Adaptive Clinical Trials: A New Paradigm in Drug Development

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Making Cancer History®

Financial Disclosure

Part owner Berry Consultants, LLC.
Designs adaptive trials for medical device and pharmaceutical companies.

Outline

- Background: Bayesian adaptive approach in drug development
- Seamless phase II/III trial from Critical Path Initiative
- Biomarker-driven trials & I-SPY2

Janet Woodcock, Director CDER FDA

“Improved utilization of adaptive and Bayesian methods” could help resolve low success rate of and expense of phase 3 clinical trials

Current use of Bayesian adaptive designs

- MDACC (> 300 trials)
- Device companies (> 25 PMAs)*
- Drug companies (Most of top 40; many biotechs)**

*http://www.fda.gov/MedicalDevicesDeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm

**http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

Some areas of application of Bayesian adaptive drug trials

- Oncology
- Migraine
- Rh Arthritis
- Lupus
- Sepsis
- Diabetes
- Obesity
- Stroke
- Gastroparesis
- Spinal Cord Injury
- HIV
- Hepatitis C
- Pre-term labor
- Constipation
- Overactive bladder
- Libido
- Alzheimer's
- Parkinson's

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FDA's $25 Million Pitch for Improving Drug Regulation

by Jennifer Couzin-Frankel on 7 October 2010, 3:17 PM | Permanent Link | 0 Comments

"Our current approach [to trials] is horribly inefficient, and we need to do something better," says Roger Lewis, an emergency medicine physician at Harbor-University of California, Los Angeles, Medical Center. Lewis helps advise a company called Berry Consultants …

conjunction with the National Institutes of Health (NIH), it announced four sizable grants, totaling $9.4 million, in regulatory science. (FDA contributed just under $1 million and NIH gave the rest.) They include support for a heart-lung system that can test potential drugs and an effort to dramatically streamline clinical trials.

"Our current approach [to trials] is horribly inefficient, and we need to do something better," says Roger Lewis, an emergency medicine physician at Harbor-University of California, Los Angeles, Medical Center. Lewis helps advise a company called Berry Consultants founded by Donald Berry, a biostatistician at M.D. Anderson Cancer Center in Houston, Texas. He and Berry, along with emergency medicine physician William Barsan at the University of Michigan, will be studying whether "adaptive" trial designs that incorporate new information in midcourse can answer medical questions. They also want to learn what concerns researchers might have about

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Bayesian adaptive trials

- Stopping early (or late)
  - Efficacy
  - Futility
- Dose finding (& dose dropping)
- Seamless phases
- Population finding
- Adaptive randomization
- Ramping up accrual

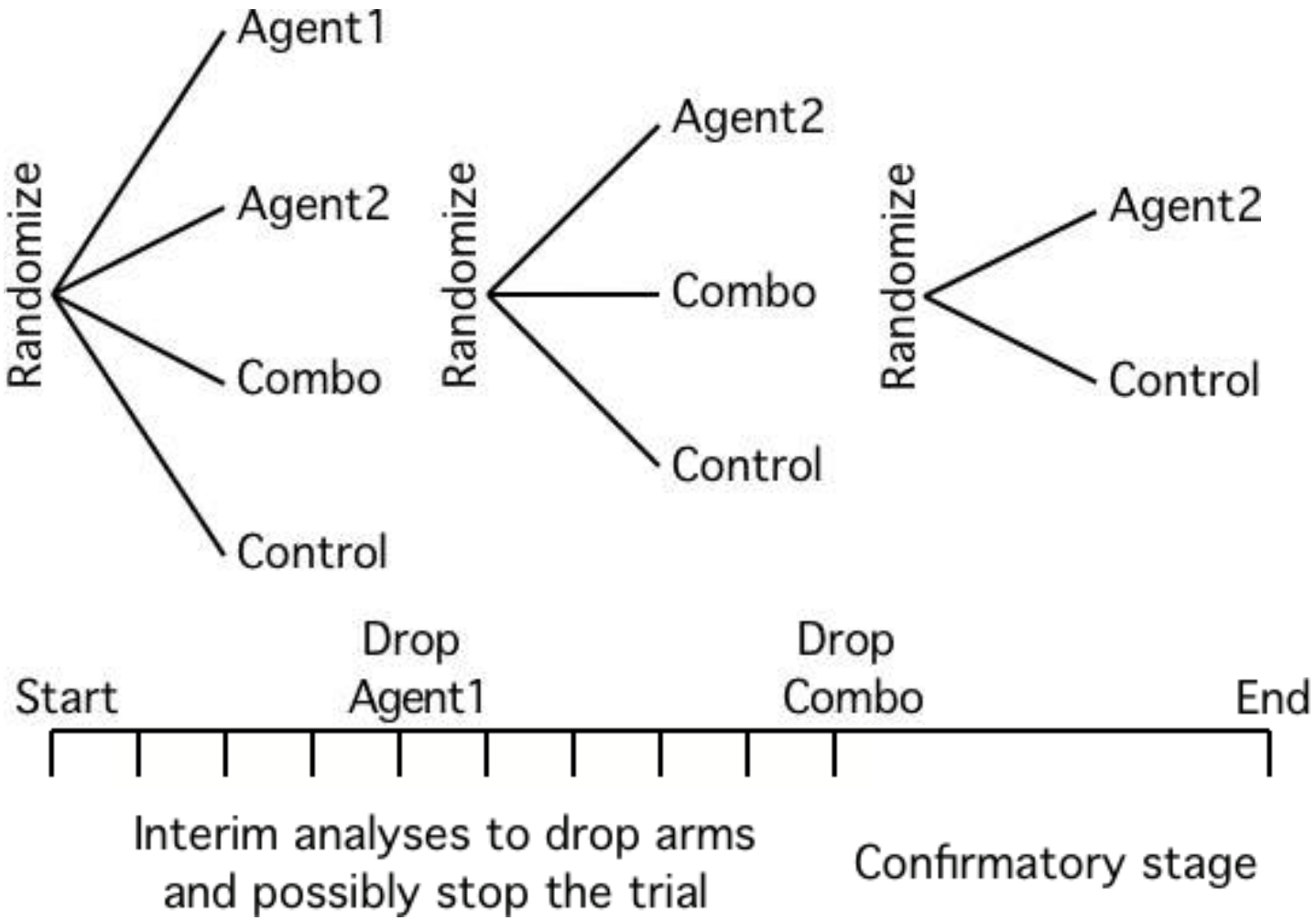
Why?

- Smaller trials (usually!)
- More accurate conclusions
- Can focus on better treatment of patients in trials

References

- Berry DA (1996). *Statistics: A Bayesian Perspective.* Duxbury. (ISBN: 978-0534234720)
- Berry DA (2006). Bayesian clinical trials. *Nature Reviews Drug Discovery.* (Free download: http://archlab.gmu.edu/people/jthompsz/Berry2006.pdf)
- Berry DA (2009). Statistical Innovations in Cancer Research. In *Cancer Medicine e.8*. Ch 35, pp 446-463. London: BC Decker. (Ed: Holland J, Frei T et al.)

Adaptive Phase II/III Trial



IoM Report on Cancer Cooperative Groups 2010

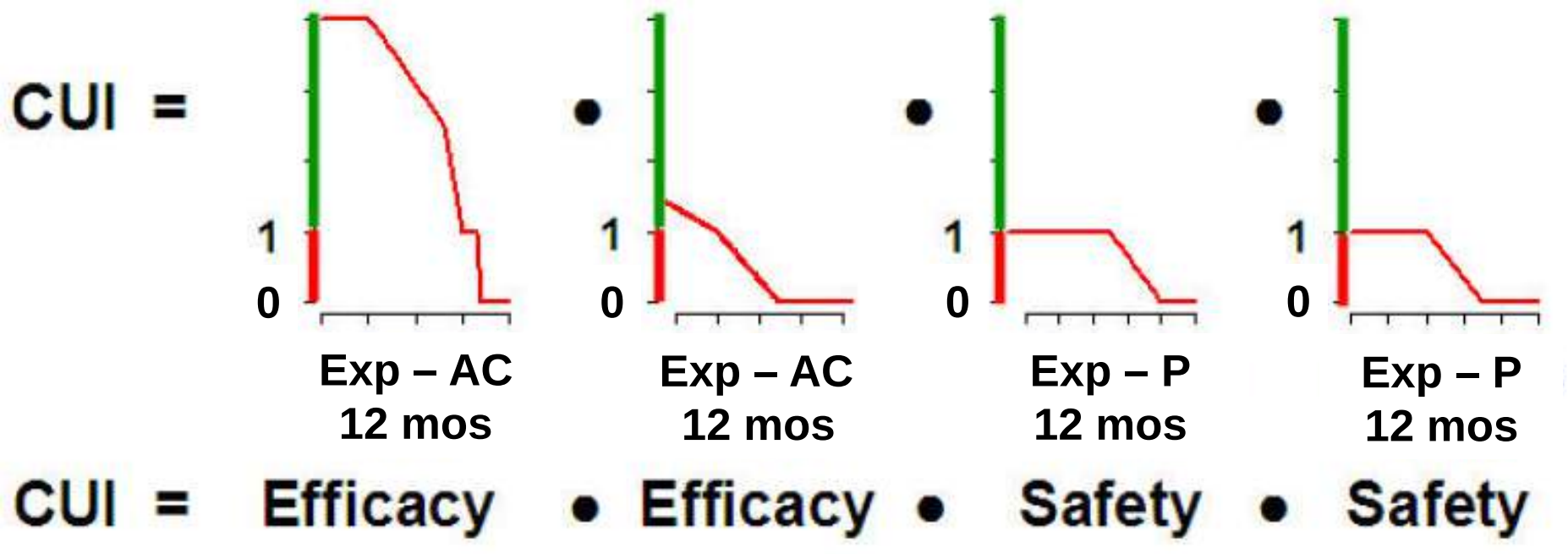
Similar Example from Critical Path Initiative

- Type II diabetes
- Seamless Phase II/III: Dose finding plus confirmation
- Active comparator & placebo
- Primary endpoint: Clinical Utility Index (12 months)

Some Details

- Longitudinal modeling
- Phase II: 7 doses experimental drug
- Phase III
  - 1 or 2 doses experimental drug
  - Sample size via predictive power considering available Phase II data
  - Adaptive transition: Bayesian predictive probs
- Both phases driven by CUI

Clinical Utility Index

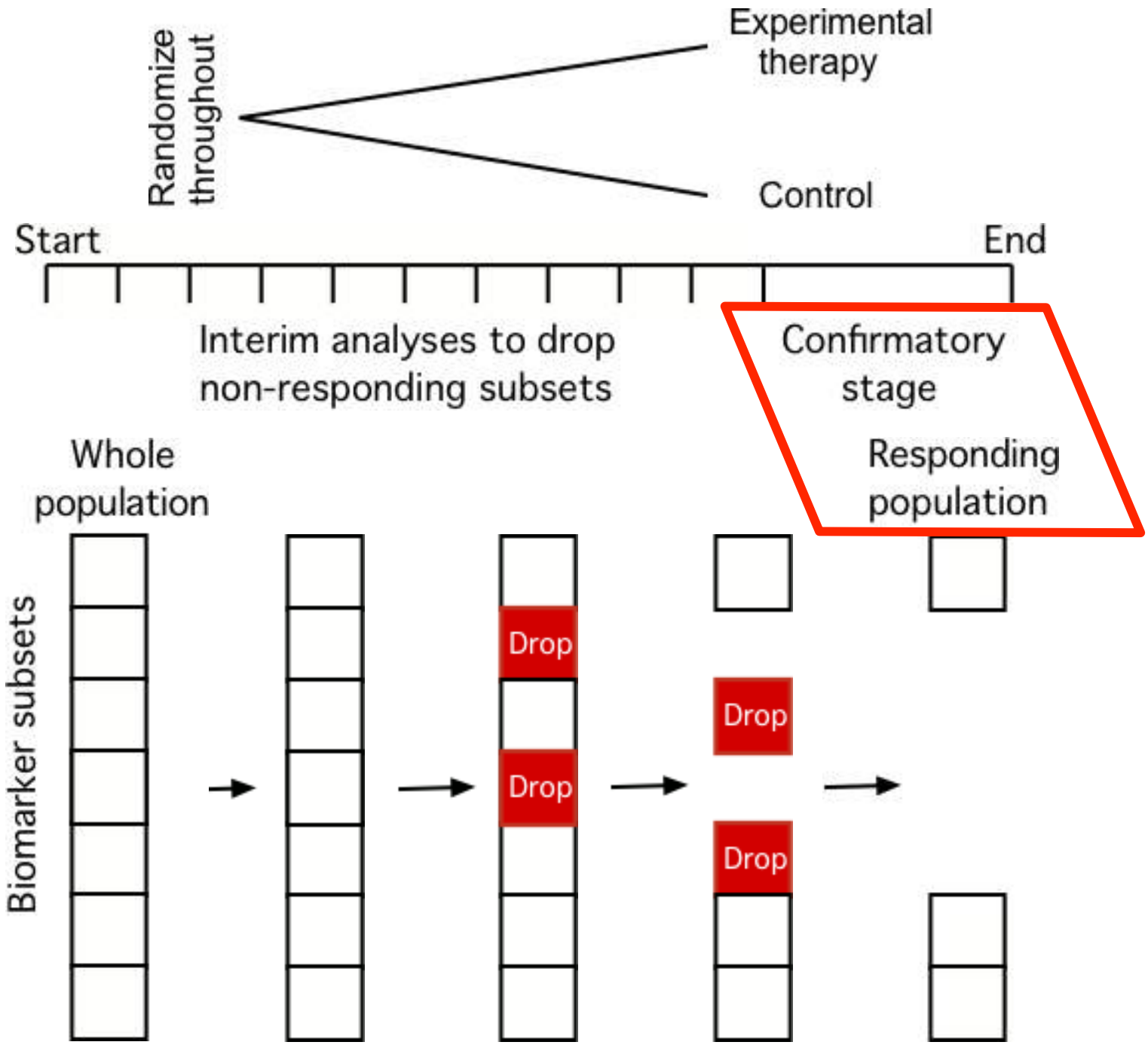


- Dose-response modeling
- Longitudinal modeling

Analogy with Composite Endpoint

Adaptive Biomarker Trial

EXAMPLE TRIAL

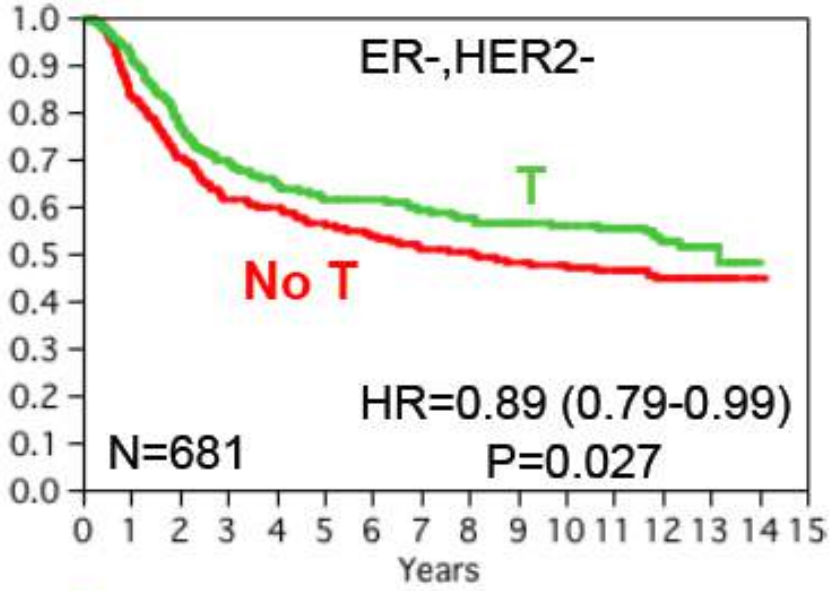


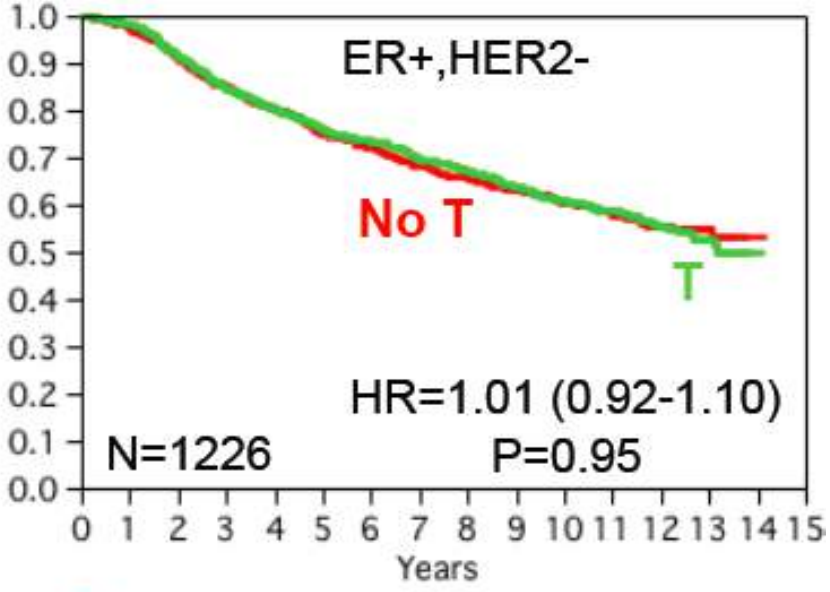
Simulations Usually Required

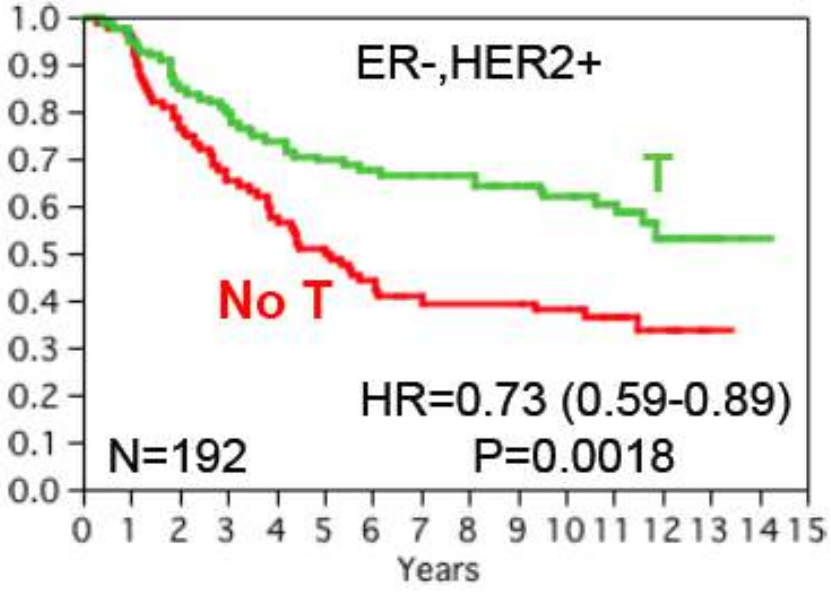
- To find operating characteristics:
  - Type I error rate
  - Power
  - Sample size distribution
- Prospective design essential
- Longitudinal modeling
- Many scenarios
- Accrual rate matters

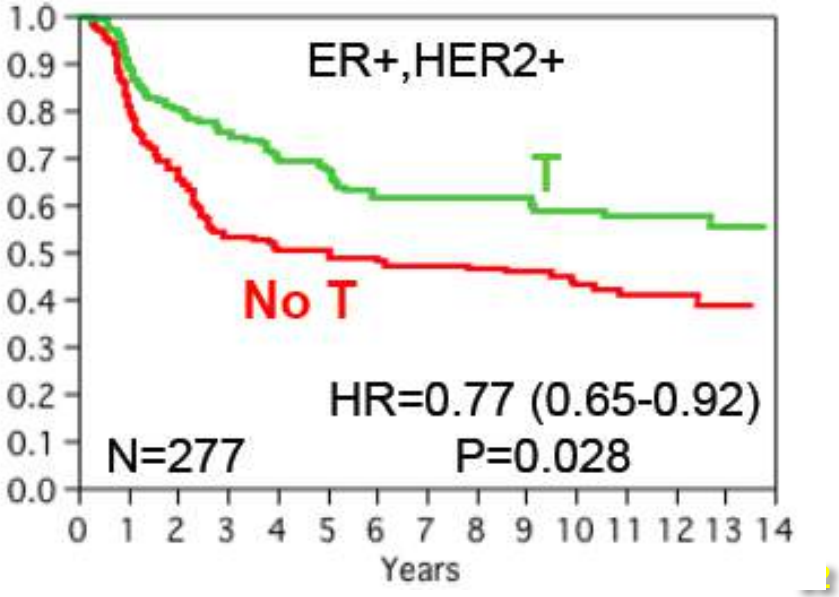
Savings possible in sample size when using biomarkers …

Relapse-free survival in CALGB 9344; n = 2376

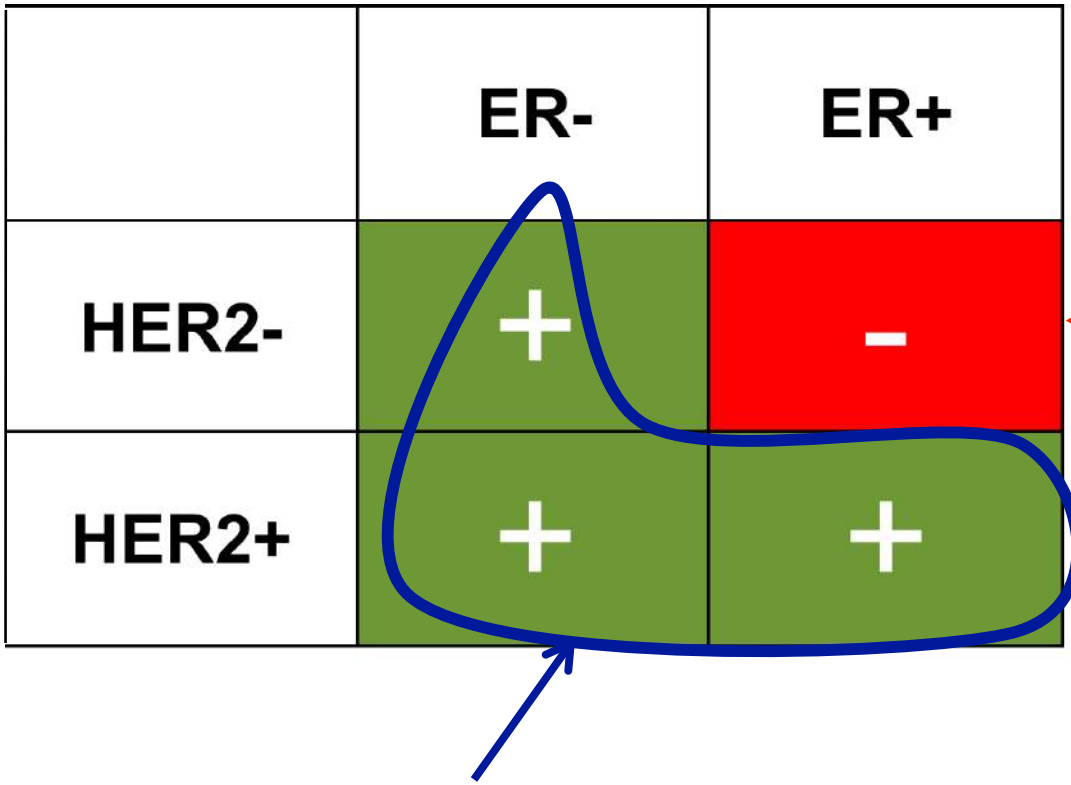








Berry et al. SABCS 2009



No paclitaxel benefit

Each subset shows a statistically significant benefit from paclitaxel with small sample size—could have been small, focused phase III

THE WALL STREET JOURNAL.
WSJ.com

THE SATURDAY ESSAY | OCT

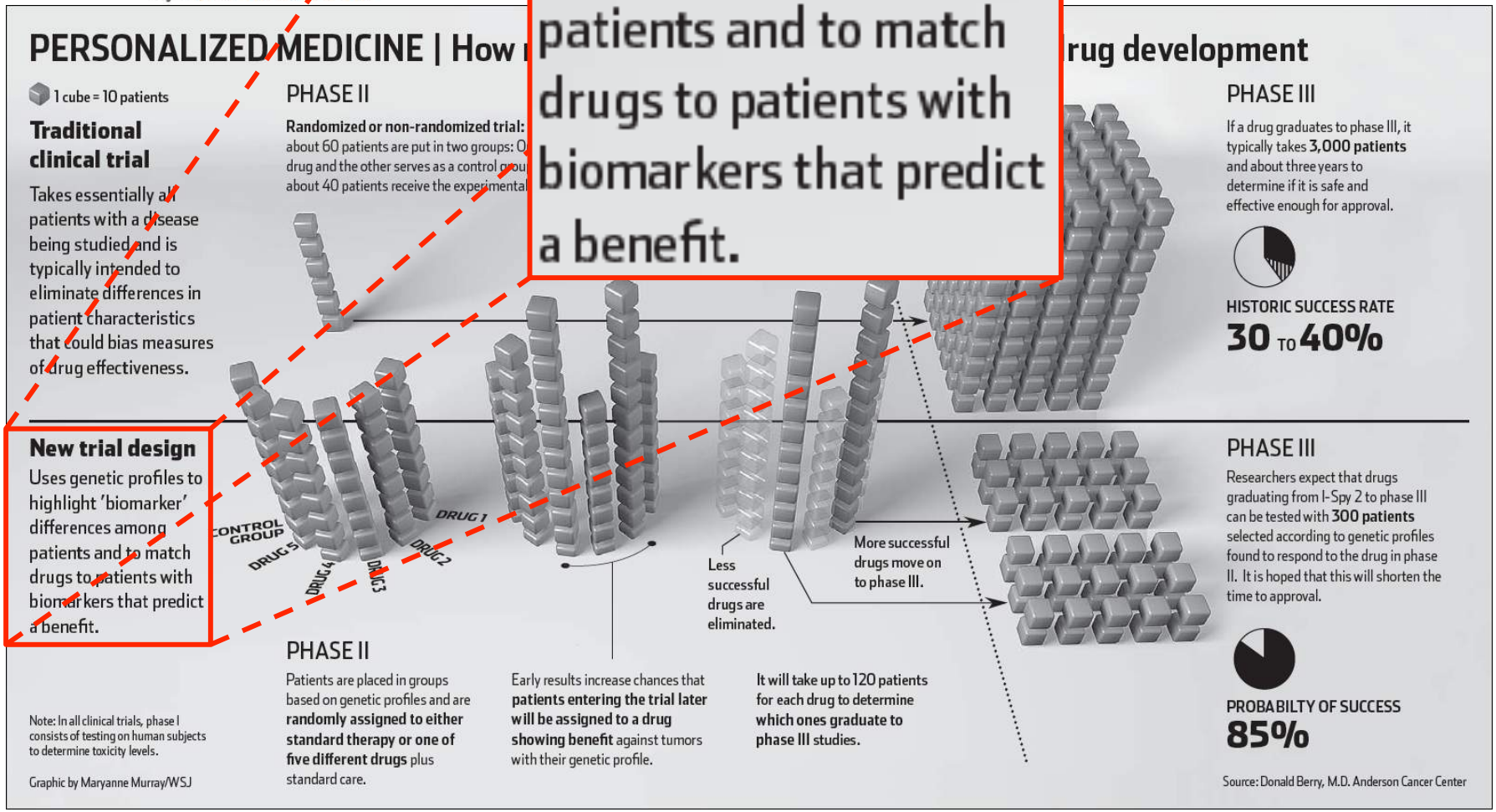
A New Rx for Med

Fed up with slow drug trials, ca ack to personalized treatments.

By RON WINSLOW

New trial design

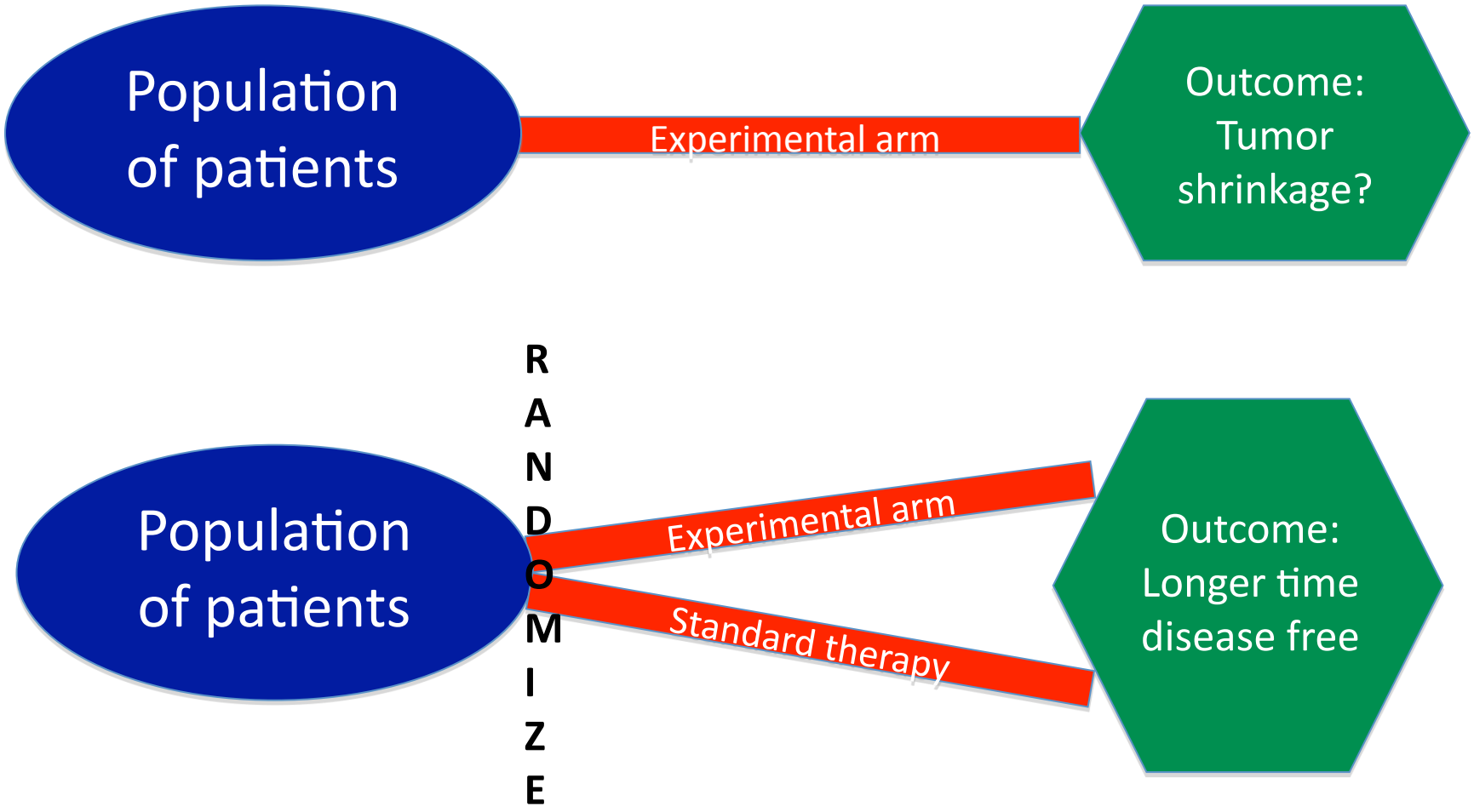
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.



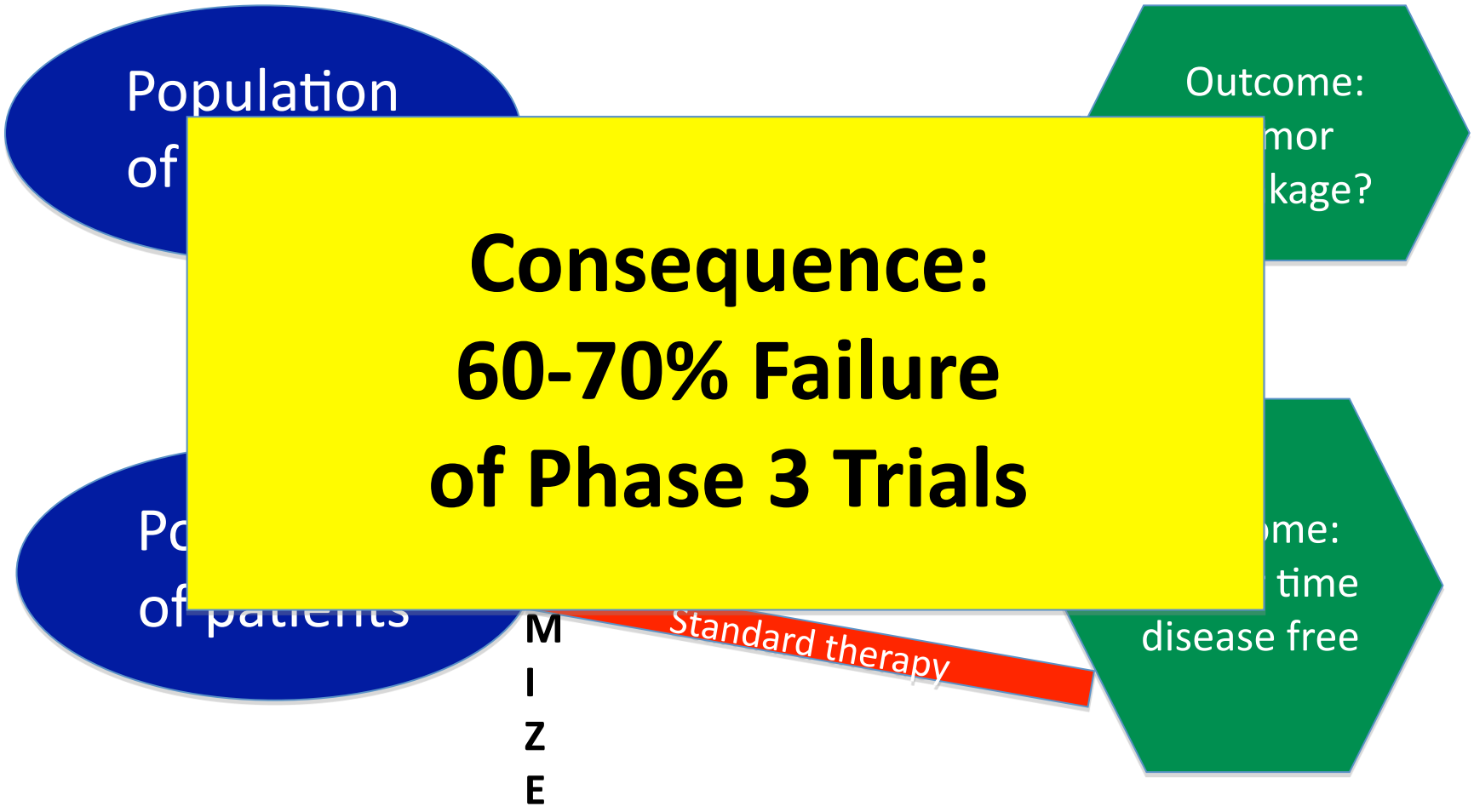
I-SPY2: The Cartoon
(Press conference* slides)

*<http://ispy2.org>

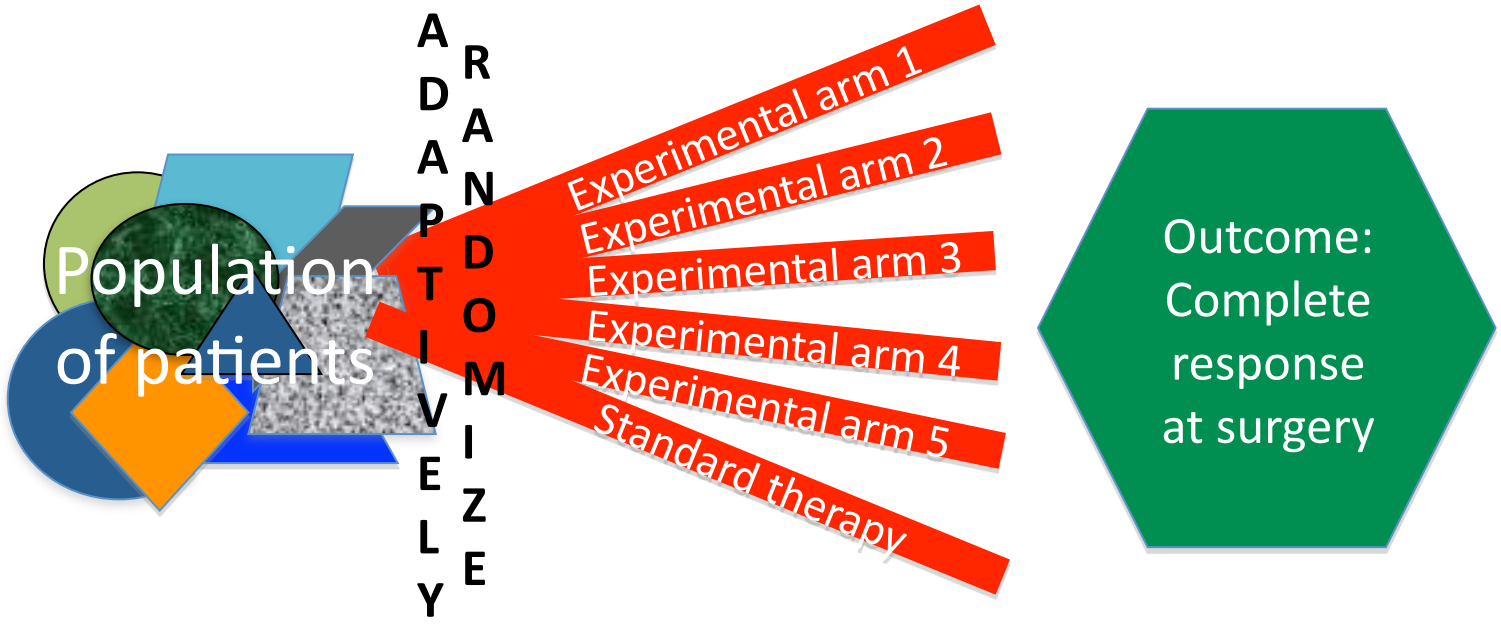
Standard Phase 2 Cancer Drug Trials



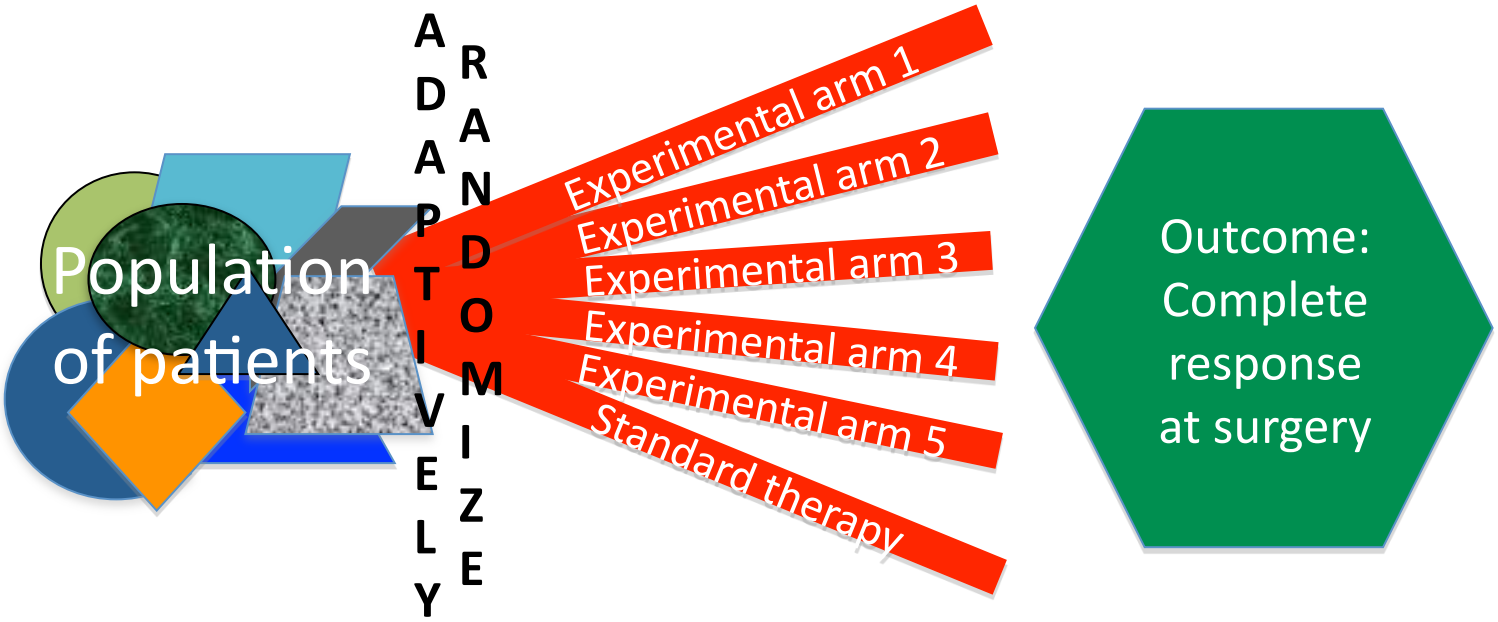
Standard Phase 2 Cancer Drug Trials



I-SPY2 TRIAL

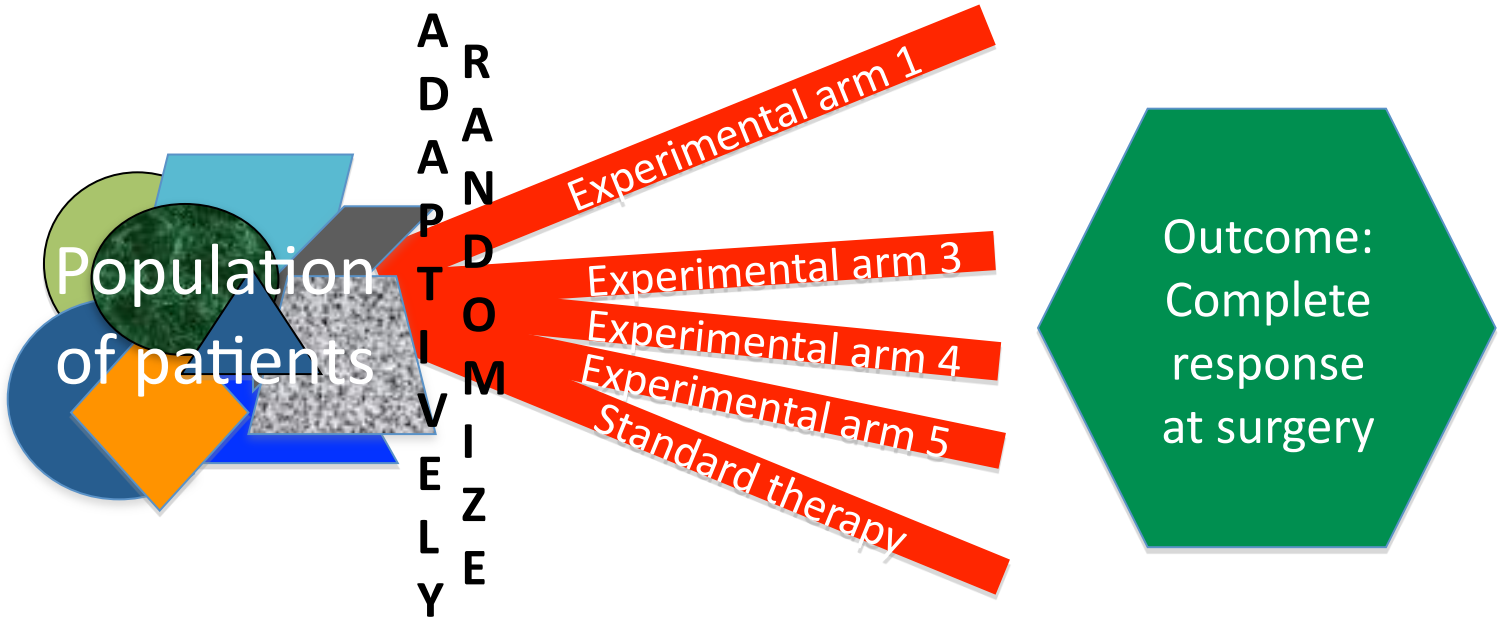

Population of patients
ADAPTIVELY RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery

I-SPY2 TRIAL



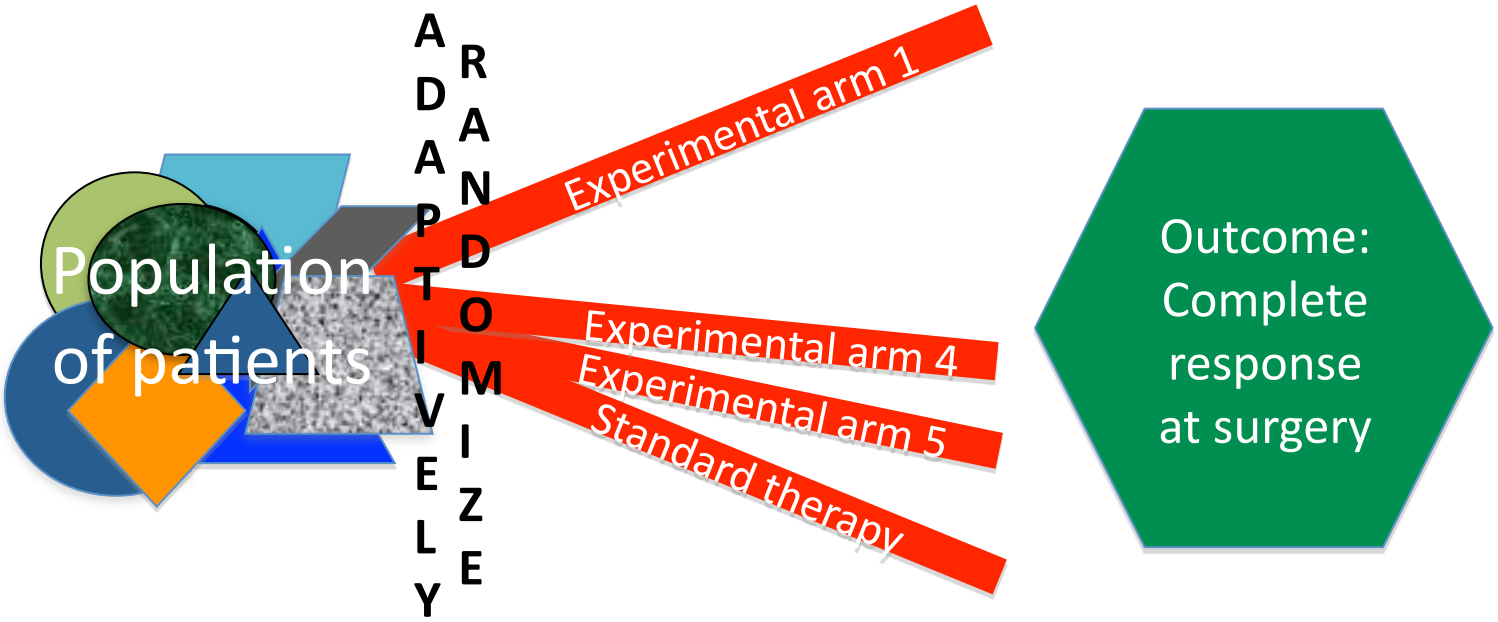
Arm 2 graduates to small focused Phase 3 trial

I-SPY2 TRIAL



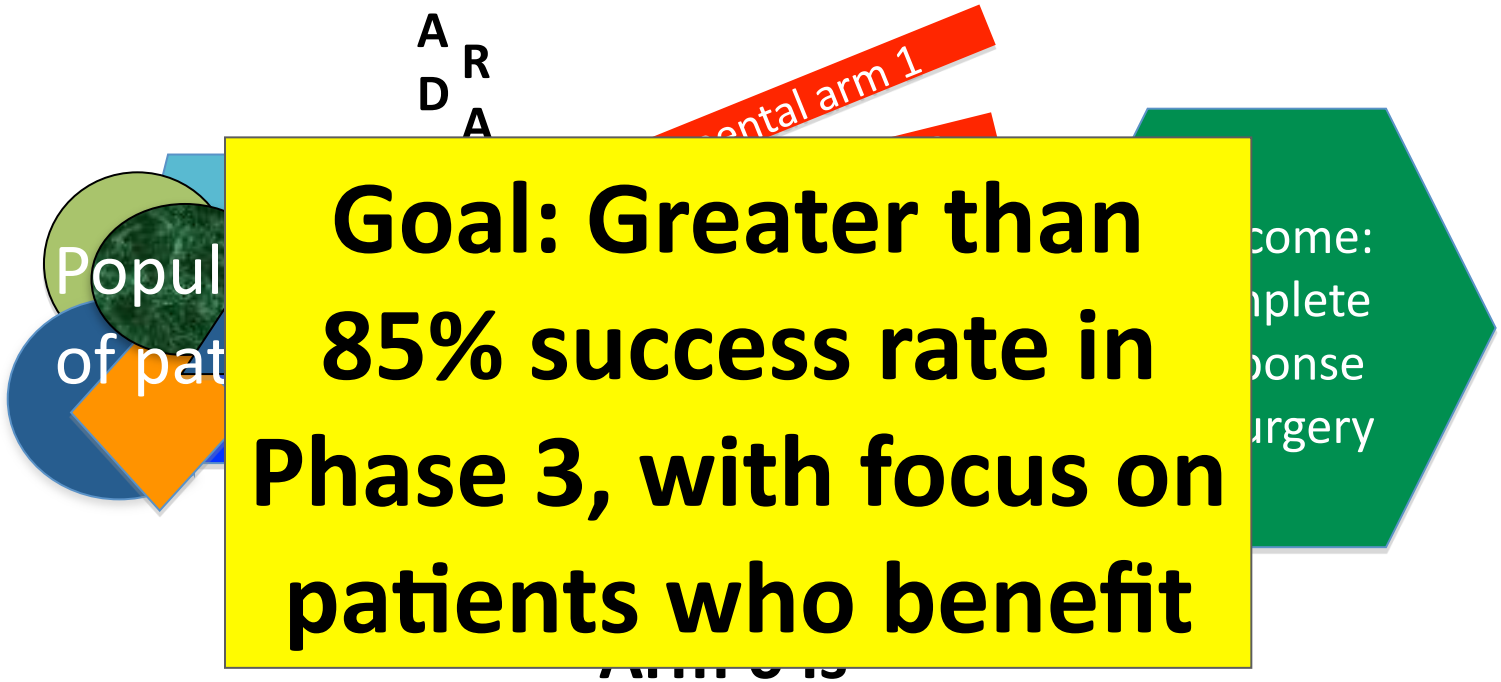
Arm 3 drops for futility

I-SPY2 TRIAL



Arm 5 graduates to small focused Phase 3 trial

I-SPY2 TRIAL



Goal: Greater than 85% success rate in Phase 3, with focus on patients who benefit

added to the mix

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

1 cube = 10 patients

Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

New trial design

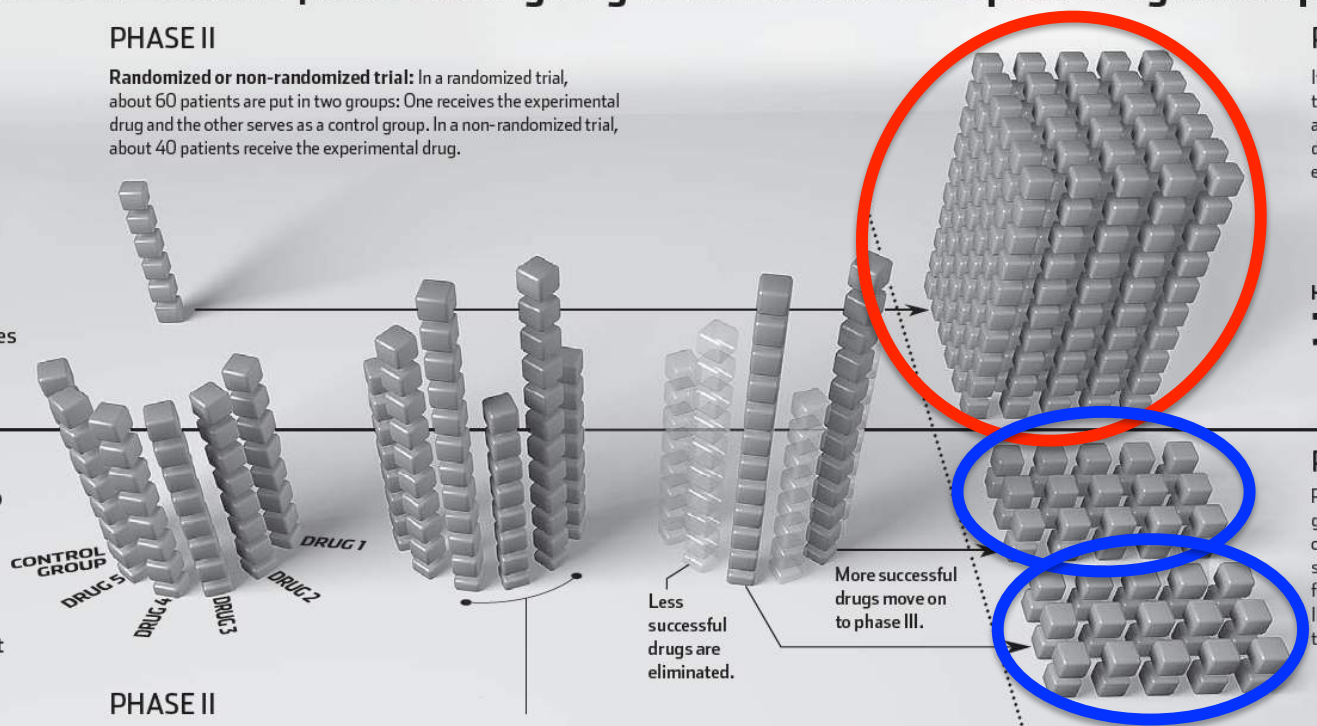
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

PHASE II

Randomized or non-randomized trial: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



PHASE II

Patients are placed in groups based on genetic profiles and are **randomly assigned to either standard therapy or one of five different drugs** plus standard care.

Early results increase chances that **patients entering the trial later will be assigned to a drug showing benefit** against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

PHASE III

If a drug graduates to phase III, it typically takes **3,000 patients** and about three years to determine if it is safe and effective enough for approval.

HISTORIC SUCCESS RATE

30 TO 40%

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with **300 patients** selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.

PROBABILTY OF SUCCESS

85%

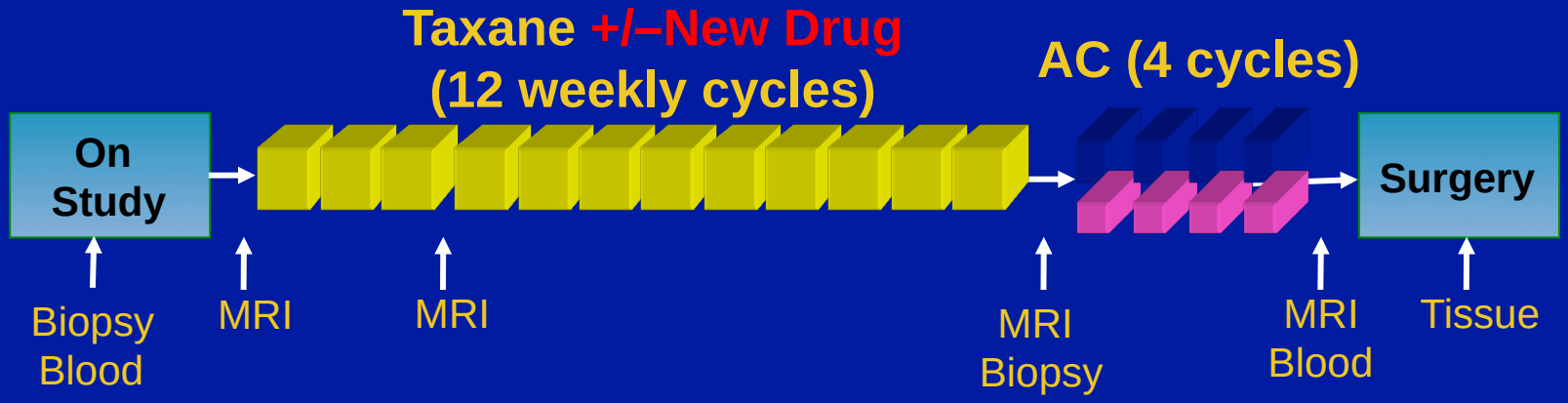
Source: Donald Berry, M.D. Anderson Cancer Center

I-SPY2 Adaptive Design Process

- PI: Laura Esserman, UCSF
- Multi-disciplinary team
- Funded by FNIH: NCI, FDA, industry, academia
- Coordinated with FDA's CDER & CDRH from inception

I-SPY2: Adaptive Phase II Neoadjuvant Breast Cancer

- Moderate to high-risk primary breast cancer
- Baseline biopsy: assess biomarkers
- Primary endpoint: pathCR
- Longitudinal modeling: MRI volume



Overview of Design

- Randomized control: T → AC
- Randomization to new drugs, balanced initially then adaptively
- Find predictive probability of success in focused 300-patient phase III trial
- Evaluate many drugs & combinations
  - Successes graduate to Phase III
  - Duds dropped for futility

Screening Process: Matching Drugs to Populations

- Many drugs; 5 to start:
  - ▲PARP inhibitor
  - ▲TRAIL agonist
  - ▲IGFR inhibitor
  - ▲Pan HER inhibitor
  - ▲Angiogenesis inhibitor
- Pair drugs/biomarker signatures

Patient strata

Estimated prevalences based on I-SPY1:

	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+

pathCR rates in I-SPY 1

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

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%

Some details

- 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 (Bayesian) prob each drug >> control; based on all current results
- Covariate modeling (across subtypes)
- Assign in proportion to current prob drug >> control, by subtype

More details

- For each possible biomarker signature B, calculate prob drug >> control in B
- If Bayesian pred prob 300-pt Phase III success < 10% for all B, drop drug
- If > 85% for some B then drug graduates
- At graduation we provide predictive probability Phase III success for each B, including B on drug's diploma

Computer Simulations: Probability graduate (power) …

- P1: True signature
- P2: All subtypes that benefit
- P3: Only subtypes that benefit
- P4: Some subtype that benefits
- P5: No subtypes that benefit

I-SPY 2 Effects

- Match drugs (& combos) with biomarker signatures
- Graduate drug/biomarker pairs to smaller (n = 300), more focused, more successful Phase III

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