Innovations in Immune Oncology Combination Clinical Trial Designs

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Disclosures

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• Scientific Advisor/Steering Committee member to Roche/Genentech, Merck, Abbvie, Janssen, Genmab, Clovis, AstraZeneca, Gamamab, Immunogen, Tesaro
Clinical Studies – Traditional Options

Like most veterinary students, Doreen breezes through Chapter 9.
Phase I: "3+3" Mantra...

**DRUG A dose and MTD set at 25%**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Dose</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
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<tr>
<td>BLR</td>
<td>True-pro Cox</td>
<td>.01</td>
<td>.09</td>
<td>26</td>
<td>47</td>
<td>.64</td>
<td>.76</td>
<td>-</td>
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<tr>
<td>% MTD</td>
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<tr>
<td>CRM</td>
<td>% MTD</td>
<td>0</td>
<td>16</td>
<td>79</td>
<td>5</td>
<td>0</td>
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<tr>
<td>3+3</td>
<td>% MTD</td>
<td>8</td>
<td>43</td>
<td>41</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>4.8</td>
<td></td>
<td></td>
<td>4.9</td>
<td>2.5</td>
<td>0.4</td>
<td>0</td>
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</table>

**Etc.**

BLR: Bayesian logistic regression
CRM: Continuous reassessment model

Eisenhauer et al.
Thall, Int J Gynecol Cancer
Two Agents: More Complicated (Arbitrary?)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Olaparib Dose</th>
<th>AZD2014 Dose</th>
<th>Dose Level</th>
<th>Olaparib Dose</th>
<th>AZD2014 Dose</th>
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<tbody>
<tr>
<td>1</td>
<td>100mg BID</td>
<td>25mg BID continuous</td>
<td>-1</td>
<td>100 mg BID</td>
<td>75 mg BID 2 days on/5 days off</td>
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<td>2</td>
<td>200mg BID</td>
<td>25mg BID continuous</td>
<td>1</td>
<td>100 mg BID</td>
<td>125mg BID 2 days on/5 days off</td>
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<tr>
<td>3</td>
<td>200mg BID</td>
<td>50mg BID continuous</td>
<td>1b</td>
<td>100 mg BID</td>
<td>100mg BID 2 days on/5 days off</td>
</tr>
<tr>
<td>4</td>
<td>300mg BID</td>
<td>25mg BID continuous</td>
<td>1c</td>
<td>200 mg BID</td>
<td>100mg BID 2 days on/5 days off</td>
</tr>
<tr>
<td>5</td>
<td>300mg BID</td>
<td>50mg BID continuous</td>
<td>1d</td>
<td>300 mg BID</td>
<td>100mg BID 2 days on/5 days off</td>
</tr>
</tbody>
</table>

“Octopus” Trial; PI: Shannon Westin
NRG-GY009: PLD With Atezolizumab and/or Bevacizumab in

Randomized Phase 2/3 Study (NCT02839707)

Enrollment Criteria

- Recurrent, platinum-resistant OC
- High-grade OC
- ≤2 prior regimens
- Measurable disease
- ECOG PS 0 or 1
- Mandatory submission of tumor tissue samples

Primary Endpoint: DLT, OS, PFS

Secondary Endpoints: ORR, safety

- ARM A: Patients receive PLD IV on day 1 and atezolizumab IV on days 1 and 8
- ARM B: Patients receive PLD IV on day 1, bevacizumab IV on days 1 and 8, and atezolizumab IV on days 1 and 8
- ARM C: Patients receive PLD IV on day 1 and bevacizumab IV on days 1 and 8
- In all arms, courses repeat every 28 days in the absence of disease progression or unacceptable toxicity

DLT, dose-limiting toxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.
Non-Monotonic Dose-Efficacy Relationship

Courtesy of Y. Yuan
Challenges of Clinical Trial Design: Immunotherapy

- Dose – Response relationship may break down
  - More = or ≠ better

- Efficacy endpoints may not be immediate or may be realized in subsequent lines of therapy
  - Can objective response be used?

- Combination IO trials have difficult attribution/mitigation strategies
  - “Who dunnit?”
  - Dose reductions?

- Unclear if duration of exposure is important for efficacy
## AE Management: Immunotherapy

<table>
<thead>
<tr>
<th>Treatment-related Adverse Event</th>
<th>Grade of Event</th>
<th>Management/Next Dose for Nivolumab monotherapy (for patients who required discontinuation of ipilimumab)</th>
<th>Management/Next Dose for Combination Nivolumab plus Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>≤ Grade 1</td>
<td>No change.</td>
<td>No change.</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>Hold nivolumab until &lt; Grade 2.</td>
<td>Hold both drugs until &lt; Grade 2.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Hold nivolumab until &lt; Grade 2.</td>
<td>Hold both drugs until &lt; Grade 2.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Off protocol therapy.</td>
<td>If event continues &gt;7 days, permanently discontinue ipilimumab</td>
</tr>
</tbody>
</table>

DART trial
Phase I-II Design Paradigm: Immunotherapy

• It is imperative to consider efficacy and toxicity simultaneously, aka “phase I-II trial”.

• The primary objective of the phase I-II trial for immunotherapy is to find the optimal biological dose (OBD), rather than the maximum tolerated dose (MTD)
Efficacy-Driven Trial Design: Immunotherapy

Adaptation – How To Measure

- Allows assessment of response to treatment **while the study is running**
- Can incorporate new findings from outside the trial
  - Redefine populations for study inclusion or exclusion
  - Incorporate new biomarker information
- Investigators can alter aspects of the study **while in process**
  - Add additional cohorts
  - Modify treatment schedule or dose
  - Redefine treatment for specific population needs
- This allows the trial to stay current with the latest updates
Advanced/Recurrent EMCA

- MMR Deficient
  - Anti-PDL1
    - 0-1 responses
      - Progression: Anti-PDL1 + Anti-CTLA4
    - Response / SD: Continue

- MMR-Proficient
  - Anti-PDL1
    - 0-1 responses
      - Progression: Anti-PDL1 + Anti-CTLA4
    - Response / SD: Continue

Analysis of response rate based on molecular subtype and total mutation load

1 If zero or one responses in the first 9-10 patients, subsequent subjects will be treated with combination Anti-PDL1 + Anti-CTLA4.
Combination Biomarker + Phase II

- **Pre-treatment tumor mRNA expression and immuno-profiling**
  - TREMELIMUMAB Q 4wks X 2 n=15
  - OLAPARIB QD X 8 wks n=15

- **Post-treatment tumor mRNA expression and immuno-profiling**
  - TREMELIMUMAB + OLAPARIB n=30

- **On-treatment tumor expression and immuno-profiling**

**Recurrent platinum resistant ovarian cancer**
Multi-candidate Iterative Design with Adaptive Selection (MIDAS)

Initial Candidates
- A (e.g. anti-OX40)
- B (e.g. anti-PDL1)
- A+B
- Control (physician’s choice)

Drop “loser(s)”
Select “graduate(s)”

Replacement of “loser(s)” and “graduates” with new candidate(s) or combinations (e.g. olaparib, cediranib)

Bx & Immunoprofiling (Pre-treatment)
Bx & Immunoprofiling (on treatment)

## Bayesian Platform Design: MIDAS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hazard Ratio</th>
<th>True toxicity rate</th>
<th>Entry Time (Months)</th>
<th>Scenario 1</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dropped due to toxicity</td>
</tr>
<tr>
<td>Control</td>
<td>1.00</td>
<td>0.15</td>
<td>0.0</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>1</td>
<td>0.83</td>
<td>0.03</td>
<td>0.0</td>
<td>0.0 (0.0)</td>
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<tr>
<td>2</td>
<td>0.56</td>
<td>0.04</td>
<td>0.0</td>
<td>0.0 (0.4)</td>
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<tr>
<td>3</td>
<td>0.42</td>
<td>0.03</td>
<td>0.0</td>
<td>0.0 (0.2)</td>
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<tr>
<td>4</td>
<td>1.25</td>
<td>0.05</td>
<td>9.3</td>
<td>0.4 (0.2)</td>
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<tr>
<td>5</td>
<td>1.67</td>
<td>0.04</td>
<td>12.7</td>
<td>0.1 (0.4)</td>
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<tr>
<td>6</td>
<td>2.50</td>
<td>0.04</td>
<td>16.3</td>
<td>0.0 (0.2)</td>
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<tr>
<td>7</td>
<td>2.50</td>
<td>0.03</td>
<td>19.5</td>
<td>0.2 (0.0)</td>
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</table>

Adaptive Basket Trial Design: BLAST

Insensitive cancer type

KEYNOTE (KN-001): Pembrolizumab Trial

- Phase I in “advanced solid tumors” (n=40)
  - Showed high efficacy in melanoma
- Added expansion cohorts:
  - Non–small cell lung cancer
  - Testing lower doses in NSCLC and melanoma
  - To provide training and validation sets for the PD-L1 biomarker expression test
  - More disease cohorts were added as more information was collected
- Incorporated aspects of:
  - Basket trial design: different diseases
  - Umbrella trial design: biomarker variability, variable prior therapies within disease cohorts
  - Adaptive trial design: additional cohorts, different dosing
- Ultimately enrolled 1260 patients
- FDA approval (melanoma) 3.5 years after study initiation without a randomized, controlled trial
  - Other data from the study has led to approval in NSCLC, head and neck cancer, Hodgkin lymphoma, urothelial carcinoma, MSI-high cancer, and gastric cancer
STAMPEDE Trial: Advanced Prostate

• Outcomes:
  • Pilot: toxicity
  • Stage I: PFS (HR ≤ 0.75)
  • Stage II: PFS (HR ≤ 0.75)
  • Stage III: PFS (HR ≤ 0.75)
  • Stage IV: OS (HR ≤ 0.75)

• Overall analysis: pairwise with multiple comparisons correction (p < 0.017)
Take Home Messages

• Clinical trial designs based on dose to response relationships provide poor guidance for immunotherapy

• Multiagent biological trials are tricky to conduct and best leverage existing and emerging information to optimize OBD identification

• Adaptive designs are most efficient for constructing the dose-toxicity trade-offs

• Seamless designs can develop information for regulatory intent