PK analyses are available in Appendix 1 (online only).

Statistical Analysis

All patients treated with zipalertinib as of the data cutoff are included in the safety population. All enrolled patients who were considered evaluable for response at the data cutoff are included in the efficacy population. Patients who received at least one dose of zipalertinib were included in PK analyses. Detailed statistical methods are available in Appendix 1.

Study Oversight

All patients provided written informed consent for study participation. The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and was reviewed and approved by the institutional review board at each participating site. Study conduct was overseen by a SRC composed of study investigators, independent reviewers, and sponsor representatives.

RESULTS

Patients

A total of 91 patients were screened and 73 patients were enrolled and treated with zipalertinib as of the data cutoff on May 9, 2022. All 73 patients are included in both the safety and efficacy population. All patients began zipalertinib treatment between December 23, 2019, and October 21, 2021.

During dose escalation, eight patients were treated at 30 mg twice a day, one at 45 mg twice a day, 14 at 65 mg twice a day, 13 at 100 mg twice a day, and 11 at 150 mg twice a day. Enrollment at 150 mg twice a day was stopped by the SRC after the first 11 patients treated at this dose had an excess number of dose reductions (three patients) and drug discontinuations (three patients), as well as events meeting DLT criteria outside the 21-day DLT evaluation period. The 100 mg twice a day dose level then entered phase 2a expansion with 36 patients planned per protocol. Three additional patients originally in screening for the 150 mg dose level were enrolled into the 100 mg dose level after closure of the 150 mg dose level, for a total of 39 patients treated at 100 mg twice a day.

Demographic information is summarized in Table 1. Enrolled patients (32 [44%] male, 41 [56%] female) had a median age of 64 years (range, 36-82) and a median of two previous systemic therapies (range, 1-9), with 66% having ≥2 previous regimens (Table 1). All patients had adenocarcinoma histology and a documented *EGFR* ex20ins mutation, with a broad spectrum of distinct ex20ins mutations represented (Appendix Table A1 [online only]). Seventy of 73 (96%) patients had received previous platinum-based chemotherapy; three patients were previously untreated (ineligible for or declined chemotherapy). Twenty-nine of 73 (40%) patients had received a previous EGFR inhibitor, including 13/73 (18%) with previous osimertinib and 3/73 (4%) with previous poziotinib or mobocertinib (Table 1). None had

TABLE 1. Summary of Patient Demographics

Characteristic	All Patients (N = 73)
Age, years, median (range)	64 (36-82)
Female, No. (%)	41 (56)
EGFR exon 20 insertion mutation, No. (%)	
Helical	2 (3)
Near-loop	52 (71)
Far-loop	9 (12)
Undetermined	10 (14)
ECOG performance status, No. (%)	
0	22 (30)
1	51 (70)
Previous systemic cancer regimens,[a] No. (%)	
0	3 (4)
1	22 (30)
2	32 (44)
3 or more	16 (22)
Median (range)	2 (1-9)
Previous EGFR TKIs (non-ex20ins), No. (%)	26 (36)
Previous afatinib or gefitinib	13 (18)
Previous osimertinib	13 (18)
Previous poziotinib and/or mobocertinib,[b] No. (%)	3 (4)
Previous PD-1/PD-L1 inhibitor, No (%)	40 (55)
History of CNS metastases, No. (%)	28 (38)

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ex20ins, insertions in EGFR exon 20; TKIs, tyrosine kinase inhibitors.
[a]Three patients with no previous therapy (declined chemotherapy).
[b]No patients received previous amivantamab.

received amivantamab. Forty (55%) patients had received an immune checkpoint inhibitor (ICI); the ICI was part of the most recent treatment regimen in 22 (30%) patients.

Safety

Treatment-emergent AEs (TEAEs) of any grade were observed in 73/73 (100%) patients treated across all dose levels, with grade ≥3 TEAEs in 39/73 (53%) patients (see details in Appendix Table A2 [online only]). TRAEs of any grade occurred in 72/73 (99%) patients treated across all dose levels, with grade ≥3 TRAEs in 17/73 (23%) patients (Table 2). The most common TRAEs of any grade occurring in ≥15% patients included rash (80%), paronychia (32%), diarrhea (30%), fatigue (21%), anemia (19%), dry skin (18%), and nausea (16%; Table 2). Anemia (10%) was the only grade ≥3 TRAE observed in ≥5% patients (Appendix Table A3 [online only]).

Fifty-eight (80%) of patients had treatment-related rash, which was grade 1 in 70%, grade 2 in 28%, and grade 3 in 2%. Diarrhea occurred in 22 patients (30%) and was grade 1 in 68%, grade 2 in 23%, and grade 3 in 9%. No patients treated at zipalertinib doses of 100 mg twice a day or lower experienced grade ≥3 diarrhea or rash. Prophylactic antidiarrheal treatment was not required, and both diarrhea and rash were generally managed with conventional supportive medications.

There were 0/8, 0/1, 1/14, 1/39, and 4/11 DLTs at the 30, 45, 65, 100, and 150 mg dose levels, respectively (Appendix Table A4 [online only]). Ten of 73 (14%) patients required dose reduction and 6/78 (8%) discontinued zipalertinib because of a drug-related AE. The six treatment-related discontinuations, two each at 65, 100, and 150 mg, were due to pneumonitis (n = 2), hepatic toxicity (n = 2), fatigue (n = 1), and allergic reaction (n = 1). In total, there were four cases of pneumonitis deemed possibly related to zipalertinib (see Appendix 1 for details). There were 2/13, 5/39, and 3/11 dose reductions at the 65, 100, and 150 mg twice a day doses, respectively. Reasons for dose reduction included rash in three patients, and one patient each for diarrhea, neutropenia, thrombocytopenia, nausea, elevated alkaline phosphatase, muscle cramps, and dyspnea (unrelated to treatment). No drug-related deaths were observed. Forty-nine of 73 (67%) patients had discontinued treatment at the time of data cutoff, while 24/73 (33%) remained on treatment. Additional details are provided in Appendix 1.

Efficacy

Objective responses (ORs) were observed across the full range of zipalertinib doses tested, including the starting dose of 30 mg twice a day (Table 3, Fig 1). Confirmed ORs occurred in 28/73 (38.4%; 95% CI, 27 to 49) patients across all dose levels, and in 16/39 (41%; 95% CI, 25 to 56) patients treated at 100 mg twice a day. The median time to response was 1.5 months (range, 1.5-6.2). Fifty-four of 73 (74%) patients experienced tumor regression at their initial 6-week disease assessment (Fig 2), including 24/73 (33%) patients with an OR, and 43/73 (59%) patients with stable disease (SD) at their first scan.

With a median duration of follow-up of 11 months, the median duration of response (mDOR) was 10 months (95% CI, 6 to not calculable [NC]) across all dose levels. At the time of the data cutoff, the mDOR had not been reached for the 16 patients treated at 100 mg twice a day or for the 12 patients treated at doses ≤65 mg twice a day. Median progression-free survival (mPFS) was 10 months (95% CI, 6 to 12) across all dose levels, 12 months (95% CI, 5 to NC) at 100 mg twice a day, and 8 months (95% CI, 5 to 13) for patients treated at

TABLE 2. Treatment-Related AEs Observed in ≥10% of Subjects Overall

	≤65 mg Twice a Day (N = 23)		100 mg Twice a Day (N = 39)		150 mg Twice a Day (N = 11)		Overall (N = 73)	
AE[a]	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17.4)	5 (13)	1 (2.6)	2 (18)	2 (18.2)	14 (19)	7 (9.6)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4.3)	3 (8)	1 (2.6)	2 (18)	1 (9.1)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0

Abbreviations: AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.
[a]CTCAE v5.0.

TABLE 3. Summary of Best Response Status Across Dose Levels

Response, No. (%)	≤65 mg Twice a Day (N = 23)	100 mg Twice a Day (N = 39)	150 mg Twice a Day (N = 11)	Overall (N = 73)
Confirmed PR[a]	8 (35)	16 (41)	4 (36.4)	28 (38.4)
SD	14 (60.9)	22 (56.4)	6 (54.5)	42 (57.5)
PD	1 (4.3)	1 (2.6)	1 (9.1)	3 (4.1)

Abbreviations: PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Per RECIST v 1.1.

doses of 65 mg twice a day or less (Appendix Fig A2 [online only]).

Among 26 patients who received zipalertinib after a previous EGFR (non-ex20ins) inhibitor, eight (31%) experienced a PR, 13 (50%) had SD, and two (8%) had progressive disease (Fig 1). Among the three patients previously treated with another ex20ins-directed TKI (poziotinib, mobocertinib, or both), there were two PRs and one SD (Fig 1). In an exploratory analysis, the OR rate (ORR) was 41.5% among patients with near-loop exon 20 insertions (n = 52) and 22% among those with far-loop insertions (n = 9; Appendix Fig A3 [online only]).

Although preclinical studies suggest that zipalertinib may not efficiently cross the normal rodent blood-brain barrier (unpublished observation), anecdotal examples of intracranial

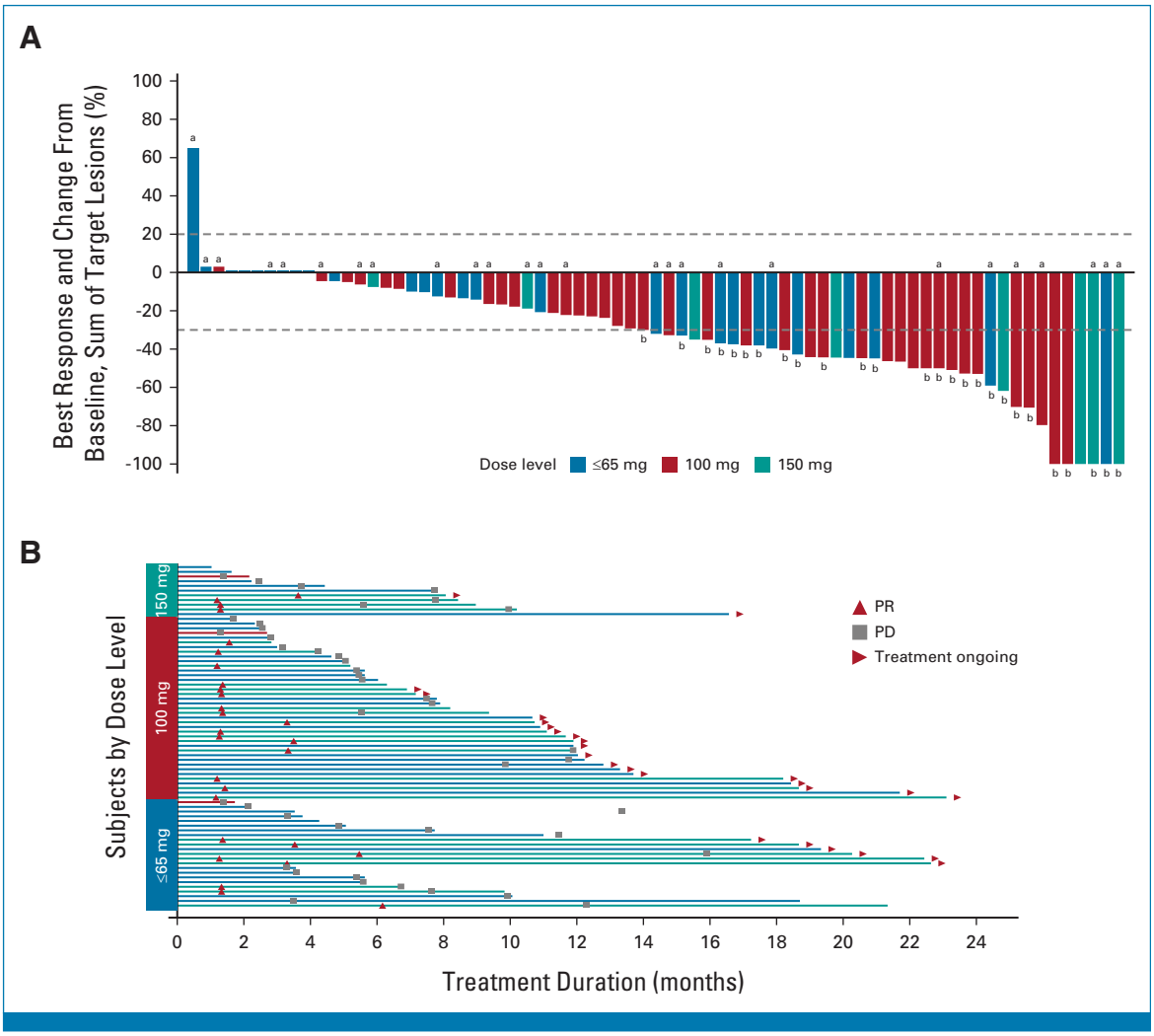

FIG 1. Clinical activity of zipalertinib in EGFR ex20ins patients with NSCLC with postbaseline target lesion assessments. (A) Waterfall plot for response of target lesions by dose level. [a]Indicates previous EGFR-targeted therapy, [b]Indicates confirmed response. (B) Swimmers plot for time to response and treatment duration by dose level. EGFR, epidermal growth factor receptor; ex20ins, insertions in EGFR exon 20; NSCLC, non–small-cell lung cancer; PD, progressive disease; PR, partial response.

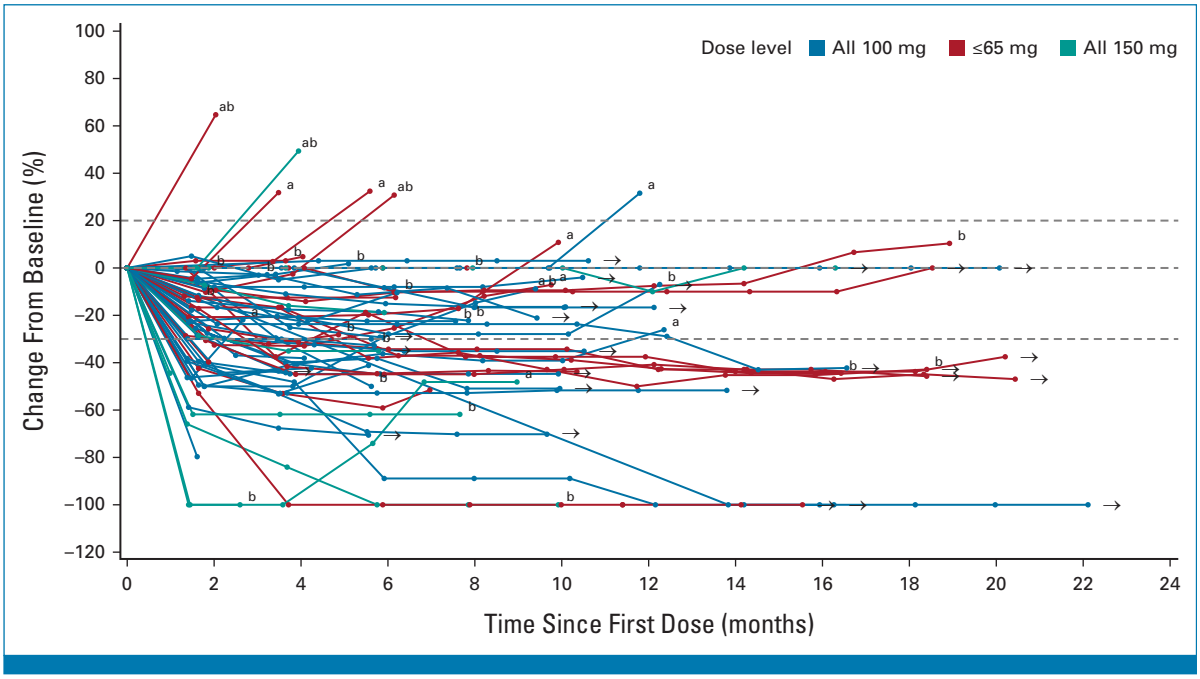

FIG 2. Tumor response over time by dose level. Spider plot of percent change from baseline in sum of target lesion diameters over time in the efficacy population (N = 73) by investigator assessment. →Treatment ongoing; [a]Growth in target lesions; [b]Growth in nontarget lesions, or new lesions.

activity were observed in patients with CNS target lesions. Eighteen patients had nontarget CNS involvement and three had CNS target lesions. Among the three patients with measurable target CNS lesions, one had both systemic and intracranial PR (Fig 3), one had systemic and intracranial SD, and one had CNS progression as the best response (details in Appendix 1).

Pharmacokinetics

Forty-seven patients were evaluable for PK after the first dose on C1D1 and 24 patients were evaluable for PK on C1D15 (Appendix Fig A4 and Appendix Table A5 [online only]). After fasting administration of zipalertinib, median time to C_{max}

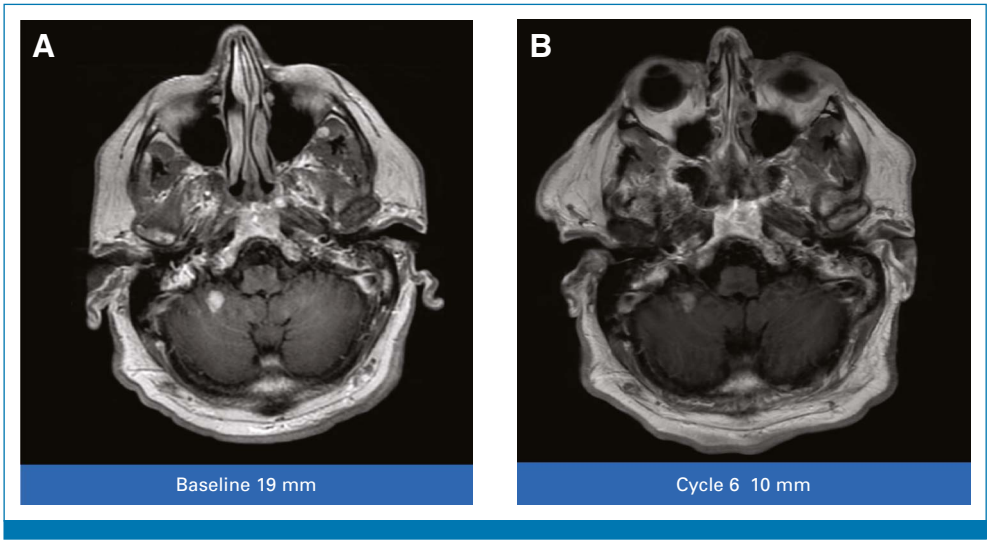

FIG 3. Intracranial response in EGFR ex20ins NSCLC patient. MRI with gadolinium enhancement (A) before and (B) after treatment with zipalertinib. EGFR, epidermal growth factor receptor; ex20ins, insertions in EGFR exon 20; NSCLC, non–small-cell lung cancer.

(T_{max}) was in the range of 0.5-1.5 hours after the C1D1 or C1D15 dose. Both C_{max} and area under the plasma concentration-time curve (AUC) increased in a dose-related manner and exhibited moderate to high variability, with intersubject variability (% coefficient of variation) in the range of 24%-86% across both days. The elimination half-life of zipalertinib is 3-4 hours after repeat twice-a-day dosing for 14 days. No notable accumulation was observed after 14 days on the basis of D15/D1 ratios of AUC_{TAU}; mean values ranged from 1.05 to 1.25.

DISCUSSION

Zipalertinib, an oral, irreversible, selective inhibitor of *EGFR* exon 20 insertions, demonstrated favorable safety and tolerability and encouraging preliminary clinical activity among patients with recurrent or metastatic *EGFR* ex20ins-mutant NSCLC previously treated with platinum-based chemotherapy. ORs were observed across the range of dose levels tested and across a diverse spectrum of ex20ins mutations. In a heavily pretreated patient population, zipalertinib led to rapid and durable tumor regression. Although data from this ongoing study are maturing, it is notable that 24 of 73 (33%) of patients remain on study at the time of the data cutoff.

While the development of effective therapies targeting *EGFR* ex20ins has been limited by EGFR-mediated toxicities, the safety profile of zipalertinib observed to date appears consistent with its high in vitro selectivity for ex20ins-mutant versus WT *EGFR*. TRAEs have generally been reversible and manageable with standard supportive care. Diarrhea was observed in 30% of patients across all dose levels, with only two cases of grade 3 diarrhea, both at the highest dose level tested. Antidiarrheal prophylaxis was not required and symptoms were well managed with standard antidiarrheal therapies. Although dermatologic toxicities were more common, with 80% of patients across all dose levels experiencing rash, these were also predominantly low grade. Only one patient (at the 150 mg dose level) experienced grade 3 rash. Dermatologic toxicities observed with zipalertinib have been well managed with conventional supportive care (topical antibiotics and/or corticosteroids, and in a smaller number of patients, oral antibiotics, antihistamines, or corticosteroids).

The safety profile of zipalertinib appears to compare favorably with that of other EGFR ex20ins-directed therapies. For example, any-grade diarrhea occurred in 91% of patients treated with mobocertinib, 92% with poziotinib, and 54% with sunvozertinib, with over 20% of patients experiencing grade ≥3 diarrhea with mobocertinib and pozotinib.[4,6,7] Although amivantamab causes less diarrhea, dermatologic toxicities including rash (84%) are more common and IRRs occur in 64% of patients.[5] Taken together, our results indicate that zipalertinib may represent a more tolerable oral treatment option for patients with *EGFR* exon 20 insertion mutations than other currently available agents.

The ORR (38.4%) and mPFS (10 months) observed to date with zipalertinib, in particular the activity observed in the largest expansion cohort of 100 mg twice a day, suggest that its efficacy may be at least comparable with, if not exceeding, other EGFR ex20ins-targeted agents, including both mobocertinib and amivantamab. Among 81 patients treated with amivantamab on the CHRYSALIS trial, the confirmed ORR was 40% and the mPFS was 8.3 months (95% CI, 6.5 to 10.9).[5] Similarly, mobocertinib led to an ORR of 28% and an mPFS of 7.3 months.[4] Moreover, we saw responses to zipalertinib in ex20ins TKI-pretreated patients, which will be further explored in a dedicated expansion cohort.

The maximum tolerated dose of zipalertinib had not been defined at the time of the data cutoff. A food effect study is underway to determine the effect of food intake on PK at the 150 mg dose level based upon the hypothesis that food coadministration may reduce AUC and C_{max} variability and reduce gastrointestinal toxicity, and that a higher dose may enhance CNS drug penetration. The outcome of this study will inform the dose selected for further clinical development.

Our study is limited by the modest number of patients treated, short duration of follow-up, and lack of uniform assessment of CNS disease, which limits conclusions about CNS activity. Central ex20ins confirmation was not required and the number of patients with far-loop and helical mutations were small. Larger cohorts will be required to more robustly assess zipalertinib's activity in these subgroups.

In summary, zipalertinib, a novel oral irreversible pyrrolopyrimidine inhibitor of ex20ins-mutant *EGFR*, demonstrated encouraging antitumor activity (as evidenced by both the ORR and PFS), with an acceptable safety profile and reduced WT EGFR-related toxicity in heavily pretreated patients with *EGFR* ex20ins-mutant NSCLC. The risk-benefit profile of zipalertinib is encouraging and zipalertinib may represent an alternative treatment option for these patients. Future clinical development plans include investigation of the safety and efficacy of zipalertinib alone and in combination with chemotherapy in treatment-naïve NSCLC, in patients with measurable CNS metastases, and after progression on currently available EGFR ex20ins-targeting agents.

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PRIOR PRESENTATION

Presented at the 2022 ASCO Annual Meeting, Chicago, IL, June 3-8, 2022.

SUPPORT

Supported and funded by Cullinan Oncology, Inc.

CLINICAL TRIAL INFORMATION

NCT04036682

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00152.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.23.00152.

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Financial support: Jeffrey Jones
Administrative support: Jeffrey Jones
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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the patients, families, and caregivers who participated in this study, and the many personnel at each study site who contributed to management of the patients and efficient conduct of the study. The authors would also like to acknowledge the support and contributions of Tracy Liu of Cullinan Oncology, and thank the Exon20 Group (Marcia Horn) for helpful advocacy, advice, and support. Zipalertinib (CLN-081/TAS6417) was discovered by Taiho Pharmaceuticals.

REFERENCES

1. Arcila ME, Nafa K, Chaft JE, et al: EGFR exon 20 insertion mutations in lung adenocarcinomas: Prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol Cancer Ther 12: 220-229, 2013
2. Remon J, Hendriks LEL, Cardona AF, et al: EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev 90:102105, 2020
3. Meador CB, Sequist LV, Piotrowska Z: Targeting EGFR exon 20 insertions in non-small cell lung cancer: Recent advances and clinical updates. Cancer Discov 11:2145-2157, 2021
4. Zhou C, Ramalingam SS, Kim TM, et al: Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: A phase 1/2 open-label nonrandomized clinical trial. JAMA Oncol 7:e214761, 2021
5. Park K, Haura EB, Leighl NB, et al: Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: Initial results from the CHRYSALIS phase I study. J Clin Oncol 39:3391-3402, 2021
6. Wang M, Yang JC, Mitchell PL, et al: Sunvozertinib, a selective EGFR inhibitor for previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations. Cancer Discov 12:1676-1689, 2022
7. Elamin YY, Robichaux JP, Carter BW, et al: Poziotinib for EGFR exon 20-mutant NSCLC: Clinical efficacy, resistance mechanisms, and impact of insertion location on drug sensitivity. Cancer Cell 40: 754-767.e6, 2022
8. Riely GJ, Neal JW, Camidge DR, et al: Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations from a phase 1/2 trial. Cancer Discov 11:1688-1699, 2021
9. Hasako S, Terasaka M, Abe N, et al: TAS6417, a novel EGFR inhibitor targeting exon 20 insertion mutations. Mol Cancer Ther 17:1648-1658, 2018
10. Udagawa H, Hasako S, Ohashi A, et al: TAS6417/CLN-081 is a pan-mutation-selective EGFR tyrosine kinase inhibitor with a broad spectrum of preclinical activity against clinically relevant EGFR mutations. Mol Cancer Res 17:2233-2243, 2019
11. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety, Tolerability, and Antitumor Activity of Zipalertinib Among Patients With Non–Small-Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Exon 20 Insertions

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No other potential conflicts of interest were reported.

APPENDIX 1. SUPPLEMENTAL DATA

Statistical Methods

Response-evaluable patients included those with measurable disease at baseline and either at least one on-treatment tumor assessment or clinical progression before the first on-treatment tumor assessment. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities, version 24.0. Responses in individual patients were determined on the basis of the assessment of the treating investigator using Response Evaluation Criteria in Solid Tumors, version 1.1. Objective responses (ORs) were confirmed by at least one sequential tumor assessment obtained at least 4 weeks from the original scan documenting a response. OR rates (ORRs) were calculated as [[(patients with a complete response + patients with a partial response [PR]) ÷ number of patients] × 100%]. A Simon two-stage design was used to assess efficacy of zipalertinib for all dose levels entering the phase I dose expansion phase.

The analysis included patients dosed in both the dose escalation and phase I dose expansion cohorts at a given dose level. The null hypothesis was an ORR of 10%, which was tested against an alternative hypothesis of ORR ≥ 40%. If 0 responses were observed in the first six patients at given dose level, no further patients would be recruited at that dose level. Otherwise, seven additional patients could be recruited and, if four or more responses are observed in total, the null hypothesis would be rejected. This design yields a one-sided type I error rate of <5% and power of >80% when the true response rate is 40%. For dose levels entering the phase 2a dose expansion phase, an additional 23 patients could be recruited. With a total of 36 patients enrolled at a dose level, the lower and upper 90% confidence limits for ORR would be within 15% of the point estimate.

The median duration of response was estimated using the Kaplan-Meier method and defined as the interval between the date of earliest response and the date of disease progression or death for any cause. Median progression-free survival was estimated using the Kaplan-Meier method and defined as the interval between the day of the first dose of study treatment to the first documentation of disease progression or death due to any cause, whichever occurred earlier. The median duration of follow-up was determined by simple frequentist median.

PK Analyses

Pharmacokinetic parameters (maximum observed plasma concentration [C_{max}], area under the plasma-time concentration curve from time zero to the last observed time point [AUC_{last}], area under the plasma concentration-time curve in a dosing interval of 12 hours [AUC_{TAU}], terminal half-life [$t_{1/2}$], and accumulation ratio [AR]) were estimated by non-compartmental analysis (Phoenix WinNonlin Build 8.0.0.3176; ICON plc, Dublin, Ireland).

Safety

Treatment-related serious AEs included pneumonitis (n = 2), diarrhea (n = 1), and hypersensitivity reaction (n = 1).

By investigator assessment, there were four cases of pneumonitis possibly related to zipalertinib (one at 65 mg twice a day, one at 150 mg twice a day, and two at 100 mg twice a day). One case of grade 1 pneumonitis resolved after a dose hold and corticosteroids with zipalertinib treatment resumed at the same dose, another patient with a history of pneumonitis with osimertinib also experienced grade 2 pneumonitis on zipalertinib, and one patient who had discontinued pembrolizumab and chemotherapy for progressive disease (PD) about 1 month before enrolling on the study experienced grade 3 pneumonitis on zipalertinib. In a fourth patient, grade 3 pneumonitis was initially considered possibly related to zipalertinib, but ultimately deemed to be unrelated to study treatment by the sponsor after the patient was diagnosed and treated for *Pneumocystis jirovecii* pneumonia on the basis of positive bronchoalveolar lavage.

There were four cases of grade 3 or 4 ALT/AST increase (one at ≤65 mg twice a day, two at 100 mg twice a day, and one at 150 mg twice a day), all in patients who had stopped pembrolizumab therapy within 50 days of initiation of zipalertinib therapy. Only one had measurable hepatic metastases. Two of the four patients discontinued zipalertinib because of AST/ALT elevation.

Reasons for treatment discontinuation included PD (30/49; 61%), AEs (12/49; 25%), withdrawal of consent (3/49; 6%) and other (2/49; 4%), and declining performance status and death (4/49; 8%).

Clinical Activity

The median number of cycles administered was 11 (range, 2-32), 11 (2-33), and 10 (1-17) for patients treated at doses of 65 mg twice a day or less, 100 mg twice a day, and 150 mg twice a day, respectively.

PRs were observed across a spectrum of diverse epidermal growth factor receptor exon 20 insertion mutations (ex20ins) mutations. In this study, near-loop mutations were the most common mutation subtype, followed by the far-loop mutations and helical region with 52, 9, and 2 patients, respectively. There were 10 patients whose site of mutation was not reported by polymerase chain reaction testing. One patient had different ex20ins mutations identified in two different tumor specimens and was included in the unknown group. In an exploratory analysis of response rate by mutation subtype, the response rate was 41.5%, 22%, and 0% in the near-loop, far-loop, and helical region mutations, respectively (Appendix Fig A3). The response rate in the unreported group was 40%.

Eighteen patients had nontarget central nervous system (CNS) involvement and three patients had CNS target lesions. Among the three patients with measurable target lesions in the brain, one patient (treated at the 100 mg dose level) achieved both a systemic and intracranial response at cycle 6, and remained in PR at cycle 16 at the time of the data cutoff (Fig 3). The second patient (treated at 100 mg) had stable disease both systemically and intracranially after 1 year on treatment. The third patient (treated at 150 mg) progressed with new lesions in the CNS at cycle 3.

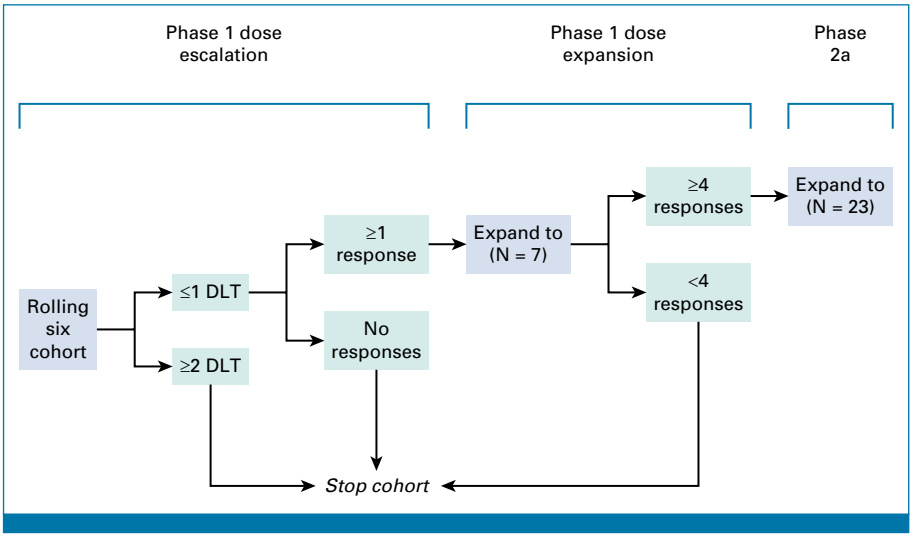

FIG A1. Phase 1/2 study design. A single-patient accelerated design was used for escalation of doses from 30 to 100 mg twice a day. At the 100 mg dose level, grade 2 toxicity occurred in the first patient, and the study transitioned to a rolling six design. Lower-dose cohorts could be expanded with a rolling six design if the dose level achieved serum drug concentrations that were associated with response in preclinical tumor models. This occurred at the first dose level of 30 mg twice a day. The SRC made decisions about expansion of cohorts at higher dose levels to six patients, and chose only to expand the 65 mg twice a day cohort. The 100 and 150 mg dose levels were expanded on the basis of safety considerations. Expansion of a dose level to 13 patients was permitted on the basis of the observation of a single response in the first six patients at any dose level. The SRC chose to expand the 65, 100, and 150 mg dose levels to 13 patients, but not the 30 or 45 mg dose levels. Expansion of the 100 mg dose level from 13 to 36 patients was based on the protocol-defined achievement of four or more responses. Although the 65 mg dose level also met this criterion, it was not expanded at the discretion of the SRC. DLT, dose-limiting toxicity; SRC, safety review committee.

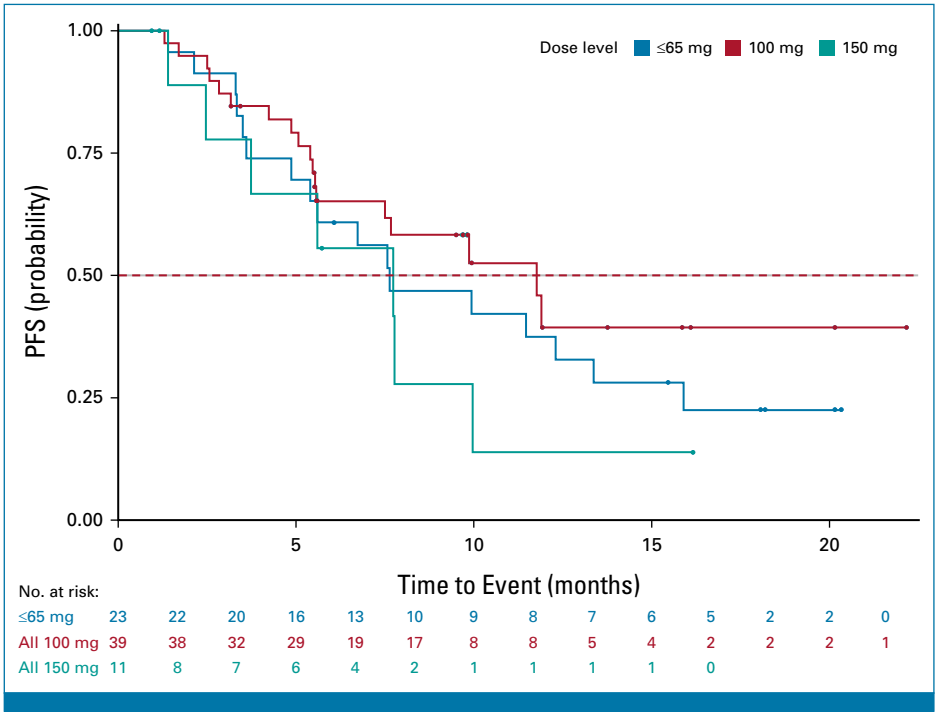

FIG A2. Kaplan-Meier curves of PFS by dose level. PFS, progression-free survival.

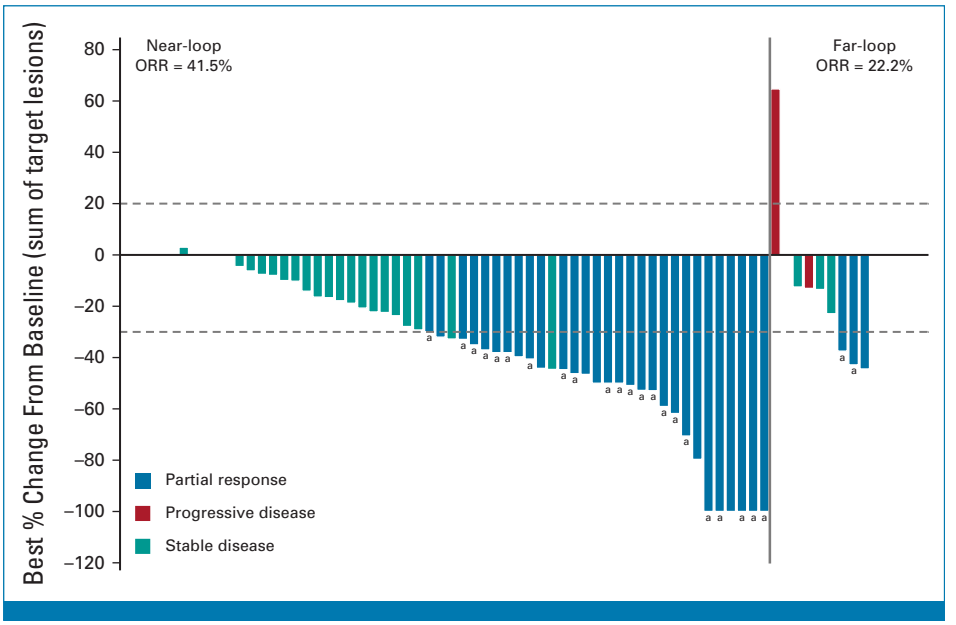

FIG A3. Tumor reduction and responses in the efficacy population by EGFR exon20ins location. Waterfall plot displaying best percent change from baseline in sum of target lesion diameters by location of EGFR exon20ins determined by local laboratory testing and investigator response. [a]Indicates response was confirmed. EGFR, epidermal growth factor receptor; ORR, objective response rate.

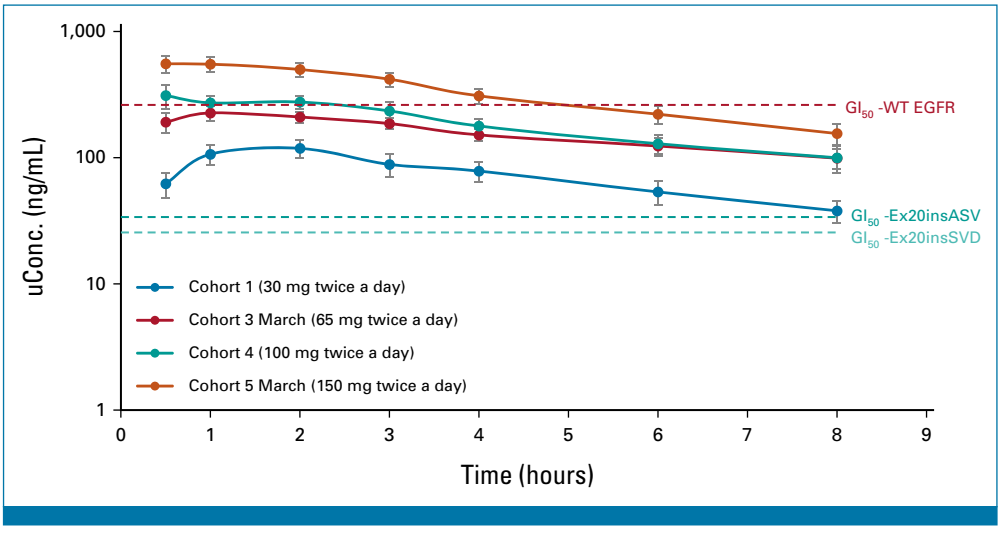

FIG A4. Average unbound plasma concentration over time for the 30, 65, 100, and 150 mg dose levels. The 50% growth inhibitory concentration of cell lines expressing wild-type and two exon 20 insertion mutation expressing cell lines. EGFR, epidermal growth factor receptor; WT, wild-type.

TABLE A1. Summary of Specific Observed EGFR ex20ins Mutations in 73 Patients With NSCLC

Exon 20 Mutation Type (No.)	Start Site	Patients, No.
Helical region (2)	762E	0
	763A	1
	764Y	0
	765V	0
	766M	1
Near-loop (52)	767A	10
	768S	12
	769V	4
	770D	13
	771N	11
	772P	2
Far-loop (9)	773H	9
	774V	0
	775C	0
Undetermined	—	10

Abbreviations: EGFR, epidermal growth factor receptor; ex20ins, insertions in EGFR exon 20; NSCLC, non–small-cell lung cancer.

TABLE A2. TEAEs Regardless of Grade Observed in ≥10% of Subjects Overall (safety analysis set)

AE Term,[a,b] No. (%)	≤65 mg Twice a Day (N = 23)	100 mg Twice a Day (N = 39)	150 mg Twice a Day (N = 11)	Overall (N = 73)
Rash	20 (87.0)	33 (84.6)	8 (72.7)	61 (83.6)
Diarrhea	7 (30.4)	18 (46.2)	4 (36.4)	26 (35.6)
Paronychia	4 (17.4)	13 (33.3)	6 (54.5)	26 (35.6)
Anemia	12 (52.2)	8 (20.5)	3 (27.3)	23 (31.5)
Fatigue	5 (21.7)	15 (38.5)	3 (27.3)	23 (31.5)
Decreased appetite	8 (34.8)	11 (28.2)	1 (9.1)	20 (27.4)
Dyspnea	6 (26.1)	13 (33.3)	1 (9.1)	20 (27.4)
Nausea	6 (26.1)	10 (25.6)	4 (36.4)	20 (27.4)
Constipation	7 (30.4)	9 (23.1)	0	16 (21.9)
Cough	4 (17.4)	10 (25.6)	2 (18.2)	16 (21.9)
Dry skin	6 (26.1)	8 (20.5)	1 (9.1)	15 (20.5)
Vomiting	4 (17.4)	9 (23.1)	1 (9.1)	14 (19.2)
Alopecia	3 (13.0)	9 (23.1)	0	12 (16.4)
Arthralgia	4 (17.4)	5 (12.8)	3 (27.3)	12 (16.4)
Headache	4 (17.4)	7 (17.9)	0	11 (15.1)
AST increased	3 (13.0)	5 (12.8)	2 (18.2)	10 (13.7)
Dizziness	2 (8.7)	6 (15.4)	2 (18.2)	10 (13.7)
Edema peripheral	4 (17.4)	4 (10.3)	2 (18.2)	10 (13.7)
Pyrexia	2 (8.7)	7 (17.9)	1 (9.1)	10 (13.7)
Stomatitis	2 (8.7)	5 (12.8)	3 (27.3)	9 (12.3)
Dry eye	1 (4.3)	7 (17.9)	1 (9.1)	8 (11.0)
ALT increased	2 (8.7)	4 (10.3)	2 (18.2)	8 (11.0)
Insomnia	2 (8.7)	5 (12.8)	1 (9.1)	8 (11.0)

Abbreviations: AE, adverse event; CPI, checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse events.

[a]CTCAE v5.0.

[b]100 mg patient with grade 3 pneumonitis confounded by recent treatment with CPI and concurrent hydropneumothorax contralateral lung; 150 mg patient with grade 3 pneumonitis confounded by concurrent Pneumocystis infection, had stopped zipalertinib 3 weeks before the event; 100 mg patient with grade 1 (to be updated as grade 2) pneumonitis treated with steroids with resolution and continued therapy; 65 mg patient with grade 2 pneumonitis who previously had pneumonitis on osimertinib.

TABLE A3. TEAEs ≥Grade 3 Observed in ≥3% of Subjects Overall (safety analysis set)

Dose Twice a Day	≤65 mg (N = 23)	100 mg (N = 39)	150 mg (N = 11)	Overall (N = 73)
AE term,[a] No. (%)				
Anemia	5 (21.7)	1 (2.6)	2 (18.2)	8 (11.0)
Dyspnea	1 (14.3)	3 (7.7)	0	4 (5.5)
Pneumonia	1 (14.3)	3 (7.7)	0	4 (5.5)
AST increased	1 (14.3)	1 (2.6)	1 (9.1)	3 (4.1)
ALT increased	1 (14.3)	1 (2.6)	1 (9.1)	3 (4.1)
Diarrhea	1 (14.3)	0	2 (18.2)	3 (4.1)
Disease progression	2 (8.7)	1 (2.6)	0	3 (4.1)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse events.

[a]CTCAE v5.0.

TABLE A4. Dose-Limiting Toxicities

Dose Level, mg/kg Twice a Day	Patients Treated, No.	DLT, Day 1-21	DLT, Day 22-EOT
30	8	0	0
45	1	0	0
65	14	0	1 (hepatic)
100	39	0	1 (pneumonitis)
150	11	2 (diarrhea)	2 (pneumonitis, hepatic)

Abbreviations: DLT, dose-limiting toxicity; EOT, end of treatment.

TABLE A5. Summary Statistics of Pharmacokinetic Parameters of Zipalertinib After Oral Doses of 30-150 mg Twice a Day

			Zipalertinib Dose Twice a Day				
Parameter	Unit	Statistic	30 mg	45 mg	65 mg	100 mg	150 mg
First dose C1D1							
C_{max}	ng/mL	GM (%CV) [n]	969 (86) [8]	2,698 (NA) [1]	2,552 (38) [14]	3,330 (39) [13]	4,788 (49) [11]
T_{max}	hour	Median (min-max) [n]	1.5 (0.5-4) [8]	1 (NA) [1]	1 (0.5-3) [14]	0.5 (0.5-3) [13]	1 (0.5-2) [11]
AUC_{LST}	ng•h/mL	GM (%CV) [n]	4,030 (81) [8]	10,151 (NA) [1]	10,674 (48) [14]	12,036 (36) [13]	20,581 (52) [11]
AUC_{TAU}	ng•h/mL	GM (%CV) [n]	5,538 (65) [7]	12,234 (NA) [1]	11,115 (39) [11]	13,674 (36) [12]	23,713 (57) [10]
$T_{1/2}$	hour	GM (%CV) [n]	3.34 (39) [7]	4.18 (NA) [1]	4.02 (32) [11]	3.67 (39) [12]	3.34 (35) [10]
Multiple dose, C1D15							
C_{max}	ng/mL	GM (%CV) [n]	1,364 (48) [7]	3,089 (NA) [1]	2,190 (47) [7]	3,827 (39) [4]	5,581 (45) [5]
T_{max}	hour	Median (min-max) [n]	1 (1-4) [7]	1 (NA) [1]	2 (0.5-3) [7]	0.5 (0.5-3) [4]	0.5 (0.5-2) [5]
AUC_{LST}	ng•h/mL	GM (%CV) [n]	5,280 (36) [7]	11,053 (NA) [1]	10,433 (54) [7]	13,861 (24) [4]	24,309 (59) [5]
AUC_{TAU}	ng•h/mL	GM (%CV) [n]	6,476 (40) [6]	12,894 (NA) [1]	12,380 (66) [6]	15,672 (34) [3]	28,326 (64) [5]
$T_{1/2}$	hour	GM (%CV) [n]	3.24 (27) [6]	4.29 (NA) [1]	4.28 (34) [6]	4.24 (52) [3]	3.89 (32) [5]
AR	NA	GM (%CV) [n]	1.13 (29) [6]	1.05 (NA) [1]	1.14 (39) [5]	1.15 (25) [3]	1.25 (23) [5]

Abbreviations: AR, accumulation ratio; AUC_{LST}, area under the plasma-time concentration curve from time zero to the last observed time point; AUC_{TAU}, area under the plasma concentration-time curve in a dosing interval of 12 hours; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GM, geometric mean; max, maximum; min, minimum; NA, not applicable; $T_{1/2}$, half-life; T_{max}, time to C_{max}.