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HARVARD MEDICAL SCHOOL

Bayesian hierarchical models for adaptive randomization in biomarker-driven studies: Umbrella and platform trials

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Motivation for biomarker-driven trials in oncology (in brief)

- Molecular heterogeneity of cancer is no longer a hypothesis, but known, measurable, and quantified.

  Personalized/precision medicine: A fundamental assumption is that using the genetic makeup of the tumor and the genotype of the patient will enable targeted therapeutics to improve clinical outcomes.

- Increased development of targeted therapies in oncology

- Components of multiplex genomic screening platforms are ~~converging~~ increasing overlapping

Motivation for biomarker-driven trials in oncology (in brief)

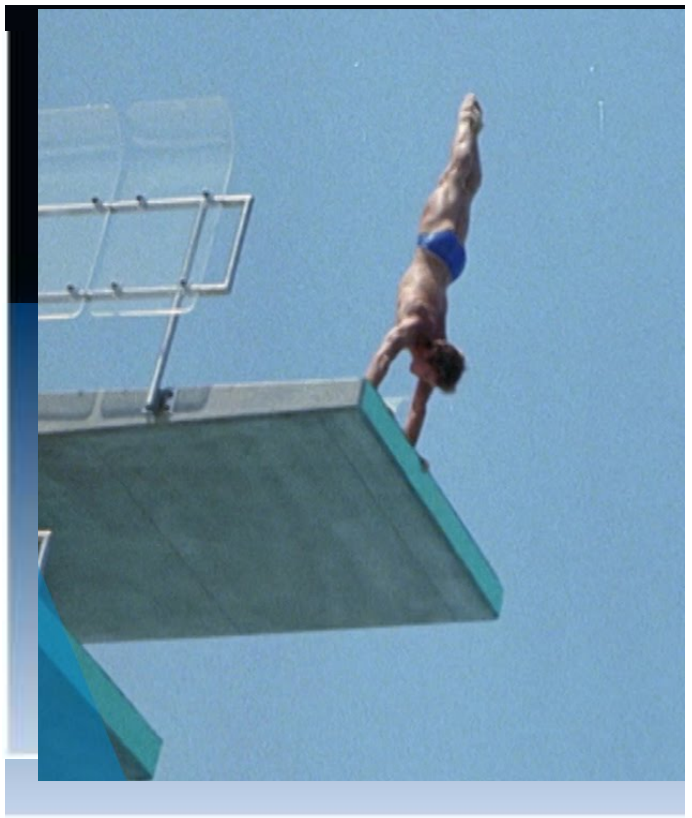
- Many innovative clinical trials designs in oncology. Important to distinguish elements:
  - Bayesian vs frequentist analysis plans
  - Comparative vs non-comparative hypotheses
  - Single-stage vs. sequential vs. continual assessment
  - Adaptive vs fixed randomization.
  - Hypotheses within or across marker-defined subgroups

Biomarker-driven designs

Integral biomarkers - Tests inherent in the design from the onset and must be performed in real time for the conduct of the trial (re: participant flow)

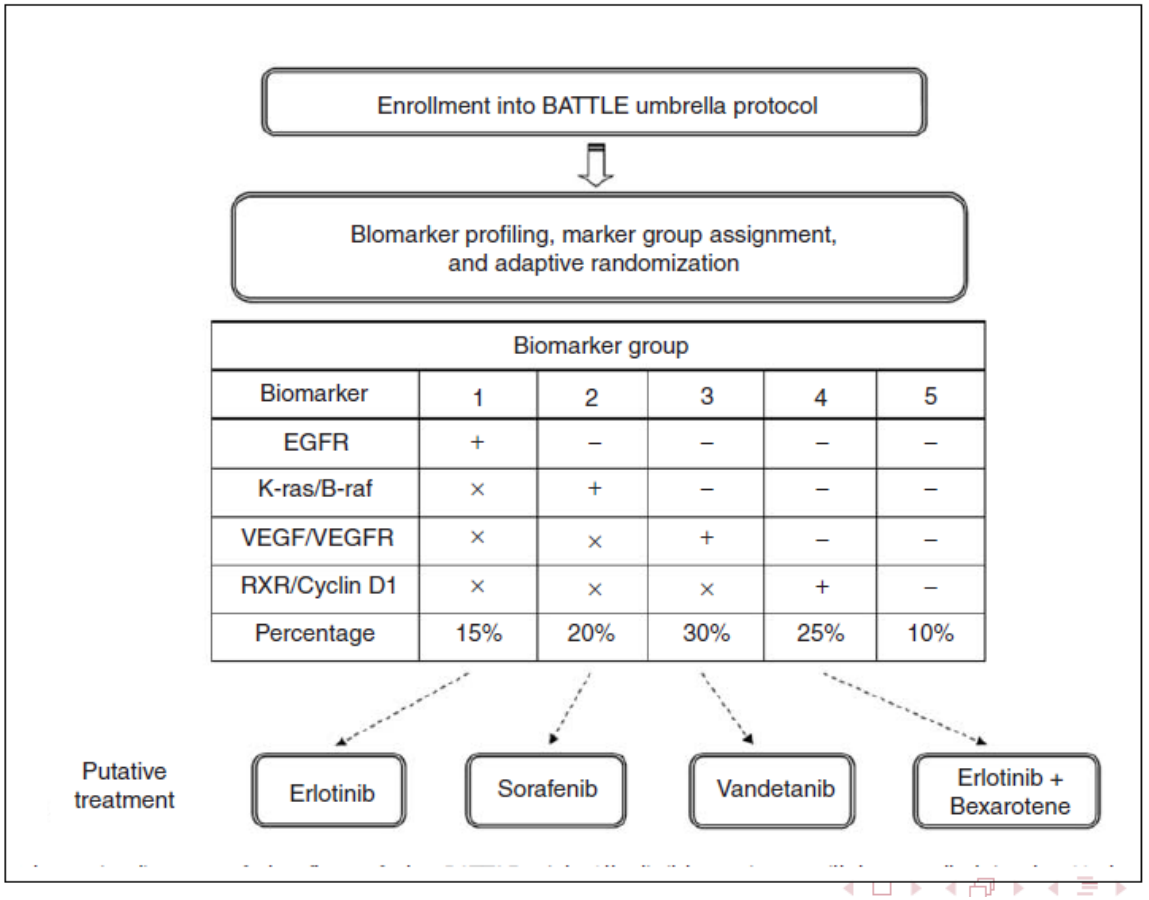
- **Single marker / treatment**
  - Enrichment designs (e.g. B31/N9831)
  - Stratified designs (TKIs and PI3Ki in Br)

- **Multiple markers / treatments**
  - Basket and Umbrella trial (BATTLE)
  - Platform trials
    - NCI-MATCH
    - I-SPY 2
  - Marker-strategy designs (SHIVA)



Herbst et al. Clin Cancer Res 2015;21:1514-1524

BATTLE: Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (PI: Kim)



Zhou et al. (2008) Clinical Trials 5:181-193 – Method (but no code) fully specified

Kim et al. (2011) Cancer Discovery 1:44-53 – Primary results

BATTLE trial design:

- Hierarchical model
- Bayesian (non-comparative) inference.
- Continual assessment
- Adaptive randomization

Kass and Steffey, 1989: Conditional independence of y_n given θ. Further, $\{\theta_{jk}|\phi\}$ are i.i.d., such that the elements of y_n are exchangeable.

$$y_n|\theta \sim p(y_n|\theta) = \prod_{jk}\prod_{i=1}^{n_{jk}} p(y_i|\theta_{jk}) \qquad \theta|\phi \sim p(\theta|\phi) = \prod_{jk} p(\theta_{jk}|\phi)$$

Binary outcome and (one possible) probit hierarchical model:

$$y_{ijk} = \begin{cases} 1 & \text{if patient } i \text{ with marker } k \text{ had a response in treatment } j \\ 0 & \text{otherwise} \end{cases}$$

$$= \begin{cases} 1 & z_{ijk} \geq 0 \\ 0 & z_{ijk} < 0 \end{cases}$$

where z_{ijk} is a latent variable that follows a Gaussian distribution.

$$z_{ijk} \sim N(\mu_{jk}, 1) \qquad \mu_{jk} \sim N\left(\phi_j, \sigma^2\right) \qquad \phi_j \sim N\left(\alpha, \tau^2\right)$$

σ^2 controls the extent of borrowing across marker groups within each treatment and α and τ^2 are the second-stage priors to the model.

BATTLE: Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (PI: Kim)

BATTLE trial design:

- Hierarchical model
- Bayesian (non-comparative) inference.
- Continual assessment
- Adaptive randomization

Futility treatment j is suspended within biomarker group k under

$$Pr\left(\Phi^{-1}(\mu_{jk}) \geq 0.5 \mid y_n\right) < 10\%$$

Efficacy likewise treatment within biomarker group (i.e. 'non-comparative')

$$Pr\left(\Phi^{-1}(\mu_{jk}) \geq 0.3 \mid y_N\right) > 80\%$$

See Zhou et al (2008) for operating characteristics w/ varying $\{\mu_{jk}\}$

BATTLE: Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (PI: Kim)

BATTLE trial design:

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- Bayesian (non-comparative) inference.
- Continual assessment
- Adaptive randomization

$$r_{jk,n} = \frac{\hat{\pi}_{jk,n}}{\sum_{w \in \Omega_{k,n}} \hat{\pi}_{wk,n}} \quad \text{where} \quad \hat{\pi}_{jk,n} = E[\Phi^{-1}(\mu_{jk})|y_n]$$

Kim (2011): *We planned to randomly assign at least the initial **80** patients equally to the 4 treatments, to allow at least 1 patient in each marker group to complete treatment, thus providing sufficient data to estimate the prior probability of [disease control]*

Barry et al. JBS 2015: The use of Bayesian hierarchical models for adaptive randomization in biomarker-driven phase II studies

Research goals:

- Evaluate properties of BATTLE (PI: Kim), as one of the first umbrella trials
- In silico simulation (R code as appendix)
- Contrast RAR and continual assessment versus traditional Simon two-stage designs

Scenarios that represent the simplest cases for using predictive biomarker(s) in a two-drug study are:

- Evaluating a novel targeted agent against a standard-of-care with a single predictive biomarker, and
- Evaluating multiple experimental agents using marker(s) selective in a complementary manner.

	Single biomarker			**Complementary biom.**	
	Marker +	Marker -		Marker +	Marker -
Trt A	θ_1	θ_0		θ_1	θ_0
Trt B	θ_0	θ_0		θ_0	θ_1

For the following illustrations: $\theta_0 = 25\%$ $\theta_1 = 50\%$

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	Single biomarker			Complementary biom.	
	Marker +	Marker -		Marker +	Marker -
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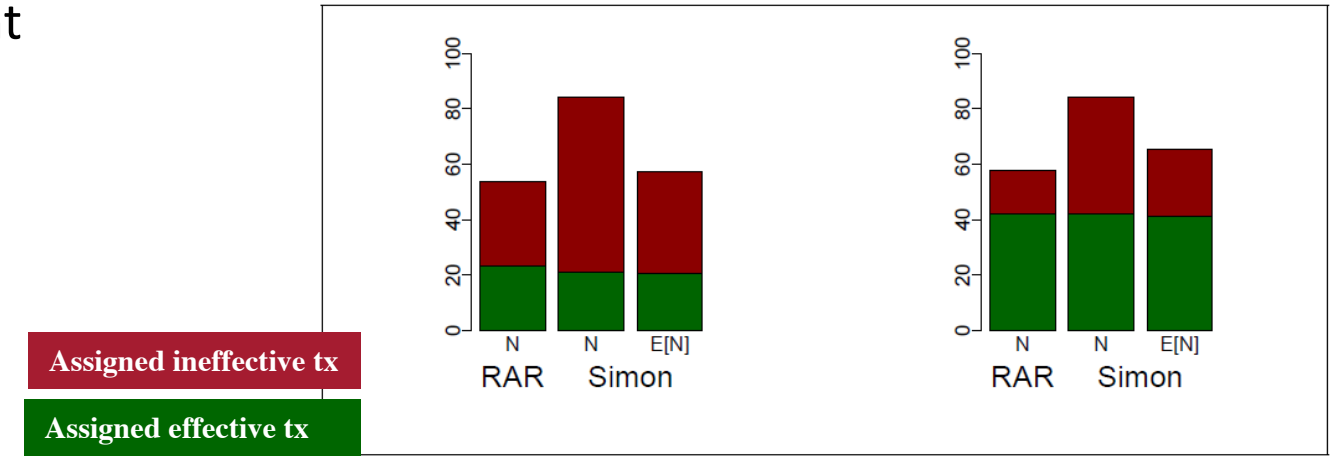
For the following illustrations: $\theta_0 = 25\%$ $\theta_1 = 50\%$

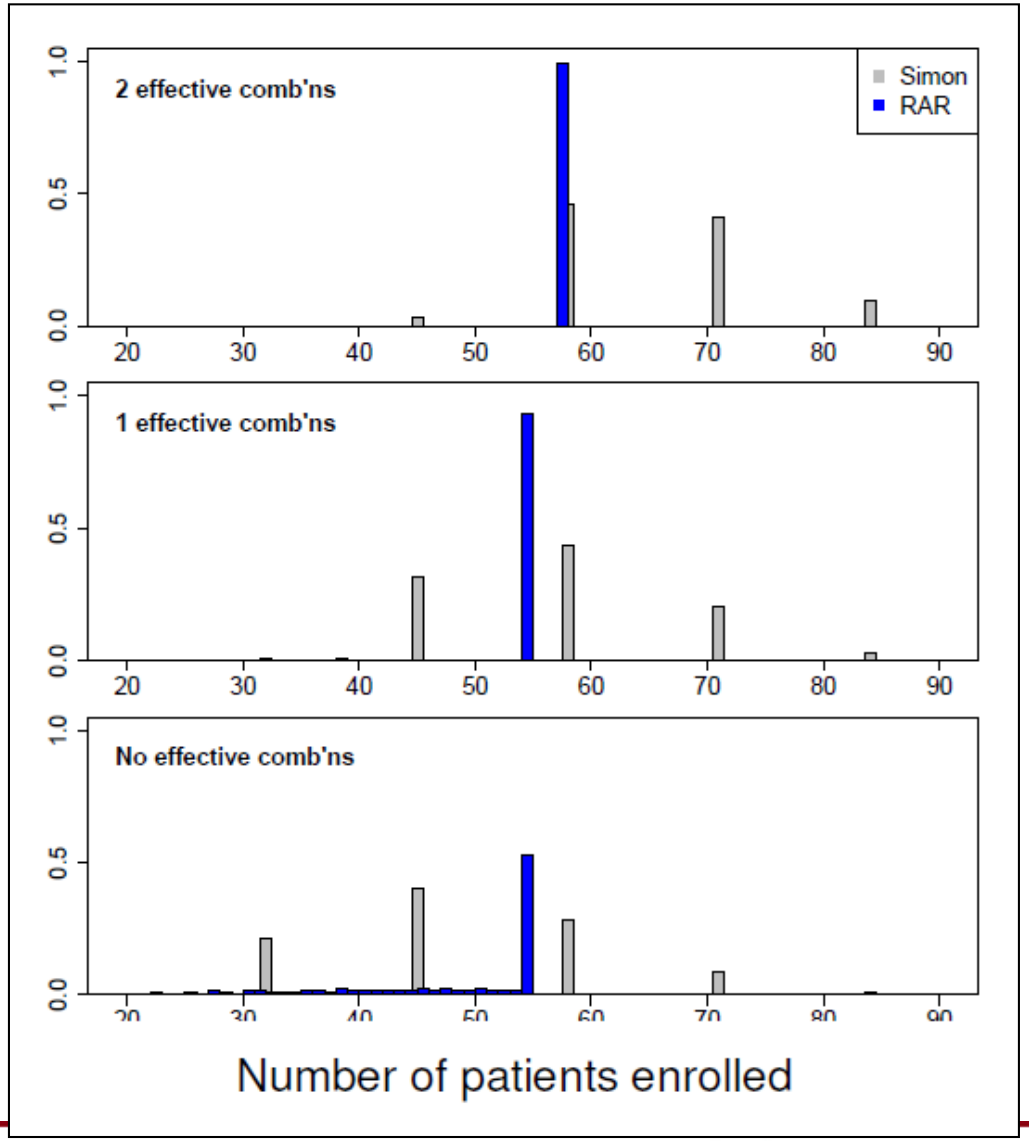


Sample sizes that achieve 80% power

Barry et al. JBS 2015: The use of Bayesian hierarchical models for adaptive randomization in biomarker-driven phase II studies

Research goals:

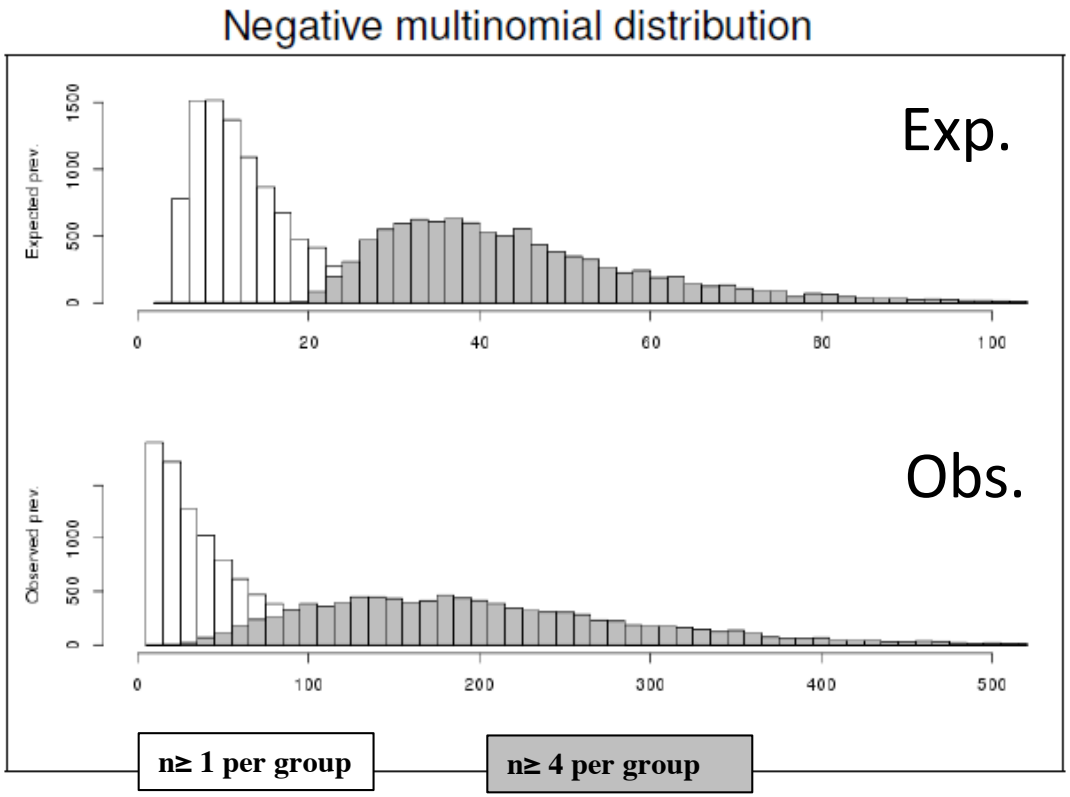
- Evaluate properties of BATTLE (PI: Kim), as one of the first umbrella trials
- In silico simulation (R code as appendix)
- Contrast RAR and continual assessment versus traditional Simon two-stage designs
- Conclusions:
  - (Nearly) equal efficiency
  - Less variability in E[N]



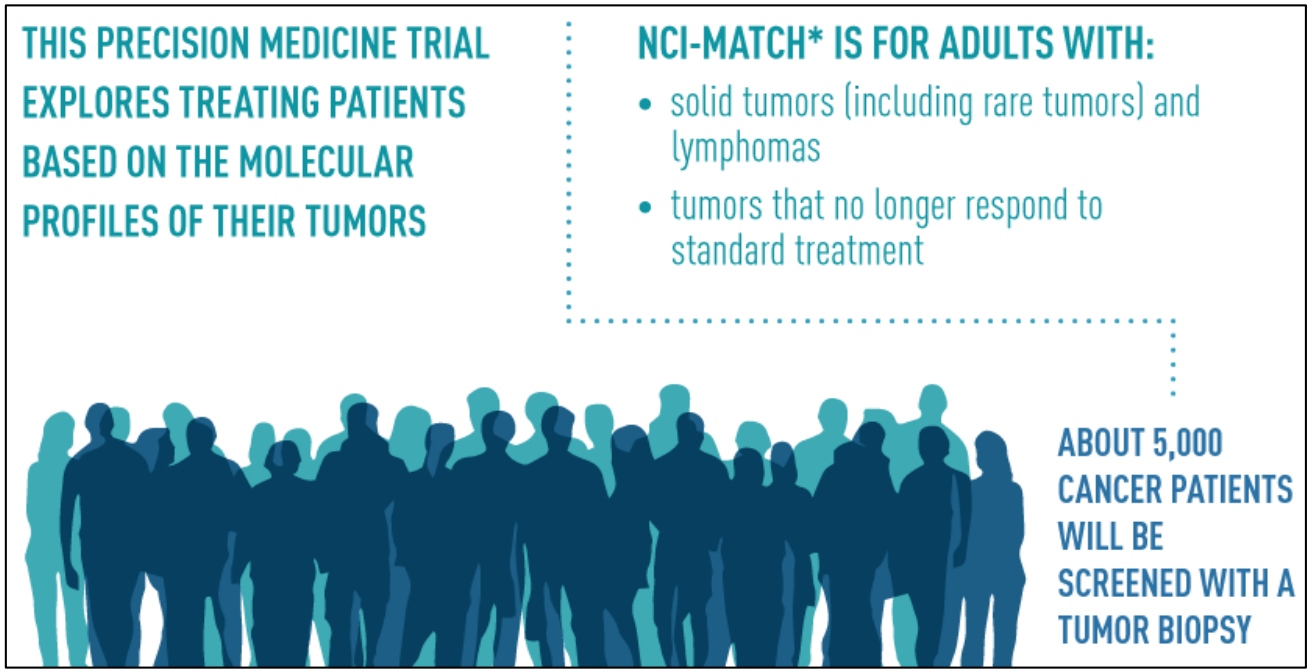
Lessons learned from BATTLE:

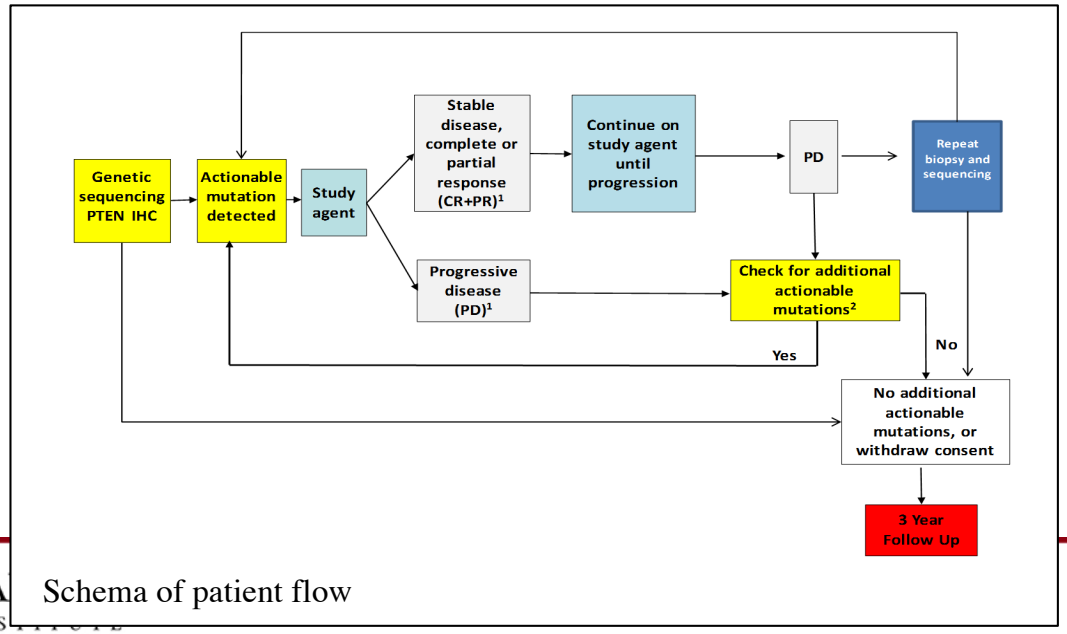
- Challenge to make reliable assumptions about prevalence of biomarkers

Group	Exp	Obs
1	10%	36%
2	20%	11%
3	30%	34%
4	25%	2%
5	10%	17%



NCI-MATCH: Molecular Analysis for Therapy Choice





Schema of patient flow

Statistical Design:

- 1° Endpoint:
  - Obj resp (RECIST1.1)
  - Null: 5%
  - Target: 25%

- Single-stage test
  - Enroll 35 pts per arm (N = 31 eval)
  - 5 or more resp.
  - $\alpha = 0.018$
  - $\beta = 0.083$

Protocol allows for expansion cohorts; not statistically driven

NCI-MATCH: Molecular Analysis for Therapy Choice

Study History	
Aug 2015	Activated with 10 initial drug arms and target N = 3000
Nov 2015	Suspended enrollment for planned evaluation 795 pts registered (739 w/ samples submitted) 645 pts completed screening 56 pts with a matching mutation (8.7%) 33 pts eligible and enrolled (5.1%) 16 pts received Tx (2.5%)
Feb 2016	Re-activated with addendum #2 Expanded eligibility to myeloma Increased to N = 5000 Increased to total of 24 treatment arms Revised estimate was 23% of pts match
Jun 2017	Reached (revised) target of N = 6000 pts 19 of 26 treatment arms still seeking patients Enrollment to sub-studies to continue through other mech's

http://ecog-acrin.org/nci-match-eay131

Snapshot of study status (Nov 2016)

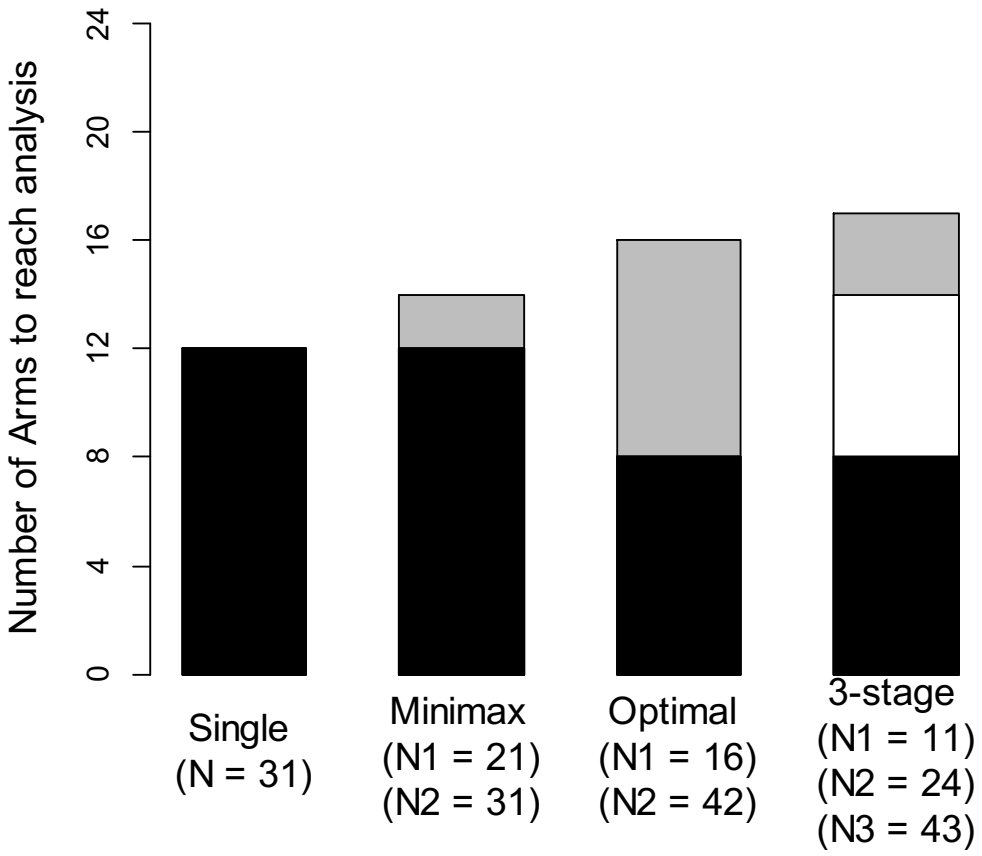
Increased
Target N: 6000 pts

24 gene alt'ns
being targeted

Arm / Target	Expected # Patients
I PIK3CA mut	137
W FGFR1/2/3	124
P PTEN loss	79
Z1A NRAS mut	70
S1 NF1 mut	66
Z1D dMMR	63
N PTEN mut	62
Q ERBB2 amp	59
B ERBB2 mut	39
C2 MET ex 14 sk	37
Z1B CCND1 amp	36
Y AKT1 mut	32

Arm / Target	Expected # Patients
R BRAF non V600	29
H BRAF V600	26
T SMO/PTCH1	18
U NF2 loss	17
C1 MET amp	14
A EGFR mut	8
G ROS1 transloc	8
S2 GNAQ/GNA11	3
E EGFR T790M	1
F ALK transloc	1
X DDR2 mut	0
V cKIT mut	0

http://ecog-acrin.org/nci-match-eay131



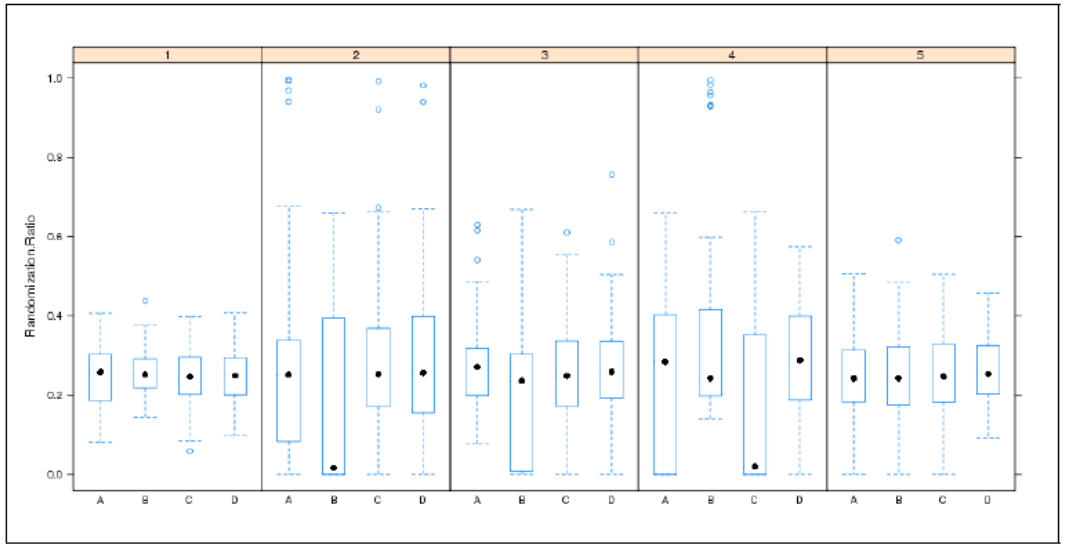
Ongoing work by R Sapigao:

- In silico simulation of the dynamic aspect of adding arms to NCI-MATCH over time and replacing completed arms
- Explore the properties of two- and three-stage designs in this framework
- Add (simulated) responses and assess Bayesian methods for continual assessment.

Lessons learned from BATTLE:

- Challenge to make reliable assumptions about prevalence of biomarkers
- Adapting w/ small n_{jk}

BATTLE: $r_{jk,n} = \frac{\hat{\pi}_{jk,n}}{\sum_{w \in \Omega_{k,n}} \hat{\pi}_{wk,n}}$ where $\hat{\pi}_{jk,n} = E[\Phi^{-1}(\mu_{jk})|y_n]$

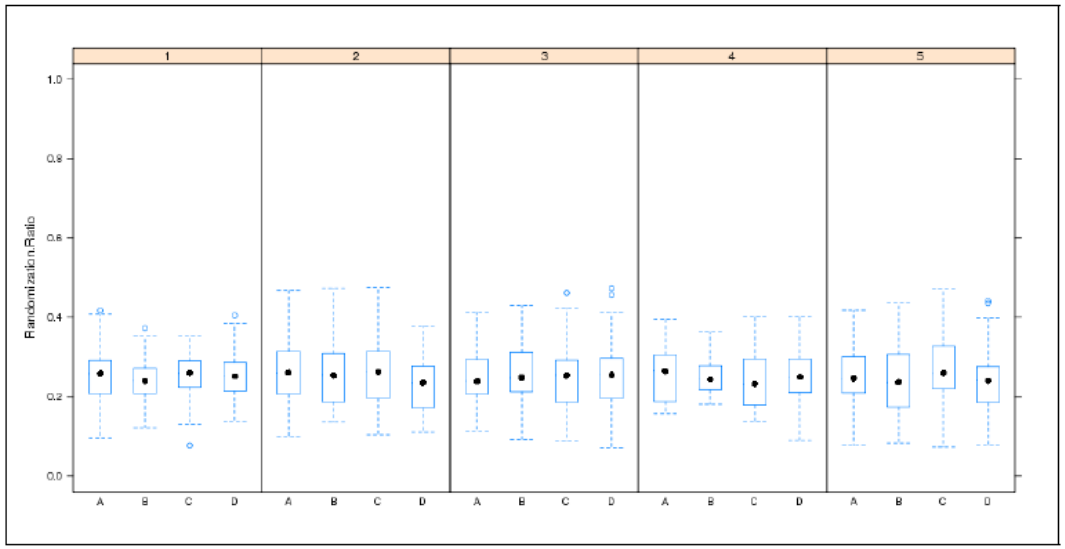


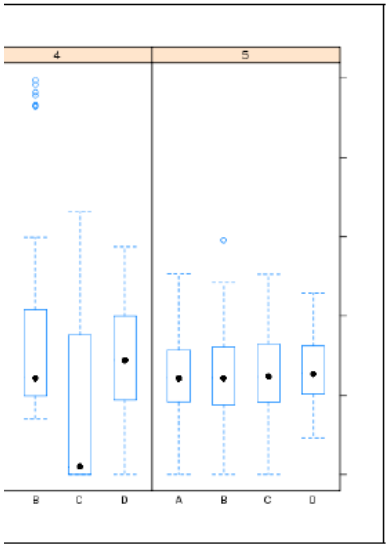
without borrowing ($\sigma^2 = 10^6$) and a non-informative prior ($\tau^2 = 10^6$).
NOTE: assuming true equipoise and no lag at $n = 97$.

Lessons learned from BATTLE:

- Challenge to make reliable assumptions about prevalence of biomarkers
- Adapting w/ small n_{jk}

BATTLE: $r_{jk,n} = \frac{\hat{\pi}_{jk,n}}{\sum_{w \in \Omega_{k,n}} \hat{\pi}_{wk,n}}$ where $\hat{\pi}_{jk,n} = E[\Phi^{-1}(\mu_{jk})|y_n]$





In Barry (in press) we advocate informative prior (e.g. $\tau^2 = 0.01$), though at $n = 97$ the likelihood will still dominate under this hierarchy.

ormative prior ($\tau^2 = 10^6$).
at $n = 97$.

Lessons learned from BATTLE:

- Challenge to make reliable assumptions about prevalence of biomarkers
- Adapting w/ small n_{jk}
- Inference w/ small n_{jk}

$$Pr\left(\Phi^{-1}(\mu_{jk}) \geq 0.3 \quad | \quad y_N\right) > 80\%$$

Table 2. Eight-week disease control status by treatment and marker groups

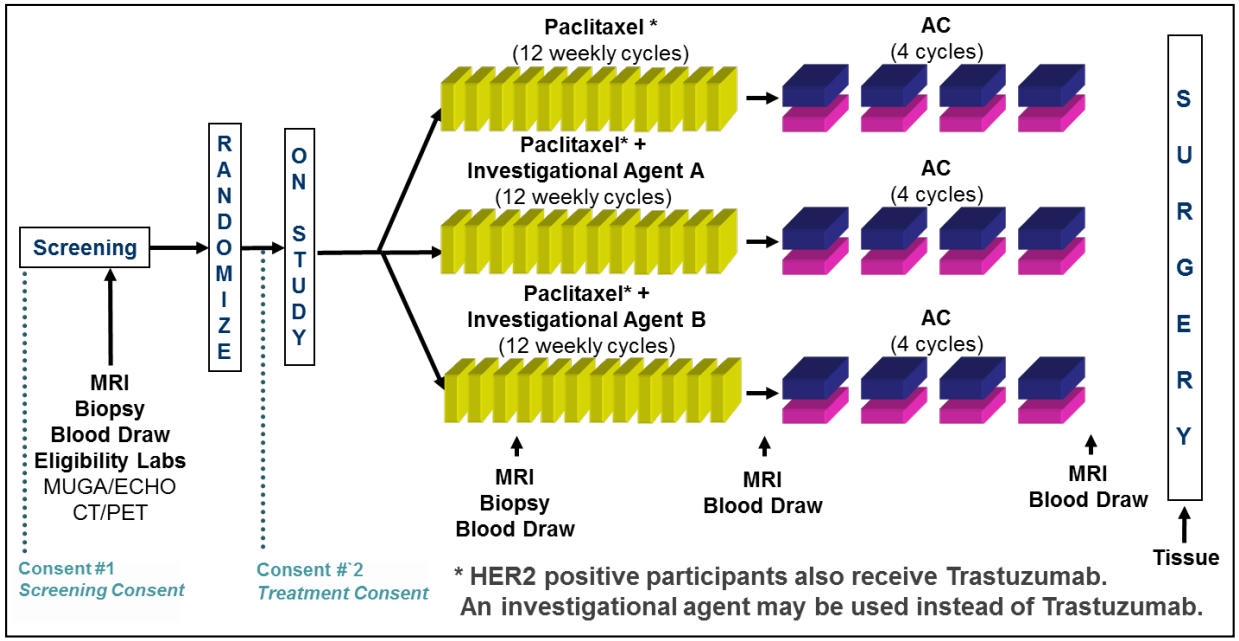
Number of patients with disease control / total number of patients (%)

Marker group	Treatment				Total
	Erlotinib	Vandetanib	Erlotinib + bexarotene	Sorafenib	
EGFR	6/17 (35%)	11/27 (41%)[a]	11/20 (55%)[a]	9/23 (39%)	37/87 (43%)
KRAS/BRAF	1/7 (14%)	0/3 (0%)	1/3 (33%)	11/14 (79%)[a]	13/27 (48%)
VEGF/VEGFR-2	10/25 (40%)[a]	6/16 (38%)	0/3 (0%)	25/39 (64%)[a]	41/83 (49%)
RXR/Cyclin D1	0/1 (0%)	0/0 (NA)	1/1 (100%)[a]	1/4 (25%)	2/6 (33%)
None	3/8 (38%)	0/6 (0%)	5/9 (56%)[a]	11/18 (61%)[a]	19/41 (46%)
Total	20/58 (34%)	17/52 (33%)	18/36 (50%)	57/98 (58%)	112/244 (46%)

[a]Cells showing effective treatments within specific marker groups defined as the probability of DCR given data is 80% or greater. Only 1 patient in the RXR/CycD1 marker group received erlotinib + bexarotene.

Likewise, $Pr > 99.9\%$ when $n_{ij} = 1$, $y_{1jk} = 1$ and $\sigma^2 \to \infty$.

I-SPY 2:
Umbrella / platform (and adaptive)



Images courtesy of Dr Rugo

Study design

- Randomized phase II
- Compare to concurrent control arm (T→AC)
- 1° endpoint: path CR
- Integral biomarkers
  - HER2
  - HR
  - Mammoprint
- Bayesian analysis plan (next slide)
- Intended to allow up to 4 experimental arms.

BATTLE trial design:

- Hierarchical model — Logistic model for pCR
- Bayesian (comparative) inference. — Threshold for 'graduation' of a regimen after 60 pts.
  Evidence (by pCR) that a future N=300 phase III study would be positive in any marker-defined subgroup: >85% PP
- Continual assessment — Threshold for futility if <10% PP in all marker-subgroups after 20 pts.

  Note: function of two parameters, π_e and π_c
- Adaptive randomization — AR is proportional to the posterior prob. a given tx is superior. Priors (appear to be) fully specified; depend on I-SPY 1

Rugo HS et al. N Engl J Med 2016;375:23-34.
Barker et al. Clin Pharmacol Ther. 2009; 86: 97– 100.

I-SPY 2: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer

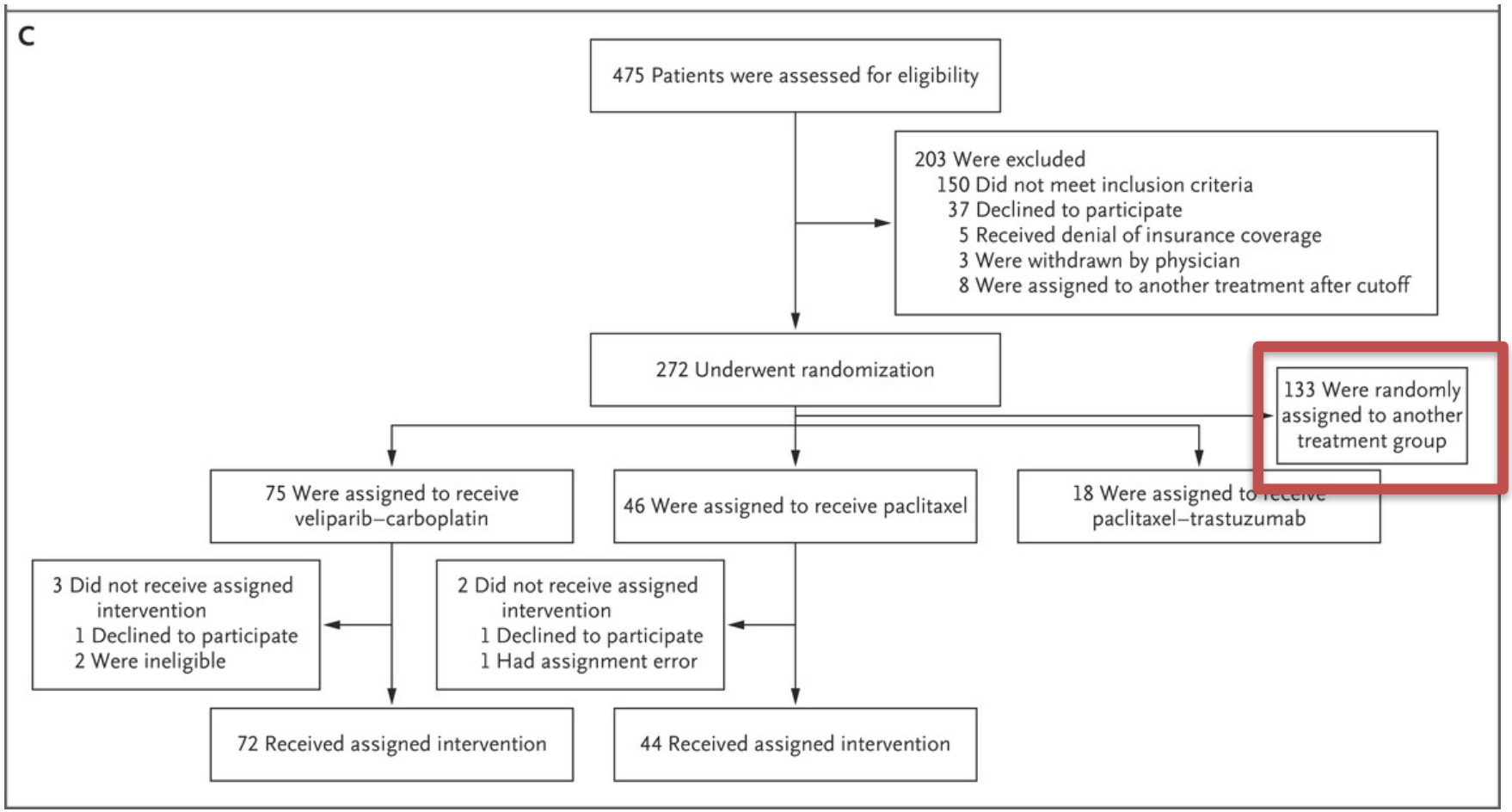
Study History	NCT00409968
Mar 2010	Activated with 3 initial experimental arms: Figitumumab, Neratinib, Veliparib + Carboplatin
Dec 2013	Results on the first regimen to 'graduate' (Veliparib + Carboplatin) were reported at SABCS by Rugo et al. **Rugo HS et al. N Engl J Med 2016;375:23-34**
Apr 2014	Results on the 2nd regimen to 'graduate' (Neratinib) were reported at AACR **Park JW et al. N Engl J Med 2016;375:11-22**
Jun 2015	Results for a 3rd regimen to 'graduate', MK-2206 [AKTi], were reported at ASCO
Jun 2017	Results for a 4th regimen to 'graduate', Pembrolizumab, were reported at ASCO

I-SPY 2: Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer

- No negative arms have been published (risk of reporting bias)
- As an ongoing study, total study-status has never been publically disseminated (to my knowledge)
- Partial information can be gleaned from clinicaltrials.gov

2010 (Target N = 800)	2012	2014	2016 (Target N = 1920)
Neratinib	Ganitumab + Metformin	AMG 386 + Trastuzumab	PLX3397
Veliparib + Carboplatin	MK-2206 +/- Trastuzumab	T-DM1 and Pertuzumab	Pembrolizumab
Figitumumab (dropped by 2012)		Pertuzumab and Trastuzumab	Talazoparib + Irinotecan
+ AMG 386		Ganetespib	Patritumab +/- Trastuzumab
+ Conatumumab (dropped by 2012)			

CONSORT: Veliparib/carboplatin



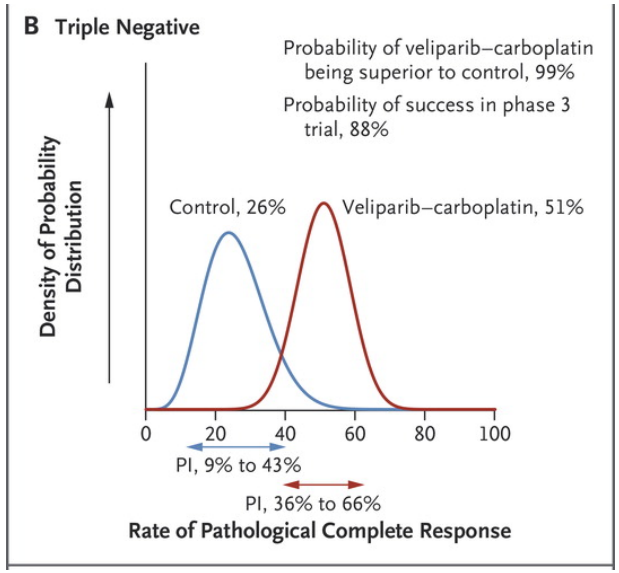
Rugo HS et al. N Engl J Med 2016;375:23-34.

Results: Veliparib/carboplatin

Table 2. Final Predictive Probabilities.*

Biomarker Signature	Estimated Rate of Pathological Complete Response (95% PI)		Probability of Veliparib–Carboplatin Being Superior to Control	Predictive Probability of Success in Phase 3 Trial
	Veliparib–Carboplatin	Control		
	percent			
All HER2 negative	33 (23–43)	22 (10–35)	91	53
Hormone-receptor positive and HER2 negative	14 (3–25)	19 (5–33)	28	8
Triple negative	51 (36–66)	26 (9–43)	99	88

* HER2 denotes human epidermal growth factor receptor 2, and PI probability interval.



"…We do not report the raw data within biomarker subtypes or signatures; our analysis carries greater precision than would a raw-data estimate"

	Veliparib + Carboplatin	Control (T → AC)
Enrolled	**N = 72**	**N = 44**
TN subset	**N = 39**	**N = 19**
pCR	20	5
No pCR	19	14

Rugo HS et al. N Engl J Med 2016;375:23-34.

* *imputed under simplified assumptions*

Comments on transparency

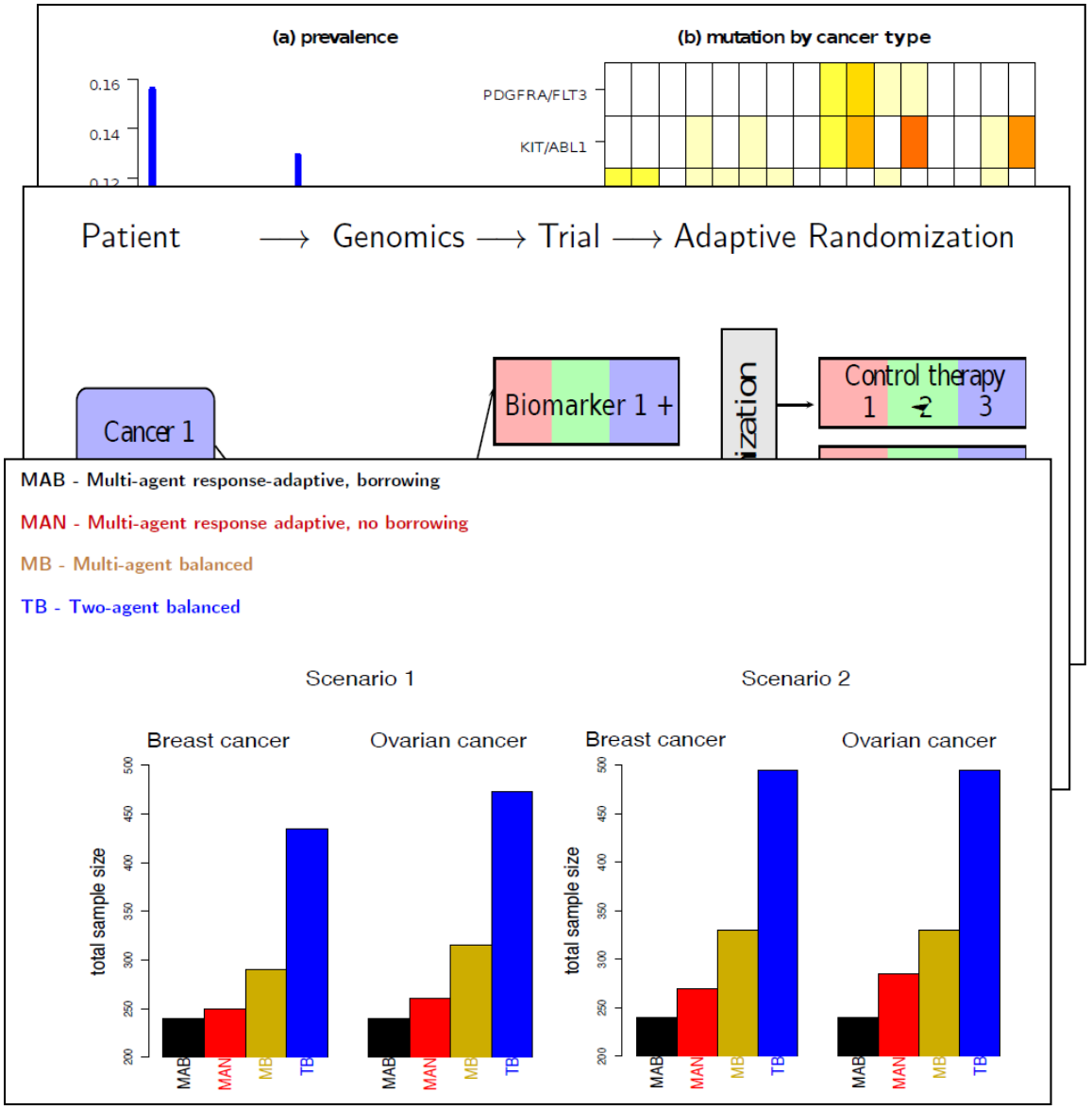
- Motivation and general approach of I-SPY 2 were published with the launch of the trial (Barker et al. 2009) Insufficient details to evaluate the specific adaptive design.
- Consistent with ICMJE policy, the protocol was provided as supplemental material to the NEJM articles.
- With multiple appendices, the statistical methods appear to be specified but will be extremely challenging to reproduce. Priors require patient-level data from I-SPY 1.
- Software has not been made public
- The decision to redact raw data from publications is concerning
- Unknown what the dissemination plans will be for negative arms

Ventz et al. Biometrics 2017: Bayesian response-adaptive designs for basket trials

Research goals:

- Develop novel methods to build off genomic platforms (Dana-Farber: Oncopanel)
- Apply RAR designs (e.g. I-SPY 2) to 'basket' trial (NCI-MATCH)
- Construct hierarchical model for adaptive allocation and continual assessment
- Use in silico simulation to tune and evaluate properties
- Provided R package(s) for models and simulation.

http://bcb.dfci.harvard.edu/~steffen/software.html



Closing remarks

- The use of master protocols (whether umbrella, basket, or platform designs) will continue to grow for trials within and across traditional disease types.
- Choice of trial design depends on many parameters:
  - Distribution of clinical outcomes, and hypothesized treatment effects
  - Marker prevalence, preliminary evidence a biomarker is predictive / prognostic, feasibility of real-time assessment, and operational resources.
- Adaptive designs give flexibility, but *always* at some cost; and it may be hard to ascertain utility
  - Response-adaptive randomization will be controversial among statisticians.
  - Adaptive enrichment designs have the potential to achieve goals of population-finding with targeted therapies.
- Adaptive platform trials are forcing us to revisit old arguments on transparency and ways to facilitate the reproducible research

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