Amsterdam UMC
Universitair Medische Centra

Immune reconstitution in multiple myeloma

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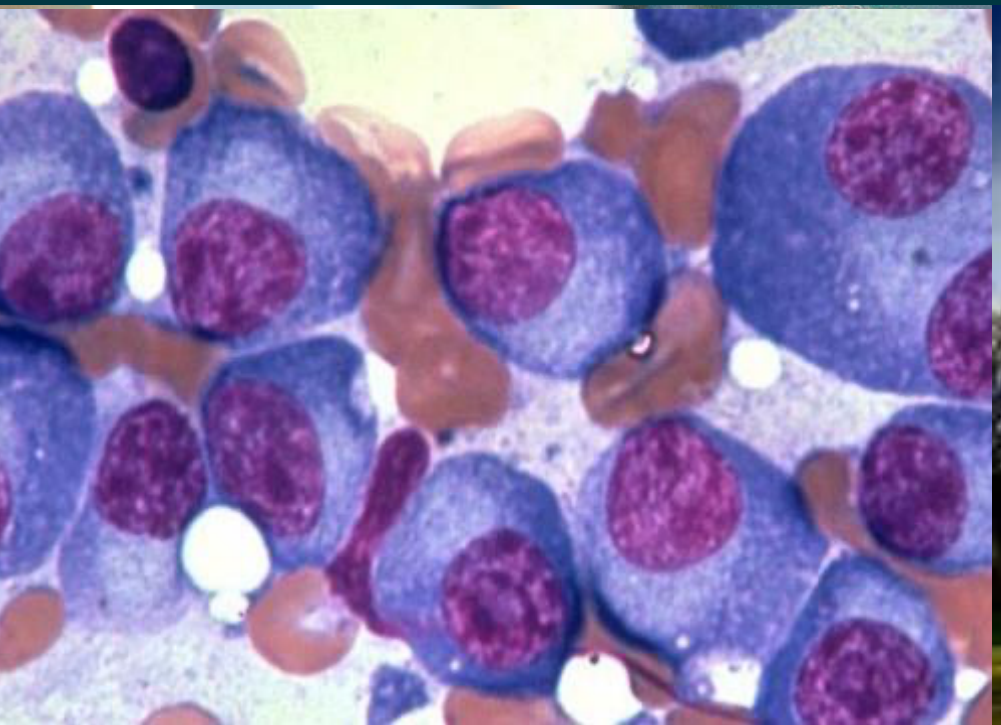
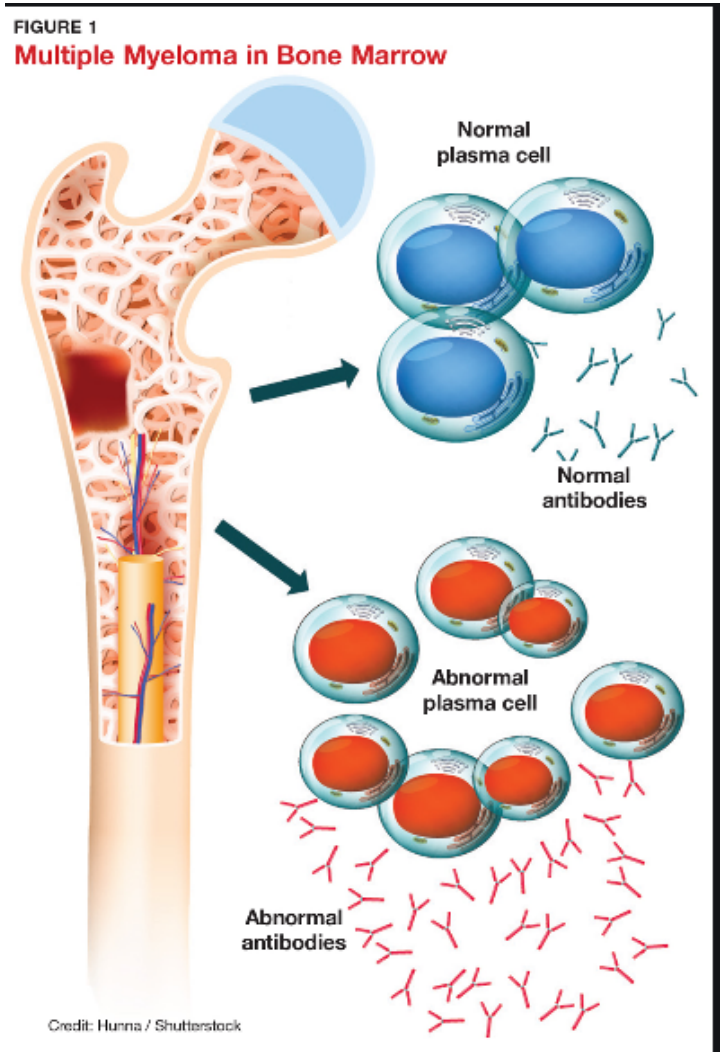


Outline

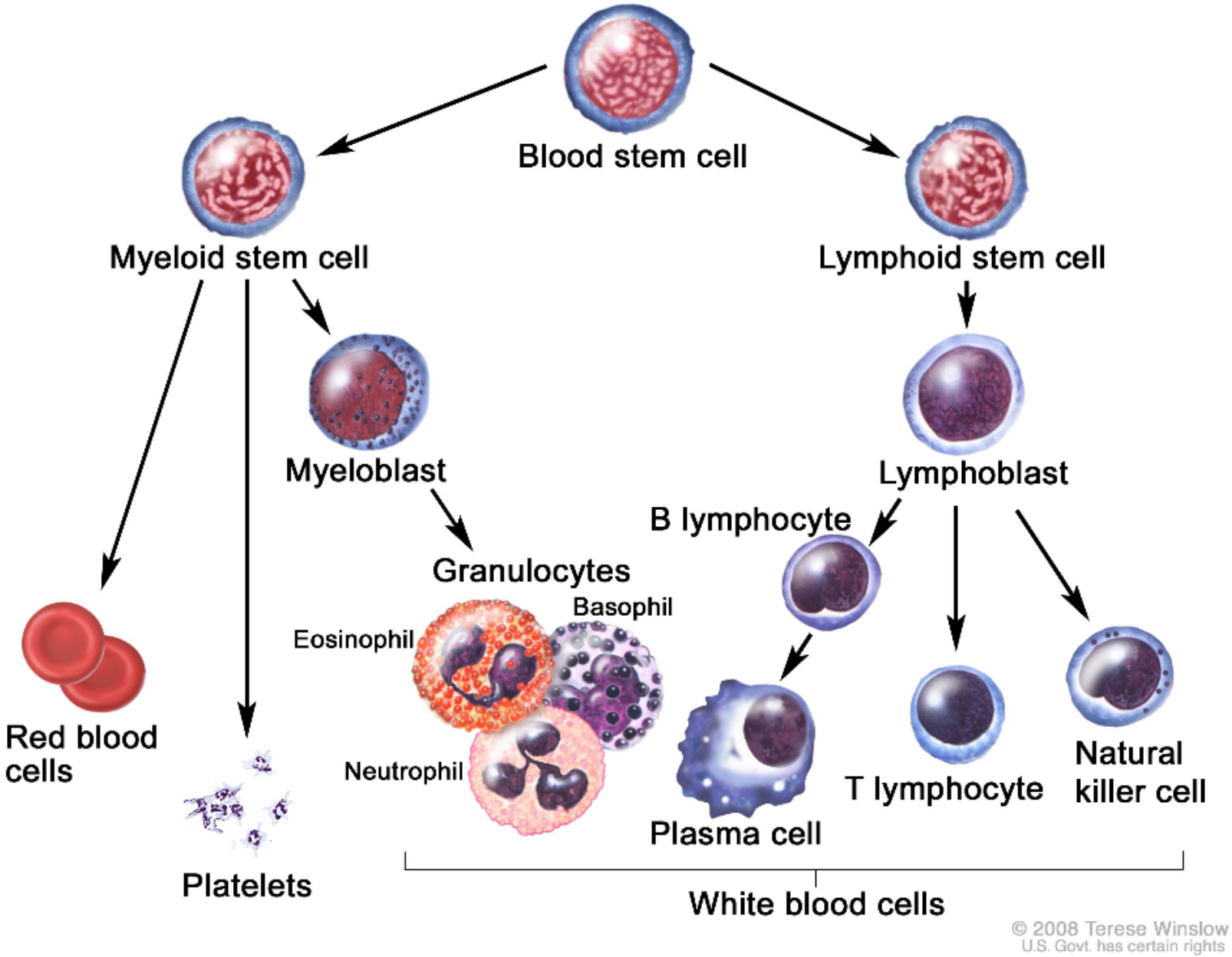
- Multiple myeloma
- Immune reconstitution
- Secundary MGUS
- Clinical meaning?

Introduction

- Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells characterized by
  - a decrease in both the number and the functionality of immune effector cells (ie, natural killer [NK] and T helper cells)
  - an increase in immune suppressor cells (ie, regulatory T-cells and myeloid-derived suppressor cells)
  - and osteoclast activation
  - leading to tumor progression, infection, and osteolytic bony lesions



Wadhera et al. *Blood*. 2011;118(11):2985-2987


Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloblast
Lymphoblast
B lymphocyte
Granulocytes
Basophil
Eosinophil
Neutrophil
Red blood cells
Platelets
Plasma cell
T lymphocyte
Natural killer cell
White blood cells
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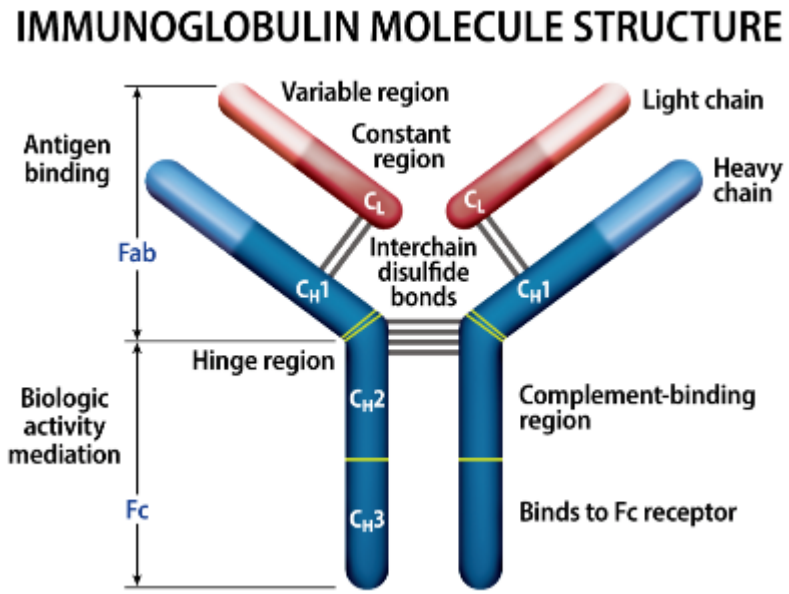
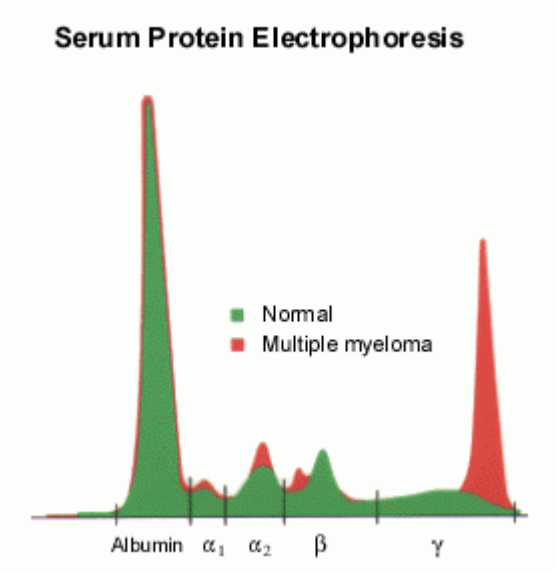
Introduction

- Malignant plasma cell clones almost always produce a single unique monoclonal heavy and/or light chain with a constant isotype
- This is represented on serum protein electrophoresis (SPEP) as an M-spike/ m-protein
- This is used as a marker for diagnosis and monitoring of disease and response in MM

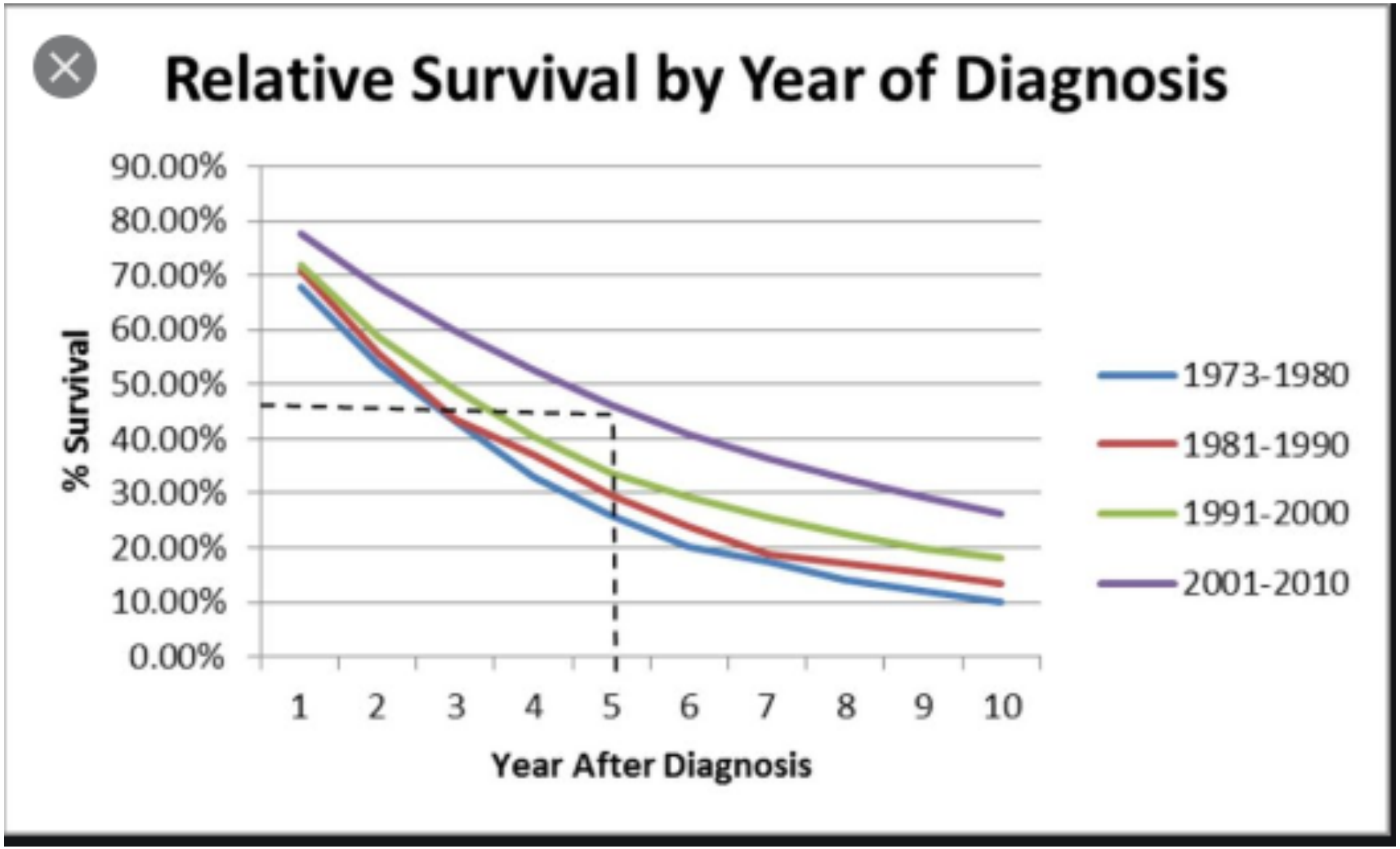




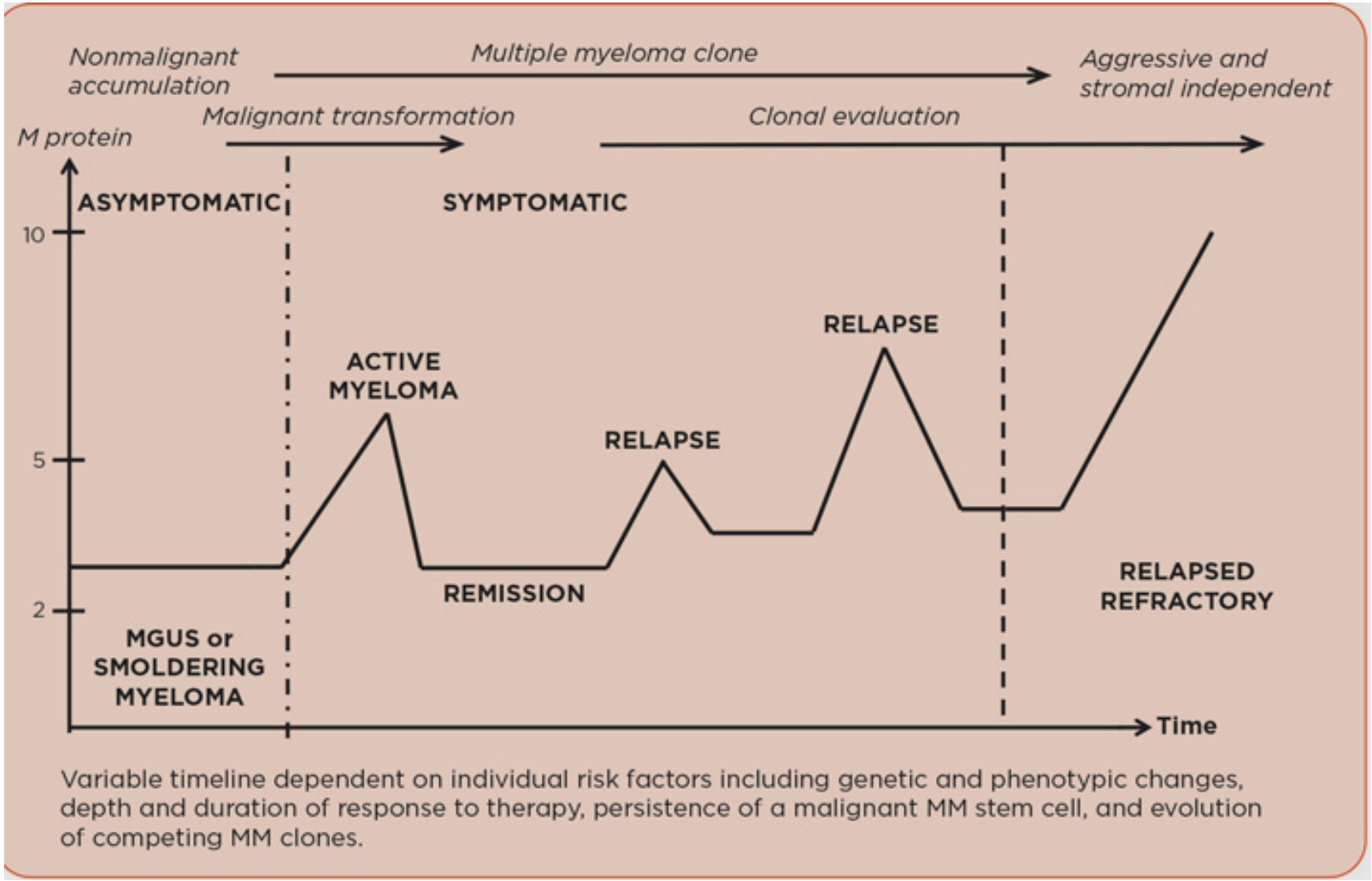
Introduction

- In the course of MM, patients may develop monoclonal bands of different isotypes to the original myeloma M-protein

- Several terms have been used to describe this phenomenon, including:
  - abnormal protein band,
  - oligoclonal protein bands,
  - transient mono- or oligoclonal gammopathy,
  - apparent isotype switch,
  - oligoclonal humoral response,
  - atypical serum immunofixation pattern,
  - clonal isotype switch (CIS),
  - and in myeloma patients, *secondary monoclonal gammopathy of undetermined significance (sMGUS)*



- During the past 2 decades, the advent of novel agents has led to significantly increased survival for patients with MM



- Howevers, unfortunately MM is still uncurable.
- MM knows a relapsing and remitting course

Keats. 2012

Introduction

- High-dose melphalan with autologous hematopoietic stem cell transplantation (ASCT) is the standard of care for fit patients with MM and is aimed at achieving long-term remission

- Robust post-ASCT immune system reconstitution has been shown to correlate with deeper responses and improved clinical outcomes

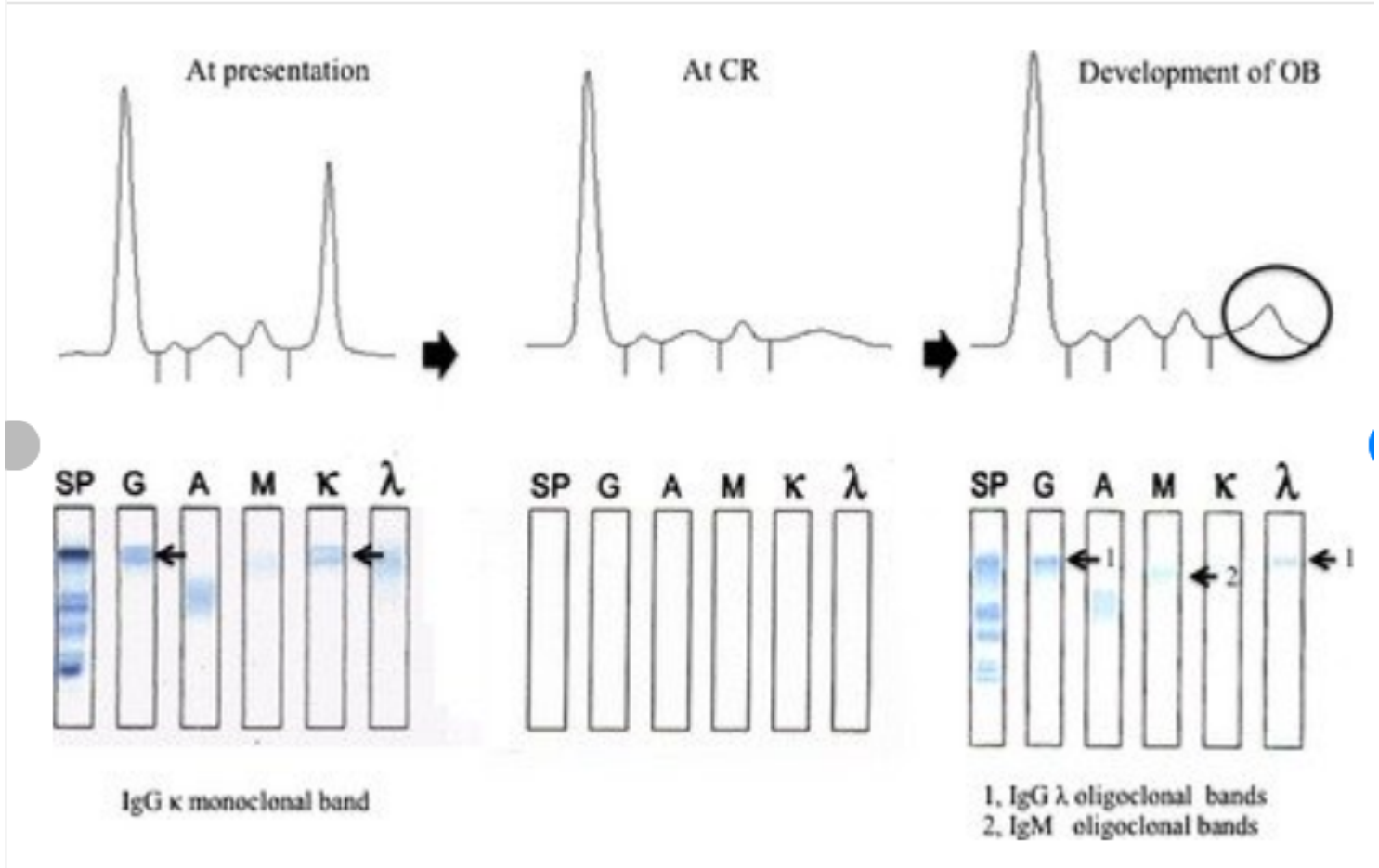
- Although currently, no ‘specific validated immune signature’ has been determined to predict superior survival among patients with MM, studies have reported on a clonal isotype switch (CIS) after ASCT

Clonal isotype switch/secundary MGUS

- Normally, MM relapse will present with the original monoclonal protein documented at diagnosis and not with the CIS protein

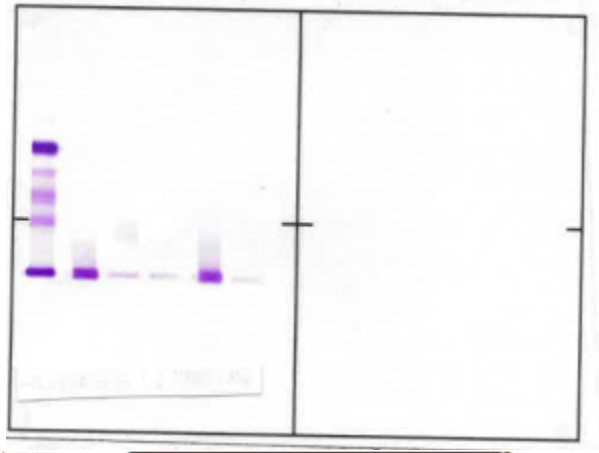
- This would suggest that the transient CIS bands might represent part of the post-transplant immune reconstitution process and might even possess some anti-MM activity?

Example of CIS/sMGUS

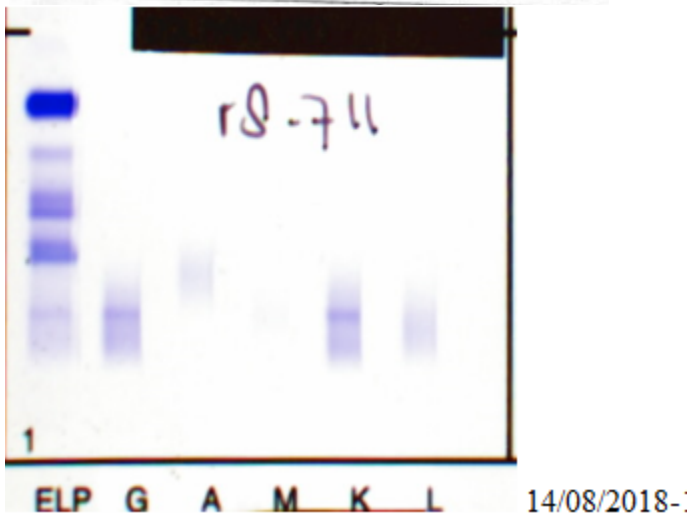


Example from our own clinic

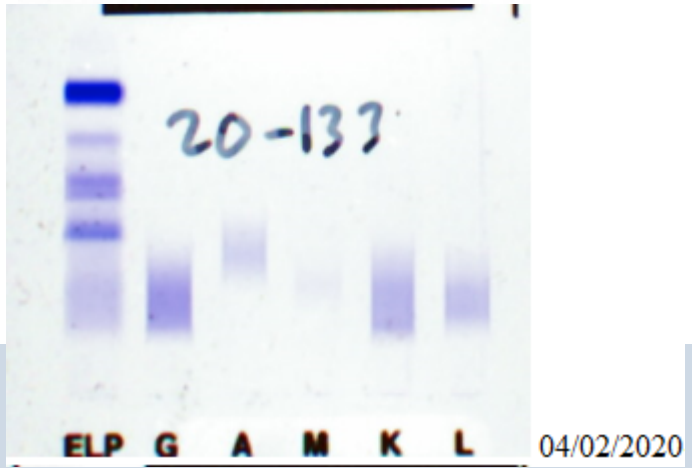
- Origineel uit Jeroen Bosch in 2015:



- MGUS uit 2018, 6 maanden na allogene SCT. Respons: CR (runt op andere hoogte dan de originele)



- Laatste gel (februari 2020): heel licht onderaan is weer een klein bandje zichtbaar. En deze runt helaas inderdaad op dezelfde hoogte als de originele M-proteïne



1. Retrospective clinical cohort study Mayo Clinic

- 1942 patients diagnosed with MM, median follow-up of 7 years
- A **secondary MGUS** developed in 128 (**6.6%**) of these MM patients
  - 34 (27%) had multiple secondary MGUS of various isotypes
- More common in patients who had undergone SCT (104 [**22.7%**] of 458 patients) than in those who had not (24 [**1.6%**] of 1484; *P* 0.001)
- Median time from diagnosis of MM to secondary MGUS; 12 months (95% CI 2-63 mo)
- The median duration of secondary MGUS was 5.9 mo

Wadhera et al. *Blood*. 2011;118(11):2985-2987

1. Retrospective clinical cohort study Mayo Clinic

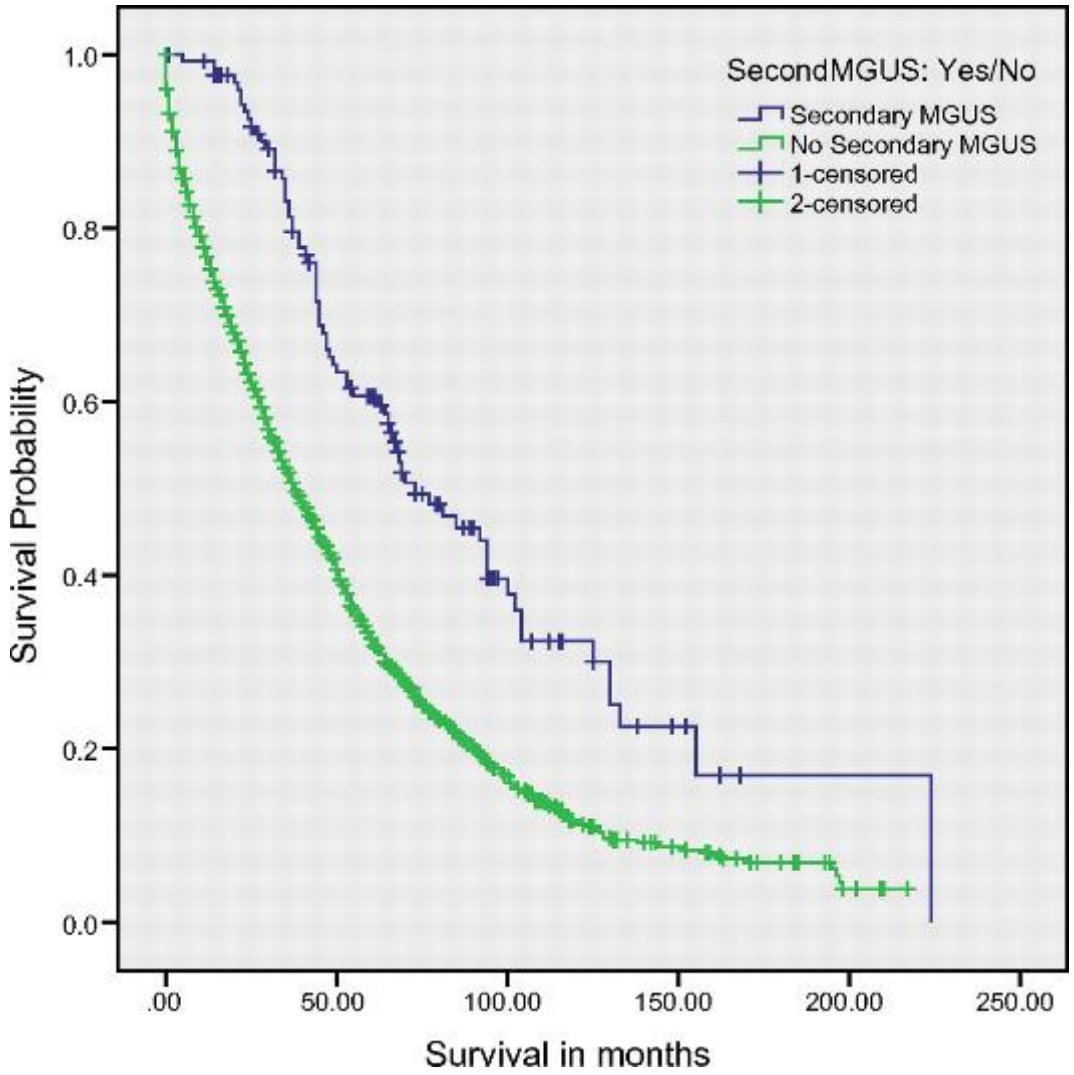
- Most secondary MGUS M proteins were small;
  - detectable by immunofixation only in 84 patients (66%),
  - 0.2 to 0.9 g/dL in 29 patients (23%),
  - and ≥1 g/dL in 15 patients (12%)

- In most patients (87%), the underlying MM was responsive to therapy at the time of secondary MGUS diagnosis

- Median overall survival (OS) of the study cohort was 41 months
- OS was significantly superior among patients who developed secondary MGUS compared with the rest of the cohort (73 vs 38 months, respectively; $P = 0.001$)

Wadhera et al. *Blood*. 2011;118(11):2985-2987

Overall survival



R. Wadhera, R. Kyle et al, Incidence, clinical course, and prognosis of secondary monoclonal gammopathy of undetermined significance in patients with multiple myeloma, Blood, 2011, Figure 1

Survival

- Survival of patients diagnosed since the year 2000 (n = 1088);

Also here, OS was superior in patients with second MGUS (n = 86) versus those without (n = 1002; median 77 vs 51 months, respectively; $P = 0.001$)

- On multivariate analysis, secondary MGUS and date of diagnosis of MM were independently predictive of OS ($P = 0.001$ for both factors)

2. Patients and Methods

- Patients with MM who had undergone ASCT from 2007 to 2016 were included in the present study
- The percentage of natural killer cells, B-cells, and T-cells was measured using flow cytometry in pre- and post- ASCT bone marrow samples
- CIS was defined as the appearance of a new serum monoclonal spike on serum protein electrophoresis and immunofixation that differed from original heavy or light chain detected at diagnosis

2. Results

- 177 patients with MM who had undergone ASCT during the study period

- A CIS was detected in 39 patients (22%)
  - Seventeen patients (46%) had only 1 new monoclonal protein
  - However, 10 (25%) had developed ≥ 4 monoclonal bands

- The newly detected monoclonal proteins were small, < 0.5 g/dL in 34 patients (87%)

- The median interval to the occurrence of a CIS was 7.1 mo (range, 1.9-32 mo)

- Patients with a relapse had an isotype that differed from a CIS, confirming the benign nature of this phenomenon

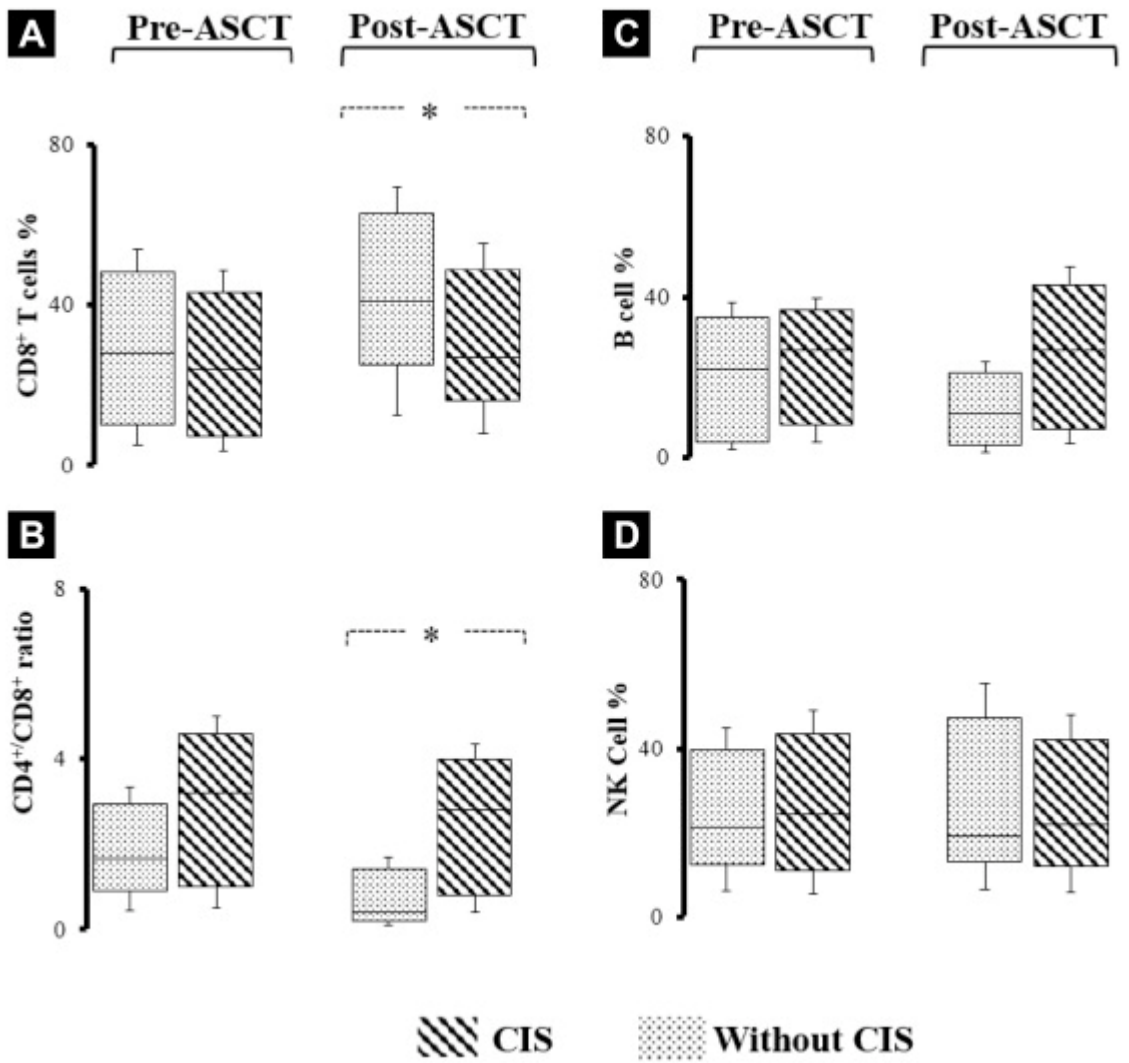
2. Correlations

- A significantly greater incidence of CIS was found in patients who had received lenalidomide, an immunomodulatory drug, before ASCT (30.4% vs. 11.2%; *P* = 0.001), patients with IgA myeloma (21% vs. 7%; *P* = 0.01), and patients who had achieved minimally a very good partial response before ASCT (52% vs. 23%; *P* = 0.023)

- Also, a CIS occurred more frequently in patients without suppressed uninvolved immunoglobulin (92% vs. 8%; *P* = 0.001)

2. Immune Subset Recovery in Patients With CIS

- The number of periph[illegible]s in MM
- No differences betwee[illegible]r monocyte counts in patients who had expe[illegible]
- Similarly, no significar[illegible] percentages or in the CD4/CD8 ratio in the p[illegible]S
- The appearance of po[illegible]entages (43% in patients without CIS v[illegible]4/CD8 ratio (0.2 vs. 2.8; *P* = .001; both with di[illegible]tive of faster T-cell compartment reconsti[illegible]

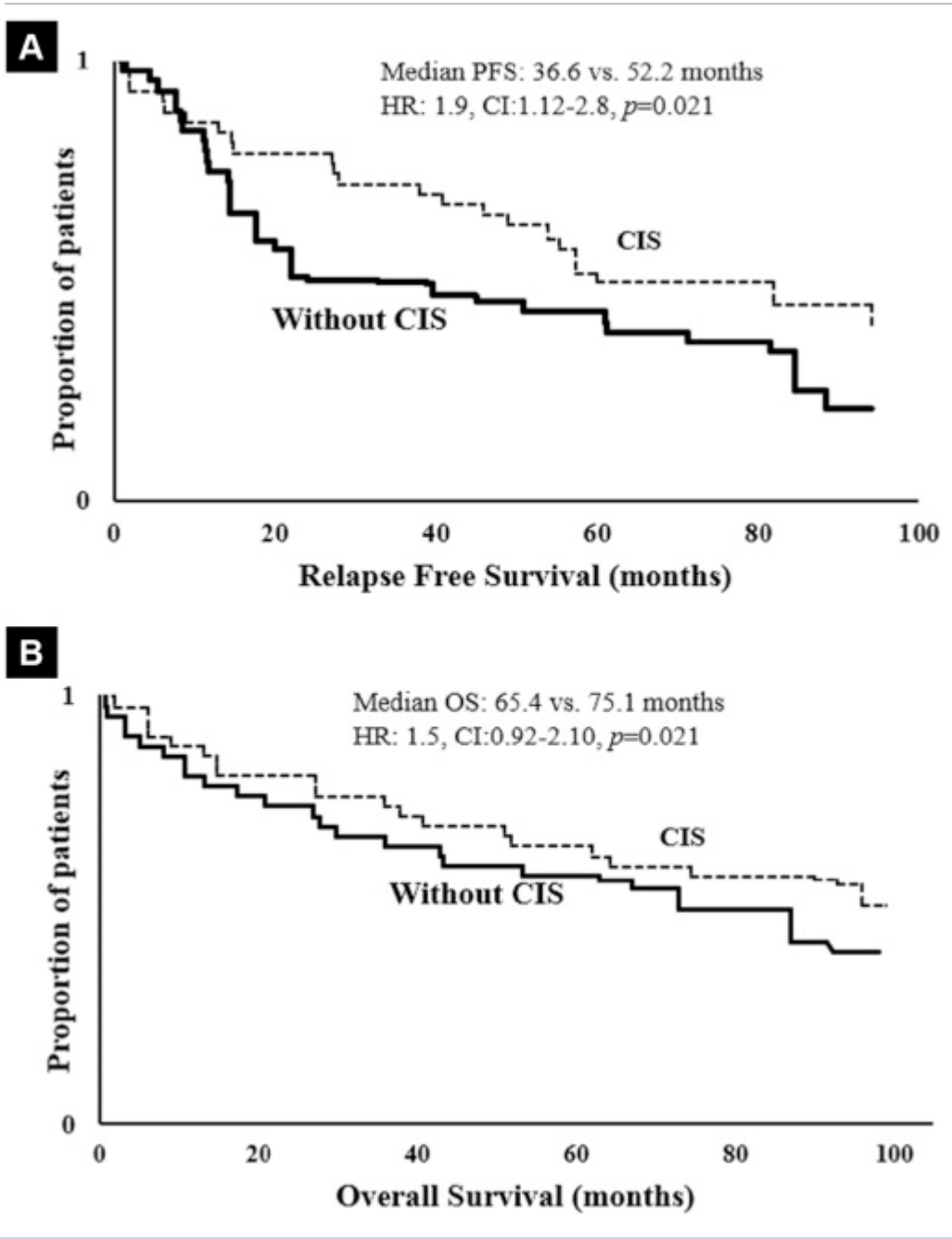


Dosani T, et al. Blood Cancer J 2017; 7:e579.
Porrata LFet al. Blood 2001; 98:579-85.
Ye et al. Clinical Lymphoma, Myeloma & Leukemia. 2019

2. PFS and OS and correlations

- The presence of post-ASCT CIS correlated significantly with improved PFS (52.2 vs. 36.6 months; *P* = 0.21) and OS (75.1 vs. 65.4 months; *P* = 0.021)
- Age, cytogenetics, response category, presence of CIS, and low lactate dehydrogenase were shown to influence PFS on univariate analysis
- Cytogenetics, lactate dehydrogenase, and CIS presence were also significantly associated with the MM response on multivariate analysis
- All patients who had experienced a relapse had an isotype different from that of the CIS, highlighting the benign nature of this phenomenon

Ye et al. Clinical Lymphoma, Myeloma & Leukemia. 2019



Ye et al. Clinical Lymphoma, Myeloma & Leukemia. 2019

2. Conclusion

- A prospective analysis of 177 patients with multiple myeloma undergoing autologous stem cell transplant

- found that 22% developed new and small concentrations of monoclonal protein after transplant that differed from that originally identified at diagnosis

- This phenomenon had a benign nature and correlated with improved survival and more robust bone marrow immune reconstitution beyond the B-cell compartment

Ye et al. Clinical Lymphoma, Myeloma & Leukemia. 2019

Discussion

- Gene sequencing of heavy chain variable region in 7 patients with post-ASCT CIS did not show a clonal relationship to the original malignant clone isotype highlighting nonmalignant B cells as the likely origin of CIS

Ye et al. Clinical Lymphoma, Myeloma & Leukemia. 2019
Guikema JE, Vellenga E, et al. Br J Haematol 1999; 104:748-54.

3. Allogeneic SCT and sMGUS/CIS

- 138 patients who had undergone allogeneic stem cell transplantations

- 67 (48.2%) patients developed sMGUS, after a median latency of 6.9 months
  - 25 patients had only one new protein band (18.0%),
  - 9 (6.5%) had 2 bands,
  - 8 (5.8%) had 3 bands,
  - and 25 (18.0%) had 4 or more

- sMGUS occurred more often in patients with deeper responses, at least very good partial response after allo SCT, compared to partial response or less (54.8% *vs.* 26.5%; *P*=0.005)

Schmitz et al. Haematologica. 2014

3. Secondary MGUS after allogeneic SCT in MM

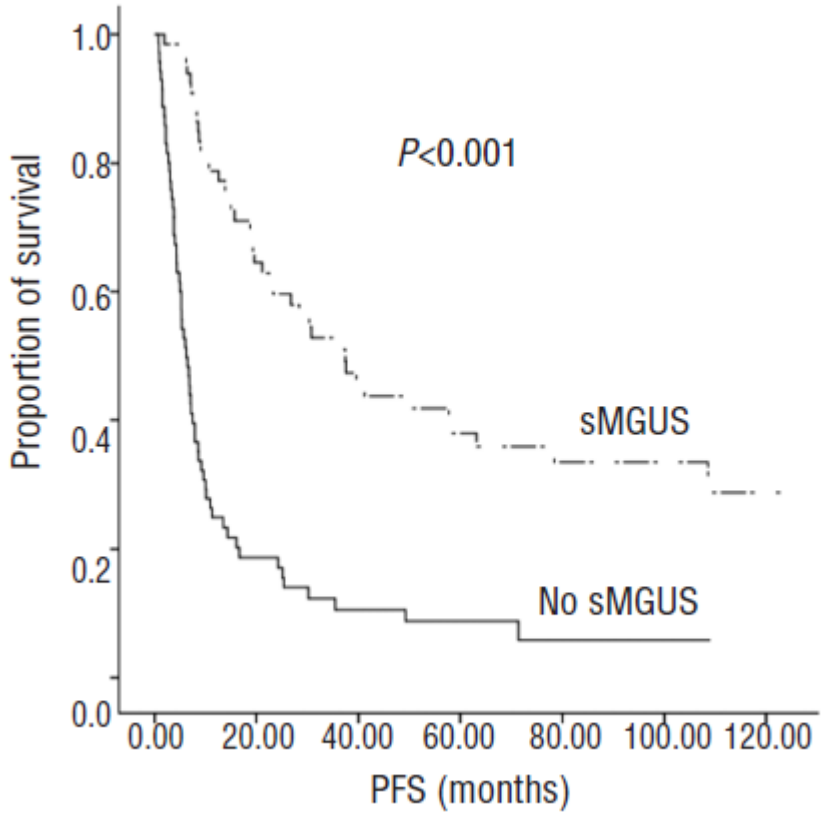
- In most cases it was not possible to quantify the level of sMGUS, mostly levels too low
  - Abnormal protein bands could be quantified in only 4 patients, with a maximum level of 11 g/L
- The median duration of all sMGUS cases was 4.47 months (range 0.0-74.5 months)
- There was no progression of sMGUS to MM or other lymphoproliferative diseases
- Clinicians should be aware of the benign nature of this phenomenon, and secondary monoclonal gammopathy of undetermined significance should not be confused with relapse or progression of disease

Schmitz et al. Haematologica. 2014

3. PFS and OS and sMGUS after allo SCT

median progression-free survival 37.5 *vs.* 6.3 months, $p<0.001$; median overall survival 115.3 *vs.* 31.0 months, $p=0.004$)

A



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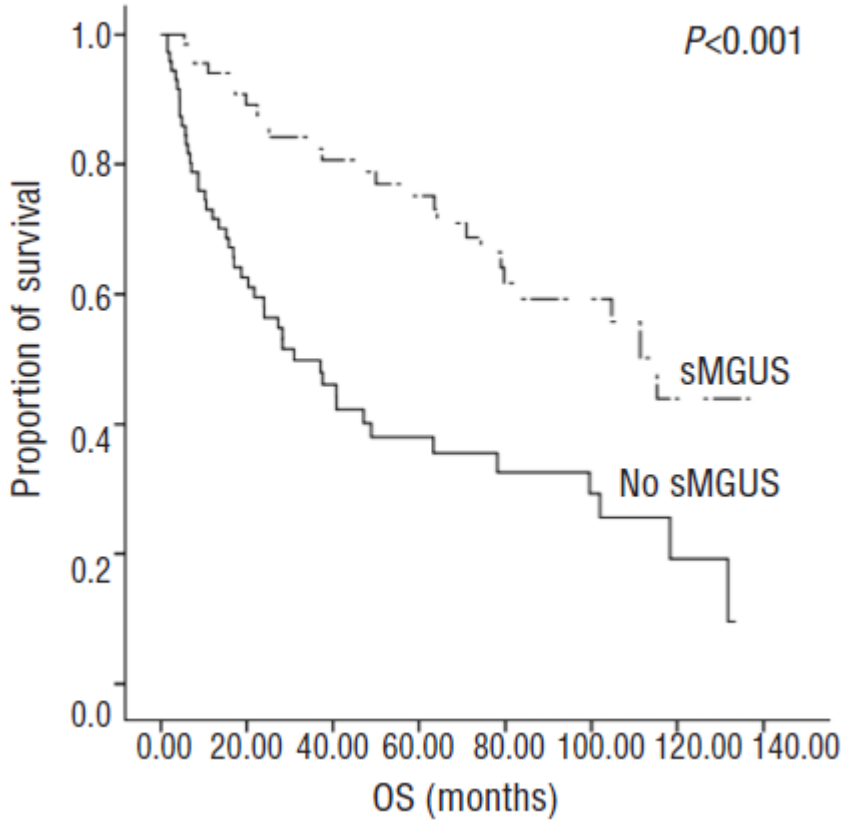

Schmitz et al. Haematologica. 2014

Overall conclusions

- The emergence of sMGUS reflects a strong humoral immune response and is a sign of immune reconstitution after allo-SCT, autologous SCT, or novel agent-containing regimens

- A higher frequency of sMGUS is observed in patients with high-quality responses, which suggests that major tumor reduction contributes to strong immune reconstitution and development of oligoclonal bands

- There is no evidence that these abnormal protein bands are related to the myeloma clone
  - Prior studies suggest that new serum M-components after auto-SCT are not produced by myeloma cells but rather by the regenerating B-cell compartment

Overall conclusions

- Furthermore, sMGUS not only occurs in patients but also after treatment for other hematologic malignancies, and even solid organ transplantations
- Development of sMGUS seems a favorable prognostic factor for PFS and OS, independent of the response achieved
- The favorable prognosis conferred by sMGUS suggests that the oligoclonal bands may also be involved in an anti-myeloma immune response
- Importantly, in order to avoid unnecessary treatment clinicians should be aware that sMGUS does not represent disease recurrence or development of a new malignancy