I-SPY 2 Clinical Trial
A Replicable Model for Accelerating Drug Development and Approval
What problem are we solving?

- New oncology drugs take 10-15 years to reach patients
- Price tag is $2 billion
- Absence of innovation in trial design/data collection tools
- Cancer is a subset of diseases
- Blockbuster approach won’t work

Current path is UN-SUSTAINABLE
Five Critical Components:

- Neoadjuvant Setting
- Molecular and Imaging Biomarker Guidance
- Multiple Drugs Tested Simultaneously
- Common Platform for Sharing Data
- Adaptive Trial Design

The Right Drug for the Right Person at the Right Time
The “Neoadjuvant” Approach Dramatically Accelerates Knowledge Turns

Metastatic Approach: 2 to 4 year knowledge turn
Adjuvant Approach: 6 to 9 year knowledge turn

Neoadjuvant Approach: 1 year knowledge turn
I-SPY 2 TRIAL Changes the Paradigm

**Five Critical Components:**

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Molecular biomarkers or gene signatures separate out tumor types.
Every tumor is profiled in I-SPY 2 so we can determine which drugs work for each tumor type.
Molecular Biomarkers Tell Us About Tumor Type
Imaging Biomarkers Tell Us Who is Responding

Pre Treatment

Complete response

Partial response

Progressive disease

Post Treatment
Generating Companion Diagnostics

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

FDA Cleared or Approved Stratification/randomization

Hypothesis Testing
Hypothesis Generating
I-SPY 2 TRIAL Changes the Paradigm

Five Critical Components:

- Neoadjuvant Setting
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The protocol and the Master IND* enable seamless addition and release of investigational agents. When an investigational agent is added to or released from the trial, only appendices require updating.

- **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.
Five Critical Components:

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• Adaptive Trial Design
I-SPY 2 TRIAL Changes the Paradigm

**Five Critical Components:**

- Neoadjuvant Setting
- Molecular and Imaging Biomarker Guidance
- Multiple Drugs Tested Simultaneously
- Common IT Platform for Sharing Data
- Adaptive Trial Design
Advantages of Adaptive Design

• Learn if the drug works better or worse than you think, as the trial progresses

• Act early
  – Drop drugs quickly if they are ineffective or harmful
  – Graduate sooner if they are clearly beneficial

• Learn, for each drug, which biomarkers are optimal

• Phase 2 conclusions will be more accurate, better treatment of patients in the trial

• Follow on 3 trials can be smaller (usually)
I-SPY 2 Participating Organizations

Sponsor and Management

Funders

Biomarker Device Providers
I-SPY 2 Goal: Optimize Success of Phase 3 Trial

- Test agents where they matter most
- Learn rapidly to tailor agents
- Drive organizational efficiency
- Use team approach
- Adaptive Trial Design
- Reduce time to market, cost of trials, accrual
I-SPY 2 Major Accomplishments

• Demonstrated that 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
• Accelerated Approval guidance issued by FDA
• Next Step: I-SPY 3 international confirmatory trial
I-SPY 2 → 3 TRIAL

I-SPY 2
drug screening trial

I-SPY 3
confirmatory trial

FDA Accelerated
Full drug approval

Esserman and Woodcock  JAMA. 2011;306(23):2608-2609
What is I-SPY 3?

- **Standing phase 3 trial**
  - Open label trial (not double blind)
  - International collaboration

- **Model to improve efficiency, decrease cost**
  - Adapt accrual number based on pCR signal
  - One trial for both pCR and EFS endpoint
  - Electronic data capture, predefined data collection plan

- **Goal is FDA Accelerated Approval within 3-5 years**
  - Shave time from start of phase 2 (first ever) to finalized accelerated approval
I-SPY 2 Projected Cost

- 6 years
- 7 drugs
- 822 patients
- 20 Sites

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**Self-Sustaining Strategy:**

- FDA Guidance offers a path to registration for new drugs
- New drugs entering I-SPY 2 will be cost neutral
- Developing I-SPY 3 for Phase 3 confirmatory trial
I-SPY 2/3 Partnership Opportunities

• Collaboration with other therapeutic areas to propagate I-SPY methodology
  – Assist in setting up research networks
  – Sharing of systems & technologies

• Seeking partners for I-SPY 3 Trial
  – Investors
  – Research networks
  – Delivery partners
Everyone working as a team

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<td>Local Sites</td>
<td>Collectively working together on trial regulatory challenges</td>
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<td>Local IRBs</td>
<td>Don Berry, Laura Esserman</td>
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<td>Imaging</td>
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<td>Imaging</td>
<td>Angie DeMichele</td>
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