KRAS Blocker Sotorasib Delays Lung Cancer Progression

The drug also showed promise for colorectal and other cancers, but it might work better in combination regimens.

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The experimental KRAS inhibitor sotorasib led to tumor shrinkage in a third of people with non-small-cell lung cancer (NSCLC), and another 56% had stable disease with no further progression, according to study results presented this week at the European Society for Medical Oncology's ESMO Virtual Congress 2020.

Amgen's sotorasib (formerly known as AMG 510) blocks a signaling protein that plays a role in cell multiplication; mutations in the gene that produces this protein can drive the development of cancer. It is a pancancer therapy, meaning it works against tumors with the targeted mutation regardless of where they occur in the body.

One mutation, known as KRAS G12C, is found in about 13% of NSCLC—far more than other targetable mutations including ALK and ROS1—about 4% of colorectal cancers and around 1% to 3% of other solid tumors. As a group, RAS mutations (which also include HRAS and NRAS) are responsible for some 30% of cancers.

Many experts considered KRAS to be "undruggable" after three decades of unsuccessful attempts. No KRAS inhibitors—or any other RAS targeted therapies—have been approved yet, but researchers last year reported that sotorasib demonstrated good activity in people with a variety of solid tumors. The new data continue to look promising.

"We have finally shown that RAS targeting and inhibition is feasible," study coauthor Marwan Fakih, MD, of City of Hope in Duarte, California, said in a press release. "We hope that this will be the first step among many to effectively treat RAS-mutant cancers, one of the most common drivers of cancer."

At ESMO, David Hong, MD, of the University of Texas MD Anderson Cancer Center in Houston, presented updated results from a subgroup of 59 people with NSCLC. A report in The New England Journal of Medicine described outcomes in a larger cohort that also included 42 people with colorectal cancer and 28 with other cancer types, all with the KRAS G12C mutation. All together, about half were women, three quarters were white and the median age was 62.

In the first part of the Phase I/II CodeBreaK100 study (ClinicalTrials.gov NCT03600883), participants were treated with different doses of sotorasib (180 to 960 milligrams), and in the second part, additional patients received the highest dose, which appeared to work best. Sotorasib was taken as a once-daily pill until patients experienced disease progression or unacceptable side effects.

The lung cancer subgroup included 59 people with previously treated locally advanced or metastatic NSCLC. All had used platinum-based chemotherapy, and most had tried checkpoint inhibitor immunotherapy.

After about a year of follow-up, 32% experienced partial tumor shrinkage, and another 56% had stable disease, yielding a disease control rate of 88%. The median duration of response was 10.9 months, and the median progression-free survival was 6.3 months—about double the expected time for heavily treated NSCLC. Among the 34 people who received the optimal dose, the overall response rate rose to 35%, and the stable disease rate remained at 56%, for a disease control rate of 91%.

The outcomes in this larger analysis did not match the 54% overall response rate among those treated with the optimal dose in an earlier analysis, but the stable disease rate was higher, and the disease control rate remained impressive.

“These latest results show that sotorasib continues to demonstrate encouraging clinical benefit in heavily pretreated patients with KRAS G12C–mutant tumors,” Hong said in an Amgen press release. “The results also establish a compelling trend in tumor shrinkage and median progression-free survival with a positive benefit-risk profile.”

According to the New England Journal report, three people with previously treated metastatic colorectal cancer (7%) saw their tumors shrink, and 67% had stable disease, for a disease control rate of 74%. The median duration of response was 6.9 months, and the median progression-free survival was 4.0 months. Four people (14%) with other cancer types—one each with melanoma, appendix, endometrial and pancreatic cancer—had a partial response, and 61% had stable disease, for a disease control rate of 75%.

“The benefits of sotorasib appear to be quite durable with at least half of metastatic colorectal cancer patients still experiencing disease control four months after the start of treatment,” Fakih said. “When you consider the poor prognosis for the metastatic setting and the lack of effective treatments for this population, controlling tumor progression for a few additional months with an oral therapy is a significant and meaningful outcome.”

Sotorasib was generally safe and well tolerated. The most common side effects were diarrhea, nausea, fatigue and elevated ALT and AST liver enzymes. Across all cancer types, 12% of study participants experienced severe (Grade 3 or 4) side effects. No dose-limiting toxicities were observed, and only one person stopped treatment due to an adverse event.

These finding are “very encouraging, showing the first step in ’drugging the undruggable,’”

Patricia LoRusso, DO, of Yale Cancer Center in New Haven, Connecticut, and Judith Sebolt-Leopold, PhD, of the University of Michigan at Ann Arbor, wrote in an accompanying editorial. They suggested that the lack of complete responses, or full remission, seen in this study might mean tumors with KRAS mutations have multiple drivers.

Fakih noted that the poorer response for colorectal cancer compared with NSCLC suggests that KRAS G12C inhibition is not sufficient for colorectal cancer and that sotorasib might work better in combination with another targeted therapy, such as an EGFR inhibitor. Hong suggested that sotorasib might also pair well with checkpoint inhibitors.

Further Phase II data on sotorasib for NSCLC are expected later this year and could put the drug on track to be considered for Food and Drug Administration accelerated approval. CodeBreaK 200, a global Phase III randomized trial comparing sotorasib against docetaxel chemotherapy for patients with NSCLC, is currently underway (ClinicalTrials.gov NCT04303780). Sotorasib is also being studied in combination regimens for various solid tumors.

Click here to read the study abstract.

Learn more about pancancer therapies and KRAS.
