Abstract S5-02: Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 TRIAL

HS Rugo, O Olopade, A DeMichele, L van 't Veer, M Buxton, N Hylton, D Yee,AJ Chien, A Wallace, I-SPY 2 Site PI's, J Lyandres, S Davis, A Sanil, D Berry, and L Esserman

University of California San Francisco Helen Diller Family Comprehensive Cancer Center; University of Chicago; University of Pennslyvania; University of Minnesota; University of Texas MD Anderson Cancer Center; I-SPY 2 Clinical Trial Sites; University of California San Diego; Berry Consultants, LLC

Abstract

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%	71%
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.