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Adagrasib in the Treatment of KRAS p.G12C Positive Advanced NSCLC: Design, Development and Place in Therapy

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Abstract: One of the most common mutations seen in lung cancers are mutations in Kristen Rat Sarcoma Viral Oncogene Homolog (KRAS), observed in 25–30% of patients with NSCLC. Mutations in KRAS result in oncogenesis via persistent activation of the MAPK/ERK pathways. Although once thought to be "undruggable", KRAS p.G12C inhibitors such as sotorasib and adagrasib have been developed. This paper focuses on adagrasib, the second KRAS p.G12C inhibitor to obtain regulatory approval by the FDA and describes the details on its study design, development and current place in therapy.

Keywords: Kristen Rat Sarcoma Viral Oncogene Homolog, sotorasib, AMG510, MRTX849, KRYSTAL, CodeBreaK, brain penetration

Background

Oncogenic driver mutations are detected in approximately 60% of non-small cell lung cancers (NSCLC).[1] Next generation sequencing (NGS) enables the identification of mutations with therapeutic implications, allowing for the use of targeted agents.[2–4] The most common mutation, however, are mutations in Kristen Rat Sarcoma Viral Oncogene Homolog (KRAS) which are seen in approximately 25–30% of patients with NSCLC.[1,5]

Notably, there is a vast heterogeneity within the subtypes of KRAS-mutated NSCLC, and prevalence rates can vary geographically. The most common KRAS mutation is the p.G12C mutation, characterized by a glycine-to-cysteine mutation at codon 12. This is estimated to be seen in 40% of patients with KRAS-mutated NSCLC. The next most common KRAS mutations are G12V (19%), and G12D (15%).[5,6] KRAS mutations have higher frequency in adenocarcinomas than squamous cell carcinomas, 37.2% vs 4.4%, respectively.[5] Patients who are current or former smokers are also more likely to harbor KRAS mutations compared to non-smokers, one study reporting 34% vs 6%, respectively. Within the smoking cohort, KRAS p.G12C is the most common mutation seen and observed in 41% of those patients.[7]

The oncogenesis of KRAS-mutated NSCLC revolves around the MAPK/ERK biochemical cascade. KRAS is one of three isoforms within the RAS group of oncogenes. It is a GTPase protein located on the cell membrane and functions to directly interact with the downstream signaling MAPK/ERK pathways, which is vital for cell survival, growth, and differentiation.[8] In KRAS mutant cells, GTP-bound KRAS remains persistently active, triggering a downstream cascade of phosphorylation and kinase activation of MEK and ERK. ERK kinases translocate to the nucleus of the cell to aid in vital cell functions. In RAS-mutant human cancer cells, these proteins exhibit single amino-acid replacements primarily residing at G12 or Q61. Thus, these RAS-mutant cells remain GTP-bound, leading to persistently activated signaling of their downstream cascade allowing for oncogenesis.[9]

Lung cancer is the main etiology of brain metastases, accounting for 40–50% of all brain metastases.[10] Up to 25–50% of patients with KRAS-mutated NSCLC are diagnosed with brain metastases.[11,12] The development of brain metastases

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in patients with KRAS-mutated NSCLC is associated with a worse overall survival (OS) and quality of life. CNS failures are seen more frequently when compared with patients without KRAS mutations.[11,13]

KRAS mutations are not only seen in NSCLC. In addition, they can be observed in 90% of pancreatic cancers and 50% of colorectal cancers.[14,15] KRAS p.G12C mutations are also seen in approximately 3.2% of patients with colorectal cancer, 3.1% of patients with small bowel cancer, 3.3% of patients with appendiceal cancers, and 3.5% of patients with cancers of unknown primary.[16] Mutations in KRAS distinctly provide negative prognostic value for patients with gastrointestinal cancers too. Among patients diagnosed with metastatic colorectal cancer, KRAS mutations were correlated with inferior progression free survival (PFS) and OS, exhibiting a multivariate hazard ratio (HR) of 1.20 (95% confidence interval [CI] 1.02–1.42) and HR of 2.99 (95% CI 2.10–4.42), respectively. Specifically, in this cohort of patients, KRAS p.G12C mutations were associated with inferior OS in comparison to tumors without KRAS p.G12C mutations with an HR of 2.26 (95% CI 1.25–4.1).[15]

Early Development of KRAS p.G12C Inhibitors

As described above, the oncogenic potential KRAS mutations lie with its ability to constitutively activate the MAPK/ERK biochemical cascade, leading to cell survival, stimulation, and differentiation.[8] This persistent activation is mediated by KRAS' ability to impair the GTPase activity of RAS by keeping it in its GTP-bound activated state. In early trials, targeting and suppressing KRAS came with hopes to halt oncogenesis. However, the first attempts to target KRAS came with challenges due to its complex structure. There are two KRAS isoforms, KRAS4A and KRAS4B, with distant structural, function, and distributional characteristics. There is varied expression of each, which resuls in reduced efficacy of early KRAS p.G12C inhibitors. In addition, KRAS p.G12C mutant cancers exhibit a lack of accessible binding sites.[17]

The initial development of small molecule novel compounds, such as ARS-853, was designed to bind KRAS p.G12C with high affinity, engage the KRAS switch II binding pocket, and covalently bind to mutant cysteine, which will halt GTP binding.[18,19] Ultimately, this novel compound was proven to selectively reduce KRAS-GTP levels by binding the GDP-bound form, effectively slowing RAS-effector signaling, inhibiting cell proliferation, and inducing cell death in KRAS p.G12C mutant cells.[18]

Another small molecule tyrosine kinase inhibitor (TKI) targeting KRAS p.G12C, adagrasib (MRTX849), was one of the first KRAS p.G12C inhibitors to be developed and advanced into the market.[20] In its early development stages, MRTX849 demonstrated the ability to near completely inhibit KRAS in vivo. It demonstrated major clinical efficacy in KRAS-mutated cancers in a group of KRAS p.G12C mutated cell lines and patient-derived xenografts. It exhibited 30% volume reduction in 17 out of 26 models (65%) after treatment of approximately three weeks. This paved its pathway as a highly compelling cancer therapeutic.[20]

A phase I/Ib component of the KRYSTAL-1 trial was performed to assess the safety, pharmacokinetics, maximum tolerated dose, recommended phase II dose, and clinical activity of adagrasib.[21] Twenty-five patients with histologically confirmed unresectable or metastatic KRAS p.G12C mutated solid tumors were enrolled. They received adagrasib at varying doses, ranging from 150 mg orally once daily up to 600 mg orally twice daily. Patients in the dose-escalation and dose-expansion cohorts were enrolled in a 96-hour single-dose PK lead-in period. Periodic imaging assessments were completed every 6 weeks, and disease responses were evaluated per RECIST 1.1. Endpoints included duration of response (DOR), PFS, and OS. The recommended phase II dose of adagrasib to show evidence of clinical activity was established to be 600 mg twice daily. The median time to reach the maximum plasma concentration after a single 600 mg dose was 4.17 hours and the half-life was 23.0 hours (range, 16.3–27.9 hours). After a median follow-up of 19.6 months, 8 of 15 (53.3%) patients with KRAS p.G12C mutated NSCLC confirmed a partial response (PR). The median DOR was 16.4 months (95% CI, 3.1 – not estimable), and the median PFS was 11.1 months (95% CI 2.6 – not estimable). Among patients with KRAS p.G12C mutated colorectal cancer who were treated with 600 mg twice daily, one of two achieved a PR. The DOR was 4.2 months. The most common treatment related adverse events (TRAE) were diarrhea, nausea, or vomiting in patients receiving 600 mg twice daily. These gastrointestinal side effects were typically self-limiting and resolved later in treatment.[21]

Later Phase Adagrasib Clinical Trials

A phase II cohort of the KRYSTAL-1 trial assessed adagrasib at the 600 mg orally twice daily recommended dose. The investigators enrolled patients with locally advanced or metastatic NSCLC with KRAS p.G12C mutations who were previously treated with at least one platinum-based chemotherapy agent and checkpoint inhibitor therapy. Patients with active, untreated central nervous system (CNS) metastases were excluded, unless the CNS metastases were adequately treated and the patients were neurologically stable. The primary efficacy endpoint was objective response rate (ORR). Secondary efficacy endpoints were DOR, PFS, OS, 1-year survival rate, and disease control, defined as complete response (CR), PR, or stable disease (SD). A total of 116 patients were treated with adagrasib. With a median follow-up of 12.9 months, the primary endpoint of ORR was 42.9% (95% CI, 33.5–52.6%). One patient (0.9%) exhibited a CR, 47 (42.0%) had a PR, and 41% (36.6%) had SD. Progressive disease (PD) without an objective response was seen in 6 patients (5.4%). The secondary efficacy endpoints revealed a median time to response of 1.4 months (95% CI, 0.9–7.2), median DOR 8.5 months (95% CI, 6.2–13.8), median PFS 6.5 months (95% CI, 4.7–8.4), and median OS 11.7 months (95% CI, 9.2 - not evaluable). Similar to the phase I/Ib dose finding portion of the trial, the most common TRAE were diarrhea (70.7%), nausea (69.8%), fatigue (59.5%), and vomiting (56.9%), mostly being grade 1 or 2. Fatigue, nausea, and increased ALT and AST were the grade 3 TRAE with the highest frequencies. Two grade 5 fatal events occurred, one for cardiac failure and one pulmonary hemorrhage. The authors concluded that in this phase II cohort, adagrasib proved sustained clinical benefit in patients with previously unresectable locally advanced or metastatic KRAS p.G12C mutated NSCLC.[22] In response to these positive results, the Food and Drug Administration (FDA) granted accelerated approval to adagrasib on December 12, 2022, for patients with KRAS p.G12C mutated locally advanced or metastatic NSCLC after receiving at least one prior systemic therapy.[23]

KRYSTAL-12 was a phase III open label clinical trial to further investigate adagrasib's efficacy in patients with KRAS p.G12C mutated unresectable or metastatic NSCLC who had previously received platinum-based chemotherapy and checkpoint inhibitor therapy. Patients were randomized to receive adagrasib 600 mg orally twice daily or docetaxel with the ability to crossover to adagrasib with PD. The primary endpoint was PFS. Secondary endpoints were ORR, DOR, OS, 1-year OS, and safety. After a median follow up if 9.4 months, there was a superior improvement in PFS with adagrasib in comparison to docetaxel, 5.49 months vs 3.84 months, respectively. The HR for PFS was 0.58 (95% CI, 0.45–0.76). In comparison to docetaxel, adagrasib also demonstrated superior ORR, 31.9% vs 9.2%, and median DOR, 8.31 months vs 5.36 months. OS data will be reported at a later date. The rates of TRAE with adagrasib were similar to prior investigational studies and did not occur significantly more frequently than docetaxel. The authors concluded that adagrasib demonstrated superior outcomes when compared to docetaxel for previously treated, unresectable or metastatic KRAS p.G12C mutated NSCLC demonstrated.[24]

Efficacy of Adagrasib in Brain Metastases

Prior studies have reported that CNS metastases may occur in approximately 25–50% of patients with NSCLC harboring a KRAS p.G12C mutation, corresponding to a poor prognosis.[25–27] The incidence of brain metastases in KRAS non-p.G12C mutations was 60%.[27] Together, this proves the importance of the development of systemic therapies to prevent and treat intracranial spread. One analysis performed preclinical studies to support KRAS p.G12C inhibitors' ability to penetrate the CNS and its efficacy in untreated brain metastases. The authors assessed the physiochemical and pharmacokinetic properties of adagrasib in mice bearing intracranial KRAS p.G12C mutant NSCLC xenografts. The subjects were treated with adagrasib, and the levels of adagrasib were monitored in the plasma, cerebrospinal fluid (CSF), and brain, as well as its antitumor activity. Adagrasib was deemed to achieve clinically relevant levels with adequate CNS penetration and exposure. In mice treated with a single dose of adagrasib, total and free plasma concentrations were 8.6 μmol/L and 43 nmol/L, respectively, at 8 hours. In addition, adagrasib was able to provide CSF levels above the IC_{50} for at least 8 hours after the dose, and CSF levels of adagrasib (52 nmol/L) were comparable to plasma levels as well. In addition, the levels of unbound brain and plasma concentrations were near identical at 8 hours indicating significant CNS penetration of adagrasib. Clinical outcomes were evaluated in two patients with metastatic KRAS p.G12C mutant NSCLC who were treated with adagrasib in the KRYSTAL-1 phase Ib clinical trial cohort with active, untreated, limited

brain metastases. The two patients had CSF concentrations of adagrasib of 34.6 nmol/L and 24.2 nmol/L, both of which were similar to the expected preclinical CSF measurements. For the two patients, interval brain imaging after 2 cycles of adagrasib demonstrated resolution of three brain metastases when compared to their imaging at diagnosis.[27]

A post-hoc evaluation of the phase II KRYSTAL-1 trial revealed 42 patients with treated CNS metastases at baseline. With the use of the modified Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria in patients who were able to be radiographically monitored, intracranial ORR was 33.3% (95% CI, 18.0–51.8%). The median duration of intracranial response was 11.2 months (95% CI, 2.99-not evaluable), median intracranial PFS was 5.4 months (95% CI, 3.3–11.6).[22] However, the retrospective nature of this analysis, the prior intracranial radiation treatment of these patients, the exclusion of untreated brain metastases, and the use of RANO-BM criteria all limit the ability to generalize this data. To further investigate this, a phase Ib cohort of the KRYSTAL-1 trial prospectively studied the use of adagrasib in patients with previously treated, locally advanced or metastatic KRAS p.G12C mutated NSCLC and untreated CNS metastases. This was the first prospective report of its kind utilizing KRAS p.G12C inhibitors. Twenty-five patients met these criteria and were treated with adagrasib. Primary objectives were to characterize the safety and intracranial activity of adagrasib and evaluate its CNS efficacy, OS, intracranial PFS, intracranial time to response, DOR, and 1-year survival rate. After a median follow-up of 13.7 months, the intracranial ORR was 42% (95%, CI 20–66.5%). Three patients had intracranial CR and five patients had intracranial PR. The median intracranial PFS was 5.4 months, intracranial time to response 2.1 months, and intracranial DOR 12.7 months. The systemic ORR was 30%, with a median DOR of 5.6 months and a median PFS of 5.3 months.[13] Overall, these prospective results proved the ability of adagrasib to penetrate the CNS and demonstrate clinically relevant CNS activity and efficacy. Lastly, in KRYSTAL-12, intracranial ORR for adagrasib vs docetaxel was 40% and 11%, respectively.[24]

Development of Sotorasib

Similar to adagrasib, sotorasib (AMG 510) is a small-molecule TKI that irreversibly inhibits KRAS p.G12C by its activity in the P2 pocket. Uniquely, its His95 groove is a novel component, which enhances binding and improves its potency 10-fold in comparison to ARS-1620.[28] The phase I trial, CodeBreaK100, evaluated the safety, pharmacokinetics, and efficacy of sotorasib in patients with previously treated, locally advanced or metastatic solid tumors harboring the KRAS p.G12C mutation. This study included 129 patients (59 with NSCLC, 42 with CRC, and 28 with other tumors) in the dose expansion and escalation cohorts. Notably, this trial also excluded patients with active, untreated brain metastases. The dose escalation cohort was treated with varying doses of sotorasib ranging from 180 mg to 960 mg daily. The primary endpoint of safety revealed that 73 patients (56.6%) had a TRAE, 15 of which (11.6%) had a grade 3 or 4 TRAE. The most common adverse events were diarrhea (29.5%), fatigue (23.3%), and nausea (20.9%). In patients with NSCLC, 32.2% (19 patients) had an objective response (CR or PR) and 88.1% exhibited disease control (objective response or SD). The median PFS was 6.2 months. The recommended dose for the expansion cohort was 960 mg daily. The mean elimination half-life was 5.5 hours.[28]

The phase II portion of CodeBreaK100 was performed to evaluate the efficacy and safety of sotorasib in previously treated, locally advanced or metastatic NSCLC with confirmed KRAS p.G12C mutations. Patients with active, untreated brain metastases were excluded. 126 patients were included and were treated with sotorasib. The primary endpoint was objective response (CR or PR). After a median follow-up of 15.3 months, objective responses were confirmed in 46 patients (37.1%), 4 (3.2%) of whom had a CR and 42 (33.9%) had a PR. The median time to response was 1.4 months, the median PFS was 6.8 months, and the median OS was 12.5 months. Similar to its phase I counterpart, TRAE occurred in 69.8% of patients, and the most common TRAE were diarrhea, nausea, fatigue, and arthralgias.[29] Data from this study led to the accelerated approval of sotorasib on May 28, 2021, for KRAS p.G12C mutated NSCLC after progression on one prior systemic therapy. Sotorasib was the first KRAS p.G12C inhibitor to garner FDA approval in the United States.[30] In 2023, the authors reported a 2-year update of this CodeBreaK100 trial. Patients treated with sotorasib experienced an ORR of 41%, median DOR of 12.3 months, PFS of 6.3 months, and OS of 12.5 months.[31]

CodeBreaK200, a phase III clinical trial, compared the use of sotorasib with docetaxel, a current standard of care second-line agent, in previously treated, KRAS p.G12C mutated NSCLC. 345 patients were included and were randomized to receive sotorasib or docetaxel. Similar to prior studies, patients with active, untreated brain metastases

were excluded. The primary endpoint was PFS. After a median follow-up of 17.7 months, sotorasib demonstrated superior PFS compared to docetaxel, 5.6 months vs 4.5 months, respectively. The HR for PFS was 0.66 (95% CI, 0.51–0.86). Sotorasib boasted a higher ORR compared to docetaxel, 28.1% vs 13.2%, respectively. Median OS was 10.6 months in the sotorasib group vs 11.3 months in the docetaxel group, which was not statistically different.[32] Of note, the FDA's Oncologic Drug Advisory Committee (ODAC) meeting recognized that the PFS benefit of sotorasib in CodeBreaK200 was not reliably measured. Instead of this ODAC meeting voting on CodeBreaK200's conditions for regulatory approval of sotorasib, scrutiny was placed on the trial's primary endpoint of PFS per BICR and whether it could be reliably determined. Despite CodeBreaK200 boasting a statistically significant primary endpoint, the difference in PFS was small between the two arms and there was no difference in OS. The FDA cited the investigators' patterns of behavior, small sample size, and minimal 5-week PFS benefit, all of which suggested a bias in favor of sotorasib.[33] Additionally, the FDA cited the investigators for concerning study conduct, such as early dropouts in the docetaxel arm. Investigator assessments of "progression of disease" may have been biased and favored the sotorasib arm, as there was crossover of patients from docetaxel to sotorasib prior to the BICR assessment. There were also questions regarding the trial's lack of adherence to imaging assessments protocols as multiple evaluations appear to have been conducted by BICR to "resolve discrepancies" between investigator and BICR. Given this situation, FDA has rejected the supplemental new drug application for sotorasib, although the drug's accelerated approval status remains in place.[32]

Acquired Resistance to KRAS p.G12C Inhibitors

Despite the recent favorable results of KRAS p.G12C inhibitors in advanced NSCLC, it is inevitable that patients will develop resistance and exhibit progression of disease. Efforts to target the MAPK/ERK pathway have led to feedback reactivation of this pathway, ultimately muting the efficacy of KRAS p.G12C inhibitors. One study utilized KRAS p.G12C mutated cell lines treated with KRAS p.G12C inhibitors, ARS-1620 and AMG 510. In all cell lines, ARS-1620 decreased the activity of the MAPK/ERK pathway signaling and total MYC protein levels at 4 hours. However, the activity began to rebound by 24–48 hours, ultimately leading to RAS-MAPK reactivation by 72 hours. They postulated that feedback RAS pathway reactivation is heterogenous and is driven by multiple alternative receptor tyrosine kinases (RTK), including an increase in wild type RAS (NRAS or HRAS) activity.[34]

Another study revealed that EGFR co-signaling may confer resistance to KRAS p.G12C inhibition, especially in colorectal cancer (CRC). This likely accounts for the paucity of proven outcomes of these agents used as monotherapy in CRC. In contrast to NSCLC cell lines harboring KRAS p.G12C mutations, CRC cells boast higher baseline RTK activation. KRAS p.G12C inhibition induces higher phospho-ERK rebound and high response to EGFR direct stimulation. These findings suggest that EGFR signaling is a major resistance mechanism of KRAS p.G12C inhibitors in CRC.[35] Targeting this collateral signaling pathway has been instrumental in the treatment of KRAS p.G12C mutated CRC.[36]

Following the development of KRAS p.G12C inhibitors, efforts have been made to further identify mechanisms of resistance to adagrasib. One group of authors performed histologic and genomic analyses of patients in the KRYSTAL-1 trial after disease progression on adagrasib. They performed NGS on available tissue biopsy samples or circulating tumor DNA (ctDNA) obtained at the time of progression on adagrasib. Results were compared to NGS data prior to adagrasib treatment. Thirty-eight patients who were treated with adagrasib and experienced SD for at least 12 weeks or an objective response followed by disease progression were included, 27 of which had NSCLC. In 32 of the 38 patients (84%), KRAS p.G12C mutation was again identified at the time of resistance. Of note the 6 patients may have had insufficient tumor shedding of ctDNA, as only plasma was available for analysis. Resistance mechanisms were identified in 17 of 38 patients (45%). They divided resistance mechanisms into three categories. The first was novel or acquired secondary mutations or amplifications in KRAS. Mutations included Y96 mutation (1 patient), H95Q and H95R mutations (1 patient), R68S and H95D mutations (1 patient), H95R mutation (1 patient), and several patients with G12D, G12V, G13D, G12R, and Q61H. The second were alterations reactivating the RTK-RAS biochemical pathway, other than KRAS. Detected pathogenic mutations included NRAS Q61K, BRAF V600E, RET, EML4-ALK, EGFR, and MAP2K1/MEK1 alterations. Multiple resistance mutations or patterns were detected in several patients as well. Finally, histologic transformation from adenocarcinoma to squamous cell carcinoma (SCC) occurred in 2 patients.[37]

Adagrasib's Place in Today's Landscape of KRAS p.G12C Mutated NSCLC

Prior to the development of KRAS p.G12C inhibitors, KRAS was deemed "undruggable." The recent accelerated FDA approvals of adagrasib and sotorasib have drastically changed the landscape of KRAS p.G12C mutated cancers.[23,30] For NSCLC, both adagrasib and sotorasib are listed as acceptable and recommended second-line therapies by the National Comprehensive Cancer Network (NCCN) for KRAS p.G12C mutated NSCLC following the administration of first-line chemotherapy plus minus immunotherapy.[38] Pharmacologic differences between the two drugs include a half-life of 5 hours for sotorasib compared to 23 hours for adagrasib. There are no head-to-head clinical trials to compare to two agents, thus neither agent is considered superior to the other. Although not ideal, cross-trial comparisons can provide means of differentiation to an extent (Table 1). The ORR for adagrasib ranged from 31.9–42.9% in its phase II and phase III trials, compared to 28.1–37.1% for sotorasib. Median PFS for adagrasib ranged from 5.49–6.5 months in its phase II and phase III trials, while the PFS for sotorasib was 5.6–6.8 months. Median OS for adagrasib was 12.6 months in its phase II trial, while OS was 10.6–12.5 months for sotorasib. Notably, in CodeBreaK200, the median OS for sotorasib was not statistically different compared to docetaxel.

As discussed earlier, patients with KRAS p.G12C mutated NSCLC have a higher incidence of brain metastases. Thus, there is significant value for providers to choose agents, which have CNS penetrance and efficacy. The landmark trials for adagrasib and sotorasib, including the phase II KRYSTAL-1 trial, phase III KRYSTAL-12 trial, phase II CodeBreaK100 trial, and phase III CodeBreaK200 trial, excluded patients with active, untreated brain metastases. Rather, these key trials

Table 1 Pivotal Trials of Adagrasib and Sotorasib for KRAS p.G12C Mutated NSCLC

Trial	ORR	PFS	OS	DOR	Intracranial Outcomes
KRYSTAL-1 Phase I/Ib trial of adagrasib in patients with previously treated, unresectable or metastatic solid tumors harboring KRAS p.G12C mutations N= 16 NSCLC patients	53.3%	11.1 months	NR	16.4 months	Prospective evaluation: Intracranial ORR: 42% (95% CI, 20.3–66.5%) Median intracranial PFS: 5.4 months Time to intracranial response: 2.1 months Median duration of intracranial response: 12.7 months
KRYSTAL-1 Phase II trial of adagrasib in patients with previously treated, unresectable or metastatic NSCLC with KRAS p.G12C mutations N= 116 pts	42.9%	6.5 months	11.7 months	8.4 months	Post hoc analysis: Intracranial ORR: 33.3% (95% CI, 18.0–51.8%) Median intracranial PFS: 5.4 months (95% CI, 3.3–11.6) Median duration of intracranial response: 11.2 months (95% CI, 2.99 to not evaluable)
KRYSTAL-12 Phase III trial of adagrasib vs docetaxel in patients with previously treated, unresectable or metastatic NSCLC with KRAS p.G12C mutations N= 301 pts	31.9% (adagrasib) vs 9.2% (docetaxel	5.49 months (adagrasib) vs 3.84 months (docetaxel)	Not yet available	8.31 months (adagrasib) vs 5.36 months (docetaxel)	Intracranial ORR: 24% (adagrasib) vs 11% (docetaxel) Intracranial Disease Control Rate: 82% (adagrasib) vs 56% (docetaxel)

(*Continued*)

Table 1 (Continued).

Trial	ORR	PFS	OS	DOR	Intracranial Outcomes
CodeBreaK100 Phase I trial of sotorasib in patients with previously treated, unresectable or metastatic NSCLC with solid tumors harboring KRAS p.G12C mutations N=129 (59 with NSCLC)	32.2%	6.2 months	N/a	N/a	
CodeBreaK100 Phase II trial of sotorasib in patients with previously treated, unresectable or metastatic NSCLC with KRAS p.G12C mutations N= 126 pts	37.1% 2-year update: 41%	6.8 months 2-year update: 6.3 months	12.5 months 2-year update: 12.5 months	11.1 months 2-year update: 12.3 months	Post hoc analysis: Intracranial Disease control rate: 87.5%
CodeBreaK200 Phase III trial of sotorasib vs docetaxel in patients with previously treated, unresectable or metastatic NSCLC with KRAS p.G12C mutations N = 345 pts	28.1% (sotorasib) vs 13.2% (docetaxel)	5.6 months (sotorasib) vs 4.5 months (docetaxel)	10.6 months (sotorasib) vs 11.3 months (docetaxel) *Not statistically significant	8.36 months (sotorasib) vs 6.8 months (docetaxel)	

focused on previously treated brain metastases. Despite this lack of randomized data, the intracranial efficacy for adagrasib appears more promising compared to sotorasib. The post-hoc analysis of patients with treated brain metastases enrolled in KRYSTAL-1 revealed that adagrasib exhibited an intracranial ORR of 33.3%, a median duration of intracranial response of 11.2 months, and a median intracranial PFS of 5.4 months. In addition, there is some; however, limited, prospective data on adagrasib's efficacy on untreated CNS metastases in patients who were included in the phase Ib expansion cohort of the KRYSTAL-1 trial. These 25 patients treated with adagrasib demonstrated an intracranial ORR of 42%, 3 of which had intracranial CR, median intracranial PFS of 5.4 months, and intracranial DOR of 12.7 months. In comparison, a post-hoc analysis of CodeBreaK100, of the 25 patients (12.7%) who had treated brain metastases, sotorasib demonstrated a 25% systemic ORR and intracranial disease control in 14 of 16 patients (87.5%).[39] Two case reports have been published reporting positive responses with sotorasib in patients with active, untreated brain metastases. The first case report illustrated a patient with KRAS p.G12C mutated NSCLC with complete radiographic and clinical resolution of active, untreated brain metastases after treatment of sotorasib. The second case report similarly demonstrated a near complete intracranial response after 6 weeks of treatment with sotorasib in a patient with KRAS p.G12C mutated NSCLC also with active, untreated brain metastases.[40,41] Altogether, there remains a lack of prospective data regarding sotorasib's intracranial efficacy.

Adagrasib in Colorectal Cancer

As described above, EGFR co-signaling is a proven resistance mechanism to KRAS p.G12C inhibitors, limiting their efficacy in KRAS p.G12C mutated CRC. EGFR blockade in combination with KRAS p.G12C inhibition has demonstrated efficacy in CRC in preclinical studies.[35] The co-administration of adagrasib and cetuximab was compared to adagrasib monotherapy in heavily pretreated, unresectable, or metastatic CRC harboring a KRAS p.G12C mutation. The primary endpoint was ORR (CR or PR) and safety. A total of 44 patients received adagrasib, 32 of which received adagrasib and cetuximab combination therapy. Adagrasib monotherapy exhibited an ORR of 19%, median DOR of 4.3 months, and median PFS of 5.6 months. In the combination therapy group, ORR was 46%, median DOR was 7.6 months, and median PFS was 6.9 months. Altogether, this superior ORR, DOR, and PFS suggest that there is enhanced clinical

benefit with the combination of adagrasib and cetuximab compared to adagrasib monotherapy.[36] Following this pivotal trial, the FDA granted accelerated approval to adagrasib plus cetuximab for patients with pre-treated, KRAS p.G12C mutated, locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.[42] This combination proved to be a new therapeutic strategy in this population and is currently the only FDA approved option for this cohort of patients. The phase III KRYSTAL-10 trial is currently ongoing and is investigating this combination in the second line setting vs chemotherapy in CRC. Of note, a recent phase II trial utilized sotorasib in 62 patients with KRAS p.G12C mutated CRC. ORR did not reach its benchmark, demonstrating a 9.7% ORR.[43]

Current Ongoing Studies with Adagrasib for KRAS p.G12C Mutated NSCLC

Multiple trials are currently ongoing to evaluate the combination of adagrasib with other novel therapeutic agents in KRAS p.G12C mutated NSCLC (Table 2). KRYSTAL-2 (NCT04330664) is an ongoing phase I/II of patients with advanced solid tumors harboring KRAS p.G12C mutations. Patients are randomized to receive adagrasib plus TNO155, a selective SHP2 inhibitor, a molecule which is shown to cause KRAS p.G12C resistance.[44,45] KRYSTAL-7 (NCT04613596) is an ongoing phase II trial of patients with treatment naïve, unresectable, or metastatic NSCLC with KRAS p.G12C mutations and are treated with first line adagrasib plus pembrolizumab. The phase III portion of the study seeks to compare the efficacy of this combination therapy vs pembrolizumab alone in patients with KRAS p.G12C mutations and PD-L1 TPS ≥50%.[46] Selection of PD-L1 positive patients aligns with results from KEYNOTE-024 in which patients with untreated advanced NSCLC with PD-L1 TPS ≥50% exhibited improved outcomes with pembrolizumab in comparison to investigators' choice of chemotherapy.[47] Preliminary efficacy data showed encouraging and promising results. In patients with PD-L1 ≥50%, ORR was 63%, and median DOR and PFS were not reached after a median follow-up of 10.1 months. No patients discontinued the combination therapy due to transaminitis or hepatotoxicity.[48]

The combination of sotorasib and immunotherapy was also studied in CodeBreaK100/101, however the sequencing of these agents was important in the outcomes and safety. Patients who were treated with concurrent sotorasib and pembrolizumab or atezolizumab led to high rates of treatment discontinuation due to grade 3 or 4 hepatotoxicity. However, lead-in with low doses of sotorasib followed by concurrent use of pembrolizumab or atezolizumab allowed for lower rates of hepatic TRAE with promising and durable efficacy.[49]

Lastly, KRYSTAL-14 (NCT04975256) is an ongoing phase I/Ib trial enrolling patients with treatment naïve or pretreated, unresectable, or metastatic NSCLC and are being treated with adagrasib with BI 1701963, a SOS1 pan-KRAS inhibitor.[50]

Second Generation KRAS p.G12C Inhibitors in Development

Despite the development and favorable results of adagrasib and sotorasib in KRAS p.G12C mutated NSCLC, clinical outcomes remain limited and patients ultimately development progression of disease. Further efforts have been made to develop newer-generation KRAS p.G12C inhibitors and are currently in active development.

Table 2 Current Ongoing Studies with Adagrasib for KRAS p.G12C Mutated NSCLC

KRYSTAL-2 (NCT04330664)	Phase I/II	Adagrasib in combination with TNO155, a selective SHP2 inhibitor, in patients with advanced solid tumors harboring KRAS p.G12C mutations
KRYSTAL-7 (NCT04613596)	Phase II	Adagrasib monotherapy and in combination with pembrolizumab in patients with treatment-naïve, unresectable, or metastatic NSCLC with KRAS p.G12C mutations and any PD-L1 TPS
KRYSTAL-14 (NCT04975256)	Phase I/IB	Adagrasib in combination with BI 1701963, a SOS1 pan-KRAS inhibitor in patients with treatment-naïve or pretreated, unresectable, or metastatic NSCLC
KRYSTAL-10 (NCT04793958)	Phase III	Adagrasib in combination with cetuximab vs chemotherapy in patients with advanced colorectal cancer with KRAS p.G12C mutations with disease progression on or after standard first-line therapy

Divarasib (GDC-6036) is a covalent second-generation KRAS p.G12C inhibitor. In preliminary studies, it has been shown to be more potent in vitro than adagrasib and sotorasib. It selectively binds to the cysteine residue and irreversibly locks the protein into its inactive state, muting its oncogenic potential.[51] A phase I trial (NCT04449874) enrolled 137 patients (60 with NSCLC, 55 with CRC, and 22 with other solid tumors) and treated them with divarasib. Their goal was to assess safety, pharmacokinetics, anti-tumor activity, and biomarkers or response and resistance. TRAE occurred in 127 (93%) of patients, of which 11% were grade 3 and 1% were grade 4. Similar to other KRAS p.G12C inhibitors, nausea, diarrhea, and vomiting were the most frequently cited adverse events. Within the NSCLC subgroup, a confirmed anti-tumor response was observed in 53.4% of patients, the median DOR was 14.0 months, and the median PFS was 13.1 months.[52] This agent is also being investigated with other anti-cancer therapies, including PD-L1 inhibitors, EGFR inhibitors, bevacizumab, GDC-1971, and inavolisib.

Olomorasib (LY3537982) is another highly potent second generation covalent KRAS p.G12C inhibitor in development for NSCLC.[53] A phase I/II study studied the use of olomorasib in patients with KRAS p.G12C mutated advanced solid tumors. This trial included 157 patients (58 with NSCLC, 32 with CRC, 24 with pancreatic cancer, and 43 with other solid tumors). Of the patients with NSCLC, 29 received prior KRAS p.G12C inhibitors and olomorasib demonstrated an ORR of 39% and a median PFS of 6 months.[54] The combination of olomorasib plus pembrolizumab in patients with KRAS p.G12C mutated NSCLC was studied in the phase I/II LOXO-RAS-20001 clinical trial. Patients with any treatment history, including those treated with prior KRAS p.G12C inhibitors, were included. Among the KRAS p.G12C-naïve patients, olomorasib demonstrated an ORR of 63%, and 75% in patients with PD-L1≥50%. In the 9 first-line patients, olomorasib exhibited an ORR of 78%.[55] An ongoing phase III trial, SUNRAY-01, is studying the use of first-line olomorasib plus immunotherapy vs olomorasib monotherapy in untreated KRAS p.G12C mutated NSCLC.[56]

Conclusion

The recent FDA approvals of adagrasib and sotorasib have drastically changed the rapidly evolving treatment landscape of previously treated, KRAS p.G12C mutated NSCLC. Despite these major advancements, patients will inevitably develop resistance. Second-generation KRAS p.G12C inhibitors, such as divarasib and olomorasib, are currently under investigation as monotherapy and in combination with other agents to overcome resistance. Further research is warranted to improve efficacy and outcomes in this cohort of patients. In addition, agents targeting KRAS beyond p.G12C are currently in progress.

Disclosure

Dr Misako Nagasaka reports personal fees from AstraZeneca, Daiichi Sankyo, Novartis, EMD Serono, Pfizer, Lilly, Regeneron, Genentech, Caris Life Sciences, Takeda, Janssen, Mirati, Blueprint Medicine, and AnHeart Therapeutics, outside the submitted work. The authors report no other conflicts of interest in this work.

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