Size, structure help poziotinib pose threat to deadly exon 20 lung cancer

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Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia
A drug that failed to effectively strike larger targets in lung cancer hits a bulls-eye on the smaller target presented by a previously untreatable form of the disease, researchers at The University of Texas MD Anderson Cancer Center report in *Nature Medicine*.

Their research provided the scientific underpinning for clinical trials under way of the drug poziotinib against non-small-cell lung cancer that has a specific alteration called an exon 20 insertion in either the epidermal growth factor receptor (EGFR) or the human epidermal growth factor receptor 2 (HER2).

"There's no effective treatment for these patients, so we're encouraged by early clinical trial results that show 7 of 11 patients (64 percent) with EGFR exon 20 mutations have confirmed tumor shrinkage after poziotinib treatment," says John Heymach, M.D., professor and chair of Thoracic/Head and Neck Medical Oncology. "We need to see if these unprecedented response rates are maintained through the remainder of the trial, but our scientific findings provide a basis for optimism."

So far, 47 patients have enrolled in MD Anderson's original phase II trial for EGFR and 12 are enrolled in the HER2 arm. The drug's owner, Spectrum Pharmaceuticals, has opened a multi-center phase II trial.

Approved targeted therapies against EGFR mutations, which improve progression-free survival (PFS) and quality of life for other patients, have only seen response rates ranging from 3 to 12 percent among patients with the exon 20 insertion. Median PFS for these patients has been just two months. So far in the MD Anderson clinical trial, median PFS has not been reached after 6.6 months.

About 3 percent of patients with either EGFR or HER2 disease have the exon 20 insertion, amounting to about 7,000 people diagnosed annually in the United States. Heymach also notes most patients with exon 20
insertions never have smoked.

'Deep dive' into exon 20

Heymach's team started to focus on exon 20 as part of its drug repurposing pipeline opened under MD Anderson's Moon Shots Program, a collaborative effort to accelerate the development of scientific discoveries into life-saving advances.

"The week we were identifying problems to focus upon in our Lung Moon Shot, I had three or four exon 20 patients and nothing to offer them at that point," Heymach said. "It was the clinic telling us where we were most needed. We decided to do a deep dive into exon 20."

Postdoctoral fellow Jacquelyne Robichaux, Ph.D., and colleagues tested 10 different targeted therapies against lung cancer cell lines with exon 20 insertions in EGFR or HER2 and found that the cells were strongly resistant to the drugs.

Working with Shuxing Zhang, PHARMD, Ph.D., associate professor of Experimental Therapeutics, the team conducted 3-D modeling of known crystal structures of EGFR and HER2. They found exon 20 insertions have "a dramatic effect" on both proteins' binding pockets—where drugs connect to block activity. These smaller, misshapen pockets pose a barrier for other targeted therapies but also suggested structural characteristics that might make a drug effective.

Smaller is better

Robichaux says the team hypothesized that smaller EGFR inhibitors that have high levels of halogenation—the presence of a group of molecules that help bind drugs to target receptors—might have greater activity against exon 20 disease. This drew them to poziotinib, an EGFR
inhibitor that had failed against the more common EGFR mutations in clinical trials.

"The structure of poziotinib had been published and showed that it was both small and highly halogenated, so we tested it against our panel of cells," Robichaux said.

Resistance tests showed poziotinib to be up to 100 times more potent against the cells than other drugs.

They compared the specificity of poziotinib and three other targeted therapies against both exon20 mutations and the more common target, T790, hit by the other drugs. Exon 20 mutations were 65 times more sensitive to poziotinib while they resisted the other three drugs.

Structural analysis showed poziotinib's size and flexibility allowed it to fit deeply into the exon 20 binding pocket, while the larger drugs either didn't fit at all or lacked the structure for deep connection.

**Tumors shrink in mouse models**

The team tested the drug in mouse models of exon 20 disease compared to afatinib, a second-generation targeted therapy that had shown some ability to inhibit the disease in cell lines.

EGFR mice treated with poziotinib had an 80 percent reduction in disease burden as measured by MRI, while those treated with afatinib had a 35 percent increase to levels almost equal to untreated controls.

HER2 exon 20 mice had a 60 percent reduction in tumor burden, compared to a 37 percent reduction by afatinib in a separate study. In both EGFR and HER2, poziotinib responses were durable at 12 weeks.
The team tested poziotinib in mice with EGFR tumors developed from a patient. Poziotinib-treated mice had their tumor burden reduced by half, while those treated with afatinib had no reduction. In a second study of mice with another patient-derived EGFR exon 20 tumor, poziotinib reduced tumors by 85 percent or more in eight of nine mice over 14 days.

**Possible application to other cancers**

Heymach's team contacted Spectrum Pharmaceuticals about their findings. The company and Heymach's group cooperated to provide poziotinib to a few patients on a compassionate use basis while preparing to launch the MD Anderson clinical trial. Updated clinical trial results will be reported in detail later.

Heymach, Robichaux and colleagues study resistance mechanisms to poziotinib to develop ways to overcome resistance.

"EGFR/HER2 exon 20 insertions occur in cancers other than lung cancer," Robichaux said. "I'm investigating whether these other types also might be sensitive to poziotinib."

MD Anderson is developing intellectual property related to the use of poziotinib for the treatment of exon 20 insertion cancers.


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