Recent Developments in Therapeutic Efficacy

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disclosure: co-founder, stockholder Agendia Inc

JCCNB
Nov 2012
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 many targeted agents are lacking
An historically fatal disease that has been turned into a chronic condition

LESSONS FROM CML
CHRONIC MYELOID LEUKEMIA
Important Observations with Targeted Therapy in Chronic Myeloid Leukemia

*The world according to Hagop Kantarjian, M.D*

- Optimal biologic-clinical dose (OBCD), not MTD
- Not all Tyrosine Kinase Inhibitors (TKIs) are equivalent: target matters; targeting agent equally important
- More potent targeted benefit
- Cancer cells may not be that smart
- Mutations as mechanism of resistance
- Early intervention yields best results
- Achieving deeper levels of minimal residual disease beyond critical threshold may not improve outcome; concept of “functional” cure rather than molecular cure
Survival in Accelerated and Blast Phase CML Diagnosed in Different Calendar Years

Accelerated Phase  

Blast Phase

Testing new agents in the metastatic setting may NOT be optimal

Population-Based CML Outcome in Sweden Overview Comparing Different Calendar Years

3173 pts Dx in 1973-2008; median age 62 yrs

Bjorkholm, JCO 29: 2514; 2011
Breast Cancer Patients at Risk for Systemic Recurrence – Problems/Opportunities

• 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
Systems Biology—at the Macro Level

- Cellular Interactions and Systems
- Subcellular Systems and Technologies
- Organism, collection of persons
- Clinical Systems Organization/Integration (high functioning microsystem)
- Branding
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

MRI Core biopsy  \(\rightarrow\) MRI Core biopsy  \(\rightarrow\) MRI

RFS at 3-Yrs  pCR, RCB Surgery
I-SPY 1 Biomarker Platforms

Establishing tissue acquisition standards across sites

Tissue: Core or Surgical

H&E, IHC, FISH

Expression Arrays

p53 GeneChip

Protein Arrays (RPMA)

<table>
<thead>
<tr>
<th>UNC, Penn</th>
<th>UNC, UCSF, NKI</th>
<th>UNC</th>
<th>GMU</th>
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CGH

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<tr>
<th>Serum</th>
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<td>Id1 proteins autoantibodies phospho proteins</td>
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Genome location

[Diagram showing genomic locations and expression patterns]
Longest Diameter, Volume, Signal Enhancement Ratio
Tumor volume based on the Signal Enhancement Ratio (SER)

**ENHANCEMENT KINETICS:**

\[
PE = \frac{\Delta S_1}{S_0}
\]

\[
SER = \frac{\Delta S_1}{\Delta S_2}
\]

Significant Volume change after one cycle predicts pCR
pCR overall and by subset

ALL (n=172)
pCR performs much better when evaluated in the context of subsets as compared to overall group

<table>
<thead>
<tr>
<th>Population</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Absolute Difference in RFS at 3 yrs</th>
<th>Absolute Difference in RFS at 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=172)</td>
<td>0.29</td>
<td>0.02</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>HR+ HER2- (n=93)</td>
<td>0.00</td>
<td>0.04</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>HR-HER2- (n=50)</td>
<td>0.25</td>
<td>0.04</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>HER2+ (n=29)</td>
<td>0.14</td>
<td>0.05</td>
<td>26%</td>
<td>42%</td>
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</table>
Refine the Selection: Enhance the signal (Outcome after NeoAdjuvant therapy)

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)

- All 11 have no pCR, though outcome excellent
- Log rank p = 0.048

Degree of Residual Disease Determines Outcome

- RCB0 (36)
- RCB1 (11)
- RCB2 (54)
- RCB3 (23)

Subset Excluding 70-Gene Low Risk Stratified by RCB (124)

- no substantial
- log rank p < 0.0001
Findings from I-SPY 1

- Patients in I-SPY 1 are most at risk of relapse, death
  - 91% of I-SPY patients had poor risk biology- (> 3cm tumors)

- pCR (and RCB – residual cancer burden) are highly predictive of outcome
  - Stronger predictor when analyzed by subgroup (Simpson’s Paradox)
  - Can be used as trial endpoint for evaluation of novel agents.

- MRI Volume change is a non-invasive way to predict pCR and RCB 0,1
  - Standard developed for MRI volume change→ automated in I SPY 2
Receptor Subtypes and Expression Profiles do NOT predict which patients within the subtypes will have a pCR

WHAT CAN WE LEARN AND USE FROM EMERGING SCIENCE?
Genomics as response predictor

- **Basic Science → Phase 1 Trial → I SPY 2**
- MYC Pathway Activation in Triple-Negative Breast Cancer is Synthetic-Lethal with CDK Inhibition (Goga)

1. MYC pathway activation predicts outcome for TN BC with residual disease after neoadjuvant chemotherapy

![Graph showing Myc Pathway: Low, Intermediate, High](image)

- Fraction disease free over time (years)
- Low, medium, high pathways
- p < 0.001

2. Small molecule CDK inhibition induces regression in MYC activated TN xenografts

- [Comparison of vehicle and dinaciclib](image)
- Phase 1b Dinaciclib 2011, Jo Chien PI

Tumor Microenvironment Could Be a Target to Overcome Poor Outcome

The combination of low Tcell/class 2 expression and high PCNA+ Tumor Associated Macrophages could explain VERY poor outcome in patients with residual disease after neoadjuvant treatment.

All cases: HR neg cases only

- low Tcell
- high TAM

p = 2.8E-05

p = 0.003
Strategies for High Risk Cancers

- Target the tumor immune environment
  - Drugs that target macrophages, e.g.
    - cfms inhibitor: Plexxikon; Amgen, IMCLONE, others
  - Drugs that reprogram the immune environment
    - T cell activation, T Regulatory Cell, NK activators: Pfizer

- Target Myc
  - CDK inhibitors: Merck

- Target Stem Cell Targets e.g. Notch, Wnt
  - Notch inhibitors: Oncomed/GSK; Merck; others

- Target PI3K:
  - TORQ 1/2 (Intellikine/Millenium)

- Target HER2:
  - TKIs, Ab toxin conjugates, Her-2/3 bivalent antibodies
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 is a Clinical Trial Process

Re-engineering of clinical care, clinical trial:

• Care
  – Neoadjuvant Setting
  – Molecular and Imaging Biomarker Guidance

• Trial
  – Adaptive Design
  – Real time data capture
  – Common Platform for Sharing Data
  – Operational Efficiency
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

• Reduce the cost, time, and numbers of patients needed to get effective drugs to market through accelerated approval
I-SPY 2 Adaptive Trial Design

**Consent #1**
- Screening
- MRI
- Biopsy
- Blood Draw
- MUGA/ECHO
- CT/PET

**Consent #2**
- Treatment Consent
- MRI
- Biopsy
- Blood Draw

**STUDY**

**RANDOMIZE**

**Paclitaxel**
- (12 weekly cycles)
- (12 weekly cycles)
- (12 weekly cycles)

**Paclitaxel +**
- Investigational Agent A
- Investigational Agent B

**AC**
- (4 cycles)
- (4 cycles)
- (4 cycles)

* 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

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

Pre Treatment

Post Treatment

Nola Hylton, PhD
UCSF Radiology and Biomedical Imaging,
- Sentinelle Aegis workstations provided to all I-SPY 2 sites
- Image data transfer from scanner to Aegis immediately after exam
- Volume computation performed by technologist or RA
- Radiologist confirmation obtained
- Image Data sent to ACRIN TRIAD
- Numerical volume data sent to I-SPY Statistical Center
- *IDE part of IND for agents being evaluated*
I-SPY 2 Adaptive Trial: Information gathered in real time for several agents

**Patient is on Study**

**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

**Key**

- MRI
- Residual Disease (Pathology)

**Surgery**

Learn, Adapt from each patient as we go along

**AC**

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

Key

- MRI
- Residual Disease (Pathology)

**HER 2 (+)**

- Paclitaxel + Trastuzumab
- Paclitaxel + Trastuzumab* + New Agent A
- Paclitaxel + Trastuzumab* + New Agent B
- Paclitaxel + Trastuzumab* + New Agent F

**HER 2 (−)**

- Paclitaxel
- Paclitaxel + New Agent F
- Paclitaxel + New Agent GH
- Paclitaxel + New Agent E

Randomize

Surgery

Learn and adapt from each patient as we go along

*Or equivalent
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): 
  \(B_1, B_2, ..., B_{256}\)

- 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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<td>HR-</td>
<td>HR+</td>
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<tr>
<td>HER2+</td>
<td>16%</td>
<td>7%</td>
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<td>HER2-</td>
<td>23%</td>
<td>6%</td>
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MammaPrint Hi-1 and Hi-2 is based on the median cut point of MammaPrint for I-SPY 2 eligible patients
Biomarker Signature #1: All

Projected frequencies based on I-SPY 1:

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MP: MammaPrint 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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MP: MammaPrint High 1 or High 2  
HR+: Hormone Receptor+: Either ER+ or PR+
### Biomarker Signature #3: HR-

Projected frequencies based on I-SPY 1:

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51%
### Biomarker Signature #4: HER2+

Projected frequencies based on I-SPY 1:

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MP: MammaPrint High 1 or High 2
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37%
Biomarker Signature #5: HER2-

Projected frequencies based on I-SPY 1:

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MP: MammaPrint High 1 or High 2
HR+: Hormone Receptor+: Either ER+ or PR+

63%
### Biomarker Signature #6: MP2

Projected frequencies based on I-SPY 1:

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MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+
Biomarker Signature #7: HR-HER2-

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34%
Biomarker Signature #8: HR-HER2+

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17%
## Biomarker Signature #9: HR+HER2+

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Biomarker Signature #10: HR+HER2-

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I-SPY 2 Adaptive Trial Schema: Screening & Randomization

Eligibility Assessment Process:

Patient presents with newly diagnosed ≥ 2.5cm invasive tumor

Core biopsy to assess eligibility

Eligibility determined by:
- Ability to tolerate MRI
- Ability to generate 44k Agilent microarray

Patient On Study
Randomized to treatment arm based on:
- ER, PR status
- HER2 Status
- MammaPrint score
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

• Biomarker IDE as part of Drug IND facilitates companion diagnostic FDA PMA approval
First part - ‘Learning’
random randomization and observation

At start of trial:
patients randomly
assigned to arm

all experimental arms
plus standard chemo
First part - ‘Learning’
random randomization and observation

At start of trial: patients randomly assigned to arm

At entry of trial: patients tumor biology assessed, ER, PR, Her2, MammaPrint-index (stratified per arm)

count=standard chemo
eperimental drug 1
eperimental drug 2
eperimental drug 3
eperimental drug 4

patients

control=standard chemo
experimental drug 1
experimental drug 2
experimental drug 3
experimental drug 4

type 1 e.g. Triple negative
type 2 e.g. ER pos MammaPrint-very high
type 3 e.g. ER pos

type 10
At start of trial: patients randomly assigned to arm

At entry of trial: patients tumor biology assessed, ER, PR, Her2, MammaPrint-index (stratified per arm)

At surgery: tumor response assessed (pCR=X) and evaluated for biology specific association

First part - ‘Learning’ random randomization and observation

control = standard chemo
experimental drug 1
experimental drug 2
experimental drug 3
experimental drug 4

patients

control = standard chemo
experimental drug 1
experimental drug 2
experimental drug 3
experimental drug 4

control = standard chemo
experimental drug 1
experimental drug 2
experimental drug 3
experimental drug 4

control = standard chemo
experimental drug 1
experimental drug 2
experimental drug 3
experimental drug 4

all experimental arms plus standard chemo

type 1
response drug 2

type 2
response drug 1

type 3

At entry of trial: assigned randomization based on patients tumor biology, ER, PR, Her2, MammaPrint-index
Biology type 2 -> drug 1 or control
Biology type 1 -> drug 2 or control

all experimental arms plus standard chemo
Continued in to - ‘Adaptive’ part
assigned randomization and evaluation

At entry of trial: assigned randomization based on patients tumor biology, ER, PR, Her2, MammaPrint-index
Biology type 2 -> drug 1 or control
Biology type 1 -> drug 2 or control

At surgery:
tumor response assessed (pCR=X) and evaluated for biology specific association

• endpoint is pCR
• “threshold” is 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair
• anticipated 100-120 patients needed per arm to find successful drug-biomarker combination or a failure
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
Qualifying Biomarker Plan

• per each investigational agent qualifying biomarker workplans are being developed, compilation of qualifying biomarker concepts
  – phosphoprotein signature
  – gene expression signature
  – additional analyses by IHC
  – specific serum markers
  – gene mutations
Qualifying Biomarkers
a Laboratory Finding to a Diagnostic Test

I-SPY 2 provides a Framework for Efficiency:
Quality Control,
Biospecimen handling and Qualifying assays performed under CLIA
Qualifying Biomarker Analysis
Lab 60 Cell Line / Sites Patient treatment/ UCSF tumor tissue

**Trial Preparation**
- I-SPY 2 investigational agents are applied to the 60 OHSU Breast Cancer Cell Lines evaluated using the Comprehensive Genomics Analysis
- Cell lines are evaluated based on response to agents to predict effectiveness of the agents by cell line

**Participant Treatment**
- Biopsy is taken from the trial participant’s tumor and predictive gene expression profile generated using Comprehensive and ‘Targeted’ Assays in a CLIA certified lab
- Trial Participants are treated with an investigational agent based on trial randomization
- Results of treatment on participants are evaluated

**Post-Treatment Analysis**
- Actual participant responses are compared to predicted responses based on cell line signature
Cancer Kinase Phospho Signature: Kinase Activity Measurement from Cell Extracts

Non-malignant (S1) and Malignant (T4)

Mixture of cell extract + Peptide + ATP

Kinase-Glo reaction

Reaction time

Measure Luminescence

Miki Kuroda Showa Univ/UCSF and Jean-Philippe Coppé UCSF

% ATP consumption of added ATP to cell extracts

-10 10 30 50 70

Baseline control (no peptide)

Control peptide (negative control)

Positive control (TK target)

EGFR target site (Src target)

AKT1 target site (Src target)

ABL1 target site (Src target)

AFAP1 target site (Src target)

STAT3 target site (Src & Hck target)
Participating Trial Sites
Trial Enrollment Overview

Registered (n=543)

Excluded (n=235)
- MammaPrint low risk, ER+, HER2-(n=79)
- Declined participation (n=54)
- Unable to obtain MammaPrint microarray (n=58)
- Unable to complete MRI (n=4)
- At investigator’s discretion (n=7)
- Did not meet eligibility criteria (n=33) [abnormal lab values (7); metastatic disease (15); other (n = 8)].

Actively Being Screened (n=22)

Randomized (n=286)

Completed Surgery (n=199)

Status as of October 15, 2012
Investigational Agent Pipeline

**Active/pending activation**

- **4 months**
  - ABT 888 (PARP Inhibitor)
  - Neratinib (Pan ErbB Inhibitor)
  - AMG 386 (TIE2 Inhibitor)
  - Anti-IGFR inhibitor + Metformin

- **9 months**
  - AKT inhibitor
  - Her-2 Targeted Combinations
  - PI3K inhibitor

- **12+ months**
  - CDK Inhibitor
  - Aurora Kinase Inhibitor

**Combinations of agents**

**Companies with signed/signing contracts:**
- Abbot, Pfizer, Amgen, Intellikine, Merck, Puma

**Companies in discussions:**
- Genentech, Millenium, Bayer, Oncomed, Merrimack, J&J, Daiichi, Plexxicon, Boehringer, Novartis
I-SPY 2 Participating Organizations

- Foundation for the National Institutes of Health
- BioMarkers Consortium
- Quantum Leap
- A Healthcare Collaborative
- UCSF
- University of California
- San Francisco
- Abbott
- A Promise for Life
- Genentech
- A Member of the Roche Group
- AMGEN
- MERCK
- Be well
- Takeda
- Millennium
- The Takeda Oncology Company
- Pfizer
- Puma Biotechnology
- Sentinelle
- Hologic
- The Women's Health Company
- UCSF
- Oregon Health & Science University
- Berkeley Lab
- Lawrence Berkeley National Laboratory
- George Mason University
- Theranostics Health
- The Partner of Choice for Personalized Medicine
- Agendia
- Decoding Cancer
Current Approach:
10-20 years for Adjuvant Drug Approval
$1-2 Billion per drug

What conditions could enable dramatic improvements in knowledge turns?
And take real time off the clock
What conditions could enable dramatic improvements in knowledge turns?
*Take real time off the clock*

A. Current Development Pathway

**Metastatic Setting**

- Phase 1 & 1B
- Phase 2
- Phase 3

**Adjuvant Setting**

- Surgery
- Chemo
- Accrual
- Phase 3
- Follow-up

B. Development Pathway

**Metastatic Setting**

- Phase 1 & 1B

**Neoadjuvant Setting**

- In high risk adjuvant setting

**Follow-up**

- Early signal

**Accelerated Approval**
Paradigm Shift: pCR as endpoint

Accelerating Identification and Regulatory Approval of Investigational Cancer Drugs

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The development of new drugs is becoming increasingly expensive—and oncology drugs, in particular, have a high clinical failure rate. The current return on capital investment in drug development by US public companies was recently reported as less than 0.3%. The low probability of success, coupled with rapidly accelerating expenses, means that drug development is increasingly the purview of only 2 organization types: a few large companies and myriad small, venture capital–funded start-up firms. At an estimated cost of $1.0 billion to $1.8 billion for developing a successful new drug, funding for such risky ventures, particularly for oncology drugs, may diminish.

The high cost of oncology drug development is not only a reflection of processes that are necessary for identifying classes of agents and the subtypes of diseases for which they are effective.

As an example, the I-SPY2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) model was developed as a precompetitive collaboration among multiple academic, pharmaceutical, biotechnology, governmental, and advocate stakeholders. I-SPY2 uses an adaptive design, modular trial process for the purpose of concurrently screening phase 2 agents in women with stage 2 and 3 breast cancer who are at increased risk for cancer recurrence and death despite standard adjuvant treatment. In this setting, pathologic complete response (pCR), measuring the complete disappearance of tumor in response to treatment prior to surgical excision, may predict recurrence-free survival (RFS)—a current regulatory standard for Food and Drug Administration (FDA) approval. The trial evaluates drugs, by class, in the context of standard and emerging biomarkers to determine whether the subgroups can be developed as pCR end points.
A research consortium including academic, pharmaceutical, and other stakeholders conducts a screening trial using a surrogate end point to identify a promising drug and biomarker. Replication of the surrogate end point during a confirmatory trial allows accelerated Food and Drug Administration (FDA) approval for the drug, and approval of the biomarker, while the trial continues through the clinical end point required for full FDA approval.
• Novel and adaptive neoadjuvant clinical trials
  – have begun to define a new regulatory path for investigational agents
  – are expected to improve the efficiency of new drug evaluation
  – accelerate the deployment of targeted agent and biomarker pairs into the adjuvant setting
THE GOAL:

• Learn **EARLY** whether agents/drugs will fail or succeed,

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

• **PREDICT** who will benefit, **PERSONALIZE** using biomarkers
Acknowledgements I-SPY 2

Local Sites
- Coordinating multi-disciplinary teams for 1 study

Local IRBs
- Collectively working together on trial regulatory challenges

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We are continually faced with great opportunities which are brilliantly disguised as unsolvable problems

Margaret Mead