Management of Multiple Myeloma: The Changing Paradigm

Frontline Therapy for Newly Diagnosed Patients
Introduction: Example Patient Case

• Insert case details here to introduce a patient who will be undergoing treatment for newly diagnosed disease

• Use this encounter with a patient to set up the main points of the presentation
  – How it was determined that the patient had active myeloma and not smoldering multiple myeloma (SMM)
  – Treatments currently available
  – Treatments they received
  – How treatment was tolerated
  – What their final outcome was and over how long a time frame these events occurred

• At the end of the presentation, the details of how the patient case was treated and the patient’s outcome will be reported
Your Personal Treatment Plan: Partnering With Your Health Care Team

Your Overall Health and Characteristics of Your Myeloma

- Age and general health
- Other conditions
- Test results
- Symptoms

Your Preferences and Personal Goals

- Eliminate vs control disease
- Willingness to tolerate side effects
- Symptom relief
- Personal lifestyle/situation

No one treatment plan is right for everyone.
Goals of Therapy

- Achieving good response (≥VGPR)
- High response rate; rapid response
- Improve performance status
- Minimal side effects
Current Treatment Approaches: Smoldering Myeloma

No active treatment*

• Close monitoring: every 3–4 months (physical exam, possible blood/urine tests)
• Bisphosphonates for bone loss or damage (pamidronate or Zometa given intravenously)

*Promising but limited studies to date.

One phase 3 study of Revlimid + Dex followed by Revlimid maintenance in patients with high-risk SMM suggests a benefit; confirmatory study is under way.

Additional studies include: Empliciti* + Revlimid ± Dex; Darzalex* (3 doses); Siltuximab; Kyprolis + Revlimid + Dex; Pembrolizumab; Ninlaro + Dex; Kyprolis

Ask your doctor if you are a candidate for a clinical trial.
# Frontline Therapy: Standard Drug Overview

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Name</th>
<th>Abbreviation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMiD (immunomodulatory drug)</td>
<td>Revlimid (lenalidomide)</td>
<td>R or Rev</td>
<td>Oral</td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>Velcade (bortezomib)</td>
<td>V or Vel or B</td>
<td>Intravenous or subcutaneous injection (under the skin)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>C</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td></td>
<td>Evomela (melphalan)</td>
<td>M or Mel</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Decadron (dexamethasone)</td>
<td>Dex or D or d</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>
Current Treatment Approaches: Active Myeloma

Are you a candidate for an autologous stem cell transplant?

YES

3–4 cycles of therapy (induction)
- Triplets (generally preferred): RVD, VTD, CyBorD, VCD
- Doublets: Vel/dex, Rev/dex
- Clinical trial

High-dose chemotherapy (melphalan) and autologous transplant

Consolidation/maintenance?

Supportive care

NO

- Any of the regimens listed for transplant candidates
- Doublets option, particularly for patients with health/side effect concerns
- Clinical trial

For t(4;14): combination including Velcade (V) or Kyprolis is critical.
**Treatment Sequence for Active Myeloma**

**NCCN Category 1* Recommendations**

<table>
<thead>
<tr>
<th>Frontline treatment</th>
<th>Maintenance</th>
<th>Relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Observation</td>
<td>Rescue</td>
</tr>
<tr>
<td>Vel/Dex</td>
<td>Observation</td>
<td>Velcade</td>
</tr>
<tr>
<td>Vel/Dex/Dox</td>
<td>Revlimid</td>
<td>Vel/Doxil</td>
</tr>
<tr>
<td>Vel/Thal/Dex</td>
<td>Thalomid</td>
<td>Kprolis/Rev/Dex</td>
</tr>
<tr>
<td>Rev/Dex</td>
<td>Clinical trial</td>
<td>Empliciti/Rev/Dex</td>
</tr>
<tr>
<td>RVD</td>
<td></td>
<td>Ninlaro/Rev/Dex</td>
</tr>
<tr>
<td>Clinical trial</td>
<td></td>
<td>Rev/Dex</td>
</tr>
<tr>
<td>SCT</td>
<td></td>
<td>Farydak/Vel/Dex</td>
</tr>
<tr>
<td>Clinical trial</td>
<td></td>
<td>Pom/Dex</td>
</tr>
<tr>
<td>Clinical trial</td>
<td></td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

*Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Key Considerations for Optimal Disease Management

1. Know the standard of care
2. What to expect on therapy
3. Assessing your response to therapy
4. Maintenance options
5. Consider clinical trials
Revlimid in Frontline Therapy

**How is Revlimid administered?**
- Capsule; usually 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-molecular-weight heparin [LMWH]) are given along with Revlimid to reduce the risk of blood clots

**What are the possible side effects?**
- Potential for blood clots
- Reduced blood counts
  - Low white blood cells (neutropenia): infections
  - Low red blood cells: anemia
  - Low platelets (thrombocytopenia) blood clotting problems
- Rash
- Fatigue
- Muscle pain (myalgia)
- Diarrhea
- Small chance of second new cancers when given with melphalan

**What combinations are being studied?**
- Revlimid + Dex with Velcade or Kyprolis
- Revlimid + Dex ± Ninlaro
- Revlimid + Dex ± Darzalex
- Revlimid + Dex ± Empliciti
- Revlimid + Dex ± Pembrolizumab
Patients Taking Revlimid: Some Patients Are More Susceptible to Blood Clots

<table>
<thead>
<tr>
<th>Key Risk Factors for Blood Clots</th>
<th>Other Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Newly diagnosed active myeloma</td>
<td>• High level of myeloma cells</td>
</tr>
<tr>
<td>• Taking other medications:</td>
<td>• Older age</td>
</tr>
<tr>
<td>− Chemotherapy (melphalan,</td>
<td>• Other medical conditions such as infections</td>
</tr>
<tr>
<td>cyclophosphamide, Doxil)</td>
<td>or disease of the lung or kidney</td>
</tr>
<tr>
<td>− Dexamethasone</td>
<td>• Obesity</td>
</tr>
<tr>
<td>− Red blood cell growth factors for anemia (erythropoietin)</td>
<td>• Family history</td>
</tr>
<tr>
<td>• History of previous blood clots</td>
<td>• Thrombophilia, a condition where clots form easily</td>
</tr>
<tr>
<td></td>
<td>• Orthopedic procedures, such as hip or knee replacement</td>
</tr>
<tr>
<td></td>
<td>• Being immobilized (for example, confined to bed, long airplane trips)</td>
</tr>
<tr>
<td></td>
<td>• Presence of central venous catheter (a special catheter often used to administer cancer drugs)</td>
</tr>
</tbody>
</table>
What Can You Do To Prevent Blood Clots?

<table>
<thead>
<tr>
<th>Risk of Blood Clots*</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Aspirin</td>
</tr>
<tr>
<td>High risk†</td>
<td>LMWH (for example, Lovenox)</td>
</tr>
</tbody>
</table>

*Also applies to other IMiDs (ie, Thalomid, Pomalyst).
†Patients with many risk factors may receive other drugs, including Coumadin, Xarelto, Pradaxa, or Eliquis (ongoing phase 3 clinical trial evaluating the use of Eliquis in the prevention of thromboembolic disease in patients with myeloma treated with IMiDs).

Talk to your doctor to see what treatments are best for YOU.
# Velcade in Frontline Therapy

## How is Velcade administered?
- Options:
  - Injection under the skin (subcutaneous), once or twice weekly
  - Intravenous once or twice weekly

## What are the possible side effects?
- Peripheral neuropathy (numbness, tingling, burning sensations and/or pain due to nerve damage)
- Occurs less often when subcutaneous or once weekly dosing is used
- Low platelets (thrombocytopenia): blood clotting problems
- Gastrointestinal problems: nausea, diarrhea, vomiting, loss of appetite
- Fatigue
- Rash

## What combinations are being studied?
- Velcade + Mel + P ± Darzalex
- Revlimid + Dex with Velcade or Kyprolis
- Thalomid + Revlimid + Velcade + Zolinza
Understanding Peripheral Neuropathy

• Peripheral neuropathy is nerve damage that causes pain, tingling, burning sensations, and numbness in the hands and feet
  – Typically improves or resolves after treatment dose is reduced or treatment is stopped
• Risk of peripheral neuropathy varies
  – Greater risk if you have pre-existing neuropathy
  – Velcade dose and type of administration

Be sure to discuss the benefits and risks of taking Velcade with your doctor if you have severe pre-existing neuropathy.
Managing Peripheral Neuropathy

- Managed by reducing the Velcade dose (with no impact on effectiveness)
- Other possible ways to prevent or reduce symptoms (less proven):
  - Vitamins and other supplements*
  - Certain medications such as gabapentin (Neurontin)

*Do not take any supplements without consulting with your doctor.

Your health care team will check for peripheral neuropathy before treatment and prior to each dose of Velcade.

Be sure to tell your health care team about any symptoms you experience.
# Measuring Response to Therapy

## Degree (or depth) of response is usually associated with better prognosis.
Some patients do well despite never achieving a CR.

*By multiparametric flow cytometry; †Allele-specific oligonucleotide PCR

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Abbreviation</th>
<th>M-Protein Reduction</th>
<th>Tests</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood</td>
<td>Urine</td>
<td>Immunofixation</td>
</tr>
<tr>
<td>Complete response</td>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>sCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunophenotypic complete response</td>
<td>iCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Molecular complete response</td>
<td>mCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>VGPR</td>
<td>&gt;90%</td>
<td>&lt;100 mg/24 hrs</td>
<td>-</td>
</tr>
<tr>
<td>Partial response</td>
<td>PR</td>
<td>&gt;50%</td>
<td>&gt;90%</td>
<td>-</td>
</tr>
<tr>
<td>Stable disease</td>
<td>SD</td>
<td></td>
<td></td>
<td>Does not meet criteria for response or progressive disease</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>PD</td>
<td></td>
<td></td>
<td>An increase of 25% in M-protein; an increase of 10% in bone marrow plasma cells</td>
</tr>
</tbody>
</table>
Testing for Minimal Residual Disease (MRD): An Emerging Approach

Talk to your doctor about types of tests available in your area.

- At diagnosis
- Partial response – 50% reduction in M protein
- Near complete remission – immunofixation positive only
- Complete remission – immunofixation negative
- Nonquantitative ASO-PCR
- Quantitative ASO-PCR
- Flow cytometry

Number of Myeloma Cells

$1 \times 10^4$
$1 \times 10^6$
$1 \times 10^8$
$1 \times 10^{12}$
Should Patients Receive Maintenance Therapy as an Option?

• What are the benefits vs risks?
• Who should get maintenance therapy?
• How long should patients get maintenance therapy?

NINLARO
Oral proteasome inhibitor

VELCADE-BASED TREATMENT
Supported by several smaller studies

REVLIMID
Reduction in myeloma progression (3 large studies)
Improved survival (1 of 3 studies)
Small risk of second cancers when used after melphalan
Additional Drugs for Newly Diagnosed Disease

- A number of new agents—though they are not yet approved in the front-line setting by the FDA—are showing promise in clinical trials
  - Kyprolis and Ninlaro have been studied as components of an induction regimens such as KRD$^{1-3}$ or IRD$^{4}$ demonstrating highly encouraging response rates

- Early-stage trials are investigating the use of monoclonal antibodies Darzalex and Empliciti as part of four-drug induction combinations.
  - Although the addition of a fourth agent has not conferred an added survival benefit in previous trials, the use of both Darzalex and Emplicit as fourth agents have now shown enough promise to advance into phase 3 testing in the induction setting.

## Ongoing Clinical Studies for Newly Diagnosed Patients

<table>
<thead>
<tr>
<th>SMM</th>
<th>Active MM (Phase 3)</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients at High Risk of Disease Progression</strong></td>
<td><strong>Induction</strong> (Transplant Candidates)</td>
<td><strong>Induction</strong> (Nontransplant Candidates)</td>
</tr>
<tr>
<td>- Revlimid vs observation</td>
<td>- Revlimid + Dex with Velcade or Kyprolis*</td>
<td>- Velcade + Mel + P ± Darzalex*</td>
</tr>
<tr>
<td>- Empliciti* + Revlimid ± Dex</td>
<td>- Revlimid + Dex ± Ninlaro*</td>
<td>- Kyprolis* + Mel + P vs Velcade + Mel + P</td>
</tr>
<tr>
<td>- Darzalex* (3 doses)</td>
<td>- Revlimid + Dex ± Darzalex*</td>
<td>- Revlimid + Dex + Empliciti*</td>
</tr>
<tr>
<td>- Siltuximab†</td>
<td>- Revlimid + Dex ± Empliciti*</td>
<td>- Thalomid + Revlimid + Velcade + Zolinza‡</td>
</tr>
<tr>
<td>- Kyprolis* + Revlimid + Dex</td>
<td>- Darzalex*</td>
<td>- Pomalyst* + Dex ± Pembrolizumab†</td>
</tr>
<tr>
<td>- Pembrolizumab†</td>
<td>- Kyprolis* + Adriamycin + Dex vs Revlimid + Velcade + Dex</td>
<td>- Revlimid + Dex ± Pembrolizumab†</td>
</tr>
<tr>
<td>- Ninlaro* + Dex</td>
<td>- Revlimid + Dex ± Pembrolizumab†</td>
<td>- Revlimid + Dex ± Pembrolizumab†</td>
</tr>
<tr>
<td>- Kyprolis*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*FDA-approved for RR disease; †Experimental therapy not yet FDA approved; ‡FDA approved for a non-MM indication
Bold = MMRC trial
When Considering a Treatment Regimen, Find Out From Your Doctor...

- What treatment options should I consider?
- What lab values and test results are important to track for a response or to monitor for side effects?
- Is there a clinical trial that might be better suited for my type of myeloma or prognosis?
- Can I bank my bone marrow?*

*Tissue banking may not be an option at some oncology offices
Conclusion: Example Patient Case

• Revisit the patient case introduced at the start of the presentation
• Use the encounter with the patient to comment on:
  – How it was determined that the patient had active myeloma and not SMM
  – Treatments received
  – How treatment was tolerated
  – What the final outcome was and over how long a time-frame these events occurred
• If possible, include any specific words of encouragement from this (or any) patient about the process
Summary: Treating Newly Diagnosed Patients

• Smoldering multiple myeloma (SMM):
  – Close monitoring plus bisphosphonates for bone loss
  – Potential for treatment for high-risk patients; clinical trials ongoing

• Symptomatic (active) myeloma:
  – Combination therapies including Revlimid and/or Velcade, along with other drugs (triplets or doublets)
  – ASCT
  – Maintenance

• Side effects of therapy can be managed
• Research to improve up-front outcomes is ongoing

*Partner with your health care team to select the treatment plan that is right for you.*