Sotorasib: First Approval

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Abstract

Sotorasib (LUMAKRAS™) is a RAS GTPase family inhibitor being developed by Amgen for the treatment of solid tumours with \textit{KRAS} mutations, including non-small cell lung cancer (NSCLC) and colorectal cancer. In May 2021, sotorasib was granted accelerated approval by the US FDA for the treatment of adult patients with \textit{KRAS} G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. This article summarizes the milestones in the development of sotorasib leading to this first approval for \textit{KRAS} G12C-mutated NSCLC.

1 Introduction

KRAS, a GTPase and member of the RAS family of proteins, is the most frequently mutated oncogene in cancer [1]. The \textit{KRAS} G12C mutation is present in approximately 13% of patients with lung cancer, 3% of patients with colorectal cancer and 2% of patients with other solid tumours [1, 2]. Unlike other mutant KRAS proteins, KRAS G12C has been shown to cycle between its active GTP-bound and inactive GDP-bound states within cancer cells [2], thereby providing a basis for the development of targeted therapies [2, 3].

Sotorasib (LUMAKRAS™) is a RAS GTPase family inhibitor being developed by Amgen for the treatment of solid tumours with \textit{KRAS} G12C mutations. Sotorasib was given orphan drug designation by the US FDA in June 2019 for \textit{KRAS} G12C-positive non-small cell lung cancer (NSCLC) and colorectal cancer [4]. The drug was granted breakthrough therapy designation for advanced or metastatic \textit{KRAS} G12C-mutated NSCLC in December 2020 [5], and a priority review was granted in February 2021 [6]. On 28 May 2021, sotorasib received its first approval in the USA for the treatment of adult patients with \textit{KRAS} G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication was approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR), and its continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s) [7]. The recommended dosage of sotorasib is 960 mg taken orally once daily (with or without food) until disease progression or unacceptable toxicity. Dosage modifications may be required because of adverse events (AEs). The recommended dose reduction levels are as follows: first reduction to 480 mg once daily; second reduction to 240 mg once daily. If patients are unable
to tolerate a dosage of 240 mg once daily, treatment with sotorasib should be discontinued [7].

Phase I/II clinical trials of sotorasib in KRAS G12C-mutated colorectal cancer and other solid tumours are currently underway in multiple countries.

### 1.1 Company Agreements

In January 2014, Amgen and Carmot Therapeutics entered into a research, development and license agreement [9]. The agreement was extended in February 2016 [10] and December 2017 [11]. Under the terms of the agreement, Carmot Therapeutics will apply its proprietary lead-identification technology, Chemotype Evolution, to discover and develop drug leads for therapeutic targets selected by Amgen [9–11].

### 1.2 Patent Information

Amgen has patent protection for sotorasib in the USA, with an estimated expiration date of 2038 [12].

### 2 Scientific Summary

#### 2.1 Pharmacodynamics

Sotorasib is a first-in-class KRAS G12C inhibitor. It binds covalently and irreversibly to the cysteine residue of the KRAS G12C mutant [7]. Consequently, the KRAS protein is locked in an inactive state and its downstream signalling effects are blocked, without affecting wild-type KRAS [7].

Cysteine proteome analysis of cells treated with sotorasib demonstrated that only the G12C-containing peptide of KRAS was covalently modified. Sotorasib inhibited KRAS signalling (as measured by ERK phosphorylation) in all KRAS G12C mutant cell lines, but not in cell lines without the KRAS G12C mutation. Sotorasib also selectively impaired the viability of KRAS G12C mutant lines. Coadministration of sotorasib with inhibitors of other cellular signalling pathways afforded evidence for synergistic effects on cell viability [13].

In preclinical tumour models, sotorasib bound rapidly and irreversibly to KRAS G12C, thereby providing durable suppression of the mitogen-activated protein kinase (MAPK) signalling pathway [14]. Once daily administration of sotorasib led to tumour regression in mouse models of KRAS G12C cancer [14]. Sotorasib was also associated...
with prolonged survival and anti-tumour immunity in KRAS G12C models [7].

The recommended dosage of sotorasib (i.e. 960 mg once daily) was not associated with large mean increases (i.e. > 20 ms) in the corrected QT interval [7].

2.2 Pharmacokinetics

Sotorasib demonstrates non-linear, time-dependent pharmacokinetics over a dose range of 180–960 mg once daily, with similar systemic exposure [i.e. area under the concentration-time curve from zero to 24 h (AUC$_{0-24h}$) and maximum plasma concentration ($C_{max}$)] across doses at steady state [7]. Steady-state concentrations of sotorasib are achieved within 22 days, with no appreciable accumulation following repeated administration (mean accumulation ratio of 0.56). The median time to reach $C_{max}$ of sotorasib is 1 h. Compared with fasting conditions, administration of a single dose of sotorasib 960 mg with a high-fat, high-calorie meal increased sotorasib AUC$_{0-24h}$ by 25%. Sotorasib is 89% bound to plasma proteins and has a mean volume of distribution at steady state of 211 L [7].

Sotorasib is largely metabolized by non-enzymatic conjugation and oxidative metabolism with CYP3As [7]. Following administration of a single radiolabeled dose of sotorasib, 74% of the dose was recovered in faeces (53% as unchanged drug) and 6% in urine (1% as unchanged drug). The mean apparent clearance of sotorasib at steady state is 26.2 L/h and the mean terminal elimination half-life is 5 h [7].

Age (28–86 years), race (white, black or Asian), sex, body weight (36.8–157.9 kg), line of treatment, Eastern Cooperative Oncology Group performance status (ECOG PS; 0 or 1), mildly or moderately abnormal kidney function (estimated glomerular filtration rate ≥ 30 mL/min/1.73 m$^2$) and mild hepatic impairment [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 2.5 × upper limit of normal (ULN) or total bilirubin < 1.5 × ULN] did not affect the pharmacokinetics of sotorasib to a clinically significant extent [7]. The effect of severely abnormal kidney function or moderate to severe hepatic impairment on the pharmacokinetics of sotorasib is not known [7].

Coadministration of sotorasib with acid-reducing agents (e.g. omeprazole [15], famotidine [7]) or repeated doses of rifampicin (a strong CYP3A4 inducer) [16] decreased sotorasib $C_{max}$ and AUC. Coadministration of sotorasib with itraconazole [a combined strong CYP3A4 and P-glycoprotein (P-gp) inhibitor] [7], metformin (a MATE1/2K substrate) [17] or a single dose of rifampicin (an OATP1B1/1B3 inhibitor) [7, 16] did not affect the pharmacokinetics of sotorasib to a clinically significant extent. Sotorasib had no clinically relevant effect on the $C_{max}$ and AUC of metformin [17], but decreased the $C_{max}$ and AUC of the sensitive CYP3A4 substrate midazolam [7] and increased the $C_{max}$ and AUC of the P-gp substrate digoxin [18]. In vitro, sotorasib may induce CYP2B6, CYP2C8 and CYP2C9 and may inhibit BCRP, but it does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 [7].

**Features and properties of sotorasib**

| Alternative names | AMG-510; LUMAKRAS™ |
|-------------------|---------------------|
| Class             | Anti-neoplastics, piperazines, pyridines, pyridones, pyrimidines, small molecules |
| Mechanism of action| KRAS protein inhibitors |
| Route of administration | Oral |
| Pharmacodynamics | Forms an irreversible, covalent bond with the cysteine residue of the KRAS G12C mutant, thereby locking the protein in an inactive state and blocking its downstream signalling effects |
| Pharmacokinetics | Non-linear, time-dependent pharmacokinetics over dose range of 180–960 mg once daily; median time to $C_{max}$ 1 h; mean Vd 211 L; mean apparent clearance 26.2 L/h; mean $t_{1/2}$ 5 h |
| Most frequent adverse events | Decreased lymphocytes, decreased haemoglobin, diarrhoea, increased AST, increased ALT, musculoskeletal pain, decreased calcium, increased ALP, nausea, fatigue, hepatotoxicity, cough |
| Grade 3 or 4 | Hepatotoxicity, increased ALT, increased AST, musculoskeletal pain, pneumonia, diarrhoea |
| ATC codes | WHO ATC code L01 (Anti-neoplastic agents) | EphMRA ATC code L1 (Anti-neoplastics) |
| Chemical name | 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-{[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one} |

$ALP$ alkaline phosphatase, $ALT$ alanine aminotransferase, $AST$ aspartate aminotransferase, $C_{max}$ maximum plasma concentration, $t_{1/2}$ terminal elimination half-life, $Vd$ volume of distribution

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2.3 Therapeutic Trials

2.3.1 Non-Small Cell Lung Cancer

2.3.1.1 Phase II (Monotherapy) Sotorasib was associated with deep and durable responses in patients with locally advanced or metastatic KRAS G12C-mutated NSCLC in the registrational phase II portion of the ongoing, multicentre, phase I/II CodeBreaK 100 trial (NCT03600883) [19]. All patients had progressed on anti-programmed cell death protein 1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) immunotherapy and/or platinum-based chemotherapy (and targeted therapy if EGFR, ALK and ROS1 alterations were identified) and had received ≤ 3 prior lines of therapy. A total of 126 patients (median age 63.5 years) received oral sotorasib 960 mg once daily until disease progression. The primary endpoint was confirmed objective response rate (ORR), assessed by blinded independent central review per RECIST 1.1 criteria [19].

At a median follow-up of 12.2 months (data cut-off 1 December 2020), the ORR was 37% [19]. The disease control rate (DCR; defined as objective response or stable disease) was 81%. The median time to response (TTR) was 1.4 months and the median DOR was 10.0 months. Median progression-free survival (PFS) was 6.8 months. At data cut-off, 43% of responders remained on treatment without disease progression [19]. Sotorasib was also associated with improvements in patient-reported outcomes, including global health status, quality of life, physical functioning and the severity of key lung cancer symptoms (e.g. cough, chest pain, dyspnoea) [20].

In exploratory analyses, the tumour response to sotorasib was seen across a range of biomarker subgroups, including patients with negative or low PD-L1 expression level and those with mutated STK11 [19]. The clinical benefit of sotorasib was also seen regardless of age (<65 vs ≥ 65 years), ECOG PS (0 vs 1), metastatic disease (yes vs no), prior lines of therapy (1 vs ≥ 2), prior anti-PD-1/PD-L1 therapy (yes vs no), TP53 co-mutation (wild-type vs mutant), STK11 co-mutation (wild-type vs mutant), KEAP1 co-mutation (wild-type vs mutant) and tumour mutational burden (low vs high) [21].

2.3.1.2 Phase I (Dose Escalation and Expansion) Sotorasib demonstrated anti-cancer activity in patients with KRAS G12C-mutated NSCLC participating in the earlier phase I portion of CodeBreaK 100 [22]. Eligible patients (aged ≥ 18 years) had histologically confirmed, locally advanced or metastatic NSCLC with the KRAS G12C mutation and had received previous platinum-based combination therapy, targeted therapies, or both. During the dose-escalation phase, patients received oral sotorasib 180, 360, 720 or 960 mg once daily in 21-day cycles until disease progression, unacceptable toxicity, withdrawal of consent or study end. A total of 59 patients with NSCLC were enrolled; of these, 90% had received previous anti-PD-1/PD-L1 therapies and 100% had received previous platinum-based chemotherapy [22].

At a median follow-up of 11.7 months (data cut-off 1 June 2020), the ORR was 32% (all partial responses) and the DCR was 88% [22]. Responses were seen across all dose levels. Among those in the 960 mg/day cohort, the ORR was 35% and the DCR was 91%. Tumour shrinkage of

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**Key clinical trials of sotorasib (Amgen)**

| Drug(s) | Indication | Phase | Status | Location(s) | Identifier |
|---------|------------|-------|--------|-------------|------------|
| Sotorasib, docetaxel | NSCLC | III | Ongoing | Multinational | CodeBreaK 200; NCT04303780; EudraCT2019-003582-18 |
| Sotorasib | NSCLC | N/A* | Recruiting | Multinational | NCT04667234 |
| Sotorasib | NSCLC | II | Not yet recruiting | Unknown | NCT04625647; NCI-2020-08103; S1900E, U10CA180888 |
| Sotorasib, PD-1/PD-L1 inhibitors | NSCLC, colorectal cancer, solid tumours | I/II | Recruiting | Multinational | CodeBreaK 100; NCT03600883; EudraCT2018-001400-11 |
| Sotorasib, anti-cancer therapies | NSCLC, colorectal cancer, solid tumours | Ib | Recruiting | Japan, USA | CodeBreaK 101; NCT04185883 |
| Sotorasib | Solid tumours | I | Recruiting | Hong Kong, Taiwan | CodeBreaK 105; NCT04380753 |
| Sotorasib | NSCLC, solid tumours | I | Recruiting | USA | NCT04887064 |

N/A not applicable, NSCLC non-small cell lung cancer, PD-1 programmed cell death protein 1, PD-L1 programmed death-ligand 1

*Expanded access protocol*

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any magnitude was seen in 71% of patients after 6 weeks. The median TTR was 1.4 months and the median DOR was 10.9 months. Median PFS was 6.3 months [22].

2.3.2 Colorectal Cancer

Sotorasib demonstrated clinical activity in patients with colorectal cancer participating in the phase I portion of CodeBreaK 100 (n = 42) [22]. All patients had received at least two previous lines of systemic therapy for metastatic colorectal cancer. At a median follow-up of 12.8 months (data cut-off 1 June 2020), 7% of patients had an ORR (all partial responses) and 74% of patients had disease control. The median duration of stable disease was 5.4 months. In the cohort receiving sotorasib 960 mg/day (n = 25), the ORR was 12% and the DCR was 80%. Median PFS was 4.0 months [22].

2.3.3 Other Solid Tumours

In patients with other solid tumours participating in the phase I portion of CodeBreaK 100 (n = 28), sotorasib was associated with an ORR of 14% and a DCR of 75% [22]. Partial responses were seen in patients with pancreatic cancer, endometrial cancer, appendiceal cancer and melanoma (all n = 1). Five patients remained on treatment at the time of data cut-off [22].

2.4 Adverse Events

Sotorasib 960 mg once daily had a manageable tolerability profile in the subset of 204 patients with KRAS G12C-mutated NSCLC enrolled in CodeBreaK 100 [7]. The most common (incidence ≥20%) AEs in patients receiving sotorasib were diarrhoea (42%), musculoskeletal pain (35%), nausea (26%), fatigue (26%), hepatotoxicity (25%) and cough (20%). The most common (incidence ≥30%) laboratory abnormalities were decreased lymphocytes (48%), decreased haemoglobin (43%), increased AST (39%), increased ALT (38%), decreased calcium (35%) and increased alkaline phosphatase (33%). The most common (incidence ≥5%) grade 3 or 4 AEs, including laboratory abnormalities, were hepatotoxicity (12%), increased ALT (11%), increased AST (9%), musculoskeletal pain (8%), pneumonia (7%) and diarrhoea (5%) [7].

Serious AEs occurred in 50% of patients receiving sotorasib, with pneumonia (8%), hepatotoxicity (3%) and diarrhoea (2%) reported most frequently (incidence ≥2%) [7]. Fatal AEs occurred in 3% of sotorasib recipients (respiratory failure, pneumonitis, cardiac arrest, cardiac failure, gastric ulcer and pneumonia). AEs led to permanent discontinuation of sotorasib in 9% of patients, with hepatotoxicity (5%) being the most common (incidence ≥2%) reason for discontinuing treatment. Sotorasib dose reductions because of AEs were required in 5% of patients and dosage interruptions because of AEs in 34% of patients. Dose reductions were most commonly (incidence >2%) for increased ALT (3%) and increased AST (3%), and dosage interruptions were required most frequently (incidence ≥2%) for hepatotoxicity (11%), diarrhoea (8%), musculoskeletal pain (4%), nausea (3%) and pneumonia (3%) [7]. Most patients reported that they were ‘not at all’ (54–79%) or ‘a little bit’ (8–33%) bothered by sotorasib side effects on the GP5 item of the Functional Assessment of Cancer Therapy-General questionnaire [20].

The US prescribing information contains a warning stating that sotorasib may cause hepatotoxicity and potentially fatal interstitial lung disease (ILD)/pneumonitis [7]. In the pooled safety population of 357 patients with NSCLC and other solid tumours with KRAS G12C mutation enrolled in CodeBreaK 100, the incidence of grade 3 hepatotoxicity was 1.4%. Grade 3 and 4 ALT/AST elevations occurred in 6% and 0.6% of patients. The median time to first onset of increased ALT/AST was 9 weeks. Grade 3 or 4 ILD/pneumonitis occurred in 0.8% of patients; one case was fatal. The median time to first onset of ILD/pneumonitis was 2 weeks [7].

2.5 Companion Diagnostic

The US FDA has approved Guardant360® CDx, a blood-based liquid biopsy companion diagnostic developed by Guardant Health, for the identification of the KRAS G12C mutation in patients with NSCLC [23]. The therascreen® KRAS RGQ PCR Kit developed by QIAGEN has also been approved by the US FDA as a tissue-based companion diagnostic to identify the KRAS G12C mutation in NSCLC tumours [24].

2.6 Ongoing Clinical Trials

In addition to the ongoing phase I/II CodeBreaK 100 trial described above (NCT03600883), the randomized, open-label, multicentre, phase III CodeBreaK 200 trial (NCT04303780) is underway. CodeBreaK 200 will evaluate the efficacy and tolerability of sotorasib versus docetaxel in patients with previously treated advanced NSCLC harbouring the KRAS G12C mutation [25]. A phase II lung cancer master protocol (Lung MAP) trial (NCT04625647) plans to evaluate the efficacy and tolerability of sotorasib in patients with stage IV or recurrent KRAS G12C-mutated non-squamous NSCLC.

The open-label, multicentre, phase Ib CodeBreaK 101 trial (NCT04185883) is currently recruiting patients. The trial will evaluate the safety, tolerability and efficacy of sotorasib alone and in combination with other anti-cancer
therapies in patients with advanced \textit{KRAS} G12C-mutated solid tumours, including NSCLC and colorectal cancer [26]. Patients are also being recruited in CodeBreaK 105 (NCT04380753), an open-label, multicentre, phase I ethnic sensitivity study which will evaluate the safety, tolerability, pharmacokinetics and efficacy of sotorasib in patients of Chinese descent with \textit{KRAS} G12C-mutated advanced/metastatic solid tumours.

Furthermore, an expanded access programme (NCT04667234) will provide treatment access to sotorasib and assess its safety in patients with previously treated locally advanced/unresectable/metastatic \textit{KRAS} G12C-mutated NSCLC who are ineligible to participate in any ongoing sotorasib clinical trial.

3 Current Status

Sotorasib received its first approval on 28 May 2021 in the USA for the treatment of adult patients with \textit{KRAS} G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy [8].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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