Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)
Objectives

• Definition
• Diagnostic criteria
• Etiology and Pathogenesis
• Diagnostic work-up
• Prognostic factors
• Patient management
**Definition**

**MGUS and SMM** are asymptomatic plasma cells disorders that are associated with a risk of progression to MM, light chain AL, WM, or related malignancy.

**MGUS** is a premalignant clonal disorder prevalent in over 4% of the general population over the age of 50, and carries a risk of progression of approximately 1% per year.

**SMM** is an heterogeneous entity that have a much higher risk of progression to frank MM (10% per year) compare with MGUS.
Benign monoclonal protein was first described by Waldenstrom in 1960\(^1\).

Kyle coined the term “monoclonal gammopathy of undetermined significance” in 1978\(^2\).

\(^{1}\) Waldenstrom J Harvey Lect 1960
\(^{2}\) Kyle RA. Am J Med 1978
## Frequency

### Monoclonal Gammopathies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>64%</td>
</tr>
<tr>
<td>Smouldering MM</td>
<td>2%</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>14%</td>
</tr>
<tr>
<td>PCL</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Plasmocytoma</td>
<td>6%</td>
</tr>
<tr>
<td>Waldenström’s Macroglobulinemia</td>
<td>2%</td>
</tr>
<tr>
<td>CLL</td>
<td>2%</td>
</tr>
<tr>
<td>NHL</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Amyloidosis Primary</td>
<td>8%</td>
</tr>
<tr>
<td>POEMS</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Other diseases</td>
<td>?</td>
</tr>
</tbody>
</table>
### Classification of Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td></td>
</tr>
<tr>
<td>Non-IgM MGUS</td>
<td>1% per year risk of progression to multiple myeloma, AL amyloidosis, or related disorder.</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>1.5% per year risk of progression to Waldenstrom macroglobulinemia; rare patients can progress to IgM multiple myeloma.</td>
</tr>
<tr>
<td>Light chain MGUS</td>
<td>Risk of progression to light chain myeloma and AL amyloidosis. Rate of progression not defined.</td>
</tr>
<tr>
<td>Smoldering multiple myeloma</td>
<td>10% per year risk of progression to multiple myeloma or related disorder for the first 5 years. Risk decreases to 3% per year for the next 5 years and 1% per year thereafter.</td>
</tr>
</tbody>
</table>

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*Note that conventionally IgM MGUS is considered a subtype of MGUS. Thus, when the term MGUS in general, it includes IgM MGUS. Since light chain MGUS was only defined in 2010, studies pertaining to MGUS prior to that time do not include patients with this entity; unless otherwise specified studies since then may also not include patients with light chain MGUS.

*Almost all patients are IgG or IgA type. Occasional patients may have IgD or IgE monoclonal proteins.*

Rajkumar V, Am J Hematol 2012
## M-protein isotypes in MGUS

<table>
<thead>
<tr>
<th>Heavy chain type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>20</td>
</tr>
<tr>
<td>IgG</td>
<td>69</td>
</tr>
<tr>
<td>IgA</td>
<td>11</td>
</tr>
<tr>
<td>Biclonal</td>
<td>3</td>
</tr>
<tr>
<td>IgD</td>
<td>1</td>
</tr>
<tr>
<td>IgE</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Light chain type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa</td>
<td>61</td>
</tr>
<tr>
<td>lambda</td>
<td>39</td>
</tr>
</tbody>
</table>

Korde N, Blood 2011
Objectives

- Definition
- **Diagnostic criteria**
- Etiology and Pathogenesis
- Diagnostic work-up
- Prognostic factors
- Patient management
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease definition</th>
</tr>
</thead>
</table>
| Monoclonal gammopathy of undetermined significance | All three criteria must be met  
Serum monoclonal protein $< 3\text{ gm/dl}$  
Clonal bone marrow plasma cells $< 10\%$, and  
Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions that can be attributed to the plasma cell proliferative disorder |
| Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma) | Both criteria must be met  
Serum monoclonal protein (IgG or IgA) $\geq 3\text{ gm/dl}$ and/or clonal bone marrow plasma cells $\geq 10\%$, and  
Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder |
| Multiple myeloma                             | All three criteria must be met except as noted  
Clonal bone marrow plasma cells $\geq 10\%$  
Presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma), and  
Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically  
  - Hypercalcemia: serum calcium $\geq 11.5\text{ mg/dl}$ or  
  - Renal insufficiency: serum creatinine $> 1.73\text{ mmol/l}$  
  - Anemia: normochromic, normocytic with a hemoglobin value of $> 2\text{ g/dl}$ below the lower limit of normal or a hemoglobin value $< 10\text{ g/dl}$  
  - Bone lesions: lytic lesions, severe osteopenia or pathological fractures |

Abbreviations: MGUS, Monoclonal gammopathy of undetermined significance; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions.
Modified, reproduced with permission from Kyle RA, Rajkumar SV. Leukemia 2009;23:3–9.
Myeloma Related Organ Damage (CRAB) updated in the IMWG 2010

- Hypercalcemia (calcium level $> 2.625$ mmol/l)
- Renal insufficiency with serum creatinine $> 176.8$ umol/l or estimated creatinine clearance $< 40$ mL/min.
- Anemia (Hb $< 10$ g/dl, or $< 2$ g/dl below the lower limit of normal).
- Bone lesions (lytic lesions, severe osteopenia with compression fractures).

Kyle RA, Leukemia 2010
MGUS and SMM: incidence

**MGUS**

- Over 50 years of age: incidence is 3.2%
  - 50-59: 1.7%
  - >70: 5.3%
- Man >> Women (4% vs. 2.7% older than age 50 years)
- 2.6 fold higher rate of MGUS in blood-related first-degree relatives of individuals with either MGUS or MM.

Across races:

- Asians lower prevalence vs. white populations.
- Africans and Afro-Americans 2 to 3 fold higher vs. white.

**SMM**

~ 10% to 15% of all cases of newly diagnosed MM.

Prevalence difficult to determine (include asymptomatic patients with lytic lesions on the skeletal survey).
Objectives

• Definition
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• **Etiology and Pathogenesis**
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The etiology still remains unclear, however the following factors play a role:

- Race (Blacks versus persons from Japan and Mexico)
- Lifestyle and socioeconomic-related risk factors (obesity, cigarette and alcohol use)
- Older age, male sex
- Exposure to pesticides
- Family history of MGUS or MM

Landgren O, Blood 2006
Cohn H, am J Med 1998
Landgren O, Blood 2010
Landgren O, Leukemia 2009
Waxman A, Blood 2010
Fernberg P, Cancer Res 2077
Familial aggregation of MGUS and SMM

• First-degree relatives of persons with MGUS and SMM have a 2- to 4-fold increase in the risk of lymphoproliferative disorders.

• This risk depends on the type of the M protein in the proband.
  
  – Relatives of patients with IgA/IgG MGUS have elevated risk of LPL and WM (RR 4.0, 95% CI, 1.5-11)
  
  – Relatives of patients with IgM MGUS had an increased risk of CLL (RR 2.0, 95% CI, 1.2-2.3).

Landgren O, Blood 2009
Kristinsson S, Blood 2008
Genetics and biologic mechanisms of familial MGUS and SMM

- Genome-wide linkage analysis (chromosomes 1q and 4q)\(^1\)
- Hyper-responsive B cells\(^2\)
- Biological factors (hyperphosphorylation of P-7 and P-8 paratag proteins)\(^3,4\)

1 McMaster M, Am J Hum Genet 2006
2 Steingrimsdottir H, Eur J Haematol 2011
3 Grass S Lancet Oncol 2009
4 Grass S Blood 2011
Figure 1. Pedigree of members of family 4, including 2 patients with MM and 2 with MGUS with a P-8 specific paraprotein carrying the hyperphosphorylated P-8.
Normal B cell differentiation

- Precursor B cell
  - Bone Marrow
  - VDJ recombination

- Immature B cell
  - IgM

- Mature B cell
  - IgM

- Short-lived plasma cell
  - IgM

- Long-lived plasma cell
  - IgG
  - IgA
  - IgD
  - IgE

- Memory B cell
- Germinal Center B cell
  - IgH Class switching
  - Somatic Hypermutation
  - Antigenic Selection

- Lymphoblast
- Lymph node
Figure 1 | Molecular processes that remodel immunoglobulin genes. Immunoglobulins (Igs) are expressed by B cells and consist of variable (V) regions, which interact with antigen, and constant (C) regions, which mediate the effector functions of Igs. To create a functional Ig, B cells must rearrange DNA segments that encode the heavy (H)- and light-chain (not shown) regions of the variable genes. a | First, through a process called ‘V(D)J recombination’, three gene segments, V\_H, D\_H, and J\_H, are joined to encode the H-chain variable region. The V regions of the κ- and λ-light chains, alternatively, are each encoded by two gene segments — the V\_L and J\_L genes (not shown). B-cell precursors first carry out D\_H\_J\_H rearrangements in H-chain genes. These D\_H\_J\_H rearrangements are followed by V\_H\_D\_H\_J\_H rearrangements, resulting in the expression of a pre-B-cell receptor if the rearrangement is productive\(^3\). About 50 functional V\_H gene segments, 27 D\_H segments and 6 J\_H segments are available in the germline, allowing the generation of a diverse repertoire of V\_H gene rearrangements. The diversity is further increased by the addition or removal of nucleotides at the joining sites of the gene segments\(^3\). The cells then carry out rearrangements at their L-chain loci (not shown). The V-region of the Ig gene is ultimately connected to the C-region of the Ig gene (C\_\_M of IgM in diagram) b | The process of somatic hypermutation is activated when B cells reach the germinal centre (GC, shown in more details in FIG. 2). This process leads to the introduction of point mutations, deletions or duplications in the rearranged V-region of Ig genes (denoted by ‘Xs’ in the figure)\(^10^2\). These mutations occur in the V-region of Ig genes — not in the downstream C\_\_M region. c | Class switching results in the replacement of the originally expressed H-chain C-region gene with that of another Ig gene. In the diagram, the C-region for IgM (C\_\_M) and IgD (C\_\_D) are exchanged for the C-region of IgG (C\_\_Y1) by recombination at the switch regions for these genes (S\_\_M and S\_\_Y1, respectively). This results in an antibody with different effector functions but the same antigen-binding domain.
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Diagnosis
Monoclonal Gammopathies

Serum Protein Electrophoresis Showing an M Component Migrating in the Slow Gamma Globulin Region. A normal result of protein electrophoresis is also shown.
Diagnostic work-up MGUS

Complete history and physical examination

LAB

- CBC
- Serum Ca/albumine and creatinine
- Serum protein electrophoresis (EF) and immunofixation (IF)
- Quantification of immunoglobulins
- 24-hour urine albumin, EF +IF

Skeletal X rays

Bm aspirate/biopsy if
  - M-protein > 15 g/l
  - IgA or IgM M-protein
  - Abnormal free light chain ratio

CT thorax/abdomen if IgM paraprotein (WM)
Other diseases associated with M-protein

• Autoimmune diseases (RA, SLE, scleroderma)
• Skin diseases (pyoderma gangraenosum)
• Liver disease (cirrhosis)
• Infectious diseases (m.tuberculosis, Hep C, HIV)
• ...............
Objectives

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• Diagnostic criteria
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• Diagnostic work-up
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MGUS and SMM prognosis

- **In MGUS** Risk of progression to multiple myeloma:
  - 1%/yr
    - Independent of age
    - Dependent on prognostic factors

- **In SMM** Risk of progression to multiple myeloma:
  - 10% per year for the first 5 years
  - 3% per year for the next 5 years
  - 1% for the subsequent 10 years.
MGUS and SMM risk of progression

MGUS predictors of risk of progression

- Size of M protein (Serum M-protein >1.5 g/dl)
- Type of Immunoglobulin (Non-IgG)
- Serum free light chain (FLC) ratio (abnormal)
- BM plasma cells (>5%)

## MGUS: risk stratification model

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>Absolute risk of progression at 20 years (%)</th>
<th>Absolute risk of progression at 20 years accounting for death as a competing risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (serum M protein &lt;1.5 g/dl, IgG subtype, normal FLC ratio (0.26–1.65))</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low-intermediate-risk (any 1 factor abnormal)</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High-intermediate-risk (any two factors abnormal)</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High-risk (all three factors abnormal)</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>

Abbreviation: MGUS, Monoclonal gammopathy of undetermined significance.

This table was originally published in *Blood*. Rajkumar SV *et al.*, Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS) *Blood*. 2005; **106**:812–817. © the American Society of Hematology.

Kyle RA, Leukemia 2010
SMM predictors of risk of progression

- Size of M protein (serum M-protein >3 g/dl)
- Serum free light chain (FLC) ratio (abnormal)
- BM plasma cells (>10%)
- Aberrant plasma cells by Immunophenotype (≥95%)
- Reduction in uninvolved immunoglobulins
- Abnormal MRI studies*

Patients with >10% plasma cells and >3gm/dl M protein are at higher risk

SMM: risk stratification model

Figure 1  Risk stratification for smoldering multiple myeloma. The model incorporates three risk factors: abnormal FLC ratio, bone marrow plasma cells $\geq 10\%$ and serum M protein $\geq 3$ g/dL. Patients with 1, 2 or 3 risk factors had 5-year progression rates of 25, 51 and 76%, respectively. Corresponding median times to progression are 10, 5.1 and 1.9 years, respectively.
Smoldering multiple myeloma: aberrant PCs by immunophenotype plus immunoparesis

- >95% aPC/BMPC + paresis: 
  - Median 23 months
  - n = 39 (28 progr.)

- > 95% aPC/BMPC or paresis: 
  - Median 73 months
  - n = 22 (10 progr.)

- No adverse factors: 
  - Median not reached
  - n = 28 (1 progr.)

*p = 0.003

Smoldering MM: Should definition be revisited?

- Early MM: Median 23 months, 82% TTP (%)
- MGUS: Median not reached, 8% TTP (%)
- p = 0.003

Mechanisms of Progression in Monoclonal Gammopathies.
Disease stages and timing of oncogenic events

- Increased DNA labeling index
- Bone destruction
- Angiogenesis

Germinal center B cell → MGUS → Smoldering myeloma → Intra-medullary myeloma → Extramedullary myeloma → Myeloma cell line

Karyotypic abnormalities:
- Primary (Ig) TLC
- Secondary (Ig) TLC

Hypermultiploidy:
- del13
- Activating mutations: N, K-ras, FGFR3
- p18 deletion
- MYC dysregulation
- p53 mutation

Gene expression profile in MGUS plasma cells differs from normal plasma cells

Gene expression profile segregate MGUS and MGUS-L MM from non MGUS-L MM
MM and MGUS express a distinct spectrum of miRNA in comparison to normal CD138+ PCs
SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies, from MGUS to myeloma status


Table 1: Frequency of CNA in monoclonal gammopathy patients

<table>
<thead>
<tr>
<th></th>
<th>Gains Median (range)</th>
<th>Losses Median (range)</th>
<th>Genomic imbalances Median (range)</th>
<th>Only gains Cases (%)</th>
<th>Only losses Cases (%)</th>
<th>Without CNA Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>1.5 (1-8)</td>
<td>1.5 (1-9)</td>
<td>5 (1-12)</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>SMM</td>
<td>3 (1-12)</td>
<td>3.5 (1-14)</td>
<td>7.5 (1-23)</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>MM</td>
<td>6.5 (1-20)</td>
<td>4 (1-29)</td>
<td>12 (1-32)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Significant comparisons: SMM vs. MM P=0.025  MGUS vs. MM P<0.001  MGUS vs. MM P= 0.033  MGUS vs. MM P= 0.006
Significantly different frequencies of gains and losses in monoclonal gammopathies

<table>
<thead>
<tr>
<th>Copy Number Gains</th>
<th>MGUS (n=20) patients (%)</th>
<th>SMM (n=20) patients (%)</th>
<th>MM (n=34) patients (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q</td>
<td>4 (20%)</td>
<td>8 (40%)</td>
<td>20 (58.8%)</td>
<td>0.013 (MGUS vs. MM)</td>
</tr>
<tr>
<td>3p</td>
<td>2 (10%)</td>
<td>5 (25%)</td>
<td>13 (38.2%)</td>
<td>0.05 (MGUS vs. MM)</td>
</tr>
<tr>
<td>6p</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
<td>9 (26%)</td>
<td>0.05 (MGUS vs. MM)</td>
</tr>
<tr>
<td>9p</td>
<td>5 (25%)</td>
<td>8 (40%)</td>
<td>20 (59%)</td>
<td>0.034 (MGUS vs. MM)</td>
</tr>
<tr>
<td>11p</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>12 (35%)</td>
<td>0.019 (SMM vs. MM)</td>
</tr>
<tr>
<td>11q</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>16 (47%)</td>
<td>0.001 (MGUS vs. MM)</td>
</tr>
<tr>
<td>19p</td>
<td>5 (25%)</td>
<td>6 (30%)</td>
<td>22 (65%)</td>
<td>0.011 (MGUS vs. MM)</td>
</tr>
<tr>
<td>19q</td>
<td>5 (25%)</td>
<td>4 (20%)</td>
<td>19 (56%)</td>
<td>0.05 (MGUS vs. MM)</td>
</tr>
<tr>
<td>21q</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>11 (32%)</td>
<td>0.004 (MGUS vs. MM)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Copy Number Deletions</th>
<th>MGUS (n=20) patients (%)</th>
<th>SMM (n=20) patients (%)</th>
<th>MM (n=34) patients (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p</td>
<td>1 (5%)</td>
<td>5 (25%)</td>
<td>15 (44%)</td>
<td>0.006 (MGUS vs. MM)</td>
</tr>
<tr>
<td>4q</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>7 (21%)</td>
<td>0.038 (SMM vs. MM)</td>
</tr>
<tr>
<td>16q</td>
<td>0 (0%)</td>
<td>6 (30%)</td>
<td>7 (21%)</td>
<td>0.02 (MGUS vs. SMM)</td>
</tr>
<tr>
<td>22q</td>
<td>0 (0%)</td>
<td>3 (15%)</td>
<td>8 (23%)</td>
<td>0.020 (MGUS vs. MM)</td>
</tr>
</tbody>
</table>
Schematic representation of percentage of cases carrying specific alterations as a major and minor subpopulations
Objectives

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MGUS and SMM Patients management

- Involves a prudent “Watch and Wait strategy” until evidence of symptomatic progression.

- Outside of clinical trials, there are no current standardized treatment options for MGUS and SMM.
MGUS: recommendations

• Repeat M-protein assessment at 3-6 months

• If stable
  – History/ lab every year, lifelong. In all ??
Low-risk MGUS

• M-protein assessment in 6 months.

• If stable can be followed every 2-3 years or when symptoms suggestive of a PC malignancy arise.

• A baseline BM examination or skeletal radiography is not routinely indicated.
  – BM is required if the patient has CRAB.

Korde N, Blood 2011
Kyle RA, Leukemia 2010
Intermediate and high risk MGUS

- A baseline BM examination
- Conventional cytogenetics and FISH
- CT scan of the thorax/abdomen if IgM paraprotein (Waldenstrom’s macroglobulinemia)
- If the results of these tests are satisfactory, M-protein assessment and CBC can be requested in 6 months and then annually for life.

Korde N, Blood 2011
Kyle RA, Leukemia 2010
Smoldering MM

- History/ lab at baseline and repeat 2-3 months
- Baseline BM biopsy and skeletal survey are mandatory
- MRI of the spine and pelvis is recommended.
- If stable can be followed every 4-6 months for 1 year and then every 6-12 months.

- **In SMM or high-risk MGUS patients** highly suspicious to harbor bone disease, MRI or PET-CT may be better than skeletal surveys.

Korde N, Blood 2011
Kyle RA, Leukemia 2010
SMM Preventive strategies

- Recently, the paradigm of delaying therapy until evidence of MM related end-organ damage is changing.

- Randomized clinical trials are evaluating the role of conventional and novel agents versus placebo in patients with SMM or asymptomatic MM (AMM).
Is it worth to early treat SMM / asymptomatic MM patients?
Non-hematologic malignancies: Oncology perspective

Early intervention
- In almost all malignancies (breast, prostate, colon cancers,...)
- Two possible objectives: To cure/erradication
  To delay progression to active disease

Outcome from a polipus to colon cancer
MM: Oncology perspective

Early intervention

Normal → MGUS → MM → Plasma cell leukemia → Cell line

Smoldering MM

Cure

Chronic disease management

Agressive clonal selection
What are the Elements of Effective therapy for a patient who HAS NO SYMPTOMS?

• Well tolerated treatment
• Reduces depth of disease
• Helps all biologic (genetic) subsets of disease
• Improves overall survival compared to observation
<table>
<thead>
<tr>
<th>Smoldering multiple myeloma: early treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional agents</strong></td>
</tr>
<tr>
<td>Initial MP vs Deferred MP$^{1,2,3}$</td>
</tr>
<tr>
<td>No benefit in ORR/TTP/OS</td>
</tr>
<tr>
<td><strong>Novel agents</strong></td>
</tr>
<tr>
<td>Thalidomide$^{4,5}$</td>
</tr>
<tr>
<td>$\sim 30% \geq \text{PR};$ high toxicity;</td>
</tr>
<tr>
<td>patients achieving PR had a shorter time to</td>
</tr>
<tr>
<td>treatment</td>
</tr>
<tr>
<td>Bisphosphonates vs abstention $^{6,7}$</td>
</tr>
<tr>
<td>No benefit in ORR/TTP/OS</td>
</tr>
<tr>
<td>Lower incidence of skeletal related events</td>
</tr>
</tbody>
</table>

**But...none of these trials discriminate the low risk patients** (that probably will not benefit from intervention) **from the high risk group**, that may be the target for therapy

Is there any trial supporting this hypothesis: early treatment but only in high-risk patients?
A Multicenter, Randomised, Open-label, Phase III Study of Lenalidomide/Dexamethasone versus Therapeutic Abstention in high-risk Smoldering MM


On behalf of Spanish Myeloma Group (PETHEMA/GEM)

QuiRedex: Study Design

• Multicenter, open-label, randomized phase III trial
  – Evaluated new treatment regimen for smoldering MM vs current standard of care

Induction
9 x 28-day cycles

Lenalidomide 25 mg/day on Days 1-21 + Dexamethasone 20 mg/day on Days 1-4, 12-15

Maintenance
28-day cycles

Lenalidomide 10 mg/day on Days 1-21 (Low-dose dexamethasone added at time of biologic progression)

Patients with high-risk smoldering MM
(N = 126)

No Treatment

2 yrs

Primary endpoint: TTP to symptomatic MM
Secondary endpoints: response, duration of response, safety and tolerability, PFS, OS

**QuiRedex: Response**

- Majority of patients responded to lenalidomide plus dexamethasone
  - Responses improved with maintenance

<table>
<thead>
<tr>
<th>Response, %</th>
<th>ITT Population With Median of 9 Induction Cycles (Range: 1-9) (n = 57)</th>
<th>After Completion of 9 Induction Cycles (n = 51)</th>
<th>After Median of 15 Maintenance Cycles (Range: 2-31) (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>86</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Stringent CR</td>
<td>7</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>CR</td>
<td>7</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>VGPR</td>
<td>11</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>PR</td>
<td>61</td>
<td>68</td>
<td>52</td>
</tr>
<tr>
<td>SD</td>
<td>14</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

QuiRedex: TTP to Symptomatic MM and OS

• Significant increase in TTP with vs without treatment

• Significantly prolonged OS with vs without treatment
  – Median 3-yr OS (from study inclusion): 93% vs 76%; \( P = .04 \)
  – Median 5-yr OS (from diagnosis): 94% vs 79%; \( P = .03 \)

**Median TTP**

- Lenalidomide/dexamethasone: NR
- No treatment: 23 mos
- HR: 6.0 (95% CI: 2.9-12.6; \( P < .0001 \))
- Median follow-up: 32 mos (range: 12-49)

QuiRedex: Safety

- 3 cases of second primary malignancies reported in treatment arm

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Lenalidomide + Dexamethasone (n = 57)</th>
<th>No Treatment (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>--</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>5</td>
<td>--</td>
</tr>
<tr>
<td>Tremor</td>
<td>13</td>
<td>--</td>
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<tr>
<td>Infection</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>5</td>
<td>--</td>
</tr>
</tbody>
</table>

QuiRedex: Conclusions

• Improved outcomes with lenalidomide and dexamethasone induction plus maintenance lenalidomide vs no treatment in smoldering MM
  – Significantly prolonged TTP, OS
• Addition of low-dose dexamethasone to maintenance lenalidomide maintained disease stabilization in most cases of biologic progression
• Well tolerated, with most adverse events grade 1/2
  – Drug-related toxicities should be considered when evaluating risk/benefit
• Question remains regarding effect of treatment at this disease stage
  – Delay progression only or alter natural history

• Preliminary encouraging data that needs further validation
Eligible patients are high or intermediate risk AMM

No Dexamethasone

PBSC collection suggested for all patients

Planned correlatives include GEP, optional MRI, Immunologic studies (SWOG)
Primum non nocere (Do No Harm)

- Risk of PN, DVT, fatigue, cytopenias, and stem cell reserve cannot be underestimated.
- Need to understand what impact (if any) early intervention has on the natural history of AMM
- Showing delay in developing MM is not sufficient when treatment at progression may be compromised by initial therapy.

Conclusions

Treatment of High risk AMM patients CANNOT be recommended for all patients at this time