Understanding Next in Class Novel Therapies in Multiple Myeloma: New Classes and Targets

March 23, 2016

Welcome and Introductions

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

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Class</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farydak® (panobinostat)</td>
<td>HDAC inhibitor</td>
<td>February 23, 2015</td>
</tr>
<tr>
<td>Darzalex™ (daratumumab)</td>
<td>Antibody</td>
<td>November 16, 2015</td>
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<tr>
<td>Ninlaro® (ixazomib)</td>
<td>Proteasome inhibitor</td>
<td>November 20, 2015</td>
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<tr>
<td>Empliciti™ (elotuzumab)</td>
<td>Antibody</td>
<td>November 30, 2015</td>
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</tbody>
</table>

* All of the approvals above are for the treatment of relapsed/refractory multiple myeloma

HDAC, histone deacetylase inhibitor.

### Faculty

- **Craig E. Cole, MD**  
  University of Michigan  
  Ann Arbor, MI

- **Amrita Krishnan, MD, FACP**  
  City of Hope  
  Duarte, CA
Myeloma Overview

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Multiple Myeloma Disease Course

Disease Burden (M-Protein)

Asymptomatic
MGUS or Indolent myeloma

Active myeloma

1st Therapy

Symptomatic
Plateau Remission

Salvage Therapy

Refractory Relapse

2nd Relapse
Brief Plateau
Refractory Myeloma

Time
Focus on Relapsed and Refractory Multiple Myeloma

<table>
<thead>
<tr>
<th>Relapsed</th>
<th>Refractory</th>
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<tbody>
<tr>
<td>When the cancer returns after treatment, usually after a period of remission or response</td>
<td>When myeloma is not responsive to therapy</td>
</tr>
<tr>
<td>Since there is no cure for multiple myeloma, it is likely that patients will relapse at some point during their disease</td>
<td>May occur in patients who never see a response from their first treatment therapies</td>
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<tr>
<td>With therapy, relapsed patients can achieve a second response</td>
<td>May occur in patients who do initially respond to treatment, but do not respond to treatment after a relapse</td>
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Proteasome Inhibitors

Craig E. Cole, MD
University of Michigan
Ann Arbor, MI
Proteasome Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
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</table>
| Velcade® (bortezomib) | • IV infusion approved for refractory (2003), relapsed (2005), and newly diagnosed MM (2008)  
                          • SQ injection approved in 2012                                           |
| Kyprolis® (carfilzomib) | • IV infusion  
                          • Approved as a single agent (2012), as DOUBLET with dexamethasone (2016), and TRIPLET with Revlimid plus dexamethasone (2016) |
| Ninlaro® (ixazomib) | • Once-weekly pill  
                          • Approved TRIPLET with Revlimid and dexamethasone (2015)                |
| Marizomib          | • IV infusion  
                          • Currently in clinical trials                                              |
| Oprozomib          | • Once-weekly pill  
                          • Currently in clinical trials                                              |

IV, intravenous; MM, multiple myeloma; SQ, subcutaneous.

Weekly Carfilzomib: CHAMPION-1 Study

- Phase I/II study of weekly carfilzomib 70 mg/m²
- Promising response rates and PFS  
  - 77% overall response rate; 63% response rate in patients refractory to bortezomib  
  - Median duration of response: 16.3 months  
  - Median PFS: 14.3 months
- Tolerable safety profile
- Next steps: Phase III ARROW study will compare once-weekly vs twice-weekly carfilzomib

PFS, progression-free survival.
High-Dose Carfilzomib: Phase III ENDEAVOR Study

- ENDEAVOR compared high-dose carfilzomib (56 mg/m²) plus dexamethasone with bortezomib plus dexamethasone
- Response and PFS was better with carfilzomib
  - In patients with 1 prior line of therapy:
    - Overall response rate was better with carfilzomib (82%) than bortezomib (66%)
    - PFS was better with carfilzomib (22.2 months) than bortezomib (10.1 months)
  - In patients with 2 or more prior lines of therapy:
    - Overall response rate was better with carfilzomib (72%) than bortezomib (60%)
    - PFS was better with carfilzomib (14.9 months) than bortezomib (8.4 months)
- More patients in the carfilzomib group developed high blood pressure and cardiac failure


Ixazomib Dose Comparison

- Study comparing 2 doses of ixazomib (4 mg vs. 5.5 mg) plus weekly dexamethasone in patients with relapsed MM who had not previously received a proteasome inhibitor
- Early results (median follow up of 10 months):
  - Overall response rate is better for the 5.5 mg ixazomib group (51%) than the 4 mg group (31%)
  - Ixazomib was well-tolerated at both doses
    - Fewer patients required dose reductions in the 4 mg group (17%) than the 5.5 mg group (43%)

Kumar SK et al. Blood. 2015;126(23):3050.
All-Oral Triplet: Ixazomib, Lenalidomide and Dexamethasone

- Phase III study comparing ixazomib, lenalidomide, and dex (triplet) with lenalidomide and dex
  - Patients had 1-3 prior lines of therapy and were not refractory to prior lenalidomide or proteasome inhibitor therapy
- Better response, duration of response, and PFS with triplet therapy
  - Overall response rate: 78.3% vs. 71.5%
  - Duration of response: 20.5 months vs. 15.0 months
  - PFS: 20.6 months vs. 14.7 months
- All-oral triplet therapy well tolerated

dex, dexamethasone; PFS, progression-free survival.

Triplet Therapy: Ixazomib, Pomalidomide and Dexamethasone

- Phase I/II study comparing ixazomib plus pomalidomide and dex (triplet) with pomalidomide plus dex (doublet)
  - Patients had received ≥2 prior lines of therapy and were refractory to an IMiD and a proteasome inhibitor
- Phase I results
  - 13 patients completed >1 cycle of triplet therapy
  - Best ORR: 62% (7 PR, 1 VGPR)
- Next steps: comparing the triplet and doublet treatments

dex, dexamethasone; IMiD, immunomodulatory drug; ORR, overall response rate; PR, partial response; VGPR, very good partial response.
Marizomib, Pomalidomide, and Dexamethasone

- Study in heavily pretreated patients
  - Including patients with high-risk genetics and refractory to prior carfilzomib treatment
- Highly active triplet
  - Partial responses: 64%
  - Partial + minimal responses: 79%
- Manageable toxicities


Oprozomib, Pomalidomide, and Dexamethasone

- Study in heavily treated patients
  - Patients had ≥2 prior treatment cycles with bortezomib and either lenalidomide or thalidomide
  - Best treatment schedule: oprozomib 210 mg twice weekly (2/7)
- Early data
  - Confirmed responses: 86%
  - Duration of response: 29-287 days
- Well tolerated

### HDAC Inhibitors

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University of Michigan  
Ann Arbor, MI

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<table>
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<tr>
<th>Drug</th>
<th>Description</th>
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</table>
| Farydak® (panobinostat) | • Oral non-selective HDAC inhibitor  
                         • Approved in combination with bortezomib and dexamethasone (2015)         |
| Ricolinostat          | • Oral selective HDAC6 inhibitor  
                         • Currently in clinical trials                                                 |
| ACY-241               | • Oral selective HDAC6 inhibitor  
                         • Currently in clinical trials                                                 |

**HDAC**, histone deacetylase inhibitor.  
Multiple Myeloma Research Foundation: [www.themmrf.org](http://www.themmrf.org)
Panobinostat Combinations

Ongoing Studies in Relapsed/Refractory Disease

- Panobinostat, lenalidomide, bortezomib, dexamethasone
- Panobinostat, lenalidomide, dexamethasone
- Panobinostat, thalidomide, bortezomib, dexamethasone-panobinostat maintenance
- Panobinostat, carfilzomib
- Panobinostat, ixazomib, dexamethasone
- Panobinostat, everolimus


Ricolinostat Triplet Regimens

- Ricolinostat, pomalidomide, dexamethasone
  - Median follow-up: 12 weeks
  - Overall response rate: 29%
- Ricolinostat, bortezomib, dexamethasone
  - Median follow-up: 3 months
  - Overall response rate: 39%
- Ricolinostat, lenalidomide, dexamethasone
  - Median follow-up: 6 months
  - Overall response rate: 55%

ACY-241

- Phase I trial ACY-241 alone followed by triplet therapy with ACY-241 plus pomalidomide and dexamethasone
  - Patients had ≥2 prior treatment cycles of lenalidomide and a PI
- Very early data after 1-3 cycles of treatment
  - ACY-241 monotherapy and combination therapy well tolerated
  - Evidence of anti-tumor activity


Antibody Therapies

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City of Hope
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Understanding Next in Class Novel Therapies in Multiple Myeloma: New Classes and Targets

**Antibody Therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Darzalex™ (daratumumab)</td>
<td>CD38</td>
<td>• IV infusion&lt;br&gt;• Approved as a single agent in relapsed/refractory myeloma</td>
</tr>
<tr>
<td>Empliciti™ (elotuzumab)</td>
<td>SLAMF7</td>
<td>• IV infusion&lt;br&gt;• Approved in combination with Revlimid and dexamethasone</td>
</tr>
<tr>
<td>Keytruda® (pembrolizumab)</td>
<td>PD-1</td>
<td>• Approved to treat melanoma and metastatic non-small cell lung cancer&lt;br&gt;• NOT APPROVED in multiple myeloma</td>
</tr>
<tr>
<td>Isatuximab (SAR650984)</td>
<td>CD38</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenous.

[www.themmrf.org](http://www.themmrf.org)

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**Daratumumab**

- Darzalex (daratumumab) is a monoclonal antibody that targets CD38
- Current approved use for daratumumab:
  - Patients who have had ≥3 lines of treatment
  - Patients who are refractory to a PI and an IMiD
  - Approved for use as a single agent

IMiD, immunomodulatory drug; PI, proteasome inhibitor.
Daratumumab Monotherapy in Heavily Treated Patients

- Study of daratumumab monotherapy
  - Combined analysis of GEN501 and SIRIUS trials
  - GEN501: ≥2 lines of treatment
  - SIRIUS: ≥3 lines or refractory to both PI and IMiD
- Early data (median follow-up: 14.8 months)
  - Overall response rate: 31%
  - Median duration of response: 7.6 months
  - Overall survival: 19.9 months

IMiD, immunomodulatory drug. PI, proteasome inhibitor.

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Daratumumab Monotherapy in Heavily Treated Patients

**Progression-Free Survival**

- Responders: NE (7.4, NE)
- MR/SD: 3.2 (2.8-3.7) months
- PD/NE: 0.9 (0.9-1.0) months

MR, minimal response; NE, not evaluable; PD, progressive disease; SD, stable disease.
**Triplet Therapy: Daratumumab, Pomalidomide, Dexamethasone**

- Phase I study in relapsed/refractory MM
  - Patients had $\geq 2$ prior therapies, including $\geq 2$ cycles bortezomib or lenalidomide but no prior pomalidomide
- Triplet shows promising activity
  - Overall response rate: 71%
  - Response in double-refractory patients: 67%
- Well tolerated
  - Similar to pomalidomide and dexamethasone doublet
- Next steps: Phase III trial

*MM, multiple myeloma.*  

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**Elotuzumab**

- Empliciti (elotuzumab) is a monoclonal antibody that recognizes a protein (SLAMF7) that myeloma and natural killer (NK) cells produce
- Approved as combination therapy (ELd, elotuzumab, Revlimid [lenalidomide], dexamethasone) in patients who have received 1-3 prior therapies

The ELOQUENT-2 trial compared the effectiveness of elotuzumab, lenalidomide, and dexamethasone (ELd) with lenalidomide and dexamethasone (Ld) in patients with relapsed, refractory multiple myeloma.

- 3-year follow-up data were presented at ASH 2015.
- Patients receiving ELd had a 30% reduction in the risk of disease progression or death compared with those treated with Ld.

**ELOQUENT-2 Update: Progression-Free Survival**

ELd-treated patients had a 30% reduction in the risk of disease progression or death vs Ld; treatment difference at 1 and 2 years was 11% and 14%, respectively.
Immunomodulatory Drugs

Amrita Krishnan, MD, FACP
City of Hope
Duarte, CA

Pembrolizumab

- Keytruda (pembrolizumab) is a monoclonal antibody that targets the programmed cell death 1 (PD-1) receptor
- Approved uses for pembrolizumab:
  - Advanced melanoma
  - Metastatic non-small cell lung cancer
- Currently in clinical trials for multiple myeloma

Multiple Myeloma Research Foundation: www.themmrf.org.
• Phase I study of pembrolizumab, lenalidomide, and dexamethasone in heavily treated R/R MM
  – Patients had ≥2 prior treatments including a PI and IMiD
• Early data (median follow-up: 9.5 months)
  – Overall response rate: 76%
  – Response in lenalidomide-refractory patients: 56%
  – Median duration of response: 9.7 months
• Combination well tolerated
  – Safety consistent with individual drug profiles

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

• Phase II study of pembrolizumab, pomalidomide, and dexamethasone in R/R MM
  – Patients had ≥2 prior treatments including a PI and IMiD
• Early data (median follow-up: 9.5 months)
  – Overall response rate: 60%
  – Response in double-refractory patients: 55%
  – Median time to best response: 2 months
• Manageable safety profile

MM, multiple myeloma; IMiD, immunomodulatory drug; PI, proteasome inhibitor; R/R, relapsed/refractory.
Other Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
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<tbody>
<tr>
<td>SAR650984</td>
<td>CD38</td>
</tr>
<tr>
<td>B-B4, nBTO62, DL101</td>
<td>CD138</td>
</tr>
<tr>
<td>Lucatumumab</td>
<td>CD40</td>
</tr>
<tr>
<td>IPH-2101</td>
<td>KIR</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PDL-1</td>
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Immunomodulatory Drugs (IMiDs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Thalomid® (thalidomide)</td>
<td>• Oral medication</td>
</tr>
<tr>
<td></td>
<td>• Given alone or with dexamethasone</td>
</tr>
<tr>
<td>Revlimid® (lenalidomide)</td>
<td>• Oral medication</td>
</tr>
<tr>
<td></td>
<td>• Approved in combination with dexamethasone</td>
</tr>
<tr>
<td>Pomalyset® (pomalidomide)</td>
<td>• Oral medication</td>
</tr>
<tr>
<td></td>
<td>• Approved in combination with dexamethasone</td>
</tr>
</tbody>
</table>
Immunomodulatory Drugs (IMiDs)

- IMiDs work against cancer cells partly by impacting the functioning of the immune system.
- As a result, IMiDs:
  - Directly effect tumor cells
  - Also effect blood vessels and other substances around the tumor (called the tumor microenvironment)
- Considered the “backbone” of many treatment combinations in multiple myeloma.

Today, you’ve heard about:

**PI combinations**
- Ixazomib, lenalidomide, dex
- Ixazomib, pomalidomide, dex
- Marizomib, pomalidomide, dex
- Oprozomib, pomalidomide, dex

**HDAC inhibitor combinations**
- Panobinostat/IMiD combinations
- Ricolinostat, pomalidomide, dex
- Ricolinostat, lenalidomide, dex
- ACY-241, pomalidomide, dex

**Antibody combinations**
- Daratumumab, pomalidomide, dex
- Elotuzumab, lenalidomide, dex
- Pembrolizumab, lenalidomide, dex
- Pembrolizumab, pomalidomide, dex

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dex, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase inhibitor; PI, proteasome inhibitor.

### Other Novel Therapies

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<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>ABT263</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, MFRG1877S</td>
</tr>
<tr>
<td>Mutant B-Raf inhibitor</td>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>

BCL, B-cell lymphoma/leukemia; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; FGFR3, fibroblast growth factor receptor 3; HSP90, heat-shock protein 90.

### Question & Answer

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Closing Remarks

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