IMPACT:
Imaging Metrics for Precision Analysis of Clinical Trial results

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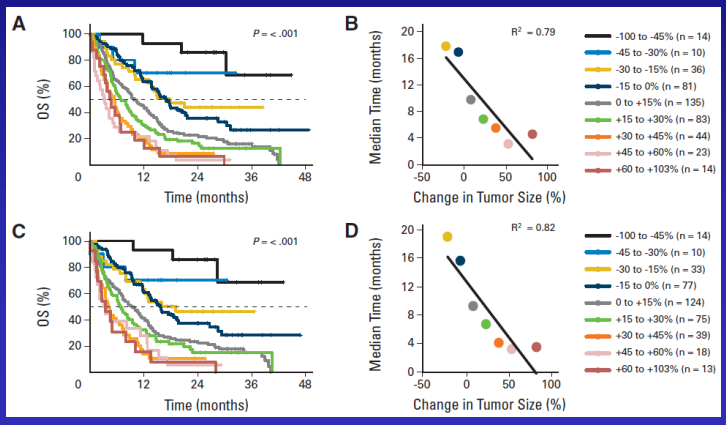
Problem statement

- Oncology drug development is inefficient
  - 62.5% of phase III trials are negative
- Therapeutic progress has inherently made drug development more difficult
  - Greater use of randomized phase II trials
  - However, trials continue to study traditional endpoints (ORR, PFS)
- A comprehensive effort to develop new trial endpoints is needed

Gan et al, JNCI, 2012

Background (1)

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

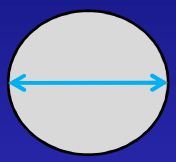


Jain et al, JCO, 2012

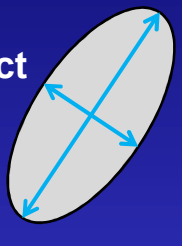
Background (2)

- Advanced imaging of whole tumor volume can better characterize the entire biology of tumor growth and response

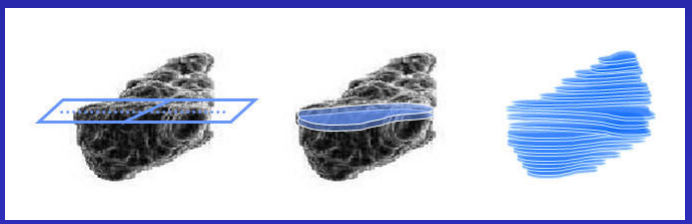
Diameter (RECIST) 1D



Cross-product (WHO) 2D



Volume 3D



Background (3)

- Some have suggested that different analytical tools will not improve clinical trial analysis:
  - Kaiser, CCR, 2012 compared PFS to growth modeling by re-sampling phase II trials
  - Used 5 large Genentech studies published in 2001-2005
  - Concluded that PFS is the best endpoint for phase III trial prediction
- We prefer to study source imaging data to ensure highest quality data input

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 phase III trial results

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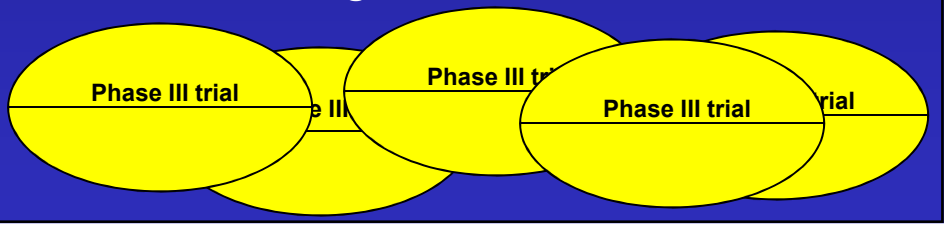
1. Assess feasibility of collection and analysis of images from completed phase III trials to:
   (A) simulate of phase II trial results and
   (B) develop quantitative metrics for improved prediction of phase III trial results
2. Assess which quantitative metrics most accurately and reliably predict 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 trials with greater than ~150 patients per arm
   - Measurable carcinomas: NSCLC, RCC, CRC
   - Collect DICOM imaging from core labs holding scans for pharma
   - IRB has approved receipt of these de-identified images at Columbia

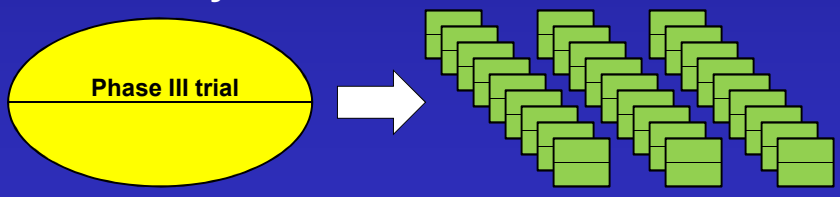


Approach (2)

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)

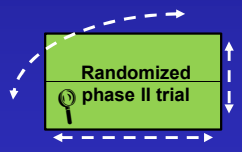
3) Develop simulated randomized phase II trials based upon existing trial data
   - Begin with measurement data from large completed clinical trials
   - Taking subsets of patients, will simulate multiple phase II trials of N patients
   - Simulation will incorporate measurement variability



Moskowitz et al, EJC, 2009

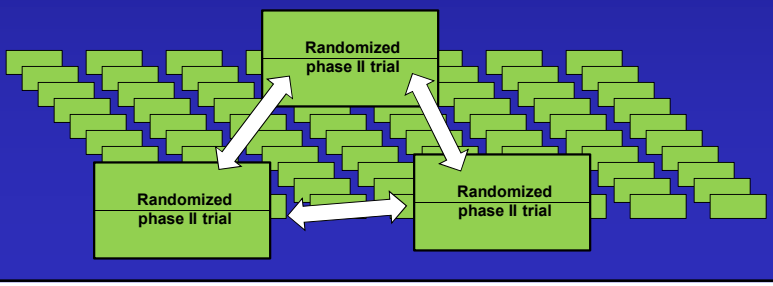
Approach (4)

4) Comprehensively study each simulated randomized phase II trial with multiple metrics
   - Entire spectrum of measurement data will be studied, not just "best response"
   - Eventually 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

Progress

1. Multiple pharmaceutical sponsors have interest in releasing data for analysis:
   - Sanofi, GSK, Genentech, Celgene
2. Positive response to date from ICL's for making imaging data available
3. Seed funding for year 1 expected from FNIH, additional funding is needed