Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

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Disclosures

Dr. Lentzsch has disclosed the following relevant financial relationships:

Consultant/Advisor: Takeda, GSK, Regeneron
Data Safety Monitoring Board: Janssen, BMS, Adaptive
Research Grant: Sanofi, Zentalis
Patent and Royalties: CAEL-101

CAR T Has Reached Standard-of-Care Status for Multiple Myeloma in the U.S.

Mar 2021 Ide-cel
Feb 2022 Cilta-cel

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

FDA Approves cilta-cabtagene autoleucel for relapsed or refractory multiple myeloma

These are the first regulatory approved CAR Ts that are not targeting CD19.
**Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma**

### Autologous BCMA CAR T in Pivotal Trials

**Idecabtagene vicleucel (Ide-cel, bb2121)**

**Ciltacabtagene autoleucel (Cilta-cel, JNJ-68284528)**

- **Binding domains**
  - VHH
  - CD3ζ
  - 4-1BB

**FDA approved**


### KarMMa-1 Study (Ide-cel)

<table>
<thead>
<tr>
<th>Response</th>
<th>CAR+ T cells</th>
<th>median PFS, mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>150 × 10⁶ (n=4)</td>
<td>2.8 (1.0–NE)</td>
</tr>
<tr>
<td>Complete response rate (%)</td>
<td>300 × 10⁶ (n=70)*</td>
<td>5.8 (4.2–8.9)</td>
</tr>
<tr>
<td>CR/sCR and MRD-negative</td>
<td>450 × 10⁶ (n=54)*</td>
<td>12.1 (8.8–12.3)</td>
</tr>
<tr>
<td>CR/sCR and MRD not evaluable</td>
<td>Ide-cel treated</td>
<td>8.8 (5.6–11.6)</td>
</tr>
<tr>
<td>VGPR</td>
<td>150 × 10⁶ (n=4)</td>
<td>2.8 (1.0–NE)</td>
</tr>
<tr>
<td>PR</td>
<td>300 × 10⁶ (n=70)*</td>
<td>5.8 (4.2–8.9)</td>
</tr>
<tr>
<td></td>
<td>450 × 10⁶ (n=54)*</td>
<td>12.1 (8.8–12.3)</td>
</tr>
<tr>
<td></td>
<td>Ide-cel treated</td>
<td>8.8 (5.6–11.6)</td>
</tr>
</tbody>
</table>

*Regulatory agency–approved dose

- PFS increased with higher target dose and depth of response
- Median PFS was 12 mos at 450 × 10⁶ CAR+ T cells
- Median PFS was 20 mos in patients with CR/sCR

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**Study discontinued. Next-generation CAR T in trial.**

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This is for educational purposes only.
KarMMa-1 Study (Ide-cel)
Long-Term Follow-Up

- OS is not decreased for older patients or those with extramedullary or triple-refractory disease
- OS is decreased in patients with R-ISS stage III

### OS in high-risk patient subgroups

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>21.7 (17.1–31.2)</td>
</tr>
<tr>
<td>≥65 y</td>
<td>28.3 (20.2–NE)</td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>NE (21.3–NE)</td>
</tr>
<tr>
<td>Yes</td>
<td>20.2 (15.5–28.3)</td>
</tr>
<tr>
<td>Triple refractory</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>31.2 (19.9–NE)</td>
</tr>
<tr>
<td>Yes</td>
<td>21.7 (18.2–NE)</td>
</tr>
</tbody>
</table>

### R-ISS Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>I–II</td>
<td>28.3 (21.7–NE)</td>
</tr>
<tr>
<td>III</td>
<td>8.8 (6.0–13.4)</td>
</tr>
</tbody>
</table>


KarMMa-1 (Ide-cel) Comparison With Other Therapies


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This is for educational purposes only.
CARTITUDE-1 Study (Cilta-cel)

- Study population
  - 3 or more prior lines of therapy
  - Triple class and CD38 mAb exposed
- Median 2-yr follow-up

ORR: 97.9% (95/97)
Best response = 
- sCR
- VGPR
- PR

Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos (95% CI)</th>
<th>27-month PFS rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Not reached (24.5–NE)</td>
<td>54.9 (44.0–64.6)</td>
</tr>
<tr>
<td>sCR patients</td>
<td></td>
<td>64.2 (51.9–74.1)</td>
</tr>
</tbody>
</table>

Overall Survival

27-month OS rate, 70.4%; median OS not reached

Cilta-cel CARTITUDE-1 vs LocoMMotion Real-World Prospective Study: PFS and OS Is Better With CAR T

- LocoMMotion (NCT04035226) patients with RRMM, triple-class exposed treated with SOC regimens
- LocoMMotion patient distribution 91% Europe, 9% U.S.

**Progression-Free Survival**

- **Unadjusted:** HR 0.19 (0.12, 0.29)
- **ATT weighted:** HR 0.15 (0.08, 0.29)

**Overall Survival**

- **Unadjusted:** HR 0.28 (0.16, 0.49)
- **ATT weighted:** HR 0.20 (0.09, 0.41)

---

**BCMA CAR T Pivotal Trials: Toxicities**

<table>
<thead>
<tr>
<th></th>
<th>Ide-Cel: Phase 2 (KarMMA-1)¹</th>
<th>Cilta-Cel: Phase 1b/II (CARTITUDE-1)²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=128</td>
<td>N=97</td>
</tr>
<tr>
<td><strong>CRS, any Gr≥ Gr 3</strong></td>
<td>84%/5%</td>
<td>95%/4%</td>
</tr>
<tr>
<td><strong>Onset day</strong></td>
<td>median (range)</td>
<td>7 (1–12)</td>
</tr>
<tr>
<td></td>
<td>1 (1–12)</td>
<td>1 (1–12)</td>
</tr>
<tr>
<td><strong>Duration, days</strong></td>
<td>median (range)</td>
<td>4 (1–97)</td>
</tr>
<tr>
<td></td>
<td>5 (1–63)</td>
<td>4 (1–97)</td>
</tr>
<tr>
<td><strong>ICANS, any Gr≥ Gr 3</strong></td>
<td>18%/3%</td>
<td>22%/11%*</td>
</tr>
<tr>
<td><strong>Drug use</strong></td>
<td>Toci: 52%</td>
<td>Toci: 69%</td>
</tr>
<tr>
<td></td>
<td>Steroid: 15%</td>
<td>Steroid: 22%</td>
</tr>
<tr>
<td></td>
<td>Anakinra: 19%</td>
<td>Anakinra: 19%</td>
</tr>
</tbody>
</table>

*Delayed-onset movement and neurocognitive symptoms noted in 12%, 8% Gr3 or higher.

### CAR T Access Remains an Issue

#### Survey of 20 centers. Responses from 15 centers.

<table>
<thead>
<tr>
<th>Annual CAR T infusions (all diseases, on/off trial) pre-/during COVID</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50–100 (&lt;50, 100–300)</td>
</tr>
<tr>
<td>CAR T infusion volume for MM in 2021</td>
<td>10–50 (&lt;5, 50–100)</td>
</tr>
<tr>
<td>Patients on wait list (since ide-cel approval)</td>
<td>20 (5–100)</td>
</tr>
<tr>
<td>Number of FDA approved CAR T slots given per month</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>Duration a patient is on waiting list</td>
<td>6 (3–8) months</td>
</tr>
<tr>
<td>Outcomes of patients on wait list</td>
<td></td>
</tr>
<tr>
<td>FDA approved CAR-T</td>
<td>25% (0%–64%)</td>
</tr>
<tr>
<td>CAR-T trial</td>
<td>25% (0%–50%)</td>
</tr>
<tr>
<td>non-CAR-T trial</td>
<td>25% (0%–50%)</td>
</tr>
<tr>
<td>hospice or death</td>
<td>25% (25%–75%)</td>
</tr>
</tbody>
</table>


### Challenges With Patient Selection for Commercial CAR T Slots

- **Maximize total benefit**: Most likely to make it to leukapheresis, most likely to make it to CAR T dosing, most likely to achieve clinical response.
- **Treat people equally**: Lottery, time spent on waiting list.
- **Priority to the worst off**: Lottery.
- **Promote/reward social value**: Lottery, time spent on waiting list.

- **Highest myeloma disease burden**: Most likely to make it to CAR T dosing, most likely to achieve clinical response.
- **Most comorbidities (ex: not eligible for clinical trials)**: Most likely to make it to CAR T dosing, most likely to achieve clinical response.
- **No other myeloma treatment option left**: Most likely to make it to CAR T dosing, most likely to achieve clinical response.

Maximize total benefit

<table>
<thead>
<tr>
<th></th>
<th>Critical</th>
<th>High</th>
<th>Medium</th>
<th>Lowest</th>
<th>Not used</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>40%</td>
<td>40%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
<td>10%</td>
<td>50%</td>
<td>30%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>40%</td>
<td>10%</td>
<td>50%</td>
<td>30%</td>
<td>20%</td>
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<tr>
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<td>50%</td>
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<tr>
<td>80%</td>
<td>10%</td>
<td>50%</td>
<td>30%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>100%</td>
<td>10%</td>
<td>50%</td>
<td>30%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Conclusions

• 2 FDA-approved CAR T-cell options: ide-cel and cilta-cel
• Ida-cel and cilta-cel have a similar safety profile
  – **CRS:** ide-cel 85% and cilta-cel 95%
  – **ICANs:** ide-cel 18% and cilta-cel 22%
• **ORR**
  – Ide-cel @450 × 10^6 CAR T cells → ORR 82.5%, CR 39%
  – Cilta-cel → ORR 92.7% and CR 82.5%
• **12 months median PFS** seems to be longer with cilta-cel:
  – Ide-cel 12 mos at 450 × 10^6 CAR T cells
  – Cilta-cel median PFS not reached → 27 months PFS 54.9%
• ? CAR T cells up front to replace ASCT?

Bispecific Antibodies for Multiple Myeloma: Clinical Safety and Efficacy

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Director, Judy and Bernard Briskin Center for Multiple Myeloma Research
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Disclosures

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Consultant/Advisor: Adaptive Biotechnologies, Artiva, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, Regeneron, Sanofi, Sutro BioPharma

Research Grant: Janssen

Speakers Bureau: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Takeda

Stock Ownership: Bristol Myers Squibb

Antibody–drug conjugate

T-cell bispecific antibodies

Bispecific Antibodies Clinical Trials in Multiple Myeloma

- AMG420 (BCMA×CD3)
- Pavurutamab (AMG701; BCMA × CD3)
- Alnuctamab (CC93269; BCMA × CD3)
- Elranatamab (PF06863135; BCMA × CD3)
- Linvoseltamab (RGN5458; BCMA × CD3)
- Teclistamab (JNJ64007957; BCMA × CD3)
- TNB-383B (BCMA × CD3)
- Talquetamab (JNJ64407564; GPRC5D × CD3)
- Cevostamab (BFCR4350A; FCRH5 × CD3)
- GBR1342 (CD38 × CD3)
- AMG424 (CD38 × CD3)


Bispecific Antibodies

Bispecific antibodies bind MM cell (multiple targets available) and to T lymphocyte

Figure 1 from Singh A, et al. Overcoming the challenges associated with CD3+ T-cell redirection in cancer. Br J Cancer. 2021 Mar;124(6):1037-1048. Available through Creative Commons Attribution 4.0 International License: http://creativecommons.org/licenses/by/4.0/
Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

BCMA (B-Cell Maturation Antigen)

- Receptor for BAFF and APRIL
- Expressed on mature B-cell subsets, PCs, and plasmacytoid DCs
- Maintains plasma cell homeostasis
  - BCMA/- mice have normal B cell #s, impaired PC survival

Figure 2 from Hengeveld PJ, Kersten MJ. B-cell activating factor in the pathophysiology of multiple myeloma: a target for therapy? Blood Cancer J. 2015 Feb 27;5(2):e282. Available through Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0 from AACR.

MajesTEC-1: Teclistamab Phase 2 Study Design

MajesTEC-1 is a first-in-human, phase 1/2, open-label, multicohort, multicenter dose-escalation study to evaluate teclistamab in patients with RRMM who previously received ≥3 prior lines of therapy and were triple-class exposed

SCREENING

Cohort A (triple-class exposed)
- Key eligibility criteria
  - Measurable MM
  - RRMM, ≥3PL
  - Prior PI, IMiD, and anti-CD38
  - No prior BCMA therapy

TREATMENT

Week 1
- Step-up doses of teclistamab SC (0.06 and 0.3 mg/kg)

Cycles 1+
- Weekly treatment dose of teclistamab SC 1.5 mg/kg
- Continue until progressive disease

POSTTREATMENT

Follow-up 2 years after LPI

Primary end point: ORR
Key secondary end points: DOR, ≥VGPR, ≥CR, sCR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

MajesTEC-1: Patient Demographics and Baseline Characteristics

- N=165
- Median age, 64 years (33–84)
- Median prior lines of therapy, 5.0 (2–14)
- Exposure status
  - Triple-class exposed, 100%
  - Penta-drug exposed, 70.3%
- Refractory status
  - Triple-class exposed, 77.6%
  - Penta-drug exposed, 30.3%
  - Refractory to last line of therapy, 89.7%


MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Teclistamab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, % (n)</td>
<td>63 (104/165)</td>
</tr>
<tr>
<td>≥Complete response rate (%)</td>
<td>39.4</td>
</tr>
<tr>
<td>≥VGPR response rate (%)</td>
<td>58.8</td>
</tr>
<tr>
<td>sCR</td>
<td>32.7</td>
</tr>
<tr>
<td>CR</td>
<td>6.7</td>
</tr>
<tr>
<td>VGPR</td>
<td>19.4</td>
</tr>
<tr>
<td>PR</td>
<td>4.2</td>
</tr>
</tbody>
</table>

- At a median follow-up of 14.1 months (range: 0.3–24.4)
  - ORR of 63% (95% CI: 55.2–70.4) represents a substantial benefit for patients with triple-class–exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate (by next-generation sequencing)
  - 26.7% at a threshold of 10^{-5}
  - In patients who achieved ≥CR, the MRD-negativity rate was 46%

### MajesTEC-1: ORR Across Subgroups

**ORR was consistent across clinically relevant subgroups, including high cytogenetic risk and penta-drug refractory subgroups**

#### Table: MajesTEC-1: ORR Across Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>65–75 years</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Baseline ISS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Baseline renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 mL/min/1.73m²</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>≤60 mL/min/1.73m²</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

#### Table: MajesTEC-1: ORR Across Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Extramedullary plasmacytomas</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>27</td>
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<tr>
<td>Prior lines of therapy</td>
<td></td>
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<tr>
<td>≤3</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>114</td>
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<tr>
<td>Refractory status</td>
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<tr>
<td>Triple class</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Penta drug</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

**Percent 0 25 50 75 100**

*MajesTEC-1: Duration of Response*

- Median DOR 18.4 months
- Median PFS 11.3 months
- Median OS 18.3 months


MajesTEC-1: Response Durability

- Responses were durable and deepening over time

MajesTEC-1: Adverse Events

**Any grade**

- Hematologic
  - Neutropenia, 70.9%
  - Anemia, 52.1%
  - Thrombocytopenia, 40%
- Nonhematologic
  - CRS, 72.1%
  - Diarrhea, 28.5%
  - Fatigue, 27.9%
  - Nausea, 27.3
  - Pneumonia, 18.2%
  - COVID-19, 17.6%
  - Neurotoxic event, 14.5%

**Grade 3/4**

- Hematologic
  - Neutropenia, 64.2%
  - Anemia, 37%
  - Thrombocytopenia, 21.2%
- Nonhematologic
  - CRS, 0.6%
  - Diarrhea, 3.6%
  - Fatigue, 2.4%
  - Nausea, 0.6
  - Pneumonia, 12.7%
  - COVID-19, 12.1%
  - Neurotoxic event, 0.6%

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BCMA-Directed Bispecific Antibodies in Development

<table>
<thead>
<tr>
<th></th>
<th>Current Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecristamab</td>
<td>Approved!</td>
</tr>
<tr>
<td>Elranatamab</td>
<td>3</td>
</tr>
<tr>
<td>AMG 701</td>
<td>1/2</td>
</tr>
<tr>
<td>REGN5458</td>
<td>1/2</td>
</tr>
<tr>
<td>CC-93269</td>
<td>1</td>
</tr>
<tr>
<td>ABBV-383</td>
<td>1</td>
</tr>
</tbody>
</table>


MagnetisMM-1: Elranatamab Monotherapy

- Dose escalation (Part 1, n=30): elranatamab 80–1,000 μg/kg weekly
- Priming cohorts (Part 1.1, n=20): single priming dose (600 μg/kg) followed 1 week later by full dose (1,000 μg/kg) q1w or q2w
- Expansion (Part 2A, n = 15): single priming dose (44 mg) followed by full dose (76 mg) weekly
  - Premedication was given with priming dose and first full dose
- Data cutoff was July 26, 2021

MagnetisMM-1: Response

- N=55, Median follow-up: 10.6 mo
- ORR: 64%
  - ≥CR: 35% (all evaluable patients MRD-negative [13/13])
  - 54% ORR in patients with prior BCMA-directed therapy

MagnetisMM-1: Adverse Events

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>2 (3.6)</td>
<td>14 (25.5)</td>
<td>25 (45.5)</td>
<td>41 (74.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (3.6)</td>
<td>8 (14.5)</td>
<td>26 (47.3)</td>
<td>0</td>
<td>36 (65.5)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>3 (5.5)</td>
<td>26 (47.3)</td>
<td>29 (52.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (12.7)</td>
<td>6 (10.9)</td>
<td>5 (9.1)</td>
<td>10 (18.2)</td>
<td>28 (50.9)</td>
</tr>
<tr>
<td>Nonhematologic, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>28 (50.9)</td>
<td>20 (36.4)</td>
<td>0</td>
<td>0</td>
<td>48 (87.3)</td>
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<tr>
<td>Injection site reaction</td>
<td>27 (49.1)</td>
<td>4 (7.3)</td>
<td>0</td>
<td>0</td>
<td>31 (56.4)</td>
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<tr>
<td>Diarrhea</td>
<td>12 (21.8)</td>
<td>8 (14.5)</td>
<td>2 (3.6)</td>
<td>0</td>
<td>22 (40.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (10.9)</td>
<td>13 (23.6)</td>
<td>3 (5.5)</td>
<td>0</td>
<td>22 (40.0)</td>
</tr>
</tbody>
</table>

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

BCMA Bispecifics

- High response rates
- Subcutaneous administration (schedule?)
- Durable?
- Efficacy after other BCMA-directed therapies
- Combination strategies
- TRIMM study: teclistamab + dara + pom

GPRC5D: G Protein-Coupled Receptor Class C Group 5 Member D

- Orphan G protein–coupled receptor of unknown function
- Limited expression in healthy human tissue, primarily in plasma cells and hair follicles
- Highly expressed in myeloma cells and associated with poor prognostic factors in multiple myeloma
- No known shed peptides or extracellular domain shedding (reduced risk for sink effect)
- Ideal target for CD3 redirection

Talquetamab: GPRC5D×CD3 Bispecific Antibody

- Talquetamab is a first-in-class antibody that binds to both GPRC5D and CD3
- Talquetamab redirects T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of multiple myeloma\(^1\)-\(^3\)
- First-in-human phase 1 study is ongoing to evaluate talquetamab in patients with RRMM (NCT03399799)


Talquetamab: Overall Response Rate

<table>
<thead>
<tr>
<th>Response</th>
<th>405 µg/kg SC QW (n=30)</th>
<th>800 µg/kg SC Q2W (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mos (range)</td>
<td>13.2 (1.1–24.0)</td>
<td>7.7 (0.7–16.0)</td>
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<tr>
<td>ORR, n (%)</td>
<td>21 (70.0)</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td>Triple-class–refractory patients, n/N (%)</td>
<td>15/23 (65.2)</td>
<td>23/34 (67.6)</td>
</tr>
<tr>
<td>Penta-drug–refractory patients, n/N (%)</td>
<td>5/6 (83.3)</td>
<td>9/12 (75)</td>
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<tr>
<td>Median tie to first confirmed response, mos (range)</td>
<td>0.9 (0.2–3.8)</td>
<td>1.2 (0.3–6.8)</td>
</tr>
</tbody>
</table>

Talquetamab: Duration of Response


Talquetamab: Safety Profile

<table>
<thead>
<tr>
<th>AEs (≥20% of Total SC population)</th>
<th>405 µg/kg SC QW (n=30)</th>
<th>800 µg/kg SC Q2W (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (66.7)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (56.7)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (40.0)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>12 (40.0)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (36.7)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Nonhematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>23 (76.7)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Skin-related AEs</td>
<td>20 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>19 (63.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Nail-related AEs</td>
<td>18 (60.0)</td>
<td>0</td>
</tr>
<tr>
<td>Rash-related AEs</td>
<td>14 (46.7)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>12 (40.0)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (36.7)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (33.3)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9 (30.0)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>9 (30.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (30.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Most common AEs were CRS, skin-related events, and dysgeusia
  - Dysgeusia managed with supportive care and dose adjustments
- Cytopenias were mostly confined to step-up and cycle 1–2 doses and generally resolved within 1 week
- Infections occurred in 46.7% of patients at 405 µg/kg SC QW and 38.6% at 800 µg/kg SC Q2W (grade 3/4: 6.7%/9.1%)
- No patients died due to drug-related AEs

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Cevostamab: FcRH5×CD3 Bispecific Antibody

• Fc receptor-homolog 5 (FcRH5)
  – Expressed on myeloma cells with near 100% prevalence
  – Expression on myeloma and plasma cells > normal B cells

• Cevostamab
  – Humanized IgG-based T-cell–engaging bispecific antibody
  – Targets FcRH5 on myeloma cells and CD3 on T cells

• Ongoing phase I dose-escalation and expansion trial (NCT03275103) evaluating safety and activity of cevostamab monotherapy in patients with RRMM


Cevostamab: Response Rate

• 51/53 patients efficacy evaluable; no response in ≤3.6/10.8 mg cohorts
• ORR* in ≥3.6 mg/20 mg cohorts
  – 53% (18/34) in all patients
  – 41% (7/17) in penta-drug refractory patients
  – 63% (5/8) in patients with prior anti-BCMA
• Median time to first response/best response: 29.5 days (range: 21–105)/57.5 days (range: 21–272)
• Response irrespective of target expression level in patients assessed to date
• MRD negativity by NGS (<10−5) detected in 6/7 evaluable patients with ≥VGPR

*Best response of PR, VGPR, CR, or sCR by IMWG uniform response criteria 2016
Cevostamab: Response Duration

- Median follow-up in responders: 10.3 months (range: 2.7–19.5)
- 8 patients with duration of response ≥6 months
- 4 patients continued in response after treatment discontinuation*


Cevostamab: Adverse Events

- Median follow-up: 8.1 months (range: 0.2–30.4)
- 28 patients with serious AEs
  - Treatment-related events (13 patients) in ≥2 patients were CRS (6 patients)
- 5 patients (9%) with AEs leading to withdrawal
  - Treatment-related events (2 patients) were pneumonitis (1 patient) and meningitis (1 patient)
- 7 pts (13%) with Gr 5 AE (malignant neoplasm progression, 5 patients; respiratory failure, 2 patients)
  - No treatment-related Gr 5 events
- 1 patient (2%) with DLT of Gr 3 pneumonia in the 3.6/90 mg cohort; MTD not reached

Conclusions

- T cell–directed therapies current state; advanced disease
- Unknown
  - Sequencing, same targets?
  - Renal failure
  - CNS disease

Options for Patients Who May Not Have Access to CAR T or Bispecifics

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Harvard Medical School
Clinical Program Leader and Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Boston, Massachusetts
Disclosures

Dr. Richardson has disclosed the following relevant financial relationships:

Consultant/Advisor: AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Karyopharm Therapeutics, Oncopeptides, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, Takeda

Research Grants: Bristol Myers Squibb/Celgene, Karyopharm Therapeutics, Oncopeptides, Takeda

Treatment of MM Is a Marathon, Not a Sprint

Strategic and Practical Considerations Key

• Treatment options rapidly diminish with each progression
• Goal in advanced RRMM: stop further progression, maintain disease control, preserve QoL

Adapted from Borrello I. Leuk Res. 2012;36:S3.
### Treatment of MM in 2022: Multiple Therapies Approved or Under Investigation

<table>
<thead>
<tr>
<th>Backbone/standard-of-care agents</th>
<th>Recent approvals / later relapse</th>
<th>Emerging therapies for MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMiDs</td>
<td>ADCs</td>
<td>BITEs/ bispecifics</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Belantamab mafodotin</td>
<td>Teclistamab (BCMA × CD3)</td>
</tr>
<tr>
<td>Bortezomib*</td>
<td>Selinexor</td>
<td>CAR NK cell therapies†</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Venetoclax</td>
<td>Teclistamab (BCMA × CD3)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Citlactagene autoleucel</td>
<td>Elirantamab† (BCMA × CD3)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Vorinostat†</td>
<td>Iberdomide†</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Melflufen††</td>
<td>Immune checkpoint inhibitors†</td>
</tr>
<tr>
<td>Marizomib†</td>
<td></td>
<td>Pavuvatamab† (BCMA × CD3)</td>
</tr>
</tbody>
</table>

**KEY TARGETS, 2022**
- Genomic abnormalities
- Target and overcome mutations
- Critical role of combination and continuous therapy
- Evolving position and timing of ASCT
- Excess protein production
- Target protein degradation
- Immune suppression
- Restore anti-MM immunity

*Also approved in combination with liposomal doxorubicin; †Not currently approved in RRMM; ‡FDA approval withdrawn. ¶Positive recommendation from CHMP for full EMA approval; §Granted FDA Breakthrough Therapy designation.


### Selected Emerging Treatment Options for MM 2022: Novel MOAs

- Novel mechanisms of action are urgently needed and are being brought forward into early relapse and NDMM
- Emerging role of cellular therapies (CAR T-cell therapies), bispecific antibodies, and more
- Continued promise of small molecules and targeted agents (eg, peptide drug conjugates, CELMoDs, venetoclax)
- Further development of novel combinations (eg, with belantamab mafodotin, selinexor, immunoconjugates)

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Immune Therapy Approaches in MM

Figure 1 from Yamamoto L, et al. Harnessing the immune system against multiple myeloma: challenges and opportunities. Front Oncol. 2021;10:606368. Copyright © 2021 Yamamoto, Amodio, Gulla, and Anderson.

Multiple Therapies Approved or Under Investigation in RRMM

Several agents have been recently approved for later relapses in RRMM; these agents are moving up the treatment algorithm and being investigated in combination regimens with the standard-of-care backbone regimens.

*Also approved in combination with liposomal doxorubicin; †Not currently approved in RRMM; ‡FDA approval withdrawn. ¶Positive recommendation from CHMP for full EMA approval; §Granted FDA Breakthrough Therapy designation.

Adapted from Richardson PG. 8th COMy World Congress, Paris, France, May 2022.
Belantamab Mafodotin: BCMA-Targeted ADC

First ADC approved in RRMM (2020)

Adapted from Figure 2 of Cho S-F, et al. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-based immunotherapy. Front Immunol 2018;9:1821.

Belantamab Mafodotin: Initial Approval Based on DREAMM-2 in Heavily Pretreated RRMM

<table>
<thead>
<tr>
<th>Patients</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Median age: 65 and 67 years</td>
<td>• 72% overall rate of keratopathy*</td>
</tr>
<tr>
<td>• High-risk cytogenetics: 42% and 47%</td>
<td>• Grade 3/4 keratopathy in 27% (2.5 mg/kg) and 21% (3.4 mg/kg) of patients</td>
</tr>
<tr>
<td>• Median prior lines of therapy: 7 and 6</td>
<td>• Grade 3/4 thrombocytopenia in 20% and 33%, anemia in 20% and 25%, respectively</td>
</tr>
<tr>
<td>• 90% and 89% lenalidomide-refractory</td>
<td>• 3% discontinued due to corneal event</td>
</tr>
<tr>
<td>• 76% and 75% bortezomib-refractory</td>
<td>• 2.5 mg/kg chosen for further studies</td>
</tr>
<tr>
<td>• 100% and 92% daratumumab-refractory</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORR</th>
<th>Belantamab mafodotin 2.5 mg/kg (n=97)</th>
<th>Belantamab mafodotin 3.4 mg/kg (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>32%*</td>
<td>35%</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>11.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>2.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>13.7*</td>
<td>14.0</td>
</tr>
</tbody>
</table>


DREAMM-5: Belantamab Mafodotin + Nirogacestat

**Rationale**
- Nirogacestat is a gamma-secretase inhibitor that may increase cell-surface levels of BCMA
- This may augment belantamab mafodotin activity by increasing target expression

**24 patients treated with combination**
- 10 in dose-escalation
- 14 in expansion cohort
- Median of 4.5 / 4.0 prior lines of therapy
- EMD in 20% / 29%
- Patients received a median of 8.5 (range 1–29) / 4.0 (1–9) cycles

**Outcomes**
- ORR: 38%
- Clinical benefit rate (≥MR): 38%
- Rate of ≥ stable disease: 75%
- Median follow-up 12–34.5 weeks (early results)

**Safety**
- 100% had AEs (83% had grade ≥3 AEs)
  - Ocular events 54% (13%)
  - Grade ≥3 thrombocytopenia 21%
- 29% had AEs leading to dose reductions
  - 13% discontinuations due to AEs


Other Novel Targeted Agents for RRMM: Selinexor

**Mechanism of Action: Inhibition of XPO1**

**XPO1 overexpression**
1. Enables cancer cells to escape tumor suppressor proteins (TSPs) mediated cell cycle arrest and induction of apoptosis
2. Correlates with poor prognosis and drug resistance

**Inhibition of XPO1 impacts tumor cells via 3 core mechanisms**
1. Increases nuclear levels and activation of TSPs
2. Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels
3. Retains activated glucocorticoid receptor in the nucleus

Selinexor is an oral selective XPO1 inhibitor; preclinical data demonstrate that, in MM models, selinexor:
- Reactivates multiple TSPs relevant to MM, inhibits NF-kB signaling and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone
- Demonstrates synergistic activity in combination with bortezomib, pomalidomide, and lenalidomide in vitro and in vivo

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>High-Risk Cytogenetics</th>
<th>Frailty</th>
<th>Previous PI Therapies</th>
<th>Previous Lenalidomide Therapy</th>
<th>No. of Prior Lines of Therapy</th>
<th># Patients</th>
<th>Overall HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;65 years</td>
<td>Yes (Del[17p] or t[4;14] or t[14;16] or 1q21)</td>
<td>Frail</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>161</td>
<td>0.74 (0.49–1.11)</td>
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<tr>
<td></td>
<td>≥65 years</td>
<td>No</td>
<td>Fit</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>241</td>
<td>0.55 (0.37–0.83)</td>
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<tr>
<td></td>
<td></td>
<td>Del[17p]</td>
<td></td>
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<td></td>
<td>3</td>
<td>192</td>
<td>0.67 (0.45–0.98)</td>
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<tr>
<td></td>
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<td>Frailty</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>210</td>
<td>0.62 (0.42–0.95)</td>
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<tr>
<td></td>
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<td>Previous PI Therapies</td>
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<td>5</td>
<td>37</td>
<td>0.38 (0.16–0.86)</td>
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<tr>
<td></td>
<td></td>
<td>Previous Lenalidomide Therapy</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>130</td>
<td>0.69 (0.40–1.17)</td>
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<tr>
<td></td>
<td></td>
<td>No. of Prior Lines of Therapy</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>272</td>
<td>0.66 (0.47–0.93)</td>
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<td></td>
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<td></td>
<td>8</td>
<td>307</td>
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<td>9</td>
<td>95</td>
<td>0.26 (0.11–0.60)</td>
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<td></td>
<td></td>
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<td></td>
<td>10</td>
<td>154</td>
<td>0.63 (0.41–0.97)</td>
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<td></td>
<td></td>
<td>11</td>
<td>248</td>
<td>0.66 (0.45–0.96)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>12</td>
<td>198</td>
<td>0.63 (0.41–0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td>204</td>
<td>0.69 (0.48–1.01)</td>
</tr>
</tbody>
</table>

Phase 3 trial (N=402)

• 195 SVd vs 207 Vd
• Median of 2 prior therapies

Efficacy

• Median PFS 13.93 vs 9.46 months (HR 0.70)
• ORR 76.4% vs 62.3%
• ≥ VGPR 44.6% vs 32.4%
• Median DOR 20.3 vs 12.9 months

Safety

• Higher rates of grade 3–4 thrombocytopenia (39% vs 17%), anemia (16% vs 10%), and cataracts (9% vs 1%) with SVd vs Vd
• Significantly lower rate of PN (32% vs 47%) and grade ≥ 2 PN (21% vs 34%)
• Grade 3 PN: 4.6% vs 8.8%

BOSTON Trial: Selinexor-Vd vs Vd in Patients With MM Who Had Received 1–3 Prior Therapies (FDA Approved)

Other Selinexor Combinations in RRMM

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>ClinicalTrials.gov</th>
<th>Setting</th>
<th>Primary endpoint</th>
<th>Initial completion</th>
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</thead>
<tbody>
<tr>
<td>BENCH</td>
<td>3</td>
<td>NCT04939142</td>
<td>1–3 prior lines, Relapsed or refractory MM</td>
<td>PFS</td>
<td>July 2024</td>
</tr>
<tr>
<td>NCI-2020-13697</td>
<td>2</td>
<td>NCT04756401</td>
<td>1–3 prior lines, Selinexor + Dara-Kd</td>
<td>MRD-negativity rate</td>
<td>September 2023</td>
</tr>
<tr>
<td>STOMP</td>
<td>1/2</td>
<td>NCT02343042</td>
<td>Multiple settings, Combinations with Pom-dex, Vd, Rd, Pom-Vd, Dara-dex,</td>
<td>MTD/RP2D ORR</td>
<td>January 2025</td>
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<tr>
<td>SELIBORDARA</td>
<td>2</td>
<td>NCT03589222</td>
<td>23 prior lines, Selinexor + Dara-Vd</td>
<td>ORR</td>
<td>August 2023</td>
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<tr>
<td>SCOPE</td>
<td>1/2</td>
<td>NCT04764942</td>
<td>≥ 2 prior lines, Selinexor-Pom-dex ± carfilzomib</td>
<td>MTD ORR</td>
<td>March 2025</td>
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<tr>
<td>EMN29</td>
<td>3</td>
<td>NCT05028348</td>
<td>1–4 prior lines, Selinexor-Pom-dex vs Elo-Pom-dex</td>
<td>PFS</td>
<td>July 2023</td>
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<tr>
<td>NCI-2014-01199</td>
<td>1</td>
<td>NCT02199665</td>
<td>≥ 2 prior lines, Selinexor + Rd, Pom-dex</td>
<td>MTD</td>
<td>July 2022</td>
</tr>
<tr>
<td>Pro2020-0369</td>
<td>2</td>
<td>NCT04661137</td>
<td>Refractory to disease progression on prior carfilzomib, pomalidomide,</td>
<td>ORR</td>
<td>January 2023</td>
</tr>
<tr>
<td>ClaSPd</td>
<td>2</td>
<td>NCT04843579</td>
<td>Selinexor + clarithromycin + Pom-dex</td>
<td>ORR, AEs</td>
<td>November 2023</td>
</tr>
<tr>
<td>SELVEDge</td>
<td>1/2</td>
<td>NCT05530421</td>
<td>Selinexor + venetoclax + dex in t(11;14)-positive RRMM</td>
<td>ORR</td>
<td>December 2025</td>
</tr>
<tr>
<td>ATG-010-IT-MM-001</td>
<td>2</td>
<td>NCT04891744</td>
<td>Selinexor + Thal-dex</td>
<td>ORR</td>
<td>December 2024</td>
</tr>
<tr>
<td>ATG-010-IT-MM-004</td>
<td>2</td>
<td>NCT04941937</td>
<td>Selinexor + Thal-dex/Rd/Pom-dex</td>
<td>ORR</td>
<td>December 2025</td>
</tr>
<tr>
<td>ATG-010-IT-MM-002</td>
<td>2</td>
<td>NCT04877275</td>
<td>Selinexor + Dooxi + Cyclo + dex</td>
<td>ORR</td>
<td>December 2024</td>
</tr>
</tbody>
</table>

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Other Novel Combinations: Dara-K-Pom-dex in RRMM

- **Dara given per APOLLO**
  - Plus weekly carfilzomib
  - Pomalidomide
  - Dexamethasone

- **24 RRMM patients; median of 2 prior regimens**
  - All had received lenalidomide and a PI
  - 54% prior pomalidomide; 13% prior carfilzomib
  - All were refractory to last prior therapy
  - 13% del17p; 8% t(14;16); 46% gain of 1q

- **12-month PFS: 86.2%**
- **Grade 3/4 hematologic AEs:**
  - Neutropenia 46%
  - Thrombocytopenia 25%
- **Non-hematologic AEs:**
  - Fatigue 42%
  - Dyspnea 36%
  - ALT/AST increased 29%
  - Insomnia 21%
  - Neuropathy 17%

- **Dara-Ixa-Pom-dex also being studied in RRMM, with ORR of 80% (28% sCR, 20% VGPR) seen to date1**

---

Ixa-Pom-Dex: Randomized Phase 2 Alliance Study A061202

- **Arm 1**
  - 28-day cycle
  - Pomalidomide 4 mg on days 1–21
  - Dexamethasone 40* mg on days 1, 8, 15, and 22

- **Arm 2**
  - 28-day cycle
  - Pomalidomide 4 mg on days 1–21
  - Dexamethasone 40* mg on days 1, 8, 15, and 22
  - Ixazomib 4 mg on days 1, 8, 15

- **Primary end point**
  - PFS
- **Secondary end points**
  - ORR, depth of response, DOR, OS, safety

- **Crossover at PD**
  - Treatment until PD, toxicity, or patient preference

- **Stratification factors**
  - High-risk vs standard-risk cytogenetics (FISH)
  - Prior PI exposure (Yes/No)
  - ISS stage I and II vs III disease at registration

- **Patients (n=80)**
  - ≥18 years of age
  - Relapsed MM
  - 1 prior line of therapy; progression on frontline lenalidomide
  - PI-naive/sensitive disease

*Arm 2 derived from Phase 1/2 study of IXA POM dex in RRMM – double refractory disease; ORR 52%, CBR 59% (n=29)

Ixa-Pom-Dex: Randomized Phase 2 Alliance Study A061202

<table>
<thead>
<tr>
<th>Response</th>
<th>Pom-dex (n=39)</th>
<th>Ixa-Pom-dex (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>43.6% (27.8%–60.4%)</td>
<td>63.2% (46.0%–78.2%)</td>
</tr>
<tr>
<td>sCR/CR</td>
<td>2.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>VGPR</td>
<td>2.6%</td>
<td>29.0%</td>
</tr>
<tr>
<td>PR</td>
<td>38.5%</td>
<td>34.2%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>5.1%</td>
<td>29.0%</td>
</tr>
<tr>
<td>Median DOR (months, range)</td>
<td>12.3 (2.8–42.3+)</td>
<td>23.7 (1.8–40.9+)</td>
</tr>
</tbody>
</table>

**Pom-dex**
- Grade 3/4 AEs included lymphopenia 26%, neutropenia 21%, anemia 13%, and fatigue 15%

**Ixa-Pom-dex**
- Grade 3/4 AEs included lymphopenia 40%, neutropenia 37%, anemia 16%, fatigue 16%, and hyperglycemia 11%
- No increase in discontinuation or dose adjustments for toxicity
- No COVID-related deaths and no treatment-related mortality in either arm

**PFS at data lock**

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Patients at Risk:</th>
<th>Pom-dex: median PFS 7.50 months (95% CI 4.90–15.32)</th>
<th>Ixa-Pom-dex: median PFS 20.35 months (95% CI 8.05–not reached)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>10–30</td>
<td>90</td>
<td>90</td>
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</tr>
<tr>
<td>30–60</td>
<td>80</td>
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<tr>
<td>60–90</td>
<td>70</td>
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<tr>
<td>90–120</td>
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</tr>
<tr>
<td>120–150</td>
<td>50</td>
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<td>50</td>
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<tr>
<td>150–180</td>
<td>40</td>
<td>40</td>
<td>40</td>
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<tr>
<td>180–210</td>
<td>30</td>
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<tr>
<td>210–240</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>240–270</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>270–300</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Preclinical findings
- MM cells exquisitely sensitive to melflufen, including melphalan- and bortezomib-resistant cells
- BMSCs more sensitive to melflufen than melphalan
- Cytoxicity of melflufen in MM cells not affected by co-culture with BMSCs
- Overcomes 17p deletion in resistant MM

**Other Novel Targeted Agents: Melflufen–Cytotoxic Drug–Peptide Conjugate**

- Melphalan flufenamide: novel targeted cytotoxic drug–peptide conjugate mechanism
- Rapidly taken up by plasma cells due to high lipophilicity
- Once inside, aminopeptidases cleave the compound and release melphalan “warhead,” where it causes maximal DNA damage to MM
- Active in melphalan and other alkylator resistance
- Potent activity in extramedullary disease
- Targeting “stemness?”
- Current dosing/dexamethasone is IV q28d; no mucositis or alopecia seen
- Granted FDA priority review in August 2020 and approved in March 2021
- FDA approval provisionally held, October 2021
- EMA review completed, CHMP recommended full approval, June 2022

HORIZON (OP-106) Phase 2 Trial in RRMM: Melflufen-dex in Pom- and/or CD38 mAb-Refractory Patients

Dosing
- Melflufen 40 mg IV on Day 1 + dex 40 mg days 1, 8, 15, and 22 in 28-day cycles

Patients
- RRMM with ≥2 prior lines, including IMiD and PI
- Refractory to Pom and/or anti-CD38 mAb

Safety
- Grade ≥3 neutropenia 79%, thrombocytopenia 76%, anemia 43%
- Grade ≥3 pneumonia 10%, hypophosphatemia 8%
- SAEs 49%; AEs leading to melflufen discontinuation 22%

Population | Median OS, months | Median PFS, months | Median DOR, months
--- | --- | --- | ---
ITT (N=157) | 11.6 | 4.2 | 5.5
Triple-class refractory (n=119) | 11.2 | 3.9 | 4.4
EMD (n=55) | 6.5 | 2.9 | 5.5

OCEAN (OP-103) Phase 3 Trial in RRMM: Melflufen-dex vs Pom-dex

- Phase 3, randomized, open-label, controlled, head-to-head, comparison study

SCREENING (day −21 to −1)
- Key eligibility criteria
  - Patients with RRMM
  - Aged ≥18 years
  - 2–4 prior lines of therapy including lenalidomide (within 18 months of randomization) and a PI
  - Refractory to lenalidomide and to last line of therapy
  - ECOG PS ≤2 (N=485)

RANDOMIZATION
- 1:1 Randomization
- Stratified by
  - Age (<75 vs ≥75 y)
  - Prior lines of therapy (2 vs 3+)
  - ISS score (I vs II or III)

TREATMENT (28-day cycles until disease progression or unacceptable toxicity)
- Melflufen (40 mg IV, day 1 of each cycle)
- Dexamethasone (40 mg PO weekly)³
- Pomalidomide (40 mg PO, days 1–21 of each cycle)
- Dexamethasone (40 mg PO weekly)³

FOLLOW-UP+
- Primary end point
  - PFS assessed by IRC per IMWG uniform response criteria
- Key secondary end points
  - ORR
  - OS
  - Safety and tolerability

ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; IMWG, International Myeloma Working Group; IRC, Independent Review Committee; ISS, International Staging System; N, intravenous; PO, orally; y, years.

Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

OCEAN (OP-103) Phase 3 Trial in RRMM: Melflufen-dex vs Pom-dex

- Superior PFS with Melflufen-dex vs Pom-dex
- No difference in OS on ITT analysis
- Post-hoc, pre-specified analysis: OS in favor of Melflufen-dex in patients without prior ASCT and in favor of Pom-dex in patients with prior ASCT
- ~ >3 years post ASCT subgroup ~ clear benefit


Other Novel Targeted Agents: Venetoclax, Selective Inhibitor of BCL-2

- Potent selective inhibitor of BCL-2
- Oncogene BCL-2 located on chromosome 11
- t(11;14) (in ~20% of MM patients) activates BCL-2 overexpression; also more common in PCL

Figure 1 from Sgherza N et al. Novel approaches outside the setting of immunotherapy for the treatment of multiple myeloma: the case of melflufen, venetoclax, and selinexor. Front Oncol. 2021; 11:716751. Copyright © 2021 Sgherza, Curci, Rizzi, and Musto.
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**Other Novel Targeted Agents: Venetoclax – Clinical Activity**

**BELLINI: Venetoclax + Vd (n=194) vs placebo-Vd (n=97)**
- Median PFS 22.4 vs 11.5 months (HR 0.63)
- Specific activity in t(11;14) RRMM patients
- Median PFS not reached vs 9.5 months (HR 0.11) in t(11;14) patients
- Median PFS not reached vs 9.9 months (HR 0.21) in patients with t(11;14) and/or high BCL2 expression
- But higher mortality overall with venetoclax+Vd (6% vs 1% grade 5 AEs)

**Phase 2 study: Venetoclax + Kd (n=49)**
- ORR 80% (92% in t(11;14) patients)
- ≥CR 41% (54% in t(11;14) patients)
- Median DOR 19.7 months
- Median PFS 22.8 months (24.8 months in t(11;14) patients)
- Grade ≥3 AEs 92%; SAEs 53%

**PCL**
- Promising preliminary findings in primary PCL and RR disease, specifically with t(11;14) or BCL-2 overexpression

**CANOVA phase 3 trial**
- Venetoclax + dex vs Pom-dex in t(11;14)-positive RRMM

---

**Multiple Therapies Approved or Under Investigation in RRMM**

<table>
<thead>
<tr>
<th>Backbone/standard-of-care agents</th>
<th>Recent approvals/later relapse</th>
<th>Emerging therapies for MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMiDs</td>
<td>ADCs</td>
<td>CELMoDs</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Belantamab</td>
<td>Teclistamab</td>
</tr>
<tr>
<td>Bortezomib*</td>
<td>Daratumumab (CD38)</td>
<td>Elranatamab†</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Isatuximab (CD38)</td>
<td>Pavurutamab†</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Eloxotumab (SLAMF7)</td>
<td>Taquetamab† (GPC3D × CD3)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Ixazomib</td>
<td>Cevostamab† (FoRHS × CD3)</td>
</tr>
<tr>
<td>Melphalan†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multiple emerging therapies for RRMM, including CELMoDs and bispecifics, are being extensively investigated and will further transform the RRMM treatment landscape in the next 5 years, with teclistamab the first to be approved, by EMA, in August 2022.

---

CELMoDs: Iberdomide and Mezigdomide (CC-92480)

Iberdomide Enhances In Vitro Immune-Stimulatory Activity vs Lenalidomide and Pomalidomide

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC50, nM</th>
<th>Ikaro</th>
<th>Aiolos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>67</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>24</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Iberdomide</td>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Figure 1 of Bjorklund CC, et al. Leukemia. 2020;34(4):1197-1201. Copyright © The Authors, 2019. Available through Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0.

Iberdomide in RRMM

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>ClinicalTrials.gov</th>
<th>Setting</th>
<th>Primary end point</th>
<th>Initial completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCALIBER-RRMM</td>
<td>3</td>
<td>NCT04975997</td>
<td>• 1–2 prior lines - Iberdomide + Dara-dex vs Dara-Vd</td>
<td>PFS</td>
<td>April 2026</td>
</tr>
<tr>
<td>ICON</td>
<td>2</td>
<td>NCT04392037</td>
<td>• 2-4 prior regimens - Iberdomide + Cd</td>
<td>PFS</td>
<td>November 2023</td>
</tr>
<tr>
<td>I2D IFM2021_03</td>
<td>2</td>
<td>NCT04998786</td>
<td>• 1st relapse - Iberdomide + Ixa-dex</td>
<td>≥VGPR rate</td>
<td>January 2025</td>
</tr>
<tr>
<td>CC-220-MM-001</td>
<td>1/2</td>
<td>NCT02773030</td>
<td>• RRMM - Iberdomide + dex, Vd, Dara-dex, Kd</td>
<td>MTD/RP2D ORR</td>
<td>May 2026</td>
</tr>
<tr>
<td>TIG-007</td>
<td>1/2</td>
<td>NCT05289492</td>
<td>• RRMM - Iberdomide + EOS88448 ± dex</td>
<td>Safety ORR</td>
<td>February 2024</td>
</tr>
</tbody>
</table>

Iberdomide is being more extensively investigated in NDMM; this is the anticipated primary treatment setting in the future.

Emerging Novel Therapies: CC-92480 (Mezigdomide), CELMoD

CC-92480, a potent CELMoD agent

Lenalidomide

Pomalidomide

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Putting the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Emerging Novel Therapies: CC-92480 (Mezigdomide), CELMoD

**First-in-Human Phase 1 Trial: CC-92480 + Dex**

- 76 heavily pretreated RRMM patients
  - 36.8% EMD
  - Median 6 prior therapies
  - 56% triple-class refractory

**CC-92480-MM-002 Phase 1/2 Study: CC-92480 + Vd**

- 19 heavily pretreated RRMM patients
  - Median time to response was 1.2 months (range 0.7–4.9)
  - Median duration of response was 10.4 months (95% CI, 9.5, not reached)

**Emerging Novel Therapies:**

- CC-92480 (Mezigdomide), CELMoD

**76 heavily pretreated RRMM patients**

- 36.8% EMD
- Median 6 prior therapies
- 56% triple-class refractory

**Grade 3/4 AEs**

- 64% neutropenia
- 32% anemia
- 18% thrombocytopenia
- 36% infections (14.5% pneumonia)

**64% neutropenia**

- 32% anemia
- 18% thrombocytopenia
- 36% infections (14.5% pneumonia)

**EMD**

- 36.8%

**Median 6 prior therapies**

- 56%

**50% triple-class refractory**

- 36.8%

**ORR: 21.1%**

- CR: 1 (1.3)
- VGPR: 2 (28.6)
- PR: 5 (62.5)
- SD: 1 (12.5)

**ORR: 40.0%**

- CR: 2 (28.6)
- VGPR: 1 (16.7)
- PR: 3 (42.9)
- SD: 1 (16.7)

**ORR: 54.5%**

- CR: 1 (16.7)
- VGPR: 1 (16.7)
- PR: 3 (50.0)
- SD: 1 (16.7)

**EMD**

- 36.8%

**Grade 3/4 AEs**

- Neutropenia
- Anemia
- Thrombocytopenia
- Infections

**First-in-Human Phase 1 Trial: CC-92480 + Dex**

- CC-92480-MM-002 Phase 1/2 Study: CC-92480 + Vd

**Conclusions and Future Directions**

**PIs, IMiDs, mAbs have produced significant improvements in PFS and OS in NDMM and in RRMM**

- Quadruplets are emerging standards of care in NDMM
- Quadruplet regimens also under investigation in non-transplant setting, with a focus on younger/fit patients
- MRD negativity a key goal of therapy; MRD-adapted therapy emerging – deferred ASCT approach
- Triplets are standards of care in early RRMM

**Next wave of immune therapies: mAbs (including ADCs, bispecifics) represent true new novel mechanisms, as well as other immuno-therapeutics (eg, CAR T cells)**

- Next-generation standards of care in NDMM and/or at first relapse?
- BCMA-targeted approaches may become a fourth pillar of NDMM treatment
- Baseline immune function is a key barrier to success and may be targetable
- Question of sequencing
- Crucially, are new therapies agnostic to mutational thrust?

**Next-generation small molecules/targeted therapy show great promise (eg, selinexor, melflufen, CELMoDS) under investigation in NDMM and RRMM**

**New insights to mechanisms of drug action are further expanding treatment/immuno-therapeutic opportunities with combinations**

- Additional novel immune therapies being investigated later in the treatment course – will move to earlier/first relapse if therapeutic potential emerges
Ongoing MM Collaborative Model for Rapid Translation of Novel Therapeutics From Bench to Bedside 2003–2022

Thank you!

Academia
Pharmaceuticals
Advocacy
MMRF/IMF
IMWG; LLS
FDA
EMEA
 NIH
NCI

Progress and Hope

14 novel drugs and 30 new FDA-approved drug combos/indications in last 18 years

Panel Discussion & Questions
Case Study 1

44-year-old man diagnosed with MM presented with extensive bone disease; BM cytogenetics revealed hyperdiploidy with trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19; kyphoplasty performed for severe L2 compression fracture

**Treatments**

<table>
<thead>
<tr>
<th>First Line</th>
<th>Second Line</th>
<th>Third Line</th>
<th>Fourth Line</th>
</tr>
</thead>
</table>
| • Lenalidomide + bortezomib + dex  
• Achieved VGPR  
• ASCT  
• Achieved CR by IF  
• Lenalidomide maintenance post-ASCT  
• Relapsed after 26 months | • Carfilzomib + pomalidomide + dex  
• Achieved VGPR  
• Pomalidomide maintenance for 1 year  
• Progressed 6 months after maintenance stopped | • Daratumumab + bortezomib + dex  
• Achieved PR  
• Biochemical progression after 12 months | • Carfilzomib + cyclophosphamide + dex  
• Achieved PR  
• Progressed after 9 month with signs of renal compromise |

**Current Status**

• 50 years old  
• Patient is active  
• Karnofsky score 80%  
• Some chronic back pain

**BM Biopsy**

• 40% clonal plasma cells

**Cytogenetics and FISH**

• Persistent hyperdiploidy  
• FISH negative for:  
  – del 17p  
  – 1q amp

**Labs**

• WBC nL  
• Hgb 10.5  
• Creatinine 2.1  
• Calcium nL
Put the CAR(T) Before the Horse: Practicalities of T Cell–Activating Therapies in Multiple Myeloma

Audience Question
What would you recommend for this patient?
A. Belantamab mafodotin as part of a clinical trial
B. Selinexor, bortezomib, dexamethasone
C. BCMA-targeted bispecific antibody
D. BCMA-targeted CAR T cell therapy

Audience Question
Have you treated a patient with CAR T cells?
A. Yes
B. No
Case Study 1

50-year-old man 6-years post diagnosis with low-risk hyperdiploid MM has progressed through 4 therapies

Patient and hematologist agree to proceed with CAR T at this time

- Patient hospitalized
- Receives BCMA CAR T
- Within 2 days, patient experiences fever (39.5°C)
- Tachycardic 120
- Mild hypotension 92/68
- No hypoxia
- No mental status change
- WBC 1.2
- Neutrophils 400

T Cell–activating therapy

Eligibility

Panel discussion questions

- What makes a patient a candidate for either bispecifics or CAR T cells?
- Is there anything about this patient that makes one treatment more suitable than the other?
- If this patient was to elect to receive CAR T cell therapy, what are the steps to take to ensure that he receives this therapy?
  - Referral process
  - Bridging therapy
  - Manufacturing slot
  - Insurance
- What other options are available for this patient if access to CAR T cells is difficult?
Audience Question

Based on the patient’s symptoms, what is the leading diagnosis?
A. CRS Grade 2
B. CRS Grade 4
C. ICANS
D. Sepsis

Audience Question

CRS management for this patient includes:
A. Fluids, acetaminophen
B. Fluids, acetaminophen, broad-spectrum antibiotics
C. Fluids, acetaminophen, tocilizumab
D. Fluids, acetaminophen, tocilizumab and broad-spectrum antibiotics
Case Study 2

73-year-old man diagnosed with IgGk MM; presented with anemia; 70% plasma cells; BM cytogenetics revealed t(4;14)

Treatments

First Line
- Lenalidomide-ixazomib-dex*
- Achieved CR
- Ixazomib maintenance
- Relapsed after 6 years

Second Line
- Daratumumab-lenalidomide + dex
- Achieved VGPR
- Len dose reduction due to diarrhea
- Light chain progression within 3 years

Third Line
- Daratumumab-pomalidomide-dex
- Progressed after 3 months

Fourth Line
- Selinexor-bortezomib-dex
- Achieved PR
- Significant fatigue, weight loss, thrombocytopenia
- Stopped therapy after 2 months
- Light chain progression

*As part of a clinical trial (ixazomib not approved for use in patients with newly diagnosed MM)

Current Status
- 82 years old
- No significant comorbidities
- Mild HTN

BM Biopsy
- 20% clonal plasma cells

Cytogenetics and FISH
- FISH
  - t(4;14)
  - del 17p

Labs
- WBC 2.5
- Hgb 9
- Creatinine 1.1
- Calcium nL
Audience Question

What would you recommend for this patient, who is now 82 and has a del(17p) clone?
A. Carfilzomib + cyclophosphamide + dexamethasone
B. Belantamab mafodotin as part of a clinical trial
C. BCMA-targeted bispecific antibody
D. BCMA-targeted CAR T-cell therapy

Audience Question

Have you treated a patient with a bispecific antibody?
A. Yes
B. No
Audience Question

What is the major risk for patients receiving T cell–activating therapies?
A. Atypical infection
B. Neurologic complications (eg, ICANS)
C. Pancytopenia
D. Recurrent CRS

Case Study 2

82-year-old man 6 years post diagnosis with MM; has relapsed from 4 prior lines of therapy.

Patient and hematologist agree to proceed with bispecific therapy at this time

- Patient hospitalized
- Received step-up dosing
- Around cycle 6 contracted COVID-19 infection
- Hospitalized 1 month
  - Multiple anti-COVID therapies in ICU and recovered
- What other options are available for this patient if access to a bispecific antibody is difficult?
- Which AEs should clinicians and patients expect on bispecific T cell–activating therapies?
  - CRS
    - Hallmark: fever
    - Grading
    - Distinguishing from infection?
    - Treatment/management
  - Neurotoxicity/ICANS
    - Features
    - Treatment/management
- Any other unique features?
  - Bispecifics: infection prophylaxis, immune globulin? PJP, pneumonia
  - COVID risk?
  - What about non-BCMA targets (skin, taste, rash)