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

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ABSTRACT

PURPOSE With the recent approval of the KRAS G12C inhibitor sotorasib for patients with advanced *KRAS G12C*-mutant non–small cell lung cancer (NSCLC), there is a new need to identify factors associated with activity and toxicity among patients treated in routine practice.

MATERIALS AND METHODS We conducted a multicenter retrospective study of patients treated with sotorasib outside of clinical trials to identify factors associated with real-world progression free survival (rwPFS), overall survival (OS), and toxicity.

RESULTS Among 105 patients with advanced *KRAS G12C*-mutant NSCLC treated with sotorasib, treatment led to a 5.3-month median rwPFS, 12.6-month median OS, and 28% real-world response rate. *KEAP1* comutations were associated with shorter rwPFS and OS (rwPFS hazard ratio [HR], 3.19; $P = .004$; OS HR, 4.10; $P = .003$); no significant differences in rwPFS or OS were observed across *TP53* (rwPFS HR, 1.10; $P = .731$; OS HR, 1.19; $P = .631$) or *STK11* (rwPFS HR, 1.66; $P = .098$; OS HR, 1.73; $P = .168$) comutation status. Notably, almost all patients who developed grade 3 or higher treatment-related adverse events (G3+ TRAEs) had previously been treated with anti–PD-(L)1 therapy. Among these patients, anti–PD-(L)1 therapy exposure within 12 weeks of sotorasib was strongly associated with G3+ TRAEs ($P < .001$) and TRAE-related sotorasib discontinuation ($P = .014$). Twenty-eight percent of patients with recent anti–PD-(L)1 therapy exposure experienced G3+ TRAEs, most commonly hepatotoxicity.

CONCLUSION Among patients treated with sotorasib in routine practice, *KEAP1* comutations were associated with resistance and recent anti–PD-(L)1 therapy exposure was associated with toxicity. These observations may help guide use of sotorasib in the clinic and may help inform the next generation of KRAS G12C-targeted clinical trials.

ACCOMPANYING CONTENT

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INTRODUCTION

KRAS is the most frequently mutated oncogene in patients with non–small cell lung cancer (NSCLC), with activating mutations in *KRAS* found in up to 30% of patients with nonsquamous NSCLC.[1,2] *KRAS G12C* is the most common subtype, present in approximately 40% of patients with *KRAS*-mutant lung cancer.[3] For decades, *KRAS* had been considered an undruggable target.[4,5] However, recent efforts aimed at developing inactive conformation-specific KRAS inhibitors[6] have led to the first KRAS-directed therapies with meaningful clinical activity.

Sotorasib is a small molecule that covalently modifies the mutant cysteine in the KRAS G12C protein, irreversibly locking KRAS G12C in an inactive conformation and blocking interaction with downstream effectors.[7] Sotorasib was granted accelerated approval by the US Food and Drug Administration (FDA) in 2021 on the basis of a multicenter, single-arm, phase II study that demonstrated a 37% objective response rate, 6.8-month median progression-free survival (PFS), and 12.5-month median overall survival (OS) for sotorasib among patients with advanced *KRAS G12C*-mutant advanced NSCLC with disease progression on previous systemic therapy.[8] In addition to sotorasib,

CONTEXT

Key Objective

Given recent approval of the KRAS G12C inhibitor sotorasib for patients with advanced *KRAS G12C*-mutant non–small cell lung cancer, there is a new need to identify features associated with activity and toxicity in the real-world setting. This multicenter retrospective study examined clinical and genomic features associated with progression-free survival (PFS), overall survival (OS), and clinically significant toxicity among patients treated with sotorasib in routine practice.

Knowledge Generated

In this real-world analysis, patients with concurrent mutations in *KEAP1* experienced shorter PFS and OS with sotorasib, while there were no significant associations between concurrent *TP53* or *STK11* mutations and activity. In addition, high-grade toxicities, particularly hepatotoxicity, were almost exclusively associated with recent anti–PD-(L)1 therapy exposure before sotorasib.

Relevance

Careful consideration of patient genomics and recent systemic therapy exposures are required for management of sotorasib in the clinic. These results may also help inform ongoing KRAS G12C-directed clinical trials.

multiple other G12C-directed agents are currently under clinical development, including adagrasib,[9] which was recently granted accelerated approval by the US FDA, as well as GDC-6036,[10] LY3537982,[11] and JDQ443.[12]

Despite the activity of sotorasib demonstrated in clinical trials, there are currently no real-world data describing clinical activity and toxicities observed among patients treated with sotorasib as part of routine care to help guide adoption in the clinic. In addition, although patterns of acquired resistance to sotorasib have been identified, including development of subclonal secondary *RAS* alterations and bypass pathway alterations,[13] our understanding of the determinants of primary response or resistance to sotorasib remains limited. Concurrent inactivating *STK11* and *KEAP1* mutations have been associated with worse outcomes to anti–PD-(L)1 therapy in NSCLC,[14,15] and concurrent *KEAP1* mutations have been associated with shorter responses to both platinum-based chemotherapy and anti–PD-(L)1 therapy.[3] However, responses to sotorasib and adagrasib have been observed across *STK11/KEAP1* mutation status in clinical trials,[8,9] and the impact of comutation status on durability of response or OS has not been reported.

To identify clinical and genomic features associated with outcomes, we conducted a retrospective analysis of patients treated with sotorasib outside of the clinical trial setting. We also sought to explore the rate of clinically significant toxicities in a real-world population, and explore associations of pretreatment clinical characteristics with development of toxicity. Our results may help inform future clinical trials, provide insights into the optimal sequencing of sotorasib in the clinic, and may have implications for other KRAS G12C-directed agents currently under clinical development.

MATERIALS AND METHODS

Study Population

We retrospectively identified patients with advanced *KRAS G12C*-mutant NSCLC who initiated sotorasib outside of clinical trials between June 2021 and August 2022 at three institutions: Memorial Sloan Kettering Cancer Center (MSKCC), New York Presbyterian/Columbia University Irving Medical Center (Columbia), and NYU Langone Perlmutter Cancer Center (NYU), all in New York, NY. The study was approved as a retrospective research protocol by the MSKCC Institutional Review Board/Privacy Board.

Clinical Data and Immunogenomic Analyses

Clinical data, including demographics, clinicopathologic features, targeted next-generation sequencing (NGS) results, clinical and radiographic outcomes, and descriptions of toxicities, were abstracted. Genomic data describing the presence or absence of concurrent *TP53*, *STK11*, and *KEAP1* comutations were identified by the tissue NGS and plasma circulating tumor DNA platforms described in the Data Supplement (Supplementary Table S1). Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) tissue NGS samples (v5, v6, and v7) were analyzed for tumor mutational burden. Normalized mutation burden was calculated as the absolute mutation burden (number of nonsynonymous mutations/sample) divided by the genomic coverage for that sample as previously described.[16] When available, PD-L1 tumor cell immunohistochemistry results obtained before sotorasib initiation were included.

Clinical Outcomes

The clinical outcomes under investigation were real-world PFS (rwPFS), time on drug, OS, and real-world response rate by investigator assessment (rwRR). rwPFS was defined as the amount of time between sotorasib initiation and either radiographic worsening or clinical progression of disease as documented in the treating physician's notes. Patients who did not have documented clinical progression but in whom sotorasib was discontinued or changed for other reasons, including toxicity or physician/patient preferences, were censored at the date of last contact or the start date of the next treatment regimen. Time on drug was defined as the amount of time between the first date and last date of sotorasib treatment, and OS was defined as the amount of time between sotorasib initiation and death from any cause. To assess real-world response, the last computed tomography scan of the chest, abdomen, and/or pelvis and/or brain magnetic resonance imaging documenting, all known sites of disease before sotorasib initiation, was reviewed and compared with the results of the first corresponding scans obtained at least 6 weeks after sotorasib initiation. Scan comparisons for assessment of response rate and rwPFS were completed manually by investigators by adapting the PRISSMM framework,[17] a structured framework to assess changes in cancer status over time. On the basis of manual review of the impression section of radiology reports, we defined categories of rwRR to include improvement, defined by cancer improving/responding, stability, defined by stability/no change or mixed changes, or worsening, defined by cancer progressing/worsening/enlarging. Real-world response (response) was defined as radiographic improvement, and real-world disease control was defined as either radiographic improvement or stability. Assessment of changes in size of brain metastases were not included in assessment of rwRR, but were included as evidence of progression of disease if a new brain lesion was identified after initiation of treatment.

Toxicity

Medical records and results of routine laboratory testing were reviewed to identify treatment-related adverse events (TRAEs) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[18] Medical records were also reviewed to identify the incidence of sotorasib dose reduction because of TRAEs, and the incidence of sotorasib discontinuation because of TRAEs, as documented in the treating physician's notes.

Statistical Analyses

All statistical analyses were performed using GraphPad Prism v9 and the survival package in R version 4.2.2. For all proportions, 95% CIs were calculated by the Wilson/Brown method. rwPFS, time on drug, and OS were estimated using Kaplan-Meier methodology, with 95% CIs for median survival times reported. 95% CIs for odds ratios (ORs) were calculated using the Baptista-Pike method. Univariate group comparisons between Kaplan-Meier curves were performed using log-rank tests, and the Mantel-Haenszel method was used to determine hazard ratios (HRs) between groups. Fisher's exact test was used to compare proportions between univariate groups. All reported *P* values are two-sided, and significance level was set at $P = .05$ for all analyses.

RESULTS

Baseline Clinical and Pathologic Characteristics

A total of 105 patients with advanced *KRAS G12C*-mutant NSCLC treated with standard-of-care sotorasib were identified and included in the analysis (Table 1). The data cutoff date was January 15, 2023, and the median duration of follow-up was 13.1 months.

Clinical Activity of Standard-of-Care Sotorasib

Among patients in our cohort, the median rwPFS was 5.3 months (95% CI, 3.6 to 6.6 months; Fig 1A), the median time on drug was 7.2 months (95% CI, 4.6 to 10.4 months; Data Supplement [Supplementary Fig S1]), and the median OS was 12.6 months (95% CI, 8.3 months to could not be evaluated [NA]; Fig 1B). Among 102 of 105 patients evaluable for response assessment, the rwRR was 28% (95% CI, 20 to 37) and the real-world disease control rate was 74% (95% CI, 64 to 81). Notably, among 13 patients who were treatment-naïve in the advanced setting (median age of 60 years and median Eastern Cooperative Oncology Group performance status [ECOG PS] of 1 at initiation), median rwPFS was 11.0 months (95% CI, 7.3 months to NA) and median OS was not reached with a median duration of follow-up of 14.1 months.

Pathologic Features and Clinical Activity of Sotorasib

We next evaluated pathologic features associated with sotorasib activity in our cohort. Most notably, *KEAP1* comutations were associated with shorter rwPFS (HR for progression or death, 3.19; 95% CI, 1.46 to 6.95; $P = .004$; Data Supplement [Supplementary Fig S2]) and OS (HR, 4.10; 95% CI, 1.64 to 10.3; $P = .003$) to sotorasib (Fig 2), with a median rwPFS of 2.0 months (95% CI, 1.4 months to NA) and median OS of 5.2 months (95% CI, 3.0 months to NA) in the *KEAP1* comutation subgroup (N = 17). Among patients with and without *STK11* comutations, no significant differences in rwPFS (HR, 1.66; 95% CI, 0.91 to 3.04; $P = .098$) or OS (HR, 1.73; 95% CI, 0.79 to 3.77; $P = .168$) were observed. We observed no significant association of *TP53*, *STK11*, or *KEAP1* mutations with real-world response (Data Supplement [Supplementary Table S2]). In addition, we observed no significant differences in OS (HR, 1.01; 95% CI, 0.53 to 1.95; $P = .973$) or real-world response (OR, 0.76; 95% CI, 0.28 to 1.97; $P > .634$) among PD-L1–negative tumors compared with PD-L1–positive tumors, and no significant differences in OS (HR, 0.96; 95% CI, 0.41 to 2.32; $P = .944$) or real-world

TABLE 1. Clinical and Pathologic Characteristics of Patients at Baseline

Clinical and Pathologic Characteristic (N = 105)	No. of Patients (%)
Age at start of sotorasib, years	
Median (min, max)	70 (51, 90)
Sex	
Female	62 (59)
Male	43 (41)
Race	
White or Caucasian	85 (81)
Black or African American	6 (6)
Asian	4 (4)
Hispanic	3 (3)
Other	3 (3)
Not available	4 (4)
Smoking status	
Current	11 (10)
Former	92 (88)
Never	2 (2)
ECOG PS at start of sotorasib	
Median (min, max)	1 (0, 4)
0-1	64 (61)
2	19 (18)
3+	3 (3)
Not available	19 (18)
Presence of previous brain metastases	
Untreated	7 (7)
Treated	28 (27)
No	70 (67)
Histologic subtype	
Adenocarcinoma	93 (89)
Squamous cell carcinoma	1 (1)
Large cell neuroendocrine carcinoma	4 (4)
Other histologies	7 (7)
No. of previous lines of systemic therapy for advanced disease	
Median (min, max)	1 (0, 5)
0	13 (12)
1	59 (56)
2	19 (18)
3+	14 (13)
Previous systemic therapy exposure	
Previous platinum-based chemotherapy	77 (73)
Previous anti–PD-1 or anti–PD-L1 therapy	86 (82)
PD-L1 IHC (22C3 or E1L3N)	
0%	43 (41)
1%-49%	19 (18)
>49%	24 (23)
Not available	19 (18)
TMB, Mut/Mb	
≤10	39 (37)
>10	13 (12)
Not available	53 (50)
KRAS G12C comutation status	
Presence of TP53 mutation	40/73 (55)
Presence of STK11 mutation	25/78 (32)
Presence of KEAP1 mutation	17/78 (22)

NOTE. PS scores on the ECOG scale range from 0 to 5, with higher numbers indicating greater disability.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; Mut/Mb, mutations per megabase; PS, performance status; TMB, tumor mutational burden.

response (OR, 0.92; 95% CI, 0.23 to 3.14; $P > .999$) among tumor mutational burden (TMB) ≤ 10 tumors compared with TMB > 10 tumors (Data Supplement [Supplementary Fig S3]).

Sotorasib Toxicity and Associations With Recent Previous Lines of Therapy

We next evaluated the incidence of, and features associated with, clinically significant toxicity from sotorasib administration. Almost all patients in our cohort initiated sotorasib at a dose of 960 mg once daily (102 of 105 patients; 97%). The most common grade 3 (G3) or higher TRAEs were elevated liver function tests (Table 2), and the most common reasons for TRAE-related discontinuation of therapy were elevated liver function tests (observed in 86% of discontinuations) and diarrhea (21% of discontinuations).

We first aimed to explore clinical features of patients who were predisposed to development of sotorasib toxicity. In particular, we explored whether previous exposure to anti–PD-(L)1 therapy was associated with G3 or higher (G3+) TRAEs to sotorasib and/or TRAE-related discontinuation of treatment. Notably, 15 of 16 cases of G3+ sotorasib-related TRAEs in our cohort were observed in patients with previous anti–PD-(L)1 therapy exposure, with 15 of 86 (17%) of patients with previous anti–PD-(L)1 therapy exposure experiencing G3+ sotorasib TRAEs. Of the 19 anti–PD-(L)1 therapy-naïve patients, only one experienced a G3+ sotorasib TRAE (Fig 3A). In addition, all 14 patients who experienced TRAE-related sotorasib discontinuation had previously been treated with anti–PD-(L)1 agents. By contrast, previous platinum-based chemotherapy did not appear to be associated with development of G3+ sotorasib TRAEs (no previous platinum exposure: five of 28 patients with G3+ TRAEs [18%], previous platinum exposure: 11 of 77 patients with G3+ TRAEs [14%]; OR, 0.77; $P = .760$), or

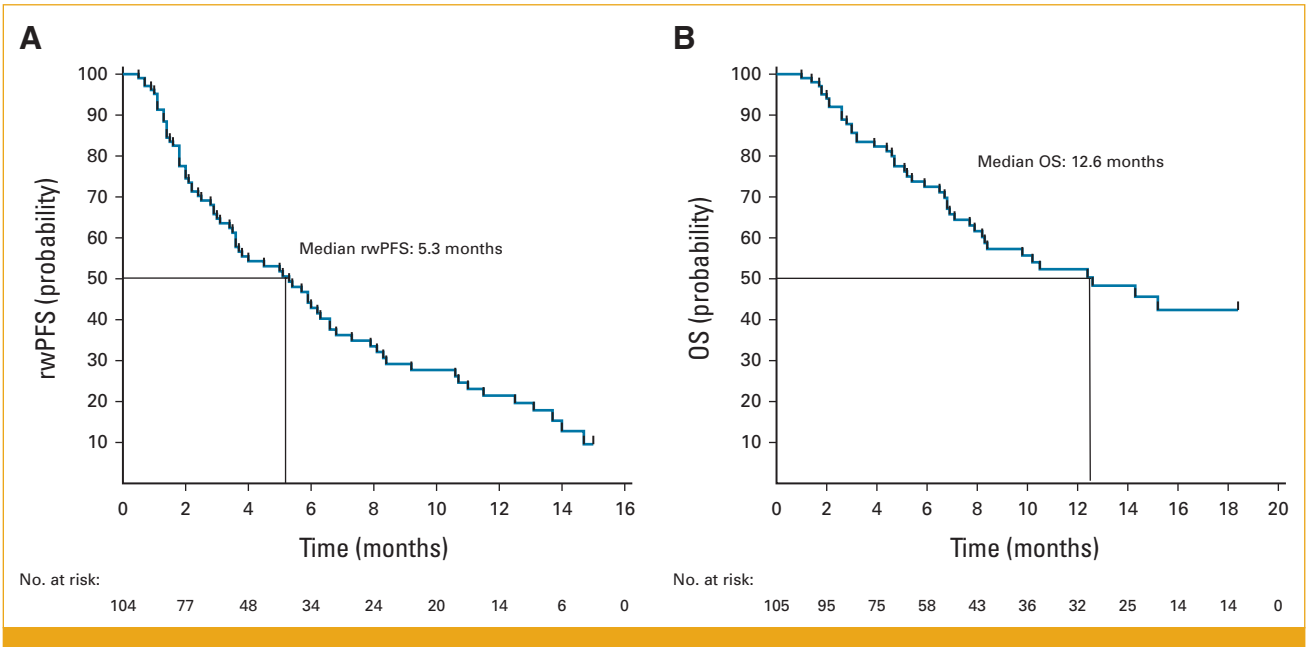

FIG 1. rwPFS and OS among patients who received sotorasib for advanced *KRAS G12C*-mutant Non–Small Cell lung cancer. Kaplan-Meier curve of (A) rwPFS and (B) OS among evaluable patients. Tick marks indicate censored data. OS, overall survival; rwPFS, real-world progression-free survival.

TRAE-related sotorasib discontinuation (no previous platinum exposure: five of 28 patients with TRAE-related sotorasib discontinuation [18%], previous platinum exposure: nine of 77 patients with TRAE-related sotorasib discontinuation [12%]; OR, 0.61; $P = .517$).

We then sought to identify the aspects of previous anti–PD-(L)1 therapy exposure that predispose patients to toxicity from sotorasib. Among the 86 patients with previous anti–PD-(L)1 therapy exposure, 25 (29%) had previously experienced an immune-related adverse event (IRAE) as defined by ASCO guidelines.[19] Previous IRAEs were not associated with development of G3+ sotorasib-related adverse events (no previous IRAEs: 10 of 61 with G3+ sotorasib TRAEs [16%], previous IRAEs: five of 25 with G3+ sotorasib TRAEs [20%]; OR, 1.28; $P = .757$). We did, however, observe a striking association between the proximity of the last dose of anti–PD-(L)1 therapy to sotorasib initiation and development of

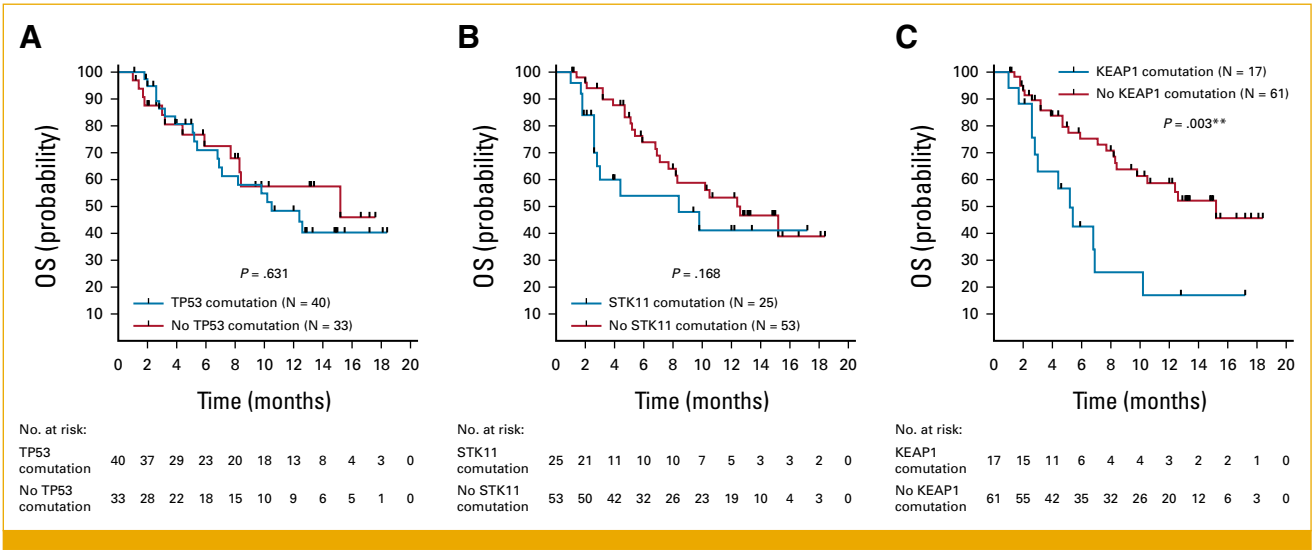

FIG 2. Influence of concurrent *TP53*, *STK11*, and *KEAP1* mutations on OS to sotorasib. Kaplan-Meier curves of OS among patients with *KRAS G12C*-mutant Non–Small Cell lung cancer with or without concurrent mutations in (A) *TP53*, (B) *STK11*, and (C) *KEAP1*. Tick marks indicate censored data. $^{**}P < .01$ for log-rank test between curves. OS, overall survival.

TABLE 2. Incidence of TRAEs, TRAE-Related Dose Reductions, and TRAE-Related Treatment Discontinuation Among Patients Treated With Sotorasib

Event	No. of Patients (%)
TRAEs	
Grade 1-2	43 (41)
Grade 3	16 (15)[a]
Grade 4	1 (1)
Grade 3 TRAEs	
ALT increased	9 (9)
Alkaline phosphatase increased	6 (6)
AST increased	6 (6)
Anemia	2 (2)
Pneumonitis	2 (2)
Blood bilirubin increased	1 (1)
Diarrhea	1 (1)
Pancreatitis	1 (1)
Grade 4 TRAEs	
Blood bilirubin increased	1 (1)
TRAE leading to dose reduction	16 (15)
TRAE leading to discontinuation of therapy	14 (13)[b]
AST, ALT, alkaline phosphatase, or bilirubin increased	12 (11)
Diarrhea	3 (3)
Nausea	2 (2)
Pancreatitis	1 (1)
Anemia	1 (1)
Pneumonitis	1 (1)
Headache	1 (1)

NOTE. All TRAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
Abbreviation: TRAE, treatment-related adverse event.
[a]Some patients had multiple grade 3 TRAEs.
[b]Some patients had multiple TRAEs leading to discontinuation of therapy.

toxicity from sotorasib; 15 of 16 cases of G3+ sotorasib TRAEs and 13 of 14 cases of sotorasib TRAE-related treatment discontinuation were observed among patients with previous anti–PD-(L)1 exposure within 12 weeks of sotorasib initiation. Among the 53 patients with anti–PD-(L)1 therapy exposure within 12 weeks of initiation of sotorasib, 15 (28%) experienced G3+ sotorasib-related TRAEs, whereas there were no cases of G3+ sotorasib AEs among the 33 patients with last anti–PD-(L)1 exposure more than 12 weeks before initiation of sotorasib (Fig 3B).

Among the 15 of 16 patients who experienced a G3+ TRAE after previous anti–PD-(L)1 therapy exposure (Table 3), patients received their last dose of anti–PD-(L)1 therapy a median of 4.6 weeks (range, 3.0 to 11.6 weeks) before sotorasib initiation, with only five of 15 patients having experienced a previous IRAE. Thirteen of these 15 patients experienced G3+ hepatotoxicity, with a median time to onset of hepatotoxicity of 6.4 weeks (range, 2.0 to 14.1 weeks). Among these 13 patients, five were treated with systemic steroids, with four experiencing clinical improvement, defined as improvement to grade 1 hepatotoxicity or better within 12 weeks of steroid initiation.

DISCUSSION

The accelerated approval of sotorasib for patients with advanced *KRAS G12C*-mutant NSCLC represented a meaningful advance in the emerging field of KRAS-directed targeted therapy. This approval has also provided an opportunity to evaluate the optimal sequencing of sotorasib in the context of other lines of therapy, and how sotorasib may be safely and effectively combined with other treatments, including platinum-based chemotherapy and/or anti–PD-(L)1 immunotherapy. To begin to address these questions, we performed a multicenter retrospective analysis of patients treated with sotorasib outside of the clinical trial setting.

Clinicians appeared to have prioritized sotorasib early in the course of care, with a median of one previous line of therapy among patients. In addition, patients in our study appeared relatively fit, with a majority of patients with an ECOG PS of 0-1 at initiation of sotorasib. Our results roughly correspond to the results of the recently presented randomized phase III study of sotorasib versus docetaxel in the second-line or later setting, in which sotorasib treatment in patients with a median of one previous line of therapy exhibited a RECIST objective response rate of 28% (95% CI, 22 to 35), median PFS of 5.6 months (95% CI, 4.3 to 7.8 months), and median OS of 10.6 months (95% CI, 8.9 to 14.0 months).[20]

Co-occurring genomic alterations underlie significant heterogeneity in disease biology and response to systemic therapy in patients with *KRAS*-mutant NSCLC, with *TP53*, *STK11*, and *KEAP1* the most commonly comutated genes in patients with *KRAS G12C*-mutant disease.[21] *STK11* and *KEAP1* comutations have previously been established as markers of resistance to anti–PD-(L)1 therapy in *KRAS*-mutant NSCLC,[14,15] and *KEAP1* comutations are associated with shorter responses to platinum-based chemotherapy in these patients.[3] However, the influence of these markers on clinical activity of KRAS-directed targeted therapies has remained unclear. In this cohort, *KEAP1* mutations were associated with shorter rwPFS and OS to sotorasib, whereas *STK11* mutations were not associated with statistically significant differences in rwPFS and OS. These results should continue to be evaluated in larger prospective studies and potentially be incorporated as stratification factors in future randomized clinical trials.

Most notably, our study sheds significant light on patients who are uniquely at risk for development of toxicity related to sotorasib. Recent anecdotal evidence and case reports[22] have suggested links between previous anti–PD-(L)1 therapy exposure and development of toxicity with sotorasib administration. We found clear associations between

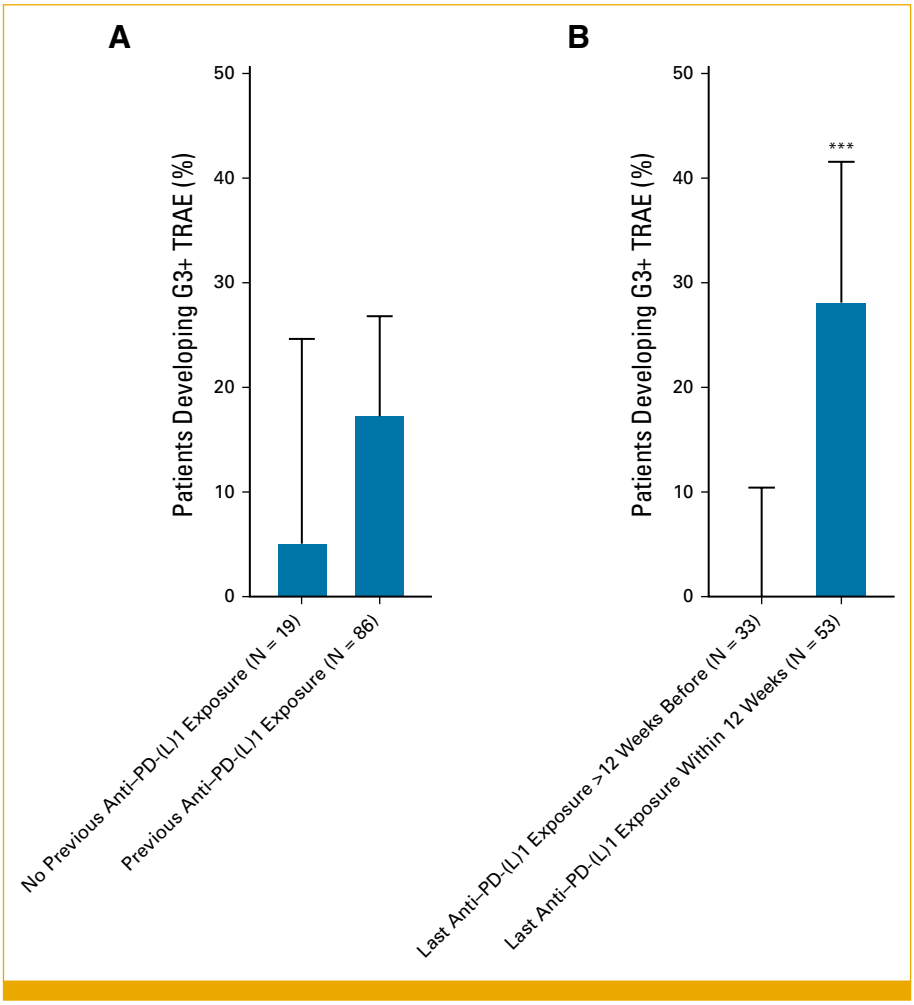

FIG 3. Influence of previous anti–PD-(L)1 therapy exposure on incidence of severe sotorasib-related adverse events. (A) Incidence of G3+ sotorasib-related adverse events among patients with no previous anti–PD-(L)1 exposure (1/19; 5%) and previous exposure (15/86; 17%). (B) Among patients with previous anti–PD-(L)1 exposure (N = 86 total), incidence of G3+ sotorasib-related TRAEs among patients with last anti–PD-(L)1 exposure more than 12 weeks before initiation of sotorasib (0/33; 0%) and among patients with last exposure within 12 weeks of initiation of sotorasib (15/53; 28%). ***P < .001 for Fisher's exact test. G3+, grade 3 or higher; TRAE, treatment-related adverse event.

previous anti–PD-(L)1 therapy exposure, specifically within 12 weeks of initiation of sotorasib, and both G3+ TRAEs to sotorasib and TRAE-related sotorasib discontinuation, with treatment-related hepatotoxicity the most common G3+ TRAE. Our results appear analogous to previous observations of severe adverse events seen with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors administered shortly after anti–PD-(L)1 therapy,[23] and help further contextualize the increased toxicity signals recently observed with combination sotorasib and pembrolizumab or atezolizumab.[24] Awareness of these findings may assist clinicians with optimal timing and sequencing of these therapies in the clinic and devising appropriate follow-up plans after sotorasib initiation among patients who are started shortly after exposure to anti–PD-(L)1 therapies. In addition, independent of the effects of dose reduction or discontinuation, whether hepatotoxicity encountered shortly after anti–PD-(L)1 therapy exposure is responsive to steroid administration is an important future consideration. Finally, whether these phenomena are observed with other KRAS G12C inhibitors, including the newly approved adagrasib, remains unclear.

Although this work is limited by the retrospective nature of the analysis and modest sample size, it reflects outcomes from real-world management of patients from multiple institutions. In this report, retrospective response assessment was completed manually by investigators using the PRISSMM framework[17] rather than RECIST version 1.1 measurements. Nevertheless, we observed relative concordance between rwPFS and time on drug in our study, and assessments linked to treatment duration in lung cancer have been identified as reasonable proxies for RECIST-defined PFS.[25] An additional challenge of real-world

TABLE 3. Patients Who Developed Grade 3 or Higher TRAEs to Sotorasib

Patient No.	Most Recent Anti–PD-(L)1 Regimen	Total Time on Anti–PD-(L)1 Therapy (weeks)	Previous IRAE to Anti–PD-(L)1 Therapy	Time Between Last Anti–PD-(L)1 Dose and D1 Sotorasib (weeks)	Time to Onset of TRAE After D1 Sotorasib (weeks)	Sotorasib TRAE	Sotorasib Dose Modification
1	None	NA	NA	NA	7.0	Anemia, G3	None
2	Carboplatin, paclitaxel, pembrolizumab	18.0	None	3.9	14.1	Hepatotoxicity, G3	Reduction
3	Carboplatin, pemetrexed, pembrolizumab	114.4	None	4.7	6.4	Hepatotoxicity, G3	Discontinuation
4	Carboplatin, pemetrexed, pembrolizumab	24.4	None	6.3	5.7	Hepatotoxicity, G4	Discontinuation
5	Atezolizumab	118.0	Pneumonitis, G1	4.6	77.7	Pneumonitis, G3	None
6	Carboplatin, paclitaxel, pembrolizumab	71.0	Colitis, G1	8.1	6.9	Hepatotoxicity, G3	Discontinuation
7	Pembrolizumab	39.7	Arthralgias, G1	7.9	3.4	Hepatotoxicity, G3; pancreatitis, G3	Discontinuation
8	Carboplatin, pemetrexed, pembrolizumab	25.0	None	3.1	11.6	Anemia, G3; pneumonitis, G3	Discontinuation
9	Pemetrexed, pembrolizumab	10.0	None	5.3	3.4	Hepatotoxicity, G3	Discontinuation
10	Carboplatin, pemetrexed, pembrolizumab	15.0	None	5.0	4.9	Hepatotoxicity, G3	Discontinuation
11	Carboplatin, pemetrexed, pembrolizumab	3.0	None	3.0	9.0	Hepatotoxicity, G3	Discontinuation
12	Carboplatin, pemetrexed, pembrolizumab	15.0	Arthralgias, G1	3.6	7.4	Hepatotoxicity, G3	Reduction
13	Carboplatin, pemetrexed, pembrolizumab	3.6	None	4.1	5.1	Hepatotoxicity, G3	Discontinuation
14	Durvalumab	60.4	None	11.6	8.0	Hepatotoxicity, G3	Reduction
15	Pembrolizumab	3.0	None	3.7	2.0	Hepatotoxicity, G3	Reduction
16	Pembrolizumab	19.0	Hepatotoxicity, G3	3.9	7.3	Hepatotoxicity, G3	Discontinuation

NOTE. Hepatotoxicity was defined by the presence of AST, ALT, alkaline phosphatase, or bilirubin elevation. The highest grade of toxicity experienced by each patient is reported. All TRAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Abbreviations: G1, grade 1; G2, grade 2; G3, grade 3; IRAE, immune-related adverse event; NA, not available; TRAE, treatment-related adverse event.

outcome analyses can be uniform collection of toxicity data. Although the frequency of TRAE-related sotorasib dose reductions and discontinuations identified in our study was similar to frequencies observed in the CodeBreaK100 study,[8] the documented frequency of grade 1-2 and G3 TRAEs was lower in our study, which may reflect differences in documentation of toxicities between clinical trial and real-world settings.

Our study suggests that sotorasib is associated with modest single-agent activity in the real-world setting, and that assessment of *KRAS* comutation status and recent exposure to anti–PD-(L)1 therapy are important considerations before sotorasib administration in the clinic. Further exploration of best strategies to mitigate toxicity is crucial to optimize targeted therapies for patients with advanced NSCLC harboring *KRAS G12C* mutations.

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Deidentified individual participant data, including clinical and genomic data, can be made available upon request.

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