Editorial Commentary

Penetrating the central nervous system sanctuary of KRAS, a target once thought "undruggable"

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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.

Keywords: Sotorasib; adagrasib; KRAS; KRASG12C; central nervous system (CNS) metastases

Submitted Feb 01, 2023. Accepted for publication Mar 23, 2023. Published online Apr 06, 2023.
doi: 10.21037/tlcr-23-71
View this article at: https://dx.doi.org/10.21037/tlcr-23-71

Although discovered back in the 1970s, the RAS family proteins were considered undruggable (1), primarily because the KRAS protein has a pocket-less structure unsuitable for fitting an effective drug. However, with concerted efforts from academia, pharmaceutical industry, and initiatives on RAS from National Cancer Institute (2), significant new strides have been made to tame this master oncogene in the last few years (3).

The discovery of a covalent inhibitor drug handle in KRASG12C protein (4) led to the development of the first in class KRASG12C off state inhibitor and ultimately to FDA accelerated approval of sotorasib/LUMAKRAS® (Amgen, USA) for previously treated advanced metastatic patients with non-small cell lung cancer (NSCLC) harboring KRAS G12C (5). Having a similar mechanism of action, another G12C inhibitor, adagrasib/KRAZATI® (Mirati Therapeutics, USA) also received accelerated FDA approval for the same setting (6).

Now that we have two "weapons" to go against KRAS G12C, how can we further improve on patient outcomes? One key consideration would be brain penetration of these inhibitors, as treatment and prevention of brain metastases would be critical on patient outcomes. The development of brain metastases in lung cancer is typically associated with worse survival (7). Furthermore, significant increase in symptoms such as fatigue, headaches and depression post the diagnosis of brain metastases have been reported by Guérin and colleagues (8), suggesting that central nervous system (CNS) disease control is crucial to maintain the quality of life (QOL) of patients.

As clinical trials excluded patients with active CNS metastases in the published sotorasib studies, there is limited data on sotorasib's CNS penetration. In the paper "Activity of Adagrasib (MRTX849) in Brain Metastases: Preclinical Models and Clinical Data from Patients with KRASG12C-Mutant Non-Small Cell Lung Cancer", Sabari and colleagues first present their retrospective analysis on brain metastases in KRAS mutant NSCLC patients, then provide a comprehensive review of the pharmacological and preclinical data on adagrasib, followed by two case studies of patients with previously untreated brain metastases who had successful response to adagrasib (9).

Of all the KRAS G12C mutant patients in the cohort, 40% (n=150) developed brain metastases at any time, highlighting the high propensity of these patients to progress in the CNS (9). The authors properly comment on

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their limitations—the retrospective nature of the analysis, comparisons only made within KRAS mutated NSCLC and the possible underestimation due to the fact that serial CNS imaging was not performed. Nonetheless, 40% is a percentage that is compelling and consistent with prior studies (10,11).

The comprehensive pharmacological and preclinical review of adagrasib shown by Sabari and colleagues highlights the favorable pharmacokinetic properties including CNS penetration. From mice models, they demonstrated that adagrasib has an IC_{50} of 980 nmol/L for inhibiting p-glycoprotein, indicating the concentration-dependent inhibition of its own efflux within a physiologically relevant range anticipated to bypass the constraints of the blood-brain barrier (9). The mice treated with 200 mg/kg of adagrasib orally yielded a total plasma concentration, free-plasma, and cerebral spinal fluid (CSF) concentrations of 8,600, 43 and 52 nmol/L, respectively, 8 hours after administration. At the 200 mg/kg dose level in mice (which had a mean steady state comparable to clinical human free-plasma concentration with the phase II adagrasib dose of 600 mg twice daily), the unbound brain to unbound plasma concentration ($K_{p,uu}$) value was approximately 1 at 8 hours, suggesting significant CNS penetration at this dose level (9).

Lastly, the authors describe two case studies of patients with previously untreated brain metastases who were given adagrasib as part of the KRYSTAL-1 study. Consistent with preclinical data, in these two patients with untreated brain metastases, the CSF concentrations of adagrasib measured above the target cellular IC_{50} and both patients demonstrated corresponding regression of brain lesions based on serial imaging. The average Kp,uu in these two patients was 0.47, which was consistent with observations from preclinical models and also exceeded values for other tyrosine kinase inhibitors with known CNS activity (9,12,13).

There may be criticism towards this study such as the number of human subjects reported was small (n=2). However, we would like to first commend the team for expanding the study drug to those with brain metastases and the patients/study team involved for diligently obtaining CSF which provided undoubtedly valuable data. While the phase Ib portion of the trial had already allowed patients with neurologically stable, asymptomatic, untreated (non-cerebellar/non-focal leptomeningeal) brain lesions <2 cm in size, the eligibility criteria were later expanded to remove the size restrictions and brain lesions and allowed for up to 25 patients (9). If 40% of KRAS G12C mutant patients were to develop brain metastases at any time, this is not a number that can be ignored. While prior studies have been traditionally hesitant regarding allowing entry of those with brain metastases, improved inclusion of such patients have been called upon by the American Society of Clinical Oncology-friends of cancer research brain metastases working group (14) and we hope to see increased inclusion of patients with brain metastases so that the trial patient population is representative of that of the "real-world".

Although Sabari and colleagues have shown the proof of concept preclinical and clinical data of adagrasib as a CNS-penetrant KRAS G12C inhibitor, there is more to be investigated. The duration of response in the brain remains a question and we will eagerly await the results of the 25 patients with brain metastases from KRYSTAL-1. Furthermore, although allowing untreated brain metastases to enroll in itself was eye-opening, we must acknowledge that many of the patients with brain metastases are treated upfront with radiation therapy or surgery, especially when symptomatic. What role could adagrasib play in these situations? Finally, there could be molecular heterogeneity between the primary site of tumor versus metastatic sites, in particular the brain (15) and differences in the tumor microenvironment has also been reported (16,17), but how would we account for that?

We are fortunate to be now in an era to have two FDA-approved KRAS G12C inhibitors. KRAS G12C, once thought "undruggable" has now become a "druggable" target. The key next steps to further improving on patient outcomes would be evaluating the potential of brain penetration of these inhibitors, as treatment and prevention of brain metastases would be critical on patient outcomes. KRYSTAL-1 team should be commended for allowing entry of those patients with untreated brain metastases. We agree that prospective interventional studies with serial CNS imaging would be the gold standard of evaluating CNS activity of tyrosine kinase inhibitors, but we must remember; this is a great start, but only a start.

Acknowledgments

The authors are grateful to SKY Foundation Inc. Partners Fund, Perry's Family Funds and U-CAN-CER VIVE Foundation for supporting studies in Dr. Azmi's laboratory.
Funding: Work in the lab of Dr. Azmi was supported by NIH R37-CA215427.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-71/coif). MN has received consulting fees from AstraZeneca, Caris Life Sciences, Daiichi Sankyo, Novartis, EMD Serono, Pfizer, Lilly and Genentech, has received travel support from AnHeart Therapeutics and is a speaker for Takeda, Janssen, Mirati and Blueprint Medicines. ASA received funding from Karyopharm, EISAI, Janssen and serves as a consultant for GLG and Guidepoint. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Nagasaka M, Azmi AS. Penetrating the central nervous system sanctuary of KRAS, a target once thought "undruggable". Transl Lung Cancer Res 2023;12(4):665-668. doi: 10.21037/tlcr-23-71