Multiple Myeloma

How to Evaluate Response To Treatment and Relapse

DR L. GARDERET

Saint Antoine Hospital, Paris
Haematology Department
What is Multiple Myeloma?

Diagnostic Tools

Response to Treatment Evaluation

Progressive / Relapse Disease

Clinical Cases
What is Multiple Myeloma?

Multiple Myeloma Epidemiology
Progression from MGUS to Myeloma
Staging Systems (Salmon-Durie and I.S.S)
Physiopathology
Diagnostic Criteria
Features of Myeloma
Progression of Myeloma
Multiple Myeloma Epidemiology

GLOBAL FIGURES

0.8% OF ALL CANCER CASES¹
1000 CASES DIAGNOSED DAILY²
750K EXISTING CASES (GLOBALLY)³

Age-standardized incidence rate is highest among industrialized countries, including the US, Europe, Australia, and New Zealand⁴


All figures accessed March 4, 2014 (myeloma.org, globocan.iarc.fr)
Multiple Myeloma Epidemiology

INCIDENCE (EU)
38900
ESTIMATED NEW CASES 2012¹

MORTALITY (EU)
24300
ESTIMATED DEATHS 2012¹

MM has a median age of diagnosis of approximately 69 years in the US, 65–70 years in the EU²-⁵

Progression from MGUS to Myeloma

What is Multiple Myeloma?

**GENOMIC INSTABILITY**
- Translocations at 14q32 (50%)
- Deletion of Chromosome 13 (50%)

**MICROENVIRONMENTAL CHANGES IN BONE MARROW**
- Increased Bone Resorption
- Increased Angiogenesis

Normal cell

Infection? Inflammation?

Monoclonal Gammopathy of Undetermined Significance

N-RAS, K-RAS (30%)
P16 Methylation (40%)
Secondary translocations?

MYELOMA
Monoclonal Gammopathy of Unknown Significance (MGUS)

- No clinical symptom
- Monoclonal peak < 3g/dL
- < 10% plasma cells in bone marrow
- No anemia, no hypercalcemia, no renal deficiency, no bone lesions

Progression to myeloma: 1% per year (+/-)
Definition

Myeloma

Tumour plasma cells in the bone marrow ≥ 10%

A monoclonal immunoglobulin in the blood and/or urine

What is Multiple Myeloma?
Bone Marrow Aspiration

Normal bone marrow aspirate: < 5% plasma cells

Abnormal bone marrow aspirate: ≥ 10% plasma cells with cytological abnormalities
What is Multiple Myeloma?

Immunoglobulin

- Antigen Binding-Site
- Disulphide Bonds
- Hinge Region
- Light Chain
- Heavy Chain

NH$_2$

COOH
Physiopathology

Marrow infiltration
Reduced normal immunoglobulins

Bone destruction
Lytic lesions
Pathologic fractures
Hypercalcemia

Monoclonal antibodies
Urine: kidney failure
Blood: hyper viscosity, cryoglobulin, cold agglutinin
Tissue: neuropathy, amyloidosis

Anemia

Marrow infiltration

Reduced normal immunoglobulins

Infection

What is Multiple Myeloma?
Features of Myeloma

<table>
<thead>
<tr>
<th>Calcium</th>
<th>May be raised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>Up to 30% of patients at diagnosis</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Leukopenia &amp; thrombocytopenia unusual at diagnosis</td>
</tr>
<tr>
<td>Bone disease</td>
<td>Lytic lesions – pathological fractures</td>
</tr>
</tbody>
</table>

Other features include increased infections, hyper viscosity and extra-medullary disease
What is Multiple Myeloma?

Xrays: Bone Lesions

[Images of X-rays showing bone lesions]
What is Multiple Myeloma?

Plasmacytoma (extra medullary)

Plasma Cell Leukemia

Plasmacytoma can be medullary or extramedullary

Plasma Cell Leukemia

• > 2000 plasma cells/mm³ or ≥ 20% plasma cells in WBC differential count

Non Secretory myeloma:

≥ 10% plasma cells in the bone marrow but no monoclonal protein neither heavy nor light chain (blood and urine)

Peripheral Smear Report

• If reported, “Circulating Plasma Cells seen”, it does not necessarily means plasma cell leukemia: it depends on the number of circulating plasma cells
## Staging Systems (1) Salmon-Durie

<table>
<thead>
<tr>
<th>I.</th>
<th>ALL OF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemoglobin &gt; 100g/L</td>
</tr>
<tr>
<td></td>
<td>Serum calcium &lt; 12mg/dL (or 3mmol/L)</td>
</tr>
<tr>
<td></td>
<td>No bone lesions</td>
</tr>
<tr>
<td></td>
<td>Low paraprotein level</td>
</tr>
<tr>
<td></td>
<td>• IgG &lt; 50g/L</td>
</tr>
<tr>
<td></td>
<td>• IgA &lt; 30g/L</td>
</tr>
<tr>
<td></td>
<td>• Urine light chain &lt; 4g/24hrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II.</th>
<th>NOT 1 OR 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemoglobin &lt; 85g/L</td>
</tr>
<tr>
<td></td>
<td>Serum calcium &gt; 12mg/dL (or 3mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Advanced lytic lesion</td>
</tr>
<tr>
<td></td>
<td>High paraprotein level</td>
</tr>
<tr>
<td></td>
<td>• IgG &gt; 70g/L</td>
</tr>
<tr>
<td></td>
<td>• IgA &gt; 50g/L</td>
</tr>
<tr>
<td></td>
<td>• Urine light chains &gt; 12g/24hrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III.</th>
<th>AT LEAST ONE OF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum creatinine: A &lt; 2mg/dL (or 177 µmol/L), B ≥ 2mg/dL</td>
</tr>
</tbody>
</table>
### Staging Systems (2)

#### I.S.S.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β2 microglobulin &lt; 3.5mg/L and albumin &gt; 35g/L</td>
<td>62</td>
</tr>
<tr>
<td>β2 microglobulin &lt; 3.5mg/L and albumin &lt; 35g/L OR β2 microglobulin 3.5 – 5.5 mg/L</td>
<td>44</td>
</tr>
<tr>
<td>β2 microglobulin &gt; 5.5 mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

**What is Multiple Myeloma?**
Cytogenetics

Often complex abnormalities:

- Hyperdiploidy (esp. odd number chromosomes)
- Translocations involving heavy chain gene e.g. \( t(4;14), t(14;16), t(14;20) \)
- Deletions 17p
- Amplification 1q, deletion 1p
- Del 13q
  - Originally seen as poor prognosis
  - Probably fellow traveller

Red= bad prognosis
Progression of Myeloma

What is Multiple Myeloma?

1. Adapted from International Myeloma Foundation; 2001

Multiple Myeloma | EBMT.ORG | #EBMT2015
Diagnostic Tools

Electrophoresis (SPEP and UPEP)
Serum and urine immunofixation
Bone marrow aspiration
To assess myeloma response, you need:

- Quantification of the serum monoclonal protein (+/- and the urines) (SPEP/UPEP and IF)

- Serum Free light Chain quantification for light chain myeloma, kappa and lambda

- Bone marrow assessment if no more monoclonal protein detectable (cytology + flow cytometry)

- Imaging (MRI and PET) are currently evaluated
Electrophoresis

Aragose gel electrophoresis, buffer pH 8.6

Electrophoretic migration
(electronegative proteins)

Electroendosmosis flow

Diagnostic Tools
What is Monoclonal Immunoglobulin?
Serum Free Light Chain Assays - An Overview
Free light chain production by plasma cells

Kappa $\kappa$

Lambda $\lambda$
SPEP and Immunofixation (IF)
IgG $\lambda$ Myeloma
SPEP and Immunofixation (IF)
Lambda Light Chain Myeloma
Why is it difficult to evaluate myeloma?

- Criteria have changed over the time (due to improvement in treatment)
- New technologies developed (Flow cytometry, ASO-PCR, NGS)
- Raw data quality suboptimal (queries+++)
- Any evaluation requires two consecutive assessments (the six week interval between consecutive assessments is no longer required)
Response to Treatment Evaluation

EMBT Criteria
2006 IMWG Criteria
2011 IMWG Criteria

What is Multiple Myeloma?
Diagnostic Tools
Response to Treatment Evaluation
Progressive / Relapse Disease
EBMT Criteria

General consideration: If one data is missing for a defined category, you downgrade to the lower category

<table>
<thead>
<tr>
<th>RESPONSE TO TREATMENT</th>
<th>EBMT CRITERIA FOR COMMON TYPE</th>
<th>EBMT CRITERIA FOR LIGHT CHAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Disease (SD)</td>
<td>Less than 25% ↓ of Monoclonal Protein (MP) in the blood</td>
<td>50-89% reduction in 24h urinary light chain excretion and monoclonal proteinuria &gt; 200 mg/d</td>
</tr>
<tr>
<td>Minimal Response (MR)</td>
<td>Between 25 and 49% ↓ of Monoclonal Protein (MP) in the blood + 50-89% reduction in 24h urinary light chain excretion (monoclonal proteinuria&gt;200 mg/d)</td>
<td></td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>Over 50% ↓ of serum MP + &gt; 90% reduction in 24h urinary light chain excretion or M proteinuria &lt; 200mg/d</td>
<td>&gt; 90% reduction in 24h urinary light chain excretion or monoclonal proteinuria &lt; 200mg/d</td>
</tr>
<tr>
<td>near Complete Response (nCR)</td>
<td>Serum MP = 0 but Serum IF &gt; 0</td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>No Monoclonal Protein (MP) in the blood + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
<td>Partial Response Criteria + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
</tr>
</tbody>
</table>

2006 IMWG Criteria

EBMT criteria plus two (for common type only) minus two (no more MR and nCR)

• VGPR (Very Good Partial Response): more than 90% decrease of MP and urine M protein < 100 mg/d OR SPEP/UPEP negative but IFs or IFu still positive
• sCR (stringent CR): CR and normal free light chain ratio and no clonal cells in bone marrow (immunofluorescence or immunohistochemistry)

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
2006 IMWG Criteria

The Free Light Chain Test

1. Very useful for light chain myeloma
2. Necessary to define sCR

Be careful, sometimes it is the difference between the involved clonal light chain – the uninvolved but it can also be the ratio involved over uninvolved!

Normal polyclonal light chains: \( k = 3.3\text{–}19.4 \text{ mg/l} \), \( l = 5.7\text{–}26.3 \text{ mg/l} \)
Normal polyclonal Free Light Chain (FLC) ratio \( k/l = 0.26\text{–}1.65 \)

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
IMWG implementation of the Free Light Chain Test for Light Chain Myeloma Evaluation

1. First assess response according to monoclonal proteinuria (>200 mg/d at least)

2. If proteinuria assessment not possible, use the serum Free Light Chain (FLC) test

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
Light Chain Myeloma assessment (EBMT Criteria)

- Minimal Response: decrease between 50 and 89% and monoclonal proteinuria > 200mg/d

- Partial Remission: more than 90% decrease in 24h monoclonal proteinuria or monoclonal proteinuria < 200mg/d

- Complete response: PR criteria + serum and urine IF < 0 + < 5% plasma cells in bone marrow

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
Light Chain Myeloma assessment (2006 IMWG Criteria) if Proteinuria Not Evaluable

- Partial response: 50-89% decrease in the difference between involved and uninvolved FLC levels

- VGPR: > 90% decrease in the difference between involved and uninvolved FLC levels

- CR: serum and urine IF < 0 and normal serum Free Light Chain ratio (0.26-1.65) and < 5% plasma cells in bone marrow (If FLC ratio not normal but individual K and L light chain values are normal: CR)

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
## IMWG Uniform Response Criteria 2006

<table>
<thead>
<tr>
<th>Partial Response (PR)</th>
<th>Electrophoresis</th>
<th>Immunofixation</th>
<th>Bone Marrow</th>
<th>Bone Disease</th>
<th>Soft Tissue Plasmacytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 50% reduction in serum and ≥ 90% reduction in urine or to &lt; 200 mg/24hrs or ≥ 50% reduction in FLC kappa/lambda difference if EP unmeasurable</td>
<td>Not required</td>
<td></td>
<td>Stable or improved</td>
<td>≥ 50% decreased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very Good Partial Response (VGPR)</th>
<th>Electrophoresis</th>
<th>Immunofixation</th>
<th>Bone Marrow</th>
<th>Bone Disease</th>
<th>Soft Tissue Plasmacytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undetectable or ≥90% reduction in serum and urine level &lt; 100mg/24hrs</td>
<td>Detectable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete Response (CR)</th>
<th>Electrophoresis</th>
<th>Immunofixation</th>
<th>Bone Marrow</th>
<th>Bone Disease</th>
<th>Soft Tissue Plasmacytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% reduction in serum &amp; urine by conventional electrophoresis</td>
<td>Undetectable</td>
<td>&lt; 5% plasma cells</td>
<td>Stable or improved</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stringent (sCR)</th>
<th>Electrophoresis</th>
<th>Immunofixation</th>
<th>Bone Marrow</th>
<th>Bone Disease</th>
<th>Soft Tissue Plasmacytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All criteria of CR and Normal FLC ratio + IHC or IF negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
### 2006 IMWG Criteria

<table>
<thead>
<tr>
<th>RESPONSE TO TREATMENT EVALUATION</th>
<th>CRITERIA FOR COMMON TYPE</th>
<th>LIGHT CHAIN if proteinuria assessment available (&gt; 200 mg/d at least)</th>
<th>LIGHT CHAIN if proteinuria assessment unavailable &gt; use the serum Free Light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response (PR)</td>
<td>Over 50% decrease of serum MP + 90% reduction in 24h urinary light chain excretion or proteinuria &lt; 200mg/d</td>
<td>&gt; 90% reduction in 24h urinary light chain excretion or proteinuria &lt; 200mg/d</td>
<td>50-89% decrease in the difference between involved and uninvolved FLC levels</td>
</tr>
<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>More than 90% decrease of Monoclonal Protein (MP) in the blood + Urine M protein &lt; 100 mg/d or SPEP/SPUP negative but IFs or IFu still positive</td>
<td>&gt; 90% decrease in the difference between involved and uninvolved FLC levels</td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>No Monoclonal Protein (MP) in the blood + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
<td>Partial Response Criteria + No serum/urine MP by Immunofixation (IF &lt; 0) + &lt; 5% plasma cells in bone marrow aspirate</td>
<td>Serum and urine IF &lt; 0 and normal serum Free Light Chain ratio (0.26-1.65) + ≤ 5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>Stringent (sCR)</td>
<td>CR and normal free light chain ratio and no clonal cells in bone marrow immunofluorescence or immunohistochemistry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Durie BGM. International uniform response criteria for multiple myeloma. Leukemia (2006) 20, 1467-1473
2011 IMWG Criteria

3 Additional Criteria

1. Minimal Response: Decrease of ≥ 25% but < 49% of MP and 24h urine MP decrease between 50 and 89%. If plasmacytoma: decrease 25-49%. No more or increase bone lesions

2. Immunophenotypic CR: Stringent CR (sCR) plus no malignant plasmacytoma by Flow (≥ 4 colours and 1 M cells minimum)

3. Molecular CR: CR + ASO-PCR negative

Criteria 2 and 3 are not yet implemented

Progressive / Relapse Disease

Progressive disease
Clinical relapse
Relapse from CR
Progressive / Relapse Disease

• All progressive/relapse categories require two consecutive assessments made at anytime

• Defining a Progressive disease is necessary to measure TTP, PFS

• Relapse from CR to define Disease Free Survival
Progressive Disease (1):

25% increase compared to the lowest value of:

- Serum MP (absolute increase at least $\geq 0.5$ g/dl)
- Or: Urine MP (absolute increase at least $> 200$ mg/24h)
- Or: for patients without measurable MP

Serum Free Light Chain test: the difference between involved and uninvolved FLC levels
(absolute increase at least $>100$ mg/L)
Progressive Disease (2):

- Or: Increase of $\geq 25\%$ bone marrow plasmocyte (absolute % at least $\geq 10\%$)
- Or: New bone lesion, plasmacytoma
- Or: Hypercalcemia ($> 2.65 \text{ mmol/L}$) attributed only to myeloma
Clinical Relapse

One or more of:

1. New soft tissue plasmacytoma or bone lesion
2. and/or: Increase in the size of existing plasmacytoma or bone lesion
3. and/or: Hypercalcemia (> 2.65 mmol/L)
4. and/or: Decrease in haemoglobin of ≥ 2g/dL
5. and/or: Rise in serum creatinine by 2 mg/dL or more (177 micromol/L or more)
Relapse from CR

1. Reappearance of serum or urine MP by IF or SPEP/UPEP
2. Or ≥ 5% plasma cells in bone marrow
3. Or any other sign of progression (new plasmacytoma, lytic bone lesion, hypercalcemia)
Clinical Cases
Common Difficulties

First question: what is the baseline?
Progression of disease or new line of treatment - usually means a new baseline

- No baseline evaluation = not evaluable
- If one data is missing for a defined category, you downgrade to the lower category
- e.g: M-Protein = 0 and IF unknown = nCR
- M-Protein >0 and IF=0: not a nCR
- Check which criteria are used EBMT and/or IMWG?
- Other…. 
Case N° 1

A patient is diagnosed with IgG kappa myeloma.

- M-spike = 60 g/L (from SPEP)
- 24-hr urine M-protein = 1000 mg
- Bone marrow biopsy had 40% plasma cells
- Patient was treated with Velcade®, Doxil® & Dexamethasone for 4 cycles
Patient was re-evaluated after the 4th cycle of VDD. The M-spike = 24 g/L & there were 15% plasma cells on the bone marrow biopsy. The patient achieved a PR.

The patient received Cytoxan for autologous stem cell mobilization. The next set of labs were obtained immediately prior to the start of the preparative regimen. The M-spike = 16 g/L & 8% plasma cells were noted on the bone marrow biopsy.
What is the patient’s disease status immediately prior to the start of the preparative regimen?

A. Stable Disease (SD)
B. Very Good Partial Remission (VGPR)
C. Partial Remission (PR)
D. I do not know - not enough information provided to make determination
The recipient from case #1 has had its autologous HSCT. Lab studies are obtained at 60 & 100 days post HSCT.

- SPEP/UPEP are negative for an M-spike at Day 60 & 100
- Serum & Urine Immunofixation are positive for IgG kappa at Day 60 & 100
- Bone marrow biopsy < 5% plasma cells at Day 100
What disease response code would you report for this recipient at 100 days post-HSCT?

A. Partial Remission (PR)

B. Very Good Partial Remission (VGPR)

C. Complete Remission (CR)

D. None of the above
Case N° 2

A 55 year old male is diagnosed with IgG lambda myeloma. Results of the initial work-up include:

- Serum M-spike = 40 g/L
- 24-hr urine M-protein = 1000 mg
- Bone marrow biopsy = 60% plasma cells

Patient receives 2 cycles of Revlimid® & Dexamethasone & then re-evaluated

- Serum M-spike = 20 g/L
- 24-hr urine M-protein = 400 mg
Case N° 2

What is the patient’s disease response after two cycles of Rev/Dex?

A. Partial Remission (PR)
B. Very Good Partial Remission (VGPR)
C. Stable Disease (SD)
The patient’s PR status was confirmed with a 2nd measurement. The patient received two additional cycles of Rev/Dex & then re-evaluated for disease response.

- Serum M-spike = 29 g/L
- 24-hr urine M-protein = 600 mg
- Bone marrow biopsy = 30% plasma cells
What is the patient’s disease response after a total of four cycles of Rev/Dex?

A. Stable Disease (SD)

B. Progressive Disease (PD)  ✔

C. Partial Remission (PR)
Case N° 2

Patient is switched to Vincristine, Adriamycin & Decadron® (VAD) and is re-evaluated after two cycles.

- Serum M-spike = 14 g/L
- 24-hr urine M-protein = 250 mg
- Bone marrow biopsy = 15% plasma cells

The plan is to give IV Cytoxan mobilization. What is the patient’s disease response to the 2 cycles of VAD?
The patient has achieved a PR after two cycles of VAD. What studies were used as a baseline to make that determination?

A. The studies obtained at diagnosis

B. The studies obtained at time of progression

C. The studies obtained after first two cycles of Rev/Dex
The patient has undergone their autologous PBSC HSCT & has been evaluated monthly for the 1st three months post HSCT.

**Day +30 Evaluation**

- Serum M-spike = 10 g/L
- Serum immunofixation (+) for IgG lambda
- 24-hr urine M-protein = 190 mg
- Bone marrow biopsy = 7% plasma cells
Day +60 Evaluation

- SPEP/UPEP- no monoclonal band
- Serum/Urine immunofixation (+) for IgG lambda
- 24-hr urine for M-protein = 90 mg
Day +100 Evaluation

- SPEP/UPEP- no monoclonal band
- Serum/Urine immunofixation (+) for IgG lambda
- 24-hr urine for M-protein = 90 mg
- Bone marrow biopsy < 5% plasma cells
What is the best disease response to HSCT that you would report at Day +100 for this patient?

A. Stable Disease (SD)
B. Partial Remission (PR)
C. Very Good Partial Remission (VGPR)
D. Complete Remission (CR)
Case N° 3

› A patient received a planned maintenance therapy (Revlimid®) starting on Day 100 Post-HSCT. At 6 months of maintenance: ‘Best response to line of therapy’ needs to be answered.

› What baseline studies would you use to determine the response he/she may have had to the Revlimid® maintenance?
Case N° 3

**A.** Use the results obtained prior to starting Revlimid®

**B.** Use the results obtained at diagnosis

**C.** Use the results obtained immediately prior to the start of the preparative regimen for HSCT
A 60 year old man receives an Auto PBSC HSCT for Multiple Myeloma. At Day +100, it is determined that he has achieved a VGPR in response to the HSCT. He’s monitored on a monthly basis & on the last set of results obtained at the time of his 6 month f/u visit he now meets the criteria for CR. He’s doing well and does not return for f/u until 3 months later. Results at that time confirm that he is in CR. He remains in CR for 2 more years.
What is the proper response code to report at 6 months?

A. Very Good Partial Remission (VGPR)
B. Partial Remission (PR)
C. Complete Remission (CR)
D. Stable Disease (SD)
When there hasn’t been a second assessment in the same reporting period to confirm the response, you report the disease status that was previously confirmed.

In this example, you would report VGPR at 6 months. At 1 year, you would report the CR & the date when the CR was first documented.
In other words, even though documentation of response requires a confirmatory measurement, the start time for date of response is the first date at which the response was noted.
Conclusions

Make your own assessment and have it confirmed by your local principal investigator of the trial
# TABLE 1

## Rules for Use of Data for Evaluation

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain (Bence-Jones) myeloma with “non-measurable” serum light chain</td>
<td>Use only 24 hour urine M-spike value for response evaluation, except for complete response (CR)</td>
</tr>
<tr>
<td>IgG, IgA or IgD myeloma with “non-measurable” serum M-spike values and measurable urine M-spike</td>
<td>Use only urine values for response evaluation except for CR or PD</td>
</tr>
<tr>
<td>Disease with “measurable” values at screening but “non-measurable” at baseline (cycle 1, day 1)</td>
<td>All assessments not meeting CR or PD should be “non-evaluable (NE)”</td>
</tr>
<tr>
<td>Missing data for 2 or more consecutive cycles</td>
<td>Consider “NE” for the specific missing cycle assessments</td>
</tr>
<tr>
<td>M-spike reported as “too small to quantitate” in responding patient</td>
<td>Assign value of 0 to allow subsequent calculation of absolute increase to determine PD</td>
</tr>
<tr>
<td>Plasmacytoma given prior radiation therapy or located only in bone</td>
<td>Not used for response assessment, except for potential PD</td>
</tr>
</tbody>
</table>

### TABLE 2

**Rules for Response Assessment**

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of 2 consecutive negative IFE and simultaneous &lt;5% BMPCs</td>
<td>CR not assigned, assess as VGPR</td>
</tr>
<tr>
<td>Extramedullary plasmacytomas (EMPs)</td>
<td></td>
</tr>
<tr>
<td>• Visits until first EMP assessment</td>
<td>Assess as NE</td>
</tr>
<tr>
<td>• Two consecutive missing EMP assessments</td>
<td>Assess as NE</td>
</tr>
<tr>
<td>• EMPs not assessed as per protocol</td>
<td>Assess as NE (consider a sensitivity analysis (ignoring EMPs))</td>
</tr>
<tr>
<td>• Patients in serologic VGPR, with 50% decrease in EMP, but still</td>
<td>Assess as PR, until EMPs have disappeared</td>
</tr>
<tr>
<td>present</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3

Rules for Determining Progressive Disease

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in a previously existing EMP or bone lesion as only source of PD</td>
<td>Request verification of radiologist reports before PD is assigned</td>
</tr>
<tr>
<td>Initiation of a new antmyeloma therapy before documented PD</td>
<td>Censor at the time of last assessment before starting the new therapy</td>
</tr>
<tr>
<td>PD only based on the BMPCs</td>
<td>Determine reason for BM exam (anemia? bone pain?) before assigning PD</td>
</tr>
<tr>
<td>Radiation therapy not for pre-planned reasons</td>
<td>Assess as PD</td>
</tr>
<tr>
<td>PD based on M-protein measurements with no confirmation</td>
<td>Censor unless that PD is considered unequivocal by unanimous agreement of IRAC</td>
</tr>
<tr>
<td>Increase in a previously existing EMP or bone lesion as only source of PD</td>
<td>Request verification of radiologist reports before PD is assigned</td>
</tr>
</tbody>
</table>