FDA Approves Second KRAS Drug for Lung Cancer

Krazati led to tumor shrinkage in 43% of previously treated NSCLC patients with KRAS G12C mutations.

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On December 12, the Food and Drug Administration (FDA) granted accelerated approval of Krazati (adagrasib), the second KRAS inhibitor for the treatment of non-small-cell lung cancer (NSCLC) with a common mutation. The approval of a new targeted therapy highlights the importance of genomic testing to determine which patients could benefit.

Targeted therapies work against cancer with specific genetic mutations or other distinct characteristics. Lung tumors can carry several mutations that make them susceptible to such drugs, but some of these—such as ALK, RET and ROS1—are rare. In contrast, the KRAS gene, which makes a protein involved in a signaling pathway that regulates cell growth, is one of the most commonly altered genes in people with cancer. Long considered "undruggable," KRAS—along with the related HRAS and NRAS genes—is implicated in around a third of all cancers. The FDA approved the first KRAS inhibitor, Lumakras (sotorasib), in June 2021.

Krazati and Lumakras both target a mutation known as KRAS G12C that is present in around 14% of NSCLC tumors. Krazati, from Mirati Therapeutics, is indicated for adults with KRAS G12C-mutated locally advanced or metastatic NSCLC who previously received at least one prior systemic therapy. The FDA also approved two companion diagnostic tests that detect the mutation in tumor tissue or blood.

The approval was based on results from the Phase I/II KRYSTAL-1 trial (NCT03785249), which evaluated Krazati (formerly known as MRTX849) in people with inoperable or metastatic solid tumors with the KRAS G12C mutation. Study participants received Krazati tablets twice daily until they experienced disease progression or unacceptable side effects. There was no placebo or comparative treatment group.

Krazati was greeted with great optimism when researchers reported initial results from a small group of patients at the International Conference on Molecular Targets and Cancer Therapeutics in 2019. Three out of five evaluable NSCLC patients (60%) who received the optimal 600 milligram dose experienced tumor shrinkage, though results were not so impressive for people with colorectal or appendix cancer.

A later analysis of 112 people with advanced lung cancer who experienced disease progression despite treatment with platinum-based chemotherapy and an immune checkpoint inhibitor was presented at the 2022 American Society of Clinical Oncology annual meeting and simultaneously published in the The New England Journal of Medicine.

In this analysis, in which all patients received the 600 mg dose of Krazati twice daily, the overall response rate was 43%, and the median duration of response was 8.5 months. Of note, one third of patients whose cancer had spread to the brain experienced tumor shrinkage. In a pooled analysis of the Phase I and Phase II study cohorts, the estimated median overall survival time was 14.1 months.

Krazati was generally safe, but most study participants experienced side effects. The most common adverse reactions include nausea, vomiting, diarrhea, decreased appetite, fatigue, musculoskeletal pain, swelling (edema), shortness of breath, liver toxicity, kidney impairment, anemia, decreased white blood cell counts, elevated liver enzymes, elevated lipase and various other laboratory abnormalities. The Krazati package insert has warnings about severe gastrointestinal symptoms, a heart rhythm abnormality known as QTc interval prolongation, severe liver toxicity and interstitial lung disease or lung inflammation.

Therapies that receive FDA accelerated approval based on overall response rate are expected to undergo further testing in larger trials to confirm their clinical benefits—such as overall survival—and the agency can rescind approval if they don't measure up. The FDA has asked Mirati to study a lower dose of Krazati.

Researchers recently reported that Krazati could safely be combined with the checkpoint inhibitor Keytruda (pembrolizumab); a similar Lumakras-Keytruda combination caused serious liver toxicity. However, the overall response rate for first-line treatment with the Krazati-Keytruda combination (49%) was not much higher than that of Krazati alone in previously treated patients, though it appeared to improve over time. Further trials are planned to compare Krazati plus Keytruda versus Keytruda plus chemotherapy in people with newly diagnosed NSCLC.

Krazati is Mirati's first commercial product. The company set the price at $19,750 per month, more than Lumakras at $17,900, according to STAT. The company is launching Mirati & Me, "a comprehensive program dedicated to supporting patients, caregivers and the oncology community including coverage and access, financial, educational and emotional support services." To learn more, visit the Mirati & Me website (www.miratiandme.com) or call 844-647-2842.

"KRAS G12C in NSCLC is an area of high unmet need and new treatment options offer patients and our community new hope for survivorship," Bonnie Addario, cofounder and chair of the GO2 Foundation for Lung Cancer, said in a Mirati press release. "I'm pleased that patients have options, there's more awareness of this disease and we are all focused on improving the journeys of people living with KRAS G12C-mutated NSCLC."

Click here for full prescribing information for Krazati.

Click here to learn more about lung cancer.
