New presurgery combination therapy may improve outcomes for women with triple-negative breast cancer

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The I-SPY 2 trial, an innovative, multidrug, phase II breast cancer trial, has yielded positive results with the first drug to complete testing in the trial. Adding the chemotherapy carboplatin and the molecularly targeted drug veliparib to standard presurgery chemotherapy improved outcomes for women with triple-negative breast cancer, according to results from the I-SPY 2 trial presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10-14.

Women with breast cancer who are likely to benefit from chemotherapy can be given that chemotherapy first, prior to surgery using a treatment strategy referred to as neoadjuvant therapy. With this approach, doctors and researchers can learn how the tumor responds to treatment. If, after completing neoadjuvant therapy, there is no residual invasive cancer detected in breast tissue and lymph nodes removed during surgery, the patient is said to have a pathologic complete response. Women with a pathologic complete response have a greater chance of long-term survival compared with women who do not have a pathologic complete response.

The I-SPY 2 (Investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) trial uses an adaptive design to learn which patients respond better to which therapies as the trial proceeds. Eligible patients are randomly assigned to standard neoadjuvant chemotherapy, including paclitaxel followed by

anthracycline-based chemotherapy, or they receive paclitaxel in combination with a novel agent followed by anthracycline-based chemotherapy before surgery. Each woman has a four-to-one chance of being randomized to receive a novel agent.

"As the trial progresses, it learns how different tumor subtypes respond to distinct novel agents, and through the adaptive trial design, women are assigned with higher probability to therapies that are performing better for patients with their subtypes," said Hope S. Rugo, M.D., professor of medicine and director of breast oncology and clinical trials education at the UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco.

The I-SPY 2 trial's adaptive statistical design was developed by the overall principal investigators for the I-SPY trial, Laura J. Esserman, M.D., M.B.A., professor of surgery and radiology and director of the Carol Frank Buck Breast Care Center at UCSF Helen Diller Family Comprehensive Cancer Center in San Francisco, and Don Berry, Ph.D., professor in the Department of Biostatistics at The University of Texas MD Anderson Cancer Center, and founder of Berry Consultants.

Rugo will be reporting trial results from one of seven experimental treatment arms that have been evaluated to date and the concurrently randomized controls. These data demonstrate that patients with triple-negative breast cancer were significantly more likely to have a pathologic complete response if they received veliparib and carboplatin in combination with standard therapy than if they received standard (control) therapy alone.

"These results predict that the veliparib/carboplatin regimen is highly likely to be superior to the control regimen for triple-negative breast cancer in a phase III trial," said Rugo.

To be eligible for enrollment in I-SPY 2, patients must have a breast tumor measuring at least 2.5 cm and be considered at high risk for early breast cancer recurrence when evaluated with the 70-gene test MammaPrint, or have triple-negative or HER2-positive disease regardless of MammaPrint results.

Seventy-one patients enrolled in I-SPY 2 were randomly assigned, using an adaptive algorithm, to the veliparib plus carboplatin regimen in combination with paclitaxel. Among these patients were 38 with triple-negative breast cancer and 33 with hormone receptor-positive and HER2-negative breast cancer. Forty-four patients with HER2-negative disease were concurrently randomly assigned to standard neoadjuvant chemotherapy of paclitaxel followed by anthracycline-based chemotherapy.

The estimated pathologic complete response rates for patients with triple-negative breast cancer were 52 percent for those receiving veliparib, carboplatin, and standard paclitaxel followed by anthracycline-based chemotherapy and 26 percent for patients treated with control therapy. These respective percentages were 33 and 22 for patients with HER2-negative breast cancer.

The researchers calculated that based on these data, there is a 92 percent Bayesian predictive probability that veliparib and carboplatin plus standard therapy would be statistically superior to standard therapy for patients with triple-negative breast cancer in a 300-patient, randomized, phase III clinical trial, based on pathologic complete response rates. If such a trial enrolled only patients with all HER2-negative breast cancers, the probability of success would drop to just 55 percent.

"These data show that the adaptive design of I-SPY 2 can generate results that will power phase III registration trials," said Rugo. "By identifying which patients benefit, we can reduce trial size, accelerate

drug development, and avoid overtreatment in the majority of patients, which is the future of drug development." Esserman and Berry are "excited by the evidence that innovations in the I-SPY 2 trial design are working—allowing us to implement more efficient, effective, and ultimately more affordable trials."

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