Combination Immunotherapy Development

**Immunotherapy Regimens**

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*July 16th, 2018*
Combination Development Differs from Traditional Single-Agent Development

Challenges

### Clinical Development

**Regulatory**
Established guidelines available in US & EU regarding NME combinations; translation to other novel combinations unclear

**Clinical Trial designs**
Defining optimal dose & schedule is critical for both safety and efficacy
Novel approaches and designs may be explored (e.g. adaptive design)

**Biomarker Development**
Increased complexity with multiple biomarkers

### Operational Execution

**Collaboration in reporting**
Safety reporting, IB, and many other aspects need to be agreed on with multiple novel molecules

**Sponsor Decision-Making**
Complexity for combining molecules internally and externally (with partner involved)

**Execution**
Efficient execution of multiple combination studies in parallel with the right data collection to support decision-making
What are the unique regulatory challenges for PD-1/PD-L1 combination therapies?

How can the impact of a second drug be assessed when combined with an existing effective drug; is there a threshold that the combination needs to meet?

How do the information needs and decision-making differ from strategies for developing novel/novel combinations?
What are the unique regulatory challenges for PD-1/PD-L1 combination therapies?

Broadly Active

Complex Biology

Massive amount of orthogonal in pathway data
A complex set of tumor, host and environmental factors govern strength and timing of anti-cancer immune responses

Immune Set Point: $\int (F_{\text{stim}}) - \int (F_{\text{inhib}}) \geq 1/\Sigma_{n=1,y} (\text{TCR affinity} \times \text{frequency})$

Chen and Mellman. *Immunity* 2013

Chen and Mellman. *Nature* 2017
Combination Therapy Approaches

- Combination with **SoC**
  - Chemotherapy in 1L NSCLC
  - Chemotherapy + bevacizumab in 1L NSCLC
- Combination with an **established in-class therapeutic**
  - bevacizumab in 1L RCC
  - bevacizumab in 1L HCC
- Combination with **established agent but in an indication where it is not established (investigational)**
  - bevacizumab in melanoma
- Combination with **new molecular entity** (new indication)
  - aCEA-CD3 bispecific in CRC
Considerations for combinations with PDL1/PD1

• PDL1/PD1 inhibitors are broadly active
• Efficacy can be measured as
  • ORR only
  • ORR, PFS, OS
  • ORR, OS only
  • PFS, OS only
  • PFS only
  • OS only
• Indication (1L vs 2L vs adjuvant)
• Subsets (eg PDL1+, TMB high, MSI high)
• Strength of SoC (eg R-CHOP in 1L DLBCL)
• Complex regimen (3 or more biologic regimen)
Clinical Study Design Options for Combination Therapies

- Add to SoC
  - Chemotherapy+bevacizumab±atezolizumab in 1L NSCLC

- Add to SoC and test contribution of parts
  - Chemotherapy±bevacizumab±atezolizumab in 1L NSCLC
  - Sunitinib vs atezolizumab±bevacizumab in 1L RCC

- Replace SoC with regimen
  - Sunitinib vs Nivolumab+ipilimumab

Add to SoC and contribution of parts in P3

Patient #, Time, Cost

representative graph
Case Study: IMPower150

Atezolizumab + bevacizumab + carboplatin + paclitaxel

Addition of atezo to a SoC

Chemo+2 biologics

First 1L NSCLC combo cancer immunotherapy

P3 readout
Combination of immunotherapy with chemotherapy

**Hypothetical curve**

- **Optimal window for initiating immunotherapy combination**
- **Return to the “equilibrium” inflammatory state**

**Individual’s cancer-immune set point**

- **Anti-PDL1/PD1:**
  - Maintenance of inflamed state?

**CD8 staining images are illustrative**

*Chen and Mellman Nature 2017*
VEGF inhibition As Immunotherapy

Hegde PS, Wallin J, Mancao C, Sem Oncol 2018

Gabrilovich et al., Nat Med 1996; Butcher et al., Cell 1991

Springer et al., Cell 1994; Motz et al., Nat Med 2014

IMpower150 is an ongoing phase III study of atezolizumab plus chemotherapy and bevacizumab.

Adding chemotherapy with or without anti-VEGF therapy to PD-L1 inhibition may further enhance the immune response.

- Stage IV non-squamous NSCLC
- Chemotherapy naïve
- PD-L1 unselected
- 1202 patients

Co-primary endpoints: PFS & OS

Maintenance: Atezolizumab, Atezolizumab + bevacizumab, Carboplatin + paclitaxel + bevacizumab

R: 1:1:1
This presentation focuses on the interim OS data for IMpower150 in all study arms in the primary study population and in key patient subgroups.
**Updated PFS ITT-WT**

PFS HR 0.59

(95% CI: 0.50, 0.70)

*P* < 0.0001

Median, 8.3 mo

(95% CI: 7.7, 9.8)

Median, 6.8 mo

(95% CI: 6.0, 7.1)

**Updated OS ITT**

OS HR 0.76

(95% CI: 0.63, 0.93)

Median, 19.8 mo

(95% CI: 17.4, 24.2)

Median, 14.9 mo

(95% CI: 13.4, 17.1)

Median follow-up: ~20 mo

Socinski et. al. ASCO 2018

Socinski et. al. NEJM 2018
A trend toward OS benefit was observed with atezolizumab + chemotherapy vs bevacizumab + chemotherapy, but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis.

Median follow-up: ~20 mo
IMpower150: INV-assessed ORR in ITT-WT

Unconfirmed ORR in ITT-WT

<table>
<thead>
<tr>
<th></th>
<th>Confirmed responses</th>
<th>Bev+CP (C)</th>
<th>Atezo+Bev+CP (B)</th>
<th>Atezo+CP (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-WT</td>
<td>n=134</td>
<td>n=197</td>
<td>n=146</td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td>40.4</td>
<td>55.3</td>
<td>41.9</td>
<td></td>
</tr>
<tr>
<td>CR rate (%)</td>
<td>0.6</td>
<td>2.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>SD rate (%)</td>
<td>40.1</td>
<td>28.9</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td>Median DOR (95% CI), mo</td>
<td>6.4 (5.7, 7)</td>
<td>11.5 (8.9, 16.2)</td>
<td>9.2 (7.4, 13.9)</td>
<td></td>
</tr>
<tr>
<td>No. of ongoing responses, n (%)</td>
<td>18 (13.4%)</td>
<td>77 (39.1%)</td>
<td>53 (36.3%)</td>
<td></td>
</tr>
</tbody>
</table>

CCOD: 22 January 2018
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of EGFR/ALK+ Patients

**Arm B vs Arm C**
- Atezo+Bev+CP (Blue line)
- Bev+CP (Red line)

**HRc, 0.54**
(95% CI: 0.29, 1.03)

No. at Risk
- Atezo+Bev+CP: 41, 39, 37, 35, 32, 30, 28, 27, 26, 25, 24, 22, 20, 18, 16, 15, 14, 13, 10, 5, 4, 2
- Bev+CP: 63, 61, 57, 49, 46, 39, 37, 36, 34, 32, 31, 29, 27, 26, 24, 22, 20, 18, 17, 12, 7, 2

**Arm A vs Arm C**
- Atezo+CP (Black line)
- Bev+CP (Red line)

**HRc, 0.82**
(95% CI: 0.49, 1.37)

No. at Risk
- Atezo+CP: 53, 51, 50, 48, 46, 44, 41, 39, 37, 35, 33, 31, 29, 27, 26, 24, 22, 20, 18, 16, 13, 8, 6, 4
- Bev+CP: 63, 61, 57, 49, 46, 39, 37, 36, 34, 32, 31, 29, 27, 26, 24, 22, 20, 18, 17, 12, 7, 2

Socinski et. al. ASCO 2018
Socinski et. al. NEJM 2018
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of Patients With Liver Metastases in the ITT-WT

**Arm B vs Arm C**
- **HR**, 0.54
- (95% CI: 0.33, 0.88)
- Atezo+Bev+CP vs Bev+CP
- Overall Survival (%)
- Time (months):
  - 9.1 mo
  - 13.2 mo
- No. at Risk:
  - Atezo+Bev+CP: 47 41 39 36 32 31 26 20 18 13 10 5 3 1
  - Bev+CP: 47 42 34 29 27 20 17 13 8 6 4 1 1 1

**Arm A vs Arm C**
- **HR**, 0.85
- (95% CI: 0.53, 1.36)
- Atezo+CP vs Bev+CP
- Overall Survival (%)
- Time (months):
  - 7.0 mo
  - 9.1 mo
- No. at Risk:
  - Atezo+CP: 42 38 35 28 19 18 15 12 9 7 5 4 1 1
  - Bev+CP: 47 42 34 29 27 20 17 13 8 6 4 1 1 1

Socinski et. al. ASCO 2018
Socinski et. al. NEJM 2018
Historical data for the benefit of bevacizumab in key clinical subgroups

JO25567: PFS benefit with bevacizumab + erlotinib vs erlotinib alone in patients with \textit{EGFR Mut+ NSCLC}^1

E4599: OS benefit with bevacizumab + carbo + pac vs carbo + pac in patients with liver metastases^2

\begin{table}
\begin{tabular}{|c|c|}
\hline
Site & HR (95\% CI) \\
\hline
Pleura & 0.86 (0.63–1.18) \\
Liver & 0.68 (0.49–0.96) \\
Bone & 0.81 (0.62–1.07) \\
Adrenal & 0.97 (0.65–1.46) \\
Overall survival & 0.79 (0.67–0.92) \\
\hline
\end{tabular}
\end{table}

VEGF suppresses anti-cancer immunity

Chen and Hurwitz, 2018 publication pending
The safety profiles of ABCP and ACP were similar to A, B and C+P individually; no new safety signals were identified with the combinations.

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### Incidence, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: atezo + CP (n = 400)</th>
<th>Arm B: atezo + bev + CP (n = 393)</th>
<th>Arm C (control): bev + CP (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median doses received (range), n</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>10 (1-43)</td>
<td>12 (1-44)</td>
<td>NA</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>NA</td>
<td>10 (1-44)</td>
<td>8 (1-38)</td>
</tr>
<tr>
<td><strong>Treatment-related AE</strong>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>377 (94%)</td>
<td>370 (94%)</td>
<td>377 (96%)</td>
</tr>
<tr>
<td>Grade 5b</td>
<td>172 (43%)</td>
<td>223 (57%)</td>
<td>191 (49%)</td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td>157 (39%)</td>
<td>174 (44%)</td>
<td>135 (34%)</td>
</tr>
<tr>
<td><strong>AE leading to withdrawal from any treatment</strong></td>
<td>53 (13%)</td>
<td>133 (34%)</td>
<td>98 (25%)</td>
</tr>
</tbody>
</table>

### Immune-related AEs in > 5 patients in any arm

<table>
<thead>
<tr>
<th></th>
<th>All grade</th>
<th>Grade 3-4</th>
<th>All grade</th>
<th>Grade 3-4</th>
<th>All grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash</strong></td>
<td>119 (30%)</td>
<td>14 (4%)</td>
<td>117 (30%)</td>
<td>9 (2%)</td>
<td>53 (14%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Hepatitis</strong>d</td>
<td>42 (11%)</td>
<td>12 (3%)</td>
<td>54 (14%)</td>
<td>20 (5%)</td>
<td>29 (7%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>36 (9%)</td>
<td>10 (3%)</td>
<td>48 (12%)</td>
<td>18 (5%)</td>
<td>29 (7%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>34 (9%)</td>
<td>1 (&lt;1%)</td>
<td>56 (14%)</td>
<td>1 (&lt;1%)</td>
<td>18 (5%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong>d</td>
<td>23 (6%)</td>
<td>8 (2%)</td>
<td>13 (3%)</td>
<td>6 (2%)</td>
<td>5 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td>11 (3%)</td>
<td>0</td>
<td>16 (4%)</td>
<td>1 (&lt;1%)</td>
<td>5 (1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>11 (3%)</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

---

a Related to any study treatment.
b Including fatal hemorrhagic AEs: Arm A: 2; Arm B: 6; Arm C: 3.
c Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality.
d In Arm A, 1 patient had grade 5 acute hepatitis and 1 patient had grade 5 interstitial lung disease. Data cutoff: January 22, 2018
Challenges with CIT Combination Development in the Future

How do the information needs and decision-making differ from strategies for developing novel/novel combinations?

- combination of novel regimen in an indication
- combination including a completely novel agent
1L HCC Phase Ib of Tecentriq + Avastin: known regimen, known pathways in disease, unapproved in indication

**Figure 2. Investigator-Assessed Response to Atezolizumab + Bevacizumab Therapy**

- **Maximum SD Reduction from Baseline (%):**
  - PR (n = 14)
  - SD (n = 5)
  - PD (n = 4)

PO, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

**Table 4. Best Overall Response (BOR)**

<table>
<thead>
<tr>
<th>BOR</th>
<th>INV-Assessed per RECIST v1.1 (n = 23)</th>
<th>IRF-Assessed per RECIST v1.1 (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>14 (61%)</td>
<td>16 (66%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (61%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (22%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (17%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

**Figure 3. Investigator-Assessed Change in Tumor Burden Over Time and Response Duration per RECIST v1.1**

Stein et al. ASCO 2018
CEA-CD3 T cell engager + atezolizumab in MSS mCRC: novel therapeutic and PDL1 inhibitor atezolizumab

Data reported by investigators, cutoff: March 3, 2017.  

Sub-group of the column to the left (n = 25 CEA-TCB + atezolizumab patients, treated at doses 5-160 mg).

MMR status unknown for 3 patients.  

Two patients were MSI-high. 

One patient had the confirmatory CT scan on March 23, 2017.

Taberner et. al. ASCO 2017

<table>
<thead>
<tr>
<th>Confirmed best overall response (RECIST v1.1), n (%)</th>
<th>Study 1: CEA-TCB monotherapy</th>
<th>Study 2: CEA-TCB + atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 31, 60-600 mg MSS, n = 28 (90%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n = 25, 5-160 mg MSS, n = 23 (92%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n = 11, 80 or 160 mg&lt;sup&gt;a&lt;/sup&gt; MSS, n = 11 (100%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (6%)</td>
<td>3 (12%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (39%)</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Disease control</td>
<td>14 (45%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16 (52%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Rapidly prioritize and Accelerate Transformative Combination Therapies

CIT=cancer immunotherapy; IND=new investigational drug application; NME=new molecular entity; LIP=late-stage investment point; SOC=standard of care

Multi-indication Indication specific umbrella protocol with SOC control arm
Multi-basket Biomarker defined subgroups for personalized healthcare
Randomized Faster and more confident decisions; potential for accelerated approval
Longitudinal At disease progression patients can reenter other combinations
Adaptable Fast-track opt-in for external and internal late-stage NMEs

2017 launch in 4 indications including 11 molecules and 22 first-in-disease combinations

Chen DS, FDA-AACR 2017
Rapid and reliable estimation of benefit over SOC

Contemporary randomized Control Arm

*Real World Data

- Create a synthetic control arm based on RWD using similar inclusion/exclusion criteria as RCT, with patients treated by the SOC
- Outcomes from RWD cohort can complement or replace those from the CT SOC arm

Meta-Analysis

Distribution

Point estimate (abstract)
Discussion

• There are a multitude of scenarios in which CIT drugs can be developed in combination with other products (SOC, investigational drug[s], novel combinations)

• Individual contribution of each component of the combination could be leveraged from historical studies, demonstrated in Phase Ib/II, or demonstrated in a multi-arm randomized Phase III study.

• **Outstanding Questions:**
  • Can real world data be leveraged to demonstrate individual contribution of a component or SOC?
  • Given level of existing data on PD-1/PD-L1 drugs, what is the level of evidence needed to establish B/R of new CIT in NME + CIT combinations?
  • What are additional considerations when developing novel-novel CIT combinations?
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Patients and their families