Biomarkers and Treatments Designing Trials

Mahesh KB Parmar

MRC Clinical Trials Unit

London

(based on a presentation given by Janet Dancey, US NCI)

Oncology Therapeutics Development

- Risk/benefit: Since benefit is survival, high risks (i.e. toxicity) are tolerated
- Most agents provide marginal benefit
  - Randomized trials required to demonstrate survival benefit
  - Surrogates for survival generally remain unclear
- Patient selection for trials (and treatment) should minimize risk and maximize potential benefit

Phase 2 Trials: Considerations

- Goal: estimate level of anti-tumour activity
- Four aspects of phase 2 clinical trial designs:
  - Defining the patient population for evaluation
    - Patient and disease related eligibility criteria
  - Defining the agent/intervention
    - Single agent, combination with active treatment
  - Selecting endpoint(s) of interest
  - Determining a level of activity that supports further development
  - Estimating sample sizes
    - Endpoint and magnitude of effect of interest
    - Level of certainty that the result is "true"
      - alpha and beta

Phase 2 Studies: Patient Population

Patient population that is most likely to tolerate and benefit from the agent

- Disease characteristics:
  - Disease type and extent
  - Prior therapy
  - Biomarkers predictive of sensitivity or resistance
- Patient characteristics:
  - Performance status
  - Adequate organ function
  - Pregnancy
  - Eligibility for special drug administration or procedures for the trial
  - Consent and availability
  - Biomarkers predictive of toxicity, drug sensitivity or resistance
- Assessable for endpoints of the study

Patient Selection: Phase 3 Trials

- Purpose: Definitively demonstrate improved patient benefit
- Selection considerations:
  - Similar to phase 2
  - Modifications may be made based on greater understanding of
    - safety,
    - activity,
    - interest in ensuring applicability to broader patient population

Phase 3 Studies: Patient Population

- Disease characteristics:
  - Disease type and extent
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  - Biomarkers predictive of sensitivity or resistance
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  - Performance status
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Why is patient selection in trials of important?

- Targets of newer agents may not be present or relevant within histologically similar tumors.
- Benefit to subgroup of patients may be masked by lack of benefit to the larger group
- *Without patient selection, there is greater uncertainty of a successful outcome for a clinical trial or for an individual patient*

Why is patient selection in trials important?

- Two Goals:
  - To improve the efficiency of drug development
  - To select the right treatment for the right type of patient

Size of trial in unselected patients

- Size of trial to detect a difference in unselected patients depends on:
  - Magnitude of the effect
  - Proportion of patients with tumors "sensitive" to agent

Effect of Molecular Heterogeneity on Trial Outcome

Betensky et al., J Clin Oncol 20:2495-2499, 2002

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- A randomised clinical trial is designed to test the effect of an experimental versus standard therapy on survival
- Assume patients have either genetic subtype 1 or 2
- Assumptions:
  - Patients treated with experimental therapy will live 50% longer if the tumor has genetic subtype 1
  - Historically, median survival is 4 years in all patients
    - genetic subtype 1, survival is 6 years
    - genetic subtype 2, survival is 2 years
  - Two-sided type I error = 0.05, and power = 80%

Effect of Molecular Heterogeneity

Adapted, Betensky et al., J Clin Oncol 20:2495-2499, 2002

- Scenario 1: Experimental treatment is ineffective for genetic subtype 2

Sample Sizes Required for 80% Power, two-sided α = 0.05

True Proportion Subtype1	Scenario 1
0.0	NA
0.1	31 209
0.3	4 259
0.5	1 693
0.7	891
0.9	526
1.0	412

Selecting Patients

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- However, in appropriately selected patients, phase 2 studies demonstrating high response rates to a targeted agent may even lead to early regulatory approval.

Agent	Histology	Target	Result
Trastuzumab	**Breast**	**Y**	**10-25% RR**
Imatinib	**GIST**	**Y**	**50% + RR**
Imatinib	**CML-CP**	**Y**	**90% RR**

- Without appropriate selection of patients even the largest trial can produce 'negative' results

Phase 2/3 Studies with Predictive Markers: 3 Principle Approaches

- Traditional: clinical trial enrolls all patients with same histology/stage of cancer
  - Retrospective evaluation of marker/treatment effects
- Targeted or enriched: enrolls only marker+ patients
- Stratified Marker and Treatment Validation: enrolls all patients and treatments evaluated separately within marker +ve and marker -ve patients

Selection of Patients Based on Biomarkers Predictive of Drug Effect: Issues

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- Disease factors relate to drug action
  - Target present/relevant
- Disease factors unrelated to target presence/relevance that may alter drug action
  - Drug efflux proteins
  - Metabolic inactivation
  - Redundant pathways
- Host related factors that may alter drug effect
  - Metabolism
  - Toxicity
- Assays/tests are not perfect
  - Bioanalytical issues of the assay
  - Sensitivity, specificity and predictive value

Phase 2/3 : Patient Selection

- The Goal: Selection of patients likely to benefit (or probably more realistically elimination of those least likely or unlikely to benefit)
- Considerations:
  - The treatment effect across patient subsets
  - Prevalence of the subset of patients with "sensitive" disease
  - Assay performance i.e sensitivity/specificity/predictive value
- Two strategies:
  - The marker is present at baseline
  - The marker changes early with treatment (will not be addressed in this presentation)
- Prospective or retrospective evaluation?

Trials Designs: Prospective and Retrospective Evaluation of Predictive Biomarkers

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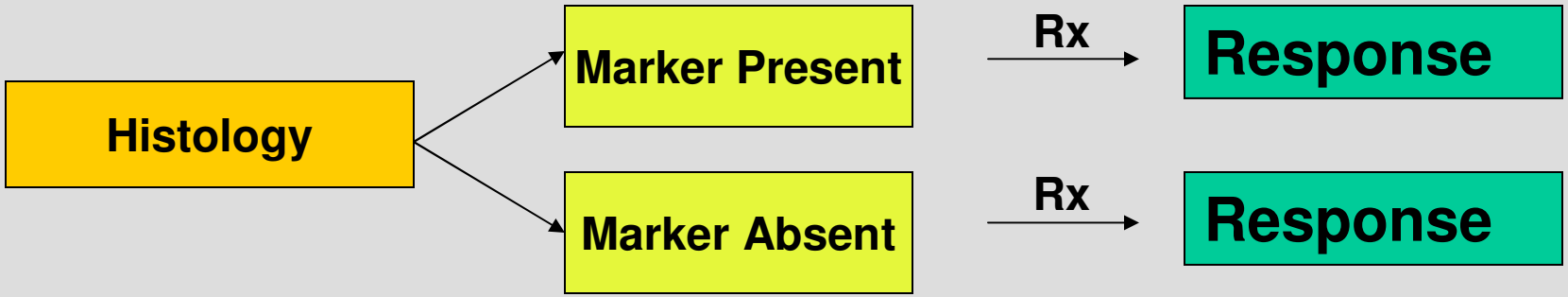
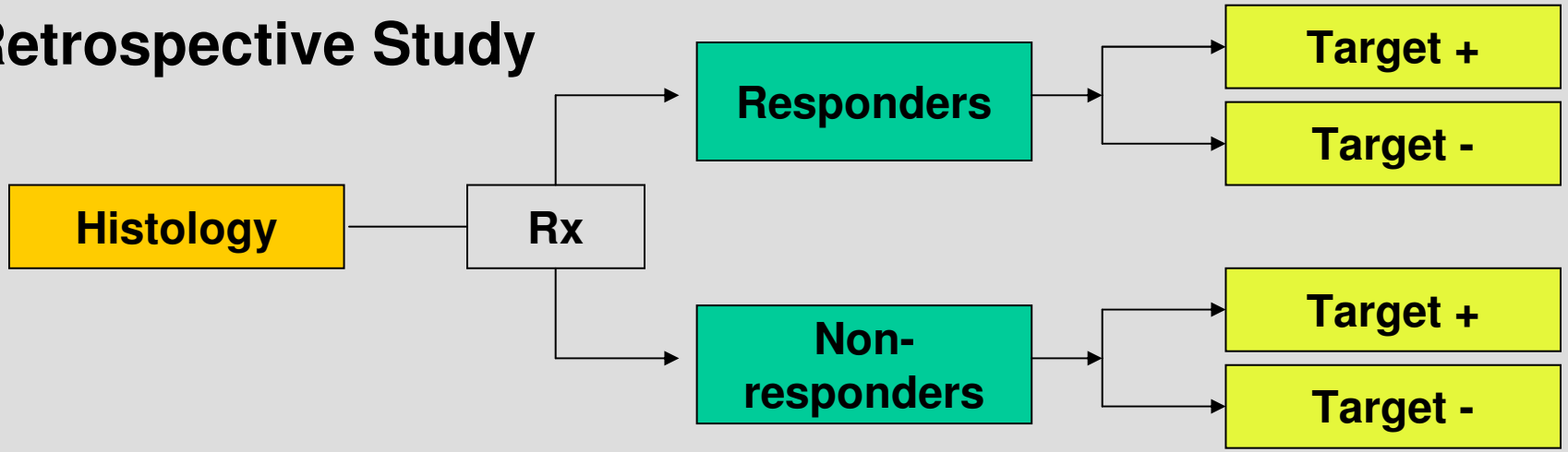
Prospective Study



Retrospective Study



Biomarkers to Select Patients: Prospective Evaluation

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- Advantage
  - Fewest numbers of patients
  - Study design guaranteed to have sufficient power to show treatment effect in marker present group
- Disadvantage
  - Must know marker to select patients
  - Rapid turnaround to determine eligibility

Biomarkers to Select Patients: Retrospective Evaluation

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- Advantages
  - Maximize accrual
  - Need not know the right marker
  - Allows refinement of marker/assay while trial ongoing
  - Allows assessment in marker+/- groups

- Disadvantages
  - Risk of insufficient numbers within marker group(s)
    - Prevalence of different marker defined subgroups
  - Collection of samples compromised
    - Incomplete submission, suboptimal handling
      - Results may not be generalizable

Prospective Clinical Trials To Assess Effects in Biomarker Defined Patient Groups

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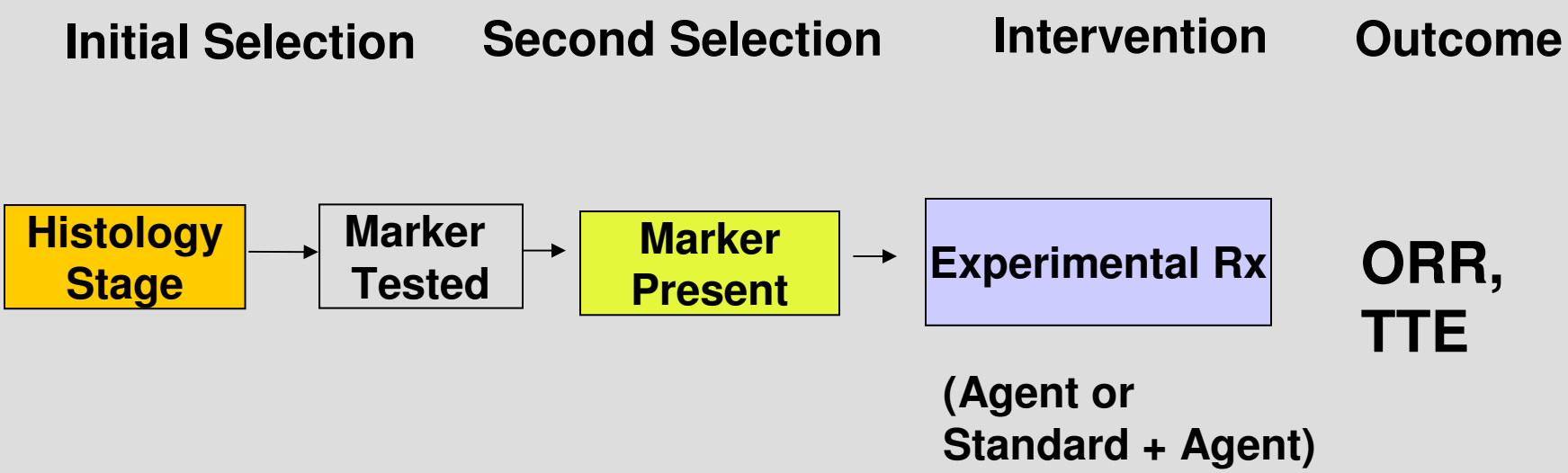
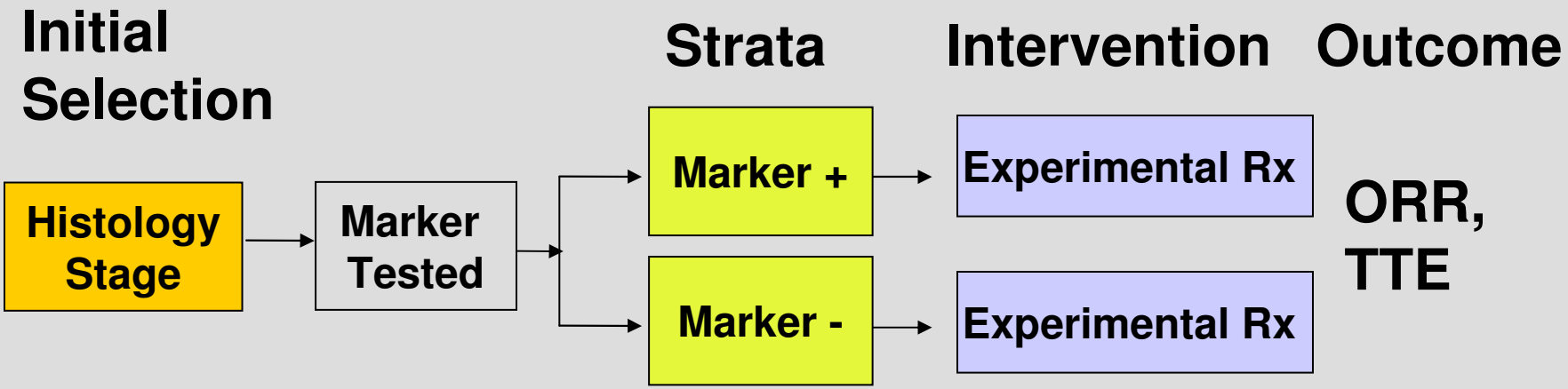
- Rationale:
  - Treatment benefit is limited to a defined group of patients
- Biomarker issues
  - Marker positive group has to have a relatively large benefit of treatment
  - Marker assessment is robust
    - Reliable, low false positive/negative rates
    - Assay failure rate (inability to assess sample and yield a result) is low
    - Turnaround time is short (delay is clinically acceptable)
  - Marker positive group prevalence is reasonable for screening and accrual
- Design Issues
  - The benefit of treatment has/has not been defined for the unselected group
- Sample Size Considerations:
  - Prevalence of the marker defined group
  - Assay failure rate, sensitivity, specificity, predictive value
  - Magnitude of benefit
  - Frequency of events in marker positive group

Non-randomised phase 2 Trial – Histologically Defined and Biomarker Defined Patient Population: Enrichment Design



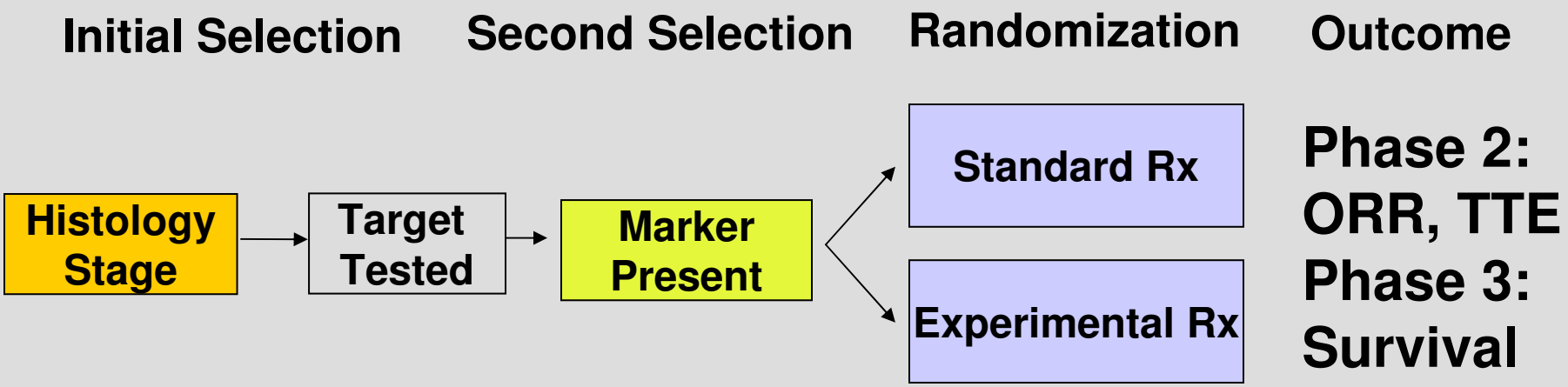
- Trial designed to assess agent activity in the marker+ group
- Marker assessment
  - Assay failure increases number of patients screened
  - False positives will dilute effect
  - False negatives will increase the number of patients screened
- Cannot tell if agent active in marker negative group
- Outcome of the marker positive group may differ from historical data assessed in unselected patients

Phase 2 Trial – Histologically Defined and Marker Defined Patient Population: Stratified Design



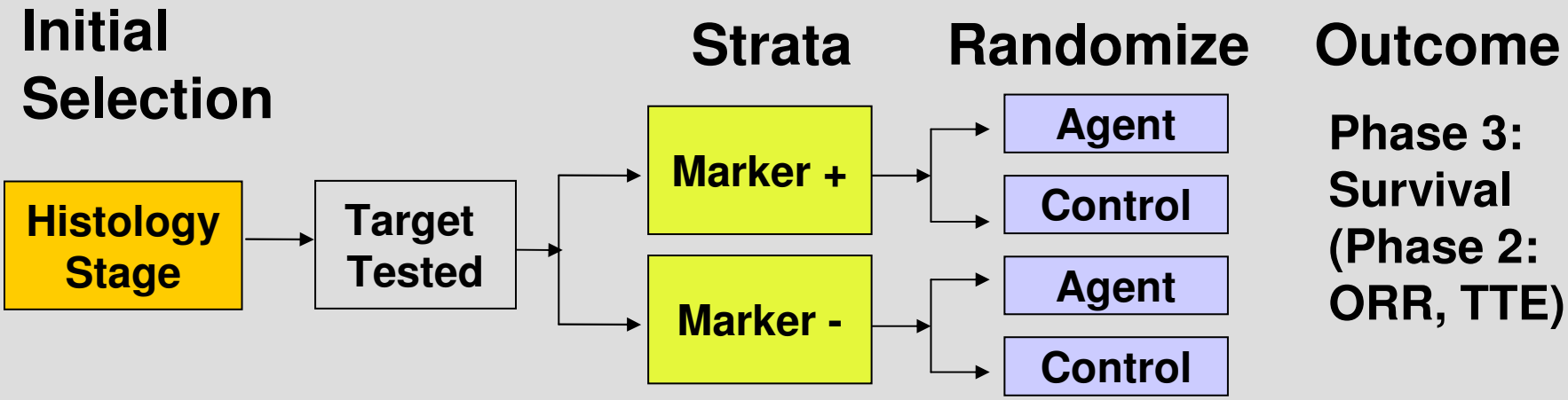
- Trial is designed to assess treatment activity in Marker+ and Marker- groups
- Marker assessment
  - Assay failure increases number of patients screened
  - False positives will dilute effect
  - False negatives will increase the number of patients screened
- Cannot distinguish between prognostic versus predictive effect of marker compared to historical data from unselected patients

Phase 2 or 3 Trial – Histologically and Molecularly Defined Patient Population: Enrichment Design (2)



- Trial designed to assess activity/effects in the marker+ group
- Marker assessment
  - Assay failure increases number of patients screened
  - False positives will dilute effect
  - False negatives will increase the number of patients screened
- Can determine prognostic versus predictive association of biomarker
- Cannot assess effect in marker negative group

Phase 3 (or 2) Trial – Histologically and Biomarker Defined Patient Populations (2): Stratified Design



- Trial is designed to assess treatment effects in Marker+ and Marker- groups
- Larger trial may be required, because of marker –ve group
- Marker assessment
  - Assay failure increases number of patients screened
  - False positives will dilute effect
  - False negatives will increase the number of patients screened
- If negative within marker groups, could analyze between treatment groups

Challenges in Data Analysis & Interpretation

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- Limitations of enrichment designs
  - Single-arm
    - Have we identified a subgroup with favorable prognosis (independent of treatment) or a group that preferentially benefits from the new treatment?
    - The biomarker defined subgroup may have a different prognosis from historical outcome data from trials done in an unselected group
      - E.g. ER+, HER2 amplification and EGFR mutations are both prognostic and predictive
    - If the outcome with standard treatment is not well defined and/or the outcome of interest is PFS/OS consider a randomized phase 2 design
  - Randomized
    - Does the new drug benefit *all* patients or only the subgroup?
- Limitations of assays to define biomarker groups
  - Assay failure increases the number of patients screened
  - False positives will dilute effect in marker+ group
  - False negatives will dilute the apparent differences in treatment effect between marker defined groups.
  - Randomized stratified design may be 4x size of a conventional study

Challenges in Acquiring Specimens

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- Patient consent
- Difficulties obtaining tissue (advanced/recurrent disease)
  - Biopsy precedes phase 2 study & unavailable
  - Risks of additional biopsy procedure
  - Exposure to prior therapy
- Relevance of original diagnostic specimen (if 2nd line) or primary tumor (if metastatic)
- Standardized collection & preservation

Challenges in Data Analysis & Interpretation of Retrospective Single Arm Studies

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- Samples sizes (with available specimens) in single arm study generally too small for definitive marker analyses
- Many endpoints, markers, and subgroups might be examined
- Combining over different studies difficult
  - Different patient populations
  - Different assay methods

Strategy to Develop Agents

- In phase 2, evaluate the effect of agent in marker +/- groups
  - Concurrently or in sequence
  - Based on results, decide whether to design phase 3 study for marker+ group, both groups, or not to select.
  - If patients are not prospectively tested for marker, consider
    - What is the power for subset analyses?
    - How to optimize specimen collection?

Phase 3 Studies with Predictive Markers: 4 Approaches

- Traditional: clinical trial comparing investigational to control treatment for all patients with same histology/stage of cancer.
  - Retrospective evaluation of marker/treatment effects
- Targeted or enriched: randomize only marker+ patients and compare treatments
- Stratified Marker and Treatment Validation: randomize all patients and compare treatments separately within marker +ve and marker -ve patients
- Marker-Based Validation: designed to demonstrate that use of marker results in better outcomes than no use of the marker