

Case Report

Sotorasib Shows Intracranial Activity in Patients with *KRAS G12C*-Mutated Adenocarcinoma of the Lung and Untreated Active Brain Metastases

Kira-Lee Koster^a Christina Appenzeller^a Arno Lauber^b Martin Früh^{a, c}
Sabine Schmid^{a, c}

^aDepartment of Medical Oncology and Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; ^bDepartment of Radiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland;

^cDepartment of Oncology, University of Bern, Bern, Switzerland

Keywords

KRAS-mutated NSCLC · *KRAS* inhibition · NSCLC with active brain metastases

Abstract

Treatment with sotorasib has shown intracranial complete responses and continued intracranial stabilization in *KRAS G12C*-mutated non-small-cell lung carcinoma (NSCLC) patients with previously treated, stable brain metastases in a post hoc analysis of the ongoing CodeBreak 100 trial. We present the case of a patient with *KRAS G12C*-mutant adenocarcinoma of the lung with active untreated brain metastases with a nearly complete intracranial response only 6 weeks after start of sotorasib illustrating the benefit of sotorasib in patients with active, previously untreated brain metastases in *KRAS G12C*-mutated NSCLC.

© 2022 The Author(s).

Published by S. Karger AG, Basel

Introduction

Findings from a post hoc analysis of the ongoing CodeBreak 100 trial showed intracranial complete responses and continued intracranial stabilization in *KRAS G12C*-mutated non-small-cell lung carcinoma (NSCLC) patients with previously treated, stable brain metastases receiving sotorasib. Patients with active brain metastases are often excluded from clinical trials. In our case report, we present the case of a patient with *KRAS G12C*-mutant adenocarcinoma of

Correspondence to:
Kira-Lee Koster, kira-lee.koster@kssg.ch

the lung with active untreated brain metastases with a nearly complete intracranial response only 6 weeks after start of treatment with the *KRAS G12C*-inhibitor sotorasib.

Case Presentation

A 61-year-old female patient with persisting fatigue was diagnosed with metastatic adenocarcinoma of the right upper lung lobe with locoregional lymph node involvement, multiple pulmonary, and one brain metastasis in the right frontal gyrus in June 2018 (clinical staging according to the PET-CT findings: cT3 cN2 cM1c). Next-generation sequencing of the tumour DNA (Ion AmpiSeq Colon and Lung Research Panel v2, Ion Torrent platform, analysis of the hotspot regions) revealed a *KRAS p.G12C* (c.34G>T) mutation in the absence of additional targetable alterations. Immunohistochemistry staining for PD-L1 was <1% of tumour cells.

First-line systemic treatment with cisplatin, pemetrexed, and pembrolizumab resulted in an overall partial response including a complete remission of the brain metastasis and maintenance therapy with pemetrexed and pembrolizumab was started in September 2018. Pemetrexed was stopped due to progressive polyneuropathy in March 2019.

In June 2019, the patient progressed in the lung necessitating haemostyptic radiotherapy due to haemoptysis and pembrolizumab was stopped as well. The solitary brain metastasis continued to be in remission. In November 2019, the patient progressed again in the lung and had symptomatic brain progression with a new lesion in the cerebellar vermis, resulting in compression of the aqueduct and consecutive hydrocephalus. A ventriculoperitoneal shunt was implanted and the lesion in the cerebellar vermis was treated with stereotactic radiotherapy; the progressive pulmonary lesion was treated with radiotherapy; in addition, treatment with pembrolizumab was resumed as the disease was otherwise stable with ongoing disease control for over a year. However, in February 2021 the patient developed progression of the known lesion in the cerebellum which was not rated as clinically significant, a new metastasis in the left periventricular white matter and further progression in the lung. Docetaxel was initiated in March 2021 with progressive disease in the lungs and in the brain with new lesions in the right frontal and temporal lobe as best response after four cycles (see Fig. 1 for schematic presentation of chronology of treatments).

In June 2021, therapy with sotorasib 960 mg daily perorally was started. After 6 weeks of sotorasib, an impressive treatment response was observed not only of the lung but also of the untreated brain metastases, lasting for 5 months (see Fig. 2). Due to systemic progression, the treatment with sotorasib was stopped and treatment with gemcitabine was started at the end of November 2021.

At the beginning of December 2021, symptomatic brain progression with behavioural changes and listlessness occurred and neurosurgical intervention with craniectomy and tumour resection was performed. The systemic treatment with gemcitabine was continued until February 2022 and stopped due to progressive disease. The patient received further systemic treatments with pemetrexed in March 2022 (re-challenge) and later on with carboplatin and paclitaxel in April 2022. Additionally, whole brain radiotherapy was performed in April 2022. Upon further progression, the patient is on best supportive care since May 2022.

Discussion/Conclusion

In the past two decades, multiple molecular alterations in NSCLC and targeted treatments for patients with actionable oncogenic alterations have been identified. *Kirsten rat sarcoma viral oncogene* (*KRAS*) mutations represent the most commonly found oncogenic driver mutations

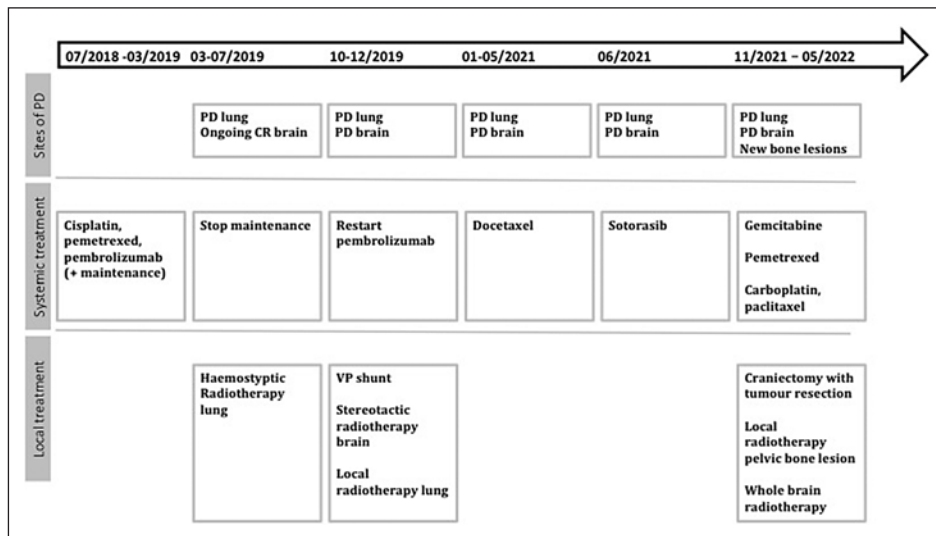


Fig. 1. History of treatment. CR complete remission, PD, progressive disease; VP shunt, ventriculoperitoneal shunt.

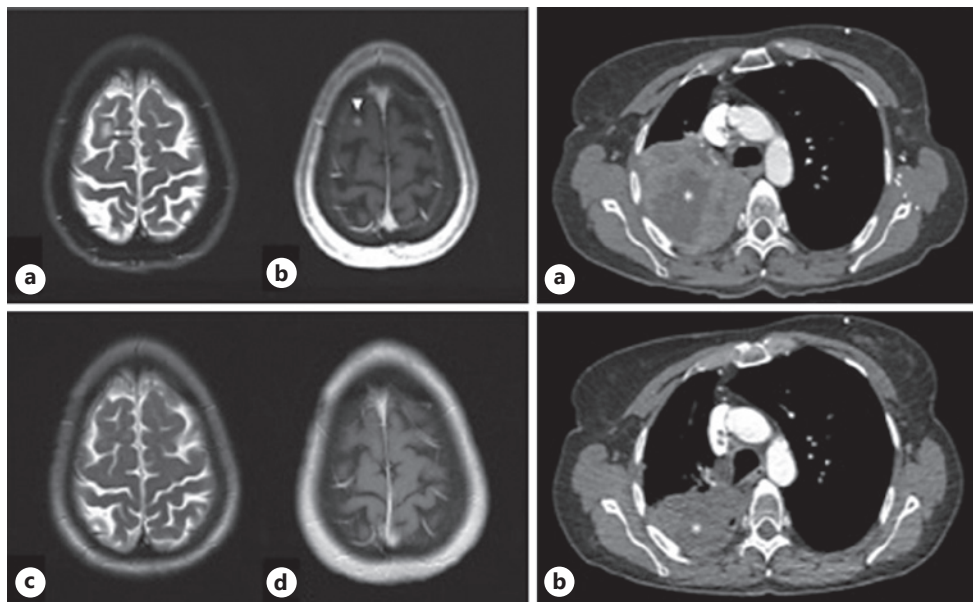


Fig. 2. Radiological response to treatment with sotorasib. Left panel: pretherapeutic axial MR images (**a**: T2 weighted, **b**: after i.v. contrast) demonstrating a contrast-enhancing metastasis (**b**: arrow head) in the right frontal lobe with adjacent parenchymal oedema (**a**: arrow). Post-therapeutic axial MR images after 6 weeks of therapy with sotorasib showing CR (**c**: T2 weighted, **d**: after i.v. contrast). Right panel: pretherapeutic contrast-enhanced chest CT (**a**) demonstrating a locally advanced primary tumour (*) of the right upper pulmonary lobe with PR after 6 weeks of therapy with sotorasib (**b**).

in patients with adenocarcinoma of the lung and can be found in up to a quarter of patients [1, 2]. The RAS proteins regulate signal transduction by activating different effectors, thereby controlling various cellular functions. *G12C*, *G12V*, and *G12D* are the predominant *KRAS* mutations with *KRAS G12C* mutations being present in approximately 13% of patients with NSCLC [1, 3].

Only recently *KRAS* stopped to be considered an undruggable target with several new agents specifically targeting *KRAS* G12C showing promising results [4, 5]. Sotorasib, a covalent *KRAS* G12C inhibitor locking *KRAS* in its inactive GDP-bound state by irreversibly binding to the switch II pocket [6], was evaluated in the phase I CodeBreak 100 trial in 129 patients with previously treated advanced or metastatic *KRAS* G12C-mutated cancer, including 59 patients with NSCLC [7]. The overall response rate (ORR) seen in patients with NSCLC was 32.2% (95% CI: 20.62–45.64) and the disease control rate (DCR) was 88.1% (95% CI: 77.07–95.09). This was confirmed in a single-group, phase II trial exclusively conducted in 126 NSCLC patients showing an ORR of 37.1% (95% CI: 28.6–46.2) and a DCR of 80.6% (95% CI: 72.6–87.2) [8]. Furthermore, a progression-free survival of 6.8 months (95% CI: 5.1–8.2) and a median overall survival of 12.5 months (95% CI: 10.0 could not be evaluated) were reported. However, patients with untreated active brain metastases such as in our case were excluded from these trials.

More recently, findings from a post hoc analysis in patients with NSCLC included in the ongoing phase 1/2 CodeBreak 100 trial showed intracranial complete responses in *KRAS* G12C-mutated NSCLC patients with stable brain metastases after previous local treatments such as radiotherapy or surgery [9]. Out of 174 patients with *KRAS* G12C-mutated NSCLC included in the post hoc analysis, 40 patients had stable brain metastases at baseline. The ORR in these 40 patients was 25% compared to 41.7% in the 132 evaluable patients without brain metastases. Sixteen of the 174 included patients (9.2%) had a baseline and at least one on treatment brain scan evaluable for response assessment, showing an intracranial DCR of 87.5% (14/16 patients).

In contrast, in our case sotorasib treatment demonstrated an intracranial response in the setting of asymptomatic but active, untreated, and measurable brain metastases with a nearly complete remission within weeks after start of treatment, questioning the need for upfront local treatment strategies in these patients. In patients with other oncogenic driver alterations such as *ALK* and *EGFR*, newer generation TKIs as osimertinib, alectinib, and lorlatinib have demonstrated intracranial activity [10–13] and local treatment of brain metastases can often be deferred [14, 15]. Whether this could be a safe strategy in patients treated with sotorasib has to be evaluated in clinical trials. One advantage of this strategy might be the avoidance or delay of toxicity of radiotherapy to the brain. Whereas we did observe an impressive response to sotorasib in our patient, duration of response was short with fast symptomatic brain progression after a few months of treatment, suggesting the need for close monitoring with brain imaging if such a deferred strategy is chosen.

Several trials addressing this question are planned or already recruiting. A currently recruiting phase 1b study is investigating sotorasib as monotherapy in *KRAS* G12C-mutated NSCLC patients with untreated brain metastases and in combination with other anti-cancer therapies in advanced solid tumours (ClinicalTrials.gov Identifier: NCT04185883). Furthermore, a phase I/II trial investigating sotorasib in combination with MVASI (a bevacizumab biosimilar) in subjects with advanced *KRAS* G12C-mutant NSCLC with small, untreated brain metastases (ClinicalTrials.gov Identifier: NCT05180422) is planned. The results of these studies including patients with *KRAS* G12C-mutated NSCLC and untreated brain metastases will shed more light on optimal management of these patients and especially intracranial activity of sotorasib.

Recently, first data on acquired resistance mechanisms to *KRAS* G12C inhibition have emerged. As seen with *EGFR* TKIs, new *KRAS* mutations as *KRAS*-dependent and activation of alternative pathways and lineage plasticity as *KRAS*-independent mechanisms of resistance are being observed [16, 17] and knowledge of type of resistance might be relevant to detect new targets and maybe overcome drug resistance in the future.

Treatment with sotorasib with deferral of local treatment could be an option in patients with NSCLC harbouring a *KRAS G12C* mutation and active untreated brain metastases. The objective intracranial response and duration of response in these patients need to be evaluated in clinical trials.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of her medical case and the accompanying images.

Conflict of Interest Statement

Kira-Lee Koster, Christina Appenzeller, and Arno Lauber declare no conflict of interest. Martin Früh: grants from BMS and Astra Zeneca; consulting fees from Astra Zeneca, Merck Sharp & Dohme, Roche, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, and Takeda; payment for expert testimony from Takeda and Roche; support for attending meetings and/or travel from Merck; and advisory board of Roche. Sabine Schmid (within last 36 months): advisory (institutional) for MSD, BMS, and AstraZeneca and research grants from University of Zürich, Swiss Cancer League Foundation, and Vontobel-Stiftung.

Funding Sources

There was no funding for this study.

Author Contributions

Kira-Lee Koster made the conceptualization, data curation, visualization, wrote the first draft, and reviewed and edited the final manuscript. Christina Appenzeller made the data curation and reviewed and edited the final manuscript. Arno Lauber made the visualization and reviewed and edited the final manuscript. Martin Früh reviewed and edited the final manuscript. Sabine Schmid made the conceptualization, data curation, and reviewed and edited the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

- 1 Sequist LV, Heist RS, Shaw AT, Fidias P, Rosovsky R, Temel JS, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. *Ann Oncol Off J Eur Soc Med Oncol*. 2011;22(12):2616–24.
- 2 Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998–2006.

- 3 Dogan S, Shen R, Ang DC, Johnson ML, D'Angelo SP, Paik PK, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2012;18(22):6169–77.
- 4 Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. *Signal Transduct Target Ther*. 2021;6(1):386.
- 5 Uprety D, Adjei AA. KRAS: from undruggable to a druggable cancer target. *Cancer Treat Rev*. 2020;89:102070.
- 6 Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575(7781):217–23.
- 7 Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, et al. KRASG12C inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383(13):1207–17.
- 8 Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med*. 2021;384(25):2371–81.
- 9 Ramalingam S, Skoulidis F, Govindan R, Velcheti V, Li B, Besse B, et al. P52.03 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(10):S1123.
- 10 Yamaguchi H, Wakuda K, Fukuda M, Kenmotsu H, Mukae H, Ito K, et al. A phase II study of osimertinib for radiotherapy-naïve central nervous system metastasis from NSCLC: results for the T790M cohort of the OCEAN study (LOGIK1603/WJOG9116L). *J Thorac Oncol*. 2021;16(12):2121–32.
- 11 Lin JJ, Jiang GY, Joshipura N, Ackil J, Digumarthy SR, Rincon SP, et al. Efficacy of alectinib in patients with ALK-positive NSCLC and symptomatic or large CNS metastases. *J Thorac Oncol*. 2019;14(4):683–90.
- 12 Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829–38.
- 13 Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med*. 2020;383(21):2018–29.
- 14 Lee J, Ahn M-J. Brain metastases in patients with oncogenic-driven non-small cell lung cancer: pros and cons for early radiotherapy. *Cancer Treat Rev*. 2021;100:102291.
- 15 Thomas NJ, Myall NJ, Sun F, Patil T, Mushtaq R, Yu C, et al. Brain metastases in EGFR- and ALK-positive NSCLC: outcomes of central nervous system-penetrant tyrosine kinase inhibitors alone versus in combination with radiation. *J Thorac Oncol*. 2022;17(1):116–29.
- 16 Awad MM, Liu S, Rybkin II, Arbour KC, Dilly J, Zhu VW, et al. Acquired resistance to KRASG12C inhibition in cancer. *N Engl J Med*. 2021;384(25):2382–93.
- 17 Zhao Y, Murciano-Goroff YR, Xue JY, Ang A, Lucas J, Mai TT, et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature*. 2021;599(7886):679–83.