Editorial Commentary

Is adagrasib just another sotorasib?—or, should we differentiate their usage according to patients' clinical presentation?

Yuko Oya[1]^, Tetsuya Mitsudomi[2]^

[1]Department of Respiratory Medicine, School of Medicine, Fujita Health University, Toyoake, Japan; [2]Fujita Healrth University, Kindai Hospital Global Research Alliance Center and Thoracic Surgery, Osaka-Sayama, Japan

Correspondence to: Tetsuya Mitsudomi, MD, PhD. Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Japan. Email: mitsudom@med.kindai.ac.jp.

Comment on: Sabari JK, Velcheti V, Shimizu K, *et al.* 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;28:3318-28.

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Although KRAS was the first oncogene cloned from human cancers, including lung cancer, in the early 1980s (1), there were few targeted therapies against KRAS until recently (2). Ostrem *et al.* found an allosteric inhibitor of KRAS in 2013 that covalently binds the cysteine of the G12C mutant form of KRAS and is accommodated by a pocket near the switch II region (3). This inhibitor locks KRAS in its GDP-bound inactive state, thereby blocking downstream signaling. Following this discovery, several companies have developed similar inhibitors, of which sotorasib and adagrasib were the first two approved by the Food and Drug Administration (FDA) for clinical use in non-small cell lung cancer (NSCLC) (4,5).

In a recent issue of *Clinical Cancer Research*, Sabari *et al.* reported the brain metastasis (BM)-specific activity of adagrasib (6). BMs are frequently observed during the treatment of advanced NSCLC, and they often significantly compromise patients' quality of life (7). Sabari *et al.* retrospectively analyzed 374 patients with NSCLC with KRAS mutations (149 with G12C mutations and 225 with non-G12C mutations) for BM. Overall, 40% of the patients with either KRAS G12C or non-G12C mutations developed BM during their follow-up period. Seventy-seven percent of the patients demonstrated synchronous BM diagnoses, defined as detection within 3 months of the initial diagnosis. However, BM may occur less frequently among patients with NSCLC with KRAS mutations than among patients with NSCLC with other driver oncogenes (8). According to a retrospective review of 579 patients with metastatic NSCLC, the incidence of BM was highest in NSCLC patients with mutation/fusion of ROS1 (36%) and ALK (34%), followed by EGFR (28%) and KRAS (28%); BM occurred in only 21% of patients with NSCLC without a driver oncogene (8). The response of BM to radiation therapy may vary depending on the oncogene that drives the cancer (9). According to a report by Arrieta *et al.* (9), the response rate to radiotherapy is higher in NSCLC patients with activated EGFR (64.5%) or ALK (54.5%) mutations than in those without driver gene mutations (35%). However, it is as low as 20% in patients with KRAS-mutated NSCLC, further underlining the need for efficacious treatments for this cohort (9).

In preclinical studies, Sabari *et al.* found that adagrasib has a high cerebrospinal fluid (CSF) concentration. The unbound brain-to-plasma partition coefficient, Kp,uu, is approximately 1 at 200 mg/kg and 0.2–0.4 at 100 mg/kg. These values are comparable to those of other targeted agents known to have high activity against BM [e.g., osimertinib (0.39), alectinib

^ ORCID: Yuko Oya, 0000-0002-3171-6031; Tetsuya Mitsudomi, 0000-0001-9860-8505.

(0.63–0.94), and lorlatinib (0.75)] (10-12). As a Kp,uu greater than 0.3 is generally indicative of good diffusion across the blood-brain barrier, central nervous system (CNS) penetration of adagrasib should efficiently occur in a dose-dependent manner. A preclinical mouse model showed that a phase II dose equivalent of adagrasib completely saturated the P-glycoprotein-dependent efflux and maximized CNS exposure. This concentration was also clinically achievable and comparable to that measured in CSF samples from patients with BM during the dose escalation portion of a phase Ib study, resulting in shrinkage of the BM. In a phase II cohort of the KRYSTAL-1 study, the intracranial (IC) objective response rate (ORR) and disease control rate were 33% and 85%, respectively (5). The IC-DOR and IC progression-free survival (PFS) were 11.2 and 5.4 months, respectively. Therefore, adagrasib for BM appears promising.

The natural question is whether this degree of activity of adagrasib against BM is also observed for sotorasib, which the FDA approved 1 year and 7 months earlier than adagrasib. Only limited data on the CNS activity of sotorasib in metastatic NSCLC are available. Although patients with active, untreated BMs were excluded from the Code-BreaK100 trial, among 16 patients with stable BM, 2 had complete response and 12 had stable disease after sotorasib therapy, resulting in intracranial disease control in 88% of these patients (13). Additionally, there are at least two case reports of a patient with BM who had a radiographic response and resolution of symptoms with sotorasib. Yeh *et al.* reported a patient with NSCLC harboring the KRAS G12C mutation with symptomatic leptomeningeal disease and multiple BMs who was treated with sotorasib monotherapy. The patient showed clinical improvement 2 weeks after starting sotorasib, and brain magnetic resonance imaging (MRI) confirmed clear radiographic improvement of many metastatic nodules and meningeal contrast enhancement, with most lesions resolved or significantly reduced in size. In this case, sotorasib was effective for untreated symptomatic BMs. However, severe hepato-toxicity mandated sotorasib discontinuation, resulting in disease progression. Therefore, sotorasib is also effective for metastases involving the CNS (14,15), although prospective trials are needed.

Outside of the activities on BM, what do we know about the difference between sotorasib and adagrasib? Adagrasib has a longer half-life than sotorasib (24 *vs.* 5.5 h) (4,5,16). In phase II trials, the ORR was higher with adagrasib (43%) than with sotorasib (37%), and the PD rate was lower with adagrasib (16% for sotorasib and 5% for adagrasib), as shown in *Table 1*. However, caution must be exercised when performing cross-trial comparisons. The median PFS is similar between these two drugs (sotorasib, 6.6 months and adagrasib, 6.5 months). Additionally, drug-related adverse events are more common with adagrasib than with sotorasib. As a result, treatment discontinuation or dose reduction is more frequent with adagrasib (sotorasib, 22% and adagrasib, 52%) (4,5). Toxicity is a key factor in the selection of these two drugs.

As with other targeted therapies for NSCLC, acquired resistance to KRAS G12C-targeted therapy is virtually inevitable. Further, the presence of co-occurring mutations in genes such as TP53, KEAP1, STK11, and others could also affect efficacy (17). Although some resistance mechanisms have been identified, they are diverse and heterogeneous, even within a single patient. A secondary mutation in KRAS is one such mechanism. These mutations can be classified into three types, based on their functional consequences. Mutations at codons 12 or 61 decrease the ability of KRAS to hydrolyze GTP, and those at G13 increase the GDP to GTP exchange. In contrast, mutations occurring at R68, H95, Y96, and Q99 decrease the affinity between KRAS and inhibitors (18). However, there is a difference between the activities of adagrasib and sotorasib against these mutations. Awad *et al.* found different mutational profiles promote resistance in sotorasib and adagrasib (18). For example, point mutations occurring at H95 that promote resistance to adagrasib resistance have no effect on sotorasib activity (18). By contrast, Koga *et al.* reported that G13D, R68M, A59S, and A59T mutants are highly resistant to sotorasib but remain sensitive to adagrasib, whereas secondary mutations occurring at M72 or Q99 promote resistance to adagrasib but remain sensitive to sotorasib (19). Therefore, there may be opportunities to use both drugs complementarily after the emergence of resistance to a single inhibitor.

In conclusion, Sabari *et al.* showed promising activity of adagrasib on BMs. Sotorasib may also have similar activity; however, more evidence is required. As both drugs are already available in clinical practice in the USA and newer G12C inhibitors will be available in the future, rational usage of these drugs to maximize their efficacy and safety should be sought.

Table 1 Summary of the difference between sotorasib and adagrasib

	Sotorasib	Adagrasib
Dose (mg)	960	1,200
Half life (hours)	5.5±1.8	24
Trial	CodeBreak100	KRISTAL-1
Design	Single-arm P2	Single-arm P2
Patients, n	126	116
Primary endpoint	ORR	ORR
ORR (95% CI) (%)	37.1 (28.6–46.2)	43 (33.5–52.6)
DOR (95% CI) (months)	11.1 (6.9–NE)	8.5 (6.2–13.8)
DCR (95% CI) (%)	80.6 (72.6–87.2)	80 (70.8–86.5)
PFS (95% CI) (months)	6.6 (5.1–8.2)	6.5 (4.7–8.4)
OS (95% CI) (months)	12.5 (10.0–NE)	12.6 (9.2–19.2)
Follow-up period (months)	15.3	12.9
Brain metastasis, n (%)	26 (20.6)	24 (21)
Intracranial ORR, DCR rates (%)	33, 85	12.5, 88
PD rate (%)	16.1	5
Dose reduction/interruption rate (%)	22.3	Dose reduction: 52; dose interruption: 61

ORR, objective response rate; DOR, duration of response; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NE, not evaluated; PD, progressive disease.

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