KRAS Inhibitors Show Promise in Early Studies

Adagrasib targets a specific cancer-causing mutation, while VS-6766 interferes with multiple steps in a cell growth signaling pathway.

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After three decades of unsuccessful attempts, researchers are finally cracking the KRAS code, as experimental drugs targeting the cancer-causing gene have shown promise in early clinical trials. KRAS mutations occur in multiple types of cancer, and KRAS inhibitors are pancancer therapies that work against tumors anywhere in the body.

Adagrasib (formerly known as MRTX849), from Mirati Therapeutics, demonstrated an overall response rate of 45% for people with advanced non-small-cell lung cancer (NSCLC) and 17% for those with colorectal cancer. Verastem's VS-6766 showed a response rate of 27% for people with various solid tumors or multiple myeloma.

The KRAS gene encodes instructions for making proteins that play a key role in signaling pathways that regulate cell growth; KRAS mutations lead to the production of abnormal proteins that allow cancer cells to grow out of control. Long considered "undruggable," therapies targeting KRAS are eagerly awaited as it is the most commonly altered gene in people with cancer. KRAS mutations, along with changes in the related HRAS and NRAS genes, are involved in around a third of all cancers.

Targeting the KRAS G12C Mutation

Researchers presented the latest results from a Phase I/II study of adagrasib, at the recent virtual Symposium on Molecular Targets and Cancer Therapeutics. The KRYSTAL-1 study (NCT03785249) enrolled people with advanced cancer who had previously been treated with other medications, including immunotherapies.

Adagrasib targets a specific mutation known as KRAS G12C, which is present in about 14% of NSCLC adenocarcinomas, about 4% of colorectal cancer and at lower rates in various other cancer types. The drug binds to KRAS G12C and locks it in an inactive state.

At last year's meeting, Pasi Jänne, MD, PhD, of Dana-Farber Cancer Institute in Boston, reported that three out of five lung cancer patients and one of the two colorectal cancer patients treated

with the optimal dose of adagrasib experienced partial tumor shrinkage.

This year, he reported updated results for 51 evaluable patients with advanced NSCLC who received 600 milligrams of adagrasib by mouth twice daily. In this group, 23 people (45%) taking any dose of adagrasib were partial responders. Another 26 had stable disease with no further progression, yielding a disease control rate of 96%. Two thirds remain on treatment. One participant initially experienced complete remission, relapsed after treatment was interrupted due to an adverse event and had a second remission after restarting the drug. Another patient experienced complete remission of a metastatic lesion in the brain.

“The fact that we are seeing responses in 45% of patients with adagrasib is incredibly meaningful as it opens up the possibility of a new treatment option for this subset of lung cancer patients,” Jänne said in a press statement.

Melissa Johnson, MD, of the Sarah Cannon Research Institute in Nashville, presented results from the same study for 18 evaluable patients with advanced colorectal cancer. In this group, three (17%) had a partial response and another 14 had stable disease, for a disease control rate of 94%.

Among six evaluable patients with other advanced solid tumors, four experienced partial remission (one each with endometrial cancer, pancreatic cancer, ovarian cancer and cholangiocarcinoma). Two people with appendix cancer had stable disease. All remain on treatment.

Adagrasib was generally safe and well tolerated. The most common side effects were diarrhea, nausea, vomiting, fatigue and elevated liver enzymes, mostly mild or moderate. Two NSCLC patients developed severe hyponatremia (low sodium). Less than 5% of side effects led to treatment discontinuation.

Mirati president and CEO Charles Baum, MD, PhD, indicated that the company expects to submit a new drug application to the Food and Drug Administration (FDA) in the second half of 2021. The company is also testing adagrasib in combination with other drugs including Keytruda (pembrolizumab) and the EGFR inhibitor Erbitux (cetuximab).

Another experimental drug targeting the same KRAS G12C mutation, Amgen’s sotorasib (formerly known as AMG 510), has also demonstrated good results. As reported at the recent ESMO Virtual Congress 2020 and in The New England Journal of Medicine, 35% of NSCLC patients treated with the optimal dose experienced partial tumor shrinkage and another 56% had stable disease, for a disease control rate of 91%. Among those with colorectal cancer, three people (7%) responded and 67% had stable disease, for a disease control rate of 74%. Amgen is expected to file for FDA approval of sotorasib later this year or in early 2021

Other KRAS Targets

KRAS G12C is not the only relevant KRAS mutation. While KRAS G12C is the most common alteration in lung cancer, KRAS G12D is predominant in pancreatic cancer. This mutation is present in about 36% of people with pancreatic cancer and 12% of those with colorectal cancer.

Mirati has announced initial data for its first-in-class KRAS G12D inhibitor, known as MRTX1133. The experimental drug appears to have a long half-life and little potential for drug interactions or off-target activity. It was found to shrink tumors, including pancreatic and colorectal cancer, in preclinical studies. The company expects to file an investigational new drug application in the first half of 2021, which will allow it to move into human clinical trials.

As previously reported, researchers at Boehringer Ingelheim are developing a novel “pan-KRAS” inhibitor that blocks a switch that activates KRAS, so it works against cancer with all major KRAS mutations, not just G12C.

Verastem is taking a different approach, targeting mutations in genes involved in multiple steps of a signaling pathway known as RAS-RAF-MEK-ERK. Its experimental drug VS-6766 blocks the activity of both RAF and MEK proteins. It has the potential to work against cancers with multiple RAS mutations, including KRAS.

As reported in The Lancet Oncology, VS-6766 administered twice weekly showed promising antitumor activity in people with various types of cancer with RAS-related mutations. The drug was previously found to be poorly tolerated with more frequent dosing, but the intermittent schedule proved to be well tolerated.

"Cancers caused by the commonly mutated KRAS gene continue to represent an important area of unmet need," Udai Banerji, MD, PhD, of the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust in London, said in a press release. “When we develop cancer drugs, we often have to walk a narrow path between on one hand effectively shrinking the tumor and on the other hand managing side effects. We need to think out of the box and use innovative intermittent schedules as a way of delivering effective and tolerable drugs.”

The Phase I portion of the study (NCT02407509) included 29 people with previously treated solid tumors with RAS-RAF-MEK pathway mutations. After the optimal dosing schedule was determined, 22 additional participants with solid tumors and seven people with multiple myeloma were enrolled in the Phase II portion and treated with the selected dose. Most had KRAS mutations, followed by HRAS and BRAF mutations.

In the expanded cohort, seven (27%) of the 26 evaluable patients had partial responses. These included three of 10 people (30%) with NSCLC, three of five (60%) with gynecological malignancies and one of six (17%) with multiple myeloma. None of the four people with colorectal cancer or the single patient with melanoma were responders. Five of the six responders with solid tumors had responses lasting more than six months.

The most common severe treatment related adverse events were rash, elevated creatine phosphokinase, low albumin levels and fatigue. Side effects were manageable, either resolving spontaneously or after dose modification.

As reported at the recent RAS-Targeted Drug Development Summit, the Phase I/II FRAME study showed that a combination of VS-6766 plus the experimental FAK inhibitor defactinib showed a

overall response rate of 56% in people with ovarian cancer with KRAS G12 mutations, according to a Verastem press release. The study was expanded to include people with pancreatic cancer, endometrial cancer with KRAS mutations and NSCLC with the KRAS G12V mutation.

Based on these findings, larger Phase II trials of VS-6766, both alone and in combination with defactinib, for people with ovarian cancer and lung cancer are expected to begin by the end of the year.

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