BRIEF REPORT

Brief Report: Real-World Efficacy and Safety of Sotorasib in U.S. Veterans with *KRAS* G12C-Mutated NSCLC

Katherine I. Zhou, MD, PhD,[a,b] Chenyu Lin, MD,[a,c] Chin-Lin Tseng, MPH,[d] Nithya Ramnath, MBBS,[e,f] Jonathan E. Dowell, MD,[g,h] Michael J. Kelley, MD[a,b,d,*]

[a]Division of Hematology-Oncology, Durham VA Medical Center, Durham, North Carolina
[b]Division of Medical Oncology, Duke University, Durham, North Carolina
[c]Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, North Carolina
[d]National Oncology Program, U.S. Department of Veterans Affairs, Durham, North Carolina
[e]Section of Hematology-Oncology, Ann Arbor VA Medical Center, Ann Arbor, Michigan
[f]Division of Hematology and Oncology, University of Michigan, Ann Arbor, Michigan
[g]Section of Hematology-Oncology, Veterans Affairs North Texas Healthcare System, Dallas, Texas
[h]Division of Hematology/Oncology, UT Southwestern Medical Center, Dallas, Texas

Received 6 February 2024; revised 13 March 2024; accepted 23 March 2024
Available online - 26 March 2024

ABSTRACT

Introduction: The *KRAS* G12C inhibitor sotorasib was approved for treating advanced NSCLC in the second line or later on the basis of the CodeBreaK100 trial. Nevertheless, data on the real-world efficacy and safety of sotorasib, and to its optimal dose, remain limited.

Methods: Patients treated with sotorasib for NSCLC through the Veterans Health Administration were retrospectively identified from the Corporate Data Warehouse. Survival, response, and toxicity data were obtained from chart review.

Results: Among the 128 patients treated with sotorasib through the Veterans Health Administration, objective response rate was 34%, progression-free survival (PFS) six months, and overall survival 12 months. Similar PFS was observed among the 16 patients who received frontline sotorasib without any prior systemic therapy for NSCLC. Toxicity leading to sotorasib interruption or dose reduction occurred in 37% of patients, whereas sotorasib discontinuation for toxicity occurred in 25%. Notably, sotorasib dose reduction was associated with substantially improved PFS and OS.

Conclusions: In this real-world study, the observed efficacy of sotorasib was similar to the results of CodeBreaK100. Patients who received frontline sotorasib had similar PFS to our overall cohort, suggesting that first-line sotorasib monotherapy may benefit patients who are not eligible for chemotherapy. Toxicities leading to sotorasib interruption, dose reduction, or discontinuation were common. Sotorasib dose reduction was associated with improved survival, suggesting that sotorasib dose reduction may not compromise efficacy.

Keywords: Sotorasib; KRAS; KRAS G12C; Non-small cell lung cancer (NSCLC); Real-world; Dose reduction

Introduction

KRAS mutations are among the most common drivers of NSCLC. The most common mutation subtype, *KRAS* G12C, occurs in 13% of lung adenocarcinomas.[1] In the CodeBreaK100 trial, sotorasib was associated with an objective response rate (ORR) of 37%, median

***Corresponding author.**

Address for correspondence: Michael J. Kelley, MD, National Oncology Program, U.S. Department of Veterans Affairs; Division of Hematology-Oncology, Durham VA Medical Center; Division of Medical Oncology, Duke University, 300 Fulton St, Durham 27705, United States. E-mail: michael.kelley@duke.edu

Cite this article as: Zhou KI, Lin C, Tseng C-L, et al. Brief report: Real-world efficacy and safety of sotorasib in U.S. Veterans with *KRAS* G12C-mutated NSCLC. JTO Clin Res Rep 2024;5:100670.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100670

progression-free survival (PFS) of 6.8 months, and median overall survival (OS) of 12.5 months in patients with *KRAS* G12C-mutated advanced NSCLC who received at least one prior line of systemic therapy.[1,2] In the phase III CodeBreaK200 study comparing sotorasib with docetaxel in the same population, sotorasib was associated with an ORR of 28.1%, median PFS of 5.6 months, and median OS of 10.6 months.[3]

Concern has been raised regarding the tolerability of sotorasib at the approved daily dose of 960 mg.[4] At this dose, in the phase II CodeBreaK100 trial, treatment-related adverse events (TRAEs) led to sotorasib interruption or dose reduction in 22.2% and sotorasib discontinuation in 7.1% of patients.[1] Similarly, in CodeBreak200, TRAEs led to sotorasib interruption in 36%, dose reduction in 15%, and discontinuation in 10% of patients.[3] Notably, no dose-response relationship was observed in the phase I trial, which evaluated daily doses of 180 to 960 mg sotorasib across multiple solid tumor types.[4,5] The U.S. Food and Drug Administration issued a postmarketing requirement to compare 240 with 960 mg daily to determine the optimal dose of sotorasib.[4] In a randomized study comparing starting doses of 240 and 960 mg sotorasib daily, 960 mg was associated with increased ORR and improved OS but also increased rates of serious TRAEs and sotorasib interruption or dose reduction.[6] The risk-benefit of dose reduction and intermediate starting doses remains unclear, particularly in less fit real-world populations.

The Veterans Health Administration (VHA) is the largest integrated health care system providing cancer care in the United States. In this national VHA study, we evaluate the real-world efficacy and safety of sotorasib among veterans with advanced NSCLC, including the relationship between dose reduction and efficacy.

Materials and Methods

Patients prescribed sotorasib through the VHA before March 1, 2023 were retrospectively identified from the Corporate Data Warehouse. Clinical and molecular data were obtained from the Corporate Data Warehouse, the VA National Precision Oncology Program database,[7] and electronic medical records, with data cutoff on April 4, 2023. All investigations were performed under an institutional review board-approved protocol, which included a waiver of informed consent. Best response and date of progression were assessed on the basis of review of clinical notes and radiology reports, not based on Response Evaluation Criteria in Solid Tumors. Toxicities were included if they led to drug interruption, dose reduction, or discontinuation. PFS and OS were measured from the time of initiation of sotorasib. Survival analyses were conducted using the Cox proportional-hazards model. Variables affecting toxicity were analyzed by chi-square analysis and logistic regression. Patients with missing data for a given variable were excluded from any analyses involving that variable. All analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).[8]

Results

Between June 2021 and February 2023, 128 patients from 72 VHA medical centers received sotorasib for *KRAS* G12C-mutated NSCLC. Patients in our cohort had a median age of 72 years, were mostly male (90%), and most typically reported White or Caucasian (77%) and Black or African American (19%) race (Table 1). Among the 92 patients (72%) examined for response, the ORR was 34%, disease control rate 71%, median time to response 2.4 months, and median duration of response four months (Supplementary Table 1). Among all 128 patients, the median duration of treatment was 6.3 months, median PFS six months, and median OS 12 months (Fig. 1*A* and *B* and Supplementary Table 1). Among the seven patients with active central nervous system (CNS) disease at the time of sotorasib initiation, four were examined for CNS response: one had a partial response; one had stable disease, and two experienced CNS progression.

Among the 16 patients who received sotorasib without any prior systemic therapy for NSCLC, the median PFS was 6.6 months and median OS 8.1 months (Supplementary Fig. 1*A* and *B*). Of the 11 patients (69%) examined for response, three patients (27%) responded. Reasons for receiving sotorasib without first-line chemotherapy included anticipated intolerance (eight), patient refusal (six), and receipt of systemic therapy for another malignancy (two). Reasons immune checkpoint inhibitors (ICIs) were not given first line included anticipated lack of efficacy of ICI monotherapy (nine), patient refusal (two), autoimmune disease (one), and not known (four).

In a univariable analysis in all 128 patients treated with sotorasib, *STK11* mutation, *KEAP1* mutation, glomerular filtration rate (GFR) greater than 60 mL/min, and Eastern Cooperative Oncology Group performance status greater than or equal to 3 were associated with decreased PFS, whereas PD-L1 tumor proportion score (TPS) greater than or equal to 50% was associated with improved PFS (Fig. 1*C*, Supplementary Fig. 2). In contrast, PFS did not markedly differ by *TP53* mutation status or by PD-L1 TPS with cutoff greater than or equal to 1% (Supplementary Fig. 3). In a multivariable analysis accounting for these five variables, only Eastern Cooperative Oncology Group performance status remained

Table 1. Characteristics of 128 Veterans with KRAS G12C-mutated NSCLC Treated With Sotorasib

Characteristic	N = 128
Age in y, median (min-max)	72 (43-93)
Sex, n (%)	
Male	115 (90)
Female	13 (10)
Race, n (%)	
White or Caucasian	98 (77)
Black or African American	24 (19)
Other	2 (2)
Not known	4 (3)
Ethnicity, n (%)	
Hispanic	3 (2)
Non-Hispanic	121 (95)
Not known	4 (3)
Rurality, n (%)	
Urban	82 (64)
Rural or highly rural	46 (36)
ECOG PS at start of sotorasib[a], n (%)	
0	8 (6)
1	38 (30)
2	21 (16)
3	9 (7)
Not known	52 (41)
Smoking status at start of sotorasib, n (%)	
Current	37 (29)
Former	88 (69)
Never	3 (2)
Histologic diagnosis, n (%)	
Adenocarcinoma	117 (91)
Squamous cell carcinoma	2 (2)
Other[b]	9 (7)
Prior lines of systemic therapy, n (%)	
0	24 (19)
1	74 (58)
2	18 (14)
3+	12 (9)
Stage at start of sotorasib, n (%)	
II	3 (2)
III	5 (4)
IV	120 (94)
Active CNS disease at start of sotorasib, n (%)	7 (5)
Starting daily dose of sotorasib, n (%)	
960 mg	111 (87)
720 mg	2 (2)
480 mg	12 (9)
240 mg	3 (2)
Survival status at data cutoff, n (%)	
Alive	71 (55)
Dead	57 (45)

Note: percentages may not add up to 100% owing to rounding.
[a]One patient categorized as ECOG PS 1 was specified as having Karnofsky performance status 80%. Of the 52 patients with unknown ECOG PS, two had ECOG PS 0-1, and three had ECOG PS 1-2.
[b]Other histologic diagnoses included not otherwise specified (six), large cell neuroendocrine (two), and carcinosarcoma (one).
Min, minimum; max, maximum; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system.

significant (hazard ratio 4.20, 95% confidence interval: 1.28–13.75).

Sotorasib was interrupted or dose reduced in 47 patients (37%) and discontinued for toxicity in 32 patients (25%). The most common adverse events leading to sotorasib interruption, dose reduction, or discontinuation were diarrhea, hepatotoxicity, and pneumonitis (Supplementary Table 2). Patients who received ICIs within three months of starting sotorasib had higher rates of sotorasib interruption, dose reduction, or discontinuation due to any toxicity (38/63 patients who received ICIs versus 25/65 patients who did not receive ICIs; Supplementary Fig. 4*A*), and higher rates of sotorasib interruption, dose reduction, or discontinuation due to diarrhea, hepatotoxicity, or pneumonitis (26/63 patients who received ICIs versus 12/65 patients who did not receive ICIs; Supplementary Fig. 4*B*).

Most patients (87%) started sotorasib at a daily dose of 960 mg. When specified, reported reasons for starting sotorasib at a lower dose included concern for intolerance (three), risk of drug interactions (two), comorbidities (two), age (one), poor performance status (one), critically ill clinical status (one), and lack of data on the appropriate initial dose of sotorasib (one). Among the 37 patients (29%) who experienced dose reduction, sotorasib was reduced to a minimum of 240 mg in 10 patients (27%), 480 mg in 23 patients (62%), and 720 mg in four patients (11%). Dose reduction was associated with improved PFS (Figure 2*A*) and a more profound improvement in OS (median OS 15.8 versus 8.8 months, Figure 2*B*). The dose dependence of this effect was unclear owing to the small subgroup sizes (Supplementary Fig. 5*A* and *B*). The association of dose reduction with survival remained substantial when patients who discontinued sotorasib for toxicity were excluded (Supplementary Fig. 5*C* and *D*).

Discussion

The CodeBreaK100 clinical trial led to the approval of the *KRAS* G12C inhibitor sotorasib for the treatment of advanced NSCLC in the second line or later.[1] In the same population, the CodeBreak200 randomized controlled trial found a PFS benefit but no difference in OS between sotorasib and docetaxel.[3] A retrospective study in 105 patients treated with sotorasib at three academic centers in New York City reported comparable efficacy to trial results.[9] Recently, a real-world study in 163 patients who received sotorasib for *KRAS* G12C-mutated advanced NSCLC through the German compassionate use program also showed similar response rates.[10] Nevertheless, data on the real-world safety and efficacy

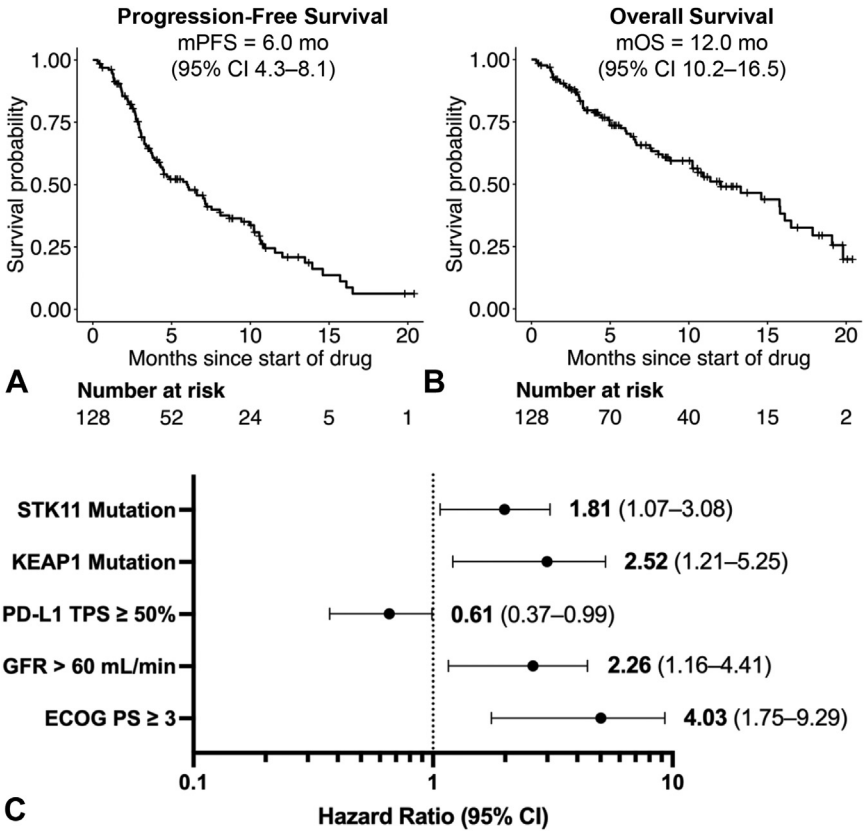

Figure 1. Survival analysis of veterans with *KRAS* G12C-mutated NSCLC treated with sotorasib. (*A*) PFS and (*B*) OS of veterans with *KRAS* G12C-mutated NSCLC treated with sotorasib. (*C*) Forest plot of factors associated with PFS based on univariable analysis, with corresponding hazard ratio in bold and 95% CI in parentheses. 95% CI, 95% confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; KEAP1, Kelch-like ECH-associated protein 1; mo, months; mOS, median overall survival; mPFS, median progression-free survival; PD-L1 TPS, programmed death ligand-1 tumor proportion score; STK11, serine/threonine kinase 11.

of sotorasib remain limited. We report on the U.S. VHA experience with sotorasib in veterans with advanced NSCLC.

Our cohort was older than the CodeBreaK100 and CodeBreak200 cohorts, less fit, more likely male, and more likely Black or African American;[1,3,9] 36 patients

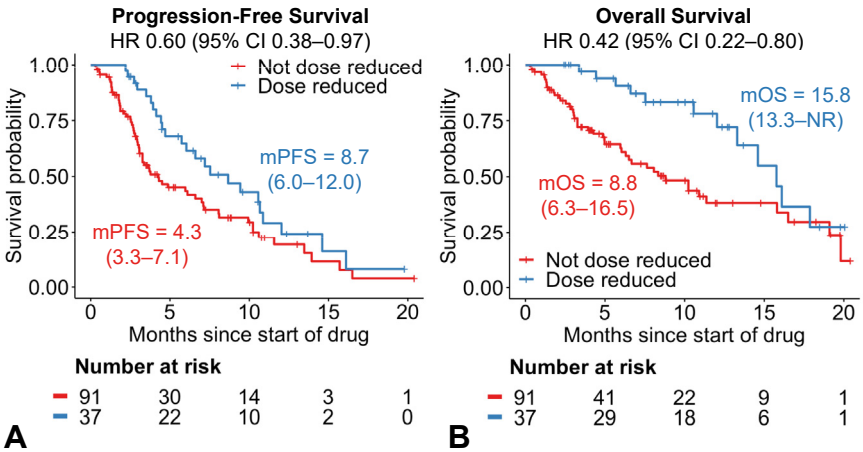

Figure 2. Association of survival with sotorasib dose reduction. (*A*) PFS and (*B*) OS of veterans with *KRAS* G12C-mutated NSCLC treated with sotorasib, stratified by whether sotorasib was dose reduced after starting treatment. mPFS or mOS and 95% CI (in parentheses) are shown in the corresponding color (red or blue) for each subgroup. CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached.

(28%) would not have been eligible for CodeBreaK100 based on performance status, renal function, or active CNS disease. Despite this older and less fit cohort, the response rate of sotorasib in our retrospective analysis was similar to clinical trial results.[1–3] Nevertheless, response data were missing in 28% of this cohort, either because response was not assessed or because records were not available, and the true ORR was likely lower than 34%. Although the *KRAS* G12C inhibitor adagrasib has intracranial activity, the CNS activity of sotorasib is less clear because patients with active untreated brain metastases were excluded from CodeBreaK100.[1,11,12] Our cohort included seven patients with active CNS disease, including one patient who had a CNS response to sotorasib, but the interpretation is limited by small sample size.

Sotorasib is approved after at least one prior line of systemic therapy. Preliminary results from the phase 1b CodeBreaK101 trial suggested promising clinical activity of frontline sotorasib in combination with chemotherapy in *KRAS* G12C-mutated advanced NSCLC.[13] For patients who are not fit for chemotherapy, it remains unclear whether frontline sotorasib monotherapy is beneficial.[14,15] In our cohort, 16 patients received frontline sotorasib off-label, typically owing to age, comorbidities, or performance status. Consistent with these population differences, these patients had shorter OS than that of the overall cohort. Nevertheless, their median PFS was similar to our overall cohort, suggesting that patients who are not candidates for chemotherapy may benefit from frontline sotorasib.

Although the approved starting dose of sotorasib is 960 mg daily, this dose is associated with greater toxicity, and the biologically optimal dose may be lower.[4,6] Owing to the retrospective study design, we only accounted for toxicities that led to sotorasib interruption, dose reduction, or discontinuation. Nevertheless, patients in our real-world cohort seemed to experience more toxicities related to sotorasib than did the clinical trial population because we observed higher rates of sotorasib interruption, dose reduction, or discontinuation for toxicity.[1,3] Surprisingly, patients in our cohort who required dose reduction had improved PFS and OS relative to patients who did not require dose reduction, which may be due to reduced toxicity at the lower dose. Although we cannot exclude confounding factors owing to the retrospective study design, this result supports the possibility that a lower dose of sotorasib may not compromise efficacy. Given the greater toxicity associated with higher doses of sotorasib,[6] lower starting doses of sotorasib may be appropriate in less fit patients. Similarly to other studies,[3,9] we found an increased risk of overlapping toxicities when sotorasib was given within three months of ICIs. Although the combination of adagrasib and pembrolizumab has shown promising clinical activity in NSCLC in a clinical trial,[16] careful attention should be paid to the tolerability of regimens combining ICIs and *KRAS* G12C inhibitors in the real world given the risk of additive toxicities.

In summary, in this real-world veteran population, sotorasib had overall similar efficacy but seemed to have higher rates of toxicity than those in clinical trials. Frontline sotorasib monotherapy may be an appropriate option for patients who are not candidates for chemotherapy. Dose reduction of sotorasib did not seem to compromise efficacy and was associated with improved survival in our cohort, providing further support for the investigation of lower doses of sotorasib in NSCLC. Additional prospective evidence is needed to clarify the relationship of sotorasib dose with drug tolerability and clinical efficacy.

CRediT Authorship Contribution Statement

Katherine I. Zhou: Conceptualization, Investigation, Formal analysis, Visualization, Writing - original draft.

Chenyu Lin: Conceptualization, Investigation, Formal analysis, Visualization, Writing - review & editing.

Chin-Lin Tseng: Software, Data curation.

Nithya Ramnath: Writing - review & editing.

Jonathan E. Dowell: Writing - review & editing.

Michael J. Kelley: Conceptualization, Writing - review & editing, Supervision.

Disclosure

Dr. Lin reported serving as a consultant for Rigel and on the advisory board of Autolus. Dr. Dowell participated in advisory boards for Mirati, Astra Zeneca, Catalyst, and Takeda. Dr. Kelley reported research funding (paid to his institution) from Novartis, Bristol-Myers Squibb, Regeneron, and Mirati Therapeutics. The remaining authors declare no conflict of interest.

Funding

Drs. Zhou and Lin were supported by the Duke Hematology and Transfusion Medicine Training Program (NHLBI T32 HL007057). Dr. Ramnath was funded by VA I50CU000182: VA Ann Arbor Lung Precision Oncology Program. Dr. Kelley was funded by the National Oncology Program, Department of Veterans Affairs.

Informed Consent

All investigations were performed under an institutional review board-approved protocol, which included a waiver of informed consent.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100670].

References

1. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with *KRAS* p.G12C mutation. *N Engl J Med*. 2021;384:2371–2381.
2. Dy GK, Govindan R, Velcheti V, et al. Long-term outcomes and molecular correlates of sotorasib efficacy in patients with pretreated *KRAS* G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreaK 100. *J Clin Oncol*. 2023;41:3311–3317.
3. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. *Lancet*. 2023;401:733–746.
4. Ratain MJ, Tannock IF, Lichter AS. Dose optimization of sotorasib: is the US Food and Drug Administration sending a message? *J Clin Oncol*. 2021;39:3423–3426.
5. Hong DS, Fakih MG, Strickler JH, et al. KRASG12C inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383:1207–1217.
6. Hochmair MJ, Vermaelen K, Mountzios G, et al. VP4-2023: sotorasib 960 mg versus 240 mg in pretreated KRAS G12C advanced NSCLC. *Ann Oncol*. 2024;35:142–144.
7. Kelley MJ. VA national precision oncology program. *Fed Pract*. 2020;37:S22–S27.
8. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021. https://www.R-project.org. Accessed May 3, 2024.
9. Thummalapalli R, Bernstein E, Herzberg B, et al. Clinical and genomic features of response and toxicity to sotorasib in a real-world cohort of patients with advanced KRAS G12C-mutant non-small cell lung cancer. *JCO Precis Oncol*. 2023;7:e2300030.
10. Stratmann JA, Althoff FC, Doebel P, et al. Sotorasib in KRAS G12C-mutated non-small cell lung cancer: a multicenter real-world experience from the compassionate use program in Germany. *Eur J Cancer*. 2024;201:113911.
11. Negrao MV, Spira AI, Heist RS, et al. Intracranial efficacy of adagrasib in patients from the KRYSTAL-1 trial with KRASG12C-mutated non-small-cell lung cancer who have untreated CNS metastases. *J Clin Oncol*. 2023;41:4472–4477.
12. Ramalingam S, Skoulidis F, Govindan R, et al. Efficacy of sotorasib in KRAS p.G12C-mutated NSCLC with stable brain metastases: a post-hoc analysis of CodeBreaK 100. *J Thorac Oncol*. 2021;16:S1123.
13. Clarke JM, Felip E, Li BT, et al. CodeBreaK 101: safety and efficacy of sotorasib with carboplatin and pemetrexed in KRAS G12C-mutated advanced NSCLC. *J Thorac Oncol*. 2023;18:S118–S119.
14. Iska S, Alley EW. Sotorasib as first-line treatment for advanced KRAS G12C-mutated non-small cell lung carcinoma: a case report. *Case Rep Oncol*. 2023;16:183–187.
15. Arbour KC, Khurana M, Dai T, Skoulidis F. Trial in progress: a phase 2 study of sotorasib as first-line treatment in patients with stage IV non-small cell lung cancer (NSCLC) whose tumors harbor a KRAS p.G12C mutation (CodeBreaK 201). *J Clin Oncol*. 2022;40:TPS9150.
16. Jänne PA, Smit EF, de Marinis F, et al. Preliminary safety and efficacy of adagrasib with pembrolizumab in treatment-naïve patients with advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *Immunooncol Technol*. 2022;16:100360.