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REVIEW ARTICLE

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Sotorasib for non-small cell lung cancer — current options and perspectives

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ABSTRACT

KRAS regulates several cellular processes, such as cell proliferation, cell cycle regulation, metabolic changes, cell survival, and cell differentiation. Abnormalities in the *KRAS* gene are found in approximately 30% of patients with non-small cell lung cancer, usually in patients diagnosed with nonsquamous cancer and more often in Caucasian patients, women, and smokers. The p.G12C variant is most frequently found in KRAS-positive patients. Sotorasib is the first drug approved for this population. The superiority of sotorasib over docetaxel after failure of immunochemotherapy was demonstrated in the CodeBreak 200 phase III study for the primary endpoint — median progression-free survival was 5.6 months [95% confidence interval (CI) 4.3–7.8] *vs*. 4.5 months (3.0–5.7); hazard ratio = 0.66 (95% CI 0.51–0.86; p = 0.0017), while the 12-month progression-free survival rate was 24.8% for sotorasib and 10.1% for docetaxel. Currently, sotorasib monotherapy, at an initial dose of 960 mg/day, is indicated for use in adults with advanced non-small cell lung cancer with the *KRAS* p.G12C mutation who have experienced disease progression after at least one previous line of systemic treatment. More randomized trials are needed to determine the optimal place of sotorasib in the systemic treatment sequence in this patient population.

Keywords: non-small cell lung cancer, *KRAS* gene, sotorasib

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Introduction

Patients diagnosed with advanced non-small cell lung cancer (NSCLC) represent a heterogeneous population. Currently, the choice of optimal systemic therapy is determined not only by the patient's clinical and morphological characteristics (performance status, comorbidities, or histological type) but also by the immunohistochemical (IHC) and molecular profile of the disease [1, 2]. In daily practice, next-generation sequencing (NGS) is increasingly used to diagnose molecular characteristics of lung cancer, allowing simultaneous assessment of multiple molecular abnormalities. Abnormalities in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene are essential from a practical point of view since they are detected in approximately 30% of patients, usually in individuals diagnosed with nonsquamous NSCLC and more often in Caucasians, women, and smokers [3]. The p.G12C variant is found most frequently and accounts for approximately 50% of patients with *KRAS* gene abnormalities [1]. Despite the high prevalence of these molecular abnormalities, attempts to develop targeted therapies have been unsuccessful for years. It was not until 2021 that the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved sotorasib, which is the first

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selective small-molecule KRAS inhibitor [4, 5]. This article summarizes the current understanding of the role of the KRAS pathway in oncogenesis, mutational analysis of the *KRAS* gene, and the efficacy and safety profile of sotorasib, including data from clinical trials and real-world experience.

The role of the KRAS pathway

The *KRAS* gene is located on the short arm of chromosome 12 (12p11.1–12p12.1) [6]. *KRAS* encodes six exons, resulting in two splice variants, KRAS4A and KRAS4B. There is a difference in the C-terminal sequence between these two variants. KRAS4A is expressed in a tissue-specific and developmentally restricted fashion, while KRAS4B is ubiquitously expressed and dominant [7]. Together with Harvey rat sarcoma viral oncogene (*HRAS*) and neuroblastoma rat sarcoma viral oncogene (*NRAS*), they encode proteins belonging to the RAS family [8]. The KRAS protein consists of several domains, each with a specific function. The G domain is responsible for binding to guanosine triphosphate (GTP) and guanosine diphosphate (GDP) and hydrolyzing GTP to GDP [9]. The G domain is critical for the switching between active (GTP-bound) and inactive (GDP-bound) states of the protein. In addition, KRAS has a flexible C-terminal structural element, also known as the hypervariable region, responsible for membrane anchoring and localization of KRAS to the cell membrane [10]. Other critical functional elements of KRAS are the switch regions, which are crucial for conformational changes during GTP binding and hydrolysis. The switch-I and switch-II regions undergo structural changes that influence the interaction of KRAS with downstream effectors [11]. Only in the GTP-bound state, turned on by extracellular stimuli, can KRAS bind and activate its effector proteins [12]. Key effector pathways downstream of oncogenic KRAS include mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), and Ras-like (Ral) GEF (RalGEF). Therefore, activated KRAS regulates several cellular processes, such as cell proliferation, cell cycle regulation, metabolic changes, cell survival, and cell differentiation. Activating *KRAS* mutations results in the high-affinity binding of GTP and loss of GTPase activity, resulting in the deregulation of RAS-dependent signaling pathways [13]. *KRAS* mutations are commonly found in various types of tumors, most often in pancreatic (88%), colorectal (45–50%), and lung cancer (31––35%) [14]. Most mutations in *KRAS* affect codons 12, 13, 61, and 146. However, mutations of codon 146 occur in colorectal cancers and hematological malignancies, while they are relatively rare in NSCLC. The most frequent *KRAS* mutations in NSCLC are p.G12C, p.G12V, and p.G12D [15]. Therefore, lung cancer cells express mutations in KRAS4A and KRAS4B splice variants [7].

Detection of *KRAS* mutations

In 1981, point mutations in the *KRAS* gene resulting in single amino acid changes in specific codons (G12, G13, and G61) were detected in lung cancer cells [16]. This finding started the era of molecular diagnostics in oncology. Today, *KRAS* is a well-characterized protooncogene, whose activating mutations are frequently detected in various tumors [14]. *KRAS* alterations are among the most frequent genetic variants detected in NSCLC [17]. *KRAS* alterations are detected in approximately 20–40% and 5% of patients with adenocarcinoma and squamous NSCLC, respectively [18]. The vast majority of *KRAS* mutations (> 95%) occur primarily at codon 12, with the most frequent alteration resulting in a substitution of glycine for cysteine at codon 12 (p.G12C) [15]. This variant is identified in approximately 40% of NSCLC patients with *KRAS* mutations. Other frequent *KRAS* substitutions are p.G12V, p.G12D, and p.G12A, detected in 21%, 17%, and 7% of NSCLC patients, respectively [19].

The emergence of targeted therapies for specific mutations, such as *KRAS* p.G12C, highlights the importance of molecular testing in guiding treatment decisions. Identifying the presence of the *KRAS* p.G12C mutation in a patient's tumor helps to select the most appropriate treatment options, and improves the chances of a favorable response. The EMA has approved molecularly targeted therapies for NSCLC patients who require the identification of variants in many different genes [20]. To administer an optimal treatment regimen in these patients, it is necessary to perform molecular tests that allow the precise detection of not only point mutations in *EGFR*, *KRAS, BRAF,* and *ERBB2* genes but also fusions of *ALK*, *ROS1, NTRK1/2/3, MET,* and *RET* genes [20]. In addition, increasing attention is being paid to the need to determine the presence of mutations in the *STK11, KEAAP1,* and *TP53* genes or the analysis of genomic signatures, such as tumor mutational burden (TMB) [21]. Therefore, according to the current guidelines of the European Society for Medical Oncology (ESMO), NGS is a method that should be routinely used to diagnose patients with advanced NSCLC [21]. In addition, numerous studies conducted on patients with advanced lung cancer have shown that the simultaneous

analysis of biomarkers is more effective than the sequential use of single-gene tests [22–25]. One of these studies found that sequential testing results in more false positives (3.3%) than simultaneous analysis of several genes (1.4%), as each additional test increases the likelihood of a false positive result. At the same time, it was found that the sequential use of single-gene tests also increases the number of nondiagnostic results (sequential tests — 6.9% *vs*. NGS — 2.7%) [22]. Studies have also shown that diagnostics conducted with sequential tests have a negative impact on the total turn-around time (TAT) or diagnostic costs [22–24]. In addition, using multiple tests also increases the risk of material exhaustion before the end of the diagnostic process in individual patients [22, 24].

Effectiveness of sotorasib — data from clinical trials

Initially, the value of sotorasib was assessed in CodeBreaK100, a multicohort dose-escalation study in patients with various solid tumors [26–28]. A total of 427 patients with the *KRAS* p.G12C mutation were enrolled. The updated results of this trial have been published on a group of 174 patients diagnosed with NSCLC, in which 52% of participants were women, 23% had brain metastases, and all individuals had received at least one line of systemic treatment (25% — three lines) [28]. Most patients had received chemotherapy and immunotherapy before qualifying for sotorasib (83%). The objective response rate (ORR) was 41% [95% confidence interval (CI) 33.3–48.4], and the disease control rate (DCR) was 84% (95% CI 77.3–88.9). In the group of patients who achieved an objective response at 12 months, 50.6% remained progression-free. Median progression-free survival (PFS) was 6.3 months with a 95% CI of 5.3–8.2, and median overall survival (OS) was 12.5 months (95% CI 10.0–17.8). The proportions of patients still alive at 12 and 24 months were 51% and 33%, respectively. Intracranial control was documented in 88% of the patients (14 of 16).

The phase III CodeBreak200 trial aimed to compare the value of sotorasib to second-line standard chemotherapy with docetaxel in patients who had failed immunochemotherapy (treatment with chemotherapy and immune checkpoint inhibitor could be concurrent or sequential) [29]. Patients were eligible if they had good performance status, had no active brain metastases, and had not previously received docetaxel for advanced disease. Patients were randomly assigned to receive sotorasib (960 mg/day) or docetaxel (75 mg/m^2). Patients were treated until disease progression, significant adverse events, or death. Crossover was allowed in this trial. In the sotorasib arm, 98% of the patients had nonsquamous NSCLC, 33% had brain metastases, and 17% had liver metastases. Before qualifying for sotorasib, 45% of the patients had received one line of therapy, and the rest had received two or more. The primary endpoint of the CodeBreak200 trial was PFS assessment.

The superiority of sotorasib over docetaxel was demonstrated for the primary endpoint: median PFS was 5.6 months (95% CI 4.3–7.8) *vs.* 4.5 months (95% CI 3.0–5.7); hazard ratio (HR) = 0.66 (95% CI 0.51–0.86; p = 0.0017), the 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel [29]. There was also a superiority of sotorasib in terms of the ORR 28.1% (95% CI 21.5–35.4) *vs.* 13.2% (8.6–19.2); p < 0.001. Clinical benefit was observed in the overall population, including patients with brain metastases. Additionally, the benefit in quality-of-life parameters was documented. The time to deterioration in global health status, physical functioning, and cancer-related symptoms (dyspnea and cough) was delayed with sotorasib. However, there were no differences in OS between groups (HR = 1.01; 95% CI 0.77–1.33), probably due to the crossover between the arms. At the time of analysis (median study follow-up 17.7 months), in both subgroups, approximately 40% of patients received systemic treatment after disease progression. Of the patients initially treated with docetaxel, 143 discontinued treatment (95 due to disease progression), and 49 patients subsequently received sotorasib [29]. It is also worth noting that in previous clinical trials (with immune checkpoint inhibitors in the second-line setting with docetaxel as a comparator), mPFS for docetaxel was approximately 3–4 months, with a 12-month PFS rate estimated at 6–8% and mOS of approximately 9 months [30–33]. In the current study, the clinical benefit was more significant in this arm. Table 1 summarizes the treatment efficacy data from CodeBreak200.

Safety profile of sotorasib

In the CodeBreak200 trial, adverse effects were observed in almost all patients from both groups. Treatment-identified adverse effects were more common in docetaxel-treated patients (86% *vs*. 70%) and similarly treatment-related severe adverse effects (23% *vs*. 11%). Fifteen percent of patients treated with sotorasib required a dose reduction and 10% required treatment discontinuation. For sotorasib, diarrhea and an increase in aminotransferase activity were observed most frequently. For docetaxel, neutropenia and fatigue

Table 1. Treatment efficacy of sotorasib in the CodeBreak200 study [29]

	Sotorasib (171)	Docetaxel (174)	HR (95% CI)	p
ORR [%]	28.1	13.2		< 0.001
DCR [%]	82.5	60.3		
mPFS [months]; 95% CI	5.6 (4.3–7.8)	4.5 (3.0–5.7)	0.66 (0.51–0.86)	0.0017
mOS [months]; 95% CI	10.6 (8.9–14.0)	11.3 (9.0–14.9)	1.01 (0.77–1.33)	0.53
12-months PFS	24.1	10.1		

CI — confidence interval; DCR — disease control ratio; HR — hazard ratio; m — median; ORR — overall response ratio; OS — overall survival; PFS — progression-free survival

Table 2. The most common adverse events of sotorasib and docetaxel in the CodeBreak200 study

	Sotorasib		Docetaxel	
	Any grade [%]	Grade ≥ 3 [%]	Any grade [%]	Grade ≥ 3 [%]
Diarrhea	34	12	19	2
Fatigue	7	1	25	6
Nausea	14	1	21	0
Anemia	3	1	18	3
Stomatitis	1	0	11	1
Alanine aminotransferase increase	10	8	0	0
Aspartate aminotransferase increase	10	5	0	0
Neutropenia	1	0	13	12
Edema peripheral	0	0	9	1
Febrile neutropenia	0	0	5	5

were the most frequently reported. Details of the safety profile are presented in Table 2.

Effectiveness of sotorasib — real-world data

The availability of sotorasib is limited in many countries. In Poland, sotorasib was reimbursed for use in patients diagnosed with advanced NSCLC and a confirmed *KRAS* p.G12C mutation after the failure of at least one line of chemotherapy and/or immunotherapy in September 2023. As a result, data from the literature documenting the value of sotorasib in daily practice are limited. Several congress abstracts have been presented recently, and these are briefly discussed below.

At the 2022 ESMO Congress, Awad et al. [34] presented the results of an international analysis of patients treated with sotorasib as part of the Expanded Access Programme (EAP). Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible for the EAP. A total of 137 patients were included in the analysis; approximately 90% had previously received platinum-based immunotherapy and chemotherapy, and 26% had brain metastases (in most cases, after previous local treatment). Median PFS in the whole analyzed population was 6.4 months. No significant differences were found in the subgroups of patients with brain metastases or ECOG 2. Treatment-related grade ≥ 3 adverse effects occurred in 23% of patients; the most common was aminotransferase elevation levels (5%). Dose reduction was required in 25% of patients [34]. The updated results of this study were presented during the European Lung Cancer Congress (ELCC) in 2023, where the results of a group of 147 patients were summarized [35]. With a median follow-up of 13.6 (95% CI 11.1–14.6) months, median OS was 9.5 (95% CI 8.6–12.0) months. The median OS rate was similar in patients with and without a history of CNS metastases. However, clinical factors such as performance status (ECOG 2), number of previous lines of treatment (> 2), and smoking status (never smokers) may have negatively influenced OS [35]. Some additional safety data were reported.

Cadranel et al. [36] presented the results of an analysis of a group of 651 patients after failure of chemotherapy, with or without immunotherapy. Fifty-one percent of patients received sotorasib immediately after failure of

immunotherapy. Due to reimbursement procedures in France, the results were presented for two cohorts of patients. The median duration of treatment with sotorasib was 7.5 (1.5–11.3) months for patients in the first group (121/130) and 3.5 (0.2–5.7) months for patients in the second group (152/549) [36].

In the 105 patients described by Thummalapali et al. [37], sotorasib treatment resulted in the ORR in 28% of patients, with median PFS and OS of 5.3 months and 12.6 months, respectively. The potential predictive value of coexisting molecular abnormalities was also demonstrated: for *KEAP1* mutations, the differences were statistically significant (for PFS HR = 3.19; p = 0.004; for OS HR = 4.10; p = 0.003). No effect on survival parameters was observed for coexisting abnormalities in the *TP53* and *STK11* genes. Furthermore, patients previously treated with immune checkpoint inhibitors had a higher incidence of adverse events. The most common was hepatic toxicity [37]. The coexistence of *KRAS* p.G12C variant with *KEAP1, SMARCA4*, and *CDKN2A* variants may limit the efficacy of sotorasib (as well as another KRAS inhibitor, adagrasib) in this patient population. However, extensive molecular profiling is not routinely performed when qualifying patients for treatment [38].

Conclusions

Currently, sotorasib monotherapy, at an initial dose of 960 mg/day, is indicated for use in adult patients with advanced NSCLC with *KRAS* p.G12C mutation who have experienced disease progression after at least one prior line of systemic treatment [39]. In the CodeBreak 200 trial, most patients received platinum-based chemotherapy and immune checkpoint inhibitors before the initiation of sotorasib. Considering the relatively high prevalence of the variant p.G12C, it is reasonable to routinely perform molecular assessment, including the *KRAS* gene, with concurrent evaluation of all clinically relevant abnormalities in NSCLC by NGS. Currently, immunotherapy or immunochemotherapy, depending on the level of PD-L1 expression, remains the standard of care for the first-line treatment of NSCLC. This also applies to patients with the p.G12C mutation in the *KRAS* gene, in whom the efficacy of immune checkpoint inhibitors is comparable to that in other patients [40–45]. Clinical trials are underway to evaluate the value of sotorasib in combination with other cancer drugs in first-line treatment (NCT05920356, NCT04933695) [46, 47]. More randomized trials are needed to determine the optimal place of sotorasib in the systemic treatment sequence in this patient population. It is important to remark on the relatively good safety profile of sotorasib, with diarrhea and liver dysfunction as the most common adverse events. At the same time, the higher risk of liver toxicity reported in the literature in patients who received immunotherapy shortly before starting sotorasib treatment should be noted [48].

In conclusion, sotorasib is the first drug to prolong PFS and significantly increase the proportion of patients who remain progression-free at 12 months in patients diagnosed with advanced *KRAS* p.G12C-mutated NSCLC after failure of systemic therapy.

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Author contributions

M.K.-W., B.W.: conceptualization, literature review, writing of draft manuscript.
Both authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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Supplementary material

None.

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