Neoadjuvant Therapy to Select the Most Effective Drug Combinations: The I-SPY 2 TRIAL

Laura Esserman, MD, MBA
Professor of Surgery, Radiology
University of California, San Francisco
Problems/opportunities

• Tumor heterogeneity
  – Among patients with high risk disease
  – Within a given tumor

• Standard therapy has made a difference, but not all benefit equally or at all

• There are hundreds of agents in the pipeline but limited ability to test them

• Biomarkers/ Companion Diagnostics for targeted agents are lacking
Women at Risk for Systemic Recurrence

• Will not be cured with surgery alone
• Order of surgery, systemic therapy has no impact on survival outcomes
• Neoadjuvant approach is an opportunity
  – Downstage tumors, refine local therapy options
  – Better understand response to therapy, prognosis
  – Accelerate targeted drug development to improve outcomes in highest risk women
  – Particularly relevant as a tool to sort out optimal treatments in the molecular era
An historically fatal disease that has been turned into a chronic condition

LESSONS FROM CML
Survival in Accelerated and Blast Phase CML Over Time

Testing new agents in the metastatic setting may NOT be optimal
Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis
I-SPY 1 \( \rightarrow \) I-SPY 2

**I-SPY 1** (2002–2008)
- Evaluation of biomarkers and imaging for predicting response to standard neoadjuvant chemotherapy

**I-SPY 2**
- Evaluate phase II drugs in combination with standard chemotherapy in a neoadjuvant setting
- Use biomarkers to stratify patients, adaptively randomize based on response to treatment
- Use imaging to measure response, pCR as endpoint
Strategies for High Risk Cancers

• Target HER2
  – TKIs, Ab toxin conjugates, Her-2/3 bivalent antibodies

• Target PI3K
  – TORQ 1,2

• Target Myc
  – CDK inhibitors

• Target the tumor immune environment
  – Drugs that target macrophages, e.g. cfms inhibitor
  – Drugs that reprogram the immune environment

• Target Stem Cell Targets
  – Notch, WNT inhibitors
Test drugs where they matter most, use biomarker and imaging guidance, collect data in real time, use adaptive design, precompetitive collaboration

CHANGE THE WAY WE TEST PROMISING NEW DRUGS
I-SPY 2 is Designed to

• Screen phase 2 agents in combination with standard chemotherapy in neoadjuvant setting
  • Endpoint is pCR
  • Design is adaptive within the trial, multiple agents, shared std arm
  • “threshold” is 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair

• Accelerate process of identifying drugs that are effective for specific breast cancer subtypes
  – Integration of biomarkers, analysis within subsets by design
  – Increase success of phase 3 or confirmatory trials
I-SPY 2 Adaptive Trial Design

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
Imaging Biomarkers Provide Functional Markers of Response, Volume Reduction Over Time

Volumetric change is automated, integrated into the trial as a standard biomarker and used as a tool for:

- early assessment of response
- assignment of randomization probabilities

Pre Treatment

Post Treatment

ACRIN 6657: MRI volume best measure (early and late) of pCR, RCB 01
Hylton, Radiology 2012

Nola Hylton, PhD
UCSF Radiology and Biomedical Imaging,
Biomarker Categories in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established Biomarkers
  - IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers
    - discovery of new response predictors

- Biomarker IDE as part of Drug IND facilitates companion diagnostic FDA PMA approval
Randomization based on Performance of drug within Biomarker signatures

- Graduate drugs/signatures from trial:
  - Based on effectiveness
  - Based on prevalence

- Biomarker signatures (2^8 combinations of subtypes): $B_1, B_2, \ldots, B_{256}$

- But restrict to (10) marketable signatures:

<table>
<thead>
<tr>
<th></th>
<th>MP Hi-1</th>
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<th>MP Hi-2</th>
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<tr>
<td>HER2+</td>
<td>16%</td>
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70 Gene Signature Hi-1 and Hi-2 is based on the median cut point of 70 Gene Signature for I-SPY 2 eligible patients
Biomarker Signature #1: All

Projected frequencies based on I-SPY 1:

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MP: 70 Gene Signature High 1 or High 2
HR+: Hormone Receptor+: Either ER+ or PR+
**Biomarker Signature #2: HR+**

Projected frequencies based on I-SPY 1:

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### Biomarker Signature #3: HR-

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Biomarker Signature #4: HER2+

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37%
### Biomarker Signature #5: HER2-

Projected frequencies based on I-SPY 1:

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**63%**
Biomarker Signature #6: MP2

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MP: 70 Gene Signature High 1 or High 2
HR+: Hormone Receptor+: Either ER+ or PR+
## Biomarker Signature #7: HR-HER2-

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MP: 70 Gene Signature High 1 or High 2  
HR+: Hormone Receptor+: Either ER+ or PR+  
34%
### Biomarker Signature #8: HR-HER2+

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Biomarker Signature #9: HR+HER2+

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## Biomarker Signature #10: HR+HER2-

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Biomarker Categories in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established Biomarkers
  - IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers
    - discovery of new response predictors

- Biomarker IDE as part of Drug IND facilitates companion diagnostic FDA PMA approval
Biomarker Testing Pre-treatment Core

• Qualifying and Exploratory Platforms:
  – Agilent 44K microarray (Agendia) (Qualifying)
  – RPMA (Petricoin) (Qualifying)
  – Cell line drug testing (Gray) (Qualifying)
  – MR volume, kinetic, functional, diffusion measures (Hylton)
  – Whole Genome Sequencing (DNA/RNA, SU2C and plans)
  – GWAS (Goetz/Giacomini/DeMichele)
  – RNAi screens (proposed)

• IDE and Qualifying Biomarkers:
  – 70 Gene Signature (high1/high2) (IDE from 44K)
  – SET-index/TFAC-predictor (Symmans) (Qualifying)
  – MR Volume (Hylton) (Qualifying)
Refine the Endpoint: Enhance the signal

Kaplan Meier curves of molecular signature dichotomized by I-SPY 2 inclusion criteria (70-Gene Low Risk HR+/HER2- vs. Not) with known pathological response (n=144).

Low 70-Gene Risk HR+/HER2- vs. Others (n=144)

All 11 have no pCR

Residual Cancer Burden
Subset Excluding 70-Gene Low Risk HR+/HER2- Cases Stratified by RCB (124)

Note: 9 patients fitting the I-SPY 2 inclusion criteria with known pathological response data do not have known RCB Class.
The protocol and the Master IND* are structured to enable seamless addition and release of investigational agents over the course of the trial

- Enrollment does NOT stop during agent transition

- When an investigational agent is added to or released from the trial only appendices require updating
  - Appendix C plus Investigational Agent Appendices

*I-SPY 2 PROTOCOL STRUCTURE*

**PROTOCOL MAIN BODY**
Contains details of the trial excluding the investigational agents

**APPENDIX C**
Summary of Investigational Agents

**INVESTIGATIONAL AGENT APPENDICES**
One (1) per Investigational Agent

*The Master IND structure allows new investigational agents to be added to the protocol without the 30-day FDA review period.*
I-SPY 2 Adaptive Trial: Information gathered in real time for several agents

**HER 2 (+)**
- Paclitaxel + Trastuzumab
- Paclitaxel + Trastuzumab* + New Agent A
- Paclitaxel + Trastuzumab* + New Agent B
- Paclitaxel + Trastuzumab* + New Agent C

**HER 2 (−)**
- Paclitaxel
- Paclitaxel + New Agent C
- Paclitaxel + New Agent D
- Paclitaxel + New Agent E

**Randomize**

**AC**
- Surgery

**Surgery**

Learn, Adapt from each patient as we go along

**Key**
- MRI
- Residual Disease (Pathology)

*Or equivalent*
Learn: Drop, Graduate, Replace Agents Over Time

**HER 2 (+)**
- Paclitaxel + Trastuzumab
- Paclitaxel + Trastuzumab* + New Agent A
- Paclitaxel + Trastuzumab* + New Agent B
- Paclitaxel + Trastuzumab* + New Agent C
- Paclitaxel + Trastuzumab* + New Agent F

**HER 2 (–)**
- Paclitaxel + New Agent F
- Paclitaxel + New Agent GH
- Paclitaxel + New Agent E

**Key**
- MRI
- Residual Disease (Pathology)

**Learn and adapt from each patient as we go along**

**Randomize**

**Surgery**

*Or equivalent*
Participating Trial Sites – 19 Sites Open to Accrual

Screening: 20+ patients per month
Trial Enrollment Overview

Registered (n=610)

Actively Being Screened (n=21)

Patients Who Did Not Proceed to the Treatment Phase (n=268)
- 70 Gene Signature low risk, ER+, HER2-(n=85)
- Declined participation (n=65)
- Sample and/or Microarray Issues (n=64)
- Unable to complete MRI (n=7)
- At investigator’s discretion (n=7)
- Did not meet eligibility criteria (n=40) [abnormal lab values (10); metastatic disease (20); other (n = 10)].

Randomized (n=321)

Completed Surgery (n=238)

3-4% metastatic disease
After staging workup

Status as of January 15, 2013
## Agent Update

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<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Status in Trial</th>
<th>HER2+ HR+</th>
<th>HER2+ HR-</th>
<th>HER2− HR+</th>
<th>HER2− HR-</th>
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<tr>
<td>Neratinib</td>
<td>Pan ErbB Inhibitor</td>
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<td>Yes*</td>
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<tr>
<td>ABT-888 (+ carboplatin)</td>
<td>PARP Inhibitor + carboplatin</td>
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<td>AMG 386</td>
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<td>MK2206</td>
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<td>TDM1 + pertuzumab</td>
<td>Antibody Toxin/HER dimer Ab</td>
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<td>Pertuzumab</td>
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<td>TORC1/TORC2 inhibitor</td>
<td>Pending Safety data</td>
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I-SPY 2 Informatics Infrastructure: TRANSCEND
Uses Common Tools, Enables Data Exchange, Real time

Reusable Infrastructure
Open Source
Developed to Support Adaptive Randomization
Collaboration with NCICB/ caBIG

Biopecimen Data Management System (caTISSUE)

Microarray Data Storage (caARRAY)

Qualifying & Exploratory Biomarkers

caINTEGRATOR

Investigators evaluate efficacy of treatment arms – as trial is underway
Scalability with THE Force:

- In one Salesforce Org can have multiple institutions with multiple trials operating with a separate DCC for each trial; Hub and spoke model
I-SPY 2 Process Collaborative by Design

- Involve key stakeholders from inception
  - NCI, FDA, FNIH Biomarkers Consortium, Academic and Clinical Partners, Pharma, Biotech, IT, Advocates

- Involve stakeholders from all sites
  - “Chaperones” for agents, biomarkers from trial investigators
  - Data in caINTEGRATOR will be open to all investigators
Everyone working as a team

- **Local Sites**
  - Coordinating multi-disciplinary teams for 1 study
- **Local IRBs**
  - Collectively working together on trial regulatory challenges
- **Data, Design**
  - Don Berry, Laura Esserman
- **Imaging**
  - Nola Hylton
- **Biomarkers**
  - Laura van’t Veer
- **Operations**
  - Angie DeMichele
- **Agent Selection**
  - Doug Yee
- **Informatics**
  - Mike Hogarth
- **Pathology**
  - Fraser Symmans
- **Advocates**
  - Jane Perlmutter
- **Project Management**
  - Meredith Buxton
- **NCI Leadership**
  - Anne Barker, Gary Kelloff
- **FDA, CDER Leadership**
  - Janet Woodcock, Karen Weiss
- **FNIH Leadership**
  - David Wholley, Sonia Pearson-White
- **Pharma, Biotech**
  - Abbott, Amgen, Agendia, Pfizer, Sentinelle, etc
A Process Model to Accelerate Knowledge Turns

Linked trial phases could provide additional efficiency and further
THE GOAL:

• **LEARN EARLY** whether agents/drugs will fail or succeed

• **ACCELERATE** approval for successful agents, biomarkers

• **PREDICT** who will benefit, **PERSONALIZE** using biomarkers