



## Sotorasib (960 mg or 240 mg) once daily in patients with previously treated KRAS G12C-mutated advanced NSCLC

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### ABSTRACT

**Background:** Sotorasib 960 mg once daily is approved to treat KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib exhibits non-dose proportional pharmacokinetics and clinical responses at lower doses; therefore, we evaluated the efficacy and safety of sotorasib 960 mg and 240 mg.

**Methods:** In this phase 2, randomized, open-label study, adults with KRAS G12C-mutated advanced NSCLC received sotorasib 960 mg or 240 mg once daily. Primary endpoints were objective response rate (ORR) and safety. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and pharmacokinetics. The study was not powered for formal statistical hypothesis testing.

**Results:** In the 960 mg group ( $n = 104$ ), ORR was 32.7 % and DCR was 86.5 %. In the 240 mg group ( $n = 105$ ), ORR was 24.8 % and DCR was 81.9 %. Median PFS was 5.4 months (960 mg) and 5.6 months (240 mg). At a median follow-up of 17.5 months, median OS was 13.0 months (960 mg) and 11.7 months (240 mg). AUC<sub>0-24 h</sub> and C<sub>max</sub> were 1.3-fold numerically higher with the 960 mg dose. Treatment-emergent adverse events (TEAEs,  $\geq 10\%$ ) for 960 mg and 240 mg doses, respectively, were diarrhea (39.4 %; 31.7 %), nausea (23.1 %; 19.2 %), increased alanine aminotransaminase (14.4 %; 17.3 %), and increased aspartate aminotransferase (13.5 %; 13.5 %).

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**Conclusions:** Patients treated with sotorasib 960 mg once daily had numerically higher ORR and DCR, and longer DOR and OS, than patients treated with 240 mg in this descriptive analysis. TEAEs were manageable with label-directed dose modifications.

**Clinical trial registration:** NCT03600883

## 1. Introduction

Sotorasib, a first-in-class, selective, irreversible small molecule inhibitor of the KRAS G12C protein, received accelerated approval from the United States Food and Drug Administration (US FDA) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) [1]. Sotorasib 960 mg has demonstrated a consistent clinical benefit across phase 1–3 clinical studies [2–5] and in real-world settings [6,7]. In the CodeBreaK 100 phase 1/2, open-label registrational trial in previously treated KRAS G12C-mutated NSCLC, objective response rate (ORR) was 37.1 %, disease control rate (DCR) was 80.6 %, median duration of response was 11.1 months, median progression-free survival (PFS) was 6.8 months, and median overall survival (OS) was 12.5 months [3]. Long-term data from the trial showed a 2-year OS rate of 33 % [4]. In the CodeBreaK 200 global phase 3 randomized controlled trial, sotorasib 960 mg significantly improved PFS over docetaxel (hazard ratio [HR] 0.66) and demonstrated a more favorable safety profile with fewer Grade  $\geq 3$  treatment-related adverse events (TRAEs) than docetaxel in previously treated KRAS G12C-mutated NSCLC [5]. Sotorasib, compared with docetaxel, also showed a higher ORR (28.1 % vs 13.2 %), faster median time-to-response (1.4 vs 2.8 months), longer median duration of response (DOR) (8.6 vs 6.8 months), and higher DCR (82.5 % vs 60.3 %) [5], with similar OS between sotorasib and docetaxel [5].

As part of the accelerated approval, the US FDA issued a post-marketing requirement to compare the safety and efficacy of sotorasib 960 mg daily and a lower daily dose [1]. In the dose escalation study (approximately n = 6 at each dose level), non-dose proportional increases in sotorasib exposure were observed at all dose levels above 180 mg once daily [2]. Therefore, drug exposure at the 240-mg and 960-mg once daily doses were anticipated to exceed the concentration associated with 90 % inhibition, based upon the 2-hour cellular pERK phosphorylation assay [8]. As such, following discussion with the FDA, a randomized dose comparison study was conducted to compare the efficacy and safety of once daily sotorasib at a dose of 960 mg and 240 mg.

## 2. Patients and methods

### 2.1. Study design, patients, and procedures

This multicenter, randomized, open-label, phase 2 study enrolled patients with previously treated locally advanced and unresectable or metastatic KRAS G12C-mutated NSCLC. Key inclusion and exclusion criteria are shown in [Supplementary Table S1](#).

Patients were randomized 1:1 to receive sotorasib once daily at a dose of 960 mg or 240 mg ([Supplementary Fig. S1](#)). Patients were stratified by the number of prior lines of therapy (1–2 vs > 2), history of central nervous system metastasis (yes or no), race (Asian vs non-Asian), Eastern Cooperative Oncology Group (ECOG) and performance status (< 2 vs 2). Sotorasib treatment continued until disease progression (assessed by blinded independent central review [BICR]), unacceptable toxicity, patient request, consent withdrawal, loss to follow-up, or death. Patients with centrally confirmed disease progression had an option to continue sotorasib treatment if their current dose was tolerable. Treatment crossover was not permitted. Dose reductions were permitted for the 960 mg group only.

The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Institutional review boards at each

participating site and regulatory authorities of participating countries approved the protocol and amendments. All patients provided written informed consent. A data reviewing team provided independent oversight of safety and efficacy throughout the trial.

### 2.2. Study endpoints

The primary endpoints were ORR (defined as complete response or partial response assessed by BICR according to Response Evaluation Criteria in Adverse Events [RECIST] version 1.1) and safety. Secondary endpoints were DOR, DCR, time to response, PFS, OS, pharmacokinetics (determination of maximum plasma concentration [ $C_{max}$ ] and area under the curve [AUC]), and patient-reported outcomes (PROs; [[Supplementary Fig. S1](#) and [Supplementary Methods](#)]). Safety assessments included treatment-emergent adverse events (TEAEs), Grade  $\geq 3$  TEAEs, serious adverse events (SAEs), and events of interest. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

### 2.3. Statistical analysis

This study planned to enroll approximately 200 patients to provide a point estimate of ORR difference between the treatment arms with acceptable precision based on its confidence interval (CI). This study was not powered to demonstrate a statistically significant difference between the efficacy endpoints but rather inform dosing based on descriptive statistics and the totality of data across efficacy, pharmacokinetic, PROs, and safety analyses.

The primary analysis was planned approximately 6 months after the last patient enrolled. Additional analyses were allowed to update the DOR when all responders had  $\geq 6$  months follow-up since the onset of response. Efficacy was evaluated in the intent-to-treat population with all randomized patients. Safety was evaluated in all patients who received  $\geq 1$  dose of sotorasib.

All efficacy, pharmacokinetic, PRO, and safety data were summarized using descriptive statistics. ORR and DCR were summarized with the use of frequency counts and percentages, with exact 95 % CIs calculated by the Clopper-Pearson method. Difference and 90 % CI were calculated from Mantel-Haenszel method to adjust for stratification factors. Time-to-event endpoints (PFS, OS, DOR) were summarized with the use of Kaplan-Meier estimates and HRs from stratified Cox proportional hazard models. Descriptive summaries for subgroups are provided.

## 3. Results

### 3.1. Patients

Between June 2021 and March 2022, 209 patients were randomized (960 mg group: 104 patients; 240 mg group: 105 patients) ([Supplementary Fig. S2](#)). Median follow-up was approximately 17.5 months. Although crossover was not permitted, 12 patients in the 240 mg group received subsequent KRAS G12C inhibitors, including sotorasib 960 mg, after ending protocol treatment. Baseline characteristics were generally balanced between the groups ([Table 1](#)) except that the proportion of patients with a history of liver metastasis was higher in the sotorasib 240 mg dose group (18.1 %) than in the 960 mg dose group (9.6 %).

**Table 1**  
Baseline characteristics.

Characteristic	Sotorasib 960 mg N = 104	Sotorasib 240 mg N = 105
Age, mean (SD), years	64.6 (8.1)	65.1 (9.7)
Male, sex, n (%)	56 (53.8)	58 (55.2)
Race, <sup>a</sup> n (%)		
White	85 (81.7)	87 (82.9)
Asian	18 (17.3)	18 (17.1)
Other	1 (1.0)	0 (0)
Region, n (%)		
Europe	76 (73.1)	74 (70.5)
Asia	18 (17.3)	18 (17.1)
North America	7 (6.7)	8 (7.6)
Rest of the world	3 (2.9)	5 (4.8)
Smoking history, n (%)		
Never	2 (1.9)	7 (6.7)
Current	20 (19.2)	12 (11.4)
Former	82 (78.8)	86 (81.9)
ECOG PS, <sup>b</sup> n (%)		
0	37 (35.6)	37 (35.2)
1	60 (57.7)	59 (56.2)
2	7 (6.7)	9 (8.6)
Histology, n (%)		
Squamous	3 (2.9)	4 (3.8)
Non-squamous	101 (97.1)	99 (94.3)
Other	0 (0)	2 (1.9)
Disease stage at diagnosis, n (%)		
Stage I	5 (4.8)	5 (4.8)
Stage II	6 (5.8)	6 (5.7)
Stage III	20 (19.2)	23 (21.9)
Stage IV	72 (69.2)	71 (67.6)
Unknown	1 (1.0)	0 (0)
Metastatic		
Yes	103 (99.0)	102 (97.1)
No	1 (1.0)	3 (2.9)
Differentiation		
Well differentiated	4 (3.8)	5 (4.8)
Moderately differentiated	13 (12.5)	15 (14.3)
Poorly differentiated	15 (14.4)	16 (15.2)
Undifferentiated	6 (5.8)	2 (1.9)
Other	0 (0)	0 (0)
Unknown	66 (63.5)	67 (63.8)
History of brain metastasis, n (%)	27 (26.0)	24 (22.9)
History of liver metastasis, n (%)	10 (9.6)	19 (18.1)
Number of previous lines of anticancer therapy, n (%)		
0	0 (0)	1 (1.0) <sup>c</sup>
1	63 (60.6)	60 (57.1)
2	27 (26.0)	26 (24.8)
3	9 (8.7)	10 (9.5)
≥ 4	5 (4.8)	8 (7.6)
Median number of previous lines of anticancer therapy	1	1
Type of previous anticancer therapy, <sup>d</sup> n (%)		
Chemotherapy	94 (90.4)	92 (87.6)
Platinum-based chemotherapy	90 (86.5)	92 (87.6)
Immunotherapy	92 (88.5)	87 (82.9)
Checkpoint inhibitor	92 (88.5)	86 (81.9)
Anti-PD-1 or anti-PD-L1	92 (88.5)	86 (81.9)
Platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 <sup>e</sup>	79 (76.0)	73 (69.5)
Hormonal therapy	0 (0)	0 (0)
Targeted biologics	11 (10.6)	9 (8.6)
Anti-VEGF biological therapy	10 (9.6)	7 (6.7)
Targeted small molecules	7 (6.7)	2 (1.9)
Other	0 (0)	3 (2.9)
Immediate prior anticancer therapy, n (%)		
Chemotherapy	47 (45.2)	57 (54.3)
Immunotherapy	49 (47.1)	42 (40.0)
Targeted biologics	4 (3.8)	2 (1.9)
Targeted small molecules	0 (0)	1 (1.0)
Unknown	2 (1.9)	0 (0)
Other	5 (4.8)	2 (1.9)
PD-L1 protein expression, <sup>f</sup> n (%)		
< 1 %	20 (19.2)	24 (22.9)

**Table 1 (continued)**

Characteristic	Sotorasib 960 mg N = 104	Sotorasib 240 mg N = 105
≥ 1 % to < 50 %	23 (22.1)	25 (23.8)
≥ 50 %	22 (21.2)	20 (19.0)
Unknown	39 (37.5)	36 (34.3)

N = number of patients randomized. n = number of patients with observed data. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed death 1; PD-L1, programmed death ligand 1; SD, standard deviation; VEGF, vascular endothelial growth factor.

<sup>a</sup> No American Indian or Alaska Native, Black or African American, or Native Hawaiian or Other Pacific Islander patients were enrolled in the study.

<sup>b</sup> Baseline ECOG is measured at cycle 1 day 1 pre-dose. Patient may have satisfied the ECOG PS enrollment eligibility during screening period, but subsequently had baseline ECOG PS = 2 prior to first dose. ECOG PS 0 = fully active, able to carry on all pre-disease performance without restriction; ECOG PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work); ECOG PS 2 = ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50 % of waking hours; ECOG PS 3 = capable of only limited selfcare, confined to bed or chair more than 50 % of waking hours; ECOG PS 4 = completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; ECOG PS 5 = dead.

<sup>c</sup> Patient received carboplatin-pemetrexed-pembrolizumab in the locally advanced setting that progressed 1 month after completing course of treatment prior to enrolling in the study with metastatic disease. Investigator did not consider this a line of therapy.

<sup>d</sup> Each patient may have had multiple prior therapies. Types of prior anti-cancer therapies were adjudicated and include therapies given in any treatment setting.

<sup>e</sup> Platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 could be in combination or across different lines.

<sup>f</sup> Local data.

### 3.2. Efficacy

Confirmed ORR (95 % CI) was 32.7 % (23.8, 42.6) with sotorasib 960 mg and 24.8 % (16.9, 34.1) with sotorasib 240 mg, resulting in a treatment difference (90 % CI) of 6.9 % (-3.4, 17.1) after adjusting for stratification factors (Table 2, Figure 1). In a prespecified subgroup analysis (Supplementary Fig. S3), ORR generally favored the 960 mg dose across patient subgroups, including those with poor prognostic factors, such as those with *KEAP1/TP53* co-mutations, and a larger tumor lesion size at baseline. The median DOR was numerically longer for the 960 mg versus 240 mg dose group (13.8 [95 % CI: 5.6, not estimable (NE)] months vs 12.5 [7.0, NE] months; Figure 1). As the estimated median DOR was not yet mature at the time of data cutoff, additional longer follow-up showed a median DOR (95 % CI) of 16.4 (5.6, 20.7) months with the 960 mg dose and 12.5 (7.0, 19.4) months with the 240 mg dose.

Tumor shrinkage was observed in 83 patients (79.8 %) with sotorasib 960 mg and 79 patients (75.2 %) with 240 mg (Figure 1). PFS was similar with both doses, with a median PFS (95 % CI) of 5.4 (4.2, 6.9) months with sotorasib 960 mg and 5.6 (4.1, 8.3) months with 240 mg (stratified HR [95 % CI] 0.95 [0.67, 1.35]; Figure 2A). Median OS (95 % CI) was 13.0 (10.7, 18.8) months with sotorasib 960 mg and 11.7 (9.5, 15.4) months with 240 mg (stratified HR [95 % CI] of 0.75 [0.53, 1.07]); Figure 2B). In a prespecified subgroup analysis, OS generally favored the 960 mg dose across multiple subgroups including those with poor prognostic factors, including patients with a history of liver metastasis (HR [95 % CI]: 0.58 [0.23, 1.46]), co-mutations in *STK11* (HR [95 % CI]: 0.41 [0.23, 0.74]) and *TP53* (HR [95 % CI]: 0.72 [0.45, 1.15]), and a larger tumor lesion size at baseline (HR [95 % CI]: 0.70 [0.43, 1.13]) (Supplementary Fig. S3). No differences in ORR or OS were observed between the 960 mg and 240 mg groups in patients with a history of brain metastases.

**Table 2**

Efficacy by BICR in patients treated with sotorasib 960 mg and 240 mg.

Outcome	Sotorasib 960 mg N = 104	Sotorasib 240 mg N = 105	Treatment Difference	
	Difference of Proportions <sup>g</sup> (90 % CI), Stratified	Difference of Proportions <sup>g</sup> (90 % CI), Unstratified		
Confirmed ORR, n (%) [95 % CI] <sup>h</sup>	34 (32.7) [23.8, 42.6]	26 (24.8) [16.9, 34.1]	6.9 (-3.4, 17.1)	7.9 (-2.3, 18.2)
Best overall response, n (%)				
Complete response	2 (1.9)	3 (2.9)		
Partial response	32 (30.8)	23 (21.9)		
Stable disease	56 (53.8)	60 (57.1)		
Non-complete response/non-disease progression	1 (1.0)	0 (0)		
Disease progression	9 (8.7)	10 (9.5)		
Not evaluable	1 (1.0)	0 (0)		
Not assessed <sup>i</sup>	3 (2.9)	9 (8.6)		
Disease control rate, n (%) [95 % CI] <sup>b</sup>	90 (86.5) [78.5, 92.4]	86 (81.9) [73.2, 88.7]	4.9 (-3.7, 13.5)	4.6 (-3.6, 12.9)
Median time to response, <sup>j</sup> months (min, max)	1.4 (1.2, 11.1)	1.4 (1.2, 8.3)		

Data cutoff date: June 23, 2023. The data cutoff date for the primary analysis was September 9, 2022 (approximately 6 months after the last patient enrolled). This article reports safety results from the data cutoff date of January 18, 2023. At the time of the safety data cutoff, OS was not mature with > 50 % of patients censored. Thus, efficacy results presented in this article were updated with data from the data cutoff date of June 23, 2023.

N = number of patients in the analysis set; n = number of patients with observed data.

Months are derived as days x (12/365.25).

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; NE, not estimable; ; ORR, objective response rate; OS, overall survival.

<sup>g</sup> The difference in proportions and two-sided 90 % CI were assessed using stratified method of Mantel-Haenszel estimate and unstratified analysis using normal approximation. Randomization stratification factors were number of prior lines of therapy in advanced disease (1–2 vs > 2), history of CNS involvement (yes vs no), race (Asian vs non-Asian), and ECOG (< 2 vs 2).

<sup>h</sup> Exact 95 % CI was calculated using the Clopper-Pearson method.

<sup>i</sup> Patients did not provide a post-baseline scan due to deaths, consent withdrawal, or adverse event.

<sup>j</sup> Time to response was calculated among confirmed responders (34 in the 960 mg group and 26 in the 240 mg group).

### 3.3. Pharmacokinetics

The pharmacokinetic profiles are shown in [Figure 3](#). Higher sotorasib exposure was observed with the 960 mg dose, with mean AUC<sub>0–24 h</sub> and C<sub>max</sub> on day 8 that were 1.3-fold numerically higher for 960 mg than for 240 mg.

### 3.4. PROs

PROs were generally similar between the sotorasib 960 mg and the 240 mg groups with overlapping CIs ([Supplementary Fig. S4](#)).

### 3.5. Safety

#### 3.5.1. TEAEs

TEAEs were similar overall, (960 mg: 97.1 %; 240 mg: 92.3 %; [Table 3](#), [Figure 4A](#)), with a higher rate of Grade ≥ 3 AEs in the 960 mg group [[Table 3](#)]). TEAEs led to dose interruptions in 45.2 % (960 mg) and 39.4 % (240 mg) of patients, and 17.3 % of patients in the 960 mg group had TEAEs that led to dose reductions ([Figure 4A](#)). TEAEs led to sotorasib discontinuation in 16.3 % of patients in the 960 mg group and 12.5 % of patients in the 240 mg group ([Figure 4A](#)), with pneumonitis leading to sotorasib discontinuation in 2.9 % of patients in the 960 mg group and 0 % patients in the 240 mg group ([Table 3](#)).

The most common AEs in patients treated with 960 mg and 240 mg sotorasib included diarrhea (39.4 %; 31.7 %), nausea (23.1 %; 19.2 %), decreased appetite (17.3 %; 10.6 %), fatigue (15.4 %; 12.5 %), vomiting (15.4 %; 9.6 %), alanine aminotransferase (ALT) increased (14.4 %; 17.3 %), and aspartate aminotransferase (AST) increased (13.5 %; 13.5 %), ([Table 3](#), [Figure 4B](#)). Median time-to-onset of gastrointestinal AEs occurred within the first two cycles (33 days for the 960 mg group; 35 days for the 240 mg group). Most diarrhea AEs were Grade 1 or 2 (960 mg: 75.6 %; 240 mg: 84.8 %). Patients in the 960 mg group had a median duration (range) of diarrhea of 24 (1 to 111) days and 29 (1 to 184) days for those in the 240 mg group. Grade 1 or 2 diarrhea events

were managed with dose interruptions, with or without dose reductions for the sotorasib 960 mg dose, along with antidiarrheal medication ([Figure 4C](#)). Dose interruptions due to diarrhea occurred in 56.1 % of patients treated with sotorasib 960 mg who reported diarrhea, for a median duration (range) of dose interruption of 9.5 (1 to 33) days; and 42.2 % of patients treated with 240 mg for a median duration of 10 (1 to 42) days. Dose reductions due to diarrhea occurred in 7.7 % of patients with sotorasib 960 mg. ([Figure 4C](#)). In this study, 25.0 % of patients in the 960 mg dose group and 20.2 % in the 240 mg dose group received antidiarrheal medication ([Figure 4C](#)).

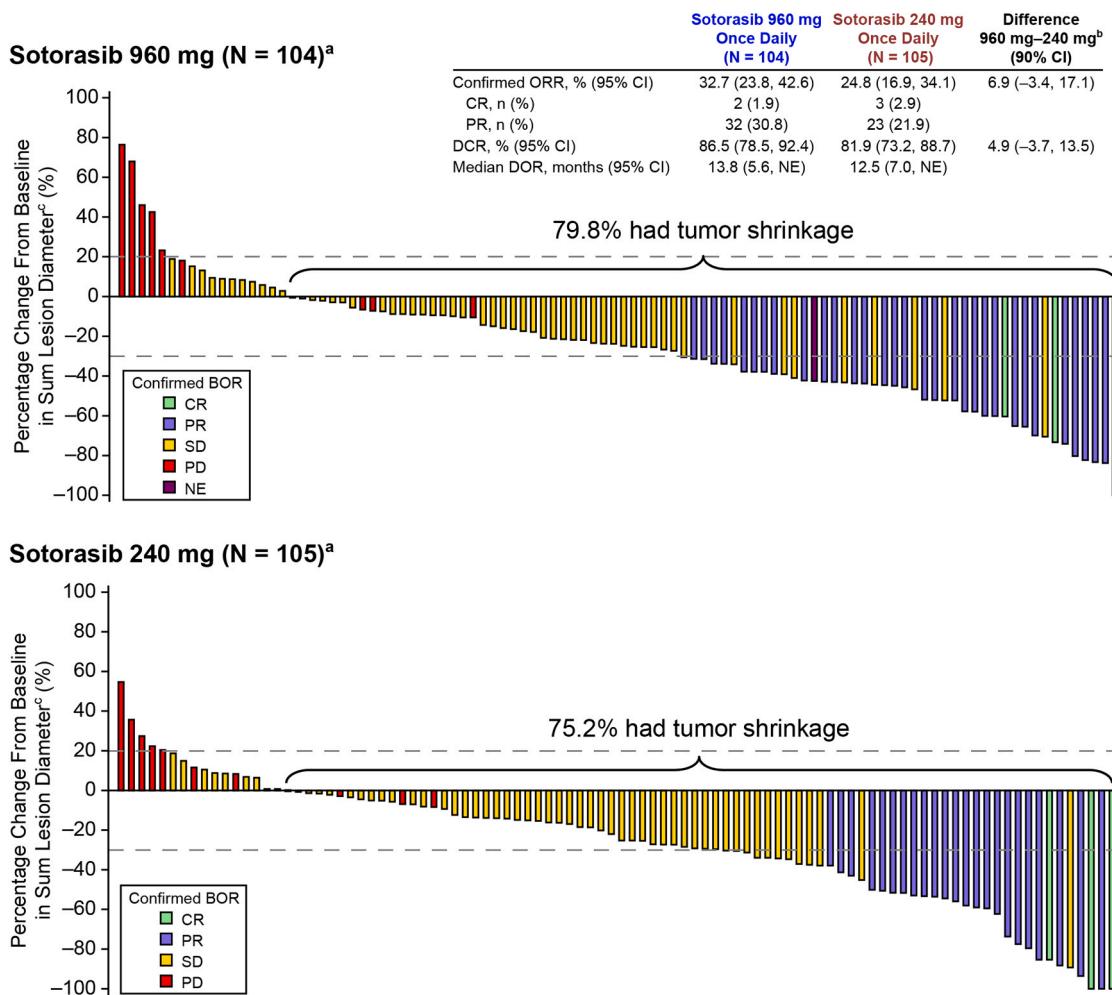
Elevated liver enzymes occurred at comparable rates overall (ALT, 960 mg: 14.4 %; 240 mg: 17.3 %; AST, 960 mg: 13.5 %; 240 mg: 13.5 %; [Table 3](#), [Figure 4D](#)). Grade ≥ 3 increase in ALT was 8.7 % with the 960 mg dose and 6.7 % with the 240 mg dose; Grade ≥ 3 increase in AST was 5.8 % with the 960 mg dose and 2.9 % with the 240 mg dose. Increased ALT or AST levels were managed by either dose interruptions for the sotorasib 240 mg dose or by dose interruptions followed by dose reductions for the sotorasib 960 mg dose. Discontinuations due to increased ALT or AST were low and comparable between doses ([Figure 4D](#)) and were managed with corticosteroids.

### 3.6. Sotorasib dose modifications and tumor response

Dose modifications for the 34 responders in the sotorasib 960 mg dose and 26 responders in the sotorasib 240 mg dose are presented in [Figure 5](#). Sotorasib dose interruptions or dose reductions (960 mg group only) did not appear to impact response durability.

## 4. Discussion

The 960 mg and 240 mg doses of sotorasib once daily showed efficacy in patients with KRAS G12C-mutated NSCLC. Yet, patients treated with the 960 mg dose had numerically higher ORR and DCR, and longer DOR and OS compared with those treated with the 240 mg dose. OS generally favored the 960 mg dose across multiple subgroups.



**Fig. 1.** Tumor response by BICR for sotorasib 960 mg and 240 mg.

Data cutoff date: June 23, 2023. The data cutoff date for the primary analysis was September 9, 2022 (approximately 6 months after the last patient enrolled). This article reports safety results from the data cutoff date of January 18, 2023. At the time of the safety data cutoff, OS was not mature with > 50 % of patients censored. Thus, efficacy results presented in this article were updated with data from the data cutoff date of June 23, 2023. Percentage change from baseline in sum of tumor diameters (of any magnitude) only considered tumor assessments prior to and included the first assessment where timepoint response was disease progression, and prior to start of next anticancer therapy.

N = number of patients randomized.

<sup>a</sup>Four patients in 960 mg group and nine patients in 240 mg group without post-baseline measurements were not included.

<sup>b</sup>Difference from the Mantel-Haenszel method accounting for stratification factors.

<sup>c</sup>Sum lesion diameter is the sum of the longest diameters of the target lesion.

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response, DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

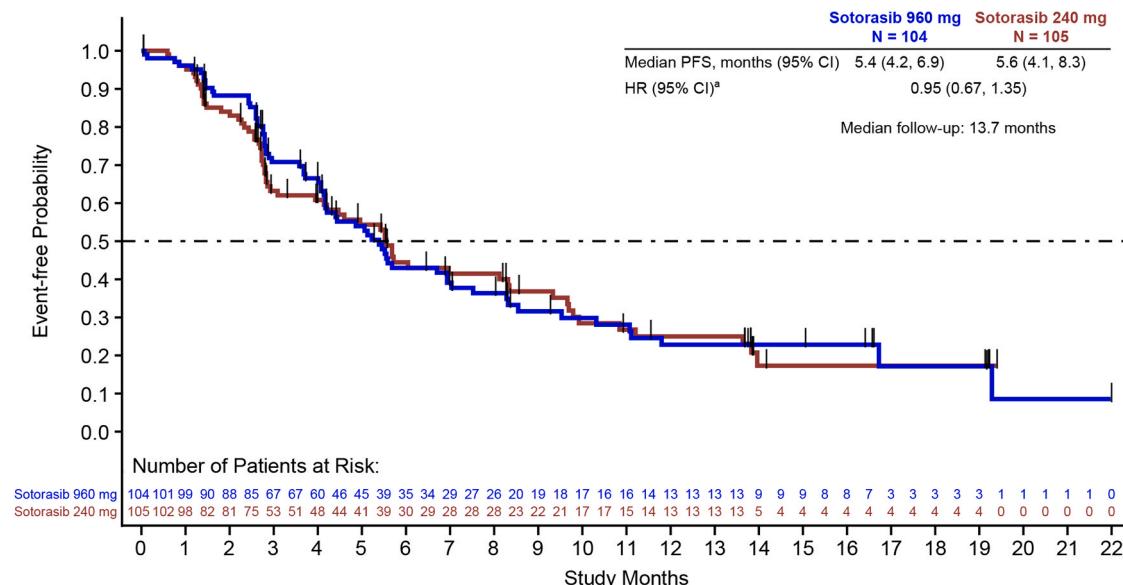
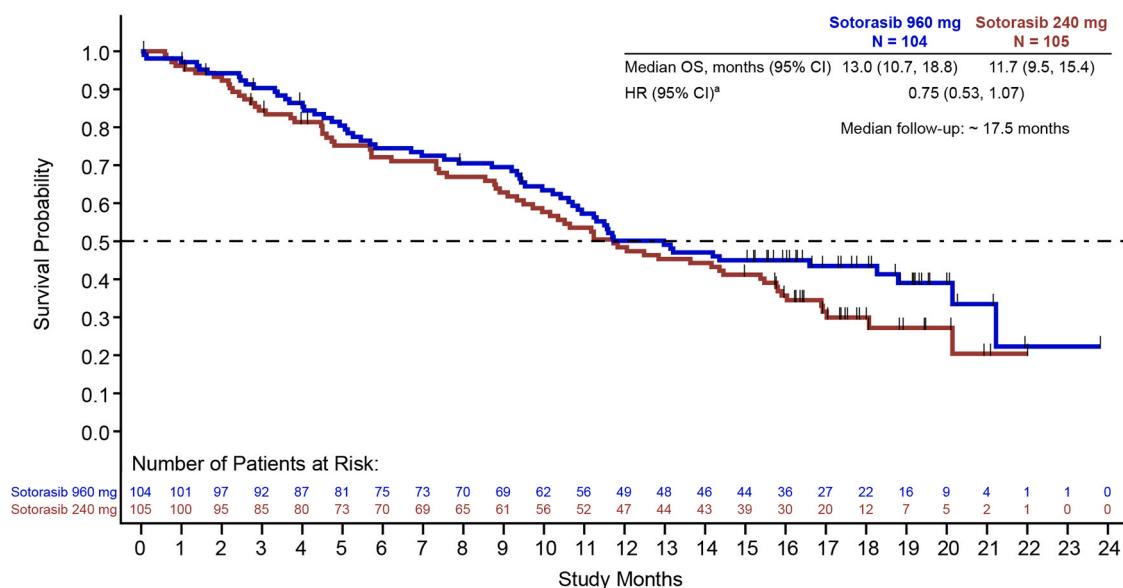
Interpretation of the efficacy data from the subgroup analyses is limited due to small patient numbers. While this study was not powered to formally test 960 mg vs 240 mg, it was sufficiently sized to understand the general shape of the dose relationship.

This dose comparison study had been designed on the assumption that drug exposure at the sotorasib 240 mg once daily dose was similar to that at the sotorasib 960 mg once daily dose. However, pharmacokinetic analysis demonstrated that sotorasib plasma exposure was numerically higher with sotorasib 960 mg than with sotorasib 240 mg.

The overall safety profile was similar between groups. Sotorasib 960 mg was associated with a higher rate of diarrhea (39.4 %) compared with sotorasib 240 mg (31.7 %); however, these AEs were mostly low grade and managed with dose modifications and/or antidiarrheal medication. The rates of increases in ALT and AST were comparable across doses. In addition, the overall safety profile of sotorasib 960 mg was consistent with safety reported for previously published data for sotorasib phase 1–3 studies [2–5]. Across the CodeBreaK trial program,

sotorasib 960 mg dose had consistently numerically higher rates of efficacy compared to the 240 mg dose [2–5]. Notably, CodeBreaK 300 tested both doses of sotorasib (960 mg or 240 mg) plus panitumumab to the standard of care in KRAS G12C metastatic colorectal cancer, where sotorasib 960 mg appeared to have a more robust benefit than sotorasib 240 mg vs standard of care [9].

According to Project Optimus, an FDA initiative that encourages early evaluation of potential doses in clinical development, dose comparison studies do not need to be powered for rigorous statistical comparisons, rather they need be sufficiently sized to understand the general shape of the dose relationship [10–12]. This study was not powered for formal statistical hypothesis testing due to practical limitations that would require enrollment of over 600 patients. Additionally, this trial was not designed to demonstrate non-inferiority. However, the efficacy of sotorasib 960 mg once daily in pretreated KRAS G12C advanced NSCLC was similar to the efficacy results from previously published sotorasib phase 1–3 studies [2–5].

**A. PFS by BICR****B. OS**

**Fig. 2.** A) PFS by BICR and B) OS in patients treated with sotorasib 960 mg and sotorasib 240 mg Data cutoff date: June 23, 2023. The data cutoff date for the primary analysis was September 9, 2022 (approximately 6 months after the last patient enrolled). This article reports safety results from the data cutoff date of January 18, 2023. At the time of the safety data cutoff, OS was not mature with > 50 % of patients censored. Thus, efficacy results presented in this article were updated with data from the data cutoff date of June 23, 2023. The sample size was not powered for formal statistical testing; dosing was assessed by totality of data. N = number of patients in the analysis set. <sup>a</sup>Stratified HR. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

## 5. Conclusions

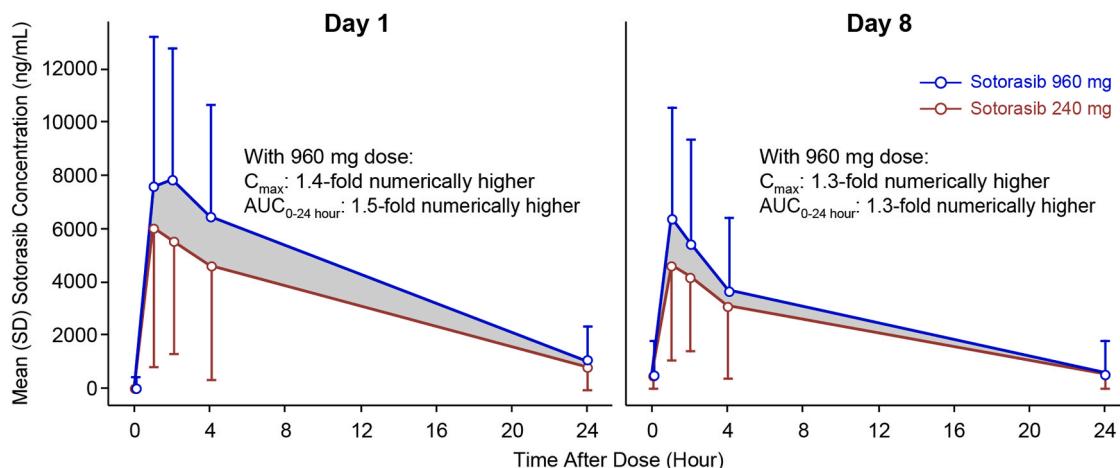
Patients treated with sotorasib 960 mg once daily had numerically higher ORR and DCR, and longer DOR and OS, compared with patients treated with sotorasib 240 mg once daily. While some AEs were numerically higher with the 960 mg dose, AEs were manageable with label-directed dose modifications. Based on results from this study and the comprehensive CodeBreaK development program, the FDA considered the post-marketing requirement fulfilled, and sotorasib 960 mg daily remains the approved dose for KRAS G12C-mutated advanced NSCLC.

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This study was supported by Amgen Inc. Amgen was involved in the design and conduct of the study, the analysis and interpretation of the data, and the decision to submit this manuscript. Amgen managed patient data collected at the study sites and provided medical writing support.

## Funding

This study was supported by Amgen Inc.



**Fig. 3.** Mean plasma concentration-time profiles for sotorasib administered at a dose of 960 mg or 240 mg once daily.

Data cutoff date: September 9, 2022. Data from 208 patients were included in the analysis. For clarity, only the top error bars are shown for sotorasib 960 mg and only the lower error bars are shown for sotorasib 240 mg.

AUC<sub>0-24 h</sub>, area under the curve from 0 to 24 h;  $C_{\max}$ , maximum plasma concentration; SD, standard deviation.

#### CRediT authorship contribution statement

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#### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **M. J. Hochmair:** Financial Interests, Personal, Other, Consulting or Advisory role: Takeda, Roche, Lilly, AstraZeneca/Daiichi Sankyo; Financial Interests, Personal, Speaker’s Bureau: Lilly, MSD Oncology, Novartis, Roche, Amgen. **K. Vermaelen:** Financial Interests, Personal, Research Grant: Bristol Myers Squibb (BMS); Financial Interests, Personal, Other, Honoraria: BMS; Financial Interests, Personal, Other, Support for Attending Meetings: AstraZeneca, BMS, Merck; Financial Interests, Personal, Other, Patents Planned/Issued/Pending: Ghent University; Financial Interests, Personal, Other, Data Safety Monitoring

Board or Advisory Board: Amgen, AstraZeneca, BMS, Merck. **G. Mountzios:** Financial Interests, Personal, Other, Honoraria: Amgen, AstraZeneca, BMS GmbH & Co. KG, Boehringer Ingelheim, MSD, Novartis, Roche, Takeda; Financial Interests, Personal, Other, Consulting or Advisory Board: Amgen, AstraZeneca/Greece, BMS GmbH & Co. KG, MSD, Novartis, Roche, Takeda; Financial Interests, Personal, Speaker’s Bureau: AstraZeneca, MSD; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: AstraZeneca, BMS GmbH & Co. KG, Ipsen, MSD, Novartis, Roche. **E. Carcereny:** No conflicts to disclose. **C. Dooms:** No conflicts to disclose. **S.-H. Lee:** Financial Interests, Personal, Other, Honoraria: Amgen, AstraZeneca/MedImmune, Lilly, Merck, Roche; Financial Interests, Personal, Other, Consulting or Advisory Role: AstraZeneca, BMS/Ono, IMBdx, Janssen, Lilly, Merck, Pfizer, Roche, Takeda; Financial Interests, Personal, Research Grant: AstraZeneca, Lunit, Merck; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Novartis. **E. Morocz:** No conflicts to disclose. **T. Kato:** Financial Interests, Personal, Advisory Board, Speaker, Consultancy: AstraZeneca, Eli Lilly, Merck Biopharma, MSD; Financial Interests, Personal, Advisory Board, Speaker: Pfizer, Amgen, Janssen; Financial Interests, Personal, Other, Consultancy: Daiichi Sankyo, Takeda, Taiho; Financial Interests, Personal, Other, Consultancy, Speaker: Chugai; Financial Interests, Personal, Invited Speaker: Ono, Novartis, BMS, Boehringer Ingelheim; Financial Interests, Personal, Advisory Board: BeiGene, GSK; Financial Interests, Personal, Advisory Board, Steering Committee: Roche; Financial Interests, Personal, Full or Part-Time Employment, Family Member: Eli Lilly; Financial Interests, Institutional, Invited Speaker: Chugai, MSD, Pfizer, Eli Lilly, AbbVie, Regeneron, Novartis, Amgen, Merck Biopharma, Haihe Biopharma, Blueprint Medicines, Turning Point, BeiGene, Gilead, GSK, Janssen, Bayer, Takeda, Daiichi Sankyo; Financial Interests, Institutional, Invited Speaker, Local PI: AstraZeneca. **T.-E. Ciuleanu:** Financial Interests, Personal, Other, Consulting or Advisory Role: Astellas Pharma, Janssen, BMS, Merck Serono, Amgen, Roche, Pfizer, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck Sharp & Dohme (MSD), Sanofi, Novartis, Servier, A&D Pharma; Financial Interests, Personal, Other, Travel Support: Pfizer, Sanofi, Boehringer Ingelheim, Merck, Servier, Ipsen, Amgen, A&D Pharma, AstraZeneca, Genentech, BMS, MSD Oncology, Eli Lilly, Janssen, Novartis, Astellas Pharma. **G. K. Dy:** Financial Interests, Personal, Other, Consulting or Advisory Role: AstraZeneca, Mirati Therapeutics, Lilly, Amgen, Regeneron, Eli Lilly; Financial Interests, Institutional, Research Grant: Amgen, AstraZeneca, Mirati Therapeutics, Lilly, Sanofi, BioAtla, Regeneron, Iovance Biotherapeutics, Revolution Medicines. **B. Parente:** No conflicts to disclose.

**Table 3**

TEAEs in patients treated with sotorasib 960 mg and 240 mg.

Events	Sotorasib 960 mg N = 104 (%)	Sotorasib 240 mg N = 104 (%)
All TEAEs	101 (97.1)	96 (92.3)
Grade ≥ 3	64 (61.5)	51 (49.0)
Grade ≥ 4	16 (15.4)	6 (5.8)
Serious TEAEs	38 (36.5)	34 (32.7)
Leading to sotorasib dose reduction/ interruption	49 (47.1)	41 (39.4)
Leading to sotorasib discontinuation	17 (16.3)	13 (12.5)
Leading to discontinuation in ≥ 2 patients in any treatment group		
Drug-induced liver injury	2 (1.9)	2 (1.9)
ALT increased	1 (1.0)	2 (1.9)
Hepatotoxicity	1 (1.0)	2 (1.9)
Pneumonitis	3 (2.9)	0 (0)
AST increased	2 (1.9)	0 (0)
ALP increased	0 (0)	2 (1.9)
GGT increased	0 (0)	2 (1.9)
Hepatitis	0 (0)	2 (1.9)
Death <sup>k</sup>	6 (5.8)	4 (3.8)
Most common TEAEs (occurring in ≥ 10 % of patients in either group)		
Diarrhea	41 (39.4)	33 (31.7)
Nausea	24 (23.1)	20 (19.2)
Decreased appetite	18 (17.3)	11 (10.6)
Fatigue	16 (15.4)	13 (12.5)
Vomiting	16 (15.4)	10 (9.6)
ALT increased	15 (14.4)	18 (17.3)
Back pain	14 (13.5)	7 (6.7)
AST increased	14 (13.5)	14 (13.5)
Arthralgia	14 (13.5)	15 (14.4)
Anemia	14 (13.5)	13 (12.5)
Dyspnea	11 (10.6)	14 (13.5)
Cough	11 (10.6)	13 (12.5)
ALP increased	10 (9.6)	11 (10.6)
TEAEs of interest		
Hepatotoxicity <sup>j</sup>	37 (35.6)	29 (27.9)
Leading to sotorasib dose reduction/ interruption	18 (17.3)	14 (13.5)
Leading to sotorasib discontinuation	6 (5.8)	11 (10.6)
Serious	6 (5.8)	6 (5.8)
Grade 3	16 (15.4)	15 (14.4)
In ≥ 2 patients		
ALT increased	8 (7.7)	7 (6.7)
AST increased	5 (4.8)	3 (2.9)
GGT increased	3 (2.9)	2 (1.9)
Hepatotoxicity	2 (1.9)	2 (1.9)
ALP increased	2 (1.9)	2 (1.9)
Drug-induced liver injury	2 (1.9)	1 (1.0)
Grade 4	6 (5.8)	1 (1.0)
ALT increased	1 (1.0) <sup>m</sup>	0 (0)
AST increased	1 (1.0) <sup>m</sup>	0 (0)
GGT increased	1 (1.0)	0 (0)
Hepatitis	1 (1.0)	0 (0)
Hepatotoxicity	1 (1.0)	0 (0)
Hepatic failure	1 (1.0)	0 (0)
Hypertransaminasemia	1 (1.0)	0 (0)
Drug-induced liver injury	0 (0)	1 (1.0)
Fatal	0 (0)	0 (0)
Renal toxicity <sup>n</sup>	19 (18.3)	10 (9.6)
Leading to sotorasib dose reduction/ interruption	3 (2.9)	0 (0)
Leading to sotorasib discontinuation	0 (0)	0 (0)
Serious	2 (1.9)	0 (0)
Grade 3	3 (2.9)	1 (1.0)
Hyponatremia	1 (1.0)	0 (0)
Creatinine increased	1 (1.0)	0 (0)
Hyperkalemia	0 (0)	1 (1.0)
Hypoalbuminemia	1 (1.0)	0 (0)
Normocytic anemia	1 (1.0)	0 (0)
Grade 4	1 (1.0)	0 (0)
Hyponatremia	1 (1.0)	0 (0)
Fatal	0 (0)	0 (0)
Pneumonitis <sup>o</sup>	4 (3.8)	1 (1.0)

**Table 3 (continued)**

Events	Sotorasib 960 mg N = 104 (%)	Sotorasib 240 mg N = 104 (%)
Leading to sotorasib dose reduction/ interruption	1 (1.0)	0 (0)
Leading to sotorasib discontinuation	4 (3.8)	0 (0)
Serious	2 (1.9)	0 (0)
Grade 3	1 (1.0)	0 (0)
Interstitial lung disease	1 (1.0)	0 (0)
Grade 4	0 (0)	0 (0)
Fatal	0 (0)	0 (0)

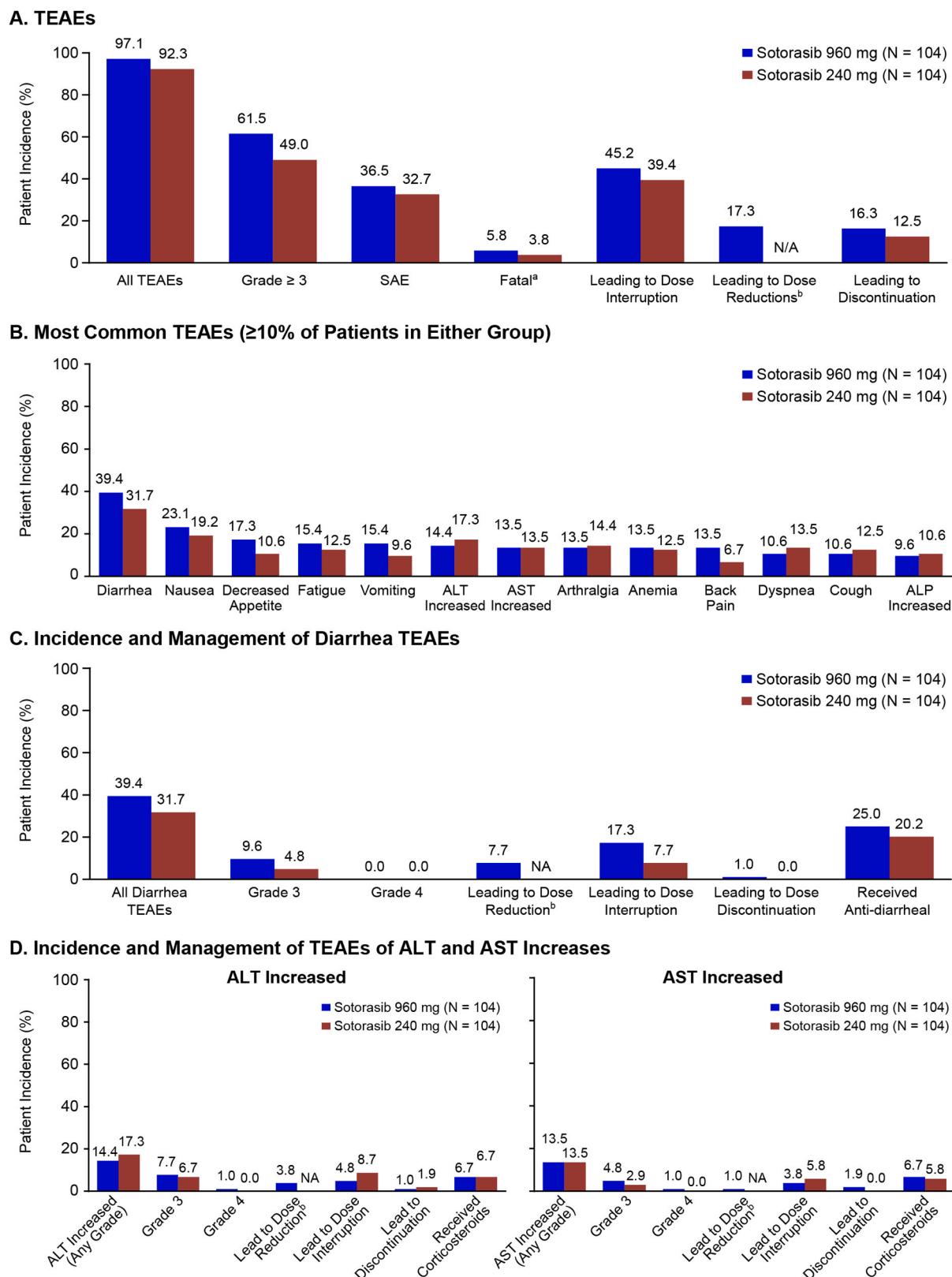
Data cutoff date: January 18, 2023.

N = number of patients in the analysis set. n = number of patients with observed data. Coded using MedDRA version 25.1. Graded using CTCAE version 5.0 criteria.

ALP, alkaline phosphatase; ALT, alanine aminotransaminase; AST, Aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; SMQ, Standardized MedDRA Queries; TEAE, treatment-emergent adverse event.

<sup>k</sup> Grade 5 fatal adverse events may have started prior to data cutoff and resulted in death after the cutoff. These events are summarized with grade 5 but deaths after data cutoff are not included in analysis.<sup>l</sup> Hepatotoxicity search strategy: Hepatic Disorders SMQ (Broad).<sup>m</sup> ALT increased and AST increased occurred in the same patient.<sup>n</sup> Renal Toxicity search strategy: Acute Renal Failure SMQ (Broad) or Chronic Kidney Disease SMQ (Broad).<sup>o</sup> Pneumonitis search strategy: Interstitial Lung Disease SMQ (Broad).

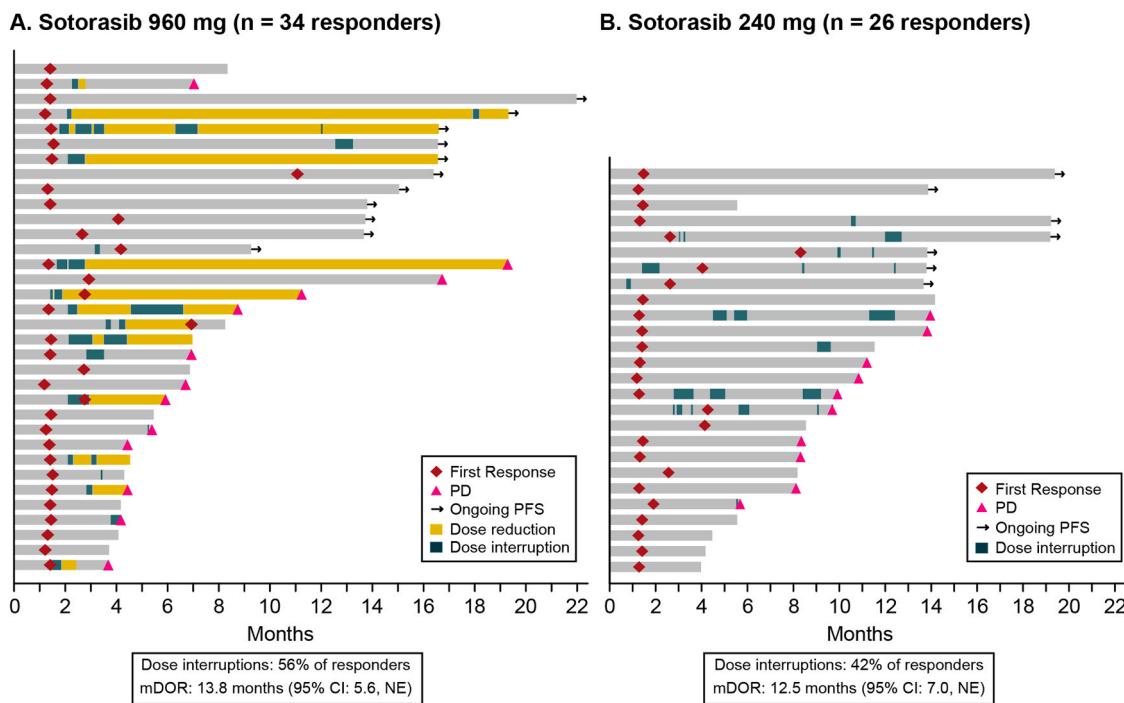
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**Fig. 4.** Safety profiles of sotorasib 960 mg and sotorasib 240 mg.

Data cutoff date: January 18, 2023.

N = number of patients in the analysis set.

<sup>a</sup>Fatal TEAEs were cardiac arrest (n = 1), cardiac tamponade (n = 1), unattributed death (n = 1), assisted suicide (n = 1), hemorrhagic stroke (n = 1), and vascular rupture (n = 1) in the 960 mg group and pneumonia (n = 2), COVID-19 (n = 1), and ovarian cancer (n = 1) in the 240 mg group.<sup>b</sup>Dose reductions were only allowed in the 960 mg group. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; N/A, not applicable; SAE, serious adverse event; TEAE, treatment-emergent adverse event.



**Fig. 5.** Dose modifications among responders who received sotorasib 960 mg and 240 mg.

Data cutoff date: June 23, 2023. The data cutoff date for the primary analysis was September 9, 2022 (approximately 6 months after the last patient enrolled). This article reports safety results from the data cutoff date of January 18, 2023. At the time of the safety data cutoff, OS was not mature with > 50 % of patients censored. Thus, efficacy results presented in this article were updated with data from the data cutoff date of June 23, 2023.

Median follow-up for DOR sotorasib 960 mg: 11.0 months (95 % CI: 5.4, 15.1); sotorasib 240 mg: 12.7 months (95 % CI: 5.7, 16.6).

Note that dose reductions were not permitted in the 240 mg group.

CI, confidence interval; DOR, duration of response; mDOR, median duration of response; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

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#### Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/>.

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#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2024.114204](https://doi.org/10.1016/j.ejca.2024.114204).

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