KRAS-Blocking Drug Sotorasib Shrinks Lung Tumors

More than 80% of lung cancer patients treated with the targeted therapy experienced remission or had stable disease.

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The experimental KRAS inhibitor sotorasib led to rapid, deep and durable responses in more than a third of people with non-small-cell lung cancer (NSCLC), according to the latest results from the CodeBreaK 100 study, presented at the virtual World Conference on Lung Cancer (WCLC).

Sotorasib (formerly known as AMG 510), from Amgen, targets a mutated protein produced by KRAS, one of the most commonly altered genes in people with cancer. Long considered "undruggable" after four decades of unsuccessful attempts, KRAS—along with the related HRAS and NRAS genes—is responsible for around a third of all cancers.

The protein is part of a signaling pathway that regulates cell growth; abnormal proteins produced by the mutated gene allow cancer cells to grow out of control. Because sotorasib targets only the mutated version of the protein, the drug spares healthy cells.

Sotorasib specifically targets a mutation known as KRAS G12C, found in around 13% of NSCLC tumors—far more common than other targetable mutations such as ALK and ROS1—about 4% of colorectal cancers and around 2% of other solid tumors. Other KRAS mutations are common in deadly pancreatic cancer. Therapies that work against cancer with a specific mutation anywhere in the body are known as site-agnostic, or pancancer, treatments.

At the 2019 American Society of Clinical Oncology annual meeting, researchers first reported that sotorasib could shrink solid tumors and delay disease progression. Other KRAS inhibitors, including Mirati's adagrasib (MRTX849), Verastem's VS-6766 and Boehringer Ingelheim's BI 1701963, have also shown promise in early studies.

In the first part of the Phase I/II CodeBreaK 100 study (ClinicalTrials.gov NCT03600883), participants with lung cancer, colorectal cancer and several other solid tumors were treated with different doses of sotorasib; in the second part, additional patients received the highest dose (960 milligrams once daily), which appeared to work best.

A report last year in The New England Journal of Medicine described interim results for people with all cancer types. At the European Society for Medical Oncology's ESMO Virtual Congress last

September, researchers presented results from the cohort of 59 people with NSCLC.

At last month's WCLC meeting, Bob Li, MD, PhD, MPH, of Memorial Sloan Kettering Cancer Center in New York City, presented results from a larger cohort of 126 advanced NSCLC patients with KRAS G12C mutations. The findings are the first from a completed pivotal Phase II NSCLC trial with a median follow-up of more than a year, according to Amgen. These latest results have not yet been published.

A majority of participants were men, the median age was about 64 years and more than 90% were current or former smokers. Everyone in this group had progressed on prior therapy—including 81% who had tried both platinum-based chemotherapy and immune checkpoint inhibitors—and had limited treatment options. They received sotorasib as a once-daily pill until they experienced disease progression or unacceptable side effects. There was no placebo or standard-of-care control arm.

After a median follow-up period of 12.2 months, the overall response rate—meaning complete or partial tumor shrinkage—was 37%, including three people (2%) with complete remission. An additional 44% had stable disease, yielding a disease control rate of 81%. The median duration of response was 10 months. While these outcomes did not match the 54% overall response rate for those treated with the optimal dose in an earlier analysis presented at the 2019 WCLC, the stable disease rate was higher, so the disease control rate remained impressive.

The median progression-free survival time—meaning patients were still alive with no worsening of disease—was 6.8 months.

Sotorasib was generally safe and well tolerated, and most side effects were mild to moderate, according to Amgen. The most common adverse events were diarrhea, nausea, fatigue and elevated ALT and AST liver enzymes. One in five patients experienced severe drug-related adverse events, and nine people (7%) stopped treatment for this reason.

"These results are encouraging and clinically meaningful for patients with advanced NSCLC harboring the KRAS G12C mutation," Li said in an Amgen press release. "These are patients who have progressive disease after standard treatment, so they need additional treatments, and the fact that we are seeing rapid tumor shrinkages and durable responses in these patients, is for me a step forward and a win for patients."

The growing number of targeted therapies for lung cancer underscores the importance of genetic testing of tumor tissue or circulating tumor DNA in a blood sample to help match patients with appropriate drugs.

Amgen has submitted study data to the Food and Drug Administration and the European Medicines Agency as well as regulatory authorities in other countries. It could become the first approved KRAS inhibitor later this year.

CodeBreaK 200, a global Phase III randomized trial comparing sotorasib versus docetaxel

chemotherapy for previously treated NSCLC patients, is currently underway (NCT04303780). Sotorasib is also being studied as a first-line treatment for lung cancer and in several combination regimens with other targeted therapies and checkpoint inhibitors for advanced solid tumors (NCT041858883).

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