
Kyoto, November 2012

Recent Developments in Therapeutic Efficacy

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disclosure: co-founder, stockholder Agendia Inc

JCCNB
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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

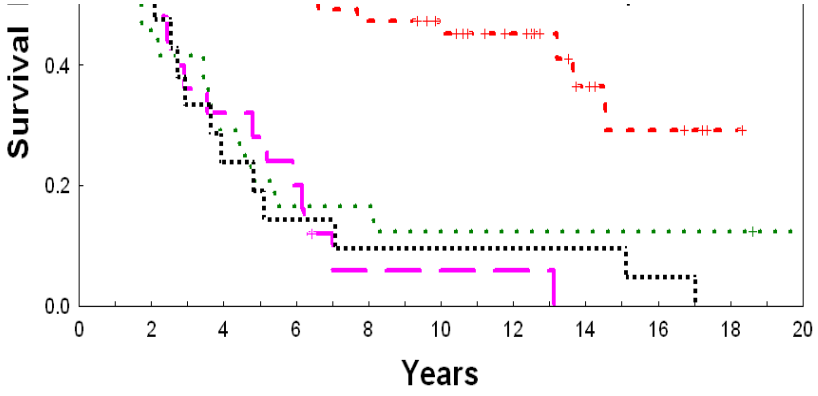
- Optimal biologic-clinical dose (OBCD), not MTD
- Not all Tyrosine Kinase Inhibitors (TKIs) are equivalent: target matters; targeting agent equally important
- More potent targeted benefit
- Cancer cells may not be that smart
- Mutations as mechanism of resistance
- Early intervention yields best results
- 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



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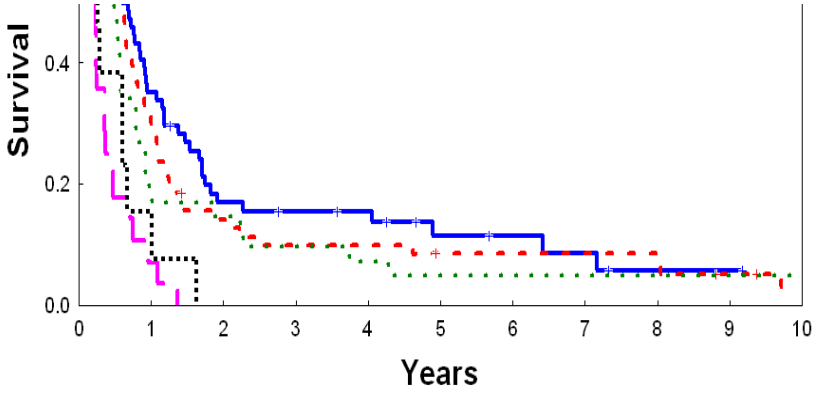

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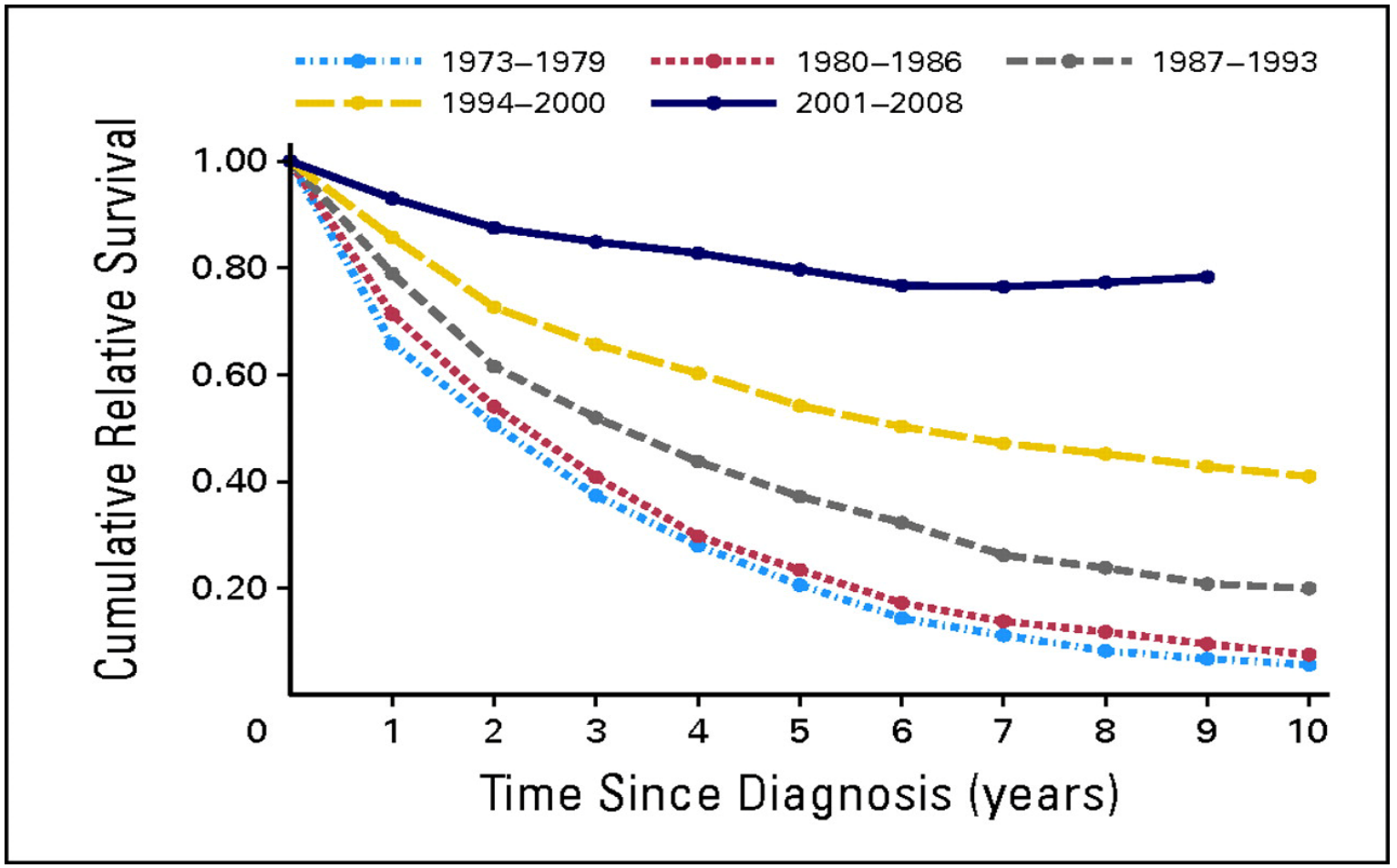
Kantarjian. Blood 119:1981;2012

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

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

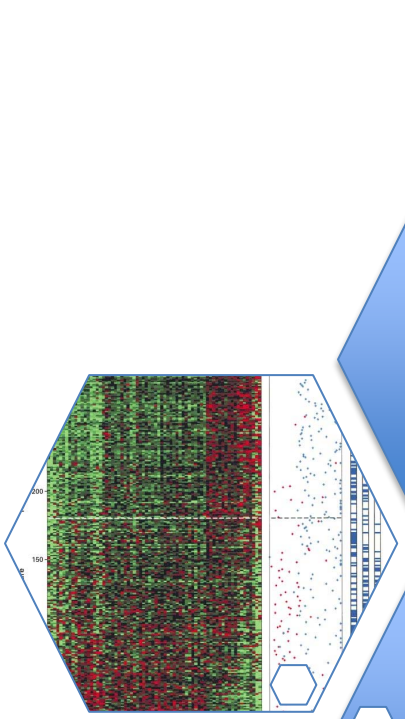


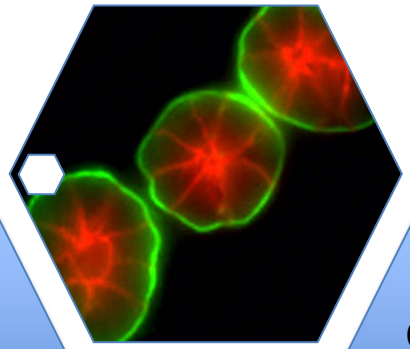
Bjorkholm, JCO 29: 2514; 2011

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

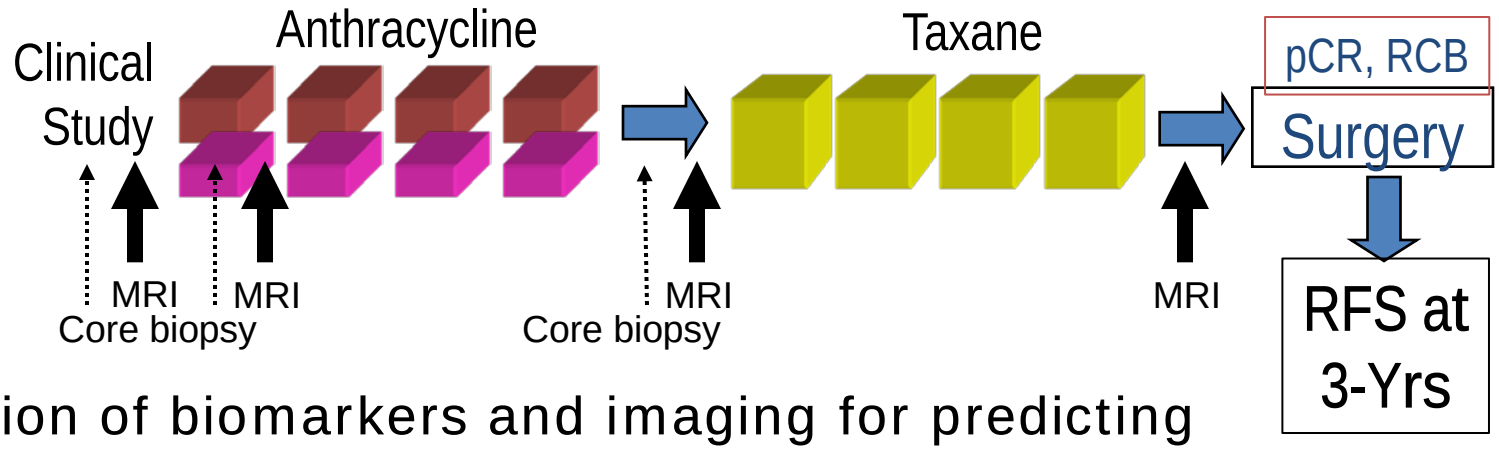
I-SPY TRIAL

Investigation of
Serial studies to
Predict
Your
Therapeutic
Response with
Imaging and Molecular
Ana-
Lysis

I SPY WITH MY LITTLE EYE ... A BIO-MARKER BEGINING WITH X...

I-SPY 1 → I-SPY 2

I-SPY 1
(2002–2008



- Evaluation of biomarkers and imaging for predicting response to standard neoadjuvant chemotherapy

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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

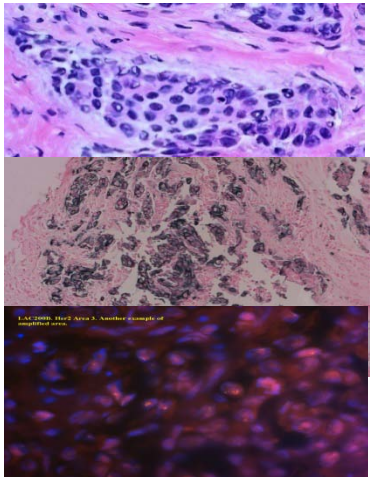
11

I-SPY 1 Biomarker Platforms

Establishing tissue acquisition standards across sites

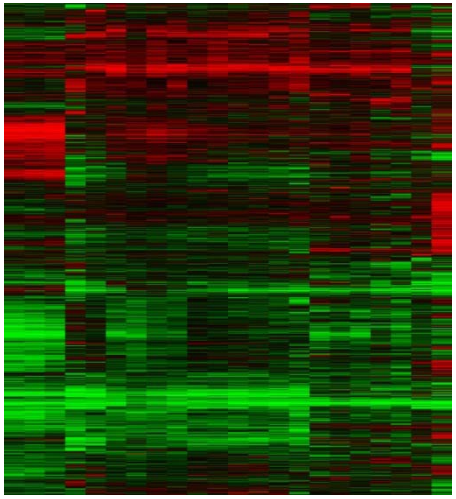
Tissue: Core or Surgical

H&E, IHC, FISH



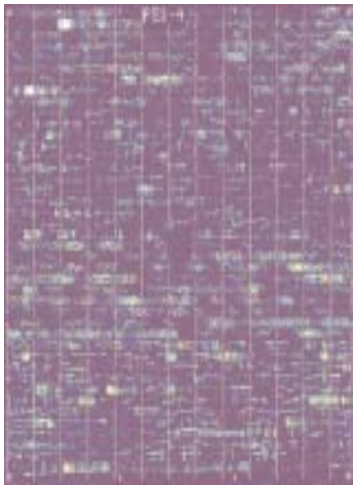
UNC, Penn

Expression Arrays



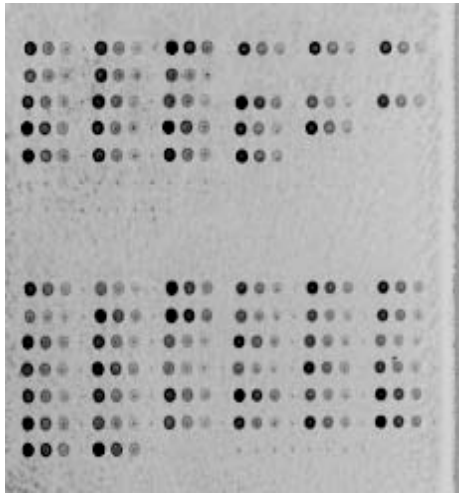
UNC, UCSF, NKI

p53 GeneChip



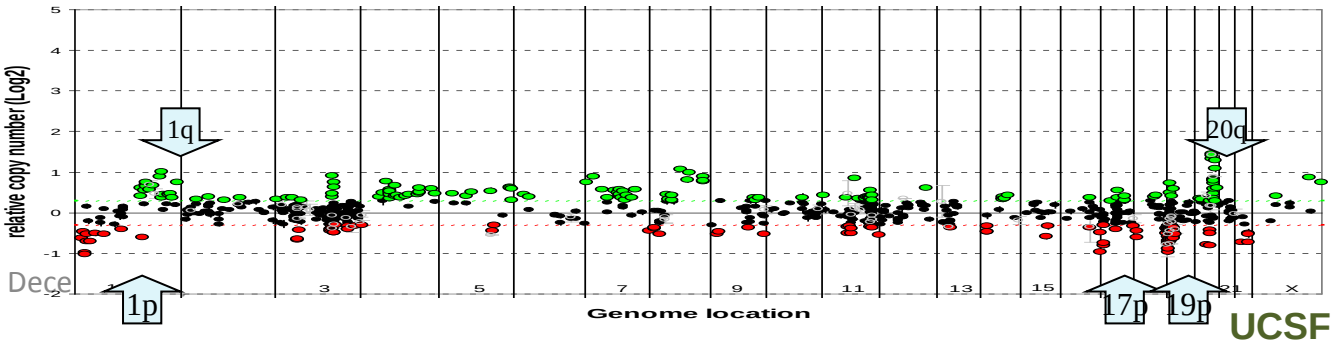
UNC

Protein Arrays (RPMA)



GMU

CGH



UCSF

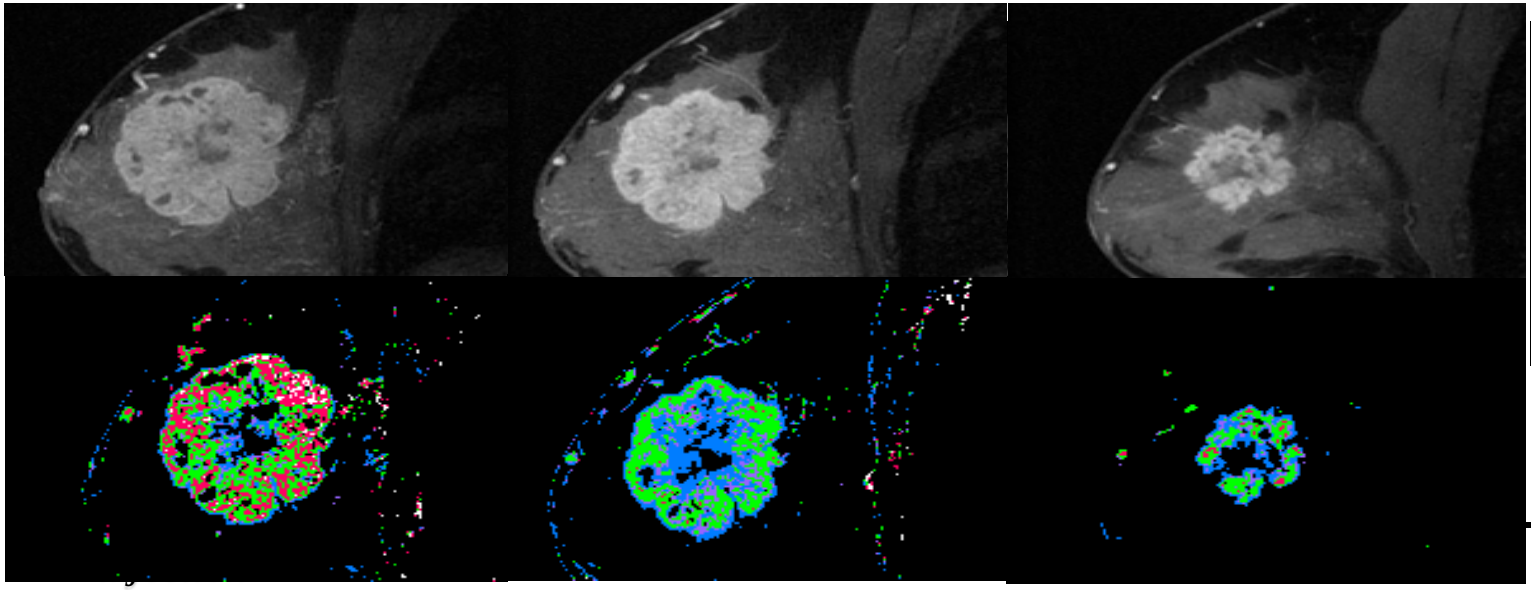
Serum

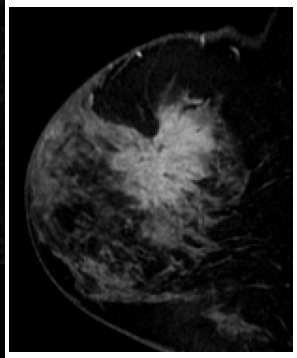
Id1 proteins
autoantibodies
phospho proteins

Longest Diameter, Volume, Signal Enhancement Ratio

Tumor volume based on the Signal Enhancement Ratio (SER)

ENHANCEMENT KINETICS:

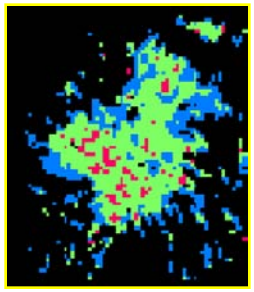




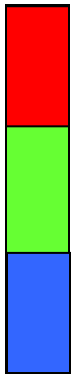
S_2

$$PE = \frac{\Delta S_1}{S_0}$$

$$SER = \frac{\Delta S_1}{\Delta S_2}$$



SER map



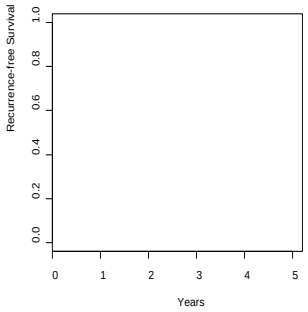
Washout
SER>1.1

Plateau
0.9≤SER≤1.1

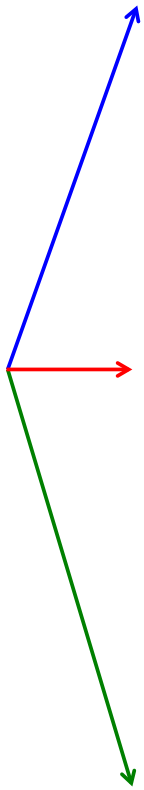
Gradual
SER<0.9

Significant Volume change after one cycle predicts pCR

pCR overall and by subset



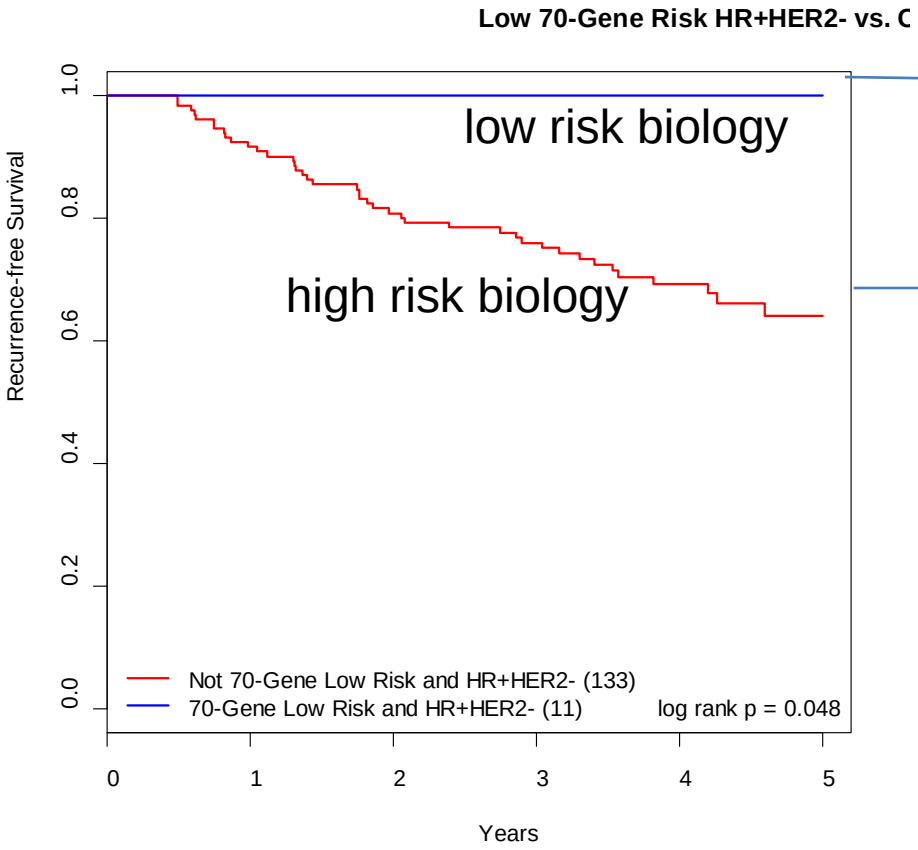
ALL (n=172)



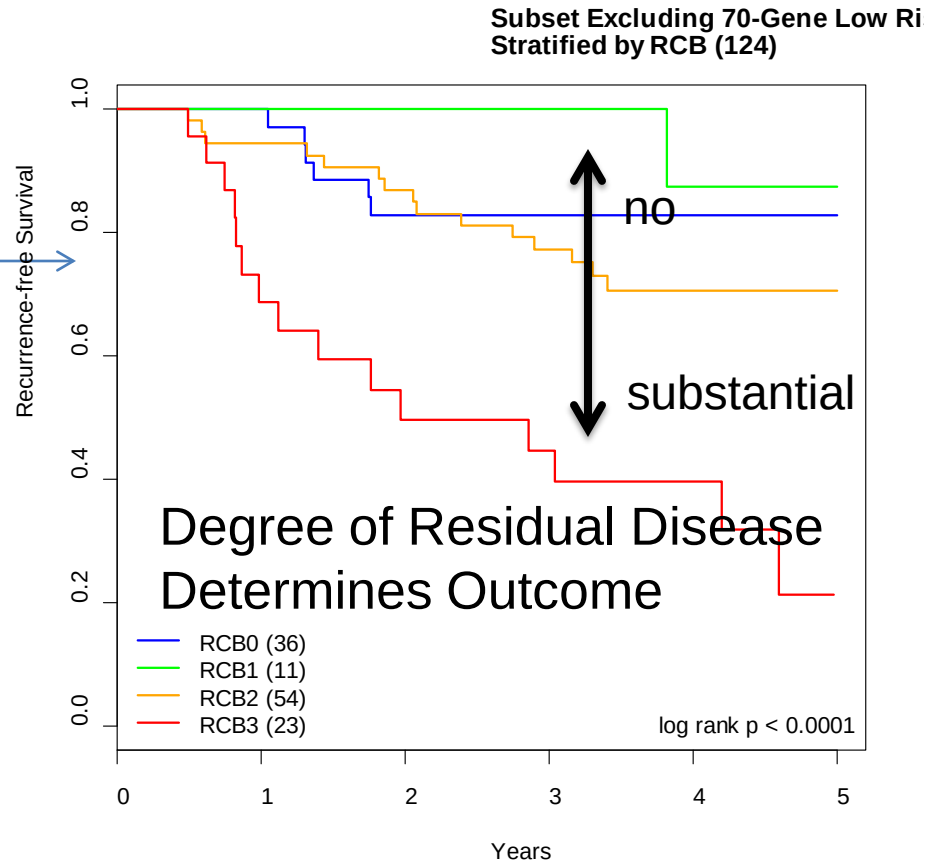
pCR performs much better when evaluated in the context of subsets as compared to overall group

Population	Hazard Ratio (95% CI)	P-value	Absolute Difference in RFS at 3 yrs	Absolute Difference in RFS at 5 yrs
Overall (n=172)	0.29	0.02	16%	23%
HR+ HER2- (n=93)	0.00	0.04	14%	22%
HR-HER2- (n=50)	0.25	0.04	34%	39%
HER2+ (n=29)	0.14	0.05	26%	42%

Refine the Selection: Enhance the signal
(Outcome after NeoAdjuvant therapy)



All 11 have no pCR,
though outcome excellent



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)

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- ($\geq$ 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

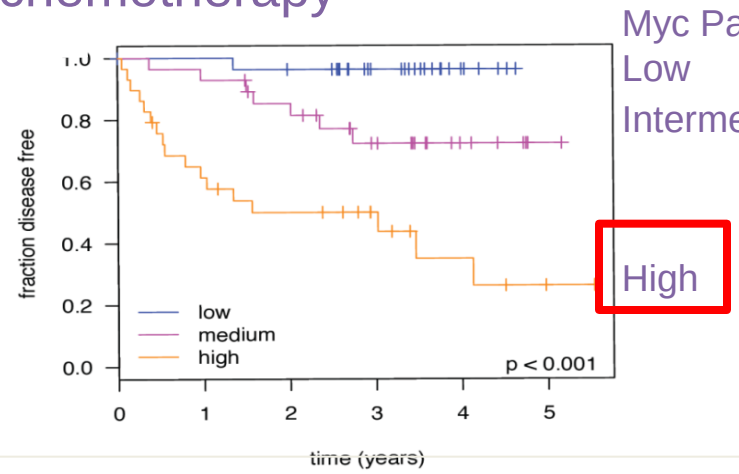
Receptor Subtypes and Expression Profiles do NOT predict which patients within the subtypes will have a pCR

WHAT CAN WE LEARN AND USE FROM EMERGING SCIENCE?

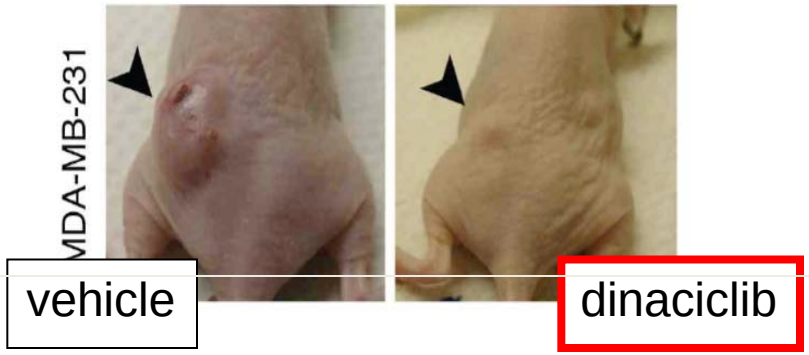
Genomics as response predictor

- ***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



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

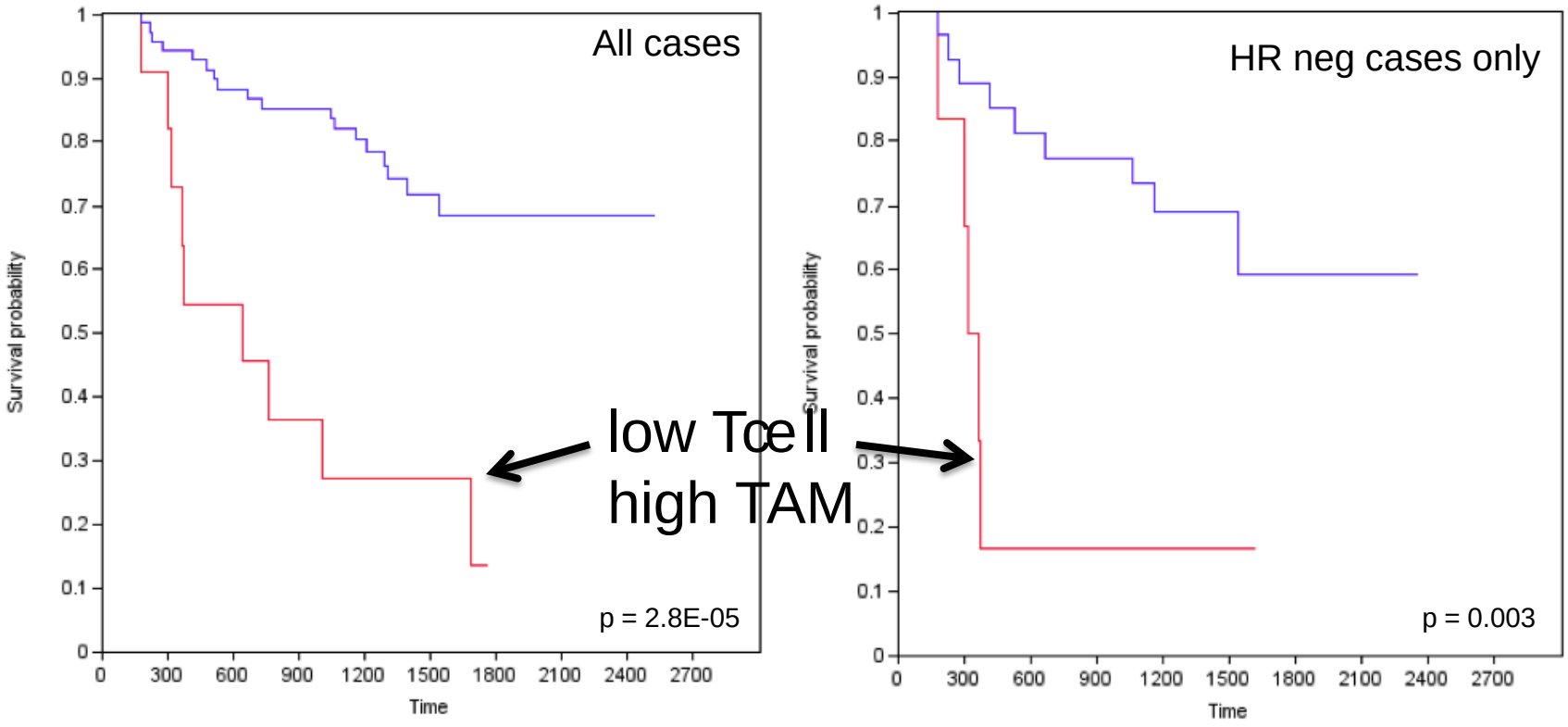


➢ Phase 1b Dinaciclib 2011, Jo Chien PI

Nature Med 2007, J Exp Med 2011

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



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

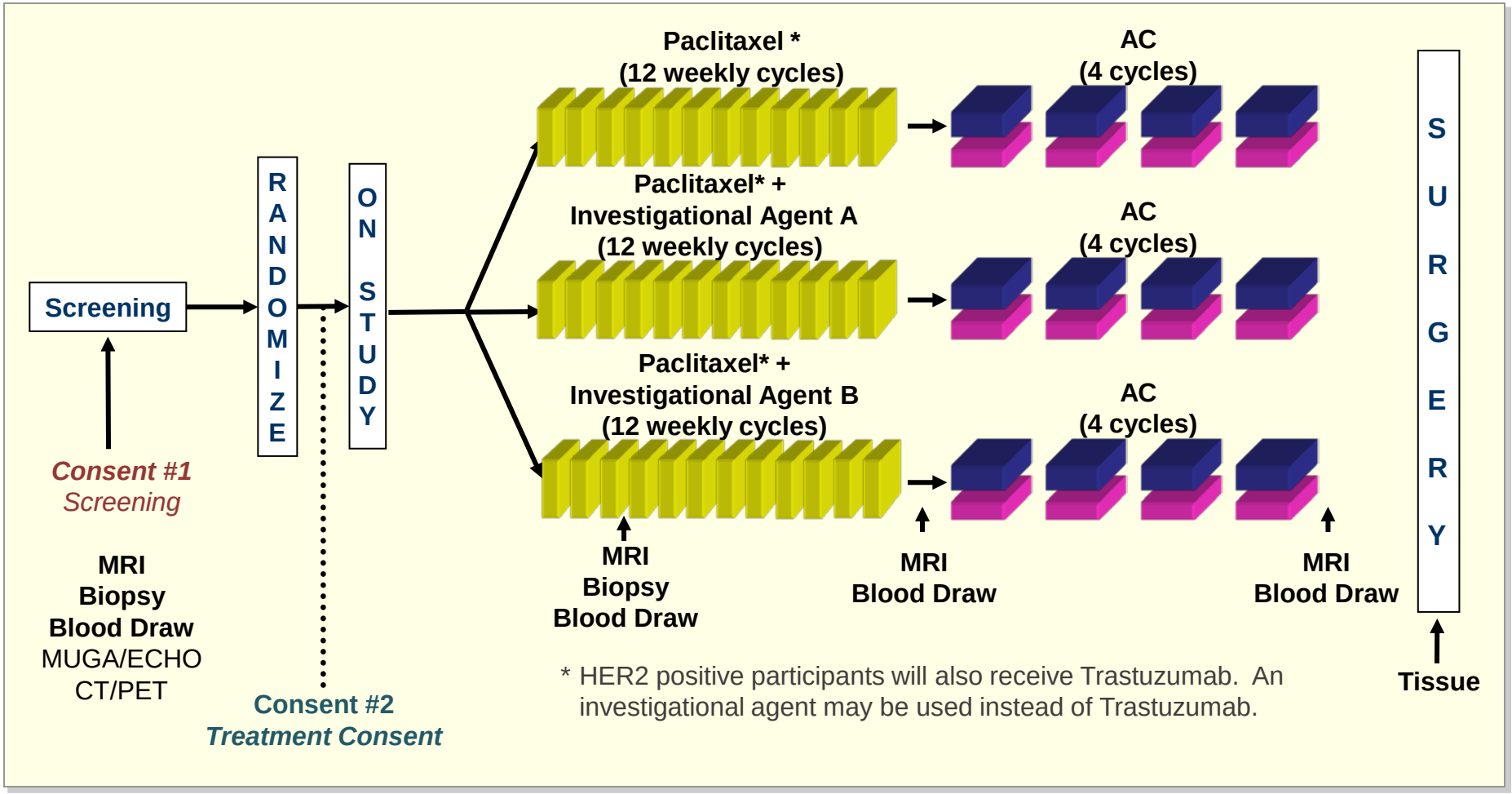
I-SPY 2 is Designed to

- 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

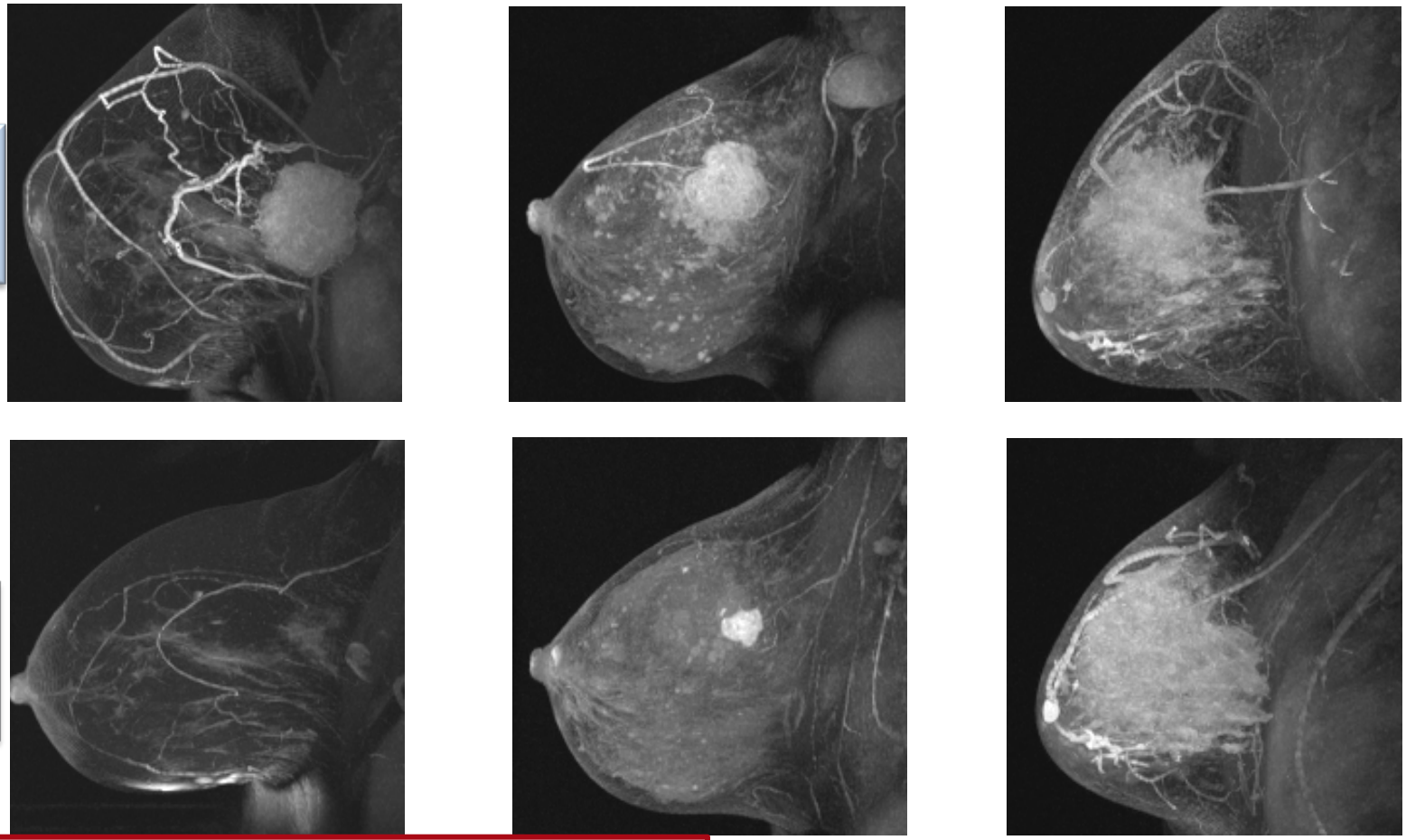
I-SPY 2 Adaptive Trial Design



Imaging Biomarkers Provide Functional Markers of Response, Volume Reduction Over Time

Pre Treatment

Post Treatment

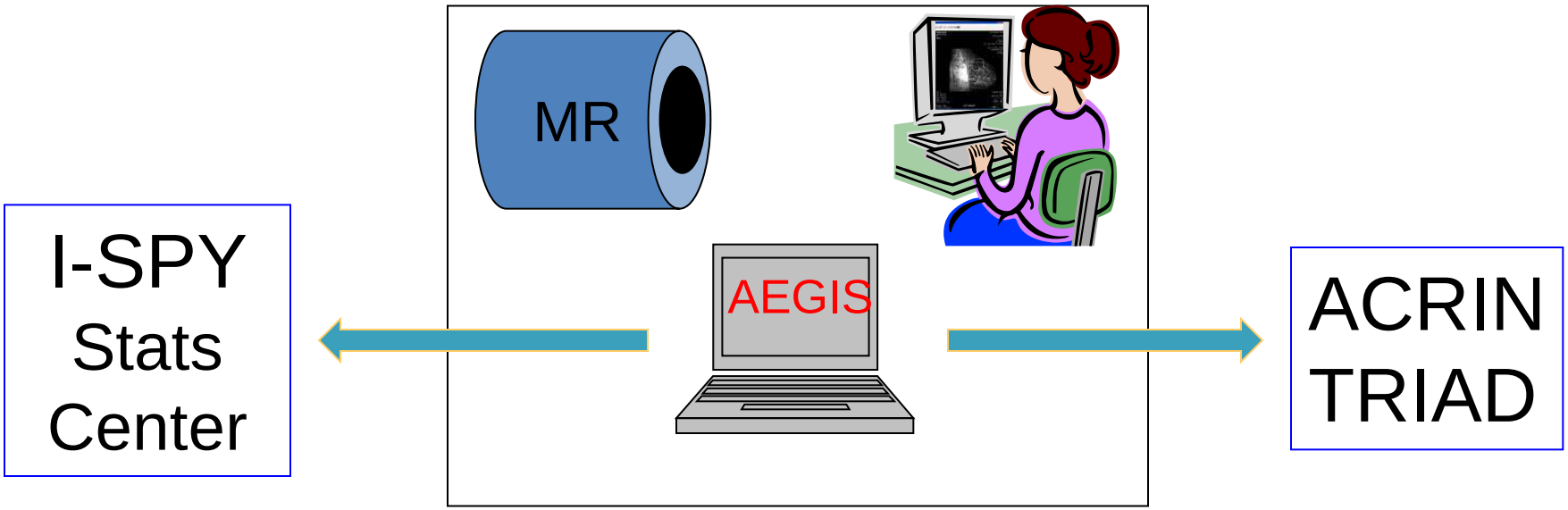


ACRIN 6657: MRI volume best measure (early and late) of pCR, RCB 01

Hylton, Radiology 2012

Nola Hylton, PhD
UCSF Radiology and Biomedical Imaging.

SER Volumetric Analysis in I-SPY 2



- 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

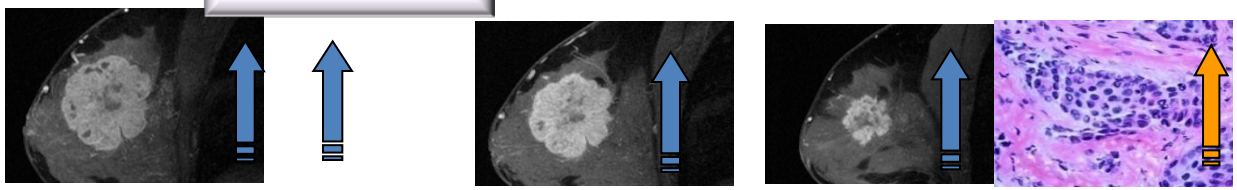
Patient is on Study

HER 2 (+)

Randomize

- Paclitaxell + Trastuzumab
- Paclitaxel + Trastuzumab* + New Agent A
- Paclitaxell + Trastuzumab* + New Agent B
- Paclitaxel + Trastuzumab* + New Agent C

AC → Surgery



Learn, Adapt from each patient as we go along

HER 2 (–)

Randomize

- Paclitaxel
- Paclitaxel + New Agent C
- Paclitaxell + New Agent D
- Pacllitaxel + New Agent E

AC → Surgery

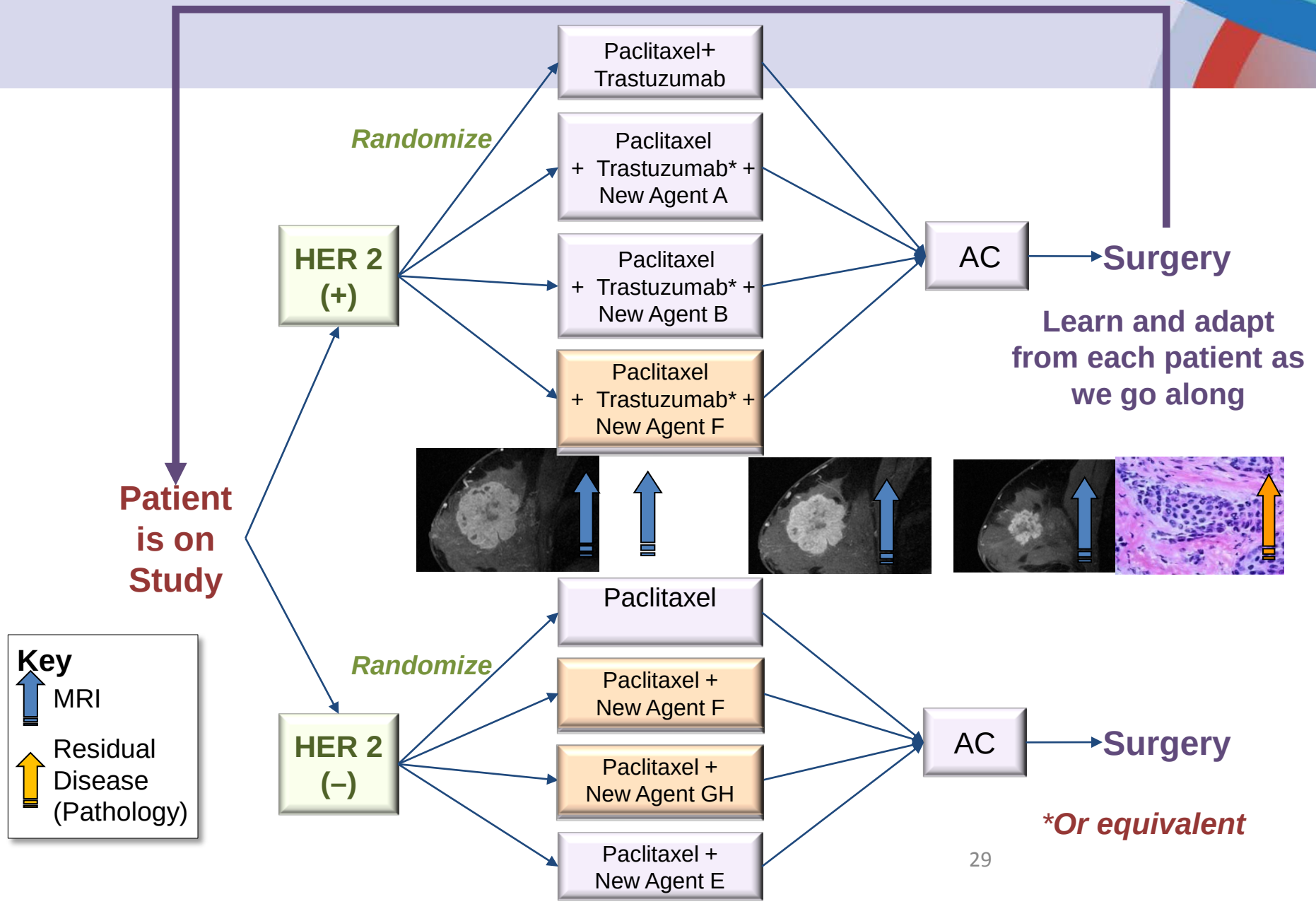
**Key*

MRI

Residual Disease (Pathology)

**Or equivalent*

Learn: Drop, Graduate, Replace Agents Over Time



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:

	MP Hi-1		MP Hi-2	
	HR +	HR-	HR+	HR-
HER2+	16%	7%	4%	10%
HER2-	23%	6%	6%	28%

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:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

100%

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:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

49%

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:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

51%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #4: HER2+

Projected frequencies based on I-SPY 1:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

37%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #5: HER2-

Projected frequencies based on I-SPY 1:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

63%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #6: MP2

Projected frequencies based on I-SPY 1:

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

48%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #7: HR-HER2-

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

34%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #8: HR-HER2+

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

17%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #9: HR+HER2+

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

20%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

Biomarker Signature #10: HR+HER2-

	MP 1		MP 2	
	HR+	HR–	HR+	HR–
HER2+	16%	7%	4%	10%
HER2–	23%	6%	6%	28%

29%

MP: MammaPrint High 1 or High 2

HR+: Hormone Receptor+: Either ER+ or PR+

I-SPY 2 Adaptive Trial Schema: Screening & Randomization

Eligibility Assessment Proc

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

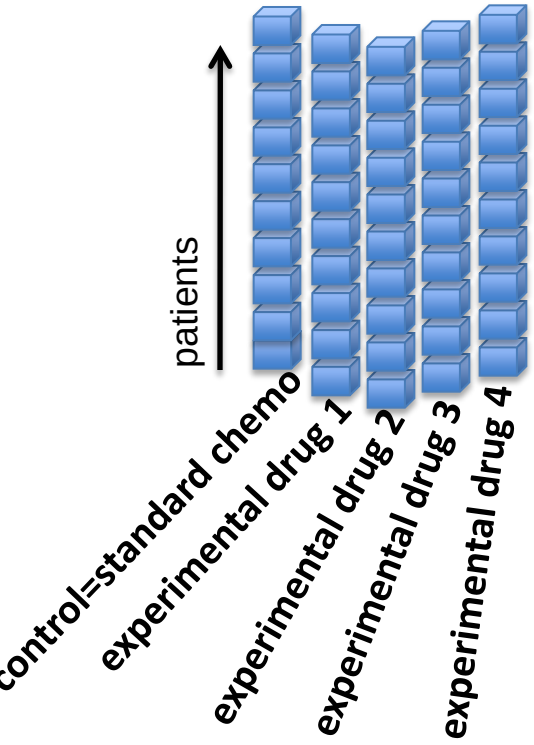
- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established Biomarkers
  - IDE Biomarkers

FDA Cleared or Approved
Stratification/randomization

- 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

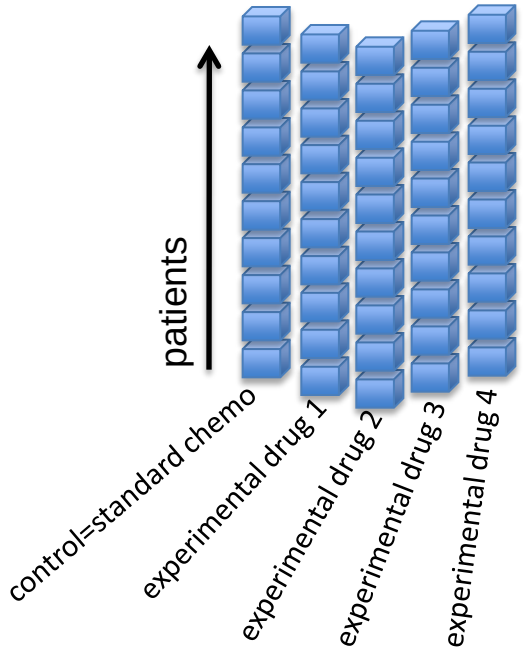


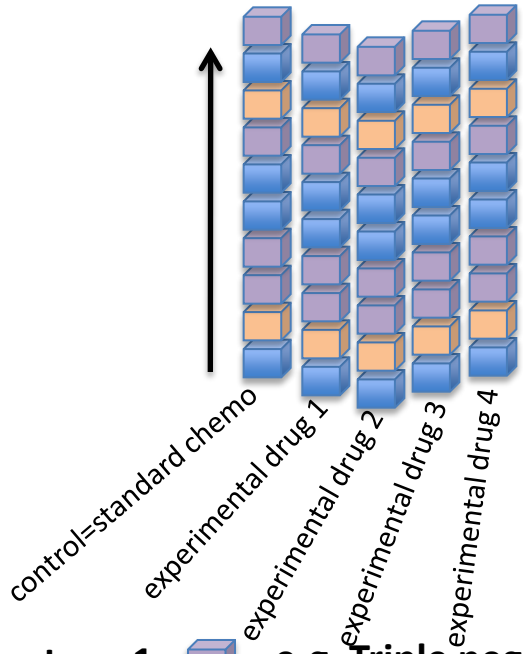
all experimental arms
plus standard chemo

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)





type 1 **e.g. Triple negative**
type 2 **e.g. ER pos MammaPrint-very high**
type 3 **e.g. ER pos**
↓
type 10

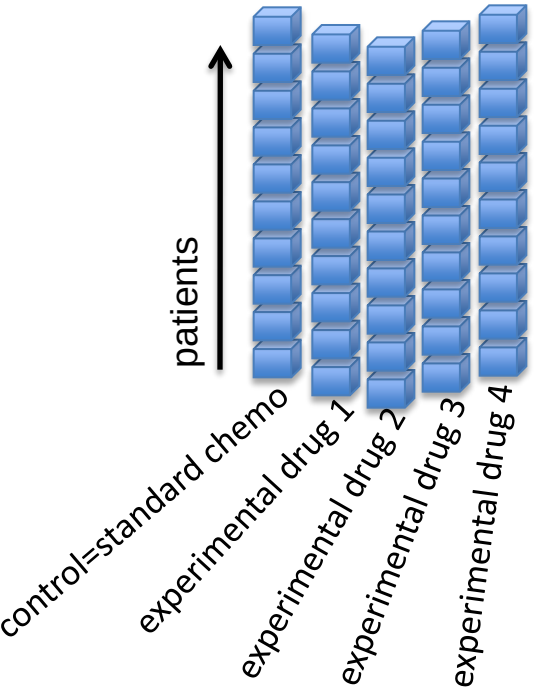
all experimental arms
plus standard chemo

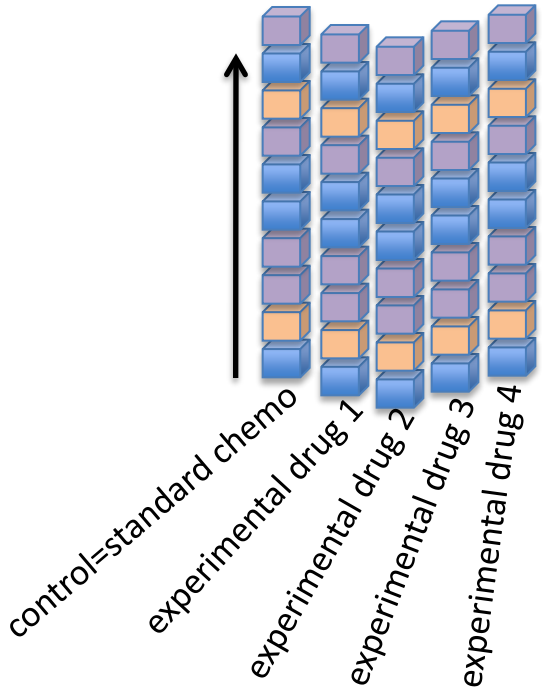
First part - ‘Learning’ random randomization and observation

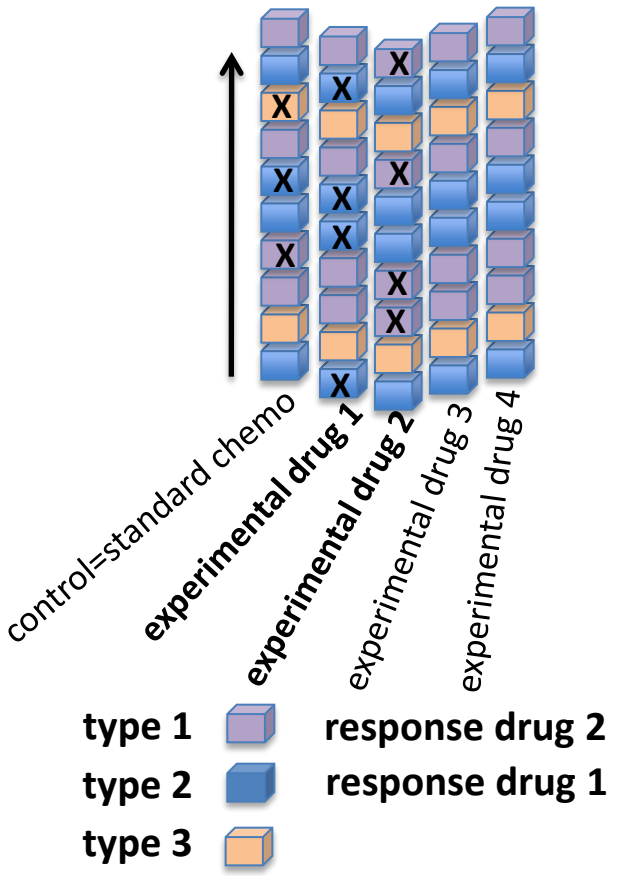
At start of trial:
patients randomly assigned to arm

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

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







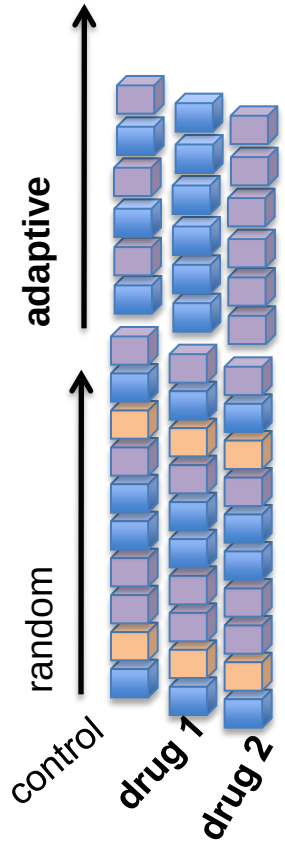
all experimental arms
plus standard chemo

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



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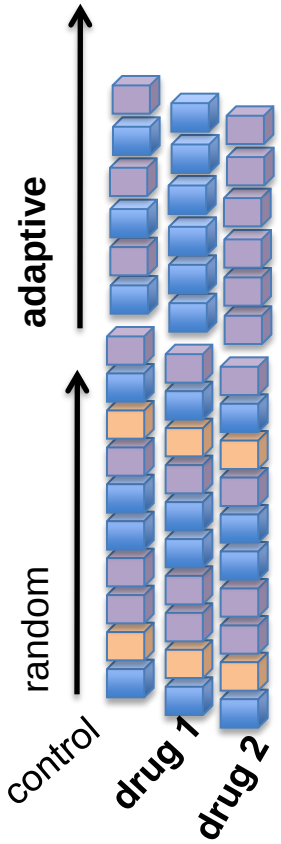
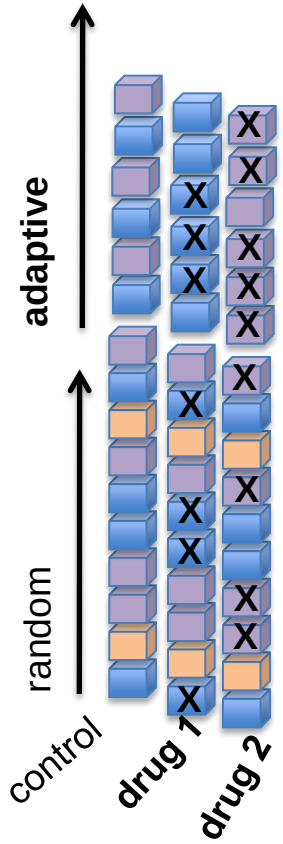


all experimental arms plus standard chemo

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

FDA Cleared or Approved Stratification/randomization

Hypothesis Testing

Hypothesis Generating

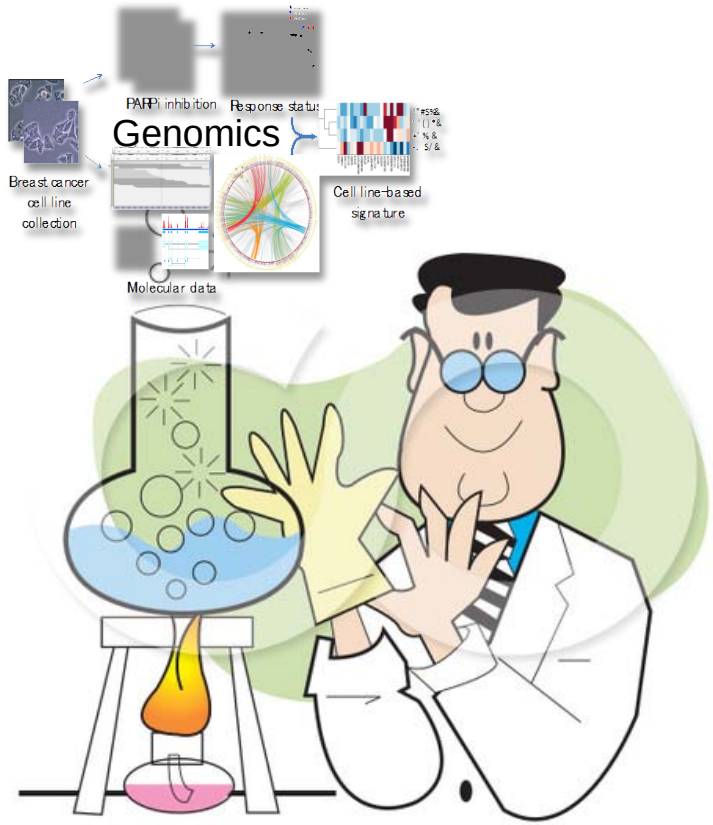
- Biomarker IDE as part of Drug IND facilitates companion diagnostic FDA PMA approval

Qualifying Biomarker Plan

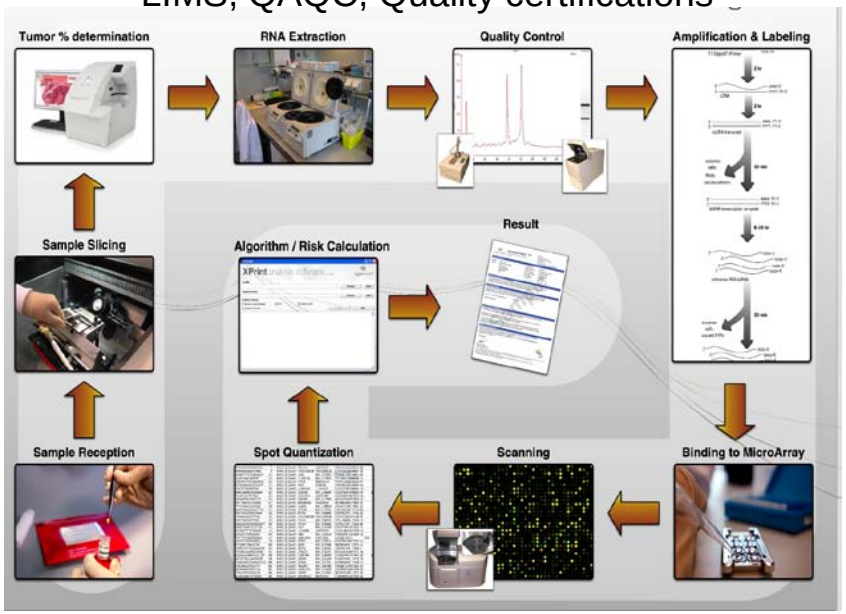
- per each investigational agent qualifying biomarker workplans are being developed, compilation of qualifying biomarker concepts
  - phosphoprotein signature
  - gene expression signature
  - additional analyses by IHC
  - specific serum markers
  - gene mutations

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



LIMS, QAQC, Quality certifications



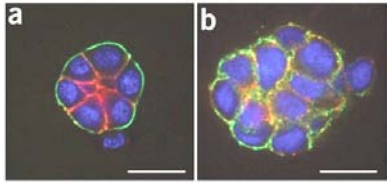
Qualifying Biomarker Analysis

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



a = normal cells b = malignant cells

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

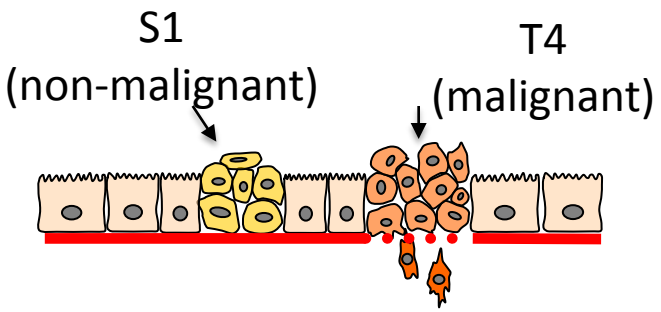
Trial Participants are treated with an investigational agent based on trial randomization

Results of treatment on participants are evaluated

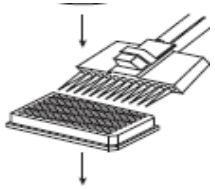
Post-Treatment Analysis

Actual participant responses are compared to predicted responses based on cell line signature

Cancer Kinase Phospho Signature:
Kinase Activity Measurement from Cell Extracts



Mixture of cell extract + Peptide + ATP



Kinase-Glo reaction

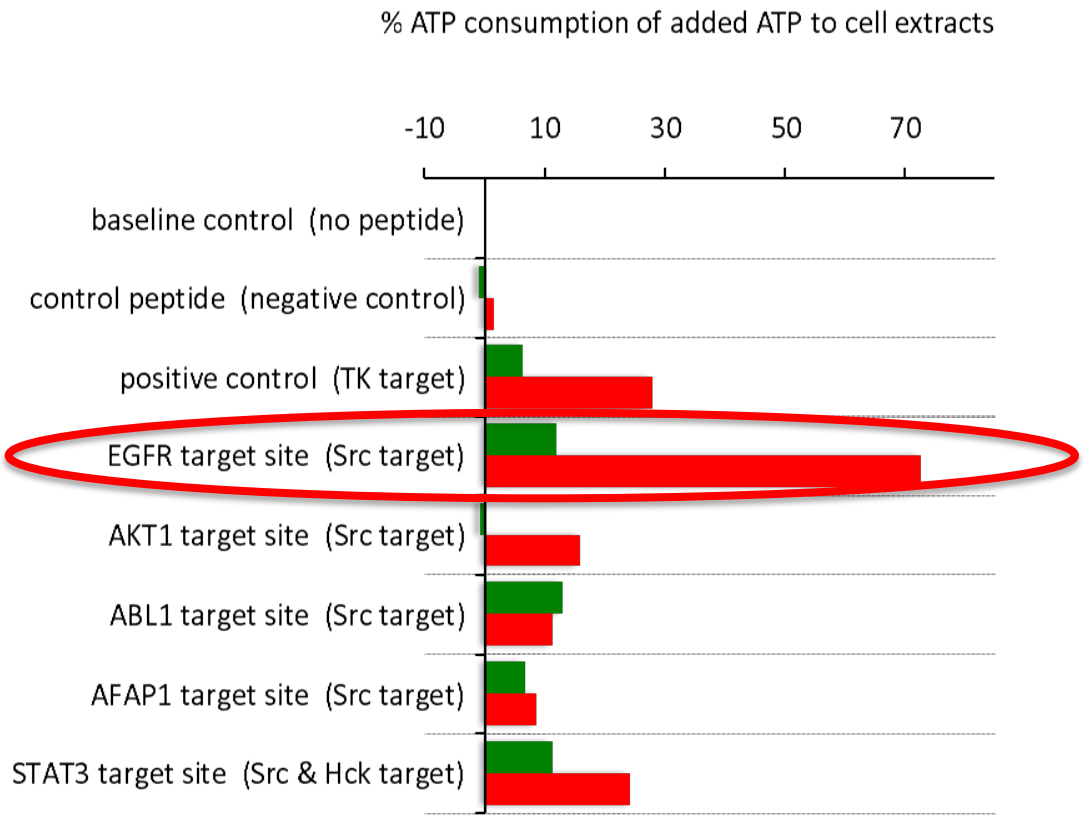
↓

Reaction time

↓

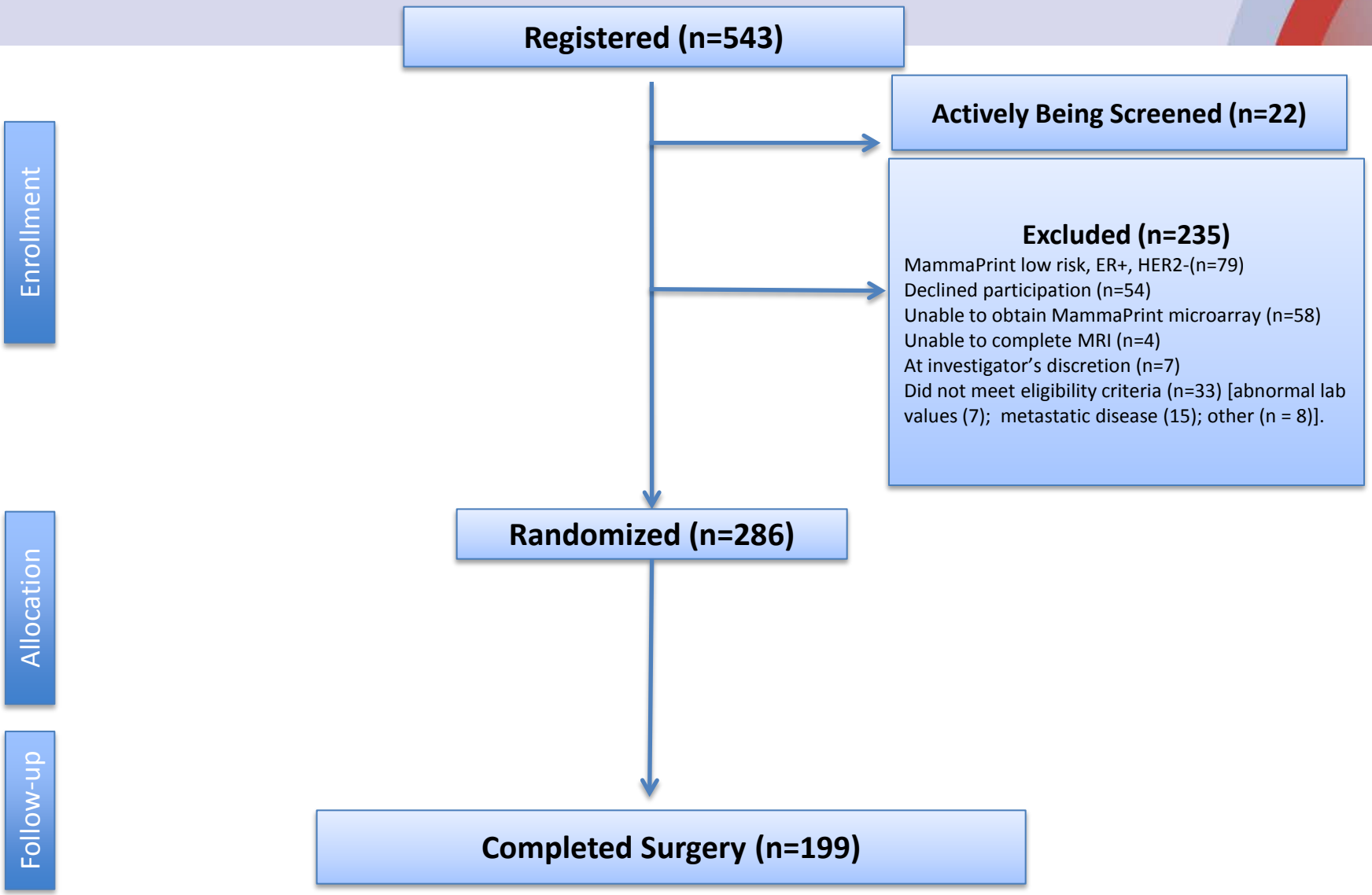
Measure Luminescence

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



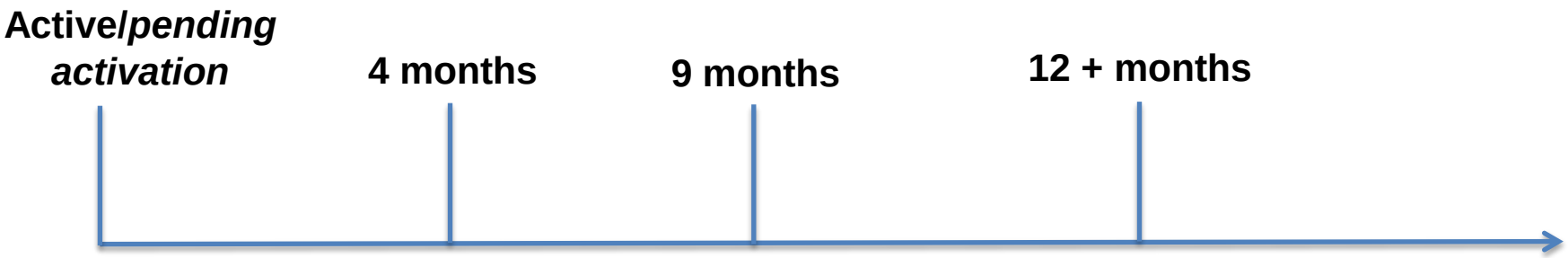
Participating Trial Sites

Trial Enrollment Overview



Status as of October 15, 2012

Investigational Agent Pipeline



Active/*pending activation*	4 months	9 months	12 + months
ABT 888 (PARP Inhibitor)	AKT inhibitor	CDK Inhibitor	Combinations of agents
Neratinib (Pan ErbB Inhibitor)	Torq 1 /2 Inhibitor	PI3K inhibitor	
AMG 386 (TIE2 Inhibitor)	Her-2 Targeted Combinations	Aurora Kinase Inhibitor	
Anti-IGFR inhibitor + Metformin			

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

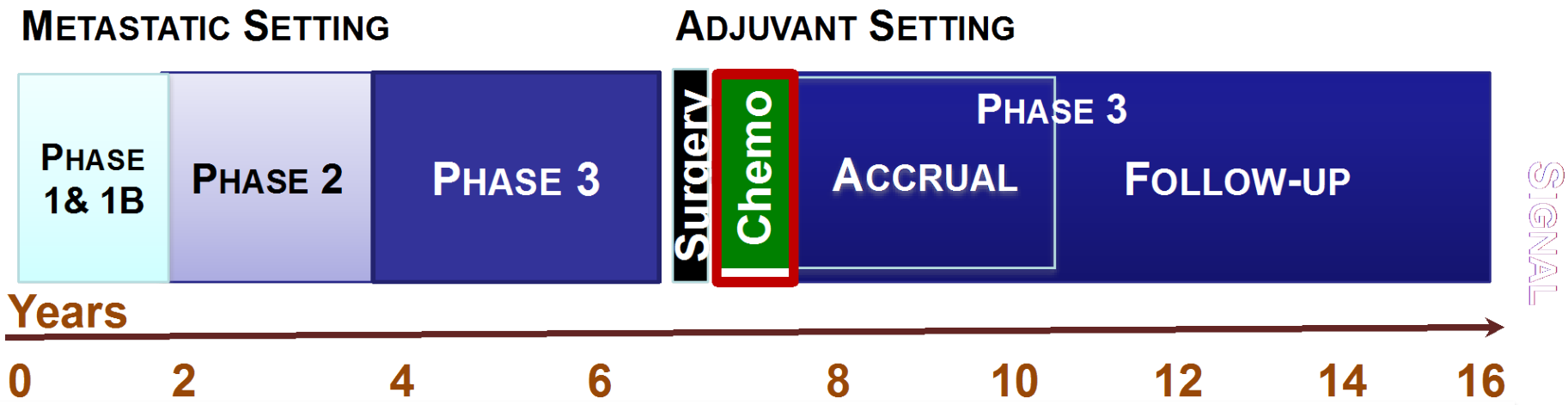
Companies in discussions:

Genentech, Millenium, Bayer, Oncomed, Merrimack, J&J, Daiichi, Plexxicon, Boehringer, Novartis

I-SPY 2 Participating Organizations

Current Approach:
10-20 years for Adjuvant Drug Approval
$1-2 Billion per drug

A. Current Development Pathway



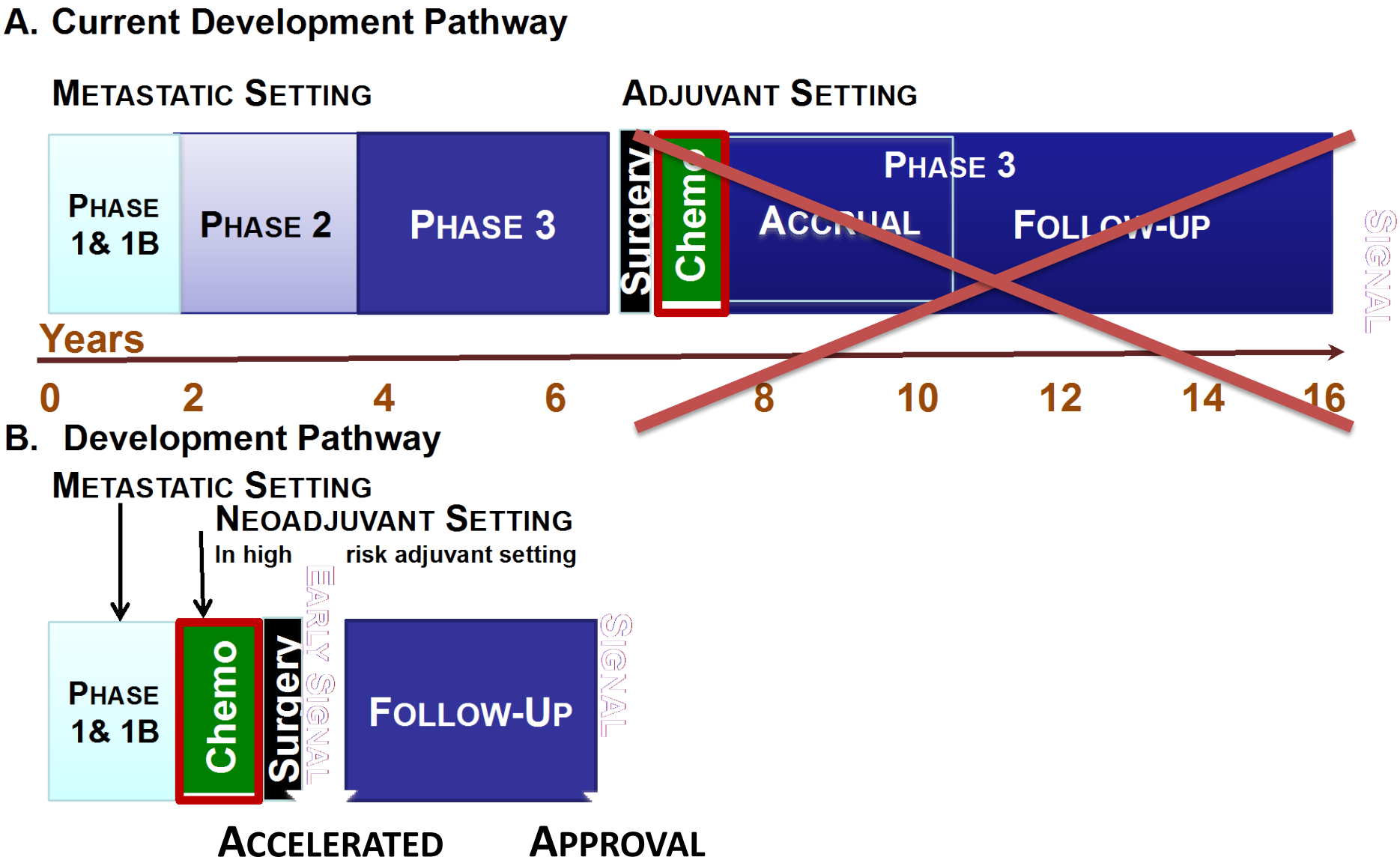
What conditions could enable dramatic improvements in knowledge turns?

And take real time off the clock

SIGNAL

What conditions could enable dramatic improvements in knowledge turns?

Take real time off the clock



Paradigm Shift: pCR as endpoint

COMMENTARY

Accelerating Identification and Regulatory Approval of Investigational Cancer Drugs

Laura J. Esserman, MD, MBA
Janet Woodcock, MD

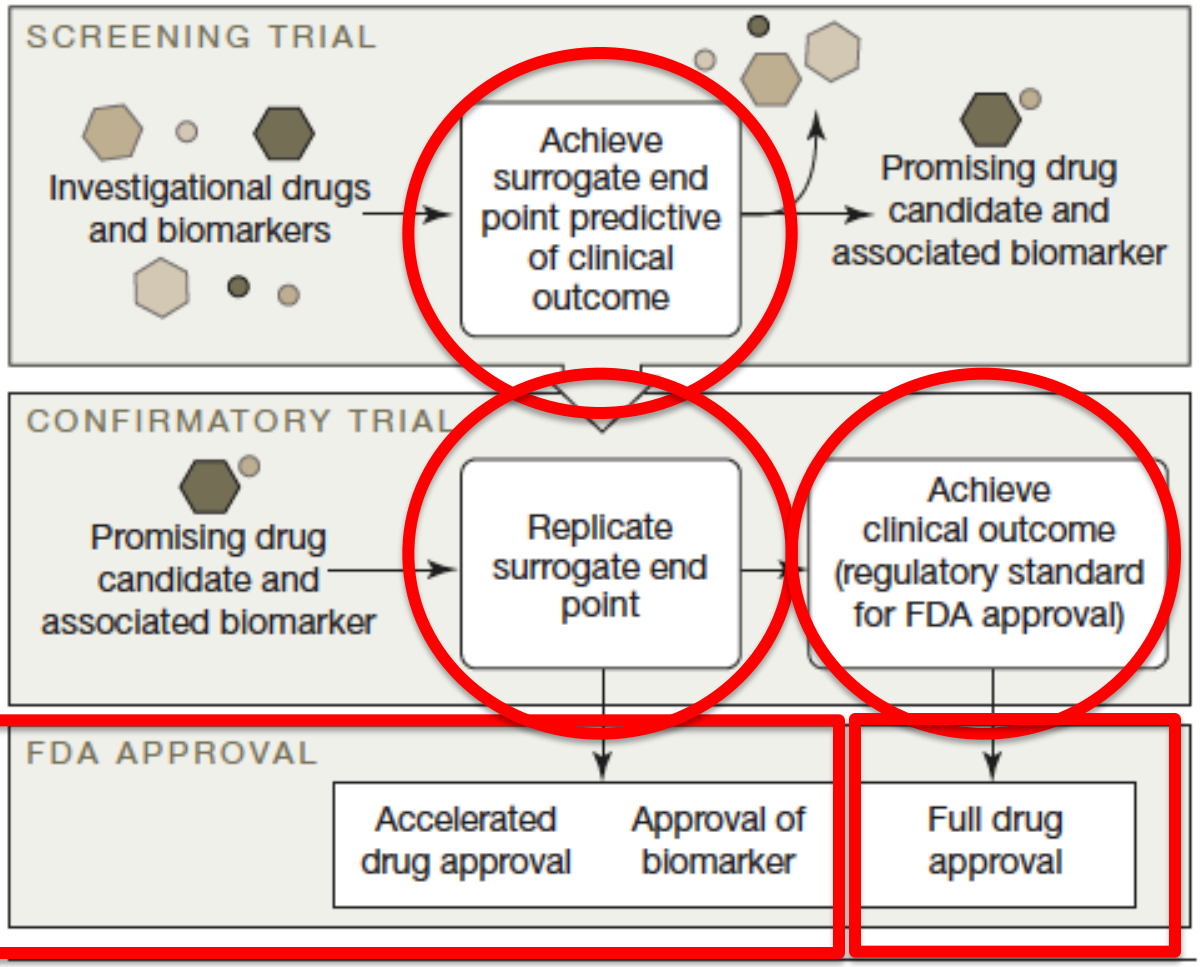
THE DEVELOPMENT OF NEW DRUGS IS BECOMING INCREASingly expensive—and oncology drugs, in particular, have a high clinical failure rate.[1,2] The current return on capital investment in drug development by US public companies was recently reported as less than 0.3%.[3] The low probability of success, coupled 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,[4] funding for such risky ventures, particularly for oncology drugs, may diminish.

The high cost of oncology drug development is not only

tifying classes of agents and the subtypes of diseases for which they are effective.[6]

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.[7] 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 deter-

Figure. Precompetitive Collaborative Research Model for Rapid Screening of Investigational Drugs and Confirmatory Testing



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.

1. pCR

2. pCR

3. survival

Getting the Right Drug to the Right Patient

- 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

I-SPY 2 TRIAL

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
Data, Design	Don Berry, Laura Esserman (Trial PI's)
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

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

Margaret Mead