Editorial Commentary

Intracranial responses with selective *KRAS*-G12C inhibitors in non-small cell lung cancer

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The recent Food and Drug Administration (FDA)-approval of adagrasib (MRTX849) has added to the armamentarium of *KRAS* G12C-mutant non-small cell lung cancer (NSCLC). The approval was based on the phase 2 KRYSTAL-1 trial (NCT03785249) which demonstrated clinical benefit in this patient population (1). Adagrasib joins sotorasib (AMG-510) as the only two FDA-approved selective *KRAS*-G12C inhibitors at this time. In phase 2 trials, both adagrasib and sotorasib showed meaningful clinical activity demonstrating a systemic objective response rate (ORR) of 42.9% versus 37.1% respectively (2,3). An area of active investigation in this space surrounds the efficacy of the selective G12C inhibitors in the central nervous system and untreated intracranial lesions.

The initial KRYSTAL-1 and CodeBreak100 trials excluded patients with active, untreated brain metastasis (4). A post-hoc analysis of the CodeBreak100 trial reported intracranial disease control in 14 of 16 patients (87.5%) (5). At 2022 American Society of Clinical Oncology Annual Meeting (ASCO22), the KRYSTAL-1 phase 1b expansion cohort which enrolled active and untreated central nervous system (CNS) metastasis demonstrated an objective intracranial response and disease control rate of 31.6% and 84.2% respectively (6). Intracranial objective responses were observed in 2 of 4 patients with non-target brain lesions and 4 of 15 with target brain lesions. The KRYSTAL-1 phase 2 trial reported an intracranial ORR of 33.3% (11/33 patients) with one intracranial complete response and a median duration of intracranial response of 11.2 months (2). A baseline CT head with contrast or brain MRI was required for study entry in both phase 2 trials.

In this translational report, Sabari *et al.* demonstrated adagrasib cerebrospinal fluid (CSF) penetration and anti-tumor activity (7). The investigators remark from their cohort of 374 patients that the incidence of brain metastasis in *KRAS*-G12C and non-G12C NSCLC patients to be around 40% which is consistent with other reports (8). Adagrasib has properties which include P-glycoprotein multi-drug resistance (MDR) pump inhibition, suggesting possible CNS penetration. To test this hypothesis, mice models were implanted with H23-Luc or LU65-Luc cell xenografts intracranially. The investigators observed that 200 mg/kg adagrasib dosing (equivalent plasma concentration to 600 mg twice daily in humans) achieved maximum CNS exposure. At 100 mg/kg twice daily dosing, brain lesion regression in animal models was observed including 2 of 5 complete intracranial responses.

In the translational report, unbound brain-to-plasma partition coefficient ($Kp_{uu,\ brain}$), predictor for blood-brain barrier (BBB) permeability, was found to be approximately 1 at 200 mg/kg and 0.2–0.4 at 100 mg/kg. For reference, the anti-EGFR tyrosine kinase inhibitor osimertinib has a $Kp_{uu,\ brain}$ of 0.39 in mice with intra-internal carotid artery injection xenograft (9). Mouse models which received intracranial implantation of xenografts could have compromised BBB integrity and permeability, and

additional model systems including intracardiac, tail vein injections, or spontaneous models would corroborate their findings.

Published sotorasib CNS activity data remains limited at this time. Two case reports describe intracranial response of untreated, active brain metastasis (10,11). In both cases, the patients were treated with sotorasib 960 mg with rapid intracranial response in less than 2 months. Additionally, here we highlight a patient case from our practice involving sotorasib and CNS control. A 74-year-old male with *KRAS* G12C-mutant oligometastatic lung adenocarcinoma involving the left frontal lobe had resection of the brain lesion followed by a course of stereotactic body radiation therapy (SBRT) and immunochemotherapy (pembrolizumab, carboplatin, pemetrexed) with further CNS progression after a year requiring stereotactic radiation therapy (SRT). The patient was started on sotorasib 960 mg with stable intracranial and improving thoracic cavity disease burden after 1 month. After 5 months of sotorasib initiation, the patient presented with seizures found to have vasogenic edema without new intracranial lesions on brain MRI and was dose reduced to 480 mg daily. A month after the dose reduction, the patient had new brain lesions on MRI and received further SRT. This case reinforces the importance of dose-dependent CNS control of the selective inhibitor. Some combinatorial strategies with *KRAS*-G12C inhibitors are being explored with different doses when combined with anti-PD1 inhibitors. How the effect of dose reduction will impact brain metastasis response and CNS penetration are important areas for future investigation.

The findings of Sabari *et al.* are important as they have demonstrated tumor shrinkage in preclinical models which has been consistent with intracranial responses noted in the KRYSTAL-1 trial. Sabari *et al.* reported in two patients a rapid intracranial response after two cycles of adagrasib (7). An oral presentation at ASCO22 discussed a patient with active, untreated CNS metastasis in the KRYSTAL-1 trial reported to have an intracranial partial response after 1 month and complete response after 5 months of starting adagrasib (6).

Current clinical practice for active focal brain lesions remains stereotactic radiosurgery. Immunotherapy regimens can have CNS activity. A phase 2 trial of monotherapy pembrolizumab in PDL-positive metastatic NSCLC reported a brain metastasis response of 29.7% (11/37) with a 5.7-month duration of CNS response (12). Further studies are needed to evaluate the response rate with selective G12C inhibitors in the context with or without immunotherapy.

Additional information on the activity of *KRAS*-G12C inhibitors on untreated, active brain metastasis will be important to understand the positioning of this class of medicines in the front-line setting. Further prospective clinical studies are required to fully characterize the CNS efficacy of both adagrasib and sotorasib as approved therapies and other selective G12C inhibitors in development including GDC-6936 (Roche), JDQ443 (Novartis), LY3537982 (Eli Lilly) among others (4).

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