Ceritinib: A potent second-generation ALK inhibitor for non-small-cell lung cancer

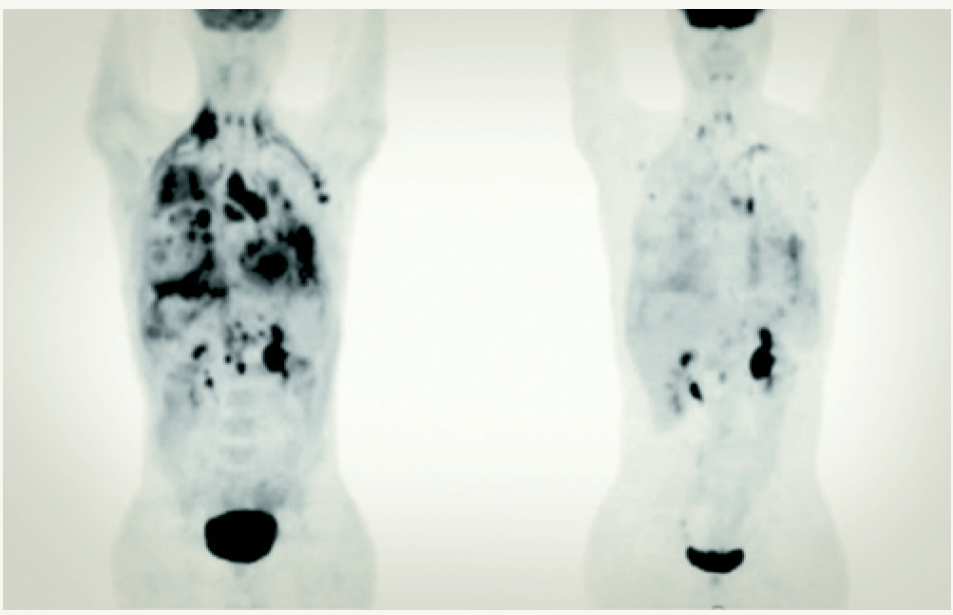
Will ceritinib prove to be a breakthrough therapy?

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the United States, yet until recently it had no effective treatments. Now, however, by gaining a better understanding of the molecular biology of NSCLC, researchers have identified genetic subtypes that can be targeted with selected inhibitors. The Massachusetts General Hospital Cancer Center has led many of the studies and trials of first- and second-generation targeted therapies for specific NSCLC subtypes. The latest results concern NSCLCs driven by chromosomal rearrangements in the anaplastic lymphoma kinase (ALK) gene that have become resistant to the first-generation ALK inhibitor, crizotinib.

In a phase I trial, ceritinib caused marked tumor shrinkage in patients with advanced cancer who had developed resistance to crizotinib as well as in those who had received other treatments, according to Alice Shaw, MD, PhD, a thoracic oncologist at the Mass General Cancer Center and lead investigator of that trial. Trial results appeared in the March 27 *New England Journal of Medicine*[1], while the March 27 *Cancer Discovery*[2] published a molecular analysis of the treatment. *(continued on page 4)*

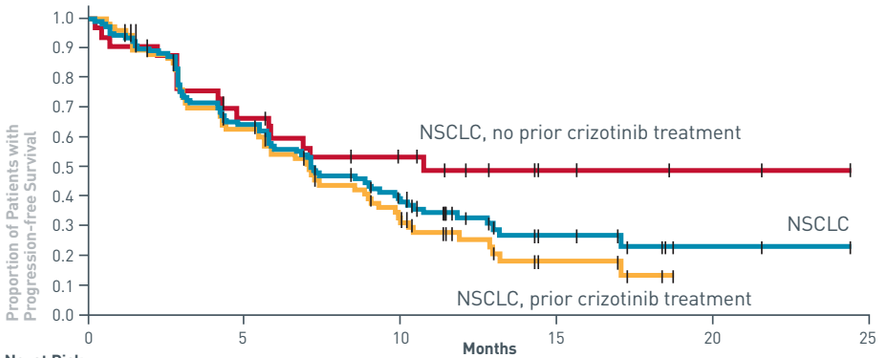
Lung Tumor Shrinkage

PET scan showing response to ceritinib in ALK-rearranged non–small-cell lung cancer (NSCLC). Positron-emission tomographic scans taken at baseline (left) and after 3.5 weeks of ceritinib treatment (right) in a patient with crizotinib-resistant disease. Subsequent computed tomographic scans after six weeks of ceritinib treatment showed a 52 percent reduction in tumor burden.



Progression-Free Survival Estimates

The median progression-free survival (PFS) for all 144 patients with advanced, ALK-rearranged NSCLC who received ceritinib at doses of 400 to 750 mg daily was 7.0 months (blue). In the subgroup of 80 patients who had received crizotinib previously (yellow), the median PFS was 6.9 months. In the 34 patients who had not received crizotinib previously (red), the median progression-free survival was 10.4 months. The PFS data for crizotinib-naïve patients is immature, as many patients are still responding to treatment.



No. at Risk						
NSCLC, no prior crizotinib treatment	34	21	13	4	2	0
NSCLC	114	66	30	9	2	0
NSCLC, prior crizotinib treatment	80	45	17	5	0	

(continued from page 3)

ALK CHROMOSOMAL REARRANGEMENT IN NSCLC

Chromosomal ALK rearrangements create a fusion protein with potent oncogenic properties. The resulting cancer cells, however, are highly sensitive to ALK inhibition. Following the 2007 discovery that about 5 percent of NSCLCs harbor ALK rearrangements, Mass General Cancer Center led a trial of the ALK inhibitor crizotinib specifically for NSCLC patients with ALK rearrangements[3]. A 60 percent response rate led to U.S. Food and Drug Administration approval of the drug for this subset of patients in 2011, a treatment that is now the standard of care. Despite excellent initial responses, however, patients develop resistance to crizotinib and relapse in one to two years. Chemotherapy, the only other treatment option for patients with advanced NSCLC, has shown modest benefit.

To identify a potentially potent next-generation ALK inhibitor, Dr. Shaw teamed up with Jeffrey Engelman, MD, director of the Center for Thoracic Cancers at Mass General Cancer Center, and other colleagues to characterize the molecular nature of crizotinib resistance in cell lines and patient biopsies. Seven acquired mutations, together with ALK fusion gene amplification, accounted for about a third of the resistance cases. In another third, the tumors activated alternative signaling pathways, including EGFR (epidermal growth factor receptor) and c-KIT (a receptor tyrosine kinase that transmits growth signals into the cell). The resistance mechanisms for the remaining third of the cases are unknown.

Dr. Shaw's team evaluated the efficacy of four investigational ALK inhibitors in cellular and animal models of ALK cancers with and without acquired crizotinib resistance. Ceritinib (LDK378, developed by Novartis Pharmaceuticals) proved the most potent and selective inhibitor. Ceritinib also suppressed downstream cancer-promoting pathways (PI3K/AKT, MEK/ERK, mTOR). In animal models, ceritinib induced a more durable response than crizotinib.

TRIAL RESULTS

The preclinical results provided a strong rationale for a multi-center phase 1 trial of ceritinib in patients with locally advanced or metastatic NSCLC, which was open to patients who had or had not previously been treated with crizotinib. The dose escalation phase of the trial enrolled 59 NSCLC patients and established a maximum tolerable dose of 750 mg/day of this oral drug. Side effects involved mainly gastrointestinal issues that resolved when treatment was reduced or stopped. Another 71 patients enrolled in an expansion phase to assess response rate and progression-free survival (PFS).

Among the 114 patients who received at least 400 mg/day, the overall response rate was 58 percent and the median PFS was seven months. Those results included patients with various resistance mechanisms and those with brain metastases. Response rates and PFS were better for patients who had not previously been treated with crizotinib. Because some patients are continuing to respond to ceritinib, data on overall survival are not available.

The positive responses to ceritinib among crizotinib-resistant NSCLC patients stand in contrast to the situation with EGFR-mutated cancers, in which fewer than 10 percent of patients with acquired resistance to first-line EGFR inhibitors respond to second-generation inhibitors.

[1] Shaw, Alice T., Dong-Wan Kim, Ranee Mehra, Daniel S. W. Tan, Enriqueta Felip, Laura Q. M. Chow, D. Ross Camidge et al. "Ceritinib in ALK-Rearranged Non-Small-Cell Lung Cancer." *The New England Journal of Medicine* 370, no. 13 (March 27, 2014): 1189–97.

[2] Friboulet, Luc, Nanxin Li, Ryohei Katayama, Christian C. Lee, Justin F. Gainor, Adam S. Crystal, Pierre-Yves Michellys et al. "The ALK Inhibitor Ceritinib Overcomes Crizotinib Resistance in Non-Small Cell Lung Cancer." *Cancer Discovery*, March 27, 2014.

[3] Kwak, Eunice L., Yung-Jue Bang, D. Ross Camidge, Alice T. Shaw, Benjamin Solomon, Robert G. Maki, Sai-Hong I. Ou, et al. "Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer." *The New England Journal of Medicine* 363, no. 18 (October 28, 2010): 1693–1703.

Preliminary data from this trial led the FDA to give ceritinib a "breakthrough therapy" designation one year ago, and to grant accelerated approval to ceritinib in April 2014.

Dr. Shaw is also involved in two phase II clinical trials of ceritinib that have completed enrollment. There are also two ongoing phase III trials that are enrolling patients. Information about these "LDK378" trials is available on clinicaltrials.gov.

MOLECULAR BASIS OF RESISTANCE

Dr. Shaw's team undertook molecular analysis of ALK resistance and ceritinib activity in cancer cell lines and mouse models, including some derived from biopsy samples of trial participants. They found that ceritinib overcomes several known mutations that cancers acquire in developing resistance to crizotinib, but its potency varies according to which resistance mechanism is involved. "Our results suggest that the majority of crizotinib-resistant tumors remain dependent on the ALK oncogene, so they are still sensitive to ALK inhibition," says Dr. Shaw, who notes that crizotinib may over time provide sub-therapeutic inhibition that a modified structure could improve.

Dr. Shaw's team also identified two new mutations that promote resistance to both crizotinib and ceritinib, and the researchers are now testing other ALK inhibitors and combinations of inhibitors. "We want to develop additional options for patients who relapse following an initially successful targeted therapy," she says. ■

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