UNDERSTANDING MULTIPLE MYELOMA AND LABORATORY VALUES

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UNDERSTANDING MULTIPLE MYELOMA

Multiple Myeloma is a cancer of the immune system, in particular of the plasma cell a mature b lymphocyte.

Plasma cells produce antibodies(immunoglobulins) that normally protect us from infection but in multiple myeloma these
are nonfunctional and are called paraproteins.

All of the paraproteins from any one individual are monoclonal (identical) because the myeloma cells are identical clones of a single plasma cell.

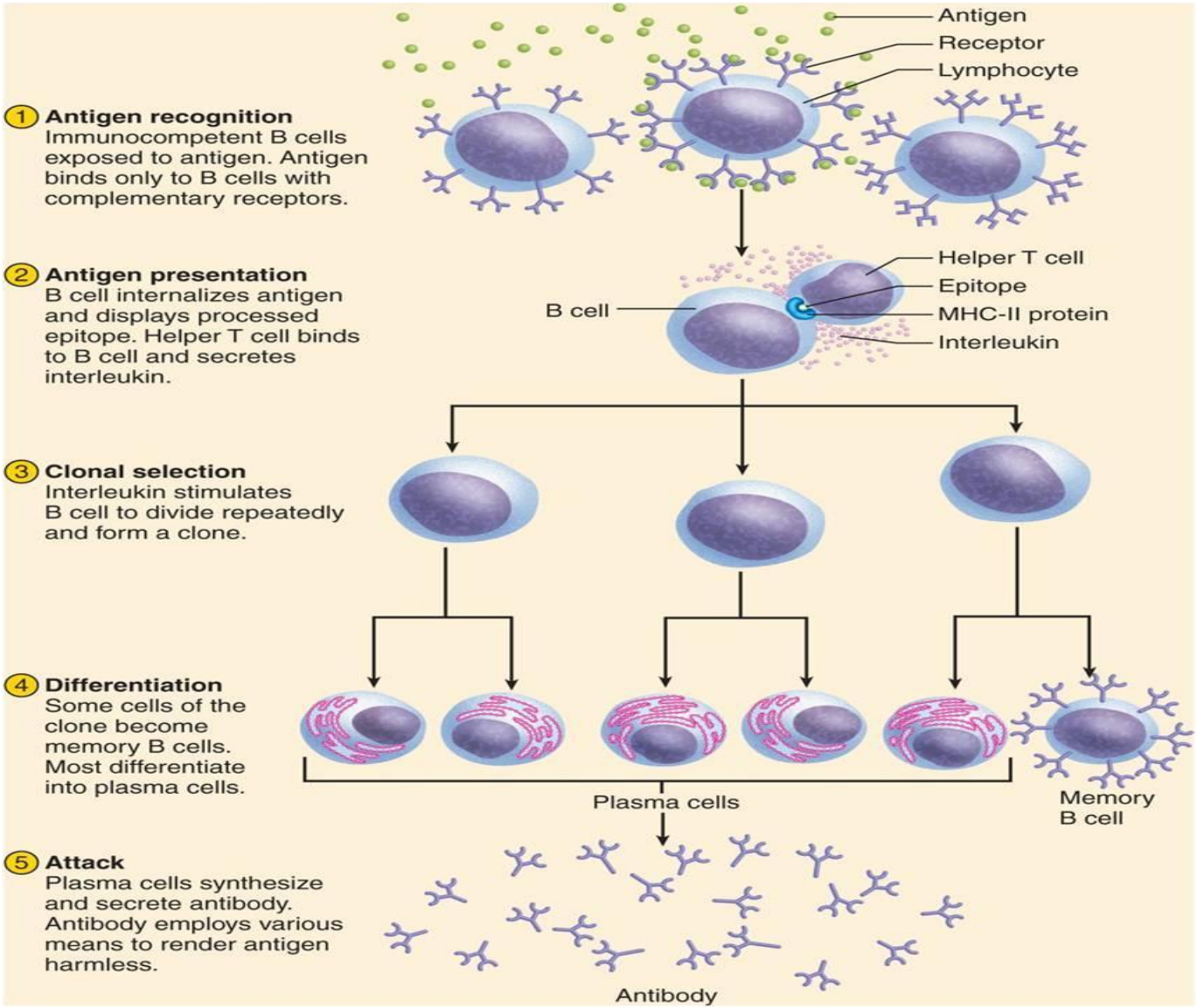
THE IMMUNE SYSTEM

Cellular Immune System

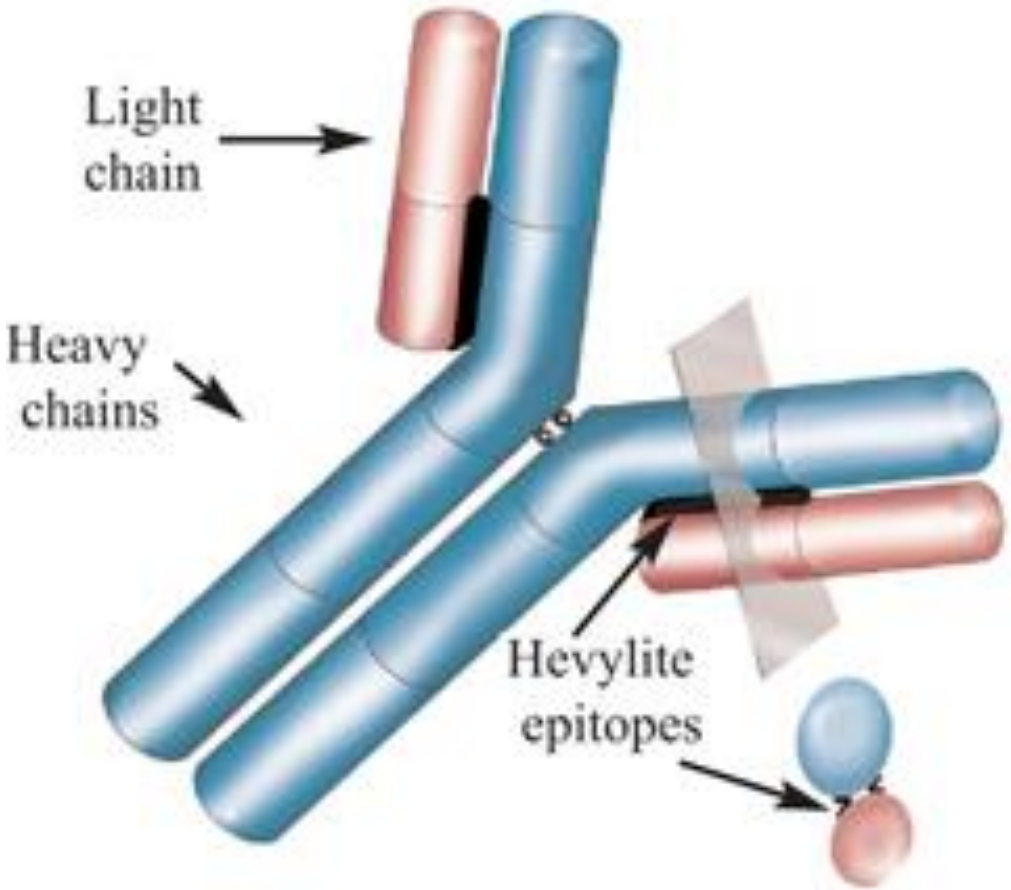
- White Blood Cells: Granulocytes
  Lymphocytes: T cells

Humoral Immune System

- B cells and antibodies


1 Antigen recognition
Immunocompetent B cells exposed to antigen. Antigen binds only to B cells with complementary receptors.
2 Antigen presentation
B cell internalizes antigen and displays processed epitope. Helper T cell binds to B cell and secretes interleukin.
3 Clonal selection
Interleukin stimulates B cell to divide repeatedly and form a clone.
4 Differentiation
Some cells of the clone become memory B cells. Most differentiate into plasma cells.
5 Attack
Plasma cells synthesize and secrete antibody. Antibody employs various means to render antigen harmless.
Antigen
Receptor
Lymphocyte
Helper T cell
Epitope
B cell
MHC-II protein
Interleukin
Plasma cells
Memory B cell
Antibody

AB BASIC STRUCTURE



Types of Antibodies

- Types of Heavy Chains
  - IgG
  - IgA
  - IgM
  - IgD
  - IgE
- Types of Light Chains
  - Kappa
  - Lambda

What happens in Multiple Myeloma?

- Malignant plasma cell makes a clone of itself and these malignant plasma cells, or myeloma cells, accumulate in the bone marrow.

- The malignant plasma cells secrete an antibody, or immunoglobulin, called the **M- protein**, or **M- spike**, or **paraprotein** or **myeloma protein**. It can be detected in the blood and/or the urine of *most* myeloma patients.

Laboratory Testing for Multiple Myeloma

Why perform lab tests?

Goals:

- Diagnosis
- Determine severity and spread (staging)
- Monitor progress of disease
- Detect complications
- Monitor the effectiveness of treatment

Comprehensive Metabolic Panel

A group of tests used to evaluate kidney and liver function, electrolyte status, and to determine calcium and total protein levels

- Total protein
- Calcium
- Creatinine

Other chemistry tests important in Multiple Myeloma

- $Beta_2$-microglobulin
- Serum albumin level
- Serum Viscosity

Complete Blood Count (CBC)

- Hemoglobin / Hematocrit

  - *measure of red blood cells*

  - *red blood cells carry oxygen*

- White Blood Cell Counts

  -*absolute neutrophil counts (ANC)*

  - *fight off and protect against infection*

- Platelet Counts

  -*platelets are responsible for stopping bleeding and blood clotting*

Quantitative Immunoglobulins

- Measures amounts of the different immunoglobulins
- Myeloma protein will be an **IgG** or **IgA**, or less commonly IgD or IgE
- Levels will help monitor the course of the disease
- Important to be aware of the levels of the normal (non-myeloma) immunoglobulins

Protein Electrophoresis and Immunofixation

- Protein electrophoresis separates the proteins in a blood or urine sample into several groups based on their size and electrical charge.

- In most patients with MM, large amounts of an abnormal immunoglobulin protein (M-spike) will appear as a large peak on the graph.

- Immunofixation is done to identify the specific type of protein that is being produced by the malignant plasma cells. The amount of protein produced may vary throughout the course of the disease, but the type generally will remain the same.

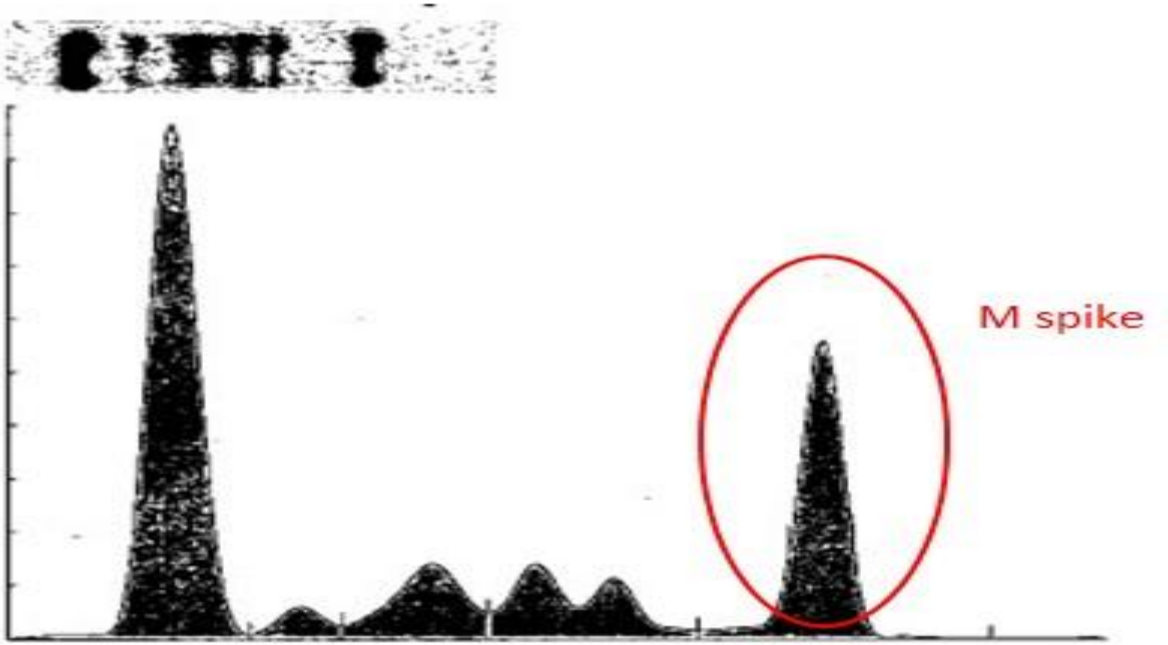
Normal Serum Protein Electrophoresis Pattern

Fraction	%	g/dL	g/dL Range	
Albumin	57.35	3.56	3.50	4.70
Alpha 1	4.95	0.31+	0.10	0.30
Alpha 2	11.92	0.74	0.50	1.00
Beta	13.42	0.83	0.80	1.40
Gamma	12.35	0.77	0.60	1.60
Total		6.20		

Figure 1

Typical normal pattern for serum protein electrophoresis.

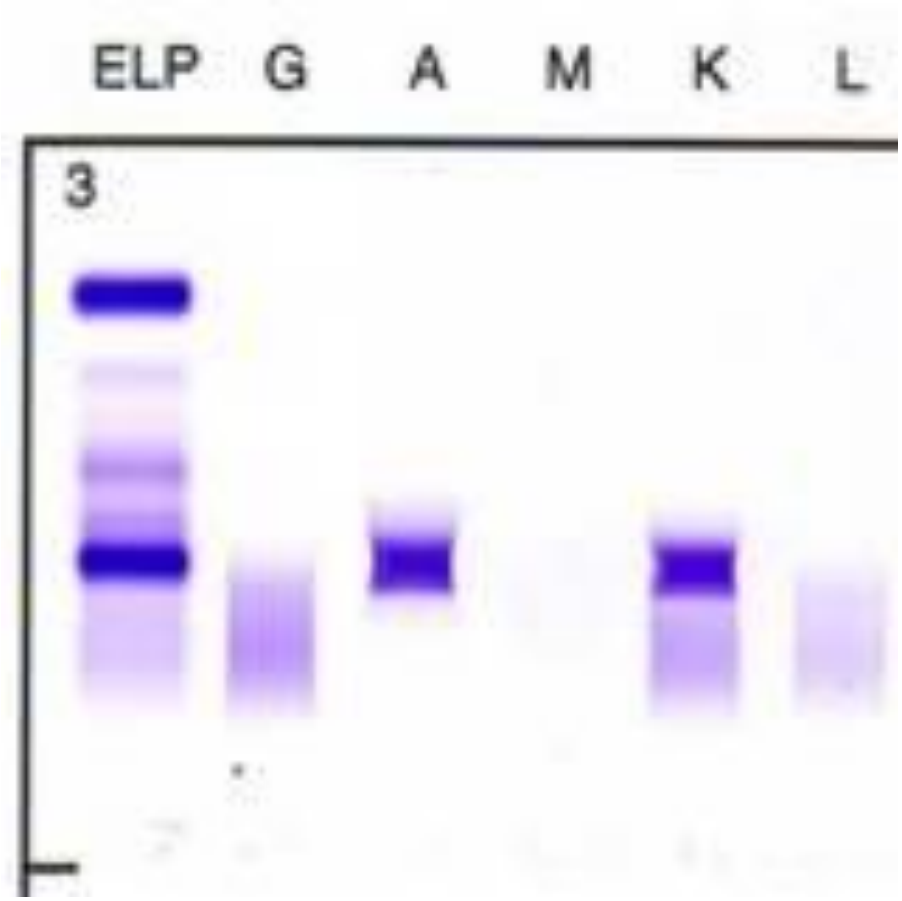
Abnormal Serum Protein Electrophoresis



Fraction	%	g/dL	g/dL Range	
Albumin	48.31	3.91	3.50	4.70
Alpha 1	2.97	0.24	0.10	0.30
Alpha 2	10.40	0.84	0.50	1.00
Beta	12.96	1.05	0.80	1.40
Gamma	25.35	2.05+	0.60	1.60
M-Spike	20.86	1.69		

Figure 2
Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.

Immunofixation Electrophoresis (IFE)



Serum Free Light Chains (FLC) or FreeLite Assay

- Measures the amount of free light chains in the serum (blood).

- In normal circumstances, plasma cells produce an excess of light chains compared to heavy chains. A small amount of these light chains will not become incorporated into intact immunoglobulins. These are “free” light chains and are released into the blood.

Serum Free Light Chains (cont'd)

- Most patients with Multiple Myeloma produce increased amounts of either kappa or lambda free light chains, which can be measured in the blood.
- Consequently, the ratio of kappa to lambda light chains is abnormal in most patients and is a sensitive indicator for this disease.
- This test may be used to monitor progression and/or treatment.

Bone Marrow Aspirate and Biopsy

- Most laboratory tests for Multiple Myeloma provide ***indirect*** information about the amount of tumor present, by measuring proteins that are secreted by the tumor into the blood and/or the urine.

- These tests do not provide the same information as looking at the tumor itself. The myeloma cells are usually only found inside the bone marrow.

Bone Marrow Aspirate and Biopsy (cont'd)

- Small fragments of bone marrow cells can be withdrawn with an aspirate needle, and a small core of bone and marrow is often removed at the same time with a different type of needle.

- Both tests are done to determine how much of the normal bone marrow is replaced by myeloma cells.

- Additional, specialized testing (cytogenetics and FISH) can be performed which can provide information about the biology of the tumor itself.

Updated IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS	Smoldering Myeloma	Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma defining events	▪ Underlying plasma cell proliferative disorder ▪ AND 1 or more myeloma defining events ▪ ≥ 1 CRAB* feature ▪ Clonal plasma cells in BM ≥ 60% ▪ Serum free light chain ratio ≥ 100 ▪ > 1 MRI focal lesion

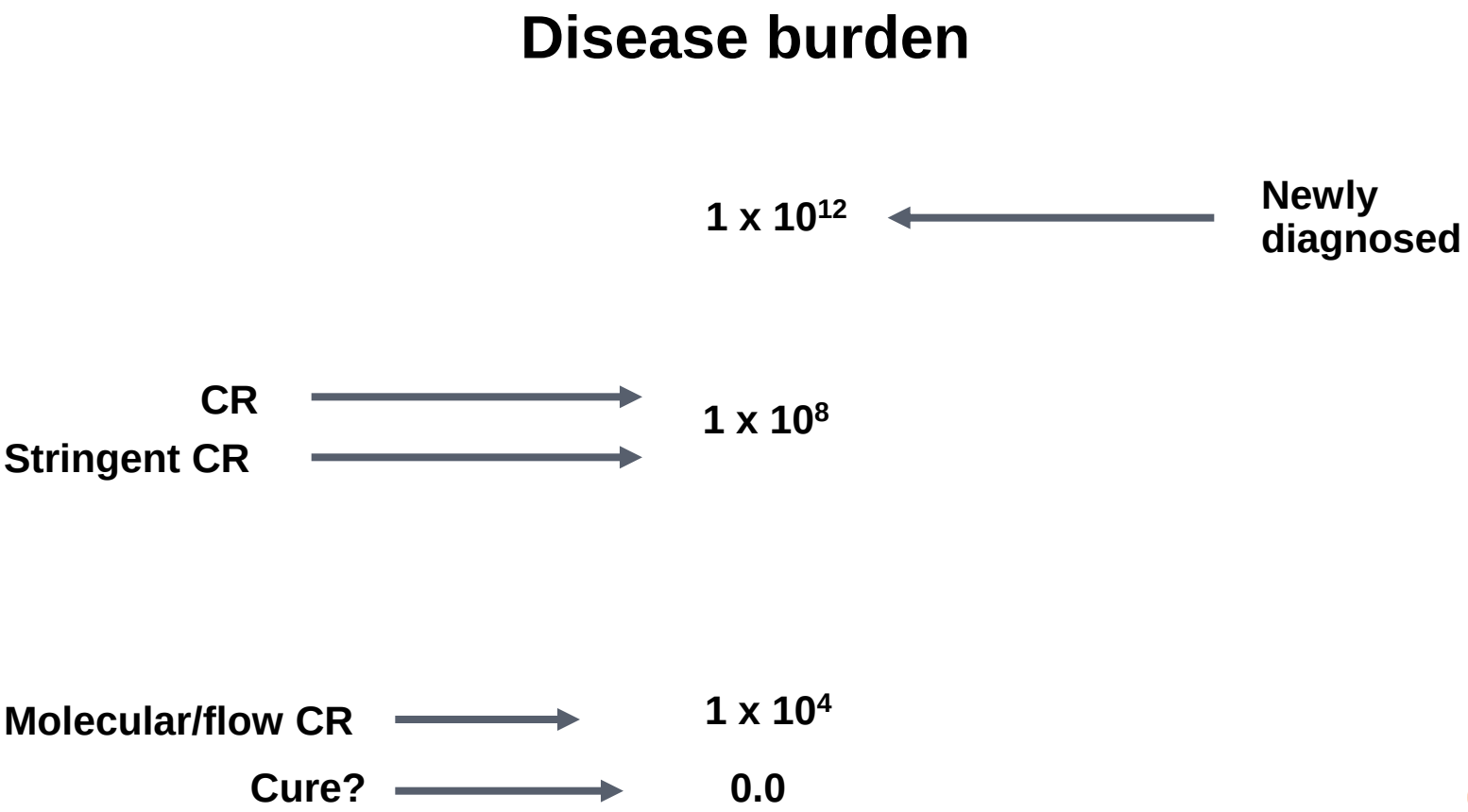
*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Response IMWG criteria

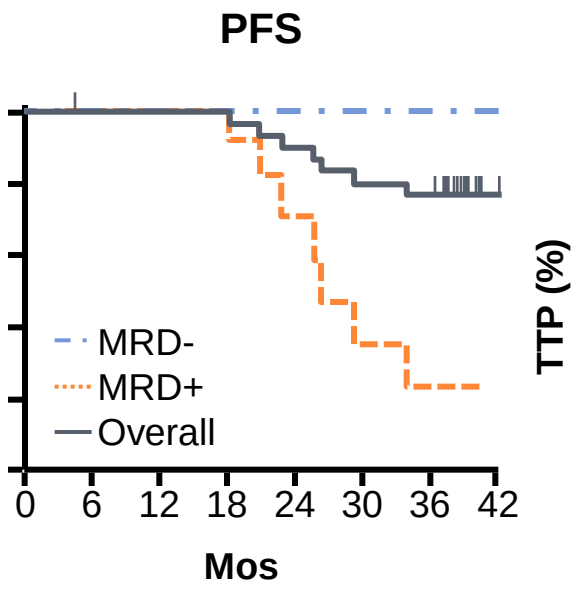
- CR Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow
- VGPR Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
- PR ≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,5 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 not measurable, and serum free light assay is also not measureable, ≥ 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

Getting to Minimal Residual Disease: New Definitions for CR

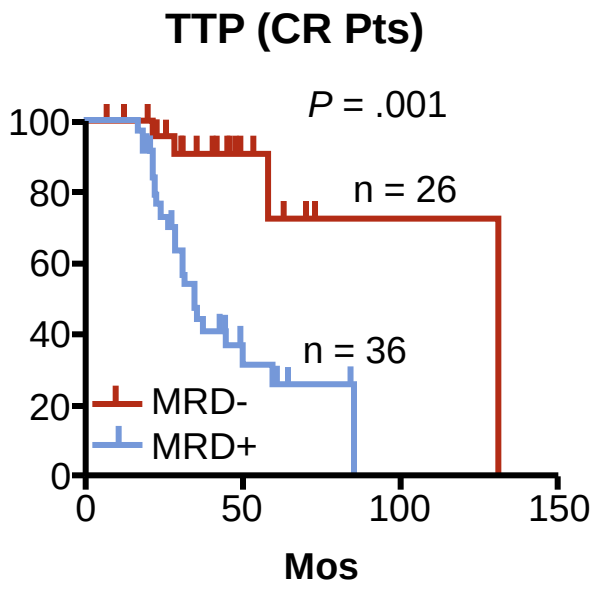


Methods for Assessing Minimal Residual Disease to Predict Outcome

8-Color Flow[1]



Next-Gen Sequencing[2]



1. Roussel M, et al. J Clin Oncol. 2014;32:2712-2717. 2. Martinez-Lopez J, et al. Blood. 2014;123:3073-3079.

Role of MRD Assessment

- Remains a research tool, but indications are that lower levels of MRD predict for better outcomes
  - Can contribute to better definition of response
  - Potential to monitor efficacy of therapy
- Best, easily exportable method and optimal time point is still under investigation
- Even pts who achieve MRD- state can relapse, so all may not be able to stop therapy
- Unsure if changing therapy based on depth of response alters survival outcomes, unsure of next steps for MRD-