Statistical Challenges in Immuno-Oncology

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Bristol-Myers Squibb
Outline

Cytotoxic vs. cytostatic agents

◆ Mechanism of action
◆ Endpoints

Immunotherapies

◆ Important issues to consider in study design and analysis
◆ Efficacy
  – Overall Survival
MOA: Cytotoxic vs. Cytostatic Agents

Cytotoxic agents
- Dose-dependent rapid cell kill or tumor shrinkage
- Lack of selectivity leads to undesired toxicity or side effects

Cytostatic agents
- Inhibit or suppress cellular growth or division which leads to delayed progression
- Minimal or less severe toxicity, prolonged duration of treatment at lower dose
Endpoints: Cytotoxic vs. Cytostatic

Cytotoxic
- OS: Clinical benefit
- BOR (WHO or RECIST): Direct cell kill action leads to tumor shrinkage

Cytostatic
- OS: Clinical benefit
- PFS/TTP: Stop or delay tumor growth
- BOR: Some may shrink tumor
Immunotherapies

Stimulate the patient’s own immune system to fight cancer

- Immune cell activation; change in tumor burden
- Toxicity or side effects caused by the modulation of immune activity

Endpoints remain similar

- OS: clinical benefit
- BOR: tumor shrinkage
Important Issues in Design and Analysis in Immuno-Oncology

Sample size determination
- Expected number of events
- Timing of analysis

Efficacy analysis
- Interim analysis strategy
- Additional analysis considerations
Typical Survival Curve – Advanced Breast Cancer

![Survival Curve Graph](image)

Patients at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>At Risk</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>120</th>
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</thead>
<tbody>
<tr>
<td>Ixa+Cape</td>
<td>123</td>
<td>102</td>
<td>80</td>
<td>52</td>
<td>38</td>
<td>21</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Cape</td>
<td>111</td>
<td>65</td>
<td>42</td>
<td>24</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>1</td>
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</table>
Ipilimumab (Yervoy) in Metastatic Melanoma

Previously Treated

Previously Untreated


*Maio et al. presented at 37th ESMO, 2012
Interferon alfa-2b (Intron-A) – Adjuvant Melanoma

Kirkwood et al., 2004, Clinical Cancer Research
Pegylated Interferon alfa-2b (Sylatron): Relapse-Free Survival – Adjuvant Melanoma

Eggermont, AMM, et al., 2012, Journal of Clinical Oncology
Study Design and Sample Size Determination

Standard study design

- Assumes exponential distribution

Unconventional study design

- Long-term survival (or “cure rate” or “functional cure”)
- Delayed clinical effect

Does unconventional study design impact sample size / power calculation?
Exponential OS Study Design

* Proportional hazards model (exponential)
Long-Term (LT) Survival

* Proportional hazards cure model
Delayed Clinical Effect

* Non-proportional hazards model
Delayed Clinical Effect with Long-Term Survival

* Non-proportional hazards cure model
Example of a Standard Study Design

Consider the following standard study design

- Exponential distribution
- Median OS: 12 vs. 16 months (HR=0.75)
- Power: 90%
- Two-sided type I error rate: 5%
- Accrual rate: 20 pts/month
- No interim analysis
- Required number of events: 512 events
- Sample size: 680 subjects
- Accrual duration: 34 months
- Study duration: 48 months
### Impact of LT Survival and Delayed Clinical Effect on Study Duration and Power

<table>
<thead>
<tr>
<th></th>
<th>Standard (exponential)</th>
<th>LT Survival</th>
<th>Delay</th>
<th>LT Survival / Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT survival</td>
<td>--</td>
<td>0.10/0.18</td>
<td>--</td>
<td>0.10/0.17</td>
</tr>
<tr>
<td>Delayed effect</td>
<td>--</td>
<td>--</td>
<td>3 m</td>
<td>3 m</td>
</tr>
<tr>
<td>Sample size</td>
<td>680</td>
<td>680</td>
<td>680</td>
<td>680</td>
</tr>
<tr>
<td># events</td>
<td>512</td>
<td>512</td>
<td>512</td>
<td>512</td>
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<tr>
<td>Hazard Ratio</td>
<td>0.75</td>
<td>0.75</td>
<td>1/0.75</td>
<td>1/0.75</td>
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<tr>
<td>Power</td>
<td>0.90</td>
<td>0.90</td>
<td>0.70</td>
<td>0.70</td>
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<tr>
<td>Study duration</td>
<td>48</td>
<td>55</td>
<td>47</td>
<td>54</td>
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</table>

* Based on 10000 simulations
Impact of LT Survival and Delayed Clinical Effect on Study Duration and Power

Long-term survival

- Results in prolonged study duration
- Higher LT survival results in longer study duration

Delayed clinical effect

- Reduces statistical power
- Longer delay results in more power loss

Expected number of events

- Can the number of events be achieved?

Follow-up duration

- Is the study designed to allow sufficient follow-up for all patients?
Interim Analysis Strategy

Necessity of interim analysis
- Interim analysis vs. final analysis only

Timing of interim analyses
- Early vs. late interim analysis

Type of interim analysis
- Superiority vs. futility
Probabilities for Stopping at Interim Analysis

<table>
<thead>
<tr>
<th>Interim sample size</th>
<th>LT Survival</th>
<th>Delay</th>
<th>LT Survival / Delay</th>
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</thead>
<tbody>
<tr>
<td>Interim sample size</td>
<td>520</td>
<td>540</td>
<td>480</td>
</tr>
<tr>
<td># events</td>
<td>256</td>
<td>256</td>
<td>256</td>
</tr>
<tr>
<td>PET&lt;sub&gt;a&lt;/sub&gt; (superiority)</td>
<td>0.25</td>
<td>0.25</td>
<td><strong>0.06</strong></td>
</tr>
<tr>
<td>PET&lt;sub&gt;a&lt;/sub&gt; (futility)</td>
<td>0.01</td>
<td>0.01</td>
<td><strong>0.08</strong></td>
</tr>
</tbody>
</table>

PET<sub>a</sub> = Probability of Early Termination when agent is active
Using O’Brien-Fleming boundaries

* Based on 10000 simulations
Interim Analysis Strategy - Conclusion

Delayed clinical effect and LT survival

- Careful consideration warranted:
  - Necessity of interim analysis
  - Timing of interim analysis
  - Type of interim analysis
Additional Analysis Considerations

Prediction of timing of analyses

- Does the long-term survival alter projected study duration?
Additional Analysis Considerations
Summary Measures

<table>
<thead>
<tr>
<th>Group</th>
<th>DEATHS / RANDOMIZED</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP I+ DT IC</td>
<td>198 / 250</td>
<td>11.17 (9.40 - 13.60)</td>
</tr>
<tr>
<td>DT IC</td>
<td>226 / 252</td>
<td>9.07 (7.75 - 10.51)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects At Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP I+ DT IC</td>
<td>250</td>
</tr>
<tr>
<td>DT IC</td>
<td>252</td>
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</table>

CA 184-024 First Line Melanoma Study

DMC analysis based on data base

Yearly OS rates
Statistical Analysis Considerations

Primary analysis
- Remains log-rank test and Cox model?

Long-term survival
- Regulatory: Median vs. OS rates
- Market access: Mean
- Cure rate models

Delayed clinical effect
- Fleming-Harrington weighted log-rank test
Summary

- Understand disease characteristics and MOA of therapy
  - Delayed clinical effect
  - Long-term survival
- Implications on study design and analyses
Reference