Frontline PARP inhibitor shrinks tumors in BRCA-positive breast patients

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All 13 newly diagnosed breast cancer patients with BRCA mutations had their tumors shrink significantly when treated with a PARP inhibitor ahead of frontline presurgical chemotherapy in a pilot study at The University of Texas MD Anderson Cancer Center.

Results of the study (abstract 153PD) will be presented Saturday at a breast cancer poster discussion session of the 2016 European Society for Medical Oncology (ESMO) Congress in Copenhagen.

Tumor shrinkage after two months of treatment with the PARP inhibitor talazoparib, measured by ultrasound, ranged from 30 to 98 percent with an average reduction in tumor volume of 78 percent among the 13 patients.

"Acknowledging that this is a small study, I can't think of any systemic therapy that gives results this consistently strong in only two months," said Jennifer Litton, M.D., associate professor of Breast Medical Oncology and leader of the study. An extension of the trial is under way.

Previously untreated patients agreed to undergo the targeted therapy treatment before proceeding to standard-of-care chemotherapy and then surgery. Patients with HER2-positive disease were excluded from the study because approved targeted agents exist for those breast cancers.

PARP inhibitors block a DNA repair pathway that tumors can use to survive DNA damage, both intrinsic and caused by therapy. BRCA1 and

BRCA2 are tumor-suppressing genes that, when mutated, account for 5 to 10 percent of all breast cancers. BRCA-related cancers are thought to be vulnerable to PARP inhibitors.

Litton is principal investigator of an international phase III clinical trial of talazoparib for patients with advanced or metastatic breast cancer. Talazoparib and other PARP inhibitors already have been through phase I safety and phase II/III efficacy clinical trials.

A first step testing drug as initial treatment

Given these early results for PARP inhibitors, Litton designed a stepwise approach to more quickly move talazoparib into the presurgical treatment setting for patients newly diagnosed with BRCA-positive breast cancer. She proposed an investigator-initiated pilot study to the drug company, to be supported by MD Anderson's Moon Shots Program, an ambitious effort to reduce cancer deaths by more rapidly developing and implementing advances in prevention, early detection and treatment based on scientific discoveries.

Litton originally expected the study to take two years to sign up 20 patients. Instead, 13 enrolled in eight months, and the results were striking enough that the study was stopped. Complete results, including pathological response after the full course of treatment through surgery, are being prepared for publication.

None of the 13 patients had to withdraw from the talazoparib treatment due to side effects, which were limited mainly to fatigue and low blood counts. There were no grade 4 toxicities. Eight of the 13 had triple-negative disease, breast cancer that does not have HER2 or hormonal targets for treatment.

"After we saw the extensive clinical response, confirmed by ultrasound,

and with a favorable toxicity profile, we really wanted to move forward into an extension to evaluate pathological response for this drug as a single treatment," Litton said.

Next study, presurgical talazoparib alone

An extension of the pilot study opened in August for 20 more patients who will take only talazoparib for six months before proceeding to surgery. Six patients have enrolled. Patients whose disease progresses will proceed to chemotherapy and then surgery.

"If this study produces similarly strong results, the next step would be to directly compare talazoparib to chemotherapy in the presurgical, curative setting," Litton said. "We might be able to delay or replace chemotherapy if we can get similar efficacy with less toxicity from treatment."

Litton noted that institutional support through the Moon Shots Program helped convince the company to provide the drug for Litton's investigator-initiated trials.

Extensive, unique biomarker research

In addition to evaluating the feasibility of enrolling patients before standard neoadjuvant therapy and the drug's toxicity profile, as well as a first estimate of clinical response, the pilot study also tapped Moon Shots Program resources for extensive biomarker evaluation.

Biopsies taken before and after PARP inhibition are evaluated for DNA and RNA changes, proteomics and immune response by Gordon Mills, M.D., Ph.D., chair and professor of Systems Biology.

Patient-derived xenografts of tumors are developed by Helen Piwnica-Worms, Ph.D., vice provost for research and professor of Experimental Radiation Oncology, and colleagues, for use in mouse models to further study tumor response to treatment.

"We will be able to learn a great deal, and not only from the tissue," Litton said. "We also have paired PDXes before and after treatment in previously untreated breast cancer. I don't know anywhere else in the world that has these types of exciting reagents."

Provided by University of Texas M. D. Anderson Cancer Center

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