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COMMENTARY

Adagrasib in KRYSTAL-12 has Not Broken the KRAS G12C Enigma Code of the Unspoken 6-Month PFS Barrier in NSCLC

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Abstract: Mutations in KRAS G12C are among the more common oncogenic driver mutations in non-small cell lung cancer (NSCLC). In December 2022, the US Food and Drug Administration (FDA) granted accelerated approval to adagrasib, a small molecule covalent inhibitor of KRAS G12C, for the treatment of patients with locally advanced or metastatic KRAS G12C mutant NSCLC who received at least one prior systemic therapy based on promising results from phase 1 and 2 trials wherein adagrasib demonstrated a median PFS of 6.5 months. Results from the phase 3 KRYSTAL-12 trial were recently presented, showing benefit with adagrasib compared to docetaxel, with participants in the adagrasib group demonstrating a PFS of 5.5 months compared to 3.8 months in the docetaxel group. However, these results fall short of the 6-month PFS benchmark that had seemed achievable from what had been seen in phase 1 and 2 trials, mirroring similarly disappointing results from the CodeBreaK 200 trial wherein sotorasib, the first-in-class KRAS G12C inhibitor, also failed to meet the 6-month benchmark also thought to be possible when examining earlier trials. These results raise the question of adagrasib's true value in the second-line treatment setting and compel us to explore more potent novel therapies, combination therapies, and more as we seek to break the 6-month PFS barrier in the treatment of KRAS G12C mutant NSCLC.

Keywords: Kirsten rat sarcoma viral oncogene homolog gene, docetaxel, sotorasib

Introduction

Mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, involved in growth factor signaling and the regulation of cell proliferation, growth, and survival, are among the most common oncogenic driver mutations in a variety of cancers.[1] KRAS mutations are among the most frequently seen in non-small cell lung cancer (NSCLC), found in more than 30% of NSCLC cases, with the KRAS G12C variant being the most common of these.[2] Importantly, KRAS is a member of the RAS family of GTPase signaling transducer proteins, which catalyzes the hydrolysis of guanosine-5'triphosphate (GTP) to guanosine diphosphate (GDP). Under normal conditions, these proteins switch between the inactive GDP-bound state and the active GTP-bound state. This switch causes a conformational change in the switch I and switch II regions, which then plays a critical role in downstream signaling.[3] For many years, KRAS was known as an "undruggable" target, due in part to its smooth structure, lack of drug-binding sites, and high affinity for GTP, which rendered drug engineering difficult.[4] However, with the 2013 breakthrough development of a compound possessing the ability to inhibit the KRAS G12C protein via the newly-identified switch II pocket came a new wave of efforts to develop KRAS inhibitors, ultimately giving rise to the development of selective small molecule inhibitors targeting KRAS G12C, including sotorasib and adagrasib.[5]

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KRAS-Mutant NSCLC Treatment Landscape

Patients with NSCLC harboring KRAS mutations are different from those with NSCLC harboring other oncogenic driver mutations, such as mutations in the epidermal growth factor receptor (EGFR), in that these patients are more frequently smokers and more frequently demonstrate high programmed death-ligand 1 (PD-L1) expression, high tumor mutational burden (TMB), and thus, responsiveness to immunotherapy.[6–8] As such, the standard treatment of KRAS G12C mutant NSCLC in the first-line setting is comprised of immunotherapy alone or in combination with platinum-based chemotherapy, which has improved overall survival (OS) from 10–20 months with chemotherapy alone to 21–28 months with the addition of immunotherapy.[9,10] Unfortunately, the majority of these patients progress on first-line therapy, and second-line treatment options, including docetaxel alone or in combination with ramucirumab, have demonstrated very limited efficacy, with a median OS of 10.5 months in patients treated with docetaxel and ramucirumab compared to 9.1 months in patients treated with docetaxel alone.[11] Thus, small molecule inhibitors of KRAS G12C represent a long awaited addition to the second-line treatment setting.

Sotorasib, the First of Its Kind

Sotorasib, a small molecule inhibitor of KRAS G12C that acts via covalent binding to the cysteine residue on the switch II pocket of the inactive KRAS GDP isoform, gained conditional FDA approval in May 2021 for the treatment of patients with locally advanced or metastatic KRAS G12C mutant NSCLC who had received at least one prior systemic therapy based on promising preclinical and clinical results. In the phase 1 CodeBreaK 100 trial, 59 patients with locally advanced or metastatic NSCLC and 70 patients of other cancer types received doses of 180 mg, 360 mg, 720 mg, and 960 mg of sotorasib, with 32% of NSCLC patients demonstrating response and 56% of NSCLC patients demonstrating stable disease. The median duration of response (DOR) was 10.9 months, and the median progression-free survival (PFS) was 6.3 months.[12] In the Phase 2 CodeBreaK 100 trial, 126 patients with locally advanced or metastatic KRAS G12C mutant NSCLC with disease progression on platinum chemotherapy or checkpoint inhibition were treated with sotorasib 960 mg daily and demonstrated a median PFS of 6.8 months, an objective response rate (ORR) of 37.1%, a disease control rate (DCR) of 80.6%, and a DOR of 11.1 months.[13]

In the global phase 3 CodeBreaK 200 trial, 345 patients with locally advanced, unresectable, or metastatic KRAS G12C mutant NSCLC previously treated with platinum chemotherapy and checkpoint inhibition were randomly assigned 1:1 to oral sotorasib 960 mg daily or intravenous docetaxel 75 mg/m^2 every three weeks. Exclusion criteria included new or progressing untreated brain lesions, symptomatic brain lesions, and previously identified driver mutations besides KRAS G12C for which other approved targeted therapies were available. Patients were stratified by number of previous lines of therapy (1, 2, or >2), ethnicity (Asian, non-Asian), and history of CNS metastases (present, absent). The primary endpoint was PFS assessed by blinded independent central review (BICR). The protocol was revised to reduce the number of patients to 330, and also to allow crossover from docetaxel to sotorasib. After a median follow-up of 17.7 months, the study met its primary endpoint with a significant increase in PFS in sotorasib-treated patients of 5.6 months compared to 4.5 months in docetaxel-treated patients (HR 0.66 [95% CI; 0.51–0.86]). Sotorasib also demonstrated an ORR of 28.1% and a DCR of 82.5% compared to docetaxel, which demonstrated an ORR of 13.2% and a DCR of 60.3%.[14] However, sotorasib failed to show an improvement in OS, with an OS of 10.6 months in the sotorasib group compared to 11.3 months in the docetaxel group, although it must be noted that the study was not powered for OS.[14]

Unfortunately, the US Food and Drug Administration (FDA) recently rejected a supplemental new drug application requesting full approval for sotorasib in the treatment of previously treated locally advanced or metastatic KRAS G12C mutant NSCLC, based on concerns regarding the trial design of CodeBreaK 200, including its high rate of early dropout in the docetaxel arm, potential for investigator bias, and potential loss of randomization.[15] Thus, the FDA requires a new confirmatory study to be completed by February 2028.

Is Adagrasib Just Another Sotorasib?

In December 2022, adagrasib, another small molecule covalent inhibitor of KRAS G12C, gained accelerated FDA approval for the treatment of patients with KRAS G12C mutant locally advanced or metastatic NSCLC after prior

treatment with platinum-based chemotherapy based on promising results from phase 1 and 2 KRYSTAL-1 trials. In the phase 1–2 KRYSTAL-1 trial, 25 patients with KRAS G12C mutant solid tumors, 15 of whom had NSCLC, were treated with oral adagrasib 150 mg daily, 300 mg daily, 600 mg daily, 1200 mg daily, and 600 mg twice daily. With the recommended phase 2 dose of 600 mg twice daily, 8 of the 15 NSCLC patients (53.3%) demonstrated a confirmed partial response, with a median DOR of 16.4 months and a median PFS of 11.1 months.[16] In the phase 2 cohort evaluating patients with KRAS G12C mutant NSCLC previously treated with both chemotherapy and immunotherapy, 116 participants were treated with oral adagrasib 600 mg twice daily and demonstrated a median PFS of 6.5 months, an overall response of 42.9%, and a DOR of 8.5 months.[17]

Highly anticipated results from the KRYSTAL-12 trial were recently presented at the 2024 ASCO Annual Meeting in Chicago, Illinois. In the global phase 3 KRYSTAL-12 trial, 453 participants with locally advanced or metastatic KRAS G12C mutant NSCLC, previously treated with platinum-based chemotherapy and immunotherapy, were randomly assigned 2:1 to oral adagrasib 600 mg twice daily or intravenous docetaxel 75 mg/m^2 every 3 weeks. Patients who received prior KRAS G12C targeted therapy and those with active brain metastases were excluded. Crossover was allowed upon confirmed progression. Primary endpoints included PFS assessed by BICR and secondary endpoints included OS, ORR, DOR, 1 year survival rate, safety, and quality of life assessment. Patients were stratified by region (non-Asia-Pacific, Asia-Pacific) and prior treatment (sequential versus concurrent chemotherapy and immunotherapy). After a median follow-up of 7.2 months, the study met its primary endpoint, with a median PFS of 5.5 months in the adagrasib group compared to 3.8 months in the docetaxel group (HR 0.58 [95% CI; 0.45–0.76]). Patients treated with adagrasib also demonstrated an ORR of 32% and a DOR of 8.3 months, compared to those treated with docetaxel, who demonstrated an ORR of 9% and a DOR of 5.4 months. Of patients with CNS metastases at baseline, 24% demonstrated intracranial response to adagrasib compared to 11% with response to docetaxel.[18]

Importantly, both sotorasib and adagrasib have demonstrated greater patient tolerability than has docetaxel. In a survey of patient-reported outcomes in the CodeBreaK 200 trial, patients who had received sotorasib experienced less bothersome side effects and less severe symptoms than patients who had received docetaxel. Furthermore, patient-reported quality of life was stable with sotorasib, but worsened with docetaxel.[19] Similarly, adagrasib seems to be better tolerated than docetaxel, with 7.7% of patients who received adagrasib discontinuing treatment due to treatment-related adverse events (TRAEs) compared to 14.3% of patients who received docetaxel.[18]

The 6-Month PFS Barrier

Unfortunately, the results of the CodeBreaK 200 trial were largely disappointing in spite of the increases in PFS, ORR, and DCR demonstrated by sotorasib-treated patients compared to docetaxel-treated patients. In particular, the PFS of 5.6 months demonstrated by sotorasib in the phase 3 trial was disheartening in light of phase 1 and 2 trials wherein patients treated with sotorasib demonstrated a PFS of 6.3 to 6.8 months, thus establishing an unsaid 6-month PFS benchmark that phase 3 trial results failed to meet. This was also true of adagrasib, which demonstrated a PFS of 6.5 months in the phase 2 KRYSTAL-1 trial, but failed to meet this 6-month benchmark in the phase 3 KRYSTAL-12 trial, instead demonstrating a PFS of 5.5 months (Table 1). Regrettably, adagrasib's PFS of 5.5 months is eerily similar to that of sotorasib, and invokes a similar sense of disappointment as it again failed to meet the 6-month PFS benchmark that had been hoped for based on earlier trials.

In spite of early enthusiasm for the development of KRAS G12C inhibitors both inherent and acquired resistance mechanisms to these targeted therapies have already become a concern and may be a significant barrier to surpassing the aforementioned 6-month benchmark. Several mechanisms of resistance to sotorasib have been proposed, including transformation from a sensitive to tolerant state via non-genetic mechanisms, as well as via acquired genetic mutations.[20] Co-mutations in STK11, KEAP, and TP53 have been reported to impact response to KRAS G12C inhibitors, leading to primary resistance.[21] In addition, tumors with co-occurring KRAS mutations that are not susceptible to the action of allele-specific KRAS G12C inhibitors could reduce response to therapy.[22] Other modes of resistance have also been identified, including mutations in several other RTKs, mutations in other RAS/MAPK pathway players, and histologic transformation.[23–25]

Table 1 Comparison of CodeBreaK 200 and KRYSTAL-12 Trial Results to Those of Phase 1 and 2 Trials

Trial	Phase 1 CodeBreaK 100	Phase 2 CodeBreaK 100	Phase 3 CodeBreak 200		Phase 1–2 KRYSTAL-1	Phase 3 KRYSTAL-12	
Drug	Sotorasib	Sotorasib	Sotorasib	Docetaxel	Adagrasib	Adagrasib	Docetaxel
Dose	960 mg PO daily	960 mg PO daily	960 mg PO daily	75 mg/m^2 IV every 3 weeks	600 mg PO twice daily	600 mg PO twice daily	75 mg/m^2 IV every 3 weeks
N for NSCLC	59	126	171	174	112	301	152
DOR (months)	10.9	11.1	8.36	6.8	8.5	8.3	5.4
PFS (months)	6.3	6.8	5.6	4.5	6.5	5.5	3.8
OS (months)	N/a	12.5	10.6	11.3	12.6	N/a	N/a

How Can We Improve?

Although earlier studies, like CodeBreaK-100 and KRYSTAL 1 were more resoundingly positive, commencing a new era of G12C mutant NSCLC treatment, we must aim to break the 6-month PFS barrier. The mere weeks won by treatment with sotorasib or adagrasib compared to docetaxel raises the question of their true value in the second-line treatment setting and begs us to do more. The excess and diversity of resistance mechanisms to KRAS G12C inhibitors should compel us to explore combination approaches, such as KRAS G12C inhibitors used in combination with other RTK inhibitors or immunotherapy, or investigate the utility of KRAS G12C inhibitors as monotherapy or combination therapy in the first-line setting.

While KRAS G12C targeted therapies have proven to have some efficacy in the second-line setting, response rates are simply not as robust as those demonstrated by targeted therapies used in the treatment of NSCLC harboring other actionable driver mutations such as EGFR, ALK, and RET.[26–28]

This decreased efficacy could be due to non-targetable co-mutations in STK11 and KEAP, which are common with those with KRAS mutations, as these co-mutations are known to be associated with a "cold" tumor microenvironment, and thus decreased responsiveness to immunotherapy.[29] Importantly, the current first-line treatment for those NSCLC patients with KRAS G12C mutations is immunotherapy plus or minus chemotherapy. However, this may need to be tailored based on genomic co-mutations in STK11 and KEAP. For example, KRAS mutant NSCLC patients with a co-occurring STK11 mutation demonstrated a PFS of 2.0 months compared to 4.8 months in those with wild type (WT) STK11 (HR 2.04 [95% CI; 1.66–2.51]), and those with a co-occurring KEAP1 mutation demonstrated a PFS of 1.8 months compared to 4.6 months in those with WT KEAP1 (HR 2.05 [95% CI; 1.63–2.59])[30] These patterns raise the question of whether KRAS inhibitors should be considered in the first-line setting in lieu of immunotherapy for patients harboring co-mutations in STK11 and KEAP1. CodeBreaK 201, for example, is an ongoing study investigating sotorasib in the first-line setting for patients with a programmed death-ligand 1 (PD-L1) score of less than 1% or an STK11 co-mutation.

It must also be acknowledged that patients with KRAS G12C are variably responsive to treatment with immunotherapy, piquing interest in the use of other predictive biomarkers, in addition to co-mutation status. As has been widely documented, higher PD-L1 expression and TMB have been associated with a more favorable response to immunotherapy.[31]

In a retrospective study following 370 patients with KRAS mutant NSCLC treated with chemoimmunotherapy or immunotherapy, patients treated with immunotherapy with a high PD-L1 tumor proportion score (TPS) $\geq$ 50% and a negative PD-L1 TPS < 1% demonstrated an OS of 20.2 months and 9.7 months, respectively, and a PFS of 5.7 months and 1.9 months, respectively, demonstrating an association between PD-L1 TPS and response to immunotherapy.[32] In another large cohort study of 1552 patients with NSCLC treated with immunotherapy, they found that patients with a TMB >19 mutations per megabase (mut/mB) demonstrated a median PFS of 11.4 months compared to 2.8 months in patients with ≤19 mut/mB (HR 0.40 [95% CI; 0.33–0.50]).[33] Aneuploidy burden, as measured by the fraction of

chromosomal arm alterations, has also been proposed as a useful biomarker in NSCLC, with higher aneuploidy burden being associated with lower response to immunotherapy.[34] These results underscore the need for further studies delineating the utility of these biomarkers in guiding the sequence of therapies offered to KRAS G12C mutant NSCLC patients.

In addition to investigating the choice between KRAS G12C inhibitors and immunotherapy in the first-line setting, we must explore combination therapy, including KRAS inhibitors used with other RTK inhibitors or with immunotherapy. This may be the most promising strategy, not only because KRAS G12C mutant NSCLC has proven to be more susceptible to the action of immunotherapy than has NSCLC harboring other driver mutations, but also because it may allow us to overcome resistance mechanisms. However, in data from the CodeBreaK 100/101 phase 1B dose exploration trial, presented at the IASLC World Conference on Lung Cancer in 2022, sotorasib used in combination with pembrolizumab or atezolizumab in patients led to a higher incidence of grade 3 to 4 TRAEs than seen with monotherapy, thus limiting the durability of response.[35] In contrast, results from the phase 2 KRYSTAL-7 trial, presented at the ESMO Congress in 2023, showed encouraging activity and tolerability with pembrolizumab and adagrasib combination therapy in KRAS G12C mutant NSCLC.[36] In addition, a phase 1/2 trial evaluating olomorasib, also a potent KRAS G12C inhibitor, in combination with pembrolizumab in KRAS G12C mutant NSCLC has shown promising results with a favorable safety profile.[37] Results from a phase 1 study presented at the IASLC World Conference on Lung Cancer in 2024 also demonstrated that the single-agent divarasib, another potent KRAS G12C inhibitor, conferred a median PFS benefit of 15.3 months in KRAS G12C NSCLC. Importantly, divarasib in combination with atezolizumab demonstrated overall manageable tolerability, thus demonstrating promise as another potential contender in the combination therapy space.[38] Further studies investigating the efficacy and tolerability of these and other KRAS G12C inhibitors in combination with immunotherapy are ongoing.

As mentioned, various preclinical and clinical studies have demonstrated the emergence of a variety of resistance mechanisms with the use of sotorasib and adagrasib. For example, resistance mechanisms via upstream alterations in EGFR and SHP2 and via downstream alterations in MEK and ERK have been described.[39] As such, several trials are currently investigating the use of KRAS G12C inhibitors in combination with MEK inhibitors, ERK1/2 inhibitors, PIK3CA inhibitors, SHP2 inhibitors, and more. However, as with combination with immunotherapy, the use of KRAS G12C inhibitors with other small molecule inhibitors may also be limited by TRAEs.[40,41] Mutations in various components of the RAS/MAPK have also been implicated in acquired resistance. Based on promising results from the phase 1 and 2 RAMP-203 trials, avutometinib, a RAF/MEK clamp targeting the RAS pathway, achieved the FDA fast track designation in January 2024 for use in combination with sotorasib in patients with metastatic KRAS G12C mutant NSCLC who received prior systemic therapy but had not received a KRAS G12C inhibitor.[42] Trials involving other investigational drugs, like FAK inhibitors and SOS inhibitors, aiming to enhance the activity of and delay resistance to KRAS G12C inhibitors are also ongoing.

Other KRAS G12C inhibitors are also in clinical development or under investigation. Recently, results from a phase 2 trial were presented at the 2024 AACR Annual Meeting in San Diego, showing that garsorasib, a potent KRAS G12C inhibitor, conferred a median PFS benefit of 7.56 months.[43] IBI351, another potent KRAS G12C inhibitor, has also demonstrated promising efficacy in a phase 2 study, wherein it demonstrated a median PFS of 9.7 months.[44] However, these and other KRAS G12C inhibitors, including sotorasib and adagrasib, are "KRAS-off inhibitors", binding to inactive, GDP-bound mutant KRAS. Alternative methods of inhibition have been proposed, allowing for the inhibition of mutated KRAS in the GTP-bound, active state, giving rise to the development of "KRAS-on inhibitors".[45] Pan-KRAS inhibitors, with the ability to target various KRAS mutants, are also under investigation.[46] Thus, these agents used as monotherapy or in combination with other drugs will be important considerations in the evolving KRAS G12C mutant NSCLC treatment landscape.

It must also be noted that 27–42% of the patients with KRAS G12C mutant NSCLC demonstrate brain metastases at the time of diagnosis, the presence of which is known to confer poorer clinical outcomes.[47–49] In recently presented findings from a post-hoc analysis of the phase 1/2 CodeBreaK 100 trial, 14 of 16 patients with previously treated brain metastases at baseline demonstrated durable intracranial disease control with treatment with sotorasib, although patients with active or untreated brain metastases were excluded from this study.[50] In addition, recent findings from a global

phase 3 trial evaluating the intracranial efficacy of sotorasib compared to docetaxel in patients with pretreated KRAS G12C mutant NSCLC demonstrated delayed time to CNS disease occurrence in patients treated with sotorasib.[51] Adagrasib has also demonstrated some CNS activity. In the KRYSTAL 1 phase 1b cohort of patients with untreated brain metastases at baseline, adagrasib demonstrated an intracranial ORR of 42% and intracranial disease control rate of 90%.[52,53] Although these studies offer some evidence that sotorasib and adagrasib possess activity against brain metastases, further studies must be done to substantiate these suggestions of CNS efficacy. Furthermore, novel therapeutics and combination strategies must also address the need for CNS penetration in patients with KRAS G12C mutant NSCLC.

As we continue in pursuit of breaking the 6-month PFS barrier in the treatment of KRAS G12C mutant NSCLC, we must continue to reimagine our treatment strategies. In doing so, we should consider emerging novel therapies, combination approaches, and sequential therapies guided by patient and tumor-specific characteristics. As such, we eagerly await the results of ongoing studies promising advancement in the evermore tailored treatment of the KRAS G12C mutant NSCLC.

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