Transforming Clinical Trials: The I-SPY TRIAL Process

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Prepared for the Biomarker Steering Committee

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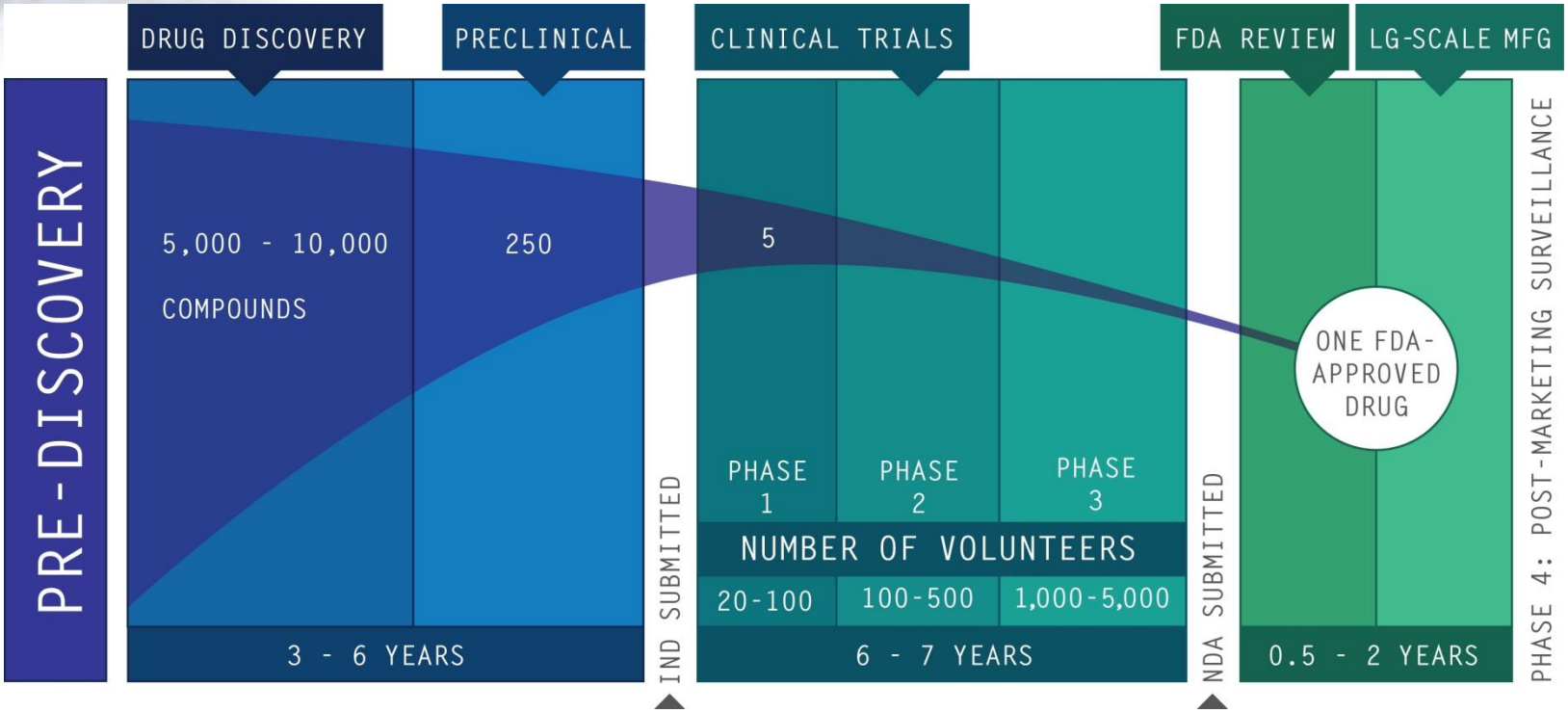
Drug Development – Current Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

It Is Time to Implement a More Efficient Clinical Trial Process

Inefficient clinical trials account for a majority for the time and cost associated with the failures of the current system

- Reduce time to conclusive results/Accelerate learning
- Reduce patient s/volunteers required
- Reduce cost of conducting trials
- Increase collaboration/Data sharing

Design Trials with the Future in Mind

Principle	Solution
Test agents where they matter most	•Neoadjuvant setting, poor prognosis cancers •Integrate advocates into trial planning
Rapidly learn to tailor agents	•Adaptive Design •Neoadjuvant therapy •Integration of biomarkers. imaging
Optimize Phase 3 trials	Graduate drugs with predicted probability of success in Phase 3 trials for given biomarker profile
Drive Organizational Efficiency	•Adaptive Design •Master IND •Test drugs by class, across many companies •Shared cost of profiling •Financial support separated from drug supply •Shared IT Infrastructure, caBIG
Use Team Approach	•Democratize access to data •Share credit and opportunity •Collaborative process for development

Neoadjuvant Approach

Building on I-SPY 1

CALGB INTERSPORE ACRIN NCICB

CALGB 150012/150007 and ACRIN 6657

Investigation of

Serial studies to

Predict

Your

Therapeutic

Response with

Imaging and Molecular

Ana-

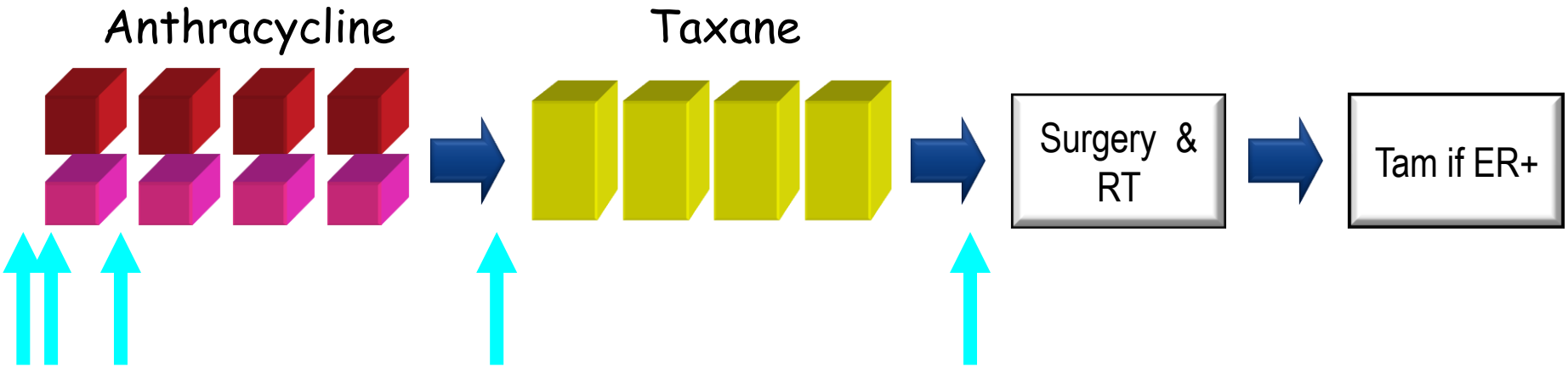
Lysis

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

I-SPY 1 Clinical Trial Backbone

CALGB 150007 / ACRIN 6657

Layered Imaging and Molecular Biomarker Studies Onto Standard Clinical Care



- Serial MRI Scans
- Serial Core Biopsies

Observations from I-SPY 1

- Patients in I-SPY are the very patients most at risk, who need novel strategies to improve survival
  - 90% of I SPY patients had poor risk biology
  - Therapies save lives in the adjuvant but not metastatic setting
- pCR (and RCB) are highly predictive of outcome in context of poor risk biology
- MRI Volume change is emerging as a non-invasive way to predict pCR

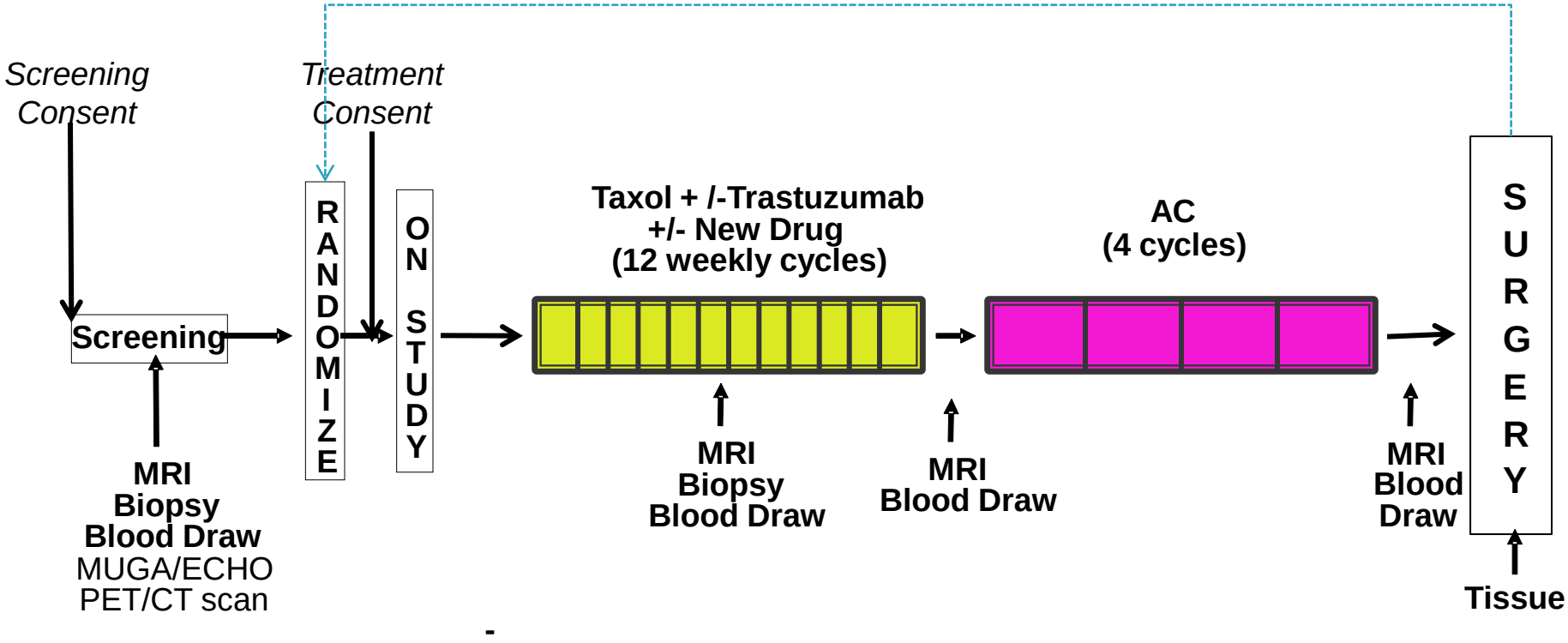
Rapidly Learn to Tailor Agents

Adaptive Design, Integration of Biomarkers

I-SPY 2 Applies Findings, Infrastructure of I-SPY 1 to Testing of New Agents

- Introduction of phase 2 agents into the neoadjuvant setting in breast cancer
- Adaptive clinical trial design
- Process for rapid, focused clinical development of oncologic therapies and biomarkers
- High potential for both accelerating development of new therapies and benefiting patients

I-SPY 2 Adaptive Trial Outline



Accrual: Anticipate 800 patients over 3–4 years

Enroll: ~20 patients per month

Participating Sites: 15–20 across US and Canada

I-SPY 2 Adaptive Trial Schema: Screening & Randomization

Eligibility Assessment Process

Patient presents with newly diagnosed ≥ 2.5cm invasive tumor

CONSENT 1
Core biopsy to assess eligibility

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

Is patient:
- MammaPrint Low
- ER Positive
- HER2 Negative?

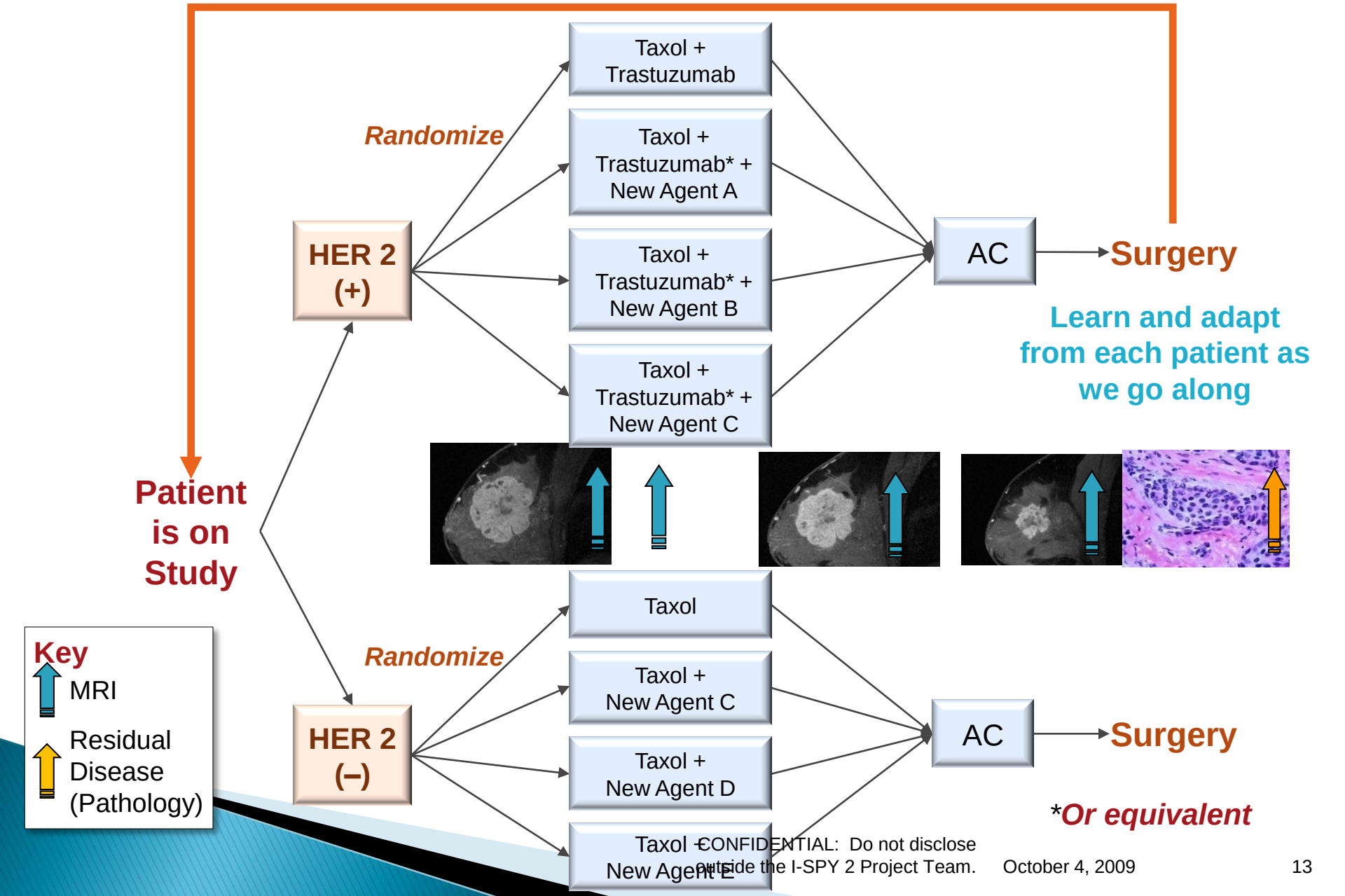
No

CONSENT 2
Patient On Study
Randomized to treatment arm based on:
- ER, PR status
- HER2 Status
- MammaPrint score

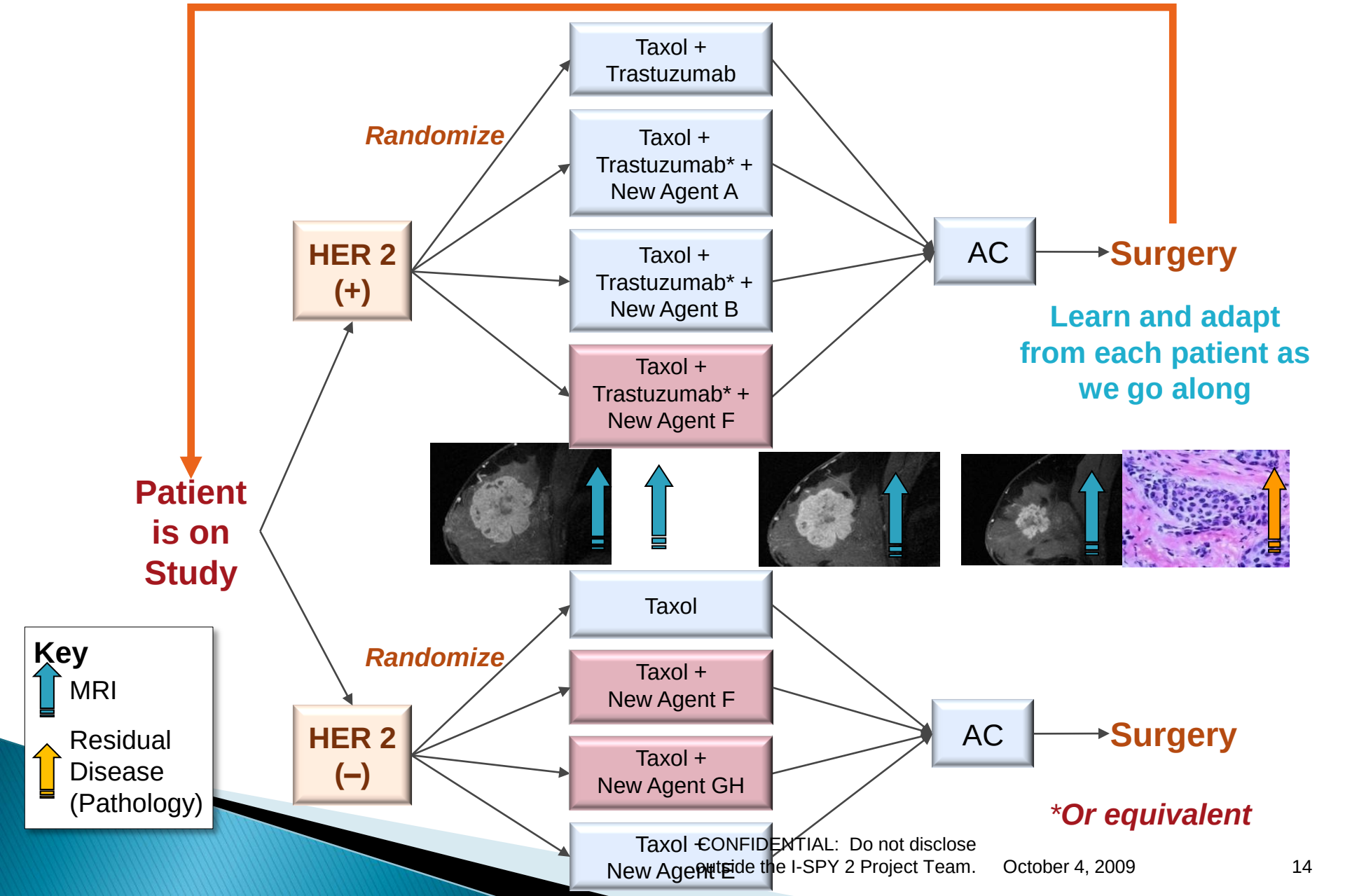
Yes

Patient not on study
Not considered good candidate for chemotherapy

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



I-SPY 2 Adaptive Trial: Learn, Drop, Graduate, and Replace Agents Over Time



I-SPY 2 is a Paradigm Shift

- Uses adaptive design in neoadjuvant setting to allow efficient learning,
  - pCR is primary endpoint
- Biomarkers, imaging and pathology endpoints help drive trial
- Qualifies biomarkers as new agent classes are tested
  - Established/ Approved Biomarkers/ IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers (
- Provides foundation of evidence for tailoring therapy

Optimize Chance of Successful Phase 3 Trials

For targeted population

Advantages of Adaptive Design

- If the drug works better or worse than you think, you will learn that as the trial progresses
- Drugs can be dropped quickly if they are ineffective or harmful, or graduated sooner if they are clearly beneficial
- Smaller trials (usually), more accurate conclusions, better treatment of patients in the trial

Statistical Considerations

- Primary endpoint: pCR (at surgery)
- Auxiliary endpoints: MRI volume over time
- (MRI not relevant in final analysis)
- Baseline covariates: ER, HER2, MP

I-SPY2 Statistical Goals

- Identify (baseline) biomarker signatures that predict drug effect on pCR
- Model relationships between baseline and longitudinal MRI to predict pCR
- Confirm observations within trial—at least partially
- Graduate drug/biomarker pairs to smaller, more focused Phase 3 trials

Patient Strata

Estimated prevalences based on I-SPY 1:

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

MP: MammaPrint High+ vs High-
HR+: Hormone Receptor+: Either ER+ or PgR+

pCR by subtype in I-SPY1*; null case in designing I-SPY2

	MP–		MP+	
	HR+	HR–	HR+	HR–
HER2+	0.47	0.67	0.35	0.55
HER2–	0.25	0.43	0.17	0.32

*** Patients w/o trastuzumab]**

Prevalence by Subtype, again

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

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

Biomarker Signatures

Biomarker Signature	Types (HR, HER2, MP)								Estimated prevalence
	+++	++-	+-+	+--	-++	-+-	--+	---	
1 (All)	X	X	X	X	X	X	X	X	100%
2 (HR+)	X	X	X	X					49%
3 (HR-)					X	X	X	X	51%
4 (HER2+)	X	X			X	X			37%
5 (HER2-)			X	X			X	X	63%
6 (MP+)	X		X		X		X		48%
7 (--)*							X	X	34%
8 (-+)					X	X			17%
9 (++)	X	X							20%
10 (+-)			X	X					29%

*Triple negative

Sponsor/SC may restrict signatures

Adaptive Randomization

- Sample size for each drug, 20 to 120 (minimum n = 60 if “graduate”)
- Maximum of 5 exp drugs at a time
- Patient enters trial, identify subtype
- Find (Bayesian) prob each drug >> control, based on all current results, including MRI
- Assign in proportion to current prob drug >> control (depends on subtype)

Dropping, Graduating Drugs

- Frequent updating through trial. For each drug and each possible biomarker signature B, find predictive probability of success in 300-pt Phase 3 trial
- If < 10% for all B then drop drug
- If > 85% for some B then drug graduates
- At graduation we give predictive probability Phase 3 success for each B, including B on the drug's diploma

Longitudinal Modeling (MRI volume is auxiliary endpoint for adaptive decision making)

- Assess predictability (depending on therapy) of pCR from interim MRI
- Based of I-SPY2 results, but “borrow” data from I-SPY1 regarding relationship

Simulations for Design Operating Characteristics

- Require completely prospective design (computationally intensive)
- For operating characteristics:
  - Type I error rate
  - Power
  - Sample size
- Many scenarios, including
  - Accrual rate
  - # exp drugs over time

Organizational Efficiencies

Master IND Accommodates Testing of Multiple agents

- Eliminates need for new protocol each time an agent is added
- Enables approval as soon as an agent is “Tier 1” ready
- Provides pharmaceutical companies a pathway for rapid development, testing of promising agents
- Provides FDA with opportunity to test more efficient process of drug qualification
- Master IND to be held by FNIH

Agent Review Process

Fall 2008

Pharmaceutical Company Focus Group

Produced broad list of candidate tier 1 and tier 2 agents

Spring 2009

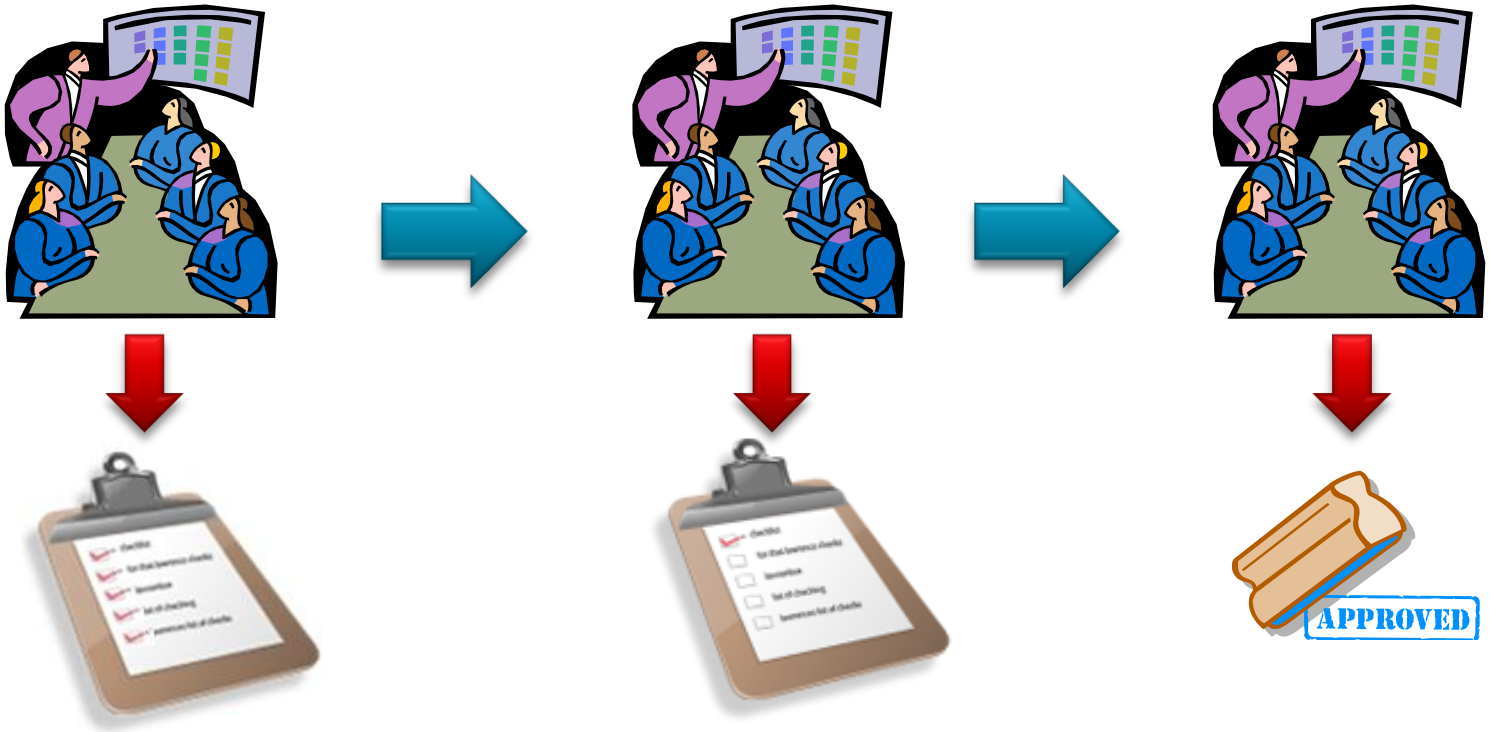
I-SPY 2 Internal Agent Review of Proposed Tier 1 Agents

Produced narrowed down list of tier 1 agents plus agents deferred to tier 2

Spring 2009

I-SPY 2 Independent Agent Review of Proposed Tier 1 Agents

Produces approved list of tier 1 agents



Agents not included in tier 1 will be reviewed quarterly for addition to the trial pipeline

Novel Agent Selection Criteria

Phase I testing completed

Compatible with standard paclitaxel therapy (i.e. no unacceptable additive toxicity)

For HER2/neu–directed agents, compatible with paclitaxel plus trastuzumab therapy

Known efficacy or rationale for efficacy in breast cancer

Fits strategic model for optimizing combinations of single/multiple molecular targeting drugs with or without standard chemotherapy

Targets key pathways/molecules in breast cancer:

Receptors	HER2, IGF1R, Death Receptor, cMET, VEGFR (multi-targeted TKI)
PI3K Pathways	PI3K, Akt, mTOR
MAPK Pathways	MEK, MAPK
Angiogenesis	AMG 386
DNA Repair	PARP

Note: Only one novel agent per target pathway will be active in the trial. The goal is to test agents by class.

Willingness of pharmaceutical company to support the trial and sufficient availability of the agent

#1 Criteria
Safety with paclitaxel is known and acceptable

Proposed Tier 1 Agents and Their Target Patient Populations

Agent	HER2+ / Any HR Cancers	HER2- / HR+ Cancers	HER2 - / HR - Cancers
ABT-888	No	Yes	**Yes**
Figitumumab (CP-751,871)	No	**Yes**	**Yes**
Neratinib (HKI-722)	**Yes***	No	No
APO/TRAIL (AMG 655)	No	**Yes**	**Yes**
AMG 386	No	**Yes**	**Yes**

* *Neratinib is anticipated to be delivered in place of trastuzumab after confirming its efficacy is at least as effective as trastuzumab in HER2+ cancers.*

Additional Agents In the Pipeline

Anticipated approval:
***Year end 2009**
***First quarter 2010**

HER2 Inhibitors	**T-DM1*** (Genentech) Pertuzumab (Genentech)
IGFR Inhibitors	OSI-906 – TKI (Imclone/Schering-Plough)
Multi-Targeted TKI	Bosutunib (Wyeth) Motesanib Diphosphate (Amgen)
Others	**PI3K*** (Genentech) **Akt*** (Merck) **Aurora A inhibitors*** (Merck) NOTCH (Oncomed/GSK) Hedgehog (Genentech) cMET (Amgen, Genentech, GSK) (/ Bcl2 (Abbott)) MEK (GSK)

Additional Organizational Efficiencies

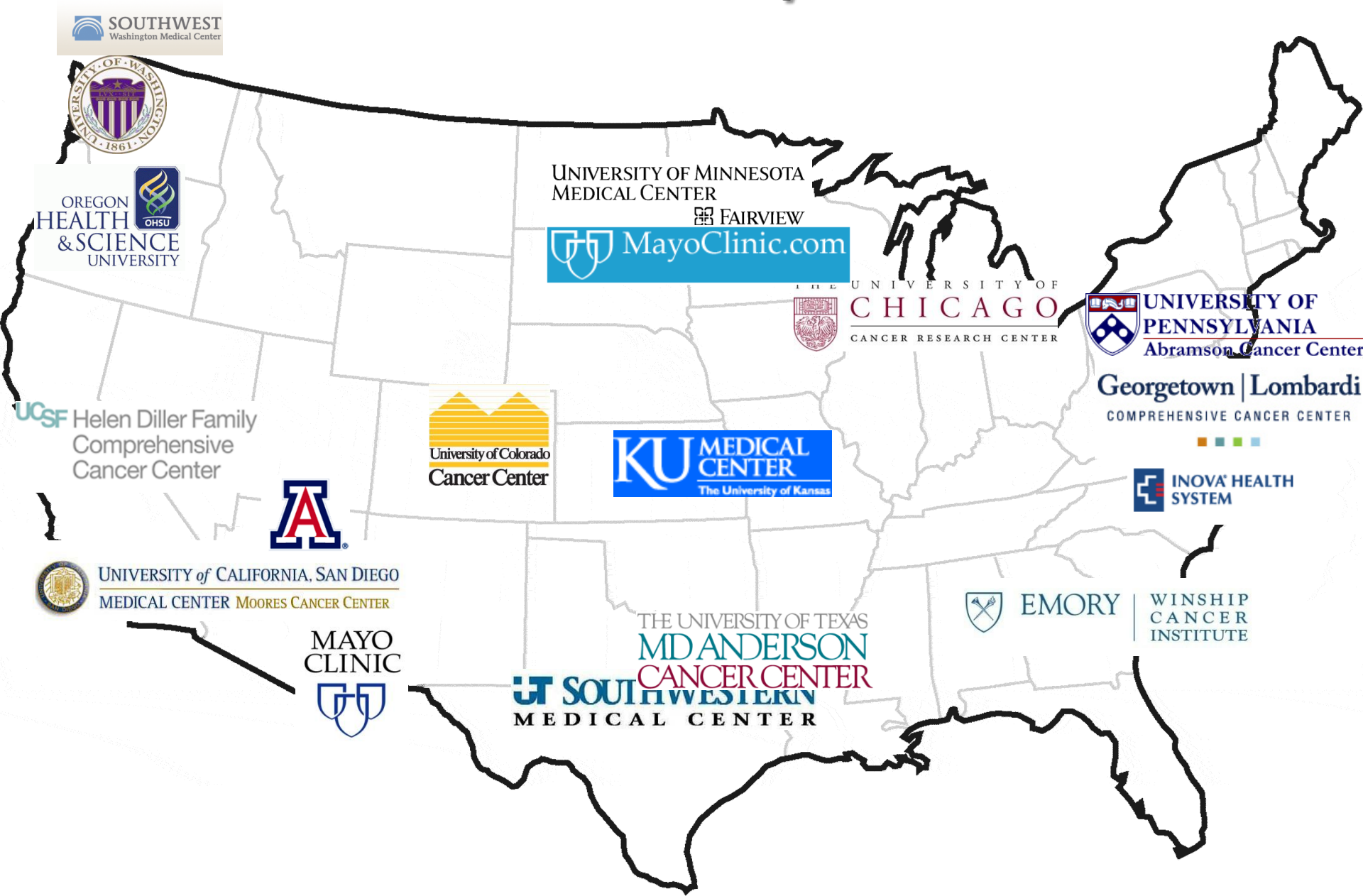
- Work designed to meet the ambitious goal of opening trial November 2009
- Simultaneous development
  - IT system for real time web based data capture, integrated with research tools
    - caTISSUE, caEXCHANGE
    - Randomization engine to support adaptive design
    - caINTEGRATOR2 to enable sharing data
  - Protocol development, iterative feedback (IRB's)
  - Qualification of agents, biomarkers
  - Site selection

Team Approach

I-SPY 2 Process Collaborative by Design

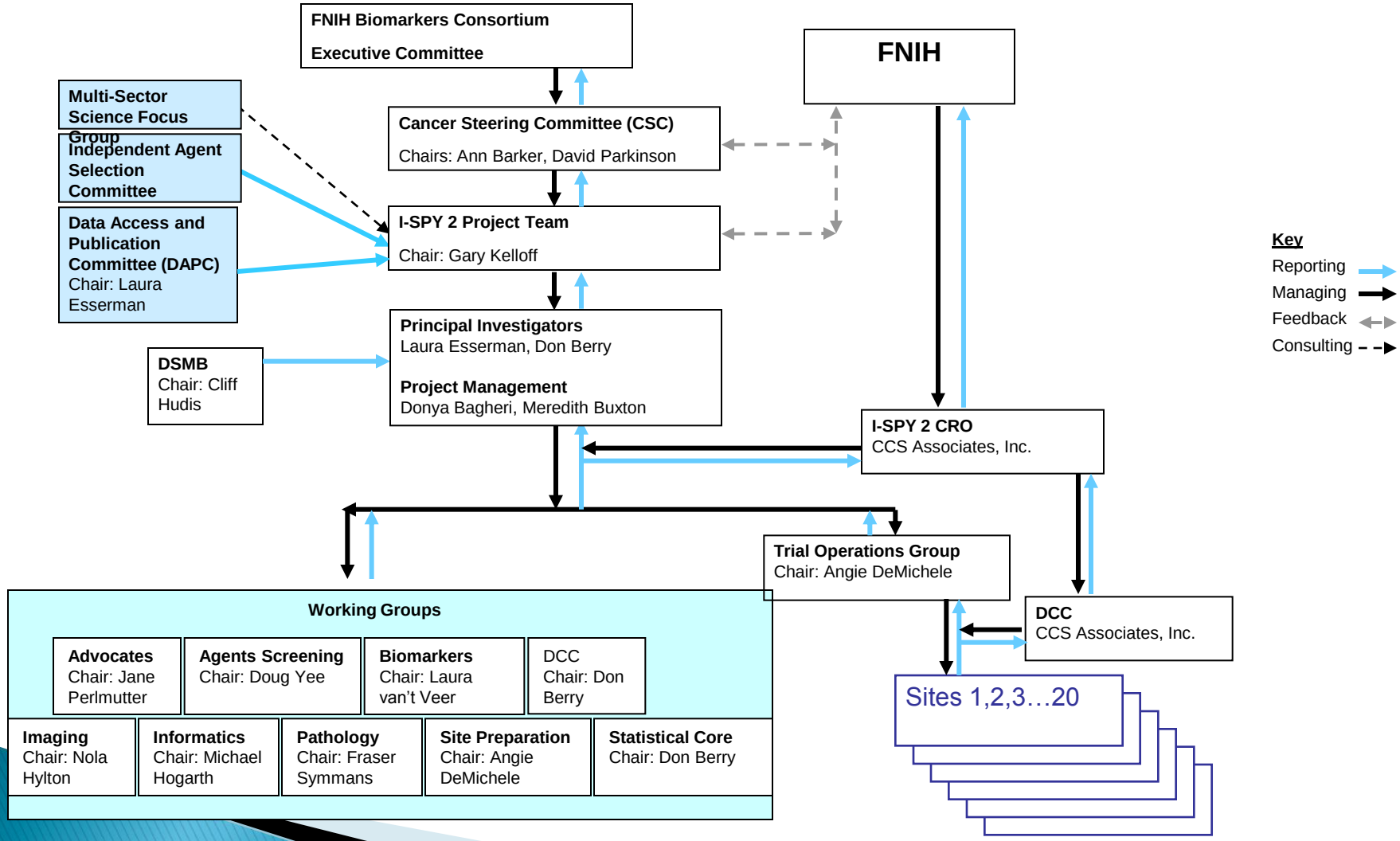
- Involve key stakeholders from inception
  - NCI, FDA, FNIH Biomarkers Consortium, Academic and Clinical Partners, Pharma, Biotech, IT, Advocates
- Involve new stakeholders as trial proceeds to approval
  - Preparation for IRB approval: 45 key stakeholders brought together for education and feedback
- Involve stakeholders from all sites
  - "Chaperones" for agents, biomarkers from trial investigators
  - Data in caINTEGRATOR is open to all investigators

Projected I-SPY 2 study sites

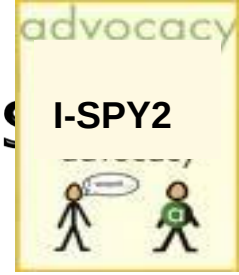


I-SPY 2 TRIAL Managed by FNIH

proposed governance structure



Unprecedented Involvement & Interes of Advocates in I-SPY2



- Advocates involved in earliest thinking and planning of I-SPY2
- Advocates assigned to all I-SPY2 scientific working groups and advisory groups
- Presentations to advocates at scientific meetings and advocacy meetings (e.g., AACR, SABCS, ASCO, NBCC, SHARE, C3)
- Regular email updates to mailing list of over 120 subscribing advocates
- Multiple advocate driven project groups

Advocate Specific Projects

Training
- Advocate Webinars
- Peer Support Consenters
- Informed Consenters

Trial Site Support
- **Recruitment & Retention Plan**
- **Local Advocates**

Patient Materials
- Recruiting Brochure
- Patient DVD & Website

Advocate Program
- **Assessment**

Protocol Review
- Especially Informed Consent

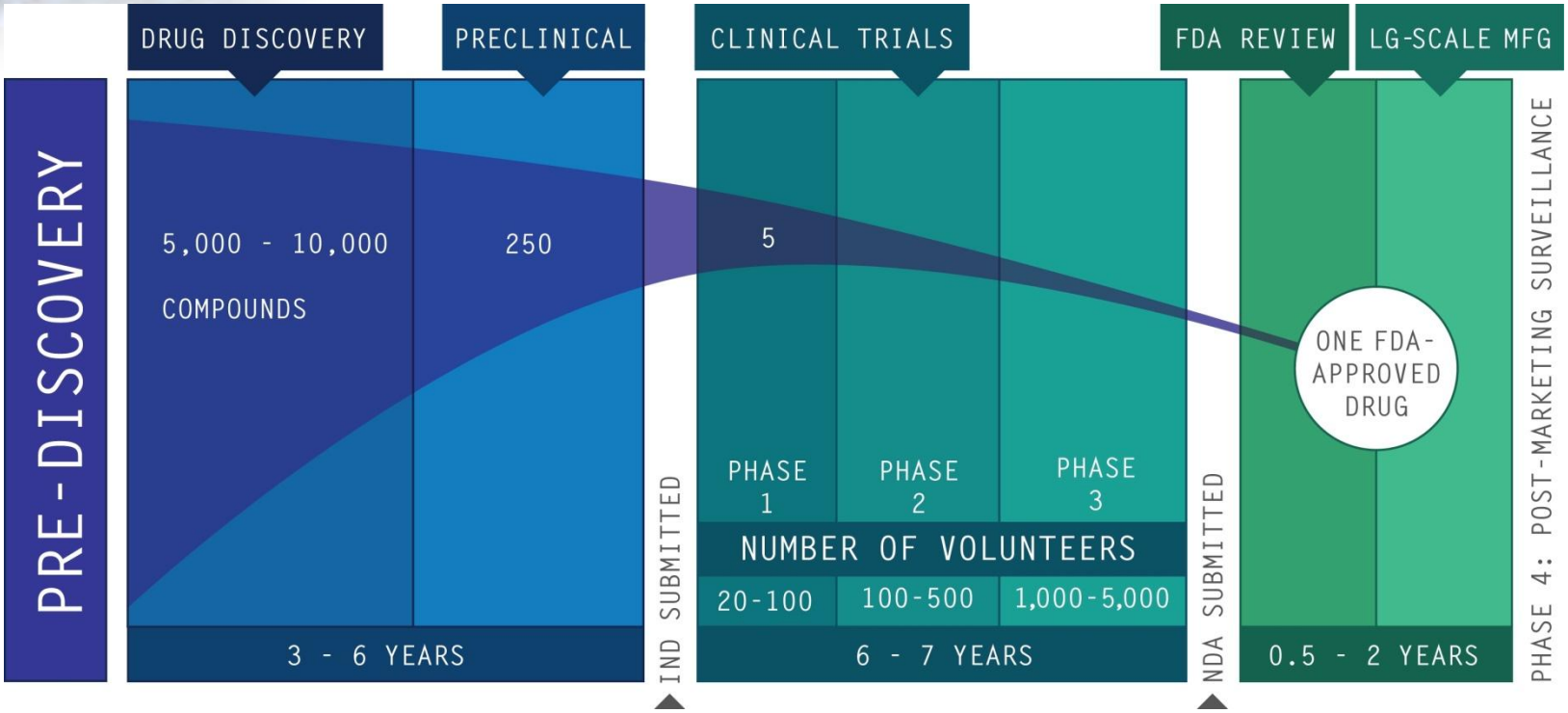
Advocate Working Groups

Dissemination
- I-SPY2 Info to Public
- Advocacy Best Practices

Value Proposition/Benefit for Partners in Public Private Partnership (PPP)

Patients	▪ Opportunity to Drive Path to Personalized Treatment ▪ Potentially More Effective Treatment/Management
FDA	▪ Provides for Evidence-Based Regulatory Policy
Pharma	▪ More Efficient Drug Development and Approval Path ▪ Better Early Response Criteria
Device Industry	▪ Larger Markets ▪ Less Risk
CMS	▪ Helps Define Reasonableness and Need
Academia/NCD	▪ Better Clinical Data ▪ More Effective Treatment/Management

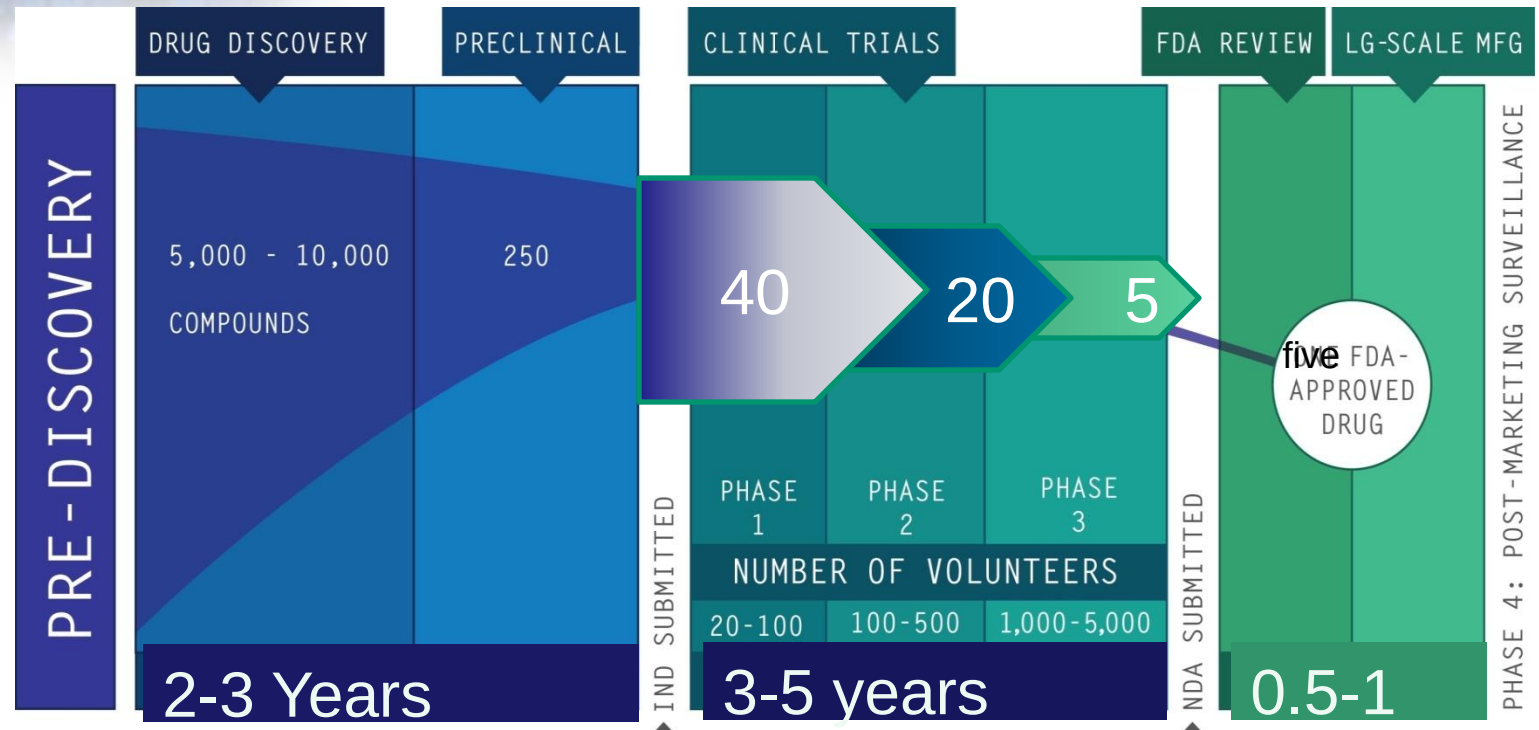
Drug Development – Current Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

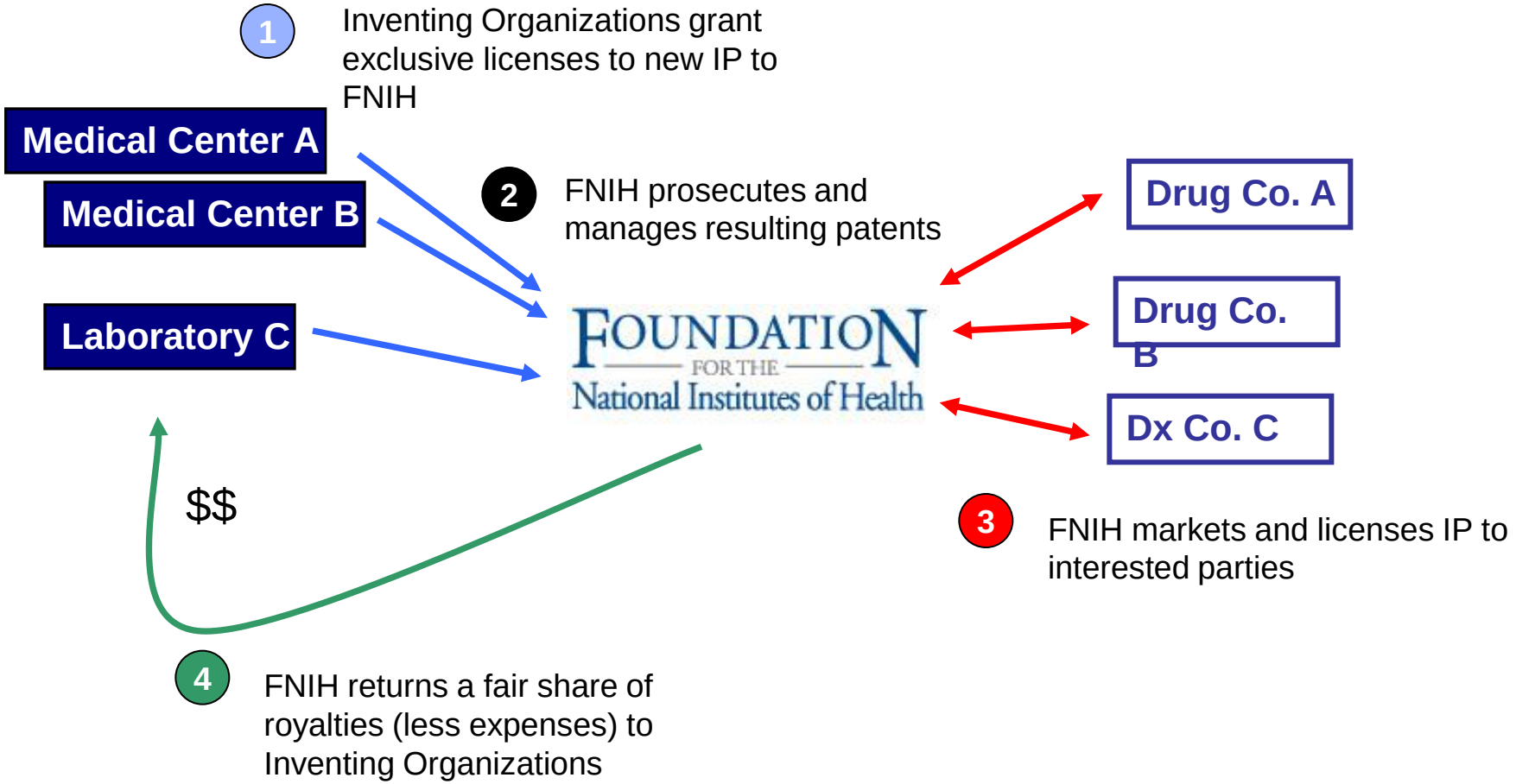
Drug Development –I SPY Model



- 5X More Products for 1/5 of the $$ (25X Improvement)
- ½ of the time, with ½ the volunteers (4X Improvement)

FNIH : Trusted Third Party

to ensure fair and appropriate licensing of new inventions arising from I-SPY 2



Potential Funding Sources

Identified: ~$6-8 million

To be raised by FNIH: $16-18 million

- Potential funding sources:
  - Safeway (~$6 million)
    - Local store campaigns will raise funds directly for nearby sites
  - Atwater Family fund (~$1-2 million)
- Cost per funder: ~3.5 million over 5 years, if 5 funders identified
    - Two Go/No-go milestones, at 20% and 40% of the total required budget

Current prospects for I-SPY 2 funding

For-Profit Companies

Abbott Laboratories
Amgen
AstraZeneca
Bristol-Myers Squibb
EMD Serono
Genentech
GlaxoSmithKline
Johnson & Johnson
Eli Lilly and Company
Merck and Co., Inc.
Novartis Pharmaceutical Corp.
Pfizer Inc.
F. Hoffmann-La Roche
Wyeth

Non-Profit Organizations

American Association for Cancer Research
American Cancer Society
American Society of Clinical Oncology Foundation
American Society for Therapeutic Radiology and Oncology
Breast Cancer Research Fund
Battelle Memorial Institute
Biotechnology Industry Organization
Coalition of Cancer Cooperative Groups
Dr. Susan Love Research Foundation
Friends of Cancer Research
Haseltine Foundation for Medical Sciences and the Arts
Living Beyond Breast Cancer
Ontario Cancer Biomarker Network
Safeway Corporation
SU2C
Susan G. Komen for the Cure
ZERO Breast Cancer

2009 Start-up Funding Needed

in order to preserve current project timelines

Activities covered would include:

- UCSF personnel
- Personnel at other sites
- Bridge funding for site setup
- Legal costs for contracts/grants

Extras

I SPY RESULTS

The Project Plan:

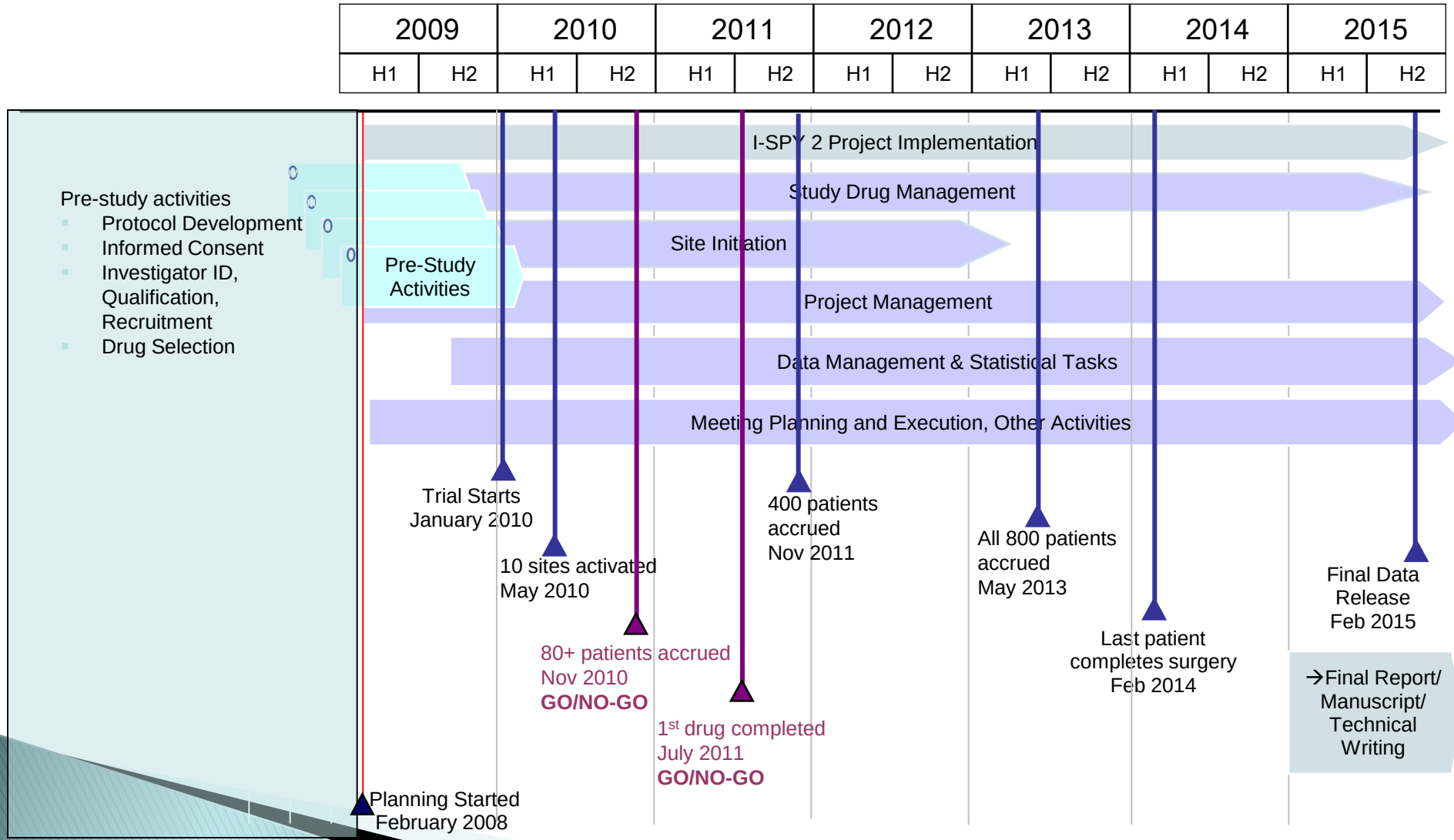
Comprehensive approach to managing both pre-existing and new intellectual property

	Treatment of IP related to:		
	Drugs	**Tools (Assay platforms)**	**Biomarkers**
Pre-existing IP	• Retained by contributing company • Research use licenses to and NDAs with Project Team only	• Companies will provide licenses via service agreements with FNIH for use in the project	• Pre-existing biomarkers (I-SPY 1)
New IP	• E.g., novel combination regimens or indications • Will be licensed back to the company (exclusively if drug-specific)	• Companies will have no early look at or proprietary rights to data or inventions • May keep proprietary tools improvements (but grant research licenses to Project Team)	• Inventors must grant interested parties a non-exclusive license for research use, and • Companies will receive option to negotiate exclusive or non-exclusive commercial license with limited field of interest

Summary of I-SPY 2 Data Release Plan

Type of Data	Purpose	Users	Release
Detailed patient data	Measure study progress and data quality	Investigators, PT only	Ongoing
Efficacy Data	Results	•Investigators & PT •Contributing Drug Cos. •Research Community	•As drugs leave study (DSMB approval) •1 week later •6 months later
Qualifying and Exploratory Biomarkers	Results	•BWG and PIs •Investigators •Research Community	•At study completion •2 weeks later •3 months thereafter (request to DAPC)
Initial Safety Data	Determine whether to continue drug; regulatory requirements	•DSMB & PIs •Contributing Drug Cos. •FDA	Ongoing for all (Drug Cos. may release some data as part of peer-reviewed manuscripts)
Follow-up Safety Data, RFS & OS (>1 yr post-treatment)	Regulatory requirements	•DSMB •Contributing Drug Cos. •FDA	Same as Initial Safety Data
Other Follow-Up Data	Results	•Investigators •Research Community	Within 3 months after completion of follow-up

The I-SPY 2 Trial will be executed over five years



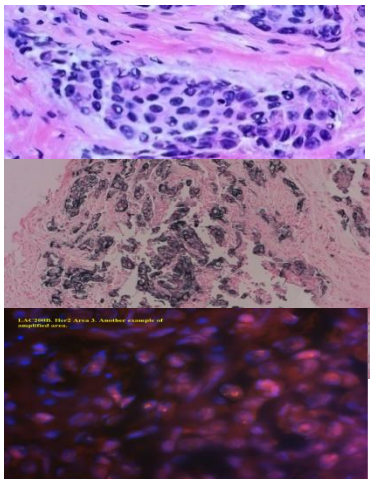
Timelines Anticipate Success

February 2009	**Site selection**	10 sites on board; Additional recruiting on-going (14 sites as of August 2009)
July 2009	**Agents finalized**	Tier 1 agents identified
August 2009	**Protocol finalized**	Undergoing review; central IRB review August 20, 2009
November 2009	**IRB approval**	Begin IRB approval process at 3 sites (UCSF, U Penn, UMN). Ongoing through June 2010
September 4, 2009	**IND application submission**	Response within 30 days
Sept-Dec 2009	**Contract negotiations**	Initiated with 3 site (UCSF, U Penn, UMN); Ongoing
January 2009	**Site/Investigator training**	
December/2009 January 2010	**First patient on-study**	Open at UCSF, UPenn, UMN first, additional sites on-study ongoing through first quarter 2010

I-SPY 1 Biomarker Platforms

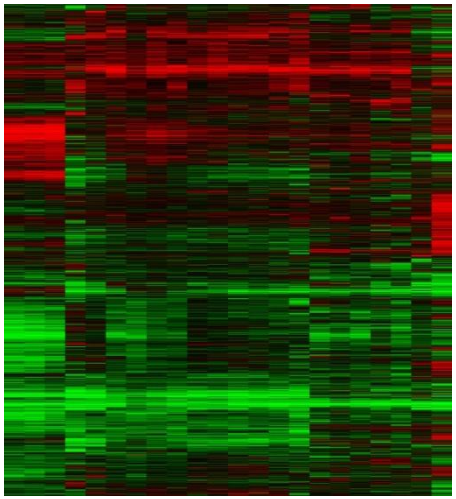
Tissue: Core or Surgical

H&E, IHC, FISH



UNC, Penn

Expression Arrays

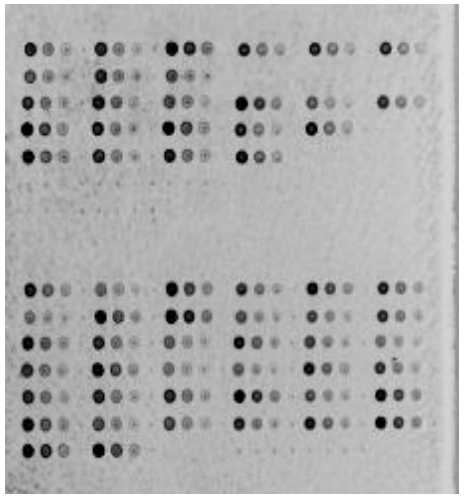


UNC, UCSF, NKI

p53 GeneChip

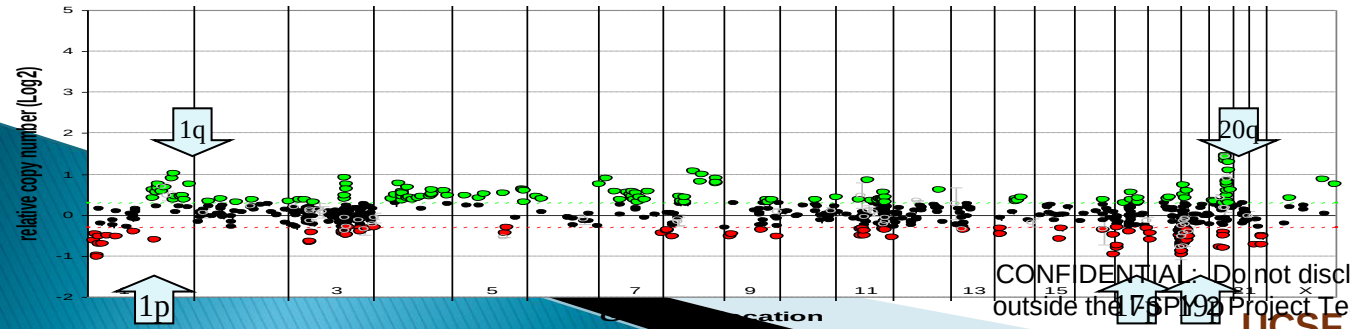
UNC

Protein Arrays (RPMA)



GMU

CGH



UCSF

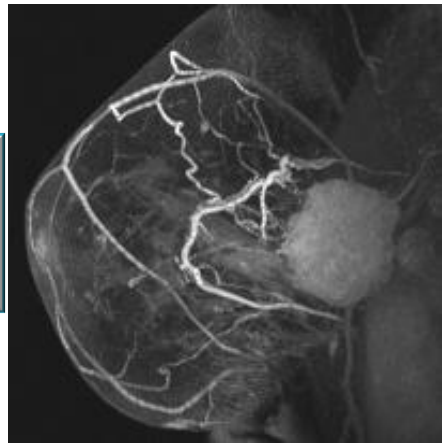
Serum

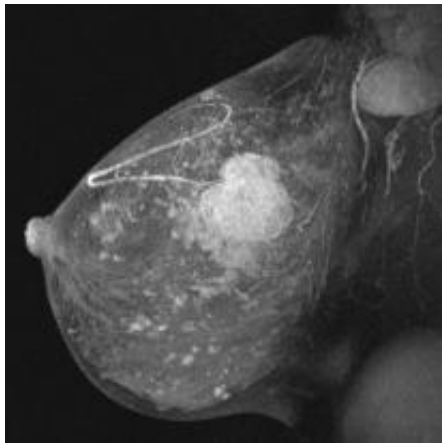
Id1 proteins
autoantibodies
phospho proteins

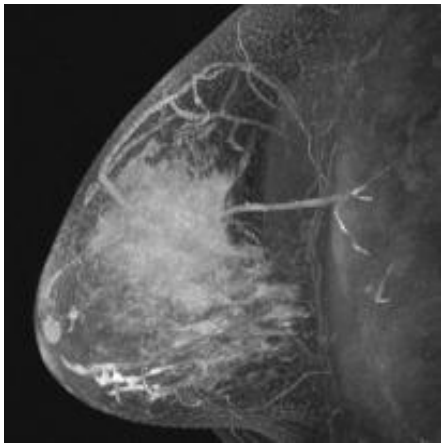
Quantitative and serial measurement of tumor response by MRI – ACRIN 6657

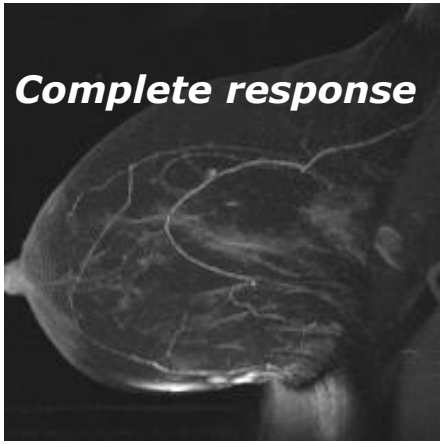
Pre Treatment

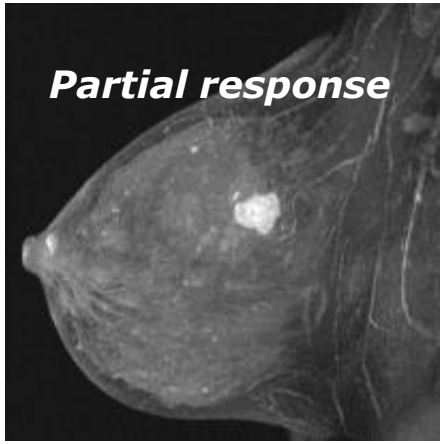
Post Treatment

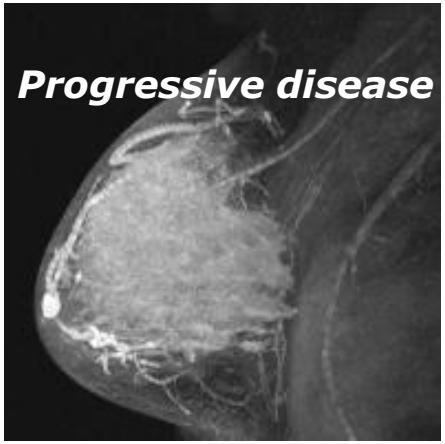




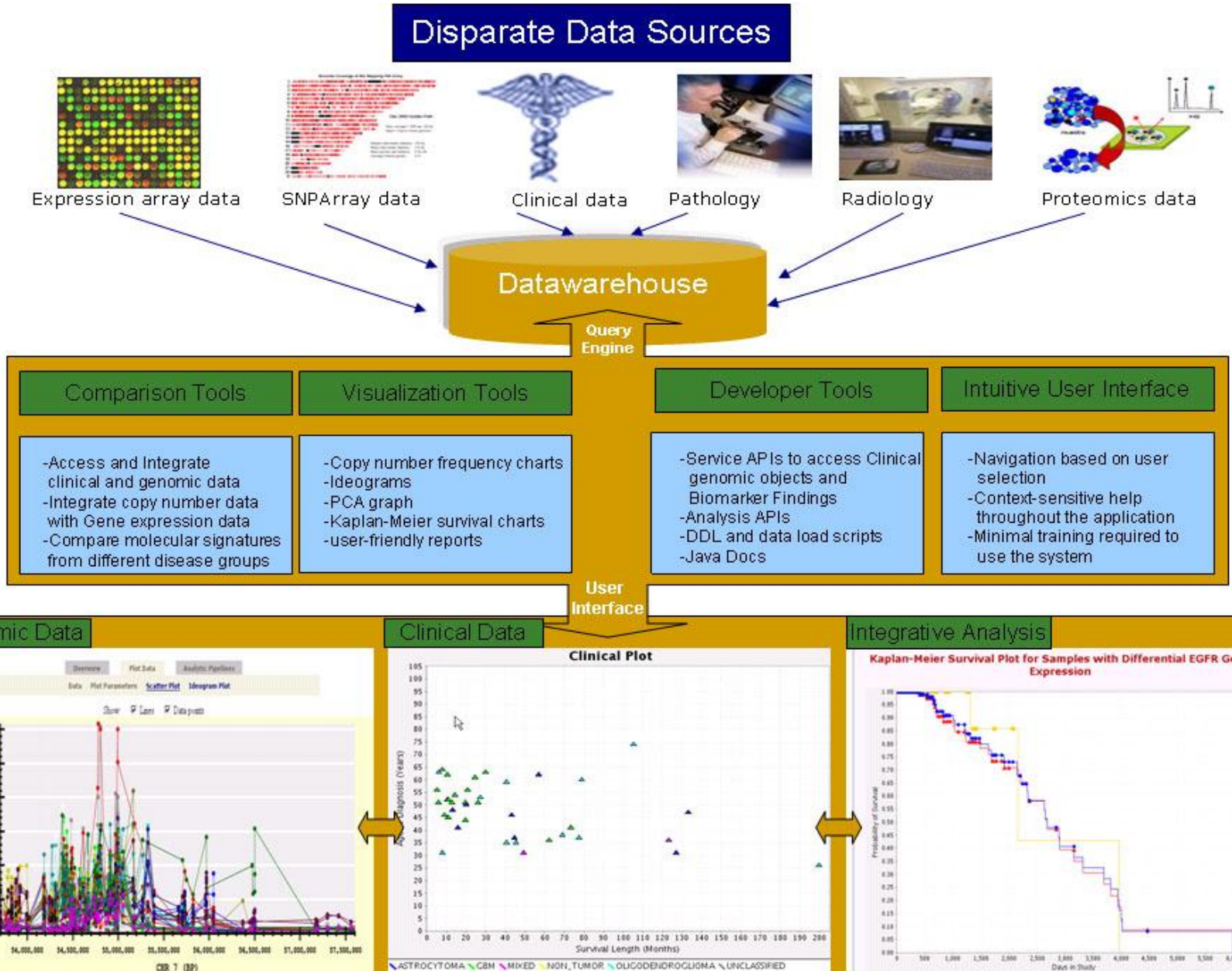








Infrastructure Builds on I SPY 1



I-SPY 2 Informatics Infrastructure:TRANSCEND

Uses Common Tools, Enables Data Exchange

Randomization Service

Patients randomized to novel treatment arm

Clinical Information System (Tolven eCHR)

Eligibility is verified, patient is registered , clinical data is captured, tracks the patient schedule, identifies labs and allows them to be viewed/resulted

calINTEGRATOR

Investigators evaluate efficacy of treatment arms – as trial is underway

caXchange (Hub)

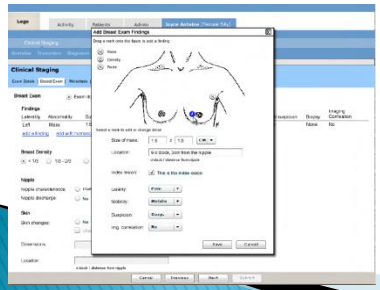
Patient visits the Physician

Biopecimen Data Management System (caTISSUE)

biospecimens are tracked

Cancer Adverse Event Reporting System (caAERS)

Identifies and tracks adverse events and any associated schedule changes

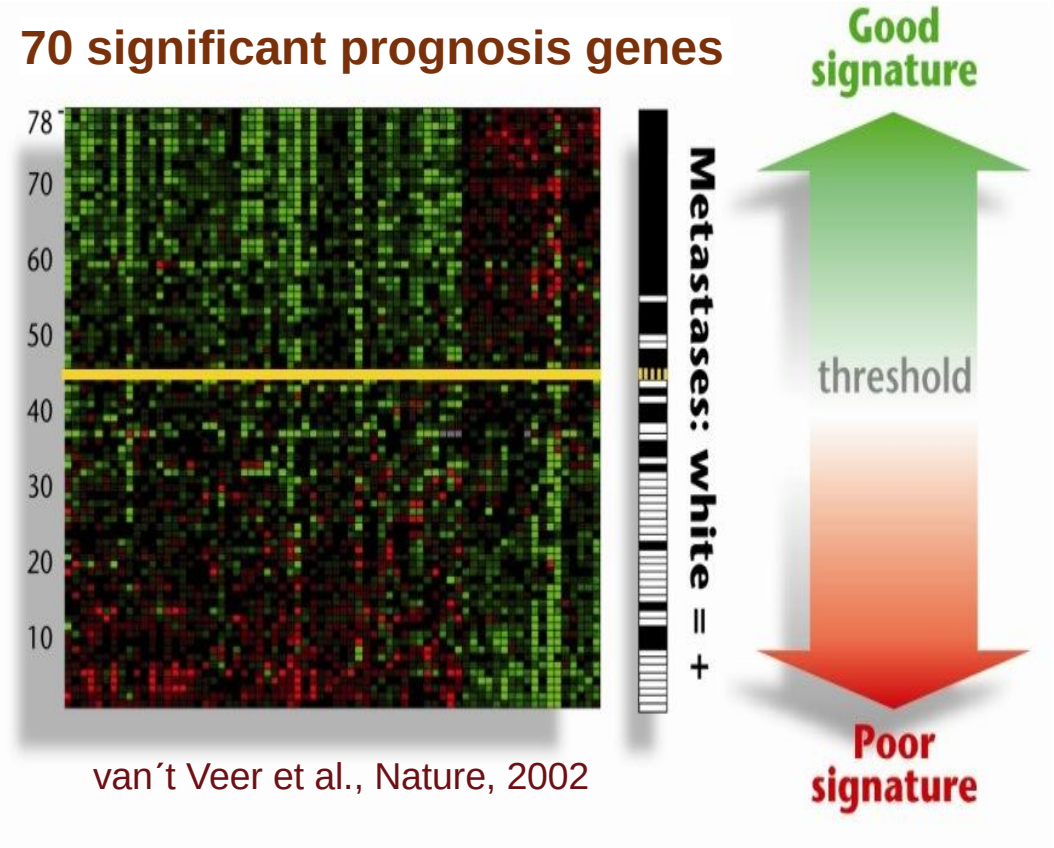


Mike

I-SPY 1: LABC are Poor Prognosis Tumors

NKI 70 Gene Profile	
"Good" Signature	9%
"Poor" Signature	**91%**

Mean Tumor Size= 6.0
Present as clinical mass
55% < Age 50



van´t Veer et al., Nature, 2002

Rates of pCR Differ Based on Biomarkers

Pathologic Complete Response (pCR)

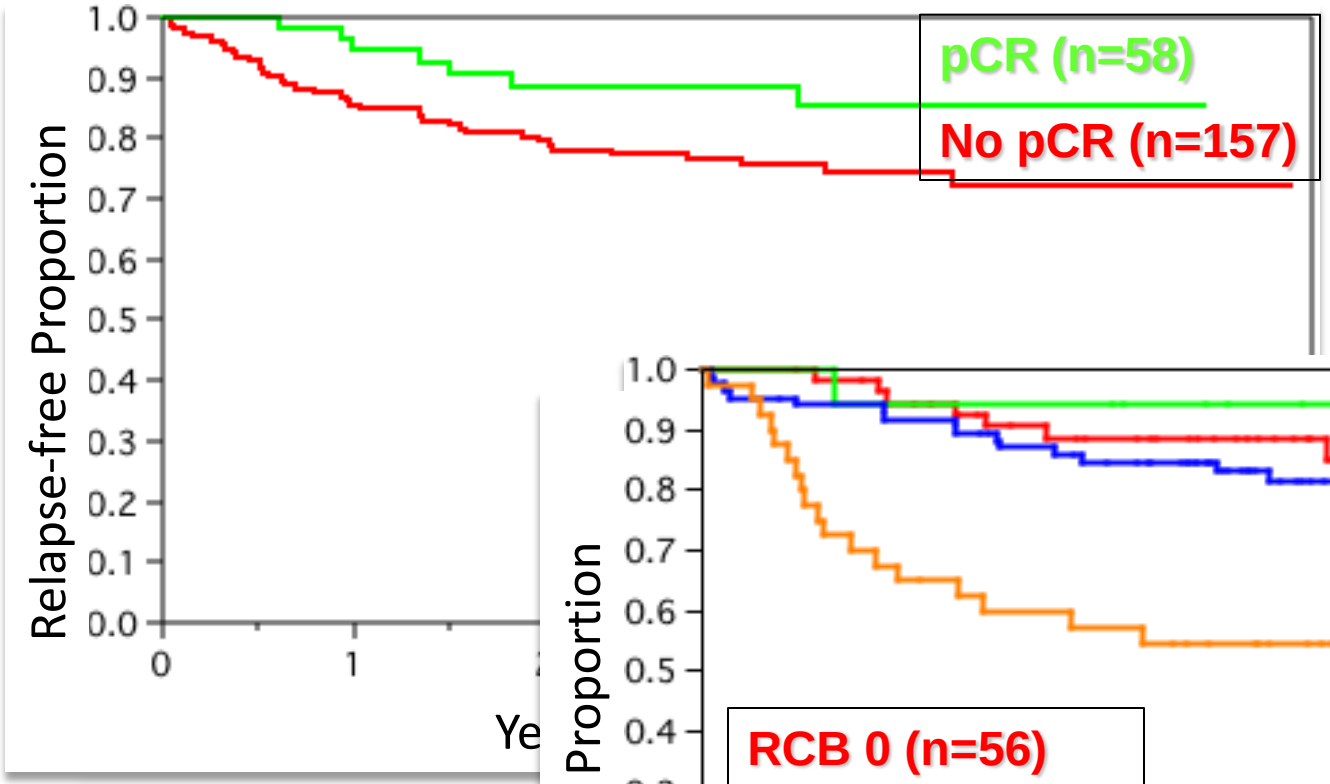
	ER+	ER-	
HER2+	33%	50%	41%
HER2-	10%	32%	18%
	15%	37%	24%

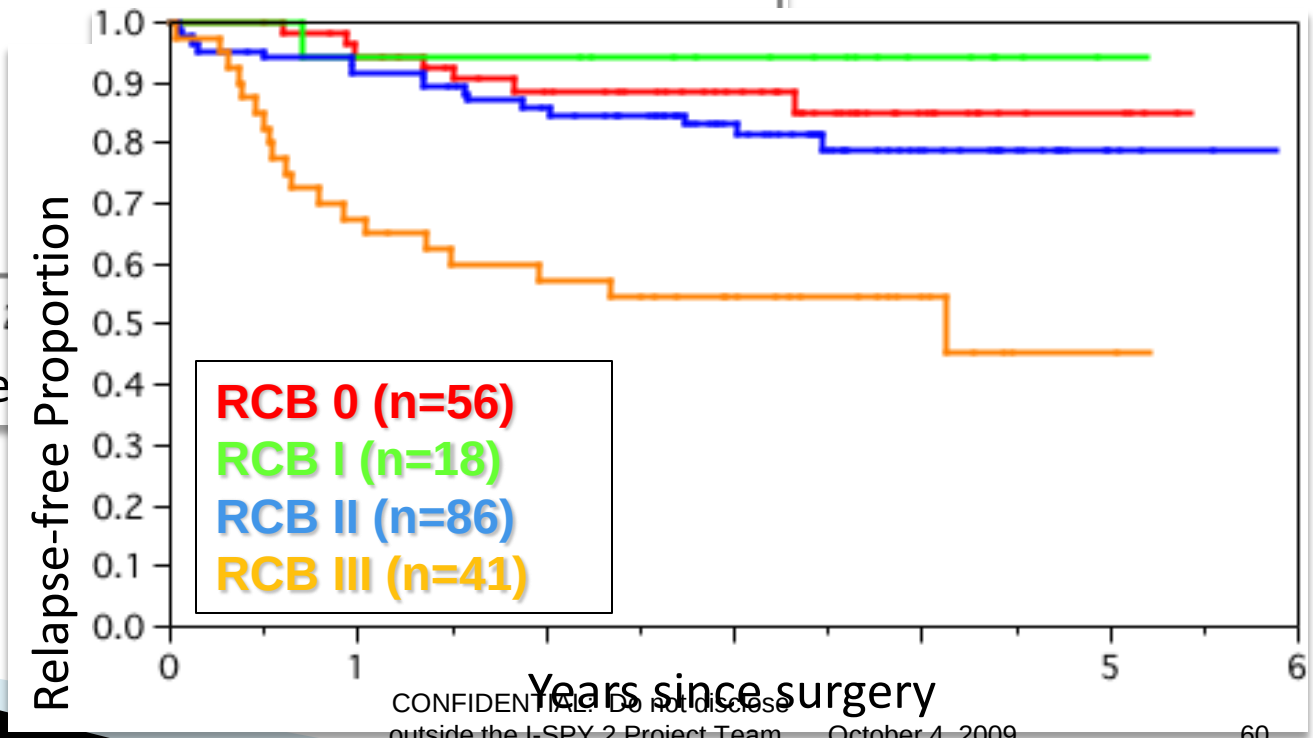
**Excludes patients who received trastuzumab (n=20)*

Effect of ER– over ER+: **22%** (p<0.01)

Effect of HER2+ over HER2–: **23%** (p<0.01)

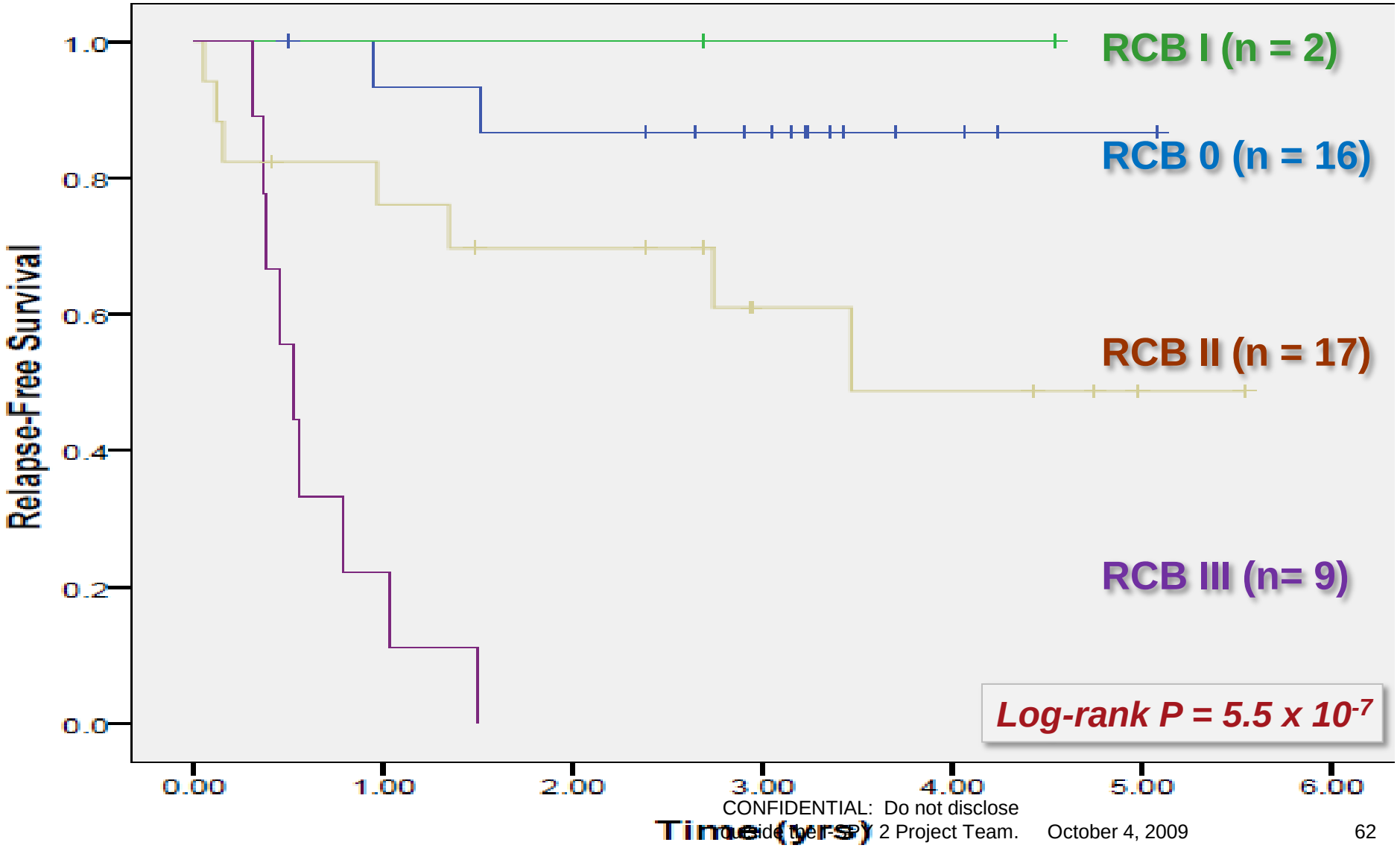
Relationship of pCR and RCB with Early Relapse for all I-SPY 1 Patients



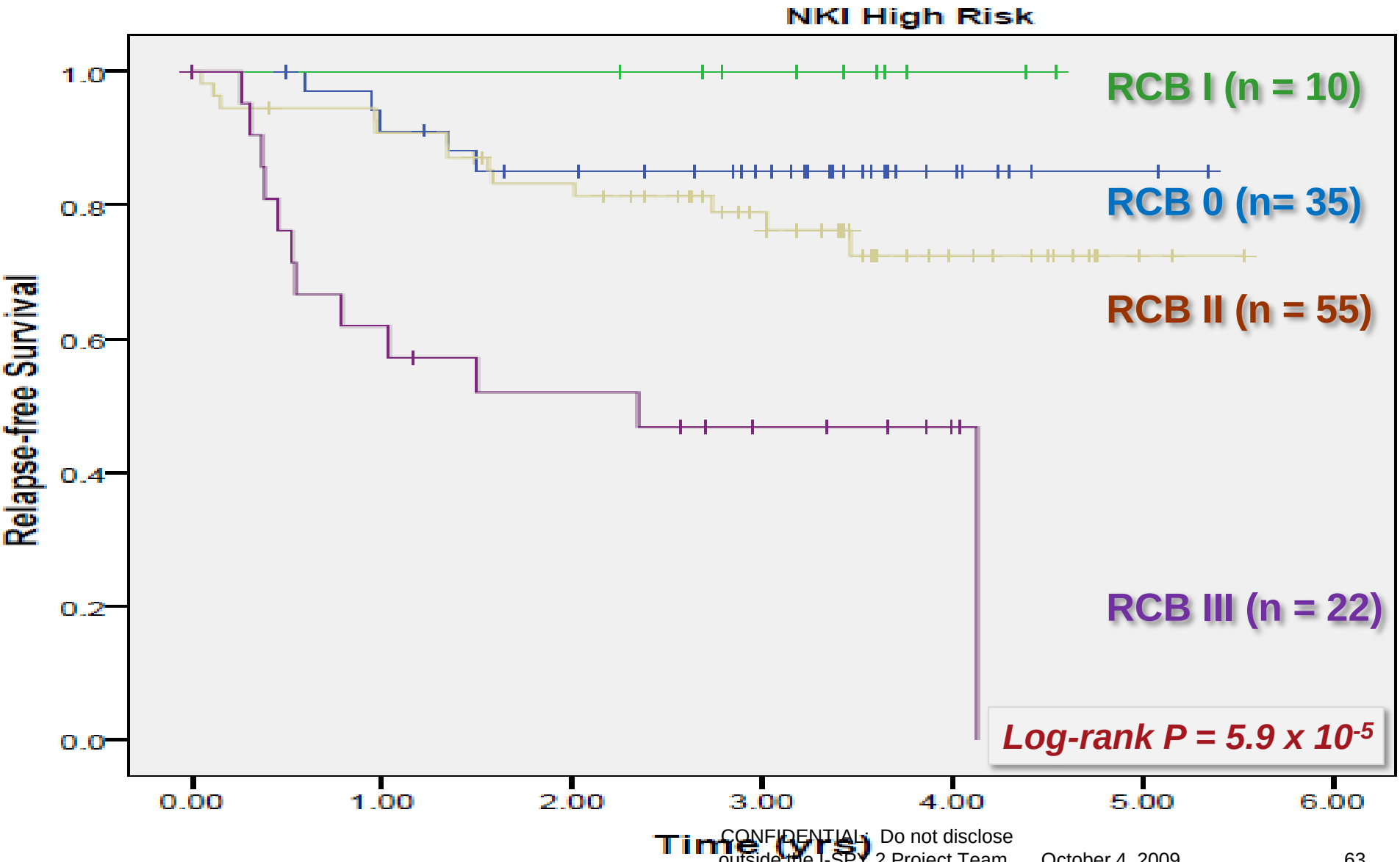


pCR and RCB are **VERY significant predictors** of early relapse in the context of a poor prognosis profile

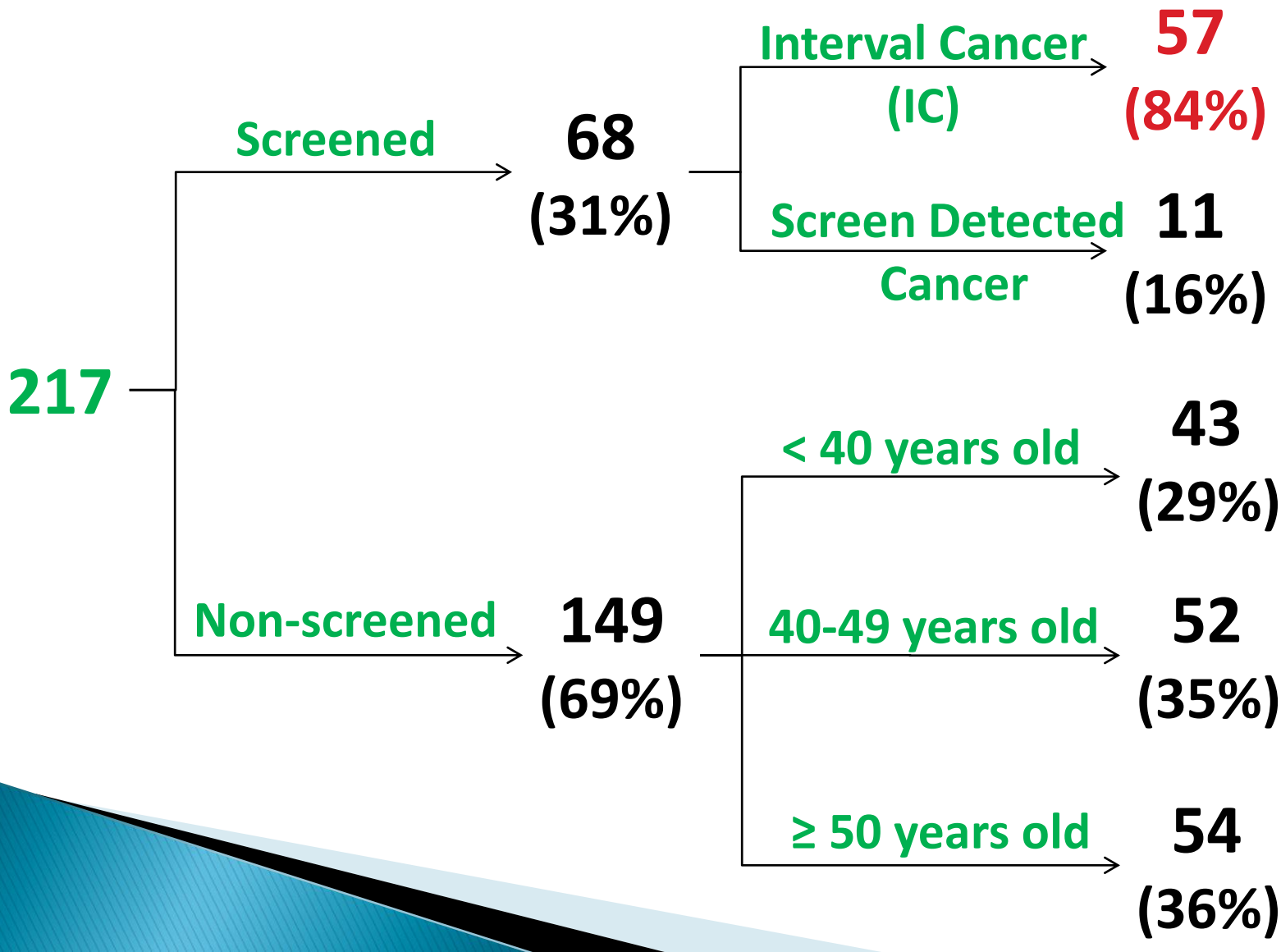
Survival Among Basal-like Tumors



Survival Among NKI-70 High Risk



Majority of LABCS in I-SPY 1 were identified during the interval between routine screenings



Estimating Expected Interval Cancer Rates in I-SPY 1

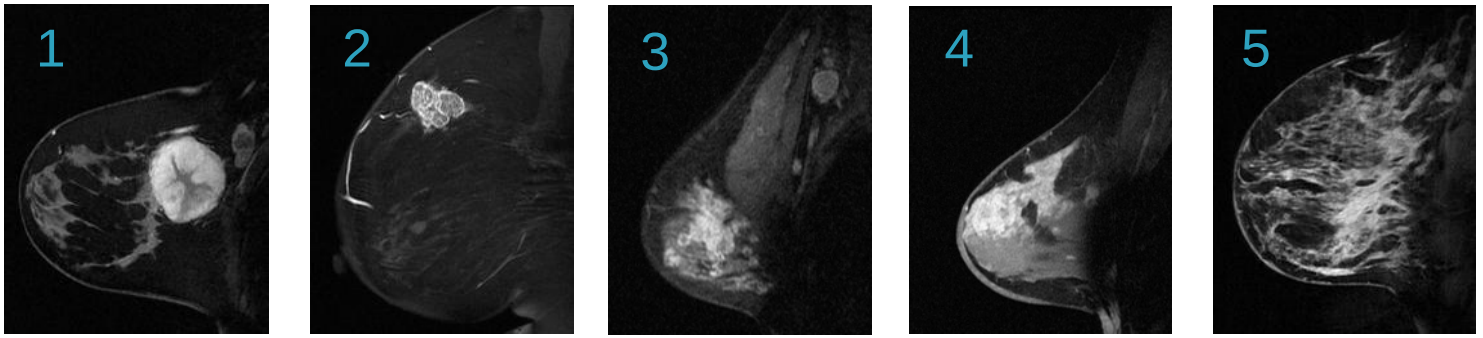
Based on rates observed in Norrbotten Mammography Screening Program*

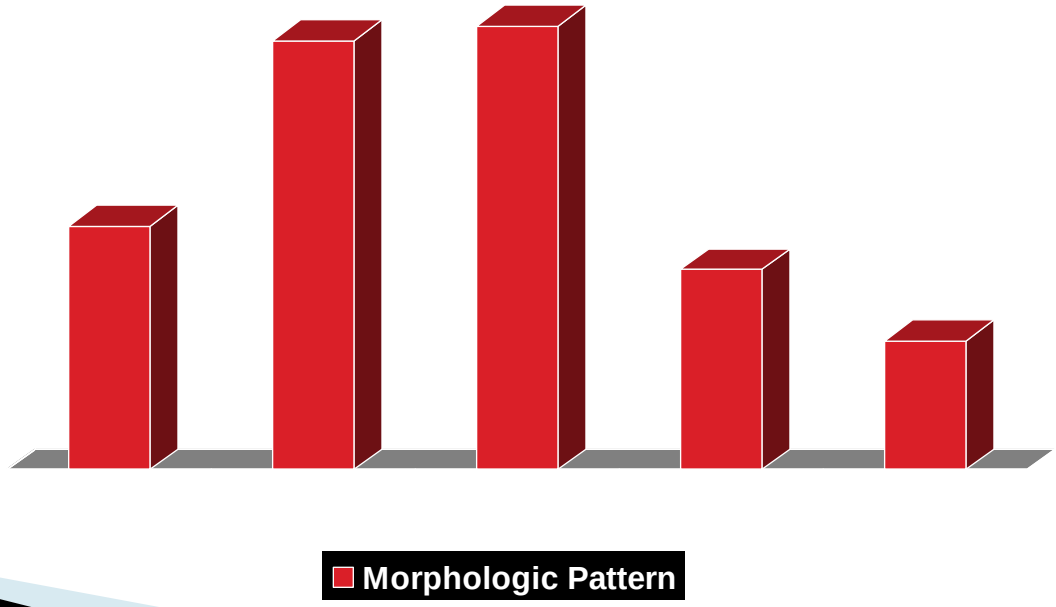
Age	Expected IC Rate	I-SPY Age Distribution	Expected IC in I-SPY
40-49	43%	34%	10
50-59	29%	53%	10
60-69	18%	13%	2
70-74	16%	0%	0

Expected IC Rate in I-SPY (22/68)	**32%**
Observed IC Rate in I-SPY (57/68)	**84%**

*Bordas, J Med Screen 2009

Morphologic Pattern





Results: Prediction of pCR

Predictor Variable	pCR = 0/1	
	OR	p-value
Clin Size2/Clin Size1	1.07	0.924
Log(LD2/LD1)	8.67	0.054
Log(Vol2/Vol1)	**19.81**	**<0.0001**
Peak SER2/Peak SER1	0.72	0.650

Adaptive Design vs. Standard Statistical Design

Adaptive

- Learn from every patient as the trial proceeds, trial "learns" degree of benefit and number of patients needed for proof
  - As evidence accumulates the level of confidence in our refined belief will increase.
- The data determines the point at which the results are robust enough to conclude that the drug/device is effective or not effective

Standard

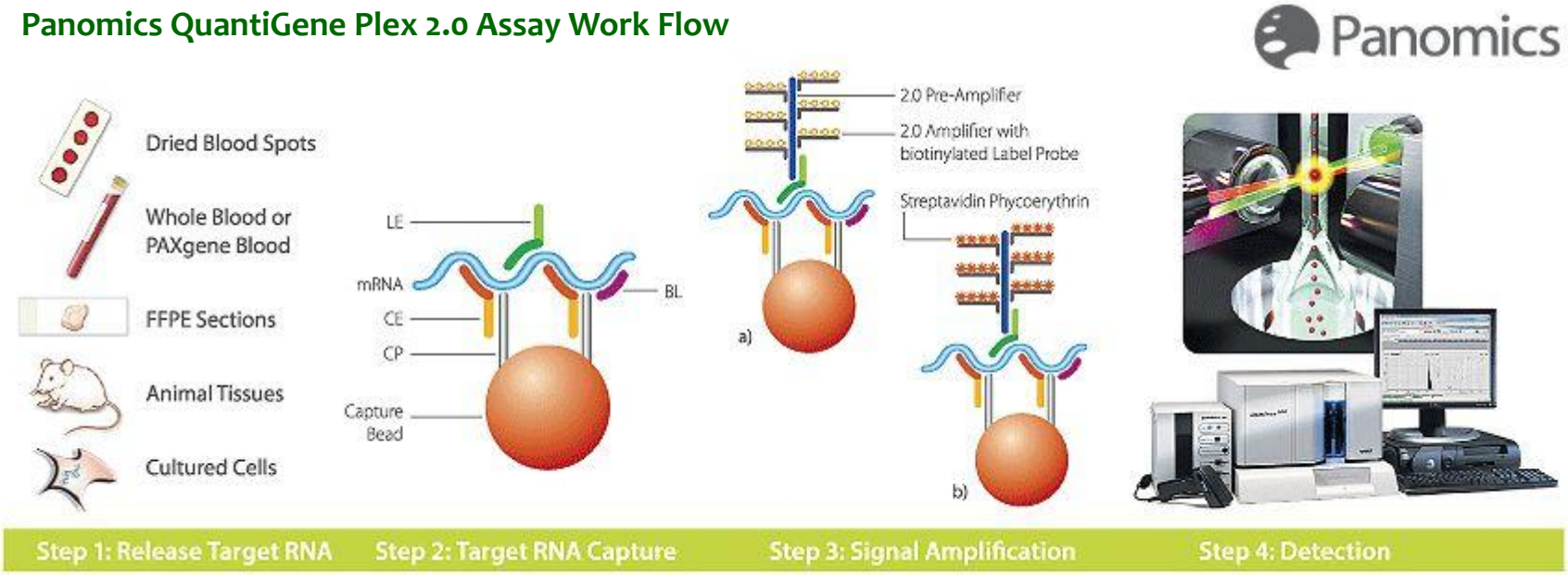
- Pre-specified number of patients based on an educated guess on how much benefit the drug will have
- Data reviewed for safety, stopping at pre-specified interim time point or the end of the trial

Qualifying Biomarker

Lawrence Berkeley National Lab 60 Cell Line Analysis using the Panomics QuantiGene Plex 2.0 Assay

The participant's tumor is matched to one of the 60 cell lines using the gene expression profile determined using the Panomics QuantiGene Plex 2.0 Assay.

Panomics QuantiGene Plex 2.0 Assay Work Flow

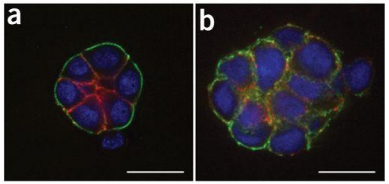


Qualifying Biomarker
Lawrence Berkeley National Lab 60 Cell Line Analysis

Trial Preparation

I-SPY 2 investigational agents are applied to the 60 LBNL Breast Cancer Cell Lines identified using the Panomics QuantiGene Plex 2.0 Assay.

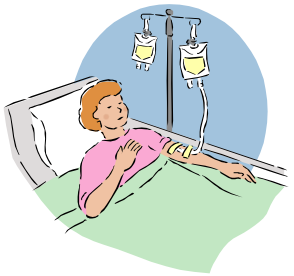
Cell lines are evaluated based on response to agents to predict effectiveness of the agents by cell line



a = normal cells b = malignant cells

Participant Treatment

Biopsy is taken from the trial participant's tumor and matched to one of the 60 cell lines based on gene expression profile using the Panomics QuantiGene Plex 2.0 Assay in a CLIA certified lab.



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

Results of treatment on participants are evaluated

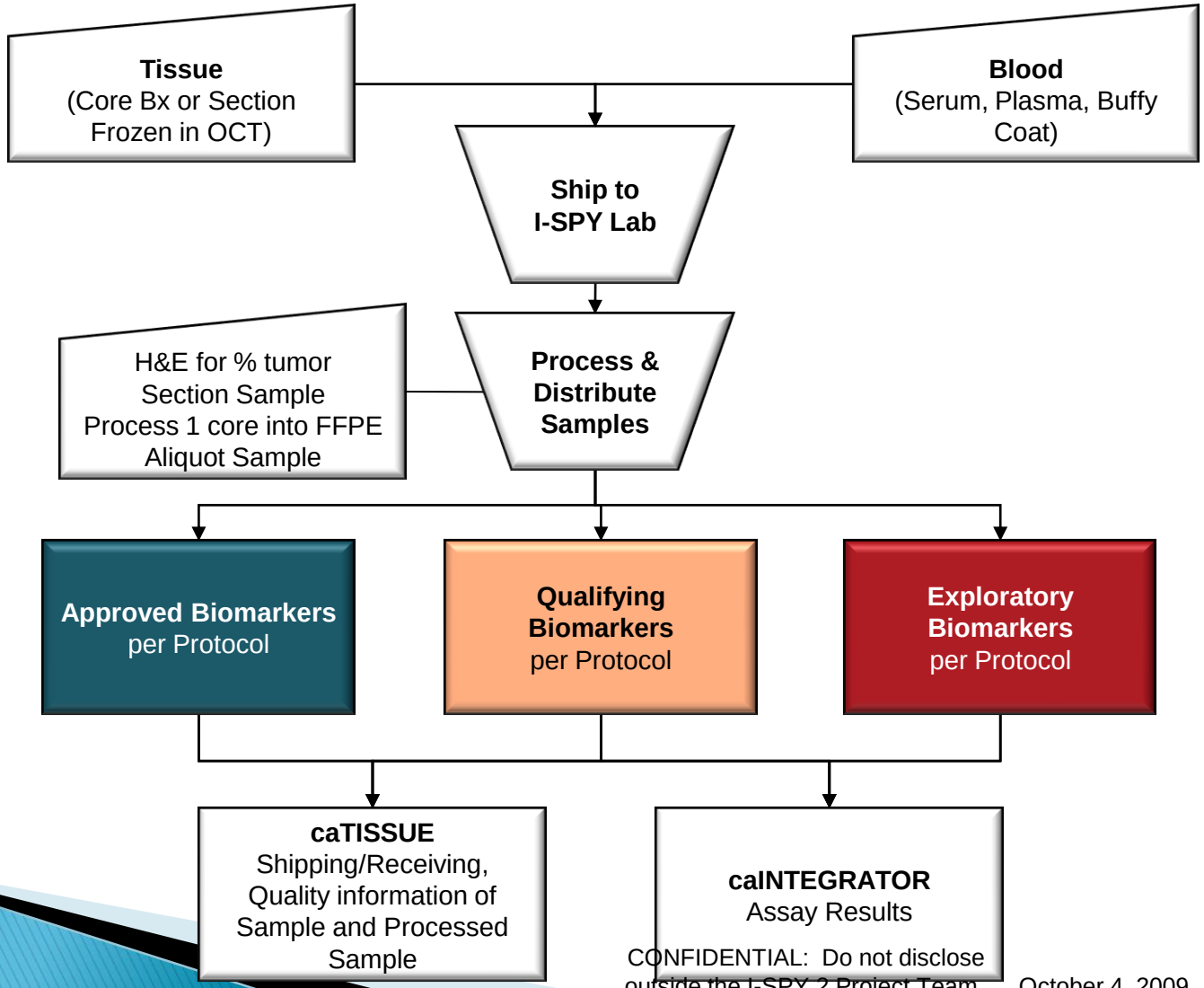
Post-Treatment Analysis

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

Recommended Tier 1 Agents

Agent	Type	Provider	Comments
ABT-888	PARP Inhibitor	Abbott	Data reviewed slightly out of date but has promising efficacy with low safety/toxicity concerns
Figitumumab (CP-751,871)	IGFR Inhibitor	Pfizer	
Neratinib (HKI-722)	Pan ErbB Inhibitor	Wyeth	
APO/TRAIL (AMG 655)	APO/TRAIL Agonist	Amgen	Efficacy not as promising as other candidate agents.
AMG 386	Angiopoietin Inhibitor	Amgen	Efficacy not as promising as other candidate agents.

Pre-Treatment, Early Paclitaxel & Pre-Surgery Samples



Simulations, null case (Type I error = 10%)

Assumptio

Subtype	S	E1	E2	E3
HR+HER2+MP+	0.35	0.35	0.35	0.35
HR+HER2+MP-	0.47	0.47	0.47	0.47
HR+HER2-MP+	0.17	0.17	0.17	0.17
HR+HER2-MP-	0.25	0.25	0.25	0.25
HR-HER2+MP+	0.55	0.55	0.55	0.55
HR-HER2+MP-	0.67	0.67	0.67	0.67
HR-HER2-MP+	0.32	0.32	0.32	0.32
HR-HER2-MP-	0.43	0.43	0.43	0.43

Average sample size

Subtype	S	E1	E2	E3
HR+HER2+MP+				
HR+HER2+MP-				
HR+HER2-MP+				
HR+HER2-MP-				
HR-HER2+MP+				
HR-HER2+MP-				
HR-HER2-MP+				
HR-HER2-MP-				
Total				

Simulations, E1 effective

Assumptions

Subtype	S	E1	E2	E3
HR+HER2+MP+	0.35	**0.71**	0.35	0.35
HR+HER2+MP-	0.47	**0.8**	0.47	0.47
HR+HER2-MP+	0.17	**0.48**	0.17	0.17
HR+HER2-MP-	0.25	**0.59**	0.25	0.25
HR-HER2+MP+	0.55	**0.84**	0.55	0.55
HR-HER2+MP-	0.67	**0.9**	0.67	0.67
HR-HER2-MP+	0.32	**0.68**	0.32	0.32
HR-HER2-MP-	0.43	**0.77**	0.43	0.43
True Signature		All	None	None

Average sample size

Subtype	S	E1	E2	E3
HR+HER2+MP+				
HR+HER2+MP-				
HR+HER2-MP+				
HR+HER2-MP-				
HR-HER2+MP+				
HR-HER2+MP-				
HR-HER2-MP+				
HR-HER2-MP-				
Total				

Arm	P1	P2	P3	P4	P5	Av Mos in Trial
E1						
E2						
E3						

Simulations, E1 = HR+, E2 = HER2-

Assumptions

Subtype	S	E1	E2	E3
HR+HER2+MP+	0.35	**0.71**	0.35	0.35
HR+HER2+MP-	0.47	**0.8**	0.47	0.47
HR+HER2-MP+	0.17	**0.48**	**0.48**	0.17
HR+HER2-MP-	0.25	**0.59**	**0.59**	0.25
HR-HER2+MP+	0.55	0.55	0.55	0.55
HR-HER2+MP-	0.67	0.67	0.67	0.67
HR-HER2-MP+	0.32	0.32	**0.68**	0.32
HR-HER2-MP-	0.43	0.43	**0.77**	0.43
True Signature		HR+	HER2-	None

Average sample size

Subtype	S	E1	E2	E3
HR+HER2+MP+				
HR+HER2+MP-				
HR+HER2-MP+				
HR+HER2-MP-				
HR-HER2+MP+				
HR-HER2+MP-				
HR-HER2-MP+				
HR-HER2-MP-				
Total				

Arm	P1	P2	P3	P4	P5	Av Mos in Trial
E1						
E2						
E3						

Conclusions

- Clinical trials can prospectively identify responding patient subpops
- False positives can be beaten down (requires potential for larger n)
- Drug companies will work together
- Not perfect, but we're getting better
- "A new day is dawning, Watson!"

Simulations

- For operating characteristics:
  - Type I error rate
  - Power (many variants)
  - Sample size distribution (mean)
- Requires completely prospective design (computationally intensive)
- Many scenarios
- Accrual rate matters
- # exp drugs over time matters

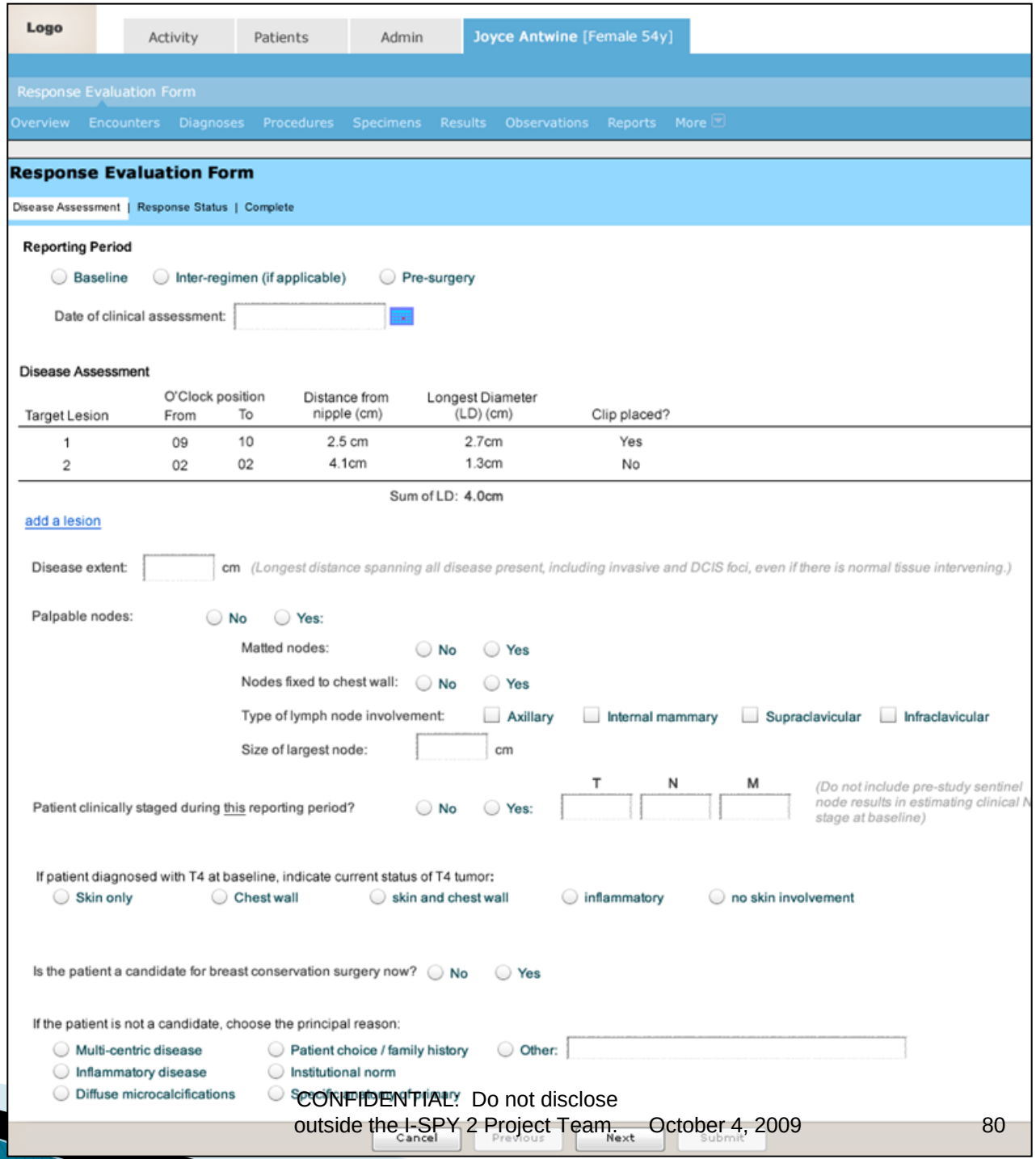
Experimental Drugs

- Sample size for each drug, 20 to 120 (minimum 60 if “success”)
- Maximum of 5 exp drugs at a time
- Patient enters trial, identify subtype
- Find prob each drug >> control; based on all current results (Bayes)
- Covariate modeling (across subtypes)
- Assign in proportion to current prob drug >> control, by subtype

Longitudinal Modeling (MRI volume is auxiliary endpoint for adaptive decision making)

- **Assess predictability (depending on therapy) of pCR from interim MRI**
- **Borrow relationship (but discounting) from I-SPY1**

Web-based eCRF Entry Screen Example



Preparing for IRB Approval

The I-SPY 2 Protocol and Informed Consent Documents are highly complex

- Adaptive trial design
- Randomization process
- Multiple novel agents from multiple pharmaceutical companies
- Biomarkers screening
- Two-stage informed consent
- Convened a meeting of 45 stakeholders-IRB chairs and PIs