Adaptive Trial Design and Personalized Therapy Trials

Donald A. Berry
dberry@mdanderson.org

Jane Perlmutter
janep@gemini-grp.com

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Financial Disclosure

Don Berry: Co-owner of Berry Consultants, LLC.

Designs adaptive clinical trials for

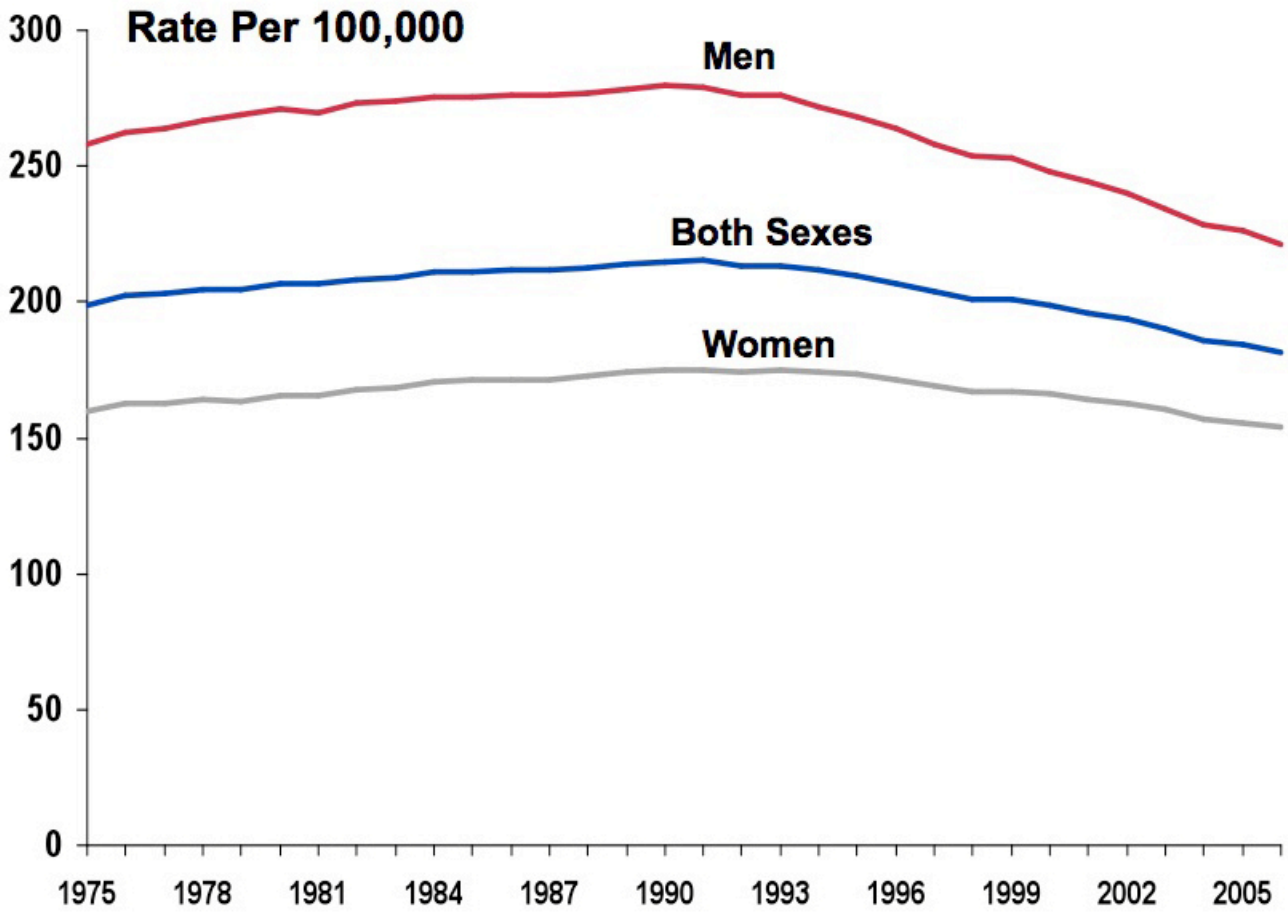
- Medical device companies
- Pharmaceutical companies
- NIH cooperative groups

Jane Perlmutter: none

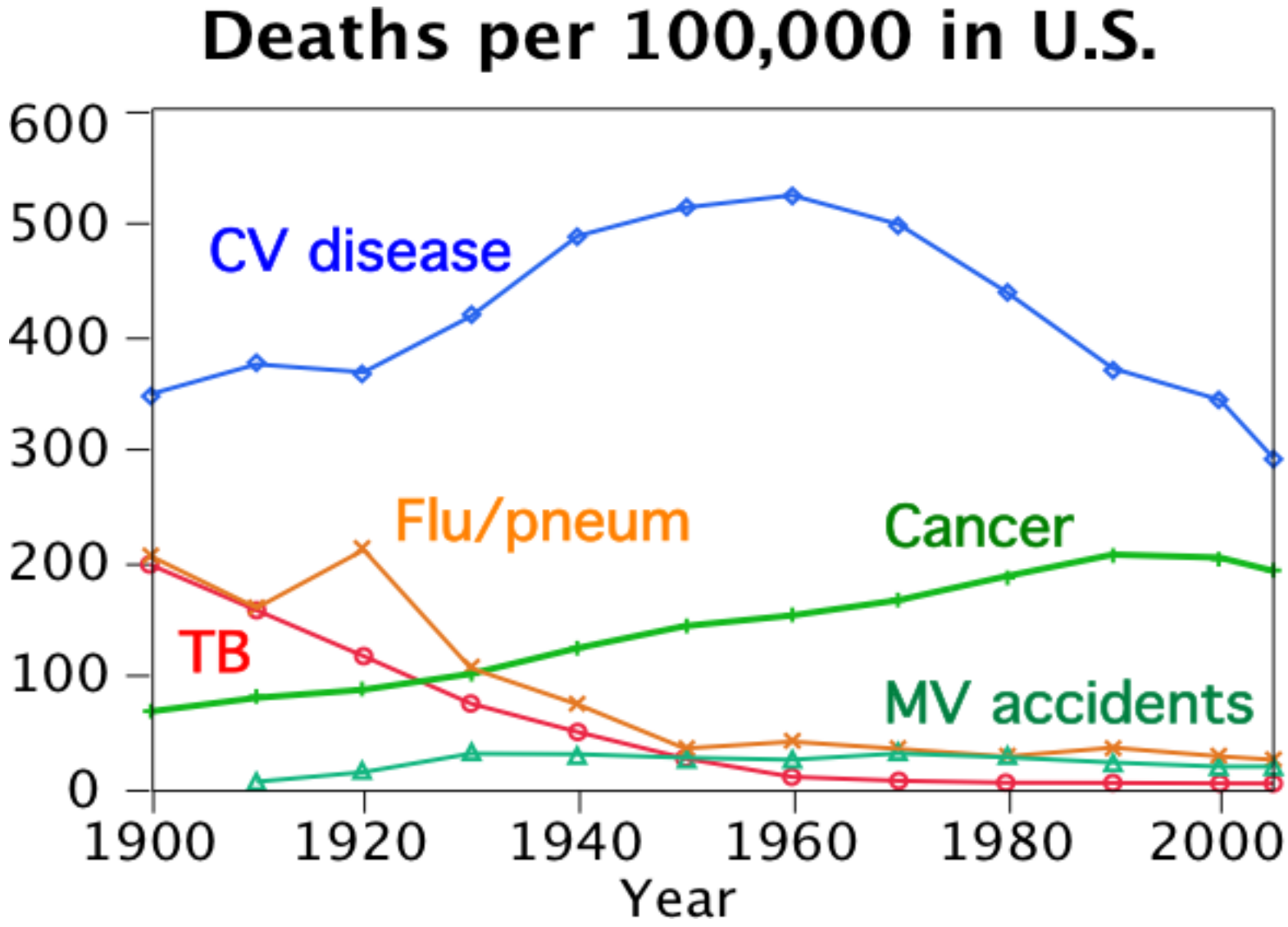
Topics

- **Background**
- Adaptive Clinical Trials
- A Detailed Example
- Next Steps/Discussion

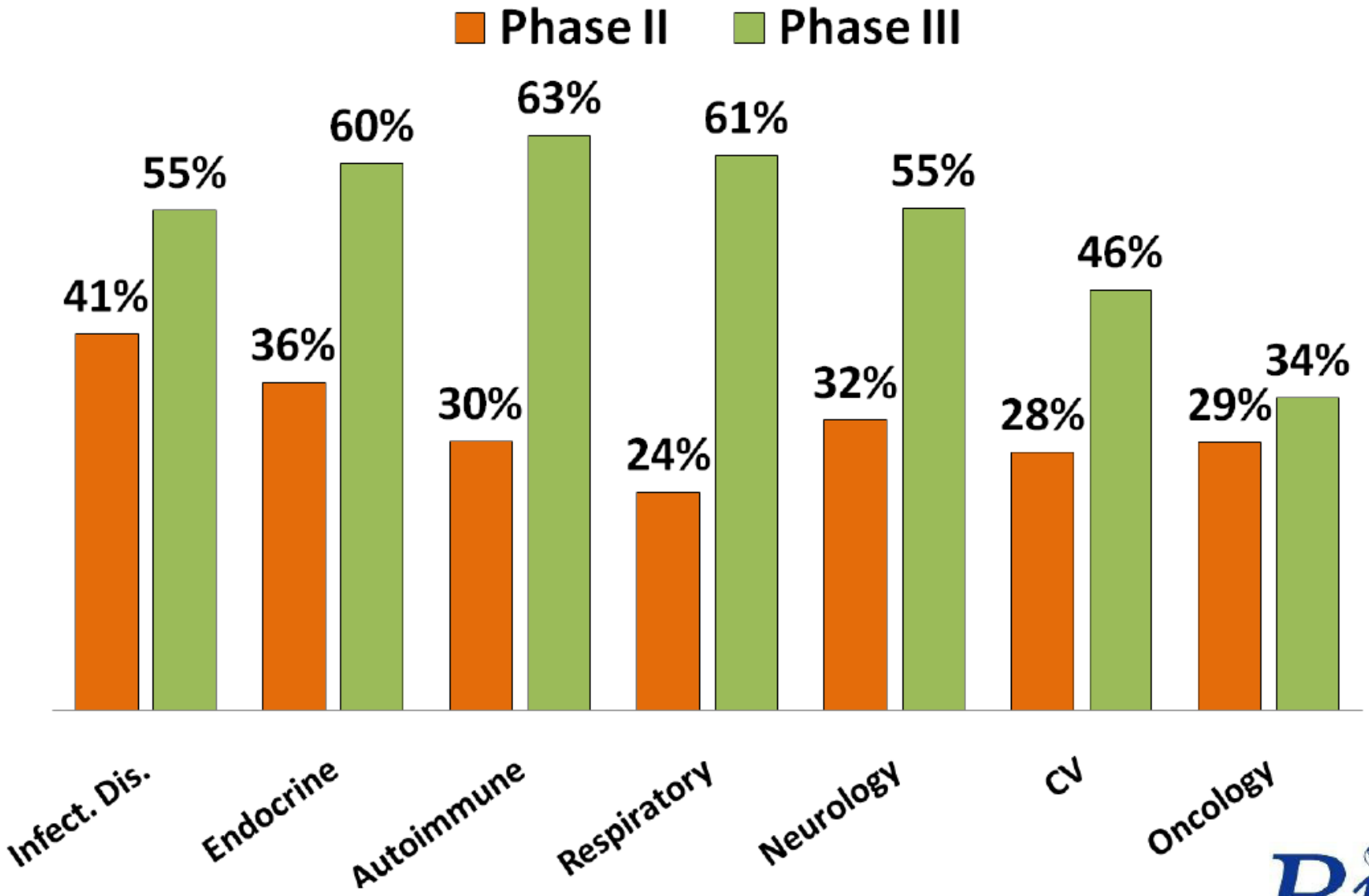
Cancer Death Rates* by Sex, US, 1975-2006



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.


Deaths per 100,000 in U.S.
600
500
400
300
200
100
0
CV disease
Flu/pneum
Cancer
TB
MV accidents
1900
1920
1940
1960
1980
2000
Year

OVERALL SUCCESS AT PHASE II AND III



biomed tracker

16 February 2011

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

Why Phase 3 Failures in Oncology?

- Ineffective drug (50%); of those:
  - Wrong endpoint in phase 2: 70%
  - No randomization in phase 2: 60%
  - Silly subsetting: 50%
  - Lottery: 30%
  - Preserving jobs: 20%
- Effective drug, lousy strategy (50%); of those:
  - Underpowered: 30%
  - Wrong dose/schedule/concomitant Rx: 60%
  - Wrong population: 70%

Janet Woodcock, Dir CDER FDA at 2006 SPORE Meetings

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

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Development of Novel Combination Therapies

Janet Woodcock, M.D., Joseph P. Griffin, J.D., and Rachel E. Behrman, M.D., M.P.H.

For example, in 2010, the Biomarkers Consortium–a public-private partnership that includes the NIH, the FDA, patient groups, and pharmaceutical and biotech–initiated a groundbreaking trial in breast cancer to predict drug responsiveness based on the presence or absence of genetic and biological markers, … I-SPY 2 (ClinicalTrials.gov NCT01042379).

cific molecules, inclu gram. Increasingly, tumors will
contributing to the pr screened for pertinent path-
of cancer cells and dependencies, as is current-
microorganisms. Although target- tively treat many tumors and in- ly done for breast cancer, and pa-

This article (10.1056/NEJMp1101548) was published on February 16, 2011, at NEJM.org.

FDA's Critical Path Opportunities Report (2006)

"uncovered a consensus that the two most important areas for improving medical product development are **biomarker development** and **streamlining clinical trials**."

http://www.fda.gov/ScienceResearch/SpecialTopicsCriticalPathInitiative/default.htm

Topics

- Background
- **Adaptive Clinical Trials**
- A Detailed Example
- Next Steps/Discussion

Adaptive Trials

- Multi-stage designs
- Fully specified at start
- Randomization can be adaptive
- Often more efficient and more attractive to patients

Adaptive Allocation Trials

- Compared to tradition trials, adaptive trials:
  - Require fewer patients—usually
  - Can provide better treatment to trial participants
  - Ideal for biomarkers
  - Take more effort to plan & execute
  - There are barriers …

“Streamlined” Trial in Adjuvant Breast Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2009 VOL. 360 NO. 20

Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

Hyman B. Muss, M.D., Donald A. Berry, Ph.D., Constance T. Cirrincione, M.S., Maria Theodoulou, M.D., Ann M. Mauer, M.D., Alice B. Kornblith, Ph.D., Ann H. Partridge, M.D., M.P.H., Lynn G. Dressler, Ph.D., Harvey J. Cohen, M.D., Heather P. Becker, Patricia A. Kartcheske, B.S., Judith D. Wheeler, M.P.H., Edith A. Perez, M.D.,

A Bayesian statistical design was used with a range in sample size from 600 to 1800 patients.

BACKGROUND

Older women with breast cancer are underrepresented in clinical trials, and data on the effects of adjuvant chemotherapy in such patients are scant. We tested for the noninferiority of capecitabine as compared with standard chemotherapy in women with breast cancer who were 65 years of age or older.

METHODS

We randomly assigned patients with stage I, II, IIIA, or IIIB breast cancer to standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide plus doxorubicin) or capecitabine. Endocrine therapy was recommended after chemotherapy in patients with hormone-receptor–positive tumors. A Bayesian statistical design was used with a range in sample size from 600 to 1800 patients. The primary end point was relapse-free survival.

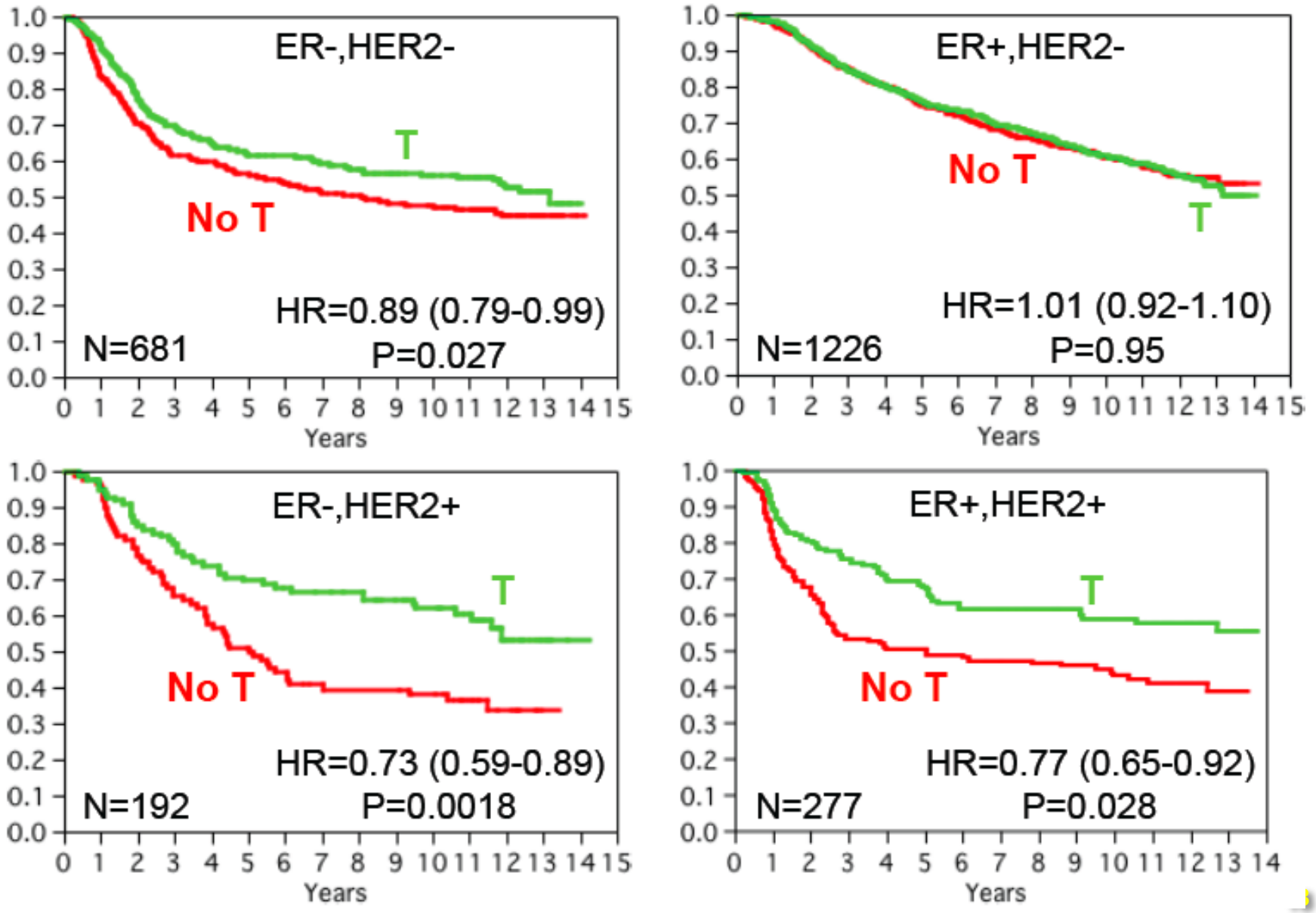
From the University of Vermont, Burlington (H.B.M.); the M.D. Anderson Cancer Center, Houston (D.A.B.); the Cancer and Leukemia Group B (CALGB) Statistical Center, Duke University Medical Center (C.T.C., P.A.K.) and Duke University Medical Center (H.J.C., J.D.W., A.A.M.) — both in Durham, NC; Memorial Sloan-Kettering Cancer Center, New York (M.T., L.N., C.A.H.); CALGB, Chicago (A.M.M., H.P.B.); the Dana–Farber Cancer Institute, Boston (A.B.K., A.H.P., H.J.B., E.P.W.); the University of North Carolina, Chapel Hill (L.G.D.); the North Central Cancer Treat-

From “Methods”

“These interim analyses were not the standard type in which the trial results are announced when a boundary is crossed. Rather, the decision to discontinue enrollment was based on a prediction that future follow-up was likely to give a meaningful answer.”

Savings possible in sample size when using biomarkers: Example from 3151-patient adjuvant breast cancer trial

Relapse-free survival in CALGB 9344; n = 2376



Berry et al. SABCS 2009

Current use of Bayesian adaptive designs

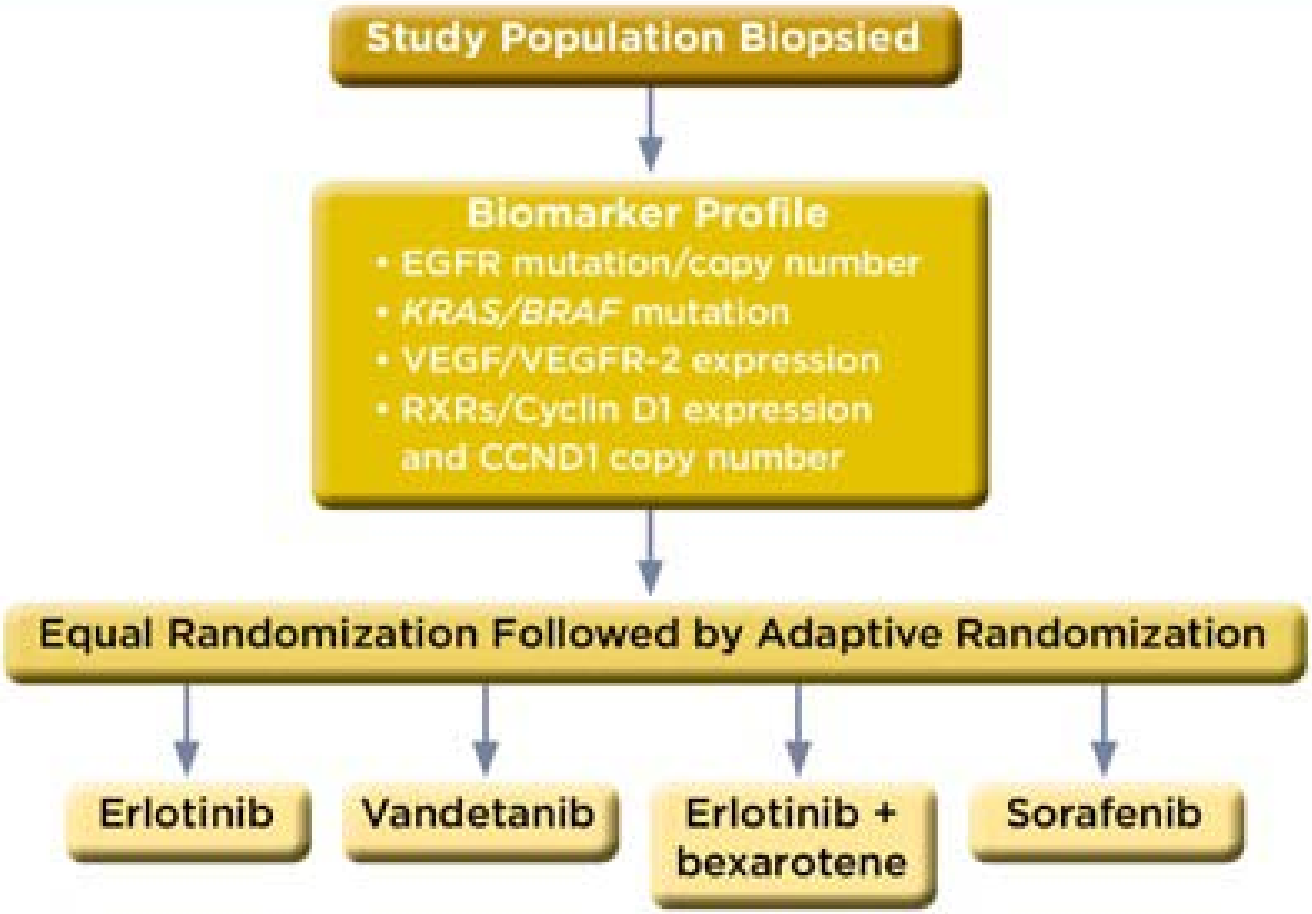
- MDACC (> 300 trials)
- Device companies (> 25 PMAs)*
- Drug companies (Most of top 40; many biotechs)**

*http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm

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

BATTLE Trial in NSCLC

Kim et al. *Cancer Discovery* 2011



BATTLE schema.

BATTLE, Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination; **EGFR,** epidermal growth factor receptor; **RXRs,** retinoid X receptors; **VEGF,** vascular endothelial growth factor; **VEGFR,** vascular endothelial growth factor receptor

BATTLE results, N (Disease Control Rate)

	EGFR mut	KRAS/ BRAF mut	VEGF/ VEGF R	RXR/Cy cD1	None	Total
Erlotinib	17 (35%)	7 (14%)	25 (40%)	1 (0%)	8 (38%)	58 (34%)
Vandetanib	27 (41%)	3 (0%)	16 (38%)	0 (--)	6 (0%)	52 (33%)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	36 (50%)
Sorafenib	23 (39%)	14 (79%)	39 (64%)	4 (25%)	18 (61%)	98 (58%)
Total	87 (43%)	27 (48%)	83 (49%)	6 (33%)	41 (46%)	244 (46%)

Is this a biomarker signature for sorafenib?

IN THE SPOTLIGHT

The BATTLE Trial: A Bold Step toward Improving the Efficiency of Biomarker-Based Drug Development

Eric H. Rubin, Keaven M. Anderson, and Christine K. Gause

Summary: Successful completion of the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer

nprove

o that

The precise biomarker hypotheses, as well as the associated type I and type II statistical errors, are not clear. Thus, the study should be considered as generating a hypothesis rather than as confirming a particular biomarker hypothesis.

TH
DE

Advances in basic cancer research have led to a widely used discovery and development approach for drugs designed to inhibit specific cancer pathways. However, clinical trial designs have not kept pace with basic research advances, and use of traditional, histology-based, "all-comers" phase I and II trial designs for these drugs has led typically to failure in

s" based on sta-
le benefit in an
all-comers population. For example, Table 1 lists 9 drugs that failed in 13 phase III trials of unselected (i.e., in the absence of a diagnostic test that predicts tumor responsiveness to a drug) patients with non-small cell lung cancer (NSCLC) during or after the completion of the BATTLE study (1). Indeed, only 2 drugs that target signaling pathways have been approved by the FDA for the treatment of unselected NSCLC patients: erlotinib [small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase] and bevacizumab [monoclonal antibody targeting vascular endothelial growth factor (VEGF)]. Clearly, the approach to developing these kinds of drugs for NSCLC and other cancers needs to change, or we will continue to waste precious clinical trial resources in futile studies.

Authors' Affiliation: Merck Research Laboratories, North Wales, Pennsylvania

Corresponding Author: Eric H. Rubin, Merck Research Laboratories, 351 North Sumneytown Pike, North Wales, PA 19454. Phone: 267-305-1717; Fax: 267-305-6042; E-mail: eric_rubin@merck.com

doi: 10.1158/2159-8274.CD-11-0036

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MELTTT in Melanoma (preliminary version)

Kevin Kim, Patrick Hwu, Mike Davies

MelTTT: Melanoma Targeted Therapy Trial (Non-Uveal)

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER *Making Cancer History®*

(1) All: BRAF/NRAS/AKT/PIK3CA Mutation Screening (T9 vs Standard Assays)
(2) All: PTEN IHC
(3) Mucosal/Acral/Unk Primary: c-KIT Sequencing

(50%) *100-200/yr*

V600 BRAF Mutation

Adaptive Randomization
n=150

PTEN IHC
PIK3CA, AKT mut

BRAFi + MEKi
BRAFi + AKTi
BRAFi + PI3Ki
BRAFi + AKTi + PI3Ki
BRAFi

Progression *Progression*

Deep Characterization And Cross-Over

100-200/yr (45%)

BRAF / CKIT WT

control

Adaptive Rand
n=250

NRAS mut, PTEN IHC
PIK3CA, AKT mut

MEKi
AKTi
PI3Ki
MEKi + AKTi
MEKi + PI3Ki

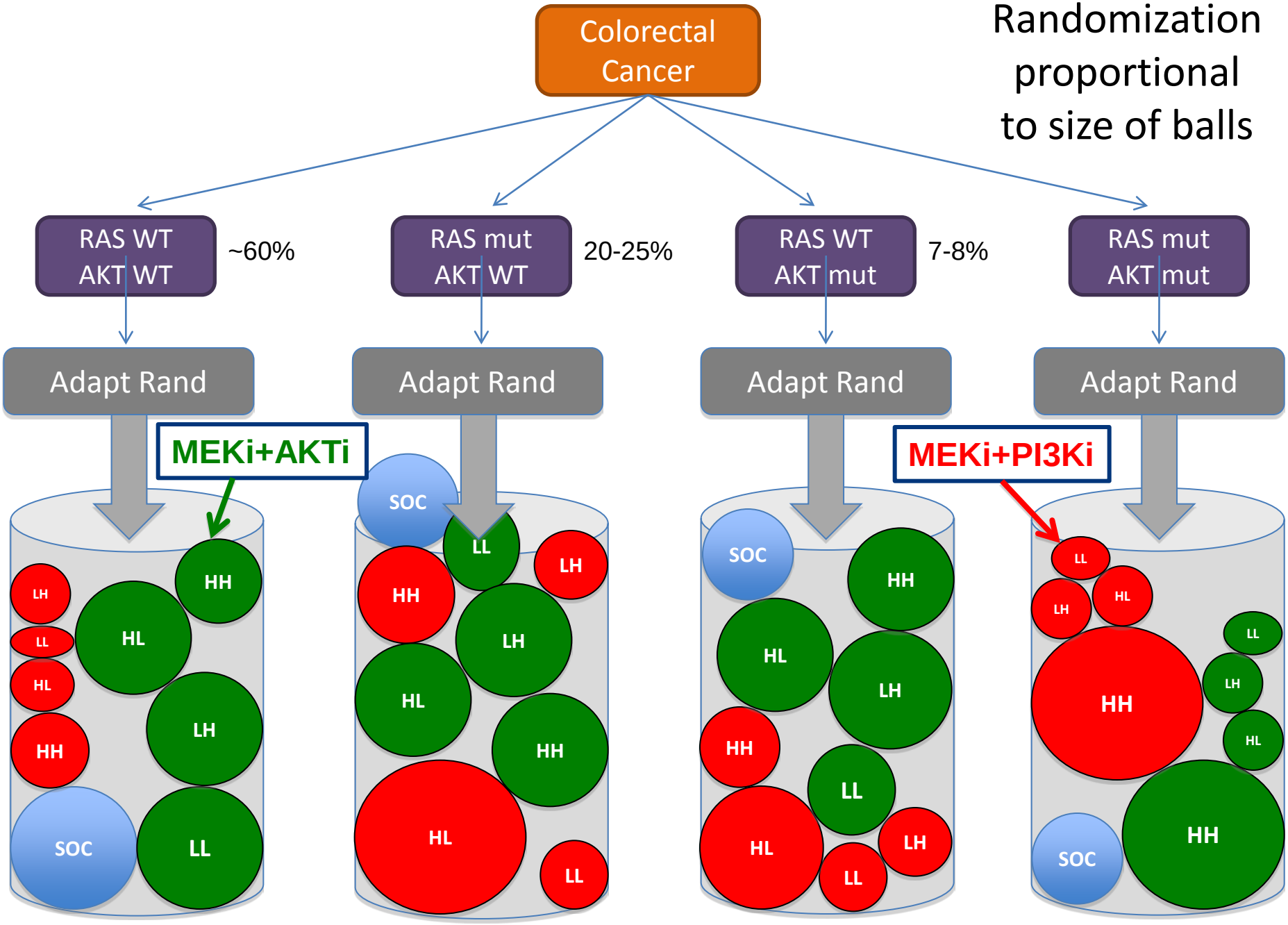
Deep Characterization Of NRAS-Mutant PD AND NRAS-WT Responders

Deep Characterization
-Deep sequencing
-Copy number analysis
-RPPA/IHC

TACTICAL Trial in Colorectal Cancer

(preliminary version)

Scott Kopetz, Cathy Eng


Colorectal Cancer
Randomization proportional to size of balls
RAS WT AKT WT
~60%
RAS mut AKT WT
20-25%
RAS WT AKT mut
7-8%
RAS mut AKT mut
Adapt Rand
Adapt Rand
Adapt Rand
Adapt Rand
MEKi+AKTi
MEKi+PI3Ki
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Topics

- Background
- Adaptive Clinical Trials
- **A Detailed Example**
- Next Steps/Discussion

I-SPY2

http://clinicaltrials.gov/ct2/show/NCT01042379?term=I-SPY2&rank=1

I-SPY 2 Clinical Trial Background

- PI: Laura Esserman (Breast Surgeon at USCF) & Don Berry (Biostatistican at MD Anderson)
- Opened in March 2008 at UCSF/Currently open in ~20 sites
- Plans to enroll 800 patients/Currently enrolled ~200 patients
- Includes many unusual partnerships
- Significant advocate involvement

I-SPY 2 Innovation

- Biomarker driven trial design
- Simultaneously validating biomarkers and assessing investigational agents
- Adaptive allocation trial design
- Unapproved agents in stage 2 and 3 patients (potentially curable)
- Multiple investigational agents from multiple companies
- Multiple funding sources
- Early involvement of FDA and NCI

THE WALL STREET JOURNAL.
WSJ.com

THE SATURDAY ESSAY | OCT

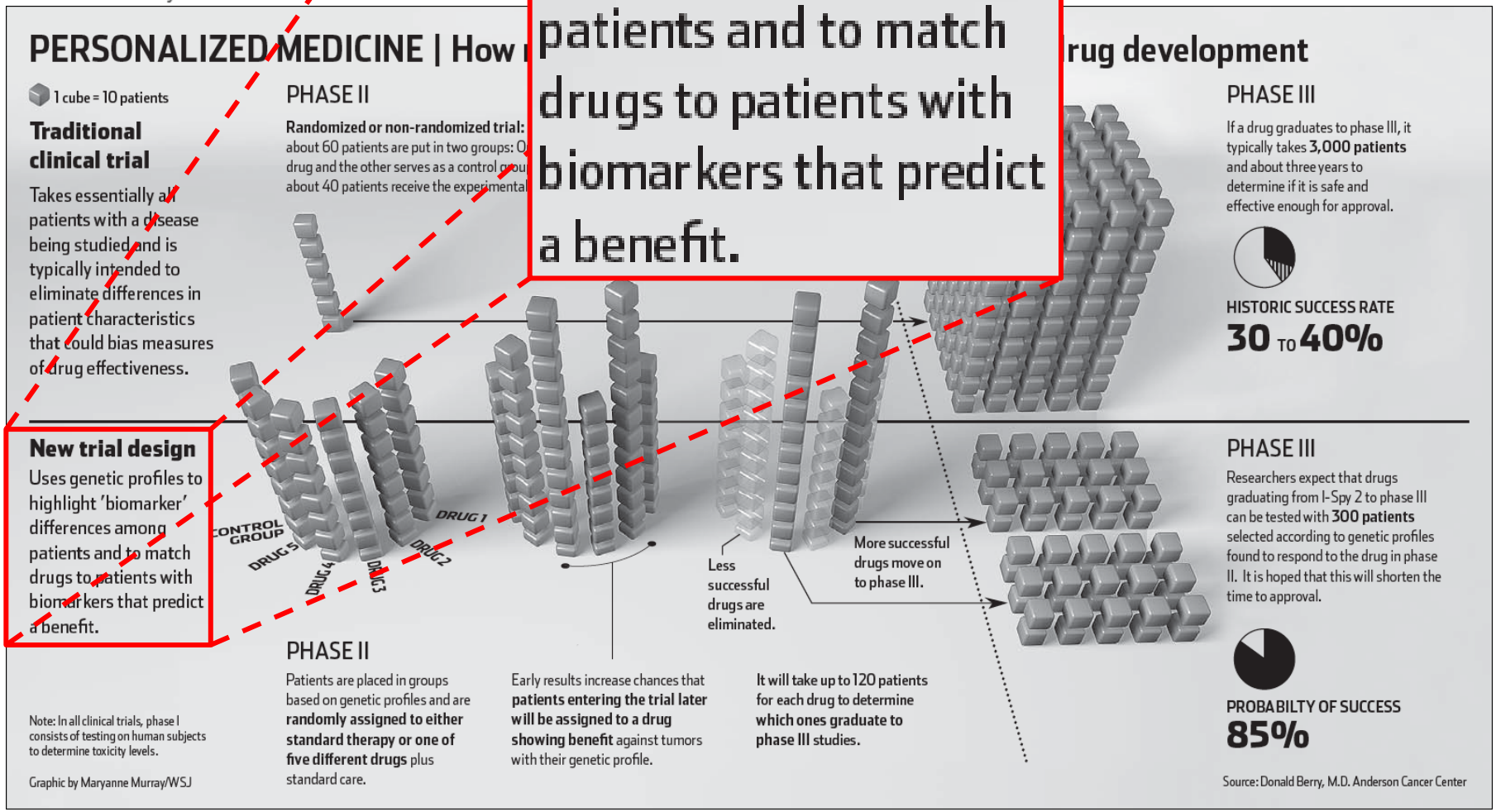
A New Rx for Med

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.



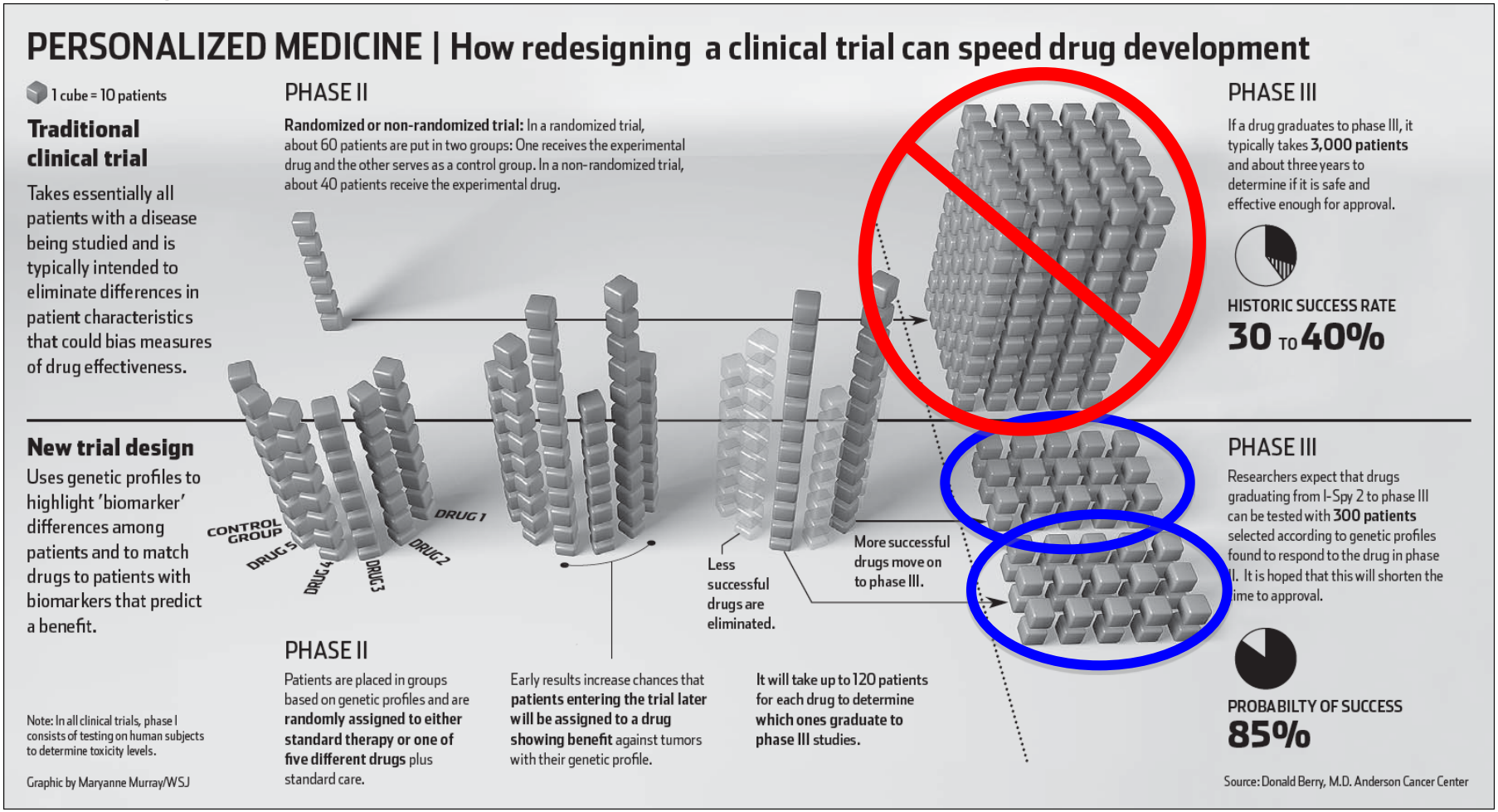
THE WALL STREET JOURNAL.
WSJ.com

THE SATURDAY ESSAY | OCTOBER 2, 2010

A New Rx for Medicine

Fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments.

By RON WINSLOW



I-SPY 2 Clinical Trial Characteristics

- Neoadjuvant trial for patients with locally advanced breast cancer
- Biomarker driven
- Adaptive allocation randomized design
- **Primary endpoint:** pathological complete response (pCR)
- **Secondary endpoints:**
  - Disease free survival (DFS)
  - Biomarker prediction of response
  - Changes in biomarkers during treatment

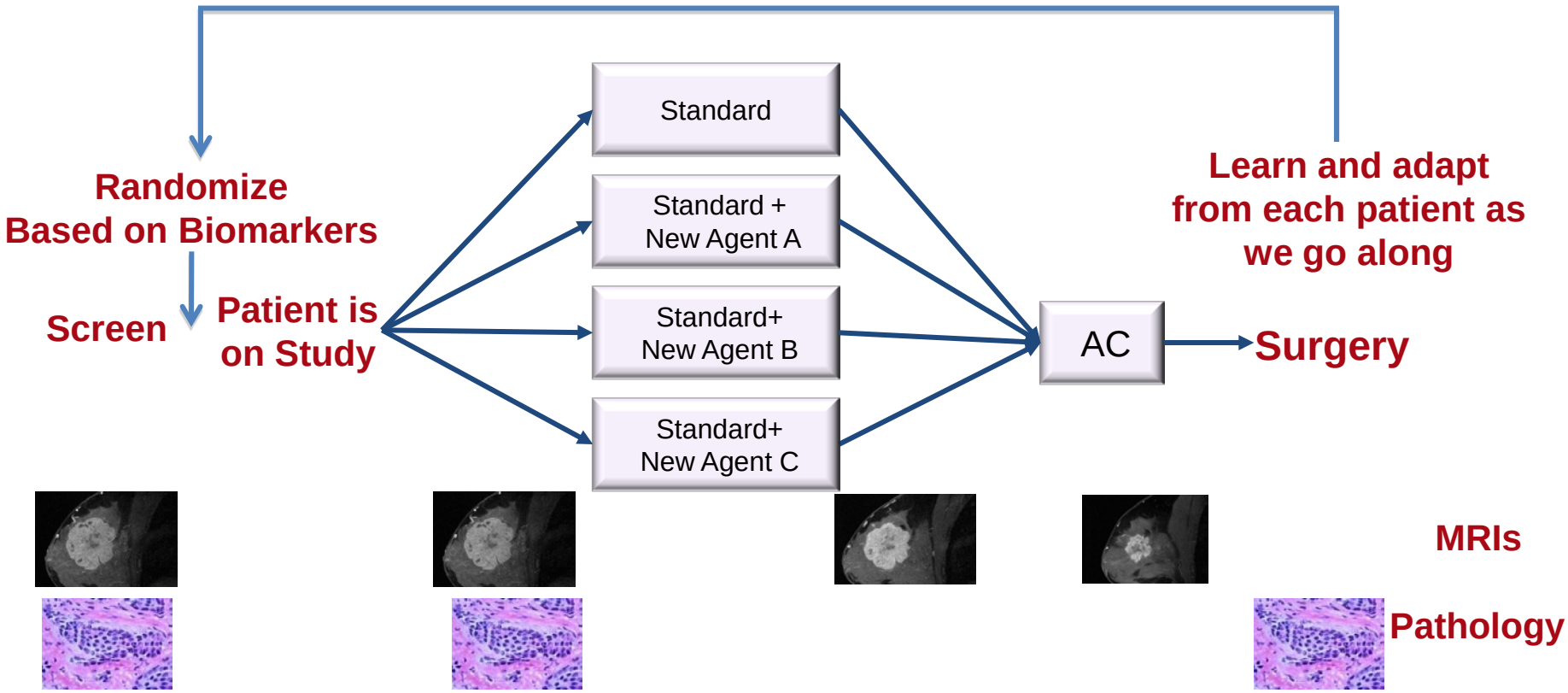
Drug Testing in I-SPY 2

- One standard of care arm; at least 20% of patients
- Up to 5 investigational agents at any time
- Expect to test about 8 agents over course of trial
- Drugs drop out when:
  - Safety concerns
  - Adequate evidence of efficacy to recommend phase 3 focused testing (graduate)
  - Adequate evidence of futility (flunk)
- When drugs leave the trial they receive detailed biomarker information (transcript)

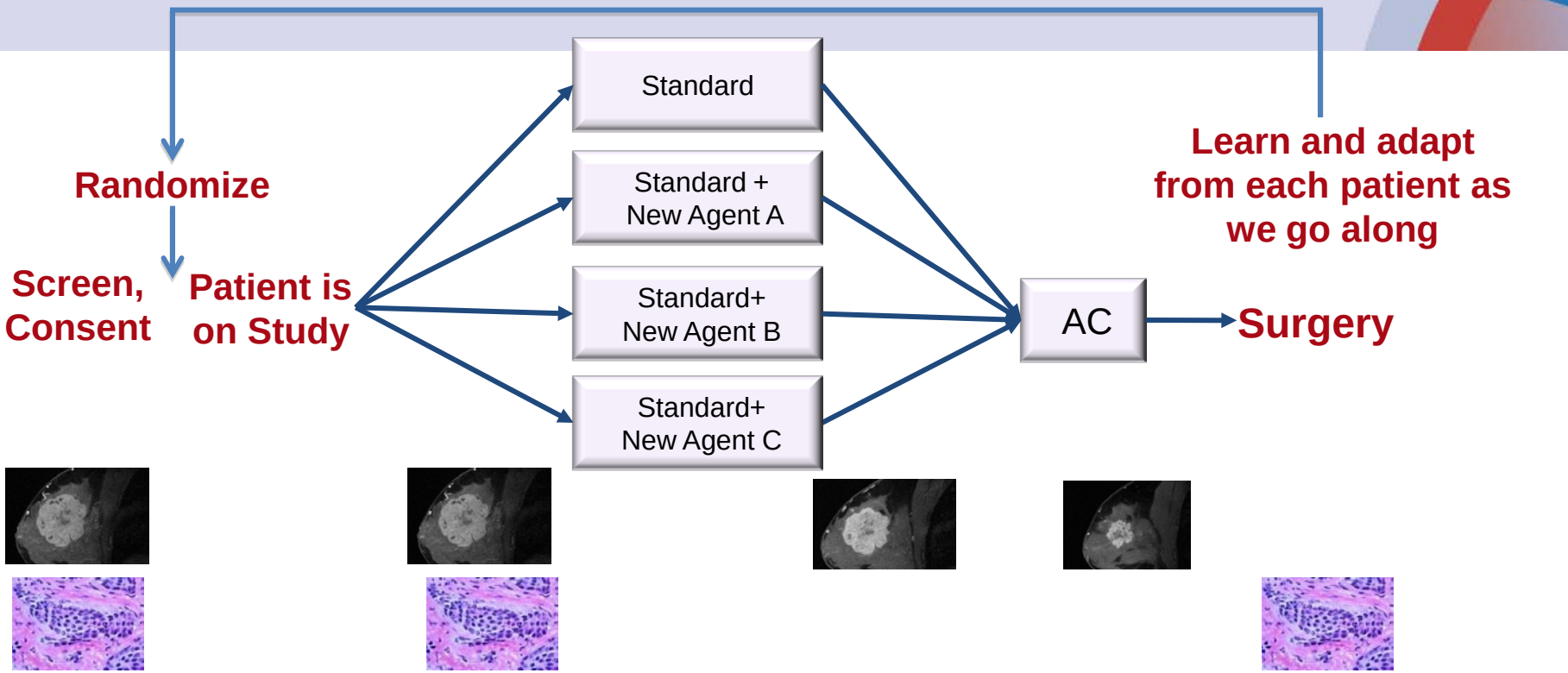
Biomarkers in I-SPY 2

Type	Role in I-SPY 2	What
Classifying	Used to assign patients to treatment arms	ER/PR HER2 MammaPrint
Qualifying	Being validated in I-SPY 2	Genetic version of ER/PR, HER2 K67, PI3K, PARP, IGFR others
MRI	Being validated as early predictor of pCR	Algorithm from I-SPY 1
Exploratory	Hypothesis generating	Stem cell markers Metabolic markers Many others

Information Gathered in Real Time for Several New Agents



Learn: Drop, Graduate, Replace Agents Over Time



Agent Pipeline

Standard+ New Agent D

Standard+ New Agent E

Standard+ New Agent F

Dropped Agents

Graduated Agents

With Transcript

Patient Prevalence

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

Predicted pCR (from I-SPY 1)

	MP Hi-1		MP Hi-2	
	HR +	HR-	HR+	HR-
HER2+	47%	67%	35%	55%
HER2-	25%	43%	17%	32%

Biomarker Profiles Associated with Drugs

Biomarker Profile	Patient Type (HR, HER2, MP)								Est. percent Patients
	+ + +	+ + -	+ - +	+ - -	- + +	- + -	- - +	- - -	
All	●	●	●	●	●	●	●	●	100%
HR+	●	●	●	●					49%
HR-					●	●	●	●	51%
HER2+	●	●			●	●			37%
HER2-			●	●			●	●	63%
MP+	●	●	●	●					48%
TNBC							●	●	34%
HR-/HER2+					●	●			17%
HR+/HER2+	●	●							20%
HR+/HER2-			●	●					29%

Summary: Traditional vs. I-SPY 2 Trail

	Traditional Approach	I-SPY 2 Approach
Phase 2 Trial		
Number of phase 2 drugs per trial	1	>8
Number of patients per phase 2 drug	60-300	<120
Follow-up Phase 3 Trial		
Role of biomarkers	None	Selected patient sample
Number of patients	>1,000	300
Probability of success	35% (historical)	85%

Summary: Lessons Learned

- Innovation is hard, but important
- Adaptive trials can be a vehicle to more rapid, cost-effective progress and identifying more effective treatments
- Use of allocation adaptive trials takes:
  - Careful planning
  - The right application
  - Persistent, visionary, charismatic leadership, unique partnerships

Summary: Lessoned Learned

- Adaptive designs are increasingly being accepted by companies, researchers and FDA
- Allocation adaptive designs are still controversial
- Allocation adaptive designs are especially helpful for:
  - Dose and schedule selection
  - Complex, biomarker driven trials

Topics

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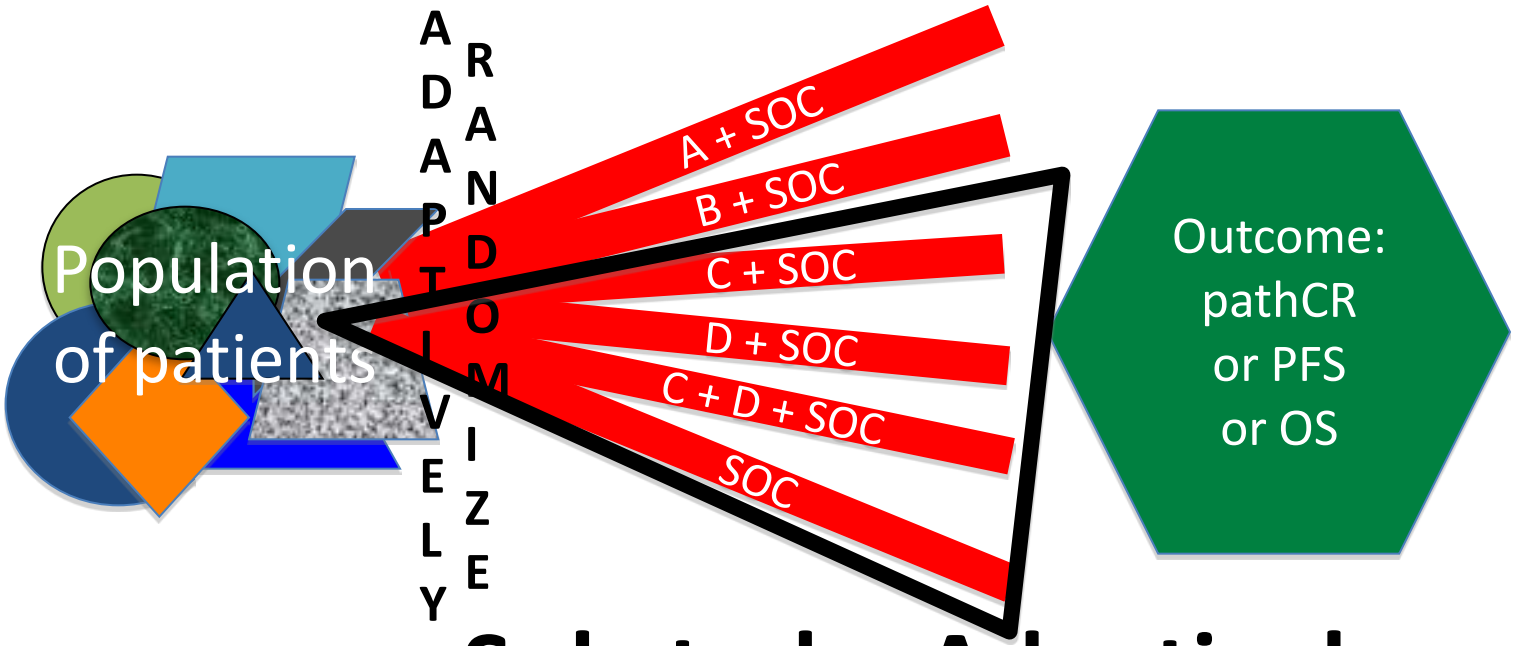
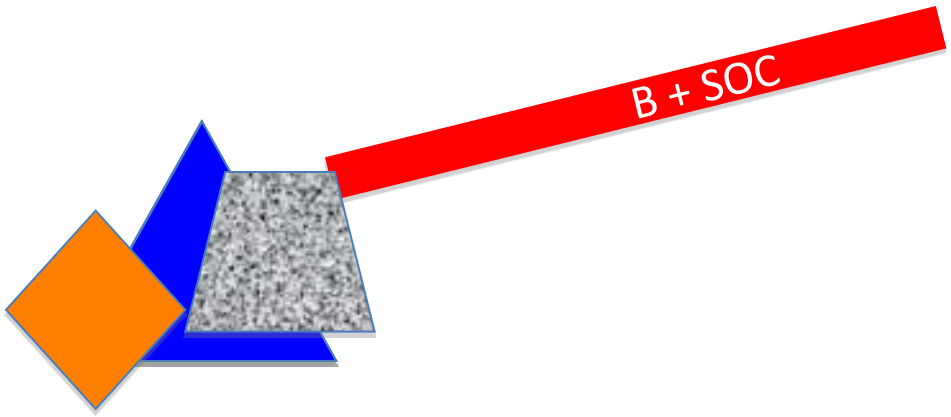
- A Detailed Example
- **Next Steps/Discussion**

I-SPY-like TRIAL for Combinations



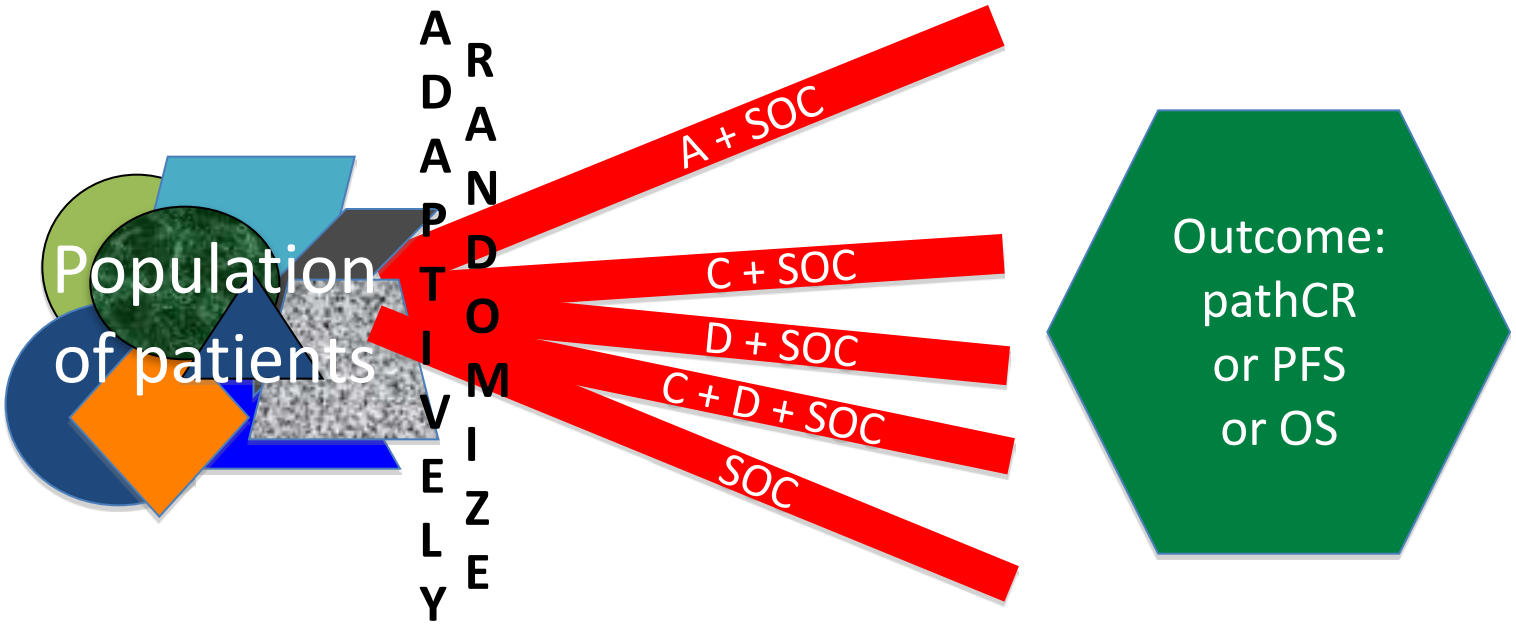
Substudy: Adaptively randomized factorial

I-SPY-like TRIAL for Combinations

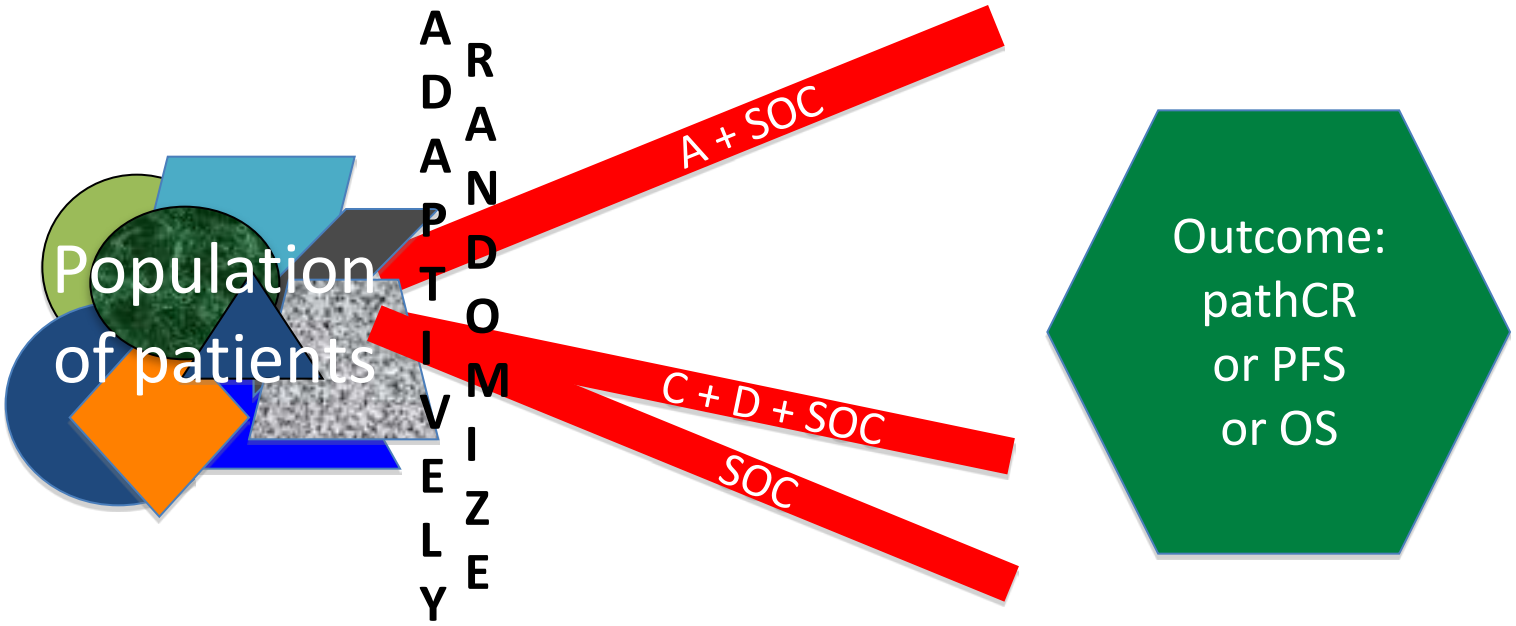


Arm B graduates
to small focused
Phase 3 trial—perhaps
seamlessly within same trial!

I-SPY-like TRIAL for Combinations

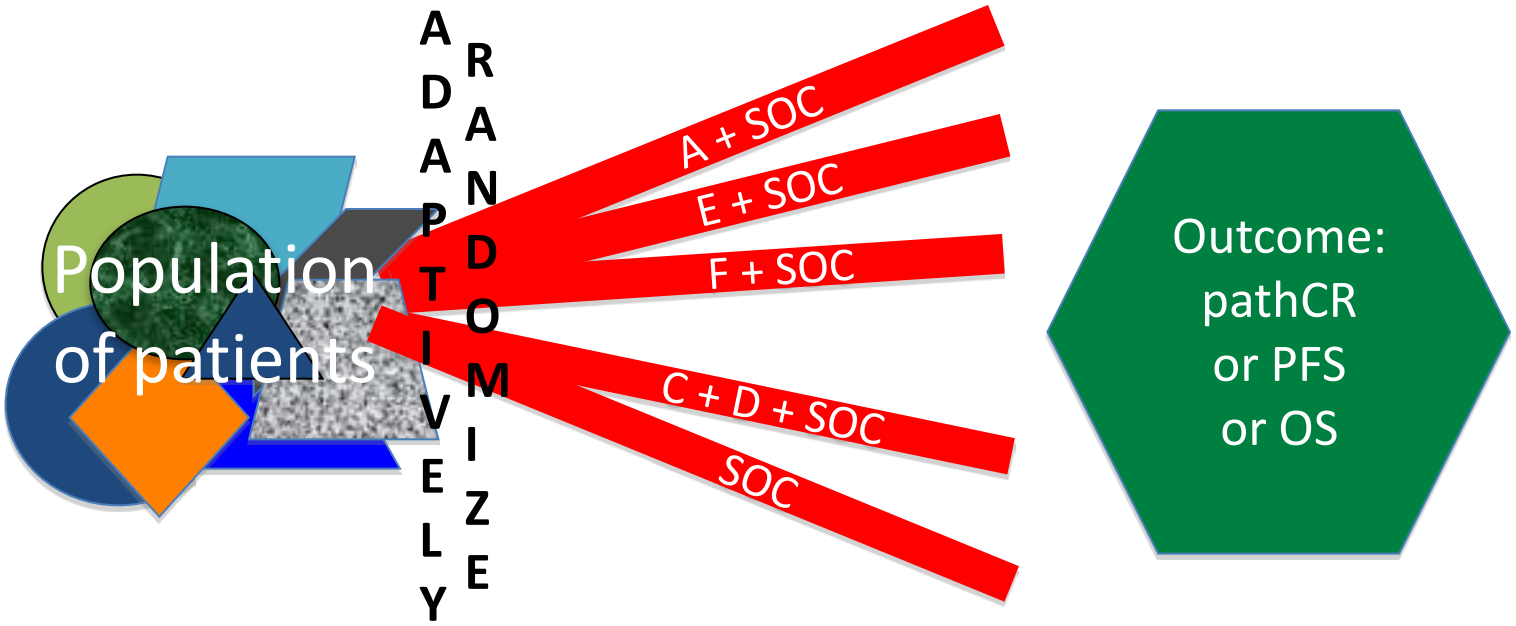


I-SPY-like TRIAL for Combinations



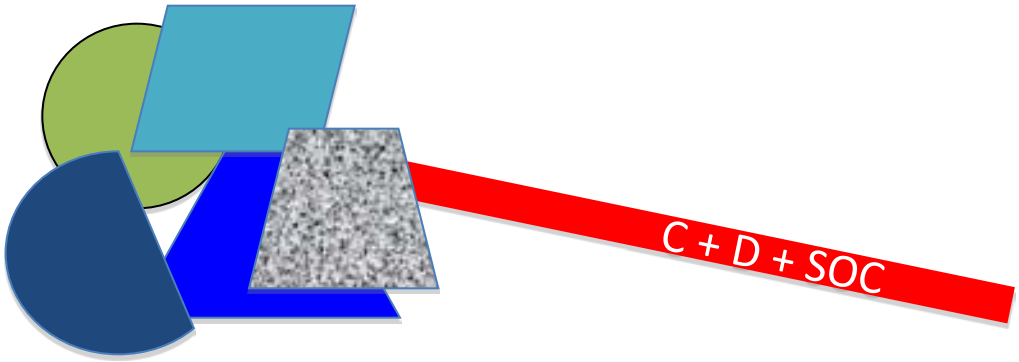
Arms C & D drop because C+D > C and C+D > D

I-SPY-like TRIAL for Combinations



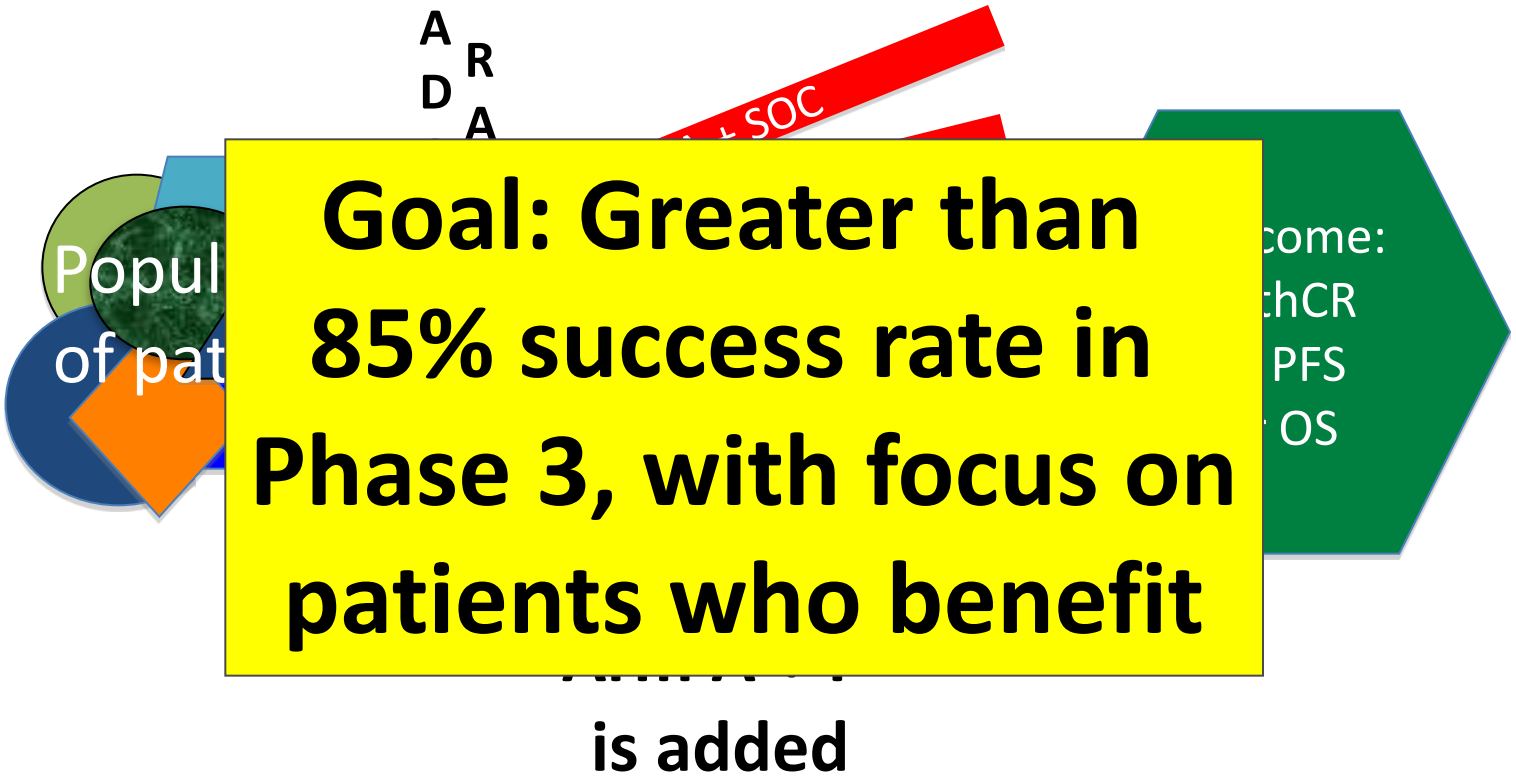
Arms E & F added

I-SPY-like TRIAL for Combinations



Arm C + D
graduates to small
focused Phase 3 trial

I-SPY-like TRIAL for Combinations

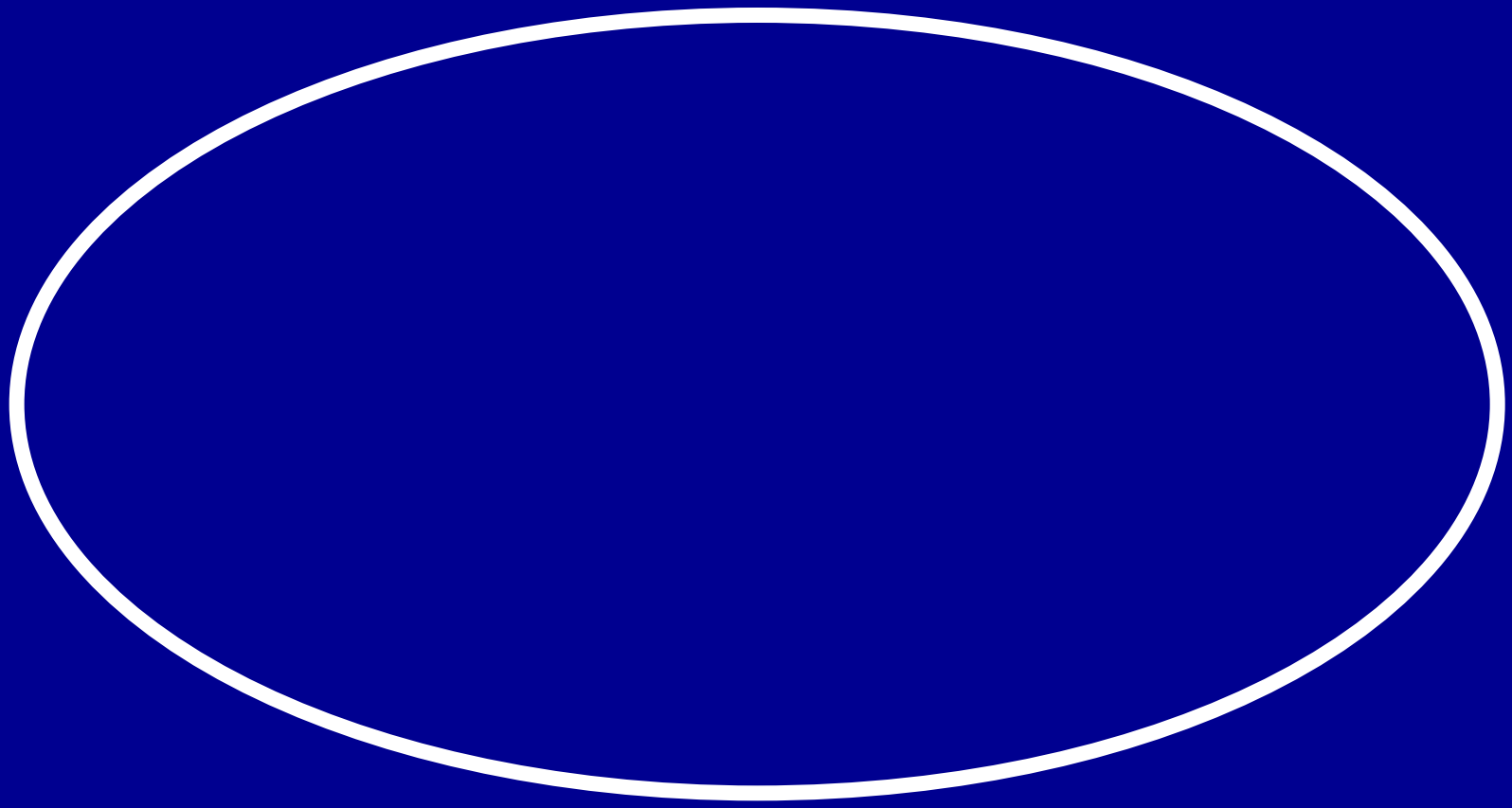


Goal: Greater than 85% success rate in Phase 3, with focus on patients who benefit

I-SPY for Targeted Agents

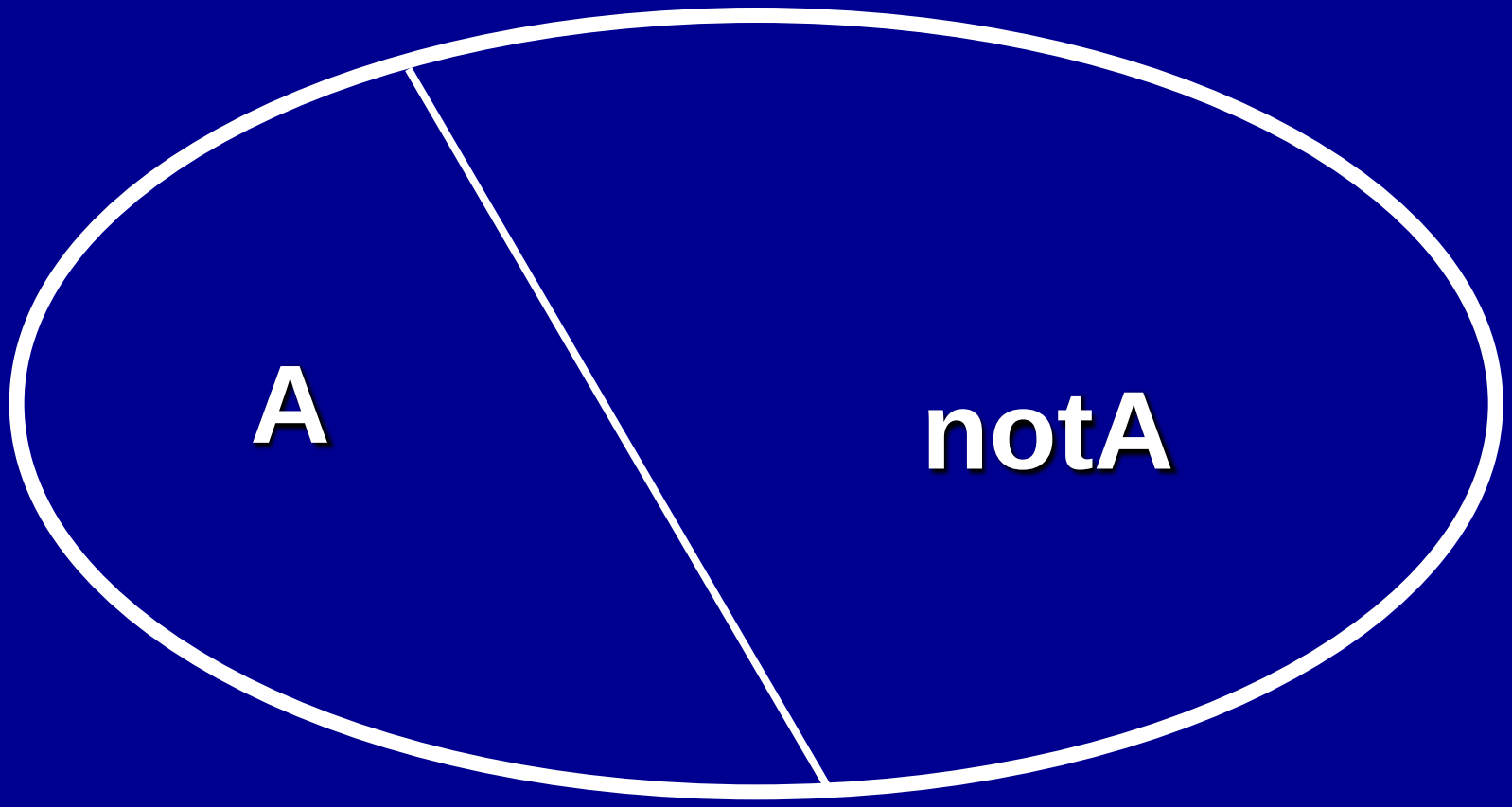
Agents Carry their Signatures into the Trial

Patient population:



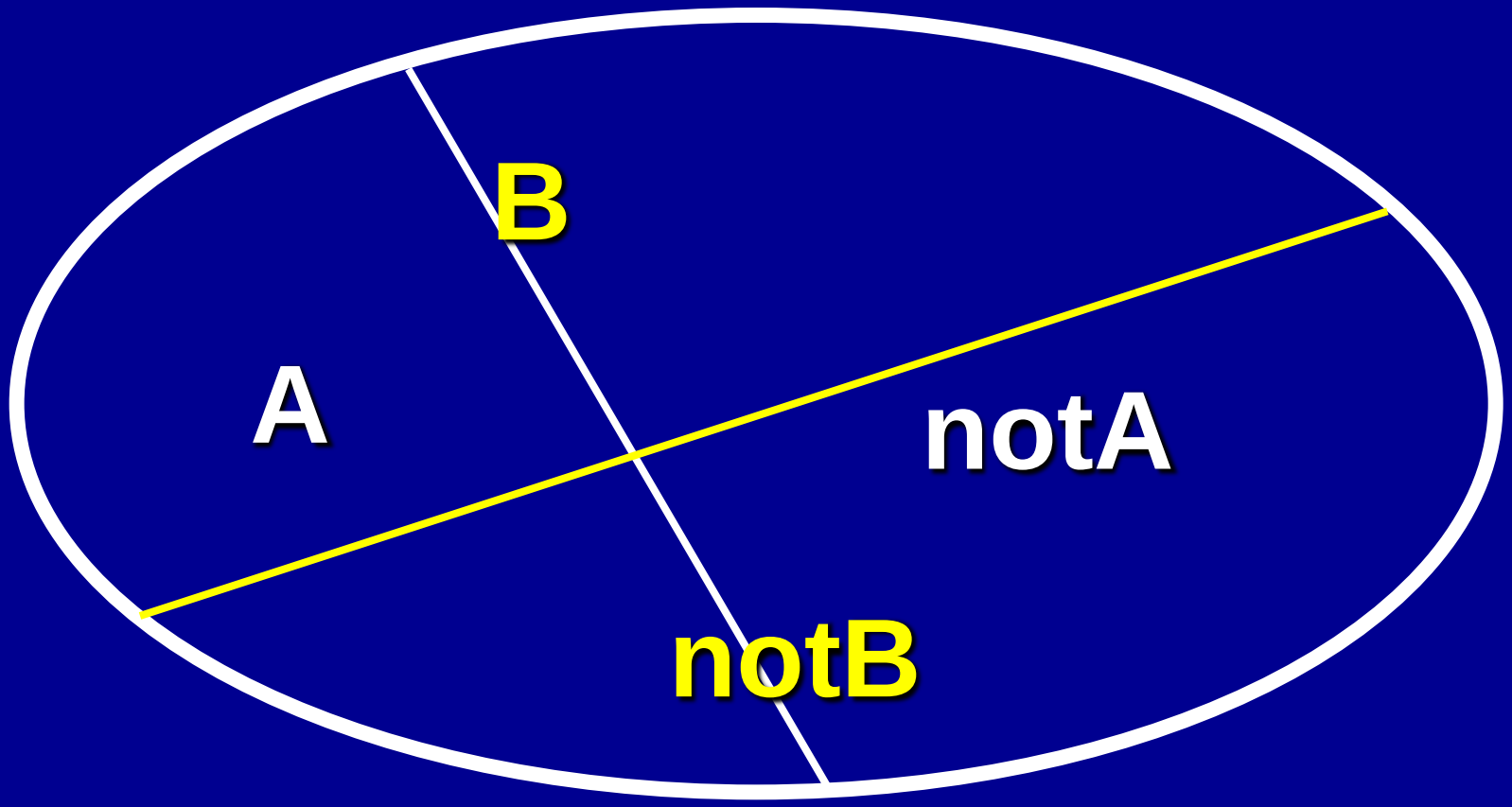
Agent A Is Added to Trial

Patient population:



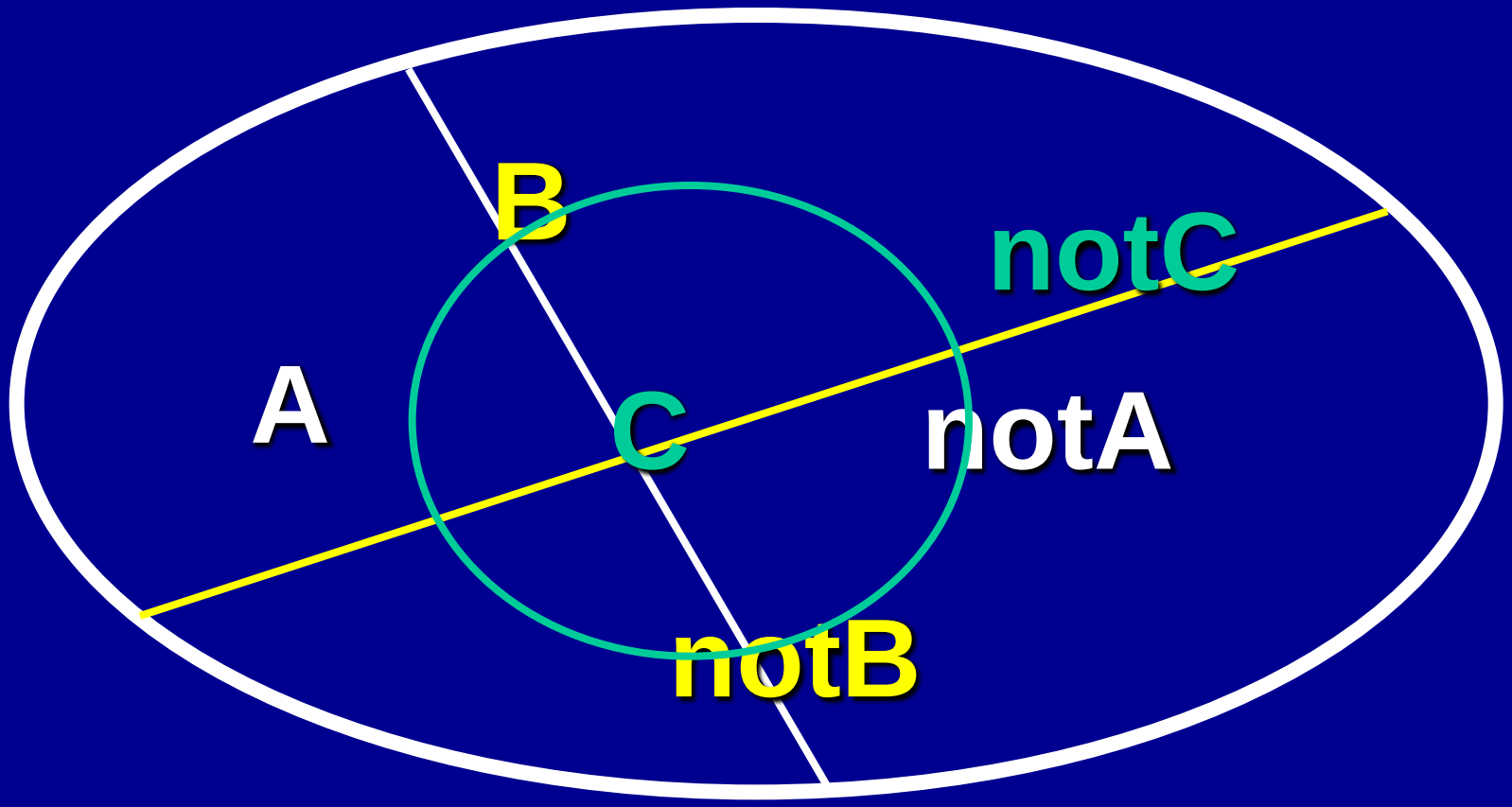
Agent B Is Added to Trial

Patient population:



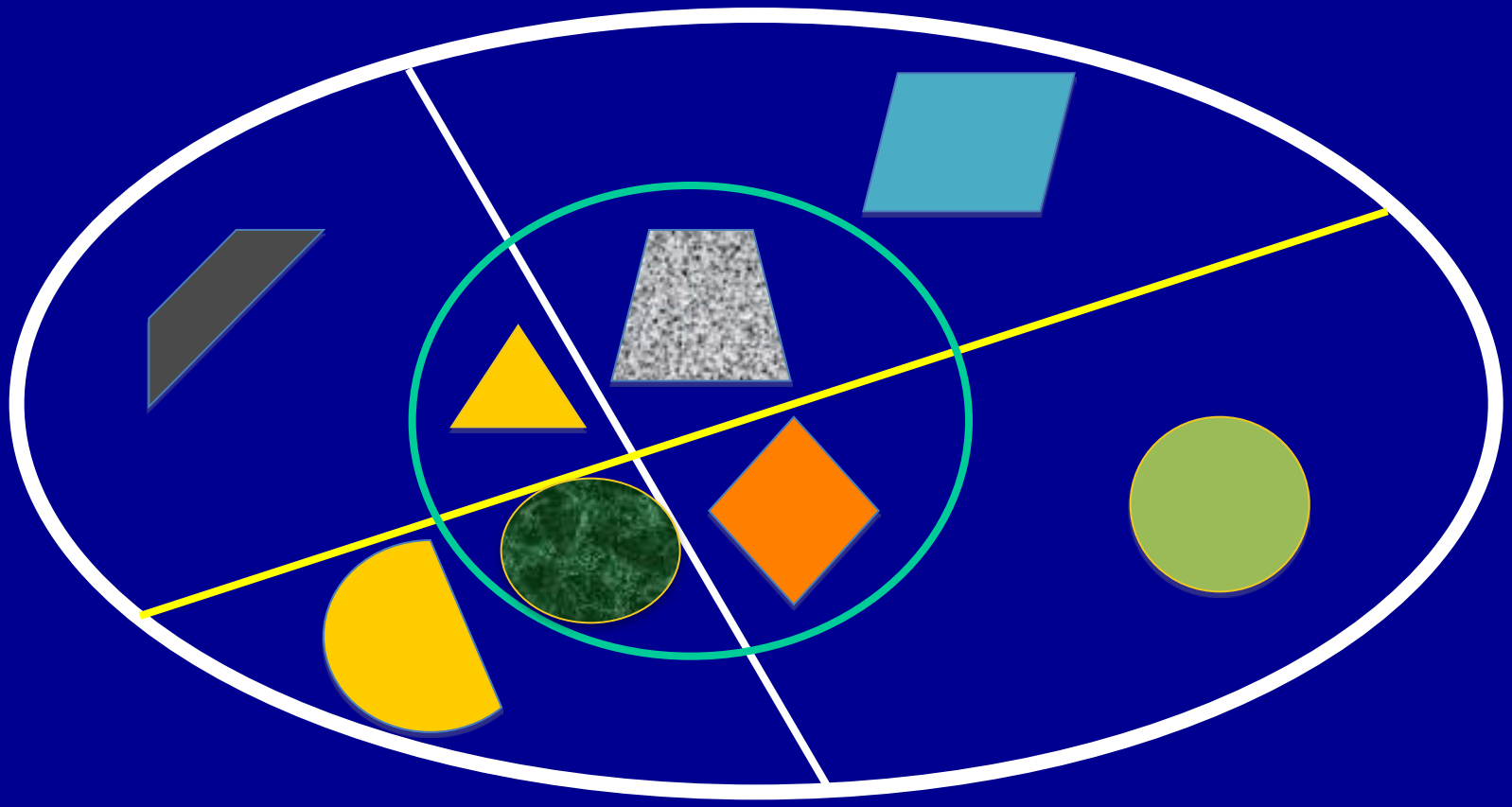
Agent C Is Added to Trial

Patient population:



3 Agents → 3 signatures, 8 cells (in analogy with I-SPY 2)

Patient population:



And So On

- Signatures defined sequentially by agents
- Signatures come and go with agents
- Adaptively randomize within cells
- Build in prior probabilities
- But explore target-negative subset

Effects of I-SPY Approaches

- Match drugs with biomarker signatures
- Savings from common control
- Better therapies move thru faster
- Successful drug/biomarker pairs graduate to small, focused, more successful Phase 3 based on Bayesian predictive probabilities
- Offspring of I-SPY 2: melanoma, colorectal cancer, Alzheimer's, HIV, acute heart failure, H1N1, …