Evaluation of patritumab/paclitaxel/trastuzumab over standard paclitaxel/trastuzumab in early stage, high-risk HER2 positive breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL

T. L. Helsten[1], S. S. Lo[2], C. Yau[3], K. Kalinsky[4], A. D. Elias[5], A. M. Wallace[1], A. Chien[3], J. Lu[6], J. E. Lang[6], K. S. Albain[2], E. Stringer-Reasor[7], A. S. Clark[8], J. C. Boughey[9], E. D. Ellis[10], D. Yee[11], A. DeMichele[8], C. Isaacs[12], J. Perlmutter[13], H. S. Rugo[3], R. Schwab[1], N. M. Hylton[3], W. Symmans[14], M. E. Melisko[3], L. J. van' t Veer[3], A. Wilson[15], R. Singhrao[3], S. M. Asare[15], A. Sanil[16], D. A. Berry[14], L. J. Esserman[3]

[1]University of California, San Diego, CA, [2]Loyola University, IL, [3]University of California, San Francisco, CA, [4]Columbia University, NY, [5]University of Colorado, Denver, CO, [6]University of Southern California, CA, [7]University of Alabama at Birmingham, AL, [8]University of Pennsylvania, PA, [9]Mayo Clinic, Rochester, MN, [10]Swedish Cancer Institute, WA, [11]Masonic Cancer Center, University of Minnesota, MN, [12]Georgetown University, Washington, DC, [13]Gemini Group, MI, [14]University of Texas, M.D. Anderson Cancer Center, TX, [15]Quantum Leap Healthcare Collaborative, CA, [16]Berry Consultants, LLC, TX

Background

Patritumab is a monoclonal antibody against HER3. Patritumab, in combination with paclitaxel and trastuzumab (PTH), was evaluated for efficacy in the neoadjuvant I-SPY 2 TRIAL in patients with early stage, high-risk HER2-positive breast cancers.

The control arm was 12 weekly cycles of paclitaxel in combination with trastuzumab (TH) followed by doxorubicin and cyclophosphamide (AC) q2-3 weeks x4 and surgery. In the PTH arm, patritumab was given q3w x 4 cycles (18mg/kg loading dose followed by 9mg/kg/dose) concurrent with paclitaxel and trastuzumab q1w x 12 weeks followed by AC q2-3w.

I-SPY 2 TRIAL (NCT01042379)

I-SPY 2: A multicenter, phase 2 platform trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents and combinations in the neoadjuvant setting for women with high-risk primary breast cancer.

Inclusion criteria: Tumor Size ≥ 2.5cm; hormone-receptor (HR)+HER2- MammaPrint (MP) high risk, HR-HER2- or HER2+

Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status, and MP

Regimens may leave the trial for one of four reasons: Futility (<10% probability of success) ; Maximum sample size accrual (probability of success ≥10% and <85%) ; Graduation (≥ 85% predictive probability of success) ; or as recommended by the independent Data Safety Monitoring Board

To date: 11 experimental regimens have been evaluated for efficacy

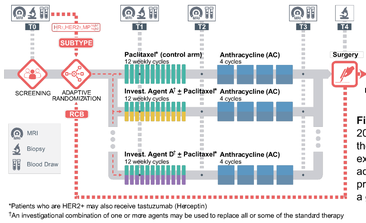


Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

*Patients who are HER2+ may also receive tastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

Methods

Women with tumors ≥ 2.5cm were eligible for screening. MP low/HR+ tumors were ineligible. Longitudinal MRI volume reduction from baseline (3 cycles after start of therapy, prior to AC, and prior to surgery) were used to predict pCR for individual patients until their pCR data becomes available. A covariate-adjusted Bayesian logistic model adjusting for time trends was used to estimate pCR probabilities and assess graduation. Analysis was modified intention-to-treat. Subjects who switched to non-protocol therapy count as non-pCR. Subjects on experimental therapy at time of arm closure are considered non-evaluable. PTH was open to HER2+ patients; and was eligible for graduation in 3 of 10 pre-defined signatures: all HER2+, HR-HER2+, and HR+HER2+.

RESULTS

PTH did not meet criteria for graduation and was stopped at the recommendation of the Safety Working Group and DSMB based on **a safety event** *(Grade 3 bilateral sensorineural hearing loss) observed in one participant.*

The participant who developed Grade 3 sensorineural hearing loss *6 days after the 2nd PTH treatment*, **did not recover her hearing after treatment was stopped**, and also reported Gr3 vulvovaginal pain, vulvitis, and vaginal inflammation.

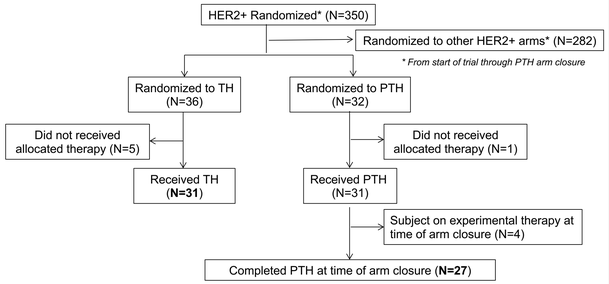


Figure 2: Evaluable population in the PTH and TH control arms

31 participants had received PTH treatment at the time accrual closed due to toxicity, among which 4 subjects receiving patritumab were changed to non-protocol therapy and removed from the analysis.

RESULTS

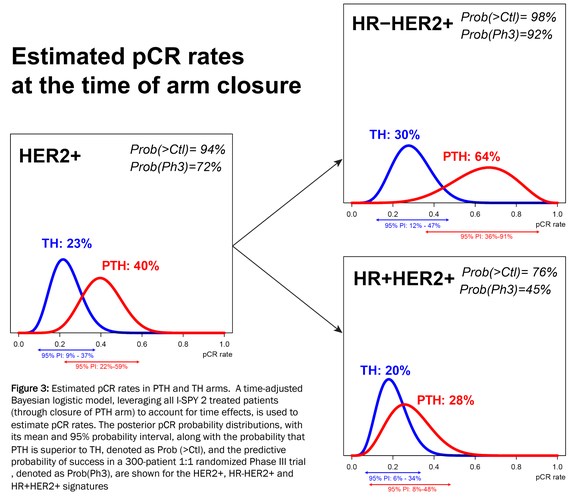


Figure 3: Estimated pCR rates in PTH and TH arms. A time-adjusted Bayesian logistic model, leveraging all I-SPY 2 treated patients (through closure of PTH arm) to account for time effects, is used to estimate pCR rates. The posterior pCR probability distributions, with its mean and 95% probability interval, along with the probability that PTH is superior to TH, denoted as Prob (>Ctl), and the predictive probability of success in a 300-patient 1:1 randomized Phase III trial , denoted as Prob(Ph3), are shown for the HER2+, HR-HER2+ and HR+HER2+ signatures

Table 1: Adverse events [≥ Grade 3] experienced by ≥5% of participants

	PTH (n=24)*	TH (n=31)
Alanine aminotransferase increased	2 (8.3%)	1 (3.2%)
Anaemia	2 (8.3%)	1 (3.2%)
Appendicitis	0 (0%)	2 (6.5%)
Diarrhoea	2 (8.3%)	1 (3.2%)
Febrile neutropenia	1 (4.2%)	3 (9.7%)
Hypertension	0 (0%)	4 (12.9%)
Hypokalaemia	**3 (12.5%)**	**1 (3.2%)**
Neutrophil count decreased	1 (4.2%)	2 (6.5%)
Premature menopausa	**3 (12.5%)**	**0 (0.0%)**

**Adverse event data available for 24 of the 27 PTH patients.*

Increased toxicity was seen on the PTH arm compared to TH alone, including Grade 3 hypokalaemia (12.5% vs 3.2%) and Grade 3 premature menopause (12.5% vs none).

One patient on the PTH arm reported a Grade 3 small intestinal obstruction which resolved with conservative management.

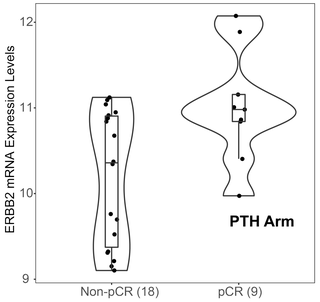
RESULTS

Biomarker of PTH Response

Higher pre-treatment ERBB2 gene expression levels are observed among patients who achieved a pCR in the PTH arm (LR p=0.007).

The association between ERBB2 levels and response remains upon adjusting for HR status (p=0.009).

Figure 4: Violin plots of pre-treatment ERBB2 mRNA expression levels by pCR status in the PTH arm. Logistic regression and the likelihood ratio (LR) test was used to assess association between pre-treatment ERBB2 mRNA expression levels and pCR.. A multivariate analysis adjusting for HR status was also performed.



CONCLUSIONS

The I-SPY 2 study aims to assess the probability that investigational regimens will be successful in a phase 3 neoadjuvant trial. PTH was stopped due to safety concerns, although there was activity in the HR-HER2+ signature. This is the first report of Grade 3 hearing loss associated with patritumab/paclitaxel/trastuzumab.

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