KRAS G12C Inhibitor Elisrasib Shows Promise for Advanced Lung Cancer

Responses were seen in patients who were not treated with prior KRAS G12C inhibitors as well as those whose disease progressed on this class of drugs.

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Next-Generation KRAS G12C Inhibitor Elisrasib Elicited Promising Response Rates in Patients With Advanced Lung Cancer

San Diego – Treatment with the investigational next-generation KRAS-G12C inhibitor elisrasib led to clinical benefit in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors harbored a KRAS G12C mutation and whose disease progressed after prior therapies, according to results presented at the American Association for Cancer Research (AACR) Annual Meeting 2026, held April 17-22.

The G12C mutation is the most common KRAS alteration in NSCLC. Two first-generation inhibitors targeting this mutation, sotorasib (Lumakras) and adagrasib (Krazati), have been approved by the U.S. Food and Drug Administration (FDA) for treatment of this patient population. However, these drugs benefit only approximately 30% of patients, half of whom experience disease progression within six months, and safety remains a challenge in the clinic, explained Byoung Chul Cho, MD, PhD, a professor in the Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine in Korea, who presented the study.

“Research is now focused on next-generation inhibitors aiming for safer, more effective, and longer-lasting results,” said Cho. “These new treatments may address challenges such as brain metastases and resistance to earlier drugs, potentially improving outcomes and redefining care for lung cancer patients with KRAS G12C mutations.”

Similar to the first-generation KRAS inhibitors, elisrasib selectively binds to mutant KRAS G12C and locks it in its inactive state, thus inhibiting its oncogenic function. However, elisrasib was designed for faster and stronger target engagement, resulting in sustained inhibition, Cho explained.

Safety and efficacy of elisrasib alone and in combination with other drugs are being tested in an ongoing Phase I/II clinical trial in patients with KRAS G12C-mutant solid tumors. Early data from a subgroup of NSCLC patients showed promising results.

The new analysis included a larger cohort of 165 patients with locally advanced or metastatic NSCLC who were previously treated with immunotherapy and/or chemotherapy. Some of them also received first-generation KRAS G12C inhibitor therapy and experienced progressive disease. Elisrasib was administered orally once daily in 21-day cycles at six dose levels ranging from 50 to 900 mg, and 600 mg was selected as the recommended treatment dose.

Median follow up time was 11.3 months in patients who had not been previously exposed to KRAS G12C inhibitor therapy (naïve) and 10.6 months in patients with G12C inhibitor-refractory disease. Grade 3 and higher treatment-related adverse events were observed in 11.5% of patients. “Elisrasib demonstrated a favorable safety and tolerability profile,” said Cho.

The efficacy analysis included 84 participants who were naïve for KRAS G12C inhibitor therapy and 31 with KRAS G12C inhibitor-refractory disease. Among the naïve cohort, for patients treated at the recommended dose of 600 mg, overall response rate and disease control rate were 58.8% (including one complete response) and 98.5%, respectively. Median progression-free survival (mPFS) was 12.2 months; median duration of response (mDoR) and overall survival (OS) rate at 12 months were 16.5 months and 72%, respectively.

“In our study, elisrasib demonstrated a significantly higher response rate and prolonged tumor responses than first-generation KRAS G12C inhibitors, indicating that its molecular design may be translating into improved clinical outcomes for patients,” said Cho. He added that elisrasib has received Fast Track and Breakthrough Therapy designations from the FDA for the indication of second-line therapy in KRAS G12C inhibitor-naïve patients.

Among patients who experienced disease progression on earlier KRAS G12C inhibitor therapy, all of whom were treated at the 600 mg elisrasib dose, overall response rate was 32.3%, and disease control rate was 83.9%. Further, mPFS, mDoR, and OS rate at 12 months were 8.1 months, 15.6 months, and 71%, respectively. Tumor responses were also observed in patients with brain metastases, a difficult-to-treat population, said Cho.

KRAS G12C-positive circulating tumor (ctDNA) was detected in 70% of patients before treatment. Molecular responses, defined as reductions of 90% or greater in the fraction of KRAS G12C-mutant ctDNA, were observed with elisrasib in 93% of G12C inhibitor-naïve patients and 80% of those whose disease had progressed on previous G12C inhibitor therapy.

“Among patients whose disease progressed on first-generation inhibitors, we found five cases of KRAS gene amplification, an important mechanism of evasion of KRAS G12C inhibitor efficacy,” said Cho. “Out of those five KRAS amplification cases, four experienced tumor shrinkage, three showed a clinical response, and the disease control rate was 100%, indicating elisrasib’s effectiveness in this biomarker-defined group.”

Cho added, “Elisrasib demonstrates the ability to provide deeper, longer-lasting tumor responses, even in cases where first-generation KRAS G12C inhibitors failed. Overall, these findings indicate that elisrasib may significantly improve treatment for lung cancer patients with KRAS G12C mutations.”

Commenting on the limitations of the study, Cho said that it was an early-phase, single-arm trial, so its primary purpose was to assess safety and early efficacy and establish the correct dose. “Although the safety and initial efficacy findings are encouraging, larger randomized studies are necessary to confirm effectiveness and tolerability. Additionally, longer follow-up will be crucial for evaluating how durable the responses truly are.”

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