Editorial Commentary

CodeBreak 200: study limitations, and future directions

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Background

In recent years, groundbreaking advancements in lung cancer research have paved the way for innovative treatments directly targeting KRAS mutations, which have long erstwhile been considered undruggable due to their high substrate [guanosine triphosphate (GTP)] affinity in the picomolar range and lack of known regulatory binding sites. KRAS mutations in non-small cell lung cancer (NSCLC) occur in hotspots most frequently in exons 2 and 3, specifically at codons 12, 13, and 61, with variable biochemical properties across the different mutants (1). Notably, the KRAS p.G12C mutation, characterized by glycine (G) to cysteine (C) substitution at codon 12 which comprises around 40% of KRAS mutations found in NSCLC or 13–16% of known oncogenic drivers in NSCLC in the Western Hemisphere, maintains near normal levels of intrinsic GTP hydrolysis in contrast to other KRAS mutations, thus able to cycle between guanosine diphosphate (GDP)-bound (inactive) and GTP-bound (active) states. This genotype-specific biochemical feature, aside from advancements in structural analysis, set the stage for the generation of mutation-selective covalent inhibitors that can irreversibly bind to the GDP-bound (inactive) form of KRAS G12C (2).

Sotorasib is the first-in-class agent in clinical development that covalently inhibits KRAS G12C by trapping it irreversibly in its inactive GDP-bound (OFF) conformation. In the phase 1/2 CodeBreak100 (CB100) trial, sotorasib demonstrated promising clinical efficacy and safety profile in patients with KRAS G12C mutated NSCLC who had been previously treated with at least one prior line of systemic therapy. This led to its accelerated approval by the United States Food and Drug Administration (US FDA) on May 28, 2021. Furthermore, sotorasib showcased its ability to provide durable clinical benefits on longer follow-up, revealing an overall response rate (ORR) of 41% and a 2-year overall survival (OS) rate of 33% (3). Encouraged by these findings, the phase 3 CodeBreak 200 (CB200) trial ensued, focusing on a head-to-head comparison of sotorasib 960 mg once daily *vs.* docetaxel 75 mg/m^2 every 3 weeks in patients previously treated for advanced KRAS p.G12C mutated NSCLC.

Highlights of CB200

CB200 is an open-label, randomized, multicenter study in which 330 patients aged 18 years and above were enrolled largely from sites outside of US (4). The trial included patients with locally unresectable or metastatic KRAS G12C mutated NSCLC following progression on at least one systemic therapy, including platinum-based chemotherapy and immune checkpoint inhibitor (unless contraindicated). Notably, patients with untreated, progressing, or symptomatic brain metastases were excluded from the study. While patients with known treated/stable brain metastases were enrolled and comprised approximately a third of enrolled patients in each group (sotorasib 33%; docetaxel 34.5%). Lastly, those with other actionable mutations for which approved therapies were available, such as EGFR or ALK, were excluded.

The primary endpoint of progression-free survival (PFS), as determined by blinded independent central review (BICR), was achieved. With a median follow-up of 17.7 months, the median PFS was 5.6 months in the sotorasib arm compared to 4.5 months in the docetaxel arm [hazard ratio (HR), 0.66; 95% confidence interval (CI): 0.51–0.86; P=0.002]. Notably, the 12-month PFS rates were 24.8% and 10.1% for sotorasib and docetaxel, respectively. Furthermore, ORR was 28.1% in the sotorasib arm and 13.2% in the docetaxel arm (P<0.001). The disease control rates (DCRs) were 82.5% and 60.3% for sotorasib and docetaxel, respectively. Finally, the median duration of response (DOR) was 8.6 and 6.8 months for sotorasib and docetaxel, respectively.

What about the choice of the control arm?

An important consideration when evaluating randomized studies is the choice of the comparator control arm. As a historical reminder, the REVEL trial demonstrated that the combination of docetaxel and ramucirumab provided a median OS benefit of 1.4 months over docetaxel alone (HR, 0.86; 95% CI: 0.75–0.98; P=0.023), albeit with increased treatment-emergent adverse events (5). The combination received US FDA approval for NSCLC second-line indication in December 2014. In the CB200 study, the use of single-agent docetaxel as the comparative control may arguably have been suboptimal for US standards. However, ramucirumab is not routinely utilized as a world-wide standard largely due to cost. In addition, there are more stringent eligibility criteria for treatment using docetaxel and ramucirumab; thus, the combination with ramucirumab does not have wide applicability in practice. In fact, real-world evidence of treatment patterns in the US reveals that approximately half of NSCLC patients (including those with KRAS G12C mutation specifically) who received second-line therapy since 2015 received docetaxel alone (6,7). OS analysis with the ramucirumab combination in the real-world setting also does not show superiority despite better real-world PFS and ORR (8). In fact, real-world OS in two separate cohorts (US and Asia) was numerically longer in patients treated with docetaxel only *vs.* combination regimens (6,7). Thus, while the choice of docetaxel as the control arm has been raised as a criticism, practical real-world considerations as outlined above provide rationale for why it remains a valid choice as a comparator arm.

What about the OS endpoint?

Another point raised as a criticism to the adoption of sotorasib is that CB200 did not show a significant difference in OS between sotorasib and docetaxel. This may partly be attributable to crossover to another KRAS G12C inhibitor among 81% of patients in the docetaxel arm who received subsequent therapy (representing 34% of the entire control group), whereas proportionately less patients in the sotorasib arm received subsequent chemotherapy (58% of patients in the sotorasib arm who received subsequent therapy, representing 21% of the entire sotorasib group). The lack of OS benefit however does not diminish the value of sotorasib, considering its overall better side effect profile. Patient-reported outcomes demonstrated improvements with sotorasib compared to docetaxel in time to deterioration of global health status, physical function, and cancer-related symptoms. Specifically, sotorasib was associated with a 31% reduction in the risk of quality-of-life (QoL) deterioration compared to docetaxel (HR, 0.69; 95% CI: 0.53–0.91; P=0.005). Moreover, sotorasib delayed physical functioning deterioration by 31% compared to docetaxel (HR, 0.69; 95% CI: 0.52–0.92; P=0.007). Indeed, lack of OS superiority is not the only endpoint of interest when other safety profile and/or QoL metrics are included, as evidenced by the preferential use of agents that did not show OS superiority to docetaxel as second-line therapy in NSCLC in randomized trials (leaving aside differences in subsequent therapy exposure, endpoints of interest, study design and statistical analyses utilized), such as 1st-generation ALK-tyrosine kinase inhibitor (TKI) crizotinib in ALK-mutated NSCLC (9) or pemetrexed (10) over docetaxel due to improved PFS and/or better side effect profile.

How about the influence of other biomarkers?

Although not reported in the original publication, an important component of the CB200 study involved gathering data on the presence of co-alteration mutations in addition to the KRAS mutational profile. Subsequently, this data was further investigated through an exploratory analysis, which was presented at the 2023 American Society of Clinical Oncology (ASCO) annual meeting (11). Investigators analyzed genomic alterations using tissue and/or plasma samples with targeted next-generation sequencing

(NGS) assays. Of the 345 patients, baseline co-alterations were well balanced across treatment arms: sotorasib demonstrated a PFS benefit over docetaxel across all key co-alteration subgroups, including those with STK11-altered, KEAP1-altered, and TP53-altered disease, as well as those with wild-type disease. The improvement in PFS with sotorasib was also observed independent of PD-L1 expression. In contrast, patients with additional KRAS alterations showed objective response to neither sotorasib nor docetaxel. Moreover, exploratory analysis identified a potential early progression signal for NOTCH1-mutated tumors in the sotorasib arm, while patients with NOTCH1 mutations who received docetaxel experienced long-term clinical benefit. These findings need further validation prospectively.

How about brain metastases?

One crucial point is that approximately 27–42% of patients with advanced NSCLC present with central nervous system (CNS) involvement at diagnosis (12). In both CB100 and CB200 trials, patients with untreated or progressing brain metastases were excluded. Adagrasib, another irreversible (OFF) inhibitor of the KRAS G12C mutation which also covalently inhibits KRAS G12C at shared but also different binding sites as sotorasib, demonstrated high cerebrospinal fluid (CSF) concentration in preclinical models (13), leading to its evaluation as monotherapy in a subgroup of KRAS G12C mutated NSCLC patients with untreated asymptomatic CNS metastases at the recommended phase 2 dose of 600 mg twice a day in the KRYSTAL-1 study. In this untreated brain metastases NSCLC cohort, confirmed intracranial (IC) ORR of 35% using the modified response assessment in neuro-oncology brain metastases (RANO-BM) criteria was observed in 20 evaluable patients, with IC DCR of 85%, median IC PFS of 4.8 months, median IC DOR of 9.7 months. Overall systemic response by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) in the 20 evaluable patients showed ORR of 30%, median PFS (mPFS) of 5.3 months, and median DOR (mDOR) of 5.6 months (14,15). Based on these data along with the registrational phase 2 cohort data from KRYSTAL-1 study (16), adagrasib received accelerated approval by US FDA on December 12, 2022, for adults with previously treated locally advanced or metastatic KRAS G12C-mutated NSCLC. Notably, in the post-hoc evaluation of adagrasib in the phase 2 cohort of KRYSTAL-1 study in NSCLC which allowed enrollment of patients with known previously treated brain metastases (i.e., presence of active brain metastases was an exclusion criterion), median IC PFS in 42 patients with CNS metastases at baseline was 5.4 months (95% CI: 3.3–11.6). That the CNS PFS among this group of patients was not better compared to those with untreated brain metastases may potentially be attributable to dose reduction required for majority of patients to manage treatment-related adverse events as well as limited duration of PFS in general.

Activity of sotorasib in NSCLC patients with untreated CNS metastases remains anecdotal despite several case reports (17-20) as CodeBreak studies published to date limited enrollment to NSCLC patients with treated brain metastases. Nonetheless, it is reassuring to see that in the pre-planned exploratory analysis of CB200 among those with known CNS metastases (sotorasib, n=58; docetaxel, n=60), median time to recurrence of CNS disease was delayed with sotorasib compared to docetaxel (15.8 *vs.* 10.5 months; HR, 0.52; 95% CI: 0.26–1.03), likely reflecting the effect of superior extracranial disease control but also indirectly raising the possibility of CNS activity as well that needs to be prospectively characterized and confirmed. Post-hoc analysis of CNS PFS showed superior outcomes with sotorasib (median, 9.6 months) *vs.* docetaxel (median, 4.5 months), HR, 0.53 (95% CI: 0.28–1.03), P=0.03 (21). *Table 1* summarizes the comparison between different treatment groups.

What about mutation testing?

Lastly, timely accessibility to biomarker testing is crucial for identifying KRAS G12C mutations and other driver oncogene mutations. A recent retrospective study by Vidal *et al.* of Flatiron Health electronic health record (EHR)-derived data from approximately 280 cancer centers (22) revealed inequities at both the practice and provider levels regarding obtaining NGS testing based on race/ethnicity for patients with advanced NSCLC treated in the community setting. This study found low overall NGS testing rate in the community (51% at best), but even worse with approximately 8% absolute lower rates among Latinx and non-Latinx black patients compared with non-Latinx white patients. Globally, testing algorithms vary even more due to regional cost-effectiveness analysis and access. Even in Europe, for example, KRAS biomarker testing is recommended to be included upfront in the Netherlands and Sweden but not in other Western European countries. Limited reimbursement was identified as a barrier to

Table 1 Comparison of IC treatment outcomes for KRAS G12C mutated NSCLC patients with known stable, treated CNS metastases receiving treatment with either adagrasib, sotorasib, docetaxel

Treatment outcomes	Adagrasib, 600 mg twice daily (n=33)	Sotorasib, 960 mg daily (n=18)	Docetaxel, 75 mg/m^2 every 3 weeks (n=13)
Median follow-up (months)	15.4	20	20
ORR (RANO-BM) (%)	33.3 (95% CI: 18 to 51.8)	33.3	15.4
IC DCR (%)	90	83.3	84.6
IC PFS (months)	5.4[†]	9.6[‡]	4.5[‡]
Concordance rate between systemic and IC disease control (%)	Not reported	88	54

[†], analysis included all 42 patients with CNS metastases at baseline; [‡], analysis included 40 and 29 patients with CNS metastases at baseline for sotorasib and docetaxel arm, respectively. IC, intracranial; NSCLC, non-small cell lung cancer; CNS, central nervous system; ORR, overall response rate; RANO-BM, response assessment in neuro-oncology brain metastases; CI, confidence interval; DCR, disease control rate; PFS, progression-free survival.

molecular testing in Central/Eastern Europe (23). It cannot be stated often enough that comprehensive testing of actionable mutations, including KRAS G12C mutation, is critical when a targeted therapy is available as OS is better among patients who are able to receive the matching targeted therapy for an identified actionable mutation compared to those with an identified actionable mutation who did not receive treatment with the matching targeted therapy (24,25).

How reliable were the PFS and OS endpoints in CB200?

During the Oncologic Drugs Advisory Committee meeting convened by the US FDA in October 2023 to review conversion of sotorasib's supplemental new drug application to full approval, there were several issues identified with the conduct of CB200 study indicating systemic bias, including investigator bias, that led to further scrutiny in the interpretation of the study results.

First, the observed improvement in median PFS (approximately 5 weeks) was deemed suspect as this was less than the protocol imaging interval of at least 6 weeks. Even though BICR assessment for progressive disease (PD) was part of the study design, there was a separate procedure to allow cross-over apart from BICR, with the study protocol enabling investigators to make the final treatment decision. Specifically, upon further review, there appeared to be investigator bias towards triggering early cross-over with premature determination of PD in the docetaxel arm (69%) compared to sotorasib (58%) by investigators relative to BICR assessment (early discordance). Conversely, there were more frequent late calls for PD in the sotorasib arm (42%) compared to docetaxel (31%) relative to BICR assessment (late discordance). While FDA performed an interval censoring sensitivity analysis of PFS which showed consistent PFS HR estimate of 0.71 (95% CI: 0.54–0.95), the estimated difference in median could be as low as approximately 5-day difference in PFS.

Additionally, within the docetaxel arm, there was also bias in terms of informative censoring noted, with a higher number of early withdrawals of 13% (23/174) in the docetaxel arm *vs.* 1% (2/171) in the sotorasib arm of patients who were randomized but did not undergo treatment, which affects the estimation of sotorasib's effect. US FDA also performed additional sensitivity analyses to evaluate the impact of crossover and early dropout on OS, with results in agreement with primary analysis but also indicating that crossover to sotorasib is unlikely to be the reason for lack of OS benefit seen.

This perhaps emphasizes the need for in-depth real-world analyses to evaluate the PFS and OS benefits of sotorasib as conducting another phase 3 trial in this setting is impractical. It is reassuring that outcomes reported from global expanded access programs, which include patients with Eastern Cooperative Oncology Group (ECOG) performance status of 2, continue to support the clinical efficacy and safety profile of sotorasib (26-28). Furthermore, the recently reported outcomes from the randomized dose comparison study of sotorasib 960 mg once daily *vs.* 240 mg once daily in patients with advanced KRAS G12C mutated NSCLC provide additional context and confirmation of

CB200 findings. While there was no statistically significant difference in PFS between the two doses, with median PFS of 5.4 (95% CI: 4.2–6.9) and 5.6 months (95% CI: 4.1–8.3), respectively, it is notable that the estimated PFS is in line with what was reported in CB200. Although there was numerically higher response rate and median OS with the higher dose, the difference is of uncertain clinical significance and at the expense of higher gastrointestinal-related adverse events (29).

Conclusions and future directions

Sotorasib is a new standard of care option for patients with advanced stage KRAS G12C mutant NSCLC who have progressed after 1st-line therapy, given its improved QoL and safety profile and around two-fold higher rate of 12-month long-term PFS, including superior control of CNS metastases, compared to docetaxel. While the benefit of sotorasib is undisputed in this 2nd/3rd line setting, its utility in 1st or earlier lines of therapy is limited by hepatotoxicity risks in sequence or in combination with immunotherapy agents (30), which play an important role in the treatment paradigm KRAS G12C mutated NSCLC. Hence, the search is still on for the "best"-in class KRAS G12C inhibitor therapy, with the playing field still looking for agents with better efficacy and safety profile as well as better predictive biomarkers, especially for combination strategies.

Lastly, to ensure that all NSCLC patients can benefit from these advancements, it is vital to overcome infrastructural and economic barriers in access to molecular testing and access to clinical trials in order to ensure the continued progress in the treatment landscape for our patient population. Presuming no changes in the formulation and pricing policies set by Amgen, adopting the 240 mg once daily dosing will significantly lower the cost barrier in terms of access to drug.

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Footnote

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