MGUS, Smoldering Myeloma and Monoclonal Gammopathies of Renal Significance

Omar Nadeem, MD
Clinical Director, Myeloma Immune Effector Cell Therapy and Center for Prevention of Progression
Multiple Myeloma Division
Dana-Farber Cancer Institute
Instructor of Medicine
Harvard Medical School
Omar Nadeem, MD

- Medical School: Ross University School of Medicine
- Residency: Dartmouth-Hitchcock Medical Center
- Fellowship: Brown University
- Instructor of Medicine at HMS
- Clinical Focus: Multiple myeloma (precursor, newly diagnosed, relapsed and refractory)
- Research focus: precursor plasma cell disorders, immunotherapeutic approaches
Disclosures

I have the following financial disclosures:

Advisory Board Participation: Janssen, BMS, Karyopharm, Takeda, GSK, Adaptive Biotechnologies, GPCR therapeutics
Research Funding: Takeda, Janssen
Objectives

- Review classification and incidence of plasma cell disorders
- Discuss risk stratification models in smoldering multiple myeloma
- Review previous and ongoing clinical trials of early therapeutic intervention in SMM
- Review practical, real-world management guidelines in MGRS
**Plasma Cell Disorders: Classification**

Updated IMWG criteria for diagnosis of multiple myeloma

<table>
<thead>
<tr>
<th><strong>MGUS</strong></th>
<th><strong>Smoldering myeloma</strong></th>
<th><strong>Multiple myeloma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• M protein &lt;3 g/dL</td>
<td>• M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)</td>
<td>• Underlying plasma cell proliferative disorder AND</td>
</tr>
<tr>
<td>• Clonal plasma cells in bone marrow &lt;10%</td>
<td>• Clonal plasma cells in bone marrow ≥10% to 60%</td>
<td>• 1 or more myeloma-defining events</td>
</tr>
<tr>
<td>• No myeloma-defining events</td>
<td>• No myeloma-defining events</td>
<td>• ≥1 CRAB* feature</td>
</tr>
</tbody>
</table>

* C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance <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)
MGUS is a Very Common Condition

- 3% of the general population at age 50 has MGUS
- This rate is 3 times higher for individuals of African descent
- This rate is 2–3 times higher for first-degree family members of myeloma patients
Current standard of care is to observe only for low- and intermediate-risk patients.

**SMM**

- Non-IgG M protein
- Abnormal serum free light chain ratio
- M protein >1.5 g/dL
Smoldering Multiple Myeloma: Heterogeneous Disease

- 51% will convert to MM in first 5 years (~10%/yr)
- 27% more will convert to MM in remaining 15 years (~2%/yr)
Risk Assessment in Smoldering Myeloma

**Mayo risk model**
Plasma cell bone marrow infiltration, serum M-component level, and serum free light chain ratio

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>N</th>
<th>Rel. Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>114</td>
<td>1.9 (1.2−2.9)</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>4.0 (2.6−6.1)</td>
</tr>
</tbody>
</table>

\( P=0.001 \)

Probability of Progression (%)

Years of Follow-Up

50% risk at 2 yrs
35% risk at 2 yrs
5% risk at 2 yrs

**Spanish model**
Aberrant PCs by immunophenotype plus immunoparesis

- >95% aPC/BMPC + paresis
- >95% aPC/BMPC or paresis
- No adverse factors

\( P=0.003 \)

% Time to Progression

Months

50% risk at 2 yrs
35% risk at 2 yrs
5% risk at 2 yrs
2/20/20 Model to Identify High-Risk SMM Patients

Risk assessment for SMM:
- 2 >2 g/dl M protein
- 20 >20 free light chain ratio
- 20 >20% bone marrow plasma cells

High-risk group (2–3 risk factors) 44.2%
Intermediate-risk group (1 risk factor) 17.9%
Low-risk group (no risk factors) 6.2%

Model does not include any biological or immune factors that may account for interpatient heterogeneity.

Developing a Risk Score Tool (n=689 pts)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLC Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>0.00</td>
<td>1.08 (0.97, 1.21)</td>
<td>0.154</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>0.00</td>
<td>1.02 (0.93, 1.11)</td>
<td>0.564</td>
<td>2</td>
</tr>
<tr>
<td>50-69</td>
<td>1.10</td>
<td>3.17 (2.40, 4.17)</td>
<td>&lt;0.001</td>
<td>8</td>
</tr>
<tr>
<td>NC (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 (reference)</td>
<td></td>
<td>1.00</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5-10</td>
<td>0.06</td>
<td>1.38 (1.04, 1.83)</td>
<td>0.002</td>
<td>5</td>
</tr>
<tr>
<td>10-15</td>
<td>1.29</td>
<td>3.23 (2.40, 4.38)</td>
<td>&lt;0.001</td>
<td>8</td>
</tr>
<tr>
<td>BMPCIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 (reference)</td>
<td></td>
<td>1.00</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>11-20</td>
<td>0.37</td>
<td>1.77 (1.31, 2.38)</td>
<td>0.024</td>
<td>1</td>
</tr>
<tr>
<td>21-30</td>
<td>1.15</td>
<td>3.14 (2.31, 4.28)</td>
<td>0.002</td>
<td>5</td>
</tr>
<tr>
<td>31-40</td>
<td>1.57</td>
<td>5.32 (3.75, 7.53)</td>
<td>&lt;0.001</td>
<td>10</td>
</tr>
<tr>
<td>41-50</td>
<td>2.00</td>
<td>7.42 (5.11, 11.30)</td>
<td>0.001</td>
<td>16</td>
</tr>
</tbody>
</table>

*689 of the original 1228 had complete data for all risk factors

<table>
<thead>
<tr>
<th>Total Risk Score</th>
<th>Predicted risk at 2 years</th>
<th>% of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.2</td>
<td>11.6</td>
</tr>
<tr>
<td>2</td>
<td>6.2</td>
<td>8.1</td>
</tr>
<tr>
<td>3</td>
<td>8.5</td>
<td>11.0</td>
</tr>
<tr>
<td>4</td>
<td>11.6</td>
<td>4.2</td>
</tr>
<tr>
<td>5</td>
<td>15.7</td>
<td>14.4</td>
</tr>
<tr>
<td>6</td>
<td>20.8</td>
<td>8.4</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>8.4</td>
</tr>
<tr>
<td>8</td>
<td>34.3</td>
<td>8.7</td>
</tr>
<tr>
<td>9</td>
<td>42.5</td>
<td>5.3</td>
</tr>
<tr>
<td>10</td>
<td>51.1</td>
<td>6.2</td>
</tr>
<tr>
<td>11</td>
<td>59.3</td>
<td>4.0</td>
</tr>
<tr>
<td>12</td>
<td>67.5</td>
<td>3.1</td>
</tr>
<tr>
<td>13</td>
<td>74.8</td>
<td>2.3</td>
</tr>
<tr>
<td>14</td>
<td>80.3</td>
<td>2.0</td>
</tr>
<tr>
<td>15</td>
<td>85.4</td>
<td>3.7</td>
</tr>
<tr>
<td>&gt;15</td>
<td>89.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Scores < 5 would give an 96% NPV (4% false negative). While score >12…72% risk at 2y

**IMWG Risk Score Tool**: Addition of High Risk FISH further adds to risk stratification

Risk score to predict progression risk at 2 years

**Developing a Risk Score Tool (n=689 pts)**

<table>
<thead>
<tr>
<th>Risk Stratification Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>7.56 (3.77 to 15.2)</td>
<td>0-4</td>
</tr>
<tr>
<td>5-8</td>
<td>17.5 (8.63 to 35.4)</td>
<td>5-8</td>
</tr>
<tr>
<td>9-12</td>
<td>31.9 (15.4 to 66.6)</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

**Total Risk score 2 year progression (%)**

Scores < 5 would give an 96% NPV (4% false negative). While score >12…72% risk at 2y
Can we identify everyone who has a precursor condition?
Nationwide Screening Studies

Iceland

United States and Canada

THE PROMISE STUDY
4.9% of individuals screened have MGUS

10.8% of individuals screened have SMM; SMM prevalence is 0.53%

One third of SMM patients have an intermediate or high risk* of progression to myeloma

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow. Thorsteinsdottir S et al. Blood. 2021;138. Abstract 151.
After 3 years of follow-up, active screening identifies a significantly higher number of individuals with malignancies and smoldering disease.

MGUS was not associated with COVID-19 susceptibility or COVID-19 severity.

These findings suggest that immunosuppression in MGUS is different than in myeloma.
Promise Study Eligibility Criteria

2 groups of U.S. adults, age 30 or older, qualify for a free screening:
1. African Americans
   AND / OR
2. People of Any Race Who Have a Parent, Sibling, or Child with:
   Multiple myeloma, another blood cancer, OR one these related conditions:
   • Monosomy D of Undetermined Significance (MDSU) 1
   • Secondary Multiple Myeloma 1
   • Waldenström Macroglobulinemia 1

We are also enrolling individuals who are 18 years of age or older and have a strong family history of blood cancer (2 or more first- and second-degree relatives).

Please sign up for the study if you qualify.

Note: The PROMISE study is for people who may have higher risk, but have not been diagnosed with any of these conditions.

If you have been diagnosed with one of these conditions, please visit our PCROAD study website to connect the people with precursor conditions.
High Prevalence of Monoclonal Gammopathy in a Population at Risk

**The PROMISE Study**

- 7,622 individuals screened*
- 6,305 patients
- 1,317 patients

**High-risk features for MM**
- Blacks (n=2,439)
- Non-Blacks with family history of HM (n=3,866)

**No high-risk features for MM**
- Negative family history of HM (n=631)
- Unknown family history of HM (n=686)

MGUS estimated in 13% to 17% of a high-risk screened population (rates increase with age).

Higher detection rates of free light chains by mass spectrometry than conventional methods.

Older adults who are Black or have a first-degree relative with a HM have an increased prevalence for MGUS.

Older individuals who are Black or have a first-degree relative with a HM may benefit from screening to allow for early detection and possible clinical intervention.

Defining Outcomes and Results

MGUS by SPEP/IFX

Confirmatory LC-MS testing

MS-MGUS

MS-MGIP

SPEP, serum protein electrophoresis; IFX, immunofixation; MS-MGUS, mass spectrometry-monoclonal gammopathy of undetermined significance; MS-MGIP, mass spectrometry-monoclonal gammopathies of indeterminate potential; LC-MS, light chain mass spectrometry
Rates of all monoclonal gammopathies* increase with age.

MGUS more prevalent in individuals older than 50 years at risk.

Higher rates of MGUS* in Blacks or individuals with a family history of HM and older than 50 years at risk.

*Free light chains detected by mass spectrometry.

HM, hematologic malignancy; MGUS, monoclonal gammopathy of undetermined significance; MGIP, monoclonal gammopathies of indeterminate potential; LC, light chain; SPEP, serum protein electrophoresis; IFX, immunofixation; MS, mass spectrometry; MGBB, Mass General Brigham Biobank.

Therapeutic Intervention for SMM
Overview of Treatment Approach

MGUS

Close monitoring (observation)

SMM

Close monitoring (observation)

If high risk:
possible myeloma drugs?*

If bone loss:
bone-targeting agents

Clinical trial participation should be considered

*Promising but only available as clinical trials.
Evolution of Myeloma Therapy

- **1962**: Oral melphalan and prednisone
- **1983**: High-dose melphalan
- **1984**: VAD
- **1986**: High-dose dexamethasone
- **1996**: Thalidomide
- **1999**: High-dose therapy with autologous stem cell support as consolidation
- **2000**: Lenalidomide, bortezomib, liposomal doxorubicin
- **2010**: Pomalidomide, Carfilzomib, Ixazomib, Panobinostat, Elotuzumab, Daratumumab, Selinexor
- **2020**: Isatuximab, Belantamab, Melflufen, Idecabtagene Vicleucel, Ciltacabtagene Auboleucel
Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D.,
Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D.,
Lucia López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D.,
Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D.,
Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D.,
Eduardo Olavarriá, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D.,
Joan Bladé, M.D., Ph.D., Juan-José Lahuentá, M.D., Ph.D.,
and Jesús-F. San Miguel, M.D., Ph.D.


HR, hazard ratio

HR for progression, 0.18
P<0.001

Progression-free survival for early treatment
Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- 92 patients to the lenalidomide arm and 90 to the observation arm
- Median follow-up is 35 months

Early Therapeutic Intervention: Lenalidomide vs Observation

Progression-Free Survival

Median follow-up: 35 months

Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria

High risk

Intermediate risk

Low risk

Progression-Free Survival Probability

Time From Randomization (Months)

High risk SMM

- Genomic profile
- Immune profile
- Spatial Imaging
- CLIA approved panels for biomarkers

Immunotherapy
- Vaccines
- T cell therapy including CART and bispecific antibodies (BCMA, GPRC5D)
- NK cell therapy
- TIGIT and other antibodies

Actionable mutations
- MAPK mutations
- T11:14 and venetoclax
- Future Mcl-1 inhibitors and 1q
- Developing novel targets: Degraders

Targeted combinations
- Elotuzumab-RD
- Ixazomib-RD
- Daratumumab-RVD
- Isatuximab-RD
- Other centers: KRD + Dara
- KRD + Transplant
- Dara Rd vs Rd

Prevention in early SMM
- Daratumumab
- Metformin
- Intermittent fasting
- Vaccines
- Lifestyle interventions

Ultimate goal: CURE
Immediate goal: No one develops end organ damage in their lifetime
### GEM-CESAR: Multicenter, Open-Label, Phase 2 Trial of Carfilzomib/Lenalidomide/Dex + SCT in SMM

#### Response category

<table>
<thead>
<tr>
<th>Response category</th>
<th>Induction (n=90)</th>
<th>HDT-ASCT (n=83)</th>
<th>Consolidation (n=81)</th>
<th>High risk (n=54)</th>
<th>Ultra-high risk (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>85 (94%)</td>
<td>82 (99%)</td>
<td>81 (100%)</td>
<td>54 (100%)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>≥CR</td>
<td>37 (41%)</td>
<td>53 (64%)</td>
<td>61 (76%)</td>
<td>41 (76%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>35 (39%)</td>
<td>18 (22%)</td>
<td>15 (19%)</td>
<td>10 (19%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (14%)</td>
<td>11 (13%)</td>
<td>5 (6%)</td>
<td>2 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (3%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MRD negative</td>
<td>27 (30%)</td>
<td>47 (56%)</td>
<td>51 (63%)</td>
<td>36 (67%)</td>
<td>15 (56%)</td>
</tr>
</tbody>
</table>

Courtesy of MV Mateos.
Precision Intervention With Elotuzumab in Smoldering Myeloma (PI: Ghobrial, DFCI 14-334)

B-PRISM: A Phase II Study of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma (DFCI 21-007)

**Inclusion Criteria:**
High risk SMM defined as having 1 of the following 2 criteria:

1. **High-risk per “20-2-20” Criteria defined as presence of any two of the following:**
   - Serum M spike ≥ 2.0 g/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%
   - OR total score of 9 using the following scoring system:
     - FLC Ratio: >10-25 = 2, >25-40 = 3, >40 = 5
     - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
     - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
     - FISH abnormality (t(4;14), t(14;16), 1q gain, or del13q = 2

2. **Presence of ≥15% BMPC and at least one of the following:**
   - Evolving pattern
   - Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
   - High risk cytogenetics defined as presence of t(4;14), t(14;16), 17p deletion, TP53 mutation, 1q gain

**Cycles 1-2**
- Daratumumab 1800mg SQ d1, 8, 15
- Bortezomib 1.3mg/m2 SQ d1, 8, 15
- Lenalidomide 25mg PO d1-21
- Dexamethasone 20mg weekly

**Cycles 3-6**
- Daratumumab 1800mg SQ d1, 15
- Bortezomib 1.3mg/m2 SQ d1, 8, 15
- Lenalidomide 25mg PO d1-21
- Dexamethasone 20mg weekly

**Cycles 7-12**
- Daratumumab 1800mg SQ d1
- Bortezomib 1.3mg/m2 SQ d1, 15
- Lenalidomide 15mg PO d1-21
- Dexamethasone 20mg d1, 15

**Cycles 13-24**
- Daratumumab 1800mg SQ d1
- Bortezomib 1.3mg/m2 SQ d1, 15
- Lenalidomide 15mg PO d1-21
- Dexamethasone 20mg d1, 15

**Primary endpoint**
- MRD negativity rate at 2 years

**Secondary endpoints**
- Sustained MRD negative disease assessed at 6 months, 1 year and 2 years
- Progression free survival to myeloma defining events (SLIM-CRAB)
- Progression free survival 2
- Duration of response
- Overall survival
- To assess safety
A Phase II Study of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Part 2

- **MRD Positive at Completion of Study**
- **Observation**

24 months

**Primary endpoint**
- Rate of MRD conversion

**Secondary endpoints**
- Sustained MRD negative disease progression free survival to myeloma defining events (SLIM-CRAB)
- Progression free survival 2
- Duration of response
- Overall survival

- Randomization of MRD positive to observation vs 2 years of daratumumab/lenalidomide. Primary end point MRD conversion to negative

- **ASCO 2022 Abstract:**
  - 20 patients have been enrolled with a median follow up of 6 months and median age of 58 years old (range 40-73).
  - Sixteen out of 20 (80%) patients met high risk criteria per Mayo 2018 model with median plasmacytosis of 20%, median M protein value of 2.6 g/dl and median FLC ratio of 28.2.
  - Seven patients had high-risk FISH: 5 with 1q duplication, 2 with t(4;14).
  - The overall response rate is 90% with 40% PR, 25% VGPR and 25% CR. All patients have achieved at least a MR and 50% achieved VGPR or greater with responses deepening over time. No patients have progressed on treatment.
  - MRD was evaluable in 16 out of 20 and 8 patients have undergone MRD testing, with MRD negativity rate of 50% (4/8) and 25% (2/8) at thresholds of 10^{-5} and 10^{-6} respectively.
  - Most common grade 3 toxicities included neutropenia (15%), ALT increased (5%), thrombocytopenia (5%), hyperglycemia (5%), hypertension (5%), diarrhea (5%), syncope (5%). No patients discontinued therapy due to toxicity.
  - Stem cells were successfully collected in all patients with mean stem cell yield of 5.78 x 10^{6} CD34+/kg cells.
V- PRISM (Precision Intervention Smoldering Myeloma): A Randomized Phase II Platform Study of Venetoclax in High-Risk Smoldering Multiple Myeloma with Translocation (11;14)- Pending

Inclusion Criteria:
Presence of t(11;14) plus 1 of the following 2 high-risk SMM criteria:

1. High risk per “20-2-20” Criteria defined as presence of any two of the following:
   - Serum M spike ≥ 2 gm/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PCs ≥ 20%
   
   OR total score of 9 using the following scoring system:
   - FLC Ratio: >10-25 = 2, >25-40 = 3, >40 = 5
   - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
   - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
   - FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2

2. Presence of ≥10% BMPC and at least one of the following:
   - Evolving pattern
   - Abnormal PC immunophenotype (>95% of BMPCs are clonal and reduction of ≥1 uninvolved immunoglobulin isotype. (Only IgG, IgA and IgM will be considered)
   - High risk cytogenetics defined as presence of t(4,14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain

Primary endpoint
- Complete Response

Secondary endpoints
- Sustained MRD negative disease assessed at 6 months, 1 year, and 2 years
- Progression free survival to myeloma defining events (SLIM-CRAB)
- Progression free survival
- Duration of response
- Overall survival
- To assess safety
Immunotherapy in SMM: Hypothesis

We believe that **immunotherapy** warrants investigation in SMM as it may:

- Prevent progression via immune stimulation and enhanced surveillance of the malignant clone
- Potentially eradicate the disease at an early stage when T cells are more functional.
- Bispecific antibodies and CAR T-cell therapy show tremendous promise in RRMM

**Potential for even greater benefit in SMM patients compared to RRMM**
Inclusion Criteria:
High risk SMM defined as having 1 of the following 2 criteria:

1. High risk per “30-20-20” Criteria defined as presence of any two of the following:
   - Serum M spike ≥ 2 g/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%
   - CRF total score of 9 using the following scoring system:
     - FLC Ratio: >10-25 = 2, >25-40 = 3, >40 = 5
     - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
     - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
     - FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2

2. Presence of ≥10% BMPC and at least one of the following:
   - Evolving pattern
   - Abnormal PC immunophenotype (>5% of BMPC are clonal) and reduction of ≥1 uninvolved immunoglobulin isotype (only IgG, IgA and IgM will be considered)
   - High risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain

Teclistamab Dosing:

Cycle 1
- Step up dose: days 1 and 3
- Treatment Dose: days 8, 15, 22

Cycle 2:
- Teclistamab (subcutaneous): Days 1, 8, 15 and 22
- Teclistamab (subcutaneous): Days 1 and 15
CAR-PRISM (PRecision Intervention Smoldering Myeloma): Ciltacabtagene Autoleucel in High-Risk Smoldering Myeloma (pending)

Inclusion Criteria:
High-risk SMM defined as having 1 of the following 2 criteria:

1. High-risk per “20-20” Criteria defined as presence of any two of the following:
   - Serum M spike ≥ 2 g/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%
   - CR total score of ≥ 3 using the following scoring system:
     - FLC Ratio: >10-25 = 2, >25-40 = 3, >40 = 5
     - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
     - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
     - FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2

2. Presence of ≥1% BMPC and at least one of the following:
   - Evolving pattern
   - Abnormal PC immunophenotype (>50% of BMPCs are clonal) and reduction of the uninvolved immunoglobulin isotype. (Only IgG, IgA and IgM will be considered)
   - High risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain

Cilta-Cel Dosing:
- First 3 patients at 0.5 x 10^6/kg cells
- Subsequent patients at 0.75 x 10^6/kg cells
- Staggered enrollment for first 3 patients
- Safety criteria
So what about the patient who presents with renal dysfunction and has a monoclonal gammopathy or abnormal serum free light chains?

- **MGUS is very common!!**
- Evaluate for alternate causes for renal dysfunction and determine chronicity
- Degree of paraprotein burden and/or light chain abnormality
  - Higher in active myeloma, can be minimal in MGRS
- Diagnostic workup for plasma cell dyscrasia to exclude multiple myeloma and AL amyloidosis
  - Bone marrow biopsy and aspirate
  - Skeletal imaging (PET/CT or MRI preferred)
  - Laboratory assessments, including 24 hour urine for UPEP/assessment of proteinuria
- If no clinical evidence of myeloma/AL amyloidosis, discuss role of kidney biopsy for further assessment to exclude MGRS
Management of MGRS: Basic Principles

- **Clone directed therapy**
  - B cell (rituximab) vs LPL /WM (rituximab/BTK inhibitor) vs plasma cell (anti-myeloma regimens)

- **Induction therapy regimens for plasma cell directed therapy**
  - Bortezomib-based regimens commonly used (in combination with cyclophosphamide)
  - Anti-CD38 monoclonal antibody daratumumab-based approaches increasingly used

- **Autologous stem cell transplantation in eligible patients**

- **Role of maintenance therapy less clear in MGRS and determined on case by case basis**

- **Consideration of renal transplantation in select patients with advanced CKD that achieve a complete hematologic remission**

- **Monitoring of disease determined by renal function, assessment of proteinuria and serum paraprotein**
Summary and Conclusions

- MGUS is very common, particularly in high risk populations

- Smoldering myeloma carries a variable risk of progression to overt myeloma, with several criteria that predict likelihood of progression

- Emerging data with early therapeutic intervention in high-risk SMM

- Immunotherapeutic approaches under study in HR-SMM

- Management of MGRS includes clone-directed therapy, with anti-myeloma combination regimens utilized for plasma cell clone
References: