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**New Presurgery Combination Therapy May Improve Outcomes for Women With Triple-negative Breast Cancer**

SAN ANTONIO — 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.”

I-SPY 2 was launched in 2010 by the Biomarkers Consortium, a public-private partnership of the Foundation of the National Institutes of Health, which includes the U.S. Food and Drug Administration, the National Institutes of Health, and major pharmaceutical companies. The trial, now sponsored by the nonprofit QuantumLeap Healthcare Collaborative, also includes patient advocacy groups and 20 academic cancer centers in the United States and Canada. Unrestricted funding for I-SPY 2 is provided by nonprofit foundations including The Safeway Foundation, several pharmaceutical companies, and other private-sector and philanthropic donors.

Rugo declares no conflicts of interest.

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The mission of the 2013 San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational, and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. For more information about the symposium, please visit [www.sabcs.org](http://www.sabcs.org).

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**Presenter:** Hope S. Rugo, M.D.

**Title:** Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 TRIAL

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**Background:** I-SPY 2 is a multicenter, phase 2 screening trial using adaptive randomization within biomarker subtypes to evaluate a series of novel agents/combinations when added to
standard neoadjuvant therapy (paclitaxel q wk x 12, doxorubicin & cyclophosphamide q 2-3 wk x 4, T/AC) vs. T/AC (control arm) for women with high-risk stage II/III breast cancer. The primary endpoint is pathologic complete response (pCR) at surgery. Our goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient biomarker-linked Phase 3 neoadjuvant trial. Experimental regimens can "graduate" in at least 1 of 10 possible signatures defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP), with a maximum number of 120 total patients enrolled. We report final efficacy results of the oral PARP inhibitor veliparib (V, ABT-888) in combination with carboplatin (carbo), 1 of 7 experimental regimens evaluated in the trial to date.

Methods: Women with tumors ≥2.5 cm by clinical exam and ≥2 cm by imaging are eligible for screening. Tumors that are MP low/HR+/HER2- are ineligible for randomization. MRI scans (baseline, 3 weeks after start of therapy, at completion of weekly T, and prior to surgery) were used in a longitudinal statistical model to improve the efficiency of adaptive randomization. V+carbo was assigned to HER2- tumors only, which limits its possible signatures to: all HER2-, HR+/HER2-, HR-/HER2-. For these 3 signatures we provide estimated pCR rates with associated 95% Bayesian probability intervals for V+carbo and concurrently randomized controls. Analysis is intent to treat with patients who switched to non-protocol therapy regarded as non-pCRs. For each signature we provide probabilities of superiority for V+carbo over control and Bayesian predictive probabilities of success in a neoadjuvant Phase 3 trial equally randomized between V+carbo and control.

Results: When V+carbo met the 85% predictive probability criterion in HR-/HER2- and all HER2-, this regimen graduated and accrual to V+carbo was stopped. V+carbo was assigned to 72 patients, and there were 62 concurrently randomized controls (44 HER2- controls). The following table shows final results based on available pCR information. Two patients assigned to V+carbo withdrew consent during treatment and are not included in the table. Signature Estimated pCR Rate (95% probability interval) Probability V+Carbo is Superior to Control Predictive Probability of Success in Phase 3 V+Carbo Control All HER2- 35% (25-45%) 20% (9-33%) 97% HR+/HER2- 14% (5-27%) 15% (5-30%) 44% 16% HR-/HER2- 52 (38-67%) 24% (9-43%) 99% 92%

Conclusion: Adaptive randomization successfully identified a biomarker signature for V+carbo on the basis of a modest number of patients. V+carbo has graduated with a triple-negative (TN) breast cancer signature, and is the subset recommended for this regimen's subsequent development. There is a suggestion that HR+/HER2- tumors benefit little from this regimen and inclusion of tumors in this subset would therefore dilute its effect in a subsequent trial. Analyses are currently underway to define additional biomarkers that may be predictive of response. The I-SPY 2 standing trial mechanism efficiently evaluates agents/combinations in biomarker-defined patient subsets, with future agents/combinations reported as available.