A Glimpse Into the Future of Myeloma Patient Management

Topic 1: Diagnosis and Risk Assessment

Current Practice

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Disclosures

Dr. Cho has disclosed the following relevant financial relationships:

*Research Grant:* Bristol Myers Squibb/Celgene, Takeda

Diagnosis and Risk Assessment

**Question 1**

*How often do you incorporate the revised International Staging System (R-ISS) measurements into your risk assessment for myeloma patients at diagnosis?*

A. Always  
B. Often  
C. Sometimes  
D. Rarely  
E. Never
Diagnosis and Risk Assessment

Question 2

How often do you incorporate genomic analysis into your risk assessment for myeloma patients at diagnosis?

A. Always
B. Often
C. Sometimes
D. Rarely
E. Never

Staging in Multiple Myeloma

- NCI defines staging as
  - Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from where it first formed to other parts of the body
- This definition is not applicable to multiple myeloma
- Staging in multiple myeloma is a risk assessment
Evolution of Myeloma Staging Systems

**International Staging System**
- Myeloma cell mass, hemoglobin, calcium, bone health, M protein, and Bence-Jones protein
- Stages I, II, or III
- Subclassification A or B (based on renal function)

**Revised International Staging System**
- ISS and LDH, and detection of CA by FISH
- High-risk CA by FISH:
  - del(17p)
  - t(4;14)
  - t(14;16)
- Stages I, II, or III

**Durie-Salmon Staging System**
- Myeloma cell mass, hemoglobin, calcium, bone health, M protein, and Bence-Jones protein
- Stages I, II, or III
- Subclassification A or B (based on renal function)

**ISS (International Staging System)** for Multiple Myeloma

- **Stage I**
  - β2M <3.5 mg/L and albumin ≥3.5 g/dL. Median survival 69 months

- **Stage II**
  - Not stage I or III. Median survival 50 months

- **Stage III**
  - β2M ≥5.5 mg/L. Median survival 33 months

B2M: beta-2 microglobulin; ISS, International Staging System; LDH, lactate dehydrogenase; CA, chromosomal abnormality; iFISH, interphase fluorescent in situ hybridization.

**Combined Prognostic Models**

**Revised International Staging System (R-ISS)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median overall survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
<td>NR</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III</td>
<td>83</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
<td>43</td>
</tr>
</tbody>
</table>


**Myeloma Staging System**

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Revised International Staging System (R-ISS)† Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-ISS Stage I</td>
</tr>
<tr>
<td><strong>ISS² stage I</strong></td>
<td></td>
</tr>
<tr>
<td>– Serum β2M level</td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 mg/L, and</td>
<td></td>
</tr>
<tr>
<td>– Serum albumin level</td>
<td></td>
</tr>
<tr>
<td>≥3.5 g/dL</td>
<td></td>
</tr>
<tr>
<td>– No high-risk CA*</td>
<td></td>
</tr>
<tr>
<td>– Normal LDH level</td>
<td></td>
</tr>
<tr>
<td><strong>All other possible combinations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ISS² stage III</strong></td>
<td></td>
</tr>
<tr>
<td>– Serum β2M level</td>
<td></td>
</tr>
<tr>
<td>≥5.5 mg/L</td>
<td></td>
</tr>
<tr>
<td>– High-risk CA* or high LDH level</td>
<td></td>
</tr>
</tbody>
</table>

5-Year OS† (%) | 82 | 62 | 40

5-Year PFS† (%) | 55 | 36 | 24

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*Deletion 17p and/or t(4;14) and/or t(14;16)
†At a median follow-up of 46 months

β2M, beta-2 microglobulin; LDH, lactate dehydrogenase; CA, chromosomal abnormality

A Glimpse Into the Future of Myeloma Patient Management

GRIFFIN: Phase 2, Randomized, Open-Label Study of Dara-RVd vs RVd in Transplant-Eligible NDMM

**Key eligibility criteria**
- NDMM
- 18–70 years
- Transplant eligible
- ECOG score ≤2
- CrCl ≥30 mL/min

**Induction:**
- Cycles 1–4
- Dara-RVd vs RVd
- Cycles: 28 days

**Consolidation:**
- Cycles 5–6
- Dara-RVd vs RVd
- Cycles: 21 days

**Maintenance:**
- Cycles 7–32
- Dara-R vs RVd maintenance
- Cycles: 28 days

**Primary end point:** sCR rate after consolidation

---

Subgroup Analysis of sCR and MRD Negativity by the 12-Months-of-Maintenance Therapy Cutoff

<table>
<thead>
<tr>
<th></th>
<th>RVd</th>
<th>D-RVd</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25/55 (45.5)</td>
<td>33/55 (60.0)</td>
<td>1.80 (0.84–3.84)</td>
</tr>
<tr>
<td>Female</td>
<td>21/42 (50.0)</td>
<td>30/44 (68.2)</td>
<td>2.14 (0.89–5.15)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>35/70 (50.0)</td>
<td>66/72 (63.9)</td>
<td>2.47 (0.83–7.39)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>11/27 (40.7)</td>
<td>11/27 (63.0)</td>
<td>1.77 (0.90–3.46)</td>
</tr>
<tr>
<td><strong>ISS disease stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>18/48 (37.5)</td>
<td>29/48 (60.4)</td>
<td>2.54 (1.12–5.79)</td>
</tr>
<tr>
<td>II</td>
<td>19/35 (54.3)</td>
<td>26/37 (70.3)</td>
<td>1.99 (0.76–5.25)</td>
</tr>
<tr>
<td>III</td>
<td>8/13 (61.5)</td>
<td>9/14 (67.1)</td>
<td>0.83 (0.18–3.68)</td>
</tr>
<tr>
<td><strong>Type or MM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>17/51 (33.3)</td>
<td>31/51 (60.8)</td>
<td>3.10 (1.38–6.96)</td>
</tr>
<tr>
<td>Non-IgG</td>
<td>29/46 (63.0)</td>
<td>29/45 (64.4)</td>
<td>1.06 (0.45–2.50)</td>
</tr>
<tr>
<td><strong>Cytogenetic risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>5/13 (38.5)</td>
<td>7/16 (43.8)</td>
<td>1.24 (0.28–5.53)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>40/80 (50.0)</td>
<td>56/79 (69.6)</td>
<td>2.29 (1.20–4.39)</td>
</tr>
<tr>
<td><strong>ECOG PS score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15/39 (38.5)</td>
<td>22/38 (57.9)</td>
<td>2.20 (0.88–5.47)</td>
</tr>
<tr>
<td>1–2</td>
<td>31/58 (53.4)</td>
<td>40/60 (66.7)</td>
<td>1.74 (0.83–3.67)</td>
</tr>
</tbody>
</table>

**D-RVd improved sCR and MRD negativity rates across most subgroups.**

Kaufman JL et al. Presented at the 7th World Congress in Controversies in Multiple Myeloma (COMy); May 7–9, 2021.
Can we refine staging even further?

- Additional chromosome abnormalities
  - 1p−, 1q21+/++, biallelic deletion of 17p, “double hit”
  - GEP
  - Somatic mutations
- Anatomic/radiographic features, clonal diversity
- Circulating plasma cells
- Define high risk, ultra high risk
  - Pursue hypothesis-driven clinical trials

Initial Staging Workup

- Bone marrow biopsy
  - FISH myeloma panel
- Radiographic assessment
  - PET, CT bone survey, MRI spine/pelvis
- Chemistries including albumin, LDH, β2M, CBC, SPEP/IFE, sFLC
Conclusion

• R-ISS is the latest step in the biologically driven risk assessment of newly diagnosed myeloma
• Appropriate staging studies are mandatory for all new symptomatic multiple myeloma patients
• Consider clinical trials for R-ISS III patients

Topic 1: Diagnosis and Risk Assessment

In the Future

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Disclosures

Dr. Manasanch has disclosed the following relevant financial relationships:

**Consultant/Advisor:** Adaptive Biotechnologies, Celgene, GlaxoSmithKline, Janssen, Sanofi, Secura Bio, Takeda

**Research Grant:** JW Pharma, Merck, Novartis, Quest Diagnostics, Sanofi

Defining Risk in Myeloma

Risk assessment for treatment personalization

Low risk = better prognosis
High risk = worse prognosis

Risk-adapted treatment
Defining Risk in Myeloma

- Retrospective study
  - 104 patients → 2014–2017
  - Available gene-expression profiling (MyPRS)
  - 99% (103 patients) had FISH available
- Patients at high risk received more treatment (triple maintenance therapy)
- Median follow-up: 33 months (1–55 months)
- 72.5% of patients received high-dose melphalan with stem cell rescue

<table>
<thead>
<tr>
<th>Criteria</th>
<th>3-Year RFS by GEP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/high-borderline (E/N=16/29)</td>
<td>41</td>
</tr>
<tr>
<td>Low/low-borderline (E/N=24/75)</td>
<td>60</td>
</tr>
</tbody>
</table>

\( P \text{ value}=0.0173 \)

FISH, fluorescence in situ hybridization; RFS, relapse-free survival

Defining Risk in Myeloma

- High-risk GEP is best predictor of early mortality due to multiple myeloma
- Mortality rate
  - HR GEP/HR FISH 21%
  - HR GEP/LR FISH 25%
  - LR GEP/HR FISH 0%
  - LR GEP/LR FISH 6%

<table>
<thead>
<tr>
<th>Criteria</th>
<th>3-Year OS by GEP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High/high-borderline (E/N=10/29)</td>
<td>71</td>
</tr>
<tr>
<td>Low/low-borderline (E/N=10/75)</td>
<td>83</td>
</tr>
</tbody>
</table>

\( P \text{ value}=0.0343 \)

GEP, gene-expression profiling; HR, high risk; LR, low risk; OS, overall survival

Defining Risk in Myeloma

Addition of ≥4 copies cm 1 (CKS1B gene) to traditional FISH high-risk abnormalities increased risk of relapse despite adequate treatment and also increased risk of death


Multiple Myeloma Genome

- Etiological events
  - Hyperdiploid
    - 3,5,7,9,11,15,19,21
  - Non-hyperdiploid
    - t(11;14)
    - t(4;14)
    - t(14;20)

- Later events
  - 1q+
  - 1p-
  - 17p-
  - Mutation
  - Methylation
  - Copy number
  - Structural

Multiple Myeloma Genome

Genetic changes characteristic of myeloma. >50% of myeloma cases have gains of odd-numbered chromosomes (hyperdiploidy)

**Structural changes**: translocations (rearrangement of chromosomes)
- Between cm 11 and 14
- **Between cm 4 and 14**
- Between cm 6 and 14
- Between cm 16 and 14
- Between cm 20 and 14

**Copy number alterations** (gains or losses of chromosomes)
- Loss of cm 17
- Gains of cm 1

Mutations
- KRAS
- NRAS
- BRAF
- TRAF2/3
- CYLD

Increasing knowledge of the multiple myeloma genome allows us to divide myeloma into different genomic abnormalities associated with specific clinical behaviors.
Clonal Evolution/Ecosystem in Myeloma

Figure 2A from Morgan GJ et al. From bench to bedside: the evolution of genomics and its implications for the current and future management of multiple myeloma. *Cancer J.* 2021 May-Jun 01;27(3):213-221.

• When could we use targeted treatment?

• **Early genomic events (translocations)** can be considered in the trunk of the tree → **disease eradication**.
  - Examples: MMSET/CCNDx inhibitors

• **Late genomic events (mutations)** → subclonal and may result in myeloma **control** but more difficult to eradicate disease.
  - Examples: BRAF/MEK inhibitors, MYC inhibitors, UTX inhibitors

**Target the trunk not the branches!**

Single-Cell Genomic Analysis

- 3 patients with relapsed MM with BRAF mutation: 1 with BRAF V600E mutation and 2 with D594N mutations
  - Treated with BRAF inhibitor dabrafenib and MEK inhibitor trametinib
- Gene expression differences as early as 7 days post treatment
- SC genomic analysis at baseline, week 1 and at progression
- Cancer cells can adapt to precision treatments
  - Increasing/decreasing expression of certain genes that give survival advantage


Diagnosis and Risk Assessment Question 1

How often do you PLAN TO incorporate the revised International Staging System (R-ISS) measurements into your risk assessment for myeloma patients at diagnosis?

A. Always
B. Often
C. Sometimes
D. Rarely
E. Never
Diagnosis and Risk Assessment
Question 2

How often do you **PLAN TO** incorporate genomic analysis into your risk assessment for myeloma patients at diagnosis?

A. Always
B. Often
C. Sometimes
D. Rarely
E. Never
Disclosures

Dr. Shah has disclosed the following relevant financial relationships:

**Consultant/Advisor:** Amgen, CareDx, CSL Behring, GlaxoSmithKline, Indapta Therapeutics, Karyopharm, Kite, Oncopeptides, Sanofi

**Research Grant:** Bluebird Bio, Celgene/Bristol Myers Squibb, Janssen, Nektar, Poseida, Sutro Biopharma, Teneobio

Smoldering Multiple Myeloma Question 1

*Do you risk stratify your SMM patients via an established risk scoring system (eg, Pethema, Mayo, etc) at diagnosis?*

A. Always  
B. Often  
C. Sometimes  
D. Rarely  
E. Never
**Smoldering Multiple Myeloma**

**Question 2**

*If regulatory approvals allow, how likely are you to treat a high-risk SMM patient?*

A. Very likely  
B. Likely  
C. Neutral  
D. Unlikely  
E. Very unlikely

---

**Defining Smoldering Multiple Myeloma**

<table>
<thead>
<tr>
<th>Monoclonal component</th>
<th>Smoldering multiple myeloma (SMM)</th>
<th>Symptomatic multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal gammopathy of uncertain significance (MGUS)</td>
<td>≥3 g/dL serum AND/OR 10%–60% AND Absent</td>
<td>Present (serum/urine) AND &gt;10% AND Present</td>
</tr>
<tr>
<td>Bone marrow plasma cells (%)</td>
<td>&lt;3 g/dL serum AND &lt;10% AND Absent</td>
<td></td>
</tr>
<tr>
<td>Myeloma-defining event</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)  
Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL)  
Anemia: hemoglobin >20 g/L below the lower limit of normal or <100 g/L  
Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

### Recommended Work-Up at Baseline in Patients With SMM

- History/physical
- CBC, CMP
- SPEP, IFE
- Serum free light chains with light chain ratio
- 24-hour UPEP with IFE
- Bone marrow biopsy
- Imaging
  - PET-CT
  - Low-dose whole-body CT
  - Whole-body MRI
  - MRI spine/pelvis

### Probability of Progression to Active Myeloma

- Probability of progression since diagnosis of SMM
  - First 5 years, 10% per year
  - Next 10 years, 5% per year
  - Next 10 years, 1% per year

**MGUS**
- Serum M protein <30 g/L
- Urine M protein <500 mg/24 h
- BMPC clone <10%
- Absence MDEs of amyloidosis

**SMM**
- Serum M protein ≥30 g/L and/or
- BMPC clone >10%, but <60% and/or
- Urine M prot ≥500 mg/24h
- Absence MDEs or amyloidosis

# Risk Factors in SMM

**Tumor burden:**
- BMPCs ≥10%
- M protein ≥3 g/L
- FLC ratio <0.125 or >8
- BJ proteinuria
- PB CTC >5 × 10E6/l

**PC characteristics:**
- t(4;14)
- del 17p
- gain 1q
- Hyperdiploidy
- Genetics

**Immunophenotypic characteristics:**
- ≥95% aberrant PC
- Immunoparesis

**Tumor dynamics:**
- Evolving M protein

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# Risk Scoring Systems in SMM

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Factors</th>
<th>Median TTP (months) or 2-yr PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Pethema&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>(1) Presence of aberrant PC &gt;95% of clonal PCs; (2) immunoparesis</td>
<td>NR</td>
</tr>
<tr>
<td>Mayo&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>(1) BMPCs ≥10%; (2) M protein ≥30 g/L; (3) FLC ratio &lt;0.125 or &gt;8</td>
<td>152</td>
</tr>
<tr>
<td>Mayo 20/20&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>(1) BMPCs ≥20%; (2) M protein ≥20 g/L; (3) FLC ratio &gt;20</td>
<td>109.8</td>
</tr>
<tr>
<td>SWOG&lt;sup&gt;6&lt;/sup&gt;</td>
<td>(1) Serum M spike ≥30 g/L; (2) involved FLC &gt;250 mg/L; (3) GEP risk score &gt; -0.26</td>
<td>3.4%</td>
</tr>
<tr>
<td>Deense risiclass&lt;sup&gt;7&lt;/sup&gt;</td>
<td>(1) M protein ≥30 g/L; (3) immunoparesis</td>
<td>5%</td>
</tr>
<tr>
<td>Barcelona Group&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Evolving M protein</td>
<td>13 (71% at 36 mos)</td>
</tr>
<tr>
<td>Pennsylvania risk score&lt;sup&gt;9&lt;/sup&gt;</td>
<td>(1) BMPCs &gt;40%; (2) sFLC ratio ≥50; (3) albumin ≤3.5g/L</td>
<td>16%</td>
</tr>
</tbody>
</table>

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A Glimpse Into the Future of Myeloma Patient Management

**20-2-20 Risk Model**

<table>
<thead>
<tr>
<th>Risk Stratification Groups</th>
<th>Patient s (n)</th>
<th>Number of Risk Factors</th>
<th>Time to Progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>143</td>
<td>0</td>
<td>110</td>
</tr>
<tr>
<td>Intermediate-risk group</td>
<td>121</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>High-risk group</td>
<td>153</td>
<td>2–3</td>
<td>29</td>
</tr>
</tbody>
</table>

**Factors**
- BMPC >20%
- M spike >2 g/dL
- FLC ratio >20

**Stratification**
- Low-risk: 0
- Intermediate risk: 1
- High-risk: ≥2

BMPC%, bone marrow-plasma cell percentage; CI 95%, confidence intervals; FLCr, involved to uninvolved free light chain ratio; OR, odds ratio


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**SMM, to treat or not?**

- Delaying symptomatic progression
- Maintain/increase quality of life by treating early
- Possibility of cure?
- Selection of resistant clone?
- Toxicity
- Costs of treatment
- Overtreatment

Slide courtesy of S. Lonial.
Observation (IMWG)

- Generally agreed upon for low- and intermediate-risk SMM
- Baseline labs/work-up
- Repeat labs 2–3 months later
- If stable → repeat every 4–6 months × 1 year
- If stable → repeat every 6–12 months
- Address new symptoms quickly


High-Risk SMM: To Treat or Not to Treat...

- NO TREATMENT
  - Observation
- TREATMENT
  - Delay symptomatic MM
    - “Mild”
  - Cure?
    - As symptomatic MM
    - Adjusted
Delaying Time to Progression

QuiRedex phase 3 trial: Rd vs observation in high-risk SMM (n=119)
Median follow-up: 75 m

<table>
<thead>
<tr>
<th>Treatment group (months)</th>
<th>Time to Progression</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (months)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Observation group (months)</td>
<td>23</td>
<td>Not reached</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.24 (0.14–0.41)</td>
<td>0.43 (0.21–0.92)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Early treatment with Rd significantly delayed the TTP to myeloma with a benefit in OS.


E3A06: Len vs Observation in Patients With Asymptomatic High-Risk SMM (n=182)

Progression-free survival was significantly longer for lenalidomide compared with observation (treatment HR, 0.28; 95% CI, 0.12 to 0.62; \( P=0.002 \))

Criteria: PCBM ≥10% and sFLC ratio >8 or <0.125

Hazard Ratios (95% CI)
- All patients, 0.28 (0.12, 0.62)
- Mayo 2008 Risk High, 0.29 (0.06, 1.49)
- Mayo 2008 Risk Intermediate, 0.37 (0.14, 0.97)
- Mayo 2018 Risk High, 0.09 (0.02, 0.44)
- Mayo 2018 Risk Intermediate, 0.52 (0.15, 1.85)
- Age <70, 0.37 (0.14, 0.98)
- Age ≥70, 0.13 (0.02, 1.01)
- Male, 0.32 (0.10, 1.03)
- Female, 0.20 (0.06, 0.70)
- ECOG PS 0, 0.30 (0.12, 0.79)
- ECOG PS 1-2, 0.22 (0.05, 1.05)
- White, 0.22 (0.09, 0.54)
- Black, 1.73 (0.10, 30.76)

\[ \text{Mayo2008: PCBM ≥10\% + MC ≥ 3g/dL} \]
\[ \text{Mayo 2018: 2/20/20} \]

- N=182, intermediate/high-risk SMM (BMPC% ≥10% and aberrant (FLC) ratio (<0.26 or >1.65)
- 1:1 randomization lenalidomide 25 mg day 1 to 21 in 28-day cycle vs observation
- Median FU 35 mnd, median time on len 23 cycles, len discontinued in 51% of patients

Early treatment with R significantly prevented the progression to MM, especially in the high-risk subgroup.

An Illustrative Example of Importance of Need for Randomized Studies in SMM With Accurate Risk Stratification/Patient Selection

E3A06: Phase 3 Lenalidomide (N=92) vs observation (N=90) for SMM
PFS by treatment arm within Mayo 2018 risk subgroup

The benefit of lenalidomide was observed in most subgroups, although many subsets are relatively small. Of note, patients in all risk groups seemed to have an HR that favored early treatment, but this was most pronounced in the Mayo 2018 high-risk category.

- 40% len discontinuation rate for adverse events
- 11.4 vs 3.5% SPM at 3 years


Effects on SMM Clone vs MM Clone: Carfilzomib, Lenalidomide, and Dexamethasone With Lenalidomide Extension in Patients With SMM or NDMM

12 high-risk SMM* 45 MM
KRd: Carf (20/36), len 25 mg d1–21, dex 20 mg d1,2 etc 4×
KRd: Carf, len, dex 10 mg d1, 2, etc 4×
lenalidomide, 24×

Response rates in relation to cycles of KRd

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>10</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>10</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Mean M-spike (d/dL)

11/12 (92%) are MRD negative by 8-color flow cytometry of the bone marrow
9/12 (75%) are MRD negative by NGS of the bone marrow

KRd: Carf, len, dex 10 mg d1, 2, etc 4×
lenalidomide, 24×

<table>
<thead>
<tr>
<th>Response rates</th>
<th>SMM</th>
<th>NDMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCR/CR/sCR</td>
<td>100%</td>
<td>56%</td>
</tr>
<tr>
<td>PR</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>VGPR</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>MRDneg (flow)†</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>MRDneg (NGS)‡</td>
<td>100%</td>
<td>92%</td>
</tr>
</tbody>
</table>

18-mo PFS

*By MAYO and/or PETHEMA criteria
†Measured only in patients with nCR/CR

Treatment Aimed at Cure: GEM-CESAR Trial for High-Risk SMM

- Multicenter, open-label, phase 2 trial

**Induction** 6×28-day cycles

- High-risk* SMM patients  
  N=90

- Carfilzomib iv  
  20/36 mg/m²  
  Days 1, 2, 8, 9, 15, 16

- Lenalidomide  
  25 mg  
  Days 1–21

- Dexamethasone  
  40 mg  
  Days 1, 8, 15, 22

Followed by ASCT

**Consolidation** 2×28-day cycles

- Carfilzomib iv  
  20/36 mg/m²  
  Days 1, 2, 8, 9, 15, 16

- Lenalidomide  
  25 mg  
  Days 1–21

- Dexamethasone  
  40 mg  
  Days 1, 8, 15, 22

**Maintenance** 24×28-day cycles

- Lenalidomide  
  10 mg  
  Days 1–21

- Dex  
  20 mg  
  Days 1, 8, 15, 22

*High-risk was defined according to the Mayo and/or Spanish models

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included, but...
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

Response category

<table>
<thead>
<tr>
<th>Response category</th>
<th>Induction (n=90)</th>
<th>HDT-ASCT (n=83)</th>
<th>Consolidation (n=81)</th>
<th>High-risk (n=54)</th>
<th>Ultra high-risk (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>85 (94%)</td>
<td>82 (99%)</td>
<td>81 (100%)</td>
<td>54 (100%)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>≥CR</td>
<td>37 (41%)</td>
<td>53 (64%)</td>
<td>61 (76%)</td>
<td>41 (76%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>35 (39%)</td>
<td>18 (22%)</td>
<td>15 (19%)</td>
<td>10 (19%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (14%)</td>
<td>11 (13%)</td>
<td>5 (6%)</td>
<td>2 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (3%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MRD negative,</td>
<td>27 (30%)</td>
<td>47 (56%)</td>
<td>51 (63%)</td>
<td>36 (67%)</td>
<td>15 (56%)</td>
</tr>
</tbody>
</table>

* Progressive disease was biological in 1 patient and clinical in 1 patient

Courtesy of MV Mateos.

A Glimpse Into the Future of Myeloma Patient Management

ASCENT: KRd-D

Study design

Primary endpoint: Rate of confirmed sCR
Secondary objectives: Safety, PFS, OS, MRD negativity

Results to date:
- 54 patients accrued
- Median patient age 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction, and 17% in induction phase
- ≥1 patient needed a dose modification
- ≥ grade 3 AE seen in 43% of patients

Quadruplet regimen KRd-D is well tolerated in high-risk SMM

AE, adverse event; CR, complete response; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; sCR, stringent complete response

Toxicity profile

Phase 2 Study of KRd Followed by Lenalidomide Maintenance in High-Risk SMM

Primary objective: determine MRD-negative CR rate
- Key secondary objectives: PFS (clinical and biochemical), ORR, DOR, duration of MRD negativity (MFC, sensitivity 10-5), and safety
- Median patient age 59 years
- 37% had disease with high-risk cytogenetic features

Benefit vs risk of KRd-R in SMM is favorable but future trials needed to confirm results

Sustained MRD negativity

Best overall response

Progression to symptomatic MM and survival

PFS

CI, confidence interval; DOR, duration of response; FE, immunofixation electrophoresis; KRd, carfilzomib, lenalidomide, dexamethasone; MFC, multiparameter flow cytometry; nCR, near complete response; ORR, overall response rate; PR, lenalidomide maintenance sCR, stringent complete response; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; VGPR, very good partial response


Conclusions

• SMM is many diseases in one
• Important to risk stratify → empower patient and provider
• Observation is still SOC in low and intermediate risk
• Debate in high risk
  – Goals of treatment
  – Pertinent endpoints

Clinical trials are liiiiiife!!!
Topic 2: Smoldering Multiple Myeloma

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Associate Professor
Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Disclosures

Dr. Manasanch has disclosed the following relevant financial relationships:

Consultant/Advisor: Adaptive Biotechnologies, Celgene, GlaxoSmithKline, Janssen, Sanofi, Secura Bio, Takeda

Research Grant: JW Pharma, Merck, Novartis, Quest Diagnostics, Sanofi
Monoclonal Gammopathies

MGUS

M protein <3 g/dL  | Bone marrow plasma cells <10%  | No symptoms
SIGNIFICANT PROPORTION OF PLASMA CELLS ARE NORMAL  
LESS IMMUNOSUPPRESSION, NORMAL UNINVOLVED IMMUNOGLOBULINS

SMM

M protein ≥3 g/dL or urine M protein ≥500 mg  | Bone marrow plasma cells 10%-60% plasma cells  | No symptoms
SIGNIFICANT PROPORTION OF PLASMA CELLS ARE ABNORMAL  
INCREASED IMMUNOSUPPRESSION

MM

M protein in the serum or urine  | Bone marrow clonal plasma cells ≥60%  
i/u FLC ratio ≥100  
>1 focal lesions on MRI  | Symptoms or lesions in the bones, kidneys; high calcium, blood counts
NORMAL PLASMA CELLS VIRTUALLY ABSENT  
SIGNIFICANT IMMUNOPRESSION – HALLMARKS MM RECURRENT INFECTIONS

Tumor burden

MGUS, monoclonal gammopathy of undetermined significance;  
SMM, smoldering multiple myeloma; MM, multiple myeloma


SMM Risk Stratification

High-risk SMM median time to progression is <2 years

PETHEMA Group Criteria (n=89)

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>Patients n (%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 (31)</td>
<td>4%</td>
</tr>
<tr>
<td>1</td>
<td>22 (25)</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>39 (44)</td>
<td>72%</td>
</tr>
</tbody>
</table>

Risk factors

- ≥95% abnormal plasma cells
- Immunoparesis

### MGUS/SMM Risk Stratification

#### SWOG Criteria

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>Patients n (%)</th>
<th>Progression at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76 (28)</td>
<td>3%</td>
</tr>
<tr>
<td>1</td>
<td>115 (42)</td>
<td>22%</td>
</tr>
<tr>
<td>≥2</td>
<td>82 (30)</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Risk factors**
- GEP70 score ≥0.26
- M protein >3 g/dL
- Involved sFLC >25 mg/dL


#### IMF/Updated Mayo Criteria

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>Patients n</th>
<th>Progression at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>522</td>
<td>6.2%</td>
</tr>
<tr>
<td>1</td>
<td>445</td>
<td>17.9%</td>
</tr>
<tr>
<td>≥2</td>
<td>396</td>
<td>44.2%</td>
</tr>
</tbody>
</table>

**Risk factors**
- Bone marrow plasma cells ≥20%
- M protein ≥2 g/dL
- Involved:uninvolved sFLC ratio ≥20

A Glimpse Into the Future of Myeloma Patient Management

**MGUS/SMM Risk Stratification**

- No approved treatments for MGUS or SMM
- Lack of prospectively validated progression models that integrate clinical, immune, and genomic markers
- 300 patients (enrolled ~200 patients)
- Bone marrow biopsy and bloodwork
- Follow-up every 6 months for 3 years
- Progression to multiple myeloma (10 – MM and 2 – amyloidosis)

**MGUS/SMM Risk Stratification**

Model comparison in the MD Anderson cohort

- PA15 all SMM patients
  - IMF (N=59): LOW 26.8, INTERMED 40.7, HIGH 35.6, SWOG (N=33): 48.5
  - Mayo (N=59): LOW 42.4, INTERMED 50.8, HIGH 30.5
- PA15 progressed SMM patients
  - IMF (N=10): LOW 80, INTERMED 70, HIGH 60
  - Mayo (N=10): LOW 40, INTERMED 50, HIGH 12.5

*Progressed in <1 year

**MGUS/SMM Risk Stratification**

Model comparison in the MD Anderson cohort (n=59)

**Best predictors**
- IMF 20/2/20 model
- GEP myeloma cells

![Graph showing patients at risk for MM progression based on IMF levels]

- IMF0: 25, 22, 9, 1
- IMF1: 17, 15, 11, 7, 1
- IMF2: 12, 8, 4, 3
- IMF3: 6, 4, 3, 2

Wald Chi-sq $P=0.0020$


---

**MGUS/SMM Risk Stratification**

Model comparison in the MD Anderson cohort (n=59)

**Best predictors**
- IMF 20/2/20 model
- GEP myeloma cells

One-way analysis of GEP score at baseline by progression to multiple myeloma

![Graph showing GEP score distribution by progression to MM]

Genomic/Immune Changes in Early Myeloma

Flow cytometry of bone marrow samples in patients with SMM. Fold change in mean fluorescence intensity (MFI) of immunosuppressive ligands on CD138+ tumor cells in bone marrow of 8 SMM patients at progression relative to the baseline is shown as a heatmap.

Manasanch E et al. Unpublished.

Genomic/Immune Changes in Early Myeloma

✓ Genomic profiling performed on 90 patients
✓ Bulk RNAseq of 144 samples from tumor and microenvironment from 38 MGUS and 52 SMM patients

Unsupervised clustering of CD138+ tumor cells RNAseq at baseline identified 3 distinct clusters (C1-C3). All SMM that progressed (n=6) belonged to C2.

Manasanch E et al. Unpublished.
Genomic/Immune Changes in Early Myeloma

- Genomic profiling performed on 90 patients
- Bulk RNAseq of 144 samples from tumor and microenvironment from 38 MGUS and 52 SMM patients

**CD138- TME RNAseq baseline samples were separated into 4 clusters (C1-C4) and 9/11 progressed patients belonged to C2 with distinct expression profiles**

Extensive changes in the immune composition between PD (n=11) vs non-PD (n=73)
- Low BL counts CD8+/CD4+ memory Resting T cells
- High CD4+ memory-activated T cells Gamma delta T cells, endothelial cells and fibroblasts, monocytes, NK cells

Manasanch E et al. Unpublished.

Genomic Alterations and Risk of Progression to MM

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Estimate (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>DNA repair pathway</td>
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<tr>
<td>Wildtype</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>5</td>
<td>5.54 (1.96 to 15.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>MYC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildtype</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>6</td>
<td>4.53 (1.74 to 11.82)</td>
<td>0.002</td>
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<tr>
<td>MAPK pathway</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildtype</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>15</td>
<td>3.84 (1.90 to 7.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T(4;14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildtype</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>5</td>
<td>2.58 (0.92 to 7.27)</td>
<td>0.072</td>
</tr>
<tr>
<td>Mayo 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>1.91 (0.66 to 5.47)</td>
<td>0.23</td>
</tr>
<tr>
<td>High</td>
<td>40</td>
<td>4.47 (1.63 to 12.26)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Isatuximab in High-Risk SMM

- 24 patients enrolled from 02/08/2017 until 12/21/2018 → Isatuximab (CD38 antibody) IV infusion weekly ×1 month, every 2 weeks for 5 months, and monthly for 24 months.¹

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Treated</td>
<td>24</td>
<td>100.0</td>
</tr>
<tr>
<td>Cycles completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>6-30</td>
<td></td>
</tr>
<tr>
<td>Responses at 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good partial response</td>
<td>5</td>
<td>20.8</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>29.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>20.8</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

- Single-agent isatuximab¹ ORR: 50% at 6 months, 62.5% best response
  50% ORR is comparable to lenalidomide single agent²
  3-year PFS: 91% lenalidomide vs 66% observation (HR=0.27)

- Single-agent daratumumab³
  Intense arm (n=41) ORR 56.1%, CR 4.9%, VGPR 24.4%, PR 26.8%, SD 43.9%

ITHACA: Lenalidomide-Dex With or Without Isatuximab

PART I: Safety Run-in (N=20)

- Isatuximab + Len-Dex (ILd)
  Isatuximab 10 mg/kg QW (Cycle 1)-Q2W (Cycles 2-12)
  Len (25 mg) Dex (40 mg) Cycles 1-9
  Len (10 mg) Dex (20 mg) Cycles 10-24
  Isatuximab 10 mg/kg Q4W Cycles 13-36
  N=20

PART II: Randomized Phase 3 study (N=300)

- Isatuximab + Len-Dex (ILd)
  Isatuximab 10 mg/kg QW (Cycle 1)-Q2W (Cycles 2-12)
  Len (25 mg) Dex (40 mg) Cycles 1-9
  Len (10 mg) Dex (20 mg) Cycles 10-24
  Isatuximab 10 mg/kg Q4W Cycles 13-36
  N=150

- Len-Dex (Ld)
  Len (25 mg) Dex (40 mg) Cycles 1-9
  Len (10 mg) Dex (20 mg) Cycles 10-24
  Total duration 24 cycles
  N=150

PFS monitoring
  Until PFS cut-off date
  Development of Myeloma-Defining Event OR Death
  Follow-up for PFS2 and OS

NCT04270409 found at clinicaltrial.gov
DETER (EAA173 ECOG): Lenalidomide-Dex With or Without Daratumumab

Step 0
PRE-REGISTRATION

Step 1
RANDOMIZATION

Stratification:
Age at time of high-risk SMM diagnosis: <65 or ≥65

Arm A
Daratumumab-Hyaluronidase SC OR Daratumumab IV
1800 mg/30,000 units SC or 16 mg/kg IV days 1, 8, 15, and 22, Cycles 1-2
1800 mg/30,000 units SC or 16 mg/kg IV days 1 and 15, Cycles 3-6
1800 mg/30,000 units SC or 16 mg/kg IV day 1, Cycles 7-24
Lenalidomide
25 mg PO daily days 1-21, Cycles 1-24
Dexamethasone
40 mg PO days 1, 8, 15, and 22 Cycles 1-6
20 mg PO days 1, 8, 15, and 22 Cycles 7-12

Arm B
Lenalidomide
25 mg PO daily days 1-21, Cycles 1-24
Dexamethasone
40 mg PO days 1, 8, 15, and 22 Cycles 1-6
20 mg PO days 1, 8, 15, and 22 Cycles 7-12

Accrual Goal: 288 patients with high-risk smoldering multiple myeloma.
Cycle: 28 days
NCT03937635 found at clinicaltrial.gov

Smoldering Multiple Myeloma Question 1

Do you PLAN TO risk stratify your SMM patients via an established risk scoring system (eg, Pethema, Mayo, etc) at diagnosis?

A. Always
B. Often
C. Sometimes
D. Rarely
E. Never
**Smoldering Multiple Myeloma**

**Question 2**

*If regulatory approvals allow, how likely do you **PLAN TO** treat a high-risk SMM patient?*

<table>
<thead>
<tr>
<th>Option</th>
<th>Likely Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Very likely</td>
<td></td>
</tr>
<tr>
<td>B. Likely</td>
<td></td>
</tr>
<tr>
<td>C. Neutral</td>
<td></td>
</tr>
<tr>
<td>D. Unlikely</td>
<td></td>
</tr>
<tr>
<td>E. Very unlikely</td>
<td></td>
</tr>
</tbody>
</table>
### Disclosures

Dr. Krishnan has disclosed the following relevant financial relationships:

**Consultant/Advisor:** Bristol Myers Squibb, GlaxoSmithKline, Janssen

**Research Grant:** Janssen

**Scientific Advisory Board:** Sutro BioPharma

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

**Stock Ownership:** Bristol Myers Squibb

### Newly Diagnosed Multiple Myeloma Question 1

**How often do you measure for minimal residual disease?**

A. Always  
B. Often  
C. Sometimes  
D. Rarely  
E. Never
Newly Diagnosed Multiple Myeloma
Question 2

How likely are you to proceed with upfront autologous stem cell transplantation in a patient who achieves complete remission and/or MRD negativity following induction therapy?

A. Very likely
B. Likely
C. Neutral
D. Unlikely
E. Very unlikely

2021 Trends

- MRD
- Tailored therapy
- Triplet regimens
- Quadruplet regimens
- Snapchat
- TikTok

- Transplant eligible vs not
- RVD for everyone
- Facebook
- Texting
Lenalidomide, Bortezomib, and Dexamethasone With Transplantation for Myeloma

RVD \times 3

CY (3 g/m²)
MOBILIZATION
stem cell
collection

Melphalan
200 mg/m² +
ASCT

RVD \times 5

RVD \times 2

Len \times 1 \text{ yr}
Salvage
ASCT at
progression


Evolving Trend: MRD Goal

<table>
<thead>
<tr>
<th></th>
<th>Transplantation</th>
<th>RVD Alone</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD negativity rate (%)</td>
<td>29.79</td>
<td>20.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HCT provides longest PFS
Incidence of SPM the same in RVD and HCT arms CHIPS?


Median follow-up 89.8 months
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA

N=750 pts (250 in each arm)

Register and Randomize → MEL 200mg/m² → VRD x 4 (N=254)

Lenalidomide Maintenance* (N=257)

MEL 200mg/m² (N=247) → Lenalidomide Maintenance* (N=247)

*Lenalidomide × 3 years: 10mg/d for 3 cycles, then 15 mg/d
Amendment in 2014 allowed lenalidomide maintenance until disease progression after CALGB 100104.


K Is the New V

This material serves as an educational resource only.
### FORTE Trial Design

**Induction**
- 4 × 28-day cycles
- Arm A: KCd (n=159)
  - K: 36 mg/m² d 1–2, 8–9, 15–16
  - C: 300 mg/m² d 1, 8, 15
  - d: 20 mg d 1–2, 8–9, 15–16, 22–23

- Arm B: KRd (n=158)
  - K: 36 mg/m² d 1–2, 8–9, 15–16
  - R: 25 mg d 1–21
  - d: 20 mg d 1–2, 8–9, 15–16, 22–23

- Arm C: KRd (n=157)
  - KRd (same as induction)

**Mobilization**
- Arm A: KCd (n=159)
- Arm B: KRd (n=158)
- Arm C: KRd (n=157)

**Consolidation**
- 4 × 28-day cycles
- Second randomization (1:1)

*20 mg/m² d 1–2, cycle 1 only
*K 70 mg/m² d 1, 15 every 28 days up to 2 years in patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards

### FORTE: PFS After First Randomization

**Rate of Sustained (1-Yr) MRD Negativity Multiparameter Flow Cytometry 10⁻⁵**

<table>
<thead>
<tr>
<th></th>
<th>Sustained MRD (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRd ASCT</td>
<td>47</td>
<td>0.02 (KRd ASCT vs KRd12)</td>
</tr>
<tr>
<td>KRd12</td>
<td>25</td>
<td>&lt;0.001 (KRd ASCT vs KCd ASCT)</td>
</tr>
<tr>
<td>KCd ASCT</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

**Progression-Free Survival**

- **KRd plus ASCT vs KCd plus ASCT**: HR 0.54, 95% CI 0.38–0.78, *P*=0.0008
- **KRd12 vs KCd plus ASCT**: HR 0.88, 95% CI 0.64–1.22, *P*=0.45
- **KRd plus ASCT vs KRd12**: HR 0.61, 95% CI 0.43–0.86, *P*=0.0084

Median follow-up: 50.9 (45.7–55.3) months

A Glimpse Into the Future of Myeloma Patient Management

FORTE: PFS by Risk After First Randomization

KCd_ASCT vs KRd_ASCT vs KRd12

Mina R et al. Presented at the 18th International Myeloma Workshop; September 8–11, 2021. Abstract OAB-004.

3-year PFS reported in the figure

GRIFFIN: Phase 2, Randomized, Open-Label Study of Dara-RVd vs VRd in Transplant-Eligible NDMM

Key eligibility criteria
- NDMM
- 18–70 years
- Transplant eligible
- ECOG score ≤2
- CrCl ≥30 mL/min

Induction: Cycles 1–4
Dara-RVd
Cycles: 21 days

Consolidation: Cycles 5–6
Dara-RVd
Cycles: 21 days

Maintenance: Cycles 7–32
Dara-R maintenance
Cycles: 28 days

Primary end point: sCR rate after consolidation
**GRIFFIN: MRD Negativity Over Time**


**GRIFFIN: PFS After 24 Months of Maintenance**

"Tomato-Tomahto/Potato-Potahto" D-RVD/I-KRD

- Carfilzomib showed high efficacy in combination treatments in first-line (eg, FORTE trial) and is superior to bortezomib in relapse
- Combination of carfilzomib and monoclonal anti-CD38 antibodies led to substantial MRD negativity rates in CANDOR\textsuperscript{1} and IKEMA\textsuperscript{2} trial in RRMM
- Endurance\textsuperscript{3} KRD vs RVD with censoring for ASCT or alternative therapy PFS: 32.8 vs 31.7 months
- BUT ENDURANCE WAS STANDARD-RISK PTS

\textsuperscript{1} Dimopoulos M et al. Lancet. 2020;396:186.
\textsuperscript{3} Kumar SK et al. Lancet Oncol. 2020;21:1317.

Impact of ASCT on Myeloma Burden Assessed by Next Generation Sequencing: MASTER Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MRD &lt;10\textsuperscript{-5} (%)</th>
<th>MRD &lt;10\textsuperscript{-6} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ASCT</td>
<td>Post-ASCT</td>
<td>Pre-ASCT</td>
</tr>
<tr>
<td>0</td>
<td>40.4</td>
<td>61.7</td>
</tr>
<tr>
<td>1</td>
<td>43.9</td>
<td>78.0</td>
</tr>
<tr>
<td>2+</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>All patients</td>
<td>40.4</td>
<td>68.8</td>
</tr>
</tbody>
</table>

*24 and 72 weeks after completion of therapy
**High Risk MM: GMMG CONCEPT**

**Isa-KRD**

**Isa-KRd Induction**

**Cycle 1**
- Isatuximab: 10 mg/kg day 1, 8, 15, 22
- Carfilzomib: 20 mg/m² day 1, 2
- Carfilzomib: 36 mg/m² day 6, 9, 15, 16
- Lenalidomide*: 25 mg day 1–21
- Dexamethasone†: 40 mg* day 1, 8, 15, 22

**Cycle 2–6**
- Isatuximab: 10 mg/kg day 1, 15
- Carfilzomib: 36 mg/m² day 1, 2, 8, 9, 15, 16
- Lenalidomide*: 25 mg day 1–21
- Dexamethasone†: 40 mg* day 1, 8, 15, 22

*Cy-based mobilization was moved in an amendment to time point after 3 induction cycles
†Dose adaption of lenalidomide according to renal function
‡20 mg in patients ≥75 years

**Arm A**
- N = 117
- Transplant-eligible and ≤70 yo
- I-KRd × 6
- I-KRd × 6
- Mobilization
- MEL200 + ASCT
- MEL200 + ASCT (if no CR)
- I-KRd × 4
- I-KR

**Arm B**
- N = 36
- Transplant-ineligible and >70 yo
- I-KRd × 6
- I-KRd × 6
- Mobilization
- MEL200 + ASCT
- MEL200 + ASCT (if no CR)
- I-KRd × 4
- I-KR

** ISA-KRD: Results Post 6 Induction Cycles**

- All evaluable patients: n=50
- ≥VGPR: 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n=4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive
  - 2 not assessable

Results of MRD assessments after induction treatment are not reported and available yet.

Progression-Free Survival

- 12-month PFS: 79.6% (68.3%; 90.9%)
- 24-month PFS: 75.5% (63.5%; 87.6%)

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What if you don’t want a transplant?

KEEP CALM
AND
JUST SAY NO
MAIA Study Design

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

Stratification factors:
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

D-Rd (n=368)
- Daratumumab (16 mg/kg IV)
  ‒ Cycles 1–2: QW
  ‒ Cycles 3–6: Q2W
  ‒ Cycles 7+: Q4W until PD
- R: 25 mg PO daily on Days 1-21 until PD
- d: 40 mg PO or IV weekly until PD

Rd (n=369)
- R: 25 mg PO daily on Days 1-21 until PD
- d: 40 mg PO or IV weekly until PD

Primary end point:
- PFS

Key secondary end points:
- ≥CR rate
- ≥VGPR rate
- MRD-negative rate (NGS; 10⁻⁵)
- ORR
- OS
- Safety

Cycle: 28 days

5-Year Follow-Up of the MAIA Trial:
Dara-Len-Dex vs Len-Dex in Transplant-Ineligible NDMM Patients

Progression-free survival

- Median follow-up: 56.2 months
- 60-month PFS rate

D-Rd; median, NR
52.5%
28.7%

Rd; median, 34.4 months

47% reduction in the risk of progression or death with DRd

Overall survival

- Median follow-up: 56.2 months
- 60-month PFS rate

D-Rd; median, NR
66.1%
53.1%

Rd; median, NR

32% reduction in the risk of death with DRd

Conclusions

• Current therapy
  – High response rates
  – Deep responses (MRD negativity)
  – Improving survival

• Future state
  – Bispecific T-cell engagers
  – CAR T
  – CURE

Dana-Farber Cancer Institute

Topic 3: Newly Diagnosed Multiple Myeloma
In the Future (but with a Real World View)

Paul G. Richardson, MD
R. J. Corman Professor of Medicine
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, Janssen, Karyopharm, Oncopeptides, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, Takeda

Research Grant: Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides, Takeda

Multiple Myeloma is Not One Disease:
Highly Complex at Diagnosis and at Relapse Due to Genomic Events and Clonal Evolution With Numerous Mechanisms of Resistance ~
Thus One Size Does Not Fit All....

High-risk cytogenetics: 17p del, 1q amplification, t(14;16), t(14;20), t(4;14)

Actionable cytogenetics: t(11;14)

Impact of therapy on long-term outcome: mutational burden, immune exhaustion, infectious complications, myelosuppression, end-organ injury (eg, renal, skeletal, cardiac, pulmonary, vascular, pny), extramedullary “escape”

Risk stratification, recognition of clonal heterogeneity...
Individualization of treatment with the advent of novel therapies


Courtesy of Nikhil Munshi MD, DFCI, personal communication.
Multiple Novel Agents Are Now Available to Treat Newly Diagnosed and Relapsed/Refractory Myeloma 2021

- Previously 15 but now 13 approved novel agents in MM...with more hopefully coming
- How do we sequence and strategize combination therapies to ensure the best outcomes for patients?

![Diagram of Myeloma Therapies with arrows indicating sequence: 1st line, 2nd line, 3rd line, and beyond]


Treating Multiple Myeloma Is a Marathon, Not a Sprint ...
...and COVID has Made it Significantly Harder

- Strategic vs tactical considerations ~
  Tolerability AND efficacy key with combination regimens, as well as practicality in the Pandemic era

Key Targets in MM 2021

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

Richardson PG et al. MMRF 2021

Treatment Landscape in Frontline Therapy of NDMM Is Evolving...

Optimal sequencing is the focus of ongoing research

The Past
LEN- or BORT-based
- MPT
- VMP
- Vd

Transplant non-eligible
- Vd
- Cvd
- PAD

Induction
- Vtd

Consolidation
- Maintenance
- LEN

Transplant eligible
- KRd
- Ixa (+/- Len)

Now and in the Future
Triplet/quadruplet combinations of LEN, PIs, mAbs
- Dara-VTd
- RVd
- RVD + Isa
- KRd + Isa
- RVd + Dara
- Len + Dara

Minimal residual disease assessment emerging as a vital research tool!

Timing of SCT ~ early vs delayed... or not at all?

Lenalidomide/Bortezomib-Based Therapy in NDMM

<table>
<thead>
<tr>
<th>Response</th>
<th>RVD(^1) (n=66)</th>
<th>RVDD(^2) (n=72)</th>
<th>VDCR(^3) (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + nCR</td>
<td>40% (57%)(^*)</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>67% (74%)(^*)</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>≥PR</td>
<td>100%</td>
<td>96%</td>
<td>88%</td>
</tr>
</tbody>
</table>

\(^*\)Phase 2 cohort (n=35)

- Active in pts with adverse cytogenetics
- Hematologic toxicity is more severe with addition of chemo (Cy or pegylated liposomal doxorubicin)
- Risk of DVT does not appear to be increased over lenalidomide/dex alone
- Risk of PN moderately increased over bortezomib alone
- Generally otherwise well tolerated, although TRM seen with VDCR

RV, lenalidomide, bortezomib, dexamethasone; RVDD, RVD with pegylated liposomal doxorubicin; VDCR, VRD + cyclophosphamide (weekly low-dose dex with VRd, vs RVD)


Bortezomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Patients With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (SWOG S0777): Response Assessment

Median follow-up 7 years

\[ P=0.006 \text{ (≥VGPR)} \]

- ORR = 78.8%
- ≥VGPR = 53.2%
- 25.6%

- ORR = 90.2%
- ≥VGPR = 74.9%
- 15.3%

Durie SGM, et al. Longer term follow-up of the randomized phase II trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020 May 11;10(5):53. This article is licensed under a Creative Commons Attribution 4.0 International License.
**SWOG S0777 (N=525): RVd vs Rd in Patients Without Immediate Intent for ASCT**

<table>
<thead>
<tr>
<th>SWOG S0777</th>
<th>RVd</th>
<th>Rd</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>264</td>
<td>261</td>
<td></td>
</tr>
</tbody>
</table>
| Median PFS, mos (95% CI) | 43 (39–52) | 30 (25–39) | One-sided $P=0.0018$
| Median OS, mos (95% CI) | 75 (65–NR) | 64 (56–NR) | Two-sided $P=0.0037$

**Initial therapy:** RVd for eight 21-d cycles vs Rd for six 28-d cycles in patients not intending to proceed to transplant, followed by Rd in both arms

Durie BGM, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020 May 11;10(5):53. This article is licensed under a Creative Commons Attribution 4.0 International License.

**SWOG S0777: Survival by Best Response**

*PFS by best response at 6 months*  
*OS by best response at 12 months*
**Carfilzomib or Bortezomib in Combination With Lenalidomide and Dexamethasone for Patients With Newly Diagnosed Multiple Myeloma Without Intention for Immediate Autologous Stem-Cell Transplantation (ENDURANCE; E1A11): A Multicentre, Open-Label, Phase 3, Randomized, Controlled Trial**

- ≥18 years of age
- NDMM (standard- or immediate-risk)
- Ineligible to undergo ASCT or who did not intend to proceed to immediate ASCT

Progression-free survival from induction randomization

- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13–18) months
- For patients ≥70 years, median PFS (95% CI) for VRd = 37 (29–NE) and KRd = 28 (24–36) months
- With censoring at SCT or alternative therapy: median PFS (95% CI) for VRd = 31.7 (28.5–44.6) and KRd = 32.8 (27.2–37.5) months
- Tolerability issues; PN with RVD vs. CVS, HTN, DVT, CNS, Renal, Pulmonary Tox with KRd

**Impact of Chromosome 1 Abnormalities Among Patients with Newly Diagnosed Multiple Myeloma: A Subgroup Analysis from the Endurance (ECOG-ACRIN E1A11) Trial**

| Comparison of KRd to VRd Among Patients With and Without +1q and del1p |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| **PFS** | **OS** | **PFS** | **OS** |
| +1q | HR 0.87 | 95% CI 0.66–1.15 | P value 0.326 | HR 0.88 | 95% CI 0.60–1.30 | P value 0.526 |
| del1p | HR 0.75 | 95% CI 0.49–1.14 | P value 0.171 | HR 0.50 | 95% CI 0.28–0.90 | P value 0.021 |
| Gain 1q | 1.46 | 95% CI 0.73–2.92 | P value 0.284 | 1.56 | 95% CI 0.64–3.78 | P value 0.326 |
| Amp 1q | No del1p | HR 0.88 | 95% CI 0.69–1.12 | P value 0.300 | HR 0.85 | 95% CI 0.60–1.21 | P value 0.377 |
| del1p | 0.80 | 95% CI 0.38–1.69 | P value 0.552 | 0.34 | 95% CI 0.13–0.89 | P value 0.028 |

Schmidt TM et al. To be presented at the 2021 ASH Annual Meeting, Abstract 467.
Early vs Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-Up Analysis of the IFM 2009 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RVD-Alone (n=350)</th>
<th>RVD + ASCT (N=350)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mos)</td>
<td>35.0</td>
<td>47.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median PFS2* (mos)</td>
<td>95</td>
<td>Not reached</td>
<td>0.76</td>
</tr>
<tr>
<td>Median second PFS† (mos)</td>
<td>36</td>
<td>25</td>
<td>0.003</td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td>Not reached</td>
<td>Not reached</td>
<td>--</td>
</tr>
<tr>
<td>8-year OS (%)</td>
<td>60.2</td>
<td>62.2</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Time from randomization to progression on next line of therapy or death
†Time from first progression to progression on next line of therapy or death


The Evolving Role Of ASCT in NDMM: High-Dose Melphalan Significantly Increases Mutational Burden in Multiple Myeloma Cells at Relapse: Results From a Randomized Study in Newly Diagnosed Multiple Myeloma

- Paired purified MM cells at diagnosis and at relapse from 68 patients using deep (75×) whole-genome sequencing to identify genomic changes induced by HDM and observed at relapse

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RVD</th>
<th>RVD → ASCT</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>45</td>
<td>23</td>
<td>--</td>
</tr>
<tr>
<td>Median follow-up (mos)</td>
<td>29</td>
<td>31</td>
<td>--</td>
</tr>
<tr>
<td>No. mutations at diagnosis</td>
<td>7137 [IQR=3741]</td>
<td>7230 [IQR=3702]</td>
<td>0.67</td>
</tr>
<tr>
<td>No. mutations</td>
<td>1745</td>
<td>5686</td>
<td>0.000014</td>
</tr>
<tr>
<td>No. indels*</td>
<td>360</td>
<td>467</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*The insertion or deletion of one or several nucleotides within a sequence

HDM causes a 4.1-fold higher mutation accumulation rate per month than RVD only (158.3 vs 38.3 mutations/month; \( P = 0.003 \)).

Selected Four-Drug Combinations Being Studied in Newly Diagnosed Myeloma (2018–2021)

Four-drug combos
- RVd-Dara¹
- RVd-Isa²
- RVd-Elo³
- KRd-Dara⁴
- KRd-Isa⁵
- KRd-Elo⁶
- IRd-Dara⁷

Other quads include:
- CyBorD + Dara
  (amyloid, MM with renal disease)


4-Drug Regimens for NDMM at ASH 2021

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 GRIFFIN Trial¹</td>
<td>Induction: Dara-RVd vs RVd  &lt;br&gt; ASCT Consolidation: Dara-RVd vs RVd  &lt;br&gt; Maintenance: R vs Dara-R</td>
<td>sCR rate by the end of post-ASCT consolidation</td>
</tr>
<tr>
<td>Phase 3 GMMG-HD7[3]</td>
<td>Induction: Isa-RVd vs RVd  &lt;br&gt; ASCT Consolidation: Isa-RVd vs RVd  &lt;br&gt; Maintenance: R</td>
<td>Rate of MRD negativity (10⁻⁵) after induction</td>
</tr>
<tr>
<td>Phase 2 IFM 2018-01[4]</td>
<td>Induction: Dara-IRd  &lt;br&gt; ASCT Consolidation: Dara-IRd  &lt;br&gt; Maintenance: R</td>
<td>Rate of MRD negativity (10⁻⁵) after consolidation and before maintenance</td>
</tr>
<tr>
<td>MASTER Trial⁵</td>
<td>Induction: Dara-KRd  &lt;br&gt; ASCT Consolidation (by MRD status): Dara-KRd</td>
<td>Rate of MRD negativity (10⁻⁵) in intent-to-treat population</td>
</tr>
</tbody>
</table>

Daratumumab Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients With Transplant-Eligible Newly Diagnosed Multiple Myeloma: Updated Analysis of GRIFFIN After 24 Months of Maintenance Therapy (ASH 2021)


New Directions ~ The Impact of the MANHATTAN Study, GRIFFIN and Others ~ Comparison Across Studies: MRD Negativity by Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination Therapy</th>
<th>ASCT</th>
<th>MRD-negativity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM09&lt;sup&gt;[1,2]&lt;/sup&gt;</td>
<td>RVd × 6 cycles</td>
<td>Yes</td>
<td>24%</td>
</tr>
<tr>
<td>GRIFFIN&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RVd-daratumumab × 6 cycles</td>
<td>Yes</td>
<td>51%</td>
</tr>
<tr>
<td>FORTE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>KRd × 8 cycles</td>
<td>Yes</td>
<td>62%</td>
</tr>
<tr>
<td>FORTE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>KRd × 12 cycles</td>
<td>No</td>
<td>56%</td>
</tr>
<tr>
<td>MANHATTAN&lt;sup&gt;5&lt;/sup&gt;</td>
<td>KRd-daratumumab × 8 cycles</td>
<td>No</td>
<td>71%</td>
</tr>
</tbody>
</table>

In 2017, where to after IFM/DFCI 2009*, with the US DETERMINATION study still not ready to report, given the profound impact of prolonged maintenance +/- ASCT?

- **Hypotheses**
  - Early MRD negative ➔ no up-front auto-transplant
  - MRD negative post-ASCT ➔ ? Role of consolidation
  - MRD negative extended period of time ➔ Continue maintenance?


In 2020 ~ IFM 2020-02 Minimal Residual Disease Adapted Strategy (the MIDAS Trial), with US DETERMINATION still not ready to report (10+ years since the start of the study with median follow up > 5 years)

Arm A
- Induction and Mobilization
- Isa-KRd (6 cycles)
- Collection of stem cells after cycle 3
- Low risk group
  - MRD NGS $<10^{-5}$
- Risk-Adapted Consolidation
- Isa-KRd (6 cycles)

Arm B
- ASCT + Isa-KRd (2 cycles)
- R: 1:1

Arm C
- ASCT + Isa-KRd (2 cycles)
- R: 1:1

Arm D
- Double ASCT
- Isa: Isatuximab
  - Iber: Iberdomide
- Iber (3 years)
- Isa + Iber (3 years)
- Risk-Adapted Consolidation
- Maintenance

Lenalidomide (3 years)
Lenalidomide (3 years)
Lenalidomide (3 years)
Lenalidomide (3 years)

Collection of stem cells after cycle 3

Low risk group
- MRD NGS $<10^{-5}$

High risk group
- MRD NGS $>10^{-5}$

Isa-KRd (6 cycles)

Induction and Mobilization

Risk-Adapted Consolidation

Maintenance

Available at www.clinicaltrials.gov/NCT04934475.
Perrot A et al. Presented at the 7th World Congress in Controversies in Multiple Myeloma (COMy): May 7–9, 2021.
A Glimpse Into the Future of Myeloma Patient Management

Selected Emerging Treatment Options for MM 2021 ~ Novel MOAs

- Drug resistance is the main cause of relapse in patients with MM and is associated with unfavorable prognosis
- Novel mechanisms of action are urgently needed, and are now being bought forward into NDMM…
- Emerging role of cellular therapies (CAR-T, bispecific antibodies and more)
- Continued promise of small molecules and targeted agents (eg, peptide drug conjugates, CELMoDs)

Figure adapted from Ramasamy K et al. Blood Rev. 2021;49:100808.

Selected Emerging Treatment Options for Testing in NDMM (2021)

- Antibody-drug conjugates (ADCs) eg, RVD + belamaf (DREAMM-9)
- Selective inhibitor of nuclear export eg, RVd + selinexor (STOMP)
- Cereblon E3 ligase modulators (CELMoDs) eg, iberdomide
- Bispecific/T-cell engaging antibodies*
- Immuno-cytokines†
- Chimeric antigen receptor (CAR) T-cell therapy eg, CARTITUDE 5


*Krishnan AY et al. To be presented at the 2021 American Society of Hematology Annual Meeting. Abstract 158;
†Vogl DT et al. To be presented at the 2021 American Society of Hematology Annual Meeting. Abstract 898;
**CARTITUDE-5: A Randomized, Phase 3, Open-Label, Global, Multicenter Study in NDMM**

- All patients will complete 6 cycles (21 days each) of RVd induction therapy prior to randomization (1:1)

**RVd + Cilta-cel Arm**
- Apheresis and 2 more cycles of RVd as bridging therapy
- Lymphodepletion daily for 3 days (fludarabine/cyclophosphamide)
- Cilta-cel as a single infusion
- No maintenance

**RVd induction (2 cycles)**

**Bridging therapy post apheresis**

**Single cilta-cel infusion**

(Administered 5–7 days after start of Flu/Cy conditioning regimen. Target dose: 0.75 × 10⁶ CAR+ T cells/kg)

**RVd (2 cycles)**

**Rd maintenance (until disease progression)**

**RVd + Rd Arm (SOC)**
- Two more cycles of RVd (8 cycles total)
- Rd maintenance therapy continues until progressive disease or unacceptable toxicity

**Screening (28 days)**
**RVD induction (6 cycles)**
**1:1 randomization (n=650)**

**Follow-up**

**PRIMARY ENDPOINT: PFS**


---

**Conclusions ~ Integration and Impact of Novel Agent Combinations in NDMM, Including Immune Therapies, and Overcoming Key Challenges…**

- Innovations (PIs, IMiDs, mAbs, HDACis) to date have produced significant improvements in PFS and OS; recent approvals will augment this, with quads emerging as a new standard
- Next wave of immune therapies: crucially, are they agnostic to mutational thrust?
- Baseline immune function is a key barrier to success and may be targetable
- mAbs (including ADCs, bispecifics) represent true new novel mechanisms, as well as other immuno-therapeutics (eg. CAR T, cellular therapies, vaccines)
- New insights to mechanisms of drug action are further expanding treatment/immuno-therapeutic opportunities with combinations
- Next-generation small molecules and targeted therapy show great promise – eg, VENETOCLAX, with SELINEXOR recently approved, and for new agents in development, eg, CeLMoDS, peptide drug conjugates
- Further refinement of prognostics, immune profiling, and MRD will guide therapy
**Ongoing MM Collaborative Model for Rapid Translation of Novel Therapeutics From Bench to Bedside 2003–2021**

**Thank you!**

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

**Newly Diagnosed Multiple Myeloma Question 1**

*How often do you PLAN TO measure for minimal residual disease?*

A. Always  
B. Often  
C. Sometimes  
D. Rarely  
E. Never
Newly Diagnosed Multiple Myeloma

Question 2

How likely do you **PLAN TO** proceed with upfront autologous stem cell transplantation in a patient who achieves complete remission and/or MRD negativity following induction therapy?

A. Very likely
B. Likely
C. Neutral
D. Unlikely
E. Very unlikely

Topic 4: Relapsed/Refractory Multiple Myeloma

Current Practice

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Multiple Myeloma Translational Initiative
Division of Hematology-Oncology
University of California San Francisco
San Francisco, California
Relapsed/Refractory Multiple Myeloma

Question 1

In what line of therapy are you most likely to use BCMA-targeted therapy (if regulatory approval allows) for your patients?

A. First relapse (triple-class refractory)
B. Second relapse
C. Third or more relapse
D. Clinical trial only

Relapsed/Refractory Multiple Myeloma

Question 2

In fourth-line relapse, which of the following would you prefer to use (if regulatory approval allows)?

A. Bispecific, T-cell engaging antibody
B. CAR T-cell therapy
C. Selinexor
D. Belantamab mafodotin
E. Other approaches
Factors in Selecting Salvage Therapy

Patient
- Age/frailty
- Performance status
- Lifestyle/patient preferences
- Drug metabolism
- Compliance/adherence
- Caregiver support
- Renal insufficiency
- Comorbidities
  - Neuropathy
  - Cardiac
  - Diabetes
  - Low blood counts

Disease
- Burden
  - ISS/LDH
  - Marrow burden
  - Biochemical vs CRAB symptoms
  - Rate of progression
  - Extramedullary
- Biology
  - LDH elevation
  - Molecular
    - del[17p], t(4;14)

Treatment
- Access/trial availability
- If previously treated
  - Depth/duration
  - Relapse >60 d vs progression
- Toxicity
  - Myelosuppression
  - Neuropathy
  - VTE
  - Secondary cancers
- Administration route
- Single or combination
- Cost and copays

Relapsed/Refractory Myeloma

Early Relapse
A Glimpse Into the Future of Myeloma Patient Management

**DRd vs Rd in Pts With Relapsed or Refractory MM (POLLUX): 4 Year Follow-Up**

**Intent-to-treat population**

- 48-mo PFS rate
- HR, 0.44; 95% CI, 0.35–0.54
- P < 0.0001
- D-Rd Median: 45.0 mo
- Rd Median: 17.5 mo

**One previous line of treatment**

- 48-mo PFS rate
- HR, 0.42; 95% CI, 0.31–0.58
- P < 0.0001
- D-Rd Median: 53.3 mo
- Rd Median: 19.6 mo


**APOLLO: Phase 3 Randomized Study of Subcutaneous Dara + Pom and Dex vs Pom and Dex in Patients With RRMM**

**Key eligibility criteria:**
- RRMM
- ≥1 prior line with both lenalidomide and a PI
- ECOG PS ≤2
- CrCl ≥30 mL/min

**D-Pd**
- D: 1,800 mg SC QW cycles 1–2, Q2W cycles 3–6, Q4W cycles 7+
- P: 4 mg PO days 1–21
- d: 40 mg PO days 1, 8, 15, 22

**Pd**
- P: 4 mg PO days 1–21
- d: 40 mg PO days 1, 8, 15, 22

**1:1 randomization**

**Post-treatment follow-up**
- Q4W for patients who discontinued treatment

**Survival follow-up**
- every 12 weeks following PD or start of subsequent therapy

**Primary end point:**
- PFS

**Secondary end points:**
- ORR, ≥VGPR, ≥CR
- MRD
- OS
- Time to response
- Duration of response
- Time to next therapy
- Safety
- HRQoL

**Cycle duration:** 28 days
- Treatment until PD or unacceptable toxicity

**Stratification factors**
- Number of lines of prior therapy (1 vs 2–3 vs ≥4)
- ISS disease stage (I vs II vs III)
**Dara-Pd vs Pd (APOLLO): PFS**

<table>
<thead>
<tr>
<th>APPLO</th>
<th>Dara-Pd</th>
<th>Pd</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month progression-free survival rate (%)</td>
<td>52</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival (months)</td>
<td>12.4</td>
<td>6.9</td>
<td>0.0018</td>
</tr>
<tr>
<td>Patients refractory to lenalidomide</td>
<td>9.9</td>
<td>6.5</td>
<td></td>
</tr>
</tbody>
</table>

Addition of DARA SC to Pd improved PFS, with a 37% reduction in the risk of progression or death.


---

**Dara-Pd vs Pd (APLLO): PFS in Pre-Specified Subgroups**

Observed treatment effect was generally consistent across subgroups.

**Carfilzomib, Dexamethasone, and Daratumumab vs Carfilzomib and Dexamethasone in RRMM: Phase 3 CANDOR Study**

**Key inclusion criteria:**
- Relapsed or refractory multiple myeloma
- 1–3 prior lines of therapy
- Partial response or better to ≥1 line

**Primary end point:** PFS

**Key secondary end points:** OS, ORR, safety

**28-day cycles until disease progression**

- **KdD (n=312)**
  - Carfilzomib 56 mg/m² IV (30 min)
  - Days 1, 2, 8, 9, 15, 16
  - Dexamethasone 40 mg (20 mg for patients >75 years old)
  - oral or IV once weekly
  - Daratumumab 8 mg/kg IV days 1, 2, cycle 1; 16 mg/kg once weekly for remaining doses of cycle 1, 2, then every 2 weeks (cycles 3–6), then every 4 weeks

- **Kd (n=154)**
  - Carfilzomib 56 mg/m² IV (30 min)
  - Days 1, 2, 8, 9, 15, 16
  - Dexamethasone 40 mg (20 mg for patients >75 years old)
  - oral or IV once weekly

**Updated Efficacy Results of the Phase 3 CANDOR Study**

- **KdD (n=312)**
  - Median treatment duration, months: 18.3
  - Median PFS follow-up, months: 27.8
  - Median PFS by ORCA, months: 28.6
  - HR (KdD/Kd) (95% CI): 0.59 (0.45–0.78)

- **Kd (n=154)**
  - Median treatment duration, months: 9.3
  - Median PFS follow-up, months: 27.0
  - Median PFS by ORCA, months: 15.2
  - HR (KdD/Kd) (95% CI): 0.59 (0.45–0.78)

**41% reduction in the risk of progression/death and a 13.4-month improvement in median PFS with KdD versus Kd**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>KdD (n=312)</th>
<th>Kd (n=154)</th>
<th>Hazard ratio for KdD vs Kd (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized subjects</td>
<td>140/312</td>
<td>85/154</td>
<td>0.59 (0.45, 0.78)</td>
</tr>
<tr>
<td>ISS stage per IXRS at screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>101/252</td>
<td>68/127</td>
<td>0.60 (0.44, 0.81)</td>
</tr>
<tr>
<td>3</td>
<td>39/60</td>
<td>17/27</td>
<td>0.57 (0.32, 1.03)</td>
</tr>
<tr>
<td>Age at baseline (years) ≤65</td>
<td>30/48</td>
<td>18/26</td>
<td>0.51 (0.35, 0.73)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>71/157</td>
<td>41/72</td>
<td>0.64 (0.43, 0.94)</td>
</tr>
<tr>
<td>Cytogenetic risk group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>30/48</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>39/107</td>
<td>28/56</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>71/157</td>
<td>28.1</td>
<td></td>
</tr>
</tbody>
</table>

**Generally Consistent PFS Benefit for KdD vs Kd Across Subgroups**


**IKEMA Study: A Phase 3 Randomized, Open-Label Study of Isatuximab + Carfilzomib and Dex vs Carfilzomib and Dex in RRMM**

Stratification factors:
- Prior line 1 vs >1
- R-ISS: I or II vs III vs not classified
- 1–3 prior lines
- No prior therapy with carfilzomib
- Not refractory to prior anti-CD38

Primary end point: PFS (IRC)
- Key secondary end points: ORR, rate of ≥VGPR, MRD negativity, CR rate, OS
- Median PFS control arm estimated at 19 months
- Prespecified interim analysis when 65% PFS events (103) as per IRC
IKEMA Study: PFS

<table>
<thead>
<tr>
<th></th>
<th>Isa-Kd</th>
<th>Kd</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression-free survival (months)</td>
<td>Not reached</td>
<td>19.15</td>
<td>0.0007</td>
</tr>
<tr>
<td>95% CI</td>
<td>–</td>
<td>15.770–NE</td>
<td></td>
</tr>
</tbody>
</table>

Isa-Kd showed improvement in PFS with 47% reduction of risk of progression or death vs Kd.

Consistent treatment effect was seen for Isa-Kd across subgroups.

### My Comments: RRMM, 1–3 Prior Lines

- Targeting CD38 = Peloton; everyone's doing it!
- Combo with carfilzomib = very effective
- …but what if you used dara in the 1st line?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>PFS triplet (mo)</th>
<th>PFS doublet (mo)</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apollo</td>
<td>DPd vs Pd</td>
<td>12.4</td>
<td>6.9</td>
<td>0.63</td>
<td>0.0018</td>
</tr>
<tr>
<td>CANDOR</td>
<td>KdD vs Kd</td>
<td>28.6</td>
<td>15.2</td>
<td>0.59</td>
<td>NA</td>
</tr>
<tr>
<td>IKEMA</td>
<td>IKd vs Kd</td>
<td>NR</td>
<td>19.15</td>
<td>0.531</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

### BOSTON Trial: Phase 3, Global, Randomized, Open-Label, Controlled Study of Selinexor + Bortezomib and Dex vs Bortezomib and Dex in Patients With MM Who Had Received 1–3 Prior Therapies

**Svd weekly** 35-day cycles
- Selinexor (oral) 100 mg D1, 8, 15, 22, 29
- Bortezomib (SC) 1.3 mg/m² D1, 8, 15, 22
- Dexamethasone (oral) 20 mg D1, 2, 8, 9, 15, 16, 22, 23, 29, 30

**Vd twice weekly** 21-day cycles Cycles 1–8
- Bortezomib (SC) 1.3 mg/m² D1, 4, 8, 11
- Dexamethasone (oral) 20 mg D1, 2, 4, 5, 8, 9, 11, 12

**Vd weekly** 35-Day cycles Cycles ≥9

Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in Svd arm vs Vd arm

Primary end point: PFS
Key secondary end points:
- ORR, ≥VGPR, Grade ≥2 PN
Secondary end points:
- OS, DoR, TTNT; safety efficacy assessed by IRC
**Boston Trial: Effect of Prior Treatment with Proteasome Inhibitors on the Efficacy and Safety of Once-Weekly Selinexor, Bortezomib, and Dex in Comparison with Twice-Weekly Bortezomib and Dex**

Conducted post-hoc analyses of the BOSTON study to determine the efficacy and safety among patients with prior proteasome inhibitor (PI) treatment.

<table>
<thead>
<tr>
<th>Overall efficacy results</th>
<th>SVd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>13.93</td>
<td>9.46</td>
</tr>
<tr>
<td>Hazard ratio (P value)</td>
<td>0.70 (0.0075)</td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td>76.6</td>
<td>62.3</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>44.6</td>
<td>32.4</td>
</tr>
<tr>
<td>DOR (months)</td>
<td>20.3</td>
<td>12.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total patients enrolled</th>
<th>SVd arm (n=195)</th>
<th>Vd arm (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior PI treatment</td>
<td>SVd Prior PI – 76% (n=148)</td>
<td>Vd Prior PI – 77% (n=159)</td>
</tr>
<tr>
<td>PI Naïve</td>
<td>SVd PI Naïve – 24% (n=47)</td>
<td>Vd PI Naïve – 23% (n=48)</td>
</tr>
</tbody>
</table>


---

**SVd is Effective Among Patients That Received Bortezomib Prior to ASCT as Induction Therapy: PFS, ORR**

![Graph showing PFS for bortezomib-treated prior to ASCT]( Mateos MV et al. Blood. 2020;136: Abstract 2297.)

Relapsed/Refractory Myeloma

Later Relapse

Rationale for Targeting BCMA

- BCMA is a cell surface protein expressed on late-stage B cells and plasma cells but virtually absent on naïve and memory B cells\(^1\)-\(^3\)
- BCMA is highly expressed on malignant plasma cells in all patients with MM\(^3\)-\(^5\)
  - BCMA ligands, BAFF and APRIL, are detected in increased levels in the circulation of patients with MM\(^3\),\(^5\)
- BCMA is essential for the proliferation and survival of malignant plasma cells\(^3\)

### House of CARs

<table>
<thead>
<tr>
<th>Trial</th>
<th>CAR T product</th>
<th>Med prior lines</th>
<th>Special sauce</th>
<th>ORR (%)</th>
<th>CRS (%)</th>
<th>Neurotox (%)</th>
<th>Survival data</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karmma-1 (phase II, n=128)</td>
<td>bb2121 (Ide-cel)</td>
<td>6</td>
<td></td>
<td>73 (82 @450 dose)</td>
<td>84</td>
<td>18</td>
<td>mPFS 8.8mo, 12.1 mo @450 dose OS 24.8</td>
<td>CAR-T Par-T in 2021!</td>
</tr>
<tr>
<td>CARTITUDE-1 (phase Ib/II, n=97)</td>
<td>JNJ-4528 (Ciltacel)</td>
<td>6</td>
<td>Bi-epitope binding to BCMA</td>
<td>97</td>
<td>92</td>
<td>20.1 (16.5 ICANS)</td>
<td>@ 18 mo: 66% prog-free; DOR 21.8 m</td>
<td>Google to the Yahoo?</td>
</tr>
<tr>
<td>LUMMICAR-2 (phase Ib/II, n=18–20)</td>
<td>CT053</td>
<td>5</td>
<td>Fully human</td>
<td>94 (n=18)</td>
<td>77–83</td>
<td>15–17</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PRIME (phase I/II, n=55)</td>
<td>P-BCMA-101</td>
<td>8</td>
<td>Piggy-bac system, centyrin technology</td>
<td>67 w/ nanoplasmid (n=6); 44–75 w/OG mfg (n=30)</td>
<td>17</td>
<td>3.8</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CRB-402 (phase I, n=69)</td>
<td>bb21217</td>
<td>6</td>
<td>PI3Ki culture to increase Tscm cells</td>
<td>68 (73 at 450 dose, 84 w/ new mfg)</td>
<td>70</td>
<td>16</td>
<td>mDOR 17 mo (all doses)</td>
<td>Memory cell phenotype in DP may correlate w/ response</td>
</tr>
<tr>
<td>UNIVERSAL (phase I, n=26–31)</td>
<td>Allo-715</td>
<td>5</td>
<td>Allo CART</td>
<td>60–67 at 320 dose</td>
<td>45</td>
<td>0</td>
<td>NA</td>
<td>Variability in LD, tx within 5 days of enrollment!! No GVH</td>
</tr>
<tr>
<td>FasT CART</td>
<td>GCO12F</td>
<td>5</td>
<td>CD19 BCMA dual CAR T, ON manufact</td>
<td>95</td>
<td>95</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**Ide-cel has arrived...now what??**

- **Label:** 4 lines of treatment
- **Our patients**
  1. VRD → ASCT → len maintenance
  2. DPD
  3. KCD
- **But what about the #myelennial patients?**
- **KRD, D-VRD may make this a little more challenging → but no one ever said single-agent dex couldn’t be a line...**
Summary of Administration Considerations for Belantamab Mafodotin

Belantamab mafodotin: humanized, afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA

FDA-approved: For patients with R/R MM after ≥4 previous therapies including an anti−CD-38 mAb, a PI, and an IMiD

Dosing
2.5 mg/kg IV once every 3 wk as infusion over 30 min

Systemic steroids not required prior to initial infusion or in combination with belantamab, but patients should be monitored for infusion-related reactions

Belantamab is only available through REMS program due to potential for ocular toxicity

Counsel patients on what to expect when receiving belantamab, including the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose


Phase 2 DREAMM-2 Study of Belantamab Mafodotin for Patients With RRMM: Efficacy and Safety

<table>
<thead>
<tr>
<th>Efficacy (13-month follow-up)</th>
<th>Belantamab mafodotin 2.5 mg/kg (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, n (%)</td>
<td>31 (32)</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Partial response</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Median DOR (95% CI), months</td>
<td>11.0 (4.2–NR)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>2.8 (1.6–3.6)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>13.7 (9.9–NR)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse reactions with incidence ≥10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belantamab mafodotin 2.5 mg/kg (n=95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th>All grades (%)</th>
<th>Grade 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratopathy</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions

- Treatment decision for RRMM depends on multiple factors
- 3 drugs >> 2 drugs
- If you didn’t use daratumumab 1st line, you have to do it in 2nd line
  - Or you will be uncool
- CAR T is coming to a peer-to-peer near you
- The future is BCMA bright
  - I suspect 2nd line by 2023
  - No worries—there’s room for new CELMoDs, alkylating agents and selinexor, new immunotherapy targets
- 60 is the new 30!

THANK YOU!
@ninashah33
#myelennial
Topic 4: Relapsed/Refractory Multiple Myeloma

In the Future

A. Keith Stewart, MBChB
Vice President, Cancer, University Health Network
Director, Princess Margaret Cancer Centre
Richard H. Clark Chair in Cancer Medicine
Toronto, Ontario, Canada

Disclosures

Dr. Stewart has disclosed the following relevant financial relationships:

Consultant/Advisor: Amgen, GlaxoSmithKline, Janssen, Oncoproteptides, Sanofi Aventis
>20% Activity a Recent Sampling

<table>
<thead>
<tr>
<th>BCMA</th>
<th>Ide-cel</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA</td>
<td>Cilta-cel</td>
<td>97%</td>
</tr>
<tr>
<td>BCMA</td>
<td>Teclistamab</td>
<td>65%</td>
</tr>
<tr>
<td>BCMA</td>
<td>REGN5458</td>
<td>73%</td>
</tr>
<tr>
<td>BCMA</td>
<td>Elranatamab</td>
<td>73%</td>
</tr>
<tr>
<td>BCMA</td>
<td>Tnb383B</td>
<td>79%</td>
</tr>
<tr>
<td>BCMA</td>
<td>CC93269</td>
<td>89%</td>
</tr>
<tr>
<td>BCMA</td>
<td>AMG701</td>
<td>83%</td>
</tr>
<tr>
<td>GPCR5</td>
<td>Talquetamab</td>
<td>70%</td>
</tr>
<tr>
<td>FCRH5</td>
<td>Cevostamab</td>
<td>55%</td>
</tr>
</tbody>
</table>

Bispecific T-Cell Engagers/Antibodies

- **AMG420**
  - Light chains: 2
  - Heavy: Half-life extender

- **AMG701**
  - Light chains: 2
  - Heavy chains: 2

- **TNB-383 B**
  - Light chains: 1
  - Heavy chains: 2

- **JNJ-7957**
  - Light chains: 2
  - Heavy chains: 2

- **XmAb**

  - CD3 binding site
  - BCMA binding site
**Expected Toxicities**

- Cytokine release syndrome (CRS)
- Neurotoxicity (ICANS)
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T
- Cytopenias
- Target unique: cytokeratin change/rash
- Infections
  - Incidence for bispecifics at RP2D not yet known

**BCMA as a Target**

<table>
<thead>
<tr>
<th>BCMA</th>
<th>Teclistamab</th>
<th>65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA</td>
<td>REGN5458</td>
<td>73%</td>
</tr>
<tr>
<td>BCMA</td>
<td>Elranatamab</td>
<td>73%</td>
</tr>
<tr>
<td>BCMA</td>
<td>Tnb383B</td>
<td>79%</td>
</tr>
<tr>
<td>BCMA</td>
<td>CC93269</td>
<td>89%</td>
</tr>
<tr>
<td>BCMA</td>
<td>AMG701</td>
<td>83%</td>
</tr>
</tbody>
</table>
Teclistamab (BCMA × CD3 Bispecific) Phase 1/2

Maximum grade CRS

Patients (%)

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>60% (44/73)</td>
<td>70% (28/40)</td>
</tr>
<tr>
<td>SC Total (n=73)</td>
<td>RP2D, 1500 μg/kg SC QW (n=40)</td>
</tr>
</tbody>
</table>

Best response in response-evaluable

Patients (%)

<table>
<thead>
<tr>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>65%</td>
</tr>
<tr>
<td>17.5</td>
</tr>
<tr>
<td>7.5</td>
</tr>
<tr>
<td>RP2D (n=40)</td>
</tr>
</tbody>
</table>

Teclistamab, a B-Cell Maturation Antigen × CD3 Bispecific Antibody, in RRMM

Duration of response RP2D (n=26)

CC-93269 (BCMA x CD3 Bispecific) Phase 1/2 Study

- IV weekly x 12, then Q2W x 6, then Q4W
- N=30, median 5 priors, 67% PI/IMID/anti-CD38 refractory
- Doses 0.15–10 mg

Maximum reported CRS grade by starting dose:

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 mg (n=3)</td>
<td>Gr 1</td>
<td>Gr 1</td>
<td>Gr 5</td>
</tr>
<tr>
<td>3 mg (n=15)</td>
<td>Gr 1</td>
<td>Gr 2</td>
<td></td>
</tr>
<tr>
<td>6 mg or 10 mg (n=12)</td>
<td>Gr 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall response rate:

<table>
<thead>
<tr>
<th>Maximum Dose</th>
<th>sCR/CR</th>
<th>VGPR</th>
<th>ORR (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 mg (n=7)</td>
<td>ORR (5%)</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>3-6 mg and 6 mg (n=14)</td>
<td>ORR (35.7%)</td>
<td>21.4</td>
<td>1.1</td>
</tr>
<tr>
<td>6-10 mg and 10 mg (n=9)</td>
<td>ORR (88.9%)</td>
<td>44.4</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Evaluation:

- Total responses ongoing: 11/13


TNB-383B

CRS (any grade):

<table>
<thead>
<tr>
<th>All Doses (n=103)</th>
<th>≥40 mg (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>52</td>
<td>70</td>
</tr>
</tbody>
</table>

Response rates at doses ≥40 mg:

<table>
<thead>
<tr>
<th>Mature (n=24)</th>
<th>Mature and Immature (n=44)</th>
<th>Triple-Class Refractory (Mature and Immature; n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 79% ≥VGPR 63%</td>
<td>ORR 64% ≥VGPR 43%</td>
<td>ORR 55% ≥VGPR 38%</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>Patients (%)</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>33</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>21</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

A Glimpse Into the Future of Myeloma Patient Management

MagnetisMM-1: Phase 1 Trial
Investigating the Safety and Efficacy
of Elranatamab as a Single Agent

What about other targets?

- CD38 ADCs
- CD38-targeted alpha interferon
- GPRC5D
- FCRH5

Talquetamab (GPRC5D×CD3) Bispecific Antibody

CRS

- SC Total (n=82): 67 patients (Any grade), 1 patient (Grade 3/4)
- RP2D, 405 ug/kg SC QW (n=30): 73 patients (Any grade), 2 patients (Grade 3/4)

Overall response rate

- SC Total (n=75): 53.3% PR, 34.7% VGPR, 9.3% CR, 50% sCR
- RP2D, 405 ug/kg SC (n=30): 6.7% PR, 4.7% VGPR, 9.3% CR, 10% sCR


Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With RRMM

Duration of response

Krishnan AY et al. To be presented at the 2021 American Society of Hematology Annual Meeting. Abstract 158.
Cevostamab Targets FCRH5

Response rate in ≥3.6/20 mg cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ORR (%)</th>
<th>PR</th>
<th>VGPR</th>
<th>CR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3.6/20 mg (n=34)</td>
<td>53%</td>
<td>12</td>
<td>6</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>3.6/20 mg-3.6/60 mg (n=16)</td>
<td>44%</td>
<td>19</td>
<td>25</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>3.6/90 mg-3.6/132 mg (n=18)</td>
<td>61%</td>
<td>6</td>
<td>11</td>
<td>28</td>
<td>17</td>
</tr>
</tbody>
</table>

CRS (n=53)
- Any grade
- Grade 3/4


Small Molecules
- Iberdomide (CC-220)
- CC-92480
- Venetoclax
**Iberdomide in Combination With Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma: Results from the Dose-Expansion Phase of the CC-220-MM-001 Trial**

Summary of responses

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iber + dex</td>
<td></td>
</tr>
<tr>
<td>(n=107)</td>
<td></td>
</tr>
<tr>
<td>ORR 26.2%</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>17.8</td>
</tr>
<tr>
<td>Iber + dex</td>
<td></td>
</tr>
<tr>
<td>Post Anti-BCMA Therapy (n=24)</td>
<td>16.7</td>
</tr>
<tr>
<td>ORR 25%</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Krishnan AY et al. To be presented at the 2021 American Society of Hematology Annual Meeting. Abstract 158.

---

**Iberdomide in Combination With Dex and Daratumumab, Bortezomib, or Carfilzomib in Patients With RRMM**

Summary of responses

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IberDd (n=37)</td>
<td></td>
</tr>
<tr>
<td>ORR 45.9%</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>35.1</td>
</tr>
<tr>
<td>IberVd (n=25)</td>
<td></td>
</tr>
<tr>
<td>ORR 56%</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td>IberKd (n=8)</td>
<td></td>
</tr>
<tr>
<td>ORR 50%</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>37.5</td>
</tr>
</tbody>
</table>

A Glimpse Into the Future of Myeloma Patient Management

Phase 1 Trial of CC-92480 Combined With Dexamethasone in RRMM

Common (> 20 % all grade) TEAEs and events of interest, n (%)

<table>
<thead>
<tr>
<th>All doses (N=76)</th>
<th>All grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>56 (73.7)</td>
<td>23 (30.3)</td>
<td>26 (34.2)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6 (7.9)</td>
<td>4 (5.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>42 (55.3)</td>
<td>24 (31.6)</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33 (43.4)</td>
<td>5 (6.6)</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>Infections</td>
<td>54 (71.1)</td>
<td>25 (32.9)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>13 (17.1)</td>
<td>11 (14.5)</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (38.2)</td>
<td>7 (9.2)</td>
<td>–</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (22.4)</td>
<td>3 (3.9)</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>4 (5.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diarthera</td>
<td>18 (23.7)</td>
<td>1 (1.3)</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (22.4)</td>
<td>1 (1.3)</td>
<td>–</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1 (1.3)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, Pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia.

Final Overall Results from BELLINI: Phase 3 Study of Venetoclax or Placebo in Combination With Bortezomib and Dexamethasone in Relapsed/Refractory MM

Significant improvement in PFS with Ven-Vd but increased mortality compared to Vd in total population. Yet, Ven-Vd showed greatest PFS improvement in patients with t(11;14) or high BCL2 expression with a favorable risk-benefit profile.
Where will these drugs fit?

- Iberdomide or CC-92580 replace lenalidomide and pomalidomide?
- Venetoclax will be included for t(11;14)
- BCMA bispecific T-cell engagers: induction/maintenance?
- GPCR / FCRH5: sequential or alternate or relapse?
- No matter: transformational!

Relapsed/Refractory Multiple Myeloma Question 1

In what line of therapy are you most likely to use BCMA-targeted therapy (if regulatory approval allows) for your patients?

A. First relapse (triple-class refractory)
B. Second relapse
C. Third or more relapse
D. Clinical trial only
In fourth-line relapse, which of the following would you prefer to use (if regulatory approval allows)?

A. Bispecific, T-cell engaging antibody
B. CAR T-cell therapy
C. Selinexor
D. Belantamab mafodotin
E. Other approaches