Zoldonrasib Elicits Objective Responses in Patients With KRAS G12D-mutated Lung Cancer

Zoldonrasib is an investigational oral RAS(ON) tri-complex inhibitor that selectively targets the G12D mutation.

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Patients with previously treated non-small cell lung cancer (NSCLC) whose tumors harbored a KRAS G12D mutation experienced clinical benefit from the oral KRAS G12D inhibitor zoldonrasib, according to results presented at the American Association for Cancer Research (AACR) Annual Meeting 2025, held April 25-30.

KRAS is among the most frequently mutated genes in human cancer, with a variety of mutations found at different rates in different tumor types.

Two inhibitors targeting the KRAS G12C mutation, which accounts for around 13% of mutations in NSCLC, have been approved by the U.S. Food and Drug Administration (FDA) for KRAS G12C-mutated NSCLC. However, around 4% of NSCLC cases harbor KRAS G12D mutations, a mutation against which there are no approved targeted therapies, explained Kathryn C. Arbour, MD, an assistant attending and thoracic medical oncologist at Memorial Sloan Kettering Cancer Center, who presented the study.

“While patients with KRAS G12D-mutated NSCLC are most commonly treated with chemotherapy and immune checkpoint inhibitors, they often do not benefit substantially from these therapies, and prognosis is poor,” Arbour said. “Therefore, developing novel therapies for this patient population is of paramount importance.”

Zoldonrasib is a novel RAS(ON) tri-complex inhibitor that selectively targets the G12D mutation. Unlike currently approved KRAS G12C-targeted therapies, which lock mutated KRAS in an inactive conformation, zoldonrasib targets the active conformation of KRAS. This may delay or prevent resistance because the cell cannot circumvent the blockade by boosting upstream signaling, maintaining KRAS in its active conformation.

Arbour and colleagues tested the safety and efficacy of zoldonrasib in a phase I clinical trial that enrolled 211 patients with KRAS G12D-mutated solid tumors who had received at least one prior

line of treatment. Ninety of these patients were treated at the recommended phase II dose of 1,200 mg daily; the maximum tolerated dose was not reached.

No grade 4 or 5 treatment-related adverse events were observed. Among patients treated at the 1,200 mg dose, one patient discontinued treatment, four patients reduced their dose, and eight patients had dose interruptions due to treatment-related side effects.

Arbour explained that while toxicities such as rash, mucositis, and transaminitis have been observed with other RAS-targeted therapies, these side effects were not observed during treatment with zoldonrasib.

“Zoldonrasib was very well tolerated at all dose levels, including the 1,200 mg once-daily dose. The most common side effects were nausea, diarrhea, and fatigue, typically low-grade and easily managed with supportive medications,” Arbour said.

The efficacy analysis included 18 patients with NSCLC who enrolled at least eight weeks before the data cutoff. Among these patients, 61% had an objective response, and 89% experienced disease control.

Arbour explained that the standard of care for patients with previously treated, KRAS G12D-mutated NSCLC is typically the chemotherapy docetaxel, which has an objective response rate of around 10% to 15%.

“Patients with tumors harboring this mutation are in need of new treatment options,” Arbour said. “The ability to target KRAS G12D in a selective manner with an oral therapy that is well tolerated will hopefully change the treatment landscape for patients with this subtype of NSCLC.”

Arbour emphasized that further studies in larger cohorts and with a longer follow-up time will be critical to assess the potential clinical impact of zoldonrasib, but she was encouraged by these preliminary results.

“These data represent a substantial advance for patients with KRAS G12D-mutated lung cancer,” she said. “We’ve shown for the first time that selectively targeting KRAS G12D is feasible and well tolerated in this distinct population of patients with NSCLC.”

Limitations of this study include the small sample size and short follow-up duration.

Funding for this study was provided by Revolution Medicines. Arbour serves on the advisory board for and has received travel reimbursement from Revolution Medicines.

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