Dose Selection Approaches for Combination Oncology/Immuno-Oncology Agents

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Proposed mechanisms of synergy
VEGF + PD-1 inhibition

Immunologic

- Elevated VEGF may inhibit dendritic cell maturation causing immunosuppression
- VEGF inhibition may reduce numbers of Tregs and tumor invading myeloid-derived suppressor cells
- VEGF therapy primes for better effect with anti PD-/PD-L1.

Empiric

- Combination dose and schedule may be based on PD modulation and MoA
- Combination dose and schedule typically anchored on approved doses

Combination dose and schedule may be based on PD modulation and MoA

Gunturi A, McDermott DF: Current treatment options in oncology 2014
Antibody combinations

• For most of biologic therapies in oncology, maximal tolerated doses become irrelevant as therapeutic effects are already achieved at lower doses

• PK interaction is highly unlikely when two monoclonal antibodies are combined

• Immunogenicity rates may be different for combination compared to monotherapy
Challenges in Dose Selection of Combination Oncology agents

• Dose-finding is primarily based on toxicity observed clinically
  • Pre-clinical toxicology studies are typically not conducted with combination agents

• Little may be known between the synergy of combination agents, as most of the information is primarily driven by Science and MoA
  • Prior information on each agent used alone in previous trials may be available
  • Activity in combination may need to benchmarked against historical data, as responses in combination may originate from combination partner

• Extremely difficult to find the right dose combination in small subset of patients from Phase I
  • Short-term endpoints (objective response rate, dose-limiting toxicities, etc.) used in Phase I may not be reflective of long-term outcome (OS)
  • DLT criteria for dose selection based on early data (1-2 cycles) and may not account for delayed toxicity

• Challenges in Dose selection of combination oncology agents
  • Sample Sizes typically are very small in early trials
  • Patient Heterogeneity may be substantial
  • Overlapping toxicities for combination agents may not be apparent in short DLT period
  • Limited pharmacodynamics data to assess biological activity

Stimulatory and Inhibitory Molecules During Immune Tumor Surveillance

Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

• PD-1 and CTLA-4 are non-redundant immune checkpoints in T-cell differentiation and function
• Anti-tumor synergy demonstrated in several synergy models
• Both agents are active in metastatic melanoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose, mg/kg</th>
<th>ORR, %</th>
<th>CR, n</th>
<th>Median OS, months</th>
<th>2- / 3-yr OS rate, %</th>
<th>Grade 3/4 treatment-related AE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab¹,²</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>10.1</td>
<td>24 / 20</td>
<td>23%</td>
</tr>
<tr>
<td>Nivolumab³,⁴</td>
<td>0.1-10</td>
<td>31</td>
<td>1</td>
<td>16.8</td>
<td>43 / —</td>
<td>14%</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab⁵</td>
<td>Nivo 0.3 + Ipi 1 Nivo 1 + Ipi 3 Nivo 3 + Ipi 1 Nivo 3 + Ipi 3</td>
<td>40</td>
<td>5</td>
<td>Not reached</td>
<td>82 (1 year)</td>
<td>53%</td>
</tr>
</tbody>
</table>


Presented By Mario Sznol at 2014 ASCO Annual Meeting
Exposure-Response analysis with Ipilimumab and Nivolumab in metastatic melanoma

• Higher doses of ipilimumab monotherapy produce greater Cminss that may be associated with increased tumor responses, longer survival, and higher rates of irAEs
  • Model-based estimates indicate that the probabilities of a CR or PR at median Cminss for the 0.3, 3, and 10 mg/kg groups were 0.6%, 4.9%, and 11.6%, respectively.
  • Overall survival at the median Cminss for ipilimumab at 0.3 mg/kg was estimated to be 0.85- and 0.58-fold lower relative to that at the median Cminss for 3 and 10 mg/kg, respectively.
  • Model-based estimates indicate that the probabilities of a grade 3 or more irAE at the median Cminss for the 0.3, 3, and 10 mg/kg doses were 3%, 13%, and 24%, respectively.

• Exposure-response of Nivolumab is relatively flat for melanoma at doses ≥1 mg/kg
CA209004 Phase I Study: Dose Cohorts
Nivolumab + Ipilimumab in Metastatic Melanoma

<table>
<thead>
<tr>
<th>Regimen Cohort No.</th>
<th>N</th>
<th>Nivolumab (mg/kg)</th>
<th>Ipilimumab (mg)</th>
<th>Treatment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>0.3</td>
<td>3</td>
<td>Nivo Q3W x 8 + IPI Q3W x 4</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>1</td>
<td>3</td>
<td>Nivo + IPI Q12W x 8</td>
</tr>
<tr>
<td>2a</td>
<td>16</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8*</td>
<td>41</td>
<td>1</td>
<td>3</td>
<td>Nivo Q3W x 8 + IPI Q3W x 4</td>
</tr>
<tr>
<td>Sequenced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>1</td>
<td>Prior</td>
<td>Nivo Q2W (Max of 48 doses)</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>3</td>
<td>Prior</td>
<td></td>
</tr>
</tbody>
</table>

*Insufficient follow-up at this data collection to report survival endpoints

Presented By Mario Sznol at 2014 ASCO Annual Meeting
CA209004 Phase I Study: Activity Summary
Nivolumab + Ipilimumab in Metastatic Melanoma

<table>
<thead>
<tr>
<th>Nivolumab (mg/kg) + IPI (mg/kg)</th>
<th>N</th>
<th>ORR(^a), %</th>
<th>CR, %</th>
<th>Aggregate Clinical Activity Rate</th>
<th>≥80% tumor burden reduction at 36 wks(^b), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent Cohorts 1-3</td>
<td>53</td>
<td>42</td>
<td>17</td>
<td>70</td>
<td>42</td>
</tr>
<tr>
<td>0.3 + 3</td>
<td>14</td>
<td>21</td>
<td>14</td>
<td>57</td>
<td>36</td>
</tr>
<tr>
<td>1 + 3</td>
<td>17</td>
<td>53</td>
<td>18</td>
<td>65</td>
<td>53</td>
</tr>
<tr>
<td>3 + 1</td>
<td>16</td>
<td>44</td>
<td>25</td>
<td>81</td>
<td>31</td>
</tr>
<tr>
<td>3 + 3</td>
<td>6</td>
<td>50</td>
<td>0</td>
<td>83</td>
<td>50</td>
</tr>
<tr>
<td>1 + 3 (\text{Cohort 8})^c</td>
<td>40</td>
<td>43</td>
<td>10(^d)</td>
<td>53</td>
<td>28</td>
</tr>
<tr>
<td>Sequenced</td>
<td>33</td>
<td>31</td>
<td>3</td>
<td>44</td>
<td>31</td>
</tr>
</tbody>
</table>

\(^a\) per RECIST, \([\text{CR+PR}] / N \times 100\); \(^b\) Best overall response; \(^c\) Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. \(^d\) 2 confirmed and 2 unconfirmed responses

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## CA209004 Phase I Study: Safety Overview
Nivolumab + Ipilimumab in Metastatic Melanoma

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Concurrent Cohorts 1-3 n=53</th>
<th>Cohort 8 n = 41</th>
<th>All Concurrent n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Gr</td>
<td>Gr 3/4</td>
<td>Any Gr</td>
</tr>
<tr>
<td>All Related AEs</td>
<td>96</td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>Select AEs</td>
<td>Gastrointestinal</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Endocrine</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>Uveitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lipase increased</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Amylase increased</td>
<td>21</td>
<td>6</td>
</tr>
</tbody>
</table>

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

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Summary: Dose Selection of Nivolumab + Ipilimumab in Metastatic Melanoma

• Based on cumulative evidence of safety/ activity, Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by Nivolumab 3 mg/kg every 2 week, was picked as a regimen for pivotal trials in metastatic melanoma

• Does the same Ipilimumab/ Nivolumab combination dose/ regimen work in other tumor types?
Challenges in Dose Selection of Combination Oncology agents

- The set of possible dose pairs is much larger than the usual interval of doses in the single-agent case
- Dose pairs are typically chosen to maximize Cancer-Killing Potential and/or Information
  - Dose of the approved drug is typically anchored, and dose of experimental drug titrated
  - Selection of the dosing schedule (weekly vs. every 3 week) also driven by schedule of the combination drug (for example, patient visits, approved cytotoxic regimen, etc.)
  - Limited precedence to select more than one combination dose pair for pivotal trials
- Several dose related questions of interest in therapeutic development of combination oncology agents
  - Dose-efficacy association
  - Dose-safety association
  - Schedule-efficacy association
  - Interactions between therapies (i.e. combinations of treatments)
- Safety/ Efficacy is typically tumor-specific and may be different for different dose combinations
Flowchart of the publications found from the Medline Pubmed search on Combination doses

847 papers found from Medline search

- 162 papers with at least 2 agents dose-escalated
- 381 papers with only one agent dose-escalated while others are fixed
- 304 other (PK/PD, single-agent, not dose-finding, comparisons,...)
Orderings between Combinations

A: \( D_{1.3} < D_{2.3} < D_{3.3} < D_{4.3} < D_{5.3} \)

B: \( D_{1.3} \rightarrow D_{2.3} \rightarrow D_{3.3} \rightarrow D_{4.3} \rightarrow D_{5.3} \)

C: \( D_{1.3} \rightarrow D_{2.3} \rightarrow D_{3.3} \rightarrow D_{4.3} \rightarrow D_{5.3} \)

Riviere et al. Annals of Oncology. 2015
Dose-Toxicity relationship for Combinational agents
Implementation of Futility Designs in Early clinical development of Oncology Combination agents

• For example, Fleming/Simon-2 Stage can be used in early clinical development of Oncology combination agents, and efficacy data can be benchmarked against historical data
Trial Designs for Optimal Dose Selection of Combination Oncology agents

• Starting doses of the drugs, as well as the dose levels and the dose-escalation steps, need to be appropriately justified with aim to
  • Ensure patient safety
  • Treat as few patients as possible at presumably infra-therapeutic doses
  • Identify the optimal drug combination for further evaluation

• Innovative Phase I trial designs are needed; dose-finding needs to be sequential and adaptive for ethical reasons
  • Balance of speed and rigor for optimal dose-finding for combinations
  • Dose-finding using alternative approaches (e.g. model-based approaches)

• CRM methods introduced with the potential to improve the precision of such studies to determine a dose with a certain toxicity threshold

• More flexible two-parameter Bayesian logistic models developed to better characterize the dose-toxicity relationship

• Futility designs can be used for Go/No Go decisions in early clinical development of combination oncology agents