Abstract Number: PD-11-01

Evaluation of the PD-1 Inhibitor Cemiplimab in Early-stage, High-risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

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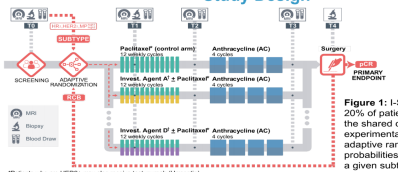
BACKGROUND

- I-SPY-2 **(Figure 1):** A multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes defined by hormone-receptor (HR), HER2, and MammaPrint (MP) status to evaluate novel agents as neoadjuvant therapy for women with high-risk breast cancer.
- Cemiplimab (Cemi) is a PD-1 inhibitor approved for the treatment of metastatic basal cancer, cutaneous squamous cell cancer, and NSCLC[1-4]. Here, we report current efficacy rates of Cemi in combination with paclitaxel followed by AC in early stage high-risk 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/HER2 status and MP.
- **Control Arm for HER2- patients:** Weekly paclitaxel x 12 wks followed by doxorubicin + cyclophosphamide (AC) q2-3 wks x 4.
- **Experimental Arms for HER2- patients:** Investigational therapy + weekly paclitaxel x 12 followed by AC .
- **To date: 24** experimental regimens have been evaluated for efficacy.

METHODS

Study Design



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

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.

Statistical Methods

- Serial MRI imaging (at 3 weeks, 12 weeks and prior to surgery) were used along with accumulating pCR data to continuously update and estimate pCR rates for trial arms. Analysis was modified intent to treat. Patients who switched to non-protocol therapy count as non-pCR.
- **Goal**: graduate regimens with ≥85% Bayesian predictive probability of success (i.e. demonstrating superiority to control) in a future 300-patient phase 3 neoadjuvant trial with a pCR endpoint within responsive signatures.
- Cemi was eligible to graduate in 3 pre-defined signatures: HER2-, HR-HER2-, and HR+HER2-. To adapt to changing standard of care, we constructed "dynamic controls" comprising 'best' alternative therapies using I-SPY 2 and external data and estimated the probability of Cemi being superior to the dynamic control.

RESULTS

Primary Efficacy Analysis

- 62 HER2- patients (39 HR+ and 23 HR-) received Cemi arm treatment.
- The control group included 350 patients with HER2- tumors (195 HR+ and 155 HR-) enrolled since March 2010.
- Estimated pCR rates (as of June 2022) are summarized in the table.

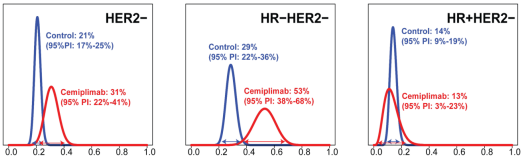


Figure 2: Estimated pCR rates in the Cemi and control arms at the time of arm closure. A time-adjusted Bayesian logistic model, based on all pts with information at the time of the closure of the Cemi arm, was used to estimate pCR rates. The posterior pCR probability distributions, with its mean and 95% probability interval, along with the probability that Cemi is superior to control, 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- (left), HR-HER2- (middle), and HR+HER2- (right) signatures.

Signature	Estimated pCR Rate (95% Probability Interval)		Probability Cemi Superior to Control	Predictive Probability of Success in Phase 3 (relative to Control)	Probability Cemi Superior to Dynamic Control
	Cemi (n=62)	Control (n=350)			
HER2-	31% (22% - 41%)	21% (17% - 25%)	0.981	0.523	
HR-HER2-	53% (38% - 68%)	29% (22% - 36%)	0.999	0.913	0.374
HR+HER2-	13% (3% - 23%)	14% (9% - 19%)	0.374	0.089	0.011

Table 1: Estimated pCR rates for the HER2-, HR-HER2-, and HR+HER2- breast cancer subtypes.

ImPrint: 53-gene Signature of Neoadjuvant Immunotherapy Response

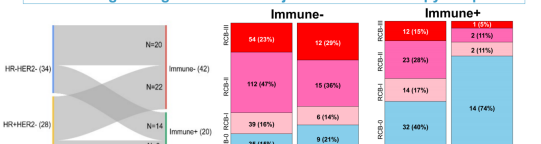


Figure: 3: A) Breast cancer subtypes by ImPrint signature. B-C) Observed RCB scores by ImPrint signature for the Cemi and control arms evaluating Immune- vs Immune+ signatures.

RESULTS

Immune-related Adverse Events

	Cemi		Control	
	All Grade	Grade 3+	All Grade	Grade 3+
Adrenal insufficiency	4 (6%)	1 (2%)	0 (0%)	0 (0%)
Hyperthyroidism	2 (3%)	0 (0%)	1 (0%)	0 (0%)
Hypothyroidism	8 (13%)	0 (0%)	0 (0%)	0 (0%)
Thyroiditis	2 (3%)	0 (0%)	0 (0%)	0 (0%)
Pneumonitis	4 (6%)	1 (2%)	4 (1%)	2 (1%)
Colitis	2 (3%)	1 (2%)	2 (1%)	1 (0%)
Hepatitis	1 (2%)	1 (2%)	0 (0%)	0 (0%)

Table 1: Immune-related adverse events. There was no difference in toxicities between the Cemi vs control arm that are non-immune related.

CONCLUSIONS

- Anti-PD-1 therapy with Cemi resulted in a higher predicted pCR rate in the HR-/HER2- breast cancer subtype at 53% compared to control at 29%.
- Cemi graduated in HR-/HER2- signature.
- We did not observe a response in the HR+/HER2- likely due to limited numbers in the randomized arm and the adaptive randomization to the Cemi/LAG-3 arm.
- The immune+ signature identifies the patients with the greatest benefit with RCB 0/1, ~84%
- Immune-mediated AE's were similar to other single IO agents + chemotherapy.[5,6]
- This data is consistent with previously published data using check point inhibitors in early-stage HR-/HER2- breast cancer.

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Acknowledgements: We are grateful to the patients who generously volunteered to participate in this study. We thank the I-SPY2 investigators, research nurses, data managers, and study coordinators for their efforts on behalf of the patients with support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835), Safeway Foundation, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF), the Biomarkers Consortium, Salesforce, Novella Clinical, CCS Associates, OHSU, and Give Breast Cancer the Boot. Support from AbbVie, Amgen, Merck, Roche/Genentech, Synta Pharmaceutical, Puma Biotechnology, Plexxikon, Daiichi Sankyo, AstraZeneca, Seagen, Dynavax, Regeneron, G1 Therapeutics, GSK, Sanofi, Eli Lilly, Apotex, Athenex, Byondis, ALX Oncology, Ambrx, Vyriad, San Francisco Foundation, Side Out Foundation, Harlan Family, Avon Foundation for Women, Alexandria Real Estate Equities, Natera, Delphi, Invitae, and Agendia. Sincere thanks to Anna Barker, our DSMB (Harold Burstein, Pat Whitworth, Christina Yau, Robert Mass, Deborah Laxague, Elizabeth Frank, Jason Connor, Tiffany Traina, Joe Koopmeiners), EOP/P1 DMC (Olumide Gbolahan, Sara A. Hurvitz, Jordan Berlin, Martin Eklund), Ken Buetow and CaBIG.