Smoldering Myeloma: when to observe and when to treat?

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Clinical Case

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

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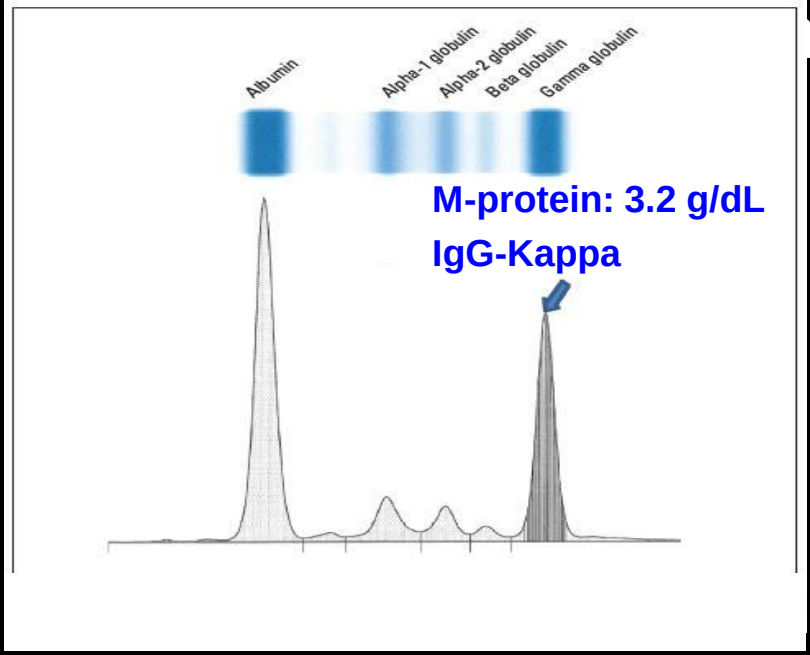

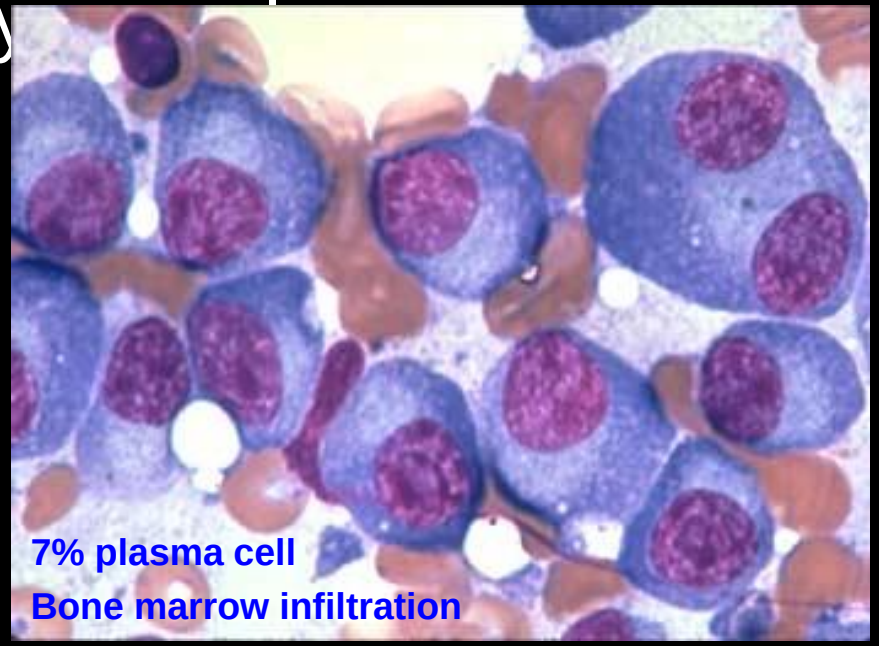

MGUS/SMM/MM: diagnostic criteria

	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

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	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**

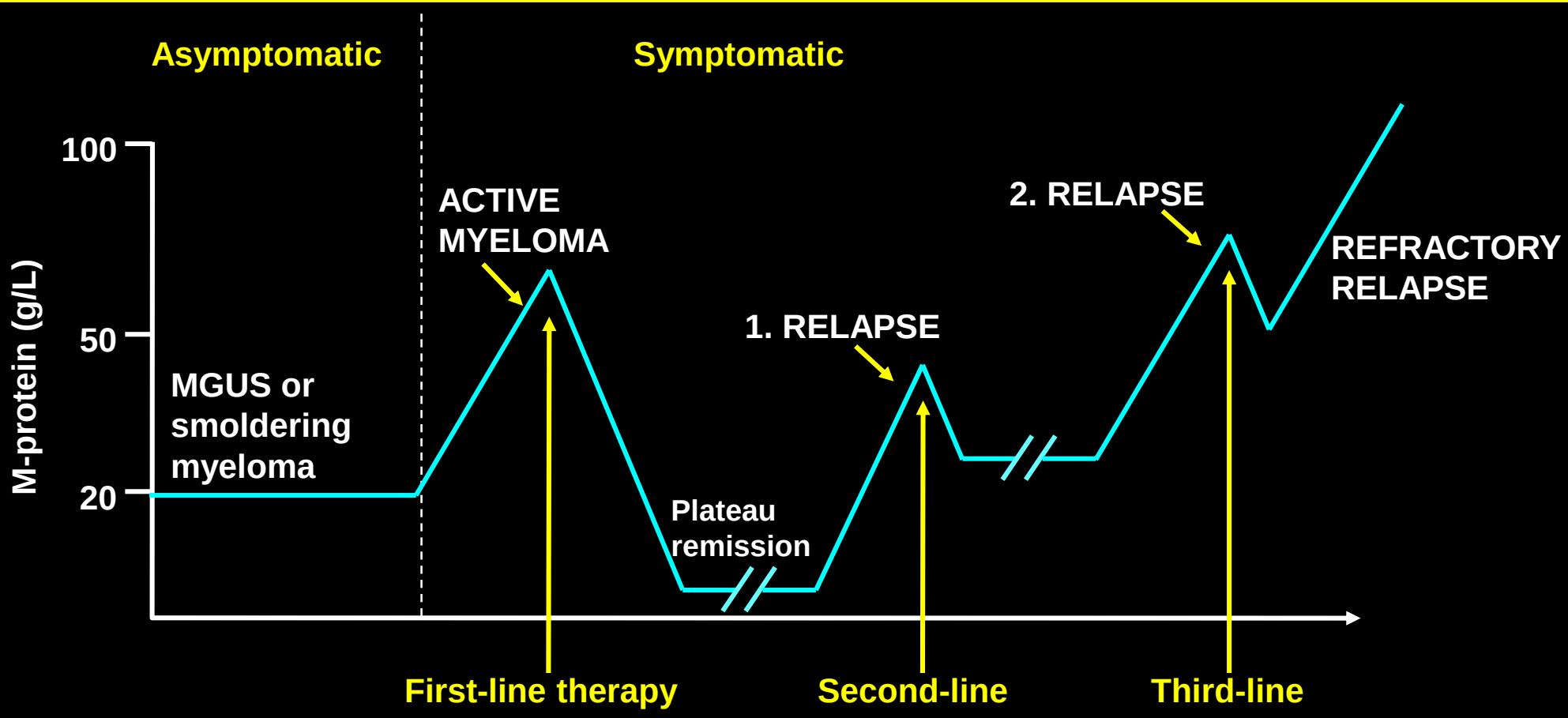
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)

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

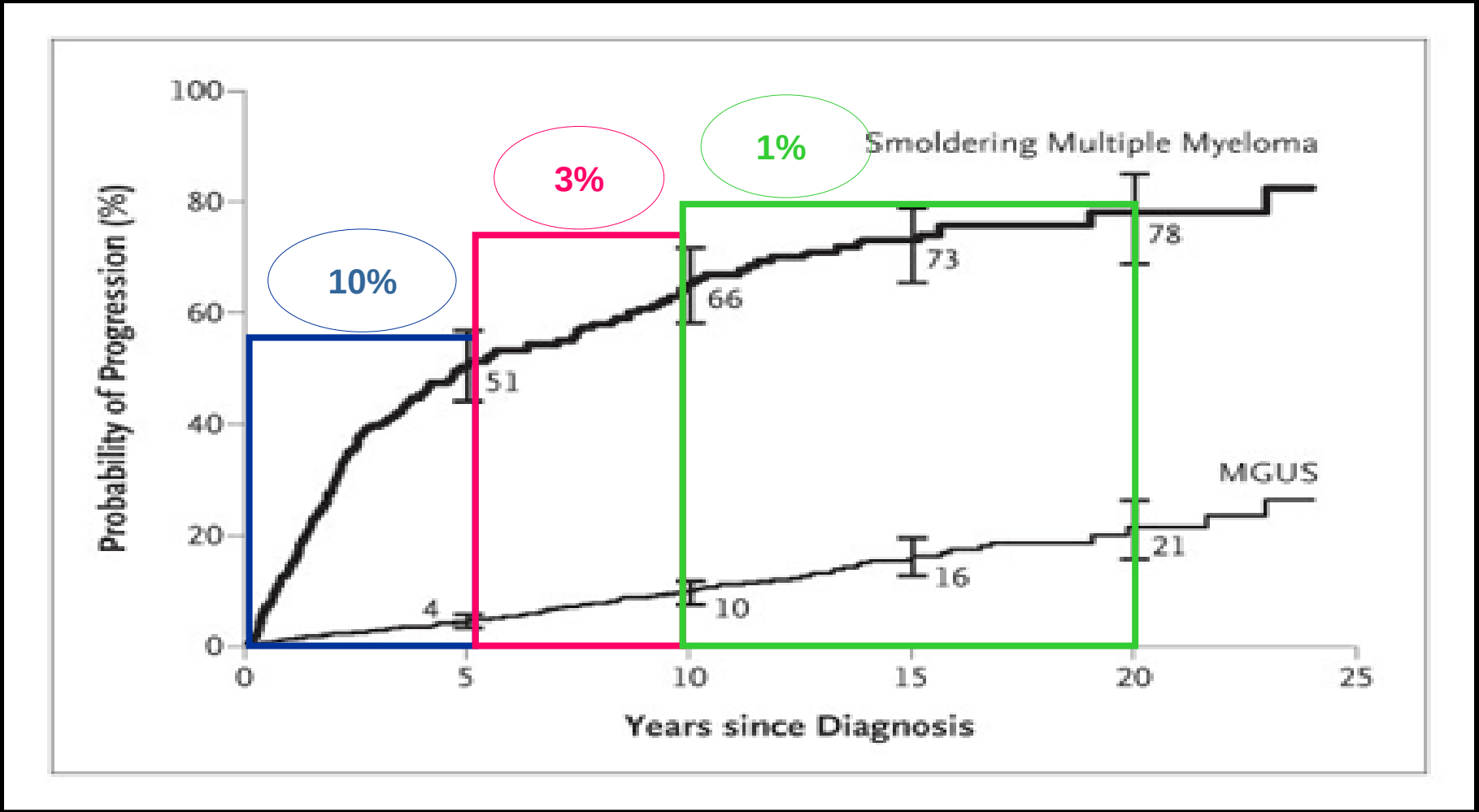
- **Differences in inmune surveillance**

  Dosani et al. Blood Cancer J. 2015

Are identical all patients with MGUS or SMM?

MGUS, monoclonal gammopathy of undetermined significance

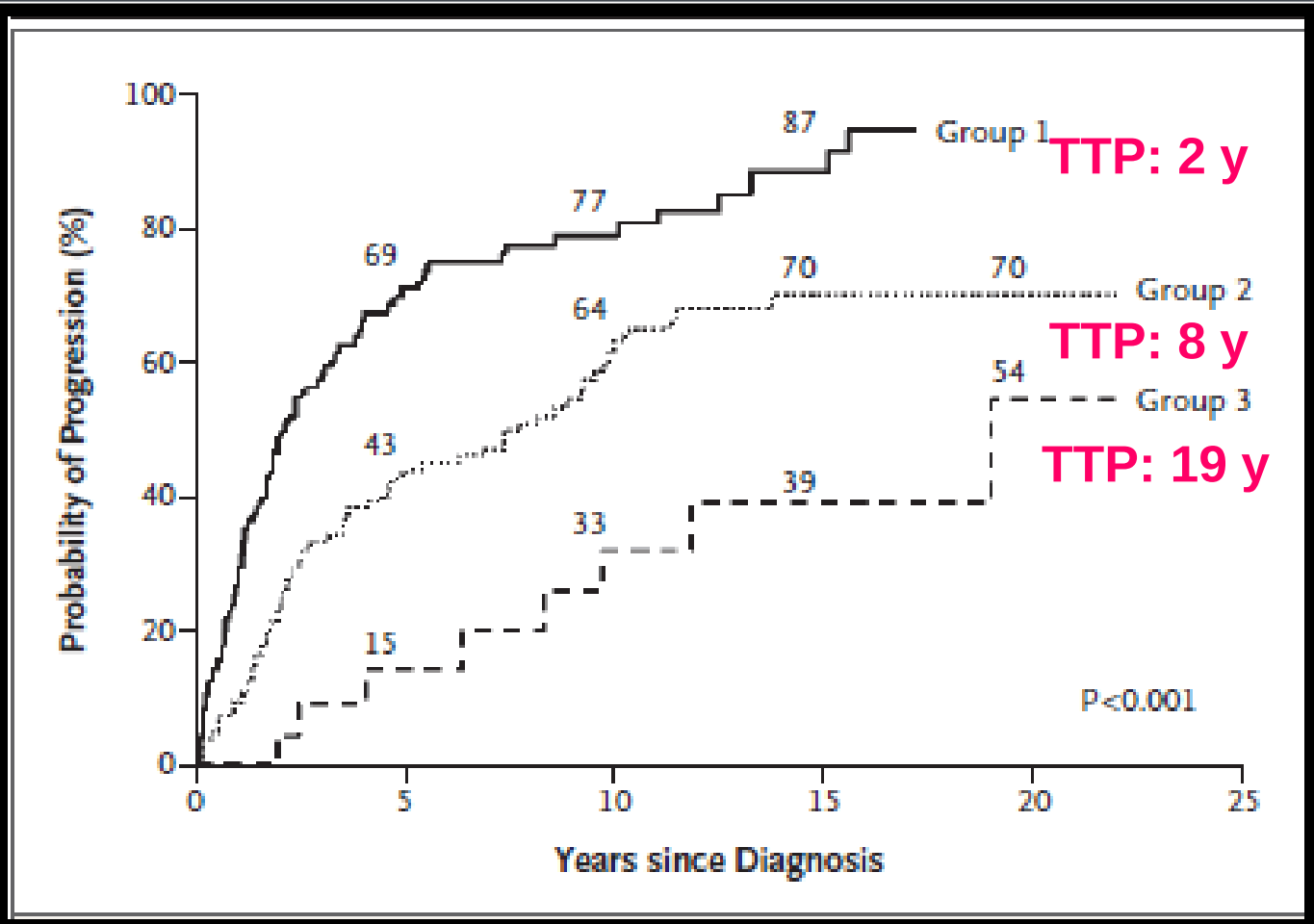
MGUS/Smoldering Multiple Myeloma: Risk of progression to active disease



Are there any risk factors predicting progression to active disease?

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

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

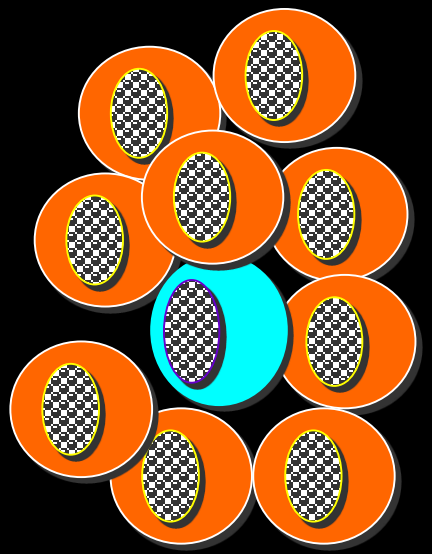
Group 1: ***PCBM ≥ 10% + MC ≥ 3g/dl***
Group 2: ***PCBM ≥ 10% + MC < 3g/dl***
Group 3: ***PCBM < 10% + MC ≥ 3g/dl***

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

Spanish Model:
Analysis of the PC compartment by flow cytometry

Clonal

MM

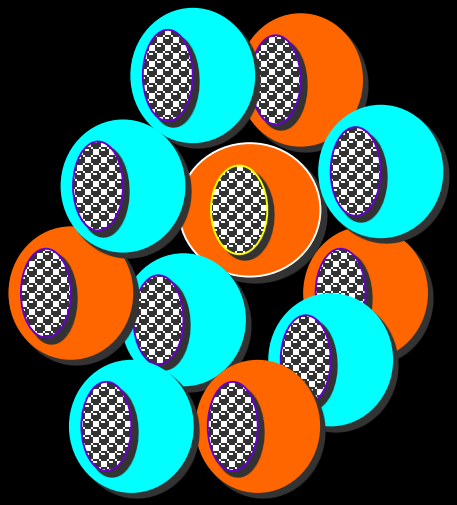


MM patients showed <5% poly-PC

versus

Poly-Clonal

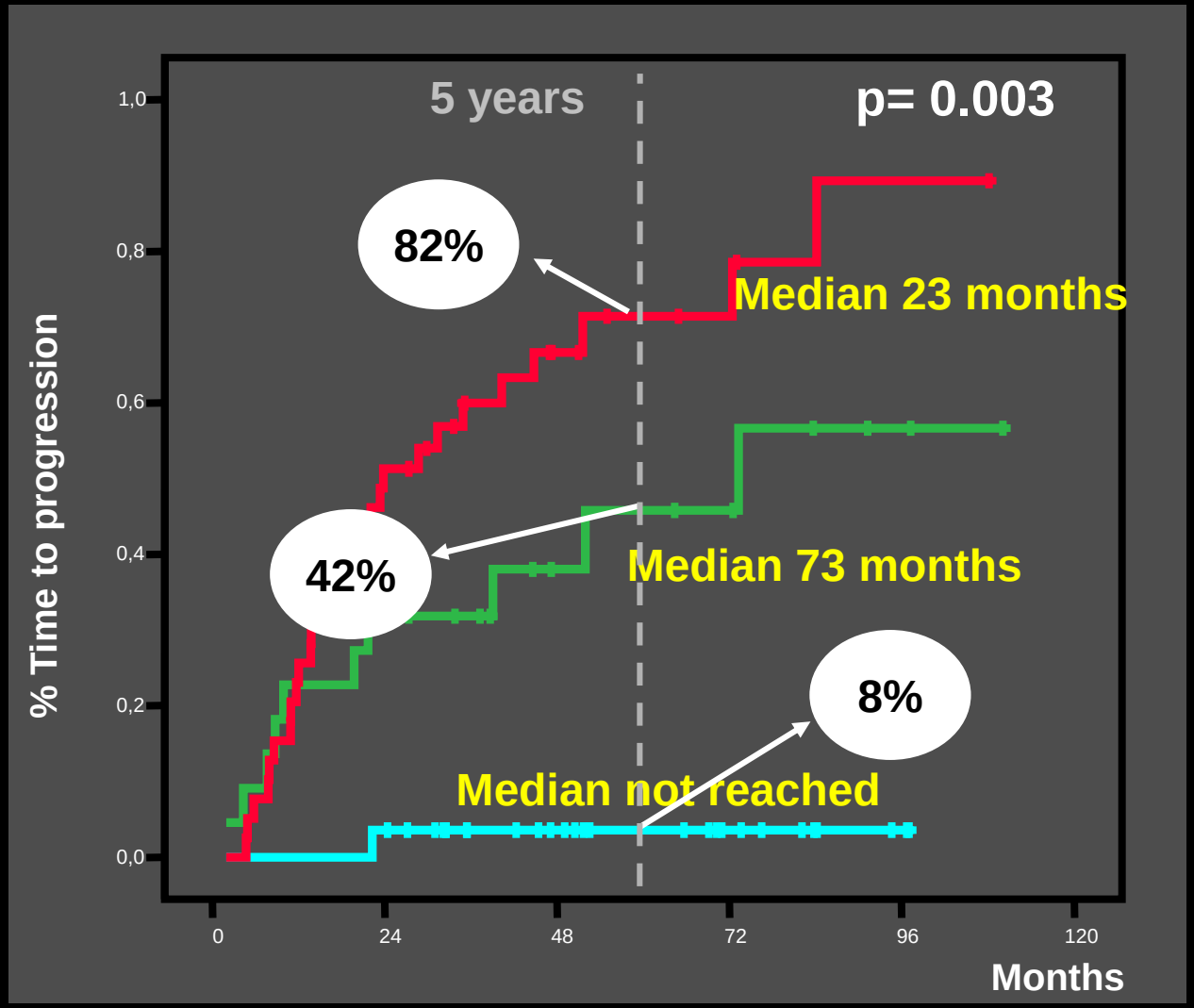
Smoldering MM



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.)

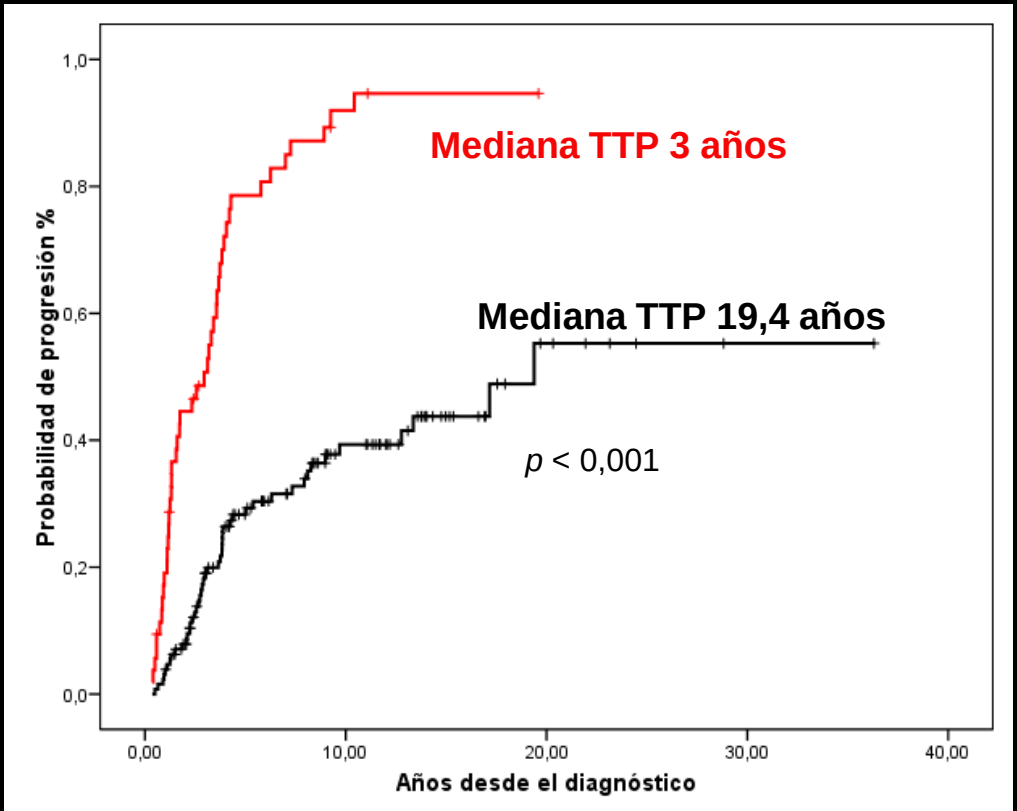
Pérez E. Blood 2007; 110:2586-92

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

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

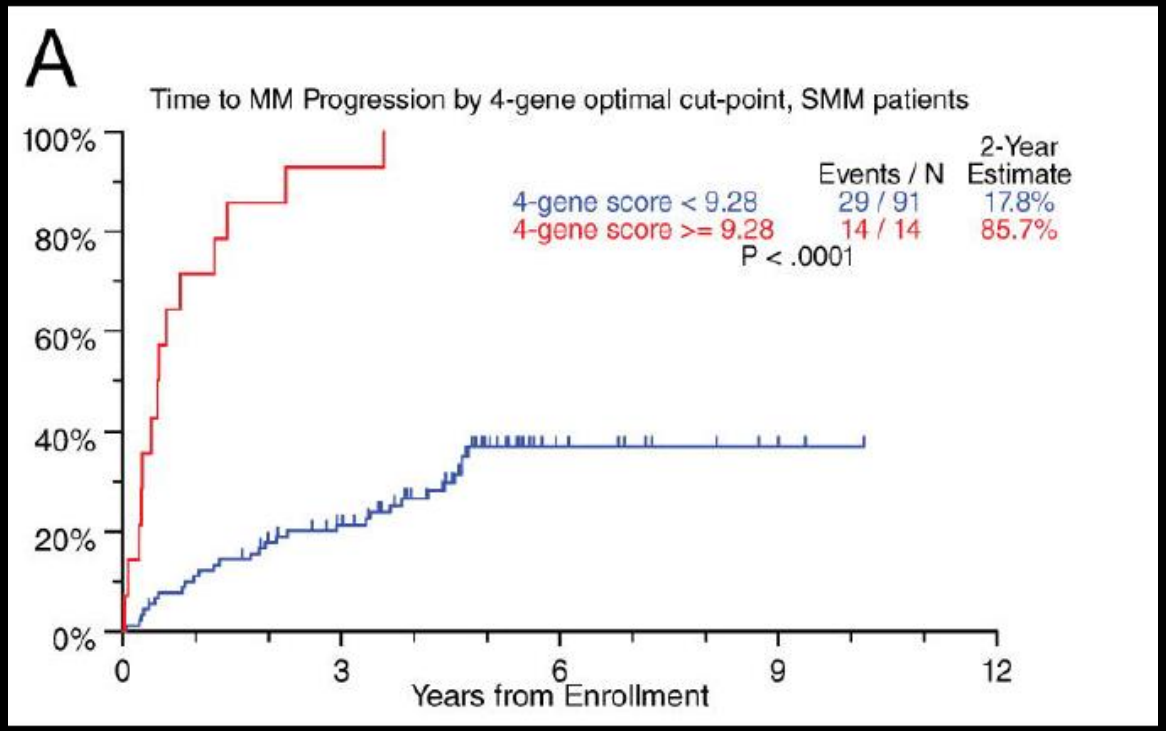
- del(17p13), t(4;14), trisomies showed significant impact on TTP

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.

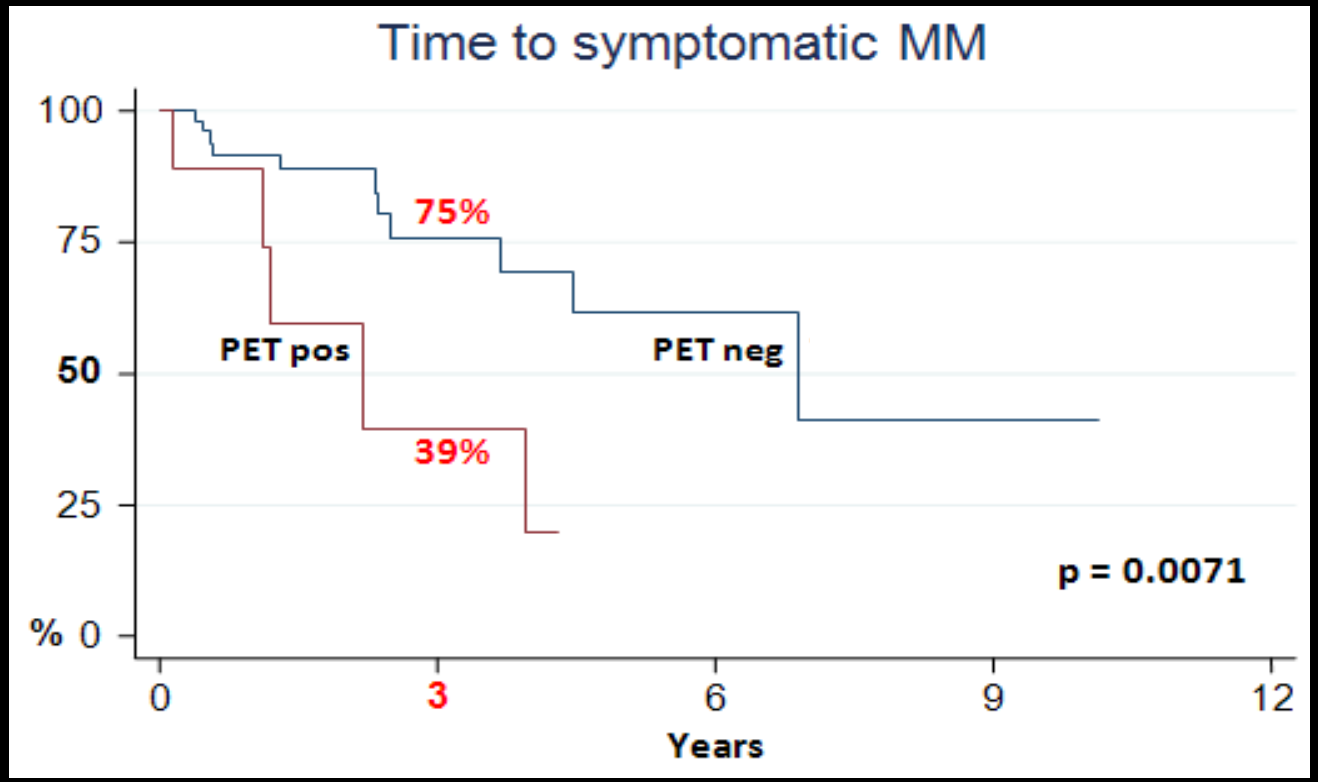


A gene signature derived from 4 genes at an optimal binary cut-point of 9.28, identified 14 patients (13%) with a 2-year therapy risk of 85.7%

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)

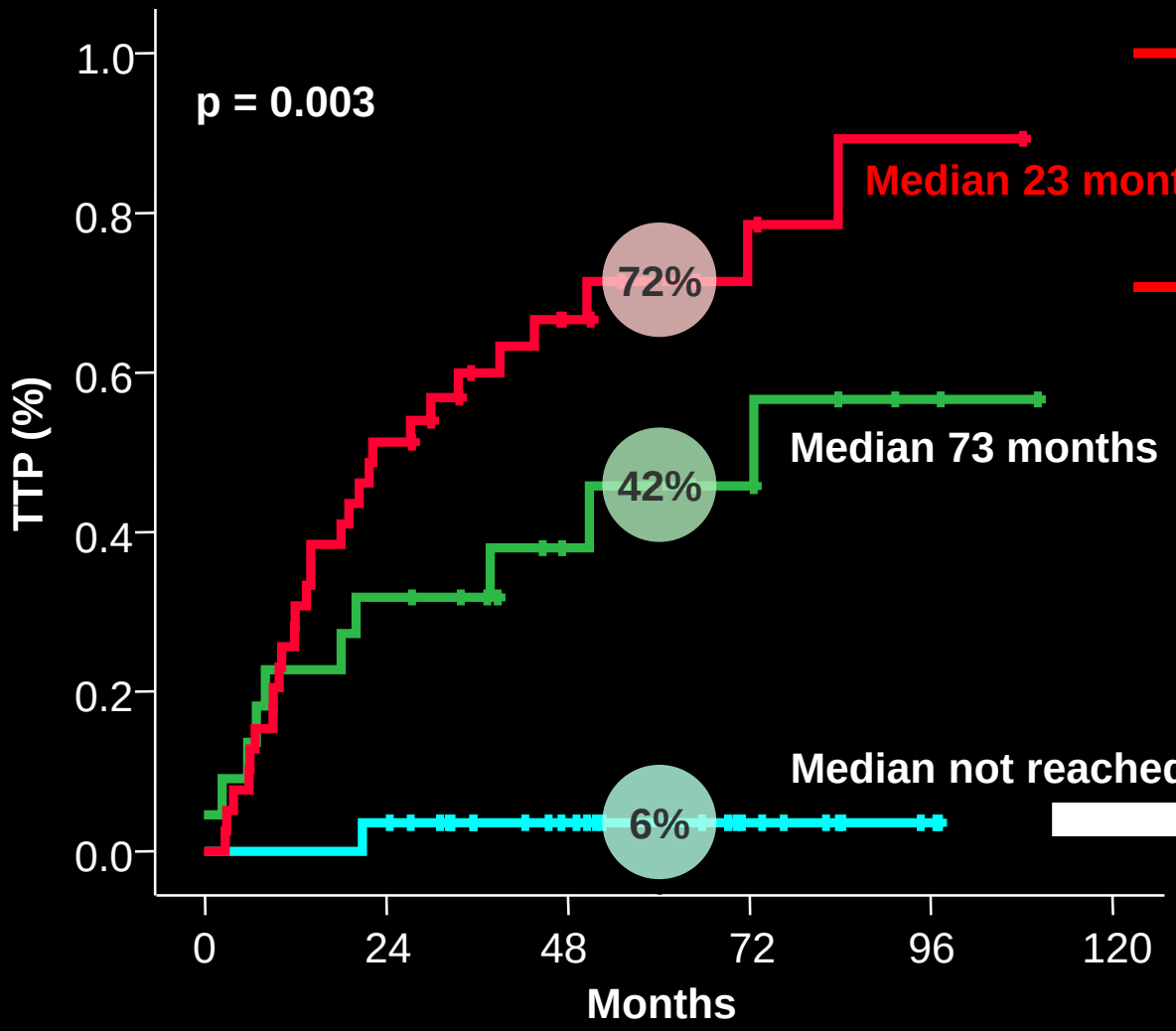
12% of patients had PET positive: 56% of them had 1 FL with a median PET SUV of 4.45 and no osteolysis was observed.



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

Zamagni E et al. ASH 2014;

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

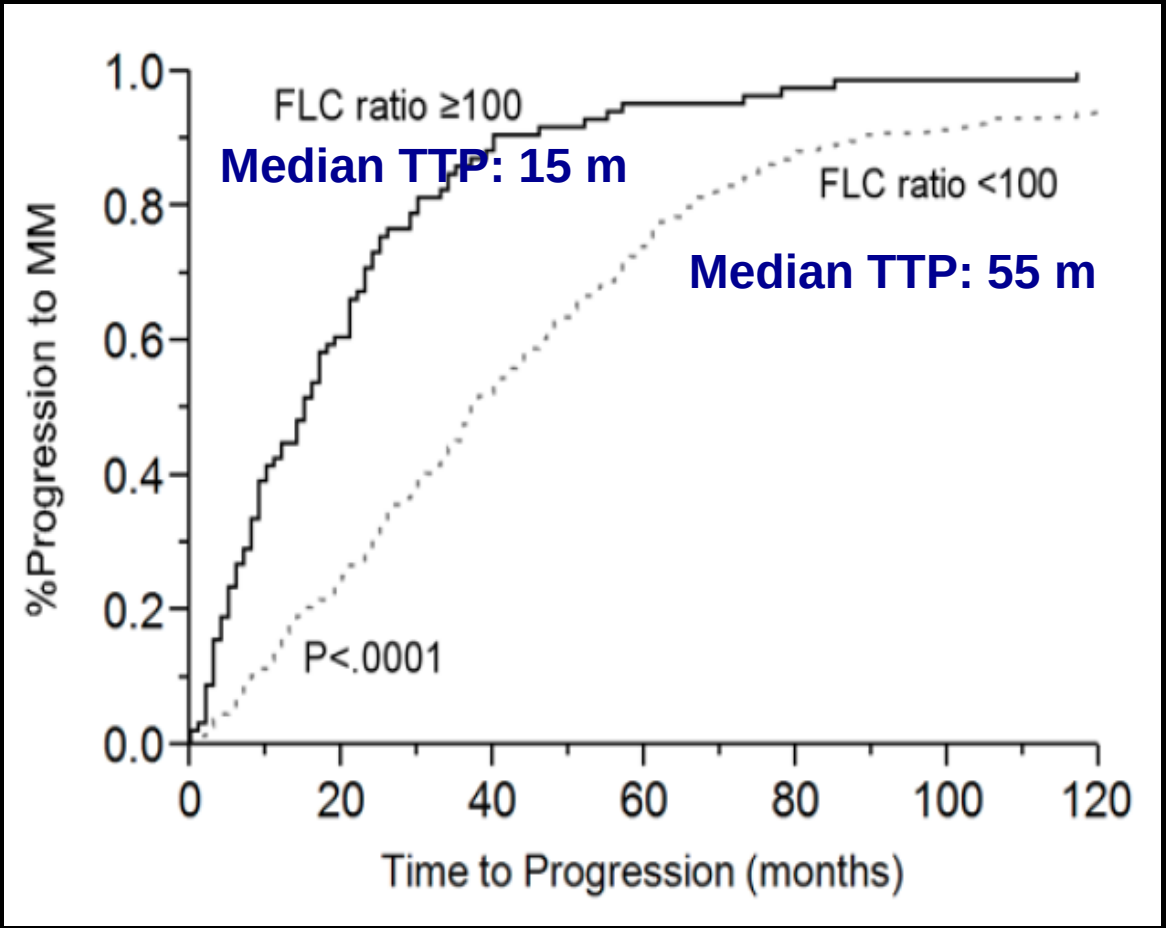
True-SMM

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

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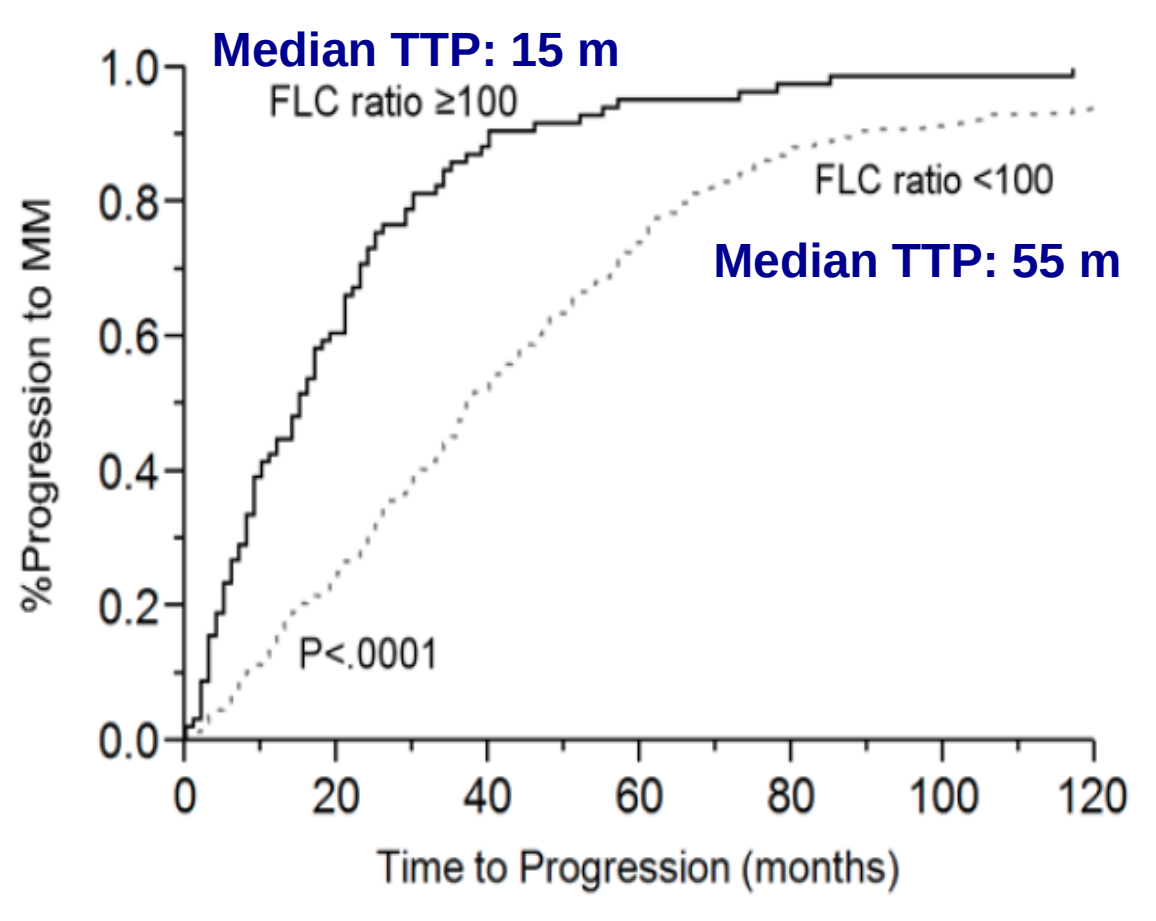

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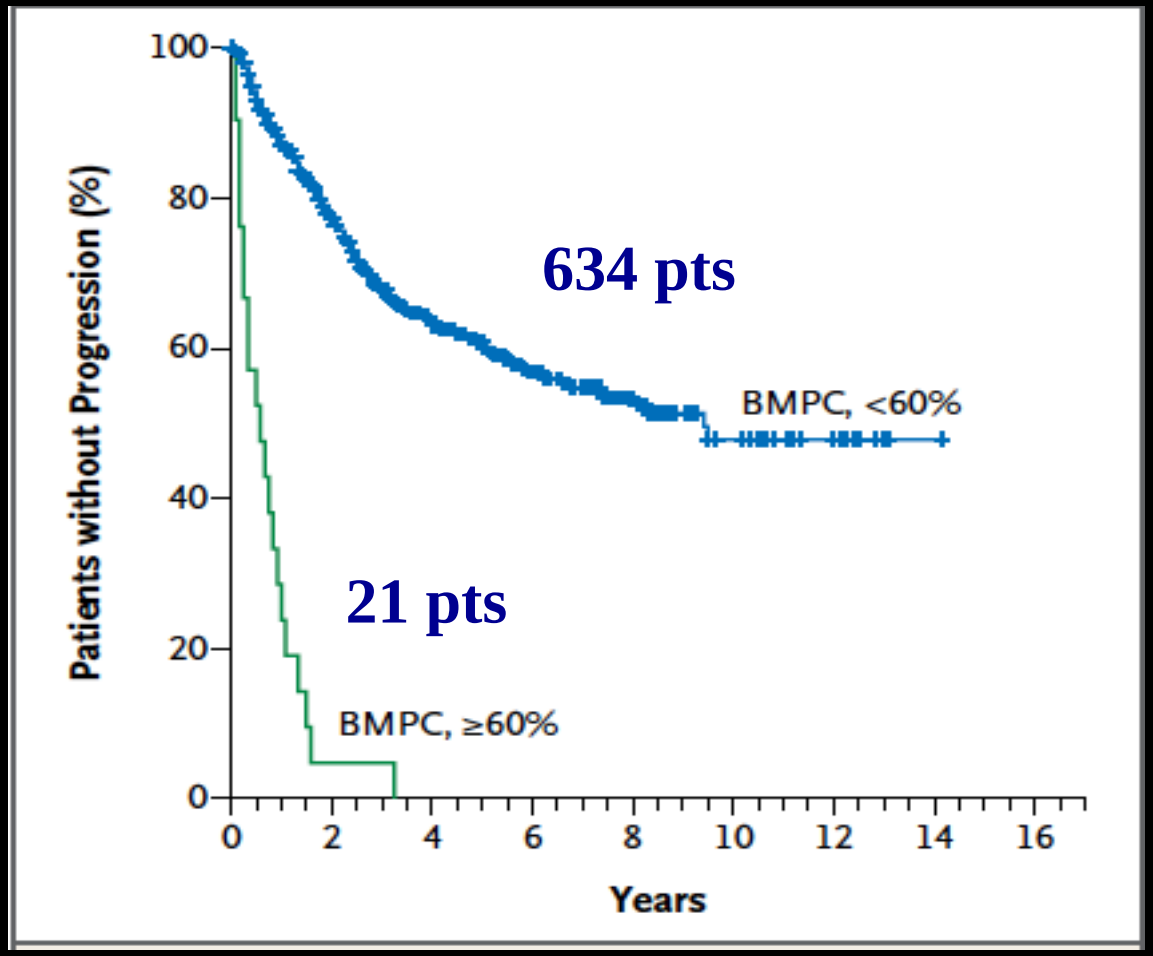
Ultra-high risk SMM: Plasma Cells in the Bone Marrow at baseline

N= 655 patients



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

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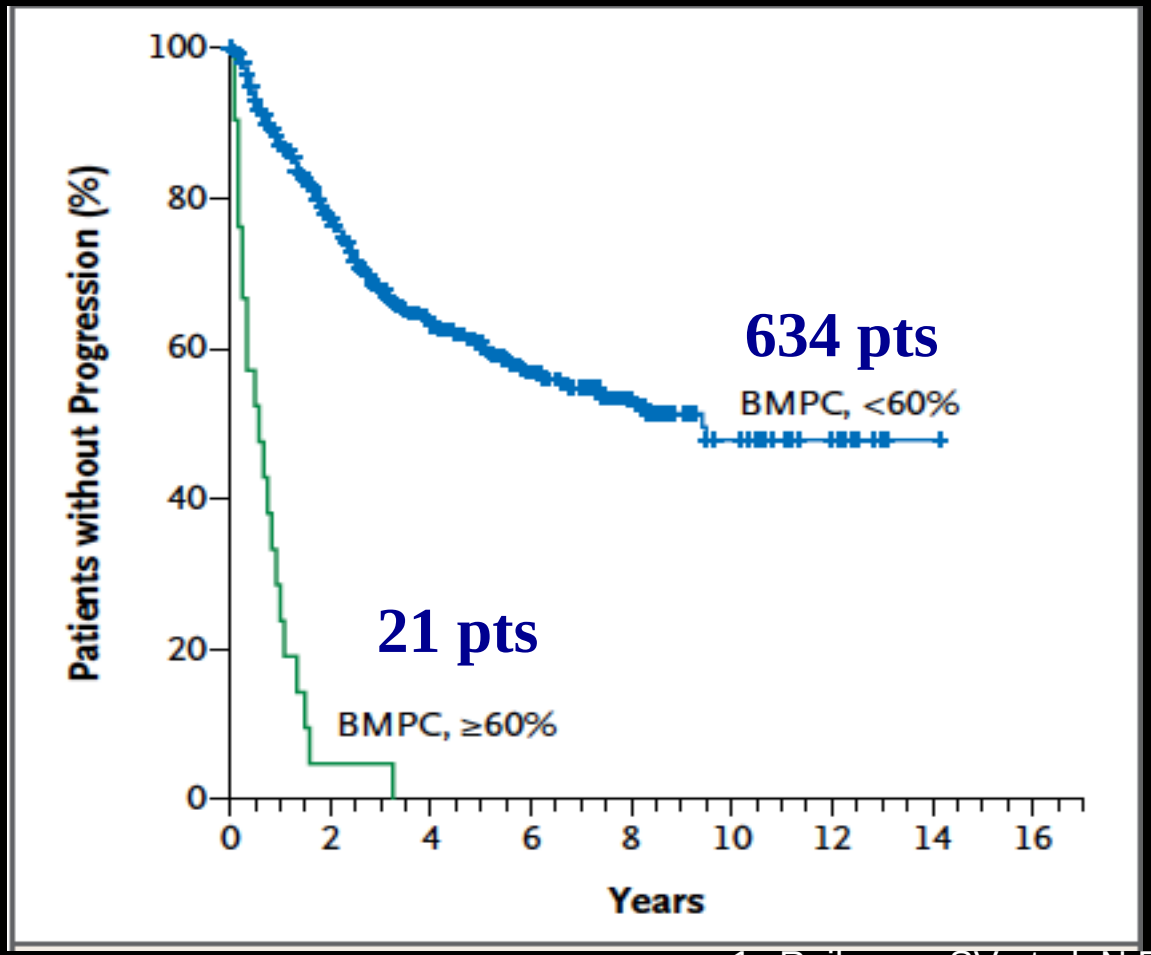

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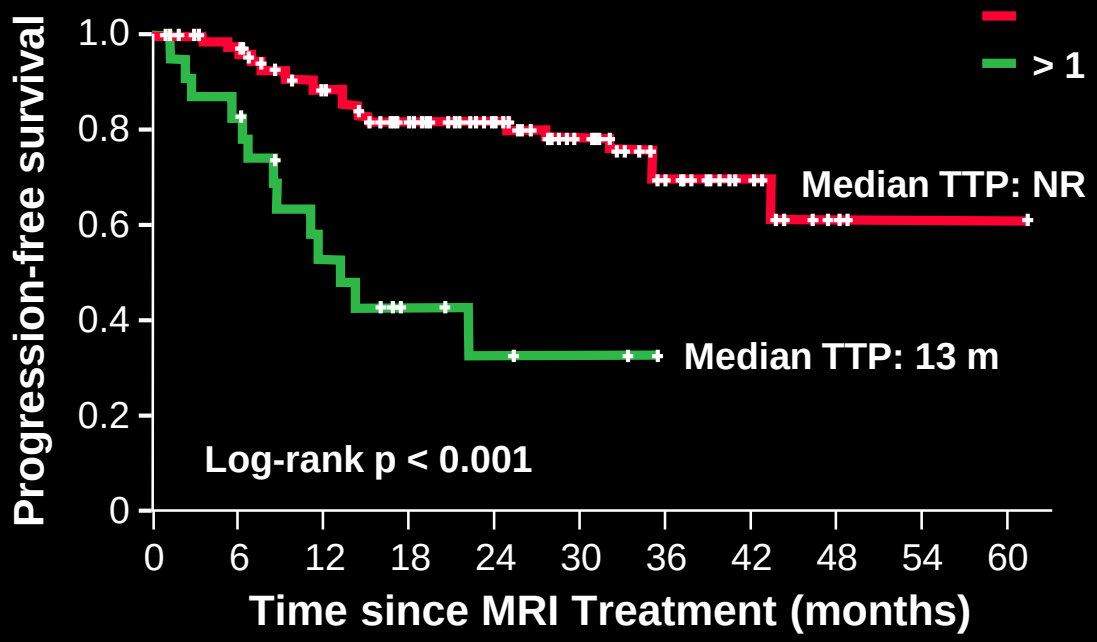
Smouldering Multiple Myeloma: Whole MRI

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*

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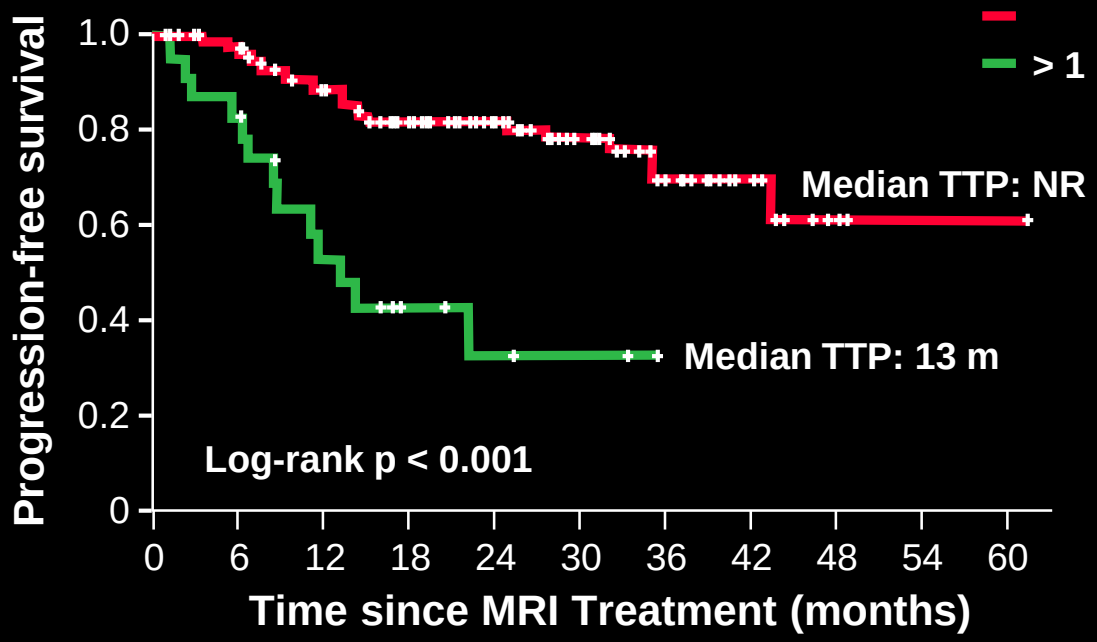
Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM

Whole MRI: 28% of pts: Focal lesions



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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.

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)**

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

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

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%)***

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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*

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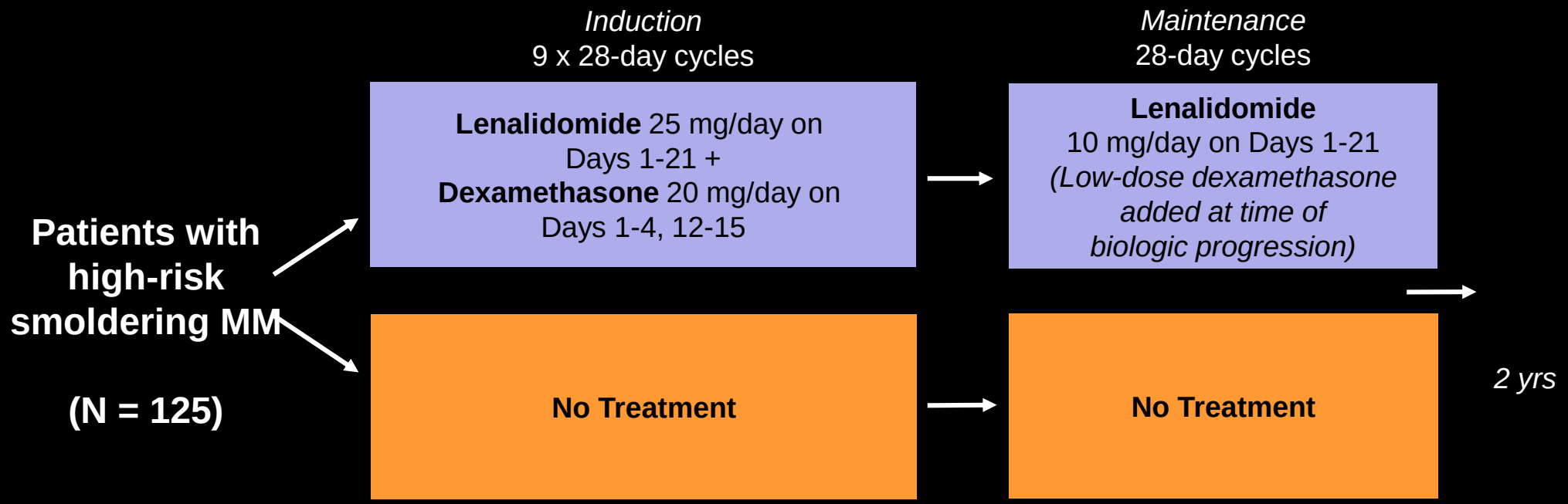
QuiRedex: Study Design

- 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

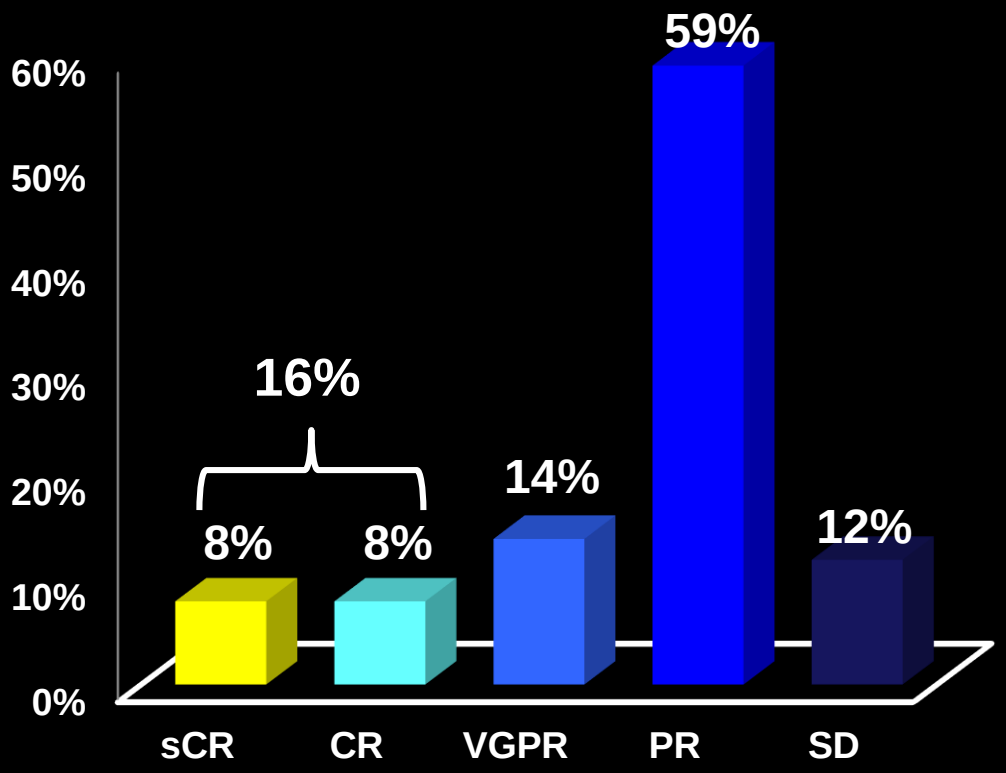
Mateos MV, et al. NEJM 2013; 369:438-47

Lenalidomide + Dex: response rate

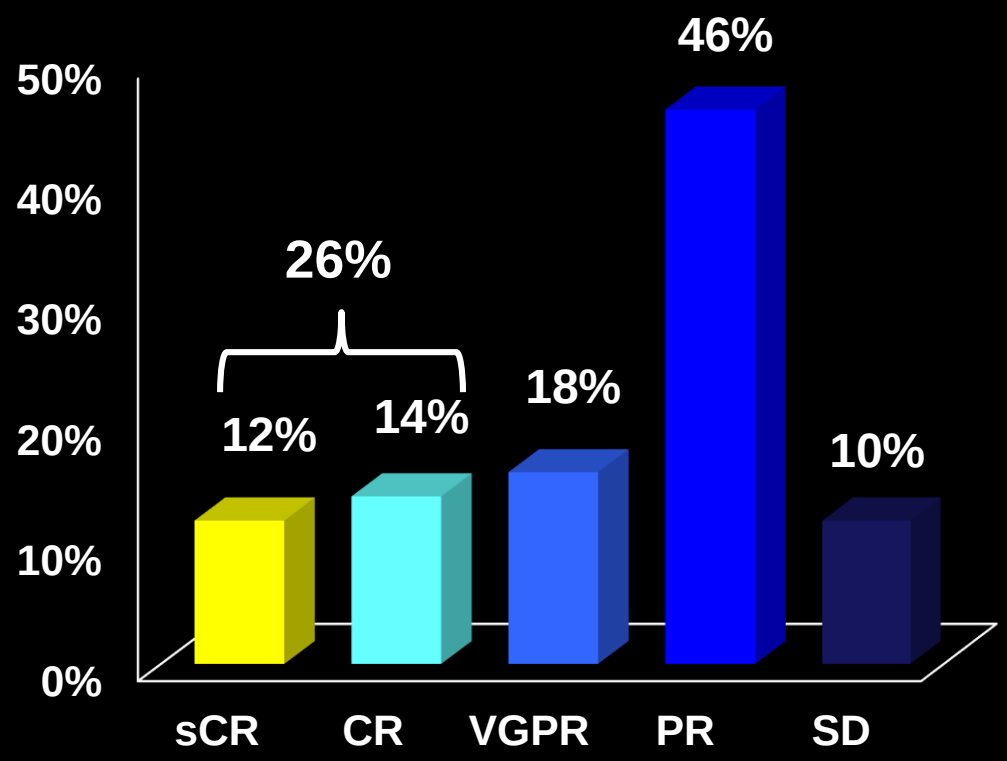
On ITT (n = 57) Median number of induction cycles: 9 (range 1–9)

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)



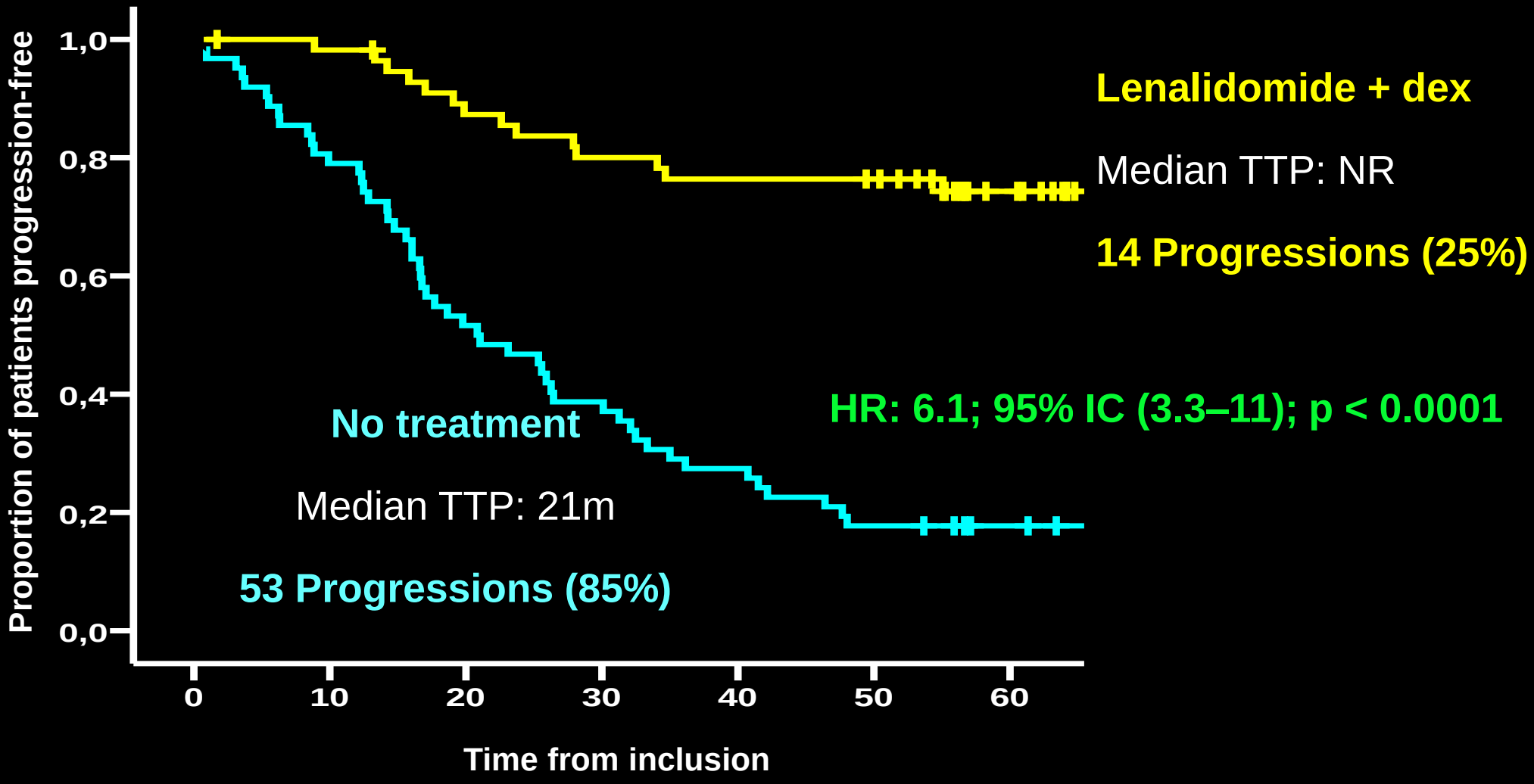
*IMWG criteria.

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

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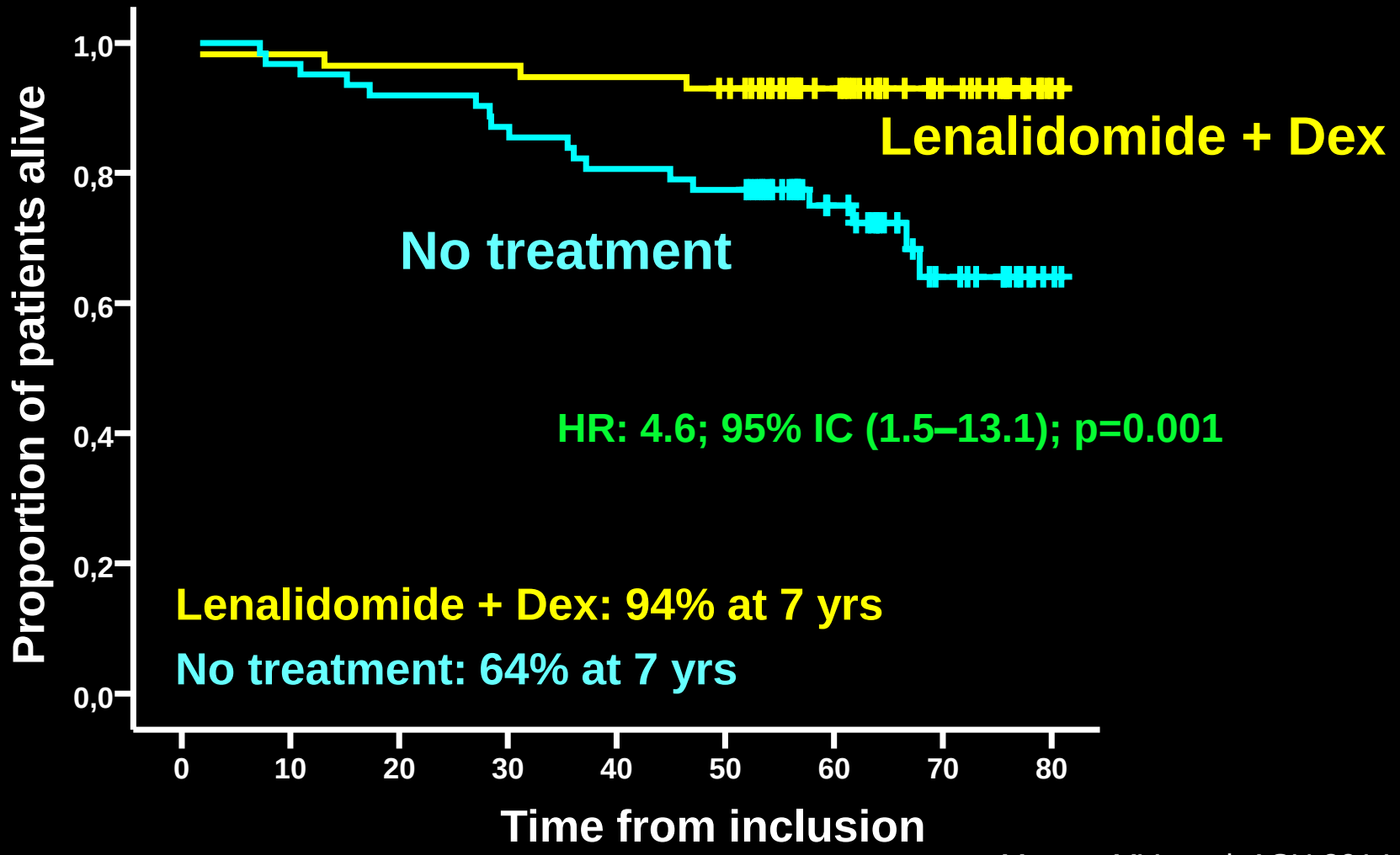


Mateos MV, et al. ASH 2014: abstract 3465

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

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: 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?

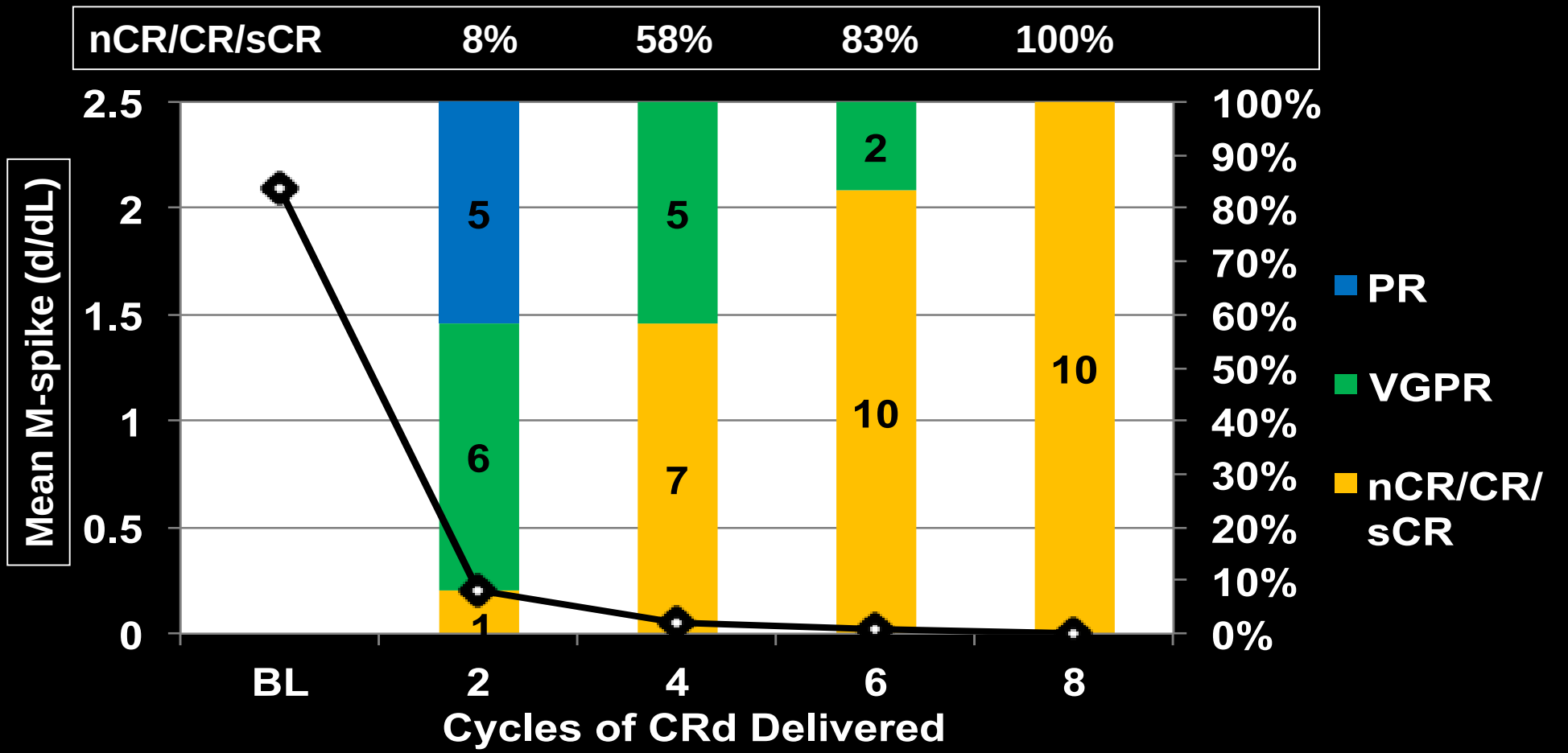
24 cycles Rev Extended Dosing

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)

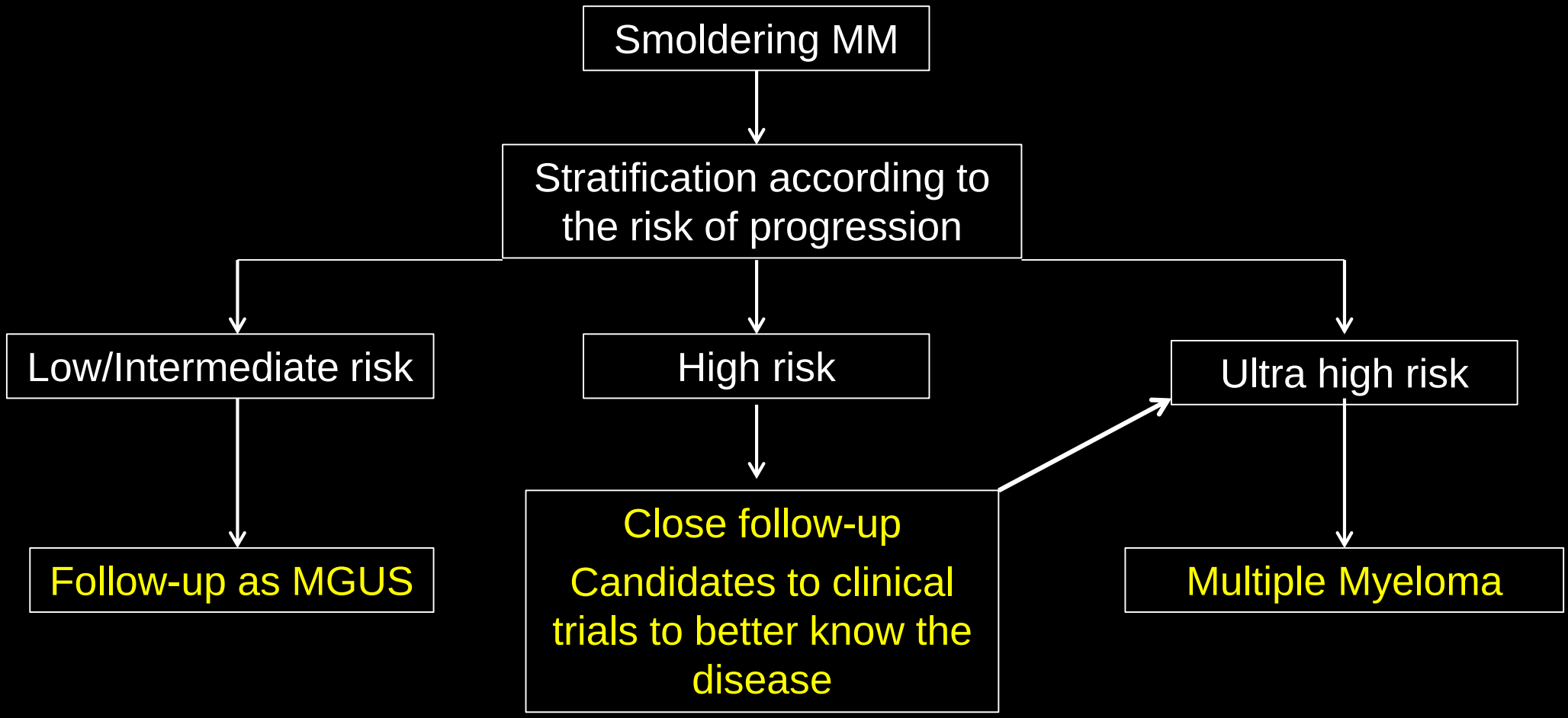
MRD ⇨

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



Acknowledgments

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