Design issues in the immunotherapy combinatorial trials

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How to rationally combine therapies and chose the best endpoints?

• Design the clinical development plans of future agents through:
  – Deeper understanding of the mechanism of action in early clinical testing
  – Pivotal trials that focus on the strengths of the new agents and the potential benefits demonstrable in clinical trials
Different effects of immunotherapy and targeted therapy for melanoma in randomized clinical trials.
### Relative merits of different endpoints in melanoma clinical trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Overall Survival</td>
<td>Gold standard</td>
<td>Quality of life not necessarily considered. Will be difficult to achieve when control groups have high survival. High patients numbers then needed. Symptom relief not taken into account. Cross over designs make overall survival outcomes difficult to achieve. Long term outcomes confounded by the clinical availability of other agents with similar mechanism of action.</td>
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<tr>
<td>Progression Free Survival</td>
<td>Outcome more rapid and allows rapid selection of agents. If very prolonged may be an endpoint of merit in its own right.</td>
<td>Not necessarily related to overall survival. Quality of life not necessarily considered.</td>
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<tr>
<td>Response Rate</td>
<td>Valuable in single arm studies if “unprecedentedly” high</td>
<td>Not necessarily a surrogate endpoint for overall survival benefit. Difficult to achieve when developing new agents with similar mechanism of action with already high response rates.</td>
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<tr>
<td>Quality of Life</td>
<td>May be a valid endpoint irrespective of effects of other endpoints.</td>
<td>No information about benefits based on time-to-event endpoints.</td>
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Examples of adapted clinical development plans (1)

- Combination of two non-antigen specific immunotherapies:
  - Anti-CTLA4 + IL-2, IL-21, IFN

- In early clinical testing, focus on detecting an increased frequency of durable tumor responses
- Focus on OS instead of PFS for pivotal clinical trials
- Long term follow up of patients to detect changes at the tail
PFS vs OS in the pivotal ipilimumab clinical trials

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfonso J. van den Eertwegh, M.D., Ph.D., Jose Lucia, M.D., Paul Longian, M.D., Julia M. Vaubel, M.D., Gerald F. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quilt, M.D., Joseph I. Clark, M.D., Jodd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tann, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.D., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

PFS

OS

HR = 0.66

> 3 years

HR = 0.72

> 3 years
Examples of adapted clinical development plans (2)

- Combination of immunotherapy and oncogene-targeted therapy:
  - Anti-CTLA4 + targeted oncogene inhibitors

- In early clinical testing, focus on detecting if the immunotherapy results in increased duration of the targeted therapy-mediated tumor responses
- Focus on PFS for pivotal clinical trials
- No need for very long follow up of patients to detect changes at the tail
Examples of adapted clinical development plans (3)

- Combination with anti-PD-1 antibodies:
  - Anti-PD-1 + anti-CTLA4
  - Anti-PD-1 + oncogene inhibitors

- Focus on PFS if compared to anti-CTLA4
- Focus on longer term OS if compared to targeted therapies