Triple-Class Refractory: Selecting BCMA-Directed Therapy?

Thomas G. Martin, MD
Clinical Professor of Medicine
Co-Director, Myeloma Program
University of California, San Francisco Medical Center
San Francisco, California
Faculty

Thomas G. Martin, MD
Clinical Professor of Medicine
Co-Director, Myeloma Program
University of California, San Francisco Medical Center
San Francisco, California

Thomas G. Martin, MD, has disclosed that he has received consulting fees from GSK and funds for research support from Amgen, Johnson & Johnson – Janssen, Sanofi, and Seattle Genetics.
Patient Scenario

- 67-year-old male presented with standard risk IgG kappa MM
  - B2M 3.4, Alb 3.6, LDH 150, Cr 1.1, Ca 8.7, FISH: hyperdiploid (+5, +9, +15)
- He has received 3 prior lines of therapy
  - RVd for 6 cycles followed by ASCT and continuous R maintenance for 36 months (progresses on maintenance – refractory to R 10 mg QD)
  - DaraKd for 19 months achieves VGPR then progresses (Triple class refractory)
  - EloPd for 6 cycles achieves PR then PD (3 prior lines: refractory to R/P/K/Dara)
- Options for triple-class drug refractory (IMiD, PI, CD38) are limited
Presurvey 5: In your current practice, what would you recommend next for this patient?

1. Triplet or quadruplet combination with previously used agents
2. Cyclophosphamide-based combination chemotherapy
3. Selinexor + dexamethasone
4. Belantamab mafodotin
5. BCMA-targeted CAR T-cell
6. BCMA-targeted bispecific T-cell engager
7. Salvage ASCT
8. Salvage AlloSCT
9. Uncertain
## Expert Recommendations

<table>
<thead>
<tr>
<th>Expert Recommendations</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>BCMA-targeted CAR T-cell</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>BCMA-targeted CAR T-cell</td>
</tr>
<tr>
<td>Thomas G. Martin, MD</td>
<td>BCMA-targeted CAR T-cell</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>BCMA-targeted CAR T-cell</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Cyclophosphamide-based combination chemotherapy</td>
</tr>
<tr>
<td>Jesús San-Miguel, MD</td>
<td>BCMA-targeted CAR T-cell</td>
</tr>
</tbody>
</table>
Poll 5: What would be your expectation for survival in patients with R/R MM?

1. Triple-class refractory: expected OS > 2 years
2. Triple-class refractory: expected OS 1-2 years
3. Triple-class refractory: expected OS < 10 months
4. Penta-refractory: expected OS > 6 months
5. Survival not measurable with novel BCMA-targeted therapies
6. Uncertain
# Expert Recommendations

<table>
<thead>
<tr>
<th>Expert Recommendations</th>
<th>Triple-class refractory: expected OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Thomas G. Martin, MD</td>
<td>&lt; 10 months</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>1-2 years</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td>Jesús San-Miguel, MD</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>
Patients with Triple-Class Refractory MM
- The unmet need with poor prognosis

• MAMMOTH Study
  • Retrospective review of R/R MM
    • 275 patients
    • PI, IMiD, and CD38 exposed
  • Median OS was < 9 months in MAMMOTH in patients with disease refractory to anti-CD38 mAbs
  • Median OS was < 6 months if penta-refractory
  • Current treatment options include conventional chemotherapy, salvage ASCT, recycling previous regimens, selinexor + dexamethasone, belantamab mafodotin and clinical trials

Median OS in MAMMOTH study from $T_0$
- mOS (95% CI), months
  - All: 8.6 (7.2–9.9)
  - Not triple-refractory: 11.2 (5.4–17.1)
  - Triple- and quad-refractory: 9.2 (7.1–11.2)
  - Penta-refractory: 5.6 (3.5–7.8)

# Triple-Class Refractory: When All Else Fails

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>HDAC / ADC XPO inhibitors</th>
<th>Monoclonal Antibodies</th>
<th>IMiDs / CELMoDs/ Novel Drugs</th>
<th>BCMA Abs Bispecifics/ ADCs</th>
<th>Cellular therapies BCMA CARs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin, Liposomal doxorubicin</td>
<td>Panobinostat/ Vorinostat</td>
<td>Next Gen 38 SAR442085</td>
<td>CC-220 (Iberdomide), CC-92480</td>
<td>Teclistamab AMG-701, CC-93269</td>
<td>Cilta-cel (JNJ-4528), Ide-cel (bb2121), Orva-cel (JCARH125)</td>
</tr>
<tr>
<td>Cyclophosphamide, Bendamustine, Melphalan</td>
<td>Belantamab Mafodotin</td>
<td>TAK-079, TAK-573, TAK-169</td>
<td>Venetoclax Melflufen</td>
<td>TNB-3838, REGN5458 PF-06863135</td>
<td>LCAR-B38M, bb21217, P-BCMA-101</td>
</tr>
<tr>
<td>PACE, HyperCAD</td>
<td>Selinexor</td>
<td>MOR202, Others</td>
<td>BFCHR4350A Talquetamab</td>
<td>MEDI2228, CC-99712 FOR46</td>
<td>Lummicar-2 (CT053) ALLO-715 ALLO-605 (TurboCAR)</td>
</tr>
</tbody>
</table>

*Blue = approved  Green = ongoing clinical trials
Immunotherapy for MM
- Targets and Therapeutics

• Current MM Targets
  • BCMA
  • GPRC5D
  • FcRH5
  • CD138
  • CD38
  • CD19
  • SLAMF7
  • ASCT2
  • CD229
  • Kappa light chain

• BCMA Therapeutics
  • CARs
    • Idecaptagene Vicleucel
    • Ciltacabtagene autoleucel
  • ADCs
    • Belantamab mafodotin
    • MEDI2228
  • Bispecific antibodies
    • Teclistamab
    • ~6 others at ASH2020

Cho. Front Immunol 2018; 9:1821
Belantamab Mafodotin (GSK2857916): A BCMA-Targeted Antibody Drug Conjugate

- **Belantamab mafodotin**
  - humanized, IgG1
  - afucosylated anti-BCMA
  - Toxin – **MMAF**
- **Phase I study**
  - Part 2: 3.4 mg/kg Q3W
  - Potent activity (ORR ~60%)
  - Ocular toxicity (~63%)
  - Thrombocytopenia (34%)

**Mechanisms of Action:**
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

**Diagram:**
- **Fc region of the antibody**
  - Target specific
  - Enhanced ADCC
- **Linker**
  - Stable in circulation
- **Drug**
  - MMAF (non-cell permeable, highly potent auristatin)

DREAMM-2 Study Design

A phase II, open-label, randomized 2-dose study in RR MM after an anti-CD38 therapy. Primary analysis of DREAMM-2 completed at median follow-up of 6.3 and 6.9 months for the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. Additional analysis was completed at 13 months of follow-up.

**Key Secondary Outcomes**
- DOR (time from ≥PR until PD or death due to PD)
- Other efficacy: CBR, PFS, OS, TTBR, TTR
- Safety, including keratopathy (MECs)

**Primary Outcome**

**ORR:** % of patients with ≥PR**

**Treatment until disease progression or unacceptable toxicity**

- Belantamab mafodotin 2.5 mg/kg IV, every 3 weeks (n=97)
- Belantamab mafodotin 3.4 mg/kg IV, every 3 weeks (n=99)

**Key baseline characteristics=>**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2.5 mg/kg</th>
<th>3.4 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior Lines</td>
<td>7 (3-21)</td>
<td>6 (3-21)</td>
</tr>
<tr>
<td>Triple class exposed</td>
<td>~100%</td>
<td>~100%</td>
</tr>
</tbody>
</table>

## Key efficacy data

<table>
<thead>
<tr>
<th>Response</th>
<th>2.5 mg/kg (N = 97)</th>
<th>3.4 mg/kg (N = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>13 months</td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>31 (32%)</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>5 (5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (11%)</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (13%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>2.8 (1.6-3.6)</td>
<td>3.9 (2.0-5.8)</td>
</tr>
<tr>
<td>Median DoR estimate, mo</td>
<td>11</td>
<td>6.2</td>
</tr>
<tr>
<td>Median OS estimate, mo</td>
<td>13.7</td>
<td>13.8</td>
</tr>
</tbody>
</table>

- ORRs were comparable in both HR and SR patients

## Key safety data

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>2.5 mg/kg (N = 95)</th>
<th>3.4 mg/kg (N = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 AE (≥20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>44 (46%)</td>
<td>42 (42%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (22%)</td>
<td>32 (32%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (21%)</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE leading to death</td>
<td>40 (42%)</td>
<td>47 (47%)</td>
</tr>
</tbody>
</table>

- Overall safety at 2.5 mg/kg
  - Keratopathy (Gr 1-4) 72%
  - Thrombocytopenia (Gr 1-4) 38%
- 2 deaths were considered potentially treatment related:
  - 2.5 mg/kg: sepsis (n = 1)
  - 3.4 mg/kg: hemophagocytic lymphohistiocytosis (n = 1)
- Overall rates of anemia and thrombocytopenia were higher in HR than SR
ADC Summary in RRMM

• What more do we need?
  1. Improved response rates and durability with combinations
     Trudel et al. ASH 2020, Abstr 725: Belantamab + Pom
     Popat et al. ASH 2020, Abstr 1419: Belantamab + Vd
  2. Improved safety
     Split/intermittent dosing of Belantamab
     Novel toxin:
       Kumar et al. ASH 2020, Abstr 179 – MEDI2228 [pyrrolobenzodiazepine dimer]
       Shah et al. ASH 2020, Abstr 3030 – STRO-001 [maytansinoid]
  3. Additional targets
     CD74/CD46/SLAMF7
  4. Mechanism of resistance
     Antigen loss
     P-glycoprotein
BCMA CAR T-Cell Studies: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Ide-cel (bb2121) PhII</th>
<th>bb21217</th>
<th>Cilta-cel (JNJ-4528)</th>
<th>Orva-cel (JCAR-H125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Dose</td>
<td>150 300 450</td>
<td>150 300</td>
<td>450</td>
<td>0.75 x 10^6 / kg</td>
</tr>
<tr>
<td></td>
<td>300 450 600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up, mos</td>
<td>13.3</td>
<td>17.6</td>
<td>4.0 3.3</td>
<td>11.5 (3.0 – 17.0)</td>
</tr>
<tr>
<td></td>
<td>9.5 8.8 2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>50% 69% 82%</td>
<td>83% 43%</td>
<td>57%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>95% 89% 92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>25% 29% 39%</td>
<td>33% 0%</td>
<td>14%</td>
<td>86%</td>
</tr>
<tr>
<td>MRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable for MRD, #</td>
<td>4 70 54</td>
<td>7 6 4</td>
<td>21</td>
<td>11 11 3</td>
</tr>
<tr>
<td>MRD- (%)</td>
<td>50% 31% 48%</td>
<td>100%</td>
<td>83.3% 100%</td>
<td>85.7%</td>
</tr>
<tr>
<td></td>
<td>72.7% 90.9% 100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>NR 9.9 11.3</td>
<td>11.1</td>
<td>NR NR NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2.8 5.8 12.1</td>
<td>NR NR NR</td>
<td>NR</td>
<td>9.3 NR NR</td>
</tr>
</tbody>
</table>

[updates at ASH2020: Cilta-cel PhII, bb2121 PhI, bb2121-7, Poseida BCMA-CAR, CD19-BCMA dual targeted CAR, Allo715-BCMA]

## BCMA CAR T-Cell Studies: Safety

<table>
<thead>
<tr>
<th></th>
<th>Ide-cel (bb2121) PhII</th>
<th>bb21217</th>
<th>Cilta-cel (JNJ-4528)</th>
<th>Orva-cel (JCAR-H125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytokine Release Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>84%</td>
<td>66%</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>Grade 3 / 4 / 5</td>
<td>4% / &lt;1% / &lt;1%</td>
<td>5% / 0% / 3%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Median Onset, Days</td>
<td>1 (1 – 12)</td>
<td>3 (1 – 20)</td>
<td>7 (2 – 12)</td>
<td>2 (1 – 4)</td>
</tr>
<tr>
<td>Median Duration</td>
<td>5 (1 – 63)</td>
<td>4 (1 – 28)</td>
<td>4 (2 – 64)</td>
<td>4 (1 – 10)</td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>18%</td>
<td>24%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Grade 3 / 4 / 5</td>
<td>3% / 0% / 0%</td>
<td>5% / 3% / 0%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Median Onset, Days</td>
<td>2 (1 – 10)</td>
<td>7 (3 – 24)</td>
<td>NR</td>
<td>4 (1 – 6)</td>
</tr>
<tr>
<td>Median Duration</td>
<td>3 (1 – 26)</td>
<td>NR</td>
<td>NR</td>
<td>4 (1 – 10)</td>
</tr>
</tbody>
</table>

[updates at ASH2020: Cilta-cel PhII, bb2121 PhI, bb2121-7, Poseida BCMA-CAR, CD19-BCMA dual targeted CAR, Allo715-BCMA]

CAR T-Cell Summary in RRMM

• What more do we need?
  1. Improved CARs
     Faster Manufacturing or Off-the-shelf
     Better T-cells – Tscm/cm
     Persistence: a good “second wave”
  2. Improved patient selection
     Early relapse (1-3 PLT)
     Frontline: replace ASCT?
     Lower burden of disease
  3. Additional targets and combinations
     GPRC5D +/- BCMA
     CD19 + BCMA
     CAR + BISPECIFIC, CAR + CelMOD
  4. Mechanism for resistance
     Antigen loss
     Myeloma “stem cell”

Teclistamab – ASCO 2020

Dosing
- Weekly step-up

STUDY ENROLLMENT AND RESULTS
- 78 patients enrolled
- 6 PLT, 31% HR cytogenetics
- 80% triple class refractory

- Toxicity:
  - CRS: overall 56%
  - Neurotox: 8% Gr 1-4 (3% Gr 3-4)
Teclistamab - Results

- 67% ORR
  - CR: n=3
  - VGPR: n=3
  - PR: n=2
  - 270 μg/kg (n=12)

- 50% ≥VGPR

- Responses deepen over time
- 16/21 patients have ongoing response

## BCMA Bispecific mAb Studies: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>AMG420</th>
<th>CC-93269</th>
<th>Teclistamab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>400 ug/day</td>
<td>6→10 mg and 6 mg</td>
<td>270 ug / kg</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Median follow-up, mos</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>70%</td>
<td>88.9%</td>
<td>67%</td>
</tr>
<tr>
<td>CR</td>
<td>50%</td>
<td>44.4%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>MRD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable for MRD, #</td>
<td>10</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>MRD- (%)</td>
<td>50%</td>
<td>NR</td>
<td>80%</td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>9.0 (range 5.8 – ≥13.6)</td>
<td>11 of 13 ongoing</td>
<td>16 of 21 ongoing</td>
</tr>
</tbody>
</table>

[Many bispecific antibody updates and new presentations at ASH 2020]

Bispecific Summary in RRMM

• **What more do we need?**
  1. Phase II study results
     - Optimized step-up dosing
     - Responses in RRMM including EMD and HR
     - Convenient schedule for long-term dosing
  2. Improved safety
     - Outpatient administration
     - Prophylactic use of tocilizumab/other CRS mitigation strategies
  3. Additional targets
     - CD38/SLAMF7/GPRC5D/FcRH5
  4. Improved response rates and durability with combinations
     - Bispecific mAb + IMiDs, PIs, CD38 Abs
     - Bispecific + CelMODs
## BCMA Therapeutics – Advantages/Disadvantages

<table>
<thead>
<tr>
<th></th>
<th>Antibody–drug conjugate</th>
<th>CAR T-cells</th>
<th>Bispecific antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-the-shelf</td>
<td>Off-the-shelf</td>
<td>Personalized</td>
<td>Off the shelf</td>
</tr>
<tr>
<td>Targeted cytotoxicity</td>
<td></td>
<td>Targeted immuno-cytotoxicity</td>
<td>Targeted immuno-cytotoxicity</td>
</tr>
<tr>
<td>Not dependent on T-cell health</td>
<td></td>
<td>Single infusion (“one and done”)</td>
<td></td>
</tr>
<tr>
<td>No lymphodepletion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available to any infusion center</td>
<td></td>
<td>Potentially persistent</td>
<td></td>
</tr>
<tr>
<td>Outpatient administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fact accredited center required (hospitalization likely required)</td>
<td>Fact accredited center required (hospitalization likely required)</td>
<td>Initial hospitalization required</td>
<td></td>
</tr>
<tr>
<td>Currently requires REMS/Ophtho</td>
<td></td>
<td>CRS and Neurotoxicity; requires ICU and Neurology services</td>
<td>CRS and Neurotoxicity possible</td>
</tr>
<tr>
<td>Single agent activity low in CD38 refractory patients</td>
<td></td>
<td>Dependent on T-cell health (manufacturing failures)</td>
<td>Dependent on T-cell health (T-cell exhaustion)</td>
</tr>
<tr>
<td>Requires continuous administration</td>
<td></td>
<td>Requires significant support social – caregiver required</td>
<td>Requires continuous administration</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relates To</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>$$$$</td>
<td>$$$$$</td>
<td>$$</td>
</tr>
</tbody>
</table>
Sequencing of BCMA Targeted Therapeutics

• As of Now ➔ Belantamab Mafodotin  [only FDA approved modality]
  • Triple Refractory => many centers chose clinical trial
Sequencing of BCMA Targeted Therapeutics

• As of Now ➔ Belantamab Mafodotin  [only FDA approved modality]
  • Triple Refractory => many centers chose clinical trial

• In 1\textsuperscript{st} /2\textsuperscript{nd} Quarter 2021 ➔ there will be a choice  [Guideline from IMS]
  • BCMA Targeted CAR T-cell (Ide-cel) ➔ Fit, well-resourced, triple refract
  • Belantamab Mafodotin ➔ less fit, limited social support, rapidly progressive
  • 3\textsuperscript{rd}/4\textsuperscript{th} Quarter ➔ potentially a second CAR – Cilta-cel may be approved
Sequencing of BCMA Targeted Therapeutics

• As of Now ➔ Belantamab Mafodotin  [only FDA approved modality]
  • Triple Refractory => many centers chose clinical trial

• In 1\textsuperscript{st} /2\textsuperscript{nd} Quarter 2021 ➔ there will be a choice  [Guideline from IMS]
  • BCMA Targeted CAR T-cell (Ide-cel) ➔ Fit, well-resourced, triple refract
  • Belantamab Mafodotin ➔ less fit, limited social support, rapidly progressive
  • 3\textsuperscript{rd}/4\textsuperscript{th} Quarter ➔ potentially a second CAR – Cilta-cel may be approved

• In 2022 and beyond ➔ other CARs, ADCs and bispecific mAbs
  • CD38 + triplet (induction) ➔ BCMA CAR consolidation ➔ BCMA – ADC early relapse
  • CD38 + doublet/triplet for induction ➔ bispecific maintenance ➔ BCMA-ADC relapse
  • BCMA-ADC + doublet induction ➔ GPRC5D CAR at relapse ➔ FcRH5 bispecific RRMM
Future Strategies in Multiple Myeloma

Where and in what combination will immunotherapy have the most Impact?

Frontline
QUAD: No transplant
MRD (+): Consolidation: CAR vs. Bispecific
MRD (-): Maintenance: Len (CELMoD)/mAb vs. Bispecific

Early Relapse (1-3 Prior Lines)
Novel CAR (Different target)
Novel Ab: ADC vs. Trivalent Ab

Late Relapse (off-the shelf)
Third party cellular therapy (NK + T)
Crispr strategies
Conclusions: Next Generation Therapeutics

• Triple Class Refractory is an UNMET Need
  • Belantamab mafodotin: BCMA-ADC → approved in this population
  • BCMA directed CAR T-cell therapeutics → will be available soon
  • Initial bispecific antibody results promising
    • Off-the-shelf products, toxicity is manageable
    • Bind BCMA, GPRC5D, FCRH5

• Need better understanding mechanisms of resistance
  • Loss of antigen
  • T cell burnout/exhaustion

• Combinations of novel-novel drugs on-going

• Sequencing of these therapeutics will be important and future sequencing studies will be important
Now, let’s return to our patient case
Patient Case Example: R/R MM

- 67-year-old male presented with standard risk IgG kappa MM
  - B2M 3.4, Alb 3.6, LDH 150, Cr 1.1, Ca 8.7, FISH: hyperdiploid (+5, +9, +15)
- He has received 3 prior lines of therapy
  - RVd for 6 cycles followed by ASCT and continuous R maintenance for 36 months (progresses on maintenance – refractory to R 10 mg QD)
  - DaraKd for 19 months achieves VGPR then progresses (Triple class refractory)
  - EloPd for 6 cycles achieves PR then PD (3 prior lines: refractory to R/P/K/Dara)
- Options for **triple-class drug refractory** (IMiD, PI, CD38) are limited
- Approved agents are available
  - Belantamab mafodotin
  - Selinexor + Dex
  - Alkylator therapy [cyclophosphamide-based, bendamustine, 2nd autologous SCT]
Assessment 5: Now, what would you recommend next for this patient?

1. Triplet or quadruplet combination with previously used agents
2. Cyclophosphamide-based combination chemotherapy
3. Selinexor + dexamethasone
4. Belantamab mafodotin
5. BCMA-targeted CAR T-cell
6. BCMA-targeted bispecific T-cell engager
7. Salvage ASCT
8. Salvage AlloSCT
9. Uncertain
Panel Discussion: BCMA-Directed Therapy