WELCOME & INTRODUCTIONS

Treatment Updates: Multiple Myeloma

Welcome to LLS Community
We are a community of blood cancer patients, survivors, and caregivers. We’re here to support you, give you trusted information and resources, and help you feel connected. No one should have to face a blood cancer diagnosis alone.

To join LLS Community, visit www.LLS.org/community.

Program will begin shortly
Lizette Figueroa-Rivera, MA
Senior Director, Education & Support
The Leukemia & Lymphoma Society
Houston, TX

Melissa Alsina, MD
Senior Member, Blood and Marrow
Transplant and Cellular Immunotherapy
Head, Multiple Myeloma BMT-CI Program
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DISCLOSURES

Treatment Updates: Multiple Myeloma

Advisory Board- GSK, Janssen
Speaker Bureau-GSK, Janssen
Research support- BMS, Blue Bird Bio

WHAT IS MULTIPLE MYELOMA?

Multiple myeloma

Normal plasma cells
Antibodies
M proteins
Bone
Bone marrow

Light chain
Heavy chains
Light chain
Multiple myeloma cells
**HOW COMMON IS MULTIPLE MYELOMA?**

- **32,270** new cases in 2020
- **140,779** living with, or in remission

- Myeloma is most frequently diagnosed among people aged **65-74**
- Median age at diagnosis **69**

- **MYELOMA represents 1.8% of all new cancer cases in the U.S.**

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**EFFECTS OF MYELOMA AND COMMON SYMPTOMS**

- Low blood counts → Weakness
- → Fatigue
- → Infection
- Decreased kidney function → Weakness
- Bone damage → Bone pain
- Bone turnover → Loss of appetite
- → Weight loss

*About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.*

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References:
MULTIPLE MYELOMA: TREATMENT PARADIGM

Goal is to achieve a deep response, obtain CR, optimize PFS and OS

Induction
RVD +/- Dara
CyBorD DRd

CyBorD: cytoxan, velcade, dexamethasone
RVD: revlimid, velcade, dexamethasone
IMiD: immunomodulating agent
PI: proteasome inhibitor

Consolidation
Auto HCT (if eligible)
or Doublet/Triplet regimens

Maintenance
IMID
PI

Relapsed/Refractory
Plethora

GRIFFIN: PHASE 2, RANDOMIZED, OPEN-LABEL STUDY OF D-RVD VS RVD IN ASCT-ELIGIBLE NDMM (N = 222)

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

Induction: Cycles 1-4
D-RVd
Cycles: 21 days

Consolidation: Cycles 5-6
D-RVd
Cycles: 21 days

Maintenance: Cycles 7-32
D-R
maintenance

RVd
Cycles: 28 days

Primary objective: sCR rate after consolidation

RESPONSES DEEPENED OVER TIME

Response rates and depths were greater for D-RVd at all time points

sCR D-RVd vs RVd: OR 2.03 standard risk, OR 0.52 high risk (median FU 13.5 mo)

MRD (10^-5) NEGATIVITY AT CLINICAL CUTOFF

MRD negative 51.0%
MRD negative & ≥CR 47.1%
≥CR (n = 79)
MRD negative 62.0%
MRD evaluable (n = 77)
MRD negative 68.8%

MRD- D-Rvd vs RVd: OR 4.72 (2.37-9.40) standard risk, OR 1.50 high risk (0.32-6.99) (median FU 22.1 mo)
Sustained MRD- 26 months 37.5% D-RVd vs 7.8% RVd, P < .0001
Sustained MRD- 212 months 28.8% D-RVd vs 2.9% RVd, P < .0001

FORTE TRIAL: EFFICACY OF KRD WITH OR WITHOUT TRANSPLANT IN NEWLY-DIAGNOSED MM

474 ND/MM patients, transplant-eligible and younger than 65 years

FORTE TRIAL: KRD-HCT AND KRD12 EQUALLY EFFECTIVE IN INDUCING HIGH-QUALITY RESPONSES

Pre-Maintenance RR, MRD

Gay F et al. ASH 2020. Abstract 141
Gay et al. JCO. 2019;37.15:8002
**FORTE TRIAL: KRD + HCT SIGNIFICANTLY PROLONGED PFS AND SUSTAINED MRD**

**Summary of Results**
- KRD-HCT significantly prolonged PFS vs. KRD12 and KCd-HCT.
- The benefit of KRD-HCT was observed in all groups of patients (ISS-1 and standard risk, 3 yr PFS 80-84%; ISS-2/3, high risk, 3 yr PFS 69-72%).
- KR maintenance also significantly prolonged PFS vs. R in all subgroups with a 30 month PFS of 81 vs. 68%, MRD neg 46 vs. 32%. No increase in maintenance discontinuation due to toxicity.

**BENEFIT WITH AUTOLOGOUS HCT**

**Summary of Results**
- HD Melphalan and auto HCT significantly reduced risk of progression or death by 30% vs. RVD.
- Frontline transplant remains standard of care for NDMM.
- More patients achieved MRD negativity with auto HCT.
- Combining transplant with most efficient quadruplets seems to be the best strategy in order to cure as many patients as possible.
## OUTCOME INCORPORATING NOVEL THERAPIES INTO ASCT PARADIGM DURING INDUCTION, CONSOLIDATION, AND MAINTENANCE

<table>
<thead>
<tr>
<th>Regimen/Trial</th>
<th>Patient characteristics</th>
<th>Best Response Post induction</th>
<th>Best Response on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>ISS-3</td>
<td>High-risk</td>
</tr>
<tr>
<td>IFM/DFCI 2009 RVD-AHCT-RVD (R 1yr)</td>
<td>350</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>FORTE KRd-AHCT-KRD (R vs KR)</td>
<td>158</td>
<td>15%</td>
<td>33%</td>
</tr>
<tr>
<td>CASSIOPEIA</td>
<td>543</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>GRIFFIN Dara RVD-AHCT-Dara RVD – (R-Dara)</td>
<td>104</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>MASTER Dara-KRd-AHCT-Dara-KRd (R)</td>
<td>81</td>
<td>20%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**MRD PREDICTS SURVIVAL (7-COLOR FLOW)**

*MRD=minimal residual disease*

**PFS by MRD**

- MFD Negative vs MFD Positive
- P=0.001

**OS by MRD**

- MFD Negative vs MFD Positive
- P=0.001

**PFS: HR 0.3, 95% CI (0.23-0.37)**

**OS: HR 0.34, 95% CI (0.22-0.51)**

MRD: INDEPENDENT PROGNOSTIC FACTOR FOR PFS

PFS by MRD:
- **Start of maintenance**
- **After 12 months of maintenance**


FIRST-LINE THERAPY WHEN TRANSPLANT IS NOT A CONSIDERATION

**Primary Therapy for Non-Transplant Candidates**

**Preferred Regimens**
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Daratumumab/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone

**Other Recommended Regimens**
- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab/bortezomib/melphalan/prednisone (category 1)
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone

**Useful In Certain Circumstances**
- Bortezomib/dexamethasone
- Cyclophosphamide/lenalidomide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
PHASE III MAIA STUDY DESIGN: ASCT-INELIGIBLE NEWLY-DIAGNOSED MYELOMA

Transplant-ineligible NDMM

ECOG PS 0-2
CrCl ≥30 mL/min (N = 737)

Stratification:
- ISS (I, II, III)
- Region (N America vs other)
- Age (<75 y vs ≥75 y)

Primary endpoint: PFS
Secondary endpoints: CR, VGPR, MRD negativity, ORR, OS, safety

Median age: 73 years (45-90)
99% of patients age ≥ 65 years

BEATING CANCER IS IN OUR BLOOD.

PHASE III MAIA: EFFICACY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Daratumumab + Rd (n = 368)</th>
<th>Rd (n = 369)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo 30 mo-PFS, %</td>
<td>NR</td>
<td>71</td>
<td>31.9</td>
<td>56</td>
</tr>
<tr>
<td>Median OS, mo Events, n (%)</td>
<td>NR</td>
<td>62 (17)</td>
<td>NR</td>
<td>76 (21)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>93</td>
<td>62</td>
<td>81</td>
<td>76</td>
</tr>
<tr>
<td>Stringent CR</td>
<td>30</td>
<td>30</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>CR</td>
<td>17</td>
<td>17</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>VGPR</td>
<td>32</td>
<td>32</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>PR</td>
<td>14</td>
<td>14</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>MRD negativity, %</td>
<td>24</td>
<td>24</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

- Median follow-up: 28 months
- Daratumumab favored in most subgroups, including age, race, ISS stages, ECOG PS scores
- Reduced risk of progression or death with MRD negativity in both arms

BEATING CANCER IS IN OUR BLOOD.
PHASE III MAIA: PRIMARY ENDPOINT—PFS

- 44% reduction in the risk of progression or death in patients receiving D-Rd

PHASE III MAIA: SAFETY

<table>
<thead>
<tr>
<th>TEAE, %</th>
<th>Daratumumab + Rd (n = 364)</th>
<th>Rd (n = 365)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>57</td>
<td>50</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Anemia</td>
<td>35</td>
<td>12</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>7</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18</td>
<td>15</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
<td>2</td>
<td>36</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>38</td>
<td>2</td>
<td>29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>14</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>DVT and/or pulmonary embolism</td>
<td>12</td>
<td>6</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>41</td>
<td>3</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Invasive second primary malignancy</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAE resulting in death</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**NDMM WITHOUT SCT**

<table>
<thead>
<tr>
<th>Study</th>
<th>SWOG 777 VRd vs Rd</th>
<th>ALCYONE VMP vs VMP</th>
<th>MAIA DaraRd vs Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>242</td>
<td>50</td>
<td>368</td>
</tr>
<tr>
<td>Median age</td>
<td>63</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>Median F/u, mos</td>
<td>55</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>ORR</td>
<td>82%</td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>44%</td>
<td>49%</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>43</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.71 (0.56-0.91)</td>
<td>N/A</td>
<td>0.56 (0.44-0.71)</td>
</tr>
<tr>
<td>OS or PFS2</td>
<td>75 mos</td>
<td>64 mos</td>
<td>78% @ 3y</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>OS 0.71 (0.52-0.96)</td>
<td>N/A</td>
<td>OS 0.69 (0.53-0.91)</td>
</tr>
</tbody>
</table>

*V for 6 mos (biw q21 d * 8 cycles)

*V for 12 mos (6 wk cycles, biw *1, qwk * 8)

**MULTIPLE MYELOMA: TREATMENT PARADIGM**

Goal is to achieve a deep response, obtain CR, optimize PFS and OS

**Induction**
- RVD+/Dara CyBorD
- DRd

**Consolidation**
- Auto HCT (if eligible)
- Doublet/Triplet regimens

**Maintenance**
- IMiD
- PI

**Relapsed/Refractory**
- Plethora

CyBorD: cytoxan, velcade, dexamethasone

RVD: revlimid, velcade, dexamethasone

IMiD: immunomodulating agent

PI: proteasome inhibitor

XPOVIO IS FROM A NEW CLASS OF DRUG, SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE)

Without XPOVIO

With XPOVIO


XPOVIO IS A NEW AGENT FOR MYELOMA PATIENTS WHO HAVE EXHAUSTED MANY OF THE EXISTING THERAPIES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</tr>
</thead>
</table>
| XPOVIO (selinexor) | 80 mg taken twice a week or 100 mg taken once a week | • In combination with dexamethasone for relapsed/refractory myeloma patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody  
• In combination with Velcade and dexamethasone for relapsed/refractory myeloma patients who have received at least 1 prior therapy |
EFFICACY OF XPOVIO IN RELAPSED/REFRACTORY MYELOMA: XPOVIO + DEXAMETHASONE

<table>
<thead>
<tr>
<th>No. Patients with ≥PR (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32 (26)</td>
</tr>
</tbody>
</table>

Previous therapies to which the disease was refractory, n (%)

- Velcade, Kyprolis, Revlimid, Pomalyst, and Darzalex 21 (25)
- Kyprolis, Revlimid, Pomalyst, and Darzalex 26 (26)
- Velcade, Kyprolis, Pomalyst, and Darzalex 25 (27)
- Kyprolis, Pomalyst, and Darzalex 31 (26)

Additional analyses showed clinical benefit with XPOVIO regardless of patient age and renal function.¹²³


XPOVIO, VELCADE, AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

More patients responded in the XPO-Vd group than in the Vd group (76.4% vs 62.3%).

Longer time until disease progression in the XPO-Vd group than in the Vd group (median 20.3 vs 12.9 months).

More patients experienced low platelet counts, fatigue, and nausea, and fewer patients experienced peripheral neuropathy in the XPO-Vd group than in the Vd group.

XPO-Vd data was approved by the FDA for use as second-line treatment in RRMM.

RRMM, relapsed/refractory multiple myeloma
SUPPORTIVE CARE STRATEGIES FOR XPOVIO

Consult with your doctor if nausea, vomiting, or diarrhea occur or persist. Begin prophylactic anti-nausea medications.

Low sodium (hyponatremia)

Maintain fluid intake.

Fatigue

Stay hydrated and active.

Low blood counts (cytopenias)

Report signs of bleeding right away. Report signs of fatigue or shortness of breath.

MELFLUFEN IS A PEPTIDE DRUG CONJUGATE

FDA APPROVED 2.27.21

1. Amino-peptidases highly overexpressed in multiple myeloma cells
2. Lipophilic melflufen rapidly traverses cell membranes
3. Amino-peptidase–potentiated release of hydrophilic alkylating moieties
4. Hydrophilic alkylating moieties binds directly to DNA
5. Melflufen and hydrophilic alkylating moieties trapped inside the cell

PHASE 2, PIVOTAL, SINGLE-ARM, MULTICENTER STUDY OF MELFLUFEN IN RRMM

Adult patients with
- Relapsed/refractory MM refractory to Pomalyst or anti-CD38 monoclonal antibody or both
- ≥ 2 prior lines of therapy, including an immunomodulatory drug and a proteasome inhibitor
- ECOG PS ≤ 2

Melflufen (IV) on day 1 + dex (oral) on days 1, 8, 15, and 22 of a 28-day cycle (until disease progression or unacceptable toxicity)

Any-grade and grade 3/4 adverse events occurred in 100% and 94% of patients, respectively
The most common grade 3/4 adverse events were low blood counts

ORR 29%
CBR 45%

PHASE 1B/2A OPEN-LABEL STUDY IBERDOMIDE + DEXAMETHASONE IN RRMM

- Relapsed/refractory MM
- Prior Revlimid or Pomalyst
- Prior proteasome inhibitor
- Documented progressive disease during or within 60 days of last antitymoma therapy

Iberdomide
(D1–21)
Dose escalation: 0.3 to 1.3 mg

+ Dexamethasone
(D1,8,15, 22)
• 40 mg (for age ≤75 yrs) or
• 20 mg (for age >75 yrs)
28-day cycles

ORR 32.2% 2 (3.4)
CBR 49.2% 10 (16.9)
DOR 84.7% 21 (35.6)

ORR 35.3% 1 (2.0)
CBR 49.2% 9 (17.7)
DOR 84.7% 7 (13.7)

ORR 29.6% 1 (3.7)
CBR 49.2% 5 (18.5)
DOR 84.7% 4 (14.8)
B-CELL MATURATION ANTIGEN (BCMA): A NEAR-PERFECT TARGET IN MULTIPLE MYELOMA

Cho SF et al. Front Immunol 2018

ANTIBODY-DRUG CONJUGATES (ADCS) IN MM

ADCs can selectively target and deliver drugs to myeloma cells

Components
Antibody
Stable linker
Toxin
## FIRST ADC APPROVED IN MM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blenrep (belantamab mafodotin)*</td>
<td>2.5 mg/kg IV over approximately 30 minutes once every 3 weeks</td>
<td>*For relapsed/refractory myeloma</td>
</tr>
</tbody>
</table>

*Black box warning: changes in the corneal epithelium resulting in changes in vision; belantamab mafodotin is available only through a restricted distribution program.

## BLENREP IN RRMM

<table>
<thead>
<tr>
<th>Blenrep (2.5 mg/kg)</th>
<th>Blenrep (3.4 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97</td>
</tr>
<tr>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Median no. lines of therapy, n (range)</td>
<td>7 (3–21)</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>31</td>
</tr>
<tr>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Median PFS (mos)</td>
<td>2.9</td>
</tr>
<tr>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td>Not reached</td>
</tr>
<tr>
<td>Not reached</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blenrep (2.5 mg/kg)</th>
<th>Blenrep (3.4 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>95</td>
</tr>
<tr>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Common adverse events, n (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1–2</td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>41 (43)</td>
</tr>
<tr>
<td>26 (27)</td>
<td></td>
</tr>
<tr>
<td>Grade 3–4</td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>26 (27)</td>
</tr>
<tr>
<td>21 (21)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (20)</td>
</tr>
<tr>
<td>33 (33)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (20)</td>
</tr>
<tr>
<td>25 (25)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events, n (%)</td>
<td>38 (40)</td>
</tr>
</tbody>
</table>

2 deaths: 1 sepsis (2.5 mg/kg) and 1 hemophagocytic lymphohistiocytosis (3.4 mg/kg)

PFS, progression-free survival; OS, overall survival
CURRENTLY AVAILABLE ADC SIDE EFFECTS

**Blenrep**
- Thrombocytopenia
- Keratopathy
- Decrease visual acuity
- Nausea
- Blurred vision
- Fever
- Infusion-related reactions
- Fatigue

**Management**
- Available only through a Risk Evaluation and Mitigation Strategies (REMS) due to the risk of ocular toxicity
- Patients receive ophthalmic examinations at baseline (within 3 weeks prior to the first dose), prior to each dose, and promptly for worsening symptoms
- Patients are advised to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment
- Patients should also avoid use of contact lenses unless directed by an ophthalmologist

CAR T-CELL THERAPY

Genetically modified T cells designed to recognize specific proteins on MM cells

CAR T cells are activated once in contact with the MM cell and can destroy the MM cell

CAR T cells can persist for long periods of time in the body

CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop “off-the-shelf” varieties

CAR, chimeric antigen receptor; MM, multiple myeloma

CAR T-cell therapy is not yet FDA-approved for patients with MM.
CHIMERIC ANTIGEN RECEPTOR T CELL

BCMA CAR-T cells vs Myeloma Cells

ANTI-BCMA CAR T
(BB2121)IDECABTAGENE VICLEUCEL (IDE-CEL)

Raje, N et al. NEJM 2019; 380:1726-37
**PHASE 1 CRB-401: BB2121 IN RR MULTIPLE MYELOMA**

- **Median age:** 61 yrs (37-75)
- **Inclusion:** > 3 lines of therapy (IMiD, PI, CD38)
- **Median # of MM therapies:** 6 (3-18)
- **Cytogenetics:** HR 27%
- **Bridging therapy:** 52%
- **Prior ASCT:** 91.9%
- **IMiD/PI E/R:** 100/80.6%
- **IMiD/PI/CD38 E/R:** 93.5/69.4%

**Safety**

<table>
<thead>
<tr>
<th>AE(s) of special interest, n (%)</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>62 (100)</td>
<td>61 (98.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>57 (91.9)</td>
<td>55 (88.7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>10 (16.1)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47 (75.8)</td>
<td>35 (56.5)</td>
</tr>
<tr>
<td>Infection</td>
<td>47 (75.8)</td>
<td>14 (22.6)</td>
</tr>
<tr>
<td>ORR</td>
<td>47 (75.8)</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 (74.2)</td>
<td>35 (56.5)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>60 (94.5)</td>
<td>32 (51.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>73 (121.1)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Neurologic toxicity</td>
<td>22 (35.5)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

- **Median time to Recovery of G3/4 Cytopenias:** 1.9 and 2.2 months
- **1 death within 8 weeks, Gr2 CRS, cytopenias, MR on D+31, hospice**
- **7 deaths within 6 months (11.3%), 1 cardiac arrest, and 6 due to myeloma**

**BB2121: ORR 75.8%, MEDIAN DOR 10.3 MONTHS**

- **All patients with a CR were MRD negative by NGS**
- **Median duration of response:** 10.3 months (95% CI 7.7 - 13.7 months)
- **Half of 8 ongoing responders have DOR > 2 yrs. Dose-related increase in DOR**
- **No decrease in DOR for older patients, higher ISS scores, extramedullary plasmacytomas or bridging therapy**
**BB2121: CAR-T CELL EXPANSION, PERSISTENCE**

*Robust Ide-Cel Expansion with Long-Term Persistence*


**Summary of Results**

- Favorable and durable responses at dose ≥ 150 x 10⁶ with median OS of 34.2 months, ½ of ongoing responders with a DOR > 2 yrs
- In pivotal phase 2 KarMMa trial: ORR was 73% (including CR rate 33%), median DOR 10.7 months, median PFS 8.8 months and OS 19.4 months
- Ide-Cel is also being explored in ongoing clinical trials:
  1. KarMMa-2: Phase 2 PD within 18 mos of 1L or inadequate response to HCT
  2. KarMMa-3: Phase 3 Ide-Cel vs. standard regimens with 2-4 prior lines of therapy
  3. KarMMa-4: Phase 1 study with high risk NDMM (R-ISS-3 per IMWG criteria)

**CARTITUDE-1: A PHASE 1B/2 OF CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) IN RRMM**

**Characteristics and Design**

- N=97 for Phase 1b + Phase 2 (Phase 2 N = 68)
- Median age: 61 years
- Inclusion: RRMM ≥ 3 lines of therapy or double refractory, prior IMiD, PI, anti-CD38
- M administered dose: 0.71 x 10⁶ (0.51 – 0.95 x 10⁶) CAR-T cells/kg
- M # of MM therapies: 6 (3-18)
- High-risk disease: 23%
- Triple refractory: 85%
- Penta refractory: 41%

Madduri, D. ASH 2020. Abstract 177

**Phase 1b portion, N = 29**

Deep, durable responses and manageable safety in RRMM
**CARTITUDE-1: ORR = 96.9% (94/97)**

**Efficacy Data**

- Median time to response: 1 month (0.9-8.5 months)
- Median time to MRD negativity: 1 month (0.8-7.7 months)
- Of evaluable patients, 93% achieved MRD negativity
- MRD – and sCR: 57.9%
- MRD – and ≥ VGPR: 86%

**Summary of Results**

- Cilta-Cel has a manageable safety profile at recommended phase 2 dose
- CRS was mostly grades ½, median time to onset of CRS was 7 days
- CAR-T related neurotoxicities occurred in 20.6% with 10.3% having Grade ≥ 3
- ORR 96.9% with sCR 67%
- Median PFS not reached, 12 month PFS rate 76.6%, OS rate 88.5%
- Cilta-Cel under further investigation in other populations of MM patients in earlier line settings (Cartitude-2 and 4)
CAR T-CELL THERAPY PATIENT JOURNEY

1. Apheresis (Manufacturing) | Patients go to the CAR T center | 1 day
2. Lymphodepletion (chemotherapy) | Standard of care therapy is permitted until CAR T cells are ready for infusion | 4–6 weeks
3. Infusion | Patient must be recovered from any toxicity incurred from bridging therapy before starting lymphodepletion | 3 days
4. Follow up | 2 weeks
5. Within 2 weeks

ADDITIONAL BCMA-DIRECTED CAR T CELLS IN MM

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase 1 study</th>
<th>LUMMICAR-2</th>
<th>CRB-402</th>
<th>PRIME</th>
<th>UNIVERSAL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>CT053</td>
<td>CT053</td>
<td>bb21217</td>
<td>P-BCMA-101</td>
<td>ALLO-715</td>
</tr>
<tr>
<td>No. patients</td>
<td>24</td>
<td>20</td>
<td>69</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>Median no. prior therapies</td>
<td>5 (2–11)</td>
<td>5 (3–11)</td>
<td>6 (3–17)</td>
<td>8 (2–18)</td>
<td>5 (3–11)</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>87.5</td>
<td>94</td>
<td>68</td>
<td>67</td>
<td>60</td>
</tr>
<tr>
<td>Complete response or better (%)</td>
<td>79.2</td>
<td>28</td>
<td>29</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>CRS, all grades (G3/4), %</td>
<td>62.5 (0)</td>
<td>79 (0)</td>
<td>70 (41)</td>
<td>17 (0)</td>
<td>45 (0)</td>
</tr>
<tr>
<td>Neurotoxicity, all grades (G3/4), %</td>
<td>4 (4)</td>
<td>16 (5)</td>
<td>22 (7)</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of response (mos)</td>
<td>21.8</td>
<td>Not reported</td>
<td>17</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Median progression-free survival (mos)</td>
<td>18.8</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*No graft-versus-host disease; †Two deaths

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; G, grade
BISPECIFIC ANTIBODIES AND BISPECIFIC T-CELL ENGAGERS (BITES)

Bispecific antibodies can target two cell surface proteins at the same time


BISPECIFIC ANTIBODIES AND BITES IN MM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Teclistamab</th>
<th>REGN54582</th>
<th>AMG-701</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bispecific or BITE</td>
<td>Bispecific</td>
<td>Bispecific</td>
<td>BITE</td>
</tr>
<tr>
<td>Target on myeloma cell</td>
<td>BCMA</td>
<td>BCMA</td>
<td>BCMA</td>
</tr>
<tr>
<td>No. patients</td>
<td>84 (IV), 65 (subq)</td>
<td>49</td>
<td>82</td>
</tr>
<tr>
<td>Median no. prior therapies (range)</td>
<td>6 (2–14)</td>
<td>5 (2–17)</td>
<td>6 (1–25)</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>69 (in 4 active IV/subq doses)</td>
<td>62.5 (at highest dose level)</td>
<td>26</td>
</tr>
<tr>
<td>CRS, all grades (G3/4), %</td>
<td>55 (0)</td>
<td>39 (0)</td>
<td>57 (10)</td>
</tr>
<tr>
<td>Neurotoxicity, all grades (G3/4), %</td>
<td>5 (3*)</td>
<td>12 (0)</td>
<td>8 (not reported)</td>
</tr>
<tr>
<td>Next steps</td>
<td>Planned phase 2 monotherapy dose is 1500 mcg/kg subq</td>
<td>Phase 1 dose escalation ongoing; phase 2 study recruiting</td>
<td>Further evaluation continuing</td>
</tr>
</tbody>
</table>

BiTE, bispecific T-cell engager; IV, intravenous; subq, subcutaneous; CRS, cytokine release syndrome; G, grade

Only IV formulation
## BISPECIFIC ANTIBODIES AND BITES IN MM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Talquetamab</th>
<th>Cevostamab (formerly BFCR4350A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bispecific or BiTE</td>
<td>Bispecific</td>
<td>Bispecific</td>
</tr>
<tr>
<td>Target on myeloma cell</td>
<td>GPRC5D</td>
<td>FcRH5</td>
</tr>
<tr>
<td>No. patients</td>
<td>102 (IV), 55 (subq)</td>
<td>53</td>
</tr>
<tr>
<td>Median no. prior therapies (range)</td>
<td>6 (2–20)</td>
<td>6 (2–15)</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>69 (at recommended phase 2 dose of 405 mcg/kg subq)</td>
<td>53 (≥3.6/20 mg doses)</td>
</tr>
<tr>
<td>CRS, all grades (G3/4), %</td>
<td>54 (3*)</td>
<td>76 (2)</td>
</tr>
<tr>
<td>Neurotoxicity, all grades (G3/4), %</td>
<td>6 (2*)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Only IV formulation

BiTE, bispecific T-cell engager; IV, intravenous; subq, subcutaneous; CRS, cytokine release syndrome; G, grade

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## KEY POINTS

- **XPOVIO** (selinexor) can help when all else has been tried (supportive care required). Could be used earlier in treatment in combination with Velcade.

- The BCMA-targeting antibody–drug conjugate Blenrep (belantamab mafodotin [belalumab]) was recently approved for the treatment of relapsed or refractory myeloma and is active as monotherapy and in combination. Blenrep is available only through REMS due to the risk of ocular toxicity.

- Iberdomide and melflufen have shown promising efficacy and tolerability.

- **CAR T** and **T-cell engaging antibodies (TCE)** represent a new wave of myeloma treatments that are highly active even in heavily pre-treated patients.

- Toxicities of CAR T and TCE mainly consist of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and low blood counts, all of which are treatable.
QUESTION & ANSWER

Treatment Updates: Multiple Myeloma

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

• Ask a question by web:
  – Type your question
  – Click enter

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

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

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

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: infocenter@LLS.org
All email messages are answered within one business day.

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Online Chats
Online Chats are free, live sessions, moderated by oncology social workers.

Banding Together Fridays Online Chat is specifically addressing questions and concerns about living with a blood cancer during COVID-19. Register now at www.LLS.org/Chat

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Patient Podcast
The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org.

LLS EDUCATION & SUPPORT RESOURCES
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer: www.LLS.org/Finances

To order free materials: www.LLS.org/Booklets
We have one goal: A world without blood cancers

THANK YOU