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CASE REPORT

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Tumor heterogeneity and its impact on sotorasib response in a patient with non-small cell lung cancer

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Abstract

Mutations in the *Kirsten rat sarcoma virus* (KRAS) gene are the most common mutations in NSCLC, and they occur in 25–40% of patients with lung adenocarcinoma. Sotorasib, a selective KRAS inhibitor, is an anticancer drug used in NSCLC patients with a G12C mutation in the *KRAS* gene. In previously treated patients, this therapy was safer and more effective than docetaxel chemotherapy. Heterogeneity refers to differences between tumor cells within a single tumor as well as in primary and metastatic lesions. It may influence the response to targeted therapies and the development of acquired resistance to these therapies. It is assumed that sotorasib efficacy is lower in patients with known tumor molecular heterogeneity, which may be common in patients exposed to tobacco smoke.

This case report presents a 63-year-old woman with advanced NSCLC and a confirmed G12C mutation in the *KRAS* gene detected with the real-time PCR technique. A later next-generation sequencing (NGS) examination did not show the presence of this mutation. However, the NGS study was performed on material from a different metastatic lesion. The negative NGS result from this material was confirmed by the real-time PCR technique. The patient had a short-term benefit from first-line chemotherapy and second-line nivolumab immunotherapy (disease stabilization). Due to progression (progression of measurable lesions and new metastases to the CNS), the patient received brain radiotherapy and then sotorasib in the third line of treatment. However, the effectiveness of KRAS inhibition was limited. Regression of the lesion with a detected mutation in the *KRAS* gene and progression of lesions without this mutation were observed. Sotorasib therapy was terminated. The woman died two years after diagnosis, not benefiting from subsequent lines of therapy.

NSCLC heterogeneity (presence of mutations in only some clones of cancer cells) may be responsible for primary and acquired resistance to molecularly targeted therapies, including KRAS inhibitors.

Keywords: *KRAS* gene, G12C mutation, sotorasib, NSCLC, heterogeneity

Introduction

Despite the development of oncology and discovery of new therapeutic methods, lung cancer is still the most common neoplastic cause of death in the world. It causes 1.8 million deaths annually. In recent years, an increase in lung cancer incidence in women was observed. Smokers still account for 90% of all cases [1].

Activating mutations in the *Kirsten rat sarcoma virus* (*KRAS*) gene occur in 25–40% of non-squamous cell carcinomas and are the most common mutation in non-small cell lung cancer (NSCLC). Mutations in the *KRAS* gene appear almost exclusively in patients with non-squamous lung cancer, primarily in patients with adenocarcinoma. These mutations do not coexist with other abnormalities in oncogenes, but

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they co-occur with mutations in tumor suppressor genes e.g. *tumor protein 53* (*TP*53), *serine-threonine kinase 11* (*STK11*), and *Kelch-like ECH-associated protein 1* (*KEAP*). The G12C (p.Gly12Cys, c.34G>T) mutation is the most common mutation in the *KRAS* gene in NSCLC patients (40% of *KRAS*-mutant patients). It occurs in 13% of patients with non-squamous cell lung cancer.

The rarer mutations in the *KRAS* gene in NSCLC patients include G12V (19% of patients with *KRAS* mutations) and G12D (15% of patients with *KRAS* mutations) [2, 3]. *KRAS* mutation frequency depends on ethnicity and sex and is more common in Caucasian patients (25%) than in Asian patients (< 10%). These patients make up 35% of adenocarcinoma cases in the US and only 13% in China. The *KRAS* mutations are more common in women than in men and in older patients, which is related to their greater exposure to tobacco smoke. These mutations are very rare in non-smokers. The occurrence of mutations in the *KRAS* gene was associated with worse prognosis in NSCLC patients and poorer effectiveness of chemotherapy. However, the prognosis for these patients has changed in the era of immunotherapy and KRAS inhibitor therapy [4].

KRAS mutations may be associated with poor overall prognosis and treatment response in advanced NSCLC [5]. Several studies have shown that *KRAS* mutations in NSCLC patients treated with chemotherapy have a negative impact on overall survival (OS) and progression-free survival (PFS). Patients with these mutations are more likely to develop liver and brain metastases and experience a more aggressive form of disease [6]. Sotorasib, a selective KRAS inhibitor, is an anticancer drug used in NSCLC patients with a G12C mutation in the *KRAS* gene. It is indicated as monotherapy in adult patients with advanced NSCLC who have progressed on at least one prior line of therapy [7].

Heterogeneity refers to differences between tumor cells within a single tumor or primary tumor and metastases. It may influence the response to molecularly targeted therapies, which has rarely been confirmed with the *epidermal growth factor receptor* (*EGFR*) gene mutations that had co-existing oncogenic mutations (e.g. in the *KRAS* gene) [8]. It seems that the efficacy of sotorasib is also lower in patients with known tumor molecular heterogeneity, which is common in patients exposed to tobacco smoke [9].

We present the case of a 63-year-old woman with advanced lung adenocarcinoma and a G12C mutation in the *KRAS* gene who did not achieve satisfactory therapeutic benefit from sotorasib therapy. However, the cancer turned out to be heterogeneous in terms of the occurrence of a G12C mutation in the *KRAS* gene.

Case report

In July 2020, a 63-year-old woman, without significant medical history, who had not smoked cigarettes for 4 years (35 pack-years) was admitted to the Department of Pneumonology, Oncology and Allergology for a dry cough. Computed tomography (CT) was performed and a 38 × 34 mm infiltrative nodal lesion was found in the left hilum obstructing the left upper lobe bronchus. Moreover, a 25 × 19 mm spiculated tumor in the upper lobe of the left lung (Fig. 1) and a 76 × 43 × 83 mm polycyclic mass with satellite nodules adjacent to the pleura in the lower lobe of the left lung were found (segment 6). The disease stage was classified as IIIB (c-T4N2M0). The patient's performance status was good — grade 1 according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.

On July 24, 2020, a percutaneous transthoracic lung biopsy was done (Fig. 2). Histopathological examination revealed lung adenocarcinoma with TTF1 expression (thyroid transcription factor 1) and napsin. Molecular tests did not show any abnormalities in the *EGFR*, *anaplastic lymphoma kinase* (*ALK*), or *ROS1 protoncogene 1* (*ROS1*) genes. There was no expression of programmed death ligand 1 (PD-L1) on tumor cells. In August 2020, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of the lung tumor located in the left lung hilum was performed. In the histopathological examination, adenocarcinoma with TTF1 expression was also diagnosed.

In August 2020, first-line platinum-based chemotherapy based was started. In October 2020, after 4 cycles of chemotherapy, a partial response on CT was obtained according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. The tumor at the upper lobe of the left lung was reduced to 26 × 17 mm, the lesion in the left hilum has been reduced to 33 × 25 mm, and the lesion located in segment 6 became more spherical, maximally 53 mm in transverse dimension (previously 76 mm). Grade 1 toxicity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (anemia and neutropenia), was observed during chemotherapy. The patient lost some scalp hair. She also reported slight nausea. Control CT in May 2021 showed disease progression.

In May 2021, second-line immunotherapy with nivolumab was started. Disease stabilization has been achieved (Fig. 3). Features of liver damage and elevated liver enzymes, CTCAE grade 2, occurred during immunotherapy. The treatment was completed after 7 cycles, in August 2021, due to the metastases to the central nervous system (CNS). A single 7.6 mm lesion

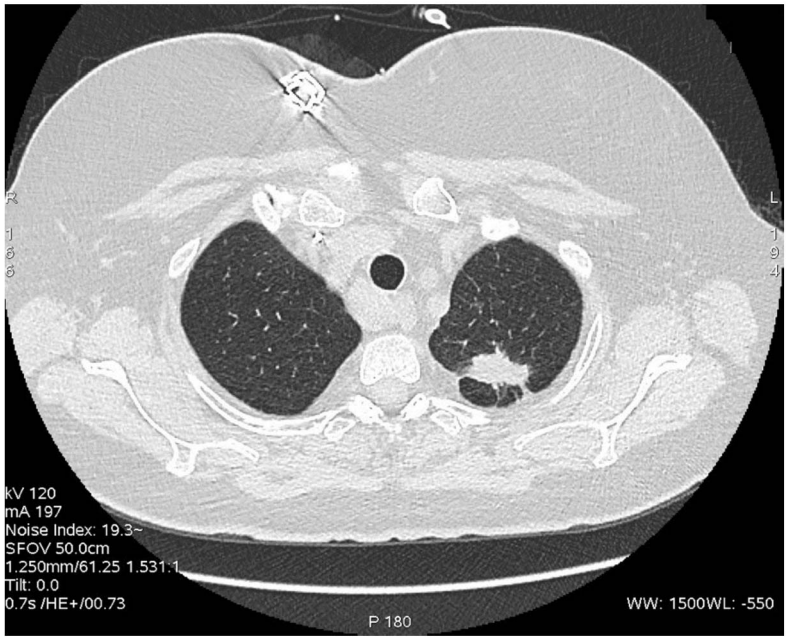

Figure 1. June 2020. High-resolution computed tomography of the chest showing the presence of a spicular tumor in the upper lobe of the left lung

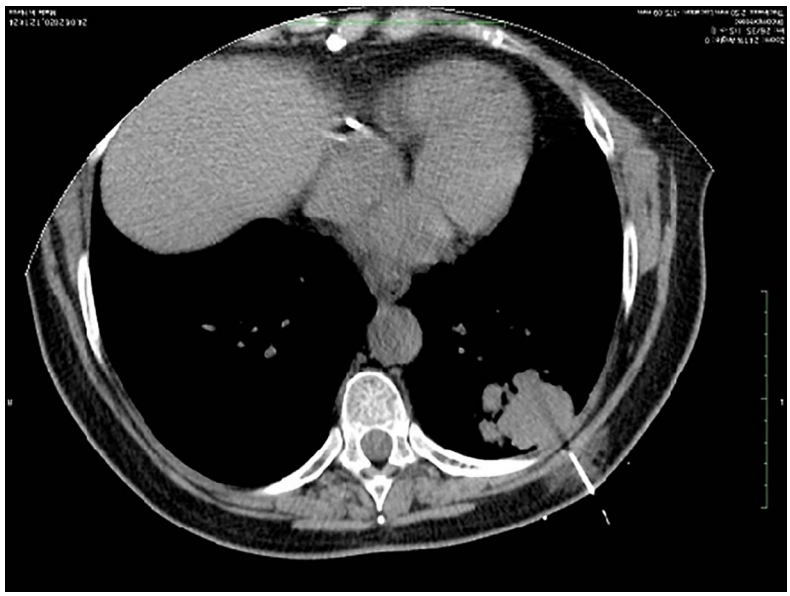

Figure 2. July 2020. The moment of lung biopsy of the 76 × 43 × 83 mm polycyclic mass with satellite nodules adjacent to the pleura on the left side

located within the white matter of the left parietal lobe was found (Fig. 4A). The patient underwent stereotactic radiotherapy of the brain lesion.

In September 2021, genetic testing was expanded to include *KRAS* gene mutation examination due to the extended access program (EAP) to sotorasib treatment. Testing was performed three times, with two different materials. Firstly, the material obtained from the percutaneous transthoracic tumor biopsy was tested for *KRAS* gene mutations using the real-time PCR (polymerase chain reaction) technique. The Entrogen test was used to detect this mutation, and the G12C mutation in the *KRAS* gene was found.

Subsequently, material obtained during bronchoscopy was tested with the NGS technique using the Oncomine Focus Assay on the Ion Torrent S5 platform, and no mutations in the *KRAS* gene were detected. The absence of mutations in the *KRAS* gene in this material was confirmed by real-time PCR using the Entrogen assay.

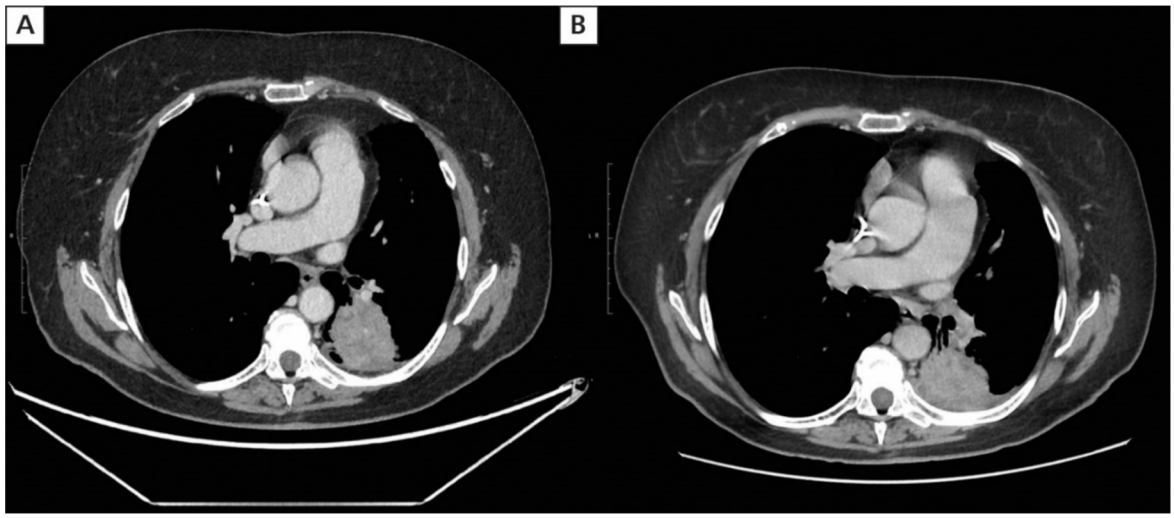

Figure 3. A. May 2021. High-resolution computed tomography of the chest showing disease progression after chemotherapy. **B.** August 2021. High-resolution computed tomography of the chest showing stabilization of lung tumor size after 7 cycles of nivolumab immunotherapy

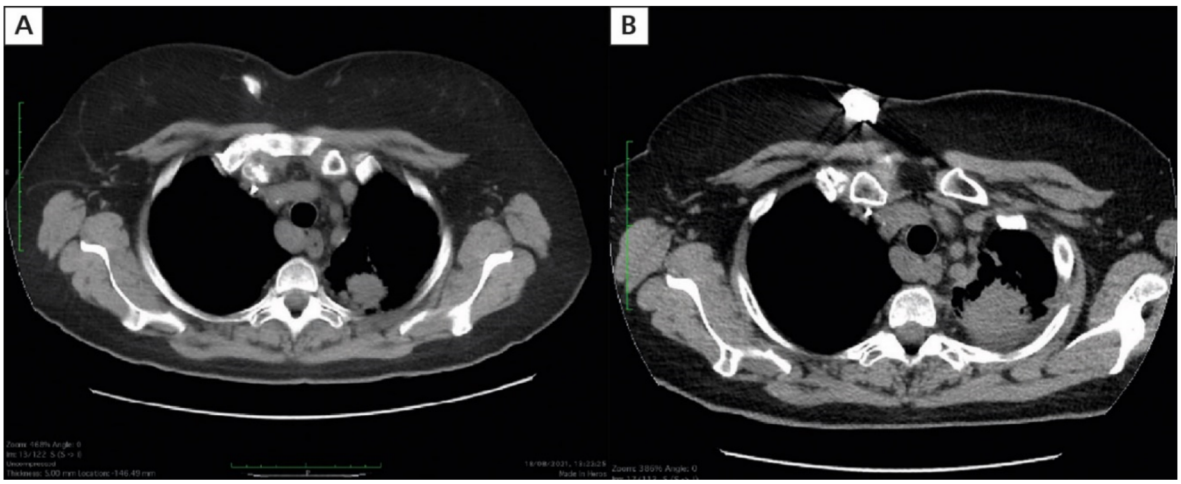

Figure 4. Progression of tumor in the apex of the left lung without G12C mutation in the *KRAS* gene; **A.** Computed tomography (CT) performed before sotorasib therapy; **B.** CT performed after two months of sotorasib therapy

In October 2021, the patient was qualified for sotorasib therapy based on the diagnosis of G12C mutation in the KRAS gene. Sotorasib therapy was well tolerated. Two different responses to treatment were observed. The tumor in the apex of the lung and lesion adjacent to the left lung hilum progressed significantly within two months of treatment (Fig. 4A, 4B). However, partial remission of the lesion in segment 6 was observed during sotorasib therapy (Fig. 5A, 5B). The G12C mutation in the *KRAS* gene was detected in the lesion in remission but was not detected in the tumor that progressed. Sotorasib therapy was discontinued in February 2022.

Then, the 4th line of treatment with docetaxel was applied from February to April 2022. Unfortunately, after two cycles of chemotherapy, progression was observed, and due to good performance status, the patient received the 5th line of treatment. Chemotherapy with gemcitabine was administered from April to July 2022 (3 cycles) without significant results. Grade 1 anemia and neutropenia accompanied subsequent chemotherapy lines. Persistent constipation occurred due to the use of opioid analgesics.

Computed tomography of the brain performed in July 2022 showed new brain metastases. The metastatic lesion in the left parieto-occipital region had enlarged to 27 mm (previously 15 mm), surrounded by a larger zone of digital swelling (Fig. 6A, 6B). A new metastatic lesion of 8 mm was found in the basolateral part of the right temporal lobe approximately.

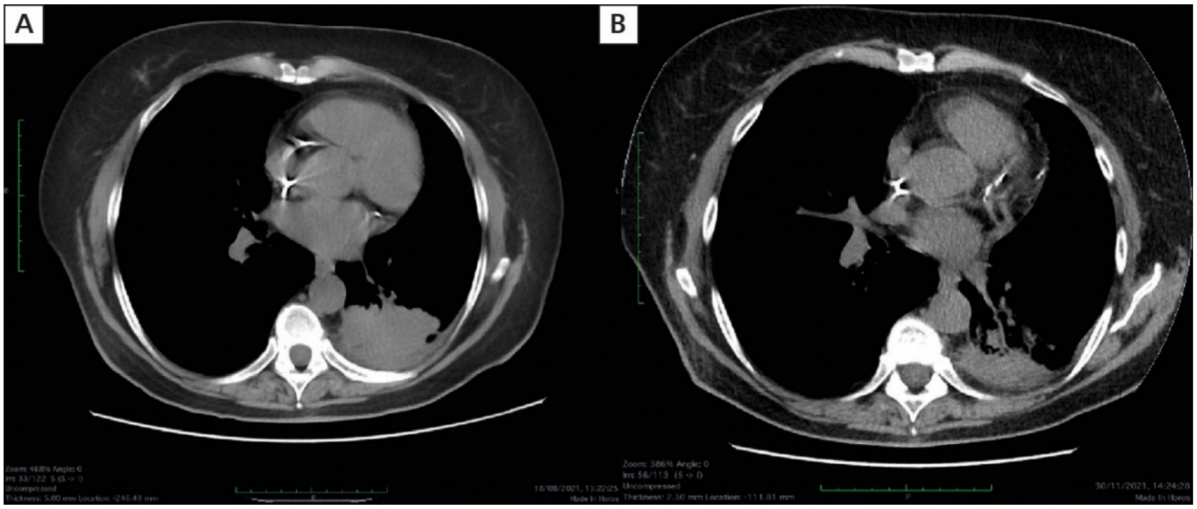

Figure 5. Remission of tumor in segment 6 with G12C mutation in the *KRAS* gene; **A.** Computed tomography (CT) performed before sotorasib therapy; **B.** CT performed after two months of sotorasib therapy

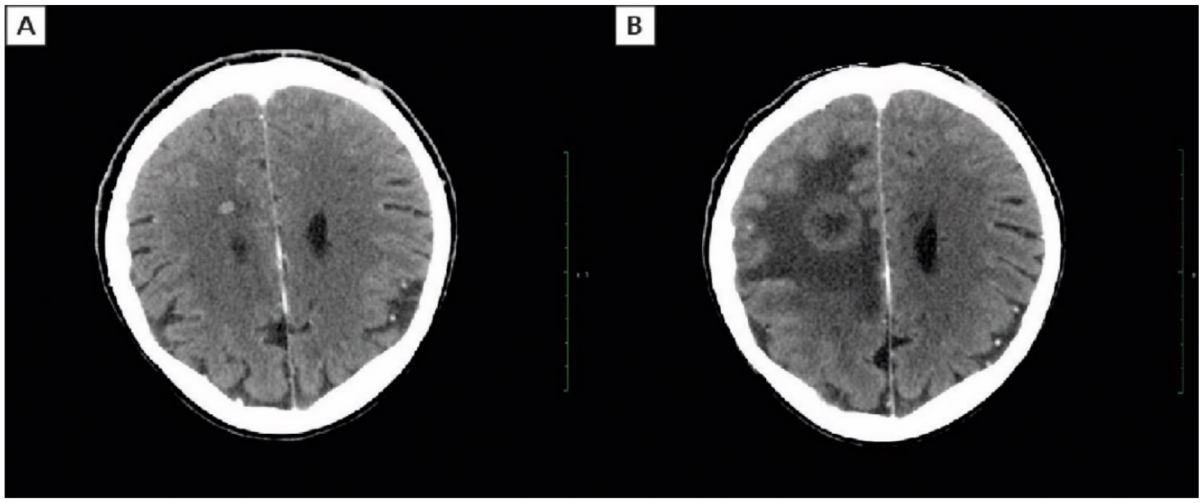

Figure 6. A. High-resolution brain computed tomography showing a single lesion of the left parietal lobe in August 2021; **B.** High-resolution brain computed tomography showing progression of brain metastases during sotorasib therapy

At that time, serious neurological symptoms appeared. Right-sided hemiparesis and untreatable severe headaches occurred. These symptoms were life-threatening for the patient, so a decision was made to surgically remove the CNS metastases. In August 2022 surgery was performed during which the tumor of the left parieto-occipital area was completely removed. Unfortunately, there was a significant progression of the disease and deterioration of the general condition. In November 2022, the woman died two years after diagnosis.

Discussion

In rare cases of metastatic NSCLC patients, a histopathological examination of biopsy material from a single neoplastic lesion may not be representative for molecular testing and may lead to therapeutic failures [10]. It seems reasonable that in patients with a mutation in the *KRAS* gene, in whom disease progresses during targeted treatment, a tumor biopsy and then molecular tests should be performed in primary and metastatic lesions.

Nowadays, molecular profiling has become essential in treatment planning in patients with metastatic NSCLC. Every year, new mutations appear that gain clinical significance, which becomes a serious diagnostic challenge. NGS provides a solution to this problem by allowing multiple variants to be detected simultaneously in a small amount of tissue. The Oncomine Focus Assay (Thermo Fisher Scientific, USA), which we used during the diagnostic process

of our patient, is used to detect clinically significant somatic mutations, including *EGFR*, *BRAF*, *KRAS*, *erb-b2 receptor tyrosine kinase* (*ERBB2*), *MET protooncogene* (*MET*) mutations and *ALK*, *ROS1*, *RET protoncogene* (*RET*), and *neurotrophic tyrosine receptor kinase 1*/2/3 (*NTRK1*/2/3) fusions. However, even NGS technology does not detect genetic abnormalities in molecularly heterogeneous tumors, which has been confirmed by our case [11].

Therefore, methods enabling molecular characterization of circulating tumor DNA (ctDNA) have been introduced into clinical practice. The secretion of ctDNA by some types of cancer cells, analyzed by NGS, can help determine the genetic makeup of heterogeneous cancer subclones. Similarly, the isolation of circulating tumor cells (CTCs) and their culture to generate CTC-derived models may be useful for defining resistance mechanisms and designing strategies to overcome them [12].

Heterogeneity is an important topic in the field of oncology and includes both inter- and intra-individual variability between organs, tissues, cells, and molecules. Heterogeneity can lead to a decrease in sensitivity to individualized treatment methods. The use of next-generation sequencing techniques greatly facilitates understanding the genetic and epigenetic basis of cancer and its heterogeneity [13]. Intratumoral heterogeneity and different responses to treatment represent a current challenge in the development of targeted therapies in lung cancer patients.

Sotorasib is a drug that specifically and irreversibly inhibits KRAS when glycine is replaced by cysteine at codon 12. Sotorasib binds to cysteine, which stabilizes the inactive form of KRAS and blocks the intracellular pathway leading to tumor cell activation. Sotorasib is used in the treatment of locally advanced or metastatic NSCLC with G12C mutation in the *KRAS* gene following prior systemic therapy.

Clinical efficacy and safety of sotorasib were confirmed in the phase II CodeBreaK 100 clinical trial. The overall response rate (ORR) in patients treated with sotorasib was 36% and the median duration of response (DoR) was 11.1 months. Moreover, median PFS reached 6.8 months and median OS — 12.5 months [8, 14]. In our analysis [15], representing the most mature clinical data, sotorasib demonstrated long-term efficacy, with no significant impact on the safety profile. The proportion of patients who achieved long-term clinical benefit, 1- and 2-year OS rates, was 51% and 33%, respectively. Oral administration of sotorasib at a dose of 960 mg once daily did not result in late severe or chronic lower-grade toxicity. The study showed relatively good treatment tolerance. The side effect profile was acceptable. Most toxicities were in grade 1 or 2 according to CTCAE. Diarrhea and nausea occurred most often. There were no treatment-related deaths, and 11.6% of patients experienced grade 3 or 4 treatment-related adverse events.

In the phase III CodeBreaK 200 clinical trial, the efficacy and safety of sotorasib and docetaxel were compared in a group of 345 previously treated NSCLC patients with the G12C mutation in the *KRAS* gene. In total, 28.1% of patients responded to sotorasib therapy and 13.2% to docetaxel therapy. Median PFS was 5.6 months in patients treated with sotorasib and 4.5 months in patients treated with docetaxel. Twelve-month PFS was observed in 24.8% of patients receiving sotorasib and only 10.1% of patients treated with docetaxel. Treatment with sotorasib showed 50.8% 1-year and 32.5% 2-year survival rates, with median OS of 12.5 months. Sotorasib was well tolerated, with fewer serious treatment-related adverse events compared with docetaxel (11% of patients *vs.* 23% of patients). For sotorasib, the most common treatment-related adverse events of grade 3 or worse were diarrhea and elevated levels of liver enzymes. Compared with docetaxel, there were fewer grade 3 or 4 adverse events (40.4 *vs.* 33.1%). For sotorasib, the most common treatment-related grade-3 or worse adverse events were diarrhea, alanine aminotransferase increase, and aspartate aminotransferase increase. The most common treatment-related adverse events of grade 3 or worse in patients receiving docetaxel were neutropenia, fatigue, and febrile neutropenia. Time to deterioration (cough, general health condition, shortness of breath) was longer in patients receiving sotorasib compared to patients receiving docetaxel [16]. Sotorasib has also been shown to be active across the spectrum of coexisting mutations, including mutations in the *TP*53, *STK11*, and *KEAP1* genes, which are associated with poor prognosis in advanced NSCLC patients [17].

The effectiveness of sotorasib in patients with advanced NSCLC has been confirmed in clinical trials and a series of case reports. It is worth asking the question: why our patient progressed despite the use of this drug? It seems that the main reason was the heterogeneity of the tumor. The histopathological and molecular examination revealed adenocarcinoma with G12C mutation in the *KRAS* gene in one tumor (due to its size, over 70 mm in diameter, it could have been a primary lesion). However, in the second lesion, adenocarcinoma was confirmed, but no mutations in the *KRAS* gene were detected. The metastases to the apex and hilum of the left lung could have arisen from a clone of cancer cells without mutations in the *KRAS* gene. On the other hand, these lesions could be a second, independent tumor. Thus, sotorasib did not affect all primary and metastatic lesions, which in turn led to further dissemination of cancer cells to the brain. Therefore, combining KRAS G12C inhibitors

with other treatment methods may improve clinical response and overcome resistance.

Jamal-Hanjani et al. [18] in their prospective study showed extensive heterogeneity within a tumor, and tumor cells within a single tumor do not necessarily have uniform characteristics, including histology and metastatic or proliferative potential. In addition, many studies have shown considerable genetic diversity in the same neoplastic process with different metastatic sites. These studies show that individualized treatment is necessary to overcome the heterogeneity of *KRAS*-mutant NSCLC and ensure the development of new effective treatment strategies. Currently, the greatest hopes are associated with combined treatment based on KRAS inhibitors and immunotherapy with immune checkpoint inhibitors [19].

Zhang et al. [20] found that gene mutations that occurred in metastases were significantly different from those that occurred in primary tumors with non-small cell carcinoma. This explains the lower effectiveness of targeted drugs in patients with known metastases and has important clinical significance in targeted therapy. On the other hand, Ottaiano et al. [21] stated that tumor heterogeneity can be divided into temporal and spatial heterogeneity. Temporal heterogeneity occurs over time within a single tumor or between different tumors in the same patient. However, spatial heterogeneity occurs in different parts of the tumor in the same patient and may result from changes in the tumor microenvironment. Tumor heterogeneity is a significant obstacle to the development of effective therapeutic strategies. According to that article, there are two best approaches to overcome tumor heterogeneity and therapy resistance: sequential treatment with next-generation drugs or combined treatment with therapies targeting different therapeutic goals. A combined treatment model increased the risk of side effects and may reduce the quality of life. It is important to remember that the approach to the patient should be individualized because both sequential and combined therapy have their advantages and disadvantages [21].

Conclusions

Undoubtedly, the future of oncology is moving towards an increased number of molecular tests and the use of targeted therapies. New studies focusing on intratumoral heterogeneity should assess the correlation between *KRAS* G12C mutation distribution in cancer cells and response to KRAS inhibitors. Further research into the significance of these genetic changes for patient prognosis and treatment response is warranted.

Article Information and Declarations

Ethics statement

Ethical approval was obtained from the Ethics Committee of the Medical University of Lublin, Poland. Consent number KE-0254/160/2021.

Author contributions

K.P.N.: conceived and designed the analysis, contributed data or analysis tools, performed the analysis, wrote the paper; I.Ch.: conceived and designed the analysis, contributed data or analysis tools, performed the analysis, wrote the paper; P.K.: c conceived and designed the analysis, contributed data or analysis tools, performed the analysis, wrote the paper; A.G.: conceived and designed the analysis, collected the data, contributed data or analysis tools; L.G.-K.: collected the data; I.P.: collected the data; J.M.: collected the data, performed the analysis.

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Conflict of interest

All authors declare no conflict of interest

Supplementary material

None.

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