



Divarasib in the Evolving Landscape of KRAS G12C Inhibitors for NSCLC

Danielle Brazel¹ · Misako Nagasaka^{2,3}

Accepted: 12 March 2024 / Published online: 13 May 2024
© The Author(s) 2024

Abstract

Kristen Rat Sarcoma viral oncogene (*KRAS*) mutations are one of the most common oncogenic drivers found in 12–14% of non-small cell lung cancer (NSCLC) and 4% of colorectal cancer tumors. Although previously difficult to target, sotorasib and adagrasib are now approved for previously treated NSCLC patients with *KRAS* G12C mutations. In preclinical studies, divarasib was 5 to 20 times as potent and up to 50 times as selective as sotorasib and adagrasib. While sotorasib met its primary endpoint in the phase III second line study against docetaxel, the progression-free survival (PFS) benefit was small and no overall survival (OS) benefit was observed. Adagrasib has demonstrated clinical benefit in the phase I/II KRYSTAL-1 study setting, however, 44.8% of patients reported grade 3 or higher toxicities. Divarasib has been studied in a phase I dose expansion cohort with promising efficacy [objective response (ORR) 53.4% and PFS 13.1 months]. Although most patients reported toxicities, the majority were low-grade and manageable with supportive care. Here we discuss these results in the context of the evolving *KRAS* G12C landscape.

Key Points

Sotorasib and adagrasib have been FDA approved for *KRAS* G12C NSCLC.

Divarasib is a potent and selective *KRAS* G12C inhibitor.

Early results show promising efficacy and safety of divarasib.

Divarasib may have the potential to change the *KRAS* G12C treatment landscape.

1 Introduction

Kristen Rat Sarcoma viral oncogene (*KRAS*) mutations are one of the most common oncogenic drivers found in 12–14% of non-small cell lung cancer (NSCLC) and 4% of colorectal cancer (CRC) tumors [1, 2]. In NSCLC, *KRAS* mutations are associated with younger age and smoking history. The *KRAS* G12C mutation consists of a glycine-to-cysteine mutation at position 12, which inhibits guanosine triphosphate (GTP) hydrolysis, keeping *KRAS* in the active state. Until recently, *KRAS* mutations had no targeted agents owing to smooth surface with lack of binding sites, small dimension, and high affinity for GTP/guanosine diphosphate (GDP) [3, 4]. In a meta-analysis and systematic review of 10,153 NSCLC patients, authors found that *KRAS* G12C-mutated tumors had worse overall survival (OS) with a hazard ratio (HR) of 1.42 [95% confidence interval (CI) 1.10–1.84] but similar disease-free survival (DFS) (HR 2.36, 95% CI 0.64–8.16) [5]. *KRAS* G12C-mutated cases had a similar OS to other *KRAS* mutations (HR 1.03, 95% CI 0.84–1.26) but a higher programmed death ligand 1 (PD-L1) expression [odds ratio (OR) 1.37, 95% CI 1.11–1.70].

Currently two *KRAS* G12C inhibitors are available for previously treated NSCLC patients: sotorasib and adagrasib. Recently, divarasib has shown similar efficacy and tolerability as prior *KRAS* G12C inhibitors. Here we discuss the phase I results of divarasib.

✉ Misako Nagasaka
nagasakm@hs.uci.edu

¹ Department of Hematology/Oncology, Scripps Clinic/ Scripps Green Hospital, 10166 N Torrey Pines Rd, La Jolla, CA, USA

² Chao Family Cancer Center, UCI Medical Center, University of California Irvine School of Medicine, 101 The City Drive, Orange, CA 92868, USA

³ St. Marianna University School of Medicine, Kawasaki, Japan

2 Preclinical Studies

2.1 Pharmacodynamics

Preclinical studies of GDC-6036 (divarasib) demonstrated a median half-maximal inhibitory concentration (IC₅₀) in the sub-nanomolar range [6]. Divarasib was over 18,000-fold more selective for mutant G12C cell lines than wild type G12C. Divarasib also demonstrated greater potency and selectivity in vitro than other *KRAS* G12C inhibitors (sotorasib and adagrasib) as presented in Table 1. Divarasib resulted in complete tumor growth inhibition in multiple *KRAS* G12C positive cell lines and xenograft cell models. On the basis of these preclinical findings, human dose projections estimated that doses under 400 milligrams (mg) would result in 90% alkylation (IC₉₀) in H2122.

2.2 Pharmacokinetics

In the phase I trial, pharmacokinetic data was evaluable in four patients with solid tumors. After a single 400 mg dose of divarasib, the average half-life was 17.6 h (+/- 2.7 h) [7]. Steady state was assessed at cycle 1 day 8 or cycle 2 day 1.

In total, 76 patients were evaluated at steady state and demonstrated mean maximum concentration was 657 nanograms per milliliter (+/- 185) and mean area under the curve was 9130 nanograms times h per milliliter (+/- 3160).

3 Phase I Study Design

Results of a phase I trial of divarasib were recently published (NCT04449874) [7]. The study design is outlined in Fig. 1. Inclusion criteria included advanced or metastatic solid tumor, *KRAS* G12C mutation, progressed on at least one line of prior therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and no active untreated brain metastases. Patients with treated brain metastases were included in the study population. A total of 137 participants were enrolled, including 60 with NSCLC, 55 with colorectal cancer, and 22 other solid tumors.

Divarasib was administered in 21-day cycles. The dose escalation included doses of 50 mg, 100 mg, 200 mg, and 400 mg daily. The primary outcomes included safety, pharmacokinetics, investigator-evaluated antitumor activity, and biomarkers of both response and resistance.

Table 1 Preclinical pharmacodynamics and pharmacokinetics of *KRAS* G12C inhibitors

	Sotorasib	Adagrasib	Divarasib
Max plasma concentration	7500 ng/mL	985 ng/mL	657 ng/mL
Recommended dose	960 mg daily	600 mg BID	400 mg daily
Half-life	5.5 h	23.0 h	17.6 h
AUC	65.3 h × mg/mL	37,139 h × ng/mL	9130 h × ng/mL

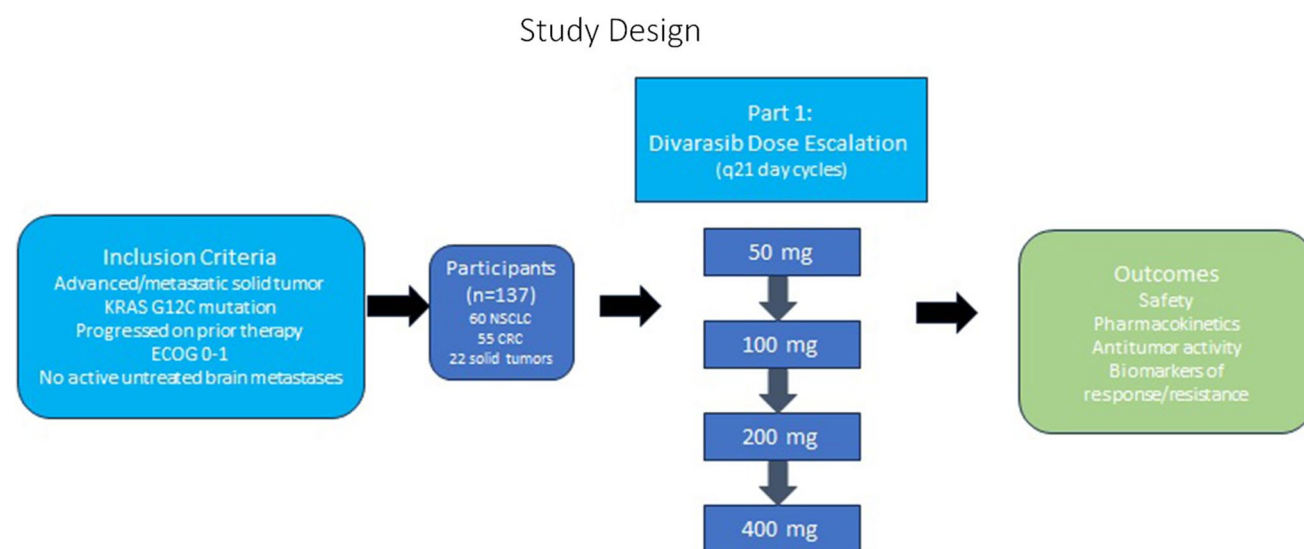


Fig. 1 Study design of the phase I divarasib study

3.1 Efficacy

Within the NSCLC cohort, investigators reported an objective response rate (ORR) of 53.4% (95% CI 39.9–66.7) with a median progression-free survival (PFS) of 13.1 months (95% CI 8.8, not reached). Within the colorectal cancer subgroup objective response rate (ORR) was 29.1% (95% CI 17.6–42.9) with a median PFS of 5.6 months (95% CI 4.1–8.2). The number of median lines of therapy was 2 (range: 0–8). The investigators note that responses were also observed in other solid malignancies. Serial circulating tumor deoxyribonucleic acid (DNA) showed a decline in KRAS G12C allele frequency associated with clinical response.

3.2 Tolerability

Adverse events were reported in 127 patients (93%) taking divarasib. This included 11% grade 3 and 1% grade 4 adverse events. There were no grade 5 events reported. The most common adverse events in the NSCLC cohort include nausea ($n = 27$, 78%), vomiting ($n = 38$, 63%), diarrhea ($n = 36$, 60%), and fatigue ($n = 16$, 27%). Dose reductions occurred in 19 (14%) and the agent was discontinued in 4 participants (3%).

4 Discussion

Divarasib has demonstrated efficacy in *KRAS* G12C-mutated NSCLC with ORR 53.4% and PFS 13.1 months. Although adverse events were frequent (93%), the vast majority were grade 1 or 2. These positive phase I results have prompted further investigation with phase II/III as well as combination agent trials which are summarized in Table 2. In colorectal cancers divarasib is being studied in combination with cetuximab, FOLFOX, and FOLFIRI (NCT04929223). Early data on the divarasib plus cetuximab combination show an ORR of 62% [8]. Although grade 3 and higher adverse events were reported in 38% of patients, treatment discontinuation was not required in most cases. In NSCLC divarasib is being studied as monotherapy in phase II/III trials (NCT03178552) and in combination with pembrolizumab (NCT05789082). Additionally, an exploratory SHP2 inhibitor, GDC-1971, is being added to divarasib (NCT04449874).

Sotorasib (Lumakras, Amgen) was one of the first *KRAS* G12C inhibitors and was approved by the Federal Drug Administration (FDA) in 2021 in the second-line treatment of NSCLC with *KRAS* G12C mutations based on Code-Break100. The trial enrolled 174 participants who received sotorasib at 960 mg daily after a median of two prior lines of therapy. In a pooled analysis of phase I/II sotorasib data, ORR was 41% (95% CI 33.3–48.4) with PFS of 6.3 months (95% CI 5.3–8.2) [9]. The duration of response (DOR) was 12.3 months (95% CI 7.1–15.0) with median OS of 12.5 months (95% CI 10.0–17.8). Importantly there were

Table 2 Ongoing trials with divarasib

Trial identifier	Agents	Phase	Study population	Number participants	Outcomes of interest	Status
NCT04929223	Divarasib + Cetuximab + FOLFOX, Divarasib + Cetuximab, Divarasib + Cetuximab + FOLFIRI	I/Ib	Metastatic colon cancer	422	ORR, DOR, DCR, AEs, plasma concentrations	Recruiting
NCT04449874	Divarasib, Divarasib + Atezolizumab, Divarasib + Cetuximab, Divarasib + Bevacizumab, Divarasib + Erlotinib, Divarasib + GDC-1971, Divarasib + Inavolisib	I	Advanced/metastatic <i>KRAS</i> G12C mutated solid tumors	498	AEs, DLT, plasma concentration, half life, area under the curve	Recruiting
NCT05789082	Divarasib + Pembrolizumab	Ib/II	<i>KRAS</i> G12C mutated advanced/metastatic NSCLC	60	AEs, ORR, DOR, PFS	Recruiting
NCT04589845	Divarasib	II	TMB high advanced/meta-static solid tumors	920	DOR, CBR, PFS, ORR	
NCT04302025	Divarasib	II	Stage IB-III NSCLC, adjuvant	85	AEs, delays in surgery	Recruiting
NCT03178552	Divarasib	II/III	Advanced/metastatic NSCLC	1000	PFS, OS, AEs, quality of life, tolerability	Recruiting

AE adverse events, CBR clinical benefit rate, DCR disease control rate, DLT dose-limiting toxicities, DOR duration of response, *KRAS* kirsten rat sarcoma viral oncogene, NSCLC non-small cell lung cancer, ORR objective response rate, OS overall survival, TMB tumor mutation burden

Table 3 Comparison of KRAS G12C Inhibitors for NSCLC

	CodeBreak 100	CodeBreak 100	CodeBreak 200	KRYSTAL-1	NCT04449874
Phase	I	II	III	I-III	I
Drug	Sotorasib	Sotorasib	Sotorasib v docetaxel	Adagrasib	Divarasib
Number NSCLC patients	59	126	171 v 174	112	
ORR	32.2%	37.1%	28.1% v 13.2%	43%	53.4%
DOR (months)	10.9	11.1	8.36 v 6.8	8.5	14.0
PFS (months)	6.3	6.8	5.6 v 4.5	6.5	13.1
OS (months)	N/A	12.5	10.6 v 11.3	12.6	N/A

no adverse events that led to treatment discontinuation. In another analysis of real-world outcomes with sotorasib in recurrent, metastatic *KRAS* G12C-mutated NSCLC, authors reported a median PFS of 9.3 months (95% CI 7.3–11.8) and median OS of 16.8 months (95% CI 12.7–22.3) [10]. Efficacy has been limited by resistance through increased expression of integrin B4 triggering AKT-mTOR bypass signaling as well as upregulated activation of the WNT-beta-catenin pathway [11]. Table 3 compares divarasib to existing *KRAS* G12C inhibitors, sotorasib and adagrasib.

The phase III CodeBreak200 compared sotorasib with docetaxel in previously treated NSCLC patients with *KRAS* G12C mutations. Sotorasib demonstrated a median PFS of 5.6 months (95% CI 4.3–7.8) versus docetaxel of 4.5 months (95% CI 3.0–5.7). However the FDA's Oncologic Drug Advisory Committee (ODAC) meeting voted that the PFS in CodeBreak200 could not be reliably determined [12]. This was a particularly interesting ODAC, where instead of voting on whether CodeBreak 200 should be used to convert the accelerated approval of sotorasib to the traditional approval, committee members were asked to vote on whether the primary endpoint of PFS per blinded independent central review (BICR) could be reliably interpreted.

While the CodeBreak 200 study met its primary endpoint, which was statistically significant, the difference in PFS was small between the two arms and there was no difference in OS. Additionally, the FDA shared concerns on the study conduct. For example, it observed that early dropouts were seen more often with the docetaxel arm, where the investigator assessments of “progression of disease” may have been biased and favored the sotorasib arm, as there were crossover of patients from docetaxel to sotorasib prior to the BICR assessment. Further concerns included lack of adherence to imaging assessment protocols as multiple evaluations appear to have been conducted by BICR to “resolve discrepancies” between investigator and BICR.

The field of *KRAS* is rapidly evolving. Especially with sotorasib falling short of initial expectations in CodeBreak 200, this leaves the door open for multiple other *KRAS* G12C competitors to continue to be developed for use in *KRAS* G12C NSCLC as well as other tumor types.

In the phase I/II KRYSTAL-1 study, patients with *KRAS* G12C-mutated NSCLC received adagrasib (Mirati Therapeutics) at 600 mg twice per day (BID). At data cut-off, 116 patients with a median of two prior lines of treatment were enrolled and ORR was 42.9% [13]. The median PFS was 6.5 months (95% CI 4.7–8.4) and median OS was 12.6 months (95% CI 9.2–19.2). The median DOR was 8.5 months (95% CI 6.2–13.8). Adagrasib demonstrated central nervous system (CNS) activity with an ORR of 33% and disease control rate (DCR) 85% in patients with stable, previously treated brain metastases [13, 14]. Adagrasib treatment-related events were common (97.4% of participants), including grade 3 or higher adverse events in 44.8% [14]. The most common toxicities include diarrhea (70.7%), nausea (69.8%), fatigue (59.5%), and vomiting (56.9%). Adagrasib was discontinued owing to adverse events in 6.9% of participants. These findings led to accelerated approval by the FDA in December 2022 for previously treated NSCLC with *KRAS* G12C mutations.

Currently, sotorasib is priced at US\$281.55 per 320 mg pill or US\$844.65 per day. Adagrasib is priced at US\$147.66 per 200 mg pill or US\$885.96 per day. Although pricing information for divarasib is not yet available, additional competitors may drive the price down to decrease the financial toxicity associated with taking newer targeted agents.

Garsorasib or D-1553 is another potent and selective *KRAS* G12C inhibitor in development. In Phase I results of patients with *KRAS* G12C-mutated NSCLC, the optimal dose was 600 mg BID [15]. In the dose expansion cohort including 79 patients, 94.5% experienced adverse events including 38% grade 3 or 4 events. In efficacy analysis of 74 patients ORR was 40.5% with median PFS of 8.2 months and median DOR of 7.1 months. In patients with brain metastases, the ORR was 17%. Studies of garsorasib are ongoing.

5 Conclusions

Divarasib is a covalent *KRAS* G12C inhibitor that in preclinical studies was 5 to 20 times as potent and up to 50 times as selective as sotorasib and adagrasib. In recently reported

phase I results, divarasib showed a similar efficacy as other KRAS G12C inhibitors. Although most patients reported toxicities, the majority were grade 1 or 2 gastrointestinal side effects that were manageable with supportive care and reversible.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest DB declares that she has no conflicts of interest that might be relevant to the contents of this manuscript. MN received consulting fees from Caris Life Sciences, honoraria from AstraZeneca, Daiichi Sankyo, Novartis, Lilly, Pfizer, EMD Serono, Genentech, Regeneron, and BMS. MN is a speaker for Mirati, Takeda, Janssen, and Blueprint Medicine and has received travel support from AnHeart Therapeutics.

Ethics approval and consent to participate Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

Author contributions DB provided clinical interpretation and drafted and reviewed all versions of the manuscript. MN provided clinical interpretation and drafted and reviewed all versions of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

- Lee JK, Sivakumar S, Schrock AB, Madison R, Fabrizio D, Gjoerup O, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. *NPJ Precis Oncol.* 2022;6(1):91.
- Nassar AH, Adib E, Kwiatkowski DJ. Distribution of KRASG12C somatic mutations across race, sex, and cancer type. *N Engl J Med.* 2021;384(2):185–7.
- Dang CV, Reddy EP, Shokat KM, Soucek L. Drugging the ‘undruggable’ cancer targets. *Nat Rev Cancer.* 2017;17(8):502–8.
- Lindsay CR, Jamal-Hanjani M, Forster M, Blackhall F. KRAS: reasons for optimism in lung cancer. *Eur J Cancer.* 2018;99:20–7.
- Wankhede D, Bontoux C, Grover S, Hofman P. Prognostic role of KRAS G12C mutation in non-small cell lung cancer: a systematic review and meta-analysis. *Diagnostics (Basel).* 2023;13(19):3043.
- Purkey H. Abstract ND11: discovery of GDC-6036, a clinical stage treatment for KRAS G12C-positive cancers. *Cancer Res.* 2022;82(12_Supplement):ND11.
- Sacher A, LoRusso P, Patel MR, Miller WH Jr, Garralda E, Forster MD. Single-agent divarasib (GDC-6036) in solid tumors with a KRAS G12C mutation. *N Engl J Med.* 2023;389(8):710–21.
- Desai J, Han S-W, Lee J-S, Shaham-Shmueli E, Massarelli E, Cervantes A. Abstract CT029: phase Ib study of GDC-6036 in combination with cetuximab in patients with colorectal cancer (CRC) with KRAS G12C mutation. *Cancer Res.* 2023;83(8_Supplement):CT029.
- Dy GK, Govindan R, Velcheti V, Falchook GS, Italiano A, Wolf J. Long-term outcomes and molecular correlates of sotorasib efficacy in patients with pretreated KRAS G12C-mutated non-small-cell lung cancer: 2-year analysis of CodeBreak 100. *J Clin Oncol.* 2023;41(18):3311–7.
- Iams WT, Balbach ML, Phillips S, Sacher A, Bestvina C, Velcheti V. A multicenter retrospective chart review of clinical outcomes among patients with KRAS G12C mutant non-small cell lung cancer. *Clin Lung Cancer.* 2023;24(3):228–34.
- Mohanty A, Nam A, Srivastava S, Jones J, Lomenick B, Singhal SS. Acquired resistance to KRAS G12C small-molecule inhibitors via genetic/nongenetic mechanisms in lung cancer. *Sci Adv.* 2023;9(41):eade3816.
- Administration, U.F.D. October 5, 2023: Meeting of the Oncologic Drugs Advisory Committee Meeting Announcement. 2023. <https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-5-2023-meeting-oncologic-drugs-advisory-committee-meeting-announcement-10052023#event-materials>.
- Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. *N Engl J Med.* 2022;387(2):120–31.
- Sabari JK, Velcheti V, Shimizu K, Strickland MR, Heist RS, Singh M. Activity of adagrasib (MRTX849) in brain metastases: preclinical models and clinical data from patients with KRASG12C-mutant non-small cell lung cancer. *Clin Cancer Res.* 2022;28(15):3318–28.
- Li Z, Song Z, Zhao Y, Wang P, Jiang L, Gong Y. D-1553 (Garso-rasib), a potent and selective inhibitor of KRAS. *J Thorac Oncol.* 2023;18(7):940–51.