Adagrasib effective for patients with KRAS G12C-mutant lung cancer and untreated brain metastases

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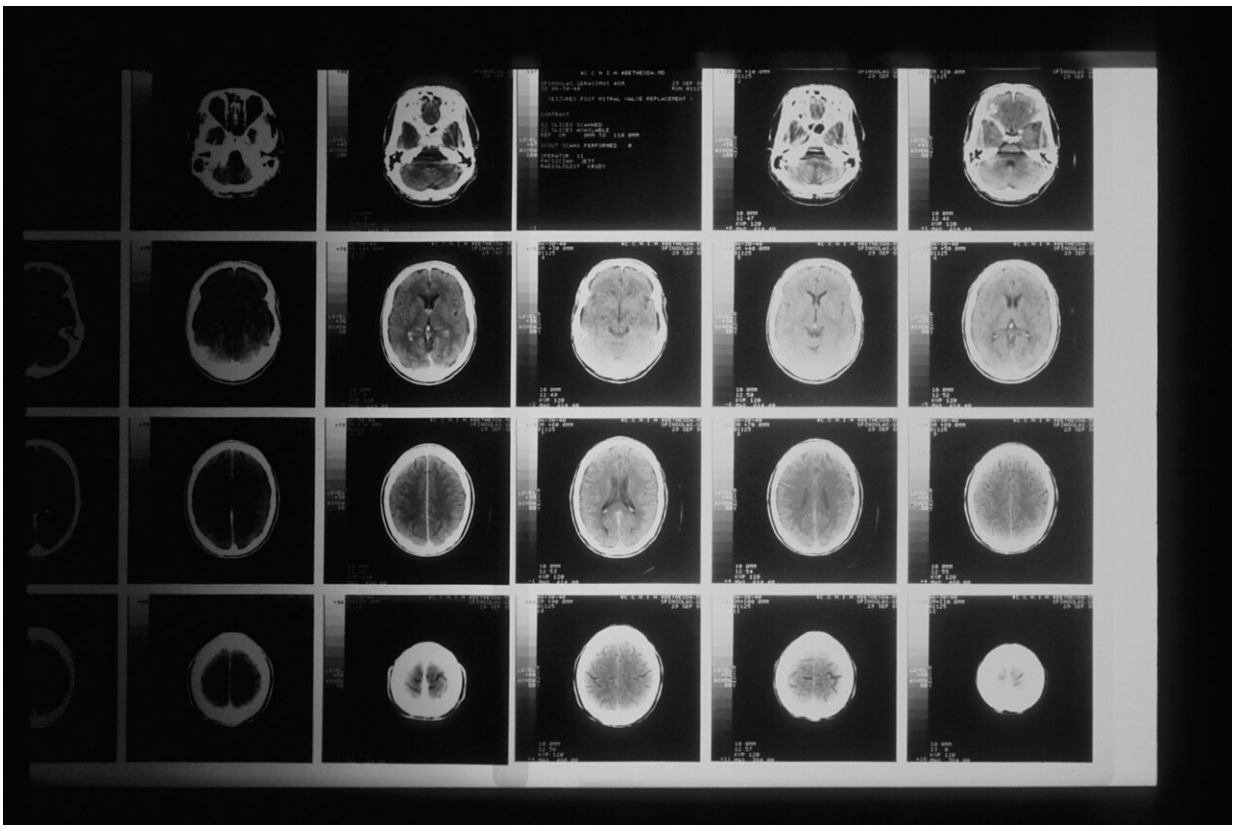

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Researchers from The University of Texas MD Anderson Cancer Center found the KRAS G12C inhibitor adagrasib showed promising activity

suppressing cancer growth not only within the lungs but also in brain metastases for patients with *KRAS G12* C-mutated non-small cell lung cancer (NSCLC).

Findings from the Phase Ib cohort of the KRYSTAL-1 trial, published today in the *Journal of Clinical Oncology*, represent the first prospective data of anti-tumor activity from a KRAS G12C inhibitor in brain metastases, providing continued evidence of the drug's efficacy.

The targeted therapy showed an intracranial disease control rate of 90%. Additionally, researchers observed a 42% objective response rate (ORR) in shrinking tumors within the brain. The median intracranial progression-free survival (PFS) was 5.4 months, while the median overall survival (OS) reached 11.4 months.

"Patients with brain metastases from *KRAS*-mutant lung cancer face a poor prognosis," said study lead Marcelo Negrao, M.D., assistant professor of Thoracic/Head and Neck Medical Oncology. "The data indicate adagrasib may offer patients a good chance of seeing response in the brain without needing additional therapy, such as radiation."

KRAS mutations occur in approximately 25-30% of NSCLC cases, with the *KRAS G12C* mutation accounting for around 13% of these instances. While radiation therapy and surgery historically have been utilized to treat brain metastases, targeted drugs with central nervous system (CNS) penetration continue to demonstrate encouraging efficacy for treatment of brain metastases.

Adagrasib targets the mutated KRAS protein, inhibiting its ability to promote abnormal cancer cell growth. The drug has obtained approval from the Food and Drug Administration for the treatment of advanced *KRAS G12C*-mutant NSCLC in adult patients who have not responded to standard systemic therapy.

This study included 25 patients with *KRAS G12C*-mutated NSCLC and untreated CNS metastases from the Phase Ib portion of the ongoing KRYSTAL-1 trial. Most participants were female (52%) with a median age of 66 years and a predominant ethnic representation of individuals identifying as white. Participants were given oral adagrasib at a 600 mg dose, twice daily.

The systemic ORR in these patients was 30%. Median intracranial duration of response was 12.7 months. 37% of patients in the study saw progression of brain metastases, and only two patients saw progression in the CNS alone. Results also reveal adagrasib continues to exhibit a manageable safety profile, with only a few CNS-specific side effects reported. These include altered taste and dizziness, both consistent with previous reports from the KRYSTAL-1 trial.

"Adagrasib is the first KRAS G12C inhibitor to prospectively demonstrate intracranial activity in patients with *KRAS G12C*-mutated NSCLC and untreated brain metastases," Negrao said. "These findings support continued clinical development of adagrasib and of its combinations for patients with KRAS G12C-mutated NSCLC."

More information: Marcelo V. Negrao et al, Intracranial Efficacy of Adagrasib in Patients From the KRYSTAL-1 Trial With KRASG12C–Mutated Non–Small-Cell Lung Cancer Who Have Untreated CNS Metastases, *Journal of Clinical Oncology* (2023). DOI: 10.1200/JCO.23.00046

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