Overview

New therapies have dramatically improved life expectancy for patients with Myeloma.

This session will provide an overview of Myeloma therapies including the 3 recently approved and those under investigation with data presented at the American Society of Hematology meeting in Orlando 12/2015.
## MAJOR MILESTONES IN MYELOMA THERAPY

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Melphalan-prednisone (MP)</td>
<td>Introduction of melphalan in the 1960s associated with improved survival. More intense chemotherapy regimens increased response rates, but no improvement in survival compared to MP</td>
</tr>
<tr>
<td>1996</td>
<td>Autologous SCT</td>
<td>Several randomized trials demonstrated a survival advantage for ASCT compared to conventional chemotherapy (CCT).</td>
</tr>
<tr>
<td>1999</td>
<td>Thalidomide (Thalomid)</td>
<td>First IMID: Improved response rates and PFS compared to dexamethasone alone. When added to MP, it improves survival compared to MP alone</td>
</tr>
<tr>
<td>2003</td>
<td>Bortezomib (Velcade)</td>
<td>First Proteasome Inhibitor (PI): improves survival compared to high-dose Dex in relapsed MM, and VMP improves survival in newly Dx pts compared to MP</td>
</tr>
<tr>
<td>2006</td>
<td>Lenalidomide (Revlimid)</td>
<td>2\textsuperscript{nd} Gen IMID: Given with weekly dex, improved survival compared with dex in relapsed myeloma</td>
</tr>
<tr>
<td>2012</td>
<td>Carfilzomib (Kyprolis)</td>
<td>2\textsuperscript{nd} Gen PI: 22% Response rate if refractory to both Vel and Rev. Also KRd better than Rd, updated approval in 2015</td>
</tr>
<tr>
<td>2013</td>
<td>Pomalidomide (Pomalyst)</td>
<td>3\textsuperscript{rd} Gen IMID: 30% Response rate if refractory to both Vel and Rev (Only works if given with weekly Dex)</td>
</tr>
<tr>
<td>Year</td>
<td>Milestone</td>
<td>Notes</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>2015</td>
<td>Panobinostat (Farydak)</td>
<td>Pan Histone Deacetylase Inhibitor. Approved in combination with Velcade for Relapsed MM</td>
</tr>
<tr>
<td>2015</td>
<td>Ixazomib (Ninlaro)</td>
<td>First Oral Proteasome Inhibitor: Given once weekly days 1/8/15 along with Rev and Dex for relapse. Much less neuropathy risk.</td>
</tr>
<tr>
<td>2015</td>
<td>Daratumumab (Darzalex)</td>
<td>Anti-CD38 Monoclonal Antibody. 29% Response rate alone. Also can be combined with Rev or Pom per ASH data. Requires 3 prior Lines of Therapy</td>
</tr>
<tr>
<td>2015</td>
<td>Elotuzumab (Empliciti)</td>
<td>Anti-SLAMF7 (CS1) Monoclonal Antibody. Must be given along with IMID such as Revlimid for activity. Requires only 1 prior line of therapy</td>
</tr>
<tr>
<td>?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overview of Updates in Newly Diagnosed Multiple Myeloma

- **SWOG S0777**: effect of adding Velcade to Rev/dex for induction therapy (VRD vs RD)

- **IFM/DFCI 2009 (BMT/CTN DETERMINATION)**: SCT in first remission after VRD induction vs collect and store and delayed SCT until Relapse. French part of study presented
Overview of Updates in Relapsed/Refractory Multiple Myeloma

- **Triple Oral Therapy**: Ixazomib (Ninlaro) combined with Rev and Dex for Relapsed MM
- **Monoclonal antibodies in combination with IMID**
  - Daratumumab (anti-CD38 mAb) + POM/Dex
  - Elotuzumab (anti-SLAMF7/CS1 mAb) + Rev/dex
  - Pembrolizumab (anti-PDL1) + Rev/dex (and + Pom/dex)
- **Anti-BCMA CAR T Cells**
- **Other promising combos not discussed here in detail:**
  - Kyprolis + Ibrutinib (btk inhibitor)
  - Kyprolis + Filanesib (Arry520 KSP inhibitor)
Newly Diagnosed
Multiple Myeloma
SWOG S0777: Background

- SWOG S0777 evaluated addition of bortezomib (Velcade) to lenalidomide/dexamethasone (VRd) induction in pts with previously untreated MM without a planned immediate ASCT after induction

SWOG S0777: Study Design

- Randomized phase III trial of VRd vs Rd

**Lenalidomide** 25 mg/day PO D1-21 +
**Dexamethasone** 40 mg/day PO D1,8,15,22
for six 28-day cycles
(eligible n = 230)

**Bortezomib** 1.3 mg/m² IV D1,4,8,11 +
**Lenalidomide** 25 mg/day PO D1-14 +
**Dexamethasone** 20 mg/day D1,2,4,5,8,9,11,12
for eight 21-day cycles
(eligible n = 243)

- Median follow-up: 55 mos
- Median time on maintenance: 385 days

Previously untreated active MM
(N = 525)

**Rd maintenance until PD, unacceptable toxicity, or withdrawal of consent**

### SWOG S0777: Response

<table>
<thead>
<tr>
<th>Confirmed Response, %</th>
<th>VRd (n = 216*)</th>
<th>Rd (n = 214*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (PR or better)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CR</td>
<td>15.7</td>
<td>8.4</td>
</tr>
<tr>
<td>• VGPR</td>
<td>27.8</td>
<td>23.4</td>
</tr>
<tr>
<td>• PR</td>
<td>38.0</td>
<td>39.7</td>
</tr>
<tr>
<td><strong>SD or better</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SD</td>
<td>15.7</td>
<td>24.3</td>
</tr>
<tr>
<td><strong>PD or death</strong></td>
<td>2.8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

SWOG S0777: Survival Outcomes

- PFS, OS increase remain significant when age-adjusted in multivariate analysis
- Other significant factors: ISS stage III, 65 yrs of age or older

<table>
<thead>
<tr>
<th>Survival, Mos</th>
<th>VRd (n = 242)</th>
<th>Rd (n = 229)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>43</td>
<td>30</td>
<td>0.712</td>
<td>.0018*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.560 - 0.906)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>75</td>
<td>64</td>
<td>0.709</td>
<td>.025†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.516 - 0.973)</td>
<td></td>
</tr>
</tbody>
</table>

## SWOG S0777: Safety

<table>
<thead>
<tr>
<th>Adverse Event, *%</th>
<th>VRd (n = 241†)</th>
<th>Rd (n = 226†)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>33</td>
<td>11</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Pain</td>
<td>12</td>
<td>4</td>
<td>.0002</td>
</tr>
<tr>
<td>Sensory</td>
<td>23</td>
<td>3</td>
<td>.004</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>22</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Only AEs at least possibly attributed to protocol therapy. †Evaluable.

**SWOG S0777: Conclusions**

- Addition of bortezomib to lenalidomide plus dexamethasone induction with continuous lenalidomide/dexamethasone maintenance significantly improves outcomes in untreated pts with MM
  - Significantly longer PFS, OS and Deeper responses

- Acceptable safety profile
  - Increased incidence of neuropathic, GI events with bortezomib (IV administration used so would change to SQ in practice)

- Investigators concluded that VRd induction followed by continuous Rd maintenance represents potential new standard of care for untreated MM

- This has now been adopted by the Mayo mSmart as new standard of care and replaces CyBorD as first line for both standard risk and intermediate risk MM (KRd for high risk)

High Dose Chemotherapy with Autologous Stem Cell Transplantation (ASCT)

- Autologous peripheral blood stem cells collected by apheresis after growth factor mobilization, frozen, later used as a “rescue” from marrow ablative effect of high dose chemo

- Introduced in the 1980’s, several randomized trials showed improved PFS and Overall Survival, so SOC since the 1990’s and remains today but studies done BEFORE novel agents

- More short term toxicity than novel therapies, in hospital 2 weeks with mucositis, nausea, diarrhea, no counts (Melphalan Misery), and need a few months away from work/crowds

- Done after 3-6 cycles of induction therapy, but can we now store stem cells and hold off on transplant until after relapse? (Dana Farber/IFM 2009 trial ongoing to confirm)

Lenalidomide until Progression in US study in both groups, 12 mo in French study.
At second interim analysis in June 2015 with median follow-up of 39 mos, the data and safety monitoring board for this trial recommended that the trial be stopped.

### IFM 2009: PFS (Primary Endpoint)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RVD (n = 350)</th>
<th>Transplantation (n = 350)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>34</td>
<td>43</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4-yr PFS, %</td>
<td>35</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## IFM 2009: Grade 3/4 AEs

<table>
<thead>
<tr>
<th>Event, %</th>
<th>RVD (n = 350)</th>
<th>Transplantation (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>31</td>
<td>89</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>78</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
IFM 2009: Conclusions

- ASCT vs RVD in pts with NDMM is associated with:
  - 31% reduced risk of progression or death (P < .001)
  - Improved TTP and rate of MRD negativity
  - Similar, low rate of mortality

- Longer follow-up required to make any conclusions about OS

- Authors concluded that ASCT should remain a standard of care for eligible pts with myeloma

- Similar, confirmatory trial ongoing in US but with continuous maintenance Rev to see if PFS equalizes

Hot Topic in Myeloma: MRD

- Lack of Minimal Residual disease by high sensitivity flow cytometry or by molecular PCR testing confirms not all Complete Remissions are the same.

- Can we use molecular testing to decide when to stop maintenance therapy or when to add additional therapy to try to achieve MRD negative status?

- Ongoing trials such as the BMT-CTN Dana Farber study are using molecular testing for MRD to help determine the effect of this finding.
IFM-DFCI 2009: PFS by MRD in Pts Achieving sCR/CR

- MRD (NGS) prior to maintenance tx
  - 125 achieved sCR/CR; 55 pts available MRD

- MRD (NGS) after maintenance tx
  - 375 achieved sCR/CR; 131 pts available MRD

IMAJEM: Premaintenance PET/CT and MRD Negativity as Predictor for PFS

- Additional data assessed MRD status (by flow cytometry) on 86 of the 134 pts in this study[1]

<table>
<thead>
<tr>
<th></th>
<th>PET/CT Positive</th>
<th>PET/CT Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD positive</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>MRD negative</td>
<td>14</td>
<td>41</td>
</tr>
</tbody>
</table>

Fisher exact test, \( P = .33 \); McNemmar test, \( P = .39 \)

Probability of PFS

Relapsed/Refractory Multiple Myeloma
TOURMALINE-MM1: Background

- All-oral triple therapy combination of PI ixazomib (Ninlaro) with Revlimid/dexamethasone (Rd) showed promising efficacy and tolerability[1]
  - Safety profile encouraging for long-term use
- Phase III TOURMALINE-MM1 trial: first interim analysis (with final PFS) reported here[2]

TOURMALINE-MM1: Study Design

- Randomized, double-blind, placebo-controlled phase III trial[1]

R/R MM pts with 1-3 prior treatments; CrCl ≥ 30 mL/min; not refractory to PIs or lenalidomide (N = 722)

Ixazomib 4 mg PO D1,8,15 + Lenalidomide 25 mg* D1-21 + Dexamethasone 40 mg D1,8,15,22 (n = 360)

Placebo D1,8,15 + Lenalidomide 25 mg* D1-21 + Dexamethasone 40 mg D1,8,15,22 (n = 362)

28-day cycles until PD or unacceptable toxicity

*10 mg for pts with CrCl ≤ 60 or ≤ 50 mL/min.

TOURMALINE-MM1: Efficacy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ixazomib + Rd (n = 360)</th>
<th>Placebo + Rd (n = 362)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>20.6</td>
<td>14.7</td>
<td>.012*</td>
</tr>
<tr>
<td>ORR, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ CR</td>
<td>11.7</td>
<td>6.6</td>
<td>.019</td>
</tr>
<tr>
<td>▪ VGPR</td>
<td>36.4</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>▪ PR</td>
<td>66.7</td>
<td>64.9</td>
<td></td>
</tr>
<tr>
<td>Median time to response, mos</td>
<td>1.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>20.5</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Median TTP, mos</td>
<td>21.4</td>
<td>15.7</td>
<td>.007†</td>
</tr>
</tbody>
</table>

- PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, PI and IMiD exposed

TOURMALINE-MM1: Conclusions

- Addition of ixazomib to Rd improved clinical outcomes with fast/durable responses in R/R MM
  - Significantly prolonged PFS vs placebo, including del(17p) pts
  - Significantly improved TTP and response rates vs placebo
- Ixazomib plus Rd has tolerable safety profile with limited additional toxicity over Rd alone
  - Quality of life preserved vs placebo
- Study investigators conclude that this all-oral triplet combination regimen could represent new standard of care for R/R MM pts[1]
  - Ixazomib approved by FDA on November 20, 2015, for use in previously treated MM[2]

Daratumumab + Pom/Dex in R/R MM: Background

- **Daratumumab**: anti-CD38 IgG1 mAb
  - Activity mediated by direct antitumor effects, ADCC and other immune-mediated apoptosis, and immunomodulation
  - Safe, active as single agent or in combination with Rd in R/R MM
  - Approved November 2015 for use in MM pts with ≥ 3 prior therapies

- **Potential synergy with pomalidomide + dexamethasone**
  - Pomalidomide increases CD38 expression in MM cells\(^1\)
  - Current phase Ib study sought to determine efficacy, safety of daratumumab plus pom/dex in heavily pretreated and highly refractory pts with R/R MM\(^2\)

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Phase Ib MMY 1001: Study Design

- Open-label, multicenter trial of daratumumab with pomalidomide/dexamethasone

Pts with R/R MM after ≥ 2 prior therapies including ≥ 2 cycles len/bort; no prior pom (N = 98)

![Drug schedule]

- Primary endpoints: safety, tolerability
- Secondary endpoint: ORR

## MMY1001: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evaluable Pts (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>71</td>
</tr>
<tr>
<td>- Stringent CR</td>
<td>5</td>
</tr>
<tr>
<td>- CR</td>
<td>4</td>
</tr>
<tr>
<td>- VGPR</td>
<td>33</td>
</tr>
<tr>
<td>- PR</td>
<td>28</td>
</tr>
<tr>
<td>MR</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>23</td>
</tr>
<tr>
<td>ORR in double-refractory pts, %</td>
<td>67</td>
</tr>
<tr>
<td>Median time to first response, mo</td>
<td>1.2</td>
</tr>
<tr>
<td>M-protein reduction ≥ 50% from baseline, %</td>
<td>77</td>
</tr>
<tr>
<td>6-mo PFS, %</td>
<td>66</td>
</tr>
</tbody>
</table>

MMY1001: Change in Paraprotein From Baseline


N = 75
In early analysis, daratumumab plus pom/dex shows promising activity in heavily pretreated R/R MM
- Rapid initial responses that are deepening over time
- 71% ORR overall; 67% ORR in pts double-refractory to PI/IMiD

Combination has tolerable safety profile similar to pom/dex alone
- No new safety concerns

Authors conclude that these results support further study of this combination in phase III trial

ELOQUENT-2: Background

- Elotuzumab: anti-SLAMF7 monoclonal antibody that acts via dual mechanism
  - Directly activates natural killer cells
  - Myeloma cell destruction by ADCC
- In primary study analysis, elotuzumab + len/dex reduced risk of progression or death by 30% vs len/dex\(^{[1]}\)
- Elotuzumab approved November 30, 2015, for use with len/dex in pts with MM and 1-3 prior therapies\(^{[2]}\)
- Current analysis presents extended 3-yr safety and efficacy follow-up\(^{[3]}\)

ELOQUENT-2: Study Design

- Randomized, open-label, multicenter phase III trial

Primary endpoints: PFS, ORR

Secondary endpoints: OS, safety, DoR, health-related QoL

Pts with R/R MM and 1-3 prior treatments (N = 646)

Elotuzumab 10 mg/kg IV QW cycles 1, 2 then Q2W +
Lenalidomide 25 mg PO D1-21 +
Dexamethasone 40 mg PO QW
(n = 321)

Lenalidomide 25 mg PO D1-21 +
Dexamethasone 40 mg PO QW
(n = 325)

28-day cycles

**ELOQUENT-2: Efficacy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elotuzumab + Len/Dex (n = 321)</th>
<th>Len/Dex (n = 325)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, mos</td>
<td>19.4</td>
<td>14.9</td>
<td>0.73 (0.60-0.89; P = .0014)</td>
</tr>
<tr>
<td>1 yr, %</td>
<td>68</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>2 yrs, %</td>
<td>41</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>3 yrs, %</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Median time to next treatment, mos</td>
<td>33</td>
<td>21</td>
<td>0.62 (0.50-0.77)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>79</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Interim OS, mos</td>
<td>43.7</td>
<td>39.6</td>
<td>0.77 (0.61-0.97; P = .0257)</td>
</tr>
</tbody>
</table>

- Infusion reactions experienced by 10% of pts; most were grade 1/2 and occurred during first treatment cycle
- PFS benefit seen with elotuzumab in all predefined subgroups

ELOQUENT-2: Conclusions

- Elotuzumab in combination with len/dex improved PFS and ORR
  - At 3-yr follow-up, pts receiving elotuzumab had 27% reduction in risk of progression or death vs len/dex alone
  - Pts in elotuzumab arm had median delay of 1 yr in time to next treatment vs len/dex arm
- Interim OS analysis shows trend in favor of elotuzumab arm
- Elotuzumab plus len/dex toxicity profile consistent with prior studies with minimal increase in toxicities vs len/dex alone
- Appears to depend on NK cell activation by both the Elo and IMID so may not work well with NK suppressive therapies in combination

Pembrolizumab + Len/Dex in R/R MM (KEYNOTE-023): Background

- PD-L1 overexpression associated with invasiveness and tumor-mediated immune suppression in MM
  - High PD-L1 in relapsed MM\(^1\)

- Pembrolizumab: highly selective anti–PD-1 mAb
  - Approved in advanced NSCLC and melanoma
  - May synergize with IMiDs\(^2\)

- KEYNOTE-023 evaluated safety, tolerability, efficacy of pembrolizumab with lenalidomide + low-dose dexamethasone in R/R MM\(^3\)

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KEYNOTE-023: Study Design

- Nonrandomized, open-label, dose-escalation phase I trial

  R/R MM pts with ≥ 2 prior treatments including a PI and IMiD (N = 50)

  Dose Determination
  3 + 3
  (n = 9)

  Dose Confirmation
  TPI Algorithm
  (n = 8)

  Dose Expansion
  (n = 33)

  Final MTD: Pembrolizumab 200 mg* IV Q2W
  Lenalidomide 25 mg
  Dexamethasone 40 mg

  *2 mg/kg ≈ 200 mg fixed dose based on pharmacokinetic studies.

- Primary endpoints: safety, tolerability (on all pts)
- Secondary endpoints: ORR, DoR, PFS, OS (on pts in first 2 stages only)

### KEYNOTE-023: Efficacy of Pembrolizumab + Len/Dex in R/R MM


<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Response-Evaluable Pts (n = 17)</th>
<th>Lenalidomide-Refractory Pts (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>13 (76)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>• VGPR</td>
<td>4 (24)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>• PR</td>
<td>9 (53)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease control rate, n (%)</td>
<td>15 (88)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Median time to first response, mos (range)</td>
<td>1.2 (1.0-6.5)</td>
<td>--</td>
</tr>
<tr>
<td>M-protein reduction ≥ 50% from baseline, %</td>
<td>76.5</td>
<td>--</td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>9.7</td>
<td>--</td>
</tr>
</tbody>
</table>
KEYNOTE-023: Conclusions

- Pembrolizumab in combination with len/dex shows promising efficacy in heavily pretreated R/R MM
  - MTD of combination defined as pembrolizumab 200 mg + lenalidomide 25 mg + dexamethasone 40 mg
- In preliminary analysis, combination has tolerable safety profile
  - Consistent with individual drug profiles
- Investigators conclude that early results support further development of pembrolizumab + len/dex in R/R MM

# Pembrolizumab + Pomalidomide/Dexamethasone in R/R MM: Efficacy

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Evaluable Pts (N = 27)</th>
<th>Double Refractory (n = 20)</th>
<th>High-Risk Cytogenetics (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>15</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>PR</td>
<td>41</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>SD</td>
<td>30</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>

- Durable responses; median time to best response: 2 mos (range 1-9)
- Median PFS, OS not reached with short 7.4-mo follow-up

CAR-BCMA T Cells in MM: Background

- BCMA: protein in TNF superfamily expressed by normal and malignant plasma cells and B cells[^1]

- Autologous T cells can be genetically modified to express CARs targeted to malignancy-associated antigens
  - BCMA a potential target for myeloma CAR T-cell therapy
  - BCMA expressed uniformly on malignant plasma cells from 60% to 70% of pts with MM

- Current study evaluated CAR-BCMA T-cell infusion for treatment of advanced MM[^2]
  - Autologous T cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion

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CAR-BCMA T Cells in MM: Study Design

- **First-in-human phase I trial**

  Pts with advanced R/R MM; ≥ 3 prior lines of therapy; normal organ function; clear BCMA expression (N = 12)

  Cyclophosphamide 300 mg/m^2
  Fludarabine 30 mg/m^2
  QD for 3 days

- **CAR-BCMA expression determined by flow cytometry**

  CAR-BCMA T cells*
  Single infusion

  *Dose escalation of CAR+ T cells/kg
  0.3 x 10^6
  1.0 x 10^6
  3.0 x 10^6
  9.0 x 10^6

CAR-BCMA T Cells in MM: Response

<table>
<thead>
<tr>
<th>Pt</th>
<th>Myeloma Type</th>
<th>CAR-BCMA Dose (T cells/kg)</th>
<th>Response</th>
<th>Response Duration, Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\kappa) light chain only</td>
<td>(0.3 \times 10^6)</td>
<td>PR</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>IgA (\lambda)</td>
<td>(0.3 \times 10^6)</td>
<td>SD</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>(\kappa) light chain only</td>
<td>(0.3 \times 10^6)</td>
<td>SD</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
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<td>(1.0 \times 10^6)</td>
<td>SD</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>IgG (\kappa)</td>
<td>(1.0 \times 10^6)</td>
<td>SD</td>
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</tr>
<tr>
<td>6</td>
<td>IgG (\lambda)</td>
<td>(1.0 \times 10^6)</td>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>IgG (\lambda)</td>
<td>(3.0 \times 10^6)</td>
<td>SD</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>(\kappa) light chain only</td>
<td>(3.0 \times 10^6)</td>
<td>VGPR</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>(\kappa) light chain only</td>
<td>(3.0 \times 10^6)</td>
<td>SD</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>IgA (\lambda)</td>
<td>(9.0 \times 10^6)</td>
<td>sCR</td>
<td>12+</td>
</tr>
<tr>
<td>11</td>
<td>IgG (\lambda)</td>
<td>(9.0 \times 10^6)</td>
<td>PR</td>
<td>6+</td>
</tr>
<tr>
<td>12</td>
<td>IgA (\lambda)</td>
<td>(3.0 \times 10^6)</td>
<td>SD</td>
<td>2</td>
</tr>
</tbody>
</table>

CAR-BCMA T Cells in MM: Pt 10

- Pt 10: chemotherapy-resistant IgA MM with 3 prior lines of therapy
  - Relapse 3 mos after ASCT + melphalan 200 mg/m² conditioning with 90% bone marrow plasma cells
  - BCMA expression on pt’s myeloma cells was uniform but dim
- After CAR-BCMA T-cell infusion, the pt experienced cytokine release syndrome (including fever, hypotension, tachycardia, high creatinine kinase, liver enzymes) which resolved within 2 wks
  - ANC < 500/µL at time of infusion and for 40 days after
  - Pt was platelet transfusion dependent for 9 wks after infusion
- Pt achieved ongoing sCR after CAR-BCMA T-cell infusion
  - Serum, urine immunofixation negative at 14 wks post infusion
  - Bone marrow negative by flow cytometry 14 wks post induction
- MM eliminated from bone marrow cells after infusion with CAR-BCMA

CAR-BCMA T Cells in MM: Pt 11

- Pt 11: advanced MM with 5 prior lines of therapy

- After CAR-BCMA infusion, pt experienced significant AEs; however, dramatic reduction in disease did occur
  - Toxicities included fever, delirium, dyspnea, hypotension, tachycardia, acute kidney injury, prolonged thrombocytopenia
  - All toxicities completely resolved

- Pt achieved PR with M-protein still decreasing
  - Markers of MM decreased rapidly after infusion
  - Evidence of MM comprising 80% of Pt 11’s bone marrow cells eliminated after CAR-BCMA infusion

CAR-BCMA T Cells in MM: Conclusions

- First demonstration that CAR T cells have activity in MM
- CAR-BCMA T cells eliminated plasma cells without causing direct organ damage
- Responses included ongoing sCR in pt with a high disease burden that was chemotherapy-resistant
- Substantial but reversible toxicity comparable to that observed in previous CAR T-cell studies
  - Highest dose level of CAR-BCMA T cells to be reserved for pts with ≥ 50% bone marrow plasma cells
- Authors conclude that CAR-BCMA T cells represent a promising novel therapy for MM

Effect of Novel Agents on Outcome in Newly Diagnosed Myeloma

OS From Diagnosis

Novel Agents + ASCT

ASCT

MM Survival Is Improving With Novel Agents

![Graph showing survival rates with follow-up from diagnosis in years. Median survival is 7.3 years.](image)

**5-Yr Survival by Age, %**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>≤ 65 Yrs</th>
<th>&gt; 65 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2010</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>2001-2005</td>
<td>63</td>
<td>31</td>
</tr>
</tbody>
</table>

Conclusions

- Between the 60’s and 2000 there was nothing better than Melphalan for Myeloma and survival was dismal.
- Survival improved with high dose chemo and ASCT.
- No new MM drugs approved for 4 decades from the 60’s until 2003 but now we have 9 highly active Novel agents approved over the past decade, 3 in 11/2015 alone!!
- Survival is continuously Improving in with combinations of Novel Agents and SCT over the past decade.
- per the IFM 2009 study, SCT in 1st remission still standard of care unless the American study using continuous maintenance cancels out the PFS advantage.
Conclusions

- With 4 new drugs approved in 2015, relapsed patients now have multiple options that can be tailored to a particular patient's circumstances (location, transportation, comorbidities, frailty, etc).

- Now most patients go through several lines of therapy and can hopefully get a chance to try most if not all of the available therapies during their lifetime.

- Not known if combinations of these new drugs will make myeloma curable or at least a chronic controllable disease, but that is still the goal.
Some of our Current MM Trials at UT Southwestern

- Phase I study of oral HDAC6 inhibitor (Ricolinostat) in combination with Pomalidomide and Dex (triple oral therapy) for Relapsed MM

- Phase I study of anti-BCMA monoclonal antibody (first in human) (plasma cell specific)

- Phase II study of Ibrutinib (oral btk inhibitor) in combination with Carfilzomib and Dexamethasone for relapsed Myeloma

- Phase III MM007 study of velcade/dex +/- Pomalidomide for rel MM

- BMT/CTN Dana Farber DETERMINATION study of early vs delayed stem cell transplant in newly Dx MM <65 y/o

- ECOG study of Rev vs Observation for high risk Smoldering MM

- Randomized Ninlaro vs standard therapy for Relapsed Amyloidosis