Innovative Clinical Trial Design

- Donald A. Berry
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Janet Woodcock
Director CDER FDA

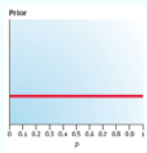
- 2006: "Improved utilization of adaptive and Bayesian methods" could help resolve the low success rate of and expense of phase III clinical trials
- 2013: FDA will need to "turn the clinical trial paradigm on its head" to allow personalized drug therapies to get on the market faster

OUTLINE

- Introduction to Bayes adaptive
- BATTLE trial in lung cancer
- I-SPY 2, brief intro for Jane
- Goldilocks and I-SPY 3
- Basket trials
- Decision analysis & rare disease

Bayesian Updating

- Paired observations, T vs C
- P(S) = P(T wins pair)
- H_0: P(S) = 1/2
- Data: SSFSS FSSSF
  SFSSS SS



Prob: 8/12

Prob: 4/12

Example: Troxacitabine in AML* (endpoint: CR by day 50)

Standard design

RANDOMIZE

Idarubicin Ara-C	n = 25
Trox Idarubicin	n = 25
Trox Ara-C	n = 25

* Giles JCO 2003

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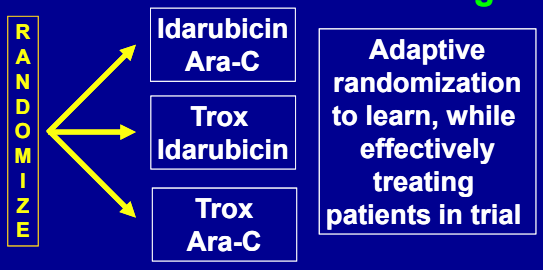
Example: Troxacitabine in AML* (endpoint: CR by day 50)

Our design



Adaptive randomization to learn, while effectively treating patients in trial

* Giles JCO 2003

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Adaptive Randomization

- Assign with higher probability to better performing therapies
- TI dropped after 24th patient
- Trial stopped after 34 patients

Summary of AML trial results

CR by 50 days:

IA 10/18 = 56%

TA 3/11 = 27%

TI 0/5 = 0%

Adaptive Randomization Compared with Balanced Randomization

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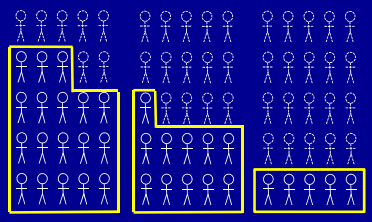
Adaptive Randomization

IA TA TI



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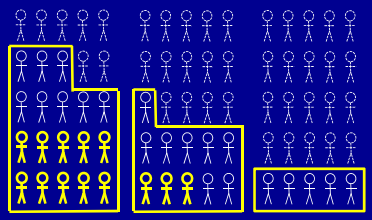
Adaptive Randomization: CRs in bold yellow

IA TA TI



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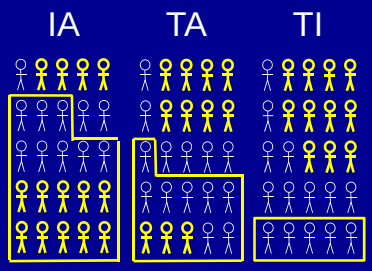
Adaptive Randomization: other 41 patients on IA



Estim: 36/75 CRs (48%)

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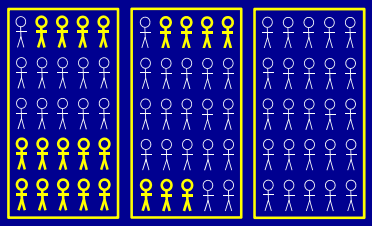
Balanced Randomization



Estim: 21/75 CRs (28%)

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Cure Magazine (2006)

"I see no rationale to further delay moving to these designs," says Dr. Giles, who is currently involved in eight Bayesian-based leukemia studies. "They are more ethical, more patient-friendly, more conserving of resources, more statistically desirable."

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However!!!!!

External impact of the trial?

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SGX Pharmaceuticals Discontinues Phase II/III Clinical Trial Of Troxatyl In Third-Line Acute Myelogenous Leukemia

Main Category: Lymphoma / Leukemia / Myeloma
Also Included In: Clinical Trials / Drug Trials
Article Date: 29 Aug 2006 - 0:00 PDT

0 tweets

The DSMB found that the study response rates were unlikely to provide evidence of a treatment benefit as a third-line treatment for patients with AML.

Current Article Ratings:

Patient / Public: Not yet rated
Health Professional: 3 (1 votes)
Article Opinions: 0 posts

Find other articles on: "troxatyl"

SG
(Na
today that it has discontinued the Phase II/III clinical trial of Troxatyl(TM) as a third-line treatment for patients suffering from acute myelogenous leukemia (AML), based upon the recommendation of the study's independent data and safety monitoring board (DSMB). The DSMB found that the study response rates were unlikely to provide evidence of a treatment benefit as a third-line treatment for patients with AML. The recommendation to discontinue the clinical trial was not made due to safety concerns.

"The response rates observed to date in our Phase II/III trial of Troxatyl are not at a level that we believe would support a New Drug Application as a third-line

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JAMA The Journal of the American Medical Association

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June 13, 2012, Vol 307, No. 22 >

Adaptive Clinical Trials
A Partial Remedy for the Therapeutic Misconception?

William J. Meurer, MD, MS; Roger J. Lewis, MD, PhD; Donald A. Berry, PhD

JAMA. 2012;307(22):2377-2378. doi:10.1001/jama.2012.4174.

Article References

There is a common "therapeutic misconception" among patients considering participation in clinical trials.[1] Some trial participants and family members believe that the goal of a clinical trial is to improve their outcomes—a misperception often reinforced by media advertising of clinical research.[2] Clinical trials have primarily scientific aims and rarely attempt to collectively improve the outcomes of their participants. The overarching goal of most clinical trials is to evaluate the effect of a treatment on disease outcomes.[3] Comparisons are usually made with placebo for conditions having no established treatments and with standard care for conditions having effective treatments. Any benefit to an individual trial participant is a chance effect of randomization and the true, but unknown, relative effects of the treatments. Available evidence is conflicting regarding whether patients receive some benefit from simply participating in a

Can advocates influence the way we think about the purpose of clinical trials?

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Joffe/Weeks, JNCI (2002)

"Many respondents viewed the main societal purpose of clinical trials as benefiting the participants rather than as creating generalizable knowledge to advance future therapy. This view, which was more prevalent among specialists such as pediatric oncologists that enrolled greater proportions of patients in trials, conflicts with established principles [from Belmont Report] of research ethics."

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BATTLE Trial in NSCLC

Kim et al. *Cancer Discovery* 2011

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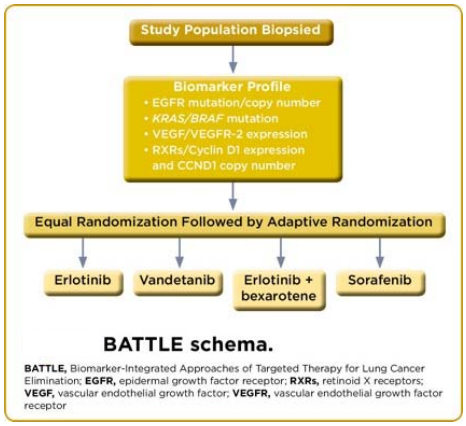

BATTLE schema.

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

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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]	[illegible]
Sorafenib	25 (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 EGFR wt a biomarker signature for sorafenib?

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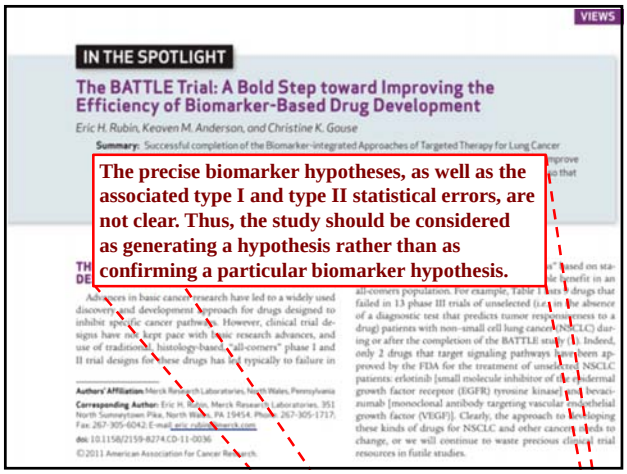

VIEWS

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

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.

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 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.

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

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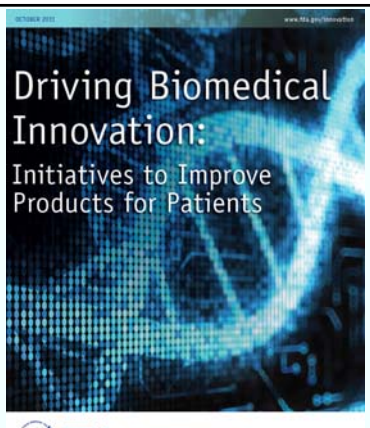
I-SPY2

http://www.ispy2.org

Berry DA. Adaptive Clinical Trials.
***Nature Reviews Clinical Oncology* (2011)**



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To respond to these challenges, FDA will hold a series of scientific meetings with academic investigators, patient groups, drug developers, statistical and methodological experts, and ethicists to achieve a common understanding of steps that can be taken when an investigational drug being studied for a serious disease with no acceptable treatment option shows exceptional promise. CDER will then publish a draft guidance on an expedited development pathway based on the outcome of these meetings.

FDA is also working on two more immediate and related steps toward expedited drug development. First, the Agency is developing a draft guidance on enrichment strategies in clinical drug development. This is a major step forward for speeding progress for targeted therapies and will lay out many strategies for selecting the patients most likely to benefit from a particular drug. These enrichment strategies are expected to improve the efficiency of clinical trials and serve as a source of expedited drug development.

Second, as a working example of an expedited pathway, CDER will publish a draft guidance on the use of pathologic complete response (pCR)—when no clinical evidence of a disease remains—as a surrogate endpoint for accelerated approval in primary high-risk breast cancer. This guidance will outline a relatively seamless pathway that could be followed from a multi-drug screening trial such as I-SPY 2 to an accelerated approval. This would speed the availability of targeted therapies for breast cancer.

U.S. Food and Drug Administration / Driving Innovation

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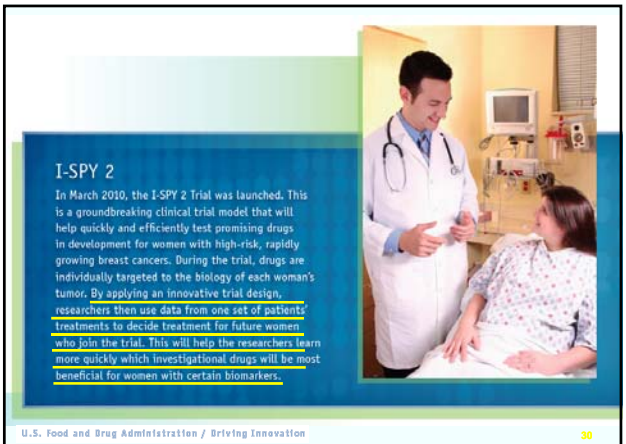

U.S. Food and Drug Administration / Driving Innovation

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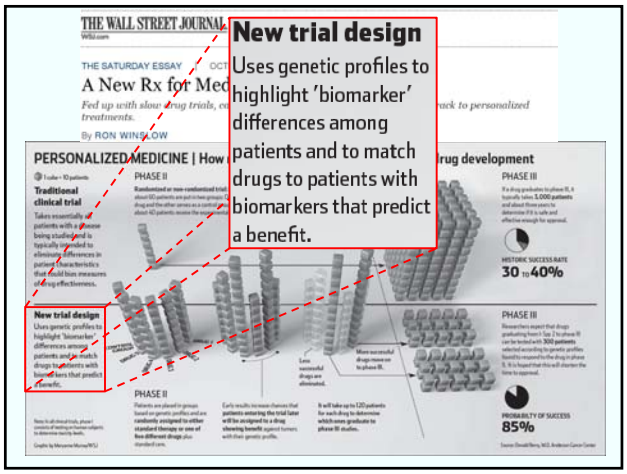
THE WALL STREET JOURNAL.
THE SATURDAY ESSAY
A New Rx for Med
Fed up with slow drug trials, ... track to personalized treatments.
By RON WINSLOW
PERSONALIZED MEDICINE | How ... drug development
PHASE II
PHASE III
Traditional clinical trial
HISTORIC SUCCESS RATE
30 TO 40%
New trial design
Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.
PROBABILITY OF SUCCESS
85%
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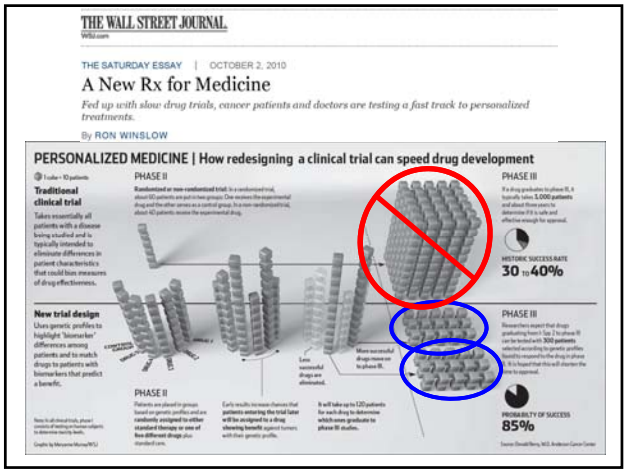
THE WALL STREET JOURNAL.
THE SATURDAY ESSAY | OCTOBER 2, 2010
A New Rx for Medicine
Fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments.
By RON WINSLOW
PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development
PHASE II
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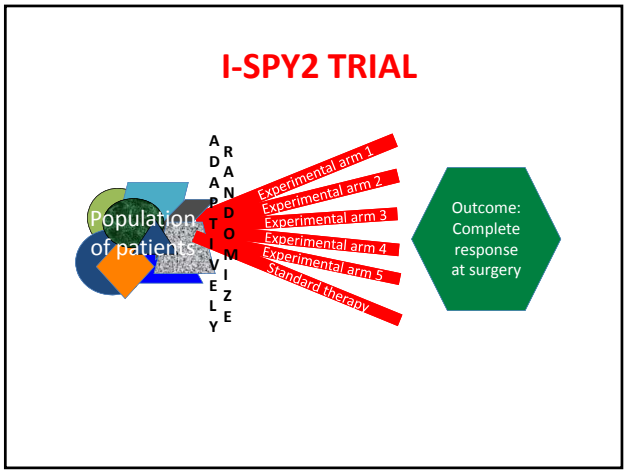
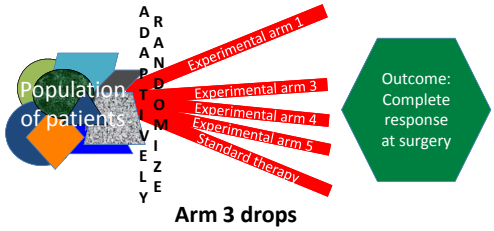

I-SPY2 TRIAL
Population of patients
ADAPTIVELY
RANDOMIZE
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery

I-SPY2 TRIAL

Arm 2 graduates to small focused Phase 3 trial

I-SPY2 TRIAL

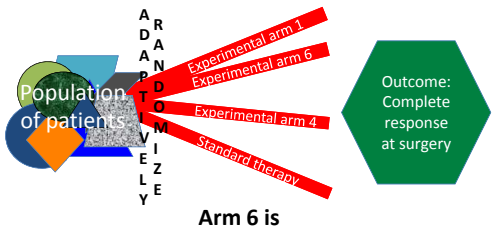


Arm 3 drops for futility

I-SPY2 TRIAL

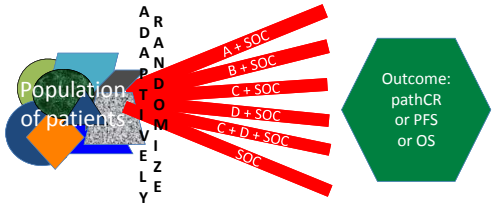
Arm 5 graduates to small focused Phase 3 trial

I-SPY2 TRIAL

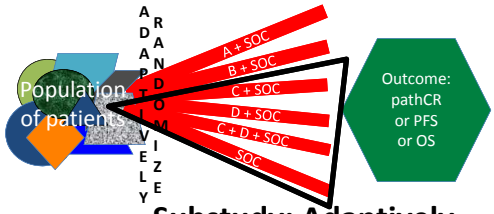


Arm 6 is added to the mix

I-SPY-like TRIAL for Combinations

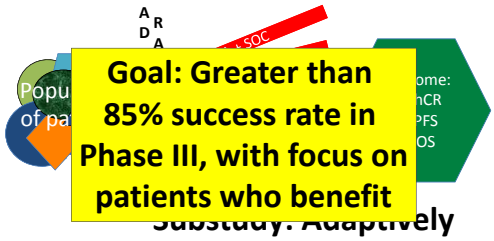


I-SPY-like TRIAL for Combinations



Substudy: Adaptively randomized factorial

I-SPY-like TRIAL for Combinations



randomized factorial

I-SPY2 Adaptive Process

- Primary endpoint: pCR (role of MRI?)
- Match drugs with up to 10 biomarker signatures
- n between 60 and 120 for "graduates"
- Currently:
  - 19 centers, US & Canada
  - ~500 pts randomized
  - First 7 exp drugs: neratinib, ABT888, AMG386, AMG479, MK2206, pertuzumab, pertuzumab+T-DM1

I-SPY2 Effects & Clones

- 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: lymphoma, HIV, melanoma, Alzheimer's, acute heart failure, scleroderma, SARI/H1N1, …

Guidance for Industry

Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
Clinical/Medical

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Designs for I-SPY 3 to address both pCR and EFS in a single trial

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Assumptions

- Focus on triple-negative neoadjuvant breast cancer as an example
- Hypothetical phase II results
  - Control pCR rate 35%
  - Experimental: pCR rates 35%, 40%, …, 70%
- Benefit in EFS due to pCR increase
- Relationship between pCR and EFS from CTNeoBC (Cortazar et al. SABCS 2012)

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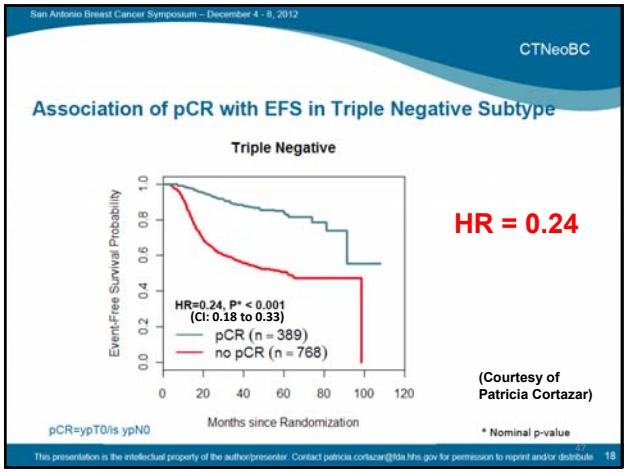
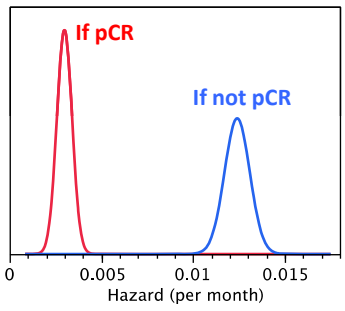


(Bayesian) Distributions of Hazards (CTNeoBC), Assuming Exponential Event Rate



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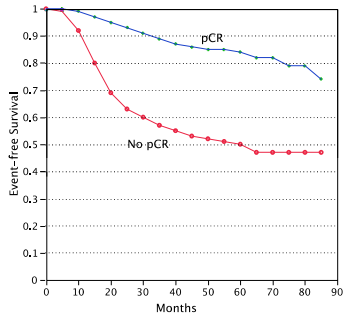
Smoothed Version of Cortazar



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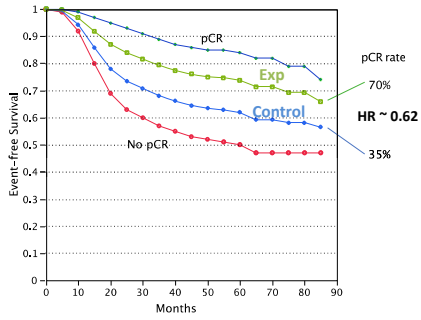
EFS for pCR Rates 70% vs 35%



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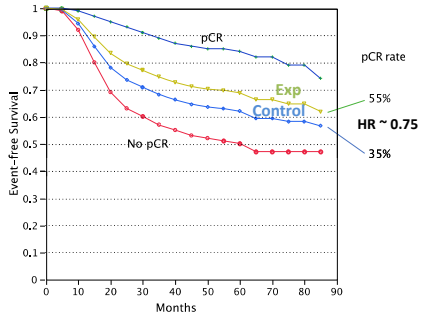
EFS for pCR Rates 55% vs 35%



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For All Designs Considered

- Accelerated approval if superiority on pCR
  - pCR analysis when all patients have surgery
  - Single final pCR comparison with control
- Full approval if superiority on EFS
  - 3 years minimum follow-up for EFS
  - Single final EFS comparison
  - Type I error rate controlled ≤ 2.5%

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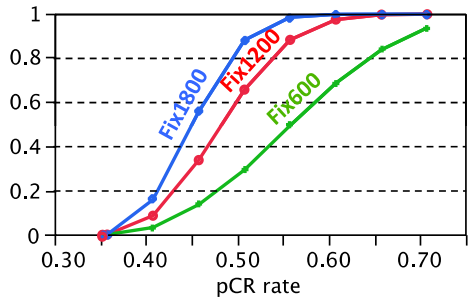
Power Via Simulations: Fixed Design

Same for Group-Sequential



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One-Look (at pCR) Design

- Maximum sample size N (= 1200)
- When 300th patient has surgery, find predictive probabilities that both pCR and EFS stat sig based on pCR results (*only*!) from I-SPY 3 (assume CTNeoBC)
  - If PP < 5% when get to N stop now for futility
  - If PP > 90% with current n then stop accrual (final n = 300 + ~120 due to delayed surgery)
  - Otherwise choose smallest sample size (multiple of 100) having PP > 90% (or go to N if none)

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Goldilocks Design

- Maximum sample size N (= 1200)
- When 300th pt has surgery, find PP of both pCR and EFS stat sig based on pCR data (only!) from I-SPY 3 (assume CTNeoBC)
  - If PP < 5% when N pts then stop for futility
  - If PP > 90% with current n then stop accrual (final n greater by ~120)
- Else continue to next 100 surgeries; repeat above until n = N
- In all cases, pCR analysis after 6 mos, EFS analysis after 3 yrs

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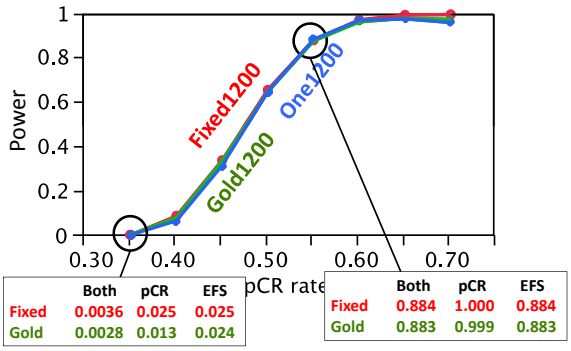
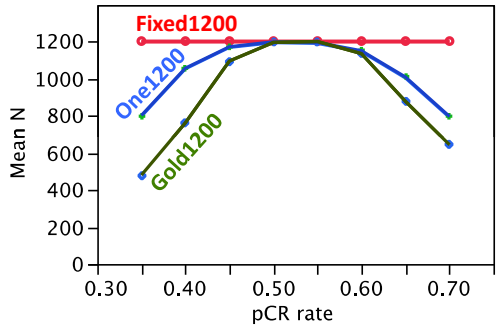
Goldilocks Vs Fixed Vs One IA



	Both	pCR	EFS
Fixed	0.0036	0.025	0.025
Gold	0.0028	0.013	0.024

	Both	pCR	EFS
Fixed	0.884	1.000	0.884
Gold	0.883	0.999	0.883

Mean Sample Size



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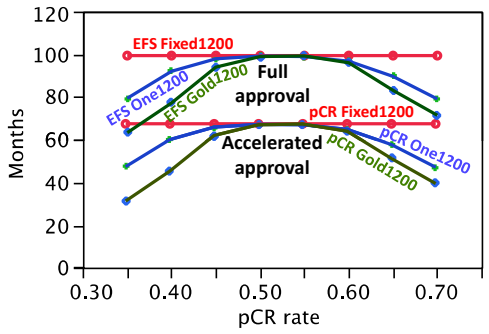
Mean Duration



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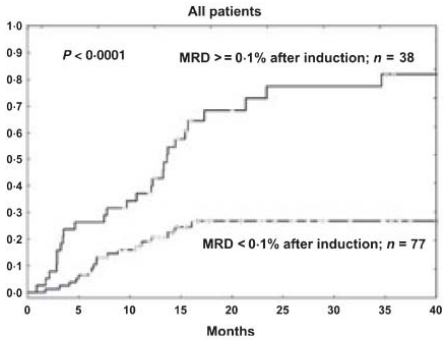
MRD a surrogate marker in leukemia?

Example: MRD/Relapse in ALL



Holowiecki BJH 2008

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Basket Trials

- Targeted drug, develop simultaneously across organ-specific cancers
- Restrict to tumors expressing target
- Population sizes small means trial sample sizes must be small

The Approaching Wall

- Ever finer grid of biomarker categories: Within 10 years every cancer patient will have an orphan disease.
- How to develop drugs in this setting?

CLINICAL TRIALS ARTICLE Clinical Trials 2013

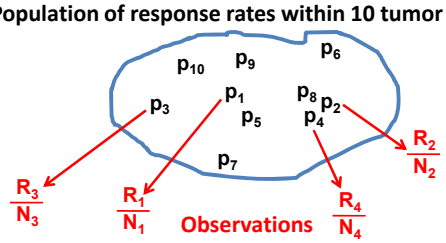
Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trials

Scott M Berry[a], Kristine R Broglio[a], Susan Groshen[b] and Donald A Berry[a,c]

Background In oncology, the treatment paradigm is shifting toward personalized medicine, where the goal is to match patients to the treatments most likely to deliver benefit. Treatment effects in various subpopulations may provide some information about treatment effects in other subpopulations.
Purpose We compare different approaches to Phase II trial design where a new treatment is being investigated in several groups of patients. We compare considering each group in an independent trial to a single trial with hierarchical modeling of the patient groups.
Methods We assume four patient groups with different background response rates and simulate operating characteristics of three trial designs, Simon's Optimal Two-Stage design, a Bayesian adaptive design with frequent interim analyses, and a Bayesian adaptive design with frequent interim analyses and hierarchical modeling across patient groups.
Results Simon's designs are based on 10% Type I and Type II error rates. The inde-

Hierarchical modeling/ Bayes borrowing assumptions

Population of response rates within 10 tumor types:



Response rates p_i have a distribution, one that is imperfectly known, even after observing the R_i/N_i

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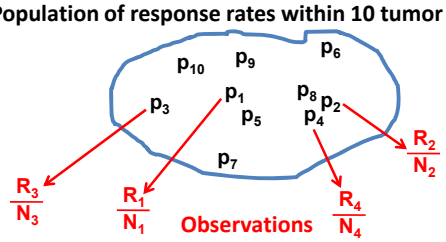
Hierarchical modeling/ Bayes borrowing assumptions

Population of response rates within 10 tumor types:



R_1/N_1 gives info about p_1 which gives info about population of p's which gives info about p_2, say. Hence "borrowing."

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Hierarchical modeling assumptions/prior

- Distribution of response rates p_i is unknown—itself has a probability distribution
- Expectations regarding p's can differ by tumor type
- Prior distribution ("hyperprior") of heterogeneity σ in population of p's is important in determining borrowing

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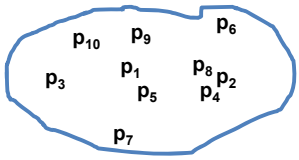
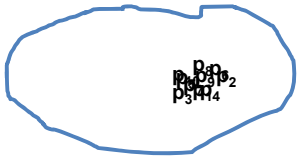
Learn about heterogeneity parameter σ from trial results

σ large:



σ small:



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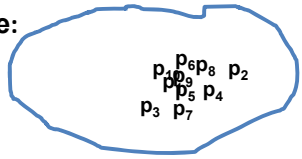
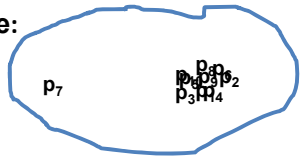
Many Possibilities …

σ moderate:



σ moderate:



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Compare Bayes with S2S (same type I and II error rates)

- Intermediate design: Bayes with no borrowing across tumor types
- Criteria:
  - Total sample size
  - Probability correct decision

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One case: 4 tumor types, all positive

		Bayes Borrow			Bayes No Borrow			S2S		
Type	*p*	Mean N	Prob Success	Prob Futility	Mean N	Prob Success	Prob Futility	Mean N	Prob Success	Prob Futility
1	0.25	20.0	0.972	0.028	24.5	0.808	0.192	31.4	0.795	0.205
2	0.30	17.4	0.988	0.012	21.7	0.914	0.086	33.0	0.902	0.098
3	0.35	14.1	0.996	0.004	18.4	0.964	0.036	34.0	0.955	0.045
4	0.40	13.5	0.998	0.002	15.6	0.984	0.016	34.6	0.980	0.020
Total		*66.0*			*80.2*			*133.0*		

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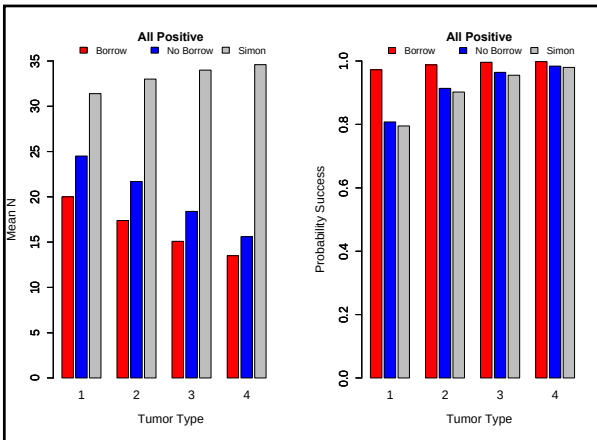

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OUTLINE

- Introduction to Bayes adaptive
- BATTLE trial in lung cancer
- I-SPY 2, brief intro for Jane
- Goldilocks and I-SPY 3
- Basket trials
- **Decision analysis & rare disease**

Designing a clinical trial is making a decision

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Standard Approach to Choosing Sample Size

- Example: time to event. Want
  - 25% reduction in hazard
  - 5% type I error, two-sided
  - 80% power
  - 2/month accrual
  - 8 mo median for control
  - 12 mos follow-up
- Answer: n = 650

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Standard Approach

- Would be an accident if this design is optimal (or even okay) when goal is delivering good medicine
- Can't be right for both
  - Disease is CHF
  - Disease is a rare pediatric cancer
- Can't be right for both
  - Product is bone marrow transplant
  - Product is a chocolate bar

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Of course investigators and regulators adjust

- For rare diseases, accept smaller trials
- For highly invasive or toxic products, consider disease severity & require stronger evidence of effectiveness
- Still: How small, how severe, how strong?
- To know whether deliver good medicine, evaluate impact on patient population

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Decision-Analytic Clinical Trial

- Deliver good medicine to patients
- Which patients?

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Ethics: Individual vs Collective

- Fundamental conflict
- Learning with time is inevitable in medicine: Better to delay getting any disease!
- But all patients should count equally *a priori*, sacrificing neither learning nor effective treatment of patients in the trial

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Decision-analytic Clinical Trial

- Goal: Effective overall treatment of patients, both
  - Those in the trial and
  - Those who come after the trial
- Maximize overall benefit in "patient horizon" N: All patients with the disease who may benefit from therapies considered

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- Goal: maximize expected number of successes in N
- Either one- or two-armed trial
- Suppose n = 1000 is right for one trial & N = 1,000,000
- Then for other N's use n =

Optimal sample size for one trial and first of two trials					
N	1,000,000	100,000	10,000	1000	100
One trial	1000	320	100	32	10
One/two	170	78	36	17	8

Ratio of sample sizes within row is general
Ratio across rows applies for particular prior distribution

Optimal allocations in a two-armed trial:

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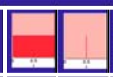
Optimal allocations to Arms 1 and 2									
	Prior distributions								
N			Succ prop			Succ prop			Succ prop
100	6	5	.63	4	8	.71	9	0	.60
1000	21	20	.65	16	30	.74	29	0	.62
10,000	70	69	.66	56	98	.75	99	0	.62
Large N	$\frac{\sqrt{N}}{2}$	$\frac{\sqrt{N}}{2}$	$\frac{2}{3}$	$\frac{\sqrt{N}}{3}$	$\sqrt{N}$	$\frac{3}{4}$	$\sqrt{N}$	0	$\frac{5}{8}$

Of course, optimal sequential assignments are even better: Bandit strategies

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"Bandit Strategies" & Google

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Berry's bandit stuff

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