Recent Advances in the Treatment & Management of Relapsed Refractory Multiple Myeloma.

Ajay Nooka MD MPH
Assistant Professor, Division of Bone Marrow Transplant
Winship Cancer Institute, Emory University
1365 Clifton Road NE, C4010, Atlanta, GA 30322

Disclosures

• Consultant: Amgen, Novartis, Spectrum pharmaceuticals
Objectives

• Examine the safety and efficacy of current and emerging treatments for patients with relapsed/refractory multiple myeloma
• Evaluate treatment options for patients who have relapsed/refractory multiple myeloma and have received prior therapies
• Discuss individualized treatment strategies for patients with relapsed/refractory MM taking into account factors such as advanced age, comorbid conditions, prior treatments, and other relevant issues
• Review recently updated clinical practice guidelines for relapsed/refractory multiple myeloma
• Analyze challenges clinicians encounter when managing relapsed/refractory multiple myeloma and discuss evidence-based strategies to overcome these barriers

Scope of the problem

• In 2016, 30,330 new myeloma cases and 12,650 deaths are expected (26,850 cases and 11,240 deaths in 2015)[1]
• Median age at diagnosis: 69 years and median age of death is 75 years[2]
• Prognosis has significantly improved, with median survival estimated between 7-10 years[3]
• Prevalence=incidence x duration, myeloma pool is increasing (expected doubling in the next 5 years)
• Disease is sensitive to treatment, but curable only in a small subset
  - Progression inevitable and all patients need salvage therapies eventually

3. Emory University myeloma patient survival 2006-2014, unpublished data
Treatment options for relapsed and refractory myeloma

Factors to consider
- Treatment related factors
- Disease related factors
- Performance status

Prior SCT
- Transplant eligible, has good PS
  - Primary refractory - SCT
  - Relapsed/refractory - SCT
- Transplant ineligible
  - If patient has previously responded to the therapy, tolerated and relapsed at least 6 months after prior drug exposure
  - Repeat prior therapy
  - Otherwise, consider
    - *Bortezomib ± Dexamethasone
    - *Bortezomib + PLD
    - *Lenalidomide + Dexamethasone
    - RVD, VTD, CFZ, CRD, VCD, RCD, DCEP, DT-PACE±V, Cytoxan, Pd, T

Relapse within first 12 months
- Newer combination strategies CRD, CPD, RVD or clinical trial
- Allogeneic transplant clinical protocol

Relapse beyond the first 12 months
- *Lenalidomide + Dexamethasone
- *Bortezomib + PLD
- *Lenalidomide + Dexamethasone
- RVD, VTD, CFZ, CRD, VCD, RCD, DCEP, DT-PACE±V, Cytoxan, Pd, T

Relapse with maintenance therapy after SCT
- Relapse within 12 months
- Relapse after 12 months

Relapse without maintenance therapy after SCT
- Relapse within 12 months
- Relapse after 12 months

Factors to consider
- Treatment related factors
- Disease related factors
- Patient related factors

Significantly improved TTP in RRMM patients in phase 3 trials

Efficacy of combinations in other phase 2 trials

- **RVD** (N = 64)
  - ORR 64%

- **RCD** (N = 31)
  - ORR 81%

- **VCD**
  - ORR 66%
  - ORR 69%


Safety of combinations in other phase 2 trials

- **RVD**
  - Grade 3/4 AEs (>10% of patients)
    - Neutropenia (30%)
    - Thrombocytopenia (22%)
    - Lymphopenia (11%)
  - Grade 3 neuropathy 3%
  - Discontinued due to AEs (5%)

- **RCD**
  - Neutropenia
  - Parasthesia
  - Dyspnea
  - Rash
  - Constipation
  - Infection
  - Somnolence

- **VCD**
  - Grade 3-4 myelosuppression: 18% of patients
  - Grade 3-4 PN: 15% of patients
  - During maintenance, grade 3-4 AEs: 25% of patients
  - Did not result in discontinuation

Pomalidomide + Low-Dose Dex in RRMM

- Pomalidomide + low-dose dexamethasone FDA approved in 2013 for treatment after ≥ 2 previous therapies (including lenalidomide and bortezomib) and progression during or within 60 days of treatment
  - Approval based on phase II MM-002 study (N = 221)\(^1\):
    - ORR of 33% with Pom + LoDex vs 18% with Pom\(^2\)
    - DoR of 8.3 mos with Pom + LoDex; 10.7 mos with Pom\(^2\)
    - Low rates of discontinuations due to AEs\(^2\)


Phase 3 MM-003: POM + LoDEX vs HiDEX
PFS and OS – ITT population

- Median number of prior therapies 5
- >90% Len refractory, 75% Len + Bort refractory

Median PFS
- POM + LoDEX (n = 302) 4.0 mos
- HiDEX (n = 153) 1.9 mos

HR = 0.50
p < 0.001

Median OS
- POM + LoDEX (n = 302) 13.1 mos
- HiDEX (n = 153) 8.1 mos

HR = 0.72
p = 0.009

Median follow-up 15.4 months

HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Pomalidomide, bortezomib and dexamethasone: phase 1/2

- Median 2 prior lines
- Prior lenalidomide 100%, prior bortezomib 57%
- Refractory to immediate prior line 28%

**OS and PFS**

- Median follow-up: 12 months N = 47
- Response rate, n (%) 40 (85)
- Median OS NA
- Event free at 6 months (%) 100
- Event free at 12 months (%) 95
- Median PFS, months 10.7 (95% CI 9.4–18.5)
- Median DoR, months 13.7 (95% CI 8.5–16.8)


**ORR and DOR**

- Median follow-up: 12 months N = 34
- Response rate, n (%) 22 (65)
- Median ORR months 7.4 (95% CI 4.4–9.9)

**Escalation**

- Median TTR, mos (95% CI) 1.1 (0.7–5.1)
- Median DOR, mos (95% CI) 5.8 (1.2–10.1)

**Phase 1/2, pomalidomide, cyclophosphamide and dexamethasone: PFS**

- Median number of prior therapies 4
- Must have been refractory to lenalidomide
- Refractory to bortezomib 71%

**Progression-free survival (months)**

- Median PFS: 9.5 vs 4.4 months (p = 0.1078)
- Median OS*: not reached vs 16.8 months (p = 0.1308)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
<th>Censored</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM-LoDEX</td>
<td>36</td>
<td>30 (83%)</td>
<td>6 (17%)</td>
<td>4.4 (2.3, 6.0)</td>
</tr>
<tr>
<td>POM-LoDEX + cyclo</td>
<td>34</td>
<td>26 (76%)</td>
<td>8 (24%)</td>
<td>9.5 (4.6, 13.6)</td>
</tr>
</tbody>
</table>

**POM-LoDEX**

- POM-LoDEX
- POM-LoDEX + cyclo

Phase 2, Pom-Cytoxan-prednisone

- Median prior therapies 3 (1-3)
- Median PFS: 10.4 months; 1-year OS: 69%
- ORR was similar in LEN- and LEN + BORT-refractory patients


Adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>25</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
</tr>
<tr>
<td>Anaemia</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
</tr>
<tr>
<td>Neurological</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

Carfilzomib in RRMM

- Carfilzomib FDA approved in 2012 for treatment of MM after ≥ 2 previous therapies, including bortezomib and an IMiD, and with progression on or within 60 days of treatment
  - Approval based on single-arm phase II PX-171-003 study (N = 266): ORR of 23.7% and median DOR of 7.8 mos\[1\]

Integrated Safety Profile of Single-Agent Carfilzomib (N=526)

- 4 phase II studies (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005)

Select AEs, %

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Related</th>
<th>Grade 3/4</th>
<th>Serious AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>55.5</td>
<td>41.4</td>
<td>7.6</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>46.8</td>
<td>26.8</td>
<td>22.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>44.9</td>
<td>35.2</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Any cardiac event</td>
<td>22.1</td>
<td>NR</td>
<td>9.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>7.2</td>
<td></td>
<td>5.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Any respiratory event</td>
<td>69.0</td>
<td>NR</td>
<td>10.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>42.2</td>
<td></td>
<td>4.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Any renal impairment</td>
<td>33.1</td>
<td>NR</td>
<td>7.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>24.1</td>
<td></td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5.3</td>
<td></td>
<td>4.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>13.9</td>
<td>NR</td>
<td>1.3</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Tolerable safety profile allows for administration of full-dose carfilzomib with low discontinuation rates


CHAMPION-1 Study Design

Treatment Schedule (Phase 1 and 2)

28 day cycles:

- Carfilzomib
  - Days 1, 8, and 15
  - Duration of infusion: 30 minutes
- Dexamethasone IV or PO
  - Days 1, 8, 15, and 22 (day 22 omitted for cycles 9+)

Both drugs given until PD or unacceptable toxicity

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Carfilzomib (mg/m²)</th>
<th>Dexamethasone (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 (3+3 dose-escalation schema)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose level 1</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Dose level 2</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Dose level 3</td>
<td>70</td>
<td>40</td>
</tr>
<tr>
<td>Dose level 4</td>
<td>88</td>
<td>40</td>
</tr>
<tr>
<td>Phase 2</td>
<td>MTD from phase 1</td>
<td>40</td>
</tr>
</tbody>
</table>

*Carfilzomib 20 mg/m² was administered to all patients on only cycle 1 day 1.

IV, intravenous; MTD, maximum tolerated dose; PD, progressive disease; PO, per oral.

Berenson J, ASH 2015 Abst 373
Efficacy

**ORR**

<table>
<thead>
<tr>
<th>Phase 1–2</th>
<th>70 mg/m² (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>eCR</td>
<td>5 (5)</td>
</tr>
<tr>
<td>CR</td>
<td>31 (30)</td>
</tr>
<tr>
<td>VGPR</td>
<td>31 (30)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (7)</td>
</tr>
<tr>
<td>SD</td>
<td>12 (12)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (2)</td>
</tr>
<tr>
<td>NC</td>
<td>2 (2)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>77 (65–85)</td>
</tr>
<tr>
<td>CBR, % (95% CI)</td>
<td>84 (75–90)</td>
</tr>
</tbody>
</table>

**DOR (SD), median months (95% CI)**: 16.3 (12.7–NA)

**TTR (SD), median months (range)**: 1.6 (0.7–7.2)

**PFS**

Median PFS (95% CI): 14.3 months (9.9–21.0)

Median follow-up: 13.2 months

ORR and CBR in Btz refr: 63% & 76% respect.

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**ENDEAVOR Study Design**

**Randomization**

1:1

N=929

Stratification:
- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

**Kd**

Carfilzomib 56 mg/m² IV
*Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)*
Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg
*Days 1, 2, 8, 9, 15, 16, 22, 23*

28-day cycles until PD or unacceptable toxicity

**Vd**

Bortezomib 1.3 mg/m² (3–5 second IV bolus or subcutaneous injection)
*Days 1, 4, 8, 11*

Dexamethasone 20 mg
*Days 1, 2, 4, 5, 8, 9, 11, 12*

21-day cycles until PD or unacceptable toxicity

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Berenson J. ASH 2015 Abst 373

Dimopoulos M, J Clin Oncol 33, 2015 (suppl; abstr 8509)
Primary End Point: Progression-Free Survival

*Intent-to-Treat Population (N=929)*

- Disease progression or death – n (%): Kd (n=464) - 171 (37) vs Vd (n=465) - 243 (52)
- Median follow-up: 11.2 months
- Median PFS – months: Kd = 18.7 vs Vd = 9.4
- HR for Kd vs Vd (95% CI): 0.53 (0.44–0.65); 1-sided P<0.0001

Dimopoulos M, J Clin Oncol 33, 2015 (suppl; abstr 8509)

New Approvals for RRMM

- Panobinostat (HDAC inhibitor) + bort/dex
- Carfilzomib (proteasome inhibitor) + len/dex
- Ixazomib (oral proteasome inhibitor) + len/dex
- Elotuzumab (anti-SLAMF7 monoclonal antibody) + len/dex
- Daratumumab (CD38-targeted monoclonal antibody) as single agent
**PANORAMA 1 Study Design**

*Randomized, Double-Blind, Phase 3 Study in Relapsed or Relapsed and Refractory MM*

- **Pts (N = 768)**
  - Rel or Rel/Ref MM (BTZ-ref excluded)
  - 1-3 prior lines of therapy
  - Stratification factors
    - Prior lines of therapy
    - Prior BTZ

**Treatment Phase 1**
- Eight 21-Day cycles (24 wks)
  - Panobinostat + bortezomib + dexamethasone
  - Placebo + bortezomib + dexamethasone

**Treatment Phase 2**
- Four 42-Day cycles (24 wks)
  - Panobinostat + bortezomib + dexamethasone
  - Placebo + bortezomib + dexamethasone

- Follow-up

- Pts with clinical benefit in Treatment Phase I, can proceed to Treatment Phase II

- **Primary endpoint:** PFS (per modified EBMT criteria per investigator)1,2
- **Key secondary endpoint:** OS
- **Other secondary endpoints:** ORR, nCR/CR rate, DOR, TTR, TTP, QoL, and safety

*Study conducted at 215 centers across 34 countries*3

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**PANORAMA Trial: Pan-Bor-Dex in Relapsed MM**

- **Panobinostat** 20 mg orally d 1,3,5,8,12 in 21-day cycles
- **Bortezomib** 1.3mg/m²
- **Dexamethasone** 20 mg

**PFS**
- Median PFS: Pan-Bor-Dex 12.9 mos, Pbo-Bor-Dex 8.1 mos
- HR 0.63, P <0.0001

**OS**
- Median OS: Pan-Bor-Dex 33.64 mos, Pbo-Bor-Dex 30.39 mos
- HR 0.87, P =0.259


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**ASPIRE Study Design**

28-day cycles

### KRd
- **Carfilzomib:** 27 mg/m² IV (10 min)  
  - Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)  
- **Lenalidomide:** 25 mg Days 1–21  
- **Dexamethasone:** 40 mg Days 1, 8, 15, 22

*After cycle 12, carfilzomib given on days 1, 2, 15, 16*

*After cycle 18, carfilzomib discontinued*

### Rd
- **Lenalidomide:** 25 mg Days 1–21  
- **Dexamethasone:** 40 mg Days 1, 8, 15, 22

**Randomization**  
N=792

**Stratification:**  
- β₂-microglobulin  
- Prior bortezomib  
- Prior lenalidomide

**Primary Endpoint: Progression-Free Survival**  
**ITT Population (N=792)**

- **KRd (n=396):** Median PFS, mo 26.3  
  - HR (KRd/Rd) (95% CI): 0.69 (0.57–0.83)  
  - P value (one-sided): <0.0001

- **Rd (n=396):** Median PFS, mo 17.0  
  - HR (KRd/Rd) (95% CI): 0.69 (0.57–0.83)  
  - P value (one-sided): <0.0001

Secondary Endpoints: Response

- Percentage of Patients
  - PR: 14.1% vs 4.3% (P < .0001)
  - VGPR: 69.9% vs 40.4% (P < .0001)
  - ORR (≥PR): 87.1% vs 66.7% (P < .0001)

* Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group.


TOURMALINE-MM1:

Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

- Ixazomib + Lenalidomide + Dexamethasone
  - Ixazomib: 4 mg on days 1, 8, and 15
  - Lenalidomide: 25 mg* on days 1-21
  - Dexamethasone: 40 mg on days 1, 8, 15, 22

- Placebo + Lenalidomide + Dexamethasone
  - Placebo: on days 1, 8, and 15
  - Lenalidomide: 25 mg* on days 1-21
  - Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria1) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

*19 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

Moneau P. ASH 2015. Abst 727
**Final PFS analysis**

- **Median PFS:**
  - IRd: 20.6 months
  - Placebo-Rd: 14.7 months

**TOURMALINE-MM1:**

- **Number of patients at risk:**
  - IRd: 360, 345, 332, 315, 298, 283, 270, 248, 233, 224, 206, 182, 145, 119, 111, 95, 72, 58, 44, 34, 26, 14, 9, 1, 0

- **Log-rank test p=0.012**
- **Hazard ratio (95% CI): 0.742 (0.587, 0.939)**
- **Number of events:** IRd: 129; placebo-Rd: 157
- **Median PFS:**
  - IRd: 20.6 months
  - Placebo-Rd: 14.7 months

**TOURMALINE-MM1:**

- **Median follow-up:** ~15 months

**Interim OS analysis @ 23 months of FU:** 81 and 90 deaths in ixazomib and placebo, respectively

**A significant, 35% improvement in PFS with IRd vs placebo-Rd**

**Improved response rates, durable responses, and improved time to progression (TTP) with IRd**

<table>
<thead>
<tr>
<th>Response rates</th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (≥PR), %</td>
<td>78.3</td>
<td>71.5</td>
<td>p=0.035</td>
</tr>
<tr>
<td>CR+VGPR, %</td>
<td>48.1</td>
<td>39.0</td>
<td>p=0.014</td>
</tr>
</tbody>
</table>

**Response categories**

<table>
<thead>
<tr>
<th></th>
<th>IRd</th>
<th>Placebo-Rd</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %</td>
<td>11.7</td>
<td>6.6</td>
<td>p=0.019</td>
</tr>
<tr>
<td>PR, %</td>
<td>66.7</td>
<td>64.9</td>
<td></td>
</tr>
<tr>
<td>VGPR, %</td>
<td>36.4</td>
<td>32.3</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 duration of response, 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>HR 0.712, P=0.007</td>
</tr>
</tbody>
</table>
**MAb-Based Therapeutic Targeting of Myeloma**

Antibody-dependent Cellular cytotoxicity (ADCC)

- Effector cells: MM
- FcR

- ADCC

Complement-dependent Cytotoxicity (CDC)

- CDC
- MM
- C1q
- C1q

Apoptosis/growth arrest via targeting signaling pathways

- Daratumumab (CD38)
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

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**ELOQUENT-2 Study Design**

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

**Key inclusion criteria**

- RRMM
- 1–3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

**Elo plus Len/Dex (E-Rd) schedule (n=321)**

- Elo (10 mg/kg IV): Cycle 1 and 2: weekly; Cycles 3+: every other week
- Len (25 mg PO): days 1–21
- Dex: weekly equivalent, 40 mg

**Len/Dex (Rd) schedule (n=325)**

- Len (25 mg PO): days 1–21
- Dex: 40 mg PO days 1, 8, 15, 22

**Assessment**

- Tumor response: every 4 wks until progressive disease
- Survival: every 12 wks after disease progression

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Co-Primary Endpoint: Progression-Free Survival

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

Extended Progression-Free Survival

PFS benefit with E-Ld was maintained over time (vs Ld):
- Overall 27% reduction in the risk of disease progression or death
- Relative improvement in PFS of 44% at 3 years
Daratumumab in monotherapy:  
Two studies: GEN501 & SIRIUS

- ≥18 years of age, ECOG status ≤2\(^2\)
- GEN501\(^1\)
  - Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
  - Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs
- SIRIUS\(^2\)
  - Open-label, multicenter, phase 2 study
  - Patients had received ≥3 prior lines of therapy, including a PI and an IMID, or were double refractory to a PI and an IMID
- DARA was approved by the FDA on November 16, 2015, based on these studies

**GEN501**
- Dose-escalation
  - Doses from 0.005-24 mg/kg (n = 32)
- Safety and response evaluated
  - Dose-expansion
    - 16 mg/kg (n = 42)
    - 8 mg/kg (n = 30)

**SIRIUS**
- Randomization
  - 16 mg/kg (n = 16)
  - 8 mg/kg (n = 18)
- Response evaluated
  - 16 mg/kg (n = 106)
  - Additional 90 patients enrolled at DARA 16 mg/kg

1. Usmani S, ASH 2015 Abst 29

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**Daratumumab in monotherapy:**  
*Two studies: GEN501 & SIRIUS – Efficacy in the combined analysis*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (sCR+CR+VGPR+PR)</td>
<td>46 (31)</td>
<td>23.7-39.2</td>
</tr>
</tbody>
</table>

**Best response**
- sCR: 3 (2)
- CR: 2 (1)
- VGPR: 14 (10)
- PR: 27 (18)
- MR: 9 (6)
- SD: 68 (45)
- PD: 18 (12)
- NE: 7 (5)
- VGPR or better (sCR+CR+VGPR): 19 (13)
- CR or better (sCR+CR): 5 (3)

- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Usmani S, ASH 2015 Abst 29
**Daratumumab in monotherapy:**

*Two studies: GEN501 & SIRIUS – PFS and OS analysis*

- For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months
- 1-year overall survival rate = 69% (95% CI, 60.4-75.6)

Usmani S. ASH 2015 Abst 29

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**Phase 1b SAR-Rd in RRMM**

*Summary of Outcomes*

**Efficacy**

- Median PFS was 6.2 months in all patients (9 months follow-up)
  - 1–2 prior lines: not reached; ≥ 3 prior lines: 5.8 months

**Response (%) n ORR sCR/VGPR/PR**

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>n</th>
<th>ORR</th>
<th>sCR/VGPR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>31</td>
<td>58%</td>
<td>23/35/6</td>
<td></td>
</tr>
<tr>
<td>LEN refractory</td>
<td>25</td>
<td>48%</td>
<td>0/28/20</td>
<td></td>
</tr>
<tr>
<td>LEN non-refractory</td>
<td>6</td>
<td>100%</td>
<td>33/67/0</td>
<td></td>
</tr>
<tr>
<td>POM refractory</td>
<td>9</td>
<td>33%</td>
<td>11/22/11</td>
<td></td>
</tr>
<tr>
<td>POM non-refractory</td>
<td>22</td>
<td>68%</td>
<td>9/27/32</td>
<td></td>
</tr>
<tr>
<td>BORT refractory</td>
<td>15</td>
<td>44%</td>
<td>0/22/22</td>
<td></td>
</tr>
<tr>
<td>BORT non-refractory</td>
<td>15</td>
<td>77%</td>
<td>15/23/38</td>
<td></td>
</tr>
<tr>
<td>CFZ refractory</td>
<td>15</td>
<td>40%</td>
<td>0/7/33</td>
<td></td>
</tr>
</tbody>
</table>
| CFZ non-refractory | 15 | 155% | 34/35/4%

**Safety**

- Infusion reactions reported only during cycle 1 (35%, 6% Gr 3) and 2 (15%, 4% Gr 3)
- Most frequent grade 3/4 AEs: neutropenia (48%), anemia (20%), thrombocytopenia (15%), febrile neutropenia (13%), pneumonia (6%)
- 10% of patients discontinued due to an AE

**Velcade-Dexamethasone +/- Elotuzumab:**

**Phase 2 trial: Study design**
- Phase 2, open-label, randomized, multicenter trial
- RRMM
- 1–3 prior therapies
- ECOG PS ≤ 2
- Prior PI (if not refractory)

**Stratification:**
- Prior PI therapy
- FcγRIIIa V allele

**Elotuzumab 10 mg/kg IV**

**Bortezomib 1.3 mg/m² IV or SC**
- 8 mg PO + 8 mg IV on elotuzumab dosing days

**Dexamethasone 20 mg PO**

**Endpoints**
- Primary
  - PFS (ITT population)
- Secondary/other
  - ORR
  - OS
  - Safety

**Premedication regimen given to mitigate infusion reactions**
- Elotuzumab IV administered over ~2–3 hours; gradual escalation to 5 mL/min permitted

**EBd (events: 67/77)**

**Bd (events: 67/75)**

**EBd**
- n=77
- Bortezomib 1.3 mg/m² IV or SC
- Dexamethasone 20 mg PO
- Median PFS (95% CI) 9.7 months (7.4–12.2)

**Bd**
- n=75
- Bortezomib 1.3 mg/m² IV or SC
- Dexamethasone 20 mg PO
- Median PFS (95% CI) 6.9 months (5.1–10.2)

**Stratified HR adjusting for prognostic factors**
- 0.62 (95% CI: 0.48–0.93; 95% CI: 0.35–1.09)
- p=0.033

At 2 years, EBd-treated patients had a 24% reduction in the risk of disease progression or death

**Velcade-Dexamethasone +/- Elotuzumab:**

**Progression Free Survival Final Analysis**

**HR 0.76 (95% CI 0.63–0.91; 95% CI 0.53–1.08); stratified log-rank p=0.1256**

**Median PFS**
- 3.7 months (95% CI 1.6–6.2)
- 6.2 months (95% CI 4.9–7.5)

**Stratified HR adjusting for prognostic factors**
- 0.62 (95% CI: 0.48–0.93; 95% CI: 0.35–1.09)
- p=0.033
**Phase II Dara + Len-Dex**

**Key eligibility**
- Measurable disease by M-protein
- Patients refractory or intolerant to LEN were excluded

**Part 1**
- Relapsed MM following 2 to 4 prior lines of therapy

**Part 2**
- Relapsed MM following ≥1 prior line of therapy (no upper limit)

**Endpoints**

**Primary endpoint**
- Incidence of adverse events

**Key secondary endpoints**
- Rate of response
- Pharmacokinetics
- Time to progression
- Duration of response
- Progression-free survival

**Part 1 - Dose escalation (N = 13)**
- Open-label, IV infusions (28-day cycle)
- Dose escalation: 3 + 3 scheme
  - DARA* IV 2-16 mg/kg + LEN PO 25 mg (Days 1-21) + DEX PO 40 mg QW

**Part 2 - Expansion cohort (N = 32)**
- Open-label, single-arm IV infusion at 16 mg/kg (28-day cycle)
  - DARA* IV 16 mg/kg + LEN PO 25 mg (Days 1-21) + DEX PO 40 mg QW

**Overall Response Rate: Dara + LEN/DEX**

<table>
<thead>
<tr>
<th></th>
<th>N = 32</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>26 (81)</td>
<td>63.6-92.8</td>
</tr>
<tr>
<td>(sCR+CR+VGPR+PR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>8 (25)</td>
<td>11.5-43.4</td>
</tr>
<tr>
<td>CR</td>
<td>3 (9)</td>
<td>2.0-25.0</td>
</tr>
<tr>
<td>VGPR</td>
<td>9 (28)</td>
<td>13.7-46.7</td>
</tr>
<tr>
<td>PR</td>
<td>6 (19)</td>
<td>7.2-36.4</td>
</tr>
<tr>
<td>VGPR or better</td>
<td>20 (63)</td>
<td>43.7-78.9</td>
</tr>
<tr>
<td>(sCR+CR+VGPR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR or better</td>
<td>11 (34)</td>
<td>18.6-53.2</td>
</tr>
<tr>
<td>(sCR+CR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **ORR = 81%**
- **Clinical benefit rate (ORR + minimal response) = 88%**

Plesner T. ASH 2015 Abst 507
PFS & OS with Dara + Len-Dex

18-month PFS rate = 72%
(95% CI, 51.7-85.0)

18-month OS rate = 90%
(95% CI, 73.1-96.8)

Eligibility criteria
- Refractory to last line of therapy
- ≥2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and bortezomib
- Pomalidomide naïve
- ECOG score ≤2
- Absolute neutrophil count ≥1.0×10^9/L, and platelet count ≥75×10^9/L for patients with <50% plasma cells (>50×10^9/L, otherwise)
- Calculated creatinine clearance ≥45 mL/min/1.73 m²

Treat 6 patients with DARA + POM-D
If ≤1 patient has DLTs
Enroll 6 additional patients
Expand up to 88 patients
ORR to Dara + Pom-Dex

- ORR = 71%
- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 73%

Chari A, ASH 2015 Abst 508

Depth and duration of response

- Median time to first response was 1.2 months
- At a median follow-up time of 4.2 months
  - Median time to best response was 2.6 months; responses are deepening over time
  - 47 of 53 (89%) responders had not progressed

Chari A, ASH 2015 Abst 508
Study Chronology

Dose Determination
3 + 3 design

Dose Confirmation
TPI algorithm

Dose Expansion

- Safety analysis: all patients enrolled in the study (N = 50)
- Efficacy analysis: patients in the dose determination and confirmation stages (N = 17)

*Pembrolizumab 2 mg/kg = 200 mg fixed dose Q2W (based upon PK/PD studies)
†Pembrolizumab IV 30 minutes (no premedication) Q2W, lenalidomide 1-21 day, dexamethasone weekly

San Miguel JF, ASH 2015 Abst 505

Keynote-023

Pembrolizumab + LD Antitumor Activity

ORR

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Total N = 17</th>
<th>Len Refractory N = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>13 (76)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Very Good Partial Response</td>
<td>4 (24)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>9 (53)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease Control Rate†</td>
<td>15 (88)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (18)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (6)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

†3 patients double refractory and 1 triple refractory (Len/Bor + Pom)
‡Disease Control Rate = CR + VGPR + PR + SD > 12 weeks.
Data cutoff date: September 22, 2015

San Miguel JF, ASH 2015 Abst 505

- Median (range) follow-up: 296 days (132-560)
- Median DOR: 9.7 month
- Median (range) time to achieve first objective response
- 1.2 month (1.0 - 6.5)
- 11% of patients upgraded the quality of response
Pembrolizumab + Pom+dex

Pembrolizumab 200 mg IV
1st 6 patients treated on day 1 only

Pomalidomide 4 mg orally

Dexamethasone 40 mg Orally
20 mg for patients > 70 yr. old

- Cycles are repeated every 28 days for responding/stable pts
- After 24 months; responding patients can continue pomalidomide and dexamethasone alone until progression.

Efficacy Pembro (Anti-PD1) + Pom-Dex

Best Response (IMWG Criteria) in 27 ev pts........ ORR: 60% (1sCR: 4 VGPR; 11 PR)
ORR 55% In double refr

Duration on Treatment for Responding Patients

Badros A, ASH 2015 Abst 506
Salvage ASCT in the Relapsed Setting: Reasonable Option?

- Data from Mayo Clinic Transplant Center suggests that ASCT2 appears safe and effective treatment for relapsed MM (N = 98)
  - ORR: 86%; median PFS: 10.3 mos; median OS: 33 mos
  - Rate of TRM: 4%, suggesting a favorable benefit-to-risk ratio
- Shorter TTP after ASCT1 predicts shorter OS post-ASCT2

<table>
<thead>
<tr>
<th>TTP After ASCT1</th>
<th>Median From ASCT2, Mos (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td>&lt; 12 mos</td>
<td>5.6 (3-8)</td>
</tr>
<tr>
<td>&lt; 18 mos</td>
<td>7.1 (6-8)</td>
</tr>
<tr>
<td>&lt; 24 mos</td>
<td>7.3 (6-10)</td>
</tr>
<tr>
<td>&lt; 36 mos</td>
<td>7.6 (7-12)</td>
</tr>
</tbody>
</table>


ASCT: Timing of Transplantation

- Median OS not significantly different at 4 yrs ($P = .3$)
  - Early ASCT: 86 mos (95% CI: 80-98); delayed ASCT: NR (95% CI: 54-NR)

Additional Targeted Therapies Under Investigation in R/R MM

- Proteasome inhibitors
  - Marizomib (NPI0052): orally available, irreversible nonpeptide PI
  - Oprozomib (ONX0912): orally available, irreversible carfilzomib derivative
- HDAC inhibitors
  - Rocilinostat (ACY1215): selective HDAC-6 inhibitor
- Selective inhibitors of nuclear export (SINE)
  - Selinexor
- CDK inhibitors
- BTK inhibitors
- Bromodomain inhibitors
- Kinesin spindle protein inhibitors
  - Filanesib (ARRY-520): inhibits spindle formation during mitosis, inducing cell death
- Akt inhibitors
- Immunotherapy- (future monoclonal antibodies in development: PD-1, CD56, CXCR4, CD74, PD-L1, ICAM-1)

Determinants of choice of therapy at relapse

- Symptomatic relapse
- Consider clinical trials
  - Relapsed myeloma (prior lines of therapy 1-3)
  - Refractory myeloma (prior lines of therapy >3)

- Transplant based in suitable pts
- Bortezomib/lenalidomide based regimen
- Lenalidomide based regimen
- Carfilzomib based regimens
- Pomalidomide based regimens
- Daratumumab based regimens

- Prior IDA
  - Good response to prior BTZ therapy and relapsed at least 6 months after prior BTZ exposure
  - Combination with HDAC inhibitors in P1 resistance
  - Renal insufficiency
  - High risk cytogenetics, (4;14)
- Good response to prior LEN therapy and LEN sensitive
- Prior PI therapy
- Peripheral neuropathy
- Partner for ixazomib
- Good response to prior LEN therapy and LEN sensitive
- Prior PI therapy
- Peripheral neuropathy
- Partner for ixazomib
- Good response to prior LEN therapy and LEN sensitive
- Prior PI therapy
- Peripheral neuropathy
- Partner for ixazomib
- Simultaneously approved as single agent for patients that have received 3 lines of therapy.
  - Good safety profile and can combine with other agents
  - Good preliminary activity among high risk pts

BTZ: bortezomib; CFZ: carfilzomib; LEN: lenalidomide; POM: pomalidomide; THAL: thalidomide; PFS: progression free survival; SCT: stem cell transplant; IMiD: immunomodulatory drugs; PI: proteasome inhibitor; HDAC inhibitors: histone deacetylase inhibitors

Nooka et al. Blood 2015
**Algorithm for using combination approaches in relapsed/refractory myeloma**

Patient with myeloma needing treatment

**Newly diagnosed**
- Assess Frailty
  - Frail
  - Fit

**Std risk**
- Relapse/Refractory
  - Symptomatic/Aggressive
    - Telomeres: modified VTD, Vd
  - Std risk
    - R or V maintenance

**Fit**
- Relapse/Refractory
  - Symptomatic/Aggressive
    - Telomeres: modified VTD, Vd
  - Std risk
    - R or V maintenance

**High risk**
- Relapse/Refractory
  - Symptomatic/Aggressive
    - Telomeres: modified VTD, Vd
  - Std risk
    - R or V maintenance

Factors that needed to be considered for choosing the optimal combination therapy:

- Treatment-related factors: severity of bone marrow involvement, performance status, cytogenetics, organ failure
- Disease-related factors: duration of prior treatments
- Treatment-related factors: tolerability
- Therapy-related factors: duration of treatment, side effects
- Response-related factors: response to prior treatments

**NCCN guidelines V2.2016 and V3.2016**

- **Exposure to myeloma agents (including alkylating agents and immunomodulatory drugs) should be limited to avoid compromising their use before disease progression.**
- **Patients who may be candidates for transplant therapy.**

**Preferred Regimens**

- **Bortezomib**
  - Bortezomib and dexamethasone
  - Bortezomib and thalidomide
  - Bortezomib, lenalidomide, and dexamethasone
  - Bortezomib, lenalidomide, and carfilzomib
  - Bortezomib and pomalidomide

- **Lenalidomide**
  - Lenalidomide and dexamethasone
  - Lenalidomide and thalidomide
  - Lenalidomide, bortezomib, and dexamethasone
  - Lenalidomide, bortezomib, and pomalidomide

- **Carfilzomib**
  - Carfilzomib and dexamethasone
  - Carfilzomib and thalidomide
  - Carfilzomib, lenalidomide, and dexamethasone
  - Carfilzomib, lenalidomide, and pomalidomide

- **Elotuzumab**
  - Elotuzumab and lenalidomide
  - Elotuzumab and pomalidomide

- **Dara**
  - Dara and lenalidomide
  - Dara and pomalidomide

- **Panobinostat**
  - Panobinostat and dexamethasone
  - Panobinostat, lenalidomide, and dexamethasone

**Other Regimens**

- **Bortezomib and dexamethasone**
  - Bortezomib and lenalidomide
  - Bortezomib and carfilzomib

- **Pomalidomide**
  - Pomalidomide and dexamethasone
  - Pomalidomide and lenalidomide

- **Ixazomib**
  - Ixazomib and lenalidomide

- **Carfilzomib**
  - Carfilzomib and lenalidomide

- **Alkylating Agents**
  - Chlorambucil

- **Monoclonal Antibodies**
  - Alemtuzumab

- **Histone Deacetylase Inhibitors**
  - Vorinostat

- **Other Treatments**
  - Gene therapy
  - Stem cell transplantation

**Summary of NCCN Guidelines V2.2016 and V3.2016**

- **Relapse/Refractory Myeloma**
  - Symptomatic/Aggressive
  - Telomeres: modified VTD, Vd
  - Std risk
    - R or V maintenance
  - Fit
    - Relapse/Refractory
      - Symptomatic/Aggressive
        - Telomeres: modified VTD, Vd
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  - High risk
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**Algorithm for using combination approaches in relapsed/refractory myeloma**

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  - Bortezomib, lenalidomide, and carfilzomib
  - Bortezomib and pomalidomide

- **Lenalidomide**
  - Lenalidomide and dexamethasone
  - Lenalidomide and thalidomide
  - Lenalidomide, bortezomib, and dexamethasone
  - Lenalidomide, bortezomib, and pomalidomide

- **Carfilzomib**
  - Carfilzomib and dexamethasone
  - Carfilzomib and thalidomide
  - Carfilzomib, lenalidomide, and dexamethasone
  - Carfilzomib, lenalidomide, and pomalidomide

- **Elotuzumab**
  - Elotuzumab and lenalidomide
  - Elotuzumab and pomalidomide

- **Dara**
  - Dara and lenalidomide
  - Dara and pomalidomide

- **Panobinostat**
  - Panobinostat and dexamethasone
  - Panobinostat, lenalidomide, and dexamethasone

**Other Regimens**

- **Bortezomib and dexamethasone**
  - Bortezomib and lenalidomide
  - Bortezomib and carfilzomib

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- Treatment-related factors: tolerability
- Therapy-related factors: duration of treatment, side effects
- Response-related factors: response to prior treatments
Conclusions

• Novel agents in combination can achieve prolonged responses even in relapsed disease
• Novel targeted therapies include agents targeted to cell surface receptors CD38 and CD138, HDAC inhibitors, cell-signaling inhibitors, and others
• Despite major advances and newer options, a few challenges that we face today are
  – how to sequence the available regimens?
  – how to personalize therapy to derive the maximize benefit (eg: biomarkers)?
  – how to tailor therapy to minimize toxicity yet retain efficacy especially in heavily pretreated patients?