Should we treat Smoldering MM patients?

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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 could offer early treatment to a selected high-risk subgroup of patients with the confidence that they are going to obtain a significant benefit

Smoldering MM: Diagnostic Criteria

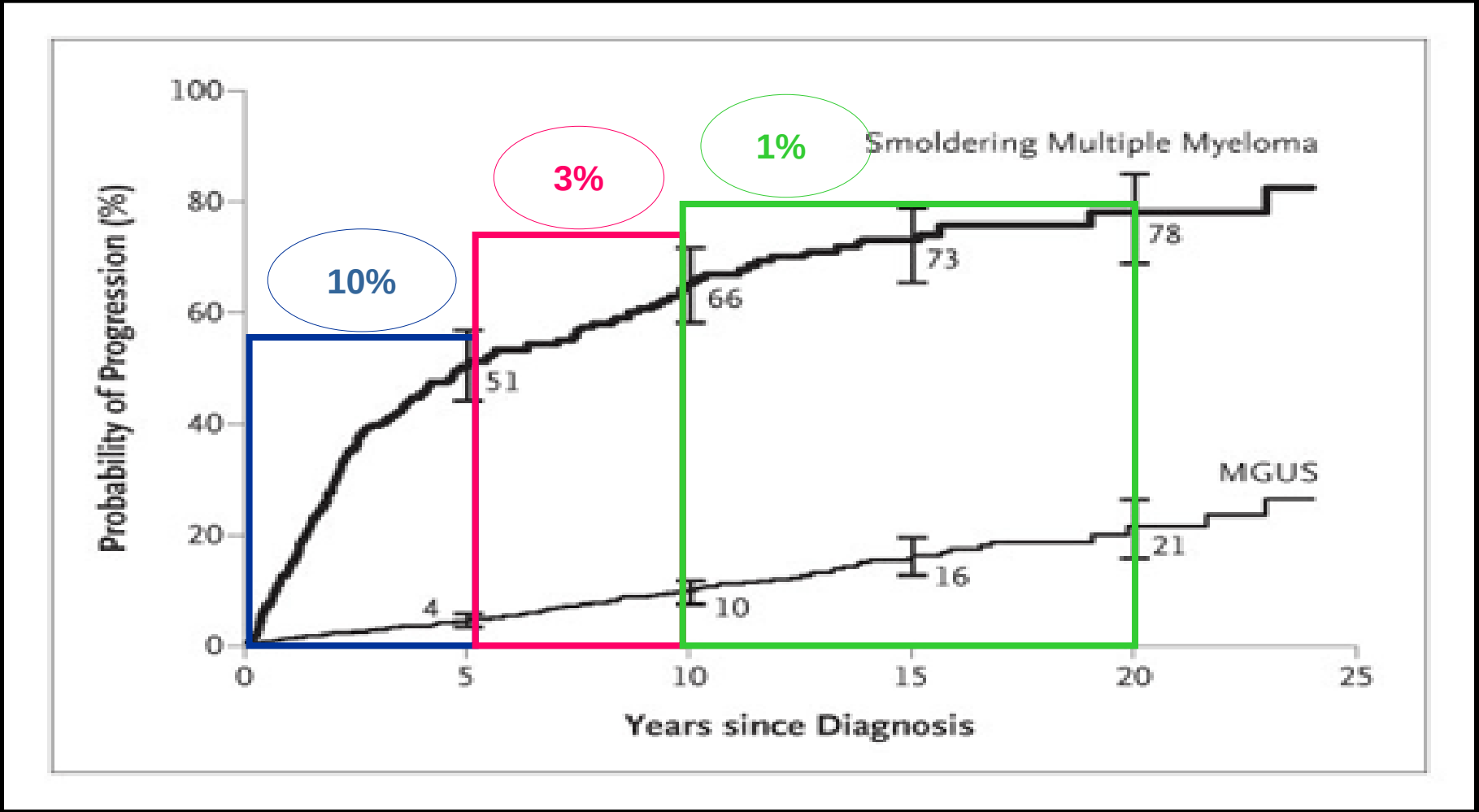
	Monoclonal Gammopathy of Uncertain Significance (MGUS)	Smoldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
Monoclonal component	< 30 g/L serum	≥ 30g/L serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10	≥ 10	> 10[b]
	AND	AND	AND
End-Organ Damage[a]	Absent	Absent	Present

a) Myeloma Related Organ or Tissue Impairment (end organ damage) related to Plasma cell proliferative process: anemia with 2 g/dL below the normal level or <10 g/dL, or serum calcium level >10 mg/L (0.25 mmol/L) above normal or >110 mg/dL (2.75 mmol/L), or lytic bone lesions or osteoporosis with compressive fractures, or renal insuficiency (creatinine >2 mg/dL or 173 mmol/L),[CRAB: Calcium increase, Renal impairment, Anemia and Bone lesion] or symptomatic hyperviscosity,, amyloidosis or recurrent bacterial infections (>2 episodes in 12 m).

b) For symptomatic multiple myeloma, a minimum level of M-component or BM plasma cell infiltration (although usually it is >10%, is not required, provided than this two features coexists with the presence of end organ damage

International Myeloma Working Group. Br J Haematol. 2003;121:749-757.

Smoldering Multiple Myeloma: Risk of Progression to Active Disease



Can we predict the risk of progression to active disease?

Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.

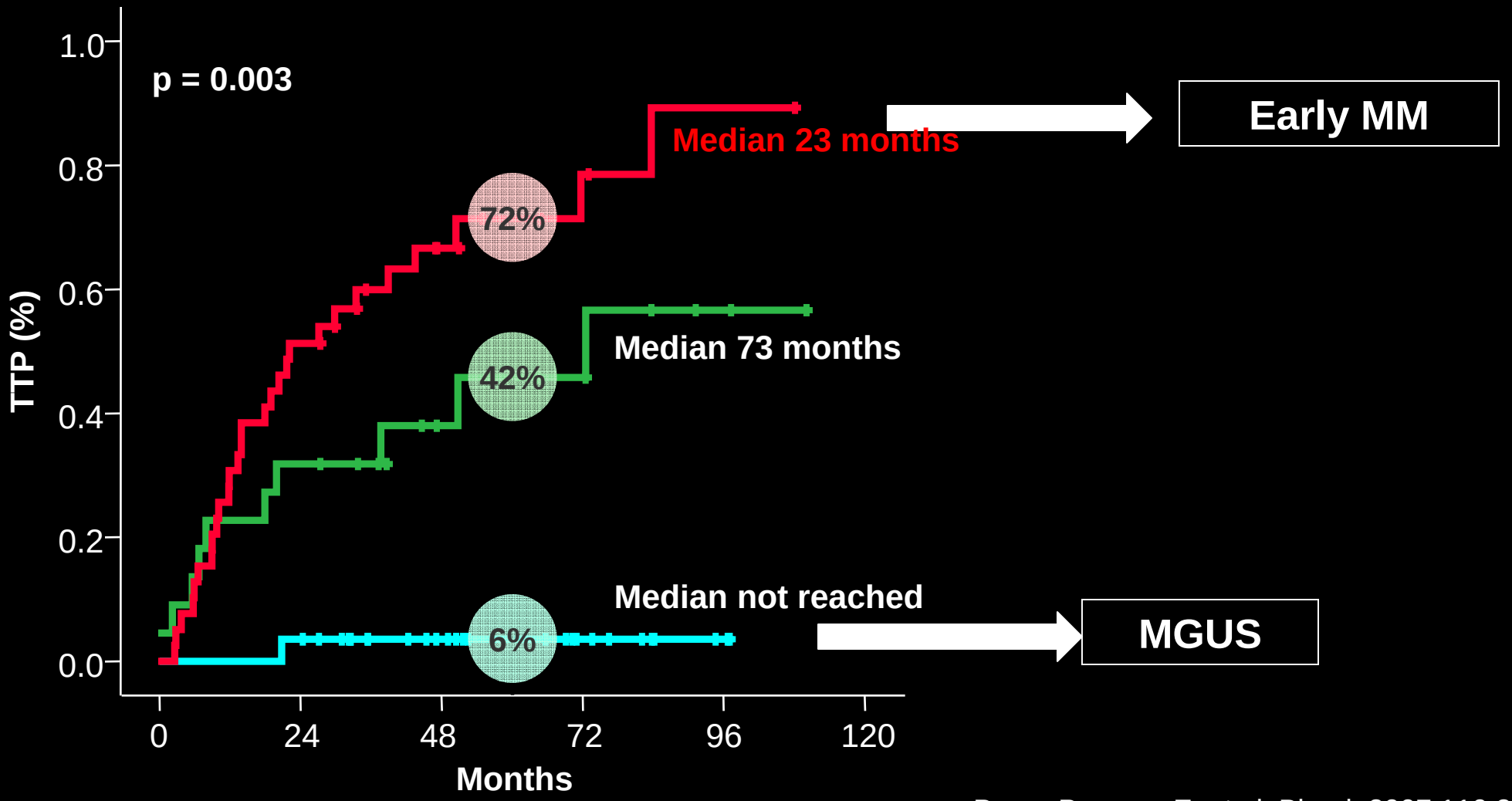
Smoldering Multiple Myeloma: prognostic factors

- 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
- Abnormal MR Imaging studies (MRI)
- Cytogenetic abnormalities

- BMPC infiltration/ PB Clonal PCs circulating/FLC ratio

** After IMWG consensus criteria*

Smoldering MM: Definition should be revisited



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

Smoldering Multiple Myeloma: Management

The standard of care is no treatment until disease progression occurs

Is there any role for early treatment in SMM patients?

Smoldering Multiple Myeloma: Management

Conventional Chemotherapy

Agents	n	ORR (%)	TTP	OS (mo)	Reference
Early MP vs Deferred MP	25 25	52 55	NR 12 m	52 53	Hjorth M, et al. Eur J Haematol. 1993;50: 95-102.
MP vs Observation	22 22	–	–	54 58	Grignani G, et al. Br J Cancer. 1996;73:1101-1107.
Early MP vs Deferred MP	75 70	40 55	–	64 71	Riccardi A, et al. Br J Cancer. 2000;82:1254-1260.

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

Smoldering Multiple Myeloma: Management

Bisphosphonates

	n	ORR (%)	TTP	OS	Reference
Pamidronate*	12	8	–	–	Martin A, et al. Br J Haematol. 2002;118: 239-42.
Pamidronate vs** observation	89 88	–	46 m 48 m	–	D'arena et al. Leuk Lymphoma. 2011;52: 771-5
Zolendronic acid vs** observation	81 82	–	67 m 59 m	–	Musto P, et al. Cancer. 2008;113:1588-95.

* Increase of bone density and decrease of bone resorption markers.

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

No anti-tumor effect

Smoldering Multiple Myeloma: Management

Thalidomide

Regimen	n	ORR (%)	TTP	OS	Reference
Thalidomide*	29	34	63% at 2 yrs	96% at 2 yrs	Rajkumar SV, et al. Leukemia 2003; 17: 775-779.
Thalidomide plus Pamidronate**	76	25	60% at 4 yrs	91% at 4 yrs	Barlogie B, et al. Blood. 2008;112:3122-125.
Thal+Zol vs Zol	68	37-0%	4.3 -3.3y	74-73% at 5y	Witzig TE, et al. Leukemia 2013; 27: 220-5

* Low ORR plus Grade 3/4 AEs in 21%; dose reduction in 100%.

**Dose reduction in 86%; 50% discontinued. Patients in ≥ PR had a shorter time to treatment (< 2 years).

None of these trial results support early treatment in patients with smoldering MM

But…none of these trials discriminate low-risk patients *(who likely will not benefit from intervention)* ***from high-risk patients who may benefit from therapy.***

QuiRedex: early treatment in high-risk SMM

MAYO CLINIC

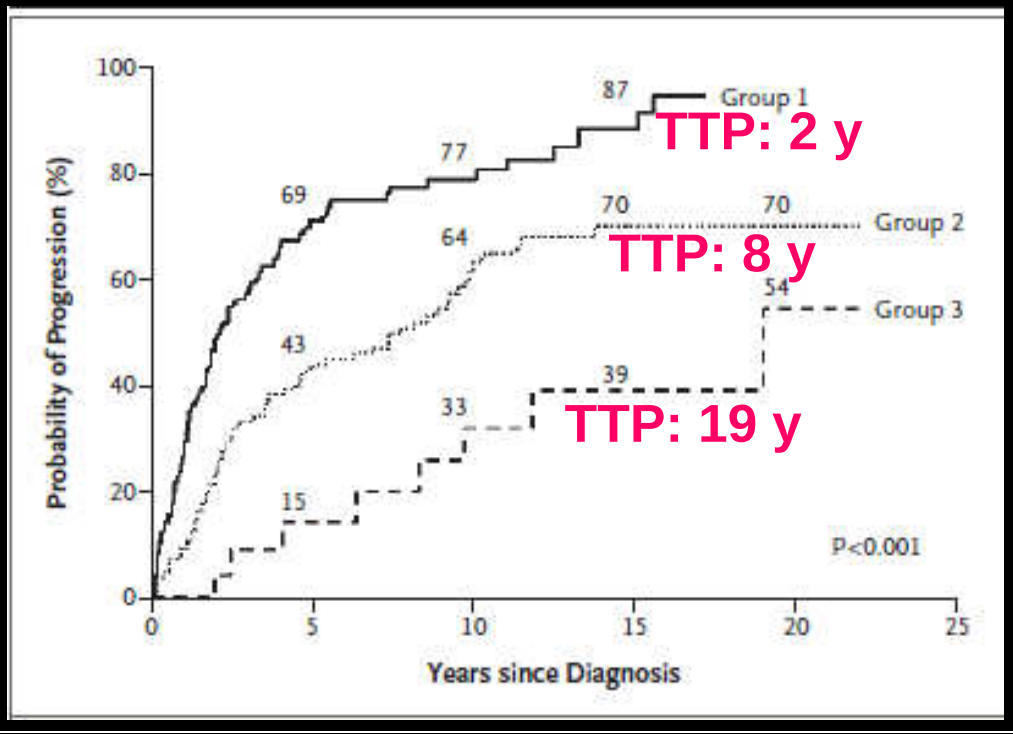
or

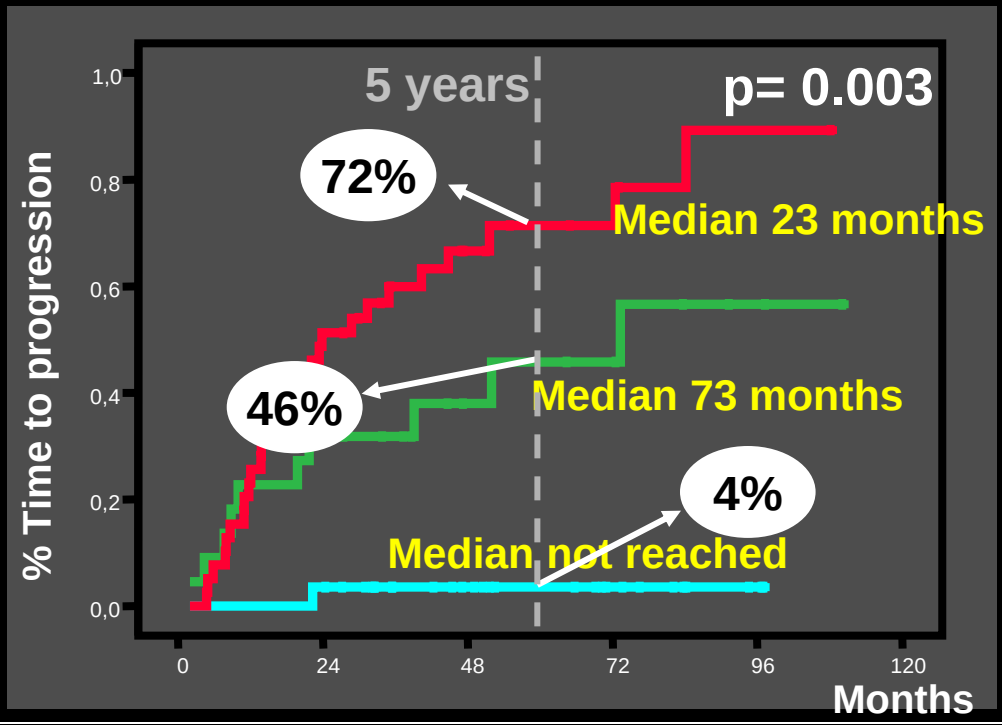
PETHEMA GEMM GRUPO ESPAÑOL DE MIELOMA

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

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

Group 1: PCBM ≥ 10% + MC ≥ 3g/dl or





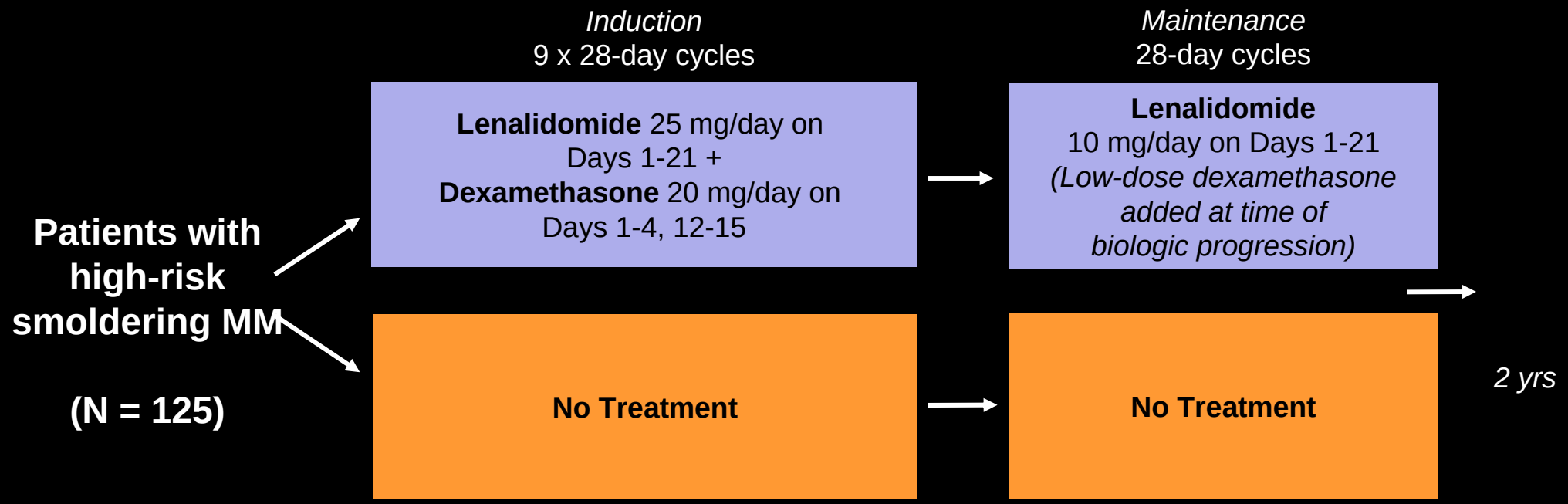
Time elapsed from diagnosis to inclusion not superior to 5 years

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

Mateos MV, et al. ASH 2011. Abstract 991.

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.

Amendment in August 2011: Stop treatment after 2 years

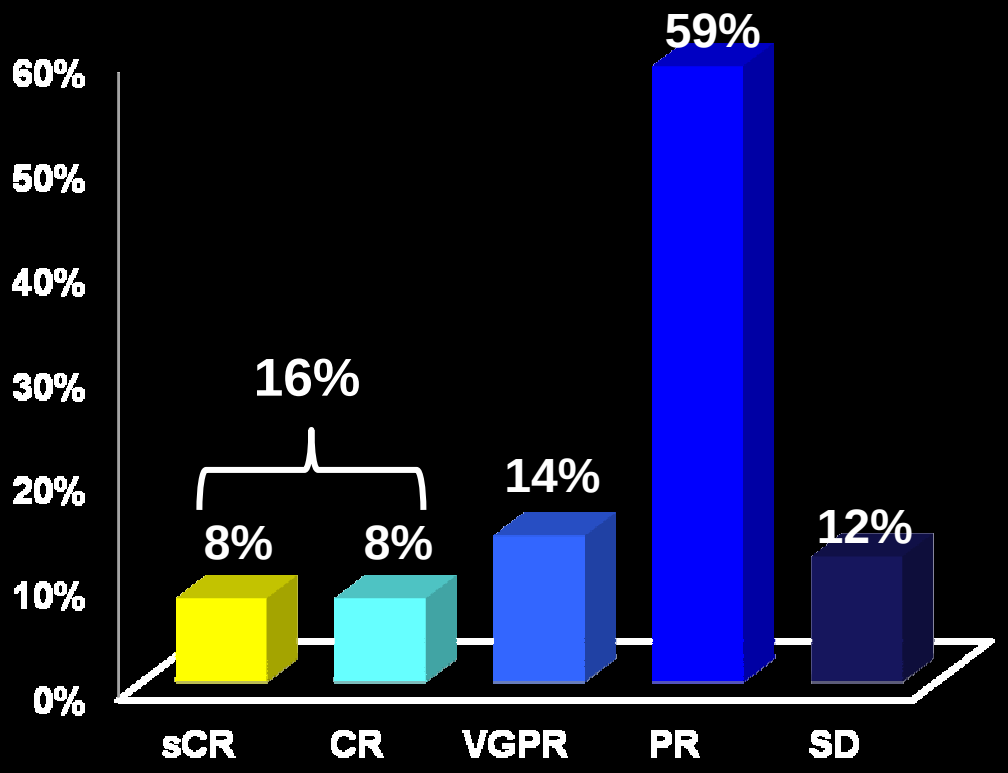
Mateos MV, et al. ASH 2011. Abstract 991.

Lenalidomide + Dex: response rate

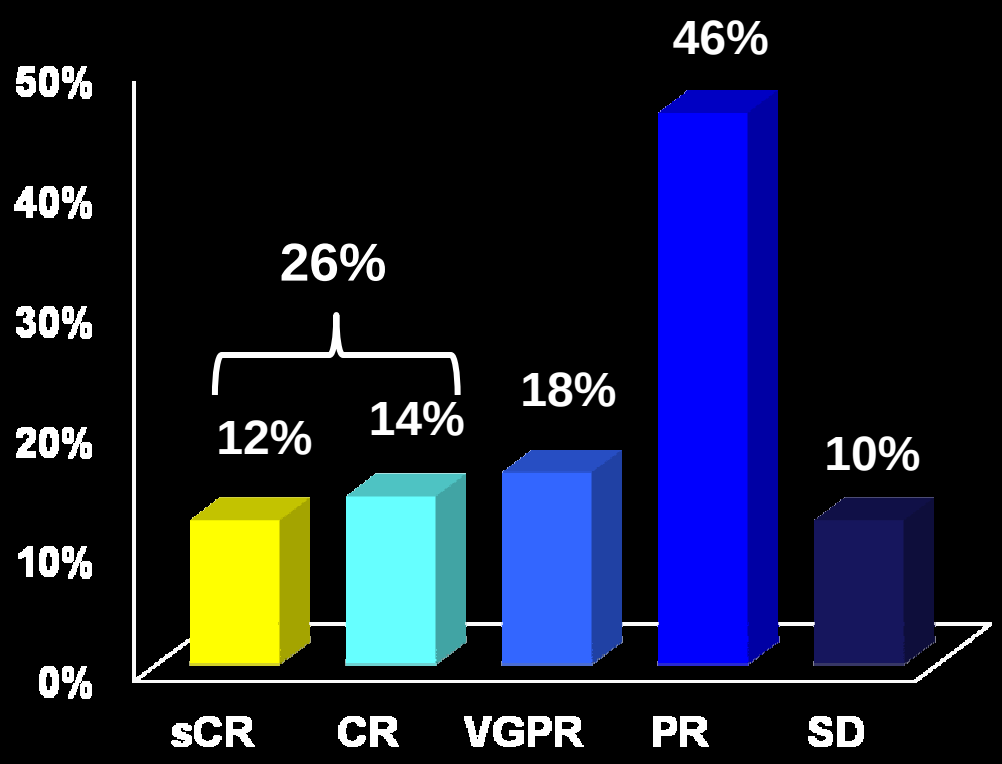
On ITT (n = 57) Median number of induction cycles: 9 (range 1–9)

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)



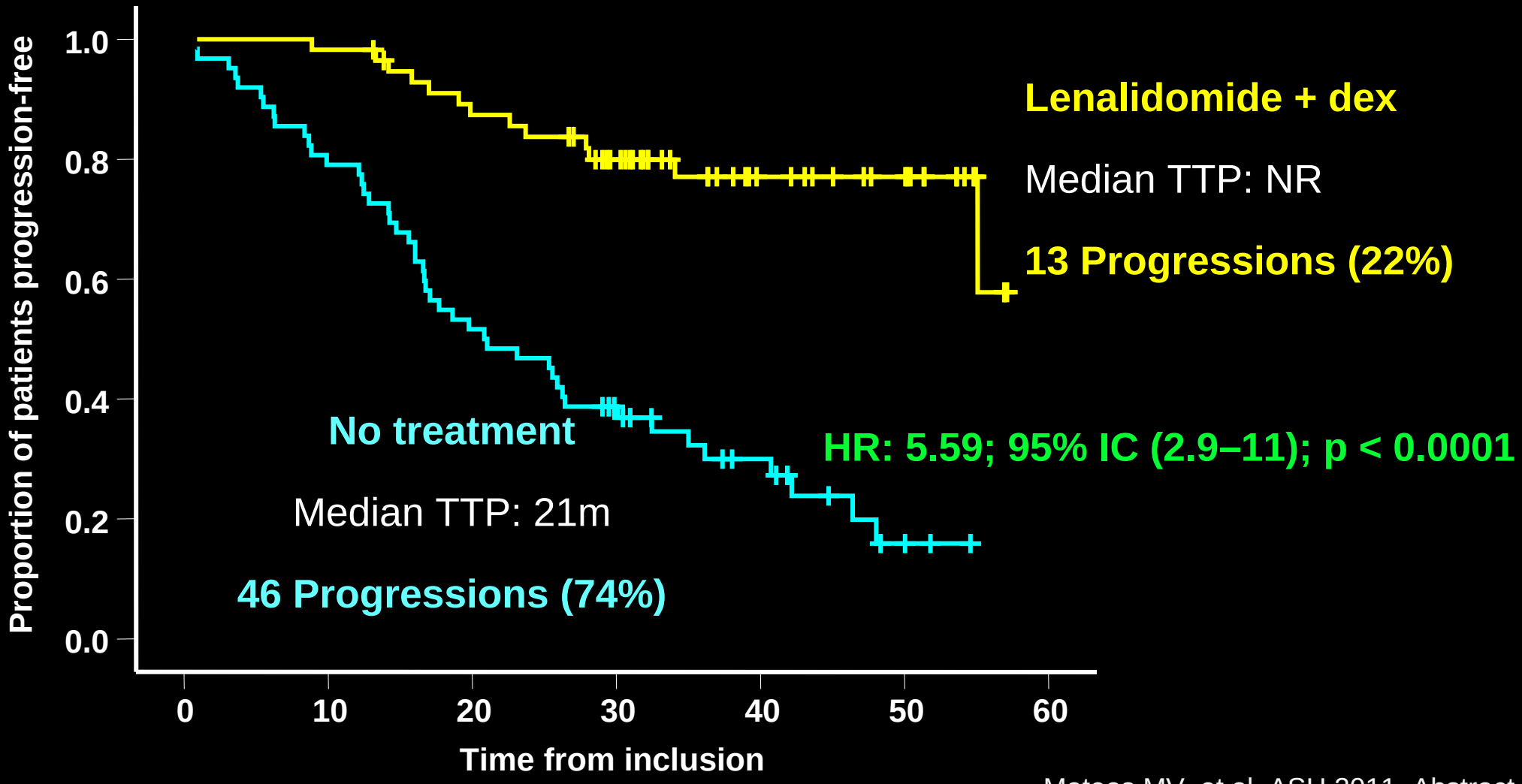
*IMWG criteria.

Mateos MV, et al. ASH 2011. Abstract 991

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

ITT analysis

Median follow-up: 40 months (range 27–57)



Mateos MV, et al. ASH 2011. Abstract 991

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

- **3 pts:** Improvement of response to PR
- **11pts:** Experienced stabilization of disease with dex
  - 10 remain stable after a median f/u of 26m (4-40)
  - 1 pts: Progressed to active disease after 12 m
- **4 pts:** Progressed to symptomatic disease

Mateos MV, et al. ASH 2011. Abstract 991

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. ASH 2011. Abstract 991

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. ASH 2011. Abstract 991

QuiRedex: toxicity profile during induction (n:125)

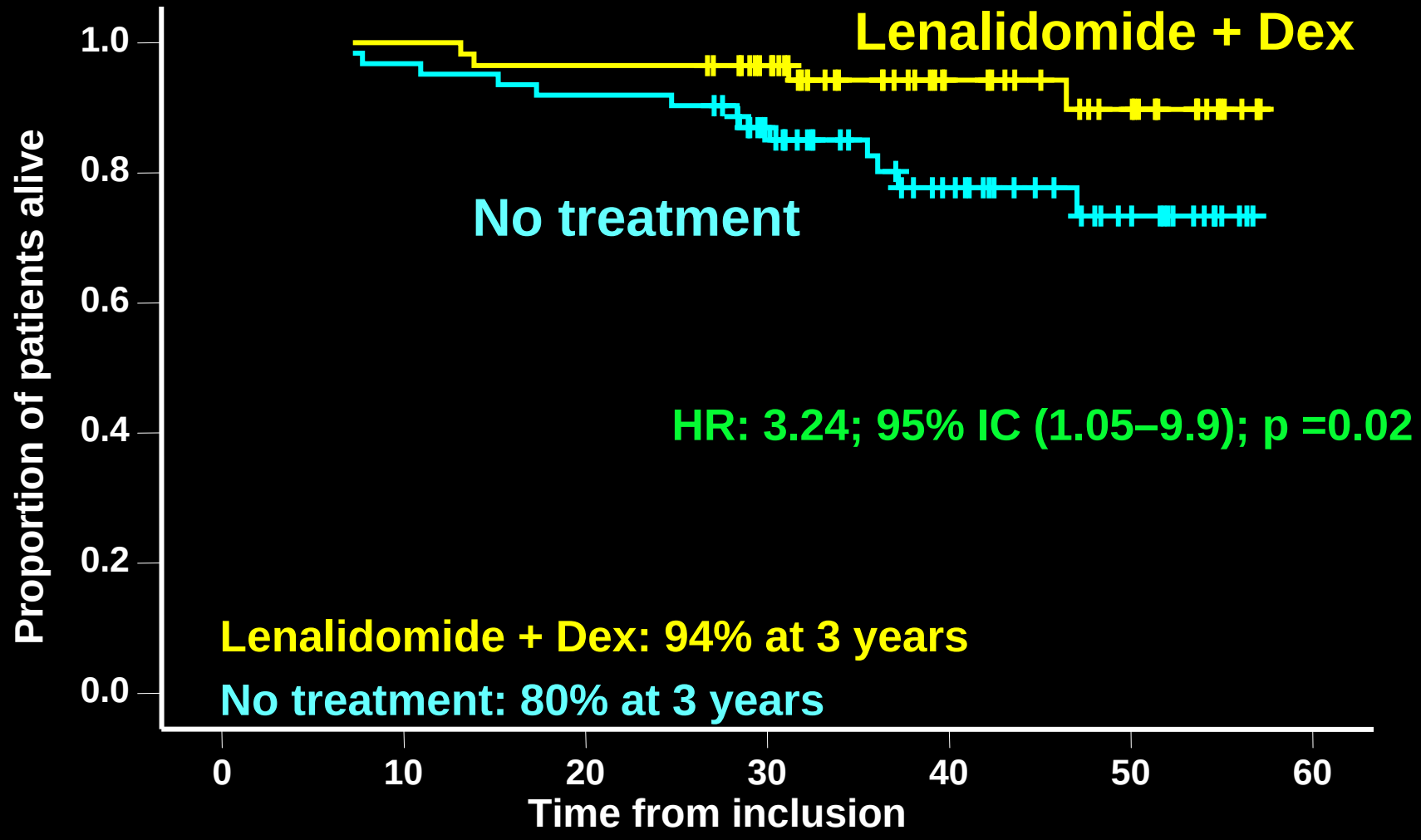
	Len-dex arm (n:62)		Abstention arm (n:63)
	G1	G2	G1-2
Anemia	11 (20%)	4 (7%)	2 (4%)
Neutropenia	3 (6%)	8 (14%)	
Thrombopenia	6 (11%)	1 (2%)	
Asthenia	6 (11%)	5 (9%)	6 (11%)
Constipation	4 (7%)	6 (11%)	1 (2%)
Diarrhea	9 (17%)	4 (7%)	2 (4%)
Rash	12 (23%)	6 (11%)	
Infection*	19 (35%)	6 (11%)	14 (26%)
DVT**	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. ASH 2011. Abstract 991

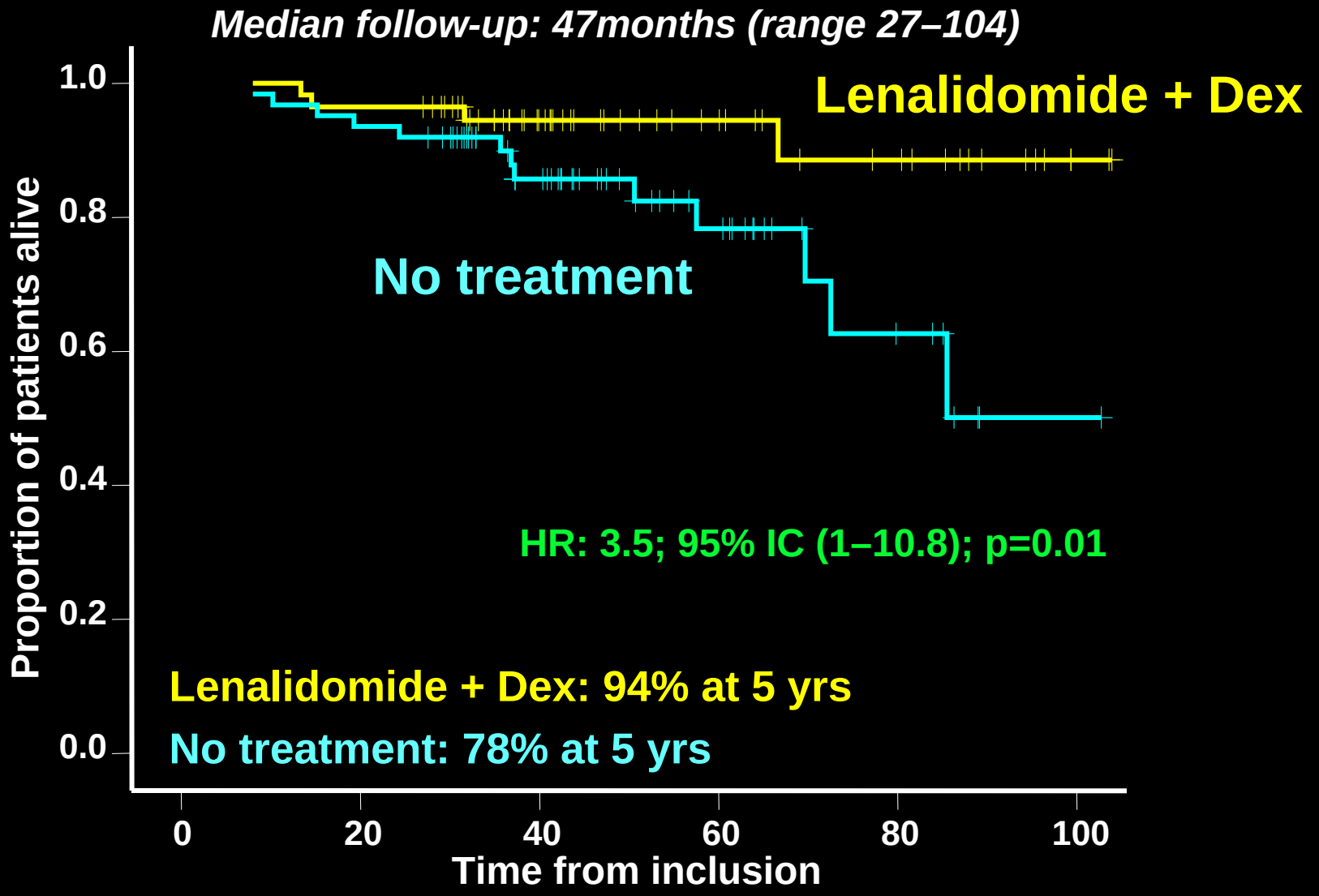
Len-dex vs no treatment: OS from inclusion (n = 119)

Median follow-up: 40months (range 27–57)



Mateos MV, et al. ASH 2011. Abstract 991

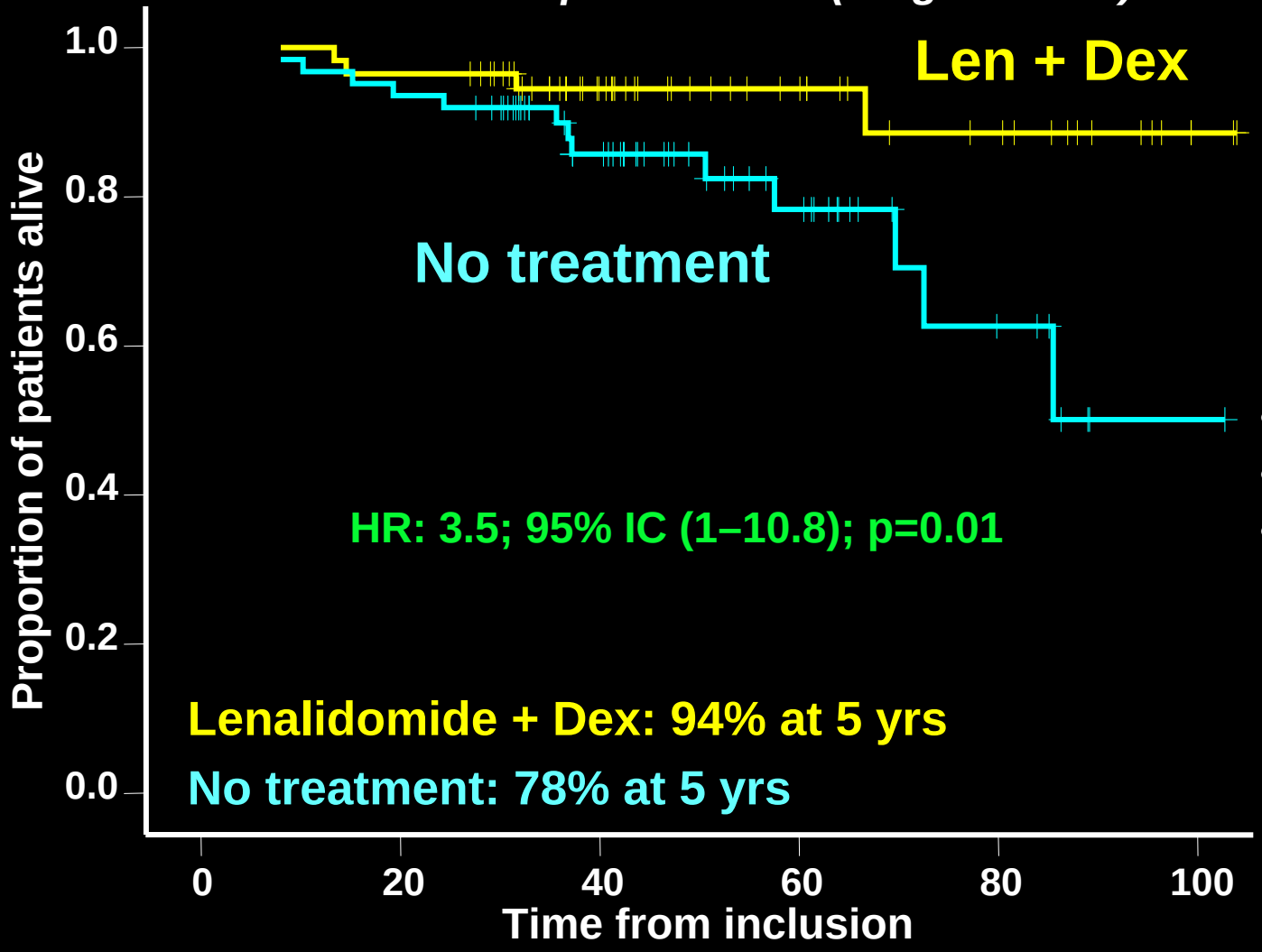
Len-dex vs no treatment: OS from diagnosis (n = 119)



Mateos MV, et al. ASH 2011. Abstract 991

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

Median follow-up: 47months (range 27–104)



Deaths: 4 pts
- **Progression disease: 2 pts**
- **Treatment-related tox: 1 pts**
- **Other: 1 pt**

Deaths: 13 pts
- **Progression disease: 9 pts**
- **Treatment-related tox: 3 pts**
- **Sudden death at home: 1 pt**

Mateos MV, et al. ASH 2011. Abstract 991

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. ASH 2011. Abstract 991

Should we treat Smoldering MM patients?

- High-risk SMM patients should be called early 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

- **Lenalidomide or observation (phase III)**[1]
- **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
- **MLN9708 and dexamethasone (phase II)**[5]
- **Carfilzomib, lenalidomide, and dexamethasone (phase II)**[6]**:**
  Very promising efficacy results will be presented tomorrow in the plenary session

1. ClinicalTrials.gov. NCT01169337.
2. ClinicalTrials.gov. NCT01441973.
3. ClinicalTrials.gov. NCT01484275.
4. ClinicalTrials.gov. NCT01302886.
5. ClinicalTrials.gov. NCT016609973.
6. ClinicalTrials.gov. NCT01572480.

Should we treat Smoldering MM patients?

- High-risk SMM patients should be called **early Multiple Myeloma**
- Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS
- Numerous clinical trials are currently ongoing in this group of patients

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

Early treatment in Early MM patients

Acknowledgments

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