PS02 – Biomarker Analysis

Discussant

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Presentations

Opportunity and Challenges in Utilizing Biomarkers for Drug Development

Mark Chang, Millenium

New Paradigms for clinical Drug Development in the Genomic Era

Richard Simon, NCI/NIH

Themes

- Terminology
- Some FDA experience
- Biomarkers: Validation or not?
- Correlation vs. Prediction
- Enrichment Strategy
- Personalized Medicine: new paradigm of statistics ?
- Adaptive design using biomarker
- Components of Variability

Terminology

- **Biomarker:**
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group ,2001)

- **A characteristic recognized as an indicator**
- **Established performance characteristics**
  - **Single Biomarker**
  - **Composite Biomarker**

Genomic Drug Trial (GDT)*

Clinical trials employing (high throughput) genomic technology to identify molecular signals including transcription, SNP or proteomic profiling in complex biological mixtures for use as *genomic composite biomarkers (GCB)* of disease, of drug exposure/drug disposition, or *of drug response including efficacy and toxicity*

* *Wang SJ, Proceedings of the Biopharmaceutical Section, American Statistical Association, 2004*

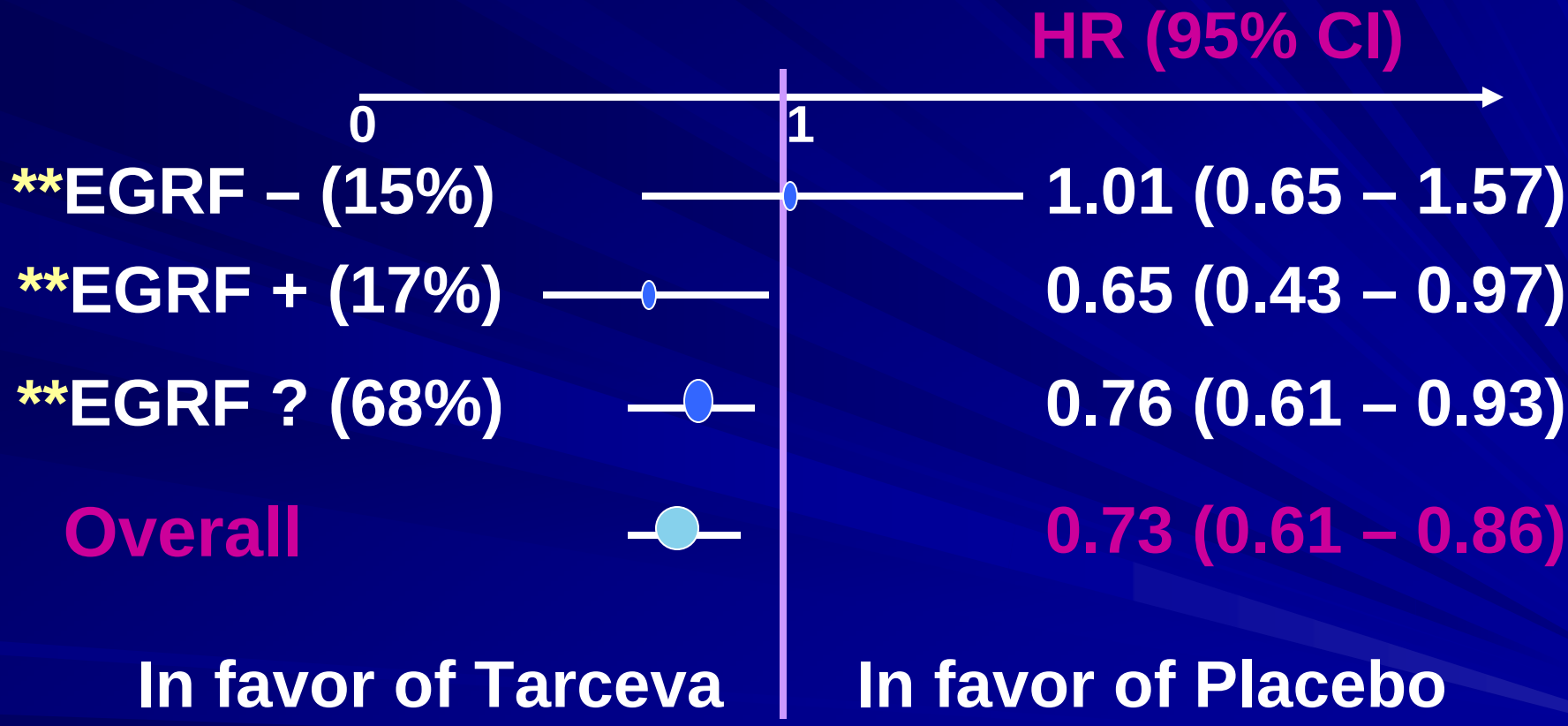
Experiences in RCT Using Single Genomic Biomarker

Her2/Neu (Herceptin)*

EGFR (Tarceva*, Iressa)

**** None of these biomarker subgroups were prospectively planned to evaluate treatment effect for targeted therapy during drug approval cycle***

If Tarceva EGFR+ subgroup is pre-specified with appropriate alpha-allocation



Overall p<0.002

* *Wang et al. 2006, The Pharmacogenomics Journal*

** *data extracted from Tarceva Package Insert*

Validation of Genomic (Composite) Biomarker?

These biomarkers are used to select responsive patient population

Genomic biomarker ≠ Surrogate biomarker

It is not about validation of surrogate biomarker (surrogate endpoint)

Rather, it is about whether the assay can be reproducibly measurable on the biomarker status

Correlation vs. Prediction

Correlation does not speak to causal effect

Correlation ≠ Prediction, especially in exploratory studies

OR is often used to describe if a biomarker is predictive of clinical outcome, e.g., in nested ca-co study

A loosely defined criteria for predictivity

Enrichment (Design #1)

- Goal: increase power of the study

Example:

GCB+ $T > C$ } ➔ Enrichment

GCB– $T = C$ Design

Severe $T >> C$ } ➔ Enrichment

Mild $T > C$ Design

Enrichment (Design #1)

- Often perceived to provide predictive ability of the therapeutic response

Concerns

Generalizability issue

Risk:Benefit

How many less sensitive patients ?

New Paradigm for PM?

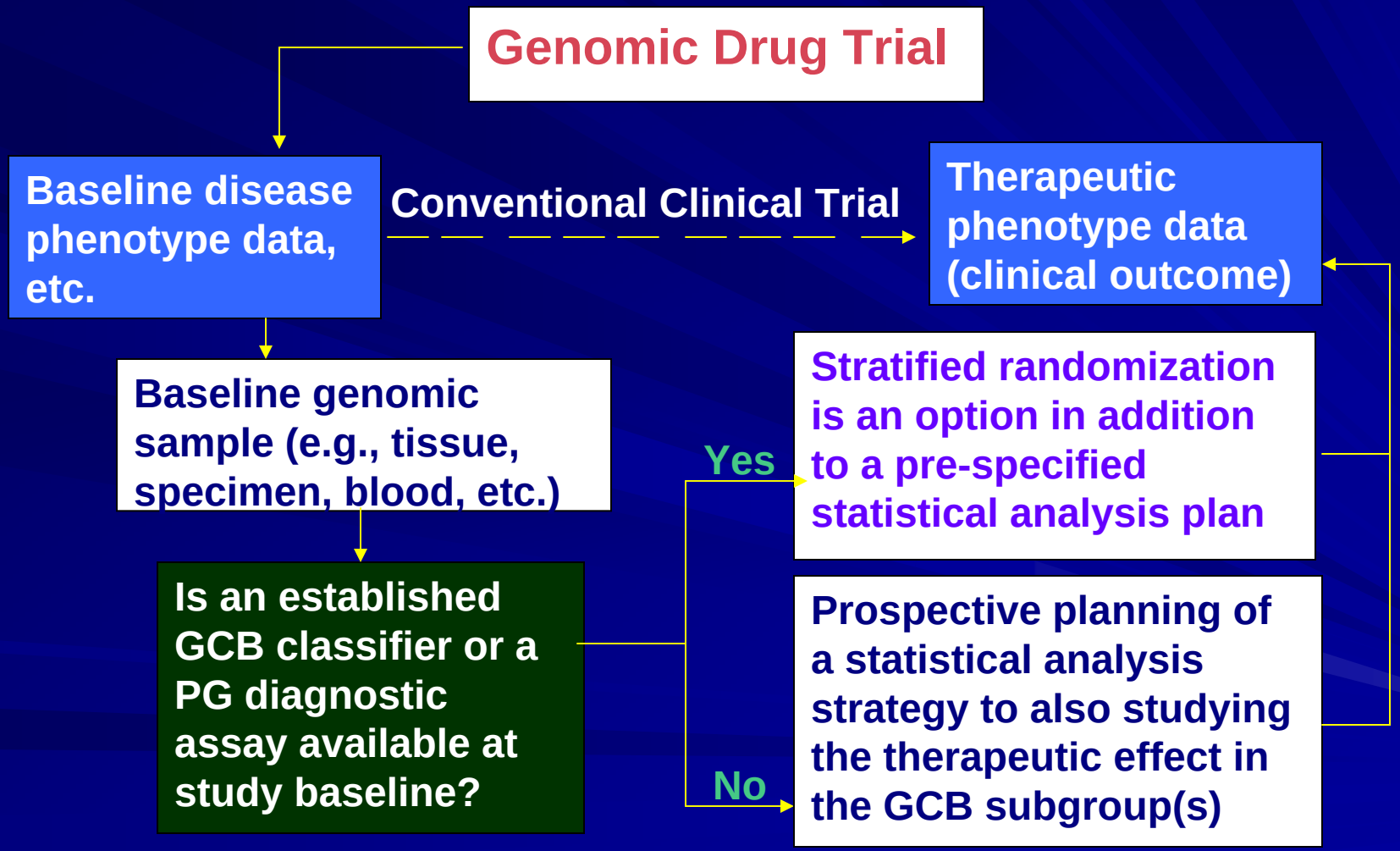
Emphasize safety and reduce statistical requirement for efficacy?

- Are we going back to pre-DESI era?
- Criteria to assess B:R balance should not be changed because of the desire to realize PM

$\Rightarrow$ lack of effect, undesirable characteristics for PM

- Prudent in research for targeted therapy, a way closer to PM
- Oncology needs predictive biomarkers (Simon, Wang, TPJ 2006)

Use of GCB profiling in Genomics Drug Trials



Wang, Temple, O'Neill, 2006

Classifier from high throughput

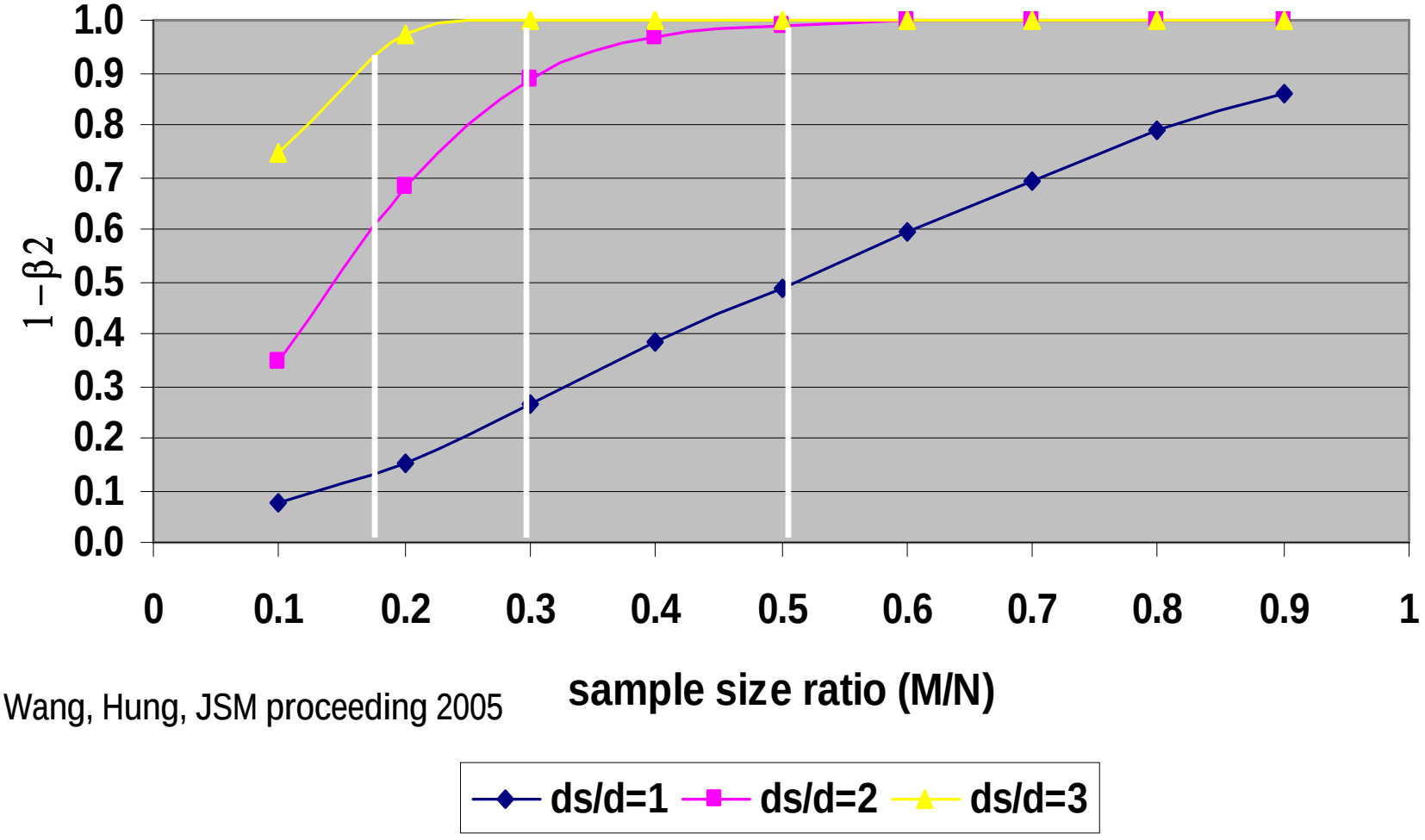
Identify a patient population that benefits from therapeutic

Q: how to identify such a patient population

- Conventional approach
- Targeted approach

  Basic concept of demonstrated drug effect remains
- Assay sufficient?

Figure 5a. Subgroup power for $\delta s/\delta$ = 1, 2 or 3, given α = 0.025, $\alpha 1$ = 0.02, 1-$\beta 1$=0.90



Wang, Hung, JSM proceeding 2005

Adaptive Design using Biomarker

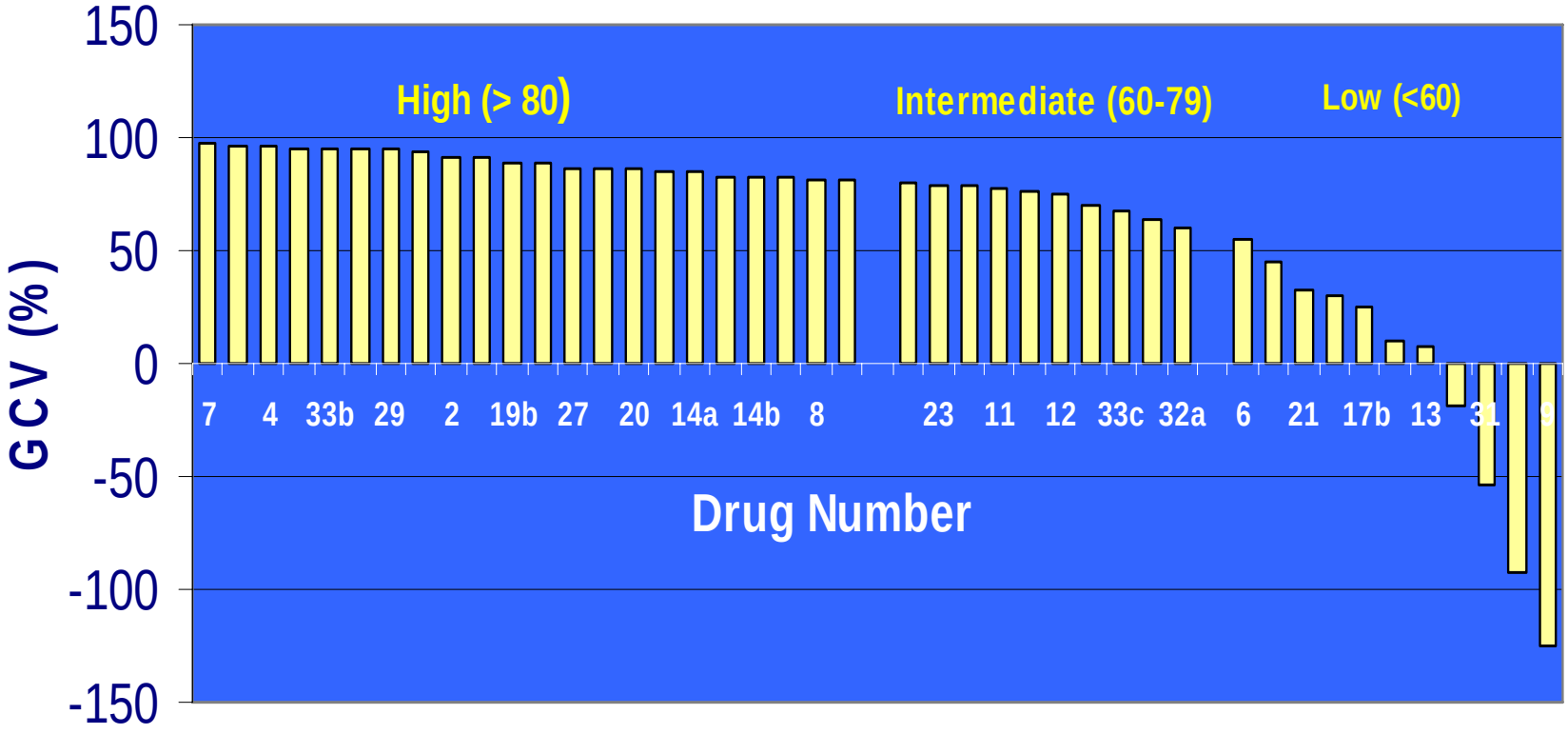
- Use of internal data
- Use of external data

Application of diagnostics to drug studies

- The more pressing elements are the reproducibility, reliability and precision of the diagnostic or imaging test that are of primary concern for evaluating the test's predictability in the targeted patient population

* *Imaging Biomarker for Clinical Prediction, Mills, Wang, Farrell, Pazdur, Woodcock, 2006*

Disease Variability → Variable Therapeutic Responses



* Lesko, Patnaik, Wang (2003): The Pharmacogenetic Component of Variability in Human Drug Exposure, Sigma/FDA Science Forum, DC, MD