Management of Multiple Myeloma:
The Changing Paradigm

Relapsed/Refractory Disease
Patient Case

• A 64-yr-old woman comes with relapsed myeloma. Her history is as follows:
  – Initial studies 3 years ago showed 55% plasma cells in the bone marrow, hyperdiploidy, IgGκ 3.5 g/dL, and multiple lytic lesions
  – Initially treated with RVD, followed by high-dose melphalan and peripheral blood stem cell transplantation
  – She achieved a CR and was on observation
  – 3 yrs later, M-protein reappears to 1.5 g/dL
• What is the right choice of therapy for her?
  – Carfilzomib/lenalidomide/dex
  – Ixazomib/lenalidomide/dex
  – Elotuzumab/lenalidomide/dex
  – Evaluation for clinical trial
What Is Relapsed/Refractory Disease?

- **Relapsed**: recurrence after a response to therapy
- **Refractory**: progression despite ongoing therapy
- **Relapsed and refractory**: progression among patients who achieve minor response or better, or who progress within 60 days of their last therapy
- **Primary refractory**: Patients who never achieve at least a MR to initial induction therapy and progress while on therapy
Treatment options for relapsed and refractory myeloma

**Symptomatic relapse**

- Consider clinical trial

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

**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
      - *Lenalidomide + Dexamethasone
      - *Bortezomib ± PLD
      - RVD, VTD, CFZ, CRD, VCD, RCD, DCEP±V, Cytoxan, Pd, Td
  - If patient has previously responded to the therapy, tolerated and relapsed within 12 months after prior drug exposure
    - Newer combination strategies CRD, CPD, RVD or clinical trial
- Allogeneic transplant clinical protocol

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

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

**Relapse with maintenance therapy after SCT**

**Relapse without maintenance therapy after SCT**

**Relapse within 36 months**

**Relapse beyond 36 months**

**Relapse beyond 18-24 months**

**Relapse within 18-24 months**

**Subsequent relapse**

**SCT2**

**Subsequent relapse**

**NCCN category 1 recommendations; RVD: lenalidomide, bortezomib and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone, CFZ: carfilzomib; CRD: carfilzomib, lenalidomide and dexamethasone; CPD: carfilzomib, pomalidomide and dexamethasone VCD: bortezomib, cyclophosphamide and dexamethasone; RCD: lenalidomide, cyclophosphamide and dexamethasone; DCEP±V: dexamethasone, cyclophosphamide, etoposide, and cisplatin ± bortezomib; DT-PACE±V: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide ± bortezomib; Pd: pomalidomide and dexamethasone; Td: thalidomide and dexamethasone; PLD: liposomal doxorubicin, PS: performance status; SCT: autologous stem cell transplant; PFS: progression free survival; SCT2: second SCT

Nooka et al. Blood 2015
Options for Relapsed/Refractory Disease Continue to Increase

When did you relapse from your initial therapy?

≤6 months
- Different therapy
- Stem cell transplant

>6 months
- Repeat initial therapy
- Different therapy
- Stem cell transplant

Clinical trial
Factors to Consider in Treatment Selection

**DISEASE-RELATED**
- DOR to initial therapy
- FISH/cytogenetics/genomics profile

**PRIOR TREATMENT-RELATED**
- Prior drug exposure
- Toxicity of regimen
- Mode of administration
- Previous SCT

**PATIENT-RELATED**
- Pre-existing toxicity
- Presence of other conditions
- Age
- General health
- Personal lifestyle and preferences

DOR, duration of response; FISH, fluorescence in situ hybridization; SCT, stem cell transplant
Options at First Relapse
**Proteasome Inhibitor: Kyprolis (carfilzomib)**

| **FDA-approved indication** | In combination with dex or with Revlimid + dex for the treatment of patients with relapsed or refractory MM who have received **one to three lines of therapy**
|                           | As a single agent for the treatment of patients with relapsed or refractory MM who have received **one or more lines of therapy**
| **How effective is it?**   | Used alone (after two or more therapies):
|                           | - 23% overall response rate (CR + VGPR + PR + MR)
|                           | - On average, responses last 7.8 months
|                           | In patients who have never received Velcade:
|                           | - 42% overall response rate
|                           | - On average, responses last 13 months
| **Who should take it?**    | High-risk features (for example, t(4;14) or 17p13 del or elevated β2-microglobulin)
|                           | History of previous neuropathy
|                           | Safe for patients with reduced kidney function
| **What combinations are used?** | Standard: Kyprolis used alone or in combination with Revlimid and dex
|                               | Under investigation: combinations with Farydak, IMiDs such as Revlimid and Pomalyst, experimental therapies (for example, SAR650984, filanesib)

*Overall response rate = complete response (CR) + very good partial response (VGPR) + partial response (PR) + minimal response (MR)*
Kyprolis (carfilzomib)

- 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\(^1\)

- Intravenously given on two consecutive days each week for three weeks (that is, days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17–28)

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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)

<table>
<thead>
<tr>
<th>Select AEs, %</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>NR</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>NR</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>NR</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>5.3</td>
<td>NR</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

Treatment Schedule (Phase 1 and 2)

28 day cycles:

**Carfilzomib**
Days 1, 8, and 15  
Duration of infusion: 30 minutes

and

**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)ᵃ</th>
<th>Dexamethasone (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1 (3+3 dose-escalation schema)</strong></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><strong>Phase 2</strong></td>
<td><strong>MTD from phase 1</strong></td>
<td>40</td>
</tr>
</tbody>
</table>

ᵃCarfilzomib 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.
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>sCR</td>
<td>5 (5)</td>
</tr>
<tr>
<td>CR</td>
<td>13 (13)</td>
</tr>
<tr>
<td>VGPR</td>
<td>31 (30)</td>
</tr>
<tr>
<td>PR</td>
<td>31 (30)</td>
</tr>
<tr>
<td>MR</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>NE</td>
<td>3 (3)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>77 (68–85)</td>
</tr>
<tr>
<td>CBR, % (95% CI)</td>
<td>84 (75–90)</td>
</tr>
</tbody>
</table>

DOR (≥PR), median months (95% CI) | 16.3 (12.7–NA)
TTR (≥PR), 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.

Berenson J, ASH 2015 Abst 373
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

Dimopoulos M. J Clin Oncol 33, 2015 (suppl: abstr 8509)
Primary End Point: Progression-Free Survival
*Intent-to-Treat Population (N=929)*

- **Proportion Surviving Without Progression**
  - Months Since Randomization
  - Kd (n=464):
    - Disease progression or death – n (%): 171 (37)
    - Median PFS – months: 18.7
    - HR for Kd vs Vd (95% CI): 0.53 (0.44–0.65); 1-sided \(P<0.0001\)
  - Vd (n=465):
    - Disease progression or death – n (%): 243 (52)
    - Median PFS – months: 9.4

- **Median follow-up: 11.2 months**

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

Randomization
N=792

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

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

Primary Endpoint: Progression-Free Survival

ITT Population (N=792)

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.3</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>HR (KRd/Rd) (95% CI)</td>
<td>0.69 (0.57–0.83)</td>
<td></td>
</tr>
<tr>
<td>P value (one-sided)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk:

<table>
<thead>
<tr>
<th></th>
<th>KRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>396</td>
<td>332</td>
<td>287</td>
</tr>
<tr>
<td>279</td>
<td>222</td>
<td>151</td>
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<tr>
<td>179</td>
<td>112</td>
<td>72</td>
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<tr>
<td>24</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proteasome Inhibitor: Ninlaro (ixazomib)

<table>
<thead>
<tr>
<th>FDA-approved indication</th>
<th>In combination with Revlimid and dex for the treatment of patients with MM who have received at least one prior therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>How effective is it?</td>
<td>78% overall response rate (PR or better)</td>
</tr>
<tr>
<td>Who should take it?</td>
<td>Relapsed or relapsed/refractory following at least one prior therapy</td>
</tr>
</tbody>
</table>
| What combinations are used? | • Standard: With Revlimid and dex  
                              • Under investigation: with Treanda or Pomalyst in RR patients or with Revlimid in newly diagnosed patients |
TOURMALINE-MM1:

Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

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

Randomization

N=722

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

Repeat every 28 days until progression, or unacceptable toxicity

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

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 criteria) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

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


Moreau P, NEJM Apr 28 2016
TOURMALINE-MM1:

Final PFS analysis

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

Interim OS analysis @ 23 months of FU: 81 and 90 deaths in ixazomib and placebo, respectively
**TOURMALINE-MM1:**

**Improvded 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**

| CR, %                           | 11.7        | 6.6                | p=0.019 |
| PR, %                           | 66.7        | 64.9               |        |
| VGPR, %                         | 36.4        | 32.3               |        |

| Median time to response, mos    | 1.1         | 1.9                |        |
| Median duration of response, mos| 20.5        | 15.0               |        |
| Median TTP, mos                 | 21.4        | 15.7               | HR 0.712, P=0.007 |

Moreau P, NEJM Apr 28 2016
# Proteasome Inhibitor: Ninlaro (ixazomib)

**How is Ninlaro administered?**
- Oral
- Days 1, 8, and 15 of a 28-day cycle

**What are the possible side effects?**
- Common side effects include:
  - Diarrhea
  - Constipation
  - Thrombocytopenia
  - Peripheral neuropathy
  - Nausea
  - Peripheral edema
  - Vomiting
  - Back pain
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)

Effector cells:

ADCC

FcR

MM

Complement-dependent Cytotoxicity (CDC)

CDC

C1q

C1q

MM

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)

• Lucatumumab or Dacetuzumab (CD40)
• Elotuzumab (CS1)
• Daratumumab (CD38)
• XmAb®5592 (HM1.24)
• huN901-DM1 (CD56)
• nBT062-maytansinoid (CD138)
• 1339 (IL-6)
• BHQ880 (DKK1)
• RAP-011 (activin A)
• Daratumumab (CD38)
### Monoclonal Antibody: Empliciti (elotuzumab)

<table>
<thead>
<tr>
<th><strong>FDA-approved indication</strong></th>
<th>• In combination with Revlimid and dex for the treatment of patients with MM who have received one to three prior therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How effective is it?</strong></td>
<td>• 78.5% overall response rate (PR or better)</td>
</tr>
<tr>
<td><strong>Who should take it?</strong></td>
<td>• Relapsed or relapsed/refractory following at least one to three prior therapies</td>
</tr>
</tbody>
</table>
| **What combinations are used?** | • Standard: with Revlimid and dex  
• Under investigation: with Revlimid and Velcade in newly diagnosed patients; with Pomalyst and nivolumab or Pomalyst and Velcade in RR patients |
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

**Endpoints:**
- Co-primary: PFS and ORR
- Other: overall survival (data not yet mature); duration of response, quality of life, safety

- All patients received premedication to mitigate infusion reactions prior to Elo administration

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.

PFS analysis used the primary definition of PFS

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

Dimopoulos M, ASH 2015 Abst 28
Monoclonal Antibody: Empliciti (elotuzumab)

How is Empliciti administered?

- IV
- Every week for the first 2 cycles and every 2 weeks thereafter

What are the possible side effects?

- Common side effects include:
  - Fatigue
  - Diarrhea
  - Pyrexia
  - Constipation
  - Cough
  - Peripheral neuropathy
  - Nasopharyngitis
  - Upper respiratory tract infection
  - Decreased appetite
  - Pneumonia
Options at Second Relapse and Beyond
**IMiD: Pomalyst (pomalidomide)**

<table>
<thead>
<tr>
<th>FDA-approved indication</th>
<th>For MM patients who have received at least two prior therapies including Revlimid and Velcade and have demonstrated disease progression on or within 60 days of completion of the last therapy</th>
</tr>
</thead>
</table>
| How effective is it?    | Patients who received two or more prior therapies, including Velcade and an IMiD  
- 29% overall response rate*  
- On average, responses lasted 7.4 months |
| Who should take it?     | Received two or more prior therapies, including Velcade and Revlimid  
- High-risk myeloma with DNA alterations, including t(4;14); preliminary data indicates effectiveness in 17p13del  
- Safe for patients with reduced kidney function  
- Patients of all ages |
| What combinations are used? | Standard: Pomalyst + dex  
- Under investigation: combinations with Vel-dex, Kyprolis-dex; experimental drugs (for example, SAR650984, Filanesib, Ixazomib) |

*Overall response rate = complete response (CR) + very good partial response (VGPR) + partial response (PR) + minimal response (MR)*
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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 302)</td>
<td>4.0 mos</td>
</tr>
<tr>
<td>HiDEX (n = 153)</td>
<td>1.9 mos</td>
</tr>
</tbody>
</table>

Median follow-up 15.4 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 302)</td>
<td>13.1 mos</td>
</tr>
<tr>
<td>HiDEX (n = 153)</td>
<td>8.1 mos</td>
</tr>
</tbody>
</table>

HR = 0.50
p < 0.001

HR = 0.72
p = 0.009


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**

<table>
<thead>
<tr>
<th>Median follow-up: 12 months</th>
<th>N = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate, n (%)</strong></td>
<td>40 (85)</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>NA</td>
</tr>
<tr>
<td>Event free at 6 months (%)</td>
<td>100</td>
</tr>
<tr>
<td>Event free at 12 months (%)</td>
<td>95</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>10.7 (95% CI 9.4–18.5)</td>
</tr>
<tr>
<td><strong>Median DoR, months</strong></td>
<td>13.7 (95% CI 8.5–16.8)</td>
</tr>
</tbody>
</table>

**ORR and DOR**

<table>
<thead>
<tr>
<th>Median follow-up: 12 months</th>
<th>N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate, n (%)</strong></td>
<td>22 (65)</td>
</tr>
<tr>
<td><strong>Median DoR, months</strong></td>
<td>7.4 (95% CI 4.4–9.6)</td>
</tr>
</tbody>
</table>

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

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

Median PFS: 9.5 vs 4.4 months (p = 0.1078)
Median OS\(^a\): 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>

### How is Pomalyst administered?

- Capsule taken once daily for 21 days out of a 28-day cycle (3 weeks on, 1 week off)
- Blood thinners (for example, aspirin or low-molecule-weight heparin) are given along with Pomalyst to reduce the risk of blood clots

### What are the possible side effects?

- Common side effects include:
  - Fatigue and weakness
  - Low white blood cell counts
  - Anemia
  - Gastrointestinal effects (constipation, nausea, or diarrhea)
  - Shortness of breath
  - Upper respiratory infection
  - Back pain
  - Fever
  - Blood clots*

*Reduced risk when taken with blood thinners
**Histone Deacetylase Inhibitor: Farydak (panobinostat)**

<table>
<thead>
<tr>
<th><strong>FDA-approved indication</strong></th>
<th>• In combination with Velcade and dex, treatment of MM patients who have received at least two prior regimens including Velcade and an IMiD (for example, Thalomid, Revlimid)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How effective is it?</strong></td>
<td>• 61% overall response rate (PR or better)</td>
</tr>
<tr>
<td><strong>Who should take it?</strong></td>
<td>• Relapsed or relapsed/refractory following at least two prior regimens including Velcade and an IMiD</td>
</tr>
</tbody>
</table>
| **What combinations are used?** | • Standard: with Velcade and dex  
  • Under investigation: with Kyprolis and experimental drugs (for example, ixazomib)                                                                                                           |
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

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

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

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\(^3\)

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-Bor-Dex</td>
<td>12.0 mos</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pbo-Bor-Dex</td>
<td>8.1 mos</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Histone Deacetylase Inhibitor: Farydak (panobinostat)

<table>
<thead>
<tr>
<th>How is Farydak administered?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral</td>
</tr>
<tr>
<td>• Taken once every other day for three doses per week of weeks 1 and 2 of a 4-week cycle (that is, on days 1, 3, 5, 8, and 12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What are the possible side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Common side effects include:</td>
</tr>
<tr>
<td>− Diarrhea</td>
</tr>
<tr>
<td>− Peripheral neuropathy</td>
</tr>
<tr>
<td>− Asthenia/fatigue</td>
</tr>
<tr>
<td>− Nausea</td>
</tr>
<tr>
<td>− Peripheral edema</td>
</tr>
<tr>
<td>− Decreased appetite</td>
</tr>
<tr>
<td>− Vomiting</td>
</tr>
</tbody>
</table>
Monoclonal Antibody: Darzalex (daratumumab)

<table>
<thead>
<tr>
<th>FDA-approved indication</th>
<th>• Treatment of patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>How effective is it?</td>
<td>• 29% to 36% overall response rate (PR or better)</td>
</tr>
<tr>
<td>Who should take it?</td>
<td>• Relapsed or relapsed/refractory following at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent</td>
</tr>
</tbody>
</table>
| What combinations are used? | • Standard: as monotherapy  
|                          | • Under investigation: with Revlimid or Velcade in newly diagnosed patients                                                         |
Daratumumab in monotherapy:

**Two studies: GEN501 & SIRIUS**

- ≥18 years of age, ECOG status ≤2
- **GEN501**
  - 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**
  - 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
  - Additional 90 patients enrolled at DARA 16 mg/kg

16 mg/kg
N = 148

---

1. Usmani S, ASH 2015 Abst 29
Daratumumab in monotherapy: 
Two studies: GEN501 & SIRIUS – Efficacy in the combined analysis

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

---

**Overall response rate (sCR+CR+VGPR+PR)**

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>3 (2)</td>
<td>0.4-5.8</td>
</tr>
<tr>
<td>CR</td>
<td>2 (1)</td>
<td>0.2-4.8</td>
</tr>
<tr>
<td>VGPR</td>
<td>14 (10)</td>
<td>5.3-15.4</td>
</tr>
<tr>
<td>PR</td>
<td>27 (18)</td>
<td>12.4-25.4</td>
</tr>
<tr>
<td>MR</td>
<td>9 (6)</td>
<td>2.8-11.2</td>
</tr>
<tr>
<td>SD</td>
<td>68 (46)</td>
<td>37.7-54.3</td>
</tr>
<tr>
<td>PD</td>
<td>18 (12)</td>
<td>7.4-18.5</td>
</tr>
<tr>
<td>NE</td>
<td>7 (5)</td>
<td>1.9-9.5</td>
</tr>
<tr>
<td>VGPR or better (sCR+CR+VGPR)</td>
<td>19 (13)</td>
<td>7.9-19.3</td>
</tr>
<tr>
<td>CR or better (sCR+CR)</td>
<td>5 (3)</td>
<td>1.1-7.7</td>
</tr>
</tbody>
</table>

**16 mg/kg (N = 148)**

**ORR = 31%**
• 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)
**Monoclonal Antibody: Darzalex (daratumumab)**

<table>
<thead>
<tr>
<th>How is Darzalex administered?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IV</td>
</tr>
<tr>
<td>• Weekly for weeks 1 to 8 then every 2 weeks for weeks 9 to 24 and then every four weeks for weeks 25 onwards</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What are the possible side effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Common side effects include:</td>
</tr>
<tr>
<td>- Infusion reactions</td>
</tr>
<tr>
<td>- Fatigue</td>
</tr>
<tr>
<td>- Nausea</td>
</tr>
<tr>
<td>- Back pain</td>
</tr>
<tr>
<td>- Pyrexia</td>
</tr>
<tr>
<td>- Cough</td>
</tr>
<tr>
<td>- Upper respiratory tract infection</td>
</tr>
</tbody>
</table>
MMY-1001 (Dara + Pom-Dex arm)

**ORR to Dara + Pom-Dex**

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

<table>
<thead>
<tr>
<th>Overall response rate (sCR+CR+VGPR+PR)</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (sCR+CR+VGPR+PR)</td>
<td>53 (71)</td>
<td>59.0-80.6</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>4 (5)</td>
<td>1.5-13.1</td>
</tr>
<tr>
<td>CR</td>
<td>3 (4)</td>
<td>0.8-11.2</td>
</tr>
<tr>
<td>VGPR</td>
<td>25 (33)</td>
<td>22.9-45.2</td>
</tr>
<tr>
<td>PR</td>
<td>21 (28)</td>
<td>18.2-39.6</td>
</tr>
<tr>
<td>MR</td>
<td>2 (3)</td>
<td>0.3-9.3</td>
</tr>
<tr>
<td>SD</td>
<td>17 (23)</td>
<td>13.8-33.8</td>
</tr>
<tr>
<td>PD</td>
<td>3 (4)</td>
<td>0.8-11.2</td>
</tr>
<tr>
<td>VGPR or better (sCR+CR+VGPR)</td>
<td>32 (43)</td>
<td>31.3-54.6</td>
</tr>
<tr>
<td>CR or better (sCR+CR)</td>
<td>7 (9)</td>
<td>3.8-18.3</td>
</tr>
</tbody>
</table>

N = 75

Chari A, ASH 2015 Abst 508
### 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

### TTP

- 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

---

San Miguel JF, ASH 2015 Abst 505
### Phase 3 Clinical Studies for Relapsed/Refractory Patients

#### Monoclonal Antibodies
- Revlimid + Dex ± Empliciti
- Velcade + Dex ± Darzalex
- Revlimid + Dex ± Darzalex
- Pomalyst + Dex ± Pembrolizumab*
- Empliciti + Pomalyst Nivolumab* + Dex

#### Currently Available Agents
- Revlimid* + Dex ± Ninlaro*
- Kyprolis* + Dex vs Velcade* + Dex
- Pomalyst* + Velcade* + low-dose Dex
- Kyprolis* (once-vs twice-weekly) + Dex

#### Expanded Access
- Revlimid* + Dex + Empliciti*
- Darzalex*
- Farydak* + Velcade* + Dex

---

*Experimental therapy not yet FDA approved

---

**Ask your doctor if you are a candidate for clinical trials.**

Many phase 1 and 2 trials of new drugs and new combinations
Conclusion: Example Patient Case

- A 64-yr-old woman comes with relapsed myeloma. Her history is as follows:
  - Initial studies 3 years ago showed 55% plasma cells in the bone marrow, hyperdiploidy, IgGκ 3.5 g/dL, and multiple lytic lesions
  - Initially treated with RVD, followed by high-dose melphalan and peripheral blood stem cell transplantation
  - She achieved a CR and was on observation
  - 3 yrs later, M-protein reappears to 1.5 g/dL

- All choices are optimal. Though she had multiple combination options available, she chose to go on combination daratumumab, lenalidomide and dexamethasone clinical trial and she remains in CR 20 months later. Other than IRR with 1st infusion, she tolerated regimen well currently has a great QOL.


#### Multiple Myeloma

**MYELOMA THERAPY**

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (cat 1)
- Lenalidomide/bendamustine/dexamethasone

**Other Regimens**

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/bendamustine/dexamethasone


#### Multiple Myeloma

**MYELOMA THERAPY**

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (cat 1)
- Lenalidomide/bendamustine/dexamethasone
- Lenalidomide/panobinostat (category 1)

**Other Regimens**

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/panobinostat/dexamethasone
Summary: Relapsed/Refractory Myeloma

Relapsed/refractory multiple myeloma is treatable

Patients typically receive multiple lines of therapy

Treatment may sometimes be continued for an extended period of time

Six new drugs (Kyprolis, Pomalyst, Farydak, Darzalex, Empliciti, Ninlaro) introduced in last 4 years

With the introduction of each new drug, potential for additional combinations

Many promising new drugs/new combinations in clinical development—consider a clinical trial