Who to Treat: a multi-assay signature approach for subgroup identification

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Proprietary
Overview

• Approximately 60% of US drug sales related to anti-cancer drugs are targeted therapies and it is estimated that a similar percentage of drugs in development have a biomarker component

• It is critical that consideration is given to advancing analytics for the discovery and commercialization of biomarkers

• Analytics should provide empirical evidence to support business decisions
Heterogeneous Population

DNA

RNA

Protein

Cool Analytics

Treatment-Specific Subgroups
A Two-Stage Multi-Marker Molecular Signature Approach

- A set of biomarkers define a multi-marker molecular signature (MMMS)
- The MMMS can be used to define a subgroup of patients with improved response profile (Li et al., 2014)

MMM Signature Framework

Stage 1 – Estimation of the multi-marker molecular signature
- Consider a working model that assumes the biomarker profile $M_i = (M_{i1}, \ldots, M_{im})^T$ can serve as a surrogate for the unknown subgroup $S$

$$h_i(t) = h_0(t) \exp(Z_i \beta + Z_i M_i^T \theta + X_i^T \alpha_0 + M_i^T \alpha) \quad (1)$$

- Penalized regression (i.e. elastic net) based on model (1) can be used to obtain a sparse estimator $\hat{\theta}$ and estimate patient specific composite scores $\hat{\gamma}_i = -M_i^T \hat{\theta}$ -> a “pseudo” biomarker or signature

Stage 2 – Subgroup identification
- A cutoff $\tau$ for the signature is identified using the max-chi square approach, and the significance for the test of enhanced treatment effect is provided via a semi-parametric bootstrap approach

- Subgroup can then be defined as all patients above a cutoff $\tau$, i.e. $S_\tau = \{i: \hat{\gamma}_i \geq \tau\}$
Ordered by increasing values for genetic score

Subgroup can then be defined as all patients above the cutoff $\tau$, i.e. $S_\tau = \{i: \hat{y}_i \geq \tau\} =$ biomarker+ subgroup for use in potential stratification in phase 3 or second phase of adaptive design.
Exemplary Case Study

• Treated + SOC vs. SOC
  – 500 total subjects; 1:1 ratio

• Biomarker data -> 23 biomarkers
  – 3 genes -> gene expression
  – 3 copy number variable regions -> copy number variation
  – 4 SNPs -> sequence variation
  – 15 burden scores -> rare mutations across 15 genes

• Can a subgroup, i.e. biomarker (+), of treated patients be identified that enjoy an enhanced treatment response?
• Can this information be used to prospectively inform trial design and/or drive decision making?
• Can the analytical framework incorporate business specific information?
Kaplan-Meier Plot: Evaluation of Treatment Effect

All Patients

Treatment Group
- Treated
- Placebo

<table>
<thead>
<tr>
<th>#Treated (%)</th>
<th>250 (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Placebo (%)</td>
<td>250 (50%)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.8125</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0582</td>
</tr>
</tbody>
</table>

Bootstrap-based treatment-by-subgroup interaction p-value = 0.004
Kaplan-Meier Plot: Treatment effect within biomarker (+) group

Within the Subgroup (size=31.8%)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>#Treated (%)</th>
<th>#Placebo (%)</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>76 (47.8%)</td>
<td>83 (52.2%)</td>
<td>0.4735</td>
<td>6e-04</td>
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</table>

Outside the Subgroup (size=68.2%)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>#Treated (%)</th>
<th>#Placebo (%)</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>174 (51.03%)</td>
<td>167 (48.97%)</td>
<td>1.0471</td>
<td>0.7202</td>
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Bootstrap-based treatment-by-subgroup interaction p-value = 0.004
Kaplan-Meier Plot: Increase biomarker (+) group -> reduce HR

Within the Subgroup (size=52%)

- Treatment Group
  - Treated
  - Placebo

<table>
<thead>
<tr>
<th></th>
<th>Treated (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Treated (%)</td>
<td>134 (51.54%)</td>
<td>126 (48.46%)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.6378</td>
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<td>P-value</td>
<td>0.0045</td>
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Outside the Subgroup (size=48%)

- Treatment Group
  - Treated
  - Placebo

<table>
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<th></th>
<th>Treated (%)</th>
<th>Placebo (%)</th>
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</thead>
<tbody>
<tr>
<td>#Treated (%)</td>
<td>116 (48.33%)</td>
<td>124 (51.67%)</td>
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<tr>
<td>Hazard Ratio</td>
<td>1.0988</td>
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<tr>
<td>P-value</td>
<td>0.5358</td>
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Concluding Thoughts

• Provides a consolidated framework to aggregate information across assay platforms and simultaneously identify a subgroup
  – Extendable across types of outcomes (i.e. binary, continuous)

• Provides empirical evidence to support decision making

• Allows prospective designation of a biomarker+ subgroup to be used in strategic planning and market differentiation

• Has the flexibility to incorporate business specific information toward informing differentiation strategies
Thank you!

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