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CASE REPORT

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Mixed response to the first-line treatment of KRAS G12C inhibitor, sotorasib, in non-small cell lung cancer: A brief report

Jiao Yang[1] | **Jie Huang**[1] | **Gongjun Yuan**[2] | **Xiao-Cheng Lin**[1,3] | **Hua-Jun Chen**[1] | **Jin-Ji Yang**[1,3]

[1]Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

[2]Department of Radiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

[3]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Correspondence
Jin-Ji Yang, Division of Pulmonary Oncology, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, 106 Zhongshan 2nd Road, Guangzhou 510080, China.
Email: yangjinji@gdph.org.cn

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Key Clinical Message

One Kirsten Ras (*KRAS*) G12C mutated non-small cell lung cancer (NSCLC) patient had improved poor performance status and obtained mixed response with the first-line KRAS-targeted treatment of sotorasib. After disease progression, partial response was achieved with chemotherapy plus immunotherapy. *KRAS* G12C mutated immunoenvironment in NSCLC may favor the immunotherapy.

Abstract

KRAS is one of the most commonly mutated genes, which used to be untargetable. The phase II CodeBreak 100 trial revealed 6.8-month median progress-free survival (PFS) and 12.5-month overall survival (OS) in previously treated *KRAS* G12C-mutant NSCLC patients treated with KRAS inhibitor, sotorasib. The specimens of the brain, lymph node (LN), and blood from the patient were analyzed by next-generation sequencing. Hematoxylin and eosin staining and immunohistochemistry were performed for pathological characterization. Computed tomography (CT) and magnetic resonance imaging (MRI) scan were used for treatment response evaluation. The patient was diagnosed in a bad Eastern Cooperative Oncology Group performance status (ECOG-PS) with metastatic *KRAS* G12C-mutated lung adenocarcinoma who had achieved mixed response to sotorasib as the first-line treatment. Although 5-month PFS of the treatment with sotorasib was not surprising, the patient achieved significantly improved ECOG-PS score from 4 to 1. Subsequently, partial response (PR) was achieved with the treatment of pemetrexed plus pembrolizumab. This case highlights superior efficacy of first-line treatment with sotorasib for the advance untreated *KRAS* G12C-mutant

patients. The high efficacy of the treatment with chemotherapy plus immunotherapy revealed that immunoenvironment of *KRAS* G12C-mutated patient may favor the immunotherapy.

KEYWORDS

KRAS inhibitor, KRAS-mutated NSCLC, mixed response, performance status, sotorasib

1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the world.[1] Kirsten Ras (*KRAS*) is one of the most commonly mutated genes in non-small cell lung carcinoma (NSCLC). KRAS used to be untargetable because of its picomolar affinity for GTP and non-favorable direct binding sites. In 2013, one secret pocket beneath the effector in switch-II region was identified.[2] KRAS (G12C) inhibitors, irreversibly binding to this pocket, allosterically alter the native nucleotide preference to favor GDP over GTP.[2] KRAS G12C inhibitors, ARS-853 and ARS-1620, were reported to significantly inhibit tumor cell growth in *KRAS* G12C-mutant lung cancer cells.[3] Comparably, sotorasib (AMG 510) showed even better inhibition of downstream MAPK signaling pathway than ARS-853 and ARS-1620 in mice.[3] Phase II CodeBreak 100 trial revealed that sotorasib achieved 37.1% objective response rate (ORR) and 80.6% disease control rate (DCR) in previously treated advanced *KRAS* G12C-mutated NSCLC patients.[4] However, the clinic trials set very strict exclusive rules and only previously treated patients with good performance status would be recruited in the ongoing KRAS G12C inhibitors related clinic trials. For the *KRAS* G12C-mutated NSCLC patients excluded from the trails, much more efforts and related information are urgently needed. Here we report that the first case of one patient was diagnosed metastatic *KRAS* G12C-mutated lung adenocarcinoma with ECOG-PS score of 4 and obtained mixed response to sotorasib in the first-line treatment.

2 | METHODS

Pathology was confirmed by hematoxylin and eosin staining and tissue-specific markers. Next-generation sequencing (NGS) of the tumor DNA from the brain tissue and the LN were conducted, respectively, at Guangdong Provincial People's Hospital using 520-gene panel (Illumina) and NGS of the cell-free tumor DNA (ctDNA) from blood using 86-gene panel (cSMART2.0). Computed tomography (CT) and magnetic resonance imaging (MRI) scan were used for treatment response evaluation.

3 | RESULTS (CASE PRESENTATION)

In February 2022, a 68-year-old man, current heavy smoker, with unstable walking was diagnosed with metastatic adenocarcinoma of the right upper lung lobe with multiple pulmonary, regional LNs involvement, bilateral pleural effusion, single left adrenal grand metastasis, and single left cerebella metastasis (clinical staging: cT1b-N3M1c, IVB).

This patient was previously healthy and had no any chronic disease. He had once urocystitis and prostatitis long time ago. He admitted completely recovery of them in local clinics with some medicine. Furthermore, there was no familial precedent of pulmonary diseases or cancer.

The patient diagnosed with *KRAS* G12C-mutated NSCLC in very poor performance status was treated and evaluated at Guangdong Provincial People's Hospital. He provided written informed consent and permission for the usage of his tumor tissue.

MRI of the brain showed one 38 × 32 mm abnormal cerebellum mass was resected on February 28, 2022. Pathologic evaluations of cervical removed brain tissue and LN were both metastatic lung adenocarcinoma (Figure 1A). NGS of the tumor DNA from the resected brain tissue, the LN and the blood revealed a common *KRAS* p.G12C (c.34G>T) mutation without any other targetable genetic alteration.

After surgery, the patient was in delirium and a deep trance with ECOG-PS score of 4. According to the clinical guideline,[5] there was no standard therapy for him except best care support. The first-line platinum-based systematic chemotherapy was not appropriate treatment recommendation for him with ECOG-PS 4. The patient was personally resistant to any intravenous chemotherapy or immunotherapy. With his agreement, the patient started the treatment with orally sotorasib 960 mg daily since April 4, 2022.

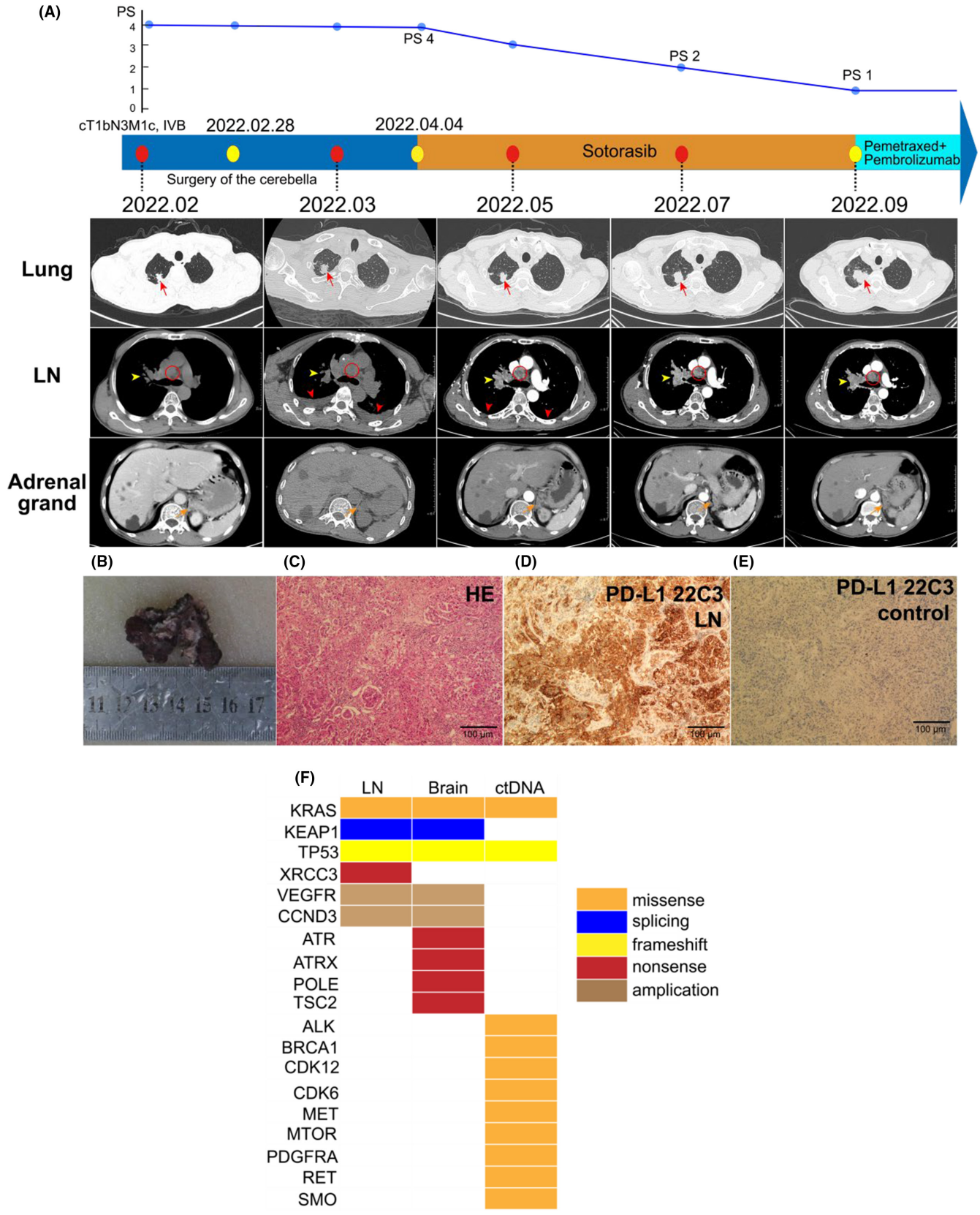

FIGURE 1 Radiological response to the treatment of sotorasib and pathological evaluation. (A) Bilateral pleural effusion had disappeared (red arrow head) and the R4 LN regressed (red circle). Primary lung lesion (red arrow), metastatic lung lesion (yellow arrow head), and metastatic adrenal grand (orange arrow) kept stabilized until September 2022. (B–E) Pathologic diagnosis result of the resected brain lesion was metastatic lung adenocarcinoma. The PD-L1 (22C3) staining in LN showed 80% positive PD-L1 expression. (F) NGS of the tumor DNA from the LN, brain, and blood revealed the *KRAS* G12C missense mutation. NGS, next-generation sequencing; LN, lymph node; ctDNA, cell-free tumor DNA.

Only mild rashes in the arms were observed shortly at the beginning of the sotorasib treatment. The evaluation of the response in May and July was both stable disease (SD) according to response evaluation criteria in solid tumors (RECIST v1.1).[6] Mixed response was observed during the treatment of sotorasib, and best overall response was SD (Figure 1). Bilateral pleural effusion disappeared since May 2022, and R4 LN regressed. Few regional LNs and adrenal grand metastasis kept stable before September. However, the primary lung lesion and few metastatic LNs progressed and new lesions appeared in the brain in September. Meanwhile the serum tumor markers, CEA, CYFRA21-1, and NSE, were all increased in September (Figure 2A). Due to progressive disease (PD), the therapy with sotorasib was stopped then.

During the 5-month PFS with the treatment of sotorasib, the ECOG-PS of the patient was gradually improved from 4 to 1. Immunohistochemistry staining for PD-L1 was 40% of brain tumor cells, and 80% of the LN tumor cells (Figure 1D). Therefore, treatment with pemetrexed plus pembrolizumab was initiated on September 21, 2022. The evaluation of the first 2 cycles was PR on November 14, 2022 (Figure 2B). The treatment was maintained till now and nicely tolerated. The recent assessment was confirmed PR on December 4, 2023. No obvious adverse was observed. It was already 14.3 months with the treatment of pembrolizumab. He was continuing benefit from the immunotherapy.

4 | DISCUSSION

KRAS mutation was found in 25%–50% NSCLC of Caucasian people, and 5%–15% among Asian population.[7–9] KRAS G12C variant was the most common mutated variant in NSCLC, which accounts for 40%–45%.[7,8] *KRAS* mutation was regarded as one poor prognostic factor, mainly because of poor response to the chemotherapy and EGFR TKI treatment.[9] Referring to the latest version of National Comprehensive Cancer Network (NCCN) guideline, the standard first-line treatment of the advanced *KRAS*-mutated NSCLC patients in ECOG-PS of 4 is best supportive care.[5]

The CodeBreak 100 trial (NCT03600883) great news with 32.2% ORR, median PFS 6.3 months in *KRAS* G12C mutated locally advanced or metastatic NSCLC.[10] Based on the excellent results, FDA granted accelerated approval to the first KRAS inhibitor, sotorasib, for the treatment of *KRAS* G12C mutated locally advanced or metastatic solid tumor in May 28, 2021. One metastatic NSCLC patient, who had end-stage renal failure with regular hemodialysis, had good response to the treatment

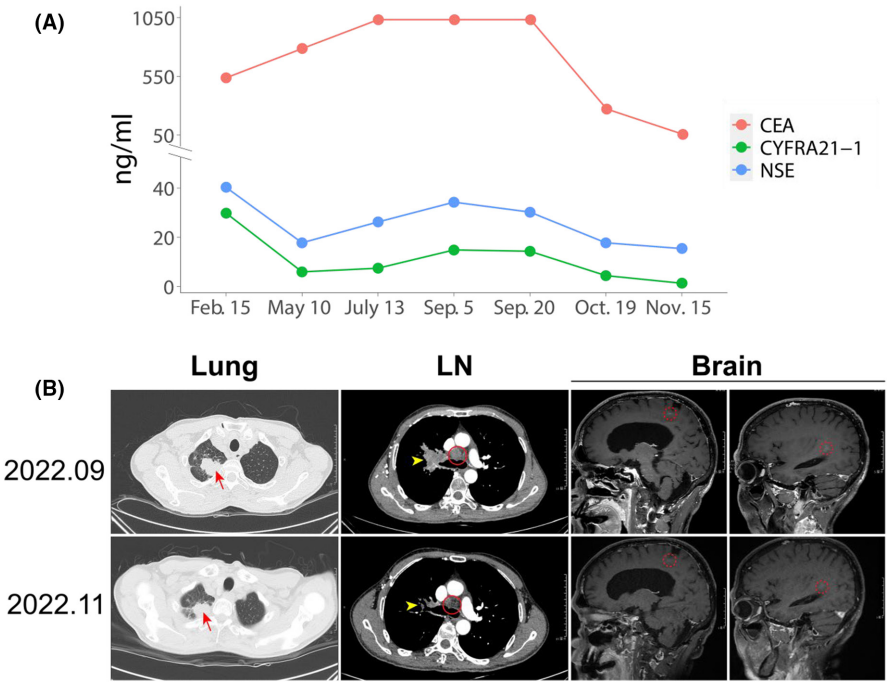

FIGURE 2 Dynamic changes of serum tumor markers and radiological examinations were observed with the chemotherapy plus immunotherapy. (A) The levels of CYFRA21-1 and NSE were decreased after the treatment of sotorasib, but gradually increased again afterwards until September. The level of CEA was constantly high before sharply reduced with chemotherapy plus immunotherapy in September. (B) Initiation of chemotherapy plus immunotherapy in September, partial response was achieved after 2-cycle treatment in November 2022. Primary lung lesion (red arrow), metastatic lung lesion (yellow arrow head), LN metastases (red circle), and metastatic brain lesions (red dotted circle) were all reduced. LN, lymph node.

with a reduced dose of sotorasib.[11] While that patient had good ECOG-PS score in early stage of NSCLC and was only observed for 5 weeks, which was not sufficient. As more investigations needed,[12] here we reported one case of advanced NSCLC with very poor ECOG-PS score, who had mixed response to the first-line treatment of sotorasib.

The patient in our case was diagnosed with ECOG-PS score of 4, who accepted the oral sotorasib as the first-line treatment. The brain of our patient was constantly stabilized for 5 months until new lesions appeared in the brain in September 2022. The post-hoc analysis of Codebreak 100 revealed the efficacy of sotorasib with intracranial complete responses and continuous intracranial stabilization in majority of previously treated NSCLC with evaluable brain metastasis.[13] Retrospective analysis and very less patients included made the conclusion in doubt. There was one report that one case with untreated active brain metastasis NSCLC had treatment response to sotorasib.[14] Consistence with the previous reports, our case indicated that sotorasib might have an efficacy to control in the brain. Recently a phase 1b trial investigation of sotorasib as monotherapy in subjects with active untreated brain metastasis NSCLC patients is ongoing (NCT04185883). And one branch of a phase I/II study is prepared to investigate sotorasib combined with MVASI in advanced *KRAS* G12C-mutant NSCLC with untreated brain metastases (NCT05180422). The results of these studies will provide more information of the intracranial activity of sotorasib soon.

Except the complete response of the bilateral pleural effusion and the regression of R4 LN, other lesions either kept stabilized or progressed after 5-month treatment of sotorasib. Intra-tumor heterogenesis may be the reason of the mixed response.[15] Through multi-regional sampling approach in previous studies, divergent genomic instability and their dynamics depicted the branch evolution and tumor development.[16] Sub-clonal evolution leads to the cancer cell population in heterogeneity and subsequently cause cancer relapse. As clonal evolution and tumor development, primary lung lesion and multiple metastatic tissues can gradually differ from each other and subsequently have distinct responses to the treatment. Therefore, mixed response was observed in our case. There will be promising results of sotorasib in the following CodeBreak 100 trial and CodeBreak 201 trial (NCT04933695) of KRAS inhibitors as first-line treatment.

After surgery, the patient in our case suffered severe delirium and deep trance. His ECOG-PS score was 4 before the start of sotorasib treatment. ECOG-PS score of the patient was astonishingly improved to 1 after 5-month PFS. Although the best evaluation of the treatment was SD, the vital ECOG-PS improvement won the patient a chance to receive chemotherapy plus immunotherapy in the following treatment. As PR was achieved in our case with immunotherapy, *KRAS* mutation might favor immunotherapy in some extent. However, the connection between *KRAS* mutation and immunotherapy needs to be explored.

5 | CONCLUSION

Overall, we present one case of poor ECOG-PS with advanced NSCLC achieved mixed response to sotorasib as first-line treatment. Sotorasib could be an optimal choice with its superior efficacy for the advance untreated *KRAS* G12C-mutant patients. These results of the ongoing sotorasib-related trials will shed more light on the optimal management of the advance untreated *KRAS* G12C-mutant patients in the near future.

AUTHOR CONTRIBUTIONS

Jiao Yang: Conceptualization; data curation; investigation; methodology; resources; visualization; writing – original draft; writing – review and editing. **Jie Huang:** Investigation; validation; visualization; writing – review and editing. **Gongjun Yuan:** Investigation; validation; visualization; writing – review and editing. **Xiao-Cheng Lin:** Validation; writing – review and editing. **Hua-Jun Chen:** Validation; writing – review and editing. **Jin-Ji Yang:** Investigation; supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All the authors declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

Data will be made available on request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Jin-Ji Yang https://orcid.org/0000-0003-0084-3908

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