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Crizotinib treatment effective against ROS1-positive lung cancer

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Treatment with the targeted therapy drug crizotinib effectively halts the growth of lung tumors driven by rearrangements of the ROS1 gene. In an article receiving Online First publication in the *New England Journal of Medicine* to coincide with a presentation at the European Society for Medical Oncology meeting, an international research team reports that crizotinib treatment led to significant tumor shrinkage in 36 of 50 study participants and suppressed tumor growth in another 9.

"Prior to this study, there were a handful of reports describing marked responses to crizotinib in individual patients with ROS1-positive lung tumors," says Alice Shaw, MD, PhD, of the Massachusetts General Hospital (MGH) Cancer Center, lead author of the NEJM report. "This is the first definitive study to establish crizotinib's activity in a large group of patients with ROS1-positive lung cancer and to confirm that ROS1 is a bona fide therapeutic target in those patients."

Crizotinib currently is FDA-approved to treat non-small-cell lung cancers (NSCLC) driven by rearrangments in the ALK gene, which make up around 4 percent of cases. An MGH Cancer Center report published in 2012 reported that 1 to 2 percent of NSCLCs are driven by rearrangements in ROS1, which encodes a protein with significant structural similarities to that encoded by the ALK gene.

The current study, an expansion of the original phase 1 crizotinib trial, enrolled 50 patients with ROS1-positive NSCLC, beginning in late 2010. Patients received twice daily doses of crizotinib. As noted above, tumor

size was significantly reduced in 72 percent of patients and tumor growth was halted in an additional 18 percent. The average duration of response was over 17 months. At the end of the study, 25 of the 50 patients were still receiving crizotinib with no evidence of tumor progression.

As with other targeted cancer therapy drugs, treatment resistance developed in a number of participants, but the effectiveness of crizotinib appeared to last longer in ROS1-positive patients than in patients with ALK-positive tumors. "Almost all patients treated with targeted therapies eventually develop resistance," explains Shaw, an associate professor of Medicine at Harvard Medical School (HMS). "Fortunately, the remissions induced by crizotinib in ROS1-positive patients are quite prolonged, and resistance appears to emerge much later, on average, than what we have seen with other targeted therapies for lung cancer and melanoma."

The authors note that development of efficient laboratory diagnostics has been critical to identification of ROS1 rearrangements and of other genetic alterations that drive tumor growth. John Iafrate, MD, PhD, medical director of the MGH Center for Integrated Diagnostics and associate professor of Pathology at HMS, who is senior author of the study comments, "This is a great example of success in personalized medicine. While NSCLC patients with ROS1 fusions are rare, if you devote the diagnostic laboratory resources to find that 1 to 2 percent of patients, you will make a real difference."

While crizotinib's FDA approval currently covers only ALK-positive NSCLC, Shaw notes that National Comprehensive Cancer Network guidelines recommend that patients with advanced lung cancer be considered for ROS1 testing and that crizotinib should be used to treat ROS1-positive patients.