Neoadjuvant/Adjuvant Standards of Care and Experimental Approaches in Breast Cancer

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#MelanomaNeoAdjuvant
Disclosures

- Scientific Consulting: Pfizer, Novartis, Calithera

- Institutional Support of Research Trials: Pfizer, Novartis, Calithera, Menarini, Genentech
The I-SPY Platform Trial

A Multicenter Consortium to Optimize Therapy in Early Breast Cancer
Thank you to the remarkable patients and families, our amazing advocates, all of the investigators, staff, and our DSMB for supporting the trial.

I-SPY™ | The right drug. The right patient. The right time.”
An inflection point

• Breast Cancer has evolved from one disease to many
  • Molecular subtyping revealed different outcomes
    • Informed better use of ER, PR, Her2, proliferation (grade/Ki-67)
  • Multigene assays have enabled us to refine patient populations and treatment
    • How much risk and when . . .

• Screening has changed the spectrum/ distribution of tumor types
  • Atypia, DCIS, Earlier stage cancers
  • But aggressive cancers still persist- in spite of “awareness” and access

• Trials, agents are evolving
  • Large trials with small benefit for all → smaller trials focused on larger benefit for subsets; better drugs have less toxicity
The Opportunity: Use early endpoints to enable interventions to rapidly evolve

Goal: Test targeted therapeutics, harness trial design, and regulatory science to get patients to the optimal endpoint and prevent recurrence
I-SPY 2 Goals

• Improve the efficiency of testing new agents:
  • Platform trial
  • Adaptive randomization
  • Testing against common controls and historic controls as the standards change
• Incorporate standards for:
  • Qualifying biomarkers
  • “Biomarker platforms”
  • Patient reported adverse endpoints
• Transform care at all participating sites  Learning system
  • Knowledge continues to increase as the trial proceeds
I-SPY 2 TRIAL Eligibility

- Tumor size $\geq$ 2.5 cm
- Candidate for preoperative chemotherapy
- Study MRI and biopsy
- Adequate organ function, PS<2

**Screening Consent** → **Assess Eligibility** → **Core Biopsy**

- HER2+ (IHC, FISH, TargetPrint)
  - Triple negative
  - Hormone Receptor + AND MammaPrint High Risk

**I-SPY2 LOW RISK REGISTRY**

- Randomized
- Consented to Assigned Arm

**Hormone Receptor Positive and MammaPrint Low Risk**

**NOT ELIGIBLE**
I-SPY 2 TRIAL Master Schema

Adaptive Randomization

Her2+ control (THP)

Her2- control (T)

Multiple experimental agents + T+/- H

12 weeks

8-12 weeks

Doxorubicin Cytoxan

S U R G E R Y

MRI, Blood Core Biopsy

MRI, Blood

MRI, Blood Core Biopsy

MRI, Blood Tissue

T=Paclitaxel, H=Trastuzumab, P=Pertuzumab
I-SPY 2 Statistical Analysis

**Primary Endpoint:**
- Pathological complete response (pCR)
- Defined as no residual invasive cancer in breast or lymph nodes (pyT0pyN0)
- Assessed using the Residual Cancer Burden (RCB) method*
- Highly reproducible between local and central pathologist review

**Intent-to-treat:**
- Patients who received therapy, but later withdrew, leave the institution, went to non-protocol therapy, or progressed are considered non-pCR

**Secondary endpoints:**
- RCB, EFS, DRFS at 3, 5 and 10 years

### Categories of Biomarkers in I-SPY 2

**STANDARD**

1. **ER/HER2 IHC; FISH**
2. **Mammaprint**
   - FDA cleared 70 gene assay (used to determine randomization eligibility)
   - IDE (filed with FDA) for 44K array

2. **MR volume**
   - used to determine response to treatment
   - IDE (filed with FDA)

**QUALIFYING**

1. **Signatures**
   1. DNA Repair Deficiency
   2. AKT pathway
   3. HER pathway
   4. Hi-2 (Mammaprint)
   5. Immune Signatures

2. **Platforms**
   1. 44k Agilent Array
   2. Reverse Phase Protein Arrays
   3. Vectra Multiplex Staining Environment

**EXPLORATORY**

1. RNA seq
2. DNA seq
3. Circulating DNA
4. Circulating tumor cells
Predicted probability of pCR: HER2- subsets

HR+HER2-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated pCR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctr</td>
<td>13%</td>
</tr>
<tr>
<td>VC</td>
<td>14%</td>
</tr>
<tr>
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</tr>
<tr>
<td>MK2206</td>
<td>17%</td>
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<td>AMG386</td>
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<tr>
<td>Ganitumab</td>
<td>14%</td>
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<td>Ganetespib</td>
<td>15%</td>
</tr>
<tr>
<td>Pembro</td>
<td>17%</td>
</tr>
<tr>
<td>Total</td>
<td>30%</td>
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</table>

HR-HER2-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated pCR rate (%)</th>
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</thead>
<tbody>
<tr>
<td>Ctr</td>
<td>22%</td>
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<tr>
<td>VC</td>
<td>51%</td>
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<tr>
<td>N</td>
<td>38%</td>
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<tr>
<td>MK2206</td>
<td>40%</td>
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<tr>
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<td>37%</td>
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<tr>
<td>Ganitumab</td>
<td>32%</td>
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<tr>
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<td>38%</td>
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<tr>
<td>Pembro</td>
<td>39%</td>
</tr>
<tr>
<td>Total</td>
<td>60%</td>
</tr>
</tbody>
</table>

No comparisons!

all patient data from 7 graduated arms + control
Predicted probability of pCR: HER2+ subsets

No comparisons!

all patient data from 4 HER+ (4/7) graduated arms + control
pCR status as predictor of DRFS and EFS
All subtypes combined

19 events in 1265 woman-years for those achieving pCR (0.0150/yr) and 169 events in 2125 woman-years for those not achieving pCR (0.0795/yr).
EFS by pCR & non-pCR: By subtype

EFS Hazard Ratio for pCR/non-pCR: By Treatment Arm

[Graph showing EFS Hazard Ratio for different treatment arms, with hazard ratios ranging from 0.00 to 1.20. The graph includes data points for Control, Non-graduates, Graduates, and Mean.]
# EFS Analysis Summary

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>pCR Rate (95% CI*)</th>
<th>EFS Hazard Ratio (95% CI)</th>
<th>DRFS Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+HER2-</td>
<td>361</td>
<td>17% (14%-22%)</td>
<td>0.14 (0.03 – 0.55)</td>
<td>0.16 (0.04 – 0.64)</td>
</tr>
<tr>
<td>HR+HER2+</td>
<td>173</td>
<td>40% (33%-48%)</td>
<td>0.15 (0.03 – 0.63)</td>
<td>0.10 (0.01 – 0.77)</td>
</tr>
<tr>
<td>HR-HER2+</td>
<td>326</td>
<td>42% (36%-47%)</td>
<td>0.18 (0.09 – 0.34)</td>
<td>0.20 (0.10 – 0.40)</td>
</tr>
<tr>
<td>HR-HER2-</td>
<td>90</td>
<td>68% (57%-77%)</td>
<td>0.14 (0.05 – 0.41)</td>
<td>0.18 (0.06 – 0.53)</td>
</tr>
<tr>
<td>ALL</td>
<td>950</td>
<td>35% (32%-38%)</td>
<td>0.19 (0.12 – 0.31)</td>
<td>0.21 (0.13 – 0.34)</td>
</tr>
</tbody>
</table>

*Based on binomial exact (Clopper-Pearson) confidence interval method.*
Key Lessons Learned: pCR> EFS/DRFS in I-SPY2

• pCR is a robust early endpoint in the setting of a well run platform trial set up as a learning system with:
  • Standards for eligibility (high risk for early recurrence)
  • Screening for metastatic disease
  • Standards for pathology assessment and multidisciplinary identification (surgeons, radiologists, pathologists)
  • Long term follow-up of all patients over time (correlation of early, intermediate and late endpoints)

• Achieving a pCR is equally prognostic across all tumor subsets
  • Enable targeted de-escalation and escalation of therapy, to both decrease toxicity and improve overall chance of survival
I-SPY2 +:
Evolving the I-SPY 2 TRIAL to include MRI-directed, adaptive sequential treatment to optimize breast cancer outcomes

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PPG I-SPY2 + TEAM:
Laura Esserman/Nola Hylton
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Adam Asare/Amrita Basu
Gillian Hirst/ Jeffrey Matthews
Hope Rugo/Andres Forero
Claudine Isaacs/Richard Schwab
Anthony Elias/Barbara Parker
All other I SPY investigators
Requirements for “multi-line” neoadjuvant trials

- Identify patients who are not on the course to pCR
- Escalate to second line therapy to achieve pCR
- Determine failure non-invasively
  - Assess when to call failure and switch
- Rational selection of second-line therapy
  - Determine whether “switching” strategies are effective
Biomarker Profiles for Prospective Treatment Assignment

*Identify the Right Population to Optimize Treatment*

**MAMMAPRINT**

<table>
<thead>
<tr>
<th>Hi2</th>
<th>Hi1</th>
<th>Low</th>
<th>Ultra-low</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>HR+ HER2−</td>
<td>HR− HER2+</td>
<td>HR+ HER2+</td>
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<tr>
<td>BASAL</td>
<td>LUMINAL B</td>
<td>LUMINAL A</td>
<td>SET Hi</td>
</tr>
<tr>
<td>SET Lo</td>
<td>SET Hi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune +</td>
<td>DRD −</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response Predictive Pathways

S1, S2, S3, S4, S5
The I-SPY Platform is Evolving

• Surrogates and endpoints are validated for the individual
• Accumulating data that combination imaging/biopsy can tell us when we have reached pCR
• Biomarker/drug combinations exist for real-time drug selection based upon individual’s tumor biology
• We can test these strategies for precision treatment in platform trials of continuous learning
  • Optimizing outcomes for individuals
  • Assessing benefits of drugs in patient subsets
  • Reducing the burden of metastatic disease
# Participating Organizations

## FUNDING PARTNERS
- William K Bowes, Jr. Foundation
- Give Breast Cancer the Boot
- University of California San Francisco (UCSF)
- The Biomarkers Consortium
- IQVIA tm (formerly known as Quintiles Transnational Corporation)
- The Breast Cancer Research Foundation
- Safeway Foundation, an Albertsons Company
- Stand Up to Cancer Netherlands
- University of Pennsylvania

## INVESTIGATIONAL AGENT PROVIDERS
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- AbbVie
- Synta Pharmaceuticals
- Genentech
- Amgen
- Plexxikon
- Dynavax

## STUDY SPONSOR
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## BIOMARKER PLATFORMS & DATA SUPPORT
- Berry and Associates
- CCS Associates
- salesforce
- Agendia
- Natera
- Hologic
- Novella Clinical
- Oregon Health & Science University (OHSU)
- UCSF
- The Translational Genomics Research Institute (TGen)