Statistical Modeling for Efficient and Adaptive Trial Designs Using Composite Endpoints

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Therapeutic development continuum

Therapy does something in a patient population

Drug does something of value better than current standard

Individualized Screening trial of Innovative GBM therapy (INSIGhT)
Potential problems with phase II

• Design issues
  – Endpoints
  – Controls

• Downtime between studies
  – “Master” protocols
  – Add/drop arms

• Inefficient use of multiplex biomarker data
Newly diagnosed unmethylated GBM

Whole exome sequencing and whole genome copy number analysis

RANDOMIZE

4-5 weeks

RT + TMZ → Adjuvant TMZ

RT + TMZ or Drug X₁ → Adjuvant Drug X₁

RT + TMZ or Drug X₂ → Adjuvant Drug X₂

RT + TMZ or Drug X₃ → Adjuvant Drug X₃

TTP ↔ SPP

Re-Bx

OS

Individualized Screening trial of Innovative GBM therapy (INSIGHt)
Adaptive trials

- Use accumulating data to decide how to modify a study in a pre-specified manner
- Types of adaptations
  - Adaptive randomization
  - Dropping arms
  - Surrogate endpoints
- Likelihood principle makes Bayesian designs natural for adaptive trials
Frequentist example

- Consider and experiment testing a probability of success of 0.35
  - SSFSSFSSSF

- Trial design for 10 observations → p=0.026 (one sided)

<table>
<thead>
<tr>
<th>Successes</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.35</td>
<td>0.013</td>
<td>0.072</td>
<td>0.176</td>
<td>0.252</td>
<td>0.238</td>
<td>0.154</td>
<td>0.069</td>
<td>0.021</td>
<td>0.004</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>p = 0.70</td>
<td>0.000</td>
<td>0.000</td>
<td>0.001</td>
<td>0.009</td>
<td>0.037</td>
<td>0.103</td>
<td>0.200</td>
<td>0.267</td>
<td>0.233</td>
<td>0.121</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Figure 1 | Probabilities for a hypothetical clinical trial.

- Alternative trial design of proceeding until 3 failures → p=0.004

\[
\pi_i^k \propto \begin{cases} 
p(\theta_k < 1 \text{ conditionally on available data})^{\gamma^{(i)}} & \text{if } k = 1, 2, 3, \\
\frac{1}{3} \exp \left( \max(n_{i,1}, n_{i,2}, n_{i,3}) - n_{i,0} \right)^{\gamma^{(i)}} & \text{if } k = 0,
\end{cases}
\]
Bayesian adaptive randomization: The movie
Newly diagnosed unmethylated GBM

Whole exome sequencing and whole genome copy number analysis

Randomize

RT + TMZ \rightarrow Adjuvant TMZ

RT + TMZ or Drug X_1 \rightarrow Adjuvant Drug X_1

RT + TMZ or Drug X_2 \rightarrow Adjuvant Drug X_2

RT + TMZ or Drug X_3 \rightarrow Adjuvant Drug X_3

Re-Bx

TTP \leftrightarrow SPP

4-5 weeks

Burroughs Wellcome Fund Innovations in Regulatory Science Award!

Individualized Screening trial of Innovative GBM therapy (INSIGHt)
Longitudinal model

• To adaptively randomize, we have to decide which arms to preferentially enroll patients to
• Which arm is doing best?
Which to choose?

- Death is binary, but *probability* of dying is not
- Factors associated with probability of dying
  - Performance status?
  - Progression?
  - Other response biomarkers?
Longitudinal model with PFS

Trippa et al. *Neuro Oncol* 2015
Therapy does something of value

Therapy does something in a patient population

Therapy does something of value to a patient

Drug does something of value better than current standard

Decision points
THANK YOU