Lung Cancer: Targets and Therapy

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COMMENTARY

CodeBreaK 200: Sotorasib (AMG510) Has Broken the *KRAS G12C*+ NSCLC Enigma Code

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Abstract: Per the US FDA sotorasib approval summary, *KRAS G12C* mutation is found in approximately 14% of adenocarcinoma of the lung, primarily in patients with a history of smoking. Until recently, targeted therapies against *KRAS G12C* have been largely unsuccessful due to the small protein size of *KRAS* and thus lack of binding pockets in *KRAS* and rapid hydrolysis of GTP to GDP by *KRAS* enzymes from abundance of GTP in the cytoplasm. Sotorasib, a first-in-class covalent *KRAS G12C* inhibitor that binds to the switch pocket II in the *KRAS G12C*-GDP "off" state, received US FDA accelerated approval on May 21, 2021 in the US, based on a Phase II dose expansion cohort of CodeBreaK 100 trial. Sotorasib at 960 mg once daily achieved an ORR of 36% (95% CI: 28%, 45%), with a median response duration of 10 months (range 1.3+, 11.1) in 124 *KRAS G12C*+ NSCLC. At the European Society of Medical Oncology (ESMO) 2022 annual meeting, sotorasib achieved a statistically significant improved PFS over docetaxel (HR = 0.66; 95% CI: 0. 51–0.86; P = 0.002). The modest magnitude of PFS improvement of 1.1 months (from 4.5 months to 5.6 months) and the ORR of 28% led to a vigorous debate on whether sotorasib was indeed a true breakthrough. In this pros and cons debate, we argue thatsotorasib has achieved a true breakthrough.

Keywords: non-small-cell lung cancer, *KRAS G12C* mutations, sotorasib, adagrasib, docetaxel, CodeBreaK

Targeting *KRAS G12C* Mutation NSCLC

From the largest pan-cancer *KRAS* mutation survey, *KRAS* mutations occurred in 35% of non-squamous cell carcinomas (SqCCs) and non-small-cell lung cancers (NSCLCs).[1] Among the *KRAS* mutations, *KRAS G12C* isotype mutation was the most common, occurring in 40% and 36% of non-SqCC and SqCC lung cancer, respectively.[1] Physiologically, *KRAS* catalyzes the rapid hydrolysis of guanosine-5'triphosphate (GTP) to guanosine diphosphate (GDP), hence it alternates between the active GTP-bound and inactive GDP-bound states. *KRAS G12C* mutations result from a cysteine substitution for glycine at codon 12, which shifts *KRAS* into a constitutively active state, resulting in hyperactivation of downstream signaling of cell proliferation, survival, and tumorigenesis pathways.[2] Until recently, targeted therapies against *KRAS G12C* mutations have been largely unsuccessful due to small binding pocket size, rapid conversion from active GTP to inactive GDP, and abundance of GTP in the cytoplasm.

Accelerated Approval Sotorasib (AMG-510) Based on CodeBreaK 100 (NCT03600883)

Sotorasib (AMG510) is a first-in-class covalent *KRAS G12C* inhibitor that targets the inactive form of *KRAS* through covalent binding to the exposure cysteine residue on the "switch pocket II" of the *KRAS*-GDP isoform.[3] Sotorasib was granted accelerated approval by the US Federal Drug Administration (FDA) on May 21, 2021 for the treatment of patients with *KRAS G12C*-mutated locally advanced or metastatic non–small-cell lung cancer (NSCLC), following at least one prior systemic therapy based on overall response rate (ORR) and duration of response (DOR) from the

Received: 4 January 2023
Accepted: 10 April 2023
Published: 20 April 2023

expansion cohort of CodeBreaK 100 patients.[4,5] Prior to this accelerated approval, sotorasib was granted Orphan Drug Designation for the treatment of *KRAS G12C*-mutated NSCLC on May 1, 2019.[5]

All *KRAS G12C* mutations in the pivotal Phase II trial were confirmed by central laboratory using the Therascreen *KRAS* RGQ PCR Kit.[5] Overall, treatment with 960 mg once daily of sotorasib demonstrated an ORR of 36% (95% CI: 28–45) among 124 patients with *KRAS G12C* mutation-positive NSCLC, who experienced disease progression after receiving immunotherapy and/or chemotherapy (but not all had been treated with chemotherapy and immunotherapy). The median DOR was 10.0 months (95% CI: 6.9–NR).[4,5] The most common adverse reactions (≥20%) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. Adverse reactions resulting in permanent discontinuation of sotorasib occurred in 9% of patients. For the 100 patients who had received both chemotherapy and immunotherapy (IO) (entry criteria for CodeBreaK 200), the ORR was 31% (95% CI: 22–41) and DOR of 10.0 months (95% CI: 6.9–NR).[5] See Table 1.

As with all FDA accelerated approvals, at least one randomized confirmatory Phase III trial had to be initiated, and patients enrolled at the time of accelerated approval. Continued approval is contingent upon verification and description of clinical benefits in a confirmed trial, which, in this instance is CodeBreaK 200. The results of this trial were presented at the annual meeting of the European Society of Medical Oncology (ESMO) 2022 and subsequently published in *The Lancet*.[6]

CodeBreaK 200 (NCT04303780) (Confirmatory Randomized Phase III Trial of Sotorasib versus Docetaxel)

CodeBreaK 200 is a global open-label study randomizing *KRAS G12C*+ NSCLC patients who had received both prior chemotherapy and immunotherapy treatment in a 1:1 ratio to either sotorasib 960 mg once daily[7] or docetaxel at 75 mg/m^2 IV every three weeks. Stratification factors included number of prior lines of therapy (1 vs 2 vs >2), race (Asian vs non-Asian), and history of brain metastasis (yes/no). Of note, patients with active brain metastases were excluded. The primary endpoint was Blind Independent Review Committee (BIRC) progression-free survival (PFS), with overall

Table 1 Comparison of Efficacy and Safety of Sotorasib in Phase II and Phase III Trials

	CodeBreaK 100*	CodeBreaK 100 (Post Chemo + IO)	CodebreaK 200**
N (sotorasib treated)	124	100	171
Prior chemotherapy	90%	100%	100%
Prior immunotherapy	91%	100%	100%
Progressive disease on enrollment	81%	NR	NR
BIRC-assessed ORR (%)	36 (95% CI: 28–45)*	31 (95% CI: 22–41)*	28.1 (95% CI: 21.5–35.4)
DOR (months)	10.0 (95% CI: 6.9 – NR)*	10.0 (95% CI: 6.9 – NR)*	10.6 (95% CI: 8.9–14.0)
DOR ≥6 months	58%*	58%*	
PFS (months)	6.8 (95% CI: 5.1–8.2)	NR	5.6 (95% CI: 4.3–7.8)
OS (months)	12.5 (95% CI: 10 – NR)	NR	10.6 (95% CI: 8.9–14.0)
Top 5 AEs	Diarrhea (50.8%) Nausea (31.0%) Fatigue (25.8%) Arthralgia (21.4%) AST increase (21.4%)	NR	Diarrhea (33.7%) Nausea (14.2%) Appetite decrease (10.7%) AST increase (10.1%) ALT increase (10.1%)

Note: *Federal Drug Administration (FDA) approval summary.
Abbreviations: AEs, adverse events; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BIRC, blind independent central review; CI, confidence interval; DOR, duration of response; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

survival (OS), ORR, safety, and quality of life as secondary endpoints. Per US FDA guidance, the protocol was amended to reduce planned enrollment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted, thus an OS was unlikely to be achieved.[6]

Overall, 171 patients were randomized to sotorasib and 174 patients to docetaxel. The median BIRC-assessed PFS with sotorasib was 5.6 months (95% CI: 4.3–7.8) versus 4.5 months for docetaxel (95% CI: 3.0–5.7), with a stratified proportional HR of 0.66 (95% CI: 0.51–0.86; p = 0.002). Importantly, 12-month PFS rate was 24.8% for sotorasib versus 10.1% for docetaxel. Sotorasib achieved a significantly higher ORR of 28.1% (95% CI: 21.5–35.1) compared to ORR of 13.2% (95% CI: 8.6–19.2) for docetaxel (p <0.001) and DCR of 60.3% (95% CI: 52.7–67.7). The DOR was 8.6 months (95% CI: 7.1–18.0) with sotorasib compared to 6.8 months (95% CI: 4.3–8.3) achieved by docetaxel. There was no OS benefit with 10.6 months achieved by sotorasib (95% CI: 8.9–14.0) versus 11.3 months achieved by docetaxel (95% CI: 9.0–14.9)[6] (Table 1).

CodeBreaK 200 Subgroup Analysis

Of the three stratification factors, both Asians and non-Asians benefited from sotorasib over docetaxel. In fact, Asian patients seemed to gain more benefit from sotorasib (HR = 0.33 95% CI: 0.14, 0.80), with a median PFS of 8.3 months for Asian patients treated with sotorasib; this finding must be viewed with caution, however, because the number of Asians enrolled was limited. Patients without brain metastasis (HR = 0.74; 95% CI: 0.53–1.03) and patients with only 1 prior line of therapy (HR = 0.70; 95% CI: 0.47–1.04) just missed the significance threshold for PFS benefit of sotorasib over docetaxel. Nevertheless, there was numerical improvement in PFS of sotorasib over docetaxel.

Docetaxel "Over-Performed" in CodeBreaK 200

Finally, the hazard ratio in a randomized Phase III trial is a comparison between the investigational arm versus the standard of care arm. The median PFS of 4.5 months achieved by patients in the docetaxel arm is the highest median PFS achieved by docetaxel in a randomized trial in the second line setting. In the REVEL trial that established a docetaxel and ramucirumab combination trial, the median PFS for docetaxel was only 3 months whereas for the combination arm it was 4.5 months.[8] In the two docetaxel versus immunotherapy monotherapy randomized Phase III trials (Keynote-010 and OAK), the median PFS achieved by docetaxel was 4.0 months in patients with any PD-L1 expression.[9,10]

Sotorasib in CodeBreaK 200 Achieved Its Pre-Specified Primary Endpoint

Another criticism of CodeBreaK 200 was that there was no OS benefit despite only 34% of the docetaxel-treated patients receiving a *KRAS G12C* inhibitor. However, the sample size of CodeBreaK 200 was reduced as per US FDA recommendation to achieve a faster read-out of the clinical efficacy data. The magnitude of the improvement in PFS of sotorasib over docetaxel may be less than what most oncologists had expected or anticipated based on the Phase II results of sotorasib in *KRAS G12C*+ NSCLC.[4] However, for regulatory purposes, CodeBreaK 200 achieved its primary endpoint of significant improvement of PFS and, per regulatory purposes, should result in full regulatory approval for sotorasib. CodeBreaK 200 results are a proof of principle that *KRAS G12C* is a targetable mutation. The commercial marketplace will determine how sotorasib is widely prescribed pending the results from other competing covalent *KRAS G12C* inhibitors.

Pending Questions About Sotorasib Dosing

In the Phase 1 dose escalation portion of sotorasib, sotorasib was dosed from 180 mg, 360 mg, 720 mg and 960 mg once daily.[11] Per the US FDA approval summary after analyzing the data submitted by Amgen, systemic exposures (ie, AUC_{0-24h} and C_{max}) of sotorasib after daily administration of doses ranging from 180 mg to 960 mg were similar (Table 1). In addition, overall response rates (ORRs) ranging from 25–50% were observed in patients with NSCLC who were treated with lower doses of sotorasib in the dose escalation portion of the trial (N ranging from 3–16 per dose level). As such, a post-marketing requirement (PMR) by the US FDA required a randomized study of two doses of sotorasib (240 mg once daily vs 960 mg once daily) (CodeBreaK 201) (NCT04933695).

The First Breakthrough Established a New Field but is Never the Last Breakthrough

We have learned in targeted therapy in lung cancer that the first positive trial established the field; however, it is not the final advance to be made. For example, when first-generation (1G) EGFR TKIs achieved greater clinical efficacy than platinum-based doublet chemotherapy, they became the standard of care.[11] However, with time, the now third-generation (3G) EGFRTKIs have consistently demonstrated statistically significant PFS over 1G EGFR TKIs.[12] Similarly, crizotinib, the first ALK TKI approved, demonstrated in the PROFILE1014 trial statistically significantly improved PFS over platinum-based chemotherapy.[13] Of note, the randomized trial of crizotinib in ALK+ NSCLC involved crizotinib demonstrating statistically significantly improved PFS over single agent chemotherapy very similar to the current CodeBreaK 200.[14]

Sotorasib is the First but Not the Only Covalent *KRAS G2C* Inhibitor to Be Approved

There are many covalent *KRAS G12C* inhibitors being developed and some of the Phase II expansion cohort results in *KRAS G12C*+ NSCLC are presented and summarized in Table 2 (1adagrasib,[15] JDQ443,[16] GDC-6036,[17] B-1553[18]). Overall, the ORR among the current *KRAS G12C*s are similar and we look forward to clinical efficacy and safety data that may differentiate these covalent *KRAS G12C* inhibitors.

Indeed, adagrasib was granted accelerated approval by the US FDA on December 12, 2022.[19] Approval was based on KRYSTAL-1, a multicenter, single-arm, open-label clinical trial (NCT03785249), which included patients with locally advanced or metastatic NSCLC with *KRAS G12C* mutations. Efficacy was evaluated in 112 patients whose disease had progressed on or after platinum-based chemotherapy and an immune checkpoint inhibitor, given either concurrently or sequentially. The main efficacy outcome measures were confirmed ORR according to RECIST 1.1, as evaluated by blind independent central review, and DOR. The ORR was 43% (95% CI: 34%, 53%) and median DOR was 8.5 months (95% CI: 6.2, 13.8).[15] The full approval of adagrasib will hinge on demonstrating clinical benefit in a pivotal Phase III trial (Table 3).

Other Confirmatory Randomized Trials of *KRAS G12C* Inhibitors versus Docetaxel (KRYSTAL-12, B-FAST, KontRASt-02)

Several of the *KRAS G12C* inhibitors have advanced past Phase II dosing and Phase III trials are on-going including adagrasib (KRYSTAL-12, NCT04685135), GDC (B-Fast, NCT03178552), JDQ433 (KontRASt-02, NCT05132075) (Table 3). The design of these pivotal trials is similar, with cross-over allowed and PFS as the primary endpoint.

Unmet Needs of Current Covalent *KRAS G12C* Inhibitors and Future Directions

As we look forward to more positive second-line randomized trials for the other *KRAS G12C* inhibitors, the results of CodeBreaK 200 and other *KRAS G12C* inhibitors have raised several therapeutic challenges and unknowns.

Efficacy of Covalent *KRAS G12C* Inhibitors in Patients with Brain Metastasis

There is a high propensity for *KRAS G12C*+ NSCLC patients to develop CNS metastasis.[20] The efficacy of these covalent *KRAS G12C* inhibitors has not been consistently demonstrated. In the CodeBreaK 100 and 200, patients with untreated brain metastases were not eligible for entry, thus limiting assessment of CNS efficacy of sotorasib.

Studies of patients with RECIST-defined measurable brain metastases, allowing asymptomatic *KRAS G12C*+ NSCLC patients with brain metastases to engage in clinical trials, are on-going.[20]

Table 2 Reported Phase II Trial of Covalent *KRAS G12C* Inhibitors

Drug	Sotorasib	Adagrasib	JDQ443	D-1553	GDC-6036
Trial name	CodeBreaK 100 (KRAS G12C+ NSCLC)	Krystalis-1	KontRASt-01		
Dosing (RP2D)	960 mg daily	600 mg twice daily	200 mg twice daily	600 mg twice daily	400 mg daily
Participants	126	116	20	32	32
Median age	63.5 years	64 years	64 years	65 years	67 years
Current/former smoker	93%	96%	Unknown	Unknown	93%
Prior immunotherapy	92.1%	98%	Unknown	Unknown	86%
Prior chemotherapy	91.3%	100%	Unknown	Unknown	90%
Median prior therapies (range)	2	2	2	2	1
Brain metastases	20.6%	21%	Unknown	Unknown	Unknown
ORR	37.1% (95% CI 28.6–46.2)	43% (95% CI 33.5–52.6)	57% (4/7)	40.6% (13/32)	53% (30/57)
DOR	11.1 months (95% CI 6.9-NR)	8.5 months (95% CI 6.2–13.8)	15.9 weeks (range 2.0–27.1)	Pending	Pending
PFS	6.8 months (95% CI 5.1–8.2)	6.5 months (95% CI 4.7–8.4)	Pending	Pending	Pending
OS	12.5 months (95% CI 10.0-NR)	12.6 months (95% CI9.2–10.2)	Pending	Pending	Pending
DCR	80.6% (95% CI 72.6–87)	80% (95% CI 70.8–86.5)	Pending	84.4% (27/32)	Pending
AEs	99.2%	97%	72.7%	78%	88.1%
Common AEs	Diarrhea (50.8%) Nausea (31%) Fatigue (25.4%)	Diarrhea (63%) Nausea (62%) Vomiting (47%)	Nausea (27.3%) Vomiting (27.3%) Fatigue (18.2%)	Elevated AST (30.5%), elevated ALT (28.8%), elevated GGT (20.3%)	Nausea (76.3%), diarrhea (61%), vomiting (54.2%)

Abbreviations: AEs, adverse events; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RP2D, recommended Phase II dose.

https://doi.org/10.2147/LCTT.S403614 DovePress

Table 3 On-Going KRASG12C Covalent versus Docetaxel Trial

Drug	Sotorasib	Adagrasib	JDQ443	GDC-6036
Trial	CodebreaK 200 (NCT04303780)	KRYSTAL-12 (NCT04685135)	KontRASt-02 (NCT05132075)	B-FAST cohort G (NCT03178552) (RO7435846)
N	345	340	360	NA
Randomized	1:1	1:1	1:1	NA
Prior chemotherapy required	Yes	Yes	Yes	NA
Prior ICI required	No	No	Yes	NA
Stage IIIB/C allowed	Yes	Yes	Yes	NA
Stratification factors	Prior lines of therapy, race, brain mets		Prior lines of treatment; ECOG PS	NA
Plasma ctDNA alone allowed	Not allowed	No	No	NA
Cross-over allowed	Yes	Yes	Yes, if and after primary endpoint is met	NA
Primary endpoint	BIRC-assessed PFS	BIRC-assessed PFS	BIRC-assessed PFS	NA
Number of clinical sites opened	274	142	NA	NA

Abbreviations: BIRC, Blind Independent Review Committee; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not available; PFS, progression-free survival.

Incorporating Immunotherapy into *KRAS G12C Inhibitors* and Deciphering the Role of *STK11*, *KEAP1*, and *NFE2L2* Genomic Co-Alterations in Response Modulation

KRAS G12C+ NSCLC has heterogeneous genomic alterations but three different mutations (*STK11, KEAP1, NFE2L2*) are of therapeutic interest. All three have been shown to negatively modulate response to immunotherapy.[21,22] Indeed, in the largest survey of *KRAS* mutations in solid and liquid tumors, STK11 and *KEAP1* mutations were positively associated with *KRAS G12C* mutation non-squamous NSCLC.[1] *KRAS G12C*+ NSCLC is more commonly found in current/former smokers whose tumors are high expressers of PD-L1.[1] Importantly, the percentage of *KRAS G12C*+ NSCLC which had PD-L1 expression of >1% were 72% (non-SqCC NSCLC) and 81% (SqCC NSCLC), respectively. Thus, combining *KRAS G12C* inhibitors with immunotherapy is the next holy grail of targeted *KRAS G12C*+ NSCLC. To date, single-agent *KRAS G12C* inhibitors (sotorasib and adagrasib) had similar efficacy in terms of ORR among *STK11, KEAP1*, and *NFE2L2* mutations.[4,15]

Combination of sotorasib with anti-PD-1 or anti-PD-L1 immunotherapy (pembrolizumab have been presented.[23] The researchers enrolled 58 *KRAS G12C* inhibitor-naïve *KRAS G12C*+ NSCLC patients and treated them in 12-dose exploration cohorts at varying doses of sotorasib (120–960 mg daily) in combination with either atezolizumab 1200mg or pembrolizumab 200mg, administered concurrently every three weeks until intolerability or disease progression. Half of the cohorts were lead-in cohorts, where patients received sotorasib monotherapy for either 21 or 42 days prior to their first dose of immunotherapy, then received atezolizumab or pembrolizumab together with sotorasib. The dose-limiting toxicity window was 21 days following initiation of combination treatment.

The 58 patients were treated with a median follow-up of 12.8 months (range: 1.6, 29.9). Median prior lines of therapy were 1 (range 0–7); 67% patients received prior IO. The median doses of sotorasib were 83 (range: 22–791), and median doses of immunotherapy were three (range: 1–26]. The most common grade 3–4 treatment-related adverse events were increased ALT and AST. Of patients with grade 3–4 hepatotoxicity, first adverse events occurrence was outside the dose-limiting window in 22 of 25 (88%) patients; most were managed with corticosteroids, and 97% of events resolved. No

fatal adverse events occurred. Grade 3–4 adverse events and adverse events leading to treatment discontinuation occurred less often in the lead-in versus concurrent cohorts. Across all 12 cohorts, confirmed response was observed in 17 of 58 patients (29%; range, 0–67). Among the 17 responders, median duration of response was 17.9 months (range: 1.5+, 23.4). For all 58 patients across cohorts, median overall survival was 15.7 months (95% CI: 9.8–17.8).[23]

Adagrasib 400 mg twice daily (less than the approved 600 mg twice daily) in combination with pembrolizumab 200 mg intravenous (IV) every 3 weeks has also reported preliminary results for 7 patients from KRYSTAL-1 and 75 patients from KRYSTAL-7 (11 with PD-L1 <1% and 62 with PD-L1 >/=1%).[24] The majority (99%) were current or former smokers.

Among the 53 evaluable patients, the ORR was 49% (95% CI: 35–63) and DCR was 89% (95% CI: 77–96) across all PD-L1 expression levels. Responses were observed in 59% (13/22) of patients with PD-L1 TPS ≥50%, in 48% (10/21) with PD-L1 TPS 1%−49%, and in 30% (3/10) with PD-L1 TPS <1%. Importantly for safety, aspartate aminotransferase (AST) and alanine transaminase (ALT) elevation each occurred in 21% of the patients with grade 3 toxicities, in 9% (AST elevation) and 8% (ALT elevation), respectively. The median time to onset for ALT and AST increase was 26 days and 37 days, respectively; only 1 patient reported new onset treatment-associated ALT/AST increase after 3 months.[24]

Moving to First-Line Treatment of *KRAS G12C*+ NSCLC

The standard of care for first-line treatment of NSCLC without activating *EGFR* or ALK fusion is chemotherapy and immunotherapy for PD-L1 <50% and either chemotherapy and immunotherapy or immunotherapy monotherapy. Regardless, in order to encompass all *KRAS G12C*+ NSCLC, based on the adagrasib and sotorasib immunotherapy combination, several clinical trials are necessary to determine the most efficacious and safe treatment approach, such as immunotherapy vs *KRAS G12C* inhibition and immunotherapy + *KRAS G12C* inhibitor for PD-L1 ≥50%. For PD-L1 <50%, a separate pivotal Phase III chemoimmunotherapy ± *KRAS G12C* inhibitor will have to be conducted. However, safety and tolerability of chemotherapy + immunotherapy + *KRAS G12C* inhibitor must be firmly established first.

Overcoming Multiple Simultaneous on-Target and off-Target Resistances

Lastly, resistance to sotorasib[25] and adagrasib[26] monotherapy has been reported. The resistance mechanisms are driven by both on-target acquired resistance mutations (mutation at the cysteine residues that abolishes the binding of covalent *KRAS* inhibitors) and off-target such as MEK bypass pathway and even receptor tyrosine kinase fusions. Thus, combination therapy with *KRAS G12C* inhibitors with other targeted therapy is another challenge, given the multiple resistance pathways that appeared at the same time. One approach is to inhibit the upstream action of *KRAS* with SH2 containing protein tyrosine phosphatase-2 (SHP2) or SOS Ras/Rac guanine nucleotide exchange factor 1 (SOS1) inhibitors. Trials with SHP2 inhibitors are on-going with both sotorasib (with RMC-4630 [NCT05054725] and BBP-398 [NCT05480865]) and adagrasib (with TNO-155 [KRYSTAL-2, NCT04330664]). Combination of adagrasib with an SOS1 inhibitor (BI-1701963) (KRYSTAL-14, NCT04975256]) has been completed. We eagerly await the results of these combination trials.

Sotorasib Activity in Advanced KRAS *G12C*+ Colorectal Adenocarcinoma and Pancreatic Adenocarcinoma

Finally, sotorasib has demonstrated clinical activity in advanced KRAS *G12C*+ colorectal and pancreatic adenocarcinoma. Results from 62 patients in the colorectal cancer arm of CodeBreaK 100 were recently published. In response to sotorasib monotherapy, ORR was 9.7% (95% CI: 3.6–19.9). Grade 3 or higher treatment-related adverse events were seen in only 10% of patients, most commonly diarrhea (3%), creatine phosphokinase increase (2%), and acute kidney injury (2%).[27] Additionally, 38 patients from the pancreatic cancer arm of CodeBreaK 100 demonstrated an ORR of 21% (95% CI: 10–37), with median PFS 4.0 months (95% CI: 2.8–5.6). The median OS was 6.9 months (95% CI: 5.0–9.1), with treatment-related adverse events in 42% of patients.[28] While the clinical activity of sotorasib was modest in KRAS *G12C*+ CRC, the ORR of 21% in KRAS *G12C*+ pancreatic adenocarcinoma gives patients with this deadly disease real hope and affirms the activity of sotorasib against *KRAS G12C* mutation across KRAS *G12C*+ solid tumors and further highlights the clinical benefit in NSCLC.

Executive Summary

1. CodeBreaK 200 achieved its primary endpoint of statistical improvement in median PFS of sotorasib over docetaxel.
2. Sotorasib also achieved higher ORR and 12-month PFS rates than docetaxel monotherapy.
3. Sotorasib has demonstrated clinical activity against other *KRAS G12C*+ solid tumors. Hence, while the absolute improvement in median PFS in CodeBreaK 200 was modest, sotorasib in CodeBreaK 200 represents the beginning of targeted therapy in *KRAS* mutated solid tumors.

Disclosure

Dr Saihong Ignatius Ou reports personal fees from Pfizer, membership of Scientific Advisory Board, stock ownership from Elevation Oncology, personal fees from DAVA Oncology LLP, personal fees from JNJ/Jassen, personal fees from BeiGene, personal fees from Lilly, stock ownership from Turning Point Therapeutics, personal fees from Roche, outside the submitted work. The authors report no other conflicts of interest in this work.

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