40-50% response rate for brigatinib after other next-gen ALK inhibitors

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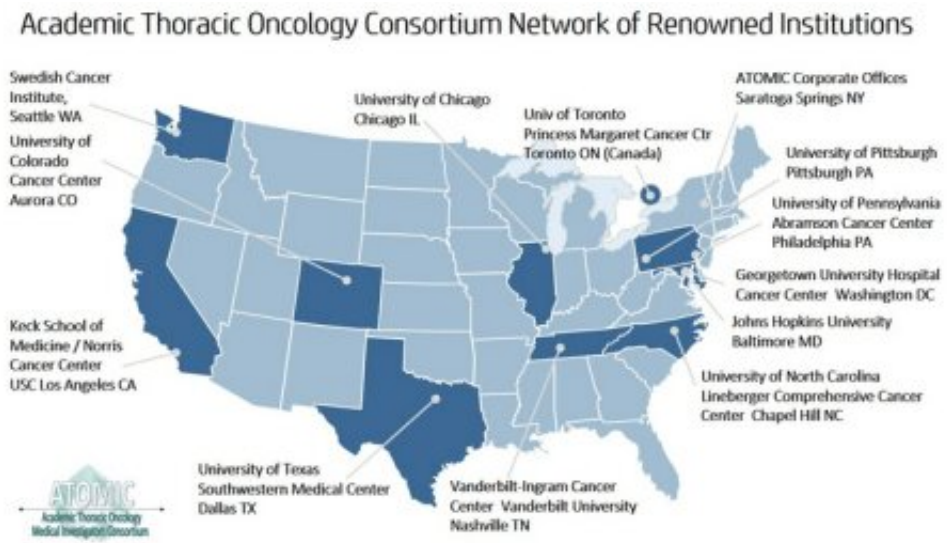

Credit: CU Anschutz Medical Campus

Crizotinib was the first drug licensed to treat ALK-positive non-small cell lung cancer (ALK+ NSCLC). Since then, a range of next-generation ALK-inhibitors including ceritinib, alectinib, and brigatinib have earned FDA approval as second-line therapies after treatment with crizotinib. However, each of these next-generation ALK-inhibitors can also be used in the first-line setting, and an important question becomes which, if any, remain useful when given after another next-generation drug? A study by the Academic Thoracic Oncology Medical Investigators' Consortium (ATOMIC) presented at the American Society for Clinical

Oncology (ASCO) Annual Meeting 2019 shows 40 percent response rate in 20 patients treated with brigatnib after first-line treatment with another next-gen ALK inhibitor (ASCO abstract 9027). A French retrospective study of 104 patients also presented at ASCO similarly demonstrated a 50 percent response rate in patients treated with brigatinib after two previous lines of ALK inhibitor therapy.

"Brigatinib is already approved for use post-crizotinib and has already shown positive data versus crizotinib in the first-line setting. Meanwhile, the world has moved around us and now we need to know the activity of this drug after a next generation ALK inhibitor," says study first author, Tom Stinchcombe, MD, of Duke Cancer Center. Study colleagues include senior author, and co-principal investigator D. Ross Camidge, MD, Ph.D., Joyce Zeff Chair in Lung Cancer Research at University of Colorado Cancer Center and Robert C. Doebele, MD, Ph.D., director of the CU Cancer Center Thoracic Oncology Research Initiative, who is performing key biomarker analyses in the ATOMIC trial.

"A single, small study had previously suggested brigatinib was not likely to be effective in this setting, presumably because not everyone responds the same way to these agents," says Doebele. "So it is very encouraging to see our own data and that of the French group paint a more encouraging picture, worthy of continued exploration."

In addition to measuring overall response rate, the study will perform detailed molecular analyses to help determine the characteristics of patients sensitive to this drug. The study was also able to capture whether patients had progressed in the body or in the brain during treatment with the first-line next-gen ALK inhibitor, allowing investigators to better understand whether brigatinib may be more useful with patients progressing in one or the other site.

"With lung cancer, people progress in different ways—sometimes in the

brain, other times in the body. If a drug has greater or lesser activity in the brain than in the body, the efficacy you quote a patient may need to be different depending on their site of progression. Only by pulling these two things apart can you actually guide someone accurately as to their chance of responding to a drug," says Camidge, who recently helped to define the Response Assessment in Neuro-Oncology guidelines, which argue for measuring a drug's effectiveness separately in the body and the brain during cancer clinical trials.

The current trial also demonstrates the ability of the ATOMIC group to successfully utilize a new clinical trial collaboration framework that occupies a middle-ground between industry-sponsored and cooperative group clinical trials.

"The middle ground used to be single center investigator-initiated trials, which allowed doctors and researchers to test their clinical research ideas fairly quickly and cheaply. But, particularly in lung cancer, with the disease fragmenting into many small disease subtypes defined by their genetic make-up, you can't do many investigator-initiated trials at just one site anymore—you'd never get enough patients. Instead, you need multiple investigators collaborating across multiple sites, supported by their own clinical research organization and that's what we've got with ATOMIC," said Camidge, who directs the consortium.

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