Editorial: Recent Approval of Sotorasib as the First Targeted Therapy for KRAS G12C-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC)

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Abstract
In the past two decades, there have been rapid advances in the number and range of regulatory approvals of targeted therapy for patients with advanced non-small cell lung cancer (NSCLC) and other cancers. The Kirsten rat sarcoma viral oncogene homolog (KRAS) gene has a high mutation rate in human cancers and is associated with some of the most aggressive types of cancer, including NSCLC, pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC). Until recently, several common and highly aggressive cancers with KRAS mutations expressing the ‘death star’ KRAS proteins were considered ‘undruggable’ and not amenable to targeted therapy. The main KRAS mutations are single-base missense mutations, with 98% occurring at codon 12 (G12C). KRAS G12C is the most common KRAS mutation in NSCLC. Sotorasib is a first-in-class specific small molecule that irreversibly inhibits KRAS G12C. Based on the results from the phase 1/2 CodeBreaK 100 safety and tolerability study, on May 28, 2021, the US Food and Drug Administration (FDA) granted accelerated approval for sotorasib for adults with advanced NSCLC and KRAS G12C mutation. This Editorial aims to present the current status of regulatory approval and the supporting clinical trial data for sotorasib, the first targeted therapy for patients with advanced NSCLC with the KRAS G12C mutation.

Keywords: KRAS • NSCLC • Targeted Therapy • Companion Diagnostic • Editorial

Preclinical studies, clinical studies, and early clinical trials on targeting human cancers with specific drugs began several decades ago [1]. However, the possibility of targeted therapy in oncology became realized for patients with advanced non-small cell lung cancer (NSCLC) almost 20 years ago [2]. The era of personalized medicine began with identifying epidermal growth factor receptor (EGFR) mutations and EGFR protein expression in patients with NSCLC [3,4]. In the past two decades, there have been rapid advances in the number and range of regulatory approvals of targeted therapy in NSCLC and other cancers [5,6]. The regulatory approvals in targeted drug therapies have required validation and regulatory approval of companion diagnostics [7]. In clinical practice and as part of the evaluation of patients by the oncology team, effective therapy for cancers such as NSCLC depends on histological and genomic classification, with the identification of biomarkers to guide targeted therapy [1,7]. Molecular diagnostics is now a standard component of the patient diagnosis and management pathway in oncology and directs the selection of the most effective treatment for the individual patient [1,7].

However, until recently, the most frequently mutated oncogene involved in the initiation and progression of some of the most common human cancers has eluded targeting and has previously been regarded as ‘undruggable’ [8]. Kirsten rat sarcoma viral oncogene homolog (KRAS) encodes the KRAS protein, and the KRAS gene has a high mutation rate in human cancers [9]. KRAS is associated with some of the most aggressive types of cancer, including NSCLC, pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC) [8,9]. The characteristics of KRAS proteins have made targeting KRAS challenging, which may have led to the KRAS protein becoming known as the ‘death star’ protein [10].

Early preclinical and drug development studies initially focused on using cyclin-dependent kinase inhibitors or indirectly targeting KRAS downstream effector signaling pathways [7,9]. These studies failed because of a lack of drug activity or selectivity [8,9]. Because patients with KRAS mutations often have a poor response to standard chemotherapy regimens, there has been an unmet and urgent need to target KRAS mutations in KRAS-driven human cancers [8]. The main KRAS mutations are single-base missense mutations, with 98% occurring at codon 12 (G12C), codon 13 (G13C), or codon 61 (Q61C) [8]. KRAS mutations occur with different mutation frequencies in several types of cancer, but G12C is the most common KRAS mutation in NSCLC [10]. As with EGFR mutations, in patients with lung cancer, KRAS mutations are affected by smoking [11]. The identification of one specific mutation involving glycine 12 to cysteine, KRAS G12C, has accelerated the development of several
irreversible inhibitors that covalently bind to KRAS G12C [12]. Currently, several novel direct inhibitors targeting KRAS G12C with similar covalent binding mechanisms are undergoing clinical trials. However, one key KRAS inhibitor has emerged as the front runner, and responses in patients with advanced NSCLC have, once again, supported regulatory approval.

Sotorasib is a first-in-class specific small molecule that irreversibly inhibits KRAS G12C by covalent binding to a pocket of the switch 2 region in the inactive GDP-bound conformation [13]. This mechanism traps KRAS G12C in an inactive state to inhibit KRAS oncogenic signaling [13]. The CodeBreak 100 phase 1 and 2 first-in-human, multicenter trial (NCT03600883) included a phase 1 portion that included patients with pretreated advanced solid tumors harboring the KRAS G12C mutation [14,15]. The results showed good efficacy and safety data for sotorasib monotherapy, particularly for the subgroup of patients with NSCLC [14,15]. The phase 2 portion of the CodeBreak 100 trial aimed to identify an indication for use in patients with advanced NSCLC and KRAS G12C mutation [14,15]. This trial was a dose-escalation and dose-expansion study [14,15]. The overall response rate (ORR) in 124 patients with advanced NSCLC with the KRAS G12C mutation treated with sotorasib was 36% (95% CI, 28-45) [14,15]. The median duration of response (DOR) was 10.0 months (95% CI, 6.9-NE) [14,15]. Adverse reactions occurred in ≥20% of treated patients and included diarrhea, fatigue, musculoskeletal pain, cough, nausea, and hepatotoxicity [14,15].

Based on the results from the phase 1/2 CodeBreak 100 safety and tolerability study, on May 28, 2021, the US Food and Drug Administration (FDA) granted accelerated approval for sotorasib (Lumakras®) (Amgen, Thousand Oaks, CA, USA) for adults with advanced NSCLC and KRAS G12C mutation, with a recommended dose of 960 mg orally once per day [16,17]. The indication also required that patients receive at least one previous systemic therapy [16,17]. The regulatory approval of sotorasib for advanced NSCLC is the first targeted therapy for NSCLC with a KRAS G12C mutation [16,17]. The review was conducted as part of the FDA Oncology Center of Excellence Project Orbis, which provides a framework for the submission and review of oncology drugs concurrently between international partners, including the UK Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, and others [18].

Also, in May 2021, the FDA approved the Guardant360® CDx (Guardant Health, Inc. Redwood City, CA, USA) for liquid biopsies and archival tissue samples using therascreen® KRAS RGQ polymerase chain reaction (PCR) kit (QIAGEN, Hilden, Germany) as a companion diagnostic for detection of KRAS p.G12C prior to treatment with sotorasib [19,20]. Approval of this companion diagnostic was based on validation studies that included NSCLC patients from the CodeBreak 100 trial in pre-treatment plasma samples and compared with archival tissue samples and matched tissue and plasma samples from other clinical trials. Currently, sotorasib is the only approved KRAS G12C inhibitor and has now been approved in more than 40 global markets.

On September 12, 2022, at the European Society for Medical Oncology (ESMO) Congress meeting, the results were reported from the phase 3 CodeBreak 200 randomized, controlled clinical trial (NCT04303780) [21]. The results showed superior PFS and a significantly higher ORR in patients with KRAS G12C-mutated NSCLC treated with sotorasib compared with intravenous docetaxel [21]. A significantly improved PFS with sotorasib was determined by Blinded Independent Central Review (BICR) compared to intravenous docetaxel in patients with advanced NSCLC who were heavily pre-treated [21]. The median PFS was 5.6 vs 4.5 months, respectively (HR, 0.66; 95% CI, 0.51-0.86; p=0.002) [21]. The proportion of patients with PFS at one year was 25% for sotorasib compared with 10% for docetaxel [21]. The data from CodeBreak 200 are currently under further regulatory review. Meanwhile, CodeBreak 201 is an ongoing phase 2 randomized trial to evaluate sotorasib as first-line targeted therapy in patients with stage IV NSCLC with a KRAS G12C mutation (NCT04933695). Also, several phase 1b studies are underway to investigate sotorasib monotherapy and sotorasib combination therapies in patients with several types of advanced solid tumors.

Conclusions

Until recently, several common and highly aggressive cancers with KRAS mutations expressing the ‘death star’ KRAS proteins were considered ‘undruggable’ and not amenable to targeted therapy. Therefore, the first approval of sotorasib for patients with advanced NSCLC and KRAS G12C mutation represents a milestone in precision oncology. Future clinical studies and trial data are required to identify tumor-specific responses to identify the best treatment option, for example, for NSCLC or PDAC. Although mechanisms exist for resistance to KRAS G12C inhibitors, some promising drug combination strategies include, for example, immune checkpoint inhibitors, which raise the hope of improved personalized treatment regimens for advanced NSCLC and other cancers.
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