

Promising trial of brigatinib shows all next-gen ALK inhibitors may not be created equal

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At ASCO 2015, Dr. Ross Camidge and colleagues report promising phase I/II clinical trial results of the drug brigatinib against ALK+ non-small cell lung cancer. Credit: University of Colorado Cancer Center

Phase I/II clinical trial results reported at the American Society for Clinical Oncology (ASCO) Annual Meeting 2015 show promising results for investigational drug brigatinib against ALK+ non-small cell lung cancer (NSCLC), with 58 of 78 ALK+ patients responding to treatment, including 50 of 70 patients who had progressed after previous treatment with crizotinib, the first licensed ALK inhibitor. Progression-free survival (PFS) in patients previously treated with crizotinib was 13.4 months.

"Although still only in an early phase trial, brigatinib is showing an objective response rate in approximately 70 percent of ALK-positive [patients](#) post-crizotinib and it's showing about a year of progression-free survival. These results are among the best in the field, offering a lot of hope to people with ALK-positive [lung cancer](#)," says D. Ross Camidge, MD, PhD, director of thoracic oncology at the University of Colorado Cancer Center and the trial's principal investigator.

In addition, robust data is emerging on [drug](#) activity in patients with brain involvement of the disease. Many lung cancer trials have traditionally excluded patients with [brain metastases](#) at baseline, expecting that the presence of metastases would create negative results that could in turn create the appearance of drug failure. Following early recognition of the importance of the brain as a potential differentiator between the activity of new drugs, the brigatinib trial includes patients with untreated brain metastases, showing a greater than 30 percent

decrease in size of brain tumors in 8 of 15 patients with [brain tumors](#) greater than 10 mm and disappearance of brain metastases in 11 of 33 patients with smaller lesions only. Brain metastases remained controlled for a median 15.6 months.

Based on these promising early results, brigatinib, developed by Ariad Pharmaceuticals, Inc., recently received Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients with ALK+ metastatic NSCLC whose tumors are resistant to crizotinib.

"Many targeted cancer treatments come with an Achilles heel, a specific way or ways that the cancer can use to escape the drug - either through growth in the brain or via a range of different crizotinib-resistance mechanisms. We're now seeing that brigatinib covers a lot of these 'escape mechanisms' potentially offering greater and more durable disease control," Camidge says.

The drug is an oral compound that inhibits the activity of ALK, which, when engaged through a gene rearrangement can drive the growth and survival of the cancer. ALK rearrangements occur in approximately 4 percent of lung cancers.

In general brigatinib is well tolerated but in a small proportion of cases early onset pulmonary symptoms can occur in which patients develop rapid shortness of breath and oxygen dependency. These symptoms were seen in 14 percent of patients treated a starting dose of 180 mg, but in only 4 percent of patients who started at 90 mg, including those patients who then escalated to 180 mg after one week of treatment.

"Beyond the dose effect, another key breakthrough in managing this rare side effect came through careful management of a patient here in Colorado. By supporting him through the 3-5 days of his symptoms, he

rapidly acclimatized and has been able to stay on the drug ever since without problems. The symptoms disappeared by themselves. This gave us the idea of maybe we could minimize the risk by getting folks through the early period at a lower dose and then escalating dosing once everything had settled down," Camidge says.

A phase II trial comparing sustained 90mg dosing of the drug, with 90mg of the drug for one week followed by escalation to 180mg is underway.

Provided by University of Colorado Denver

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