

# CLINICAL NEEDS/VALUES OF IMAGING BIOMARKERS

OR

## WHAT THE HECK IS AN IMAGING BIOMARKER ANYWAY

Walter Stadler, MD, FACP  
University of Chicago

### My Top Words

#### Most fuzzy and overused

- Correlative study
- Targeted therapy
- Biomarker
- Response
- Surrogate

#### Least fuzzy and underused

- Variability/Heterogeneity
- Control
- Qualification
- Predictive biomarker
- Prognostic biomarker
- Pharmacodynamic biomarker

## Oncologic Therapeutics

- All drugs are “targeted”
  - If they weren’t they wouldn’t work
- Some of our best drugs are “dirty”
  - They hit multiple targets
- We don’t have “better targeted” drugs
  - We have more drugs and targets
- True drug mechanism often discovered after drug effectiveness is demonstrated
  - Putative mechanism may be wrong

## Why Biomarkers?

- Individualized therapy
  - Most likely to benefit
  - Least likely to experience toxicity
  - Early identification of benefit
  - Early identification of resistance
- Understanding drug mechanism of action
- Understanding patient/disease heterogeneity

## Biomarker Definition

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Clin Pharm Ther 69:89, 2001

## Biomarkers

- Diagnostic marker
  - Information on disease presence/absence
  - e.g.: 1cm spiculated nodule on chest CT
- Prognostic marker
  - Information on disease natural history, regardless of therapy
  - e.g.: ECOG performance status
- Predictive marker
  - Information on relative benefit from a specific therapy
  - e.g.: ER status and benefit from tamoxifen
- Pharmacodynamic marker
  - Information on therapy effect on host or tumor
  - e.g.: neutropenia following paclitaxel therapy
- Treatment resistance marker
  - Information regarding progression/resistance to ongoing therapy
  - e.g.: Secondary EGFR mutations

## Biomarker Qualification

- Known valid biomarker:
  - A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, or clinical significance of the results.
- Probable valid biomarker:
  - A biomarker that is measured in a an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, or clinical significance of the results..
- Exploratory biomarker:
  - A biomarker that does not meet the criteria for probable or known valid biomarker

Goodsaid & Frueh, AAPS J, 9:105, 2007

## Surrogate Endpoints

- Subset of pharmacodynamic biomarkers intended to serve as a substitute for a clinically meaningful endpoint
  - Relapse free survival in adjuvant breast cancer
  - Cytogenetic complete response in CML
  - Few if any “perfect” surrogate endpoints in oncology (Prentice criteria)
    - How good is “good enough”

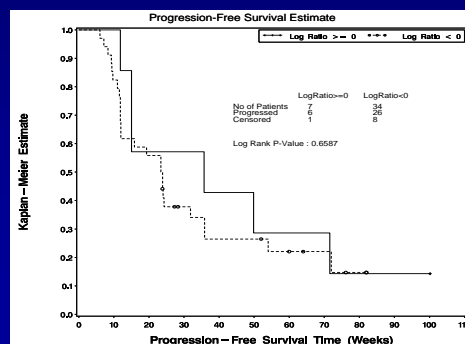
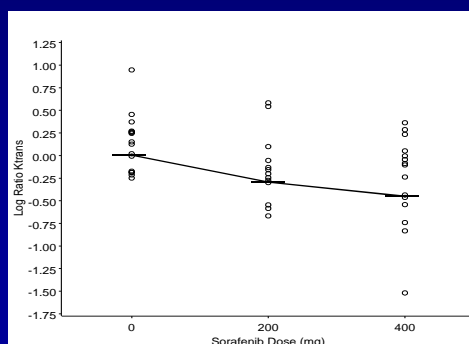
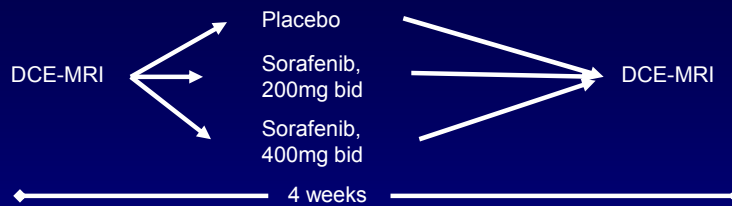
## The Two-Variable Problem

- Cannot test an unknown/exploratory biomarker and an unknown drug in the same trial

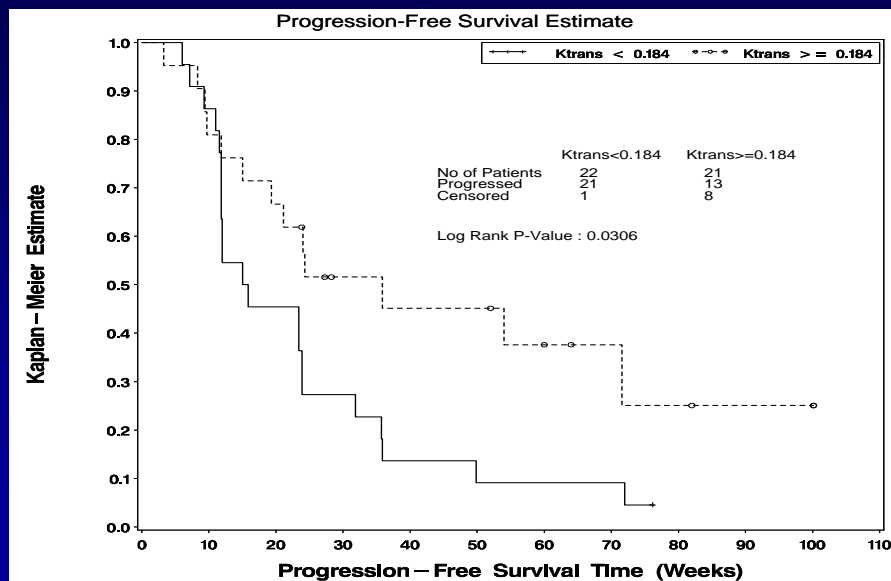
## DCE-MRI As an Antiangiogenic Biomarker

- Utilizes standard 1.5T MRI with gadolinium contrast
- Kinetics of contrast uptake and washout reflect tumor “vascularity”
- Changes detectable soon (1-30 days) following therapy with antiangiogenic agent
- Preliminary studies suggested that changes correlate with drug benefit and outcome

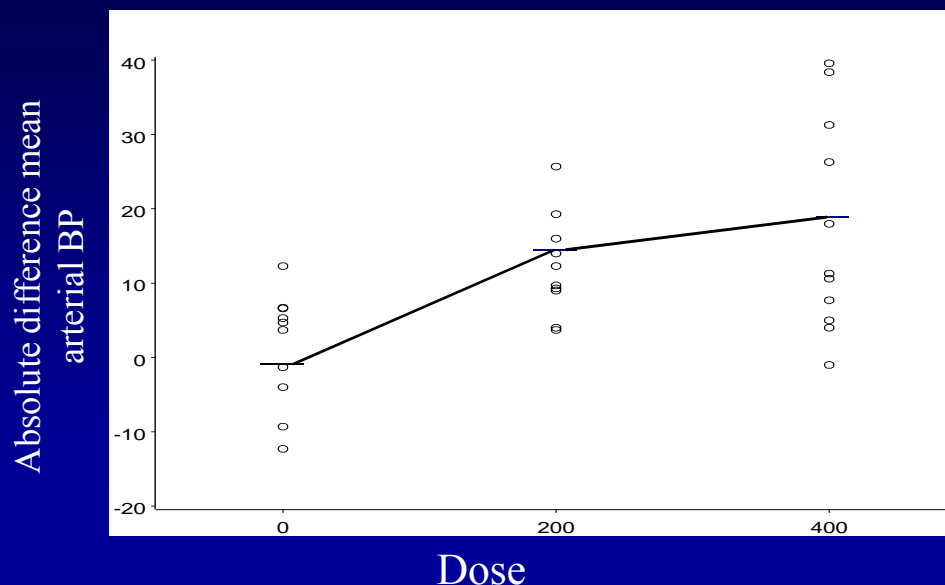
# DCE-MRI $K^{trans}$ as Pharmacodynamic Biomarker



# Baseline $K^{trans}$ is Prognostic For Time to Progression



## BP Is a Pharmacodynamic Marker



## Conclusions – Quantitative Imaging

- Numbers derived from cool technology and pretty pictures still require testing
  - Assay validity
  - Biomarker qualification
- The hypothesized utility of a biomarker must be specified a priori
  - Diagnostic, pharmacodynamic, predictive, etc
- A change with therapy may or may not be “good”