Immuno-Oncology Opportunities and Challenges In Moving Toward a Cure for Multiple Myeloma

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Immunology Is in Our Blood
Mechanism of action of IMiDs: Cereblon Binding substrate adaptor of the CRL4CRBN E3 ubiquitin ligase

**Mechanism of Lenalidomide**

- **CUL4A**
- **DDB1**
- **ROC1**
- **E2**
- **Ubiquitin**
- **Substrate**

**IKZF1, IKZF3 casein kinase 1A1**
IMiDs/CeMDs Are Highly Effective Oral Drugs That Activate Multiple Components Of The Immune System

**T-Cell Effects**
- Activation and proliferation
- ↑ Immune synapse formation
- ↑ CD8+ T-effector cell activity
- Stimulation of cytotoxic CD8+ and helper CD4+ T cells
- ↑ Dendritic cell antigen presentation

**NK-Cell Effects**
- ↑ Number and activity of NK cells
- ↑ Enhanced ADCC
- ↑ Immune synapse formation and direct NK killing

**Malignant B-Cell Effects**
- ↑ p21WAF-1, AP-1
- ↓ CDK2, CDK4, CDK6, Rb
- ↓ Akt, Gab1 phosphorylation
- ↑ G0/G1 arrest; ↓ proliferation

**Microenvironment Effects**
- ↑ Anti-inflammatory cytokines: IL-2, IL-8, IL-10, IFN-γ, TNF-α
- ↓ Inflammatory cytokines: IL-1, IL-6, IL-12, TNF-α

Cancer Progress by Defined Health
New York, NY | March 8-9, 2016

Mechanisms of PD Pathway–induced Immunosuppression in the Tumor Microenvironment

- The PD pathway has at least 5 interacting molecules and 7 consequences of blockade of PD-L1 on the PD-L1/PD-1 interaction

Chen L. et al., J Clin Invest. 2015;125(9):3384–3391
Blocking the PD-1/PD-L1 pathway may enhance anti-tumor responses in patients with MM

Increased PD-L1 and PD-1 expression on MM cells and T cells from patients with myeloma

Shorter PFS is observed in patients with MM and elevated vs normal serum levels of soluble PD-L1

BMPC, bone marrow plasma cell; MM, multiple myeloma; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

Blocking the PD-1/PD-L1 pathway may enhance anti-tumor responses in patients with MM

In vitro treatment with anti–PD-L1 induces myeloma cell killing by NK cells and CD8+ T cells.

DC, dendritic cell; MM, multiple myeloma; NK, natural killer; PD-1, programmed death-1; PD-L1, programmed death ligand-1.

Combining durvalumab with IMiD® agents is hypothesized to enhance their anti-tumor effects by preventing PD-1/PD-L1—mediated immune quiescence.

**Increased apoptotic/dead MM cells from RRMM BM treated with anti-PD-1 or anti-PD-L1**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Anti-PD-L1</th>
<th>Anti-PD-1</th>
<th>LEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptotic/dead MM Cells (fold)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*P < .05

**Increased IFNγ expression by effector cells from RRMM BM treated with anti-PD-1 and anti-PD-L1 ± LEN**

**BM, bone marrow; BMMC, bone marrow mononuclear cells; IFNγ, interferon gamma; LEN, lenalidomide; MM, multiple myeloma; NK, natural killer; NKT, natural killer T cells; PD-1, programmed death-1; PD-L1, programmed death ligand-1; RRMM, relapsed/refractory multiple myeloma.**

Combining durvalumab with IMiD® agents is hypothesized to enhance their anti-tumor effects by preventing PD-1/PD-L1—mediated immune quiescence

PD-1/PD-L1 blockade combined with LEN or POM enhances CTL-mediated killing of MM cells in the presence of DCs

CTL, cytotoxic T lymphocyte; DC, dendritic cell; GFP, green fluorescent protein; LEN, lenalidomide; MM, multiple myeloma; PD-1, programmed death-1; PD-L1, programmed death ligand-1; POM, pomalidomide.

Combining durvalumab with IMiD® agents is hypothesized to enhance their anti-tumor effects by preventing PD-1/PD-L1—mediated immune quiescence.

A phase 1 trial of LEN and PD-1 blockade in RRMM demonstrated promising results with reduced serum M-protein levels in the vast majority of patients and a robust ORR,¹ which is historically consistent with LEN Tx in this population²

- The ORR was 76%, and 94% of patients experienced reduced serum M-protein levels¹

LEN, lenalidomide; ORR, overall response rate; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SD, stable disease; Tx, treatment; VGPR, very good partial response.

## Expanding Leadership in Multiple Myeloma

### Building on the IMiD® Backbone Across All Lines of Multiple Myeloma

<table>
<thead>
<tr>
<th>1L</th>
<th>2L</th>
<th>3L+</th>
<th>Drugs in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk / Aggressive Disease</strong></td>
<td><strong>SCT Induction</strong></td>
<td><strong>SCT Maintenance</strong></td>
<td><strong>NSCT</strong></td>
</tr>
<tr>
<td>RVd +/- MAb</td>
<td>R + Ixa, R + Dara</td>
<td>RVd Rd + Mab</td>
<td>Pom/Imn Triplets</td>
</tr>
<tr>
<td>RVd Rd + Mab</td>
<td>R</td>
<td>Rd RVd Rd + Mab</td>
<td>Rev Triplets</td>
</tr>
<tr>
<td><strong>Standard Risk</strong></td>
<td><strong>SCT Induction</strong></td>
<td><strong>SCT Maintenance</strong></td>
<td><strong>NSCT</strong></td>
</tr>
<tr>
<td>RVd Rd + Mab</td>
<td>R</td>
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</tr>
</tbody>
</table>

**I/O Combos:**
- Durvalumab
- BCMA
- CART(bb2121)
- Anti-CD47
- NK cells

**Next-gen HDACs:**
- Ricolinostat
- ACY-241

**Next-gen PIs:**
- Marizomib

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**Revlimid** (lenalidomide) capsules

**Pomalyst** (pomalidomide) capsules
INITIAL CLINICAL TRIALS IN HEMATOLOGIC MALIGNANCIES

- Relapse or refractory MM
- Newly Diagnosed HR MM
- Relapsed or refractory MDS
- Newly diagnosed high risk MDS and AML
- Relapse or refractory NHL, CLL, HL
- Newly Diagnosed High Risk DLBCL
Initial 6 Ph1/2 Studies in Hematologic Malignancies
Focus on combinations with biologic relevance from Celgene pipeline

**Multiple Myeloma**
- MM-001 Pomalidomide combination for r/rMM ≥ 3L
- MM-002 Lenalidomide combination for NDMM (NTE high risk, elderly; & TE post ASCT maintenance)

**NHL**
- NHL-001 Multiple durvalumab combination arms in parallel (r/r NHL/CLL/HL)
  a) Rituximab + Lenalidomide (R²) (NHL only)
  b) Ibrutinib
  c) Rituximab + Bendamustine
  d) monotherapy (include HD)
- DLBCL-001 1L High Risk DLBCL: Combination with Rituximab + Lenalidomide (R²) + CHOP

**MDS/AML**
- MDS-006 CC-486 + durvalumab for HMA failed MDS
- MDS-001 Vidaza + durvalumab for HR front-line MDS & AML
• B cell maturation antigen (BCMA) is a member of the TNF receptor superfamily.
• BCMA binds B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). BCMA is expressed by plasma cells and some mature B cells.
• Mice deficient in BCMA are healthy and have normal numbers of B cells, but reduced survival of plasma cells.
• BCMA RNA is near universally detected in multiple myeloma (MM) cells, and BCMA protein is detected on the surface of malignant plasma cells from patients with MM.
NCI BCMA CART Myeloma Trial Update NCT02215967

### Dose Levels (x10^6/kg)
1. 0.3
2. 1.0
3. 3.0
4. 9.0

**Gammaretrovirus transduction**

**CD28-CD3 zeta OKT3 activation**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Rx (median No. regimens)</td>
<td>7</td>
</tr>
<tr>
<td>Myeloma subtype</td>
<td></td>
</tr>
<tr>
<td>- IgG</td>
<td>4</td>
</tr>
<tr>
<td>- IgA</td>
<td>3</td>
</tr>
<tr>
<td>- light chain only</td>
<td>5</td>
</tr>
</tbody>
</table>

**Kochenderfer, Late Breaker, ASH 2015**
NCI BCMA CART Trial
Dose Related Myeloma Eradication with CRS

<table>
<thead>
<tr>
<th>Dose Level (x 10^6/kg)</th>
<th>N</th>
<th>Best Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>3</td>
<td>SDx2, PRx1</td>
<td>mild fever</td>
</tr>
<tr>
<td>1.0</td>
<td>3</td>
<td>SDx3</td>
<td>mild fever</td>
</tr>
<tr>
<td>3.0</td>
<td>4</td>
<td>SDx3, VGPRx1</td>
<td>Moderate CRSx1</td>
</tr>
<tr>
<td>9.0</td>
<td>2</td>
<td>sCRx1, PRx1</td>
<td>Severe CRSx2</td>
</tr>
</tbody>
</table>

Cytokine Release

CART Persistence

Kochenderfer, Late Breaker, ASH 2015
NCI BCMA CART Trial
Rapid Elimination of Myeloma Tumor Burden at Highest Dose Level

**Patient 10 - sCR**

Baseline | Week 4
--- | ---
CD138 | CD138

**Patient 11 - PR**

Baseline | Week 8
--- | ---
BCMA | BCMA

**IgA Normalization**

*SPEP/IEP negative
Flow negative*

![Graph showing IgA normalization](image)

**Del17p**

*Add (1q)*

![Graph showing Del17p and Add (1q)](image)
### CRB-401 (NCT02658929)
*(Refractory Multiple Myeloma)*

<table>
<thead>
<tr>
<th>U.S.-based, 6-10 clinical sites – including NCI</th>
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<tr>
<td>• Diagnosis of MM with relapsed or refractory disease and have had at least 3 different prior lines of therapy including proteasome inhibitor (e.g., bortezomib or carfilzomib) and immunomodulatory therapy (e.g., lenalidomide or pomalidomide)</td>
</tr>
<tr>
<td>• N = 40 patients, standard 3+3 Design based on CAR+ T cells doses</td>
</tr>
<tr>
<td>• Primary endpoint = Determine the maximally tolerated dose and recommended phase 2 dose (RP2D)</td>
</tr>
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<td>• Subjects must have received 3 prior regimens including a proteasome inhibitor (bortezomib, carfilzomib) and immunomodulatory agent (lenalidomide, pomalidomide)</td>
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<tr>
<td>• Following screening, enrolled subjects will undergo a leukapheresis procedure to collect autologous mononuclear cells for manufacturing of bb2121.</td>
</tr>
<tr>
<td>• Following manufacture of the drug product, subjects will receive one cycle of lymphodepletion prior to bb2121 infusion</td>
</tr>
</tbody>
</table>
The MM IO pipeline has 29 trials in development.

There are 10 new trials included in this update, of these, 3 are new checkpoint inhibitor trials, 2 are new CAR-T trials and the remaining are due to the inclusion of new mechanisms (CD-19 and BCMA).

**Notable changes since last quarter:**

- Two phase II trials with pembrolizumab are planned for initiation in 1Q 2016
  - NCT02603887 aims to test single agent pembrolizumab in patients with intermediate and high risk smoldering MM
  - NCT02636010 will test pembrolizumab as consolidation therapy in MM patients with residual disease
- Bluebird Bio initiated a Phase I trial of its anti-BCMA CAR-T program bb2121 in adults with R/R MM (NCT02658929)
- Another Anti-BCMA CAR-T trial is also underway in patients with R/R MM (NCT02546167), which is being run out of the Abramson Cancer Center
Evolution of Treatment Options in Multiple Myeloma

- Alkylators
- Corticosteroids
- Proteasome Inhibitors
- IMiDs/CelMods
- HDACi
- SLAMF7; CD38 antibodies
- Cellular therapies
- Checkpoint inhibitors
- Antibody drug conjugates
- T cell engagers
Development Thoughts

- Route of administration, duration of therapy, cost and adverse event profile will contribute to physician and patient choice in addition to efficacy
- Biomarker and risk group definition may guide choice of combination/sequence
- Randomized studies will be increasingly costly to source SoC agents
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<tr>
<td></td>
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<td>RVd Rd + Mab</td>
<td></td>
<td>CC-122</td>
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<tr>
<td><strong>Maintenance</strong></td>
<td></td>
<td>R</td>
<td></td>
<td>CC-220</td>
</tr>
<tr>
<td></td>
<td>RVd Rd + Mab</td>
<td>Rd + Mab</td>
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<td>I/O Combos:</td>
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<tr>
<td><strong>NSCT</strong></td>
<td>RVd</td>
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<td></td>
<td>Durvalumab</td>
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<td>Ricolinstat</td>
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**Note:**
- RVd: Revlimid® (lenalidomide) capsules
- Pom: Pomalyst® (pomalidomide) capsules