Statistical Challenges in the Study of Adolescent and Young Adult Cancers

Lisa M. McShane, Ph.D.

Biometric Research Branch
Division of Cancer Treatment and Diagnosis
National Cancer Institute

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Challenges

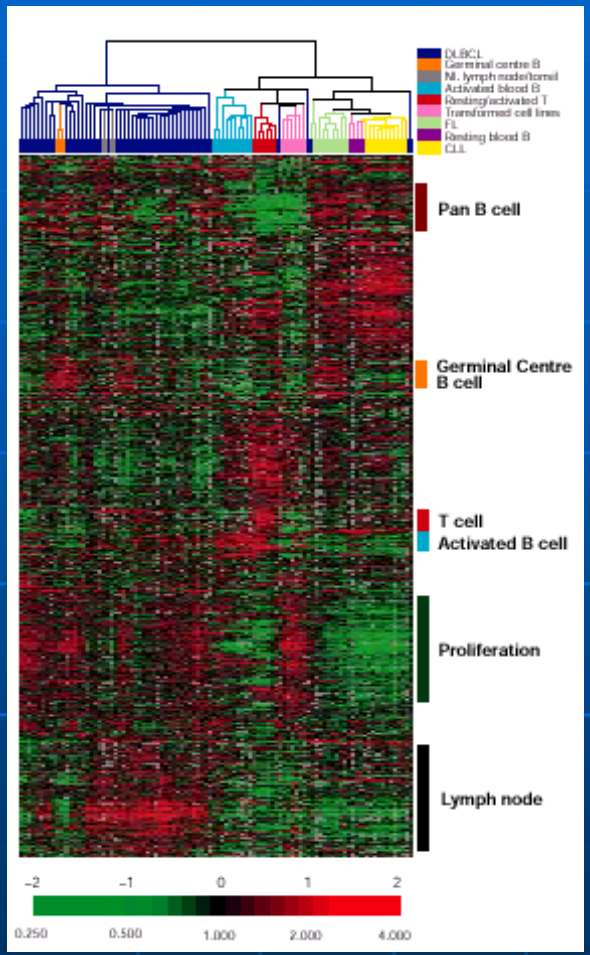
- Understand the biology
- Exploit the biology to hypothesize better prevention, detection, and treatment strategies*
- Clinical trials to test hypotheses under the constraints of rare diseases

***This talk will focus on biology and treatment strategies.**

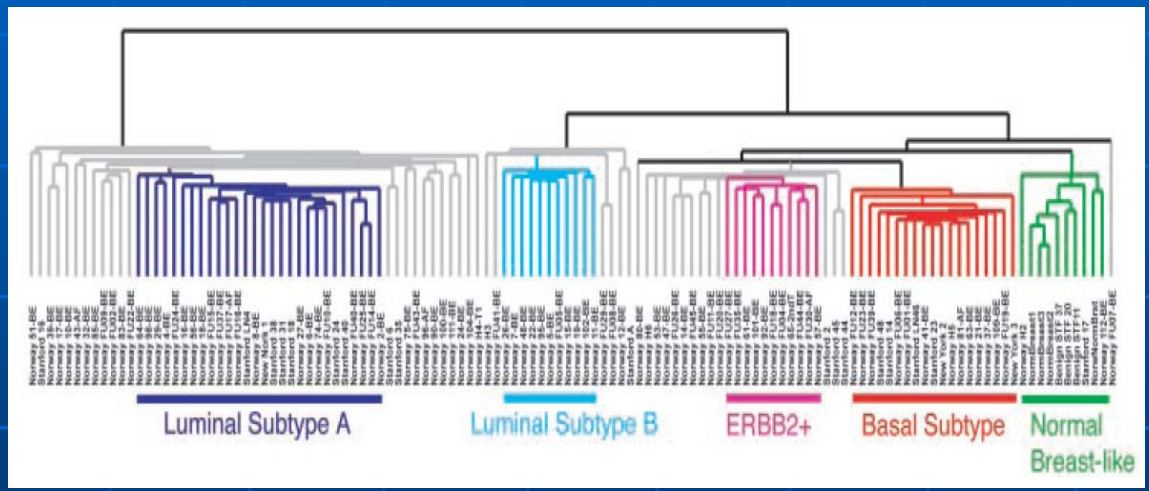
Understanding the biology: Molecular profiling

- DNA – mutations, polymorphisms, and copy number alterations (e.g., SNP chips)
- Cytogenetics
- RNA - Gene expression microarrays, multiplex RT-PCR
- Protein – IHC marker panels, other proteomic assays

Biological Subgroups in Adult Cancers



Alizadeh et al., *Nature*, 2000 (lymphoma)



Perou, *Nature* 2001; Sørlie, *PNAS* 2001; Sørlie, *PNAS* 2003 (breast cancer)

Molecular Profiles of AYA Cancers

- One or more biological subgroups?
- Mapping from child and/or adult subgroups?
  - Similar to adult subgroups, but shifted toward over-representation of aggressive subtypes?
  - Completely different biology?
- Association of “natural” biological subgroups in AYA with age?
  - Continuum?
  - Natural breakpoints?

What could the biological subgroups tell us?

- Etiology
- Prognostic
- Predictive (therapy selection)

Interesting biology may or may not be prognostic or predictive. Maybe it will suggest new targets for therapy.

Prognostic Marker*

Measurement associated with clinical outcome in absence of therapy or with application of standard therapy that all patients are likely to receive.

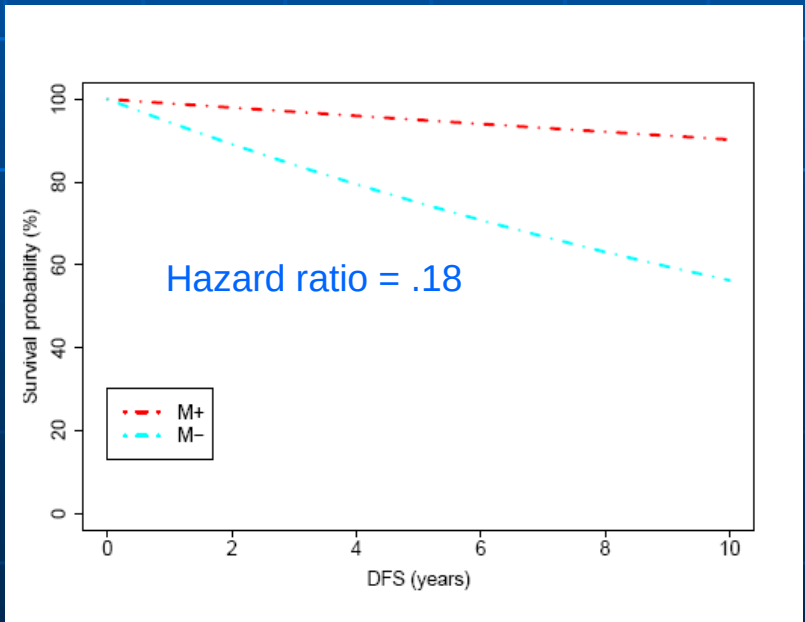
- Examples
  - Pathologic stage
  - Histologic grade
- Importance
  - Highly favorable group might avoid treatment
  - Might suggest aggressiveness of treatment
  - Might suggest more intensive monitoring
  - Might suggest target for therapy

***Think of subgroup membership as a "marker".**

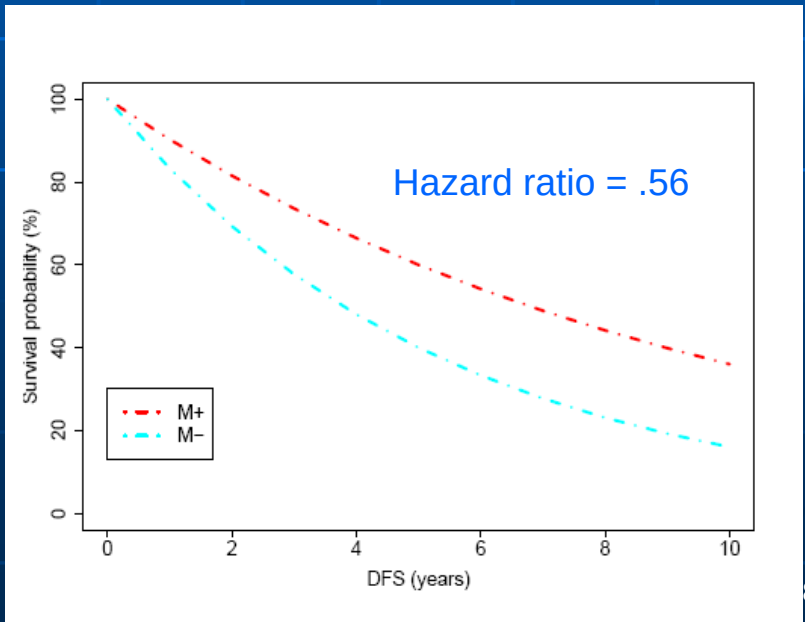
Prognostic Marker Issues

- Correlation with outcome not necessarily sufficient to impact clinical decisions

Good prognosis group may forego additional therapy



Is this prognostic information helpful?



Predictive Marker*

Measurement associated with response or lack of response to a particular therapy.

Example

- ER/PgR for endocrine therapy benefit in breast cancer

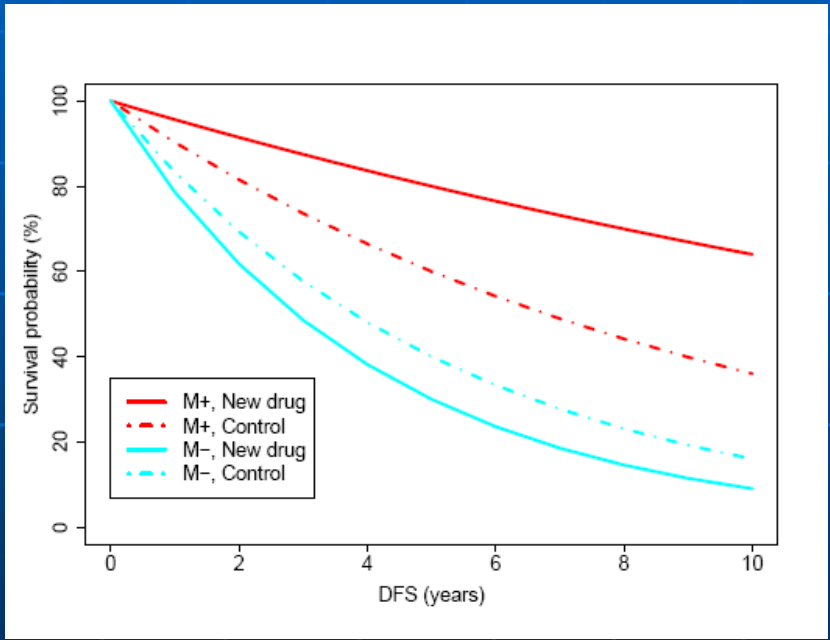
Statistical wisdom

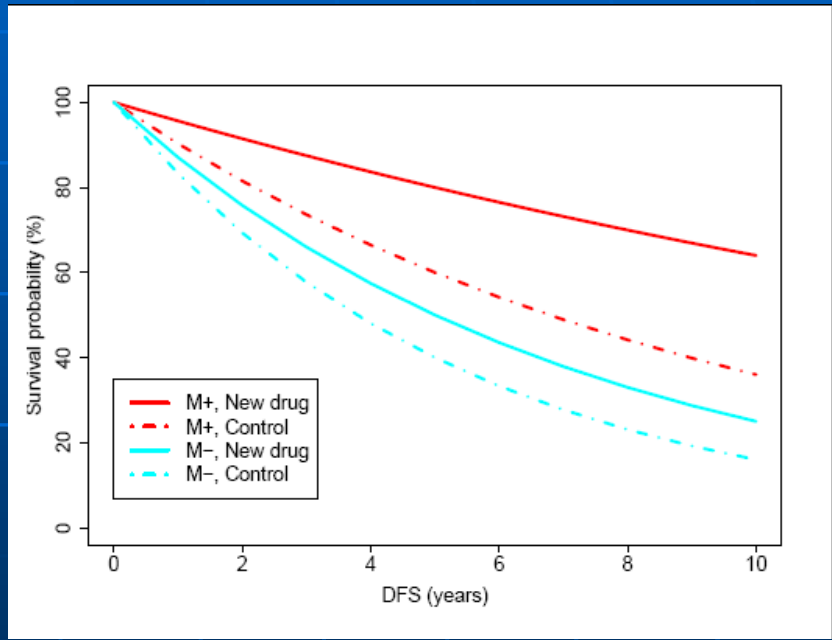
- Test for treatment by marker interaction

***Think of subgroup membership as a "marker".**

Predictive Marker

What is a treatment by marker interaction, and are they all created equal?





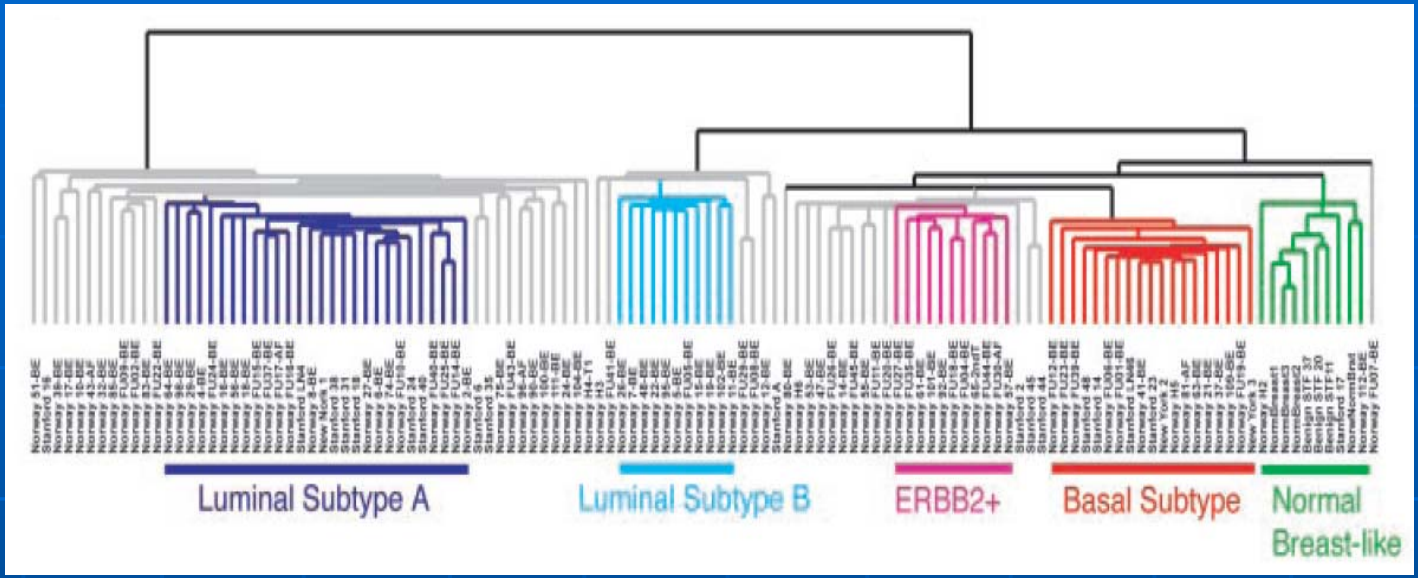
Qualitative interaction

- New drug better for M+ (h.r. = 0.44)
- Control drug better for M– (h.r. = 1.31)
- Interaction = 0.44/1.31 = 0.33

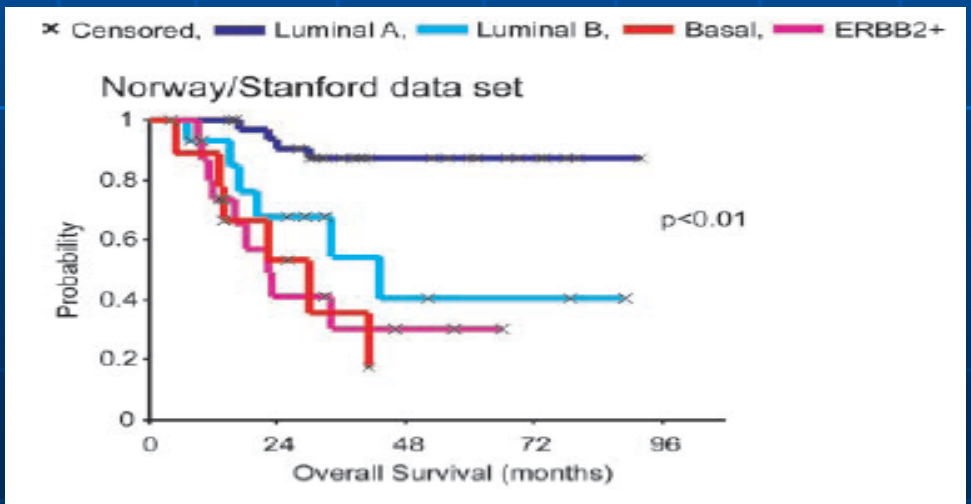
Quantitative interaction

- New drug better for M+ (h.r. = 0.44)
- New drug better for M– (h.r. = 0.76)
- Interaction = 0.44/0.76 = 0.58

Clinical Value of Clusters?



122 breast cancer samples, ~500 "intrinsic" genes



- Biologically interesting
- Prognostic for outcome
- Select therapy (predictive)?

(Perou, *Nature* 2001; Sørlie, *PNAS* 2001; Sørlie, *PNAS* 2003)

Analyzing Molecular Profiles

- Unsupervised analyses
  - Search for subgroups ignoring phenotype or outcome information
  - Examples: Clustering algorithms such as hierarchical clustering, K-means, SOMs
- Supervised analyses
  - Use phenotype or outcome information to directly derive distinguishing features or classifiers
  - Feature identification: multiple testing issues
  - Classifier building: discriminant analysis, nearest neighbor, SVM, neural nets
  - Not necessarily biologically homogeneous within a phenotype or outcome group

Strategy

- Search for biological subtypes
- If subtype exists in pediatric or adult populations, examine existing information relating biology to treatment success
- Conduct efficient trials to find better treatments
  - Phase I - dose & toxicity assessment
  - Phase II – single-arm vs. randomized
  - Phase III – stratification, enrichment, factorial designs & others
  - Add-ons to pediatric and/or adult trials
- Meta-analyses may be required

Phase I Considerations

- Pharmacokinetic/pharmacodynamic differences between AYA and pediatric or adult patients may suggest dose/schedule alterations
- Few co-morbidities and other medications
- Greater impact and/or susceptibility for long-term & delayed toxicity

Phase II Considerations

- Single arm trials
  - May require less than half sample size of some randomized phase II trials with comparable type I (α) and type II (β) error
  - Historical control data required
  - Impact of selection biases unintended (e.g., drift), or intended (e.g., targeted subpopulation)
  - Benchmark of RR may be more stable historically and less subject to evaluation bias than endpoint such as PFS

Phase II Considerations (cont.)

- Randomized phase II trials
  - Guard against selection bias
  - Don’t require availability of historical controls
  - May require more than twice the sample size of single arm phase II trial with comparable type I and type II error

(Reference: Rubinstein et al., *JCO* 2005)

Phase II Considerations (cont.)

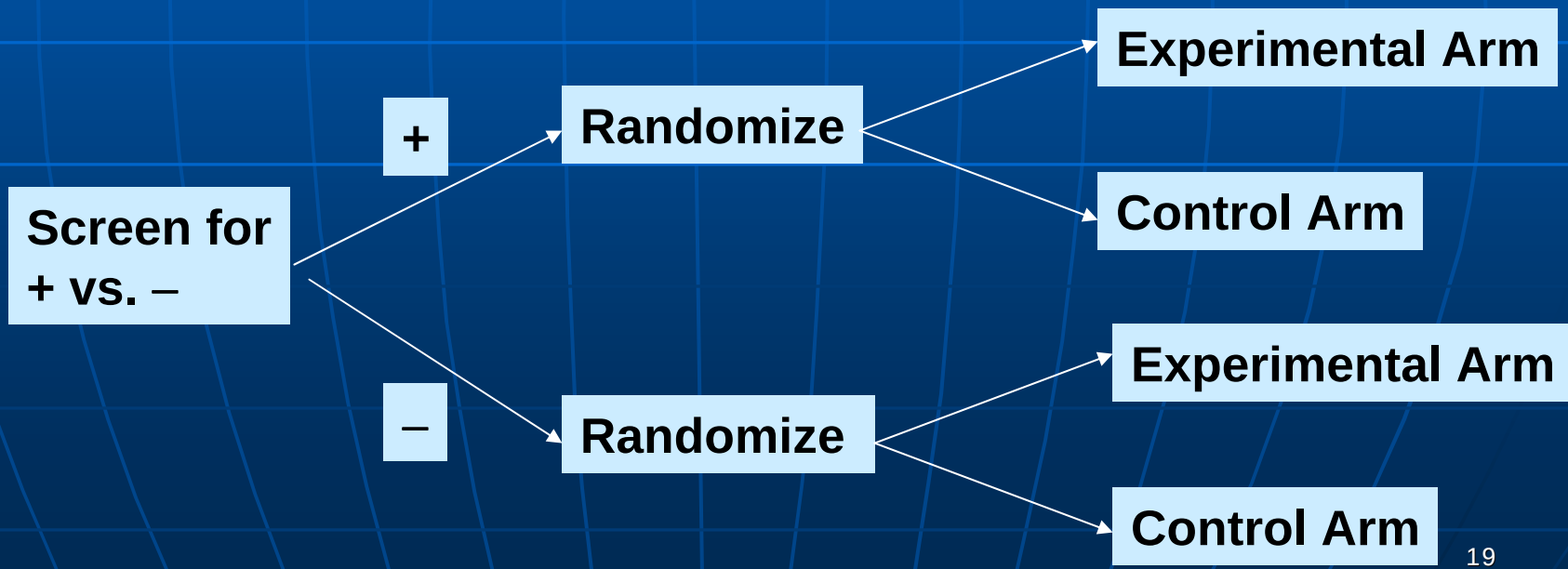
- Randomized phase II trials (cont.)
  - Examples of randomized designs
    - Selection design
      - Appropriate for prioritizing between two experimental regimens when no a priori preference (e.g., based on cost, toxicity)
      - Not appropriate for comparing experimental agent to standard treatment control arm (50% chance of choosing experimental arm if truly no difference)
      - Possible neither experimental regimen is effective

Phase II Considerations (cont.)

- Randomized phase II trials (cont.)
  - Examples of randomized designs (cont.)
    - Screening design
      - Compare experimental regimen to standard treatment control arm
      - Economize on sample size by using larger than usual type I and type II errors, and targeting larger effect size (e.g., $\alpha=\beta=0.20$, PFS hazard ratio = 1.5 or RR difference = 20%)
    - Other designs
      - Randomized phase II (2 experimental regimens) plus reference control arm
      - Phase II/III

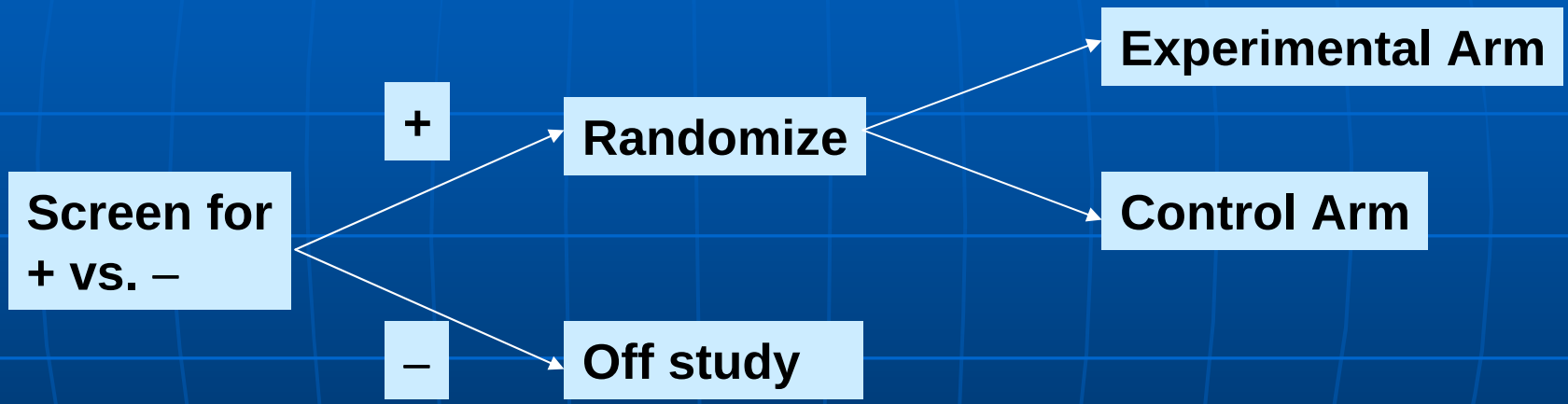
Phase III Considerations

- Stratified design
  - Control for variability added by prognostic subgroups
  - Possibly conduct different trials in different prognostic groups



Phase III Considerations

- Enrichment design
  - Expect benefit only in "+" subgroup
  - Avoid dilution of treatment effect by "–" group



  - Efficiency (relative to all-comers design) depends
    - Proportion of patients in targeted "+" subgroup
    - Treatment effect (relative to control) in excluded patients
  - No information about treatment benefit in "–" subgroup

Phase III Considerations (cont.)

- Factorial design
  - 2×2 design: Test treatments (A, B) simultaneously
  - Patients serve “double duty”

Median OS (yrs)

	A-	A+
B-	4	8
B+	6	12

No interaction (additive)

Median OS (yrs)

	A-	A+
B-	8	4
B+	6	12

Qualitative interaction

Median OS (yrs)

	A-	A+
B-	4	6
B+	6	12

Quantitative interaction

  - Problematic interpretation in presence of interactions

Phase III Considerations (cont.)

- Other designs – e.g., adaptive, Bayesian
  - Extensive planning
  - Intensive monitoring
  - Usually require short term endpoints
  - Required sample size may or may not be smaller
  - Receive a lot of hype

Meta-analyses

- Pool across studies to evaluate an effect of interest, e.g., treatment effect, prognostic effect
- Overcome inadequate samples size in individual studies or because interest is in subgroups
- Understand heterogeneity in results
- Understand generalizability of result
- Draw conclusion, practice guideline

Meta-analysis Conduct

- Focused, clinically meaningful question
- Identify relevant, high quality studies
- Search broadly to avoid publication bias
- Two main approaches
  - Trial summary data (effect estimates with variance estimates)
  - Individual patient level data

Meta-analysis Methods

- Test for between-study **heterogeneity**
- **Weighted average** of trial-specific effects
- **Test average effect** against null value (e.g., no treatment effect)
  - **Random effect model** (trials effects have a distribution around some mean value)
  - **Fixed effect model** (no between-trial heterogeneity)

Summary Recommendations

- Invest in biology studies
- Leverage knowledge already acquired in pediatric and adult studies regarding biological variability and treatment effects in AYA-overlapping subgroups
- Consider efficient trial design options, but understand the trade-offs
- Consider possibility of meta-analyses to examine treatment or prognostic questions
- Coordinate expanded collection of specimens with standardized pathologic and clinical data