Monoclonal gammopathy & Multiple myeloma
Clinical scenario

- 62 y/o woman admitted due to persisted low back pain for months.
- compression fracture s/p vertebroplasty
- pale conjunctiva
### Lab examination

<table>
<thead>
<tr>
<th>RBC</th>
<th>Hb</th>
<th>Hct</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
<th>Plt</th>
<th>WBC</th>
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<tr>
<td>M/ul</td>
<td>g/dl</td>
<td>%</td>
<td>fL</td>
<td>pg</td>
<td>g/dl</td>
<td>K/ul</td>
<td>K/ul</td>
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<td>7.8</td>
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<th>Baso</th>
<th>Mono</th>
<th>Lym</th>
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<tr>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<tr>
<td>73.7</td>
<td>1.1</td>
<td>1.4</td>
<td>10.1</td>
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<th>aPTT</th>
<th>INR</th>
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<td>17.8</td>
<td>36.9</td>
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<table>
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<th>BU N</th>
<th>Cr</th>
<th>Na</th>
<th>K</th>
<th>Ca</th>
<th>Alb</th>
<th>T.P.</th>
<th>T-bil</th>
<th>ALT</th>
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<tr>
<td>mg/dl</td>
<td>mg/dl</td>
<td>mEq/l</td>
<td>mEq/l</td>
<td>mEq/l</td>
<td>g/dl</td>
<td>g/dl</td>
<td>mg/dl</td>
<td>U/L</td>
</tr>
<tr>
<td>19</td>
<td>0.8</td>
<td>133</td>
<td>3.5</td>
<td>6.7</td>
<td>1.6</td>
<td>14.4</td>
<td>0.6</td>
<td>23</td>
</tr>
</tbody>
</table>
Brief history-x-ray
X-ray

RBC
Can this patient have different result?
Albumin/Globulin ratio

- Serum protein: albumin(50~60%), globulin, other proteins  <normally: A/G ratio slightly over 1>
- Low albumin/Globulin ratio (A/G reverse)
  - Albumin underproduction / loss
  - Disturbance in synthesis of immunoglobulins
    - Polyclonal gammopathy
    - Monoclonal gammopathy
Serum protein electrophoresis

Normal pattern on serum protein electrophoresis

Monoclonal protein

Polyclonal hump

“M spike”

gamma
Polyclonal gammopathy

- Inflammatory or reactive
  - Chronic liver disease, especially chronic active hepatitis (61%)
  - Connective tissue disease (22%)
  - Chronic infection (6%)
  - Lymphoproliferative disease (5%)
  - Non-hematologic malignancy (3%)
  - Others (3%)
Monoclonal gammopathy

- Plasma cells produce a homogenous monoclonal M protein
- Malignant or potential malignant

**Immunofixation**
Monoclonal gammopathy

Monoclonal Gammopathies
Mayo Clinic
1960-2008

n=39,929

- MGUS: 58% (23,179)
- Multiple myeloma: 17.5% (6,974)
- Amyloidosis: 9.5% (3,781)
- Lymphoproliferative: 3% (1,298)
- SMM: 4% (1,494)
- Solitary or extramedullary: 2% (774)
- Macro: 2% (940)
- Other: 4% (1,489)
Mechanisms of disease progression

Figure 1. Mechanisms of Disease Progression in the Monoclonal Gammopathies.
# Multiple pathogenesis of MM

## Multistep progressive disease

### Cytogenetic abnormalities
- **Hyperdiploidy** (50% of patients)
- **Non-hyperdiploidy** (50% of patients)

### Other molecular alterations
- **Increased expression of cyclin D1, D2, and D3**
- **Oncogenic activation or mutation (RAS, FGFR3)**
- **MYC dysregulation, TP53 mutation**

## Bone marrow microenvironment

## Bone resorption

## Angiogenesis

**Figure 1.** Multistep Pathogenesis of Multiple Myeloma.
M protein <3g/dl and \[ \geq 3g/dl \text{ or} \]
Bone Marrow <10% Plasma cells \[ \geq 10\% \text{ Plasma cells} \]
Clinical Picture Asymptomatic No end-organ damage Asymptomatic No end-organ damage Symptomatic End-organ damage present
Therapy Observation only Observation only Therapy required
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td><strong>MGUS</strong></td>
<td>All 3 criteria must be met:</td>
</tr>
<tr>
<td></td>
<td>• Serum monoclonal protein $&lt; 3$ g/dL</td>
</tr>
<tr>
<td></td>
<td>• Clonal BM plasma cells $&lt; 10%$, and</td>
</tr>
<tr>
<td></td>
<td>• Absence of end-organ damage such as (CRAB)</td>
</tr>
<tr>
<td><strong>Smoldering multiple myeloma</strong></td>
<td>Both criteria must be met:</td>
</tr>
<tr>
<td><em>asymptomatic</em></td>
<td>• Serum monoclonal protein (IgG or IgA) $\geq 3$ g/dL and/or clonal BM plasma cells $\geq 10%$, and</td>
</tr>
<tr>
<td></td>
<td>• Absence of end-organ damage</td>
</tr>
<tr>
<td><strong>Multiple Myeloma</strong></td>
<td>All 3 criteria must be met except as noted:</td>
</tr>
<tr>
<td></td>
<td>• Clonal BM plasma cells $\geq 10%$</td>
</tr>
<tr>
<td></td>
<td>• Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma), and</td>
</tr>
<tr>
<td></td>
<td>• Evidence of end organ damage due to plasma cell proliferative disorder</td>
</tr>
</tbody>
</table>
**CRAB**

- **HyperCalcemia:** Serum calcium ≥11.5 mg/dL
- **Renal insufficiency:** Serum creatinine >2 mg/dl)
- **Anemia:** Normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL
- **Bone lesions:** Lytic lesions, severe osteopenia, or pathologic fractures
Disease status

- Monoclonal gammopathies of Undetermined Significance (MGUS)
- Smoldering MM
- Symptomatic MM
Monoclonal gammopathies of Undetermined Significance (MGUS)
age-adjusted prevalence
Monoclonal gammopathies of Undetermined Significance (MGUS)

- Median age at diagnosis: 70 years
- IgG (70%): most common
- Kappa (62%): more common than lambda
- Risk of progression: 1% per year

Risk of progression
Predictors of Malignant Transformation in MGUS

- Serum M protein at the time of diagnosis
  (x2 risk with every 1 g/dl increment in M protein)
- Non-IgG MGUS (IgA, IgM)
- Abnormal FLC (free light chains) ratio
- Bone marrow plasma cell (BMPC) content
- Presence of circulating plasma cells in PB
Risk factors for progression of MGUS

- Serum M spike < 1.5 g/dL
- IgG subtype
- Normal FLC ratio

Blood. 2005; 106:812-817
Monoclonal gammopathies of Undetermined Significance (MGUS)

- Smoldering MM
- Symptomatic MM
Smoldering (Asymptomatic) Multiple Myeloma

- ~15% of newly diagnosed MM
- Risk of progression is higher
- No survival advantage from chemotherapy before symptomatic disease
- Close follow-up once every 3 to 6 months
- Early therapy with bisphosphonates, thalidomide, and lenalidomide to delay progression? ongoing clinical trials
Progression probability

![Graph showing progression probability over years since diagnosis for Smoldering Multiple Myeloma and MGUS]

Probability of Progression - Smoldering to symptomatic

abnormal FLC ratio
BM plasma cells >10%
serum M protein >3 g/dl
Monoclonal gammopathies of Undetermined Significance (MGUS)

- Smoldering MM
- Symptomatic MM
Multiple Myeloma

Sarah Newbury, the first reported patient with multiple myeloma

Blood. 2008;111:2962-2972
History

1844
First documented case

1845
Abnormal urine protein, later termed Bence Jones protein


1895
Description of plasma cells

1928
First large case series of myeloma

1939
Serum protein spike identified

1956
Light chain types (later termed kappa and lambda) recognized

1975
Durie-Salmon staging system

2005
International staging system

2005
Cytogenetic classification

1947
Melphalan (N. Blokhin)

1958
Corticosteroids (R. E. Maas)

1962
Autologous transplantation (T. J. McElwain and R. L. Powles)

1999
Thalidomide (S. Singhal and B. Barlogie)

2002
Bortezomib (R. Z. Orlowksi)

2002
Lenalidomide (P. G. Richardson and K. C. Anderson)

Treatment
Multiple Myeloma

- Clonal proliferation of malignant plasma cells
- Incidence:
  - 4.5 per 100,000 per year in United States
  - Blacks > Whites; Male > female
  - Taiwan: 1.41/100,000 per year (2003)
  - 1% of all malignancies
  - 10% of all hematologic malignancies
- Median age at diagnosis: 71 years
Etiology

- Radiation exposures
  - atomic bomb
  - radiation-related occupation
- Workplace exposures
  - agricultural occupations
  - benzene
- Lifestyle factors
  - cigarette smoking and alcohol
  - socioeconomic status
  - hair dyes
- Precursor medical conditions
  - MGUS
  - chronic antigenic stimulation
  - viral infection (HIV, HCV, HHV8)
Clinical Manifestations

- Bone lesions: 79%
- Bone pain: 66%
- Hb<12 g/dl: 73%
- Fatigue: 32%
- Cr>2 mg/dl: 19%
- Ca>11 mg/dl: 13%
- Wt loss (>9kg): 12%

Percent of patients
Anemia

- Normochromic, normocytic anemia in most patients
  - Bone marrow replacement/infiltration
  - Kidney damage (relative erythropoietin deficiency)
  - Cytokines, like TNF-α and IL-1, may inhibit erythropoiesis
Hypercalcemia

- anorexia, N/V, polyuria, polydipsia, increased constipation, weakness, confusion, or stupor…

Management

- Vigorous hydration (isotonic saline)
- Biphosphonate: pamidronate, zoledronic acid
- Corticosteroids
- Calcitonin (for rapid reduction of calcium or refractory to bisphosphonates alone)
- Hemodialysis
Monoclonal proteins

- Over-production of immunoglobulin or fragment
  - IgG: 52%
  - IgA: 20%
  - Free light chain only: 16%
  - IgD: 2%
  - IgM: <1% (MGUS, lymphoma, WM, amyloidosis)

- 90%: reductions at least 1 of uninvolved Ig
- 97%: either an intact Ig or a free light chain by SPEP
- Non-secretory myeloma: no identifiable M component (~1 to 3%)
Bone Disease

- 75%: punched-out lytic lesions, osteoporosis, or fractures
- Vertebrae, skull, ribs, sternum, proximal humerus, femur (long bones) most frequently
- Bone pain is not commonly precipitated by movement
  - the proliferation of tumor cells
  - activation of osteoclasts that destroy bone
  - suppression of osteoblasts that form new bone
- X-ray is superior to Tc-99m MDP bone scan
- Tc-99m sestamibi scans (MIBI): as sensitive as plain radiographs
Therapy of myeloma bone disease

- **Biphosphonates**
  - Inhibit dissolution of the hydroxyapatite crystals
  - Down regulate the major osteoclast functions
  - Reduce the likelihood of a skeletal event about 50%

- Pamidronate or zoledronic acid: 1 or more lytic lesions on skeletal radiography

- Adverse events: pyrexia, renal function impairment, myalgias, hypocalcemia, osteonecrosis of the jaw (ONJ)
Figure 1. Time to the Onset of Osteonecrosis of the Jaw in Patients with Myeloma Receiving Zoledronic Acid or Pamidronate.

Among patients receiving zoledronic acid, the occurrence of osteonecrosis of
Renal insufficiency

- Causes: *cast nephropathy* (myeloma kidney) and *hypercalcemia*
- Dehydration, hyperuricemia, nephrotoxic drugs
- Bence Jones proteinuria or IgD myeloma: highest rate of renal insufficiency
- Metabolic acidosis
- Myeloma kidney: tubular > glomeruli diseases
- Management: maintain high urinary output in those with high monoclonal light chains in the urine, treat underlying problem
Infection

- High risk of bacterial infections
- Bacterial sepsis: 0.8~1.4 infection / patient / year
- Tumor fever is rare in myeloma patients
- Encapsulated organisms: *S. pneumoniae, H. influenzae*
  → receive vaccinations
- Staphylococcus aureus & GNB increased markedly after diagnosis → responsible > 90% of deaths from infection
Hemostatic abnormalities

- Bleeding is more common
  - Thrombocytopenia
  - Uremia
  - Hyperviscosity
  - Interference with coagulation factors
Investigation if suspected myeloma

- H&P
- CBC, differential, platelet count
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24 h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]
## Diagnostic criteria for MM

- **Monoclonal protein in serum and/or urine**
- **Clonal BM plasma cells or plasmacytoma**
- **Myeloma-related organ or tissue impairment**
  - CRAB
  - Symptoms of hyperviscosity; amyloidosis; recurrent bacterial infection

International Myeloma Working Group
# Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Durie-Salmon Criteria</th>
<th>ISS Criteria</th>
</tr>
</thead>
</table>
| I     | All of the following:  | Serum beta-2 microglobulin < 3.5 mg/L  
|       | - Hemoglobin value > 10 g/dL | Serum albumin ≥ 3.5 g/dL  
|       | - Serum calcium value normal or ≤ 12 mg/dL |  
|       | - Bone x-ray, normal bone structure) or solitary bone plasmacytoma only |  
|       | - Low M-component production rate |  
|       |   - IgG value < 5 g/dL; |  
|       |   - IgA value < 3 g/dL |  
|       |   - Bence Jones protein < 4 g/24 h |  
| II    | Neither stage I nor stage III | Neither stage I nor stage III |
| III   | One or more of the following: | Serum beta-2 microglobulin ≥ 5.5 mg/L  
|       | - Hemoglobin value < 8.5 g/dL |  
|       | - Serum calcium value > 12 mg/dL |  
|       | - Advanced lytic bone lesions |  
|       | - High M-component production rate |  
|       |   - IgG value > 7 g/dL; |  
|       |   - IgA value > 5 g/dL |  
|       |   - Bence Jones protein > 12 g/24 h |  

**Subclassification Criteria**

- **A** Normal renal function (serum creatinine level < 2.0 mg/dL)
- **B** Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)
Prognosis

- Median survival: 3 years

### TABLE 3. International Staging System for Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Frequency (% of patients with myeloma)*</th>
<th>Median survival (mo)</th>
<th>Proportion of patients with Durie-Salmon stage III myeloma (%)</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
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<tr>
<td>Serum albumin ≥3.5 g/dL and serum β₂-microglobulin &lt;3.5 µg/mL</td>
<td>29</td>
<td>62</td>
<td>38</td>
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<tr>
<td>Stage II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither stage I nor III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum β₂-microglobulin ≥5.5 µg/mL</td>
<td>34</td>
<td>29</td>
<td>70</td>
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</tbody>
</table>
NCCN Guidelines Version 1.2013
Multiple Myeloma

CLINICAL PRESENTATION
Smoldering (asymptomatic)\(^a,b,c\)

PRIMARY TREATMENT
Observe at 3-6 mo intervals (category 1) or Clinical trial

FOLLOW-UP/SURVEILLANCE
- Quantitative immunoglobulins + quantitation of M protein (serum and urine)
- CBC, differential, platelets
- BUN, creatinine, calcium
- Bone survey annually or for symptoms
- Bone marrow aspirate and biopsy as clinically indicated
- Serum free light chain assay as clinically indicated
- MRI as clinically indicated
- PET/CT scan as clinically indicated
- Multi-parameter flow cytometry as clinically indicated

Progression to symptomatic myeloma\(^d\)

See Active (symptomatic) Myeloma below

Active (symptomatic)\(^a,d\)

Myeloma therapy\(^f\), bisphosphonates\(^g\) + adjunctive treatment\(^g\) as indicated

Stem-cell harvest (adequate for 2 transplants), if candidate for transplantation (Refer for evaluation by stem cell transplant center)

Response\(^e\) →

See Response After Primary Therapy (MYEL-4)

No response\(^e\) →

See Additional Treatment (MYEL-6)
Response after therapy

**ACTIVE (SYMPTOMATIC) MYELOMA**

- Response after primary therapy
  - Autologous stem cell transplant (category 1)
  - OR
  - Allogeneic stem cell transplant in clinical trial
  - OR
  - Continue myeloma therapy until best response

**FOLLOW-UP/SURVEILLANCE**

- Quantitative immunoglobulins + quantitation of M protein at least every 3 mo
- CBC, differential, platelets
- BUN, creatinine, calcium
- Bone survey annually or for symptoms
- Bone marrow aspirate and biopsy as clinically indicated
- Serum free light chain assay as clinically indicated
- MRI as clinically indicated
- PET/CT scan as clinically indicated

Monitor as above and/or maintenance therapy
### Treatment

**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>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Therapy for Transplant Candidates</strong> (Assess for response after 2 cycles)</td>
<td><strong>Primary Therapy for Non-Transplant Candidates</strong> (Assess for response after 2 cycles)</td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone (category 1)</td>
<td>• Bortezomib/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Lenalidomide/low-dose dexamethasone (category 1)</td>
</tr>
<tr>
<td>• Bortezomib/doxorubicin/dexamethasone (category 1)</td>
<td>• Melphalan/prednisone/bortezomib (MPB) (category 1)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide&lt;sup&gt;4&lt;/sup&gt;/dexamethasone</td>
<td>• Melphalan/prednisone/lenalidomide (MPL) (category 1)</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone (category 1)</td>
<td>• Melphalan/prednisone/thalidomide (MPT) (category 1)</td>
</tr>
<tr>
<td>• Lenalidomide&lt;sup&gt;4&lt;/sup&gt;/dexamethasone (category 1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance Therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bortezomib</td>
<td>• Interferon (category 2B)</td>
</tr>
<tr>
<td>• Lenalidomide&lt;sup&gt;5&lt;/sup&gt; (category 1)</td>
<td>• Steroids (category 2B)</td>
</tr>
<tr>
<td>• Thalidomide (category 1)</td>
<td>• Thalidomide + prednisone (category 2B)</td>
</tr>
</tbody>
</table>

NCCN Guidelines Version 1.2013
Thalidomide

- Immune modulatory drugs (IMiDs)
  - Antiangiogenic
  - Modulate adhesion molecules of myeloma cells and their surrounding stroma
  - Modulate cytokines
  - Affect natural killer cells
- Adverse effects: sensory neuropathy, constipation, fetal malformation, fatigue, somnolence, skin problems, Steven-Johnson syndrome, hepatitis
Lenalidomide (Revlimid)

- A small-molecule derivative of thalidomide
- IMiD class
- More potent and much more expensive
- Induces apoptosis of myeloma cells
- Anti-angiogenesis
- Stimulates host anti-myeloma T- and natural killer cell immunity
- Adverse effects: myelosuppression, neuropathy, fatigue
Bortezomib (Velcade)

- Proteasome inhibitor
- Myeloma cells: dependent on proteasome-regulated proteins for their growth and interaction with stromal cells
  - Growth arrest, induce apoptosis, inhibit angiogenesis
- Adverse events: GI disturbance (diarrhea), peripheral neuropathy, myelosuppression, fatigue
Bortezomib - A Proteasome Inhibitor

Modified from Cancer Treat Rev. 2003, May Suppl1:33-39
Treatment

- mSMART (Mayo Stratification for Myeloma And Risk-adapted Therapy)

- A consensus opinion: genetically determined risk status and the various treatment strategies

mSMART 2.0: Classification of Active MM

High-Risk

- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk*

- FISH
  - t(4;14)‡
- Cytogenetic Deletion 13 or hypodiploidy
- PCLI >3%

Standard-Risk*†

- All others including:
  - Hyperdiploid
  - t(11;14)**
  - t(6;14)

* Note that a subset of patients with these factors will be classified as high-risk by GEP
† LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis
‡ Prognosis is worse when associated with high beta-2 M and anemia
**t(11;14) may be associated with plasma cell leukemia

Kumar et al. Mayo Clin Proc 2009 84:1095-1110,
Revised and updated: June 2010
Newly Diagnosed Myeloma Eligible for Transplantation

**High Risk**
- VRD x 4 cycles
- ASCT
  - Bortezomib-based maintenance

**Intermediate Risk**
- VCD x 4 cycles
- ASCT; 2nd ASCT if not in CR or VGPR
  - Bortezomib maintenance for 2 years

**Standard Risk**
- Rd x 4 cycles
- Early ASCT
- Delayed ASCT
  - Lenalidomide maintenance if not in CR or VGPR following ASCT

*For patients who choose delayed ASCT, dexamethasone usually discontinued after 12 months, and continued long-term lenalidomide is an option for patients who are tolerating treatment well.*
Newly Diagnosed Myeloma Not Eligible for Transplantation

High Risk
- VRD x one year
  - Bortezomib maintenance

Intermediate Risk
- VCD x one year
  - Bortezomib maintenance for 2 years if possible

Standard Risk
- Rd*

*Dexamethasone usually discontinued after 12 months; continued long-term lenalidomide is an option for patients who are tolerating treatment well.
## Response criteria

### RESPONSE CRITERIA FOR MULTIPLE MYELOMA

**International Myeloma Working Group Uniform Response Criteria - CR and Other Response Categories**

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR, stringent complete response</td>
<td>CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow (^2) by immunohistochemistry or immunofluorescence (^3)</td>
</tr>
<tr>
<td>CR, complete response</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow (^2)</td>
</tr>
<tr>
<td>VGPR, very good partial response</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level &lt; 100 mg per 24 h</td>
</tr>
</tbody>
</table>
| PR, partial response              | ≥ 50% reduction of serum M-protein and reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h  
If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria  
If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%  
In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required |
<p>| SD, stable disease (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates) | Not meeting criteria for CR, VGPR, PR or progressive disease |</p>
<table>
<thead>
<tr>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response criteria for multiple myeloma</strong></td>
</tr>
<tr>
<td><strong>International Myeloma Working Group Uniform Response Criteria - Disease Progression and Relapse</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse Subcategory</th>
<th>Relapse Criteria</th>
</tr>
</thead>
</table>
| Progressive disease | Progressive Disease: requires any one or more of the following:  
  - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)  
  - Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)  
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.  
  - Bone marrow plasma cell percentage: the absolute % must be ≥ 10%  
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas  
  - Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder |
| Clinical relapse | Clinical relapse requires one or more of:  
  - Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice  
  - Development of new soft tissue plasmacytomas or bone lesions  
  - Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion  
  - Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L]  
  - Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L]  
  - Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more] |
| Relapse from CR | Any one or more of the following:  
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis  
  - Development of ≥ 5% plasma cells in the bone marrow  
  - Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) |

NCCN Guidelines Version 1.2013
Take home message

- Multiple pathogenesis of disease development
- MGUS: M protein < 3g/dl, BM plasma cell < 10%
- Smoldering MM: M protein > 3g/dl or plasma cell > 10%
- Multiple myeloma: CRAB
- Treatment choice: based on if candidate for Autologous SCT
Thanks for your attention!