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Will tarloxotinib finally break the HER2 barrier in lung cancer?

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Robert C. Doebele, M.D., Ph.D., reports promise of tarloxotinib against HER2+ lung cancer. Credit: University of Colorado Cancer Center

The HER2 gene is a well-known driver of breast cancer, where changes in this gene are found in about 1-in-5 cases of the disease. HER2 also contributes to about 3 percent of lung cancers, representing about 6,500 patients per year. But while drugs like trastuzumab and lapatinib have

proven effective in silencing the action of HER2 in breast cancer, there are currently no approved HER2-targeted therapies for the treatment of lung cancer.

Now, a University of Colorado Cancer Center study presented at the 30th annual EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics shows the promise of an innovative new strategy against HER2-driven lung cancers (with EGFR involvement, which is also a well-known driver of lung cancer). Tarloxotinib, a potent HER2/EGFR inhibitor, is unique in that the drug only becomes active in low-oxygen conditions, such as those commonly found in tumor tissue. By pairing a potent HER2/EGFR inhibitor with a targeting mechanism specific to tumors, researchers show that tarloxotinib is far more active against lung cancer cell lines than even the most successful existing HER2/EGFR inhibitors, with minimal effect on surrounding, healthy tissues.

"We are very excited about this drug. When it's near healthy cells, it's inactive; when it's near tumor cells, it's very active. This could provide a new therapeutic approach for patients with HER2 lung cancer," says Robert C. Doebele, MD, Ph.D., director of the CU Cancer Center Thoracic Oncology Research Initiative. Dr. Doebele is a co-founder of Rain Therapeutics Inc., a clinical stage biotechnology company developing tarloxotinib as its lead drug candidate.

Tarloxotinib is one in a class of anti-cancer agents known as "prodrugs," in which inactive molecules are transformed by specific conditions inside the body into active molecules. In the case of tarloxotinib, oxygen molecules scavenge electrons from the prodrug to keep it inactive. In the absence of oxygen, tarloxotinib fractures into its active form.

The current study shows that in healthy, high-oxygen tissues, it takes about an hour for the body to clear half of any administered molecules

of tarloxotinib; in low-oxygen tumor tissues, the same clearance takes about 80 hours. This makes tarloxotinib about 50 times more active in low-oxygen conditions than it is in normal-oxygen conditions. And low-oxygen conditions, aka "hypoxia," are a hallmark of cancer, in which the growth of tumor tissue often outpaces the growth of blood vessels needed to supply the tumor with oxygen.

"The problem is that the concentration of HER2/EGFR inhibitor needed to affect HER2/EGFR lung cancer is so high that these drugs have come with too many side effects to be clinically useful. We hope that our approach with this prodrug will solve that problem, delivering the HER2/EGFR inhibitor where it's needed without compromising function in healthy tissues," says Adriana Estrada-Bernal, Ph.D., the study's first author.

More information: At noon (GMT) on November 13, the group will present data describing the therapeutic effect of tarloxotinib on mouse models of lung cancer. Collaborators at the University of Auckland will present the following additional data:

Presentation Title: The hypoxia-activated EGFR/HER2 inhibitor Tarloxotinib is activated by the plasma membrane reductase STEAP4
Date: November 16, 2018, 10:00 a.m. GMT

Presentation Title: Targeting tumour hypoxia with tarloxotinib improves the therapeutic efficacy of checkpoint blockade
Date: November 16, 2018, 10:00 a.m. GMT

Provided by CU Anschutz Medical Campus

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