

Campus researchers helped move lung cancer drug to market

'Paradigm Shift' Brings Lung Cancer Advance

By Todd Neff

A novel drug targeting a specific type of lung cancer is now Food and Drug Administration-approved, and research work done on the Anschutz Medical Campus played an important role in making it happen.

The work at the University of Colorado Cancer Center included studying patients in clinical trials as well as improving the molecular test that determines if a patient's cancer cells have the genetic quirk that puts tumors in the new drug's crosshairs.

Crizotinib, which Pfizer sells as Xalkori™, is a twice-daily pill that targets a particular sort of lung cancer, one triggered by ALK fusion, a problem with the anaplastic lymphoma kinase (ALK) gene. It's the first new lung cancer drug approved in six years.

Roughly 85 percent of all lung cancer patients have non small-cell lung cancer. 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 in the United States alone who could benefit from the new treatment.

Striking results. In its phase 1 and phase 2 trials, crizotinib proved to be very effective on non small-cell lung cancer among those with ALK fusion. Roughly 90 percent of the more than 100 patients enrolled in the phase 1 trial saw their tumors shrink; 60 percent of them shrank more than 30 percent, a threshold known as "objective response."

Paul Bunn, MD, a School of Medicine lung cancer specialist, said 5 percent of patients would typically show such shrinkage in phase 1 trials.

The median time to progression – the time it takes for cancer finally to outwit the drug and begin to grow again – was 10 months, eight months longer than expected, Bunn said. Eighty percent of patients were alive a year later; normally, just 20 percent might have been, he added.

Ross Camidge, MD, PhD, who treated more than 50 patients in crizotinib trials at UCH, said some patients are still alive nearly two years after they began treatment.

UCH was one of five U.S. sites for the trial, which also included institutions in Australia and South Korea, Camidge said. The phase 1 trial started out testing the drug's use as an MEK inhibitor, which is implicated in esophageal, gastric, and kidney cancers, among others.

At the time, ALK had not been associated with lung cancer at all, Camidge said.

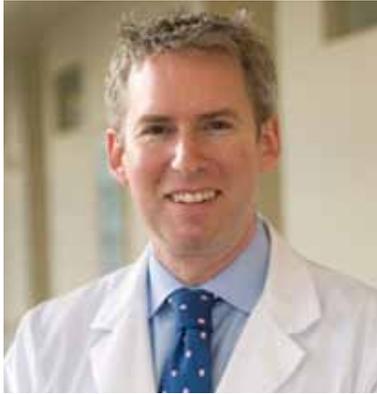


Xalkori (crizotinib) shot (courtesy Pfizer).

Meanwhile, in the lab... But the research work of School of Medicine cytogeneticist Marileila Varella Garcia, PhD, helped enhance an existing test to spot ALK fusion in lymphoma that could also reliably detect the problem in lung cancers, Camidge said. With improved diagnostics available, one could efficiently sort out patients likely to respond to crizotinib.

That capability, in turn, evolved into an Abbott Molecular test the FDA approved concurrently with crizotinib. Called the Vysis ALK Break Apart FISH Probe Kit, it works by illuminating the area around the ALK gene on chromosome 2. Sometimes chromosome 2 breaks at a weak point in ALK. Cancer-

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Ross Camidge, MD, PhD

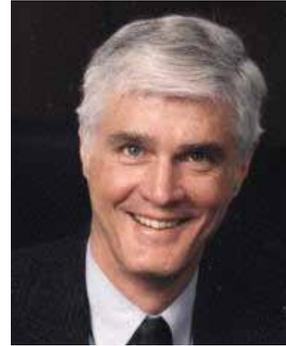
Pairing a cancer treatment with the results of a genetic test represents a radically different approach to cancer drug development.

Had crizotinib taken the typical path, patients with and without ALK fusion would have received it. Those without the ALK fusion would have experienced only side effects (which include vision disorders, nausea, diarrhea, vomiting, edema, and constipation). But the financial cost would have been steep. Although patient assistance programs are available,

causing ALK fusion happens when the ALK gene fuses back together in a different orientation with another gene, usually EML4, creating an EML4-ALK fusion, Bunn explained. Genes in this faulty layout illuminate differently in the new screen.



Marileila Varella Garcia, PhD



Paul Bunn

the drug costs \$9,600 a month. Thanks to the test, physicians can be confident the patients receiving it stand to benefit.

Still, the new approach to drug development is hard. Researchers must understand the molecular drivers of the disease, devise a way to screen for them, and come up with a therapy.

But Camidge says it's definitely worth doing. The results, as crizotinib has shown, can be striking, leading to faster approval and more enthusiastic clinical use.

“In lung cancer, there are now two such tests, for ALK and EGFR (epidermal growth factor receptor). Bunn predicts more will join them in the coming years. “The fact that you’re testing for molecular changes – for multiple genetic changes before selecting treatment – is a paradigm shift for treating lung cancer patients,” Bunn said.”

Camidge has seen the results of this shift up close.

“Even people who were suspicious of the idea of entering into a clinical trial say it’s the best thing they ever did,” Camidge said. “It’s been an amazing trip.”