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Remarkable intracranial response to sotorasib in a patient with $KRA_S^{G12C}$-mutated lung adenocarcinoma and untreated brain metastases: A case report

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Abstract

Sotorasib is a \( KRAS^{G12C} \) inhibitor that recently received approval for use in locally advanced or metastatic \( KRAS^{G12C} \)-mutated non-small cell lung cancer. CodeBreaK100, the phase II clinical trial leading to the approval of sotorasib, excluded patients with untreated brain metastases; there have been no reports describing efficacy of sotorasib on untreated brain metastases. We present a case of a patient with active untreated brain metastases with resulting disorientation and weakness who demonstrated radiographic response and complete resolution of neurologic symptoms with sotorasib. Our case illustrates the intracranial activity of sotorasib, but additional studies are needed to characterize the intracranial response rate and duration of response in these patients.
### Introduction

Activating Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations are found in approximately 20%-35% of lung adenocarcinoma, making it one of the most prevalent genomic drivers in non-small cell lung cancer (NSCLC).\(^1\) Mutations in KRAS lead to cellular dysregulation and oncogenic transformation of signaling pathways, resulting in uncontrolled cell proliferation. While targeted therapy for other activating drivers in NSCLC has become standard, efforts to target KRAS mutations in NSCLC have been disappointing until recently. Sotorasib (AMG 510, Amgen, Thousand Oaks, CA) is a small-molecule that specifically binds inactive GDP-bound $\text{KRAS}^{\text{G12C}}$, trapping it in an inactive state and preventing oncogenic signaling.\(^2\)

Sotorasib was granted accelerated approval by the US Food and Drug Administration (FDA) in May 2021 for $\text{KRAS}^{\text{G12C}}$-mutated locally advanced or metastatic NSCLC after at least one line of systemic therapy based on the results of the phase II CodeBreaK100 study. The objective response rate (ORR) was 37.1%, with a disease control rate (DCR) of 80.6% and a median duration of response (DoR) of 11.1 months.\(^3\) While the trial included patients with evidence of metastatic brain disease, patients with active, untreated brain metastases were excluded. Here, we report a case of $\text{KRAS}^{\text{G12C}}$-mutated NSCLC with active, untreated brain metastases, demonstrating profound clinical and radiographic response to sotorasib.

### Case Presentation

A 61-year-old man presenting with worsening headaches was found to have a presumed left occipital hematoma. A chest CT revealed a 4.0 cm right upper lobe (RUL) lung mass, and bulky right hilar and mediastinal lymphadenopathy. He underwent endobronchial ultrasound bronchoscopy with a transbronchial fine-needle aspiration of the right paratracheal and hilar
lymph nodes, which revealed poorly differentiated lung adenocarcinoma (Figure 1A). In the setting of subsequent progressive headaches and confusion, a repeat MRI of the brain showed a mildly rim-enhancing, left occipital lesion with mass effect that was increased in size compared to imaging two weeks earlier. He was treated with dexamethasone and subsequently underwent a surgical left occipital craniotomy with tumor resection. Pathology revealed metastatic poorly-differentiated adenocarcinoma of lung primary origin (Figure 1B). Tumoral PD-L1 expression (Dako 22C3) was high in both the brain and the lymph node at 80% and 90%, respectively. Blood-based next-generation sequencing (NGS; Guardant 360, Guardant Health, Redwood, CA) revealed a KRAS$^{G12C}$ mutation without other genomic alterations. Tissue-based NGS (Caris Life Sciences, Phoenix, AZ) of the right paratracheal node showed KRAS G12C, TP53 V157F, and ARID2 E101* mutations.

He received post-operative stereotactic radiosurgery to the cranial resection cavity and started treatment with pembrolizumab 200 mg every three weeks. An MRI of the brain obtained one month after initiation of pembrolizumab showed postsurgical changes without evidence of enhancing lesions. His clinical course was complicated by thyroiditis with progression to grade 2 hypothyroidism, for which he received thyroid replacement therapy. On restaging imaging, the RUL mass was stable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, following four cycles of pembrolizumab. Cycle five was delayed due to hospitalization for weakness and fatigue thought to be secondary to grade 3 immunotherapy-related hypothyroidism. His dose of thyroid replacement therapy was increased, and he was discharged after improvement with supportive care.

Within a week of hospital discharge, he presented with severe disorientation and profound weakness, prompting re-admission. Work-up for reversible causes of encephalopathy
was unrevealing. A repeat MRI of the brain revealed significant progression with innumerable brain metastases (Figure 2A, D) and leptomeningeal enhancement consistent with leptomeningeal disease, and the patient was subsequently initiated on corticosteroid therapy. Given these findings and the poor prognosis, his family elected for open access hospice care but agreed to a trial of sotorasib 960 mg daily, starting 2 months after his last dose of pembrolizumab. No further radiation to the brain was delivered. After 2 weeks of sotorasib, the patient had remarkable clinical improvement in his mental status and strength. An MRI of the brain after one month of sotorasib revealed clear radiographic improvement in the numerous enhancing lesions, with most lesions resolved or significantly smaller (Figure 2B, E). A CT of the chest at that time demonstrated a reduction in size of the RUL mass (Figure 3) and right hilar and subcarinal lymph nodes. The patient’s clinical course was complicated by the development of grade 3 transaminitis, which occurred 2 months after initiation of sotorasib. Sotorasib was held, and he was treated with a course of corticosteroids with improvement in the transaminitis. As he had a remarkable response to sotorasib, the patient was rechallenged at lower doses of sotorasib (720 mg daily, then later 480 mg daily). Upon each rechallenge, his transaminitis worsened, leading to permanent discontinuation of sotorasib. He received sotorasib for 3.5 months before discontinuation. A repeat brain MRI one month after discontinuation of sotorasib showed ongoing intracranial response (Figure 2C, F). Six weeks after sotorasib discontinuation, the patient began third-line carboplatin, pemetrexed, and bevacizumab and remains on third-line therapy at the time of submission. A timeline of the patient’s treatment course is summarized in Figure 4.

Discussion
Here, we present a patient with $KRAS^{G12C}$-mutated lung adenocarcinoma with metastasis to the brain who experienced a remarkable intracranial response to sotorasib. To the best of our knowledge, this is the first report to demonstrate activity of sotorasib for symptomatic, untreated brain metastases. The patient exhibited clinical improvement shortly after initiation of sotorasib, with imaging demonstrating an objective response to sotorasib.

Brain metastases are a relatively common occurrence in $KRAS^{G12C}$-mutated NSCLC. A retrospective analysis from Massachusetts General Hospital identified 149 patients with $KRAS^{G12C}$-mutant NSCLC; 60 (40%) of those patients developed brain metastases. The 12-month cumulative incidence of brain metastases from the time of diagnosis of metastatic $KRAS^{G12C}$-mutant NSCLC was 48.2%. The majority of brain metastases were identified at the time of initial diagnosis.

Limited data on central nervous system (CNS) activity of sotorasib in metastatic NSCLC exists. In the CodeBreaK 100 trial, patients with active, untreated brain metastases were excluded. In a post-hoc analysis of CodeBreaK100, patients with stable brain metastases previously treated with radiation or surgery had a median overall survival (OS) of 8.3 months and a median progression-free survival (PFS) of 5.3 months with disease control rate of 77.5% and median duration of response of 11.1 months. Of note, 14 of 16 patients (87.5%) with evaluable brain metastases achieved intracranial disease control. These results suggest patients with previously-treated brain metastases benefit from sotorasib with continued intracranial stabilization, but the effect of sotorasib on treatment-naive metastatic disease has not been determined. In CodeBreaK 101 (NCT04185883), there is a cohort for patients with active, untreated brain metastases, which will help to elucidate the intracranial activity of sotorasib.
Adagrasib (MRTX849, Mirati Therapeutics, San Diego, CA) is another small molecule
KRASG12C inhibitor which shows promise for use in KRASG12C-mutated NSCLC with brain
metastases. Adagrasib demonstrated cerebrospinal fluid penetration and extended survival in
preclinical models, as well as brain metastasis regression in 2 patients with NSCLC and
untreated brain metastases. In the KRYSTAL-1 trial, 25 patients with active, untreated CNS
metastases received adagrasib. The intracranial ORR per modified RANO criteria by blinded
independent central review (BICR) was 32%, suggesting CNS specific activity of adagrasib.
Prospective data are needed to confirm these early signals of efficacy and to determine the depth
and durability of CNS response to small molecule inhibitors in KRASG12C-mutated NSCLC.

The continued use of sotorasib in our patient was limited due to grade 3 immune-
mediated hepatitis. Begum et al. first reported a case of severe immune checkpoint-mediated
hepatotoxicity triggered by sotorasib in a patient who had received pembrolizumab 14 weeks
prior to sotorasib initiation. Grade 3 or higher transaminitis was reported at a rate of
approximately 6% in CodeBreaK 100 and 8% in CodeBreaK 200, while occurring at a rate as
high as 31% in a retrospective study of 32 patients who had received sotorasib within 90 days of
immune checkpoint therapy. Clear guidance for the management of hepatotoxicity with
sotorasib is an unmet area of need, particularly in patients who have received previous immune
checkpoint inhibitor therapy.

Conclusion

In summary, our case demonstrates the intracranial activity of sotorasib in a patient with
KRASG12C-mutated NSCLC and active, untreated brain metastases complicated by
leptomeningeal disease. Further studies are needed to understand the intracranial response rate and duration of response associated with sotorasib in patients with $KRAS^{G12C}$-mutated NSCLC.
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Figure legends

Figure 1. Hematoxylin and eosin (H&E) stain of cell block preparation of the right paratracheal lymph node (A), showing solid sheet/nest of malignant cells, some with intracytoplasmic mucin. H&E stain of sections from the right parietal brain tumor (B) demonstrating malignant cells with large pleomorphic nuclei, frequent multinucleation, and increased mitoses. Tumor cells are positive for cytokeratin 7, TTF-1 and Napsin A (not pictured), supporting metastasis from pulmonary primary origin. The adjacent brain parenchyma shows abundant reactive changes including reactive gliosis, chronic inflammation, and patchy hemorrhage.

Figure 2. Magnetic-resonance imaging, T1 post-contrast phase, axial brain. Pre-sotorasib (A, D), one month after sotorasib treatment (B, E), and four months after sotorasib initiation (C, F). Numerous metastases demonstrated in multiple levels in A and D, with improvement in B, C, E and F, respectively.

Figure 3. Computed tomography contrast-enhanced axial scan of the right upper lobe lung mass in the lung window (A and B) and soft tissue window (C and D). Pre-sotorasib (A, C; 4.0 x 2.1 cm) and one month after sotorasib (B, D; 3.2 x 1.5 cm) treatment.

Figure 4. Timeline of the patient’s treatment course spanning from the initial diagnosis to most recent follow up at time of the report. PemCBev: carboplatin, pemetrexed, bevacizumab.
References


Figure 2

Pre-sotorasib | 1 month after sotorasib | 4 months after sotorasib

A | B | C

D | E | F
Initial diagnosis
KRAS G12C
PD-L1 80-90%

Pembrolizumab
4 months
RT to cranial resection cavity

Sotorasib
3.5 months
960 mg QD
720 mg QD
480 mg QD

PemCBev
2 months +

Left occipital craniotomy