Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer: Results from the I-SPY 2 Trial


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Pembrolizumab and Breast Cancer

• Tumors can co-opt the PD-1 pathway to evade immune surveillance\(^1\)

• Pembrolizumab is a humanized monoclonal antibody against PD-1; modest single agent activity in heavily pretreated breast cancer
  – RR in TNBC < 10\(^%\); in HR+ disease 12.0\(^%\) \(^3\)

• Safety of pembrolizumab plus paclitaxel available prior to inclusion:
  – KEYNOTE 021 trial in advanced NSCLC\(^4\)

• The I-SPY 2 Trial tested the ability of pembrolizumab to improve pathologic complete response (pCR) rates over standard therapy

The I-SPY 2 TRIAL Standing Platform

• Phase II, adaptively-randomized neoadjuvant trial
  – Goal: efficiently identify promising agents to take to phase III

• Multiple concurrent experimental arms; 13 agents to date

• Adaptive randomization minimizes number of patients needed to determine efficacy

• “Graduation” for efficacy = reach an 85% predicted probability of success in a 1:1 randomized 300 patient phase III trial
Trial Enrollment Overview

Registered (n=2048)

- Actively Being Screened (n=37)
- Did Not Proceed to the Treatment Phase (n=840)

Randomized (n=1171)

Completed Surgery (n = 1020)

Status as of June 1st, 2017
I-SPY 2 TRIAL Eligibility

Screening Consent → Assess Eligibility → Core Biopsy

**Screening**

- Tumor size $\geq 2.5$ cm
- Candidate for preoperative chemotherapy
- Study MRI and biopsy
- MammaPrint (MP)
- Adequate organ function, PS<2
I-SPY 2 TRIAL Eligibility

1. Screening Consent
2. Assess Eligibility
3. Core Biopsy
   - Hormone Receptor Positive and MammaPrint Low Risk
   - I-SPY2 LOW RISK REGISTRY
   - NOT ELIGIBLE
I-SPY 2 TRIAL Eligibility

Screening Consent → Assess Eligibility → Core Biopsy → HER2+ (IHC, FISH, TargetPrint)
Triple negative HR+, MP High Risk → Randomized Consented to Assigned Arm → ELIGIBLE
Primary Endpoint: pCR

- Defined as no residual invasive cancer in the breast or lymph nodes (ypT0/is and ypN0)
  - Intent-to-treat
  - Protocol-defined non-pCR:
    - Switch to non-protocol assigned therapy (e.g. addition of carbo)
    - No surgery
    - Withdrawal from the trial

- Pembrolizumab was studied in 3 HER2 negative “biomarker signatures”
  - All HER2-
  - HR+/HER2-
  - HR-/HER2- (triple-negative breast cancer; TNBC)
I-SPY 2 TRIAL Schema: HER2- Signatures

Adaptive Randomization

Paclitaxel

Paclitaxel + Pembro

Other HER2- Arms

Doxorubicin Cyclophosphamide

12 weeks

MRI, Blood Core Biopsy

MRI, Blood Core Biopsy

MRI, Blood

8-12 weeks

MRI, Blood

MRI, Blood Tissue
I-SPY 2 Adaptive Randomization

Randomization
(Probabilities based on performance of each drug within each subtype)

Outcome
MRI $\rightarrow$ pCR model

Update probabilities

New patient accrues; assess subtype
Not Every Regimen Graduates for Efficacy

Drop for Toxicity

0% 10% 85% 100%

Drop for Futility
Toxicity

Maximum accrual reached (n=75 Her2-) > STOP

Graduate for Efficacy

DSMB meets monthly
I-SPY 2 TRIAL Schema: HER2- Signatures

Adaptive Randomization

Paclitaxel

Paclitaxel + Pembro

Other HER2- Arms

12 weeks

Doxorubicin
60 mg/m²
Cyclophosphamide
600 mg/m² × 4

8-12 weeks

Control
Paclitaxel 80 mg/m² every wk x 12

Experimental
Paclitaxel 80 mg/m² every wk x 12
Pembro 200 mg every 3 wks x 4
# Demographics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Pembrolizumab (n=69)</th>
<th>Control (n=180)</th>
</tr>
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<tbody>
<tr>
<td><strong>Median Age, yrs (range)</strong></td>
<td>50 (27-71)</td>
<td>47 (22-77)</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>81.2</td>
<td>76.7</td>
</tr>
<tr>
<td>African American</td>
<td>8.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Asian</td>
<td>4.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Other</td>
<td>5.8</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>HR Status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>58.0</td>
<td>52.8</td>
</tr>
<tr>
<td>Negative</td>
<td>42.0</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>Median tumor size, cm (range)</strong></td>
<td>3.6 (1.9-13.0)</td>
<td>3.95 (1.2-15.0)</td>
</tr>
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<td><strong>Nodal Status</strong></td>
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<tr>
<td>Positive</td>
<td>37.7</td>
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<tr>
<td>Negative</td>
<td>52.2</td>
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</tr>
<tr>
<td>Missing</td>
<td>10.1</td>
<td>5.6</td>
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I-SPY 2 Results Reporting

• The I-SPY 2 Bayesian model generates predictive probability distributions of pCR rates by signature
  – Estimated pCR rates
  – Actual pCR rates not reported; biased by the adaptive randomization

• Format of results presented
  – Estimated mean pCR rates by signature
  – Probability that experimental arm is superior to the control for a given signature
  – Predicted probability of success in a 1:1 randomized 300 patient phase 3 trial
Results Format: Estimated Probabilities for pCR

Distribution of pCR Rates

- Curves: probability distribution of pCR rate
- Blue=control; Red=experimental arm
- Midpoint of curves: estimated pCR rate
- Separation: strength
- Width: certainty
Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

<table>
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<tr>
<th>Signature</th>
<th>Estimated pCR Rate (95% Probability Interval)</th>
<th>Probability Pembro Superior to Control</th>
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<td>0.44 (0.33 – 0.55)</td>
<td>0.17 (0.11 – 0.23)</td>
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<td>0.30 (0.17 – 0.43)</td>
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The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population. The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.
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pCR Probability Distributions by Signature

**HER2−**
- **Control:** 17%
- **Pembrolizumab:** 44%
- 95% PI: 11% - 23%
- 95% PI: 33% - 55%

**HR−HER2−**
- **Control:** 22%
- **Pembrolizumab:** 60%
- 95% PI: 13% - 30%
- 95% PI: 44% - 75%

**HR+HER2−**
- **Control:** 13%
- **Pembrolizumab:** 30%
- 95% PI: 7% - 19%
- 95% PI: 17% - 43%
## Select treatment-related adverse events

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From start of treatment to 30 days after surgery (3 months after last dose of pembrolizumab)
Up to 60 days after treatment for those not undergoing surgery
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## Adverse Events of Special Interest (including immune-related toxicities)

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<td>4.3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Adrenal Insufficiency^</td>
<td>8.7 (6)</td>
<td>7.2 (5)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2.9 (2)</td>
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<tr>
<td>Pneumonitis</td>
<td>2.9 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.4 (1)</td>
<td>1.4 (1)</td>
</tr>
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<td>Pruritis</td>
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*includes both hyperthyroidism and hypothyroidism
^includes primary and secondary causes of AI
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Primary and Secondary Adrenal Insufficiency

• Adrenal insufficiency reported in 6 patients
  – At least 3 were related to hypophysitis (secondary AI)
  – 5 presented after completion of AC (10-12 weeks after last pembro dose)
  – 1 presented during pembro treatment (5 weeks after 1st pembro dose)
  – Variable presentation (N/V, fatigue, weakness)
  – Patients on replacement therapy

• Primary and secondary AI are known toxicities of pembrolizumab
  – Rates across all studies are 0.8% and 0.6%

• Due to the toxicities observed, serial screening AM cortisol levels have been incorporated into trial, in addition to ongoing serial thyroid function testing
Conclusions

- Pembrolizumab x 4 cycles plus paclitaxel has graduated for all HER2-signatures studied
  - Near Tripling of the estimated pCR rate in TNBC (60% vs 20%)
  - More than doubling of the estimated pCR rate in HR+/HER2- (34% vs 13%)
  - First agent to graduate in HR+/HER2- signature

- Adrenal insufficiency was observed at a higher rate than previously reported in advanced cancer; pts are doing well on replacement therapy; follow-up of patient outcomes is ongoing

- This is the first report regarding the incidence and time course of immune-mediated toxicities in early stage breast cancer
Future Work

• An experimental arm where pembrolizumab is continued for the anthracycline-based portion of the I-SPY 2 will begin enrollment soon (8 cycle arm)

• I-SPY2 is a biomarker-rich clinical trial with multiple platforms and serial tumor specimens
  – Studies to identify those most likely to benefit or have complications are ongoing
I-SPY 2 TRIAL Study Team

I-SPY 2 Working Group Chairs:
- Laura Esserman: Principal Investigator
- Don Berry: Principal Investigator, Study Statistician
- Angela DeMichele: Co-PI, Site Operations
- Doug Yee: Co-PI, Agents
- Laura van ’t Veer: Co-PI, Biomarkers
- Fraser Symmans: Co-PI, Pathology
- Nola Hylton: Co-PI, Imaging
- Michael Hogarth: Co-PI, Informatics
- Jane Perlmutter: Lead Advocate, Advocates
- Hope Rugo & Richard Schwab: PI/Co-PI, Safety
- Michelle Melisko: Co-PI, Quality of Life

Site PIs:
- UCSD: Anne Wallace; USC: Julie Lang; Swedish: Erin Ellis;
- UMich: Doug Yee; Mayo: Judy Boughey; UCSF: Jo Chien;
- Georgetown: Claudine Isaacs; UChicago: Rita Nanda;
- Loyola Chicago: Kathy Albain; UColorado: Anthony Elias;
- UPenn: Amy Clark; Oregon HSU: Kathleen Kemmer;
- UTSouthwestern: Barbara Haley; U Alabama: Andres Forero-Torres
- Columbia: Kevin Kalinsky; Moffitt: Heather Han;

Sponsor: Quantum Leap Healthcare Collaborative: Dave Mandelkern, Nancy Lisser, Mike Bankert, Adam Asare, Smita Asare
Funding: Safeway, Bill Bowes, Quintiles, J&J, Genentech, Amgen, Give Breast Cancer the Boot, Harlans, Side-Out, Avon, Alexandria
Oversight: Anna Barker/ASU, Gary Kellogg/NCI
FDA: Janet Woodcock, Richard Pazdur

I-SPY 2 Program Management Office (PMO)
- Exec Director, I-SPY Trial Operations: Smita Asare
- Operations Manager: Ruby Singhrao
- Kat Steeg, Lorena Kanu, Julie LeDuc, Jill Parker, Reggie Gladney, Evan Sirchuk

Safety: Sausan Abouharb, Linda Doody, Monina Angeles, CCSA
Data Analysis and IT Team
- Ashish Sanil, Christina Yau, Adam Asare, Karen Kimura, Garry Peterson, Amy Wilson

I-SPY 2 Lab, Biomarkers and Translational Research
- Lamorna Brown-Swigart, Gillian Hirst, Denise Wolf, Jeff Matthews, Chip Petricoin and Julie Wulfkuhle

I-SPY Imaging Lab: Jessica Gibbs, M Watkins
Business Development: Daniel Dornbusch

I-SPY 2 Agents Committee
- Kathy Albain, Christopher Benz, Jo Chien, Amy Clark, Angela DeMichele, Laura Esserman, Andres Forero-Torres, Teresa Helsten, Claudine Isaacs, Brian Leyland-Jones, Minetta Liu, Stacy Moulder, Rita Nanda, Funmi Olopade, John Park, Barbara Parker, Hope Rugo,, Doug Yee, Paula Pohlmann, Richard Schwab, Patricia LoRusso, Anthony Elias, Patricia Haugen, Pamela Miunster, Lajos Pusztai; Heather Beckwith, Larissa Korde (CTEP)

Thank you to the remarkable patients and families, and all of the investigators, staff, our DSMB and advocates, past and present, supporting the trial.
I-SPY 2 Participating Organizations

Sponsors and Managers
- Quantum Leap
- A Healthcare Collaborative

Funders, Operations
- UCSF
- Novella Clinical
- SAFEWAY
- William K. Bowes, Jr. Foundation

Investigational Agent Providers
- Merck
- Amgen
- Genentech
- Plexxikon
- Abbvie
- Pfizer
- Synta Pharmaceuticals
- Puma Biotechnology

Biomarker Device Providers
- Oregon Health & Science University
- Salesforce
- UCSF
- Berkeley Lab
- Lawrence Berkeley National Laboratory
- George Mason University
- TheraNostics Health
- Agendia