VOL-PACT:
Volumetric CT 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
  – 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, JNQI, 2012
**Problem statement**

- Two randomized trials in 1\textsuperscript{st}-line NSCLC:
  - Carbo/taxol plus placebo
  - Carbo/taxol plus vorinostat

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>RR</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramalingam et al, JCO, 2010</td>
<td>94</td>
<td>Carbo/taxol: Carbo/taxol</td>
<td>12.5%</td>
<td>4.1m</td>
</tr>
<tr>
<td>Belani et al, ESMO, 2009</td>
<td>253</td>
<td>&amp; vorinostat: Carbo/taxol  &amp; 29.3%</td>
<td>5.5m</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; vorinostat:             &amp; 34.0%</td>
<td>6.0m</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; 22.4%</td>
<td>4.3m</td>
<td></td>
</tr>
</tbody>
</table>

**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
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:

**RECIST partial response rate**

- Tumor diameter decrease, %

**Area of response**

- In patients with minor response area under curve, as a fraction of CR in all patients
Furthermore, advanced imaging of the whole tumor volume can characterize the biology of tumor growth and response.

Diameter (RECIST) 1D

Volume 3D

Cross-product (WHO) 2D

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