Efficacy of T-DM1+Pertuzumab over Standard Therapy for HER2+ Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

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COI

• Dr. DeMichele receives institutional research support from Pfizer, Novartis, Johnson & Johnson, Calithera, Incyte and Genentech, and has participated in scientific advisory boards for Pfizer and Novartis.
Therapeutic Landscape for Her2+ Breast Cancer

• **Her2+ breast cancer is curable** with chemotherapy plus Her2-directed therapy

• In the neoadjuvant setting
  – pCR (pathologic complete response) is an excellent surrogate for long-term survival outcomes
  – Not all patients achieve a pCR

• **Goal:** To determine if new Her2-directed therapies can improve pCR rate over standard chemotherapy plus trastuzumab

(This is a bold statement. Could be interpreted as HER2+ BC which is not true. Could be interpreted as *some* HER2 which may be true. There is no question that therapy dramatically improves outcomes; distinguishing between “cure” and “greatly slows the course of disease” is almost impossible in early BC, including in HER2+ BC. The statement is certainly wrong in metastatic BC. And there’s good evidence that it’s correct in early BC.)
The I-SPY2 TRIAL Platform

• Phase II, adaptively randomized trial of multiple agents/combinations
  – Patients are randomized to receive one of several experimental arms for Her2+ disease
  – Comparator is standard neoadjuvant therapy
  – Endpoint is pathologic complete response (pCR)

• Match therapies with breast cancer subtypes
  – Reduce the cost, time, and number of patients needed to get effective drugs to market

We are reporting one of the experimental arms of I-SPY 2: T-DM1 + Pertuzumab in HER2+ disease

[[Important to say "neoadjuvant" somewhere]]
T-DM1 + Pertuzumab

T-DM1 (ado-trastuzumab emtansine)
- Antibody-drug conjugate: trastuzumab linked to DM-1 (maytansine)
- Inhibits microtubules > cell cycle arrest and cell death
- Toxicities: Thrombocytopenia, transaminitis

Pertuzumab
- Monoclonal antibody to HER2
- Binds at critical heterodimerization site, different site from trastuzumab
- Toxicities: Diarrhea, fatigue, rash, nausea

Rationale for I-SPY2 Entry
- T-DM1 superior to docetaxel/trastuzumab in front-line metastatic setting
- T-DM1+ Pertuzumab safe, high response rate in front-line metastatic setting

TDM 4450 and 4373 Trials

Gwin and Spector, CCR, 2014
I-SPY 2 TRIAL SCHEMA

SCREENING

Adaptive Randomization

NEW PATIENT

TREATMENT

Paclitaxel* (control)

Paclitaxel* + Agent A

12 weeks

6-12 weeks

[[Every time I see this slide I think of Poseidon with his trident.]]

[10% of U.S. males are red colorblind. It’s hard for us to see the “Adaptive Randomization” and “12 weeks” because they’re on a dark background.]]
I-SPY2 TRIAL Eligibility

Screening

• Tumor size ≥ 2.5 cm
• Candidate for preoperative chemotherapy
• Able to have MRI and biopsy
• Adequate organ function, PS<2
I-SPY2 TRIAL Eligibility

[[You seem to be talking about the overall trial here ....]]

**Screening**

- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Able to have MRI and biopsy
- Adequate organ function, PS<2

**Treatment**

- If HR- or HER2+ or Mammaprint high-risk
- Meet all agent-specific eligibility criteria
I-SPY2 TRIAL Eligibility

Screening

- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Able to have MRI and biopsy
- Adequate organ function, PS<2

Screening

Assess Eligibility

Patient Eligible & Randomized

Treatment Consent, Patient On Study

Treatment

- If HR- or HER2+ or Mammaprint high-risk
- Meet all agent-specific eligibility criteria
I-SPY2 TRIAL Treatment Plan

Experimental regimen
• T-DM1: 3.6 mg/kg iv
  Pertuzumab: 840 mg load, followed by 420 mg
• Every 3 weeks x 4
• AC x 4 > Surgery

Control regimen
• Paclitaxel 80 mg/m2
• Trastuzumab 4 mg/kg load, then 2 mg/kg
• Weekly x 12
• AC x 4 > Surgery

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Here you’re talking about the T-DM1 comparison only. It’s not that what’s on this slide is the “I-SPY 2 TRIAL Treatment Plan.” The “R” for randomization is misleading in at least 3 ways.
Accelerated Approval of Pertuzumab

9/2013: FDA granted accelerated approval to pertuzumab in the neoadjuvant setting
THP was already an open arm of the trial
I-SPY2 Executive Committee determined that paclitaxel/trastuzumab was no longer an appropriate clinical option
Randomization to the paclitaxel/trastuzumab arm stopped (randomization probability set to zero)
Time adjusted analysis was utilized to compare enrolling Her2+ arms to all prior trial control patients receiving paclitaxel/trastuzumab moving forward

[[See notes.]]
Primary Endpoint: pCR

• Defined as **no residual invasive cancer in the breast or lymph nodes (ypT0/is and ypN0)** or receive non-protocol therapy
  – If do not have surgery: “non-pCR” by ITT

• Endpoint is assessed in overall group and within up to 10 pre-specified “biomarker signatures”
  – By receptor subtype (HR, Her2) and Mammaprint Score

• 3 signatures applicable for patients with Her2+ disease:
  – All Her2+, HR+/Her2+, HR-/Her2+
• 3 signatures applicable for HER2+ disease:
HR-/
HER2+
HR+/HER2+
All HER2+
New patient enrolled
assess subtype

Randomize

I-SPY2 RANDOMIZATION ENGINE
New patient enrolled; assess subtype

Randomize

Update outcome data

Update & apply longitudinal model

Update predictive probabilities

I-SPY2 RANDOMIZATION ENGINE
New patient enrolled; assess subtype

Randomize

Update outcome data

Update & apply longitudinal model

Update predictive probabilities

I-SPY2 RANDOMIZATION ENGINE

Assess termination rule by arm
Randomize

Update outcome data

Update & apply longitudinal model

Update predictive probabilities

I-SPY2 RANDOMIZATION ENGINE

Assess termination rule by arm

New patient enrolled; assess subtype

Stop futility
Graduate

Randomize

New patient enrolled; assess subtype

Update outcome data

Update & apply longitudinal model

Update predictive probabilities

I-SPY2 RANDOMIZATION ENGINE

Assess termination rule by arm

Graduate
New patient enrolled; assess subtype

Randomize

Update outcome data

Update & apply longitudinal model

Update predictive probabilities

Assess termination rule by arm

Continue

Update randomization probability within each subtype

Update predictive probabilities in each arm
Update patient outcome data

Randomize to exp arm or ctl

Update prob each exp arm > ctl for each subtype

For each exp arm determine adaptive randomization prob within each subtype

Add new exp arms accrual permitting

Update pred prob each exp arm >> ctl in phase 3 for each signature

Update & apply longitudinal model

Termination rule per arm

Continue

Graduate

Stop futility

New patient accrued; assess subtype

I-SPY 2
Threshold for Graduation

- Graduation Threshold = 85% predictive probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)
  - Probability is calculated from estimated pCR rates per signature
  - If pCR data is not available, use MRI volume response

- A drug “graduates” when the probability threshold is reached -> accrual to that arm then stops
  - Final probabilities are recalculated when all patients have gone to surgery and pathology data are complete
Not Every Drug Graduates for Efficacy

Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)
Not Every Drug Graduates for Efficacy

Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)
Not Every Drug Graduates for Efficacy

Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)

0% 10% 85% 100%

Drop for Futility

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

Graduate for Efficacy
Not Every Drug Graduates for Efficacy

Based upon predicted probability of success in a randomized phase 3 neoadjuvant trial (N=300, pCR endpoint)

Drop for Futility

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

Graduate for Efficacy

Drop for Toxicity
Format for Reporting I-SPY 2 Results

• The I-SPY 2 Bayesian model finds the probability distribution of pCR rates by signature
  – Actual pCR rates are biased by the adaptive randomization and are not provided

• 3 analyses presented
  (mean)
  – Estimated pCR rates by signatures
  – Probability that the drug is better than the control for each signature
  – Predicted probability of success in a 300 patient phase 3 trial based on estimated pCR rates (Threshold)
Consort Diagram for T-DM1 + Pertuzumab

Screened Patients (N=1540)

Randomized (N=878)

HER2+ Patients (N=249)

T-DM1+P→AC (N=52)

Received allocated intervention (N=52)

HER2- Patients (N=629)

Randomized to 5 other Investigational arms (N=165)

[You can’t subtract like this because of shared controls]

Received allocated intervention (N=31)

Screen Fail (N=601)

Did not receive allocated intervention (N=1)

[You might say orally that we’re now over 950 randomized]

[[see notes for this slide]]
# Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T-DM1+P-&gt;AC (n=52)</th>
<th>TH-&gt;AC (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>48 (33-72)</td>
<td>50 (29-71)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42 (80.7%)</td>
<td>25 (81%)</td>
</tr>
<tr>
<td>African American</td>
<td>4 (7.7%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (9.6%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latina</td>
<td>8 (15%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>HR Status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>35 (67%)</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>MRI Tumor Diameter (cm), median (range)</td>
<td>3.25 (1.5 – 12.0)</td>
<td>3.5 (1.3 – 11.7)</td>
</tr>
</tbody>
</table>
T-DM 1 + Pertuzumab Graduated in all 3 HER2+ Signatures: All HER2+, HR+/HER2+, and HR-/HER2+

<table>
<thead>
<tr>
<th>Arm</th>
<th>Estimated pCR Rate (95% PI)</th>
<th>Prob(&gt;Ctrl)</th>
<th>Prob(Ph3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All HER2+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TH-&gt;AC</td>
<td>0.22 (0.05 – 0.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-DM1+P-&gt;AC</td>
<td>0.52 (0.36 – 0.68)</td>
<td>0.995</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>HR- HER2+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TH-&gt;AC</td>
<td>0.33 (0.06 – 0.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-DM1+P-&gt;AC</td>
<td>0.64 (0.39 – 0.88)</td>
<td>0.98</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>HR+ HER2+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TH-&gt;AC</td>
<td>0.17 (0.00 – 0.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-DM1+P-&gt;AC</td>
<td>0.46 (0.26 – 0.66)</td>
<td>0.991</td>
<td>0.93</td>
</tr>
</tbody>
</table>

P= pertuzumab
TH = paclitaxel + trastuzumab
pCR Probability Distributions by Signature

**HER2+**
- Prob(>Ctl)= 99.5%
- Prob(Ph3)=94%
- TH→AC: 22%
- T-DM1+P→AC: 52%

**HR–HER2+**
- Prob(>Ctl)= 98%
- Prob(Ph3)=90%
- TH→AC: 33%
- T-DM1+P→AC: 64%

**HR+HER2+**
- Prob(>Ctl)= 99.1%
- Prob(Ph3)=93%
- TH→AC: 17%
- T-DM1+P→AC: 46%

95% PI: 5% - 39%
95% PI: 6% - 59%
95% PI: 0% - 34%
95% PI: 36% - 68%
95% PI: 39% - 88%
95% PI: 26% - 66%
# Adverse Events Grade ≥ 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>T-DM1+P-&gt;AC (n=52)</th>
<th>TH-&gt;AC (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available for Evaluation, n</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (14%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 (11%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (8%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

- Data summarized from files “Output_AE_Paclitaxel_Trastuzumab.txt” and “Output_AE_T-DM1_Pertuzumab.txt” received from Amy 4/1/2016
- 16 patients missing AE data in TDM1 arm
- Summary excludes baseline adverse events (3 patients on the TDM-1+Pertuzumab arm have no on-treatment events)
- CTCAE Term experienced by >5% of patients on the TDM-1+Pertuzumab Arm are listed
The THP regimen also graduated in I-SPY2
(paclitaxel/trastuzumab/pertuzumab)

(Abstract # XX, Poster Tuesday 4/19/16)
Conclusions

- I-SPY 2 adaptive trial has identified biomarker signatures for T-DM 1 + pertuzumab:
  - T-DM1 + Pertuzumab has graduated in all HER2+ signatures, including the HR+ and HR- subsets of HER2+

- T-DM 1 + pertuzumab is well tolerated, with only minor toxicity reported
  - Details....

- I-SPY 2 is a biomarker rich trial; additional response predictors are under investigation

- Based on these strong efficacy results, tolerability and favorable toxicity profile, additional combinations with T-DM1 are being explored

(Passive voice is a problem here. Who’s doing the exploring?)
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
Meredith Buxton: Co-PI, Project Management
Jane Perlmutter: Lead Advocate

Site PIs:
UCSD: Anne Wallace; USC: Julie Lang; Swedish: Hank Kaplan; MDAnderson: Stacey Moulder; UMinn: Doug Yee
Mayo: Judy Boughhey; UCSF: Jo Chien; Georgetown: Claudine Isaacs
U.Chicago: Rita Nanda; Loyola Chicago: Kathy Albain; U.Colorado: Anthony Elias;
U.Penn: Amy Clark Oregon HSU: Kathleen Kemmer;
UTSouthwestern: Barbara Haley U Alabama: Andres Forero British Columbia CA: Stephen Chia; Moffitt: Susan Minton

I-SPY Program Management Office (PMO)
Meredith Buxton: Exec Director, I-SPY Program
Julia Lyandres Clennell: Operations Director
Ashish Sanil, Christina Yau, Denise Wolf: Data Analysis
Karen Kimura, Garry Peterson, Amy Wilson: IT
Gillian Hirst: Biomarkers / Lamorna Brown-Swigart:
I-SPY 2 Lab
Ruby Singrao, Tayeba Maktabi, John Nespeco, Mamta Shah, Brigitte Cronier, Julia Chambers: PMO Office

I-SPY 2 Agents Committee
Kathy Albain, Christopher Benz, Stephen Chia, Jo Chien, 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, Debu Tripathy, Doug Yee, Amy Clark, Paula Pohlmann, Richard Schwab, Patricia LoRusso, Anthony Elia, Melissa Paoloni, Patricia Haugen

Sponsor: QuantumLeap Healthcare Collaborative: Melissa Paoloni, Cabot Brown
Funding: Safeway, Bill Bowes, Quintiles, J&J, Genentech, Amgen, Give Breast Cancer the Boot, Harlans, Side-Out, Avon, Alexandria
Oversight: Anna Barker/ASU, Gary Kelloff/NCI
FDA: Janet Woodcock, Richard Pazdur

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

Sponsors and Managers
Quantum Leap
A Healthcare Collaborative

Funders, Operations
UCSF University of California San Francisco
Novella Clinical A Quintiles Company
Safeway Ingredients for life...

Investigational Agent Providers
AbbVie
Genentech A Member of the Roche Group
Amgen
Medivation
Merck Be well
Plexxikon
Synta Pharmaceuticals
Puma Biotechnology

Biomarker Device Providers
Oregon Health & Science University
Salesforce
UCLA
George Mason University
Berkeley Lab Lawrence Berkeley National Laboratory
Agenda decoding cancer

Foundation National Institutes of Health
William K. Bowes, Jr. Foundation
The biomarkers consortium
T-DM1 + Pertuzumab vs. Paclitaxel + Trastuzumab

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- Prob(>Ctl) = 99.5%
- Prob(Ph3) = 94%
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- Prob(Ph3) = 90%
- TH → AC: 33%
- T-DM1 + P → AC: 64%

**HR+HER2+**
- Prob(>Ctl) = 99.1%
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- TH → AC: 17%
- T-DM1 + P → AC: 46%

THP vs. Paclitaxel + Trastuzumab

**HER2+**
- Prob(>Ctl) = 99.8%
- Prob(Ph3) = 96%
- TH → AC: 22%
- THP → AC: 54%

**HR-HER2+**
- Prob(>Ctl) = 99.8%
- Prob(Ph3) = 98%
- TH → AC: 33%
- THP → AC: 74%

**HR+HER2+**
- Prob(>Ctl) = 99%
- Prob(Ph3) = 91%
- TH → AC: 17%
- THP → AC: 44%