Tarloxotinib promising against NRG1-fusion cancers

April 1 2019

Robert C. Doebele, MD, PhD, and colleagues show that the prodrug tarloxotinib is active against NRG1-fusion cancers no matter where the cancer lives in the body. Credit: University of Colorado Cancer Center

A study by University of Colorado Cancer Center and Rain

Therapeutics, Inc. presented at the American Association for Cancer Research (AACR) Annual Meeting 2019 shows that the clinical-stage drug, tarloxotinib, is active against NRG1-fusion cancers, in addition to the HER2/EGFR cancers for which the drug was originally designed. Though tumors with NRG1 alterations represent only 0.2 percent of all cancers, laboratory results suggest the drug's action is consistent across cancer sites, representing approximately 3,500 new cases per year.

"This is a relatively new genetic target recently identified in breast, lung, ovarian and many other cancer types, and there are currently no approved therapies targeting NRG1 fusions. We're very hopeful that tarloxotinib could meet this need," 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 a unique prodrug, pairing a targeted therapy called a kinase inhibitor with a molecule that ensures the drug only becomes active in low-oxygen conditions, such as those commonly found in tumor tissue. Indeed, its name comes from targeting low oxygen. 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. By pairing a potent kinase inhibitor with a targeting mechanism specific to tumors, Doebele and colleagues have previously shown that tarloxotinib is far more active against HER2/EGFR lung cancer cell lines than even the most successful existing HER2/EGFR inhibitors, with minimal effect on surrounding, healthy tissues. A clinical trial of tarloxotinib, RAIN-701 (NCT03805841) is now recruiting patients with EGFR exon 20 mutations or HER2 activating mutations, cancer subtypes for which there are no currently approved drugs.

"We are very excited about the potential to offer an effective and more

tolerable approach to treating patients suffering from HER-driven cancers, including NRG1 fusions," says Avanish Vellanki, co-founder, chairman and chief executive officer of Rain Therapeutics. "When tarlox is near healthy cells, it's inactive and avoids the side effects characteristic of many other drugs in development for these types of cancers."

The current study shows that tarloxotinib not only inhibits HER2- and EGFR-altered cancers directly (including cancers with HER3 alterations, which is a member of the EGFR pathway), but takes a step back in the series of unfortunate events to block gene over-activation, even if these genes are not themselves altered.

"NRG1 is another way to activate HER2 and HER3. In our cell line and xenograft models, we show that tarloxotinib is even more effective at silencing these cancers driven by NRG1 than its already-promising results against HER2 and EGFR directly," Doebele says.

The study highlights a shift in the field of anti-cancer drug design from drugs targeting cancers depending on their site in the body (e.g. lung cancer or breast cancer), to "tumor agnostic" drugs that target genetic abnormalities driving cancer, no matter where it lives in the body.

"This way what seems like a rare disease—say it's only 0.2 percent of lung cancer—isn't so rare after all. Once you look at 0.2 percent of all cancers, you're talking about a significant number of patients who could benefit," Doebele says.

The current study tested tarloxotinib in cell lines and xenograft models of NRG1 gene fusion positive ovarian and breast cancer. The drug was greater than 45 times more active in the low-oxygen conditions near tumors than it was in healthy tissues, and 10 times more potent than the existing HER2/EGFR inhibitor, afatinib, against these models, leading to

what the study describes as, "a profound, durable and dose dependent anti-tumor response."

Additional studies presented at AACR describe the activity of tarloxotinib against genetic changes including exon 20 insertions and acquired resistance such as T790M/C797S that have limited the effectiveness of existing therapies targeting EGFR (abstract 2200/8), and also describe the role of STEAP4 in reducing tarloxotinib from its inactive into its active form, implying that STEAP4 may be a biomarker of response to the drug, allowing for patient selection in future clinical trials (abstract 4025/18).

Provided by CU Anschutz Medical Campus