Smoldering Myeloma: when to observe and when to treat?

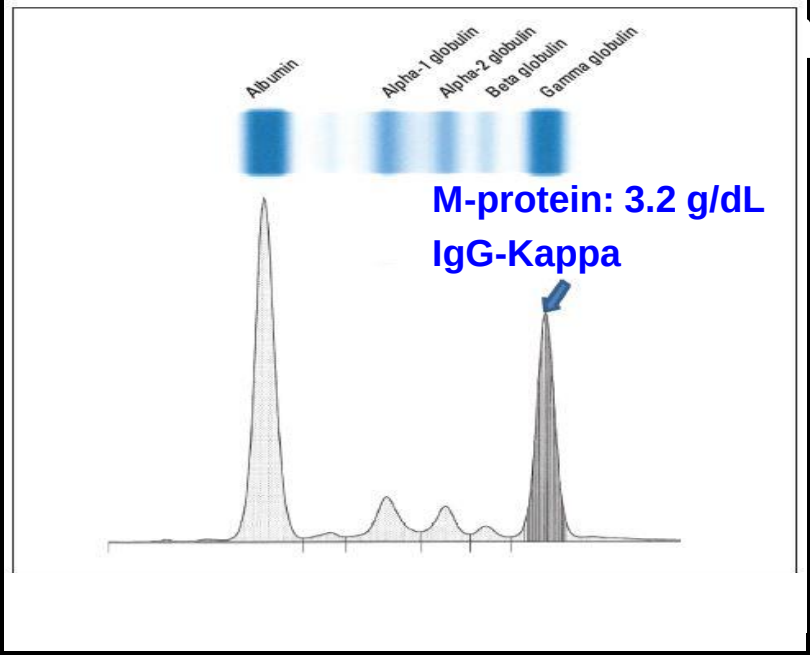
María-Victoria Mateos
University Hospital of Salamanca- IBSAL
Salamanca. Spain

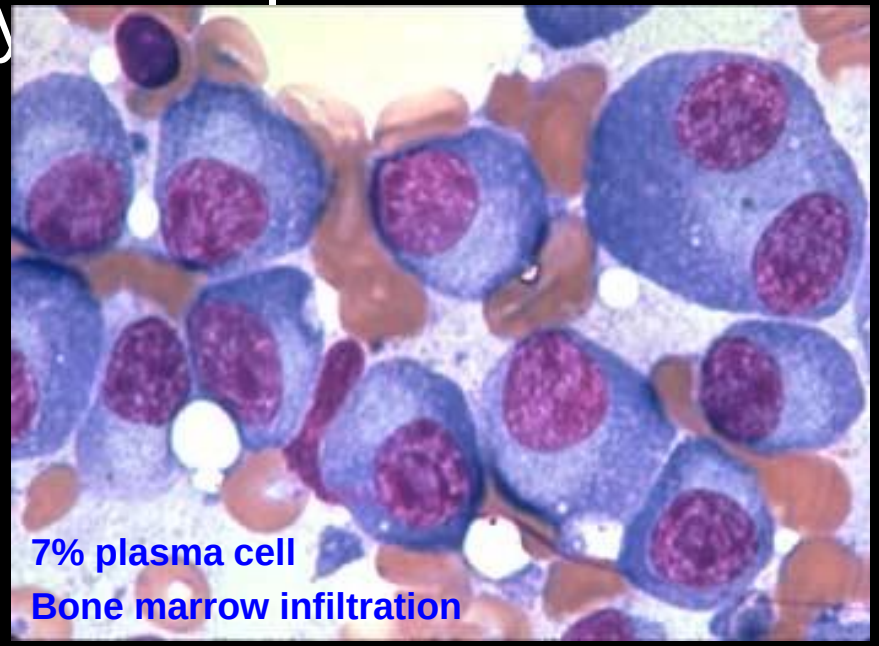
Clinical Case

- 52 years-old man
- Asymptomatic.
- Routine analysis
- Elevated total serum proteins (10.2 g/dL) with normal albumin
- Hemogram and biochemistry normal

Clinical Case

- 52 years-old man
- Asymptomatic.
- Routine analysis
- Elevated total serum proteins (10.2 g/dL) with normal albumin
- [illegible]nistry





MGUS/SMM/MM: diagnostic criteria

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10%	10-60%	> 10%[b]
	AND	AND	AND
End-organ damage	Absent	Absent	Present

Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡

Rajkumar SV. Lancet Oncology 2014

Smouldering MM: diagnostic criteria

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10%	10-60%	> 10%[b]
	AND	AND	AND
End-organ damage	Absent	Absent	Present

Concomitant diseases that can mimic MM:

-Increase of serum Cr due to diabetes or hypertension

-Anemia due to idon-vitamin deficiency, chronic disease,..

-Diffuse osteoporosis

-Hyperparatiroidism

-Single asymptomatic bone lesion

Rajkumar SV. Lancet Oncology 2014

Recommended work up at 3 months in patients with Smouldering MM

- **Medical History and physical examination**
- **Hemogram**
- **Creatinine and calcium values**
- **Protein studies**

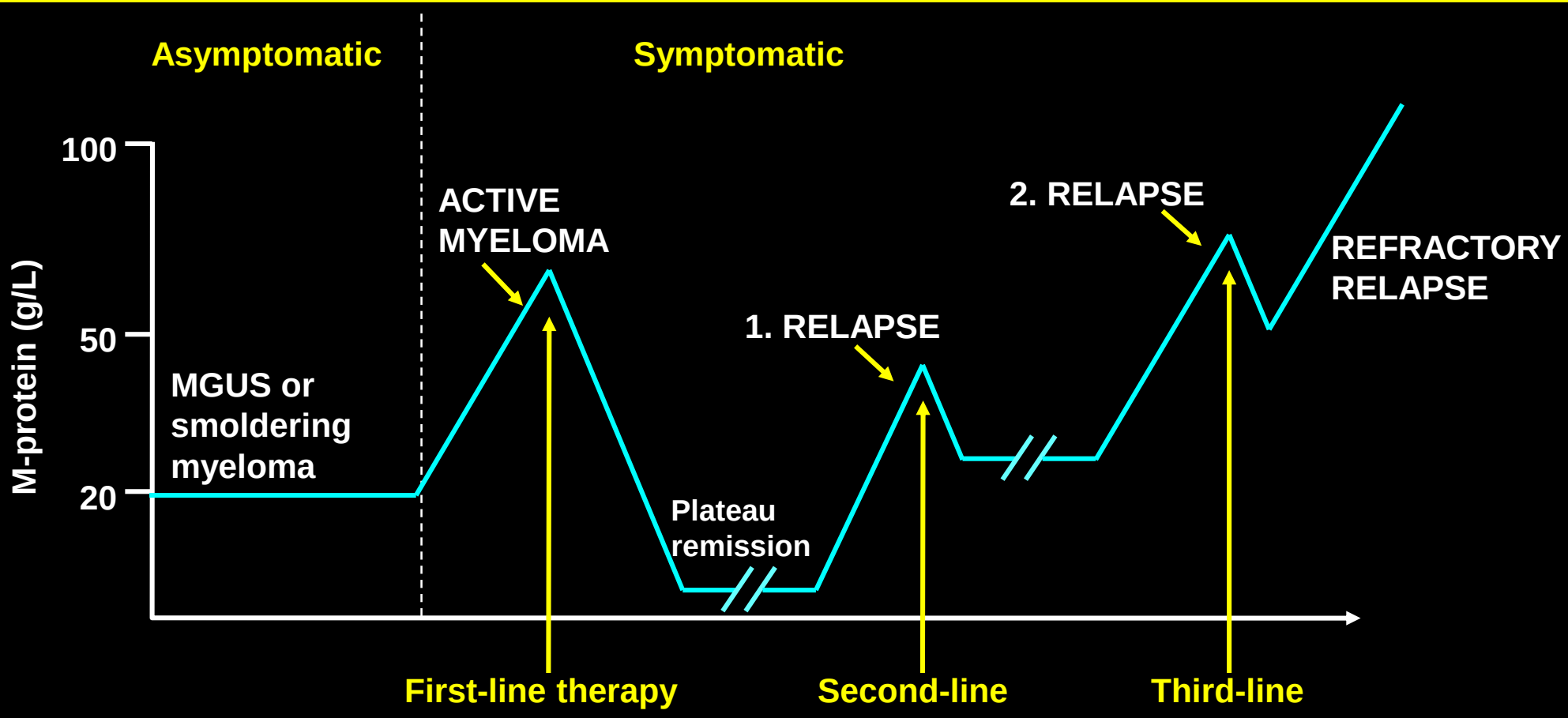
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)

If results show stabilization of the disease, diagnosis of SMM is confirmed

Mateos MV et al. Current hematologic malignancy reports. 2013; 8(4): 270-6

What is the next step?

Natural History of MM



Myeloma is always preceeded by MGUS or Smoldering Myeloma

MGUS, monoclonal gammopathy of undetermined significance

Transition from MGUS/SMM to MM

- **Expansion of altered clones already present in MGUS patients**

  López Corral et al. Leukemia 2012

- **Branching model→ Key molecular events leading to disease evolution→ distinct patterns of driver mutations**

  Walker et al. Nature Reviews Cancer 2012

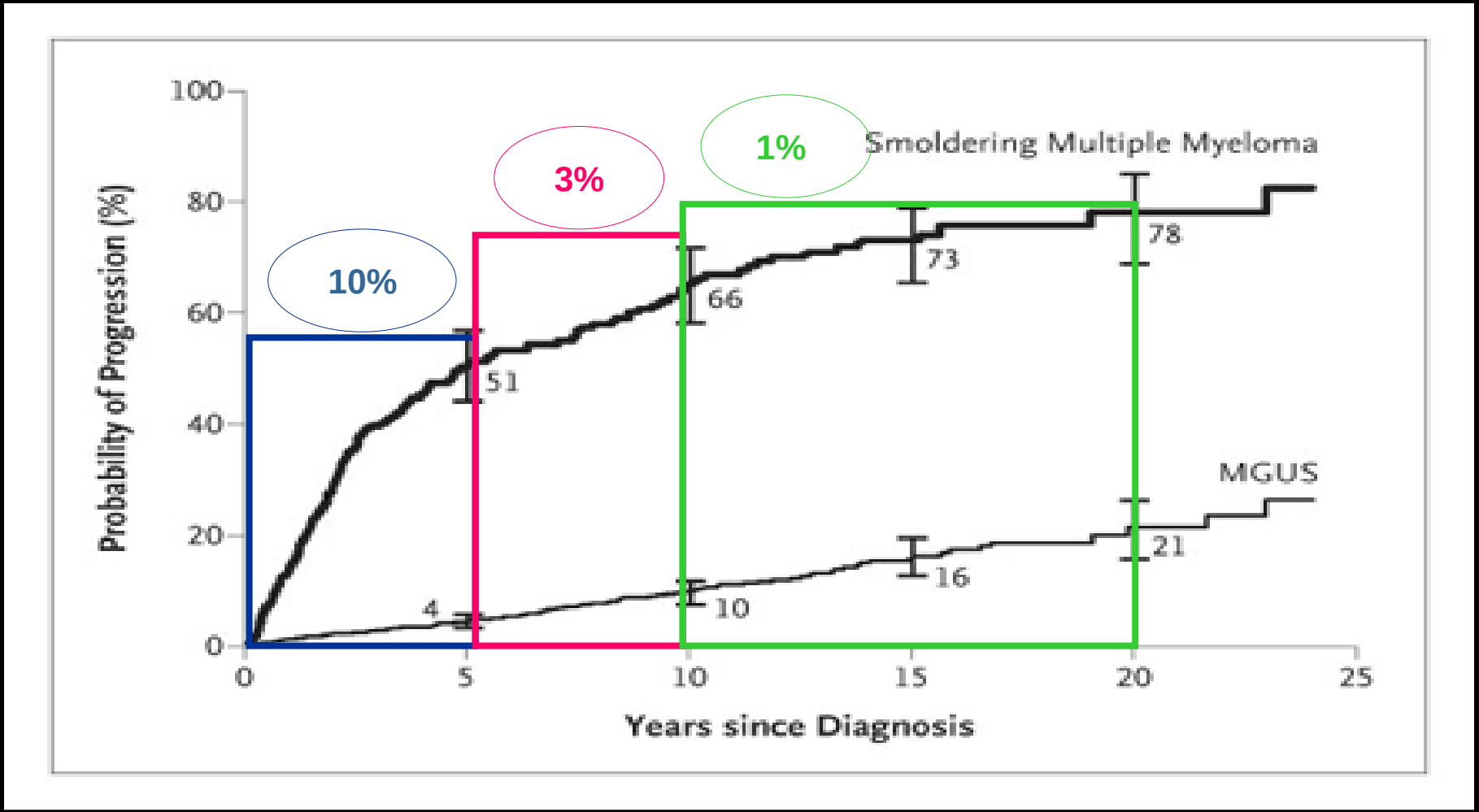
- **Differences in inmune surveillance**

  Dosani et al. Blood Cancer J. 2015

Are identical all patients with MGUS or SMM?

MGUS, monoclonal gammopathy of undetermined significance

MGUS/Smoldering Multiple Myeloma: Risk of progression to active disease



Are there any risk factors predicting progression to active disease?

Kyle R. N Engl J Med 2007; 356:2582-90

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Abnormal sFLC ratio
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Evolving MM
- Cytogenetic abnormalities

** After IMWG consensus criteria*

Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000; Hillengass J, 2010

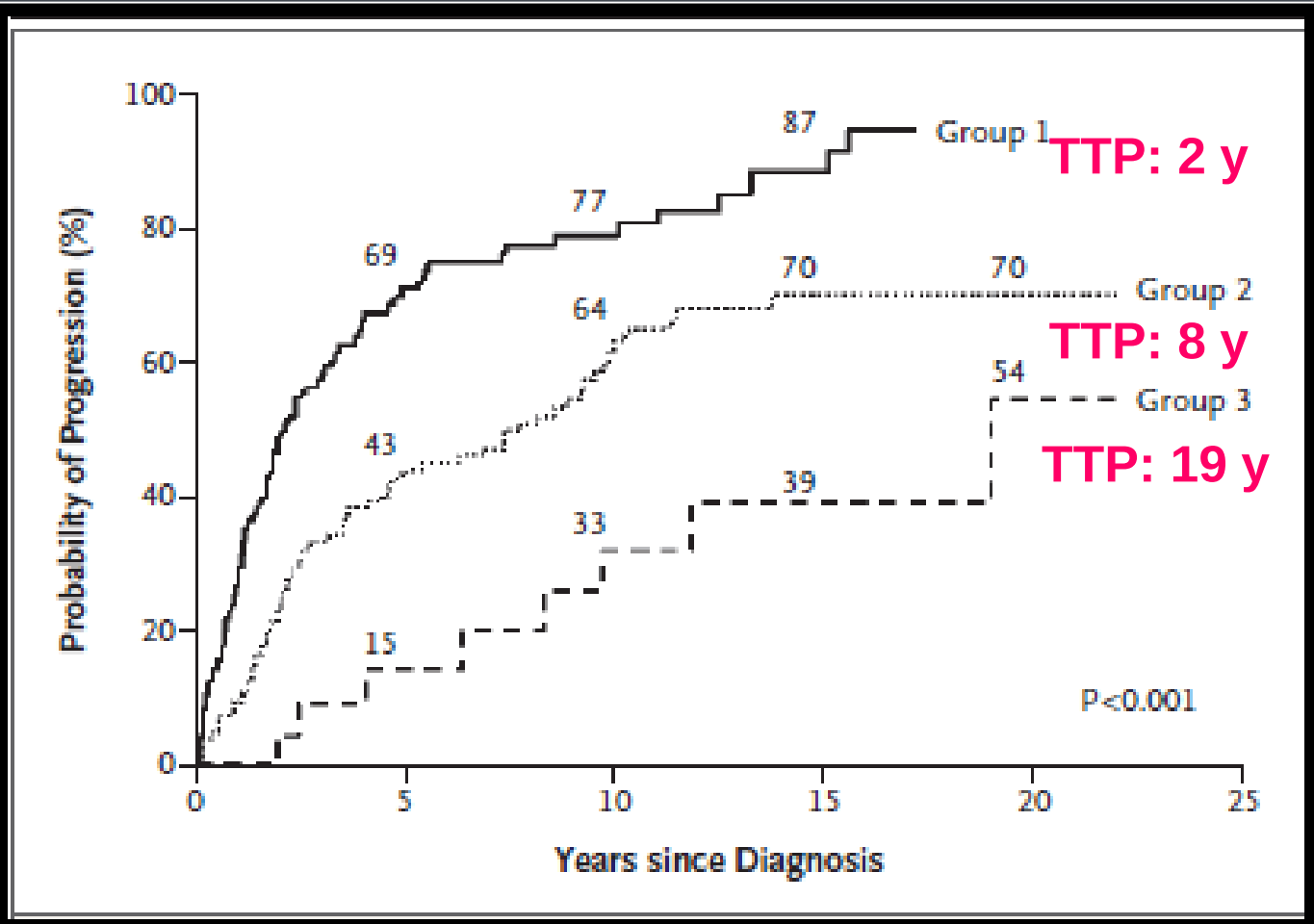
Smouldering Multiple Myeloma: prognostic factors

- **Serum level of Monoclonal Component (>3g/dl)**
- **Plasma Cells Bone Marrow infiltration (PCs>10%)**
- **Aberrant Plasma Cells by immunophenotype (≥ 95%)**
- **Reduction in uninvolved immunoglobulins**
- **Abnormal sFLC ratio**
- **Evolving MM**
- **Cytogenetic abnormalities**

** After IMWG consensus criteria*

Rosiñol et al, 2003; Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000

Mayo risk model: PCs BM infiltration and Serum M-component level



TTP: 2 y

TTP: 8 y

TTP: 19 y

50% risk at 2 yrs

Group 1: ***PCBM ≥ 10% + MC ≥ 3g/dl***
Group 2: ***PCBM ≥ 10% + MC < 3g/dl***
Group 3: ***PCBM < 10% + MC ≥ 3g/dl***

Kyle R. N Engl J Med 2007; 356:2582-90

Smouldering Multiple Myeloma: prognostic factors

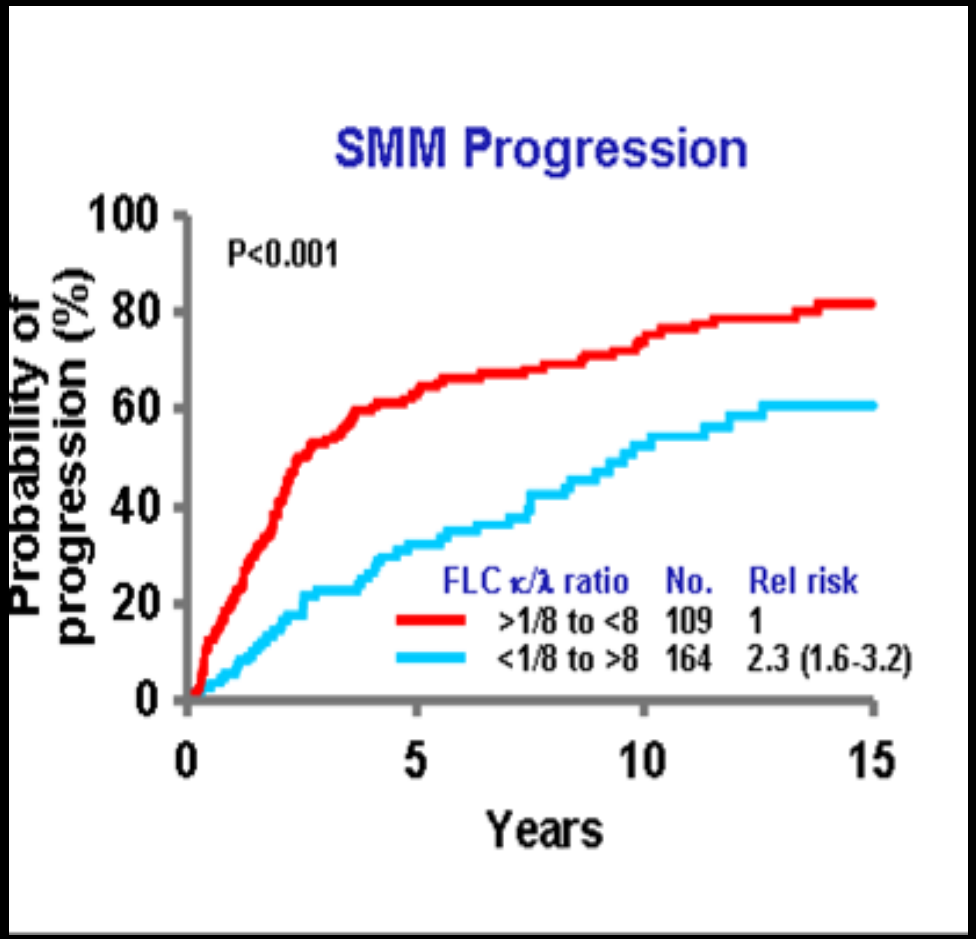
- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- **Abnormal sFLC ratio**
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Evolving MM
- Cytogenetic abnormalities

** After IMWG consensus criteria*

Rosiñol et al, 2003; Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000

Smouldering Multiple Myeloma: serum immunoglobulin free-light chain (FLC) ratio (n:273)

Serum FLC ratio <0.125 or > 8

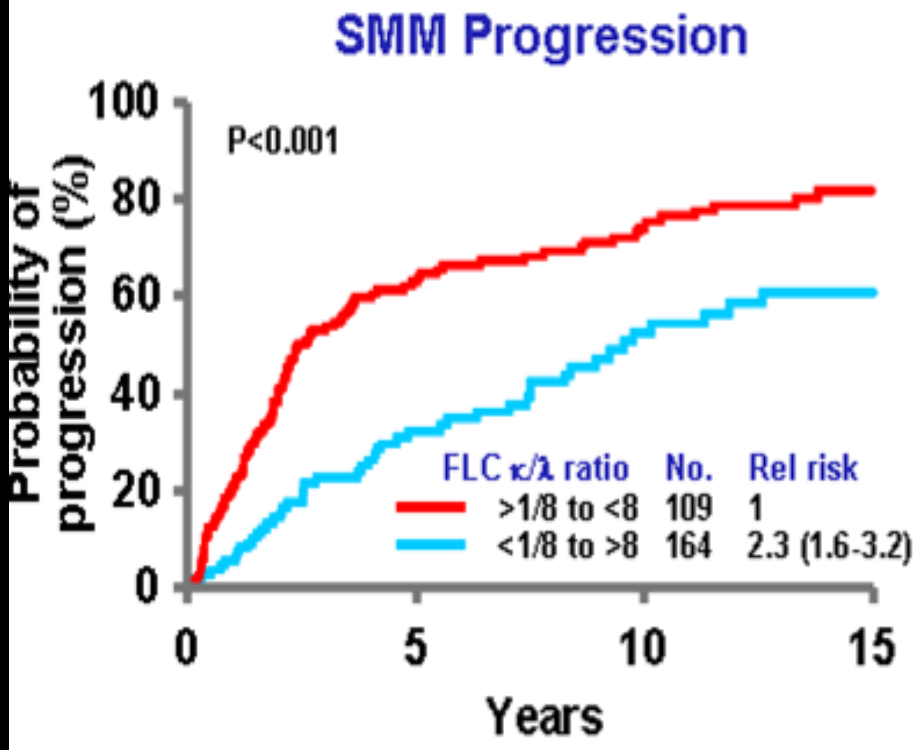


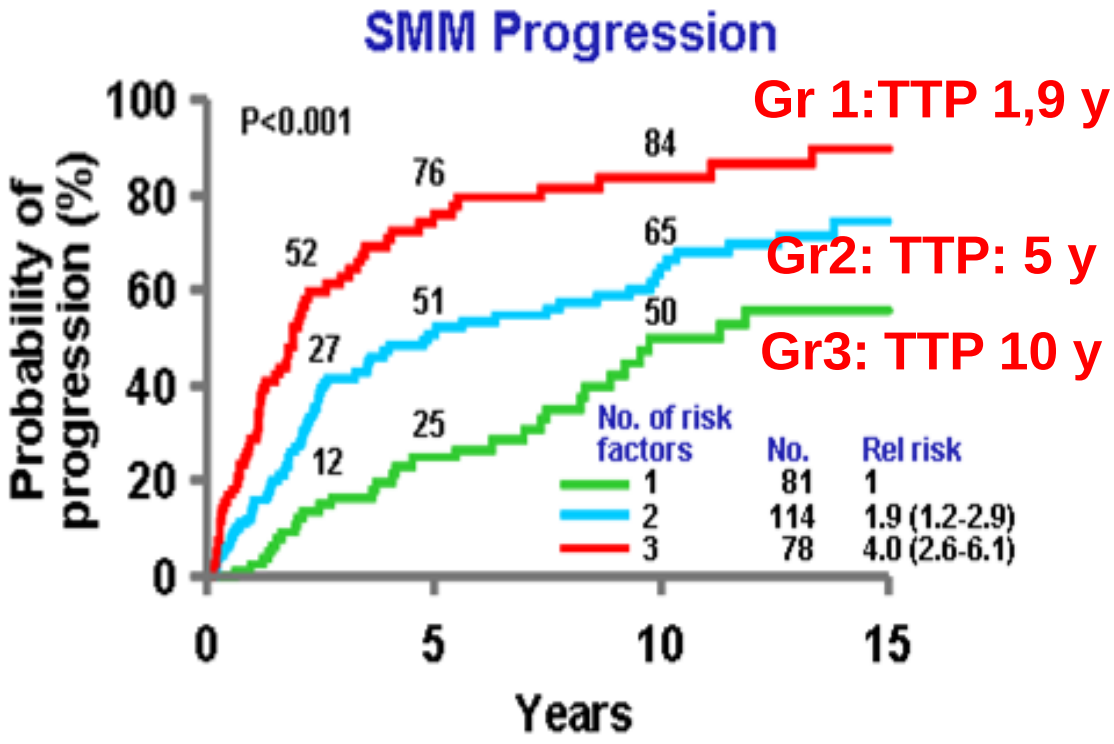
Dispenzieri A. Blood 2008; 111:785-9

Mayo Clinic model: serum immunoglobulin free-light chain (FLC) ratio (n:273)

Serum FLC ratio <0.125 or > 8

PCsBM Infiltration ≥ 10%
Serum M protein ≥ 3 g/dL
Serum FLC ratio <1/8 or >8





Dispenzieri A. Blood 2008; 111:785-9

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Abnormal sFLC ratio
- **Aberrant Plasma Cells by immunophenotype (≥ 95%)**
- **Reduction in uninvolved immunoglobulins**
- Evolving MM
- Cytogenetic abnormalities

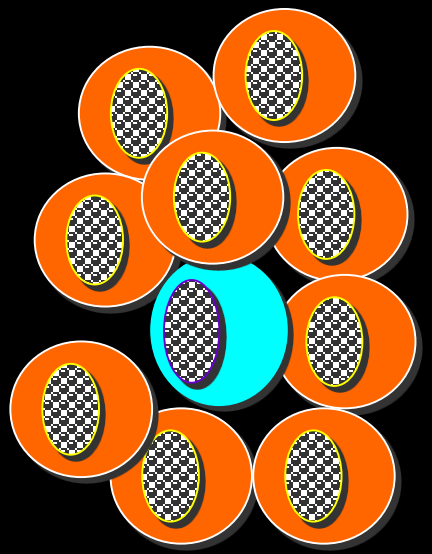
** After IMWG consensus criteria*

Rosiñol et al, 2003; Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000

Spanish Model:
Analysis of the PC compartment by flow cytometry

Clonal

MM

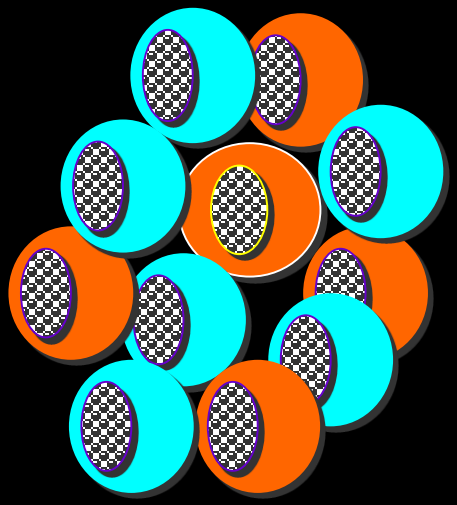


MM patients showed <5% poly-PC

versus

Poly-Clonal

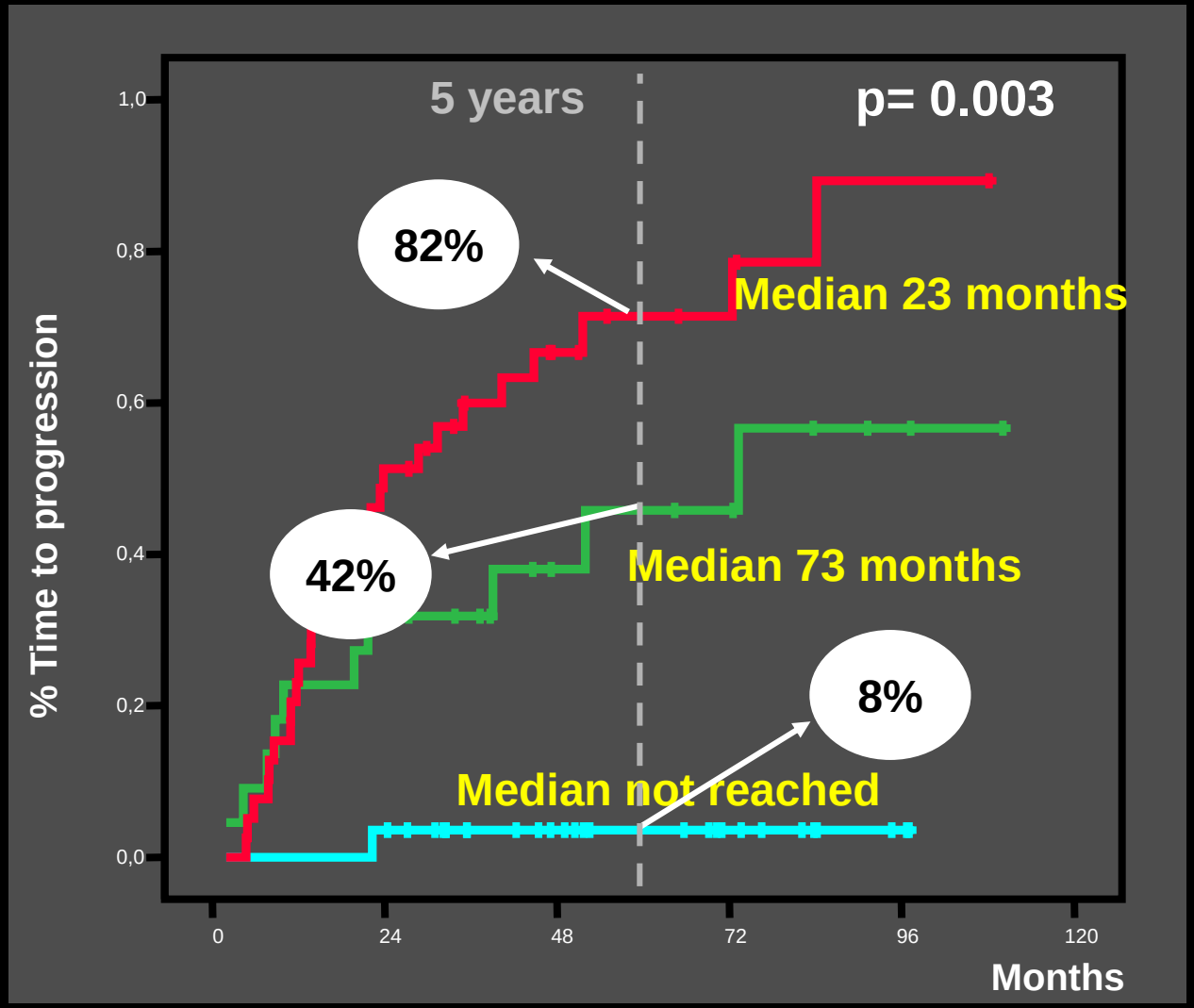
Smoldering MM



Clonal & Polyclonal PC coexist

1. Ocqueteau M, Am J Pathol 1998, 152: 1655

Spanish model: Aberrant PCs by immunophenotype plus immunoparesis



>95% aPC/BMPC + paresis
n= 39 (28 progr.)

50% risk at 2 yrs

>95% aPC/BMPC or paresis
n= 22 (10 progr.)

No adverse factors
n= 28 (1 progr.)

Pérez E. Blood 2007; 110:2586-92

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Abnormal sFLC ratio
- **Evolving MM**
- Cytogenetic abnormalities

** After IMWG consensus criteria*

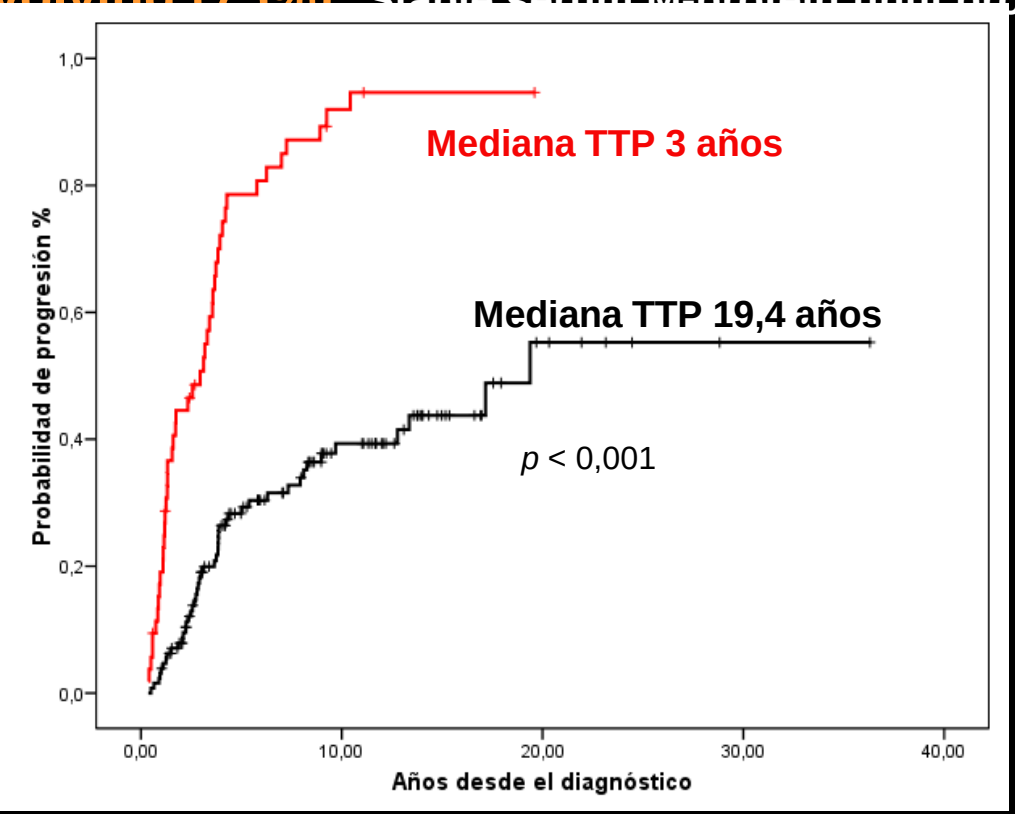
Rosiñol et al, 2003; Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000

Evolution pattern of the M-spike: evolving vs nonevolving (n:207)

Evolving SMM (52 (25%)): at least 10% increase within the first 6 months from diagnosis when MP was ≥30 g/L or progressive increase in MP in each of the annual consecutive measurements during

a period of 3 years in patients with an initial MP < 30 g/L

Non-evolving (75%): Stable serum M-protein until progression occurs



Evolving SMM

- Risk progression at 2 years: 45%
- Risk progression at 5 years: 78%
- IgA isotype:
  (41,2% frente a 23,8%, p=0,02)

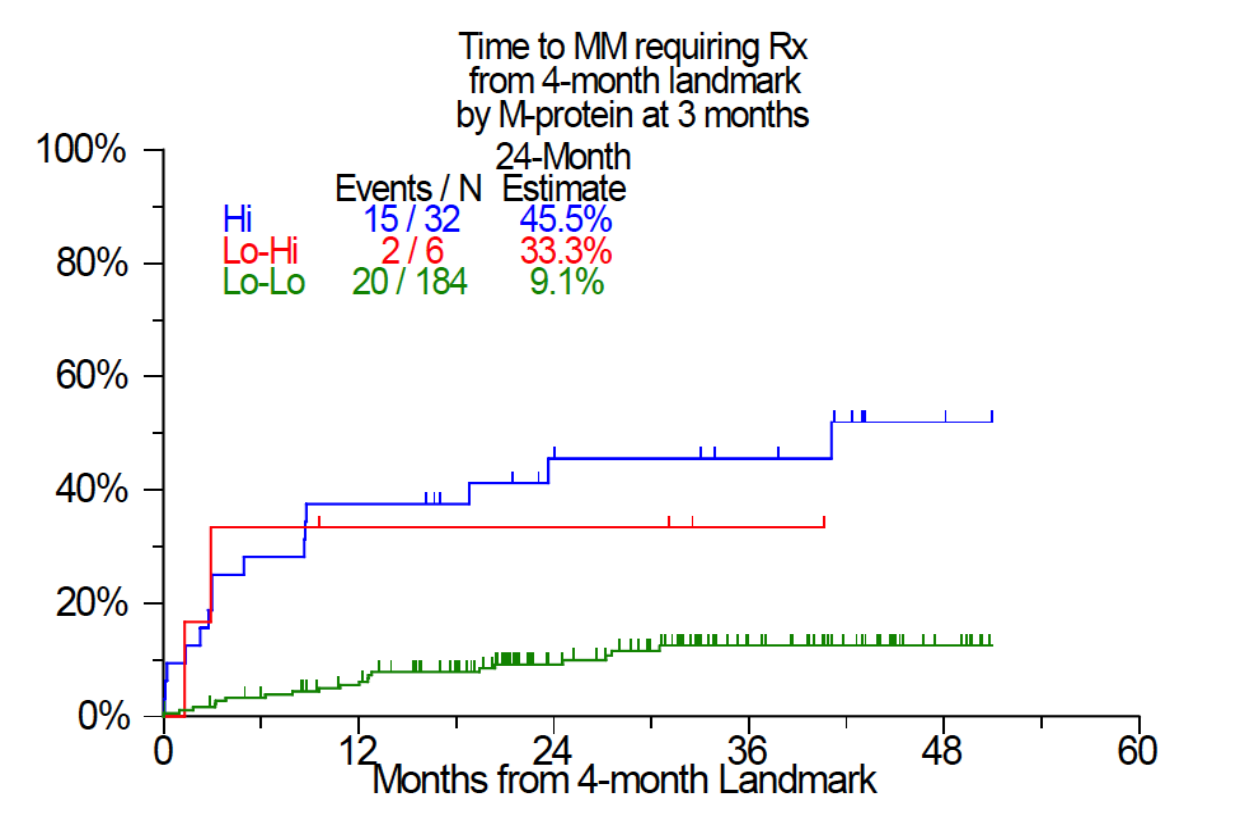
Fernández Larrea C et al. ASH 2014

Evolution pattern of the M-spike: SWOG experience (n:222)

Hi (32pts): High M spike (≥3g/dL) at baseline

Lo-Hi (6 pts): Pts with an increase in M spike to ≥3g/dL in 3 months time

Lo-Lo (184 pts): Patients who retained a M spike (<3g/dL) throughout the 3-months period



Dhodapkar MV et al. Blood 2013; Nov 3 epub ahead of print

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Abnormal sFLC ratio
- Evolving MM
- **Cytogenetic abnormalities**

** After IMWG consensus criteria*

Rosiñol et al, 2003; Kyle et al, 2007; Perez-Persona, 2007; Dispenzieri et al, 2008; Rosiñol et al, 2003; Dimopoulos et al, 2000

Prognostic significance of whole MRI for patients with SMM

- **Retrospective study:** whole body MRI
  - 157 pts with SMM, 138 pts with MGUS, 249 pts MM

- **Results**

	MGUS patients	SMM patients
Focal lesions	23.9%	34.4%
Diffuse infiltration	53%	45.9%
Adverse prognostic factors for PFS	Presence and no. of focal lesions, severe diffuse infiltration Multivariate analysis: number of focal lesions (p=0.0005)	Plasma cell percentage, moderate diffuse infiltration (but not focal lesions), beta2-microglobulin

Hillengass et al. ASH 2012 (Abstract 2911), poster presentation

Del(17p), t(4;14), and +1q21 predict progression from smoldering to symptomatic MM (n=248)

- **del(17p13), t(4;14), +1q21 showed significant impact on TTP**

	TTP	P
All pts	4.9 years	
+1q21 versus no gain of 1q21	3.7 years 5.3 years	0.013
del(17p13) versus no del(17p13)	2.7 versus 4.9 years	0.019
t(4;14) versus no t(4;14)	2.9 versus 5.2 years	0.021
HD versus NHD	3.9 versus 5.7 years	0.036

- **Multivariate analysis:** t(4;14), +1q21, HD, reduction of uninvolved immunoglobulins and risk score defined by Kyle et al. as independent factors for adverse outcome
- **Conclusion:** specific chromosomal aberrations drive transition from asymptomatic to symptomatic disease

Neben et al. JCO 2013; October 21 Epub ahead of print

Primary molecular cytogenetic abnormalities and risk of progression in SMM (n=351)

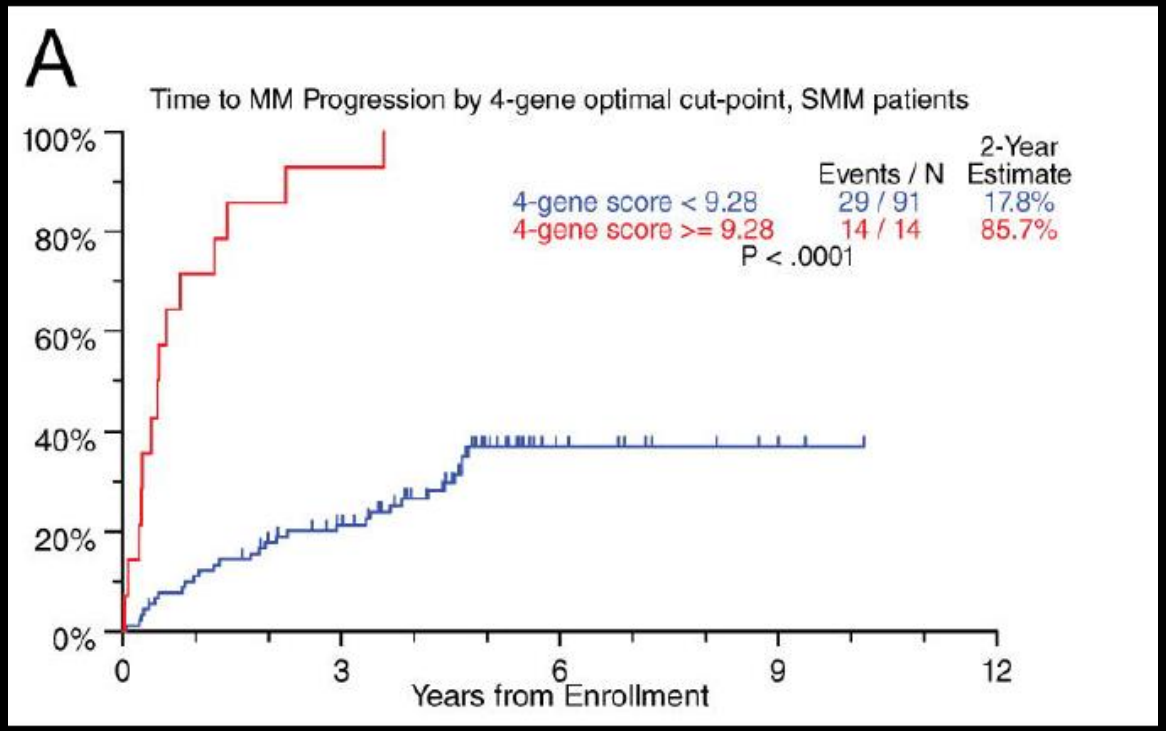
- del(17p13), t(4;14), trisomies showed significant impact on TTP

Cytogenetic abnormalities	TTP
High-risk subgroup	
t(4;14, del(17p)	24 months
Intermediate-risk subgroup	
Trisomy (ies) withouth IgH translocation	34 months
Standard/low-risk subgroup	
T(11;14), other, or no abnormalities	55 months/NR

Rajkumar SV. Leukemia 2013; 27(8): 1738-44

Gene Expression Profiling of purified CD138+ tumor cells in SMM an (n: 105)

The validated 70-gene model (GEP-70) identified SMM patients with GEP70>-0.26 with a 51% of progression risk at 2 yrs.

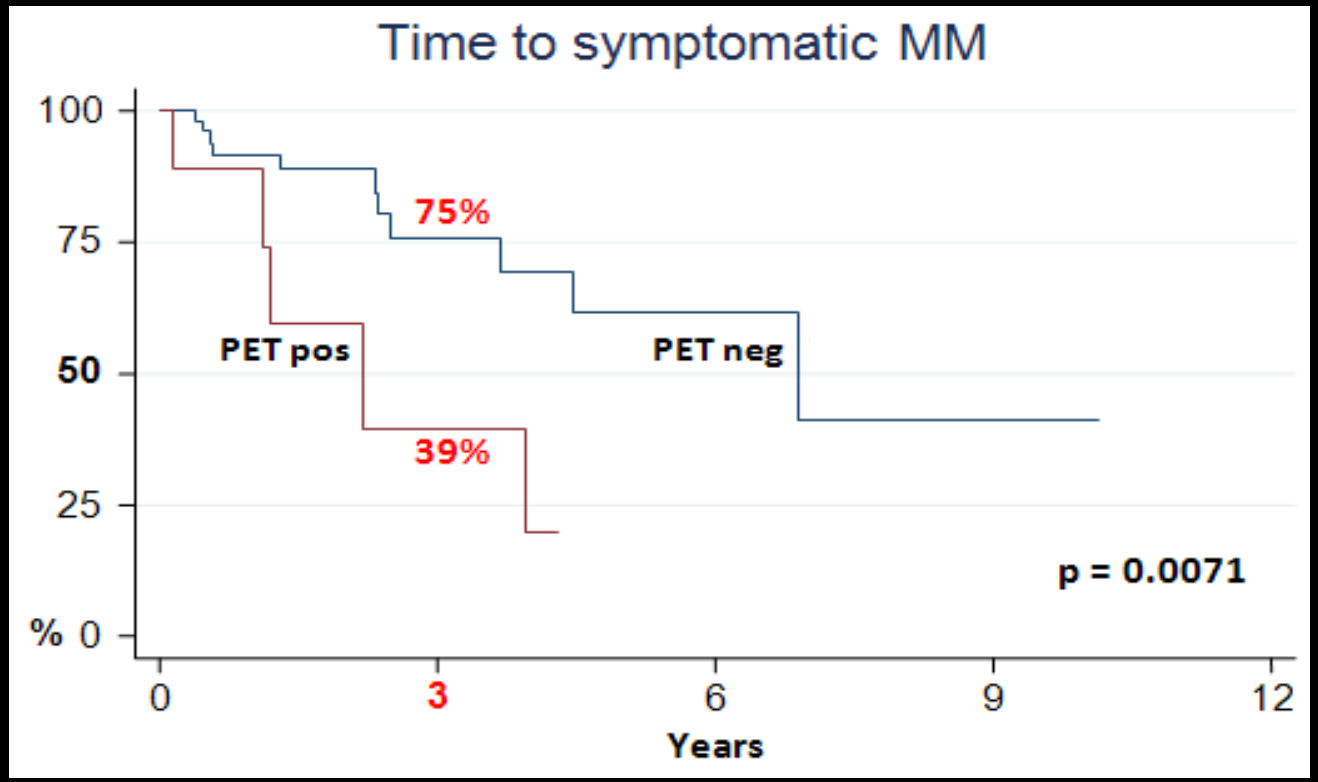


A gene signature derived from 4 genes at an optimal binary cut-point of 9.28, identified 14 patients (13%) with a 2-year therapy risk of 85.7%

Dhodapkar MV et al. Blood 2013
Khan RC et al. ASH 2014

PET-CT in SMM patients as predictor of progression to symptomatic MM (n: 73)

12% of patients had PET positive: 56% of them had 1 FL with a median PET SUV of 4.45 and no osteolysis was observed.

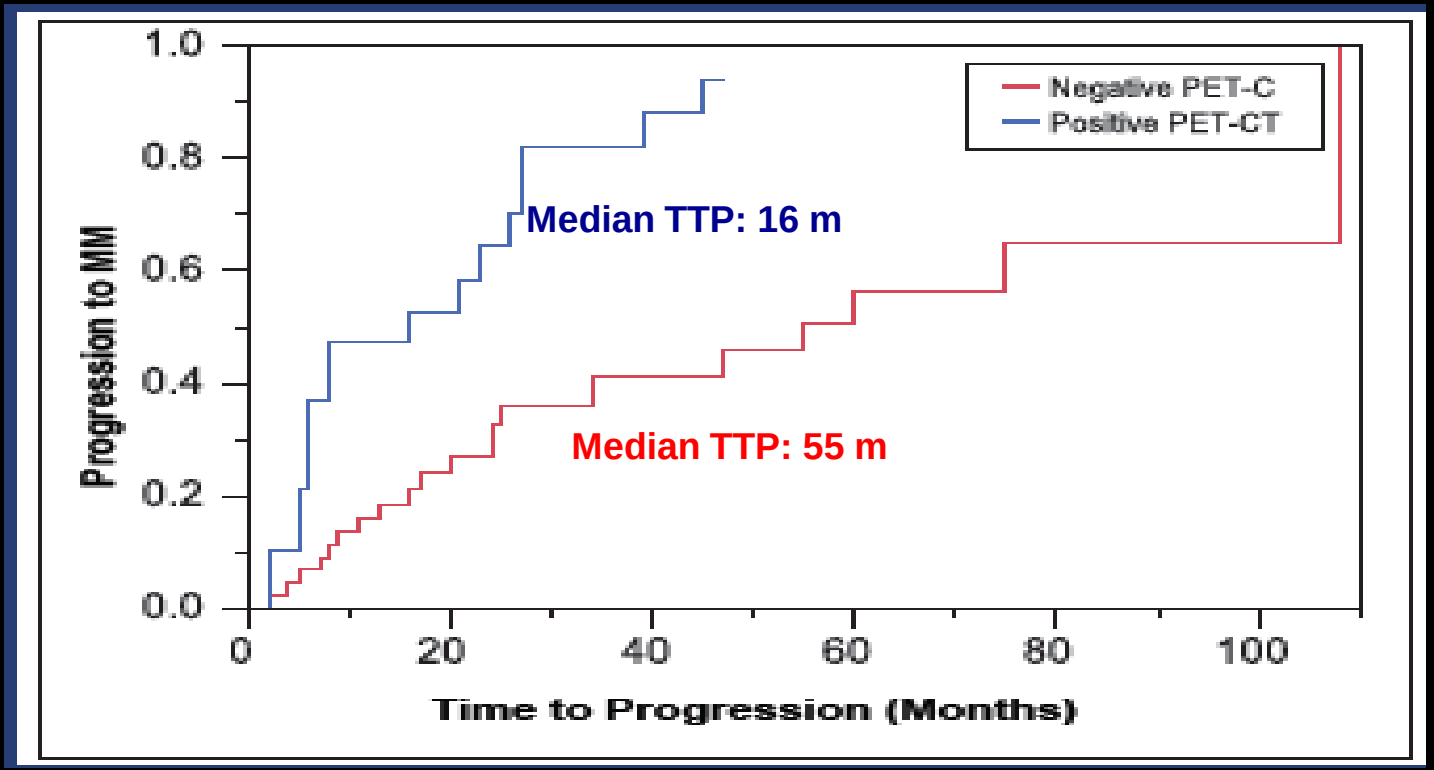


Relative risk of skeletal progression was 4.0 (95% CI 1.3-12, P= 0.013)

Zamagni E et al. ASH 2014;

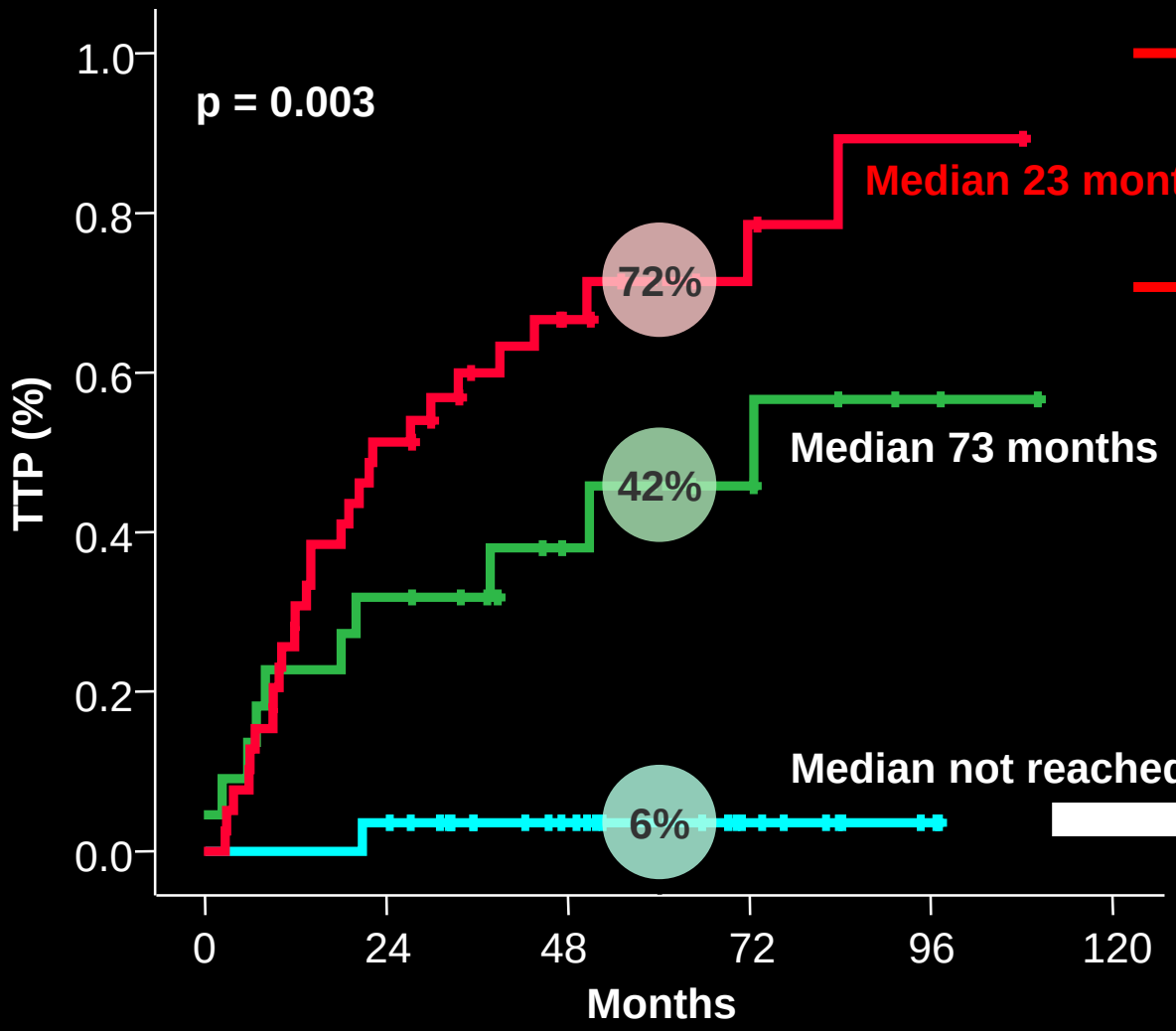
Smouldering Multiple Myeloma: PET/CT (n:202)

Positive PET/CT: 41% of the patients



Dykstra B, Kumar S, et al. ASH 2014

Smoldering MM: Heterogeneous disease



Ultra high risk sMM:
70-80% of prg risk at 2 yrs

High risk sMM:
50% of prg risk at 2 yrs

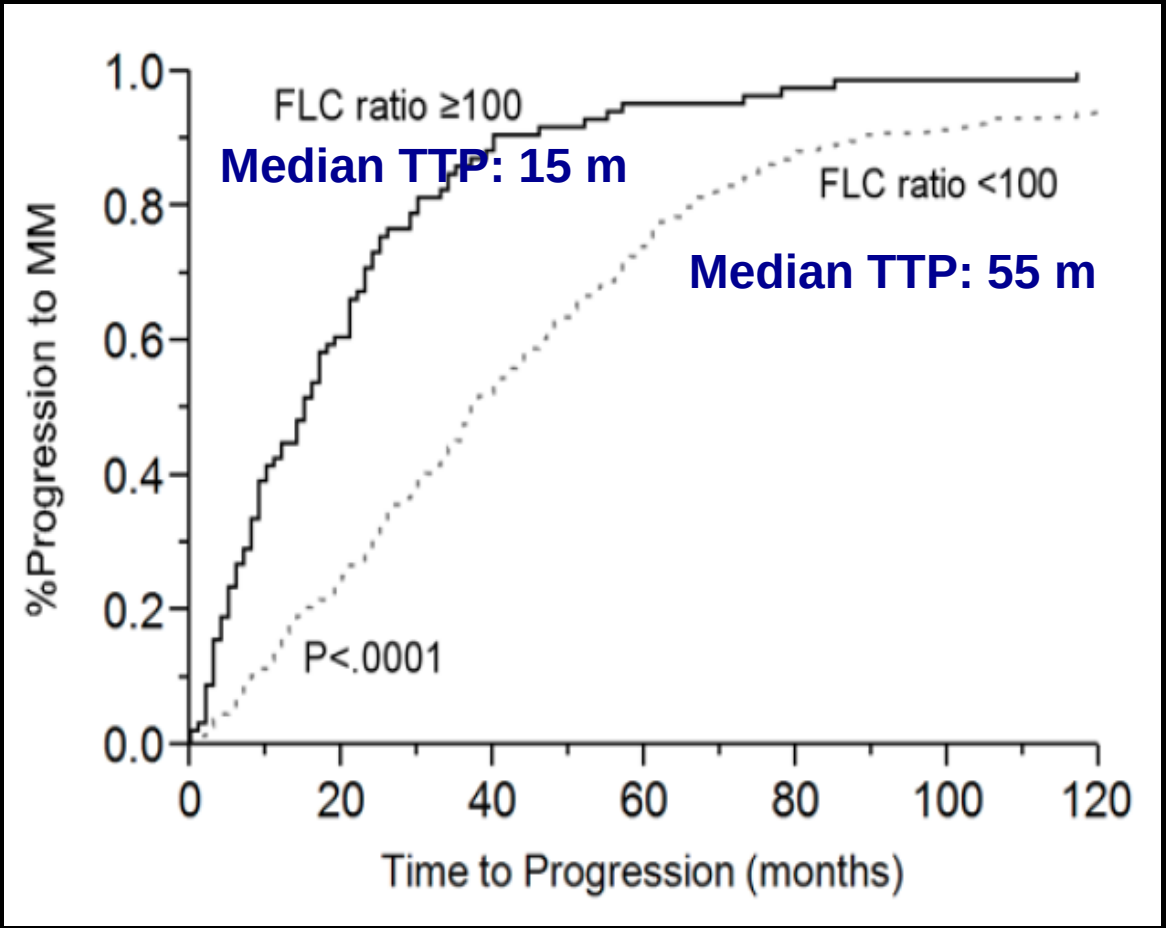
True-SMM

MGUS

Perez-Persona E, et al. Blood. 2007;110:2586-92.

Ultra-high risk SMM: Serum involved/uninvolved free-light chain (FLC) Ratio

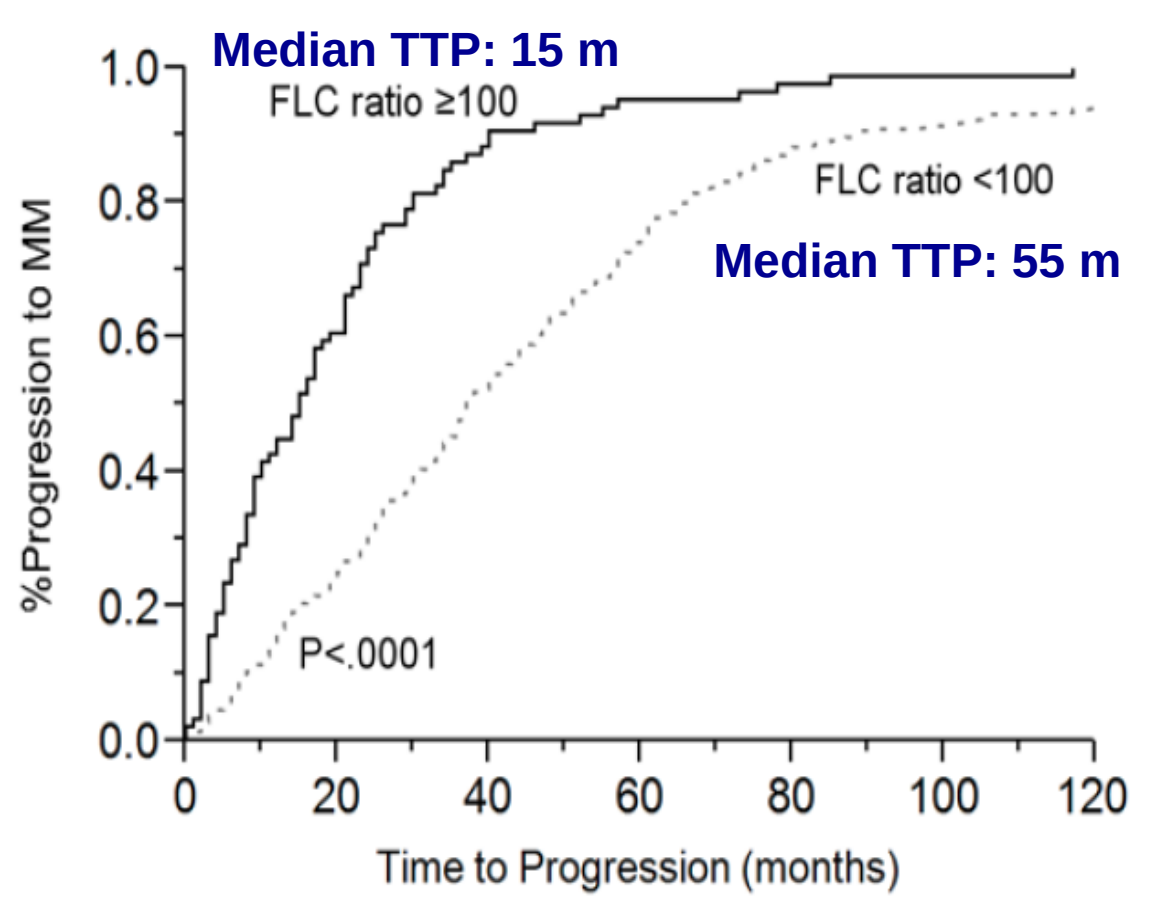
N= 586 patients



1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53
3. Waxman AJ, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8607)

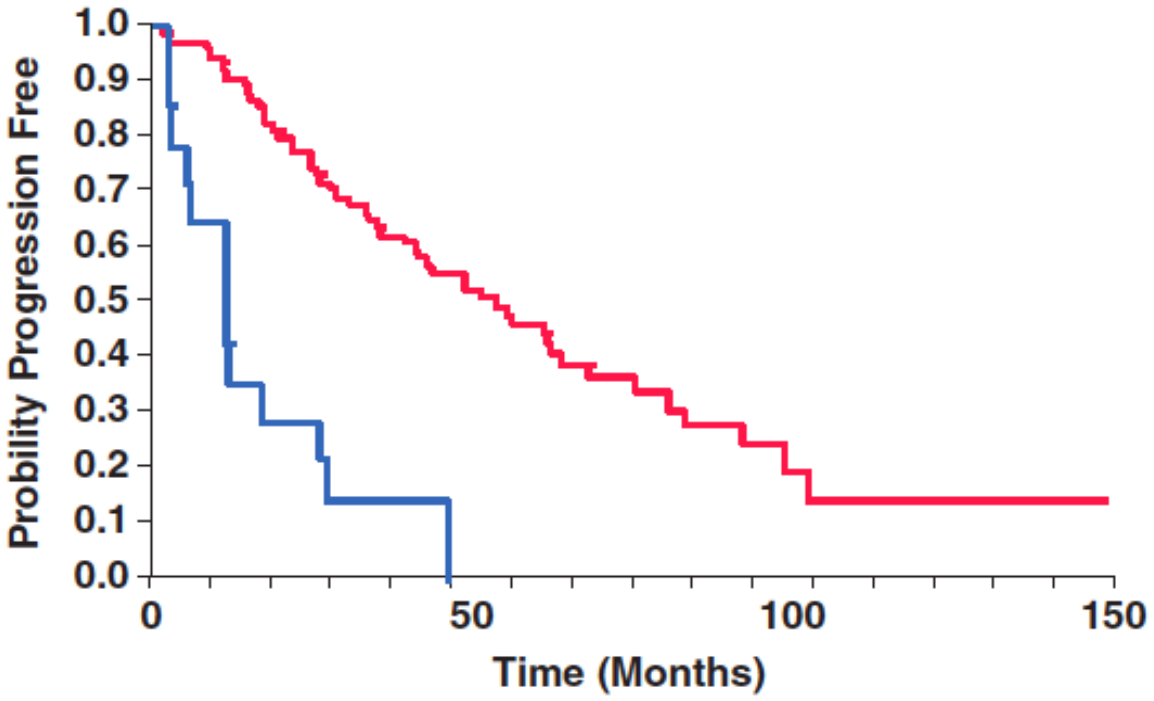
Multiple Myeloma: Serum involved/uninvolved free-light chain (FLC) Ratio

N= 586 patients



1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53
3. Waxman AJ, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8607)

Ultra-high risk SMM: peripheral blood plasma cell circulating (>5x10^6/L and/or 5% per 100 cytoplasmic Ig-positive PB mononuclear cells)



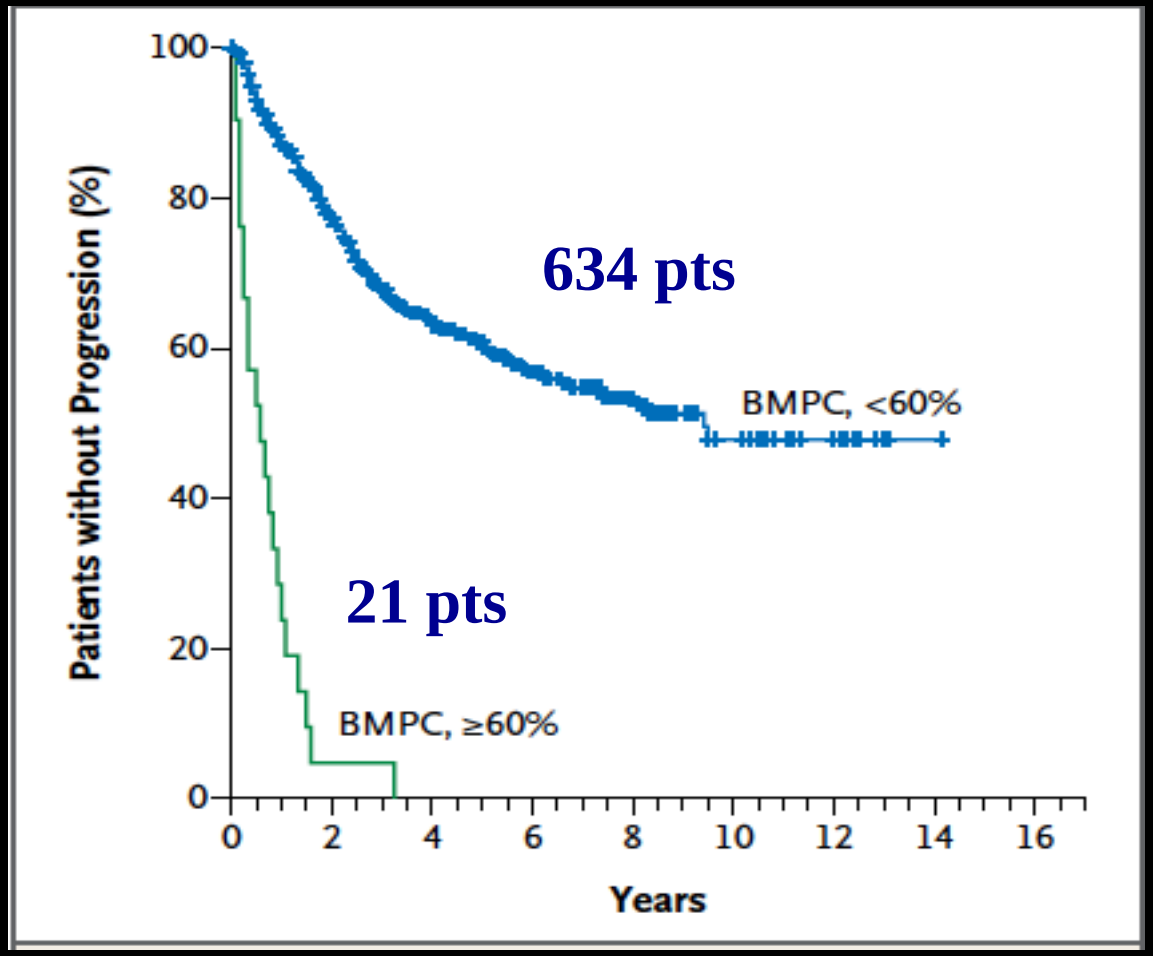
		Median TTP (months)
High circ PC	14 pts (15%)	12
Low circ PC	77 pts (85%)	57

P value: <0.001

Bianchi et al. Leukemia 2013;27: 680-5

Ultra-high risk SMM: Plasma Cells in the Bone Marrow at baseline

N= 655 patients

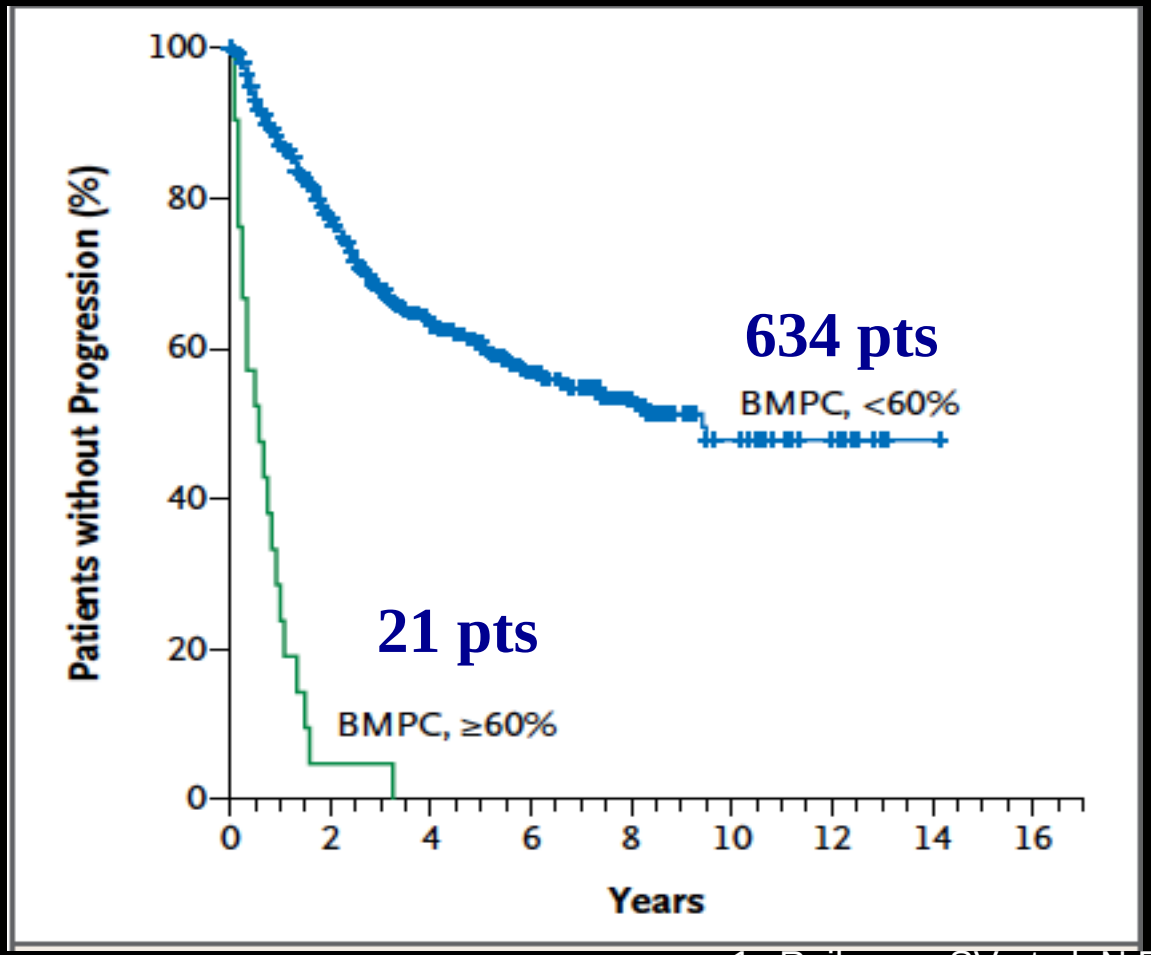


"In these patients (3.2%), median TTP was 7m and 95% of them progressed to symptomatic MM within 2y" [1]

1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

Multiple Myeloma: Plasma Cells in the Bone Marrow at baseline

N= 655 patients

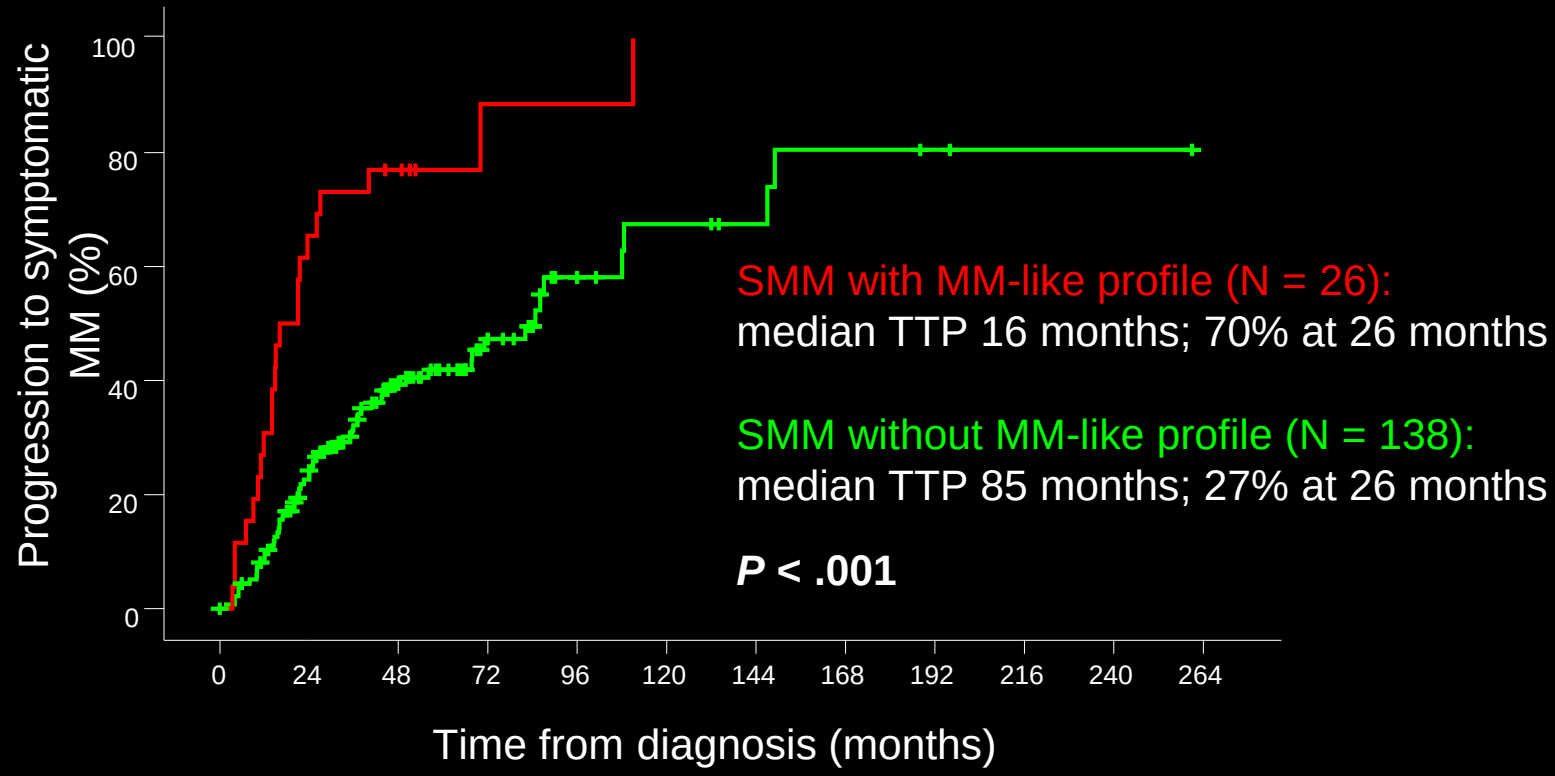


1. Rajkumar SV et al. N Engl J Med 2011; 365:474-475
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

Ultra-high risk SMM: Automatized flow cytometry immunphenotyping (n:164 pts)

164 pts with SMM have been compared with a phenotypic dataset that included 497 MGUS and 698 symptomatic MM patients.

26 pts (16%) had MM-like profile.



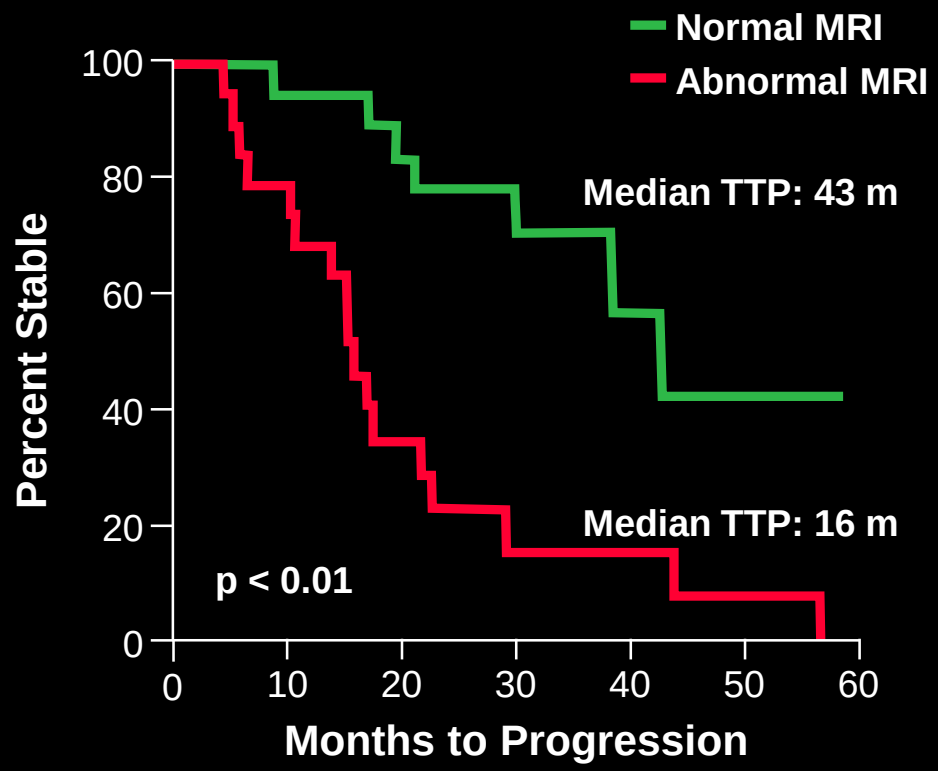
Paiva B, Mateos MV et al. *Data unpublished*

Smoldering Multiple Myeloma: MRI

43 pts with asymptomatic MM

Spinal MRI: 50% of pts: marrow involv

Patterns: Diffuse, variegated and **focal**

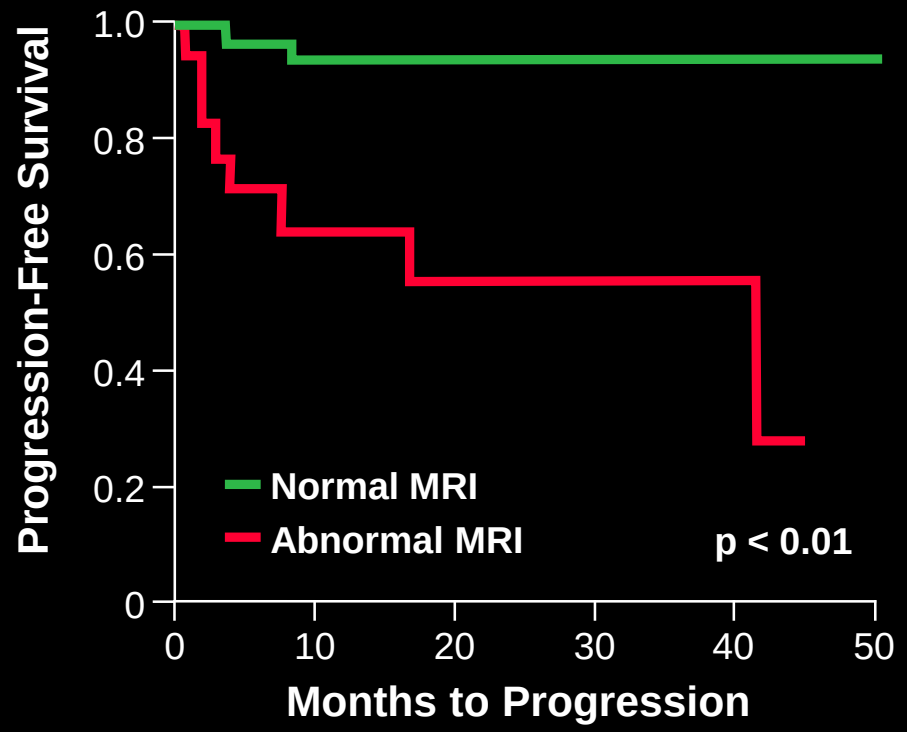


Moulopoulos et al. J Clin Oncol 2005; 13:251-6

55 pts with stage I MM

Spinal MRI: 31% of pts: marrow involv

Patterns: Diffuse, variegated and **focal**

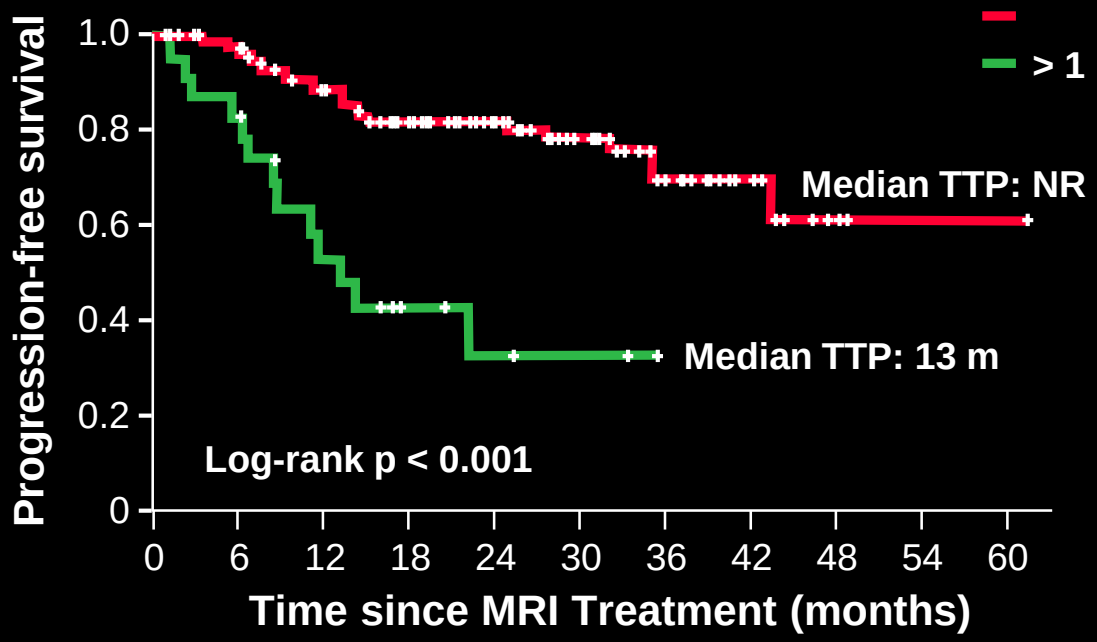


Mariette et al. Br J Hematol 1998; 104:723-9

Smouldering Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM

Whole MRI: 28% of pts: Focal lessions



0 or 1 FL	126	106	81	64	49	36	20	11	3	1	1
More than 1 FL	23	19	10	5	3	2					

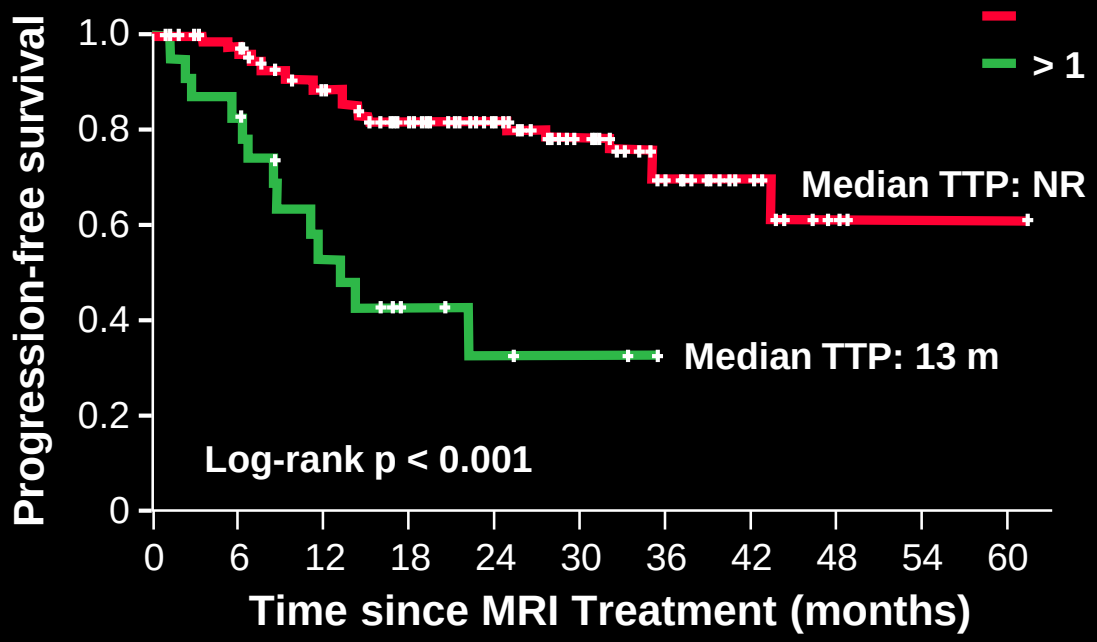
***> 1** Focal lession plus diffuse pattern → adverse prognosis*

1. Hillengass J, et al. J Clin Oncol 2010;28:1606-1610
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM

Whole MRI: 28% of pts: Focal lesions



0 or 1 FL	126	106	81	64	49	36	20	11	3	1	1
More than 1 FL	23	19	10	5	3	2					

***> 1** Focal lession plus diffuse pattern → adverse prognosis*

1. Hillengass J, et al. J Clin Oncol 2010;28:1606-1610
2. Kastritis E, et al. Leukemia. 2013 Apr;27(4):947-53

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Rajkumar et al. Lancet Oncology 2014; 15: e538-48

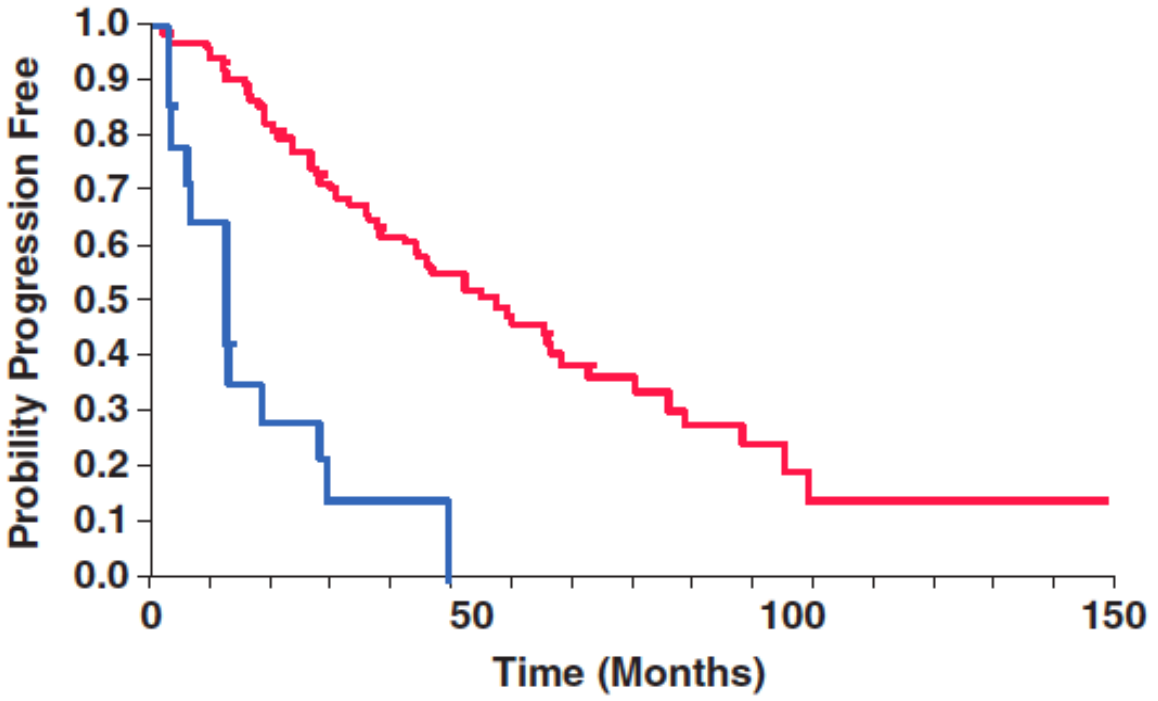
Recommended work up at baseline in patients with Smouldering MM

- **Medical History and physical examination**
- **Hemogram**
- **Creatinine and calcium values**
- **Protein studies**

  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)
- **Bone Marrow aspirate+/- biopsy**
- **Skeletal survey/Low-dose CT/PET-CT**
- **MRI of the spine and pelvis/ Whole-body MRI**

Mateos MV et al. Current hematologic malignancy reports. 2013; 8(4): 270-6.

Ultra-high risk SMM: peripheral blood plasma cell circulating (>5x10^6/L and/or 5% per 100 cytoplasmic Ig-positive PB mononuclear cells)

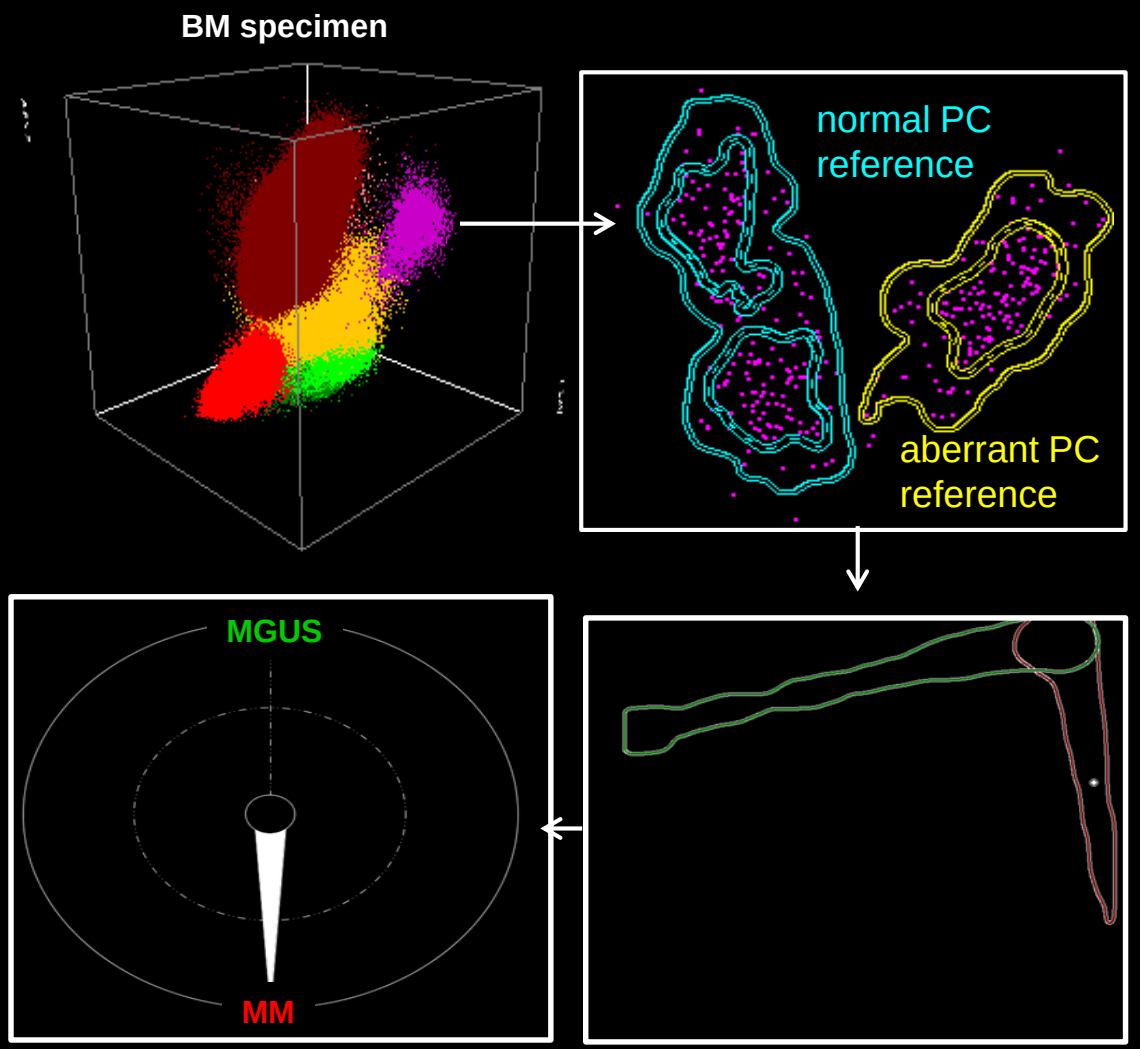


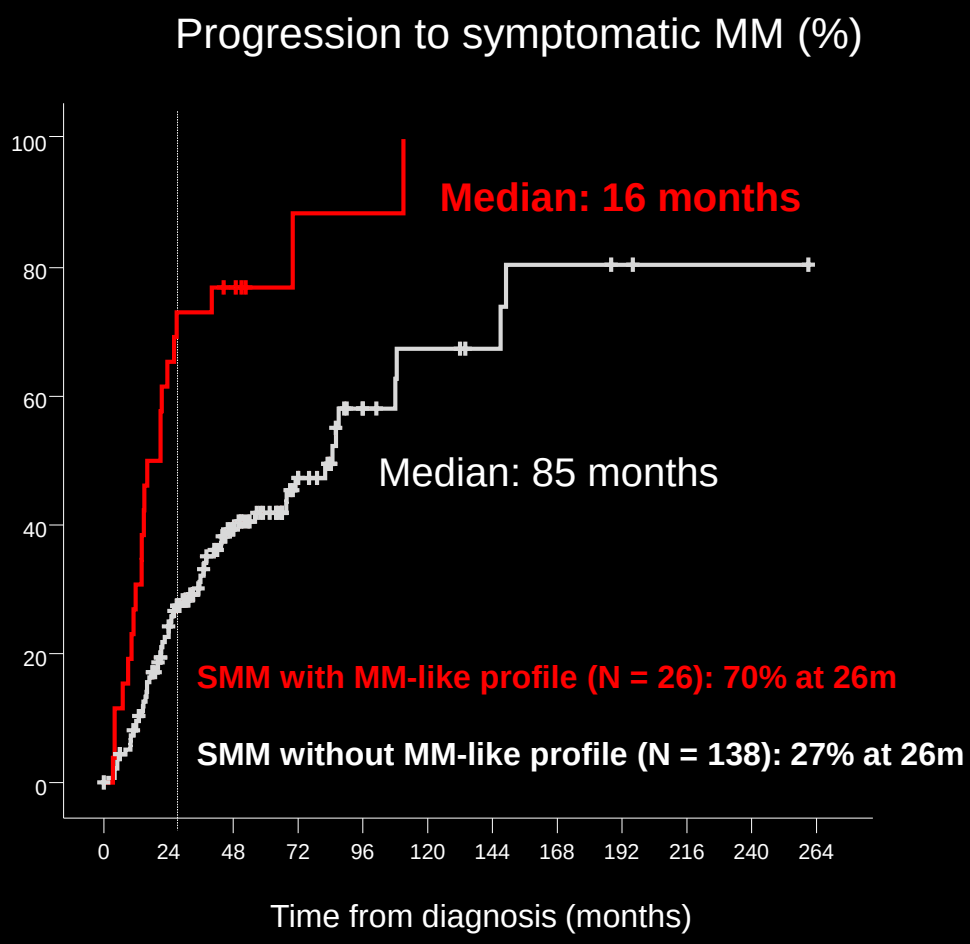
		Median TTP (months)
High circ PC	**14 pts (15%)**	12
Low circ PC	**77 pts (85%)**	57

P value: <0.001

Bianchi et al. Leukemia 2013;27: 680-5

Ultra high-risk SMM: automated MFC immunophenotyping of BMPCs





Paiva B, et al. Leukemia. 2013;27:2056-2061 (updated results)

Smoldering Multiple Myeloma: Risk models

Identification of high risk SMM→ 50% of progression risk at 2y

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglogulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** **≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs)**
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

Smoldering Multiple Myeloma: Risk models

- Are all these risk models similar?

Smoldering Multiple Myeloma: Risk models

Identification of high risk SMM→ 50% of progression risk at 2y

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglogulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** **≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs)**
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

Each model appears to identify patients at high risk, with some but not complete overlap

Smoldering Multiple Myeloma: Risk models

- Are all these risk models similar?
- Are concordant all risk models?

Smoldering Multiple Myeloma: Risk models

Identification of high risk SMM→ 50% of progression risk at 2y

- ***Mayo Clinic:*** ≥10% clonal plasma cell bone marrow infiltration, and ≥30g/L of serum M-protein, and serum-free light ratio >0.125 or <8
- ***Spanish:*** ≥95% of aberrrant plasma cells measured by flow plus >25% decrease in one or both uninvolved immunoglogulins
- ***Heidelberg:*** Tumor mass defined by Mayo risk model plus t(4;14)/del17p/gains of 1q/
- ***Japanese:*** Beta 2-microglobulin ≥ 2.5 mg/L plus M-protein increment rate > 1 mg/dL/day
- ***SWOG:*** serum M-protein ≥2 g/dL plus involved free light chain >25 and GEP >-0.26 (71% of risk progression at 2 yrs)
- ***PENN:*** **≥ 40% clonal PCBM infiltration plus sFLC ratio ≥ 50 plus Albumin □ 3.5 mg/dL (81% of risk at 2 yrs)**
- ***Czech & Heidelberg:*** immunoparesis plus serum M-protein ≥ 2.3 g/dL plus involved/uninvolved sFLC > 30 **(81% of risk at 2 yrs)**
- ***Barcelona:*** evolving pattern plus serum M-protein ≥ 3 g/dL plus immunoparesis **(80% of risk at 2 yrs)**

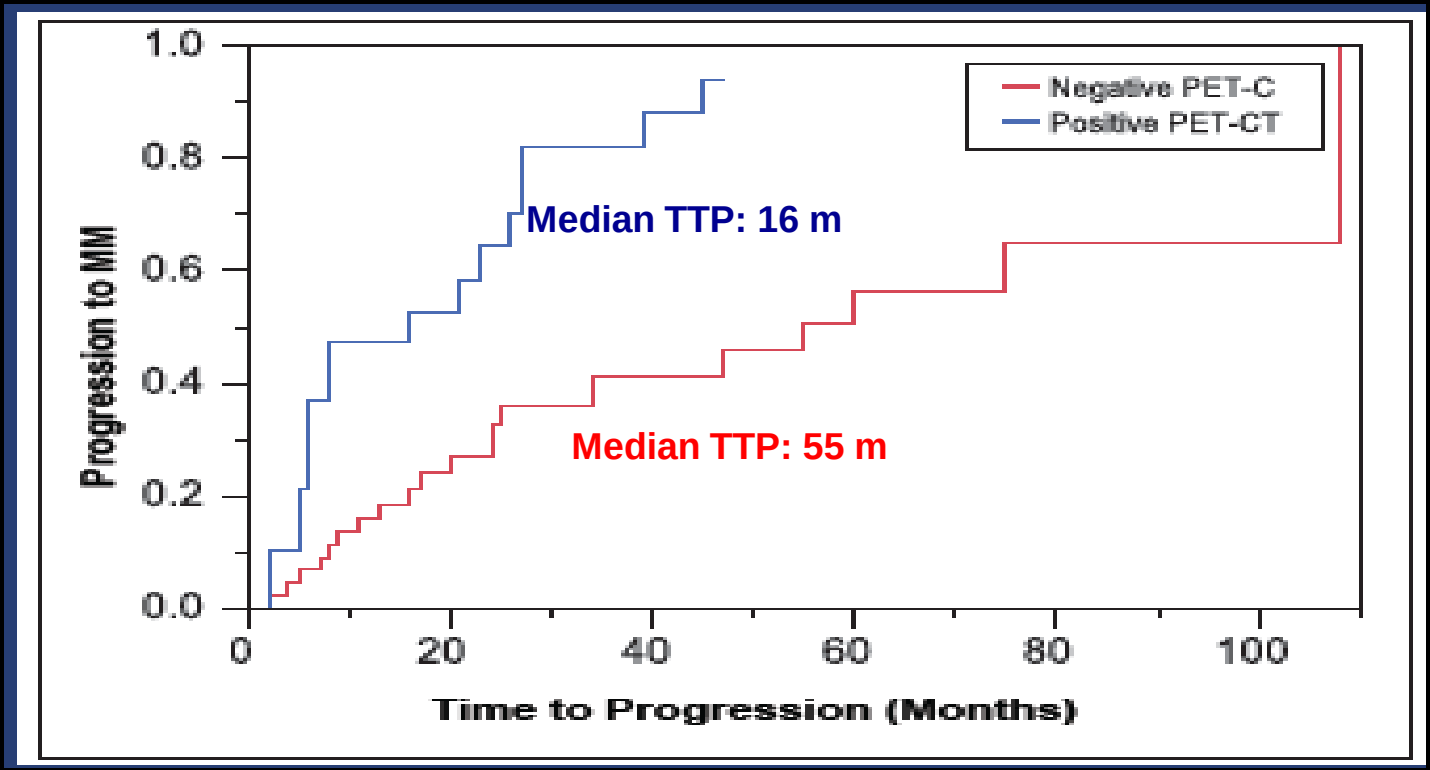
Texto de rajkumar

Smoldering Multiple Myeloma: Management

- Management should be risk-adapted
- **Low risk SMM** should be followed as MGUS-like pts: annually
- **Intermediate risk SMM** should be followed as true SMM pts: every 6 months
- **Ultra high-risk** should be considered **MM** and be treated
- **High-risk** SMM can benefit from early treatment

Smouldering Multiple Myeloma: PET/CT (n:202)

Positive PET/CT: 41% of the patients



In patients with positive PET-CT, those with underlying osteolysis had increased incidence of progression (77% at 2 yrs)

Dykstra B, Kumar S, et al. ASH 2014: abstract

Smoldering Multiple Myeloma

Features for identifying high-risk SMM→ 50% of progression risk at 2y

- ***Tumor burden:***
  ≥10% clonal plasma cell bone marrow infiltration, and
  ≥30g/L of serum M-protein, and
  serum-free light ratio >0.125 or <8

- ***Immunophenotyping characterization and immunoparesis***
  ≥95% of aberrrant plasma cells measured by flow
  >25% decrease in one or both uninvolved immunoglogulins

- ***Primary molecular cytogenetic abnormalities***
  t(4;14)/del17p/gains of 1q/trisomies/hyperdiploidy
- ***GEP-70***
  >-0.26

- ***PET/CT***
  positive with no osteolysis

Features for identifying ultra high-risk SMM→ 80-90% of progression risk at 2 y

- >1 focal lesion plus diffuse pattern in whole body MRI/ PET-CT positive with underlying osteolysis in TC
- ≥60% of clonal plasma cell in bone marrow biopsy
- Involved/uninvolved serum FLC ratio >100

Smoldering Multiple Myeloma: Management

Management should be risk-adapted

- **Why observation for asymptomatic patients?**

Advanced cancer is usually incurable. In most malignancies (lung, colon, prostate, breast, …) early detection and intervention is a pre-requisite for cure.

Smoldering Multiple Myeloma: Management

Agents	ORR (%)	TTP	OS	Reference
Early MP* vs Deferred MP	52 55	No benefit	No benefit	Hjorth M, et al. Eur J Haematol. 1993 Grignani G, et al. Br J Cancer. 1996 Riccardi A, et al. Br J Cancer. 2000
Thal+Zol vs Zol**	37 0	No benefit	No benefit	Witzig TE, et al. Leukemia 2013
Bisphosphonates***vs observation	0	No benefit	No benefit	Martin A, et al. Br J Haematol. 2002 D'arena et al. Leuk Lymphoma. 2011 Musto P, et al. Cancer. 2008

**Abandon: No differences in survival and potential risk of secondary leukemias*

***Low efficacy&high rates of discontinuation due to PN*

****Skeletal related events lower in the bisphosphonate groups* ***(39% vs 73% and 55% vs 78%)***

Smoldering Multiple Myeloma: Management

Agents	ORR (%)	TTP	OS	Reference
Early MP* vs Deferred MP	52 55	No benefit	No benefit	Hjorth M, et al. Eur J Haematol. 1993 Grignani G, et al. Br J Cancer. 1996 Riccardi A, et al. Br J Cancer. 2000
Thal+Zol vs Zol**	37 0	No benefit	No benefit	Witzig TE, et al. Leukemia 2013
Bisphosphonates***vs observation	0	No benefit	No benefit	Martin A, et al. Br J Haematol. 2002 D'arena et al. Leuk Lymphoma. 2011 Musto P, et al. Cancer. 2008

Low, intermediate and high risk patients were included

**Abandon: No differences in survival and potential risk of secondary leukemias*

***Low efficacy&high rates of discontinuation due to PN*

****Skeletal related events lower in the bisphosphonate groups* ***(39% vs 73% and 55% vs 78%)***

QuiRedex:
early treatment in high-risk SMM

MAYO CLINIC

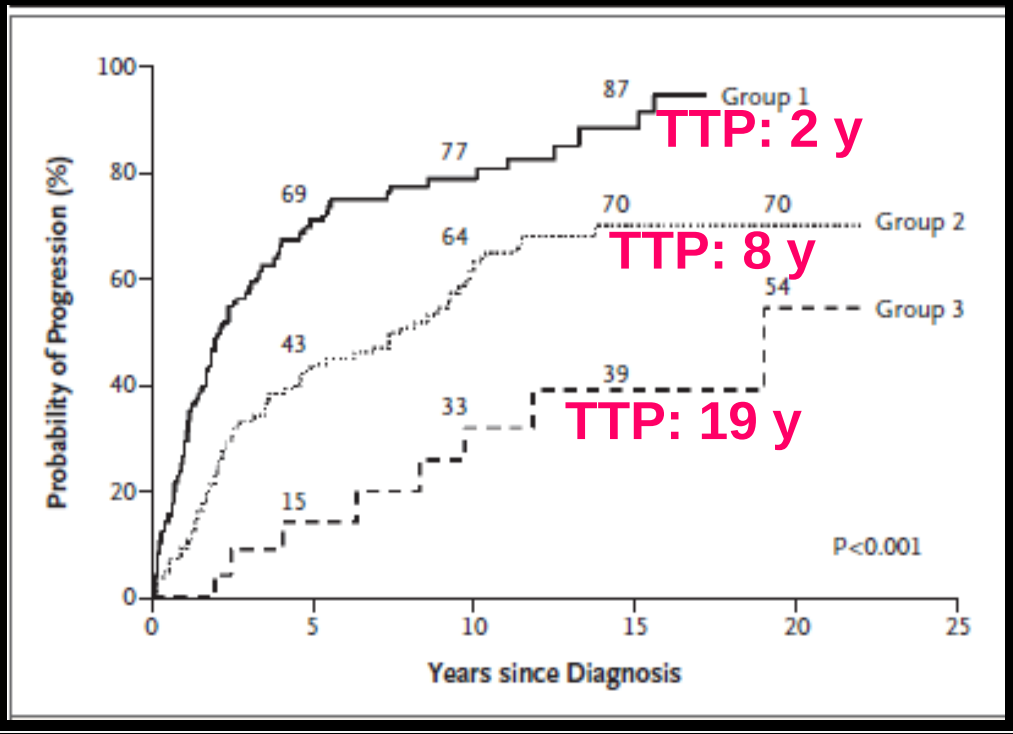
or

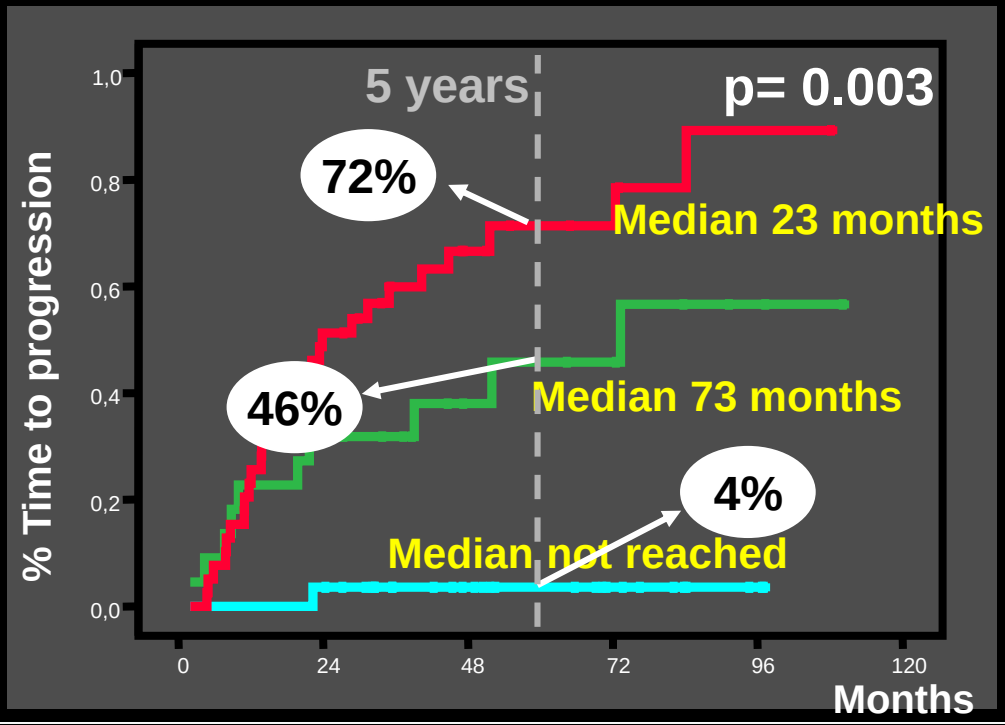
PETHEMA GEMM GRUPO ESPAÑOL DE MIELOMA

PCs BM ≥ 10% or **M-protein** ≥ 30 g/L

but **BM aPC/nPC** ≥ 95% plus **immunoparesis**

Group 1: PCBM ≥ 10% + MC ≥ 3g/dl or





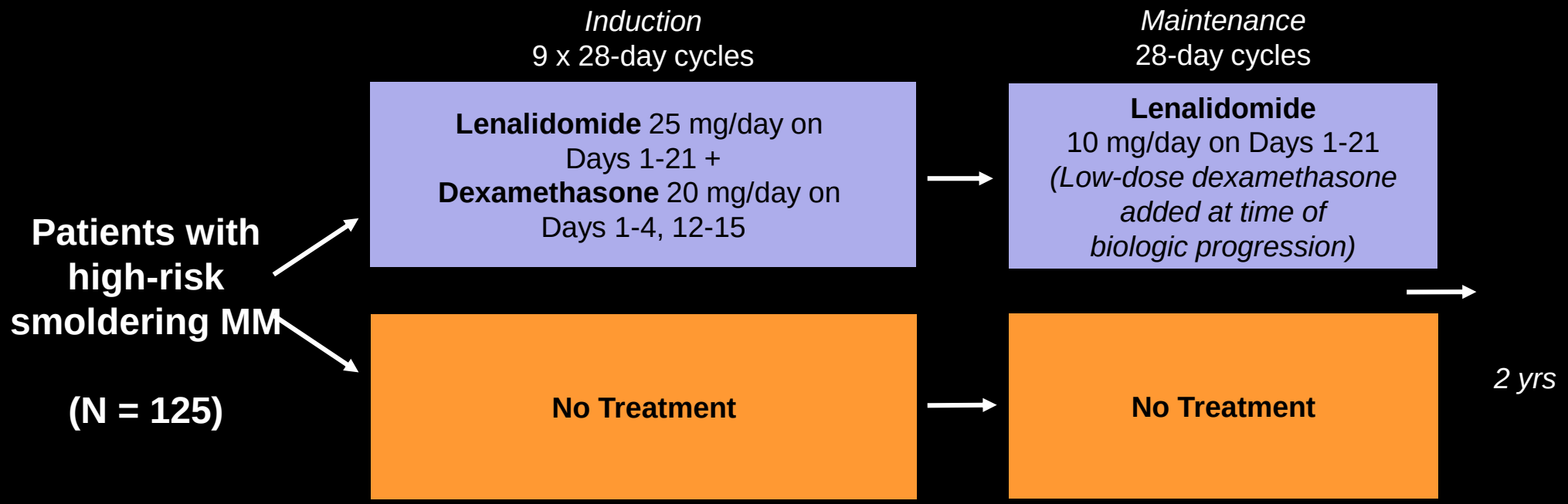
Time elapsed from diagnosis to inclusion not superior to 5 years

No CRAB (hypercalcemia, anemia, bone lesions, renal impairment) **or symptoms**

Mateos MV, et al. NEJM 2013; 369:438-47

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial



In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

High-risk was defined according to the Mayo and/or Spanish models

Mateos MV, et al. NEJM 2013; 369:438-47

QuiRedex: Objectives

Primary objective

- **Time to progression** to symptomatic MM

Secondary objectives

- Response rates
- Duration of response
- Safety and tolerability
- Overall survival

External CRO: monitoring data

Independent Data Monitoring Committee: Inclusion criteria and primary endpoint

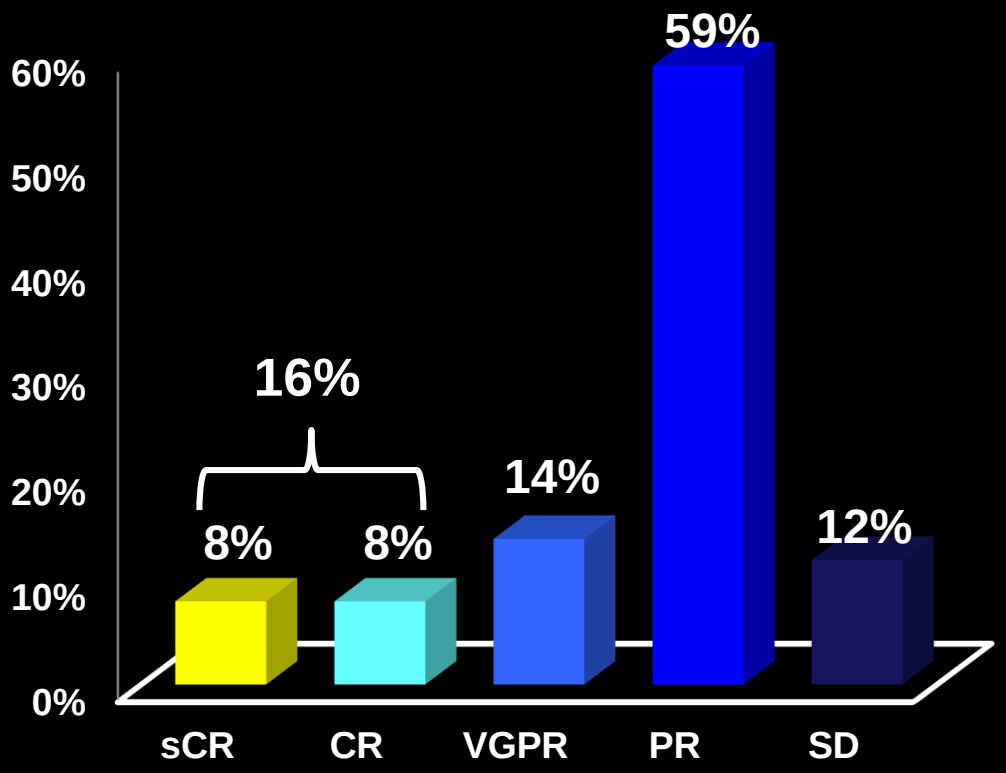
Mateos et al. submitted for publication

Lenalidomide + Dex: response rate

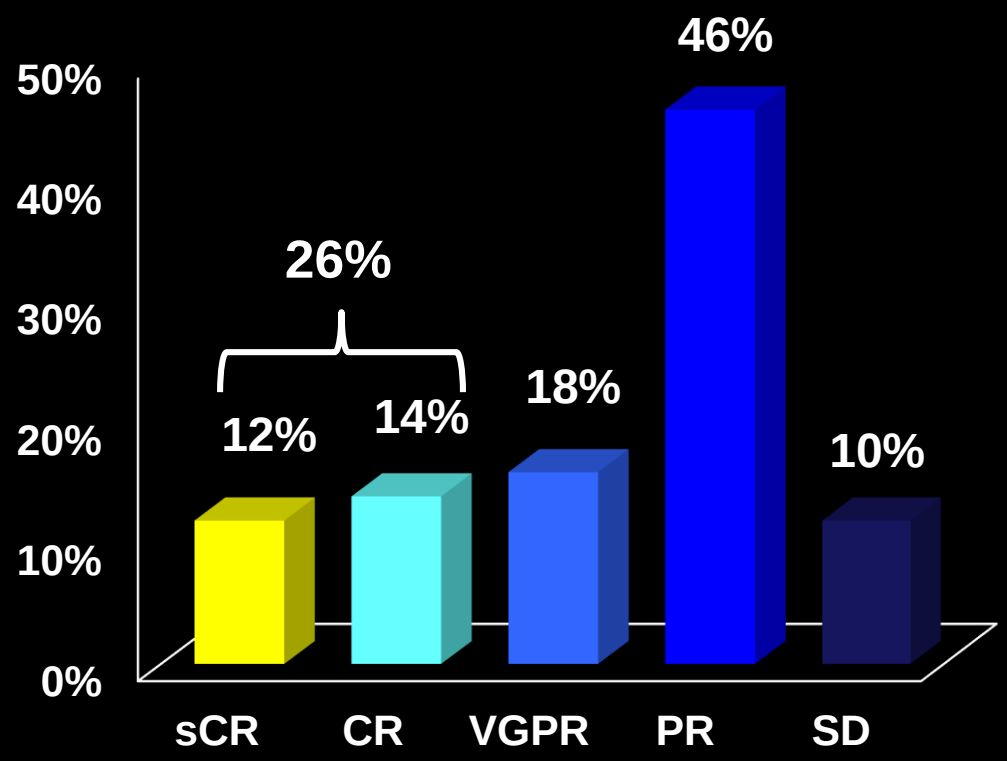
On ITT (n = 57) Median number of induction cycles: 9 (range 1–9)

ORR: 80%; ***sCR: 7%, CR: 7%; VGPR: 11%; PR: 65%;*** **SD: 21%**

After 9 induction cycles (n = 51)



After a median of 15 maintenance cycles (2-41) (n=50)



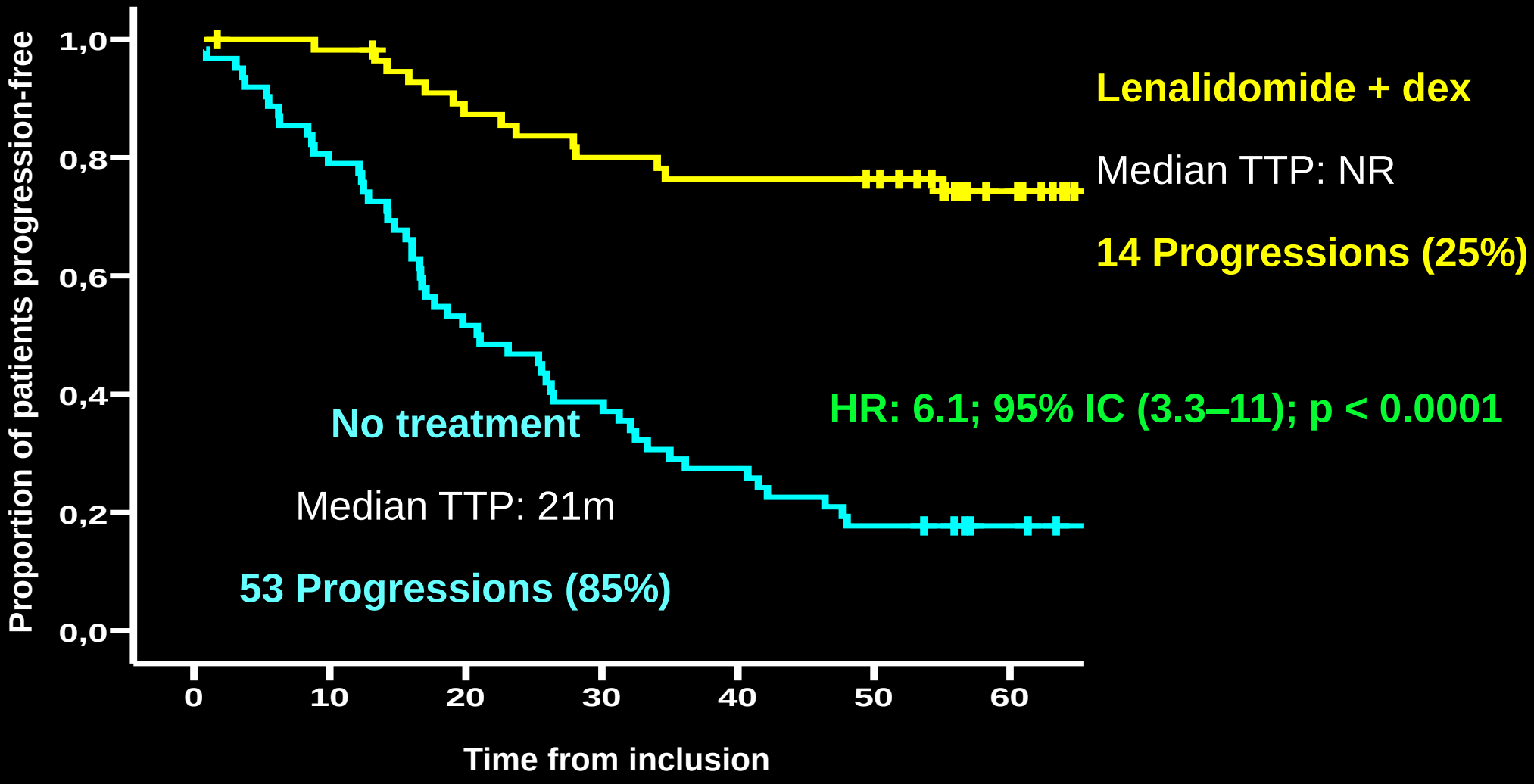
*IMWG criteria.

Mateos MV, et al. NEJM 2013; 369:438-47

Len-dex vs no treatment: TTP to active disease (n = 119)

ITT analysis: updated analysis

Median follow-up: 64 months (range 49–81)



Mateos MV, et al. ASH 2014: abstract 3465

Len-dex: biological progressions (n:57 pts)

At last f/u of maintenance therapy

24 biological progressions

Dex was added according to the protocol in 18 pts*

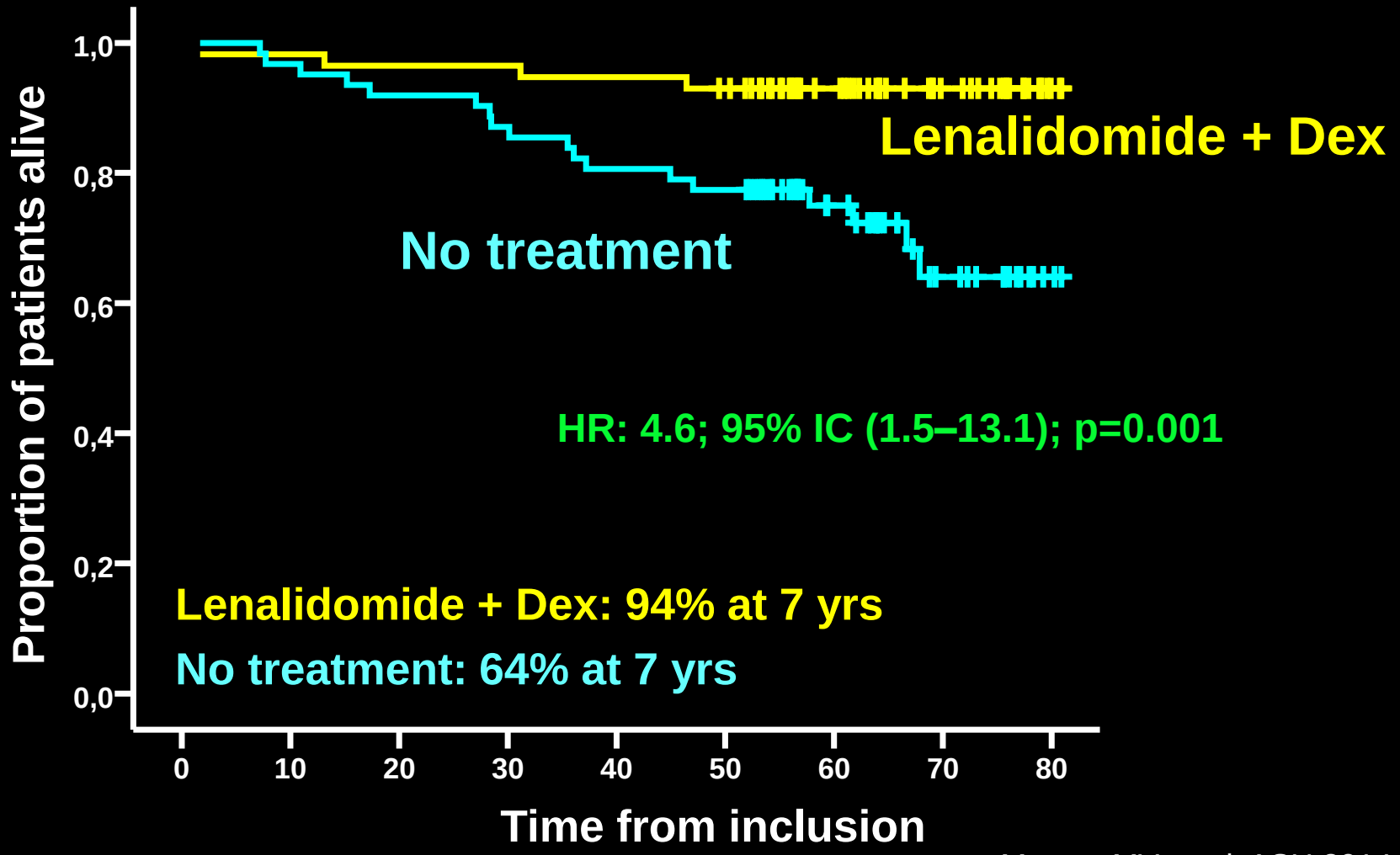
4 out of the 6 patients in which dex was not added → progressed

- **10pts: Experienced stabilization of disease with dex**
  - **7 remain stable after a median f/u of 50 m**
  - **3 pts: Progressed to active disease**

Mateos MV, et al. ASH 2014. Abstract 3465

Len-dex vs no treatment: OS from inclusion (n = 119)

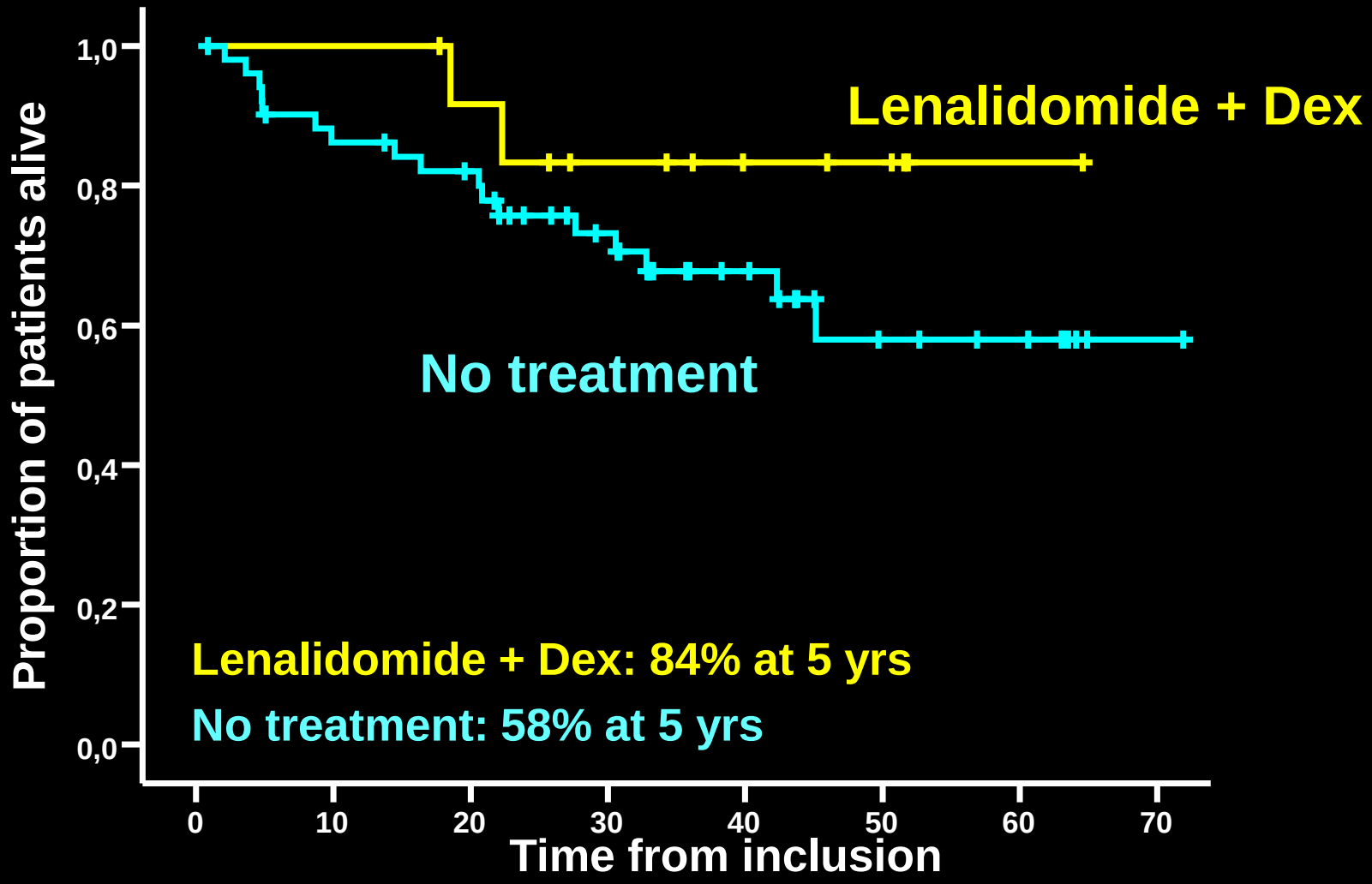
Median follow-up: 64 months (range 49–81)



Mateos MV, et al. ASH 2014: abstract 3465

Len-dex vs no treatment: OS from progression to active disease (n = 119)

Median follow-up: 64 months (range 49–81)



Mateos MV, et al. ASH 2014. Abstract 3465

Len-dex: toxicity profile during induction (n:62)

	G1-2	G3
Anemia	15 (28%)	1(2%)
Neutropenia	11 (20%)	3 (5%)
Thrombocytopenia	7 (13%)	1 (2%)
Asthenia	11 (20%)	4 (7%)
Constipation	10 (18%)	-
Diarrhea	13 (24%)	1 (2%)
Rash	18 (33%)	2 (4%)
Infection*	25 (46%)	4 (6%)
DVT**	3 (5%)	

- *One infection was Grade 4*

***DVT prophylaxis with Aspirin (100mg) in 1 pt, oral anticoagulation in 1 pt with low INR levels and no px in the other one*

Mateos MV, et al. NEJM 2013; 369:438-47

QuiRedex: toxicity profile during induction (n:62)

	G1	G2
Anemia	11 (20%)	4 (7%)
Neutropenia	3 (6%)	8 (14%)
Thrombopenia	6 (11%)	1 (2%)
Asthenia	6 (11%)	5 (9%)
Constipation	4 (7%)	6 (11%)
Diarrhea	9 (17%)	4 (7%)
Rash	12 (23%)	6 (11%)
Infection*	19 (35%)	6 (11%)
DVT**	1 (2%)	2 (4%)

Mateos MV, et al. NEJM 2013; 369:438-47

QuiRedex: toxicity profile during induction (n:125)

	Len-dex arm (n:62)		Abstention arm (n:63)
	G1	G2	G1-2
Anemia	11 (20%)	4 (7%)	2 (4%)
Neutropenia	3 (6%)	8 (14%)	
Thrombopenia	6 (11%)	1 (2%)	
Asthenia	6 (11%)	5 (9%)	6 (11%)
Constipation	4 (7%)	6 (11%)	1 (2%)
Diarrhea	9 (17%)	4 (7%)	2 (4%)
Rash	12 (23%)	6 (11%)	
Infection*	19 (35%)	6 (11%)	14 (26%)
DVT**	1 (2%)	2 (4%)	
SPM -Hematologic -Non hematolog	1 patient (PV) 3 patients*		1 patient (MDS)

*2 prostate cancers, 1 breast cancer

Mateos MV, et al. NEJM 2013; 369:438-47

Abstention arm: outcome after progression to symptomatic disease

Abstention arm
(n=46 pts)

Median age: 74 yrs

Treatments received:

58% bz-based comb (VMP)

28% ASCT

13% len-based comb

8% MP or conventional QT

60% of pts alive at 3 yrs after progression

VISTA trial: 3 yr-OS: 69%

Mateos MV, et al. NEJM 2013; 369:438-47

High-risk Smoldering Multiple Myeloma

- Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS

- Numerous clinical trials with several drugs are currently ongoing in this group of patients

Current Studies in High-Risk Smoldering MM

- **Biomarker study of elotuzumab (phase II)[2]**
- **Siltuximab (anti IL6) or no treatment (phase II)[3]**
- **Biomarker study of BHQ880 (anti DKK1) (phase II)[4]:**
  Data presented at ASH2012: no antitumor effect but anabolic activity
- **Lenalidomide or observation (phase III)[1]**
- **Elotuzumab-Lenalidomide-dex**
- **Carfilzomib, lenalidomide, and dexamethasone (phase II)[5]:**

1. ClinicalTrials.gov. NCT01169337.
2. ClinicalTrials.gov. NCT01441973.
3. ClinicalTrials.gov. NCT01484275.
4. ClinicalTrials.gov. NCT01302886.
5. ClinicalTrials.gov. NCT01572480.

Phase II trial for high-risk SMM: E3A06 Lenalidomide alone vs no treatment

Study open for high-risk smoldering myeloma pts ≥18 years old
Lenalidomide single agent (25 mg on days 1-21)

44 pts included. Median f/u: 17m

12 pts: (33%)≥PR

11 pts: G3-4 AEs: neutropenia/fatigue the most frequent

These results were encouraging to proceed to the Phase 3 trial in which lenalidomide will be compared with therapeutic abstention in high risk SMM

- Each cycle is 28 days

Lonial S, et al. *ASH abstract #3174*

Phase II trial for high-risk SMM: Carfilzomib/Revlimid/dex

Study open for high-risk smoldering myeloma pts ≥18 years old

8 cycles CRd Combination Therapy

Carfilzomib 20/36 mg/m^2,
day 1, 2, 8, 9, 15, 16

Lenalidomide 25 mg/day,
day 1-21

Dexamethasone 20/10 mg
day 1, 2, 8, 9, 15, 16, 22, 23

SD or better?

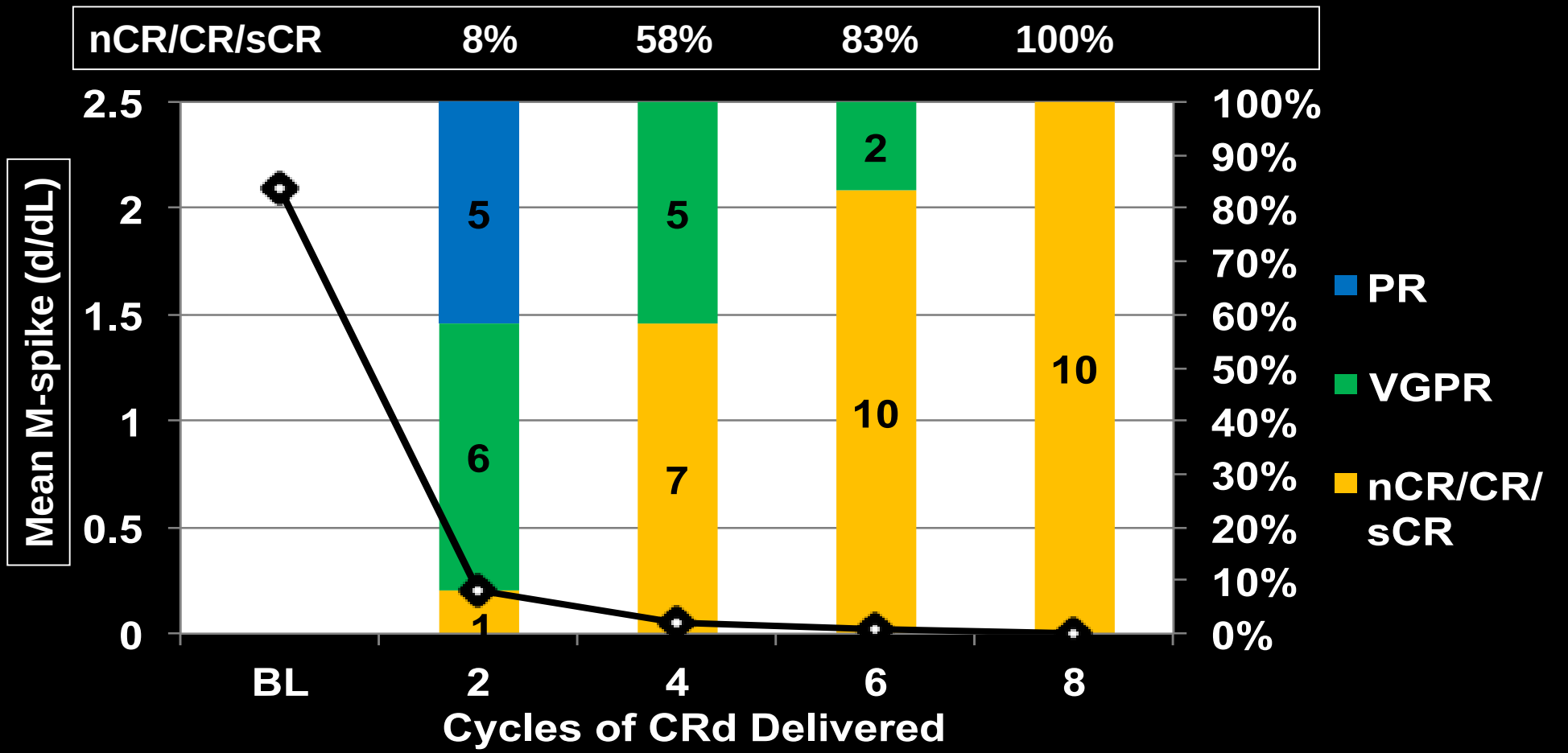
24 cycles Rev Extended Dosing

Lenalidomide 10 mg/day,
day 1-21

- Each cycle is 28 days
- Stem cell harvest after ≥4 cycles of CRd for patients <70-75 yrs
- C1D1/2 – Carfilzomib dose is 20 mg/m^2
- C1- 4 – Dex dose is 20 mg, C5- 8 – Dex dose is 10 mg

Landgren, et al. *ASH2014: abstract 4746*

Response rates in relation to cycles of KRd



11/12 (92%) are MRD negative by 8-color flow cytometry of the bone marrow

Landgren, et al. *ASH2014: abstract 4746*

Curative Estrategia Smoldering Alto Riesgo (CESAR trial) (n:90)

Induction 6 cycles of KRd

MRD ⇨

↓

ASCT (melphalan 200)

MRD ⇨

↓

Consolidation (2 cycles of KRd)

MRD ⇨

↓

Maintenance (Len-dex for 2yrs)

MRD ⇨

Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective

20 centers

Smoldering Multiple Myeloma

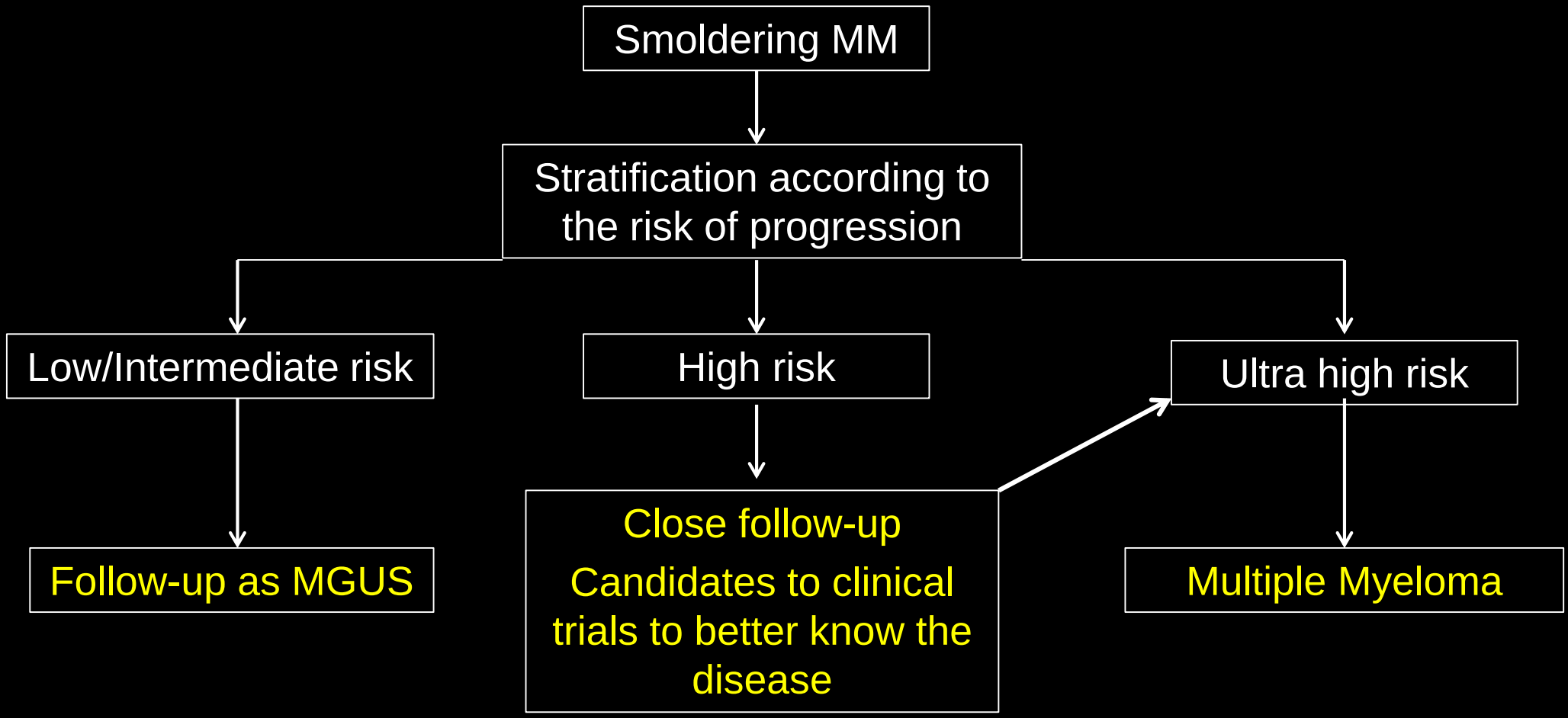
- **Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS**

- **Numerous clinical trials with several drugs are currently ongoing in this group of patients**

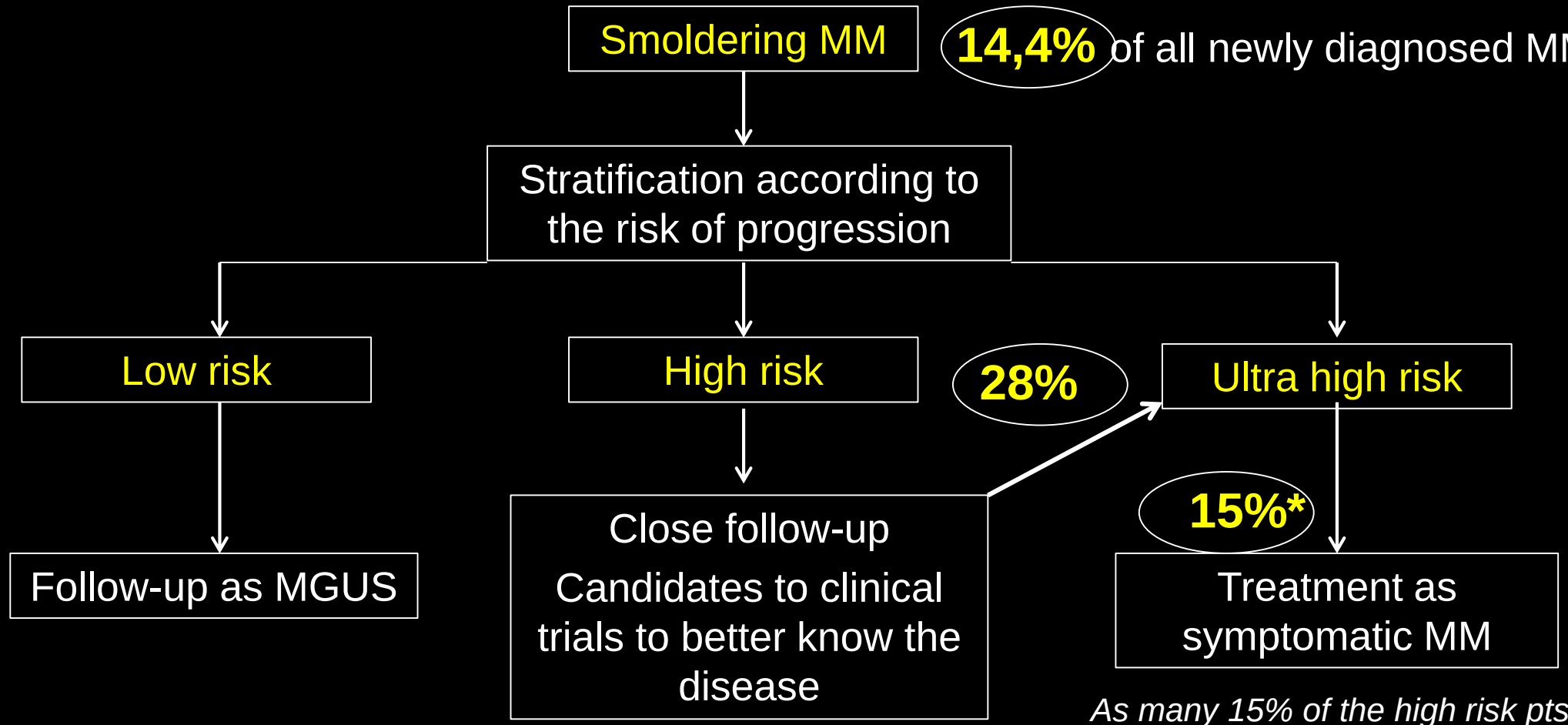
These results support to change the current treatment paradigm for this patient population

Early treatment in selected asymptomatic MM patients

Smoldering Multiple Myeloma



Smoldering Multiple Myeloma



Using the World population as reference, the age standardized incidence of smoldering multiple myeloma is 0.44 per 100.000, and high-risk disease 0.14 per 100.000

Kristinsson S et al. NEJM 2013

Acknowledgments

Investigators including cases in trials of the Spanish Myeloma Group, and most of all, the patients!