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Original Article

Pooled safety analysis and management of sotorasib-related adverse events in *KRAS* G12C-mutated advanced non-small cell lung cancer

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Abstract

Introduction: We describe the safety of sotorasib monotherapy in patients with *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC) and discuss practical recommendations for managing key risks.

Methods: Incidence rates of treatment-related adverse events (TRAEs) were pooled from 4 clinical trials: CodeBreaK 100 (NCT03600883), CodeBreaK 101 (NCT04185883), CodeBreaK 105 (NCT04380753), and CodeBreaK 200 (NCT04303780) and graded according to CTCAE v5.0. Adverse events were deemed sotorasib-related per investigator causality assessment.

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Results: In the pooled population (n = 549), TRAEs were reported in 388 (70.7%) patients (grade 1: 124 [22.6%]; grade 2: 117 [21.3%]; grade ≥ 3: 147 [26.8%]). Gastrointestinal and hepatic TRAEs, including diarrhea (171 [31.1%]), nausea (80 [14.6%]), elevated alanine aminotransferase (ALT; 68 [12.4%]), and elevated aspartate aminotransferase (AST; 67 [12.2%]) were the most common (≥10%). Dose interruption and dose reduction of sotorasib resulted in the resolution of >90% of diarrhea events; median time to resolution were 18.0 days and 22.0 days, respectively. Similar trends were observed for elevated ALT and AST events. Patients who stopped immunotherapy <3 months before initiating sotorasib had a higher incidence of treatment-related hepatotoxicity (80/240 [33.3%]) than those who stopped immunotherapy ≥3 months before initiating sotorasib (26/188 [13.8%]). Treatment-related pneumonitis/interstitial lung disease (ILD) and corrected QT (QTc) prolongation were observed in 9 (1.6%) and 4 (0.7%) patients, respectively. Two (0.4%) patients died with TRAEs, 1 with ILD whose ultimate cause of death was disease progression, and the other with an unknown cause.

Conclusions: Sotorasib has a well-characterized safety profile in patients with *KRAS* G12C-mutated advanced NSCLC, and key risks are manageable with dose modification.

Key words: *KRAS* G12C; management; non-small cell lung cancer; pooled analysis; safety; sotorasib; treatment-related adverse events.

Implications for practice

Sotorasib is a first-in-class, selective KRAS^{G12C} inhibitor taken once daily for pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer. Results from this study, which pooled analysis of treatment-related adverse events (TRAEs) across 4 CodeBreaK clinical trials, demonstrated that sotorasib 960 mg once daily has a consistent and manageable safety profile with low rates of treatment discontinuation. The most common TRAEs were gastrointestinal- and hepatic-related, primarily low-grade, and managed by dose interruption and/or dose reduction with or without antidiarrheal medications or corticosteroids.

Introduction

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is one of the most frequently mutated genes in human cancer. *KRAS* G12C is the most common *KRAS* mutation in non-small cell lung cancer (NSCLC), occurring in 13% of patients.[1,2] Until the availability of KRAS^{G12C} inhibitors, limited second-line treatment options were available for *KRAS* G12C-mutated advanced NSCLC, including docetaxel, a chemotherapeutic agent.[3,4] Although docetaxel has been a standard of care treatment in this patient population, it is associated with toxicities, including neutropenia, anemia, alopecia, peripheral edema, hypersensitivity reactions, asthenia, nail dystrophy, fatigue, nausea, and vomiting.[5,6]

Sotorasib is a first-in-class small molecule that selectively and irreversibly inhibits the KRAS^{G12C} protein and has a pharmacokinetic profile that allows for once daily (QD) dosing.[7] Sotorasib 960 mg QD received accelerated approval from the United States Food Drug and Administration (FDA) in May 2021, offering a targeted treatment alternative for molecularly unique patients with advanced NSCLC harboring a *KRAS* G12C mutation and treated with at least one prior systemic therapy.[8] In addition, sotorasib has been approved in other regions, including the European Union and Japan.[9,10] Accelerated approval was based on the findings of the phase II CodeBreaK 100 study (n = 126; NCT03600883).[11] In response to an FDA post-marketing requirement to evaluate sotorasib at the conditionally approved dose versus a lower dose, it was demonstrated that 960 mg QD provided a more favorable benefit-risk profile compared with 240 mg QD and confirmed an FDA recommended dose of 960 mg QD.[12] Alongside sotorasib, the only other KRAS^{G12C} inhibitor available under accelerated approval by the FDA is adagrasib, which is based on the outcomes of the phase 1/2 KRYSTAL-1 study in 116 patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who had received at least one previous systemic therapy.[13]

The CodeBreaK 200 phase 3, randomized, multicenter trial was the first-ever global study to compare the efficacy and safety of a KRAS^{G12C} inhibitor to standard of care docetaxel. The trial did not meet the requirement to convert sotorasib from conditional to full approval in the US. However, sotorasib (n = 171) demonstrated a significantly superior improvement in progression-free survival vs docetaxel (n = 174) and had a more favorable safety profile with fewer treatment-related adverse events (TRAEs). The most common sotorasib-related adverse events (AEs; ≥ 10%) of any grade reported in the CodeBreaK 200 study were diarrhea (34%), nausea (14%), decreased appetite (11%), elevated alanine aminotransferase (ALT; 10%), and elevated aspartate aminotransferase (AST; 10%) levels.[14] In this pooled safety analysis of 549 patients treated with sotorasib across the NSCLC clinical development program from August 27, 2018 to September 9, 2022, we provide the largest safety evaluation for any KRAS^{G12C} inhibitor and further characterize AEs of interest that were observed across the clinical trials, and provide practical recommendations based on real-world experience to manage sotorasib-related AEs.

Materials and methods

Study designs and patients

To further characterize the safety profile of sotorasib, data were pooled from phase I to III studies of patients treated with sotorasib monotherapy at a dose of 960 mg QD. Studies included CodeBreaK 100 (NCT03600883; phase I, phase II [part A and part B]), CodeBreaK 101 (NCT04185883; phase I subprotocol G), CodeBreaK 105 (NCT04380753; phase I), and CodeBreaK 200 (NCT04303780; phase III). The data from these CodeBreaK studies were collected by the investigators using electronic case report forms and reposed in the clinical trial database maintained by the sponsor. The study designs and eligibility criteria have been previously reported.[11,14-16] Briefly, patients had *KRAS* G12C-mutated advanced NSCLC and disease progression after prior anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) therapy or platinum-based combination chemotherapy (Supplementary Table S1). An exception was the phase I part of the CodeBreaK 100 trial, which included a cohort of 39 patients who were treatment-naïve in the metastatic setting. Patients must not have received antitumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy [except for patients with history of completely resected breast cancer

with no active disease for over 3 years on long-term adjuvant endocrine therapy], or investigational agent) within 4 weeks of study day 1; within 15 days of study day 1 for CodeBreaK 101. Patients were treated with sotorasib until disease progression or unacceptable toxicity. Dose modifications were recommended for TRAEs; as specified in the study protocols, if a patient experienced a grade 3 or 4 TRAE, sotorasib was withheld until recovery to grade 1 or baseline and resumed at the next lower dose level. A maximum of 2 dose reductions, from 960 mg to 480 mg QD and from 480 mg to 240 mg QD, were permissible. Sotorasib was discontinued if a patient was unable to tolerate the minimum dose of 240 mg QD. The trials were approved by institutional review boards or independent ethics committees at each participant site and conducted in accordance with the principles of the Declaration of Helsinki.

Safety assessments

All AEs that occurred after the first dose of sotorasib through 30 days after the last dose were collected and graded in worsening severity from 1 to 5 according to the National Cancer Institute CTCAE, version 5.0. Causality assessments were performed by investigators to determine relatedness to sotorasib. An AE deemed related to sotorasib, per the investigator's assessment, was considered a TRAE. Events of interest for this analysis included gastrointestinal (GI) AEs and hepatotoxicity. Hepatotoxicity was analyzed using the Hepatic Disorders Standardized MedDRA query narrow search of preferred terms, which are validated, pre-determined terms that have been grouped together following expert review (Supplementary Table S2).[17] Time to onset was defined as the period from the start date of sotorasib (Cycle 1 Day 1) to the start date of the event reported by the investigator. Duration of dose interruption was defined as the period from treatment interruption due to the event until treatment resumption. Where a patient had multiple dose interruptions within 1 cycle, the duration of dose interruption was the sum of each period. Time to resolution was defined as the period from the onset of an event until recovery as reported by the investigator. With multiple events within 1 cycle, the time to resolution would be the sum of each period. In an event of disease progression, TRAEs were not collected unless they were serious and were deemed unresolved at the time of discontinuation of sotorasib. The effects of age (< 65 years vs ≥ 65 years; < 75 years vs ≥ 75 years), sex, race, and region on the frequencies of TRAEs were also assessed.

Statistical analyses

All analyses were descriptive. Frequencies were summarized for demographic (sex, race, and smoking status), clinical (prior lines of therapy and response to last immediate prior treatment), and pathological (site, stage, and metastases) variables. Continuous variables were summarized using descriptive statistics (median [interquartile range, IQR]).

Results

Patient demographics

A total of 549 patients with *KRAS* G12C-mutated advanced NSCLC were included in this pooled safety analysis. The data cutoff date for CodeBreaK 100 (phase I [n = 88] and phase II [part A; n = 126]), CodeBreaK 101 (subprotocol G; n = 6), CodeBreaK 105 (n = 10), and CodeBreaK 200 (n = 215; including 46 patients who crossed over from the docetaxel to the sotorasib arm) was August 2, 2022; and September 9, 2022, for CodeBreaK 100 (phase II [part B; n = 104). The median age of the patients was 65 (range, 32–88) years and a majority were White (437 [79.6%]) and Asian (89 [16.2%]) (Table 1). A total of 294 (53.6%) patients were male. Most patients had a history of smoking (former: 433 [78.9%] or current: 88 [16.0%]), had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 (183 [33.3%]) or 1 (356 [64.8%]), and had stage IV disease at screening (528 [96.2%]); 161 (29.3%) patients had a history of brain metastases and 271 (49.4%) patients received ≥2 prior lines of therapy. A total of 428 (78.0%) patients were treated with prior immunotherapy before initiating sotorasib, with approximately half of the patients (225 [52.6%]) having received immunotherapy within 12 weeks prior to initiating sotorasib (Table 1). With a median duration of follow-up of 19.4 months, the median duration of sotorasib treatment was 4.8 (range, 0–41) months.

Summary of treatment-related adverse events

TRAEs were reported in 388 (70.7%) patients (Table 2). Grade 1 and grade 2 TRAEs were reported in 124 (22.6%) and 117 (21.3%) patients, respectively, with grade ≥3 events occurring in 147 (26.8%) patients. The frequencies of TRAEs were similar across patient subgroups such as age, sex, race, and region (Supplementary Tables S3–7). The most common TRAEs occurring in ≥5% of patients were diarrhea (171 [31.1%]), nausea (80 [14.6%]), elevated ALT (68 [12.4%]), elevated AST (67 [12.2%]), fatigue (46 [8.4%]), elevated alkaline phosphatase (38 [6.9%]), decreased appetite (34 [6.2%]), and vomiting (34 [6.2%]) (Table 3). TRAEs were managed with dose interruption in 156 (28.4%) patients, dose reduction in 60 (10.9%) patients, and sotorasib discontinuation in 44 (8.0%) patients (Table 2). The most common TRAEs managed with dose interruption were diarrhea (61 [11.1%]), elevated ALT (31 [5.6%]), and elevated AST (28 [5.1%]). The most common TRAEs managed with dose reduction included diarrhea (28 [5.1%]), elevated ALT (15 [2.7%]), and elevated AST (8 [1.5%]; Table 3). The most common TRAEs managed with sotorasib discontinuation included elevated ALT (any grade: 11 [2.0%] patients; grade 3: 5 [0.9%] patients), and elevated AST (any grade: 8 [1.5%] patients; grade 3: 3 [0.5%] patients; Table 3); none were grade 4. Two (0.4%) patients died with TRAEs, 1 with interstitial lung disease (ILD) whose ultimate cause of death was disease progression, and the other with an unknown cause (Table 2).

Incidence and management of treatment-related adverse events of interest

Gastrointestinal adverse events

Diarrhea (171 [31.1%] patients), nausea (80 [14.6%] patients), and vomiting (34 [6.2%] patients) were the most common (≥5%) treatment-related GI AEs (Table 3). GI AEs were mostly manageable with dose interruptions and supportive care; low rates of sotorasib discontinuation occurred due to these events.

Diarrhea

Overall, grades 1, 2, and 3 treatment-related diarrhea events occurred in 78 (14.2%), 53 (9.7%), and 40 (7.3%) patients,

Table 1. Baseline demographics and disease characteristics.

	Sotorasib 960 mg daily (*N* = 549)
Sex, *n* (%)	
Male	294 (53.6)
Female	255 (46.4)
Median age, years (range)	65.0 (32–88)
Race, *n* (%)	
White	437 (79.6)
Asian	89 (16.2)
Black or African American	9 (1.6)
Multiracial	1 (0.2)
Other	12 (2.2)
Unknown	1 (0.2)
Smoking history, *n* (%)	
Former	433 (78.9)
Current	88 (16.0)
Never	25 (4.6)
Unknown	3 (0.5)
ECOG PS, *n* (%)	
0	183 (33.3)
1	356 (64.8)
2	10 (1.8)
Disease stage at initial diagnosis, *n* (%)	
I	35 (6.4)
II	37 (6.7)
III	97 (17.7)
IV	370 (67.4)
Unknown	10 (1.8)
Stage IV disease at screening, *n* (%)	528 (96.2)
Histopathology type, *n* (%)	
Adenocarcinoma	526 (95.8)
Squamous cell carcinoma	9 (1.6)
Large cell carcinoma	6 (1.1)
Other[a]	8 (1.5)
Site of metastases[b], *n* (%)	
Bone	230 (41.9)
Brain	161 (29.3)
Liver	81 (14.8)
Prior lines of therapy, *n* (%)	
0	39 (7.1)
1	239 (43.5)
2	175 (31.9)
>2	96 (17.5)
Prior surgery, *n* (%)	238 (43.4)
Prior radiotherapy, *n* (%)	331 (60.3)
Prior immunotherapy before sotorasib initiation, *n* (%)	428 (78.0)
Time interval between prior immunotherapy and sotorasib, *n* (%)	
<8 weeks	146 (26.6)
≥8 to <12 weeks	79 (14.4)
≥12 to <16 weeks	46 (8.4)
≥16 to <20 weeks	24 (4.4)
≥20 weeks	133 (24.2)
Best response to previous anticancer therapy[c], *n* (%)	
CR	3 (0.5)
PR	97 (17.7)
SD	147 (26.8)
PD	181 (33.0)
Non-PD/non-CR	11 (2.0)
Unable to evaluate	16 (2.9)
Unknown/NA/ND	47 (8.6)
Missing	8 (1.5)

[a]Includes sarcomatoid (3 [0.5%]); bronchoalveolar carcinoma (2 [0.4%]); others (2 [0.4%]); and undifferentiated (1 [0.2%]). [b]Metastasis history/body site (brain, liver, and bone) was derived per study-specific data collection. [c]as per investigator.
Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; ND, not done; PD, progressive disease; PR, partial response; SD, stable disease.

respectively (Table 3). There were no grade 4 diarrhea TRAEs. The median time to first onset of diarrhea was 45 (IQR, 24–72) days. Of the 171 patients with treatment-related diarrhea, management with dose interruption occurred in 61 (35.7%) patients, dose reduction in 28 (16.4%) patients, and discontinuation in 3 (1.8%) patients (Table 4). The median duration of sotorasib interruption due to diarrhea was 8.0 (IQR, 4.0–11.0) days. Antidiarrheal medication was administered in 114/171 (66.7%) patients, with the most common being loperamide. Prior immunotherapy did not have an impact on incidence of treatment-related diarrhea events.

A total of 331 treatment-related diarrhea events were reported after a more detailed investigation of these 171 patients; 301 (90.9%) events were resolved as per investigators and 29 (8.8%) were unresolved with the status of one (0.3%) event unknown. Of the unresolved events, 4 had resolved only after discontinuation of sotorasib; 19 patients had diarrhea ongoing at the time of death from disease progression; 4 patients were lost to follow-up; and 2 patients continued on sotorasib after improvement to grade 1. Of the 96 treatment-related diarrhea events that led to dose interruption and 34 that resulted in dose reduction, 91 (94.8%) and 31 (91.2%) events resolved, respectively, without administering antidiarrheal medication. Additionally, a combination of antidiarrheal medication was used with dose modifications (Supplementary Figure S1). The median time to resolution of treatment-related diarrhea events following dose interruption with and without antidiarrheals was 18.0 days ([IQR, 11.0–33.0] and [IQR, 10.0–33.0] days, respectively], and that following dose reduction with and without antidiarrheals was 22.0 days ([IQR, 7.0–85.0] and [IQR, 9.0–76.0] days, respectively; Supplementary Table S8). There was no apparent difference in rate and time to resolution of diarrhea events, including grade ≥3 events, when antidiarrheal medication was used in addition to dose interruption and/or reduction suggesting that dose modifications alone were effective in resolving diarrhea events (Supplementary Figure S1 and Supplementary Table S8). However, the analysis was not designed to directly assess the impact of antidiarrheals on

rate and time to resolution and small patient numbers preclude the ability to draw firm conclusions.

Nausea and vomiting

Nausea and vomiting TRAEs were predominantly low grade (Table 3). The median time to first onset of nausea was 22.0 (IQR, 7.5–61.5) days, and the median time to first onset of vomiting was 40.5 (IQR, 16.0–84.0) days (Table 4). Of the 34 patients with treatment-related vomiting, sotorasib was discontinued in 1 (2.9%) patient. No patients discontinued due to nausea.

Patients were managed with supportive care including antiemetics (for nausea, 30/80 [37.5%] patients; for vomiting, 15/34 [44.1%] patients). Antiemetics commonly prescribed included ondansetron and/or prochlorperazine. For patients who have not received olanzapine, the American Society of Clinical Oncology guideline for antiemetics in oncology recommends the addition of olanzapine to their current antiemetic regimen if they experience nausea and vomiting despite optimal prophylaxis. For patients who have received olanzapine, the guideline recommends the addition of a drug of a different class (eg, neurokinin-1 receptor antagonist, benzodiazepine, dopamine receptor antagonist).[18] Out of 108 and 43 reported treatment-related nausea and vomiting events, respectively, a total of 81 (75.0%) and 35 (81.4%) resolved. Of the 27 patients with unresolved nausea, 18 died from disease progression, 4 died from concurrent illnesses (eg, pneumonia), 5 withdrew consent or transitioned onto a different trial. Of the 8 patients with unresolved vomiting, 6 died from disease progression, and 2 died from other causes (pneumonia and multiple organ failure).

Table 2. Summary of treatment-related adverse events.

Adverse event, *n* (%)	Sotorasib 960 mg daily (*N* = 549)
Any grade[a]	388 (70.7)
Grade 1	124 (22.6)
Grade 2	117 (21.3)
Grade 3	127 (23.1)
Grade 4	18 (3.3)
Leading to interruption of sotorasib	156 (28.4)
Leading to reduction of sotorasib	60 (10.9)
Leading to discontinuation of sotorasib	44 (8.0)
Fatal AEs	2 (0.4)

[a]For patients with multiple events under the same category, only the worst grade was reported.
Abbreviation: AE, adverse event.

Hepatic adverse events

Treatment-related hepatotoxicity of any grade was observed in 118 (21.5%) patients. Hepatotoxicity events were primarily characterized by asymptomatic elevations in ALT and AST, which were observed at any grade in 68 (12.4%) and 67 (12.2%) patients, respectively; grade 3 or higher ALT and AST elevations were observed in 38 (6.9%) and 27 (4.9%) patients, respectively (Table 3). A total of 512 events were reported for treatment-related hepatotoxicity, with 476 (93.0%) of these events being resolved as assessed by the investigators. The 36 unresolved hepatic events were reported among 23 patients; 11 had resolved events after discontinuation of sotorasib; 9 patients had events ongoing as they died from disease progression, and 3 patients were lost to follow-up.

Among patients with any grade treatment-related ALT (n = 68) and AST (n = 67) elevations, the median time to first onset was 45.0 (IQR, 41.5–65.0) and 46.0 (IQR, 42.0–66.0) days, respectively (Table 5). Management with dose interruption occurred in 31 (45.6%) and 28 (41.8%) patients, dose reduction in 15 (22.1%) and 8 (11.9%) patients, and treatment discontinuation in 11 (16.2%) and 8 (11.9%) patients, respectively (Table 5). The median duration of sotorasib interruption due to elevated ALT and AST was 16.5 (IQR 10.0, 31.0) and 14.0 (IQR 7.0, 26.0) days. A total of 30 (44.1%) and 29 (43.3%) patients received corticosteroids, most

Table 3. Most common (≥ 5%) treatment-related adverse events.

	Sotorasib 960 mg daily (*N* = 549)							
Event, *n* (%)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Leading to dose interruption	Leading to dose reduction	Leading to discontinuation
Diarrhea	171 (31.1)	78 (14.2)	53 (9.7)	40 (7.3)	0	61 (11.1)	28 (5.1)	3 (0.5)
Nausea	80 (14.6)	46 (8.4)	27 (4.9)	7 (1.3)	0	16 (2.9)	1 (0.2)	0
ALT increased	68 (12.4)	18 (3.3)	12 (2.2)	36 (6.6)	2 (0.4)	31 (5.6)	15 (2.7)	11 (2.0)
AST increased	67 (12.2)	20 (3.6)	20 (3.6)	25 (4.6)	2 (0.4)	28 (5.1)	8 (1.5)	8 (1.5)
Fatigue	46 (8.4)	31 (5.6)	13 (2.4)	2 (0.4)	0	3 (0.5)	1 (0.2)	0
ALP increased	38 (6.9)	13 (2.4)	17 (3.1)	8 (1.5)	0	10 (1.8)	3 (0.5)	4 (0.7)
Decreased appetite	34 (6.2)	20 (3.6)	11 (2.0)	3 (0.5)	0	5 (0.9)	1 (0.2)	0
Vomiting	34 (6.2)	17 (3.1)	15 (2.7)	2 (0.4)	0	6 (1.1)	1 (0.2)	1 (0.2)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Management of gastrointestinal treatment-related adverse events.

	Sotorasib 960 mg daily (*N* = 549)					
	Diarrhea (*n* = 171)		Nausea (*n* = 80)		Vomiting (*n* = 34)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Median time to onset, days (IQR)	45.0 (24.0, 72.0)	46.0 (32.0, 76.0)	22.0 (7.5, 61.5)	15.0 (12.0, 45.0)	40.5 (16.0, 84.0)	16.5 (11.0, 22.0)
Patients managed with dose interruption, *n* (%)	61 (35.7)	34 (19.9)	16 (20.0)	5 (6.3)	6 (17.6)	1 (2.9)
Median duration of dose interruption, days (IQR)[a]	8.0 (4.0, 11.0)	4.0 (1.0, 9.0)	7.0 (4.0, 17.0)	4.0 (2.5, 13.0)	13.0 (4.0, 21.0)	21.0 (21.0, 21.0)
Patients managed with dose reduction, *n* (%)	28 (16.4)	12 (7.0)	1 (1.3)	1 (1.3)	1 (2.9)	0 (0.0)
Patients managed with discontinuation, *n* (%)	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Use of antidiarrheal, *n* (%)	114 (66.7)	34 (19.9)	20 (25.0)	2 (2.5)	6 (17.6)	0 (0.0)
Use of antiemetic, *n* (%)	31 (18.1)	7 (4.1)	30 (37.5)	3 (3.8)	15 (44.1)	2 (5.9)

Percentages are based on *n* for each TRAE except where noted.
[a]Duration of dose interruption is defined as number of days with dose interruption per episode. If consecutive TRAEs under the same preferred term had an end and start within 1 calendar day, they were collapsed as 1 episode.
Abbreviation : IQR, interquartile range.

Table 5. Management of hepatotoxicity treatment-related adverse events.

	Sotorasib 960 mg daily (*N* = 549)					
	Hepatotoxicity[a] (*n* = 118)		ALT increased (*n* = 68)		AST increased (*n* = 67)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Median time to onset, days (IQR)	45.5 (41.0, 64.0)	63.0 (43.0, 82.0)	45.0 (41.5, 65.0)	63.0 (43.0, 70.0)	46.0 (42.0, 66.0)	64.0 (43.0, 87.0)
Patients managed with dose interruption, *n* (%)	67 (56.8)	54 (45.8)	31 (45.6)	29 (42.6)	28 (41.8)	19 (28.4)
Median duration of dose interruption, days (IQR)[b]	20.0 (11.5, 34.0)	17.0 (7.0, 27.0)	16.5 (10.0, 31.0)	12.0 (6.5, 18.0)	14.0 (7.0, 26.0)	9.5 (4.0, 21.0)
Patients managed with dose reduction, *n* (%)	28 (23.7)	16 (13.6)	15 (22.1)	8 (11.8)	8 (11.9)	4 (6.0)
Patients managed with discontinuation, *n* (%)	30 (25.4)	19 (16.1)	11 (16.2)	5 (7.4)	8 (11.9)	3 (4.5)
Use of corticosteroid, *n* (%)	61 (51.7)	40 (33.9)	30 (44.1)	17 (25.0)	29 (43.3)	13 (19.4)
Median duration of corticosteroid use, days (IQR)	20 (14, 43)	17 (7, 36)	21 (13, 40)	12 (7, 30)	14 (7, 30)	9 (5, 30)

Percentages are based on *n* for each TRAE except where noted.
[a]Defined using hepatic disorders standard MedDRA query narrow search; preferred terms included in Supplementary Table S2.
[b]Duration of dose interruption is defined as number of days with dose interruption per episode. If consecutive TRAEs under the same preferred term had an end and start within 1 calendar day, they were collapsed as 1 episode.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; TRAE, treatment-related adverse event.

commonly prednisolone, for elevated ALT and AST events, for a median duration of 21.0 (IQR, 13.0–40.0) and 14.0 (IQR, 7.0–30.0) days. Grade 3 to 4 ALT and AST elevation events were generally transient and managed with dose interruption in 29 (42.6%) and 19 (28.4%), dose reduction in 8 (11.8%) and 4 (6.0%), and discontinuation in 5 (7.4%) and 3 (4.5%) patients, respectively.

Treatment-related ALT and AST elevations were resolved with dose interruption (68/70 [97.1%] and 56/58 [96.6%] events) and/or dose reduction (18/19 [97.4%] and 10/11 [90.9%]; Supplementary Figures 2 and 3). Corticosteroid treatment in combination with dose interruption resulted in high rates of resolution of treatment-related ALT and AST elevations (38/39 [97.4%] and 31/32 [96.9%] events). Further,

corticosteroid treatment in combination with dose reduction resulted in the resolution of treatment-related ALT and AST elevations (10/11 [90.9%]) and 3/4 [75.0%] events). All events of grade ≥3 ALT and AST elevations (100%) were managed with either dose interruption and/or dose reduction with or without corticosteroids (Supplementary Figures 2 and 3).

Dose interruption resolved the elevated ALT levels in 21.0 (IQR, 11.0–35.0) days with or without corticosteroids and elevated AST in 20.0 (IQR, 7.0–26.0) days with corticosteroids and in 20.0 (IQR, 6.5–28.0) days without corticosteroids (Supplementary Table S8). Dose reduction resulted in the resolution of elevated ALT in 43.0 (IQR, 29.0–84.0) days with corticosteroids or in 25.0 (IQR, 11.0–43.0) days without corticosteroids and elevated AST in 22.0 (IQR, 8.0–43.0) days with corticosteroids and in 22.0 (IQR, 14.0–43.0) days without corticosteroids. A higher incidence of treatment-related hepatotoxicity was observed in patients treated with prior immunotherapy (106/428 [24.8%]) vs those who were not treated with immunotherapy (12/121 [9.9%]) before initiation of sotorasib. Patients who had stopped immunotherapy less than 3 months before initiating sotorasib had a higher incidence of treatment-related hepatotoxicity (80/240 [33.3%]) than those who stopped immunotherapy 3 months or more before initiating sotorasib (26/188 [13.8%]; Supplementary Table S9). There was no apparent difference in resolution rates by use and timing of prior immunotherapy.

Other severe hepatic events were evaluated. No patient met Hy's law criteria without the presence of a reasonable alternative etiology for the laboratory abnormalities.[19] Shifts from baseline to grade 4 ALT elevations (1.8%) or grade 4 AST elevations (0.9%) rarely occurred (Supplementary Table S10). Of the 118 patients with hepatotoxicity TRAEs, drug-induced liver injury (DILI) was reported in 8 (6.8%) patients; however, further review of these events showed no evidence of severe DILI with hepatic encephalopathy, coagulopathy, or other sequelae of decompensated liver disease. Overall, no patient experienced severe (4+) or fatal (5+) DILI in accordance with the Drug-Induced Liver Injury Network severity grading criteria.[20,21]

Other TRAEs

Treatment-related fatigue was observed in 46 (8.4%) patients, with grade ≥3 events observed in 2 (0.4%) patients (Table 3). Fatigue was managed with dose interruption in only 3 (6.5%) patients and dose reduction in 1 (2.2%) patient.

Treatment-related pneumonitis/ILD was observed in 9 (1.6%) patients, of which 5 experienced grade ≥3 events. Treatment-related pneumonitis/ILD was managed with dose interruption in 3 patients and dose reduction in 1 patient. Patients were monitored for new or worsening pulmonary symptoms indicative of ILD or pneumonitis (eg, dyspnea, cough, fever). Seven patients discontinued treatment due to pneumonitis/ILD. As noted above, 1 patient died with ongoing treatment-related ILD; cause of death was determined to be progression of underlying NSCLC. The median time to first onset for pneumonitis/ILD was 74.0 (IQR, 38.0–127.0) days and the median time from onset to resolution was 42.0 (IQR, 24.0–55.0) days.

In this study, treatment-related QTc prolongation rarely occurred ($n = 4$ [0.7%]). Three events were grade 1, which required no change in sotorasib administration, and 1 event was grade 3, which led to sotorasib interruption and resumption at the initial dose. None of these events required hospitalization prior to resolution, and they were confounded by other comorbidities or concurrent illnesses (eg, electrolyte abnormalities).

Discussion

In this extensive pooled safety analysis of 549 patients with *KRAS* G12C-mutated advanced NSCLC, sotorasib 960 mg QD demonstrated a consistent and manageable safety profile, with low rates of treatment discontinuation. Grade ≥3 events were managed with dose modification; a subset of these patients resumed sotorasib at 960 mg after treatment interruption or prior dose reduction at investigator discretion. The most common TRAEs across these 4 CodeBreaK clinical studies were GI- and hepatic-related and were primarily low grade; QTc prolongation was rarely observed, reducing the notable risk of drug–drug interactions that could negatively impact the QTc profile of patients with *KRAS* G12C-mutated advanced NSCLC. Safety findings from this analysis were consistent with the real-world data reported from the sotorasib global expanded access program, which included a clinical trial-ineligible population that had approximately 21% of patients with ECOG PS 2 from Brazil, Israel, Italy, Spain, Taiwan, and US.[22]

The most common (> 5%) sotorasib-related GI AEs were diarrhea (31%), nausea (14.6%), and vomiting (6.2%), which were mostly low grade. Sotorasib-related diarrhea, including grade 3, was effectively managed with dose interruption or dose reduction with or without antidiarrheal medications in more than 90% of events; no grade 4 or fatal diarrhea event was reported. Dose interruption alone and in combination with antidiarrheals resolved sotorasib-related diarrhea events in a median of 18 days, with grade ≥3 diarrhea resolving in approximately 12 days with the same management strategy. Further, dose reduction alone and in combination with antidiarrheals resolved sotorasib-related diarrhea in 22 days, with grade ≥3 diarrhea resolving in 10 days. One plausible reason why the duration of grade 3 diarrhea events was longer compared to diarrhea events of any grade might be that antidiarrheal treatment and sotorasib dose modification rates were greater in patients with grade 3 diarrhea. For instance, 34 of 40 patients (85%) with grade 3 diarrhea received antidiarrheal treatment in addition to dose modification, whereas 114 of 171 patients (67%) with diarrhea of any grade received antidiarrheal treatment. GI toxicities have been observed across the class of commercially available and investigational $KRAS^{G12C}$ inhibitors.[23] For example, adagrasib has reported diarrhea (63%), nausea (62%), and vomiting (47%) as the most common GI TRAEs in the phase II cohort of 116 patients with previously treated *KRAS* G12C-mutated advanced NSCLC from the KRYSTAL-1 study.[24] To minimize treatment-related GI events, antidiarrheals and antiemetics can be prescribed concomitantly, and patients can be instructed on the use of these medications and actions to take at the first incidence of nausea or diarrhea.

Treatment-related hepatotoxicity has been reported with $KRAS^{G12C}$ inhibitors.[23] Sotorasib-related hepatotoxicity occurred in 21% of patients and primarily presented as asymptomatic, transient transaminase elevations. Sotorasib-related ALT and AST elevations occurred in 12.4% and 12.2% of patients, respectively. In the phase II cohort of the KRYSTAL-1 study, adagrasib was associated with ALT and

AST elevations which were observed in 28% and 25% of patients, respectively.[17] In the current study, more than 90% of the sotorasib-related events related to ALT and AST elevations, including grade ≥3, were effectively managed with dose interruption or dose reduction with or without corticosteroids. Corticosteroid use did not show an effect on the resolution of ALT and AST elevations, considering that dose modification of sotorasib resulted in similar resolution rates and resolution with and without corticosteroid use. However, the relatively small numbers of patients with dose modification due to transaminase elevations may have been too small to detect any significant differences by corticosteroid use. Hepatic events resolved in 93% of cases; <6% of patients discontinued treatment. The remaining unresolved cases were attributed to various reasons, including disease progression prior to event resolution or loss to follow-up.

Treatment-related hepatotoxicity has been observed in a higher proportion of patients who had received sequential and recent immunotherapy before initiating sotorasib treatment. Results from 2 retrospective studies in patients with *KRAS* G12C-mutated advanced NSCLC demonstrated that severe sotorasib-related hepatotoxicity occurred in 67% of the patients with sequential anti-PD-(L)1 therapy followed by sotorasib treatment[25] and grade ≥3 hepatotoxicity was observed in a majority of patients who were treated with anti-PD-(L)1 therapy 6.4 weeks before initiating sotorasib.[26] Treatment with systemic steroids resulted in clinical improvement to grade 1 hepatotoxicity in 80.0% of patients within 12 weeks of steroid initiation.[26] In the current pooled safety analysis, the impact of prior immunotherapy before sotorasib initiation was consistent with the literature findings where patients treated with prior immunotherapy less than 3 months before sotorasib initiation exhibited a higher incidence of treatment-related hepatotoxicity compared with those who stopped immunotherapy 3 months or more before initiating sotorasib. Regardless of the interval between prior immunotherapy and sotorasib initiation, these events were manageable with dose modification of sotorasib with or without corticosteroids. As indicated in the USPI, liver function should be monitored before the start of sotorasib treatment, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated with more frequent testing in patients who developed transaminase and/or bilirubin elevations. These data also reinforce the importance of following the recommended testing frequency for patients starting sotorasib less than 3 months after discontinuing immunotherapy. Corticosteroids may be considered for treating severe hepatotoxicity. To summarize, we demonstrate that dose reduction and interruption of sotorasib are key to the resolution and management of treatment-related diarrhea and hepatic AEs. Further supportive care with antidiarrheals and corticosteroids can be used at the discretion of the treating physician.

A limitation of this analysis is the generalization of these results to real-world patients, as this analysis included clinical trial populations only from the CodeBreaK global development program; patient eligibility criteria for each trial can differ from the real-world practice setting. For instance, most patients included in this pooled analysis had ECOG PS ≤1 and 1.8% with ECOG PS 2. Further, TRAEs were not assessed after the patients stopped sotorasib and moved to post-trial follow up. Additionally, these trials were ongoing during the coronavirus disease 2019 pandemic and hence, recruiting patients and procuring data was challenging. Notwithstanding these limitations, this is the largest and most comprehensive safety assessment of a $KRAS^{G12C}$ inhibitor. Results from this study demonstrate that sotorasib has a well-characterized safety profile in patients with *KRAS* G12C-mutated advanced NSCLC and can be well managed, with supportive guidance available and prescribing information.

Under its accelerated approval status, sotorasib is available for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. The sotorasib development program remains active with studies in earlier treatment settings ongoing, including the CodeBreaK 202 (NCT05920356) global, phase 3, randomized study of sotorasib versus pembrolizumab in combination with platinum doublet chemotherapy as first-line treatment for PD-L1 negative, *KRAS* G12C-mutated advanced NSCLC.

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Conflicts of interest

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Data availability

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

Supplementary material

Supplementary material is available at *The Oncologist* online.

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