



Complete response to sotorasib as neoadjuvant treatment in patient with locally advanced primary pulmonary sarcoma harboring *KRAS* mutation: a case report

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Background: Primary pulmonary sarcoma (PPS) is very rare relative to other subtypes of lung cancer. Therefore, evidence-based treatment options for PPS patients have remained unclear. Identification of actionable cancer driver mutations in patients with non-small cell lung cancer (NSCLC) has provided the chance to use targeted treatments and improve patient clinical outcomes. In addition to epidermal growth factor receptor (*EGFR*), the wide use of high-throughput genomic profiling with next-generation sequencing (NGS) has also identified other cancer driver genes such as Kirsten rat sarcoma (*KRAS*), human epidermal growth factor receptor 2 (*HER2*), and mesenchymal epithelial transition (*MET*).

Case Description: In our study, we reported a locally advanced PPS patient harboring *KRAS* G12C mutation. The clinical stage before neoadjuvant treatment was stage IIIB (c.T3N2M0). The direct *KRAS* G12C inhibitor sotorasib (AMG-510) was used as neoadjuvant treatment and the patient achieved complete response (CR). Then, the patient underwent video-assisted thoracoscopic surgery (VATS) with reserved spontaneous breathing for surgical resection. The pathological evaluation was indicative of pathological CR (pCR). Further follow-ups are required to evaluate the long-term clinical benefit of neoadjuvant treatment with sotorasib and surgical resection with VATS.

Conclusions: To our knowledge, it was the first study to use sotorasib for a PPS patient harboring *KRAS* G12C mutation in a neoadjuvant setting. Further follow-ups are required to evaluate the long-term clinical benefit of neoadjuvant treatment with sotorasib and surgical resection with VATS.

Keywords: Case report; primary pulmonary sarcoma (PPS); Kirsten rat sarcoma G12C (*KRAS* G12C); video-assisted thoracoscopic surgery (VATS); complete response (CR)

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Introduction

Primary pulmonary sarcoma (PPS) is a rare type of mesenchymal tumor of the lung (1). Previous studies of PPS have been limited to small retrospective cases; therefore, evidence-based treatment options for PPS patients remain undefined (2). In other common types of lung cancer, patients harboring actionable cancer driver mutations could benefit from personalized targeted therapies (3). Tyrosine

kinase inhibitors (TKIs) such as gefitinib, erlotinib, and osimertinib are usually recommended for non-small cell lung cancer (NSCLC) patients with common sensitizing mutations of epidermal growth factor receptor (*EGFR*), including exon 19 deletion, L858R, and T790M (3,4). In addition to *EGFR*, other driver genes such as Kirsten rat sarcoma (*KRAS*), human epidermal growth factor receptor 2 (*HER2*), and mesenchymal epithelial transition

(*MET*) also play important roles in cancer pathogenesis and progression (5). The widely used technique of high-throughput genomic profiling with next-generation sequencing (NGS) could be used to describe the mutation profile of different oncogenes and provide treatment suggestions (6).

In this study, we report the case of a patient with locally advanced PPS. The NGS test identified the *KRAS* G12C mutation. Sotorasib (AMG-510) is a small molecule that specifically and irreversibly inhibits the *KRAS* G12C mutant protein (7). In the case described herein, sotorasib was used as neoadjuvant treatment. The patient archived complete response (CR) and underwent video-assisted thoracoscopic surgery (VATS) with reserved spontaneous breathing for surgical resection. We present the following article in accordance with the CARE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4248/rc>).

Case presentation

A 75-year-old male patient presented to our hospital due to lung mass in the right upper lobe. The patient received positron emission tomography-computed tomography (PET-CT), which indicated atelectasis in the upper lobe of the right lung and enlarged lymph nodes in the mediastinum featured by hypermetabolism (*Figure 1A*). Bronchoscopy showed that the upper lobe of the right lung was obstructed by neoplasm. A biopsy indicated sarcoma with mucinous degeneration, but tumor differentiation remained undefined and undifferentiated sarcoma could not be excluded. After consultation with the pathologist, it was suggested that the tumor was PPS. Further multidisciplinary (MDT) discussion determined that the tumor was unresectable, therefore immune checkpoint inhibitor (ICI) in combination with chemotherapies were used as the neoadjuvant treatment. The clinical stage before neoadjuvant treatment was stage IIIB (c.T3N2M0). From 5 August to 7 August 2021, pembrolizumab 200 mg in combination with nab-paclitaxel 300 mg and carboplatin 500 mg were administered to the patient. After one treatment cycle, no obvious change in tumor lesion was observed (*Figure 1B*). The treatment response was assessed as stable disease (SD).

The patient underwent an NGS test covering 520 cancer-related genes to identify potential actionable therapeutic targets. The NGS analysis identified genetic alterations including *KRAS* G12C, *PTEN* G165fs, *TP53* R273S,

FGFR1 copy number amplification, and *MYC* copy number amplification. The tumor mutation burden (TMB) was 8.97 mutations/Mb and the status of microsatellite instability (MSI) was stable. Given the presence of *KRAS* G12C mutation, neoadjuvant treatment of the patient was switched to sotorasib. The dosage of sotorasib was initiated at 480 mg per day. After 1 week, the dose was increased to 720 mg per day. The subsequent CT scan indicated that the tumor lesion in upper lobe of right lung had disappeared, and the obstruction of lung tissue had re-dilated (*Figure 1C*). The patient achieved CR after 4 weeks of sotorasib treatment. In total, the patient received sotorasib for 8 weeks. No adverse events were observed during treatment. On 22 November 2021, the bronchoscope observed neoformation in the intersegmental bronchial crest of the upper lobe of the right lung. The CT scan indicated that the hypermetabolic lesion had disappeared (*Figure 1D*). The most recent follow-up in February 2022 indicated that the patient has remained disease-free (*Figure 1E*). The biopsy indicated no structural staining, fibrous hyperplasia, or tumor cells (*Figure 2*). The size of the lymph nodes in the mediastinum remained unchanged and the metabolic status was slightly decreased, which was likely to be inflammatory reactive hyperplasia. The yc.stage after neoadjuvant treatment was yc.T0N0M0. No contraindications for surgical resection were observed.

On 29 November 2021, the patient underwent right upper lobectomy and lymph node dissection. The preoperative assessment indicated adequate cardiopulmonary function, as well as heart enlargement and aortic and coronary artery wall calcification. During VATS-based surgical resection, the patient was able to retain spontaneous breathing instead of endotracheal intubation. The patient was discharged after surgery. No tumor residuals or metastasis were observed in the lung and lymph nodes during postoperative pathological evaluation (*Figure 2*) and the yp.stage was yp.T0N0M0, which indicated that the patient had achieved pathological CR (pCR). The carcinoembryonic antigen (CEA) level had decreased from 8.79 ng/mL (before surgery) to 5.93 ng/mL (after surgery). The disease-free survival (DFS) after surgery was 3 months and the overall survival (OS) was 6 months. The treatment and follow-up timeline of the patient since diagnosis is summarized in *Figure 3*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for

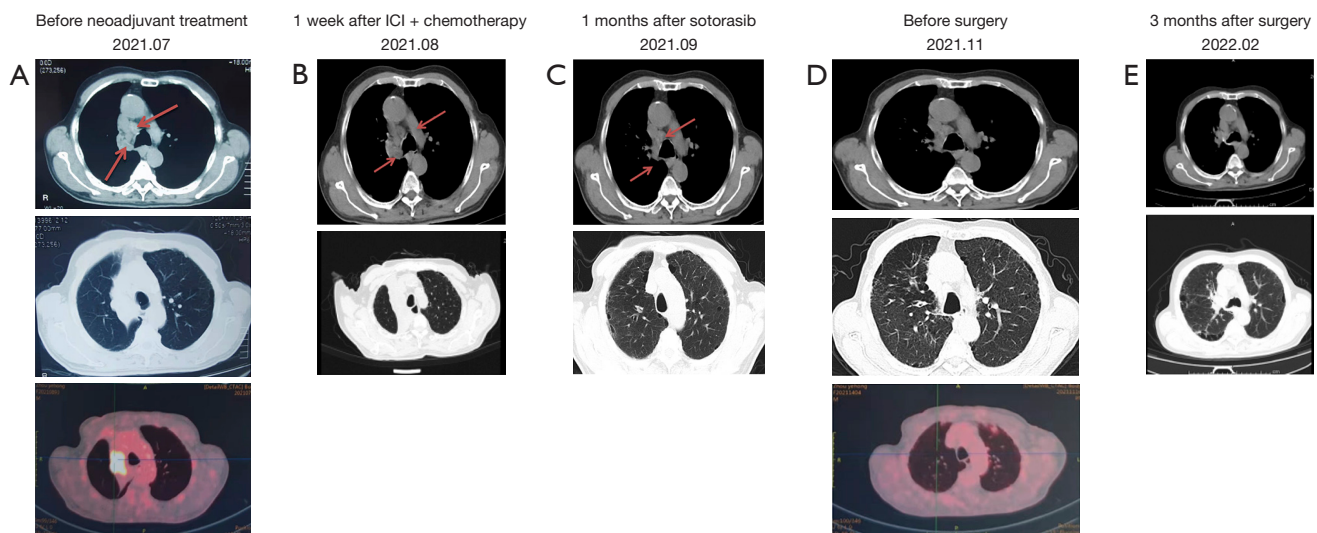


Figure 1 Clinical evaluation of the patient by CT and PET-CT. (A) Before neoadjuvant treatment; (B) 1 week after ICI + chemotherapy; (C) 1 month after sotorasib; (D) before surgery; (E) 3 months after surgery. Red arrows, tumor lesions. ICI, immune checkpoint inhibitor; CT, computed tomography; PET, positron emission tomography.

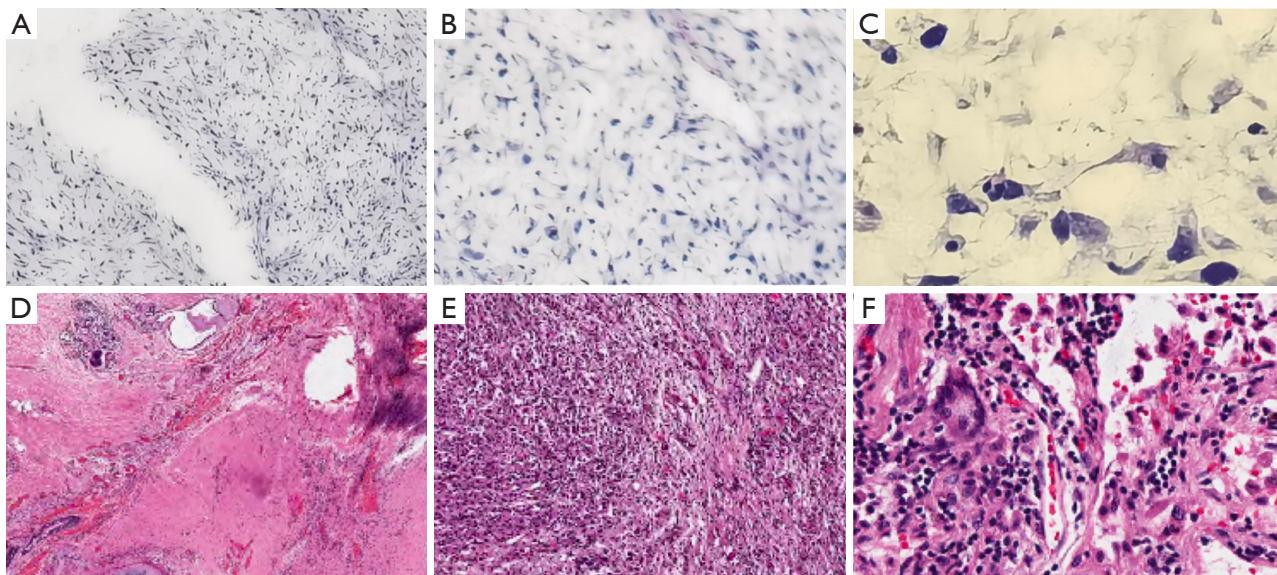


Figure 2 Pathological evaluation of the patient before (A-C) and after surgical resection (D-F). (A-C) HE staining 4 \times , 100 \times , 200 \times ; (D-F) HE staining 4 \times , 100 \times , 200 \times . HE, hematoxylin-eosin.

publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Surgical resection is usually considered as the main treatment

option for PPS. However, some patients may not be suitable for surgery at the time of diagnosis. The use of neoadjuvant treatment for PPS had remained undefined given the rarity of this tumor type. In our study, the patient started with ICI and chemotherapy, but the treatment effect was limited. According to results of NGS testing, the neoadjuvant treatment regimen was changed to sotorasib, a covalent

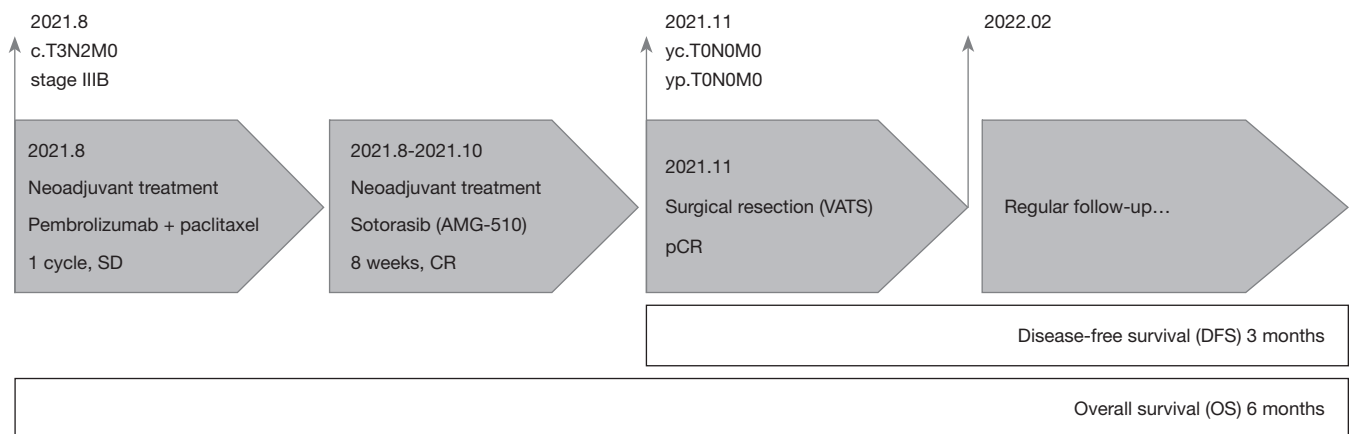


Figure 3 Summary of treatment timeline. SD, stable disease; CR, complete response; VATS, video-assisted thoroscopic surgery; pCR, pathological complete response.

inhibitor targeting *KRAS* G12C mutation. The amino acid residue G12 of *KRAS* is a mutational hot spot in different cancer types in which G12D is the leading mutation in pancreatic and colorectal cancer and G12C mainly occurs in lung cancer (8). These missense mutations are believed to have unique structural and functional consequences on the RAS protein (9). In our case, sotorasib was used as neoadjuvant treatment for a PPS patient with *KRAS* G12C mutation. The patient achieved CR in week 4 and had maintained CR in week 8 before surgical resection (yc.stage T0N0M0).

The patient received surgical resection through VATS with reserved spontaneous breathing in order to minimize the injury of cardiopulmonary function due to double-lumen endotracheal intubation and general anesthesia. The use of VATS with reserved spontaneous breathing could reduce the adverse reactions caused by endotracheal intubation and mechanical ventilation, as well as the length of hospital stay and postoperative pulmonary complications. The pathologic evaluation after surgical resection was pCR.

Conclusions

To our knowledge, it was the first study to use sotorasib for a PPS patient harboring *KRAS* G12C mutation in a neoadjuvant setting. Further follow-ups are required to evaluate long-term clinical benefit of neoadjuvant treatment with sotorasib and surgical resection with VATS.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4248/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-4248/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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