Defining & Treating High Risk Multiple Myeloma

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LEVINE CANCER INSTITUTE
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• Speaker: Amgen, BMS, Janssen, Sanofi.

Presented by: Saad Z. Usmani, MD FACP, @szusmani
MM Is Not One Disease

- MGUS to Active MM transition period is different among patients. Diagnosis is made at variable time-points during the transition, so degree of end organ damage is different.

- Management strategies are focusing on changing myeloma to a chronic illness for majority of patients, probably curative for a subset – high risk disease remains a challenge.

- Advances in understanding myeloma biology has led to new therapeutic targets.
  - MM Pathways
  - BM microenvironment
  - Immune regulation and modulation

Martinez-Lopez J et al Blood 2011
Usmani et al Leukemia 2012
ISS and R-ISS

ISS

Stage I
β2-microglobulin < 3.5 mg/L and Albumin ≥ 3.5 g/dL

Stage II
Not stage I or II

Stage III
β2-microglobulin ≥ 5.5 mg/L

R-ISS

Stage I
ISS stage I and No high-risk FISH and Normal LDH

Stage II
Not stage I or II

Stage III
ISS stage III and High-risk FISH or High LDH

Median OS: not reached
Median PFS: 66 mo

Median OS: 83 mo
Median PFS: 42 mo

Median OS: 43 mo
Median PFS: 29 mo

Defining High Risk Disease At Diagnosis in 2021

- Clinical Phenotypes
  - EMD and pPCL

- MM Biology
  - Cytogenetics/FISH
    - Translocation (14;16) – MAF over-expression
    - Translocation (14;20) – MAFB overexpression
    - Gain & Amplification of chromosome 1q21 – overexpression of several proteasome genes
    - Deletion 17 p – monoallelic loss is bad, biallelic loss is worse.
  - ? Translocation (4;14)
  - Poor Risk by Gene Expression Profiling

- Gene mutations
  - BRAF, K-RAS, N-RAS (low incidence at diagnosis, usually late events)
Blind Spots

- Poor assessment of MM disease biology at diagnosis and relapse:
  - Highly dependent on the quality of random pelvic bone biopsy
  - Can fix by creating SOP for sample ‘pecking order’.
  - No assessment of FDG avid focal bone lesions or EMD
  - Can fix by concomitant biopsy of such lesions as ‘routine’ practice, not patient friendly.
  - Only examine at finite timepoints
  - Harder fix as biopsies are not patient friendly, this is not CLL 😊.
- This leads to the ‘unexpected’ poor responders or unexpected ‘early relapse’ we see in the clinics.

- We are still learning how to incorporate immunome and BM microenvironment status in MM patient assessment.

- We are still optimizing how best to assess depth of response/detect MRD status.
Current Treatment Strategies
### Survival of High-Risk Subgroup in Randomized, Controlled NDMM Trials (Pre-2010)

<table>
<thead>
<tr>
<th>FISH</th>
<th>N1/N2</th>
<th>End point</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 1 (%)</th>
<th>Arm 2 (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)</td>
<td>26/24</td>
<td>3-y OS</td>
<td>VAD/ASCT/thalidomide*</td>
<td>VAD/ASCT/bortezomib*</td>
<td>44</td>
<td>66</td>
<td>HOVON65/GMMG- HD4</td>
</tr>
<tr>
<td>98/106</td>
<td>4-y OS</td>
<td>VAD</td>
<td>VD</td>
<td></td>
<td>32</td>
<td>63*</td>
<td>IFM-2005</td>
</tr>
<tr>
<td>21/23</td>
<td>2-y OS</td>
<td>Thalidomide*</td>
<td>Placebo*</td>
<td></td>
<td>67</td>
<td>87</td>
<td>TT2</td>
</tr>
<tr>
<td>21/29</td>
<td>2-y OS</td>
<td>Thalidomide-TT2</td>
<td>Bortezomib TT3</td>
<td></td>
<td>67</td>
<td>97*</td>
<td>TT2 vs TT3</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>21/16</td>
<td>3-y OS</td>
<td>VAD/ASCT/thalidomide</td>
<td>PAD/ASCT/bortezomib*</td>
<td>17</td>
<td>69*</td>
<td>HOVON65/GMMG-HD4</td>
</tr>
<tr>
<td>119/54</td>
<td>4-y OS</td>
<td>VAD</td>
<td>V D</td>
<td></td>
<td>36</td>
<td>50</td>
<td>IFM-2005</td>
</tr>
<tr>
<td>Nonhyperdiploid</td>
<td>92</td>
<td>3-y OS</td>
<td>VTD</td>
<td>VMP</td>
<td>53</td>
<td>72*</td>
<td>PETHEMA</td>
</tr>
<tr>
<td>Unfavorable FISH</td>
<td>152/141</td>
<td>3-y OS</td>
<td>CTD</td>
<td>VAD-cyclophosphamide</td>
<td>58</td>
<td>56</td>
<td>MRC IX intensive</td>
</tr>
<tr>
<td>96/90</td>
<td>3-y OS</td>
<td>CTD</td>
<td>Placebo MP</td>
<td></td>
<td>34</td>
<td>26</td>
<td>MRC IX nonintensive</td>
</tr>
<tr>
<td>99/98</td>
<td>3-y OS</td>
<td>Thalidomide</td>
<td>Placebo</td>
<td></td>
<td>45</td>
<td>69*</td>
<td>MRC IX maintenance</td>
</tr>
</tbody>
</table>

Sonneveld P et al, Blood 2016
Total Therapy 3A & 3B GEP-Defined High-Risk NDMM Outcomes

Event-Free Survival

Overall Survival

UARK 2003-33 = TT3A
UARK 2006-66 = TT3B

Estimated median PFS = 26 months

Nair B et al., Blood 2010
Randomized Phase II (1:1)

**ARM A**
**RVd**

**Induction**
**21-Day Cycle**
*(8 Cycles)*

- Bortezomib 1.3 mg/m² SC
  - Days 1, 4, 8, 11
- Lenalidomide 25 mg PO
  - Days 1-14
- Dexamethasone 20 mg PO
  - Days 1, 2, 4, 5, 8, 9, 11, 12

**ARM B**
**RVd-Elotuzumab**

**Induction**
**21-Day Cycle**
*(8 Cycles)*

- Bortezomib 1.3 mg/m² SC
  - Days 1, 4, 8, 11
- Lenalidomide 25 mg PO
  - Days 1-14
- Dexamethasone 20 mg PO
  - Days 1, 2, 4, 5, 8, 9, 11, 12
- Elotuzumab 10 mg/kg IV
  - Day 1, 8, 15

**Bortezomib 1.0 mg/m² SC**
- Days 1, 8, 15

**Lenalidomide 15 mg PO**
- Days 1-21

**Dexamethasone 12 mg PO**
- Days 1, 8, 15

**Elotuzumab 10 mg/kg IV**
- Day 1, 15

**Maintenance**
**28-Day Cycle**

Bortezomib 1.0 mg/m² SC
- Days 1, 8, 15
Lenalidomide 15 mg PO
- Days 1-21
Dexamethasone 12 mg PO
- Days 1, 8, 15

**Off-Protocol at Progression/Relapse**

**Primary Endpoint**
PFS: 82% power and a one-sided $\alpha = 0.1$ to detect a HR=1.75 between the two treatment arms or an increase in median PFS from 2 years to 3.5 years in the RVd-Elo arm compared to the RVD arm.

**Secondary Endpoints**
ORR, OS, Safety

1. **One cycle of prior therapy allowed prior to enrollment**
2. **Stem cell collection allowed after cycle 2 on protocol. ASCT allowed off-protocol at progression/relapse**

Opened to all National Clinical Trials Network members

Usmani SZ et al. Lancet Haematol 2021
SWOG 1211 – Key Inclusion Criteria

- Newly diagnosed multiple myeloma
- Subjects had to meet one of the following high-risk criteria:
  - **Poor Risk Score by Gene Expression Profiling**
  - **One or more of the following cytogenetic/FISH abnormalities:**
    - Translocation (14;20)(q32;q12)
    - Translocation (14;16)(q32.3;q23)
    - Deletion (17p)
    - Chromosome 1q21 gain/amplification
  - **Primary plasma cell leukemia (PPCL)**
  - **Elevated serum LDH twice above the institutional ULN**
SWOG 1211 Phase II – PFS and OS

Progression Free Survival

Overall Survival

Usmani SZ et al. Lancet Haematol 2021
# Summary of High-Risk Subsets in Contemporary NDMM Trials Compared to S1211 Randomized Phase 2 Study

<table>
<thead>
<tr>
<th>Study / Total Patients</th>
<th>High Risk Definition</th>
<th>No. of High Risk MM Pts</th>
<th>ORR</th>
<th>Median PFS; HR (CI)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-1211¹\nN=100</td>
<td>GEPh⁹, Del17p, t(14;16), t(14;20), Amp1q21, elevated LDH, pPCL</td>
<td>RVd = 52 RVd-Elo = 48</td>
<td>RVd= 88% RVd-Elo = 83%</td>
<td>RVd= 34 mos. RVd- Elo = 31 mos. HR 0.97; 80% CI = (0.697, 1.344)</td>
<td>RVd = NR RVd-Elo = 68 mos.</td>
</tr>
<tr>
<td>SWOG-0777²\nN= 525</td>
<td>Del17p, t(14;16), or t(4;14)</td>
<td>Combined n = 44</td>
<td>Not reported</td>
<td>Rd = 16 mos. RVd = 38 mos. HR 0.61; 95% CI = (0.28, 1.03)</td>
<td>Not reported</td>
</tr>
<tr>
<td>MAIA³\nN= 737</td>
<td>Del17p, t(14;16), or t(4;14)</td>
<td>DRd = 48 Rd = 44</td>
<td>Not reported</td>
<td>HR 0.85 (0.44–1.65)</td>
<td>Not reported</td>
</tr>
<tr>
<td>ALCYONE⁴\nN= 706</td>
<td>Del17p, t(14;16), or t(4;14)</td>
<td>D-VMP = 53 VMP = 45</td>
<td>Not reported</td>
<td>HR 0.78 (0.43–1.43)</td>
<td>Not reported</td>
</tr>
<tr>
<td>CASSIOPEIA⁵\nN= 1085</td>
<td>Del17p or t(4;14)</td>
<td>Dara-VTd = 82 VTd = 86</td>
<td>sCR HR 0.83 (0.42–1.66)</td>
<td>HR 0.67 (0.35–1.30)</td>
<td>Not reported</td>
</tr>
<tr>
<td>BMT-CTN-0702⁶\nN= 758</td>
<td>ISS 3, Del13, Del 17p, t(4;14), t(14;16), t(14;20)</td>
<td>Tandem = 72 ASCT/RVD = 76 ASCT = 75</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

The ‘high risk’ MM definition is not uniform across the contemporary randomized phase III trials and accounts for a small subset of study populations.

The Emory Experience: RVd Induction, Consolidation and Maintenance in HRMM
KRd in TE NDMM (Phase II)

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>76</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>59 (40-76)</td>
</tr>
<tr>
<td>≥65</td>
<td>21 (27.6)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (59.2)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>65 (85.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (14.5)</td>
</tr>
<tr>
<td><strong>ISS stage</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td>II</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td>III</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td><strong>Cyto genetic risk by FISH†</strong></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>27 (35.5)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>11 (14.5)</td>
</tr>
<tr>
<td>Ultra-high risk‡</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>Standard</td>
<td>49 (64.5)</td>
</tr>
<tr>
<td><strong>Serum β2-microglobulin, mg/L</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>45 (59.2)</td>
</tr>
<tr>
<td>≥3.5</td>
<td>24 (31.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (9.2)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; ISS, International Staging System.

*All data in the table are n (%), unless otherwise designated.
†Defined per International Myeloma Working Group (IMWG): t(4;14), del(17p), t(14;16), t(14;20), nonhyperdiploidy and gain(t(1q)).
‡High risk = 3 cytogenetic abnormalities.

KRd in TE NDMM (Randomized Phase II)

Trial design

474 NDMM patients, transplant-eligible and younger than 65 years

4x KCd
K: 36^ mg/m^2 d 1-2,8-9,15-16
C: 300 mg/m^2 d 1,8,15
d: 20 mg. d 1-2,8-9,15-16,22-23

4x KRd
K: 36^ mg/m^2 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

Single ASCT
Intensification with high-dose melphalan followed by autologous stem-cell reinfusion

4x KCd
K: 36 mg/m^2 d 1-2,8-9,15-16
C: 300 mg/m^2 d 1,8,15
d: 20 mg. d 1-2,8-9,15-16,22-23

4x KRd
K: 36 mg/m^2 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

R
R: 10 mg days 1-21, until progression or intolerance

KR
K: 36 mg/m^2 d 1, 2, 15, 16 up to 2 years*
R: 10 mg days 1-21, until progression or intolerance

*20 mg/m^2 on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m^2 days 1, 16 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.
NDMM, newly diagnosed multiple myeloma; R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); KR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

Gay F al, ASH 2020;abstract 141
KRd in TE NDMM (Randomized Phase II)

**Progression-free survival: Random 1**

**Subgroup Analyses**

<table>
<thead>
<tr>
<th>KRd ASCT vs KCd ASCT</th>
<th>KRd ASCT vs KRd12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td><strong>Overall</strong></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Interaction-p</td>
<td>Interaction-p</td>
</tr>
<tr>
<td>0.53 (0.37 - 0.77)</td>
<td>0.64 (0.44 - 0.94)</td>
</tr>
<tr>
<td>0.47 (0.26 - 0.85)</td>
<td>0.56 (0.31 - 1.03)</td>
</tr>
<tr>
<td>0.57 (0.35 - 0.93)</td>
<td>0.70 (0.43 - 1.15)</td>
</tr>
<tr>
<td>0.52 (0.30 - 0.91)</td>
<td>0.57 (0.32 - 1.01)</td>
</tr>
<tr>
<td>0.47 (0.26 - 0.84)</td>
<td>0.51 (0.28 - 0.94)</td>
</tr>
<tr>
<td>0.56 (0.36 - 0.86)</td>
<td>0.66 (0.43 - 1.01)</td>
</tr>
<tr>
<td>0.36 (0.16 - 0.81)</td>
<td>0.44 (0.18 - 1.05)</td>
</tr>
</tbody>
</table>

**Favors KRd ASCT**

**Favors KCd ASCT**

**Favors KRd ASCT**

**Favors KRd12**

**SIMILAR HR IN STANDARD AND HIGH RISK PATIENTS TREATED WITH KRD ASCT**

PFS, progression-free survival; Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd ASCT, KCd induction-ASCT-KCd consolidation; KRd ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Gay F al, ASH 2020;abstract 141
KRd in TE NDMM (Randomized Phase II)

PFS in ITT pre-maintenance patients: NGS (10^-5)

Median FU: 45 months from R1

**Subgroup analysis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Interaction-p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.34 (0.22 - 0.52)</td>
<td>-</td>
</tr>
<tr>
<td>Age &lt;60</td>
<td>0.41 (0.24 - 0.69)</td>
<td>0.3078</td>
</tr>
<tr>
<td>Age ≥60</td>
<td>0.26 (0.13 - 0.51)</td>
<td>-</td>
</tr>
<tr>
<td>ISS I</td>
<td>0.41 (0.21 - 0.79)</td>
<td>0.4774</td>
</tr>
<tr>
<td>ISS II/III</td>
<td>0.30 (0.18 - 0.52)</td>
<td>-</td>
</tr>
<tr>
<td>FISH Standard</td>
<td>0.44 (0.25 - 0.76)</td>
<td>0.0895</td>
</tr>
<tr>
<td>FISH High</td>
<td>0.20 (0.10 - 0.41)</td>
<td>-</td>
</tr>
<tr>
<td>LDH &lt;ULN</td>
<td>0.31 (0.19 - 0.51)</td>
<td>0.685</td>
</tr>
<tr>
<td>LDH &gt;ULN</td>
<td>0.37 (0.16 - 0.86)</td>
<td>-</td>
</tr>
<tr>
<td>R-ISS I</td>
<td>0.45 (0.18 - 1.13)</td>
<td>0.5042</td>
</tr>
<tr>
<td>R-ISS II/III</td>
<td>0.32 (0.20 - 0.51)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Lower risk of progression or death with MRD NEG**

**Lower risk of progression or death with MRD POS**

ITT population: NGS-POS patients included those who were MRD-POS and those who did not achieve ≥CR (excluding CR patients not evaluable by NGS).

PFS, progression-free survival; ITT, intention-to-treat; NGS, next-generation sequencing; FU, follow-up; R1, first randomization (induction/consolidation treatment); HR, hazard ratio; p, p-value; MRD, minimal residual disease rate; NEG, negative; POS, positive; CI, confidence interval; ISS, International Staging System stage; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal; R-ISS, Revised ISS stage; CR, complete response.

Gay F al, ASH 2020;abstract 141
# Daratumumab Meta-Analysis in High Risk NDMM

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### 1.1.1 Newly Diagnosed High Risk Multiple Myeloma

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAIA</td>
<td>-0.5621</td>
<td>0.301</td>
<td>48</td>
</tr>
<tr>
<td>CASSIOPEIA</td>
<td>-0.4005</td>
<td>0.3313</td>
<td>82</td>
</tr>
<tr>
<td>ALCYONE</td>
<td>-0.2485</td>
<td>0.3038</td>
<td>53</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI):**
- 183
- 175
- 100.0%
- 0.67 [0.47, 0.95]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.54$, df = 2 ($P = 0.76$); $I^2 = 0$

Test for overall effect: $Z = 2.25$ ($P = 0.02$)

### 1.1.2 Relapsed/Refractory High Risk Multiple Myeloma

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLLUX</td>
<td>-0.9943</td>
<td>0.3676</td>
<td>35</td>
</tr>
<tr>
<td>CASTOR</td>
<td>-0.8916</td>
<td>0.3414</td>
<td>41</td>
</tr>
<tr>
<td>CANDOR</td>
<td>-0.5447</td>
<td>0.3364</td>
<td>48</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI):**
- 124
- 98
- 100.0%
- 0.45 [0.30, 0.67]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.93$, df = 2 ($P = 0.63$); $I^2 = 0$

Test for overall effect: $Z = 3.98$ ($P < 0.0001$)

---

Smith G et al., JAMA Onc 2020
The LCI Approach to High-Risk NDMM

Transplant Eligible:
- KRd × 4 cycles
- Consider DRVd × 4 cycles
  - Stem cell mobilization; adequate stem cell harvest (≥4 × 10^6 CD34 cells/kg) ASCT
  - Consolidation Tx for patients who do not achieve serologic CR
  - IMiD/Pl maintenance

Transplant Ineligible:
- RVd-Lite Induction × 6-8 cycles
- IMiD/Pl maintenance
- Consider DRd until relapse, progression or intolerance

Usmani S, personal communication
Approach to Bulky EMD or pPCL

**Induction**
- Age ≤ 65 years: V(T/R)D-PACE (x 2 cycles)
- Age > 65: RVd +/- Dara
  - (CyBorD for IP before RVd transition as OP) for 4-6 cycles

**Transplant Eligible**
- Mel-200 Auto-SCT followed by RVd maintenance until relapse/progression
- RIC-AlloSCT consideration for age ≤ 65 years.

**Transplant Ineligible**
- RVd maintenance until relapse/progression

*IN ABSENCE OF BETTER THAN PR TO INDUCTION, APPROACH AS PRIMARY REFRACTORY AND SWITCH TO 2ND LINE REGIMEN.

Consider CSF Analysis at Diagnosis and IT Chemotherapy Given High Proportion of CNS Involvement at Diagnosis/Relapse

Usmani S, personal communication
Emerging Treatment Strategies
Response-Adaptive Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) in Newly Diagnosed Multiple Myeloma

**MRD tested by NGS (clonoSEQ®) to $10^{-5}$ sensitivity**

Bhutani M et al, ASH 2020; 1388
KarMMa: High-risk subgroups

- >33% of patients had high-risk cytogenetics
- 51% had a high tumor burden
- Patients heavily pre-treated, with 47% having received >1 prior regimen per year (84% triple refractory)

Response rate by subgroup:

Efficacy
- ORR ≥65% and CR ≥20% across all high-risk groups except R-ISS stage III
- Presence of EMD and baseline tumor burden did not substantially affect ORR
- Median PFS ≥7.5 months in patients with high tumor burden, bridging therapy and >1 prior regimen/year (≥8.9 months with target dose – 450 x 10^6 CAR+ T cells)
- Median duration of response ≥9.2 months in all high-risk groups except R-ISS stage III (10.3 months with target dose)

Safety
- No new safety signals
- Incidence of CRS comparable with that of overall ide-cel treated population

Ide-cel yielded early, deep and durable responses in patients with high-risk and aggressive disease features

EMD, extra-medullary disease; IMiD, immunomodulatory disease; IMWG, International Myeloma Working Group; PD, progressive disease; PI, protease inhibitor
CARTITUDE 2: High-Risk Cohort

Screening

Cohort A (n=20)
- Progressive disease after 1–3 lines of MM therapy, including PI and IMiD
- Lenalidomide refractory
- No prior exposure to a BCMA-targeting agent

Cohort B (n=20)
- 1 prior line of MM therapy containing PI and IMiD
- Early relapse (≤12 months after frontline therapy or ASCT)
- No prior exposure to a BCMA-targeting agent

Cohort C (n=20)
- Prior treatment including PI, IMiD, anti-CD38 antibody
- Prior exposure to a BCMA-targeting agent, excluding cellular therapy

Cohort D (n=20)
- <CR after 4–8 total cycles of frontline therapy, including induction, high-dose therapy, and ASCT, with or without consolidation

Cohort E (n=20)
- Newly diagnosed MM
- High risk (ISS stage III) disease
- Not intended for ASCT

Apheresis

Bridging therapy (as needed) → R bridging → D-VRd Induction

Cyclophosphamide (300 mg/m²) + fludarabine (30 mg/m²) × 3 days

Cilta-cell infusion (target dose: 0.75×10⁶ [0.5–1.0×10⁶] CAR+ viable T cells/kg)

R maintenance → D + R consolidation

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*Due to age ≥65 y, age 18–65 y with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with ASCT, or refusal of high-dose chemotherapy with ASCT as initial treatment. ASCT=autologous stem cell transplantation; BCMA=B-cell maturation antigen; CR=complete response; D + R=daratumumab and lenalidomide; D-VRd=daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD=immunomodulatory drug; ISS=International Staging System; PI=proteasome inhibitor; R=lenalidomide

Einsele et al., ASTCT 2021
KarMMa-4: High Risk NDMM

Multicenter, open-label, phase 1, single-arm study of ide-cel in high-risk NDMM (R-ISS stage III disease per IMWG criteria)

**Endpoints**
- **Primary (Safety)**
  - Optimal target dose (DLT rate/safety)
- **Secondary (Efficacy)**
  - CR, improvement of CR, MRD neg, ORR, DOR, PFS, TCR, and OS
  - Feasibility and time to start of LEN maintenance
  - PK

**High risk (HR) definition**
R-ISS III at diagnosis as defined by IMWG¹:
- ISS stage III and
  - Cytogenetic abnormalities t(4;14), del(17p), and/or t(14;16) or
  - Serum LDH > ULN

ClinicalTrials.gov identifier: NCT04196491.
BMT-CTN SOSS 2021 Concept: Incorporation of BCMA Directed TCT Strategy

Usmani S, personal communication

Assumptions:
S1211 – no identified regimen better than RVD
MRD negativity (10^-5) is an important goal in HR-MM

- Revised ISS-3
- Revised ISS-2 with:
  - FISH for t(4;14), t(14;16), t(14;20), Del17p, ≥ 3 copies of chromosome 1q21
  - Genomic: GEP70^{th}, SKY92^{th}, biallelic TP53 deletion, c-Myc rearranged / mut
  - Imaging: >3 FDG avid bone lesions on PET-CT
- Extra-medullary disease at diagnosis
- Circulating plasma cells >5% at diagnosis
SWOG 2021 Concept: Incorporation of BCMA Directed Bispecific In Induction/Maintenance Strategy

Induction

NDMM High Risk
*allow 1 prior cycle of therapy off protocol

Randomize

RVd-Dara X 8 cycles

Maintenance

RV-Dara to progression

Dara plus Anti-BCMA bispecific Ab to progression

Allow SC Collection & Storage s/p 4 cycles

- Revised ISS-3
- Revised ISS-2 with:
  - FISH for t(4;14), t(14;16), t(14;20), Del17p, > 3 copies of chromosome 1q21
  - Genomic: GEP70th, SKY92th, biallelic TP53 deletion, c-Myc rearranged / mut
  - Imaging: >3 FDG avid bone lesions on PET-CT
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Phase I/II Study of Carfilzomib, Lenalidomide, Dexamethasone and the Anti-B-Cell Maturation Antigen (BCMA) Antibody Drug Conjugate Belantamab Mafodotin in Newly Diagnosed, High-Risk Multiple Myeloma

Usmani S, personal communication
## Frequency of Karyotypic Abnormalities in pPCL

### Table 2. Frequency of the major genomic aberrations by FISH and/or SNP array in the two prospective PPCL series of GIMEMA and IFM clinical trials.

<table>
<thead>
<tr>
<th>Genomic aberration</th>
<th>GIMEMA study PPCL cases pos/tested (%)</th>
<th>IFM study PPCL cases pos/tested (%)</th>
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<tbody>
<tr>
<td>t(11;14)</td>
<td>9/23 (39%)</td>
<td>16/32 (50%)</td>
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<tr>
<td>t(4;14)</td>
<td>3/23 (13%)</td>
<td>2/32 (6%)</td>
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<tr>
<td>t(14;16)</td>
<td>7/23 (30%)</td>
<td>5/32 (16%)</td>
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<tr>
<td>del(13q)</td>
<td>17/23 (74%)</td>
<td>19/32 (59%)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>8/23 (35%)</td>
<td>9/32 (28%)</td>
</tr>
<tr>
<td>1q gain</td>
<td>10/21 (48%)</td>
<td>17/32 (53%)</td>
</tr>
<tr>
<td>1p loss</td>
<td>8/21 (38%)</td>
<td>5/32 (16%)</td>
</tr>
<tr>
<td>MYC locus rearrangement</td>
<td>2/15 (13%)</td>
<td>9/32 (28%)</td>
</tr>
</tbody>
</table>

FISH: fluorescence *in situ* hybridization; SNP: single-nucleotide polymorphism; PPCL: primary plasma cell leukemia; GIMEMA: Gruppo Italiano Malattie Ematologiche dell’Adulto; IFM: Intergroupe Francophone du Myélome; pos: positive; del: deletion.

Venetoclax is a selective, orally available small-molecule BCL-2 inhibitor¹; active in R/R MM³

Venetoclax (daily dose up to 1,200 mg) has an acceptable safety profile in R/R MM, predominantly in patients with t(11;14) abnormality and favorable BCL-2 family profile

In contrast to the CLL experience, TLS appears to be uncommon in MM; ramp-up dosing has not been necessary

Venetoclax Is Active Combined With Bortezomib/Dexamethasone \textsuperscript{1}

- N = 66 patients with R/R MM

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>ORR</th>
<th>ORR</th>
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<tr>
<td></td>
<td>All Patients (N = 66)</td>
<td>Nonrefractory (n = 37)</td>
<td>Refractory (n = 28)</td>
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<tr>
<td>Prior PIs</td>
<td>ORR = 67%</td>
<td>ORR = 92%</td>
<td>ORR = 32%</td>
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<td>PR</td>
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<tr>
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</tr>
</tbody>
</table>

\textsuperscript{1} Moreau P et al. \textit{Blood}. 2017;130:2392-2400.
... And With Carfilzomib/Dexamethasone$^1,a$

- N = 42 patients with R/R MM

- ORR = 79%

- ORR = 76%

- ORR = 77%

- ORR = 71%

- ORR = 79%

- ≥ CR: 38%

- Data cutoff: September 17, 2018. $^a$ One patient died within the first 2 weeks of dosing; no data available.

Conclusions

• Recognize MM is not one disease, need small enrichment design clinical trials for high-risk disease.
• Achieving and sustaining MRD negativity matters for HRMM>SDMM.
• PI/IMiD based induction/maintenance.
• Do not throw out Melphalan from the schema.
• Potential strategies to eradicate MRD in TE/TI HRMM:
  • CAR-T cell strategies (BCMA, GPRC5D, SLAMF7, FCRH5, etc.)
  • Bispecific antibody strategies (BCMA, GPRC5D, FCRH5, etc.)
  • Antibody-Drug Conjugates (BCMA, SLAMF7, etc.)
• For TI elderly MM, use of immune modulation to re-establish immune surveillance and equilibrium.
  • Role for immune profiling signatures.
• For pPCL: Strategies incorporating BCL2 inhibition being explored.
  • CelMods, PROTACs, etc.
Acknowledgements