Experimental Pan-KRAS Inhibitor Enters Clinical Trials

A novel drug that blocks multiple cancer-causing mutations shows promise, especially for combination therapy.

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Experimental drugs that target KRAS mutations—the most common cancer-causing gene alterations—were the stars of the show at the recent International Conference on Molecular Targets and Cancer Therapeutics, jointly sponsored by the American Association for Cancer Research (AACR), the National Cancer Institute and the European Organization for Research and Treatment of Cancer.

One candidate, which blocks a switch that activates KRAS, has now advanced to a Phase I clinical trial thanks to promising preclinical data.

The KRAS gene encodes instructions for making proteins that play key roles in signaling pathways that regulate cell growth, and KRAS mutations lead to the production of abnormal proteins that allow cancer cells to grow out of control. KRAS alterations are thought to drive approximately 15% of all metastatic cancers, including 90% of pancreatic cancer, about 40% of colorectal cancer and around 30% of lung cancer. After three decades of futile efforts, some experts had concluded that KRAS was “undruggable,” but this year has finally seen some breakthroughs.

As previously reported, one small study presented at the conference showed that 60% of non-small-cell lung cancer (NSCLC) patients treated with an optimal dose of Mirati Therapeutics’ MRTX849, which targets a mutation known as KRAS G12C, experienced tumor shrinkage. These findings follow an initial report at this year’s American Society of Clinical Oncology annual meeting, with additional data presented at the World Conference on Lung Cancer, showing that Amgen’s KRAS G12C inhibitor AMG 510 led to tumor regression in 54% of lung cancer patients treated with the best dose. Response rates were lower, however, for colorectal cancer and appendix cancer.

KRAS G12C, which occurs in around 13% of people with NSCLC, 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, and several others are often found in colorectal cancer, for example.

Researchers from Boehringer Ingelheim in Germany presented preclinical data from its program to develop drugs that target multiple cancer-causing KRAS mutations, dubbed pan-KRAS therapies. One of these, BI 1701963, targets “all major oncogenic KRAS mutations” and could potentially block around 15% of all cancers, according to a company press release.

BI 1701963 binds to SOS1, a protein that acts as a molecular switch to turn KRAS from an inactive to an active state and enabling it to trigger cell growth pathways. KRAS is normally turned off in healthy cells but activated in cancer cells. Both normal (wild-type) and mutated KRAS proteins rely on SOS1, so blocking it should interfere with KRAS activation regardless of mutation status.

Preclinical studies showed that a precursor to BI 1701963 blocked the growth of tumors with a variety of G12 and G13 KRAS mutations. Its activity was stronger when it was combined with MEK inhibitors, which block later steps in KRAS-triggered signaling pathways. Combining direct KRAS inhibitors with other types of therapy could prevent or delay the development of drug resistance.

BI 1701963 is now being evaluated in a Phase I study, the first stage of human clinical trials after an agent has demonstrated promising activity and acceptable safety in laboratory and animal studies. The trial will include people with a variety of solid tumor types.

Boehringer Ingelheim indicated that BI 1701963 will be evaluated both alone and in combination with Mekinist (trametinib), one of three MEK inhibitors approved as part of combination therapy for melanoma. Ultimately, the company hopes to test its KRAS inhibitors with the experimental MEK inhibitor LNP3794, which it is developing with Lupin.

“Our pan-KRAS inhibitor has been designed to target a broad range of oncogenic KRAS variants, including all major G12 and G13 oncoproteins. Effective targeting of the most prevalent KRAS mutant alleles that have so far proved elusive could enable us to develop much-needed new therapy regimens for patients with gastrointestinal and lung cancers who have limited treatment options available,” said Norbert Kraut, PhD, Boehringer Ingelheim’s head of global cancer research.

Click here to see the full Targets conference program.
