# VOL-PACT:
# Volumetric CT for Precision Analysis of Clinical Trial results


Lawrence H. Schwartz, MD, Chair of Radiology,
Columbia University Medical Center

Geoffrey R. Oxnard, MD, Lowe Center for Thoracic Oncology,
Dana-Farber Cancer Institute

Mithat Gonen, PhD, Dept of Epidemiology & Biostatistics,
Memorial Sloan-Kettering Cancer Center

Michael Maitland, MD PhD, Dept of Medical Oncology,
University of Chicago

Binsheng Zhao, DSC, Dept of Radiology,
Columbia University Medical Center




# Problem statement

- Oncology drug development is inefficient
  - 62.5% of phase III trials are negative
- Therapeutic progress has inherently made drug development more difficult
  - More active drugs leads to greater use of randomized phase II trials
  - However, trials continue to study traditional endpoints (ORR, PFS)
- Development of new, modern trial endpoints is needed

Gan et al, JNCI, 2012

# Problem statement

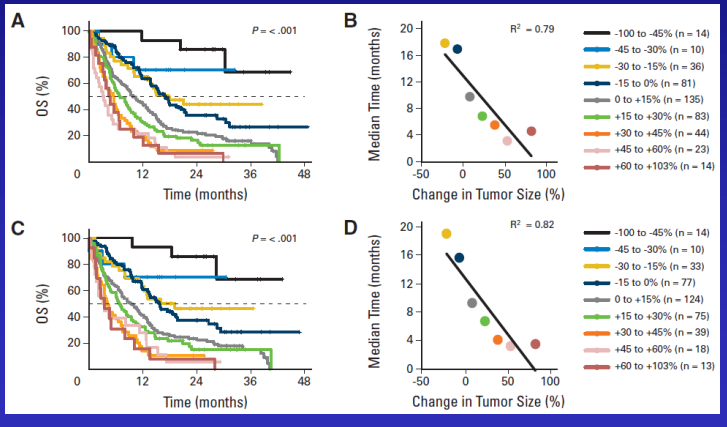
- **Two randomized trials in 1st-line NSCLC:**
  - **Carbo/taxol plus placebo**
  - **Carbo/taxol plus vorinostat**

| Ramalingam et al, JCO, 2010 | | Belani et al, ESMO, 2009 | |
|---|---|---|---|
| NCI-supported consortia | | Industry sponsored | |
| 94 patients | | 253 patients | |
| Carbo/taxol: | 12.5% RR<br>4.1m PFS | Carbo/taxol: | 29.3% RR<br>5.5m PFS |
| & vorinostat: | 34.0% RR<br>6.0m PFS | & vorinostat: | 22.4% RR<br>4.3m PFS |
| **A POSITIVE TRIAL** | | **A NEGATIVE TRIAL** | |



# Background

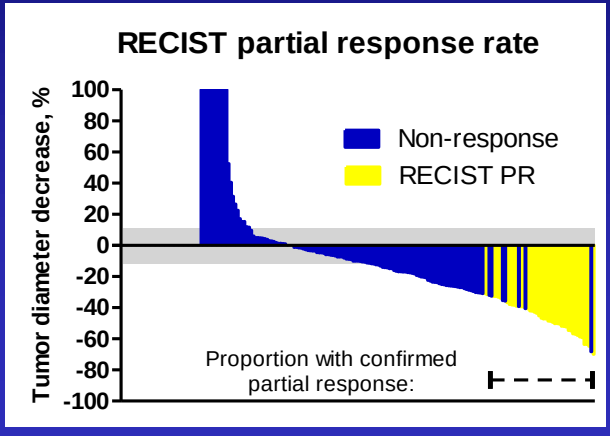
- **It has recently been shown that a greater magnitude of response is associated with a better prognosis for an individual patient**




Jain et al, JCO, 2012

# Background

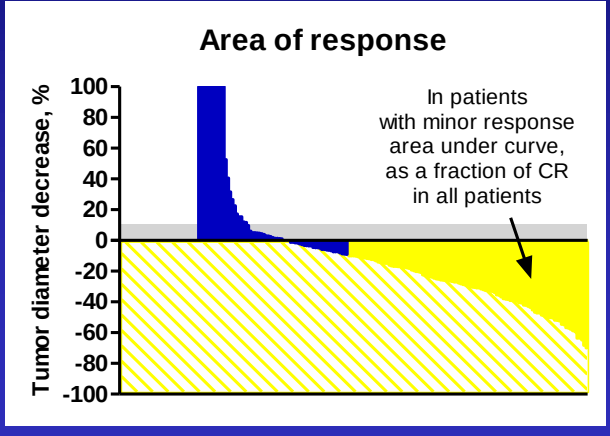
- Yet, conventional trial endpoints do not measure quantitative improvements in response magnitude:






# Background

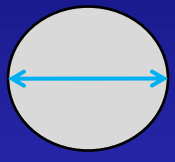
- Yet, conventional trial endpoints do not measure quantitative improvements in response magnitude:



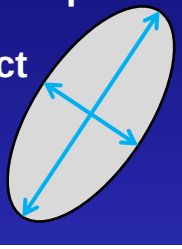
# Background

- Furthermore, advanced imaging of the whole tumor volume can may characterize the biology of tumor growth and response

Diameter (RECIST) 1D



Cross-product (WHO) 2D



Volume 3D



# Background

- Some have suggested that different analytical tools will not improve clinical trial analysis:
  - Kaiser, CCR, 2012 compared PFS to growth modeling by re-sampling data from 5 large Genentech studies published in '01-'05
  - Concluded that PFS is the best endpoint for phase III trial prediction
- We worry that use of case report forms rather than source imaging is a fundamental weakness of such analyses

# Hypothesis

1. Quantitative analysis of tumor response as a continuous variable will improve the ability of randomized phase II trials to accurately predict phase III results
2. Detailed assessment of the entire tumor burden using volumetric CT will improve efficiency and accuracy of phase II trial analysis

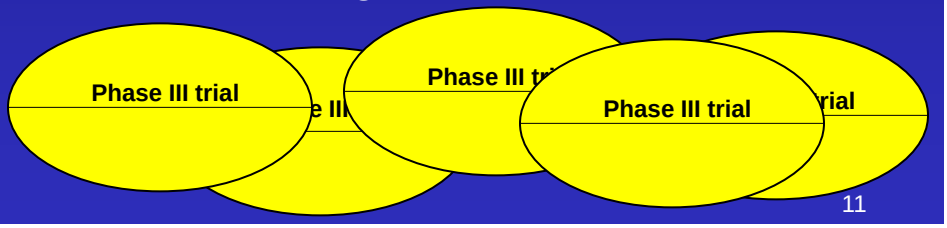


# Aims

1. Assess feasibility of collection and analysis of images from completed phase III trials to:
   (A) simulate of phase II trial results and
   (B) develop quantitative metrics for improved prediction of trial results
2. Assess which quantitative metrics most accurately and reliably predict phase III results across different trials
3. Quantify the added value of volumetric tumor measurement as compared to conventional measurement only

# Approach (1)

1) Collection of existing trial data
   - Focus on large completed landmark trials (>300 patients)
   - Measurable carcinomas: NSCLC, RCC, CRC
   - Collect DICOM imaging from imaging core labs holding scans for pharma
   - IRB has approved receipt of these de-identified images at Columbia



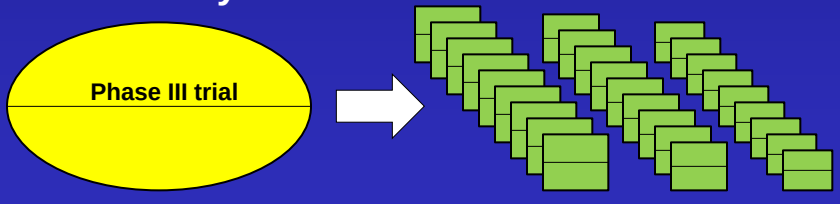



# Approach (2)

2) Generate semi-automated tumor measurements
   - DICOM images will be studied at a lab experienced with volumetry (e.g. Schwartz lab, Columbia University)
   - Computer generated tumor contours will be corrected as needed by an experienced technician
   - Measurements in 1D, 2D, 3D will be calculated for all lesions >= 1cm (up to 10 lesions) at each time point

# Approach (3)

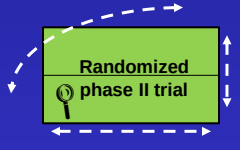
3) Develop simulated randomized phase II trials based upon existing trial data
   - Begin with measurement data from large completed clinical trials
   - Taking subsets of patients, will simulate multiple phase II trials of N patients
   - Simulation will incorporate measurement variability




Moskowitz et al, EJC 2009

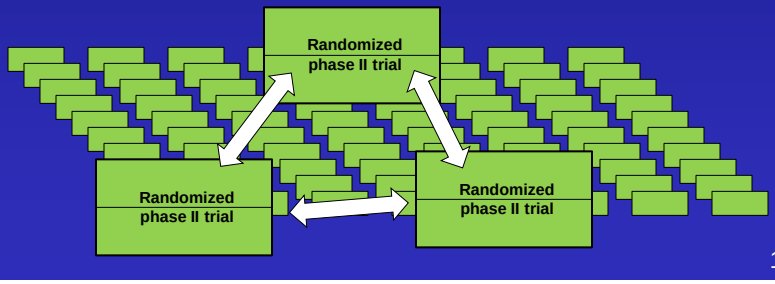
# Approach (4)

4) Comprehensively study each simulated randomized phase II trial with multiple metrics
   - Entire spectrum of measurement data will be studied, not just "best response"
   - Will include statistical modeling of tumor growth & regression



# Approach (5)

5) Compare multiple simulations of the same trial to assess the reliability of each metric
   - The variance of each metric will be calculated across 1000 simulations
   - Change in variance with change in N will be studied for each metric






# Approach (6)

6) Correlate each trial metric with the hazard ratio (HR) from the parent phase III trials in multiple ways:
   - Pearson and rank correlation
   - Linear regression
   - ROC curves on various dichotomized versions of the HR
   - Sensitivity/specificity/predictive values on various dichotomized versions of the metric and HR

# Value statement

1. New metrics could provide greater clarity for go/no-go decisions regarding phase III drug development
2. More efficient phase II trials will allow earlier results and more innovative studies (dose finding, subset analyses)
3. The metrics from the proposed analysis could then be applied to other settings like biomarker development and prognostication



# Key strengths

1. Collaboration between multiple academic and pharma parties, with FDA representation
2. Comprehensive analysis of source image data
3. No bias towards a specific trial analytic
4. FNIH supported effort in pre-competitive space
5. Leverages a growing movement toward data sharing in cancer research