Welcome and Introductions

Joan Levy, PhD
Multiple Myeloma Research Foundation
Norwalk, CT
Recent FDA Approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panobinostat (Farydak®)</td>
<td>February 23</td>
</tr>
<tr>
<td>Carfilzomib (Kyprolis®)</td>
<td>July 24</td>
</tr>
<tr>
<td>Daratumumab (Darzalex™)</td>
<td>November 16</td>
</tr>
<tr>
<td>Ixazomib (Ninlaro®)</td>
<td>November 20</td>
</tr>
<tr>
<td>Elotuzumab (Empliciti™)</td>
<td>November 30</td>
</tr>
</tbody>
</table>

1. Carfilzomib was approved on this date for a new indication: for use with lenalidomide and dexamethasone to treat relapsed multiple myeloma with 1–3 prior lines of therapy.

Overall Trends in 2016

- Heavy emphasis on new treatments for relapsed/refractory multiple myeloma (RRMM) this year
- Lots of research on novel immunotherapies, mostly combined with chemotherapy, for RRMM
  - Daratumumab (Darzalex), isatuximab, pembrolizumab (Keytruda), elotuzumab (Empliciti)
- Several studies of other novel therapies for RRMM
  - Venetoclax (Venclexta), carfilzomib (Kyprolis), ixazomib (Ninlaro), panobinostat (Farydak)
- Confirmation of the roles of autologous stem cell transplant (ASCT) and post-ASCT maintenance therapy
Immunotherapy

David H. Vesole, MD, PhD, FACP
John Theurer Cancer Center
Hackensack, NJ

Daratumumab

- Daratumumab (Darzalex) is a monoclonal antibody that binds to the CD38 molecule
  - CD38 is highly expressed by myeloma cells
- Approved by the FDA for RRMM
  - Patients must have tried at least 3 other therapies, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or be double-refractory to a PI and an IMiD

RRMM, relapsed/refractory multiple myeloma
Daratumumab


CASTOR trial: Daratumumab for RRMM

- CASTOR is a multicenter, phase 3, randomized, open-label controlled trial
- All patients had RRMM with at least one previous line of therapy
  - Patients had a median of 2 prior lines of therapy
- Compared daratumumab + bortezomib + dexamethasome (DVd) to bortezomib + dexamethasome alone (Vd)

IMiD, immunomodulatory drug; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma

CASTOR Design and Results

- Relapsed/refractory
- ≥1 prior therapy
- Not refractory to VEL

Daratumumab + VEL + DEX
(DVd, N = 251)

VEL + DEX
(Vd, N = 247)

Endpoints:
- PFS
- OS, ORR, CR, VGPR
- MRD
- Time to progression
- Time to response
- Duration of response

Response

<table>
<thead>
<tr>
<th></th>
<th>DVd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>not reached</td>
<td>7.2</td>
</tr>
<tr>
<td>ORR, %</td>
<td>83</td>
<td>63</td>
</tr>
<tr>
<td>≥ CR, %</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>≥ VGPR, %</td>
<td>59</td>
<td>29</td>
</tr>
</tbody>
</table>

- 61% reduction in risk of disease progression or death for DVd vs. Vd

CR, complete response; DEX, dexamethasone; MRD, minimal residual disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; VEL, bortezomib (Velcade); VGPR, very good partial response

CASTOR Design and Results


PI-based Studies

<table>
<thead>
<tr>
<th></th>
<th>Daratumumab DVd vs Vd</th>
<th>Carfilzomib Kd vs Vd1</th>
<th>Panobinostat PVd vs Vd2,3</th>
<th>Elotuzumab EVd vs Vd4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.39 (0.28-0.53)</td>
<td>0.53 (0.44-0.65)</td>
<td>0.63 (0.52-0.76)</td>
<td>0.72 (0.59-0.88)</td>
</tr>
<tr>
<td>PFS Median mo</td>
<td>NE</td>
<td>18.7</td>
<td>12.0</td>
<td>9.7</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>59%</td>
<td>54%</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>≥ CR</td>
<td>19%</td>
<td>13%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>NE</td>
<td>21.3</td>
<td>13.1</td>
<td>11.4</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.77 (0.47-1.26)</td>
<td>0.79 (0.58-1.08)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.61 (0.32-1.15)</td>
</tr>
</tbody>
</table>

**POLLUX**

- The “twin” study to CASTOR
- Same study design as CASTOR, except instead of adding bortezomib and dexamethasone to the daratumumab, investigators added lenalidomide (Revlimid) and dexamethasone
- Study design was notated as DRd (n = 286) versus Rd (n = 283)
- All eligibility criteria and endpoints were the same, except for exclusion of patients refractory to lenalidomide (instead of to bortezomib as in CASTOR)


**POLLUX Results**

<table>
<thead>
<tr>
<th>Response</th>
<th>DRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>not reached</td>
<td>18.4</td>
</tr>
<tr>
<td>ORR, %</td>
<td>93</td>
<td>76</td>
</tr>
<tr>
<td>≥ CR, %</td>
<td>43</td>
<td>19</td>
</tr>
<tr>
<td>≥ VGPR, %</td>
<td>76</td>
<td>44</td>
</tr>
</tbody>
</table>

- 63% reduction in risk of disease progression or death for DRd vs. Rd
- Treatment effects were consistent across all subgroups and regardless of prior lenalidomide exposure
- DRd doubled the complete response rates and quadrupled the rate of negativity for minimal residual disease

CR, complete response; DRd, daratumumab, lenalidomide, and dexamethasone; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response

## Lenalidomide-based Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>POLLUX DRd vs Rd</th>
<th>ASPIRE KRd vs Rd&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ELOQUENT-2 ERd vs Rd&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>TOURMALINE-MM1 NRd vs Rd&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR</td>
<td>0.37 (0.27-0.52)</td>
<td>0.69 (0.57-0.83)</td>
<td>0.73 (0.60-0.89)</td>
<td>0.74 (0.59-0.94)</td>
</tr>
<tr>
<td>ORR</td>
<td>93%</td>
<td>87%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>76%</td>
<td>70%</td>
<td>33%</td>
<td>48%</td>
</tr>
<tr>
<td>≥CR</td>
<td>43%</td>
<td>32%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>NE</td>
<td>28.6</td>
<td>20.7</td>
<td>20.5</td>
</tr>
<tr>
<td>OS HR</td>
<td>0.64 (0.40-1.01)</td>
<td>0.79 (0.63-0.99)</td>
<td>0.77 (0.61-0.97)</td>
<td>NE</td>
</tr>
</tbody>
</table>

K, carfilzomib; E, elotuzumab; N, ixazomib.


## Isatuximab

- Isatuximab (ISA) is a novel monoclonal antibody that is effective and well tolerated as a monotherapy
- Like daratumumab, it targets CD38 molecules

ISA + REV + DEX

- Phase 1 study of isatuximab (ISA) plus lenalidomide (REV) and dexamethasone (DEX)
- As a phase 1 study, the goal was to identify the maximum tolerated dose (MTD) and the optimal dose schedule, to determine how to prescribe it in future studies and eventually in practice
- Subjects had RRMM with at least 2 prior therapies (median 4–6 prior lines of therapy)

DEX, dexamethasone; ISA, isatuximab; REV, lenalidomide (Revlimid); RRMM, relapsed/refractory multiple myeloma


ISA/REV/DEX Results

- The combination had an acceptable safety profile, with adverse events similar to those of the individual drugs
- No drug-drug interactions were seen between ISA and REV
- Overall response rate was 57%, and median duration of response was 7.6 months

Conclusion: a phase 3 trial of ISA/REV/DEX at 10 mg/ kg once weekly/once every 2 weeks will begin soon

DEX, dexamethasone; ISA, isatuximab; REV, lenalidomide (Revlimid)

Infusion-related Reactions

- One common toxicity seen with anti-CD38 monoclonal antibodies like DARA and ISA is infusion-related reactions (IRRs)
- Most reactions are mild to moderate, and the great majority (≥ 90%) occur during the very first infusion
- Very few patients needed to discontinue DARA or ISA due to IRRs (<1% in CASTOR and POLLUX)

Immune Checkpoint Antibodies

How the Anti-PD-1 Antibody Works

Without the antibody

When PD-L1 binds with PD-1, the cancer puts the brakes on immune cells (T cells) and blocks attacks on cancer cells.

With the antibody

Nivolumab removes the brakes on T cells by preventing PD-L1 from binding with PD-1, thereby reactivating T cells and allowing them to attack cancer cells.
Pembrolizumab and the PD-1 Pathway

- Pembrolizumab (Keytruda) is a highly selective humanized monoclonal antibody directed against the cell surface receptor programmed cell death-1 (PD-1), allowing the immune system to attack tumor cells
- PD-1 inhibitors do not work alone, but they work synergistically (together) with IMiDs like REV to fight myeloma
- Keynote presentation at ASCO described using a combination of pembrolizumab plus REV/DEX in patients who previously did not respond to a PI and an IMiD

Pembrolizumab and the PD-1 Pathway


Pembrolizumab + REV/DEX

- Patients had heavily pretreated RRMM (median 4 prior therapies), 86% had received a stem cell transplant, and 75% were refractory to lenalidomide
  - 49% were unresponsive to two, three, or four medications
- Acceptable safety profile, with adverse events similar to those seen using pembrolizumab in solid tumors
- ORR was 50%, and disease control rate (CR, PR or SD) was 98%

Conclusion: Results are promising; phase 3 studies of pembrolizumab are now underway

CR, complete response; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SD, stable disease

CAR-BCMA T Cells in MM: Background

- BCMA: protein in TNF superfamily expressed by normal and malignant plasma cells and B cells
- 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
  - Autologous T cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion


Slide credit: clinicaloptions.com
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, uniform BCMA expression on MM cells (N = 12)

Cyclophosphamide 300 mg/m² Fludarabine 30 mg/m² QD for 3 days

CAR-BCMA T cells* Single Infusion

*Dose escalation of CAR+ T cells/kg
0.3 x 10⁶
1.0 x 10⁶
3.0 x 10⁶
9.0 x 10⁶

- CAR-BCMA expression determined by flow cytometry


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

Ali SA, et al. ASH.
Transplant, Maintenance and Novel Therapies

Angela Dispenzieri, MD
Mayo Clinic
Rochester, MN

Stem Cell Transplants v. Chemotherapy in Newly Diagnosed Myeloma

- High-dose chemotherapy (HDM) with ASCT has traditionally been the standard of care for younger, fit patients with NDMM
- In recent years, novel agents have dramatically increased response rates and extended survival in previously untreated MM patients, questioning the role of upfront ASCT in NDMM
- Are stem cell transplants still the best option for NDMM?

ASCT, autologous stem cell transplant; HDM, high-dose melphalan; NDMM, newly diagnosed multiple myeloma

EMN02/HO95 MM Trial: Study Design

VCD x three-four 21-d cycles
Bort 1.3 mg/sm twice weekly; CTX 500 mg/sm d1-8;
Dex 40 mg on day of and after bort

CTX (2-4 g/sm) + G-CSF + PBSC collection

R1

VMP x 4 cycles (n=497)

R2

VRD x two 28-d cycles
Bort 1.3 mg/sm, twice weekly;
len 25 mg d1-21;
dex 20 d1-2-4-5-8-9-11-12

Lenalidomide 10 mg/day, d1-21/28

ASCT x 1 (n=488)
ASCT x 2 (n=207)

No consolidation therapy


Transplant(s) v. Chemotherapy

• Progression-free survival at 3 years:

<table>
<thead>
<tr>
<th></th>
<th>2 ASCTs</th>
<th>1 ASCT</th>
<th>VMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.1%</td>
<td>63.0%</td>
<td>57.5%</td>
</tr>
</tbody>
</table>

• No information yet on whether there is a survival benefit

• No information on whether the 2 cycles of consolidation therapy before starting lenalidomide maintenance provides benefit

ASCT, autologous stem cell transplant; VMP, bortezomib (Velcade), high-dose melphalan, and prednisone

Maintenance after Transplantation

- Upfront ASCT is the standard of care, but many patients relapse, even with complete response to ASCT
- Lenalidomide maintenance after ASCT reduces the risk of progression by 50%

Objective: to assess the effect of post-ASCT lenalidomide maintenance on OS using data from previous studies
- 3 studies fulfilled all criteria
- Mean follow-up time of 80 months
- 7-year OS = 62% in lenalidomide arm vs. 50% in control arm (2.5-year increase in median survival)

Conclusion: post-ASCT lenalidomide maintenance can be considered the standard of care
Venetoclax

- Background: BCL-2 and MCL-1 promote myeloma survival
- Bortezomib (B; Velcade) inhibits MCL-1, and venetoclax (VEN; Venclexta) is a BCL-2 inhibitor that enhances the efficacy of B
- This phase 1b/2 study combined VEN with B and dexamethasone (D) for 11 cycles, with VEN alone after that, in patients with RRMM, to determine dosing and to evaluate safety and efficacy
- The 45 enrolled patients had a median of 4 previous therapies, and 32 had had ASCT. Most had received prior B (N = 38) and lenalidomide (Revlimid; N = 36) therapy

ASCT, autologous stem cell transplant; RRMM, relapsed/refractory multiple myeloma

Multiple Myeloma Highlights: 2016 ASCO Annual Meeting and 21st Congress of EHA

Venetoclax + Bortezomib Results

- Overall response rate (ORR) was 51%

<table>
<thead>
<tr>
<th>Lines of therapy</th>
<th>1-3 prior</th>
<th>4-6 prior</th>
<th>≥ 7 prior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>83%</td>
<td>38%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Response rates were also higher in those with no prior B treatment and in those who were not refractory to B
- Best responses were seen in patients with a t(11;14)

Conclusion: VEN + B + D has an acceptable safety profile and evidence of anti-tumor activity in RRMM

B, bortezomib; D, dexamethasone; MTD, maximum tolerated dose; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; VEN, venetoclax

Carfilzomib + Pomalidomide + Dexamethasone (KPd)

- Multicenter, single-arm study
- This study combined 28-day cycles of carfilzomib, pomalidomide, and dexamethasone (KPd)
- Patients were refractory to lenalidomide but naïve to (or sensitive to) PIs such as carfilzomib
- Goals: determine MTD (phase 1b) and efficacy (phase 2)

MTD, maximum tolerated dose; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma

Carfilzomib + Pomalidomide + Dexamethasone (KPd) Results

- 84% of 55 treated patients achieved a partial response or better; 72% achieved this after only 4 cycles of KPd

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration, months</td>
<td>12.9</td>
<td>NR</td>
</tr>
<tr>
<td>1-year rate</td>
<td>53%</td>
<td>91%</td>
</tr>
<tr>
<td>2-year rate</td>
<td>22%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Conclusion: Results warrant further investigation of KPd in randomized trials

Ixazomib + Pomalidomide + Dexamethasone (IPd)

- Triplet combinations to attack different pathways to eradicate MM cells are commonly used upfront and in RRMM
- Ixazomib (Ninlaro) was approved by the FDA in November 2015 in combination with lenalidomide (Revlimid; LEN) and dexamethasone for RRMM with at least 1 prior therapy
- An all-oral regimen of Ix + POM + DEX (IPd) could be useful in LEN-refractory RRMM

IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma


**Ixazomib + Pomalidomide + Dexamethasone (IPd) Results**

- Preliminary results of the phase 1/2 trial of IPd in 32 patients
- Eligibility: RRMM, 1–5 previous therapies, including a PI and LEN, and refractory to LEN
- ORR = 44% (including 28% partial response and 16% very good partial response)
- IPd was well tolerated

**Conclusion:** IPd is an active regimen

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**Ongoing Trials to Watch**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOURMALINE</td>
<td>Lenalidomide, and dexamethasone + Ixazomib (or placebo) in newly diagnosed MM (NDMM)</td>
</tr>
<tr>
<td>ELOQUENT-1</td>
<td>Lenalidomide and dexamethasone + Elotuzumab (or placebo) in NDMM</td>
</tr>
<tr>
<td>DRd v Rd</td>
<td>Lenalidomide and dexamethasone ± Daratumumab in non-transplant NDMM</td>
</tr>
<tr>
<td>E1A11</td>
<td>Carfilzomib, lenalidomide, dex versus Bortezomib, lenalidomide, dex in NDMM</td>
</tr>
<tr>
<td>DVMP vs VMP</td>
<td>4 drugs vs 3 drugs in-transplant NDMM</td>
</tr>
<tr>
<td>Ixazomib maintenance</td>
<td>Ixazomib maintenance vs placebo post-ASCT</td>
</tr>
</tbody>
</table>

Find more trial information at: [www.myelomatrials.org](http://www.myelomatrials.org); [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
### Novel Therapies to Watch For (1)

<table>
<thead>
<tr>
<th>Antibody (Target)</th>
<th>Proteasome inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-B4, DL101 (CD138)</td>
<td>Marizomb*</td>
</tr>
<tr>
<td>Lucatumumab (CD40)</td>
<td>Oprozomb</td>
</tr>
<tr>
<td>IPH-2101 (KIR)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab (PD-L1)*</td>
<td>HDAC inhibitors</td>
</tr>
<tr>
<td>Nivolumab (PD-1)</td>
<td>Ricolinostat</td>
</tr>
<tr>
<td>Durvalumab (PD-L1)</td>
<td>ACY-241</td>
</tr>
<tr>
<td>Indatuximab (CD38)</td>
<td></td>
</tr>
</tbody>
</table>

* Drugs studied in the

### Novel Therapies to Watch For (2)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>KSP inhibitors</td>
<td>Filanesib (ARRY-520)*</td>
</tr>
<tr>
<td>BTK inhibitors</td>
<td>Ibrutinib*, AVL-292</td>
</tr>
<tr>
<td>CDK inhibitors</td>
<td>PD0332991*, SCH727965, AT7519*</td>
</tr>
<tr>
<td>BCL antagonist</td>
<td>Ventoclax*</td>
</tr>
<tr>
<td>HSP90 inhibitors</td>
<td>Ganetespib (STA-9090)*</td>
</tr>
<tr>
<td>SINE XPO1 antagonists</td>
<td>Selinexor (KPT-330)*</td>
</tr>
<tr>
<td>FGFR3 inhibitor/antibodies</td>
<td>TKI258*, MFGR1877S</td>
</tr>
<tr>
<td>Mutant B-Raf inhibitor</td>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>

* Drugs studied in the

Question & Answer

Angela Dispenzieri, MD
Mayo Clinic
Rochester, MN

David H. Vesole, MD, PhD, FACP
John Theurer Cancer Center
Hackensack, NJ

Closing Remarks

Joan Levy, PhD
Multiple Myeloma Research Foundation
Norwalk, CT

To learn more about the MMRF, please visit:
www.multiplemyeloma.org
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