Non-BCMA Bispecific Antibodies

October 11, 2023

Tech Support
1-719-234-7952
Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation

Submit your questions throughout the program!
MMRF Research Initiatives

1. MMRF Myeloma Accelerator Challenge (MAC) Grants
   - Broad, multi-institutional research grants designed to advance clinical trial concepts in the areas of
     - High-risk newly diagnosed multiple myeloma (NDMM)
     - High-risk smoldering myeloma (SMM)
   - Each research network will be funded up to $10M over 3 years

2. MMRF Horizon Adaptive Platform Trials
   - Paired with MAC grants
   - Done in collaboration with 13 MMRC sites
   - Trials in relapsed/refractory myeloma, high-risk NDMM, high-risk SMM

For more information, visit themmrf.org

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Speakers

Ajai Chari, MD
University of California, San Francisco
San Francisco, California

Suzanne Trudel, MD, FRCPC
University of Toronto
Princess Margaret Hospital
Toronto, Ontario, Canada

Nicholas Lenoir
Patient
Spring Hill, Florida
Myeloma Targets Beyond BCMA

Ajai Chari, MD

University of California, San Francisco
San Francisco, California

Bispecific Antibodies

Bispecific antibodies are also referred to as dual-specific antibodies, bifunctional antibodies, or T cell–engaging antibodies.

Bispecific antibodies can target two cell surface molecules at the same time (one on the myeloma cell and one on a T cell).

Many different bispecific antibodies are in clinical development; three approved for use in myeloma!

Availability is off-the-shelf, allowing for immediate treatment.

Myeloma Cell Targets for Bispecific Antibodies

**BCMA**
- Highly expressed only on the surface of plasma cells
- Myeloma patients have significantly higher serum BCMA levels than healthy individuals

**GPRC5D**
- Highly expressed on myeloma cells in the bone marrow
- Lowly expressed on hair follicles but not on other healthy cells
- Expression on myeloma cells is independent of BCMA

**FcRH5**
- Selectively expressed on B cells and plasma cells

**Bispecific Antibodies Under Investigation**

<table>
<thead>
<tr>
<th>Target (MM cell × T cell)</th>
<th>Bispecific antibody</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA × CD3</td>
<td>Tecvayli (teclistamab)</td>
<td>✓ Approved</td>
</tr>
<tr>
<td></td>
<td>Elrexfio (elranatamab)</td>
<td>✓ Approved</td>
</tr>
<tr>
<td></td>
<td>Linvoseltamab</td>
<td>Clinical studies</td>
</tr>
<tr>
<td></td>
<td>Alnuctamab</td>
<td>Clinical studies</td>
</tr>
<tr>
<td></td>
<td>ABBV-383</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>GPRC5D × CD3</td>
<td>Talvey (talquetamab)</td>
<td>✓ Approved</td>
</tr>
<tr>
<td></td>
<td>Forimtamig (RG6234)</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>FcRH5 × CD3</td>
<td>Cevostamab</td>
<td>Clinical studies</td>
</tr>
</tbody>
</table>

Overall response rates 60% to 70% in heavily pretreated myeloma patients

High proportion of patients achieving VGPR or CR
Talvey in Patients With Relapsed/Refractory Multiple Myeloma

Phase 1/2 study (MonumenTAL-1) in RRMM

288 patients—with or without prior T cell—redirecting therapies—received treatment with Talvey at 2 different doses (0.4 mg/kg every week and 0.8 mg/kg every other week) subcutaneously.

Now approved for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a PI, an IMiD, and an anti-CD38 monoclonal antibody!

IMiD, immunomodulatory drug; PI, proteasome inhibitor

PFS and Duration of Response of Recently Approved Therapies in Relapsed/Refractory Myeloma

T cell redirection therapies
For >4 LOT and IMID/PI/anti-CD38 exposed

LOT, line of therapy; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PFS, progression-free survival; DOR, duration of response.
This is not a head-to-head comparison and cross-trial comparisons should not be interfered from these data.
Data represent two populations, PFS includes all patients, DOR includes responding patients only.
Expected Toxicities With Bispecific Antibodies

- Cytokine release syndrome (CRS)
- Infections
- Cytopenias
- Neurotoxicity (ICANS)
- Off-target effects (with GPRC5D targeted agents)
- Cytokeratin changes/rash
- Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome

Talvey in Patients With Relapsed/Refractory Myeloma

<table>
<thead>
<tr>
<th>Most frequent adverse events, %</th>
<th>0.4 mg/kg</th>
<th></th>
<th>0.8 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>44.8</td>
<td>31.5</td>
<td>45.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35.0</td>
<td>30.8</td>
<td>28.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27.3</td>
<td>20.3</td>
<td>29.7</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>79.0</td>
<td>2.1</td>
<td>74.5</td>
</tr>
<tr>
<td>Taste disorder (dysgeusia)*</td>
<td>72.0</td>
<td>NA</td>
<td>71.0</td>
</tr>
<tr>
<td>Infections</td>
<td>58.7</td>
<td>19.6</td>
<td>66.2</td>
</tr>
<tr>
<td>Skin related*</td>
<td>55.9</td>
<td>0</td>
<td>73.1</td>
</tr>
<tr>
<td>Nail related*</td>
<td>54.5</td>
<td>0</td>
<td>53.8</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>41.3</td>
<td>2.1</td>
<td>41.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24.5</td>
<td>3.5</td>
<td>27.6</td>
</tr>
</tbody>
</table>

* Taste- and skin-related side effects led to discontinuations in 5 patients

# GPRC5D-Associated Side Effects

<table>
<thead>
<tr>
<th>Affected area</th>
<th>Symptoms and effects</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash, skin peeling</td>
<td>Relatively benign, not painful, self-limiting, and manageable with emollients</td>
</tr>
<tr>
<td>Nails</td>
<td>Nail thinning and loss</td>
<td>Mostly aesthetic but take time to resolve</td>
</tr>
<tr>
<td>Oral</td>
<td>Difficulty swallowing, dry mouth, taste changes</td>
<td>Can lead to weight loss; have longer duration and can affect quality of life. Most successfully managed with dose modification. Supportive measures may be used (eg, NaCl mouth rinse, artificial saliva spray, diet modification)</td>
</tr>
</tbody>
</table>

Myeloma patients respond well to treatment, and GPRC5D-associated side effects improve over time, becoming more tolerable; notable reduction in side effects is seen with dose modification.


**Products applied twice daily**
- Ammonium lactate 12% cream
- Triamcinolone 0.1% cream
- Emollients

- Oral antihistamines as needed

5 patients who had grade 3 rash
• Starts ~C2, lasts for months
• Avoid frequent/long durations of water immersion
• Frequent application of emollients (Vaseline/Aquaphor)
• Vitamin E oil
• File to smooth the edges and corners of the nail plates
• Clear nail polish or nail hardeners
• Biotin supplements may be helpful

Talvey Use in Practice

Administered subcutaneously according to step-up dosing schedule and then weekly or every 2 weeks thereafter

Patients are to be hospitalized for 48 hours for monitoring of side effects after they have completed their step-up dosing, at a REMS-certified facility

REMS, risk evaluation and mitigation strategy
Talvey Combinations: Tecvayli + Talvey in Patients With Relapsed/Refractory MM

PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; CRS, cytokine release syndrome; EMD, extramedullary disease


Progression-free survival, 20.9 months; duration of response, not yet evaluable.

Talvey Combinations; Talvey + Darzalex in Patients With 3 or More Prior Lines of Therapy

PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response


Progression-free survival, 19.4 months; duration of response, 20.3 months.
Future Direction With Talvey

• Phase 2 pilot study of Tecvayli + Darzalex and Talvey + Darzalex in patients with high-risk* newly diagnosed multiple myeloma, with an early rescue intervention guided by minimal residual disease (MRD) assessment (GEM-TECTAL)

*One or more of the following high-risk features: del(17p), t(4;14), t(14;16), or 1q amplifications detected by fluorescence in situ hybridization, Revised International Staging System stage 3, and presence of extramedullary disease
Forimtamig a GPRC5D × CD3 Bispecific Antibody in Patients With Relapsed/Refractory Multiple Myeloma

### Phase 1 study of 105 patients

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>Number of Patients</th>
<th>Overall Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>52</td>
<td>71.2</td>
</tr>
<tr>
<td>&gt;4 Prior lines of therapy</td>
<td>49</td>
<td>63.3</td>
</tr>
<tr>
<td>Triple-class refractory</td>
<td>81</td>
<td>60.5</td>
</tr>
<tr>
<td>Penta-drug refractory</td>
<td>45</td>
<td>57.8</td>
</tr>
<tr>
<td>Prior BCMA-targeted therapy</td>
<td>29</td>
<td>51.2</td>
</tr>
<tr>
<td>Antibody-drug conjugate</td>
<td>19</td>
<td>47.7</td>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>5</td>
<td>42.9</td>
</tr>
<tr>
<td>CAR T cells</td>
<td>5</td>
<td>66.7</td>
</tr>
<tr>
<td>High risk cytogenetics (include del(17p), t(4;14), t(14;16))</td>
<td>33</td>
<td>63.4</td>
</tr>
<tr>
<td>1q21 gain</td>
<td>15</td>
<td>86.7</td>
</tr>
<tr>
<td>ISS III</td>
<td>24</td>
<td>70.8</td>
</tr>
<tr>
<td>Soluble BCMA &gt;327 ng/mL</td>
<td>54</td>
<td>55.6</td>
</tr>
<tr>
<td>Soluble BCMA &lt;327 ng/mL</td>
<td>55</td>
<td>80.0</td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td>28</td>
<td>50.0</td>
</tr>
</tbody>
</table>


Cevostamab a FcRH5 × CD3 Bispecific Antibody in Patients With Relapsed/Refractory Multiple Myeloma

### Best response rates in efficacy-evaluable patients by dose level

- **20–90 mg dose level (N=83)**
  - sCR: 8.4%
  - CR: 10.8%
  - VGPR: 20.5%
  - PR: 15.7%
  - sCR: 10.8%
  - CR: 15.7%
  - VGPR: 25.0%
  - PR: 23.3%
  - ORR: 36.1%
  - ORR: 66.7%

- **132–198 mg dose level (N=60)**
  - sCR: 1.7%
  - CR: 1.7%
  - VGPR: 20.5%
  - PR: 33.3%
  - sCR: 1.7%
  - CR: 1.7%
  - VGPR: 20.5%
  - PR: 23.3%
  - ORR: 56.7%

Fixed-Duration Therapy With Cevostamab

At the time of this presentation, no patients who achieved an sCR have relapsed!

Expected Toxicities With Bispecific Antibodies

- Cytokine release syndrome (CRS)
- Infections
- Cytopenias
- Neurotoxicity (ICANS)

ICANS, immune effector cell-associated neurotoxicity syndrome
Pretreatment With Tocilizumab Reduces Incidence and Severity of Cytokine Release Syndrome With Cevostamab

Phase 1 study evaluating the use of tocilizumab (an IL-6 antibody) prior to the first dose of cevostamab.

- Significantly lower rate of CRS in the TCZ PT group
- TCZ PT had no negative impact on response rates


Bispecific Antibodies Are Associated With an Increased Risk of Infections

A pooled analysis of 1,185 RRMM patients in 11 different clinical trials treated with single agent bispecific antibodies (with no prior use of different bispecifics)

- Majority of patients (72%) treated with BCMA-targeted bispecific antibodies

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>38.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Infections</td>
<td>50</td>
<td>24.5</td>
</tr>
<tr>
<td>CRS</td>
<td>59.6</td>
<td>NR</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>COVID-19</td>
<td>NR</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Hypogammaglobulinemia occurred in 75.3% of patients with intravenous immunoglobulin used in 48%.

Death was reported in 110 patients of which 28 (25.5%) were reported to be secondary to infections.

Certain precautions should be used when using bispecific antibodies to mitigate the risk and/or identify and treat infections promptly.

Bispecific Antibodies: Infection Risk and Current Mitigation Strategies

- CRS can mask signs of infection
  - Tocilizumab and steroids are used for CRS treatment and prevention but are also immunosuppressive
  - These agents can increase the risk of infections as well as masking signs of infection
- Neutropenia is an established risk for infection
  - Bispecific antibodies activate effector T cells and may activate immunosuppressive T regulatory cells
  - These T regulatory cells are postulated to be responsible for cytopenias seen with bispecific antibody therapy
  - Tocilizumab is known to induce neutropenia

MajesTEC-1 Safety Data

- Hypogammaglobulinemia is linked with increased risk of severe infections, particularly:
  - Bacterial infections
  - Respiratory tract infections
  - GI infections
  - Viral infections

CRS (72.1% pts) and CRS management

Hypogammaglobulinemia (74.5% pts)

Neutropenia (71% pts)

IVIG Infusion Reduces Risk of High-Grade Infections

- Serious infections are very common, including opportunistic infections (e.g., CMV, PCP)
- Infection risk continues to accumulate over time, even in deep remissions
- Profound hypogammaglobulinemia/agammaglobulinemia is universal in responders
- IVIg appears to be largely protective for severe infections

Lancman et al, Blood Cancer Discovery 2023
Infection Prevention

Avoid crowds
Ensure handwashing, hygiene
Growth factors
IVIG for hypogammaglobulinemia
Immunizations (no live vaccines)
COVID-19 prevention
Zoster and PJP prophylaxis
Consider CMV monitoring

IVIG, intravenous immunoglobulin; PJP, Pneumocystis jiroveci pneumonia; CMV, cytomegalovirus

Cevostamab Combinations: Cevostamab-Pomalyst-Dexamethasone in Relapsed/Refractory Myeloma

Phase 1b study (CAMMA 1) in RRMM (≥2 prior lines of therapy, including ≥1 IMiD and ≥1 proteasome inhibitor)

8 patients received treatment with cevostamab (intravenously), Pomalyst, and dex.

<table>
<thead>
<tr>
<th></th>
<th>Cevostamab-Pom-Dex (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, n</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Adverse events (grade 3/4), n</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Gr 3: 1 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Gr 4: 3 (37.5%)</td>
</tr>
<tr>
<td>CRS</td>
<td>All Gr: 7 (87.5%)</td>
</tr>
<tr>
<td></td>
<td>Gr 3: 2 (25%)</td>
</tr>
</tbody>
</table>

Evolution of Bispecific Antibodies

Bispecific antibodies: dual targets

Trispecific antibodies: triple targets

Key Points

- Bispecific antibodies are very active even in heavily pretreated patients.
- Side effects of bispecific antibodies include cytokine release syndrome, confusion, and low blood counts, and confusion (rare)—all of which are treatable.
- Infections have emerged as a more challenging toxicity but, with experience, strategies are forming to mitigate the risks.
- Bispecific antibodies represent an off-the-shelf immunotherapy; three bispecific antibodies have been approved since October 2022.
- Several additional bispecific antibodies are under clinical evaluation. Different bispecifics and different targets are on the way.
Patient Experience

Questions & Answers
Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

Learn more and find your event today! themmrf.org/get-involved/mmrf-events
# Upcoming Patient Education Events

**Save the Date**

For more information or to register, visit themmrf.org/educational-resources

<table>
<thead>
<tr>
<th>Program</th>
<th>Date and Time</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Myeloma Society Annual Meeting FAQs Livestream</td>
<td>Tuesday, October 17 4:00 PM – 5:00 PM (ET)</td>
<td>Jesus Berdeja, MD Nick Barkemeyer, PA</td>
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<tr>
<td>Patient Summit Virtual</td>
<td>Saturday, October 21 11:00 PM – 4:00 PM (ET) 9:00 AM – 2:00 PM (MT)</td>
<td>Gurbakhash Kaur, MD Amrita Krishnan, MD Robert Rifkin, MD</td>
</tr>
<tr>
<td>Non-BCMA Bispecific Antibodies FAQs Livestream</td>
<td>Monday, October 30 2:00 PM – 3:00 PM (ET)</td>
<td>Hearn Jay Cho, MD, PhD</td>
</tr>
<tr>
<td>Patient Summit Boston, MA</td>
<td>Saturday, November 11 9:00 AM – 2:00 PM (ET)</td>
<td>Shonali Midha, MD Clifton Mo, MD Omar Nadeem, MD Kim Noonan, NP Paul Richardson, MD</td>
</tr>
<tr>
<td>Patient Summit Virtual</td>
<td>Saturday, January 13, 2024 12:00 PM – 5:00 PM (ET) 9:00 AM – 2:00 PM (PT)</td>
<td>Ajai Chari, MD Tom Martin, MD Sagar Lonial, MD</td>
</tr>
</tbody>
</table>
Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation

Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
- This partnership is one facet of the MMRF’s commitment to improve diversity and representation in myeloma clinical studies
- MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673
Thank you!