Myeloma Crowd

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Lombardi Comprehensive Cancer Center
Steps to make an informed treatment decision

Diagnosis and Treatment

• Ask your doctor for your specific diagnosis and write it down
  – Your specific diagnosis is important in determining treatment
• Gather information about all your treatment options
  – Ask your doctor to explain the treatment options

Refer to *Questions to Ask Your Healthcare Provider*
Goals of Treatment

• Ask your doctor
  – What is the goal of treatment?
  – Is my cancer curable?
  – What are the options for my treatment?
  – Why are you recommending these options for me?

• Ask yourself
  – What are my personal goals for treatment?
    • Your goals are an important part of your treatment decision process.
  – Do I have the information I need to make an informed decision?

Take an active role in making treatment decisions for yourself
Ask Questions, Seek a Second Opinion

• Bring a family member, friend or other advocate to take notes and for support

• Ask who on the cancer care team can answer additional or follow up questions

• Seek a second opinion for diagnosis and/or treatment
Personal Medical Records

- Establish a file and keep it with you for reference
  - Specific diagnosis, including the subtype
  - Laboratory reports
  - Radiology reports
  - Current medications you are taking (including vitamin supplements)
  - Past and current treatments you have had for cancer
  - Medical history
  - List of your healthcare providers and contact information/business cards
Standard Treatment

- Standard treatment is treatment that experts agree is appropriate, accepted, and widely used.

- As with any treatment, it will have side effects.

- For some blood cancers, the standard treatment may only be somewhat effective.
  - In these instances, you may want to consider a clinical trial.
Talk to your doctor about all of your treatment options—Standard treatment or clinical trials

Ask as many questions as you have, until the answers are clear to you.
Clinical Trials

• Ask about therapies being studied in a clinical trial
  – Ask if a clinical trial might be right for you
  – Ask about benefits and risks of both standard treatment and treatment in the clinical trial and how they differ

• There are risks and benefits in standard treatment and in clinical trials

• Ask about side effects of each treatment option and how these will be managed

Having more information will help you make decisions and manage challenges
First Randomized Trial in MM

- A controlled trial of urethane treatment in multiple myeloma
- Randomized 83 patients with treated or untreated multiple myeloma to receive urethane or a placebo consisting of a cherry- and cola-flavored syrup
- No difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier

First Randomized Trial in MM: Results

<table>
<thead>
<tr>
<th></th>
<th>Median Survival, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urethane</strong></td>
<td>A: 8</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>A: 15</td>
</tr>
</tbody>
</table>
How do clinical trials work?

Phase I investigates for safety and side effects, dosage and best way to give treatment—includes 20 or more people

Phase II determines effectiveness and safety—typically includes fewer than 100 (may include up to 300) people

Phase III looks at effectiveness, side effects and safety in comparison with other treatments—includes 100s to 1000s of people

Phase IV gathers more information after FDA approval & drug is on market
Placebos are rarely used in cancer clinical trials
Clinical trials

• Are an important option for everyone
• Can be for people newly diagnosed, with limited disease or advanced disease
• Are appropriate for people of different age, gender, and race, depending on the purpose and phase of the study
• Take into account all the above factors as well as stage of disease, other treatments used and presence of any other illness

Remember…communication with your healthcare team is important in making treatment decisions about standard treatment or clinical trial treatment
Why Do So Few Cancer Patients Participate in Clinical Trials?

Patients may:

• Be unaware of clinical trials
• Lack access to trials
• Fear, distrust, or be suspicious of research
• Have practical or personal obstacles
• Face insurance or cost problems
• Be unwilling to go against their physicians’ wishes
Why Do So Few Cancer Patients Participate in Clinical Trials?

Doctors might:

- Lack awareness of appropriate clinical trials
- Be unwilling to “lose control” of a person’s care
- Believe that standard therapy is best
- Be concerned that clinical trials add administrative burdens
Goals of Therapy

• High response rate
• Depth of response (MRD?)
• Improve performance status and quality of life
• Not limit PBSC mobilization (for younger pts)
• Current issues:
  – Role of transplant
  – Optimal duration of therapy

How deep of a response should we aim for?
Myeloma treatment paradigm

- **Induction** followed by continuous therapy
- **Consolidation**
- **Maintenance**
- **Relapse**

**SCT eligible**

**SCT ineligible**

**Tumor Burden**

- Induction followed by continuous therapy
Getting to Minimal Residual Disease (MRD): New Definitions for CR

- **S.S. Patient**
- **Disease burden**
  - CR
  - Stringent CR
  - Molecular/Flow CR
  - ?Cure?

Newly diagnosed: $1 \times 10^{12}$

- $1 \times 10^8$
- $1 \times 10^4$
- 0.0

Bortezomib Lenalidomide Combinations
Time To Progression

Overall Survival

Kapoor P et al. JCO 2013;31:4529-4535
Minimal Residual Disease (MRD)

- Techniques using PCR and Multi Parameter Flow (MPF) are the best ways to get closer
- PCR is able to identify at lower levels than MPF

Rawstron A C et al. JCO 2013;31:2540-2547
Induction Regimens

• Three classes of drugs are being used in the management of multiple myeloma patients:
  – Proteasome inhibitors: borezomib, carfilzomib, ixazomib
  – Immune modulatory drugs: thalidomide, lenalidomide, pomalidomide
  – Corticosteroids: dexamethasone, prednisone

• The choice of initial induction therapy can be influenced by the underlying medical conditions of the patients and their prognostic features.
### MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosourea) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

#### Primary Therapy for Transplant Candidates
(assess for response after 2 cycles)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>Bortezomib/dexamethasone (category 1)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bortezomib/doxorubicin/dexamethasone (category 1)</td>
<td>Carfilzomib&lt;sup&gt;7&lt;/sup&gt;/lenalidomide&lt;sup&gt;5&lt;/sup&gt;/dexamethasone</td>
</tr>
<tr>
<td>Bortezomib/lenalidomide&lt;sup&gt;9&lt;/sup&gt;/dexamethasone (category 1)</td>
<td>Ixazomib/lenalidomide&lt;sup&gt;5&lt;/sup&gt;/dexamethasone</td>
</tr>
<tr>
<td>Lenalidomide&lt;sup&gt;5&lt;/sup&gt;/dexamethasone (category 1)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Lenalidomide&lt;sup&gt;5&lt;/sup&gt;/dexamethasone</td>
</tr>
</tbody>
</table>

#### Primary Therapy for Non-Transplant Candidates
(assess for response after 2 cycles)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>Bortezomib/dexamethasone&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bortezomib/lenalidomide/dexamethasone (category 1)</td>
<td>Carfilzomib/lenalidomide/dexamethasone (category 2B)&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lenalidomide/low-dose dexamethasone (category 1)&lt;sup&gt;6,9&lt;/sup&gt;</td>
<td>Ixazomib/lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>

#### Maintenance Therapy

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
</tr>
<tr>
<td>Lenalidomide&lt;sup&gt;8&lt;/sup&gt; (category 1)</td>
</tr>
</tbody>
</table>

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<sup>1</sup>Selected, but not inclusive of all regimens.

<sup>2</sup>Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.

<sup>3</sup>Subcutaneous bortezomib is the preferred method of administration for patients with pre-existing or high-risk peripheral neuropathy.

<sup>4</sup>Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

<sup>5</sup>Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

<sup>6</sup>Triplet regimens should be used as the standard for patients with previously treated multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

<sup>7</sup>Optimal dosing in this regimen has not been defined.

<sup>8</sup>There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.


<sup>10</sup>Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
Newer Myeloma Drugs Are Associated With Better Clinical Response


![Graph showing the response rate of pts treated with different induction regimens. The x-axis represents the induction regimens (VAD, Dex, CTD, Thal-Dex, VCD, Len-Dex, VTD, VRDC, RVD, KRd). The y-axis represents the response rate of pts treated (%). The bars are color-coded with red for ≥ VGPR and green for OR. The graph illustrates the variation in response rates across different regimens.](image-url)
Phase IIIB UPFRONT Trial: VD, VTD, and VMP in Transplant-Ineligible MM Pts

8 cycles induction: VD, VTD, or VMP; 5 cycles of V maintenance
No statistically significant difference in survival outcomes
1-year PFS estimates: 57.4% (VD), 63.8% (VTD), 67.3% (VMP)
2-year OS estimates: 73.7% (VD), 73.6% (VTD), 77.6% (VMP)

Kaplan-Meier analysis of (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat population.
Phase IIIB UPFRONT Trial: VD, VTD, and VMP in Transplant-Ineligible MM Pts

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- No statistically significant difference in survival outcomes
  - 1-year PFS estimates: 57.4% (VD), 63.8% (VTD), 67.3% (VMP)
  - 2-year OS estimates: 73.7% (VD), 73.6% (VTD), 77.6% (VMP)

<table>
<thead>
<tr>
<th>Grade ≥ 3 AEs, %</th>
<th>VD Induction</th>
<th>VTD Induction</th>
<th>VMP Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 grade 3+ AE</td>
<td>74</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>19</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

### mSMART – Off-Study

**Transplant Eligible**

<table>
<thead>
<tr>
<th>Standard-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14), t(6;14), Trisomies</td>
<td>t(4;14)</td>
<td>Del 17p, t(14;16), t(14;20)</td>
</tr>
<tr>
<td>4 cycles of VRd</td>
<td>4 cycles of VRd</td>
<td>4 cycles of KRd</td>
</tr>
<tr>
<td>Collect Stem Cells (^a)</td>
<td>Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT</td>
<td>Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT</td>
</tr>
<tr>
<td>Autologous stem cell transplant (preferred)</td>
<td>VRd x 4 cycles</td>
<td></td>
</tr>
<tr>
<td>Len maintenance for at least 2 years (^b)</td>
<td>Rd until progression (^c)</td>
<td>Bortezomib-based maintenance for 2 years (^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carfilzomib or Bortezomib-based maintenance for 2 years (^b)</td>
</tr>
</tbody>
</table>

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\(^a\) If age > 65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor

\(^b\) Duration based on tolerance; consider risks and benefits for treatment beyond 2 years

\(^c\) Continuing Rd for patients responding to Rd and with low toxicities

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Treatment sequence

Induction

Consolidation

Post consolidation

Relapse

Front line treatment

Maintenance

Relapsed

OLD

VAD
DEX
SCT
Nothing
Prednisone
Thalidomide
Few options

NEW

VD
Rev/Dex
CyBorD
VRD
KRD
Dara-VMP
Dara-KRD
SCT
RD/VRD
Nothing
Thalidomide?
Bortezomib?
Lenalidomide?

Bortezomib
Lenalidomide
Carfilzomib
Pomalidomide
Daratumumab
Elotuzumab
Panobinostat
Bendamustine
Venetoclax
Nelfinavir
CAR T cells
The Expanding MM Therapeutic Armamentarium

**MM Therapies Introduction**
- 1958 Melphalan
- 1962 Prednisone
- 1969 Melphalan + prednisone
- 1983 Autologous transplantation
- 1986 High-dose dexamethasone (dex)

**FDA Approved in MM**
- 1986 High-dose dexamethasone (dex)
- 2003 Bortezomib 3rd line
- 2005 Bortezomib 2nd line
- 2006 Lenalidomide (len) + dex 2nd line
- 2006 Thalidomide + dex 1st line
- 2007 Doxorubicin + bortezomib 2nd line
- 2008 Bortezomib frontline
- 2012 Carfilzomib 3rd line
- 2014 Bortezomib retreatment
- 2015 Pomalidomide 3rd line
- 2015 Panobinostat 3rd line
- 2015 Ixazomib, Daratumab, Elozumab, Panobinostat

When to Consider Retreatment

• Differences between biochemical relapse and symptomatic relapse need to be considered.

• Patients with asymptomatic rise in M-protein can be observed to determine the rate of rise and nature of the relapse.
  – Caveat: patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse.

• CRAB criteria are still listed as the indication to treat in the relapsed setting—however, in patients with progression, treatment can avoid CRAB.
  – C: Calcium elevation (> 11.5 mg/L or ULN)
  – R: Renal dysfunction (serum creatinine > 2 mg/dL)
  – A: Anemia (Hb < 10 g/dL or 2 g < normal)
  – B: Bone disease (lytic lesions or osteoporosis)
Considerations in Patients With Relapsed/Refractory Myeloma

- Previous therapy
- Response to previous therapy
- Patient characteristics and other prognostic factors
  - Older than 65 yrs of age
  - Increased $\beta_2$-M, decreased serum albumin, low platelet count
  - Cytogenetic abnormalities: del(13q), t(4;14)
  - Renal dysfunction
    - Up to 50% of patients with MM have renal dysfunction
    - Between 20% and 30% of patients have concomitant renal failure
  - Extensive bone disease; extramedullary MM

**Therapy for relapsed disease**

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**NCCN Guidelines Version 2.2016**  
**Multiple Myeloma**

**MYELOMA THERAPY**

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

<table>
<thead>
<tr>
<th>Therapy for Previously Treated Multiple Myeloma</th>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repeat primary induction therapy (if relapse at &gt;6 mo)</td>
<td>• Bortezomib (category 1)</td>
<td>• Bendamustine</td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone</td>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td>• Bortezomib/lenalidomide/dexamethasone (category 1)</td>
<td>• Carfilzomib</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone</td>
<td>• Bortezomib/thalidomide/dexamethasone</td>
<td>• Carfilzomib/dexamethasone</td>
</tr>
<tr>
<td>• Carfilzomib</td>
<td>• Carfilzomib/dexamethasone</td>
<td>• Carfilzomib/lenalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td>• Carfilzomib/lenalidomide/dexamethasone (category 1)</td>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DECEP)</td>
<td>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</td>
</tr>
<tr>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DECEP)</td>
<td>• High-dose cyclophosphamide</td>
<td>• Lenalidomide/dexamethasone³ (category 1)</td>
</tr>
<tr>
<td>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</td>
<td>• Lenalidomide/dexamethasone³ (category 1)</td>
<td>• Panobinostat/bortezomib/dexamethasone¹⁰ (category 1)</td>
</tr>
<tr>
<td>• High-dose cyclophosphamide</td>
<td>• Panobinostat/bortezomib/dexamethasone¹⁰ (category 1)</td>
<td>• Pomalidomide¹¹/dexamethasone³ (category 1)</td>
</tr>
<tr>
<td>• Lenalidomide/dexamethasone³ (category 1)</td>
<td>• Pomalidomide¹¹/dexamethasone³ (category 1)</td>
<td>• Thalidomide/dexamethasone³</td>
</tr>
</tbody>
</table>

¹Selected, but not inclusive of all regimens.
²Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
³Prophylactic anti-coagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
⁴Consideration for appropriate regimen is based on the context of clinical relapse.
⁵Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.
⁶Indicated in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.
⁷Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

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**First Relapse Off-Study**

<table>
<thead>
<tr>
<th>Relapsing after Auto Transplant</th>
<th>Relapsing after Non-Transplant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Maintenance</td>
<td>On Therapy/ Maintenance</td>
</tr>
<tr>
<td>Off-therapy/ Unmaintained</td>
<td>Off-therapy/ Unmaintained</td>
</tr>
<tr>
<td>CyBorD if Rev maintenance; Rd, or KRd if Vel maintenance²</td>
<td>Not Eligible for ASCT</td>
</tr>
<tr>
<td>Rd or CyBorD if standard-risk²; CyBorD or Vrd if high risk²</td>
<td>Transplant Eligible</td>
</tr>
<tr>
<td>Not Eligible for ASCT</td>
<td>Auto SCT</td>
</tr>
<tr>
<td>Repeat first-line Rx if remission off therapy &gt;12months; if not, CyBorD if relapsing after IMiD based Rx; otherwise Pom/dex or KRd</td>
<td></td>
</tr>
</tbody>
</table>

*Consider 2nd auto if eligible and >18 months unmaintained or >36 months maintained response to first auto.

---

**Second or later Relapse**

**Off-Study**

**Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)**

- **Dual-Refractory** (Bortezomib and Lenalidomide)**²
- **Triple-Refractory** (Bortezomib, Lenalidomide and Carfilzomib)**²
- **Triple-Refractory** (Bortezomib, Len, and Pomalidomide)**²

- KRD or Pom/dex to maximum response or 18 months, then Rd
- PCD, PVO or Car-Pom-Dex to maximum response or 18 months, then Pom/dex
- KRD or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom/dex

* If single refractory refer to First Relapse algorithm; **Auto transplant is an option, if transplant candidate and feasible; Doublets such as Cy+Pred, Pd or Kd could be considered in patients with indolent disease.

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**MYEL-D**

(2 OF 2)

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## COMPARISON OF PHASE 3 TRIALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Overall Response(%)</th>
<th>Complete Response (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOURMALINE-1</td>
<td>IRd* vs Rd</td>
<td>78.5 vs 71.5</td>
<td>11.7 vs 6.6</td>
<td>20.6 vs 14.7</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>KRd vs Rd</td>
<td>87.1 vs 66.7</td>
<td>31.8 vs 9.3</td>
<td>26.3 vs 17.6</td>
</tr>
<tr>
<td>ELOQUENT-2</td>
<td>ERd vs Rd</td>
<td>79 vs 66</td>
<td>5 vs 9</td>
<td>19.4 vs 14.9</td>
</tr>
<tr>
<td>ENDEAVOR</td>
<td>Kd vs Vd</td>
<td>83 vs 66</td>
<td>11.6 vs 7.8</td>
<td>18.7 vs 9.4</td>
</tr>
<tr>
<td>CASTOR</td>
<td>DVd vs Vd</td>
<td>83 vs 63</td>
<td>19 vs 9</td>
<td>61% vs 27%</td>
</tr>
<tr>
<td>POLLUX</td>
<td>DRd vs Rd</td>
<td>93 vs 76</td>
<td>43 vs 19</td>
<td>78% vs 52%</td>
</tr>
</tbody>
</table>

*I = Ixazomib (Ninlaro); R = Lenalidomide (Revlimid); K = Carfilzomib (Kyprolis)*

*E = Elotuzumab (Empliciti); D = Daratumumab (Darzalex)
Treating Relapsed/Refractory Myeloma

**Carfilzomib-Based Salvage**
- Intolerance or resistance to bortezomib
- Dexamethasone-sparing treatment as part of a combination
- Intolerance to IMiDs

**Pomalidomide-Based Salvage**
- Lenalidomide refractory
- Refractory to standard-dose PI
- Pts with del(17p)?

**Other Salvage**
- Refractory to pomalidomide and carfilzomib
- Monoclonal antibody candidate
- Clinical trials
Treating Indolent, Slow-Growing Myeloma in First Relapse

IMiD-Based Salvage
- Initial treatment with bortezomib
- May consider single agent without dexamethasone
- Underlying PN

PI-Based Salvage
- Initial treatment with IMiD
- Previous bortezomib therapy but good or long response
- Renal dysfunction

Transplant-Based Salvage
- Transplant not part of initial therapy
- Long remission posttransplant
Treating Aggressive Myeloma With Rapid, Multiple Relapses

Likely Combination Therapy
Do Not Wait for Symptomatic Relapse

Chemotherapy-Based Salvage
- DCEP vs DT-PACE
- Oral vs IV chemo
- Performance status of pt plays important role

Chemotherapy + Novel Agent
- Combinations of lenalidomide/ bortezomib and other chemotherapy agents

Transplant-Based Salvage
- Likely to be short lived
- Rapid disease control
- Reconstitute marrow
mSMART 2.0: Classification of Relapsed MM

High-Risk
- Relapse <12 months from transplant or progression within first year of diagnosis
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- High risk GEP

Intermediate-Risk
- FISH
  - t(4;14)
  - 1q gain
- High PC S-phase

Standard-Risk
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)


v4 //last reviewed Dec 2015
First Relapse Off-Study

**On maintenance**
- Fit Patients
  - KPd or DVd if Rev maintenance
  - DRd if Vel maintenance
- Indolent Relapse or Frail patients
  - DVd or ICd if Rev maintenance
  - IRd or DRd if Vel maintenance

**Off-therapy/ Unmaintained**
- Fit Patients
- Indolent Relapse or Frail patients
  - IRd or Rd-Elo*

*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto;
Smoldering Myeloma: Background

• Smoldering MM currently defined as:
  – M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
  – Clonal plasma cells in BM 10% to 60%
  – No myeloma-defining events (≥ 1 CRAB feature or ≥ 1 biomarker of malignancy)

• Biomarkers of active myeloma
  – Clonal plasma cells in BM ≥ 60%
  – Serum FLC ratio ≥ 100
  – > 1 MRI focal lesion ≥ 5 mm on MRI
  – CRAB criteria

Risk of Progression in Pre-CRAB MM

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL above ULN)
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)


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GEM-CESAR: Phase II Study Design

- Multicenter, open-label trial

**Induction**
- 6 x 28-day cycles
- Patients with high-risk* smoldering MM (N = 90)
- Carfilzomib IV 20/36 mg/m² Days 1, 2, 8, 9, 15, 16
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg Days 1, 8, 15, 22

**Consolidation**
- 2 x 28-day cycles
- High-dose Melphalan 200 mg/m² followed by ASCT
- Carfilzomib IV 20/36 mg/m² Days 1, 2, 8, 9, 15, 16
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg Days 1, 8, 15, 22

**Maintenance**
- 24 x 28-day cycles
- Lenalidomide 10 mg Days 1-21
- Dexamethasone 20 mg Days 1, 8, 15, 22

- Primary endpoint: MRD negative rate (by flow cytometry) after induction, ASCT, consolidation/maintenance, and 3 and 5 yrs after maintenance

- Secondary endpoints: response, TTP, PFS, OS, safety

*High risk defined per Mayo and/or Spanish models (pre-2014 diagnostic criteria)

- Pts with both BM PCs ≥ 10% and serum M-protein ≥ 3g/dL, or 1 plus > 95% aberrant BM PCs by immunophenotyping plus immunoparesis

GEM-CESAR: Efficacy After KRd Consolidation and Rd Maintenance

<table>
<thead>
<tr>
<th>Response Category, n (%)</th>
<th>Induction (n = 71)</th>
<th>HDT ASCT (n = 42)</th>
<th>Consolidation (n = 35)</th>
<th>Maintenance (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>69 (98)</td>
<td>42 (100)</td>
<td>35 (100)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>sCR</td>
<td>21 (30)</td>
<td>22 (52)</td>
<td>24 (69)</td>
<td>24 (83)</td>
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<tr>
<td>CR</td>
<td>9 (13)</td>
<td>2 (5)</td>
<td>2 (6)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>VGPR</td>
<td>27 (38)</td>
<td>12 (29)</td>
<td>7 (20)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>PR</td>
<td>12 (17)</td>
<td>6 (14)</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>MRD negative, %</td>
<td>31</td>
<td>50</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Relapse from CR, n (%)</td>
<td>2 (3)</td>
<td>--</td>
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<tr>
<td>Clinical progression, n (%)</td>
<td>--</td>
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</tbody>
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