Early returns hint at strong successor to crizotinib

New Hope for Lung Cancer Patients

By Todd Neff

The University of Colorado Cancer Center’s run in advancing targeted lung cancer therapies continues, this time with an experimental drug called brigatinib.

The center established itself as a central player in ALK-positive non-small cell lung cancer in the run-up to the U.S. Food and Drug Administration’s approval of crizotinib in 2011. It served as one of just five U.S. centers in the phase 1 clinical trial and developed the gene test to identify patients who might benefit from the drug. Crizotinib, which Pfizer named Xalkori, was the first new lung cancer drug in six years.

Crizotinib has been a success: Results from a phase 3 trial published in late 2014 showed that those taking twice-daily crizotinib pills saw their cancer progression halted for nearly 11 months as compared to seven months progression-free survival among a control group treated with chemotherapy.

But like many other cancer drugs, crizotinib isn’t forever. Over time, cancer tends to mutate around agents sent in to fight it, and so it is in this case. Brigatinib, developed by Cambridge, Mass.-based Ariad Pharmaceuticals, is designed to take over when crizotinib has run its course.

Brigatinib, like crizotinib, is a pill targeting a particular sort of lung cancer, one triggered by ALK fusion, a problem with the anaplastic lymphoma kinase (ALK) gene. Roughly 85 percent of all lung cancer patients have non-small cell lung cancer (NSCLC). Of those, perhaps 5 percent have ALK fusion. But with a disease as common as lung cancer, those numbers still add up to around 10,000 people with ALK-positive NSCLC in the United States alone. Often, they’re young, and either light smokers or nonsmokers altogether. For many of them, brigatinib offers new hope (see related story, this issue).

Ross Camidge, MD, PhD, Joyce Zeff Chair in Lung Cancer Research at the University of Colorado Cancer Center, has led crizotinib as well as brigatinib trials at UCH. At the American Society for Clinical Oncology (ASCO) meeting in June, he and colleagues reported preliminary results of phase 1/phase 2 brigatinib clinical trials launched in September 2011, and Camidge is also leading the national and international phase 2 trial of the drug.

The researchers reported that 58 of 78 patients with ALK-positive NSCLC responded to treatment, including 50 of 70 who had previously been taking crizotinib. Those who had been on crizotinib saw their cancer’s progression halted for a median of 47 weeks. Also, there’s good news for the 50 percent or so of crizotinib patients who develop brain tumors as that drug fails with time. Brigatinib shrank brain tumors by 30 percent or more in six of the 12 patients with measurable lesions in their brains, and completely erased small, nonmeasurable brain lesions in eight of 26 patients whose initial scans showed them. As a group, their brain tumors were held in check for nearly 19 months.

During the phase 1 trial, one of the problems had been rare cases of rapid onset breathing difficulties within a few days of starting...
the drug. As these weren’t happening in everyone, it took some detective work to figure out what was going on. As Camidge and the study team started to look at these cases more closely and to listen to the stories that other patients were telling, it seemed that the effect seemed to happen more commonly at higher starting doses of the drug and, importantly, a number of patients seemed to have had milder symptoms that cleared up spontaneously even though they had continued to take the drug.

Based on these observations, the ongoing phase 2 trial, called ALTA, looks at starting patients at either 90 milligrams a day or starting at 90 milligrams each day for a week before doubling the dose.

Brigatinib isn’t the only next-generation ALK-positive non-small cell lung cancer inhibitor. Novartis’s ceritinib (trade name Zykadia) was approved in April 2014 for the treatment of ALK- positive lung cancer after progression on crizotinib, and Roche’s alectinib has also been shown to help these patients in clinical trials. The company is waiting to see if it will be approved by the FDA too.

“It is always good to have options for your patients,” says Camidge. “And it’s only when you try these side by side that you can see each drug’s individual liabilities and merits. Just as with so much in oncology, one size is never going to fit all.”