Entrectinib effective, well-tolerated against ROS1 and NTRK lung cancers, especially with brain metastases

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Robert C. Doebele, MD, PhD. Credit: CU Anschutz Medical Campus

Pooled analysis of three phase 1 and 2 clinical trials published online ahead of print in the journal Lancet Oncology show that the drug entrectinib is effective and well-tolerated against advanced ROS1 and NTRK fusion-positive non-small cell lung cancers (NSCLC). Results of the trials STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267), and ALKA, show 77 percent response rate to entrectinib in 53 patients with ROS1+ NSCLC, with a median progression-free survival of 19 months and a median duration of response of 24.6 months. In 54 patients with NTRK+ NSCLC, 57 percent responded to entrectinib, with a median progression-free survival of 11.2 months and a median duration of response of 10.4 months. Based on the early promise of these trials, in August 2019 the U.S. Food and Drug Administration granted entrectinib accelerated approval for the treatment of metastatic ROS1+ NSCLC and for advanced tumors across cancer types defined by NTRK fusion. The current journal articles update these findings that led to approval.

"For a drug to get simultaneous approval for use against two different targets is somewhat unique. I don't know of this ever happening before," says Robert C. Doebele, MD, Ph.D., director of the University of Colorado Cancer Center Thoracic Oncology Research Initiative, senior author on the ROS1 study, and first author on the NTRK study.

About 2 percent of lung cancers are driven by the improper fusion of the gene ROS1 with one of a handful of possible genetic partners, resulting in a cancer-causing ROS1 fusion gene. About 1 percent of all solid tumors, including but not limited to lung cancers, are similarly caused by NTRK fusion genes. The FDA-approved drug crizotinib can silence the action of ROS1 fusion genes in some cases, but can't reach cancers that have metastasized to the brain. And, unfortunately, 36 percent of patients with ROS1+ NSCLC already have brain metastases at the time of advanced disease diagnosis, and many more will go on to develop brain metastases during the course of care.

"For ROS1+ lung cancer, entrectinib represents a new and better standard of care due to entrectinib's effectiveness against ROS1 in the body and especially due to its activity against ROS1+ brain metastases," Doebele says. "For NTRK cancers, the picture is a little more complex and I think it depends on an NTRK+ cancer's chance of developing brain metastases. Personally, if I were a patient and felt there was any chance of me getting brain mets, I would want this brain-penetrating drug."

Included in these phase 1 or 2 studies were adults with locally advanced or metastatic ROS1+ or NTRK+ NSCLC who had received previous treatment not including other ROS1 inhibitors. Patients received entrectinib at a dose of at least 600 mg orally once per day, with at least 12 months follow-up. Doebele describes the drug as "well tolerated with a manageable safety profile," with side effects including weight increase (8%) and neutropenia (4%). Eleven percent of patients had serious treatment-related adverse events, the most common of which were nervous system disorders (3%) and cardiac disorders (2%). No treatment-related deaths occurred.

"The genes ROS1 and NTRK are on a growing list of known genetic drivers of non-small cell lung cancer. In addition to showing the benefit of entrectinib against cancers caused by these fusion genes, these results highlight the importance of genetic testing in NSCLC, especially when patients are diagnosed with the condition in the absence of other risk factors," Doebele says. "Only by testing for genes like ROS1 and NTRK can we match these genetic drivers of cancer with drugs like entrectinib."

More information: Ulrik Lassen, Entrectinib for ROS1 fusion-positive NSCLC and NTRK fusion-positive solid tumours, *The Lancet Oncology* (2019). DOI: 10.1016/S1470-2045(19)30789-2