THERAPEUTIC STRATEGIES TARGETING B-CELL MATURATION ANTIGEN (BCMA) IN MM

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## Disclosures

<table>
<thead>
<tr>
<th>Consulting Agreements</th>
<th>Amgen Inc, Bioclinica, Bristol-Myers Squibb Company, Celgene Corporation, CRISPR Therapeutics, Janssen Biotech Inc, Karyopharm Therapeutics, Kite Pharma Inc, Servier, Takeda Oncology</th>
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<tr>
<td>Contracted Research</td>
<td>AbbVie Inc, Acetylon Pharmaceuticals Inc, Amgen Inc, bluebird bio, Bristol-Myers Squibb Company, Celgene Corporation, Constellation Pharmaceuticals, Curis Inc, Genentech, Glenmark, Janssen Biotech Inc, Kesios Therapeutics Ltd, Lilly, Novartis, Poseida Therapeutics, Sanofi Genzyme, Takeda Oncology, Teva Oncology, Vivolux</td>
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<td>Data and Safety Monitoring Board</td>
<td>Prothena</td>
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Case Presentation: Dr Lamar

48-year-old man

- Diagnosis: IgG-kappa multiple myeloma
  [1q-/1q+, t(4;14), del(13)]
  - Multiple plasmacytomas
  - Testicular involvement
  - Multiple lytic spinal lesions
- VRd → rapid PD
MOVING BEYOND THE NAKED MONOCLONAL ANTIBODIES...

• Antibody Drug Conjugates (ADC)
• Bispecific antibodies or BiTEs
• Chimeric Antigen Receptor T Cells (CART)

• Most important target to date - BCMA
BCMA (B Cell Maturation Antigen)

- Member of the TNF receptor superfamily
- Receptor for BAFF and APRIL
- Expressed on cell surface
- Expression largely restricted to plasma cells and some mature B cells (absent on naive and memory B cells)
- Important in B cell maturation and long lived plasma cell survival

GSK2857916 (Belantamab mafodotin) an Antibody Drug Conjugate Against BCMA

**Background**

- **Antibody**
  - Humanized, afucosylated IgG1 anti-BCMA ab
- **Payload:**
  - MMAF (monomethyl auristatin-F)

**Four mechanisms of action:**

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signaling inhibition

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ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F


GSK2857916 (Belantamab mafodotin): Results from Part 2 of Study BMA117159 (DREAMM-1)

Population
- 35 pts in expansion phase
- 3.4 mg/kg IV q 3 wk
- Med priors 5
- 40% dara exposed/refractory

AEs of interest
- IRR 29% (Gr 1/2 in first dose only)
- Gr 3 Thrombocytopenia 26%
- Corneal events 69%
  (blurred vision, photophobia, dry eyes)

Efficacy
- Entire population (n=35)
  - ORR 60% (most ≥ VGPR)
  - Med PFS 12.0 mos
  - Med DOR 14.4 mos
- Dara exposed/refractory (n=14)
  - ORR 42.9%
  - Med PFS 6.8 mos


DREAMM studies underway in many combinations in the relapsed and frontline settings
Bispecifics

- Targets in MM
- BCMA:CD3
- GPRC5D:CD3
- CD38:CD3
- FcRH5:CD3
AMG 420 (BCMA:CD3 BiTE): Updated Results of a First-in-Human Phase 1 Dose Escalation Study

Population
42 pts in dose escalation
Med prior therapies 4
MTD 400 µg/d CIV
CIV infusions 4wks on, 2 wks off

Toxicity
3 DLTs
Gr 3 CRS (@ 800µg/d)
Gr 3 PN (@400 and 800µg/d)
2 Deaths - unrelated
ARDS due to flu/aspergillosis
Hepatitis due to adenovirus

Efficacy
- Entire population (n=42)
  - ORR 31%

- @MTD 400µg/d (n=10)
  - ORR 70%
  - 5 of 7 with MRD- CR*
  - Med DOR 9 mos

*MRD@10⁻⁴

Topp et al. ASCO 2019, Abstract 8007
# Bispecific T Cell Engagers/Antibodies

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Structure</th>
<th>Trial ID</th>
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<tbody>
<tr>
<td>AMG-420</td>
<td>BCMA</td>
<td>BiTE</td>
<td>NCT02514239</td>
</tr>
<tr>
<td>AMG-701</td>
<td>BCMA</td>
<td>BiTE-HLE</td>
<td>NCT03287908</td>
</tr>
<tr>
<td>CC-93269</td>
<td>BCMA</td>
<td>BsAb</td>
<td>NCT03486067</td>
</tr>
<tr>
<td>PF-06863135</td>
<td>BCMA</td>
<td>BsAb</td>
<td>NCT03269136</td>
</tr>
<tr>
<td>REGN-5458</td>
<td>BCMA</td>
<td>BsAb</td>
<td>NCT03761108</td>
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<td>TNB-383B</td>
<td>BCMA</td>
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<td>NCT03933735</td>
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<td>JNJ-64007957</td>
<td>BCMA</td>
<td>DuoBody</td>
<td>NCT03145181</td>
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<td>JNJ-64007564</td>
<td>GPRC5d</td>
<td>DuoBody</td>
<td>NCT03399799</td>
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<tr>
<td>GBR 1342</td>
<td>CD38</td>
<td>BsAb</td>
<td>NCT03309111</td>
</tr>
<tr>
<td>AMG-424</td>
<td>CD38</td>
<td>BsAb (XmAb)</td>
<td>NCT03445663</td>
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<tr>
<td>BFCR4350A</td>
<td>FcRH5</td>
<td>BsAb</td>
<td>NCT03275103</td>
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HLE, half-life extended; BsAb, bispecific antibody

Costa et al. ASH 2019 Oral Session: Abs 143, Sat 12/7/19:10:30am

Cooper et al. ASH 2019 Poster Session: Abs 3176, Sun 12/8/19
CAR T Cells: Mechanism of Action

**T cell**
- Expression of CAR
- Viral DNA Insertion

**Tumor cell**
- CAR enables T cell to recognize tumor cell antigen
- Antigen
- CAR T cells multiply and release cytokines
- Tumor cell apoptosis
**Chimeric Antigen Receptors**

**Antigen Binding Domain**

**Activation Domains**

**VH**

**VL**

**Antigen binding domain**

**Hinge region**

**Costimulatory Domain:** CD28 or 4-1BB

**Enhances proliferation, cytotoxicity and persistence of CAR T cells**

**Signaling Domain:** CD3ζ chain

**Proliferation and activation of CAR T cells**

**CAR T-cell-mediated killing of tumor cells**

**scFv**

Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

**Hinge region**

Essential for optimal antigen binding

**Costimulatory Domain:** CD28 or 4-1BB

Enhances proliferation, cytotoxicity and persistence of CAR T cells

**Signaling Domain:** CD3ζ chain

Proliferation and activation of CAR T cells

CAR T-cell-mediated killing of tumor cells
## BCMA-DIRECTED CAR T CELLS IN MULTIPLE MYELOMA

<table>
<thead>
<tr>
<th></th>
<th>BB2121 (BLUEBIRD)</th>
<th>LCAR-B38M (LEGEND)*</th>
<th>JCARH125 (JUNO)</th>
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<tbody>
<tr>
<td>Ag-binding domain</td>
<td>scFv (M)</td>
<td>2-VHH (C)</td>
<td>scFv (H)</td>
</tr>
<tr>
<td>Special Qualities</td>
<td>Low tonic activity</td>
<td>2 epitopes</td>
<td>Equal # CD4/CD8</td>
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<tr>
<td>Population</td>
<td>33</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td># Prior Tx</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>CART Dose</td>
<td>50-800 x10^6</td>
<td>0.5(0.07-2.1)x10^6/kg</td>
<td>50-450 x10^6</td>
</tr>
<tr>
<td>ORR</td>
<td>85%</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>CR</td>
<td>45%</td>
<td>68%</td>
<td>27%</td>
</tr>
<tr>
<td>CRS All Grades (Grade 3/4)</td>
<td>76%(6%)</td>
<td>90%(7%)</td>
<td>80%(9%)</td>
</tr>
<tr>
<td>Neurotox All Grades (Grade 3/4)</td>
<td>42%(3%)</td>
<td>2%(0%)</td>
<td>25%(7%)</td>
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<tr>
<td>Med PFS</td>
<td>11.8 mos</td>
<td>15 mos</td>
<td>NR</td>
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Raje et al, NEJM 2019; Zhao et al, J Hem Onc 2018, Mailankody et al, ASH 2018

*Wang et al. ASH 2019 Oral Session: Abs579, Mon 12/9/19: 7:30a*
FUTURE DIRECTIONS OF MOST ADVANCED CART PRODUCTS

• Race to FDA Approval in the USA
  – Global Pivotal Trial (KarMMa) has completed enrollment
    • bb2121 dose range: $150-450 \times 10^6$ CAR+ T cells
  – Legend/Janssen enrolling on pivotal trial of JNJ-68284528 (LCAR-B38M)

• Use Beyond the Refractory Setting
  – Trials in earlier phase of disease
    • KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
    • KarMMa 2 – cohort of pts with early relapse, bb2121 as 2\textsuperscript{nd} line
  – In conjunction with ASCT/Consolidation in MRD
    • KarMMa2, SZ-CART-MM 02 (BCMA and CART19)
  – Upfront in high risk patients
    • Studies in development
OVERCOMING RELAPSE OF CART THERAPY

- Increase persistence of CARTs - Select/augment memory phenotype
  - bb21217\(^1\)
    - same construct as bb2121 but cultured w/ PI3Ki
    - 12 patients reported – ORR 83.3%, detectable CART out to 9 mos
  - P-BCMA-101\(^2\)
    - piggyBac – non viral DNA delivery using transposons
    - CRS 9%, no Gr3/4; peak expansion 14-21 ds
- Decrease potential of BCMA escape/augment expression
  - Gamma secretase inhibitors
  - Dual and Tandem CARTs
    - Tandem BCMA and CD19 CAR
    - Dual BCMA and CD19
    - Dual BCMA and CD38
- Off the shelf
  - Allogeneic CART
    - “Better” T cells
    - Readily available

How Will All These Modalities Fit Into Our Treatment Paradigm?
SOME UNANSWERED QUESTIONS

• ADCs
  – Will they be better than naked monoclonal antibodies or just different?
  – Is plan to replace the naked MoAbs?
    • DREAMM studies with belantamab mafodotin planned in many current daratumumab indications
  – Ocular toxicity of BM could be an issue – but this is payload specific
    • Will tox limit combination potential?
    • Will tox limit ability to be given continuously?
• CAR Ts vs BiTEs/Bispecifics
  – One time infusion vs frequent dosing/continuous infusion
  – Complex procedure vs “off the shelf”
• Targeting BCMA via ADCs, BiTEs or CAR Ts have produced impressive results in the relapsed/refractory setting
  – Is there a rational way of sequencing them?
  – Is there a role for retreatment?
• Will failure of one anti-BCMA therapy negate use of another?
  – Will depend on mechanisms of resistance
  – Clinical trials need to include patients who have relapsed post other anti BCMA therapies
    • CT103A, fully human BCMA CART – 4 pts with prior murine BCMA CAR – 100% RR, 3 sCR, 1VGPR (AB440, IMW 2019)

Li et al. ASH 2019 Oral Session: Abs 582, Mon 12/9/19: 8:15a