The I-SPY Master Trials: A Model for Accelerating the Pace of Getting the Right Drugs to the Right Patients

Laura Esserman MD MBA
Professor of Surgery and Radiology
Director, Carol Franc Buck Breast Care Center
University of California, San Francisco

The Problem for Patients

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

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

Many new therapeutic options- little chance to rapidly get them to patients

Access to new investigational drugs depends on where in the world you live

The Problem for Companies

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

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

Cancer is a subset of diseases

Blockbuster approach won't work

Current path is UN-SUSTAINABLE

COMMENTARY

Knowledge Turns:
Indicators of time it takes for an experiment to proceed from hypothesis ➔ result ➔ new hypothesis ➔ new result

Efficiency in the Health Care Industries
A View From the Outside

Andrew S. Grove, PhD

THE HEALTH SCIENCE/HEALTH CARE INDUSTRY AND THE microchip industry are similar in some important ways: both are populated by extremely dedicated and

Knowledge Turn for Metastatic ➔ Adjuvant ➔ Practice: **20 years**

Knowledge Turn for Neoadjuvant Phase 2 ➔ Phase 3 ➔ Practice: **2-3 years**

services.

To be sure, there are additional fundamental differences between the 2 industries. One industry deals with the well-defined world of silicon, the other with living human beings. Humans are incredibly complex biological systems, and working with them has to be subject to safety, legal, and ethical concerns. Nevertheless, it is helpful to mine this comparison for every measure of learning that can be found.

plex experiment. The test chips are monitored as an experiment progresses. If they show negative results, the experiment is stopped, the information is recorded, and a new experiment is started.

This concept is also well known in the health sciences. It is embodied in the practice of futility studies, which

The difference is this: whereas the surrogate "end point" in the case of microchip development—the test chip failure—is well defined, its equivalent in the health sciences is usually not. Most clinical trials fall back on an end point that compares the extent by which a new drug or therapy extends life as compared with the current standard treatment. Reaching this end point usually takes a long time; thus, knowledge turns are slow. In many instances, a scientist's career can continue only through 2 or 3 such turns. The re-

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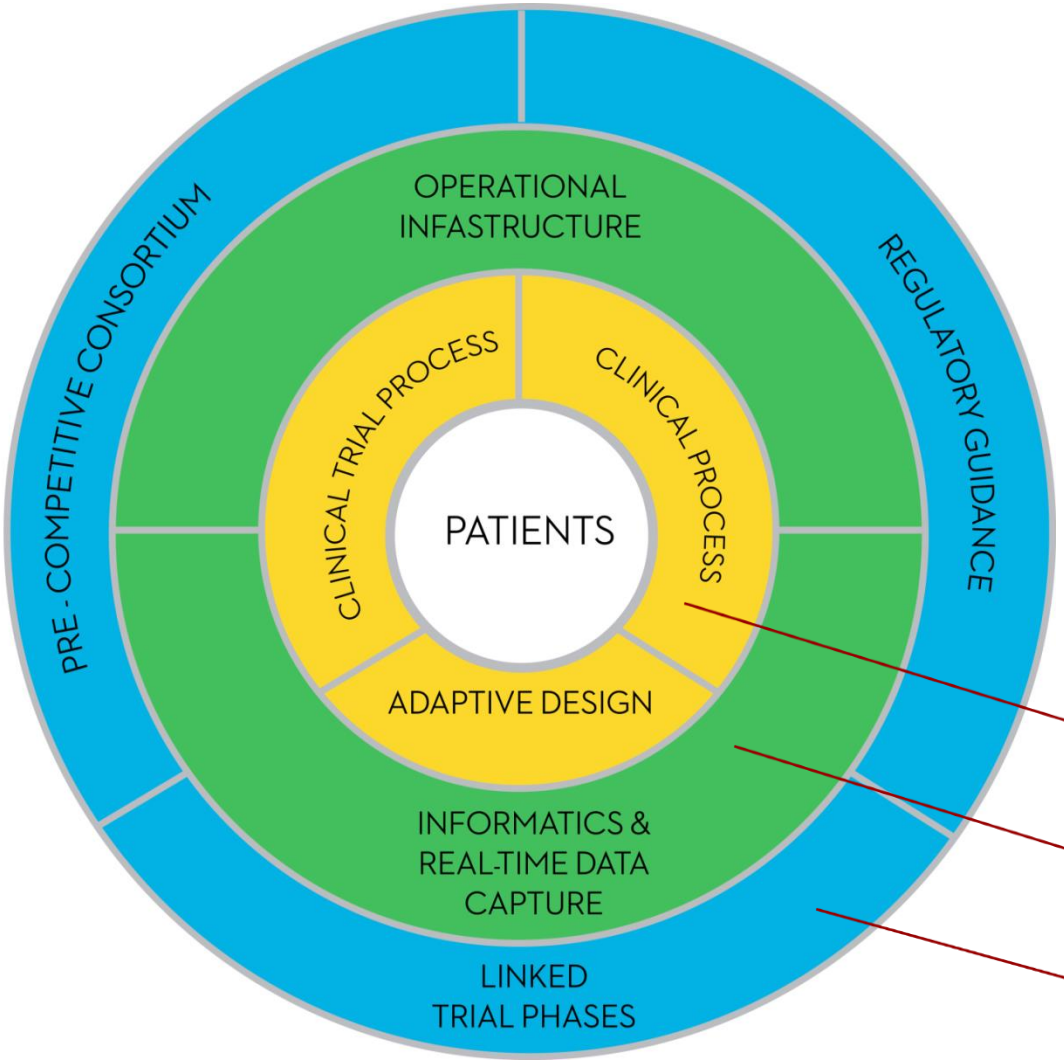
A Process Model to Accelerate Knowledge Turns



Linked trial phases could provide additional efficiency and further

Core

Structural

Alignment

Optimize the Clinical Care Process

Women at Risk for Systemic Recurrence

- Will not be cured with surgery alone

- Order of surgery, systemic therapy has no impact on survival outcomes

- Neoadjuvant approach is an opportunity
  - Downstage tumors, refine local therapy options
  - Better understand response to therapy, prognosis
  - Accelerate targeted drug development to improve outcomes in highest risk women
  - Particularly relevant as a tool to sort out optimal treatments in the molecular era

An historically fatal disease that has been turned into a chronic condition

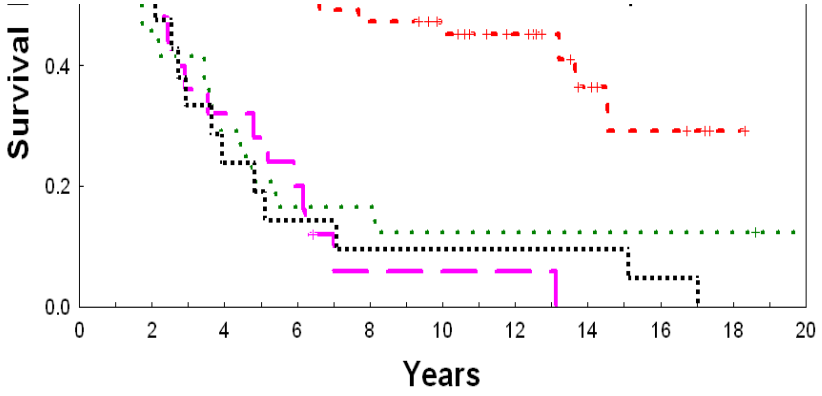
LESSONS FROM CML

Survival in Accelerated and Blast Phase CML Over Time

Accelerated Phase

Blast Phase

Testing new agents in the metastatic setting may NOT be optimal



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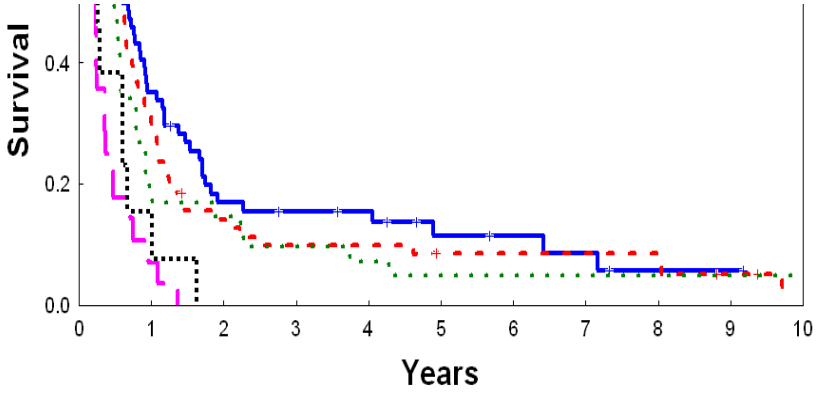

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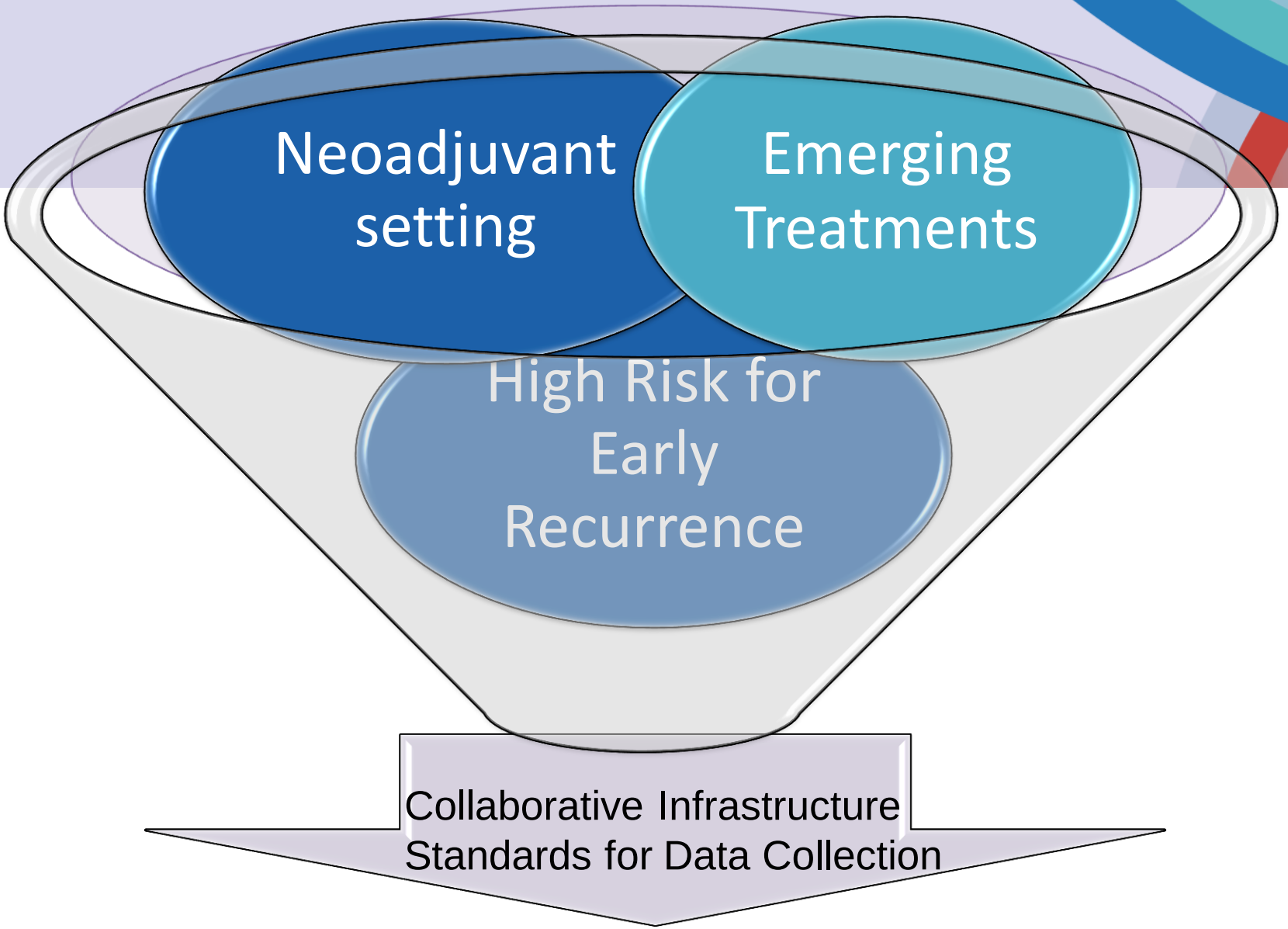

Neoadjuvant setting
Emerging Treatments
High Risk for Early Recurrence
Collaborative Infrastructure
Standards for Data Collection

I-SPY 2

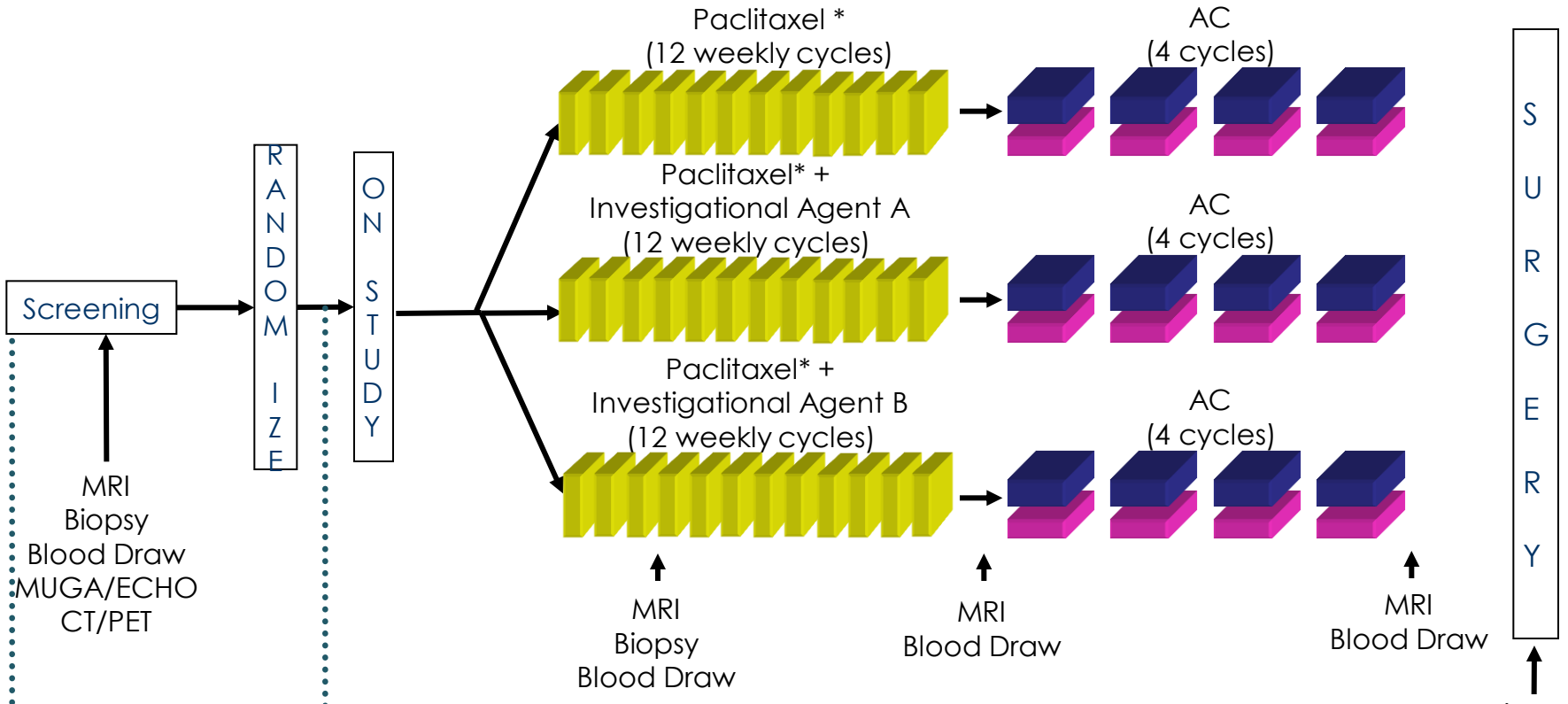
I-SPY 2 is Designed to

- Screen phase 2 agents in combination with standard chemotherapy in neoadjuvant setting
  - Endpoint is pCR
  - Design is adaptive within the trial, multiple agents, shared std arm
  - “Graduation” indicates an 85% predicted likelihood of success in a 300-patient phase 3 trial for drug biomarker pair

- Accelerate process of identifying drugs that are effective for specific breast cancer subtypes
  - Integration of biomarkers, analysis within subsets by design
  - Increase success of phase 3 or confirmatory trials

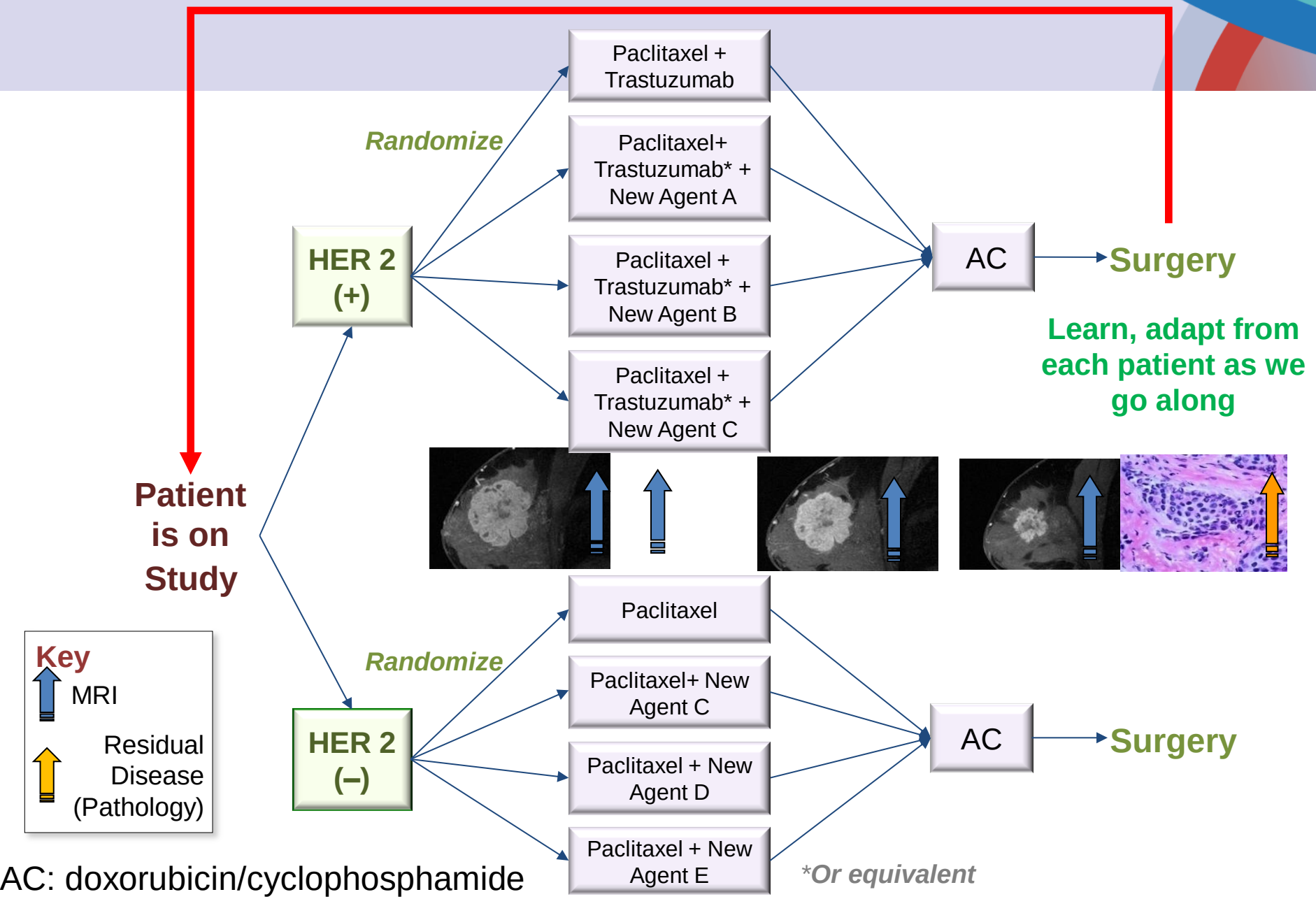
- Reduce the cost, time, and numbers of patients needed to get effective drugs to market through accelerated approval

Summary of Study Plan



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

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



AC: doxorubicin/cyclophosphamide

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

Patient is on Study

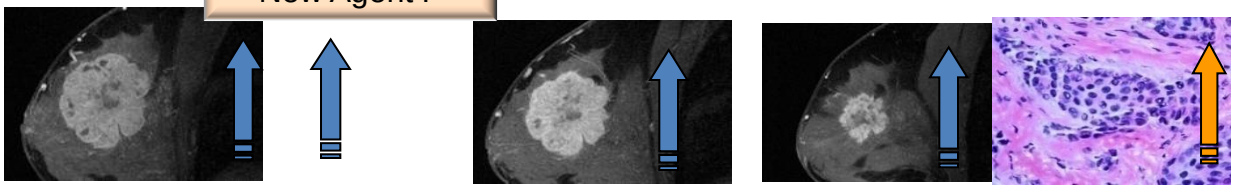
HER 2 (+)

Randomize

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

AC → Surgery

Learn, adapt from each patient as we go along



HER 2 (–)

Randomize

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

AC → Surgery

*Or equivalent

Key

MRI

Residual Disease (Pathology)

I-SPY 2 is a Standing Trial with a Master Protocol

I-SPY 2 Participating Organizations

Sponsors and Managers

QuantumLeap
A Healthcare Collaborative

UCSF
University of California
San Francisco

SAFEWAY
Ingredients for life.

William K. Bowes, Jr.
Foundation

Foundation for the National Institutes of Health
THE biomarkers CONSORTIUM

Investigational Agent Providers

abbvie

AMGEN

Genentech
A Member of the Roche Group

MERCK
Be well

SYNTA
PHARMACEUTICALS®

Puma Biotechnology

Biomarker Device Providers

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

UCSF
University of California
San Francisco

BERKELEY LAB
LAWRENCE BERKELEY NATIONAL LABORATORY

GEORGE MASON UNIVERSITY

sentinelle MEDICAL

HOLOGIC
The Women's Health Company

THERANOSTICS HEALTH
The Partner of Choice for Personalized Medicine

agendia
decoding cancer

Biomarker Categories in I-SPY 2

- When a drug leaves the trial, we learn the probability of success to predict response for
  - Established, IDE Biomarkers
    - HR, HER2, Mammaprint: 10 signatures
  - Qualifying Biomarkers
  - Exploratory Biomarkers
    - new response predictors

FDA Cleared or Approved
Stratification/randomization

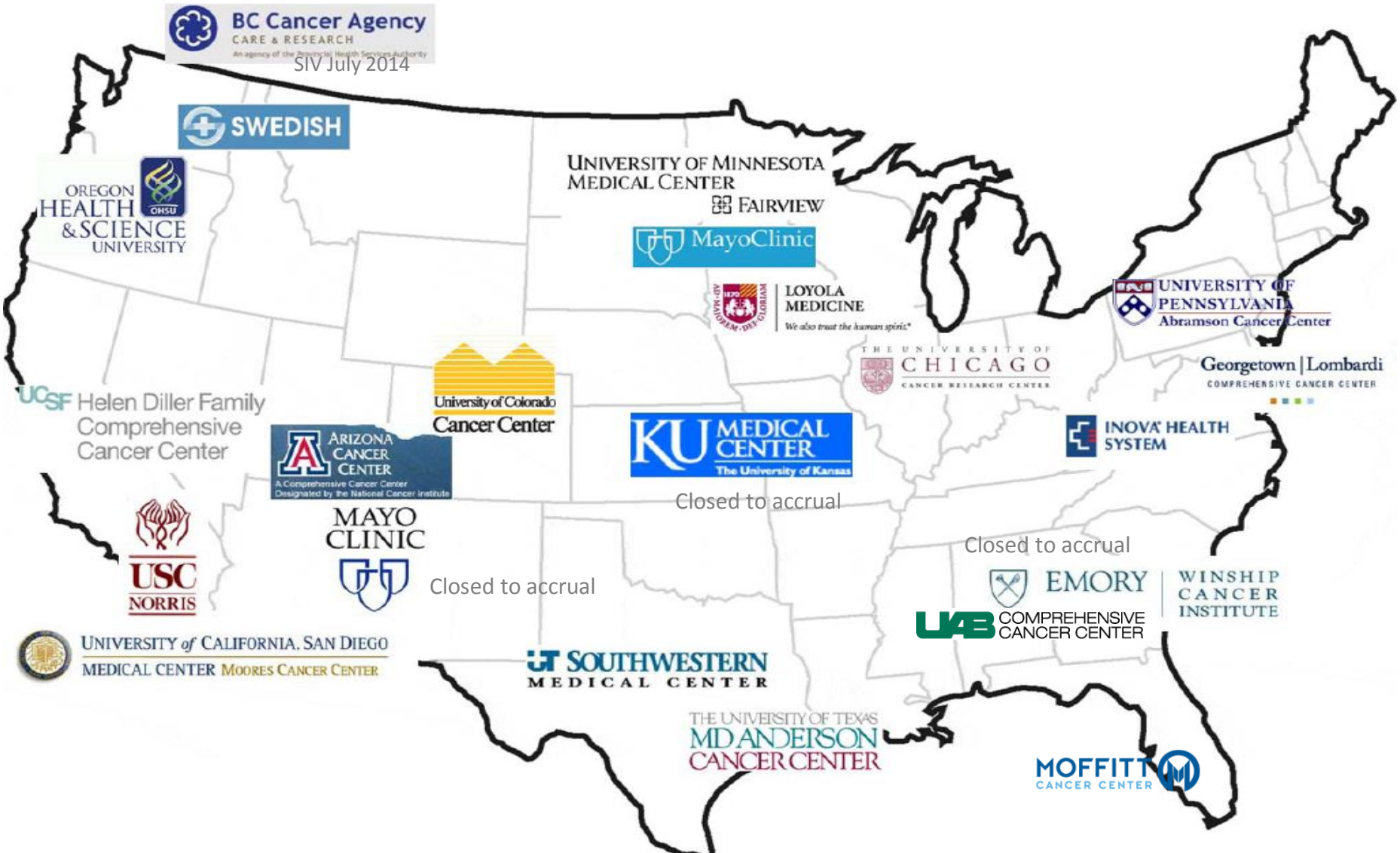
Hypothesis Testing

Hypothesis Generating

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

Participating Trial Sites – 20 Sites Open to Accrual

>1200 patients screened, >30 patient/month, >550 have completed surgery



I-SPY 2 TRIAL Study Team

I-SPY 2 Working Group Chairs:
Laura Esserman: Principal Investigator
Don Berry: Principal Investigator, Study Statistician
Angela DeMichele: Co-PI, Trial Operations
Doug Yee: Co-PI, Agents
Laura van't Veer: Co-PI, Biomarkers
Fraser Symmans: Co-PI, Pathology
Nola Hylton: Co-PI Imaging
Michael Hogarth: Co-PI, Informatics
Meredith Buxton: Co-PI, Project Management
Jane Perlmutter: Lead Advocate

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

Sponsor: QuantumLeap Healthcare Collaborative: Melissa Paoloni, Alan Hu
FNIH Biomarker Consortium**:** David Wholley & Sonia Pearson-White
Funding: Safeway, Bill Bowes, Quintiles, J&J, Genentech, Amgen, Give Breast Cancer the Boot, Harlans, Side-Out, Avon, Alexandria
Oversight: NCI: Anna Barker/ASU, Gary Kelloff
FDA: Janet Woodcock, Richard Pazdur

Agent Chaperones

ABT888:	**Hope S. Rugo, Funmi Olopade**
Neratinib:	John Park, Minetta Liu
AMG 386:	Kathy Albain, Brian Leyland-Jones
AMG479:	Doug Yee, Paul Haluska
MK2206:	Debu Tripathy, Jo Chien
Pertuzumab:	Stephen Chia, Stephen Chui
Pertuzumab: /T-DM1:	Angie DeMichele, Stacy Moulder

Site PIs:
UCSD: Anne Wallace**; USC:** Debu Tripathy
U Arizona: Julie Lang/ Rebecca Viscusi**; Swedish:** Hank Kaplan
MDAnderson: Lajos Pusztai/ Stacey Moulder; **UMinn:** Doug Yee
Mayo: Judy Boughey**; Mayo Scottsdale:** Donald Northfelt
UCSF: Jo Chien**; Georgetown:** Minetta Liu/Claudine Isaacs
U.Chicago: Rita Nanda; **Inova Fairfax:** Kristen Edmiston
Loyola Chicago: Kathy Albain**; U. Kansas:** Qamar Khan
U.Colorado: Anthony Elias**; U.Penn:** Angela DeMichele
Oregon HSU: Steven Chui**; ; UTSouthwestern:** David Euhus
U Alabama: Andres Forero **British Columbia CA:** Stephen Chia

I-SPY Milestones

- Demonstrated that pCR endpoints work better by subtype
- Enlisted multiple pharma companies into same trial
- Developed I-SPY 2 infrastructure
  - IT systems to support adaptive learning
  - New methods to distribute credit
- Successful integration of adaptive randomization, including real time data collection and use in driving ongoing randomization
- Demonstration of the standing trial concept
  - multiple arms, single backbone and Master IND
  - 8 drugs introduced into the study, several in the pipeline
- Graduation of 2 agents, with biomarker signatures
  - Neratanib (Puma Biotechnology) (Dec 4, 2013): HER2+ HR-
  - Veliparib (AbbVie) (Dec 13, 2013): HER2- HR- (triple negative)
- Accelerated Approval guidance issued by FDA
  - Next step: I-SPY 3 international trial

Compressing the Timeline

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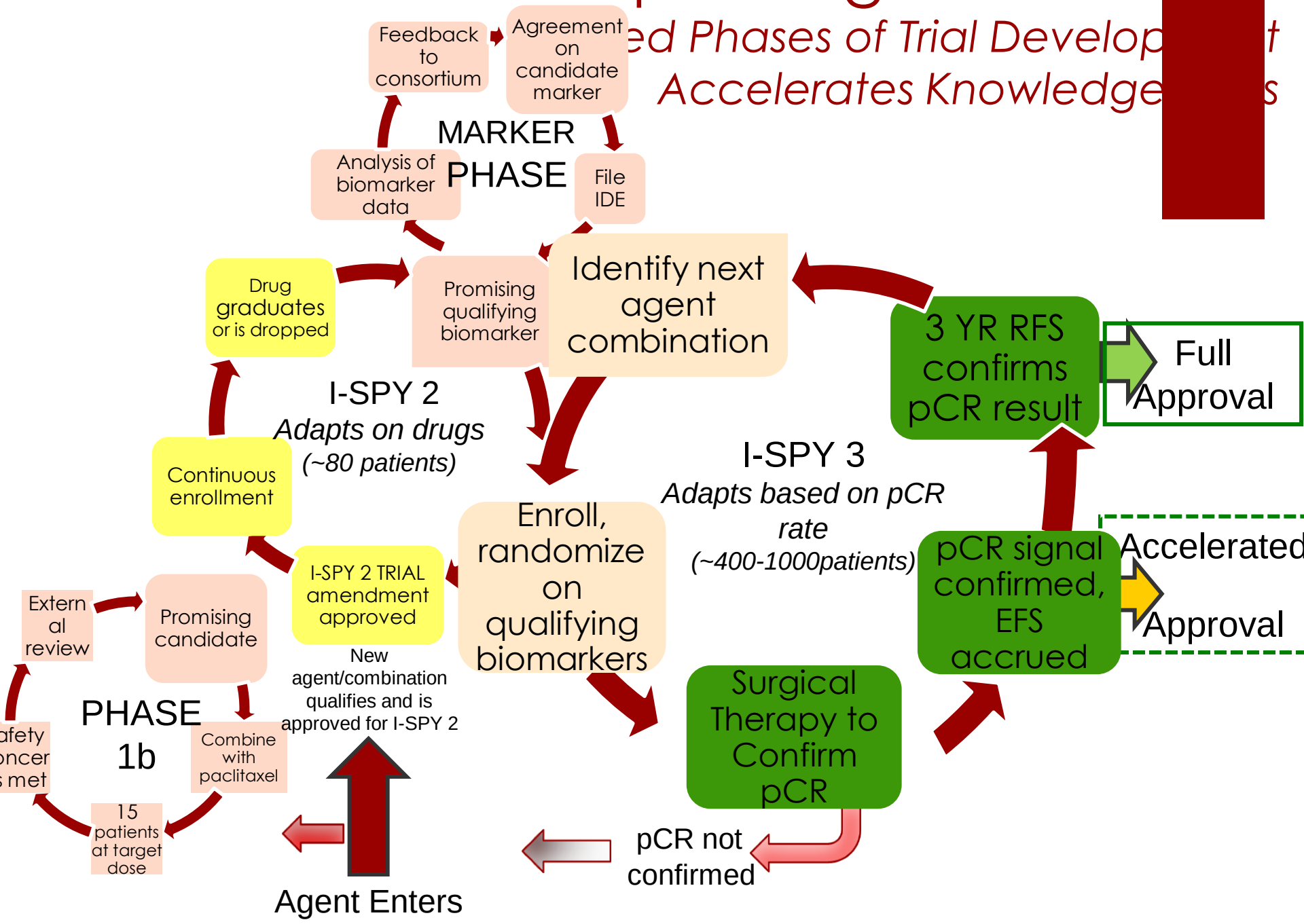
Accelerates Knowledge s



The Value of A Consortium Model

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