IMMUNO-ONCOLOGY
CHALLENGES IN DEVELOPING
NOVEL-NOVEL COMBINATIONS

Characterizing The
Contribution of Monotherapy Components

Ramy Ibrahim, MD
Pralay Mukhopadhay, PhD
Hesham A. Abdullah, MD, MSc, RAC

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CURRENT REGULATORY VIEW ON NOVEL-NOVEL COMBINATIONS

• Contribution of Components (CoC): Requirement for demonstrating the contribution of each agent to the activity of the combination to the extent possible and needed
  – Depends on the level of enhanced activity expected with the combination vs individual monotherapy components
COMBINATIONS CAN CONVERT NON-IMMUNOGENIC TUMORS TO IMMUNOGENIC

Padmanee Sharma and James P. Allison SCIENCE 2015 • VOL 348
PRECLINICAL DATA INDICATES POTENTIAL SYNERGY OF PD-L1/CTLA-4 COMBINATION

Tumor Volume vs Time After Tumor Cell Implantation

- Anti-PD-L1 10 mg/kg BIW
- Anti-CTLA-4 10 mg/kg BIW
- Anti-PD-L1 + Anti-CTLA-4
POTENTIAL LONG-TERM SURVIVAL WITH IO MONOTHERAPY OR COMBINATION

Adapted from Urba W, et al. Discussion session at ASCO 2013.
DOSE SELECTION DESIGN FOR DURVALUMAB + TREMELIMUMAB IN ADVANCED NSCLC

Study 006 Design: Zone-based dose escalation and Phase Ib expansion phase

Population: Stage III-IV NSCLC patients who have failed systemic therapy (no restrictions on number of prior therapies)

1st endpoint: Safety (28-day DLT period)
2nd endpoint: Efficacy (RECIST response Q8 wks)
Exploratory endpoints: Peripheral pharmacodynamics, tumour PD-L1 status

*DLT, dose-limiting toxicity
COMBINATION CAN POTENTIALLY ADDRESS SUBPOPULATIONS IN AREAS OF UNMET MEDICAL NEED

Response rates at doses selected for pivotal studies

Monotherapy = M10 mg/kg Q2W in NSCLC (all lines) in 1108 (data cut-off = 27 Feb 2015); Combination therapy = M10-20/T1 in 006 (data cut-off = 15 Apr 2015); ORR = Overall response rate

TREME DOSE SELECTION KEY TO OPTIMIZING B/R OF COMBINATION

- Related Grade 3/4 AEs and discontinuations due to related AEs were lowest in the 1 mg/kg Q4W tremelimumab cohorts
- AEs did not appear related to dose or schedule of durvalumab

<table>
<thead>
<tr>
<th></th>
<th>M10-20 Q4/2W</th>
<th>M10-20 Q4/2W</th>
<th>M15 Q4W</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>T1 mg/kg</td>
<td>T3 mg/kg</td>
<td>T10 mg/kg</td>
</tr>
<tr>
<td>n=56</td>
<td>n=34</td>
<td>n=9</td>
<td></td>
</tr>
<tr>
<td>Related AE</td>
<td>35 (63%)</td>
<td>30 (88%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Related G3/4 AE</td>
<td>16 (29%)</td>
<td>18 (53%)</td>
<td>7 (78%)</td>
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<tr>
<td>Related death</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Related serious AE</td>
<td>10 (18%)</td>
<td>17 (50%)</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Related AE leading to</td>
<td>4 (7%)</td>
<td>12 (35%)</td>
<td>4 (44%)</td>
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<tr>
<td>discontinuation</td>
<td></td>
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SUMMARY

• Biology of the combination is complex
• Preclinical data may support scientific hypothesis for synergistic effect
  – Where appropriate & relevant animal models or systems can be identified
• Monotherapy dose may differ from that used in combination
  – Impact on evaluating CoC
• Clinical activity & tolerability burden of combination drive B/R optimization through dose selection
• Combinations may address unmet need not fulfilled by monotherapies
  – Challenge with extent of monotherapy data to be generated in these areas
COMBINATIONS HAVE POTENTIAL TO ADDRESS DIFFERENT ESCAPE MECHANISMS

ADC, antibody-drug conjugate; CART, chimeric antigen receptor T-cell therapy; IDO, indoleamine 2,3-dioxygenase; TKI, tyrosine-kinase inhibitor

Optimising T-cell function and memory
- PD-L1
- CTLA-4
- OX40
- PD-1
- CART
- TIM-3

Inhibition by micro-environment
- IDO
- CCR4
- STAT3
- CXCR2


ADC, antibody-drug conjugate; CART, chimeric antigen receptor T-cell therapy; IDO, indoleamine 2,3-dioxygenase; TKI, tyrosine-kinase inhibitor
THE PROMISE OF COMBINATIONS BEYOND CTLA-4 + PD-L1

PD-L1 + OX40 and CTLA-40 + OX40

Pre-clinical1 data with PD-L1

- **PD-L1**
  - CR=0/10

- **OX40**
  - CR=1/10

- **PD-L1 + OX40**
  - CR=5/10

Pre-clinical1 data with CTLA-4

- **CTLA-4**
  - CR=2/14

- **OX40**
  - CR=3/14

- **CTLA-4 + OX40**
  - CR=10/14

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1 Mouse model used in experiments, CR = complete response, McGlinchey et al. Poster AACR 2014
TLR7/8 AGONIST IN COMBINATION WITH CTLA-4 AND PD-L1

Triggers Innate Immunity + Promotes Adaptive Immune Response

Evidence of Abscopal Effect

Potential Synergy with Checkpoint Inhibitors

Singh M et al J Immunol 2014;193:4722-4731
CONTRIBUTION OF COMPONENTS: 4-ARM PHASE II OR III TRIAL

- Characterizing CoC in purist form through randomized controlled 4-arm design
- Ideally, conducted within context of Phase II
CHALLENGES WITH ADDRESSING COC FOR IMMUNOTHERAPIES

• Complex study designs requiring large sample size and longer duration of follow-up
• May be difficult to enroll monotherapy arms
  • If no preliminary evidence of activity (e.g. anti-CTLA4 in NSCLC)
• Challenging to drop arms early based on surrogate endpoints
• Dose-selection for monotherapy vs combination
• How much evidence is enough?
  • Need to generate data across tumor types and lines of therapy within tumor?
• Regulatory expectations across global & regional health authorities
POSSIBLE SOLUTIONS TO CONSIDER

• Relying more on small randomized Phase II trials or on single-arm activity

• Adaptive designs
  – Introducing flexibility in level of evidence required to drop a monotherapy arm
    • Seamless Phase II/III designs
    • Working with regulators to define acceptable thresholds for dropping arms
    • Opportunities to share data with health authorities before making decisions

• Conducting 3-arm trials with only one monotherapy component
  – Understanding the contribution of one-arm relative to the combination may be enough in many situations

• Further clarifying regulatory hurdle on level of evidence required
  – A “pyramid” approach of gathering more data in Phase I & II versus III
  – Alignment across global regulatory authorities on expectations for CoC
**PROPOSED FRAMEWORK – EVALUATING TOTALITY OF DATA**

- **Preclinical**
  - Demonstration of unique mechanism of combination vs monotherapy in vitro (e.g., gene expression)
  - Demonstration of unique pharmacodynamics of combination vs monotherapy in vivo
  - Assess potential for synergistic antitumor activity in vivo, where appropriate

- **Phase I**
  - Monotherapy & combination
  - Late lines
  - Multiple tumor types
  - Sufficiently sized to allow for precision around ORR estimate and evaluate duration of response (DoR) relative to historical data
  - Biomarkers for patient selection
  - Pharmacodynamic biomarkers confirming unique effect of combination vs monotherapy

- **Phase II**
  - IF ORR data suggest improvement over SoC:
    - Randomized 3 or 4-arm POC study (with biomarker evaluation) if Phase 1 data indicative of monotherapy activity
    - Consider adaptive designs or leave flexibility in error control to enable early decision-making
    - Recommend following for additional surrogate measures (e.g., PFS) and longer-term outcomes (OS)
    - Once CoC characterized in 1 or more tumor types, consider leveraging available data to inform future study designs in other lines of therapy within same tumor type or other indications (different tumors)

- **Phase III**
  - Proceed with Combo vs SoC, unless prior clinical experience provides compelling evidence for 1 or both monotherapies and suggests potential for favorable B/R compared to historical control or SoC

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