Combination of PI3-kinase and PARP Inhibitors May Offer New Treatment Option for Triple-negative Breast Cancers

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- PI3-kinase inhibitors sensitized tumors to PARP inhibitors.
- Combination significantly prolonged progression-free survival in mouse model.

PHILADELPHIA — The simultaneous inhibition of two separate and seemingly unrelated pathways could potentially provide an effective treatment for women with triple-negative breast cancer, according to results of two studies published in the November issue of *Cancer Discovery*, a journal of the American Association for Cancer Research.

Triple-negative breast cancers do not express three common targets of breast cancer treatments: the estrogen receptor, progesterone receptor and HER2/neu. As a result, women with triple-negative breast cancer have few treatment options. In early-phase clinical studies, those women with triple-negative breast cancer with BRCA1 gene mutations had some clinical benefit from treatments with poly-ADP-ribose-polymerase (PARP) inhibitors. However, the activity of the PARP inhibitors is short-lived.

“We are in desperate need of new therapies for triple-negative breast cancer, which is a type of breast cancer that is very aggressive and occurs mostly in young females,” said José Baselga, M.D., Ph.D., chief of the division of hematology and oncology at Massachusetts General Hospital Cancer Center in Boston.

In their study, Baselga; Yasir Ibrahim, Ph.D., a postdoctoral fellow at Vall D’Hebron Institute of Oncology in Barcelona, Spain; and Maurizio Scaltriti, Ph.D., faculty assistant and lab coordinator at Massachusetts General Hospital Cancer Center, hypothesized that inhibiting PI3-kinase, a key component of a signaling pathway frequently activated inappropriately in triple-negative breast cancer, would replicate the conditions present in BRCA-mutated breast cancers, thereby increasing sensitivity to PARP inhibitors.

They found that if PI3-kinase function was blocked in a BRCA-proficient triple-negative breast cancer cell line, DNA damage would occur due to BRCA protein downregulation, and that this resulted in activation of PARP to repair the damage.

“In a way, with PI3-kinase inhibitors, we are converting BRCA-proficient triple-negative breast cancer into BRCA-deficient breast cancer and, therefore, these cells

become sensitive to PARP inhibition," Baselga said.

In the second study, Lewis C. Cantley, Ph.D.; Gerburg Wulf, M.D., Ph.D.; and colleagues used an endogenous mouse model of BRCA1-deficient breast cancer. They observed that mice with a BRCA1 mutation also had molecular indicators of strong activation of the PI3-kinase pathway, suggesting that the tumors might be vulnerable to PI3-kinase inhibitors.

When the mice were treated with a PI3-kinase inhibitor, tumor doubling was delayed from five to 26 days. Given that BRCA-mutated tumors are also known to respond to PARP inhibitors, the researchers combined the two medications and found that this delayed tumor doubling to more than 70 days.

"We saw in vivo synergy that led to dramatic prolongation of progression-free survival in these mice of more than two to three months, which in the life of a mouse is very long," said Wulf, staff physician in the division of hematology and oncology at Beth Israel Deaconess Medical Center. "This is an unusual observation that makes us hopeful that it is worthwhile to explore in an early-phase clinical trial."

Both studies received funding from Stand Up To Cancer Dream Team Translational Research Grants.

Cantley, who conducted the research while director of the cancer center at Beth Israel Deaconess Medical Center in Boston, and his colleagues have worked with Novartis and AstraZeneca, the two companies that manufacture the PI3-kinase inhibitor (BKM120) and the PARP inhibitor (Olaparib) to initiate a clinical trial combining the two drugs in humans.

Cantley said it is extremely unusual for two unapproved drugs to be combined in a cancer clinical trial, especially when the two drugs are produced by separate companies. Yet the preclinical results were sufficiently compelling to accelerate the initiation of this trial. The trial, led by Ursula Matulonis, M.D., director of medical gynecologic oncology at the Dana-Farber Cancer Institute in Boston, is now open and starting to enroll patients with triple-negative breast or ovarian cancer.

"This is truly an amazing story where essentially the same week that the paper is coming out showing an observation, the clinical trial is starting," Cantley said. "This type of bench-to-bedside process typically takes five to 10 years but was dramatically accelerated by the collaborative efforts of the Stand Up To Cancer-funded PI3-Kinase Dream Team."

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