Augtyro Expands Treatment Options for Lung Cancers With ROS1 Fusions

Augtyro (repotrectinib) shrinks non-small-cell lung cancer tumors that have a genetic change called ROS1 gene fusion.

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By Edward Winstead

In November 2023, the Food and Drug Administration (FDA) approved repotrectinib (Augtyro) for the treatment of some advanced lung cancers that have a genetic change called a ROS1 gene fusion.

Nearly 40% of the participants with NSCLC who had previously been treated with another ROS1-targeted drug, such as crizotinib (Xalkori) or entrectinib (Rozlytrek), had a response.

FDA's approval of repotrectinib for advanced or metastatic NSCLC with ROS1 fusions includes the drug's use as an initial treatment and as a second-line treatment in those who previously received a ROS1-targeted drug.

The trial, called TRIDENT-1, evaluated repotrectinib in people with advanced solid tumors, including 127 participants who had ROS1 fusion–positive lung cancers.

For many of these individuals, the response to repotrectinib lasted for several years.

"Repotrectinib can lead to long-term responses for patients with ROS1 fusion–positive lung cancers, including those who have and have not received prior targeted therapy," said Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center, who led the TRIDENT-1 study.

Treatment with repotrectinib also shrank tumors that had spread to the brain, a common location for lung metastases, the researchers reported.

Repotrectinib can overcome some ROS1 mutations that cause drug resistance

Some lung tumors develop genetic mutations in ROS1 that can cause crizotinib and entrectinib to stop working. Repotrectinib was designed to be effective against tumors with these resistance mutations, including one called G2032R.

In the TRIDENT-1 trial, 10 of 17 participants (59%) whose tumors had the G2032R mutation had a response to repotrectinib. The trial was funded by Bristol Myers Squibb, the drug's maker.

"Although repotrectinib can overcome resistant mutations that other ROS1 inhibitors cannot overcome, the drug does not seem to have more side effects than other ROS1-targeted drugs," said Luis Raez, MD, who directs the Thoracic Oncology Program at Memorial Cancer Institute in Florida and was involved in the study.

An important next step, several experts said, will be to conduct studies that can help doctors determine how best to use the different ROS1-targeted drugs in individual patients.

Expanding treatment options for advanced lung cancers with ROS1 fusions

ROS1 fusions occur when part of the gene breaks off and attaches to another gene. In lung cancer cells with the ROS1 fusion, the ROS1 protein produced as a result of these fusions is overly active, leading to uncontrolled cell growth and tumors. ROS1 fusions are present in up to 2% of people diagnosed with NSCLC.

The fusions are typically found in people who have little or no history of smoking, but they have also been detected in heavy smokers.

Repotrectinib blocks the activity of the ROS1 fusion protein. Although crizotinib and entrectinib can shrink some lung tumors with ROS1 fusions, these drugs are not effective against tumors with certain other ROS1 mutations that make the protein overly active. The need for new treatments has led researchers to develop the next generation of ROS1-targeted therapies.

Repotrectinib, which patients take as a capsule, is among the first approved treatments to emerge from this work. In addition to ROS1, the drug targets other proteins that fuel cancer cell growth, including ALK and several forms of NTRK proteins.

Lasting tumor responses to repotrectinib

In the TRIDENT-1 trial, 56 of 71 participants (79%) who had not previously received a ROS1-targeted drug had a response lasting at least 18 months. The median time before the disease worsened, known as progression-free survival, was nearly 36 months.

Among those who had previously received a ROS1-targeted drug, 21 of 56 participants (38%) had a response. The median progression-free survival for this group was 9 months.

A small number of people in both groups had complete responses to treatment, meaning their cancer disappeared entirely.

Repotrectinib also appeared to be effective against lung tumors that had spread to the brain. Of the participants with brain metastases, 8 of 9 participants (89%) who had not previously received

a ROS1-targeted drug had their brain tumors shrink. Brain tumors shrank in 5 of 13 participants (38%) who had previously received a ROS1-targeted drug.

For many of these patients, the treatment responses lasted at least 1 year.

The most common treatment-related side effect of repotrectinib was dizziness. This effect could be managed by reducing the dose of the drug or temporarily interrupting the treatment schedule, the researchers wrote.

Other common side effects included a bad taste in the mouth (dysgeusia) and an abnormal touch sensation, such as burning or prickling, that occurs without an outside stimulus (paresthesia). Three percent of participants stopped taking repotrectinib due to treatment-related side effects.

Limitations of the TRIDENT-1 clinical trial

A limitation of the TRIDENT-1 trial was that repotrectinib was not directly compared with other ROS1-targeted drugs in a randomized phase 3 clinical trial, Dr. Raez said. In addition, the trial included a relatively small number of participants, largely because NSCLC with ROS1 fusions is uncommon, he added.

In the absence of trials that directly compare the available ROS1-targeted drugs in patients, Dr. Drilon said oncologists should consider factors such as the durability of responses and safety when selecting treatments.

“It appears as though repotrectinib has the longest progression-free survival of the three approved ROS1-targeted therapies,” he said. And for patients who have already received a ROS1 inhibitor, repotrectinib is the only approved option right now, he added.

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