HIGHLIGHTS IN THERAPY: MULTIPLE MYELOMA

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WELCOMING REMARKS
HIGHLIGHTS IN THERAPY: MULTIPLE MYELOMA

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DISCLOSURES
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HIGHLIGHTS IN THERAPY - OVERVIEW

1. Introduction
2. Understanding Multiple Myeloma
3. Current Treatments for Multiple Myeloma
4. Emerging Approved Immunotherapies
5. Managing Side Effects
6. Quality-of-Life Considerations
7. Patient and Caregiver Resources
8. Conclusion

WHAT IS MULTIPLE MYELOMA?

Plasma cell neoplasm
• Characterized by malignant plasma cells infiltrating the bone marrow, and sometimes other organs and tissues
• Symptoms depend on tumor burden and complications by plasma cell clones
• The clones produce monoclonal immunoglobulin, cytokines, and other factors that interfere with bone metabolism, kidney function, hematopoiesis, immune mechanisms, and other organ systems

HEMATOPOIESIS

- **V<sub>L</sub>**: light chain variable domain;
- **C<sub>L</sub>**: light chain constant domain;
- **V<sub>H</sub>**: heavy chain variable domain;
- **C<sub>H1</sub>–C<sub>H3</sub>**: heavy chain constant domains 1–3.

THE IMMUNOGLOBULIN MOLECULE

- Antigen binding site
  - **C<sub*L</sub>**, **C<sub>H</sub>**, **C<sub>H1</sub>**, **C<sub>H2</sub>**, **C<sub>H3</sub>**
- Hinge region
SERUM PROTEIN ELECTROPHORESIS (SPEP)

WHAT ARE SERUM FREE LIGHT CHAINS (FLC)?
EPIDEMIOLOGY OF MULTIPLE MYELOMA - USA

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases in 2023</td>
<td>35,730</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.8%</td>
</tr>
<tr>
<td>Estimated Deaths in 2023</td>
<td>12,590</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>2.1%</td>
</tr>
<tr>
<td>Prevalence (2020)</td>
<td>170,405 people with myeloma in the USA</td>
</tr>
</tbody>
</table>


CLINICAL PRESENTATION OF MULTIPLE MYELOMA

Signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains:

- Anemia – 73%
- Bone pain – 58%
- Elevated creatinine – 48%
- Fatigue/generalized weakness – 32%
- Hypercalcemia – 28%
- Weight loss – 24%, one-half of whom had lost ≥9 kg
**MULTIPLE MYELOMA - DIAGNOSTIC CRITERIA SINCE 2014**

Clonal bone marrow plasma cells >10% OR biopsy proven plasmacytoma
+ “CRAB” Criteria (Classic):
   - HyperCalcemia
   - Renal failure
   - Anemia
   - Bone lesions

New additions with 2014 IMWG (Biomarker driven):
- Serum free light chain ratio (involved/uninvolved) ≥100
- 1 or more focal bone lesions on MRI (>5 mm in size)
- >60% clonal plasma cells on bone marrow examination

IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging.

**CURRENT TREATMENT OF NEWLY DIAGNOSED MM IN 2023**

**Transplant Eligible**
- 4 drug combinations
  - Dara-RVd or Dara KRd
- 3 drug combinations:
  - RVd, KRd,
  - VCd (renal failure)

**Maintenance**
- Standard: Lenalidomide
- High risk: PI/IMiD, CD38/IMiD

**Autologous stem cell transplantation**

**Not Transplant Eligible**
- Dara Rd
- RVd

**Supportive Care**

Dara, daratumumab; Dara KRd, carfilzomib, lenalidomide, dexamethasone; IMiD, immunomodulatory drugs; PI, proteasome inhibitor; RVd, lenalidomide, bortezomib, dexamethasone.
**PRIMARY ENDPOINT: sCR BY THE END OF CONSOLIDATION**

**Primary endpoint met at pre-set 1-sided alpha of 0.1**

- sCR by end of consolidation
  - 42.4% D-RVd vs 32.0% RVd
  - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided P=0.068

**Post-consolidation depth of response**

- ORR: 99.0%
- ORR: 91.8%
- sCR: 91.5%
- sCR: 91.5%
- VGPR: 90.9%
- VGPR: 73.2%

Cl, confidence interval; sCR, stringent complete response.

**GRIFFIN: TIME TO MRD NEGATIVITY**

- Median time to MRD negativity ($10^{-5}$)
  - D-RVd: 8.5 months
  - RVd: 34.6 months for RVd
- At the $10^{-6}$ threshold, time to MRD negativity
  - D-RVd: 33.9 months
  - RVd: not reached
- Time to MRD negativity was shorter for D-RVd versus RVd; however, as a caveat, MRD was not assessed as frequently as response

**GRIFFIN: PFS IN THE ITT POPULATION**

- Median follow-up: 49.6 months
- Median PFS was not reached in either group
- PFS was longer for D-RVd/D-R versus RVd/R, with a clinically meaningful 55% reduction in the risk of disease progression or death
- The separation of the PFS curves occurred beyond 1 year of maintenance and suggests a benefit of prolonged D-R maintenance therapy

ITT, intent to treat; PFS, progression-free survival.
PERSEUS TRIAL: LBA-1: RANDOMIZED PHASE 3 TRIAL

Key eligibility criteria:
- Transplant-eligible NDMM
- Age 18-70 years
- ECOG PS ≤2

4 cycles of 28 days

Induction

VRd
- V: 1.3 mg/m² SC
- Q: 10mg PO Days 1-21
- R: 25 mg PO Days 1-21
- d: 40 mg PO Days 1-4, 9-12

Consolidation

VRd
- V: 1.3 mg/m² SC
- Q: 10mg PO Days 1-21
- R: 25 mg PO Days 1-21
- d: 40 mg PO Days 1-21, 5-8, 10-12

Maintenance

R
- R: 10 mg PO Days 1-28 until PD

Discontinue DARA therapy only upon confirmed loss of CR without PD or recurrence of MRD

Primary endpoint: PFS
- Overall ≥CR rate, overall MRD-negativity rate, OS

Key secondary endpoints: Overall ≥CR rate, overall MRD-negativity rate, OS

PERSEUS OUTCOMES: DARA-RVD VS RVD

Disease Progression or Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events</th>
<th>NRI</th>
<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Scene</td>
<td>36,211</td>
<td>61205</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Female</td>
<td>34,144</td>
<td>42149</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>30,282</td>
<td>81267</td>
<td>NE</td>
<td>NE</td>
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<tr>
<td>Charlson</td>
<td>28,994</td>
<td>1997</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>WHO</td>
<td>47,310</td>
<td>91313</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Other</td>
<td>3,235</td>
<td>6,11</td>
<td>NE</td>
<td>NE</td>
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<tr>
<td>ISS disease stage</td>
<td>18,186</td>
<td>35178</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>0</td>
<td>33,114</td>
<td>43123</td>
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</tr>
<tr>
<td>1</td>
<td>13,554</td>
<td>20200</td>
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<td>NE</td>
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<tr>
<td>Type of multiple myeloma</td>
<td>28,210</td>
<td>56213</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IgG</td>
<td>33,178</td>
<td>3195</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Cyto genetic risk</td>
<td>35,264</td>
<td>42266</td>
<td>NE</td>
<td>NE</td>
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<tr>
<td>High-risk</td>
<td>24,796</td>
<td>38178</td>
<td>NE</td>
<td>44,1</td>
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<tr>
<td>Endpoints:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>38,226</td>
<td>60210</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>OS</td>
<td>22,154</td>
<td>43124</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death (95% CI)

- Scene: 0.51 (0.34-0.77)
- Female: 0.25 (0.16-0.35)
- Age <65: 0.39 (0.20-0.70)
- Charlson: 0.97 (0.53-1.78)
- WHO: 0.42 (0.33-0.50)
- Other: 0.48 (0.31-0.70)
- ISS disease stage: 0.56 (0.30-0.93)
- 0: 0.48 (0.26-0.83)
- 1: 0.57 (0.22-1.39)
- Type of multiple myeloma: 0.51 (0.21-1.21)
- IgG: 0.48 (0.24-0.98)
- Cyto genetic risk: 0.55 (0.22-1.36)
- High-risk: 0.54 (0.22-1.36)
- Endpoints: 0.40 (0.25-0.64)

**PERSEUS: OVERALL ≥CR RATES**

**P value (2 sided) was calculated with the use of the Stratified Cochran-Mantel-Haenszel chi-squared test**

CR, complete response.


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**Table 2. Summary of Tumor Response and MRD Status (Intention-to-Treat Population).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>D-VRd (N=355)</th>
<th>VRd (N=354)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response — no. (% [95% CI])</td>
<td>343 (96.6 [94.2–98.2])</td>
<td>332 (93.8 [90.7–96.1])</td>
<td>—</td>
</tr>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>246 (69.3)</td>
<td>158 (44.6)</td>
<td>—</td>
</tr>
<tr>
<td>Complete response</td>
<td>66 (18.6)</td>
<td>50 (14.2)</td>
<td>—</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>26 (7.3)</td>
<td>68 (19.2)</td>
<td>—</td>
</tr>
<tr>
<td>Partial response</td>
<td>5 (1.4)</td>
<td>16 (4.5)</td>
<td>—</td>
</tr>
<tr>
<td>Complete response or better — no. (%)</td>
<td>312 (87.9)</td>
<td>248 (70.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Very good partial response or better — no. (%)</td>
<td>338 (95.2)</td>
<td>316 (89.3)</td>
<td>—</td>
</tr>
<tr>
<td>Stable disease — no. (%)</td>
<td>4 (1.1)</td>
<td>9 (2.5)</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>—</td>
</tr>
<tr>
<td>Response could not be evaluated — no. (%)</td>
<td>6 (1.7)</td>
<td>12 (3.4)</td>
<td>—</td>
</tr>
<tr>
<td><strong>MRD status:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD-negative status — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^3 sensitivity threshold</td>
<td>267 (75.2)</td>
<td>168 (47.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10^4 sensitivity threshold</td>
<td>231 (65.3)</td>
<td>114 (32.2)</td>
<td>—</td>
</tr>
<tr>
<td>Sustained MRD-negative status, assessed at 10^3 sensitivity threshold, for ≥12 mo — no. (%)</td>
<td>230 (64.8)</td>
<td>105 (29.7)</td>
<td>—</td>
</tr>
</tbody>
</table>

MRD, minimal residual disease.

PERSEUS: COMMON ADVERSE EVENTS

- **Neutropenia**
  - Any grade: 69% DRVD, 58% RVD
  - Grade 3 or 4: DRVD 29%, RVD 17%
- **Thrombocytopenia**
  - Any grade: DRVD 48%, RVD 34%
  - Grade 3 or 4: DRVD 29%, RVD 17%
- **Peripheral neuropathy**
  - Any grade: DRVD 53%, RVD 51%
  - Grade 3 or 4: DRVD 4.3%, RVD 4%
- **Infections**
  - Any grade: DRVD 86%, RVD 76%
  - Grade 3 or 4: DRVD 35%, RVD 27%


PERSEUS: SUMMARY

- **GRIFFIN phase 2 trial** – increased rates of sCR, MRD (-), and improved PFS with Dara RVD
- **Large global phase 3 trial** – confirms benefit of upfront treatment with CD38/IMID/PI/Dexamethasone in conjunction with autologous HCT
- **Daratumumab and lenalidomide maintenance a reasonable option based on GRIFFIN, PERSEUS**
- **Benefit of quad even in high-risk subgroups**

MRD, minimal residual disease; PFS, progression-free survival; sCR, stringent compete response.
DARA RVD ADMINISTRATION: THE FRED HUTCH APPROACH

- **28-day cycles (plan for 4-6 before ASCT, or until deepest response):**
  - Daratumumab subQ per package insert
  - Bortezomib 1.3 mg/m² on Days 1, 8, 15 (2x weekly okay if acute cast nephropathy)
  - Lenalidomide 25 mg Days 1-21 out of 28
  - Dex 20 mg weekly for first 1-2 cycles, then plan to stop

- **No post-ASCT consolidation!**
  - At Day +80, move to lenalidomide maintenance. For high-risk cytogenetics, add q14day proteasome inhibitor
  - We do not give daratumumab + lenalidomide maintenance
  - **No dex during maintenance.** Zero benefit and very real risk of long-term toxicities, e.g., visually significant cataracts (Banerjee 2023)

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Median PFS 67 months for transplant

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ASCT, autologous stem cell transplant.


Richardson PG et al *NEJM*. 2022.
**DARA-RD VS RD: MAIA TRIAL – STUDY DESIGN**

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)

**Key eligibility criteria:**
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥30 mL/min

**Randomization:** 1:1

**Primary endpoint:**
- PFS

**Key secondary endpoints:**
- ≥CR rate
- ≥VGPR rate
- MRD-negative rate (NGS; 10^-5)
- ORR
- OS
- Safety

---

**MAIA TRIAL: DARA-RD VS RD UPFRONT TREATMENT FOR ASCT-INELIGIBLE NDMM PATIENTS**

Figure: Progression-free survival (A) and overall survival (B) with D-Rd and Rd in the intent-to-treat population.

A. **60-month PFS**

![Progression-free survival graph](image)

B. **60-month OS**

![Overall survival graph](image)

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Kumar S et al. ASH 2022

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ASCT, autologous stem-cell transplant.
A DEXAMETHASONE SPARING-REGIMEN WITH DARATUMUMAB AND LENALIDOMIDE IN FRAIL PATIENTS WITH NEWLY-DIAGNOSED MULTIPLE MYELOMA: EFFICACY AND SAFETY ANALYSIS OF THE PHASE 3 IFM2017-03 TRIAL

IFM 2017-03 – Study design

Primary endpoint: PFS
Interim analysis endpoints: 12-months-therapy data cut:
- Overall response rate,
- VGPR or better rate,
- NRD rate,
- Occurrence of grade 3 or more side effects

Deeper responses were obtained with DR at all time points, including at early time points
MANAGEMENT OF RELAPSED MULTIPLE MYELOMA IN 1+ LINE OF THERAPY IN 2024

Most patients:
RVD or Dara RVD → autologous HCT → Lenalidomide maintenance
OR
Dara RD / RVD → lenalidomide maintenance

1-3 Lines of therapy
CD38 + IMiD: Carfilzomib, pomalidomide, dexamethasone
CD38 + PI: Carfilzomib + either Daratumumab/Isatuximab and dexamethasone

Progression of Disease
4+ Lines of therapy

1. BCMA CAR T cells: Cilta-cel, or Ide-cel
2. BCMA Bispecific: Tecristamab, elrantamab
3. GPRC5D Bispecific: Talquetamab

Post-BCMA relapse
Clinical trials
GPRC5D bispecific: Talquetamab (if not already given)

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR T CELLS)

1. A patient’s leukocytes are collected by apheresis
2. Patient receives lymphocyte-depleting chemotherapy prior to T-cell infusion
3. Patient receives CAR T-cell infusion

Ex vivo cell processing
T-cell activation
CAR transduction
T-cell proliferation

Virus: retrovirus, lentivirus
Electroporation, RNA/DNA
CAR T-CELL MANUFACTURING

- Leukapheresis
- Selection of T cells from a leukapheresis product
- Activation of the enriched T cells with magnetic beads and cytokines
- Transduction with lentiviral vector containing the CAR
- Expansion of the CAR T cells: goal is to reach appropriate dose, this can take several days
- Cell harvest and formulation of final product for cryopreservation

TOXICITIES FROM CAR T-CELL THERAPY

- Cytokine release syndrome
- ICANS – aka neurotoxicity
- Prolonged cytopenias
- B-cell aplasia and hypogammaglobulinemia
- Secondary malignancy
WHAT IS CYTOKINE RELEASE SYNDROME (CRS)?

- Pro-inflammatory syndrome caused by excessive immune activation from CAR T cell therapy
- If not recognized and treated early, results in substantial morbidity and mortality
- Hallmark of this syndrome is fever, hypotension, hypoxia

WHAT IS NEUROTOXICITY ASSOCIATED WITH CAR T-CELL THERAPY?

• Neurotoxicity – also more recently known as “Immune Effector Cell-Associated Neurotoxicity Syndrome” – ICANS

• Predominant symptoms: Ranges from mild confusion, lethargy, word finding difficulties, to more severe states such involving global encephalopathy such as coma, persistent vegetative states

• Important – has resulted in deaths in some patients receiving CAR T-cell therapy

• Dexamethasone – mainstay of treatment – treat early, don’t delay!

EARLIER USE OF BCMA CAR T

KarMMA-3 – Otero P et al, NEJM 2023

Ide-cel/Abecma: BCMA targeted chimeric antigen receptor T-cell therapy, approved by FDA in 2020

Multiple myeloma
2-4 prior lines of therapy
Triple class exposed

Primary endpoint:
PFS
Crossover ALLOWED

2:1 Randomization

SOC therapy, n=132
n.b. KdDara or IsaKD not permitted as SOC; 5 approved regimens

Probability of Progression-free Survival

Overall Response

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Standard Regimen</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Ide-cel</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Months since Randomization

Probability of Progression-free Survival

Overall Response

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Standard Regimen</th>
<th>0.55</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Ide-cel</td>
<td>0.73</td>
</tr>
</tbody>
</table>

5 approved regimens

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>Standard Regimen</th>
<th>0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Ide-cel</td>
<td>0.01</td>
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</tbody>
</table>

Crossover ALLOWED
KARMMA-3: UPDATED ANALYSIS

Otero P et al, ASH 2023

**TREND OF OS BENEFIT WITH IDE-CEL AMONG TREATED PATIENTS**

- This is an exploratory analysis of the treated population without adjusting for crossover.

- Based on Kaplan-Meier approach.
- Stratified HR based on the univariate Cox proportional hazards model. CI is 2-sided.
- Kaplan-Meier survival curves showed a significant OS benefit with IDE-CEL compared to standard regimens, with a hazard ratio of 0.83 (95% CI, 0.58-1.18).

* OS, overall survival.
CARTITUDE 1 STUDY DESIGN

- Primary Objectives
  - Phase 1b: Determine safety and RP2D
  - Phase 2: Efficacy

- Eligibility criteria, in brief
  - PD per IMWG
  - 3 or more prior therapies
  - Prior exposure to IMiD, PI, CD38
  - Measurable disease


CARTITUDE-1: FINAL RESULTS

PFS by CR and sustained MRD neg:

- All pts: median PFS 34.9 months
- > CR, median PFS 38.2 months
- 12 mo sustained MRD neg: 30 mo PFS 74.9%
- 12 mo sustained MRD neg, > CR: 30 mo PFS 78.5%

Lin Y et al, ASCO 2023
CARTITUDE-4: STUDY DESIGN AND ENDPOINTS

**Primary endpoint**
- PFS\(^a\)

**Secondary endpoints**
- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

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**CARTITUDE-4: PRIMARY ENDPOINT – PFS (ITT POPULATION)**

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected

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\(^a\)PFS: Progression-free survival; CR: Complete response; ORR: Overall response rate; MRD: Minimal residual disease; OS: Overall survival; SOC: Standard of care; PFS: Progression-free survival; mPFS: Median progression-free survival

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<table>
<thead>
<tr>
<th>Week</th>
<th>Cilta-cel arm</th>
<th>SOC arm</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>60</td>
</tr>
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<td>6</td>
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<td>18</td>
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<td>21</td>
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<td>27</td>
<td>0.625</td>
<td>0.3125</td>
</tr>
<tr>
<td>30</td>
<td>0.3125</td>
<td>0.15625</td>
</tr>
</tbody>
</table>

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mPFS: not reached (95% CI, 22.8–NE)
mPFS: 11.8 months (95% CI, 9.7–13.8)

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Cilta-cel, cilta-cel, autologous t-cell therapy, CAR-T, clonal expansion of T cells, complete response, CR, Lymphodepletion, lymphocyte depletion, lymphocyte expansion, lymphocyte transduction, lymphocyte transduction and expansion.
# BSABS FOR MM: APPROVED AND IN DEVELOPMENT

<table>
<thead>
<tr>
<th>Agent name</th>
<th>ORR</th>
<th>MRD (−)**</th>
<th>PFS</th>
<th>CRS</th>
<th>Infections</th>
<th>Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecristamab*</td>
<td>63%</td>
<td>26.7%</td>
<td>mPFS 11.3 mos</td>
<td>72%</td>
<td>G3-4, 44%</td>
<td>Y – 11 days</td>
</tr>
<tr>
<td>Elranatamabβ</td>
<td>61%</td>
<td>90%</td>
<td>12 mos PFS 58%</td>
<td>57%</td>
<td>G3-4 35%</td>
<td>Y – 3 days</td>
</tr>
<tr>
<td>ABBV-383bβ</td>
<td>57%</td>
<td>73%</td>
<td>mPFS 10.4 mos</td>
<td>57%</td>
<td>41% all G</td>
<td>Y – 48 hrs D1</td>
</tr>
<tr>
<td>Linvoeltamab (REGNS5458)α</td>
<td>51%</td>
<td>4/10 pts</td>
<td>NA</td>
<td>38%</td>
<td>Not reported</td>
<td>Y</td>
</tr>
<tr>
<td>Alnaciamab</td>
<td>43%</td>
<td>Not reported</td>
<td>NA</td>
<td>77%</td>
<td>Not reported</td>
<td>Y</td>
</tr>
<tr>
<td>GPRC50xCD3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talquetamabβ</td>
<td>68%</td>
<td>69%</td>
<td>mDOR 10.2 mos</td>
<td>80%</td>
<td>G3-4 7%</td>
<td>Y, 11 days</td>
</tr>
<tr>
<td>FcRHS5xCD3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cevostamabβ</td>
<td>56.7%</td>
<td>7/10 pts</td>
<td>mDOR 11.5 mos</td>
<td>80%</td>
<td>~20%</td>
<td>Y</td>
</tr>
</tbody>
</table>

*FDA Approvals 10/2022, 8/23.
** In Evaluable patients.

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**Impaired MM cell lysis (Immunosuppressive components)**
- OC
- BMSC
- Treg
- PD-1/PD-L1 axis
- sBCMA
- APRIL
- TGF-β
- IL-6

**Improved MM cell lysis (Upregulation of effector cell activity/function)**
- CD8+ ratio ↑
- CD8+/CD4+ T cell ↑
- Central memory T cell ↑
- Effector memory T cell ↑
- Stem cell-like memory T cell ↑
- Enhanced surface expression of MM antigen

**Additive/synergistic effects with other agents**
- DARA
- ELO
- POM
- LEN
- GSK

**Effective MM cell killing**
- Activated T cell
- Proliferation, Activation, Differentiation

**Enhance cytolytic effect**
- BiAb
- Perforins
- Granzymes
- INF-γ, TNF-α, IL-3, IL-6, IL-10, granzyme B

**Promote T and NK cell function**
- LEN
- NKp30
- NKp46
- POM

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45 Cho SF et al Frontiers Oncology 2022.
QUALITY-OF-LIFE CONSIDERATIONS/MANAGING SIDE EFFECTS

- Treatment-related side effects
  - Peripheral neuropathy
  - Lenalidomide side effects
  - Fatigue

- Mobility and strength
  - Sarcopenia

- Diet and multiple myeloma

TREATMENT-RELATED SIDE EFFECTS

- Peripheral neuropathy
  - What is it? General dysfunction of nerves.
    - Autonomic, sensory, motor
  - Sensory – pain, tingling, coldness, burning, and numbness
  - Motor – weakness, atrophy of muscles
  - Autonomic – lightheadedness when standing, dry mouth, diarrhea, erectile dysfunction

Ref: Weisman J “Healthy Nerves.”
ADVICE FOR PERIPHERAL NEUROPATHY

• Decrease alcohol intake – alcohol has direct toxicity to nerves

• Stop smoking – causes constriction of blood vessels that nourish nerves

• Eat a diet rich in fruits, vegetables, especially dark green leafy vegetables that contain B vitamins (need to discuss latter with your physician first if on blood thinners)

• Muscles use nerves to stay healthy – use them!

Ref: Weisman J "Healthy Nerves."

INTERVENTIONS FOR NEUROPATHY

• Vitamins – Multicomplex B vitamins; B6 should NOT exceed 150 mg daily, folic acid, and vitamin E (B6 > 200 mg daily can CAUSE neuropathy)

• Cramping – stretching of calf muscles

• For pain, burning – medications (always discuss with your physician)
  • Gabapentin – can cause drowsiness, fatigue
  • Pregabalin – same as gabapentin
  • Duloxetine
  • Tricyclics (amitryptiline, and others)
FATIGUE IN MULTIPLE MYELOMA

• Fatigue is COMMON in multiple myeloma – related to both the disease and sequelae, but also related to treatment

• Grade 3 or higher fatigue in DETERMINATION 6%

• PERSEUS Trial:
  • 24% any grade fatigue with DRVD
  • 2.4% grade 3 or higher fatigue

• Interventions:
  • Exercise
  • Dose reductions of treatment

LENALIDOMIDE TOXICITY MANAGEMENT

• Gastrointestinal: diarrhea, cramping
  • Heather’s tummy fiber
  • Colestipol 1-2 G divided daily; discuss with your physician, may impair absorption of other medications

• Neutropenia
  • Growth factor support, neupogen or Neulasta
  • Dose reductions

• Fatigue
  • Dose reductions
  • Changing treatment schedule, frequency

• VTE prevention
  • Anti thrombotic therapy (aspirin or apixaban/similar)
**MOBILITY AND STRENGTH - SARCOPENIA**

Intrinsic risk factors:
- Muscle degeneration
- Hormone disorder
- Mitochondrial damage
- Chronic inflammation

Healthy muscle

Extrinsic risk factors:
- Physical inactivity
- Sedentary lifestyle
- Obesity
- Other factors

Sarcopenic muscle

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**SARCOPENIA IN MULTIPLE MYELOMA**

- Sarcopenia is common in multiple myeloma patients:
  - In a single center study of MM pts undergoing auto HCT, sarcopenia (<81% high density muscle) was present in 72/142 pts (51%) and was associated with cardiovascular events\(^1\)
  - Sarcopenia had a negative prognostic impact independent of ISS stage, age, and HR FISH in 322 patients with newly diagnosed MM\(^2\)
  - In an analysis of 61 patients receiving either ide-cel and cilta-cel commercially, 47/61 (77%) met criteria for sarcopenia; sarcopenia associated with higher risk of developing neurotoxicity\(^3\)
  - In a study of 341 patients with newly diagnosed MM, low muscle radiodensity was associated with higher disease stage, anemia, and renal failure, but not with OS\(^4\)

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**MANAGEMENT OF SARCOPENIA/FRAILTY**

- Physical exercise
  - Resistance training – Hillengass et al, IMS 2023: supervised resistance training in a pilot study; no grade 3 or higher AEs, and no new fractures

**Intervention**

- Cohort 1 (Resistance Training): 6 months, twice weekly, supervised resistance training
- Cohort 2 (Walking): 6 months, remote prompts to a fitness tracker to reach the recommended 150-300 active minutes per week

**Results (6MWT* and 30SST**)**

*6 Min Walk Test, **30 Second Sit to Stand, Brackets represent significant differences*

**IMPACT OF DIET ON MULTIPLE MYELOMA**

- Beneficial Diet (variety of intake)
  - Whole Fruits & Vegetables
  - Whole Grains & Fiber
  - Beans & Legumes
  - Fish
  - Animal Products & Processed Foods

- Gut Microbiome
  - Diversity
  - Dysbiosis

- Butyrate producing bacteria
- Nitrogen producing bacteria
- Bile-tolerant bacteria

- Circulation
  - Butyrate
  - Ammonium
  - Glutamine

- Bone Marrow Microenvironment
  - Th17 cells
  - Eosinophils

- Immune System
  - Inflammation
  - Anti-Tumor Immunity
  - Proinflammatory cytokines
  - IL-17
  - IL-5
  - IL-8

**Outcomes**

- Progression to Multiple Myeloma
- Sustained MRD negativity
- Progression-Free Survival
- Overall Survival
- Gastrointestinal toxicities
- Comorbidities

SUMMARY

- Improving outcomes for newly diagnosed MM – with introduction of quad regimens, unprecedented improvements in survival
- Relapsed multiple myeloma seeing gains due to introduction of newer immune based therapies – which would not have been possible without clinical trials!
- Quality of life on treatment still a major issue
  - Neuropathy
  - Fatigue
  - GI issues
  - Strength, energy
- Future research needs to focus not simply on improving survival (and someday finding a cure!) but also on making life more manageable when receiving these treatments.

ASK A QUESTION

HIGHLIGHTS IN THERAPY: MULTIPLE MYELOMA

Ask a question by phone:
Press star (*) then the number 1 on your keypad.

Ask a question by web:
Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.
LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an Information Specialist about disease, treatment and support information, resources and clinical trials:

Call: **(800) 955-4572**
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: [www.LLS.org/InformationSpecialist](http://www.LLS.org/InformationSpecialist)
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: [www.LLS.org/ContactUs](http://www.LLS.org/ContactUs)

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CLINICAL TRIAL SUPPORT CENTER

Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process. [www.LLS.org/Navigation](http://www.LLS.org/Navigation)

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NUTRITION CONSULTATIONS

Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email. [www.LLSNutrition.org](http://www.LLSNutrition.org)

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LLS EDUCATION & SUPPORT RESOURCES

**Online Chats**

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit [www.LLS.org/Chat](http://www.LLS.org/Chat).

**Education Videos**

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit [www.LLS.org/EducationVideos](http://www.LLS.org/EducationVideos).

**Patient Podcast**

*The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit [www.TheBloodline.org](http://www.TheBloodline.org).
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers:

www.LLS.org/Finances

To order free materials: www.LLS.org/Booklets

THANK YOU

This program is supported by

[Logos of Genentech, Biogen, and Johnson & Johnson]

Please complete our program evaluation

We have one goal: A world without blood cancers