I-SPY 2 Changing the Options for High Risk Women

Director, Anne M. Wallace, MD, FACS
Professor of Clinical Surgery
UCSD Moores Cancer Center
Understanding Breast Cancer – Past, Present and Future

• It's easy to walk into a surgeon’s office with a diagnosis of breast cancer and hear surgery can be scheduled this week.

• It's common to think that quickly having surgery to “remove both breasts” will allow longer survival.

• Common cancer care is often naively practiced. Understanding the details is crucial; algorithms are important but individualized care is critical.
Example

• 58 year old female with a 5cm triple negative breast cancer – biologically aggressive
• Large breasted, no family history
• Urges her community provider to do bilateral mastectomies and then she “wont need chemotherapy”. He somehow agrees and never ensures that she understand her disease; he is practicing in the “past”
• Came to UCSD for second opinion at urging of her friends
Example, continued

• We see her. She has a complete misconception over how cancer behaves, the role of chemo and radiation therapy, etc.

• After undoing all the information she had heard and spending time explaining the significance of triple negative disease, we offer her chemotherapy via the i-spy clinical trial instead of surgery first. The absolute necessity to have systemic therapy is explained; surgery is not a trade off

• The trial will allow her an 80% chance of getting not only the standard chemotherapy but a parp inhibitor or other biologic agent with the promise of vastly improving response

• The role of SURGERY FIRST IN STAGE 2 TRIPLE NEGATIVE DISEASE is minimal. Bilateral surgery is aggressive, time consuming, full of complications and would have disqualified her from the chance to obtain life saving agents for her disease – the FUTURE

• She changed her care to UCSD that day
Recurrence and Local Treatment

• Recurrence of high risk breast cancer influenced by
  – Stage at presentation
  – Stage after chemotherapy and response to therapy,
  – NOT by type of surgery

• Distant recurrence is the biggest risk and a reflection of poor biology

_Cureton et al Annals of Surgical Oncology 2014_
Optimize the Clinical Care Process

**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
## Recurrence by Treatment Type

In the I SPY 1 Trial, in the setting of serial MRI

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</tr>
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<td>90 (44%)</td>
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<td>Mastectomy</td>
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*Cureton ASBS 2012, Annals of Surgical Oncology 2014*
The Problem for Patients

30-50% of women with breast cancer are still die of their disease.

It takes 10-15 years for new oncology drugs to reach patients.

Many new therapeutic options—little chance to rapidly get them to patients.

Access to new investigational drugs depends on where in the world you live.
The Problem for Companies

The cost to bring a new drug to the market is approximately $2 billion

Absence of innovation in trial design/data collection tools to improve the efficiency and decrease the cost of trials

Cancer is a subset of diseases

Blockbuster approach won’t work

Current path is UN-SUSTAINABLE
I-SPY2 TRIAL

Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular Analysis 2
Compressing Trial Timelines and Finding Better Treatments:
General I-SPY2 Overview

• I-SPY 2 is a clinical trial for women with newly diagnosed locally advanced breast cancer
• Goals:
  – To test whether adding investigational drugs to standard neoadjuvant chemotherapy is better than the standard chemotherapy
  – To try to match particular investigational agents with patients who stand to benefit the most from them, based upon the biology of the patient’s disease
  – To use the information from each study participant to help decide treatment for future women who join the trial
I-SPY 2
High Risk for Early Recurrence
Neoadjuvant setting
Emerging Treatments
Collaborative Infrastructure Standards for Data Collection
General I-SPY2 Overview

- 80% of patients receive an investigational drug in addition to standard chemotherapy.
- Patients are assigned to various treatment arms on the basis of the biological characteristics of their disease.
  - Extra molecular tests are performed in screening to determine the appropriate treatment arm.
- The trial uses serial MRI imaging to track the progress of the patient’s tumors.
General I-SPY2 Overview

• I-SPY2 is collaborative trial
  – 19 locations nationally
  – Sponsored by the Biomarkers Consortium, a partnership led by the Foundation for the National Institutes of Health (FNIH), includes:
    • Food and Drug Administration (FDA)
    • National Institutes of Health (NIH)
    • A large number of partners from major pharmaceutical companies

Safeway/Vons – led the philanthropic Funding at the beginning
19 Sites Currently
I-SPY 2 Participating Organizations

Sponsors and Managers
- Quantum Leap
- UC San Francisco
- Safeway
- William K. Bowes, Jr. Foundation
- The Biomarkers Consortium

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

Biomarker Device Providers
- Oregon Health & Science University
- UCSF
- George Mason University
- THERANOSTICS Health
- Agendia
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
  - “Graduation” indicates an 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

- Reduce the cost, time, and numbers of patients needed to get effective drugs to market through accelerated approval
Summary of Study Plan

- MRI
- Biopsy
- Blood Draw
- MUGA/ECHO
- CT/PET

Consent #1
Screening Consent

Consent #2
Treatment Consent

Paclitaxel* (12 weekly cycles)
Paclitaxel* + Investigational Agent A (12 weekly cycles)
Paclitaxel* + Investigational Agent B (12 weekly cycles)

AC (4 cycles)
AC (4 cycles)
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* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
I-SPY 2 Adaptive Trial:
Introduce several new agents for a given profile

Patient is on Study

Key
MRI
Residual Disease (Pathology)

AC: doxorubicin/cyclophosphamide

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

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

Surgery
Learn, adapt from each patient as we go along

AC
*Or equivalent

Residual Disease (Pathology)
MRI
Trial Enrollment Overview

- Registered (n=1361)
  - Actively Being Screened (n=37)
    - Patients Who Did Not Proceed to the Treatment Phase (n=568):
      - MammaPrint low risk, ER+, HER2- (n=161)
      - Declined participation (n=125)
      - Sample and/or Microarray Issues (n=99)
      - At investigator’s discretion (n=16)
      - Did not meet eligibility criteria and other (n=167)
  - Randomized (n=756)
    - Completed Surgery (n=638)

Status as of Feb 15, 2015
### 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, Trial 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

#### Agent Chaperones
- **ABT888:** Hope S. Rugo, Funmi Olopade
- **Neratinib:** John Park, Minetta Liu
- **AMG 386:** Kathy Albain, Brian Leyland-Jones
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#### Site PIs:
- **UCSD:** Anne Wallace
- **USC:** Debu Tripathy
- **U Arizona:** Julie Lang/Rebecca Viscusi
- **Swedish:** Hank Kaplan
- **MD Anderson:** Lajos Pusztai/Stacey Moulder
- **UMinn:** Doug Yee
- **Mayo:** Judy Boughey
- **Mayo Scottsdale:** Donald Northfelt
- **UCSF:** Jo Chien
- **Georgetown:** Minetta Liu/Claudine Isaacs
- **U Chicago:** Rita Nanda
- **Inova Fairfax:** Kristen Edmiston
- **Loyola Chicago:** Kathy Albain
- **U Kansas:** Qamar Khan
- **U Colorado:** Anthony Elias
- **U Penn:** Angela DeMichele
- **Oregon HSU:** Steven Chui
- **UT Southwestern:** David Euhus
- **U Alabama:** Andres Forero
- **British Columbia CA:** Stephen Chia

#### I-SPY Project Management Office
- Meredith Buxton: Director, I-SPY Program
- Julia Lyandres: New Agents/Trial Operations
- Sarah Davis, Ashish Sanil: Informatics
- Susan Flynn: Biomarkers
- Christina Yau, Densie Wolf: Data Analysis
- Lamorna Brown-Swigart: I-SPY 2 Laboratory

#### Sponsor:
- QuantumLeap Healthcare Collaborative: Melissa Paoloni, Alan Hu
- FNIH Biomarker Consortium: David Wholley & Sonia Pearson-White

#### Funding:
- Safeway, Bill Bowes, Quintiles, J&J, Genentech, Amgen, Give Breast Cancer the Boot, Harlans, Side-Out, Avon, Alexandria

#### Oversight:
- NCI: Anna Barker/ASU, Gary Kellogg
- FDA: Janet Woodcock, Richard Pazdur
I-SPY Milestones

- Demonstrated that pCR endpoints work better by subtype
- Enlisted multiple pharma companies into same trial
- Developed I-SPY 2 infrastructure
  - IT systems to support adaptive learning
  - New methods to distribute credit
- Successful integration of adaptive randomization, including real time data collection and use in driving ongoing randomization
- Demonstration of the standing trial concept
  - multiple arms, single backbone and Master IND
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- Graduation of 2 agents, with biomarker signatures
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- Accelerated Approval guidance issued by FDA
  - Next step: I-SPY 3 international trial
Compressing the Timeline

Linked Phases of Trial Development Accelerates Knowledge Turns

MARKER PHASE

- Analysis of biomarker data
- Agreement on candidate marker
- File IDE

I-SPY 2
Adapts on drugs (~80 patients)

- I-SPY 2 TRIAL amendment approved
- Promising qualifying biomarker
- Continuous enrollment
- Drug graduates or is dropped

I-SPY 3
Adapts based on pCR rate (~400-1000 patients)

- Surgical Therapy to Confirm pCR
- pCR signal confirmed, EFS accrued

PHASE 1b

- Promising candidate
- Enroll, randomize on qualifying biomarkers
- Combine with paclitaxel
- New agent/combination qualifies and is approved for I-SPY 2

PHASE 3 YR RFS confirms pCR result

- pCR not confirmed
- pCR signal not confirmed

External review

Surgical Therapy to Confirm pCR

Agent Enters

Full Approval

Accelerated Approval

Agreement on candidate marker

File IDE

Feedback to consortium

Identify next agent combination

Promising qualifying biomarker

Drug graduates or is dropped

Continuous enrollment

Enroll, randomize on qualifying biomarkers

I-SPY 2 TRIAL amendment approved

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Combine with paclitaxel

15 patients at target dose

Safety concern met

Adv. (157) 04/2021
The Value of A Consortium Model:

*Building Capacity worldwide*

- The power of a consortium enables innovation
  - No one group can effect change on their own
  - Allows companies to participate in meaningful change that would otherwise be seen as self-serving if they went alone
- Promotes international collaboration and dialogue
- Ensures drugs will be more available across the world at the same time
- A faster more efficient process for approving more drugs at a lower cost
Why UCSD Succeeds

• 194 patients screened; 102 enrolled
• Neoadjuvant trials must have Surgical leads or patients go to surgery BEFORE trial ever gets considered
• TEAM approach – RESEARCH COORDINATOR must be outstanding
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- UCSF
- SAFEWAY

**Investigational Agent Providers**
- abbvie
- Genentech
- AMGEN
- SYNTA

**Biomarker Device Providers**
- Biocad
- Micromedex
- Roche Diagnostics
- Siemens Healthcare
- sentinelle HOLOGIC
- sentinel

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**Summary of Study Plan**

**I-SPY 2 TRIAL**

**Screening**
- MRI
- Biopsy
- Blood Draw
- MUGA/ECHO

**Tissue**
- Surgical Residual Disease (Pathology)

**Procedure**
- Randomize
- AC
- Surgery

**Patient is on Study**
- HER 2 (+)
- HER 2 (-)

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

**I-SPY 2 Adaptive Trial:** Introduce several new agents for a given profile

*HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.*

*Or equivalent*
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  - Sarah Davis, Ashish Saini: Informatics
  - Susan Flynn: Biomarkers
  - Christina Yau, Dersie Wolff: Data Analysis
  - Lamorna Brown-Swift: I-SPY 2 Laboratory

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  - U. Southern State: David Euhus
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  - British Columbia: Stephen Chia

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- **Funding:** Safeway, Bill Bowes, Quellines, HJ. Genentech, AstraZeneca, Genentech, the Broad Institute, Seattle Cancer Care Alliance, Merck

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