Implementing a National Cancer Clinical Trials System for the 21st Century, Workshop #2

Session #5: Accelerating Innovation Through Effective Partnerships

Accelerating Innovation in Statistical Design

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Outline

- Goals
- Design approaches
- Cautions and caveats
- Conclusions

Statistical Design Goals

- Interpretable results
- Efficient
- Informative for future

Changing Landscape

- NCTN
  - Fewer, but larger cooperative groups
  - More access to trials from outside of groups
- Oncology
  - Cancer types dividing into ever-smaller disease subgroups
  - Therapies targeting “rare” molecular subgroups
  - Expectations for bigger treatment effects in smaller subgroups

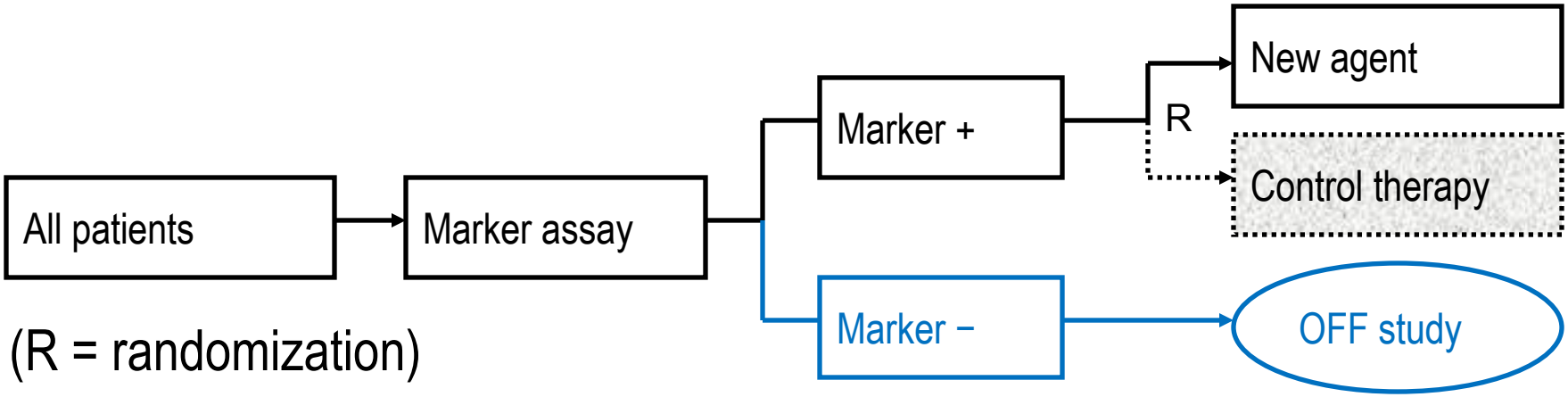
Statistical Design Features Discussed

- Biomarker-based
  - Single targeted agent/single biomarker
  - Multiple targeted agents/multiple biomarkers
- Multi-arm trials
- Adaptive features
- Intermediate endpoints

Biomarker-Based Designs

- Basic phase III designs and hybrids
  - Enrichment design
  - Completely randomized design
  - Randomized block design
  - Biomarker-strategy design
- References
  - Sargent et al., J Clin Oncol 2005; 23:2020-2027
  - Freidlin et al., J Natl Cancer Inst 2010; 102:152-160
  - Clark & McShane, Stat Biopharm Res 2011; 3:549-560

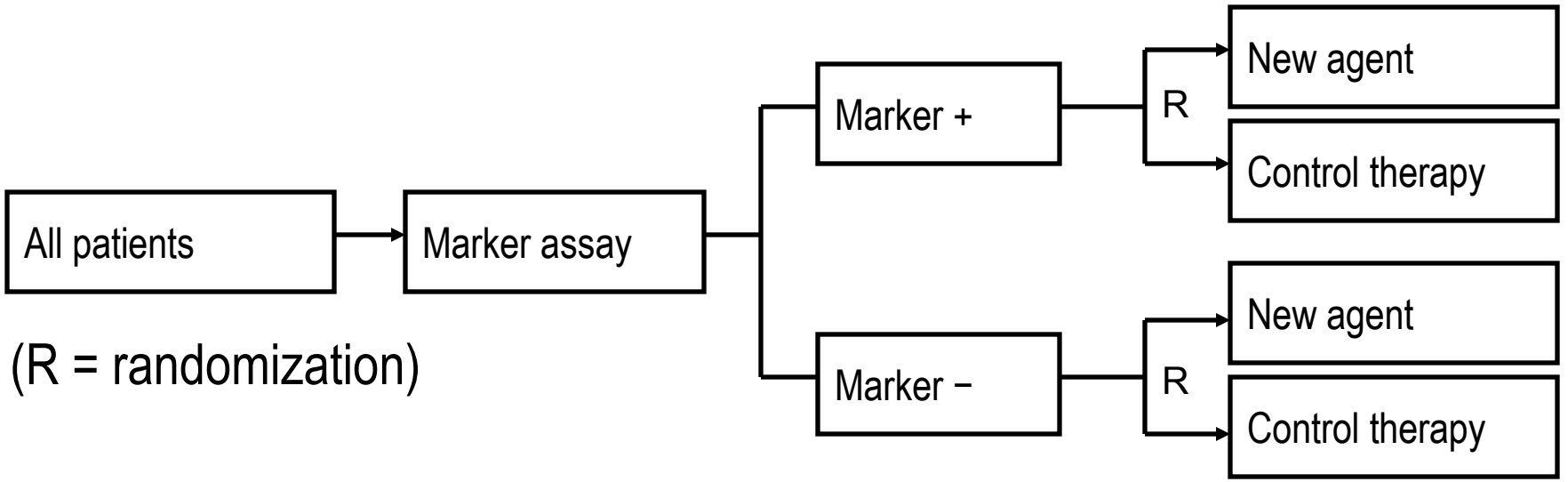
Biomarker-Enrichment Design



(R = randomization)

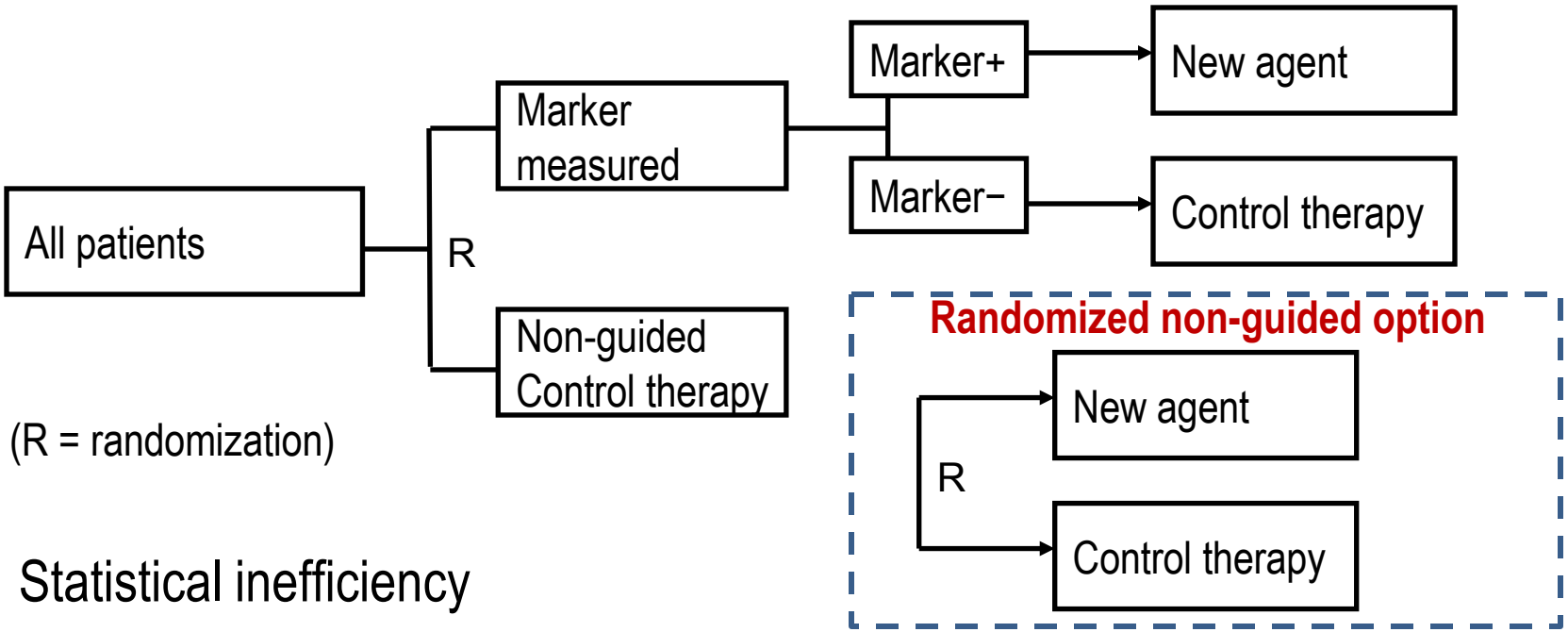
- Based in knowledge of biology (New agent→ Molecular target)
- Control therapy arm controls for biomarker prognostic effect
- Variation: Standard therapy ± new agent
- Limitations:
  - Off-target effects of new agent not fully evaluated
  - Regulatory indication limited to Marker+ group
  - Biomarker refinement outside of Marker+ group difficult

Biomarker-Stratified Design



- Reasonable basis for biomarker candidate (target gene or pathway), but still equipoise for randomization
- Allows maximum information
  - Controls for prognostic effect of biomarker
  - Directly compares new agent to control therapy in *all* patients
- Allows retrospective evaluation of biomarkers measured by different method (e.g., protein, RNA, DNA) or alternative biomarkers in pathway
- Variation: Standard therapy ± new agent

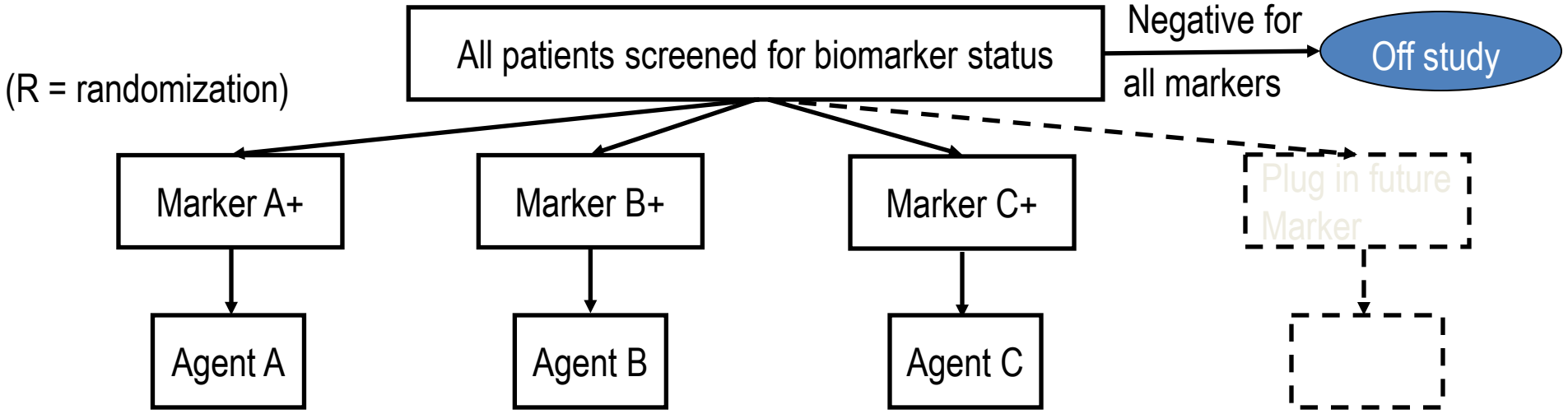
Biomarker-Strategy Design



(R = randomization)

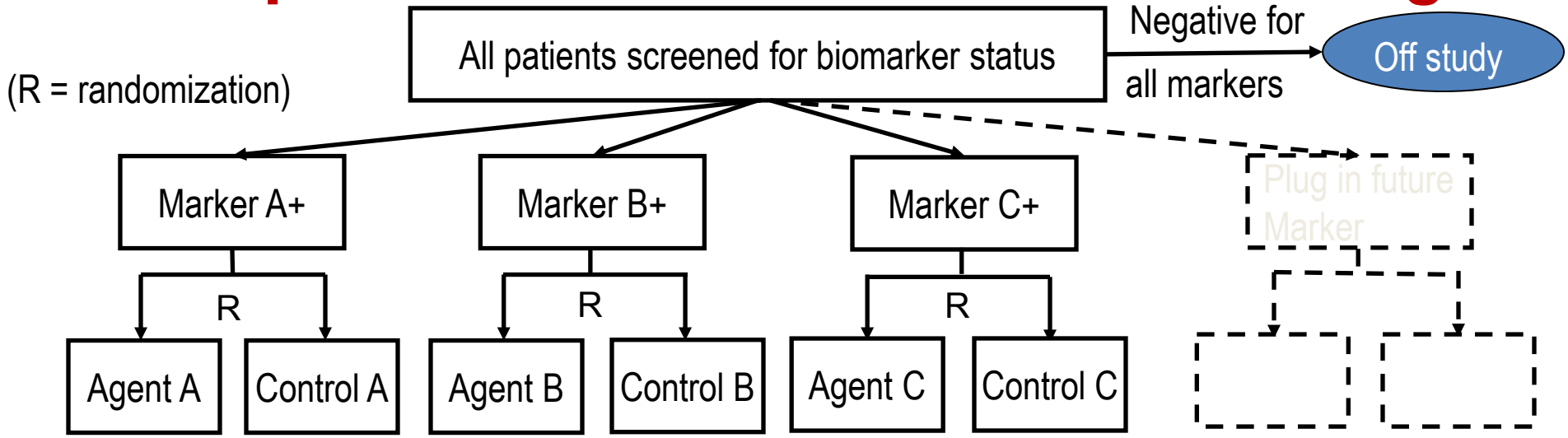
- Statistical inefficiency
  - Marker– patients receive same therapy on both arms
  - If randomize non-guided group, **even more inefficient**
- Biomarker-guided treatment sounds attractive
- Might be necessary for complex multi-biomarker guided strategies
- Must measure biomarker in non-guided arm to distinguish prognostic effect
- Non-guided randomization allows assessment of new agent effect in Marker– group, but it is terribly inefficient

Multiple-Biomarker Signal-Finding Design



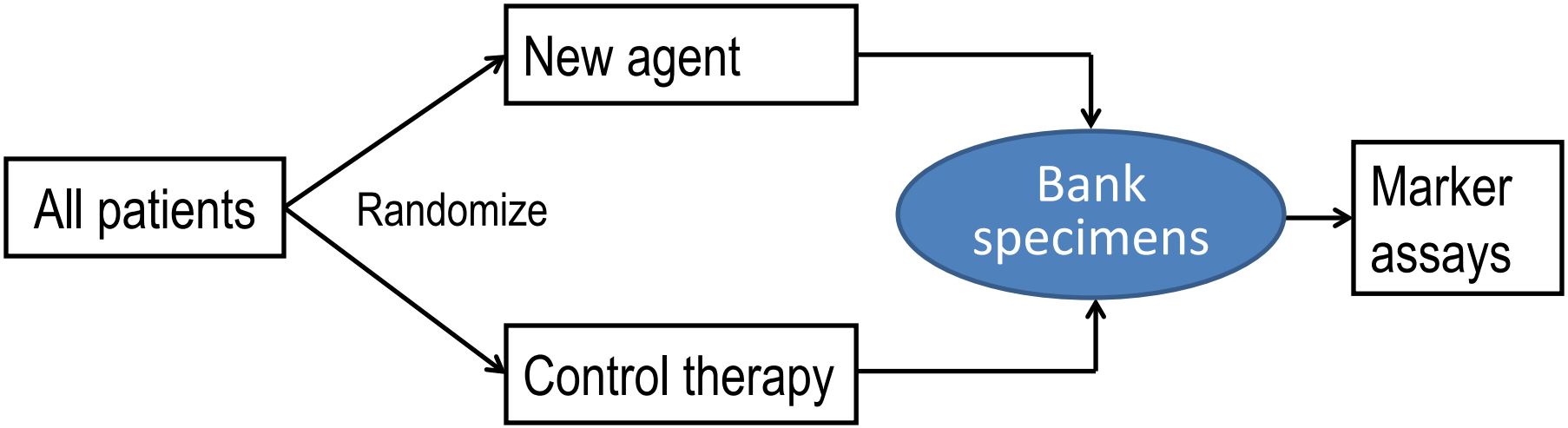
- Endpoint: ORR, rate PFS or SD > x months
- Multiple single arm studies (1- or 2-stage, 30-40 patients per subgroup)
- Limitations:
  - Can't assess off-target or prognostic effects
  - Biomarker refinement outside of Marker+ group difficult
  - Handling overlapping biomarkers: Randomize? Prioritize?
  - Differential efficacy by disease site?
- Efficiencies
  - Common entry for biomarker testing, multiplex biomarker assays possible
  - Master IND for multiple drugs

Multiple-Biomarker Rand. Enrich. Design



- Multiple biomarker-enrichment designs
- Control therapy arm controls for biomarker prognostic effect
- Variations: Standard therapy ± new agent; randomize Marker–
- Limitations:
  - Can't assess off-target effects
  - Biomarker refinement outside of Marker+ group difficult
  - Handling overlapping biomarkers?
- Efficiencies
  - Common entry for biomarker testing, multiplex biomarker assays possible
  - Master IND for multiple drugs

Prospective-Retrospective Biomarker Study

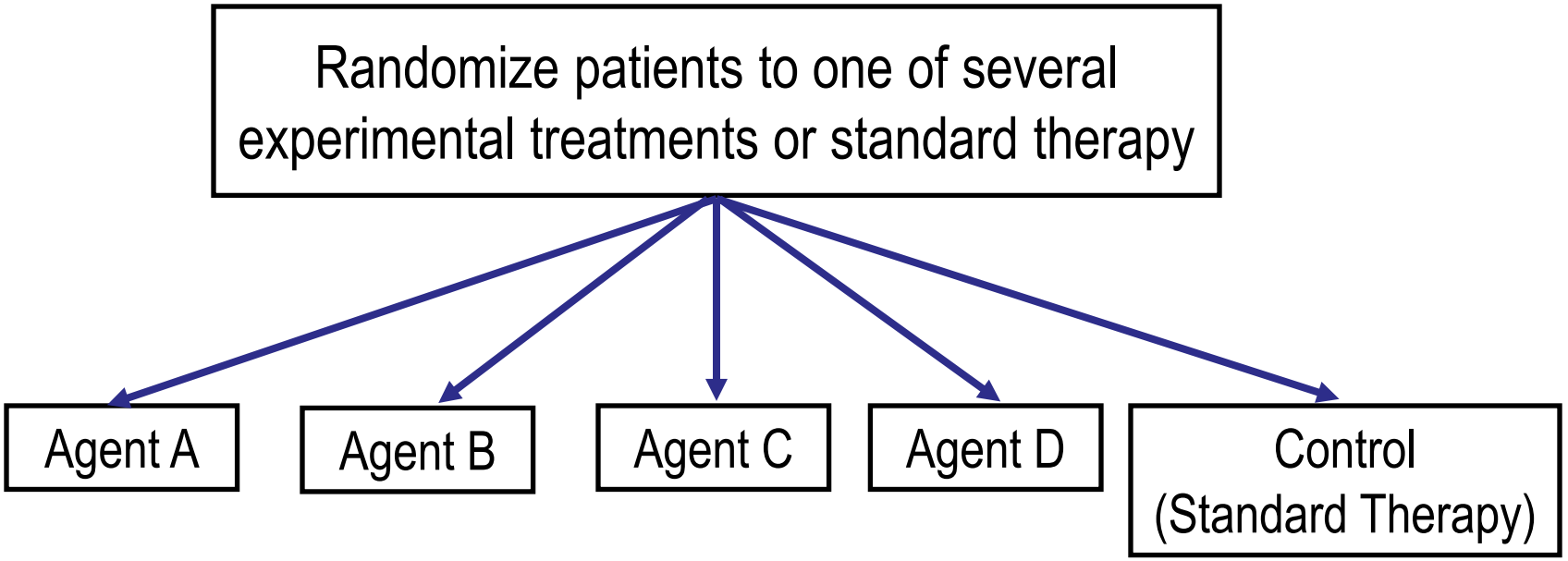


- Completed clinical trial – uncertain target or non-targeted therapy
- Flexibility to evaluate multiple biomarkers
- Variation: Standard therapy ± new agent
- Pre-specified statistical analysis plan
- Specimens processed under appropriate conditions
- Cases with specimens representative of full cohort
- **Sample size planned to answer treatment question might not be sufficient to answer biomarker question**

Lingering Questions for Biomarker-Based Designs

- Centralized or local biomarker-based testing?
  - Extreme heterogeneity in biomarker testing can attenuate treatment effects
  - For which marker assay(s) do the study results apply?
  - Assurance of reliable testing for individual patients?
  - Regulatory issues (e.g., IDEs)?
  - What if no FDA-cleared/approved test is available?
- What to do with discordant local positive/central negative) patients?
  - Useful for detecting unanticipated off-target effects? (not “typical” negatives)
  - Not enough to reliably answer a question
  - Primary statistical analysis: Enroll all or centrally confirmed cases only?

Multi-Arm Trial: Multiple Agents vs. Control



- Compare each experimental therapy to control
- Interim monitoring: Drop non-performing arms early
- Example: E2805 (locally advanced renal cell cancer)
  - Is adjuvant sunitinib better than placebo?
  - Is adjuvant sorafenib better than placebo?

Multi-Arm Trial Efficiency

Reduction in sample size in a multi-arm trial relative to conducting *K* independent two-armed trials assuming one-sided α = 0.025, power to detect a 25% reduction in hazard for DFS (for each experimental agent relative to placebo), and the accrual and follow-up periods the same for all trials

Number of experimental arms (*K*)	No multiplicity adjustment to significance level	With Bonferroni multiplicity adjustment to significance level	
		80% power	90% power
2	25%	9%	11%
3	33%	11%	14%
4	37%	12%	15%

Freidlin et al., Clin Cancer Res 2008;14:4368-4371

Factorial Designs

		Agent B	
		Yes	No
Agent A	Yes	AB	AX
	No	XB	XX

Estimate effect of Agent A

Estimate effect of Agent B

(X = no additional therapy beyond base treatment)

- Factorial designs
  - Yes/No for each of k ≥ 2 drugs to form 2^k treatment groups
  - Each treatment group used in multiple drug comparisons
  - **Requires assumption of *no important interactions between drugs***

Multi-Arm Trials

- Advantages
  - Efficiency through “re-use” of arms
  - Direct comparisons on common patient population
  - Popular with patients due to greater chance of receiving an experimental therapy
- Challenges
  - Difficulty maintaining blinding across several different treatment types
  - Inclusion/exclusion criteria must cover all agents
  - Interactions & overlapping toxicities in factorial designs
  - Cooperation among multiple drug companies, if applicable

Adaptive Design

- An **adaptive** design clinical study is a study that includes a ***prospectively*** planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study

Reference: FDA Draft Guidance on Adaptive Design Clinical Trials for Drugs and Biologics (Feb 2010; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf)

Typical Adaptable Design Features

- Study eligibility criteria (enrollment or analytic subset)
- Treatment regimens (e.g., dose, schedule, duration)
- Total sample size of the study (including early termination)
- Randomization procedure (e.g., randomization ratio)

(Refer to FDA guidance for many more options. . .)

Adaptations can occur ONLY while the study remains unequivocally blinded

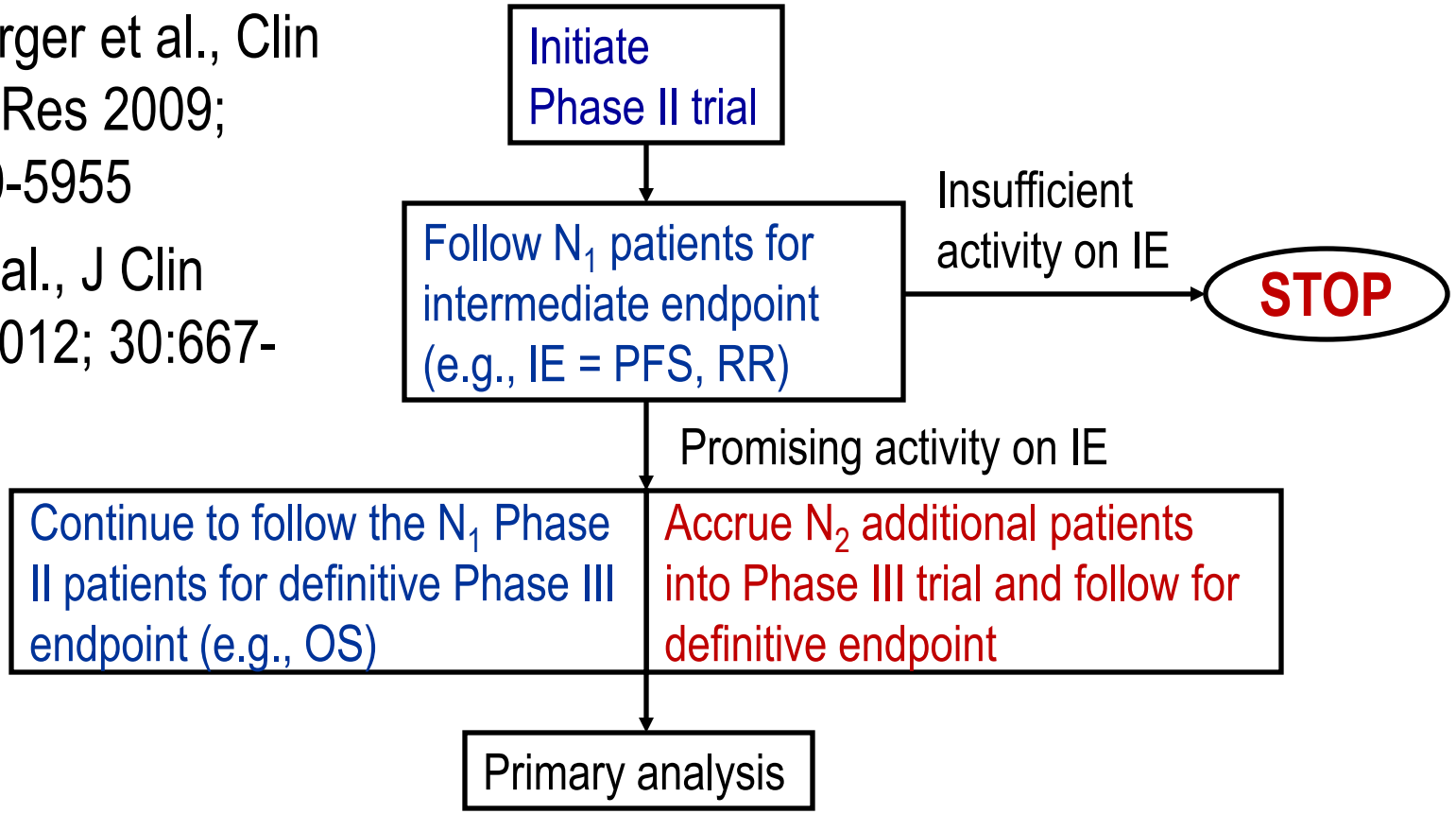
Examples of Adaptive Design Features in Current NCI Trials

- Interim monitoring (full cohort)
  - Efficacy
  - Futility
- Termination for slow accrual
- Dropping ineffective arms or non-benefiting patient subgroups (interim monitoring in subgroups)
- Seamless Phase II/III designs

Phase II/III Designs

Hunsberger et al., Clin Cancer Res 2009; 15:5950-5955

Korn et al., J Clin Oncol 2012; 30:667-671



- Issues
  - Choice of intermediate endpoint
  - Define "promising" activity for Phase II (error rates, timing)
  - Accrual suspension to allow Phase II data to mature

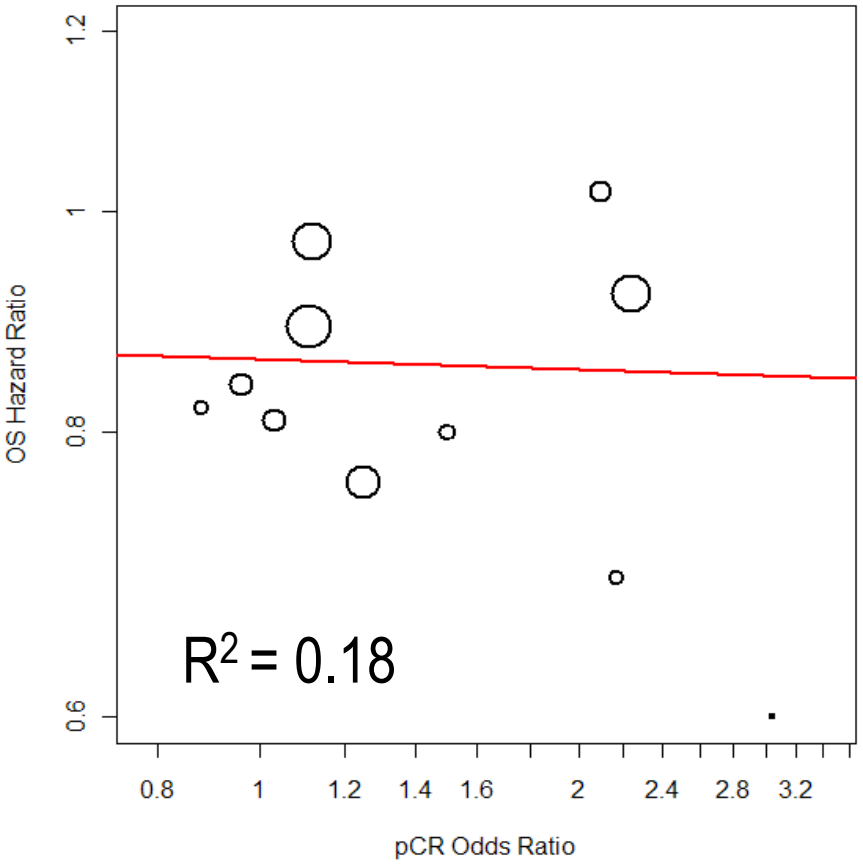
Intermediate Endpoint

- An endpoint obtained earlier than the definitive clinical endpoint (e.g., response, progression)
- Influenced by the intervention
- Correlated with the definitive clinical endpoint
- Not as strong as a surrogate endpoint, which must provide the same inference as if the true endpoint (e.g., overall survival) had been observed
- May be specific to patient population and mechanism of action of the drug

pCR as Intermediate Endpoint in Breast Cancer:

Results from Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC)

(Presented by Dr. Patricia Cortazar at San Antonio Breast Cancer Symposium 2012)



- 12 neoadjuvant RCTs
- 12,993 patients
- Long term EFS and OS
- pCR = absence of invasive cancer in the breast and axillary nodes, DCIS allowed

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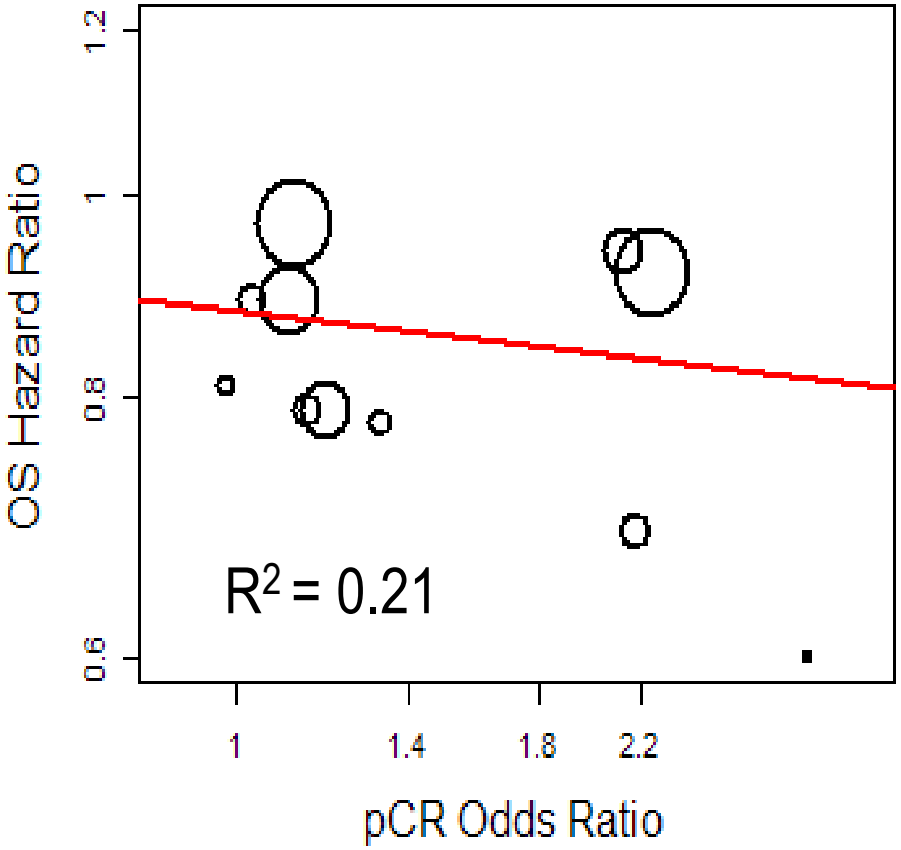

Only slightly better association after *excluding* HR+ grade 1-2 cases

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Potential for NCTN

- Answer clinically meaningful questions not likely to be addressed by industry (e.g., compare agents from different companies)
- National & international coverage
- Capability to conduct large trials and find rare tumor subtypes
- Leverage resources (including specimen collections) and expertise across the network