Abstract CT227: Neratinib plus standard neoadjuvant therapy for high-risk breast cancer: Efficacy results from the I-SPY 2 TRIAL

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Abstract

Background: I-SPY 2 is a multicenter, phase II neoadjuvant trial in women with high-risk stage II/III breast cancer using adaptive randomization within biomarker subtypes to evaluate novel agents added to standard chemotherapy. Primary endpoint is pathologic complete response (pCR). Goal is to identify regimens that meet a high Bayesian predictive probability of statistical significance in a neoadjuvant 300-patient phase III trial defined by hormone-receptor (HR), HER2 status, and MammaPrint (MP). Experimental regimens may “graduate” in 1 of 10 signatures, with a maximum of 120 patients. We report efficacy results for neratinib (N).

Methods: Tumors ≥2.5cm by clinical exam & ≥2cm by imaging are eligible for screening. MP low risk/HR+/HER2- tumors are ineligible for randomization. Patients receive chemotherapy (paclitaxel qwk x 12, doxorubicin and cyclophosphamide q2-3 wk x 4, T->AC). HER2- pts were randomized to N+T->AC vs. T->AC

and HER2+ pts to N+T->AC vs. trastuzumab+T->AC. Analysis is intent-to-treat with pts who switch to non-protocol therapy regarded as non-pCRs. We provide estimated pCR rates (95% Bayesian probability intervals), probabilities of superiority of neratinib over control, and Bayesian predictive probabilities of success in an equally randomized phase III trial.

Results: Neratinib met the predictive probability criterion in HR-/HER2+, “graduated”, and accrual ceased [115 N patients (65 HER2+), 78 concurrently randomized controls (22 HER2+)]. The table shows results for all 10 signatures. Two patients (1 N and 1 control) withdrew consent and are not included.

Conclusion: I-SPY 2's standing trial mechanism efficiently evaluates agents in biomarker-defined patient subsets. In a modest number of patients, adaptive randomization successfully identified a biomarker signature (HR-/HER2+) for neratinib's further development. All HER2+ and MP+ tumors may also benefit from this regimen, consistent with preclinical data. Evaluation in I-SPY 3, a phase III registration trial, is planned.

Signature	Estimated pCR Rate (95% probability interval)		Probability NeratinibIs Superior to Control	Predictive Probability of Success in Phase III
	Neratinib	Control		
ALL	32% (28-36%)	23% (19%-28%)	92%	44%
HR+	23% (18%-28%)	17% (11%-22%)	81%	40%
HR-	43% (37%-49%)	31% (24%-38%)	89%	53%
HER2+	39% (33%-45%)	23% (15%-30%)	95%	73%
HER2-	26% (21%-32%)	24% (18%-29%)	63%	20%
MP+*	45% (38%-53%)	29% (20%-39%)	91%	66%
HR-/HER2-	36% (29%-43%)	30% (23%-38%)	72%	34%
HR-/HER2+	55% (46%-64%)	32% (22%-43%)	94%	78%
HR+/HER2+	31% (24%-37%)	17% (10%-24%)	91%	65%
HR+/HER2-	14% (8%-19%)	16% (10%-21%)	39%	12%

* MammaPrint 44K Array Low/High score was adjusted to MammaPrint High1 (MP-) or High2 (MP+), using a pre-defined median cut-point of I-SPY 1 participants, who fit the eligibility criteria of I-SPY 2.

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