

Aspects of Novel and Traditional Clinical Trial Design

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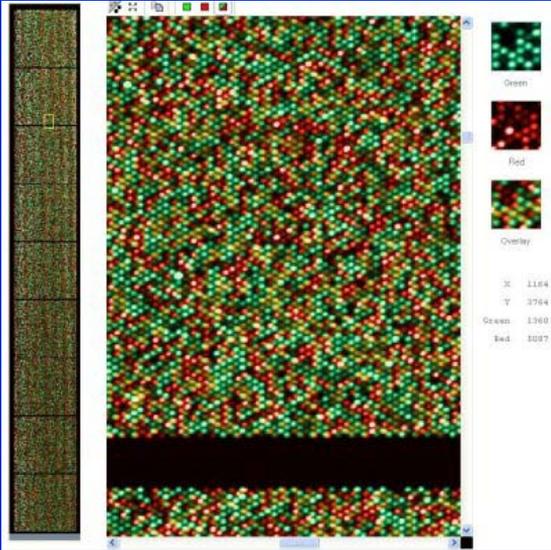
Goals

- Through better understanding of biology, identify better therapies
- Move promising therapies into clinical trials rapidly
- Conduct clinical trials efficiently
- Conduct “smart” trials based on biological understanding of the disease and mechanism of action of the therapeutic

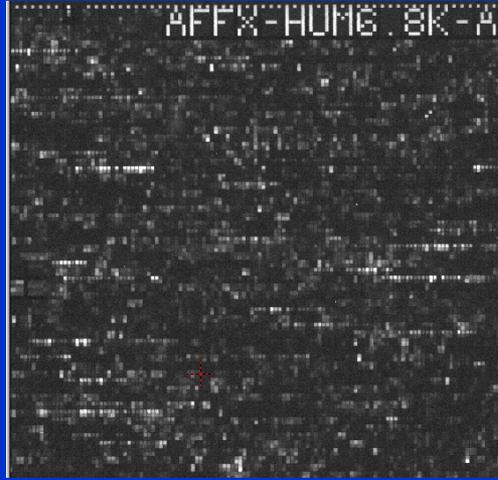
Guiding Principles

- Few therapies will benefit all cancer patients, especially in the era of molecularly targeted therapeutic agents
- Identification of the patients who will or will not benefit from a new therapy is becoming as important as developing the therapeutic agent itself
- Strive for BIG benefits for targeted patient group

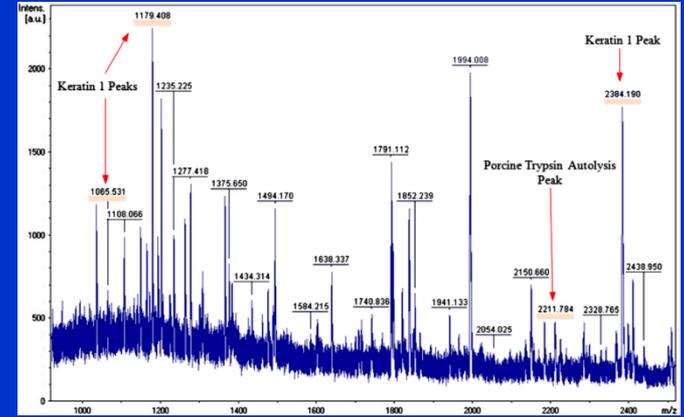
Rich Sources of Biological Information



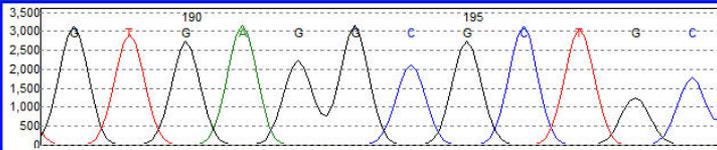
Illumina SNP bead array



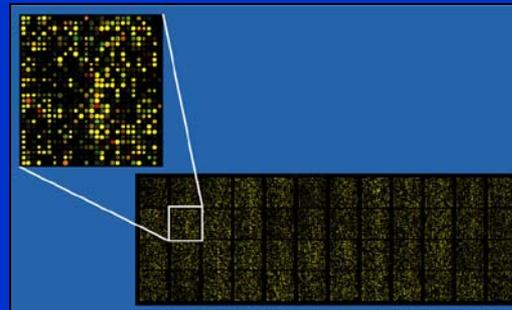
Affymetrix expression GeneChip



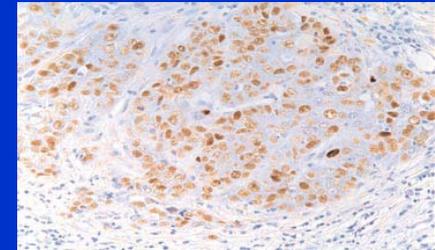
MALDI-TOF proteomic spectrum



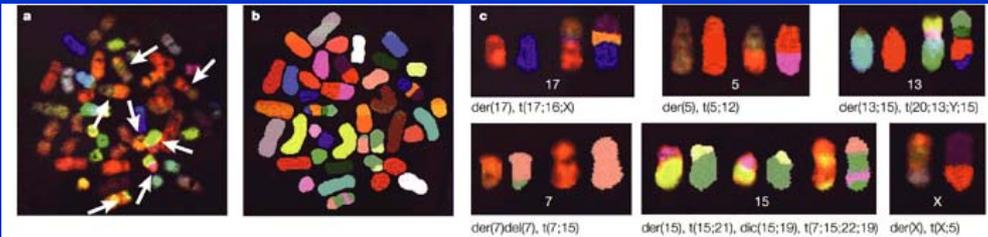
Mutation sequence surveyor trace



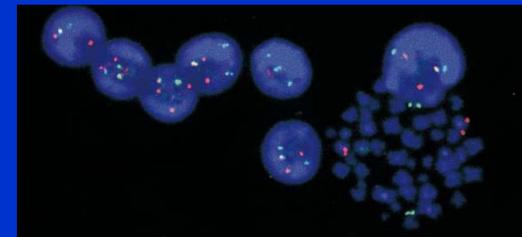
cDNA expression microarray



p53 IHC stain of breast cancer



SKY analysis of AML cells



FISH analysis of BCR-ABL in ALL

Definitions

- **Biomarker** (<http://www.cancer.gov/dictionary>): Biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.
- **Biomarker signature**: A *collection* of biomarkers that are combined and assessed for patterns having biological or clinical significance, usually through development of mathematical models or predictors.

Targeted Therapy Success Stories

- Trastuzumab: HER2 (breast)
- Imatinib: Ph⁺ CML, KIT⁺ GIST
- Erlotinib: EGFR mutation (lung)
- Crizotinib: ALK rearrangements (lung)
- Vemurafenib: BRAF V600E mutation (melanoma)

Types of Trials

- Phase 0: Demonstrate biological activity in patients
- Phase I: Dose finding and toxicity
- Phase II: Early evaluation of efficacy
 - Single arm
 - Randomized
 - Biomarker-directed
 - Neoadjuvant “window of opportunity”
- Phase III: Definitive evaluation of efficacy
 - Multi-arm trials
 - Biomarker-based designs
- Other: Hybrid I/II, II/III

Phase 0 Trials

- Demonstrate biological activity in patients
- Very low doses of experimental drugs administered to patients
- Drug's pharmacokinetics (the body's effect on the drug) and pharmacodynamic (the drug's effect on the body) evaluated through a series of blood tests or imaging studies
- Requires known drug target, reliable biomarker assay, or potentially molecular imaging

Phase I Trials

- Dose finding & toxicity
- For cytostatic target-based agents, might need to supplement traditional endpoints with biological or pharmacokinetic endpoints to define the optimal doses
- Consider selective evaluation pharmacogenomic markers (e.g., SNP gene variants) for early detection of toxicity risk indicators

Phase II Trials - Issues

- Endpoints
- Targeted vs. all-comers
- Trial types
 - Single arm
 - Randomized trials
 - Biomarker-directed
 - Neoadjuvant “window of opportunity” trials

Phase II Trials

- Endpoints
 - Tumor response based on shrinkage in advanced disease not relevant for cytostatic targeted agents
 - Progression evaluation can be very subjective, drift over time (e.g., changes in imaging methods) and vary from observer to observer
 - Biological endpoints require “qualification”

Phase II Trials

- Single arm trials
 - May require less than half sample size of some randomized phase II trials with comparable type I (α , “false positive”) and type II (β , “false negative”) error
 - Historical control data required
 - Impact of selection biases unintended (e.g., drift), or intended (e.g., targeted subpopulation)

Phase II Trials

- Single arm trials in targeted subset of patients
 - Cautionary note about effect of enrichment on appropriateness of historical response rate (RR)

Table 1. Effect of enrichment for biomarker-positive cases on the probability of falsely concluding that a new therapy increases the response rate when a single-arm phase II study is designed using assumptions from an unselected population

Historical response rate in the unselected population (%)	Historical response rate in the subpopulation enriched for biomarker-positive cases (%)	Sample size	No. observed responses required to conclude that the response rate is increased by the new therapy	Actual probability of falsely concluding that the new therapy increases the response rate in the enriched subpopulation
10	15	30	6	0.29
10	20	30	6	0.57
20	25	36	11	0.27
20	30	36	11	0.53
30	35	39	16	0.26
30	40	39	16	0.51

NOTE: Single-arm phase II studies are typically designed to test against benchmark historical response rates in the range of the example rates provided in column 1. When the historical response rate in the subpopulation enriched for biomarker-positive cases is unknown, it is often assumed to be the same as in the unselected population. Column 2 presents the (unknown) historical response rate in the subset of patients who are positive for the biomarker. Sample size (column 3) and required observed response rate (column 4) are calculated to satisfy two conditions: (a) control the probability of falsely concluding that the true response rate has been increased from the historical rate in the unselected population to be ≤ 0.10 and (b) provide at least 0.90 probability of concluding that the new therapy has increased the response rate when the new therapy has a true response rate that represents an absolute increase of 20% compared with the historical response rate in the unselected population.

(McShane et al., *Clin Cancer Res* 2009)

Phase II Trials (cont.)

- Randomized phase II trials
 - Guard against selection bias
 - Historical control data not required
 - May require more than twice the sample size of single arm phase II trial with comparable type I and type II error

(Rubinstein et al., *J Clin Oncol* 2005)

Phase II Trials (cont.)

- Randomized phase II trials (cont.)
 - 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 Trials (cont.)

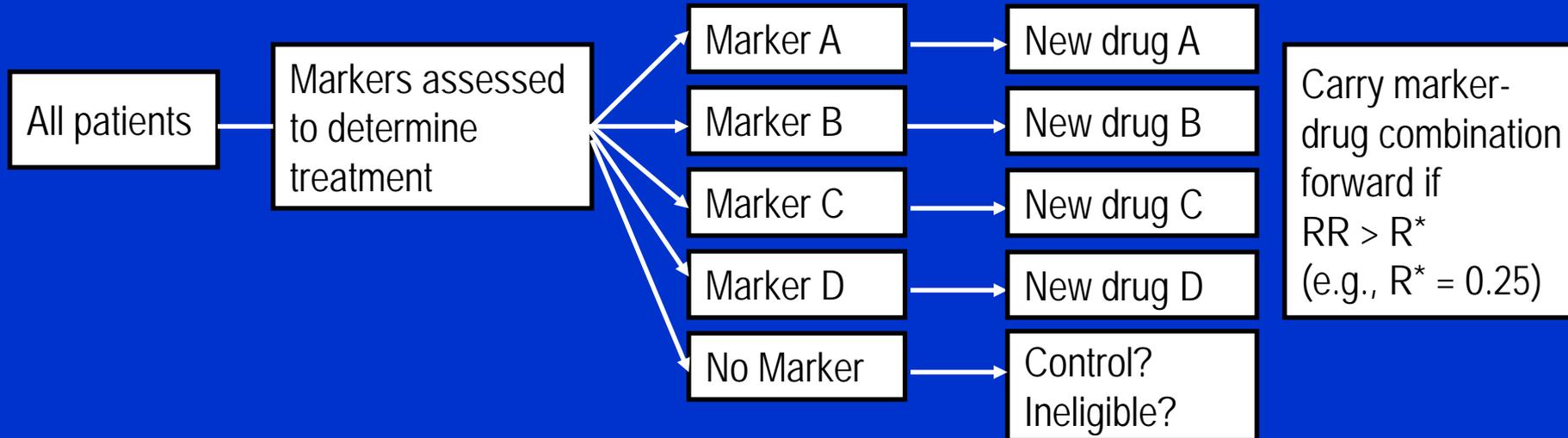
- Randomized phase II trials (cont.)
 - Screening design
 - Compare experimental regimen to standard treatment control arm
 - Economize on sample size by using larger than usual type I and type II errors, and targeting larger effect size (e.g., $\alpha=\beta=0.20$, PFS hazard ratio = 1.5 or RR difference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

Phase II Trials (cont.)

- Neoadjuvant “window of opportunity” trials
 - Alternative to conventional Phase II trials with therapy (often targeted) prior to definitive surgery
 - Assessment of tumor response (clinical and pathologic) and biomarker-based response at time of surgery
 - Interim assessments if tumor biopsy-accessible
 - Possible downstaging and less surgery, modification or elimination of adjuvant (post-surgery) therapy
 - Longer term follow-up required to establish clinical benefit
 - Examples: breast, lung, bladder

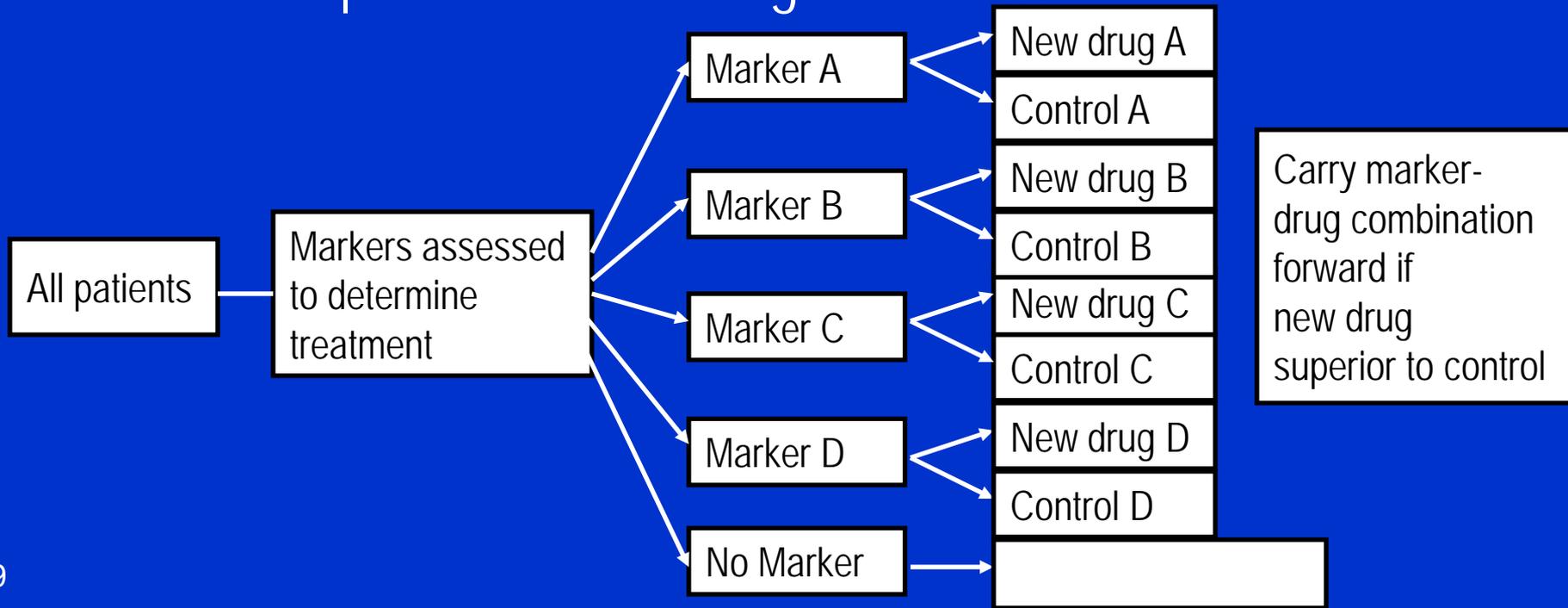
Phase II Trials (cont.)

- Biomarker panel directed (non-randomized)
 - Appropriate when expected response rate in patient population is very low (e.g., < 5-10%)
 - May require follow-up with randomized phase II trials before proceeding to phase III depending on magnitude of response and subgroup prevalences
 - Add or drop drugs or markers over time



Phase II Trials (cont.)

- Biomarker panel directed (randomized)
 - Effectively multiple parallel phase II designs, one per marker-defined subgroup
 - Control treatments potentially differ by marker subgroup
 - Addresses possibility of prognostic effects of subgroups
 - Add or drop markers and drugs over time



Phase III Trials - Issues

- Multi-arm trials
- Definitive evaluation of predictive (“treatment-selection”) biomarkers

Multi-Arm Trials

- Control (standard) arm versus several experimental drug arms
 - Apply group sequential methods to each experimental arm versus control comparison to adaptively drop non-performing arms
 - Increasingly used
 - Reference: Freidlin et al. (Clin. Ca. Res, 2008)
- Factorial designs
 - Yes/No for each of two or more drugs to form 2^k treatment groups
 - Each treatment group used in multiple drug comparisons assuming no important interactions

Multi-Arm Trials

- Advantages
 - Efficiency through “re-use” of arms
 - Direct comparisons on common patient population
- Logistical issues
 - Difficulty maintaining blinding across several different treatment types
 - Interactions may be problematic in factorial designs
 - If multiple drugs involved, may require cooperation among multiple drug companies

Prognostic and Predictive Biomarkers in Context of Phase III Trials

- **Prognostic:** Biomarker associated with clinical outcome in absence of therapy (natural course) *or with standard therapy all patients are likely to receive*
 - Treatment vs. no treatment following surgery
 - Aggressiveness of treatment
- **Predictive (Treatment-selection):** Biomarker associated with response (benefit) or lack of response (benefit) to a particular therapy relative to other available therapy
 - Select one treatment vs. another treatment

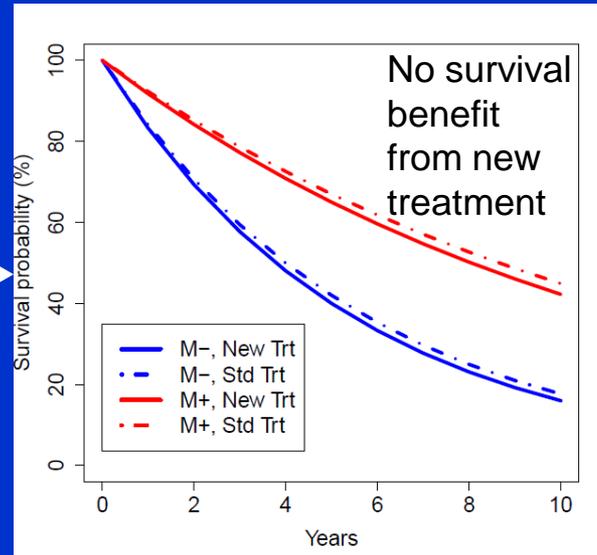
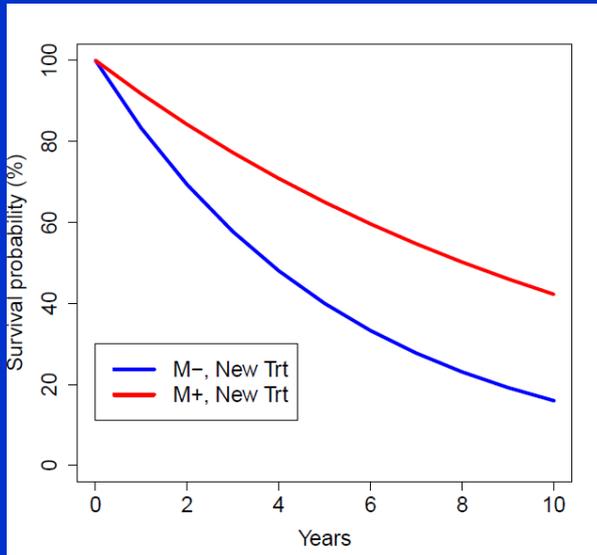
Phase III Evaluation of Predictive Biomarkers

- Ideally, predictive tests should be developed in parallel with new therapeutics (“co-development”)
- In reality, test and therapeutic development are not always synchronized
- A biomarker-based test might be “good enough” for use in development and testing of a therapeutic but not be optimized for clinical use when the therapeutic is ready

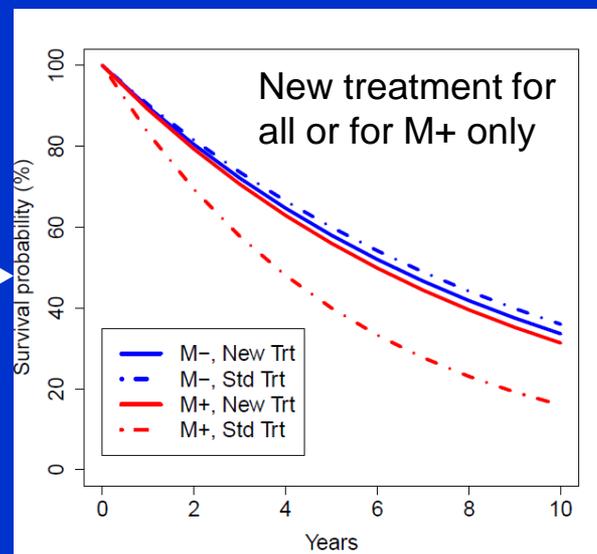
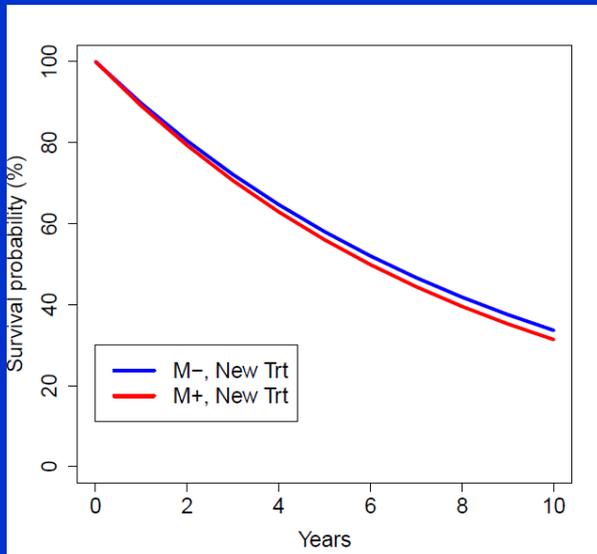
Phase III Trials with Candidate Predictive Biomarkers

- Basic principles
 - Prognostic vs. predictive
 - Treatment-by-biomarker interactions
- Comparison of randomized designs (Freidlin et al., *JNCI*, 2010)
 - Enrichment design
 - Completely randomized design
 - Randomized block design
 - Biomarker-strategy design
- Power and sample size considerations
 - Prospective vs. retrospective

Prognostic vs. Predictive: Importance of control groups



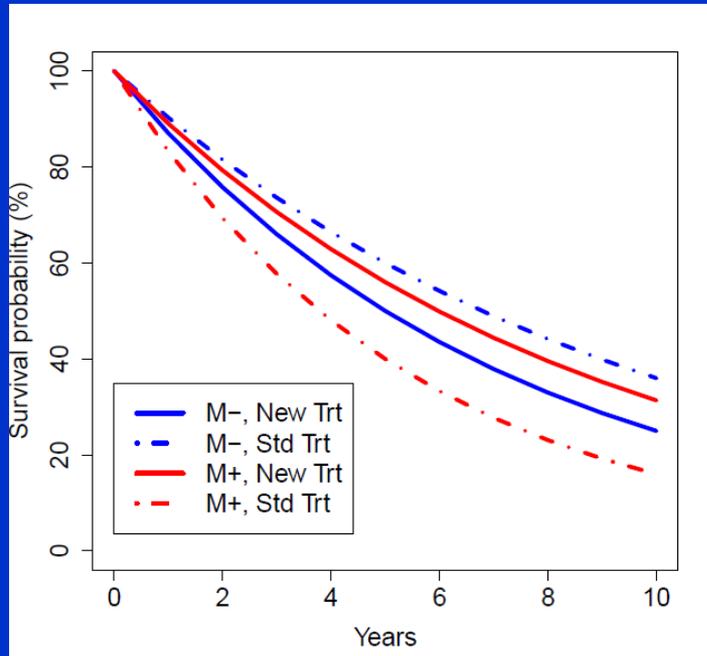
Prognostic
but not
predictive



Prognostic
and predictive

When is a biomarker useful for guiding treatment decisions?

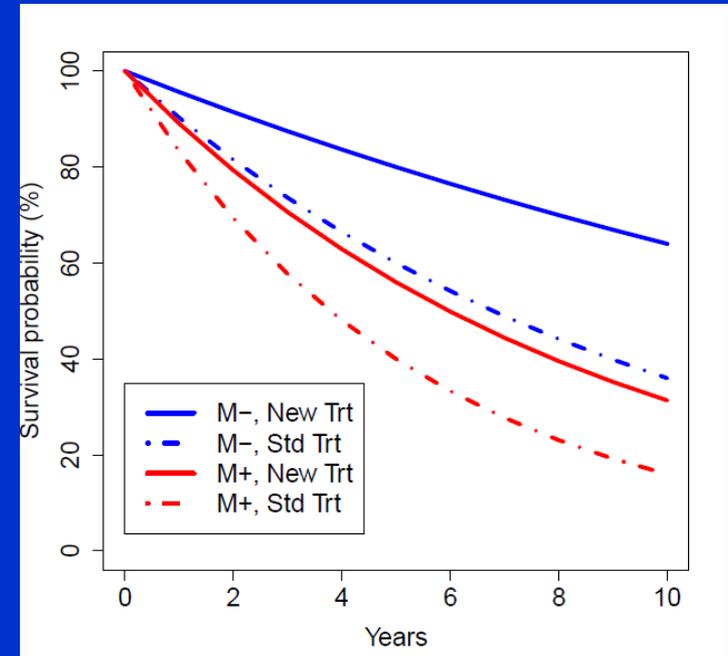
Prognostic and predictive;
New treatment for M+ only



Qualitative interaction

- Std Trt better for M- ($HR_- = 1.36$)
- New Trt better for M+ ($HR_+ = 0.63$)
- Interaction = $0.63/1.36 = 0.47$

Prognostic and predictive;
New treatment for all



Quantitative interaction

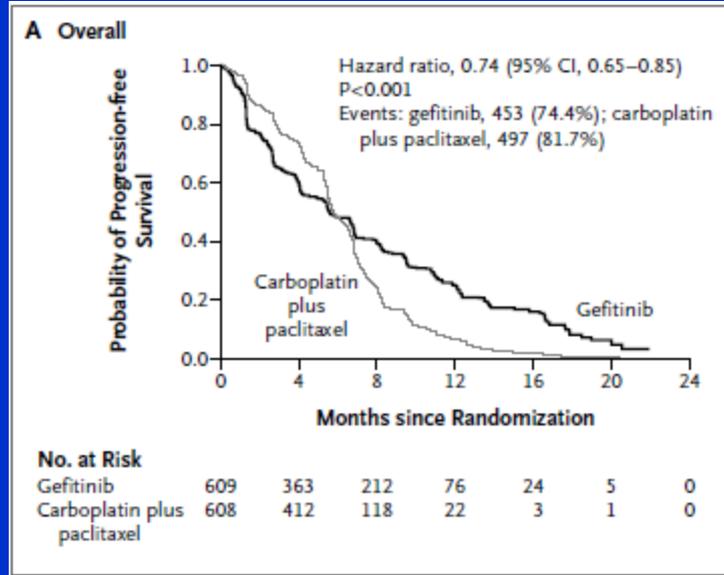
- New Trt better for M- ($HR_- = 0.44$)
- New Trt better for M+ ($HR_+ = 0.63$)
- Interaction = $0.63/0.44 = 1.45$

Example from NSCLC: EGFR mutation as a predictive biomarker

Mok et al.
N Engl J Med; 361: 947-57

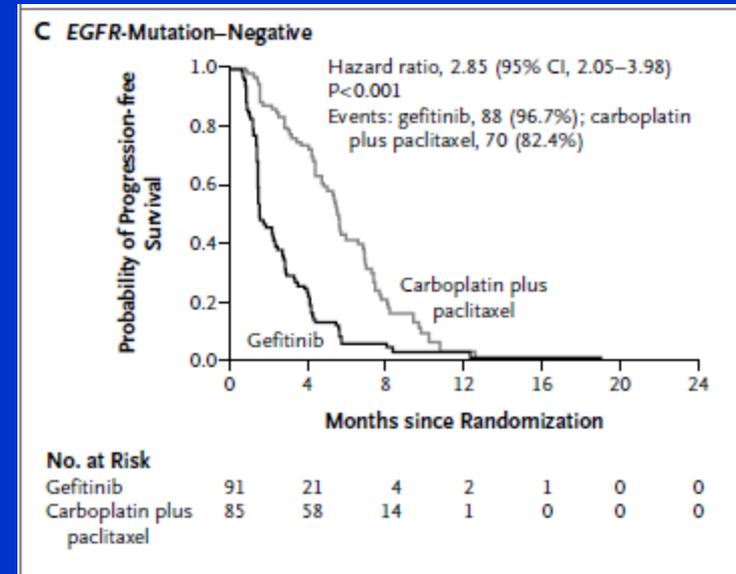
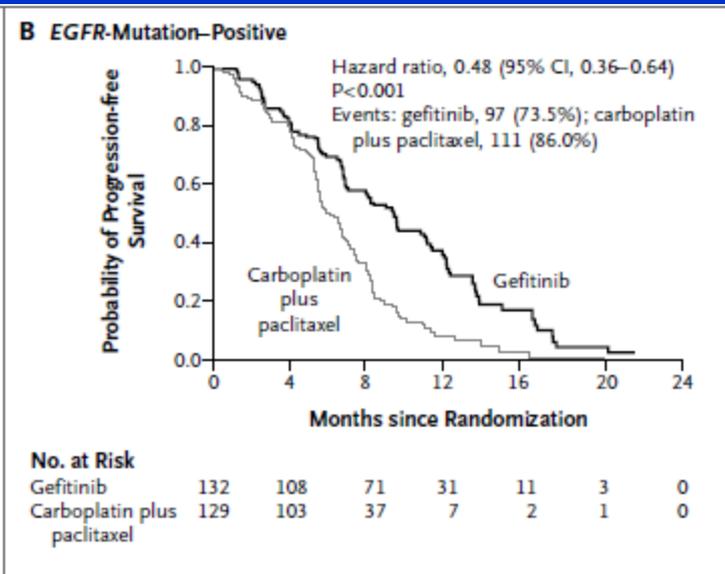
EGFR mutation is:

- Positive prognostic factor
- Positive predictive factor for gefitinib benefit



IPASS: Phase III
 1st line advanced adeno
 NSCLC

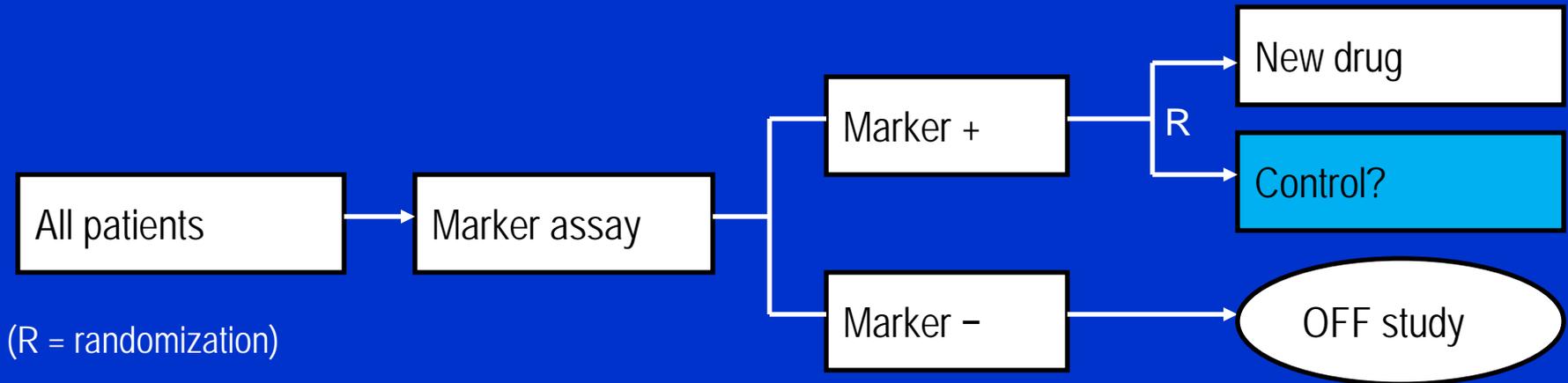
gefitinib
 vs.
 carboplatin+
 paclitaxel



Predictive Marker Study Design

Enrichment Design

Only marker+ patients are randomized and/or treated

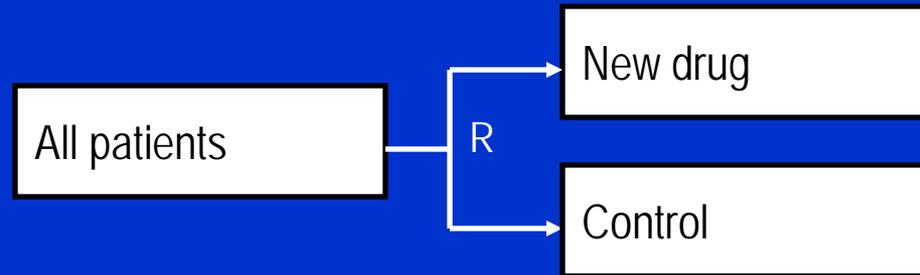


- Does new drug benefit marker negative patients also?
- Inclusion of control arm preferred, but if no control arm
 - Is good outcome due to better prognosis alone?
 - Is the historical comparator appropriate (e.g., Marker +)?
- Need to know the “right” marker and have good marker assay
- Limits possibilities for future marker refinement (conditional on patient inclusion by first enrichment)

Predictive Biomarker Study Design

Completely Randomized Design

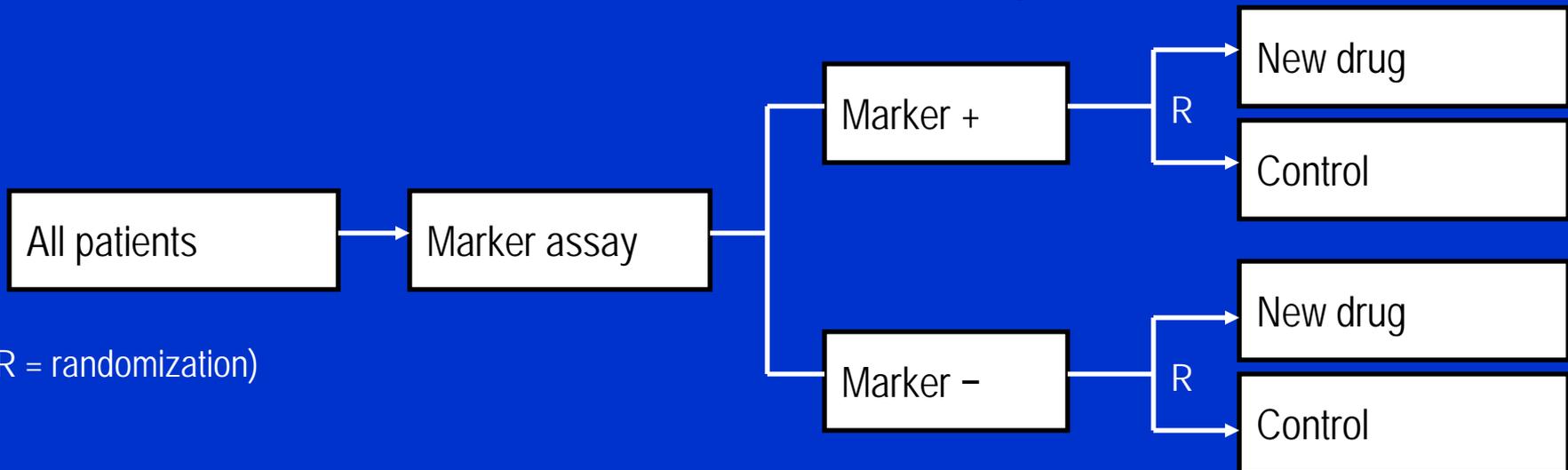
Biomarker tested on all patients, but result not used for randomization



(R = randomization)

Randomized Block (Stratified) Design

Biomarker tested pre-randomization, stratification by biomarker

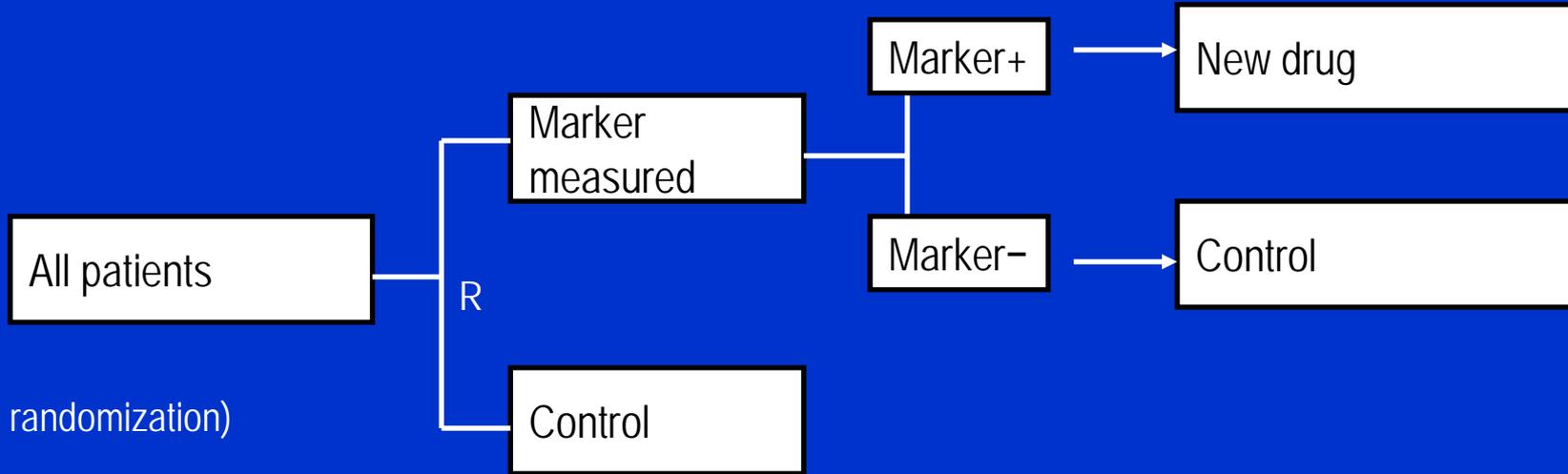


(R = randomization)

Predictive Biomarker Study Design

Biomarker-Strategy with Control Design

Randomize to use of biomarker versus no biomarker evaluation

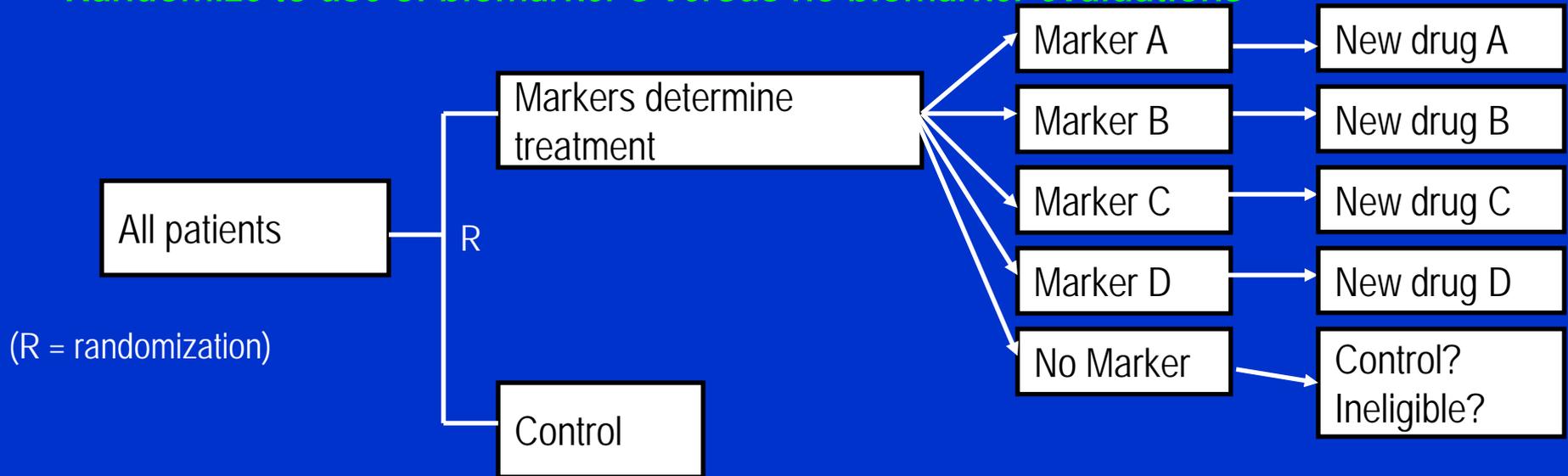


- Cannot compare new drug and control in marker negative patients (unless also randomize to new drug, worsening inefficiency)
- Statistically very inefficient if marker positive prevalence is low (many patients would receive same treatment on both arms)
- Marker-guided treatment attractive to patients and clinicians
- Might be necessary for complex multi-marker guided strategies
- Can't separate prognostic and treatment effects unless marker measured in control arm patients

Predictive Biomarker Study Design

Multiple-Biomarker-Strategy with Control Design

Randomize to use of biomarker s versus no biomarker evaluations



- Must measure markers on the patients randomized to the control treatment in order to separate prognostic and predictive effects
- Provides direct measure of patient willingness to follow marker-assigned therapy (but that could change as new evidence emerges)
- Marker guided treatment attractive to patients or clinicians
- Required sample size depends on marker prevalences, prognostic and treatment effects
- To power for marker-specific conclusions (desired) can require screening very large number of patients

General Sample Size Considerations

- Depends on design
- Substantially larger sample size than required for typical treatment or prognostic study
- Studying low prevalence biomarkers will be extremely challenging
- Aim for large effect sizes
- Sample size might not be sufficient to “retrofit” a predictive biomarker to a completed treatment trial

General reference for randomized clinical trial designs with biomarkers: Freidlin et al., JNCI 2010

Summary

- New biological characterizations of cancer bring new challenges for clinical trial design
- Patient participation in clinical trials will likely need to increase to take full advantage of potential for tailored therapies
- Clinical trials enterprises will need to be more efficient
- We need to aim for new therapies that will result in bigger benefits to patients

Acknowledgements

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