Editorial Commentary

Evaluating the intracranial activity of adagrasib

Rupesh Kotecha[1,2], Alonso La Rosa[1], Tugce Kutuk[1], Manmeet S. Ahluwalia[2,3], Minesh P. Mehta[1,2]

[1]Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA; [2]Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA; [3]Department of Medical Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA

Correspondence to: Rupesh Kotecha, MD. Miami Cancer Institute, Baptist Health South Florida, 1R203, 8900 N Kendall Drive, Miami, FL 33176, USA. Email: rupeshk@baptisthealth.net.

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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Brain metastasis represent the most common intracranial malignancy in adults, with lung cancer patients accounting for the largest proportion of brain metastasis' primary site of origin (1). Due to improvements in intracranial imaging and standardization of intracranial screening at cancer diagnosis and during surveillance, it is expected that two out of every five patients with non-small cell lung cancer (NSCLC) will be diagnosed with brain metastasis at some point during their disease course (2). During this same period, the near uniform adoption of tissue and liquid testing for molecular alterations in NSCLC has deepened our understanding of the varying risks of developing brain metastases as a function of molecular subgrouping. For example, recent studies have revealed that patients with epidermal growth factor receptor (*EGFR*)-mutated and anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC have a 23% to 31% risk of brain metastasis at diagnosis and another 50% to 60% will develop intracranial relapse during their disease course (3-5). Although these two molecular subgroups now have multiple Food and Drug Administration (FDA) approved targeted therapies with demonstrated central nervous system (CNS) penetration, a significant proportion patients with NSCLC do not harbor such molecular alterations with actionable targets, and therefore remain understudied.

The kirsten rat sarcoma viral oncogene (*KRAS*) mutation is present in approximately one in every four NSCLC patients, occurring most frequently in codons 12, 13, and 61 [90% are glycine in codon 12, and predominantly with cytosine (42%, *KRAS*^{G12C})] (6-8). The incidence of brain metastasis in *KRAS*-mutated patients is approximately 40% (similar to the *EGFR*-mutated subgroup), and these incidence rates are recapitulated in those with the common codon 12 mutation (85%) and *KRAS*^{G12C} variant (42.3%) (8). It is not clear whether there exists higher brain tropism due specifically to the presence of *KRAS*-mutation or a specific variant (*KRAS*-mutated *vs.* *KRAS*$^{wild\text{-}type}$: 33% *vs.* 40%, P=0.17; *KRAS*^{G12C} *vs.* other *KRAS* mutation: 40% *vs.* 41%, P=0.74) (9). Recent molecularly-stratified prognostic studies in NSCLC brain metastasis patients have demonstrated the importance of *EGFR*-mutation and *ALK*-rearrangement on patient survival, but the impact of *KRAS*-mutation has not been similarly evaluated (10). Furthermore, the observation of *KRAS*-mutation switching between a primary tumor and brain metastasis (occurring in approximately 10% of cases) and its impact on patient prognosis and outcome remains understudied (11). Finally, the inability to previously target this specific mutation has limited our understanding of the ultimate impact of *KRAS*-mutation on patient outcome.

In a recent publication, Sabari *et al.* expand our understanding of the impact of *KRAS*-mutation on NSCLC brain metastasis by reporting results from three different datasets: a retrospective review of patients with *KRAS*-mutated NSCLC and brain metastasis, preclinical studies evaluating CNS concentrations of *KRAS* inhibitors, and clinical outcomes in two patients treated on a prospective clinical trial (12). For the retrospective cohort analysis, of

374 patients with *KRAS*-mutated metastatic NSCLC (40% $KRAS^{G12C}$, 60% *KRAS* non-G12C mutant) around 90% of the patients developed brain metastases during their disease course, and almost half of them presented with intracranial disease within 12-month of metastatic disease diagnosis. These data support a high propensity of *KRAS*-mutated metastatic NSCLC patients for developing brain metastasis (12). These results are supported by a recent study from Vassella and colleagues who reported that *KRAS* mutation was present in 58% of primary NSCLC tumors which ultimately metastasized to the brain, significantly higher in proportion than metastases to other sites (13). In addition, Sabari *et al.* reported that 77% of patients developed brain metastasis within 3 months of diagnosis of metastatic disease (synchronous), rather than metachronous development. In contrast, Vassella *et al.* found no difference in mutation profile between synchronous and metachronous brain metastasis presentation. However, neither of the studies differentiated whether discordance in mutation status between the primary tumor and the intracranial metastasis accounted for synchronous versus metachronous presentations. It would be interesting to identify if the presentation chronology can be related to the molecular heterogeneity between the primary and intracranial disease (14). Vassella *et al.* also analyzed a subset of 54 patients where primary and brain metastasis samples were available, and reported that most of the driver alterations observed in the primary were preserved in the brain metastasis (26%) (13). However, alterations exclusive to primary tumors were observed in 22% and in brain metastases only in 26%. Similarly, Jiang *et al.* recently reported significantly higher genomic heterogeneity between primary tumors and brain metastasis (median 6.8% of shared mutations) than between primary tumors and liver metastases (median 66.3% of shared mutations; P=0.005) (15). Finally, Rau *et al.* studied concordance in *KRAS* status in primary NSCLC and brain metastasis, finding only a 50% concordance for *KRAS* mutation (in codon 12 and 13) but 100% when subdivided in *KRAS*—codon 12 only mutations (16). Therefore, there is much still to learn about how the mutational heterogeneity between the primary and CNS metastatic tumors influences the cadence, chronology, biological behavior, and eventual outcome of *KRAS*-mutated NSCLC patients developing brain metastases.

Sabari and colleagues also report on CNS concentrations of adagrasib. Initially, the efflux ratio was only 13 in MDCK-MDR cell permeability assays, suggesting limited CNS exposure. Yet, concentration-dependent inhibition allows adagrasib to gain access to the CNS by bypassing the physiochemical constraints of the blood-brain barrier. When they measured the penetration into the CNS after oral administration of adagrasib, they found that at the 200 mg/kg dose level, the unbound brain to unbound plasma concentration (Kp,uu) of adagrasib at 8 hours was 1, indicating significant penetration. This finding demonstrated time and dose-dependent penetration to the CNS with increasing CNS exposure (12). Although similar preclinical studies in other molecular subgroups are limited, comparable experiments with NSCLC targeted therapies also demonstrate similar levels of CNS penetration and are summarized in *Table 1*. Sabari and colleagues were also able to demonstrate intracranial activity in their preclinical experiments with LU99-Luc $KRAS^{G12C}$-mutant NSCLC implanted mice. Adagrasib treated mice experienced an improvement in overall survival ($P<0.05$) and complete tumor responses were observed in 40% (2/5). These results are similar to *EGFR* exon 19 deletion xenograft brain metastases preclinical models which demonstrated dose-dependent tumor regression and improved overall survival with the CNS-penetrant agent osimertinib, whereas more limited outcomes were seen with rociletinib and gefitinib, which have inferior CNS-penetrance (18).

In this report, Sabari and colleagues also provide two case examples of patients with metastatic $KRAS^{G12C}$-mutated NSCLC who were enrolled in the phase Ib limited brain metastasis cohort of KRYSTAL-1 and received adagrasib. These selected examples are obviously preliminary, and as such warrant discussion of the key inclusion criteria and treatment strategy of the overall trial. As is commonly observed in clinical trials evaluating the role of systemic therapies alone in patients with brain metastasis, the cohort consists of highly-selected patients who are neurologically stable, asymptomatic, with an Eastern Corporative Oncology Group (ECOG) performance status of ≤1, have lesions smaller than 2 cm, are corticosteroid-naive for ≥2 weeks, and are not receiving any antiepileptic therapy. Patients also must have discontinued the most recent course of systemic or radiation therapy >2 weeks prior to the first adagrasib dose. It is important to note that such strict inclusion criteria, needed to be able to safely defer upfront effective local therapy of brain metastases, often limit the external validity or generalizability to a larger patient population (20). Moreover, even in well-selected patients who respond to upfront systemic therapy alone, local intervention is frequently needed due to the lack of durability of benefit from systemic

Table 1 Preclinical data on the CNS concentrations of various therapeutic agents for NSCLC

Reference	Mutation	Medication	Efflux ratio	Concentration	Outcomes
Sabari *et al.*, 2022 (12)	*KRAS*^{G12C}	Adagrasib	13 (MDCK-MDR1)	CSF concentration (nmol/L) =52	Brain CR =40%
				Brain Kp,uu =1 (8 hours)	Increased OS ($P_{adjusted}$ <0.05)
Colclough *et al.*, 2021 (17)	*EGFR*	Icotinib	3.4 (MDCK-BCRP)	Brain Kp,uu =0.12	–
		Poziotinib	3.5 (MDCK-BCRP)	Brain Kp,uu =0.06	–
		Erlotinib	6.9 (MDCK-BCRP)	Brain Kp,uu =0.084	–
		Gefitinib	22.4 (MDCK-BCRP)	Brain Kp,uu =0.0092	–
		Afatinib	53.1 (MDCK-BCRP)	Brain Kp,uu =0.0062	Intracranial efficacy 16%, extracranial efficacy 72%
		Osimertinib	3.2 (MDCK-BCRP)	Brain Kp,uu =0.21	–
Ballard *et al.*, 2016 (18)	*EGFR*	Osimertinib	13.4 (MDCKMDR1)	Brain/plasma C_{max} ratio =3.41	Tumor regression 83%
			5.4 (MDCK-BCRP)	Brain Kp,uu =0.39	
		Gefitinib	–	Brain/plasma C_{max} ratio =0.21	–
		Rociletinib	5.38 (MDCK-MDR1)	Brain/plasma C_{max} ratio <0.08	Tumor regression not achieved
		Afatinib	4.62 (MDCK-MDR1)	Brain/plasma C_{max} ratio <0.36	–
			54.6 (MDCK-BCRP)		
Kodama *et al.*, 2014 (19)	*ALK*	Alectinib	1.32	Brain/plasma concentration at Tmax was between 0.63 and 0.94	–

CNS, central nervous system; NSCLC, non-small cell lung cancer; *KRAS*, kirsten rat sarcoma viral oncogene; MDCK-MDR, multidrug-resistant canine kidney; CSF, cerebrospinal fluid; *EGFR*, epidermal growth factor receptor; BCRP, breast cancer resistance protein; *ALK*, anaplastic lymphoma kinase.

therapy alone (21). Finally, although systemic therapy alone trials often do not restrict the number or size of intracranial lesions, more recent results from such studies have revealed that certain subgroups with significant intracranial disease burden may warrant upfront local therapy. One such example is the NIVOREN study, in which no objective responses were reported in patients treated with systemic therapy alone if they had multiple brain metastases or if any individual lesions were larger than 1 cm (22).

The first case is a 67-year-old female who was initially diagnosed with stage IIIA NSCLC and progressed to metastatic disease after upfront platinum-based chemotherapy, and before any definitive local thoracic treatment. She also appeared to have asymptomatic brain metastasis. Although dimensional or volumetric assessments are not provided, the extent of the patient's intracranial disease appears quite minimal, as depicted in *Fig. 4* of the original publication (12). Although difficult to ascertain from the single axial slices provided in the figure, these lesions are likely below the RECIST 1.1 minimum measurement threshold (23). It is important to note that these thresholds were established as there are concerns over reproducibility and interpretation of changes in such small lesions. Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) provides guidance for investigators who choose to lower the minimum size limit of measurable disease to 5 mm and these appear even below this threshold (24). The second case is a 66-year-old male diagnosed with *de novo* metastatic NSCLC with brain metastases. In the month following diagnosis, the patient received palliative radiotherapy followed by carboplatin, pemetrexed, and pembrolizumab until progressive disease was noted. Following two cycles of adagrasib, the best overall response was stable disease but decrease in the size of three brain metastases. It is important to note that these represent the best responses and although details are provided up to 2 cycles, the durability of the response for intracranial disease is unknown. Again, these two examples are encouraging, but do not establish delay or avoidance of local therapy for brain metastases as a generally acceptable

clinical standard.

As *KRAS*-targeting agents penetrate into clinical practice, the selection of one particular agent over another is typically governed by patient characteristics, medical comorbidities, and institutional practice patterns, but will likely also be based on the presence or absence of brain metastasis given the current data. The FDA approved the use of the *KRAS* small-molecule inhibitor sotorasib for patients with *KRAS*^{G12C}-mutated NSCLC based on a phase II study (CodeBreaK100 trial) of 126 previously-treated patients with a 37% objective response rate and median duration of response of 11.1 months (25). However, patients with untreated brain metastases were excluded from this trial. A post-hoc analysis also reported that among 40 patients with evaluable brain metastasis at baseline, the intracranial disease control rate was 87.5% (14/16 patients) (26), but in the setting of previously treated disease, the ultimate activity of sotorasib alone cannot be adequately assessed. This is currently being investigated as a substudy of the CodeBreaK101 protocol (NCT04185883). Of relevance, in a case report evaluating the intracranial response to sotorasib in a single patient with active brain metastasis without upfront local treatment, the patient initially achieved an intracranial complete response, but the duration of response was limited to less than 6 months, and ultimately, symptomatic brain metastasis progression resulted in an urgent resection (27). A recent phase 2 study published by Jänne *et al.* (28) evaluated adagrasib in previously treated patients with chemotherapy and PD-1 or PD-L1 therapies. Among 112 patients with measurable disease at baseline, the confirmed objective response rate was 42.9%. In this study, using the RANO-BM criteria, they identified 42 patients with CNS metastases at baseline and reported a median intracranial progression-free survival of 5.4 months. In a subset of 33 patients who could be evaluated radiographically, the intracranial confirmed response rate was 33.3%, and the median duration of intracranial response was 11.2 months. However, a substantial proportion of patients had received prior radiotherapy before entry, therefore confounding the true effect of the drug. Therefore ongoing studies, like KRYSTAL-1 will provide more data on the intracranial activity of adagrasib alone, especially in untreated brain metastases (29). Finally, as these therapies become more commonplace, it is important to monitor for acquired resistance even after a favorable initial response. In one recent series of 38 patients with *KRAS*^{G12C}-mutated lung and gastrointestinal cancers treated with adagrasib, 45% acquired resistance mechanisms at disease progression (30). Therefore, selection of the optimal treatment, and consideration of local therapy in the setting of acquired resistance *vs.* switching systemic therapy requires even more complex, and less scientifically-grounded, decision making.

Ultimately, in the era of precision medicine, several systemic therapies are available for patients with metastatic NSCLC with a wide spectrum of published intracranial response rates and durability (*Figure 1*). As patients require systemic therapy for their metastatic disease, the question of which type of local therapy that should be integrated, the timing, and even the ultimate need for that local therapy itself continues to be questioned. For specific molecular subgroups, advances in systemic therapies with superior intracranial penetration have resulted in delayed intracranial relapse rates for those without brain metastasis (33), increased intracranial responses in those with brain metastasis (31), and improved survival (34). Yet, the minimum threshold of CNS activity with systemic therapy alone to preclude the use of local interventions has yet to be established. The most recent American Society of Clinical Oncology (ASCO)-Society for Neuro-Oncology (SNO)-American Society of Radiation Oncology (ASTRO) guidelines recommend that select patients with mild symptoms controlled with supportive therapy may reasonably defer local therapy while receiving CNS-active systemic therapy (35). However, the definitional threshold of "CNS activity" remains unspecified, and obviously varies substantially based on the selected agent. It remains unclear which metric should define this: CNS concentration, best intracranial response rate, overall CNS response rate, durability of response, clinical benefit rate, time to CNS progression, or intracranial progression-free survival. The field clearly needs to provide meaningful rigor to such an important measure. In the meantime, as the intracranial responses from adagrasib can currently be described as modest at best, the most meaningful trial should compare adagrasib alone *vs.* adagrasib and modern local therapies, such as SRS. Brain metastasis progression can result in neurologic symptoms, cognitive decline, the need for additional medications, hospitalizations, emergent surgeries, detriment in quality of life, and potentially limit survival (21,36). In fact, previous studies evaluating the paradigm of systemic therapy alone for patients with active brain metastasis with agents with modest CNS activity, similar to that of the current *KRAS*-agents, have demonstrated reduced survival (37). Therefore, before removing effective local treatments from the armamentarium, one should

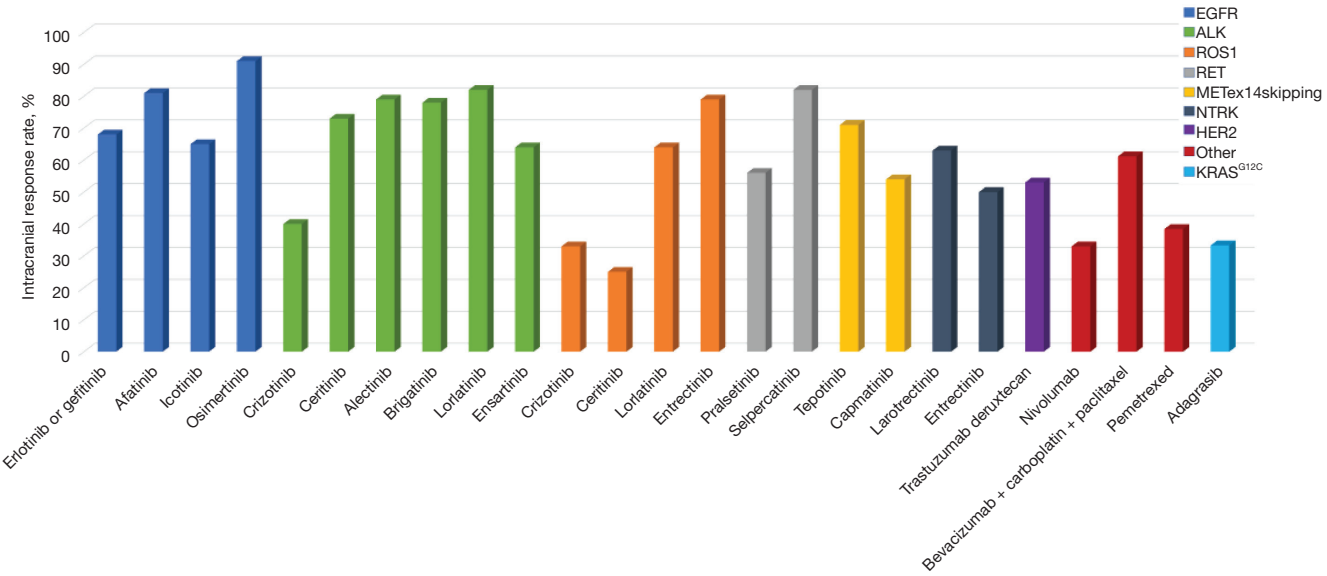

Figure 1 Published intracranial response rates for various systemic therapies using in patients with brain metastasis from NSCLC (31,32). EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ROS oncogene 1; RET, rearranged during transfection; NTRK, neurotrophic tyrosine kinase; NSCLC, non-small cell lung cancer.

design appropriate trials to compare the risks/benefits of systemic therapy alone versus systemic and local interventions.

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Footnote

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