Should we treat some patients with stage I Multiple Myeloma?

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What is a stage I Multiple Myeloma?

Clasification	Criteria	
Stage I *Durie&Salmon*	Hb > 10g/dl Normal calcium No bone lessions	Low MC: -IgG<5g/dL -IgA<3g/dL -Prot BJ<4g/24h
Stage I *ISS*	Symptomatic patients	Beta2M< 3.5g/L Albumin ≥ 3.5mg!dL
Smoldering MM *IMWG*	No end organ damage	**≥ 3 g/dL serum** AND/OR **≥ 10% PCBM**

Durie BG. Cancer 1975;36(3):842-54
Greipp PR. JCO 2005; 23(15):3412-20
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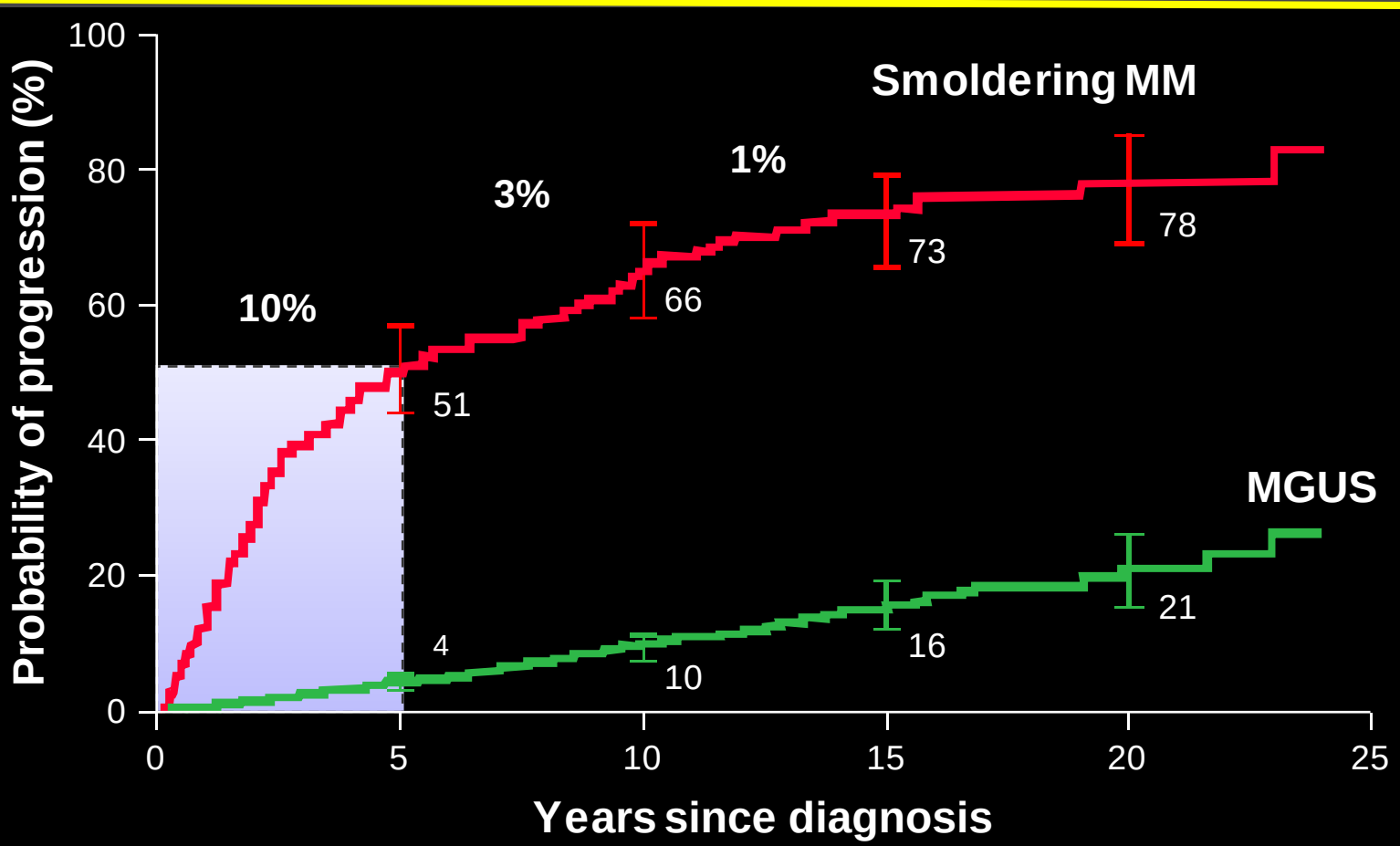
Is SMM an uniform entity?

Smoldering MM: risk of progression to active disease



Are there any risk factors predicting progression to active disease?

Kyle RA, et al. N Engl J Med. 2007; 356:2582-90.

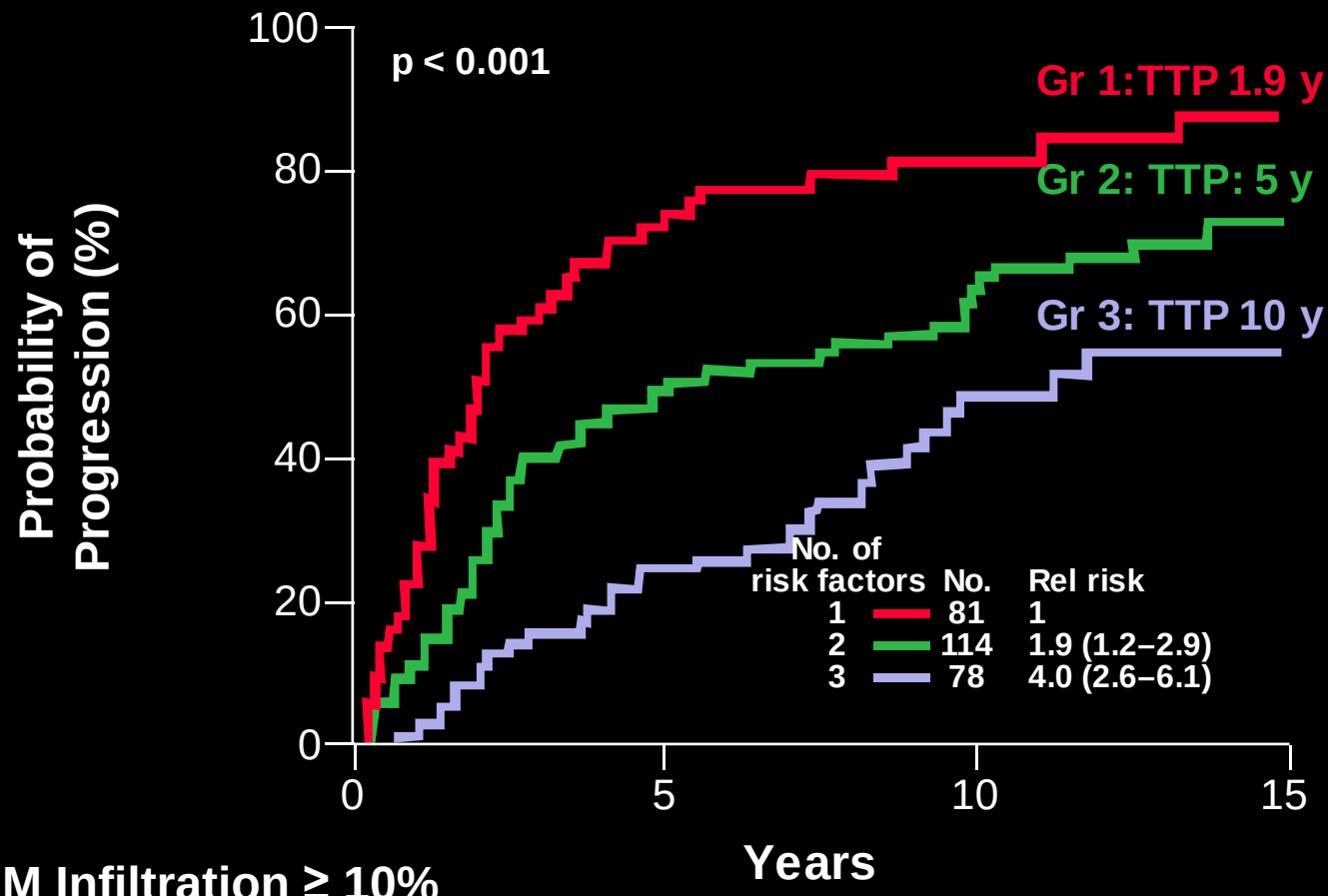
Smoldering MM: risk of progression to active disease

- Serum level of monoclonal component (> 3 g/dL)
- Plasma cell bone marrow infiltration (PCs > 10%)
- Abnormal sFLC ratio
- Aberrant plasma cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Evolving MM
- Abnormal MRI studies

* After IMWG consensus criteria.

Kyle RA, et al. N Engl J Med. 2007;356:2582-90. Perez-Persona E, et al. Blood. 2007;110:2586-92. Dispenzieri A, et al. Blood. 2008;111:785-89. Rosiñol L, et al. Br J Haematol. 2003;123:631-6. Dimopoulos MA, et al. Blood. 2000;96:2037-44. Hillengass J, et al. J Clin Oncol. 2010;28:1606-10.

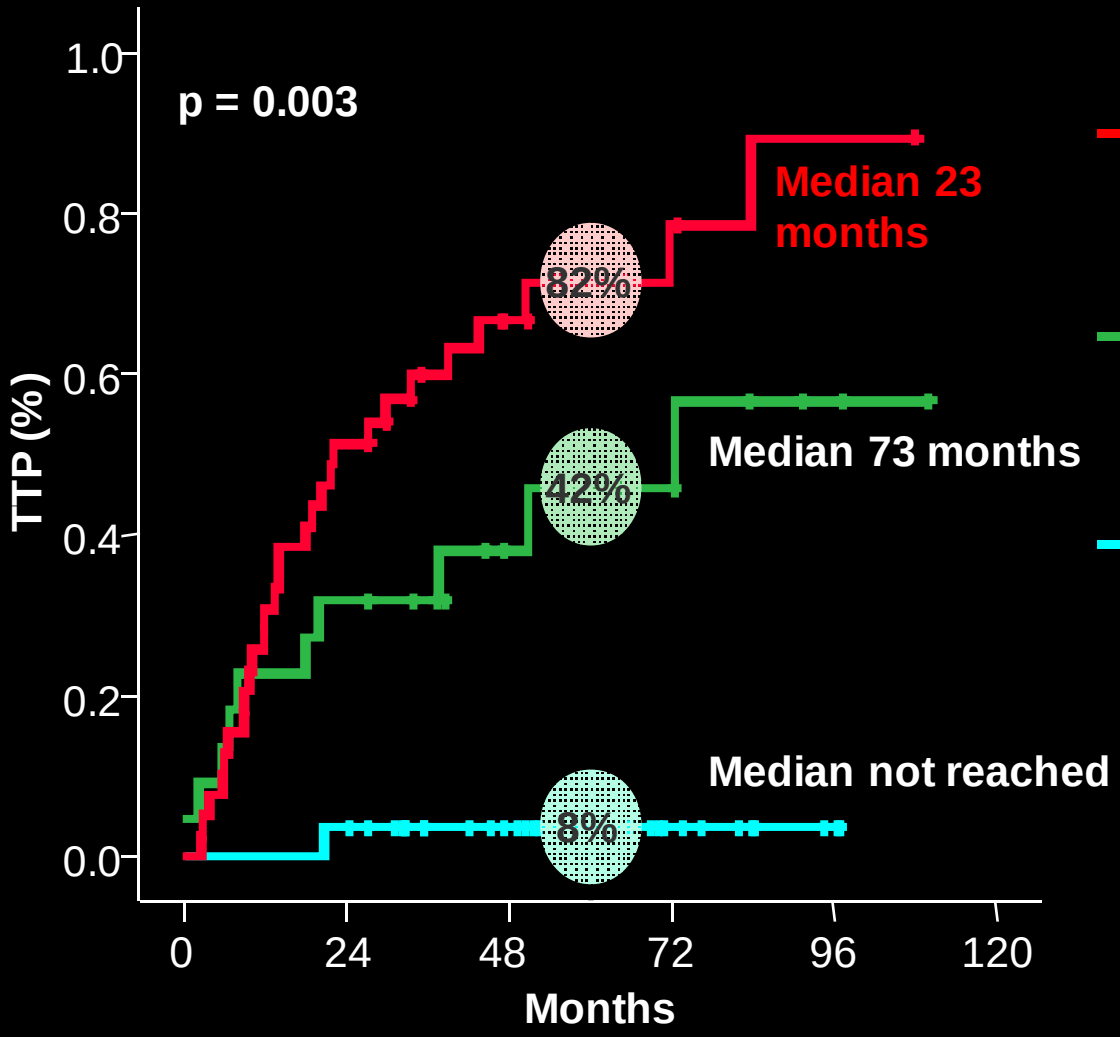
Smoldering MM: PCs BM infiltration and serum M-component level plus sFLC ratio



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

Kyle RA, et al. N Engl J Med. 2007; 356:2582-90
Dispenzieri A, et al. Blood. 2008;111:785-9.

Smoldering multiple myeloma: aberrant PCs by immunophenotype plus immunoparesis



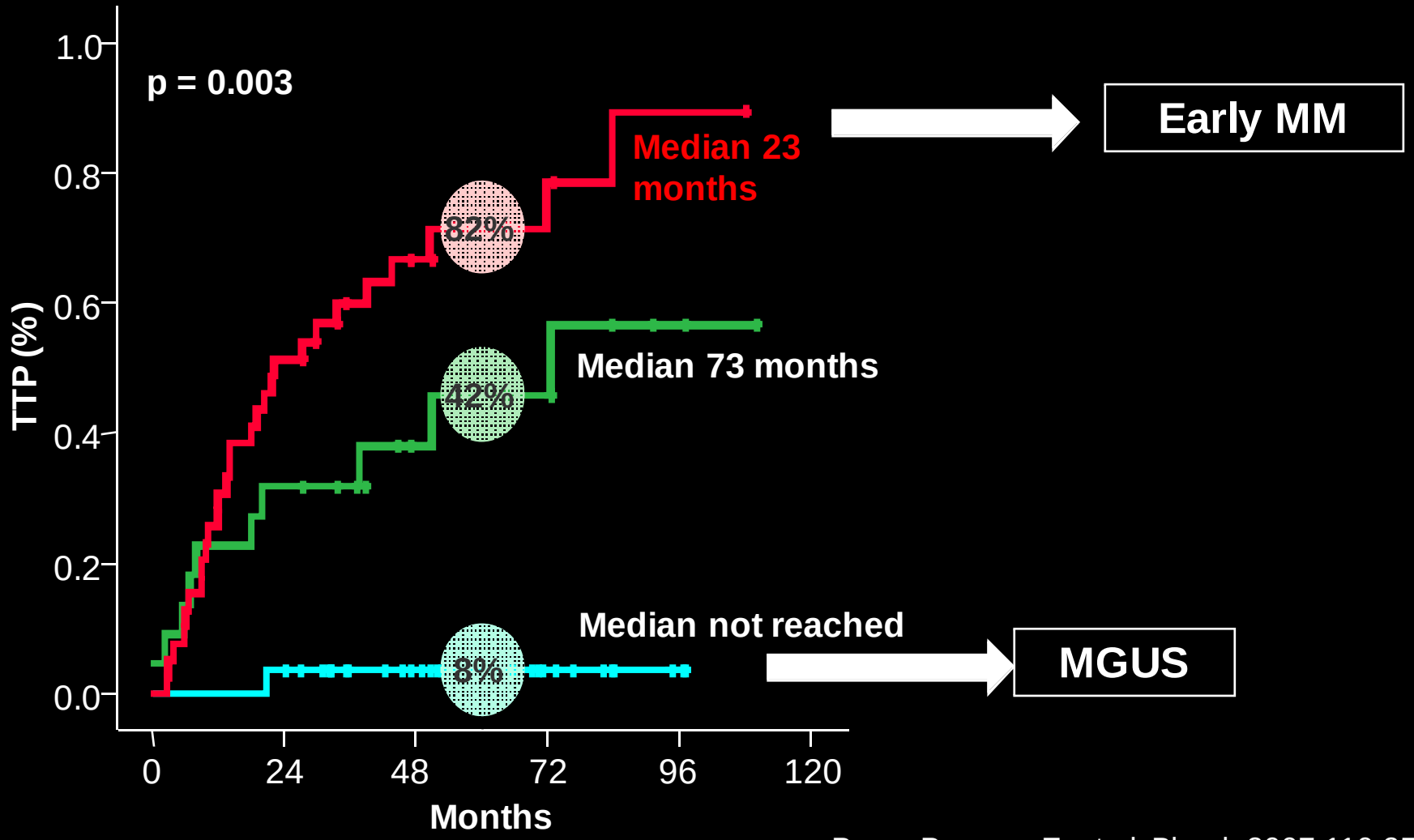
>95% aPC/BMPC + paresis
n = 39 (28 progr.)

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

No adverse factors
n = 28 (1 progr.)

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

Smoldering MM: Should definition be revisited?



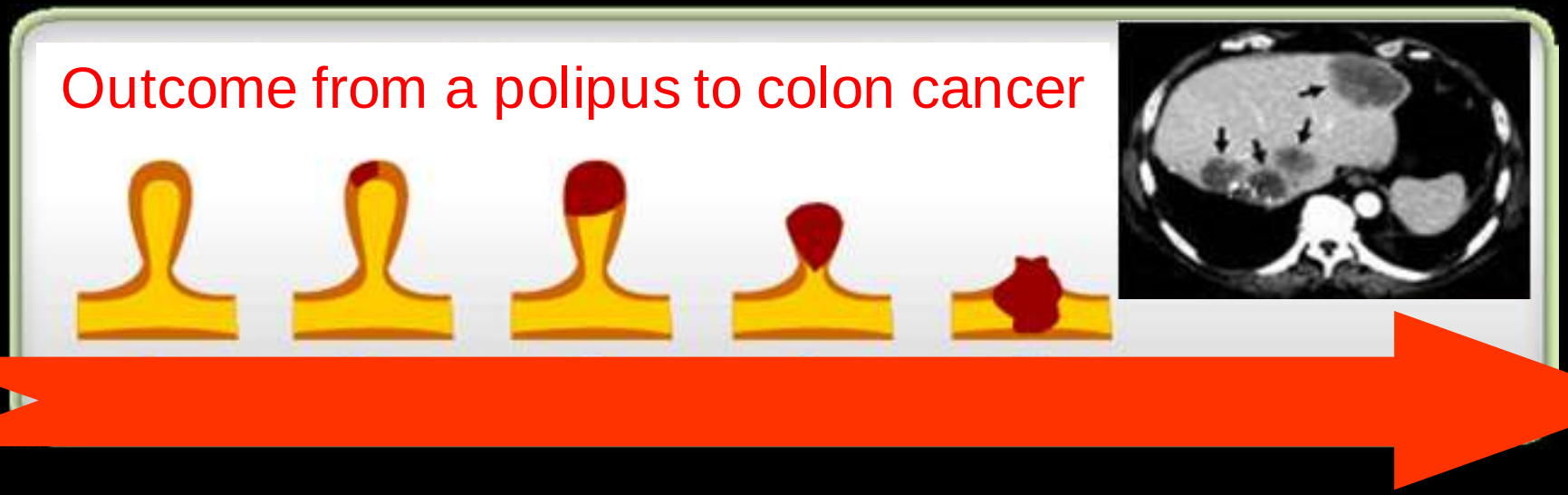
Perez-Persona E, et al. Blood. 2007;110:2586-92.

Is it worth to early treat asymptomatic Myeloma patients?

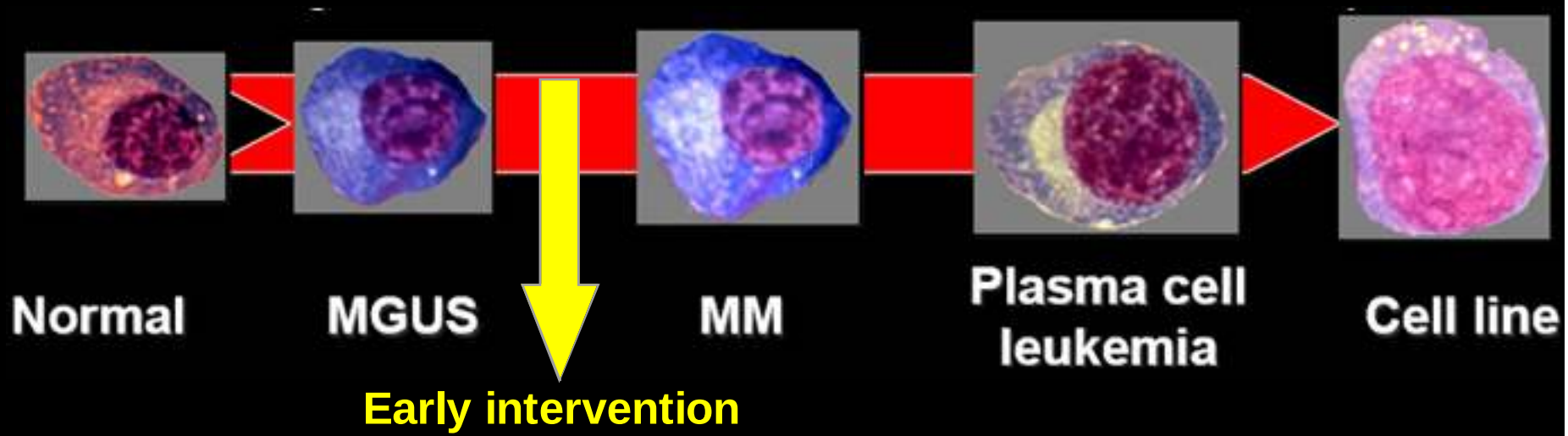
Non-hematologic malignancies: Oncology perspective

Early intervention

- In almost all malignancies (breast, prostate, colon cancers,...)
- Two possible objectives: To cure/erradication
  To delay progression to active disease



MM: Oncology perspective



Early intervention

Agressive clonal selection

Cure

Chronic disease management

Is there any trial supporting *early treatment in smoldering MM patients*?

Smoldering multiple myeloma: early treatment

Conventional agents	
Initial MP vs Deferred MP[1,2,3]	No benefit in ORR/TTP/OS
Novel agents	
Thalidomide[4,5]	~ 30% ≥ PR; high toxicity; patients achieving PR had a shorter time to treatment
Bisphosphonates vs abstention [6,7]	No benefit in ORR/TTP/OS Lower incidence of skeletal related events

1.Hjorth M, et al. Eur J Haematol. 1993;50:95-102.
2.Grignani G, et al. Br J Cancer. 1996;73:1101-07.
3.Riccardi A, et al. Br J Cancer. 2000;82:1254-60.
4. Rajkumar SV, et al. Am J Hematol 2010; 85(10):737-40
5. Barlogie B, et al. Blood. 2008;112:3122-25.
6. Musto P, et al. Leuk Lymphoma. 2011;52(5):771-775
7. Musto P, et al. Cancer. 2008;113:1588-95.

But…none of these trials discriminate the low risk patients *(that probably will not benefit from intervention)* ***from the high risk group, that may be the target for therapy***

Is there any trial supporting this hypothesis: early treatment but only in high-risk patients?

QuiRedex: Len-dex vs no treatment

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

or

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

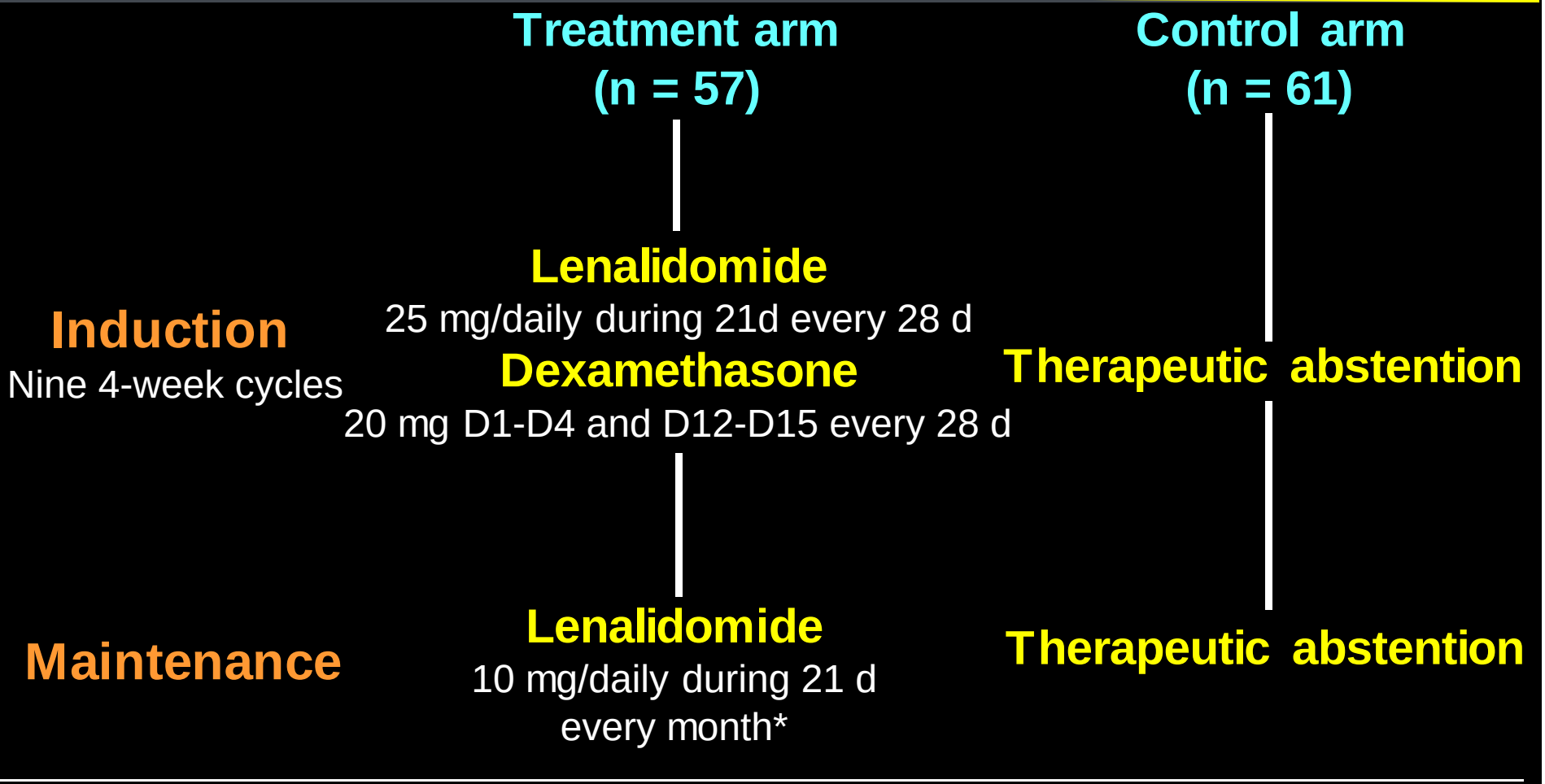
but **BM aPC/nPC** ≥ 95% plus **immunoparesis**

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. Blood. 2010;116:[abstract 1935]. Updated data presented at ASH 2010.

Schedule of therapy (n:126 pts)



** Low-dose Dex will be added at the moment of biological progression*

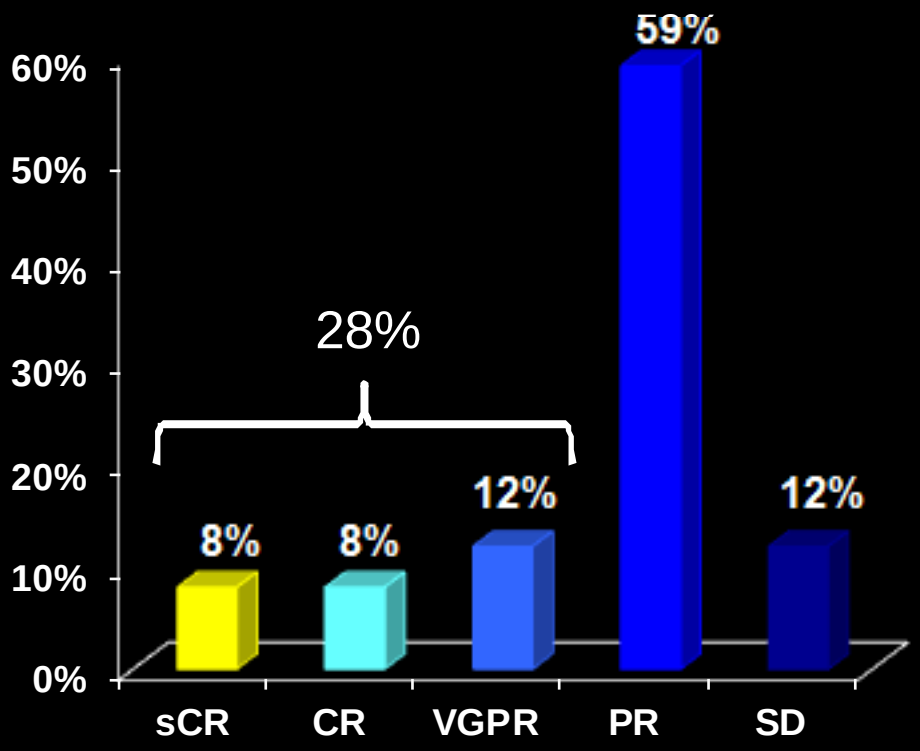
Mateos MV, et al. Blood. 2010;116:[abstract 1935]. Updated data presented at ASH 2010.

Lenalidomide + Dex: response rate

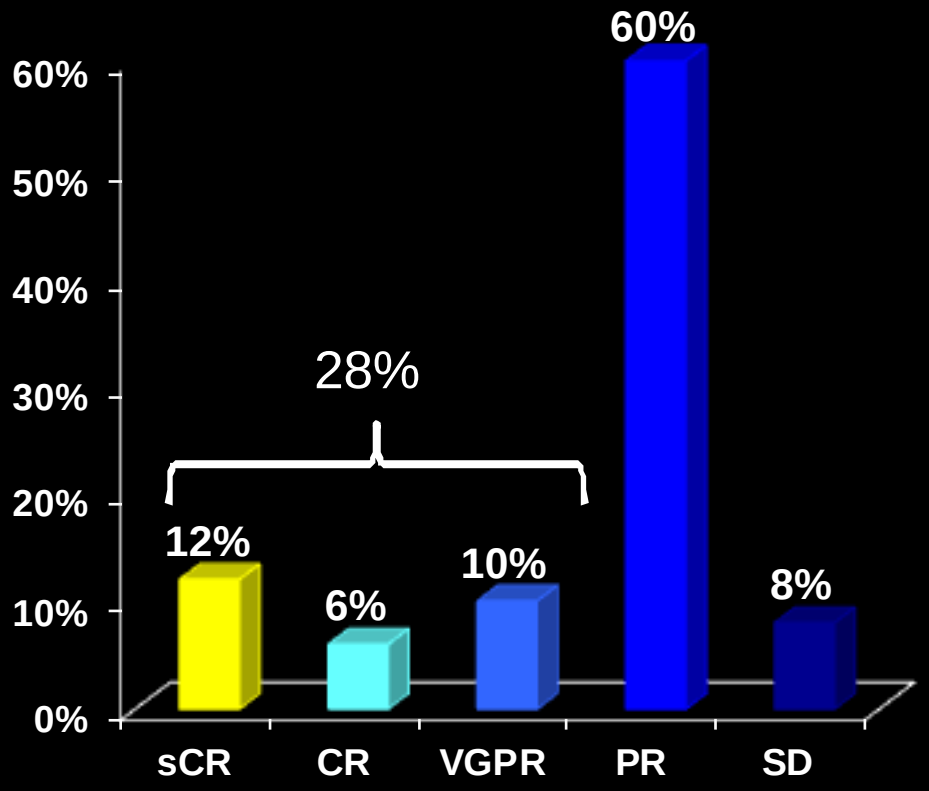
On ITT (n = 57) Median number of cycles: 9 (range 1–9)

ORR: 81%; ***sCR: 7%, CR: 7%; VGPR: 11%; PR: 56%;*** **SD: 19%**

After 9 induction cycles (n = 51)



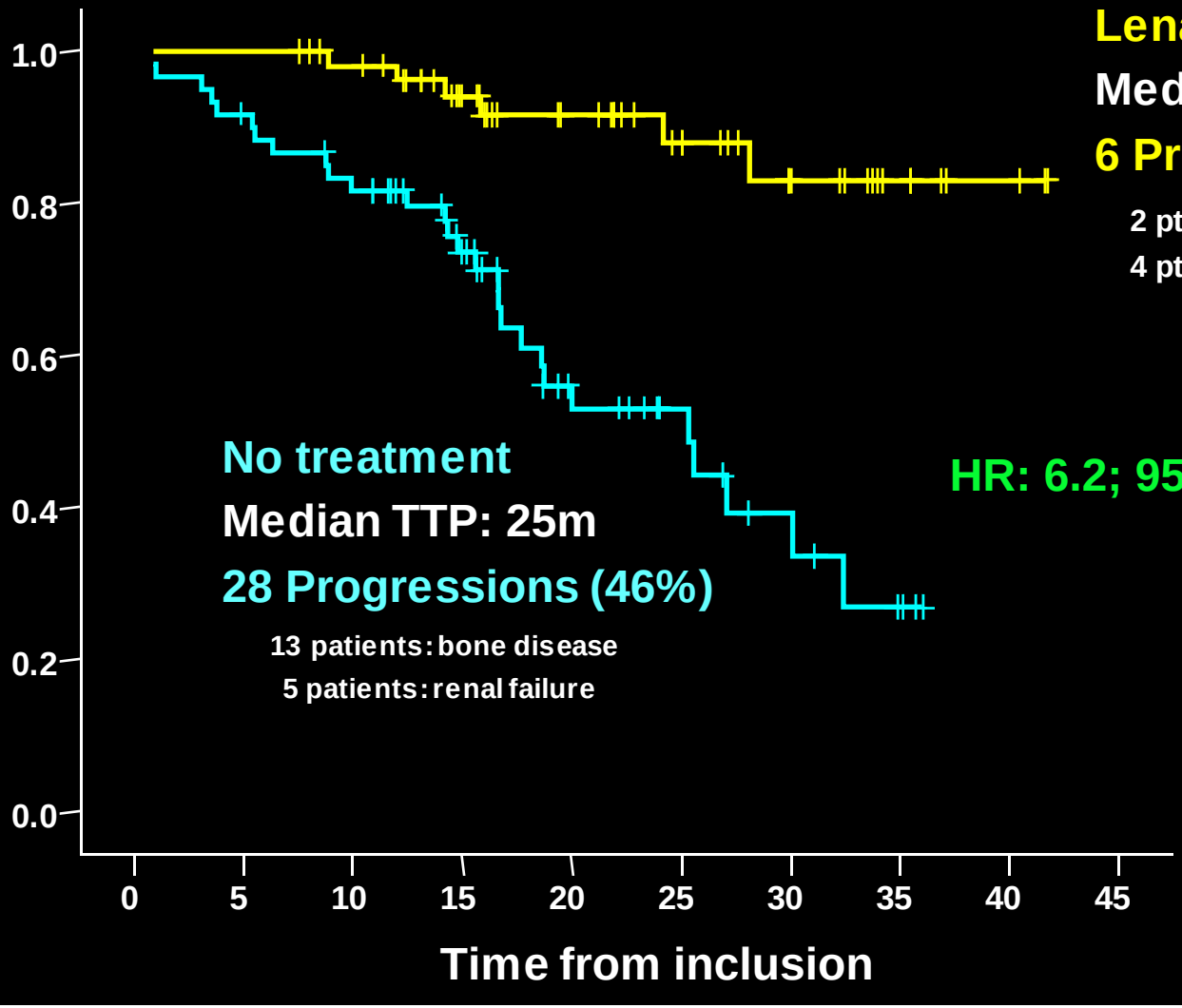
After a median of 6 maintenance cycles (1-21) (n=50)



*IMWG criteria.

Len-dex vs no treatment: TTP to active disease (n = 118)

Median follow-up: 22 months (range 5–42)



Lenalidomide + dex

Median TTP: NR

6 Progressions (10%)

2 pts:early disc followed by progression

4 pts:symptomatic progressions

No treatment

Median TTP: 25m

28 Progressions (46%)

13 patients: bone disease

5 patients: renal failure

HR: 6.2; 95% IC (2.6–15); p < 0.0001

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

At last f/u of maintenance therapy

12 biological progressions (1 during induction)

Dex was added according to the protocol

- **9 pts: Experienced stabilization of disease with dex**
  - **7 remain stable after a median f/u of 11 m *(1 pt achieved again PR)***
  - **2 pts: Progressed to active disease after 4 and 12 m**
- **2 pts: Withdrawal of informed consent**
- **1 pt: Progression to active disease before dex was added**

Len-dex in high-risk SMM

- **Effective** as induction and maintenance therapy
- Addition of **low dose dex** is able to **control** the disease
- Significant benefit in terms of **TTP,**

…….. but

Important questions remain opened

What about toxicity?

Len-dex: toxicity profile during induction (n:57)

	G1-2	G3
Anemia	9(15%)	1(2%)
Neutropenia	11(20%)	2(3.5%)
Thrombocytopenia	6(11%)	-
Asthenia	7(15%)	4(7%)
Constipation	10(18%)	-
Diarrhea	3(5.5%)	2(3.5%)
Rash	10(17%)	1(2%)
Parestesias	3(5.5%)	-
Tremor	4(7%)	-
Infection	7(12%)	2(3.5%)
DVT	3(5.5%)	

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

Len toxicity profile during maintenance (n:50)

	G1	G2	G3
Anemia	3(5%)	1(2%)	-
Neutropenia	1(2%)	1(2%)	-
Thrombocytopenia	1(2%)	1(2%)	-
Asthenia		1(2%)	-
Parestesias		1(2%)	-
Tremor	1(2%)		-
Infection	2(4%)	1(2%)	1(2%)

Len-dex in high-risk SMM

- **Effective** as induction and maintenance therapy
- Addition of **low dose dex** is able to **control** the disease
- Significant benefit in terms of **TTP**
- **Toxicity** profile acceptable,

……. but

Important questions remain opened

What about second primary malignancies?

Second primary malignancies in Len-dex (n:57)

2 patients (3.5%)→ Polycythaemia vera and prostate cancer

54 yrs old man. No CA After induction and 10 maint. cycles **Hb: 15g/dl** **JAK2+** ↓ **Polycythaemia Vera**	We went back to the sample obtained at the moment of inclusion in the study (frozen DNA) **JAK2+** **Hb: 16g/dl**
68 yrs old man. No CA After induction and 9 maint. cycles **PSA x2** **Prostate enlargement** ↓ **Bx: Prostate Cancer**	We went back to the medical records **PSA x2** plus **prostate hyperplasia** since 2006 Follow-up by Urologist

None of these cases can be attributed to treatment with Len-dex

No SPM detected in the abstention arm

Flow cytometric analysis of dysplastic features in SMM patients treated with LenDex

In none of the patients treated with LenDex we have observed evolution into a specific dysplastic phenotypic profile, only non-specific changes on individual antigens were observed

Immunophenotypic characteristics of BM cell compartments	**SMM at diagnosis (n=18)**	**SMM after induction (n=20)**	***** p-value***
No abnormalities	7 (39%)	8 (40%)	.6
Single abnormalities	9 (50%)	7 (35%)	.6
≥2 abnormalities	2 (11%)	5 (25%)	.1

The frequency of single abnormalities present in ≥2 cell lineages slightly increased after induction: 6% vs. 15% of pts

Len-dex in high-risk SMM

- **Effective** as induction and maintenance therapy
- Addition of **low dose dex** is able to **control** the disease
- Significant benefit in terms of **TTP**
- **Toxicity** profile acceptable
- There is no **safety warnings** at the present time

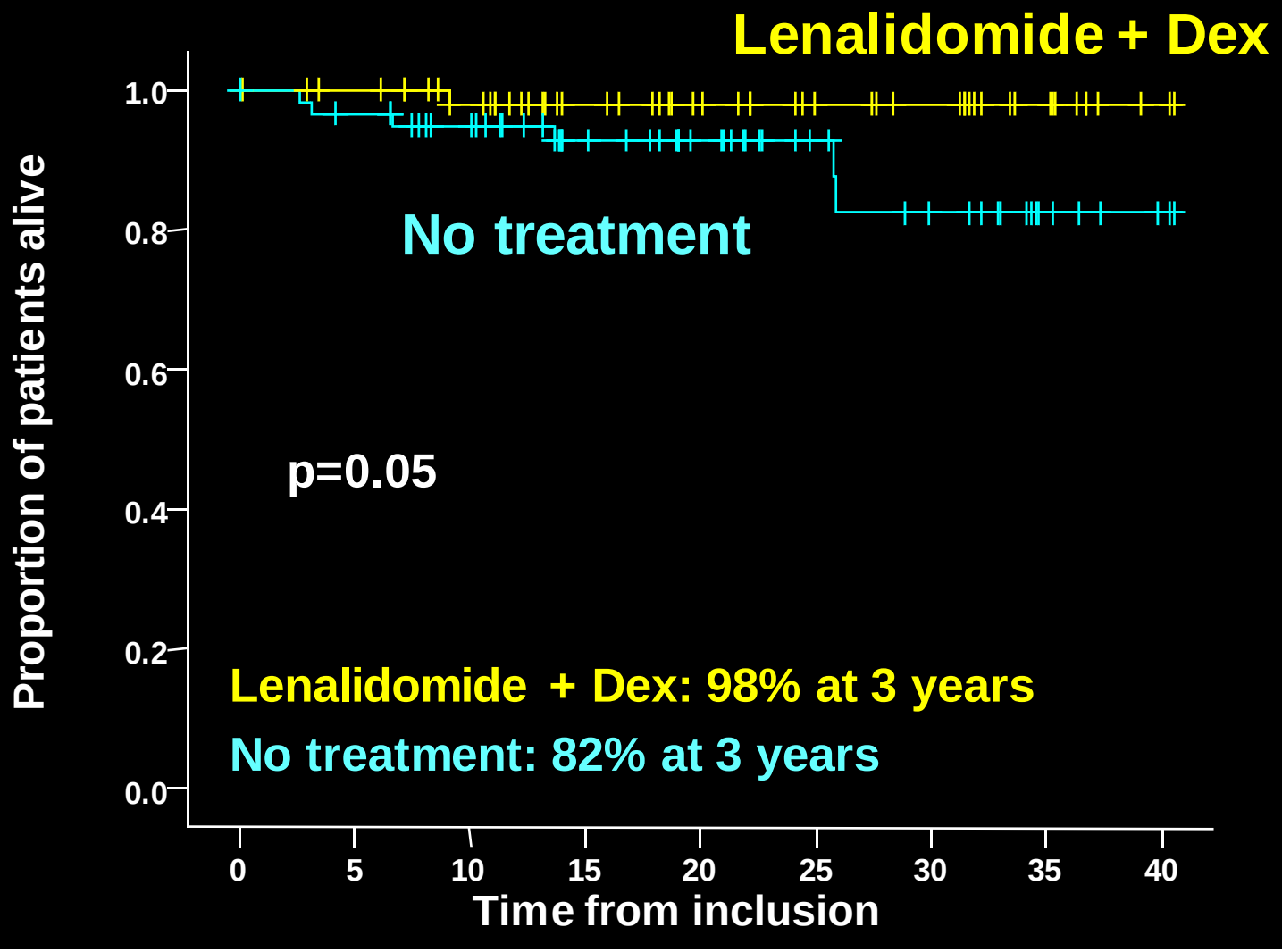
……. but

Important questions remain opened

What about overall survival?

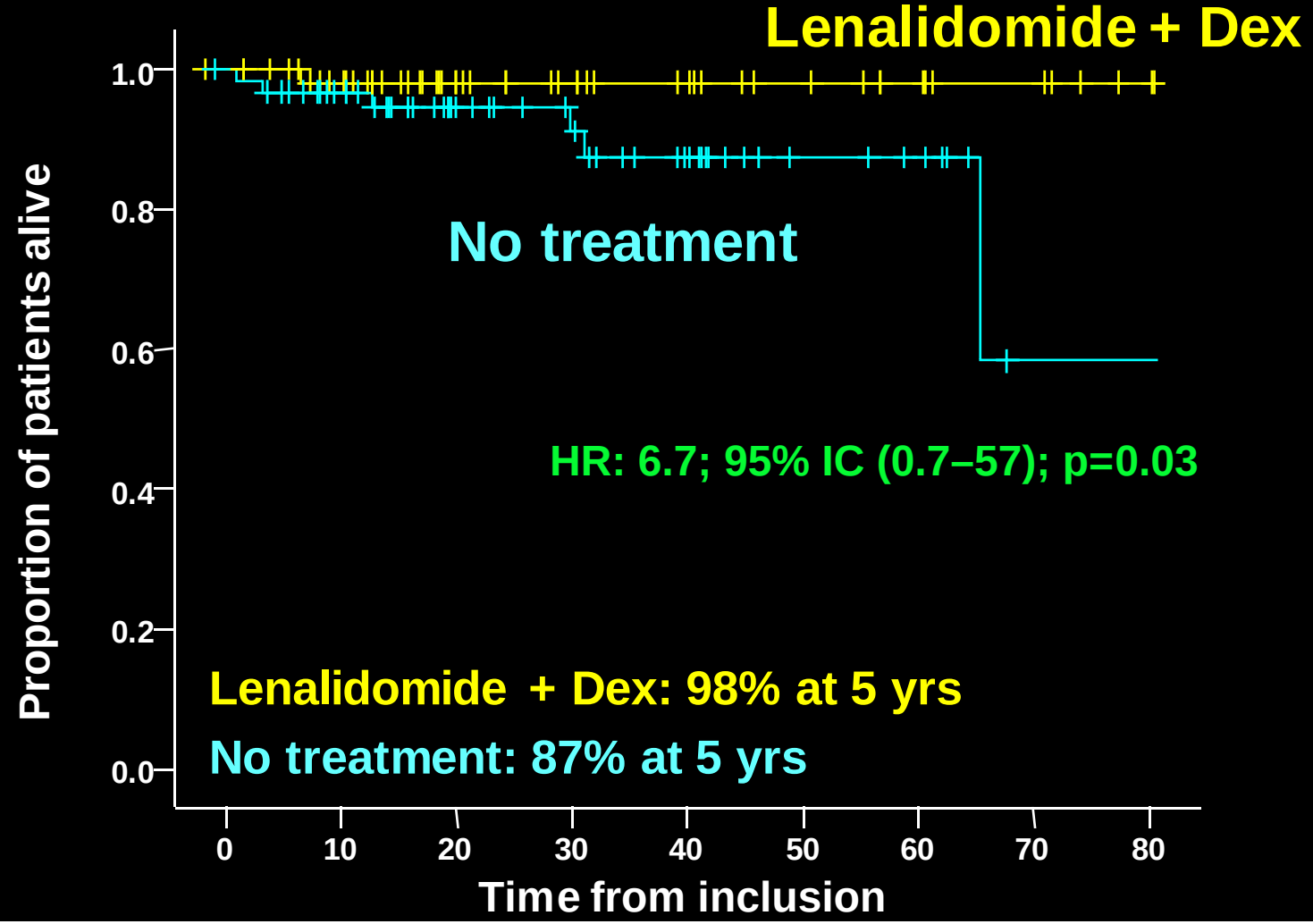
Len-dex vs no treatment: OS from inclusion (n = 118)

Median follow-up: 22 months (range 5–42)



Len-dex vs no treatment: OS from diagnosis (n = 118)

Median follow-up: 29months (range 5–89)



Len-dex in high-risk SMM

- **Effective** as induction and maintenance therapy
- Addition of **low dose dex** is able to **control** the disease
- Significant benefit in terms of **TTP**
- **Toxicity** profile acceptable
- There is no **safety warnings** at the present time
- At least, a trend to a benefit in **Overall Survival**

Should we treat some patients with Stage I MM?

- Len-dex is a promising and atractive option
- All efforts to plan an early treatment in asymptomatic MM patients should be focused on high-risk patients
- Long term follow-up is required to actually confirm the benefit, especially in OS
- Results of other trials that they are being conducted are needed

In the near future, we will probably be able to offer early treatment to a selected high-risk of patients with the confidence that they are going to obtain a significant benefit