Challenges of Modelling Immuno-Oncology

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Survival With IOs vs. Targeted Therapies

Source: Ribas et al. 2012
Key Challenges of Modelling IOs

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences in biomarkers</td>
<td>Increases heterogeneity between trial / label populations</td>
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<tr>
<td>Long-term treatment benefits may be different</td>
<td>Questions around extrapolation of survival curves and long-term QoL</td>
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<tr>
<td>No gold standard for treatment duration</td>
<td>Major driver of cost-effectiveness and can influence model structure</td>
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<tr>
<td>Treatment sequences more complex</td>
<td>Increases heterogeneity between trials questioning feasibility of NMAs, influences model structure</td>
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<tr>
<td>Treatment switching pre and post progression</td>
<td>Increases the uncertainty of long-term extrapolation</td>
</tr>
<tr>
<td>Changes in surrogate outcome</td>
<td>Determines model structure</td>
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</tbody>
</table>

Multiple Biomarkers Depending on Tumor Type

- Biomarkers (e.g. EGFR, ALK, HER2, PD-L1) play a pivotal role in treatment selection and vary by tumor type
- Multiple PD-L1 diagnostic assays exist with different attributes
- Rapidly emerging new biomarkers e.g. tumor mutational burden
Lack of Data on the Long-Term Benefit of IOs

- **Survival**
  - Delayed effect
  - Potential for plateau in survival curves
  - Long-term survivors (“cure”)
  - Potential sustained benefit beyond treatment discontinuation

- **Quality of life impact**
  - Uncertainty due to lack of historical data
  - Trials usually collect data until end of treatment or disease progression

Source: Schadendorf et al. 2015

Treatment Duration

- Patients may get treatment beyond progression (purple arrows)
- Patients may experience sustained benefit beyond treatment discontinuation (green arrows)
- Stopping rules may be considered for patients with long-term benefit

Source: Muro 2016, Pembrolizumab

Source: Boku 2017, Nivolumab
Hyperprogression

- A novel aggressive pattern of hyperprogression in a fraction of patients treated with anti–PD-1/PD-L1\(^1\)
- Incidence varies with age, therapeutic area and biomarker status (e.g. EGFR, MDM2)\(^2\)
- There is no standardized definition available, but usually based on tumor growth rate\(^1,3\)

Medical records from all patients (N = 218) prospectively treated in Gustave Roussy by anti–PD-1/PD-L1 within phase I clinical trials
Source: Champiat at. 2017


Pseudoprogression

- Due to the immunotherapy mechanism of action, pseudoprogression can be observed
- Defined as tumor growth when the tumor inflates due to its own necrosis
- RECIST assessment of PFS can confuse pseudoprogression with true tumor progression
- To account for pseudoprogression, treatment beyond disease progression was authorized

Source: West 2015
Durable Response Prolongs Survival

Example in advanced melanoma

Example in advanced renal cell carcinoma

PFS as Surrogate Outcome for OS?

Takeaway:
- No significant correlation between median OS, PFS, and gains in medians
- 10 RCTs showed 18% greater improvement in OS than PFS
- PFS cannot adequately capture the benefit of PD-1 inhibitors in patients with solid tumors
PFS as Surrogate Outcome for OS?

Example in recurrent squamous-cell carcinoma of the head and neck

Source: Ferris et al. 2016

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Early Response to IO Agents May Be Predictive of Improved OS

Responses to immune-targeted agents follow unconventional pattern and appear to be early indications of long-term survival outcomes

Source: D'Angelo et al, 2018; Anagnostous et al, 2017
Increasing Level of Treatment Switch in IO Trials

- Treatment switch pre and post progression increases the uncertainty of extrapolating long-term overall survival.

- Implies that sequential modelling by explicitly tracking treatment sequences may be necessary to reconcile treatment pattern in trials and to reflect clinical practice.

<table>
<thead>
<tr>
<th>Investigational Drug</th>
<th>Clinical Study</th>
<th>Comparator Arm</th>
<th>Investigational Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>CheckMate 017</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>CheckMate 057</td>
<td>2%</td>
<td>-</td>
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<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE-010</td>
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<td>1%</td>
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<tr>
<td>Atezolizumab</td>
<td>POPLAR</td>
<td>5%</td>
<td>-</td>
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<tr>
<td>Atezolizumab</td>
<td>OAK</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>JAVELIN 200</td>
<td>26%</td>
<td>4%</td>
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