WHAT ARE THE MOST RELEVANT BIOMARKERS TO IDENTIFY HIGH-RISK PATIENTS WITH SMM?

Friday, April 5, 2013

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Cedars Sinai Samuel Oschin Cancer Center
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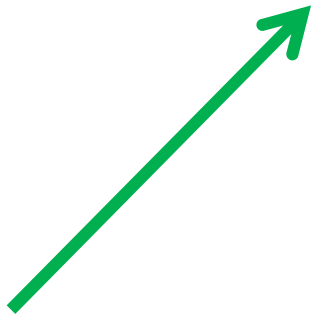
CURRENT STATUS OF BIOMARKERS

WHAT ACTIONS TO TAKE



WHICH TESTS TO USE

** After IMWG consensus criteria*

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**
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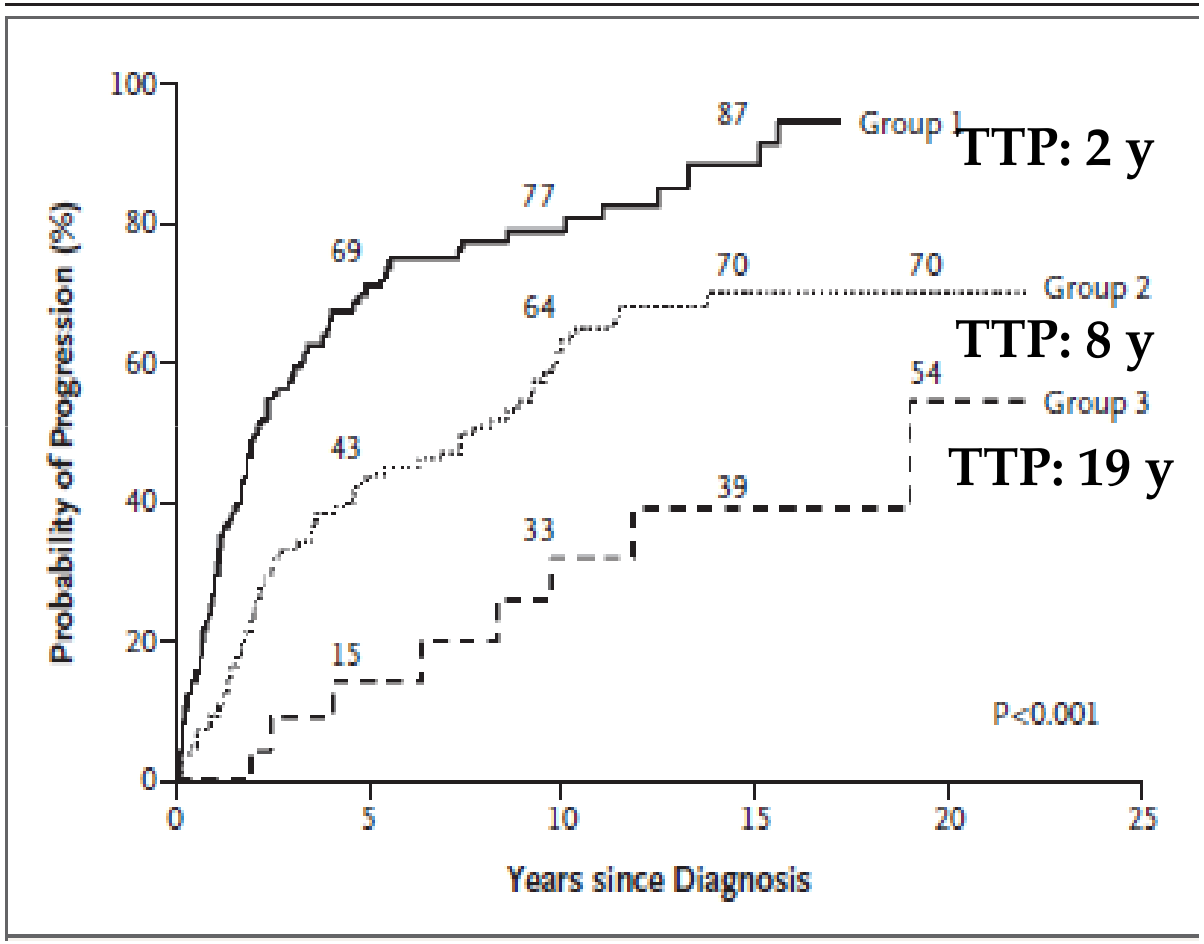
SMOLDERING MULTIPLE MYELOMA: PCs BM INFILTRATION & SERUM M-COMPONENT LEVEL



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

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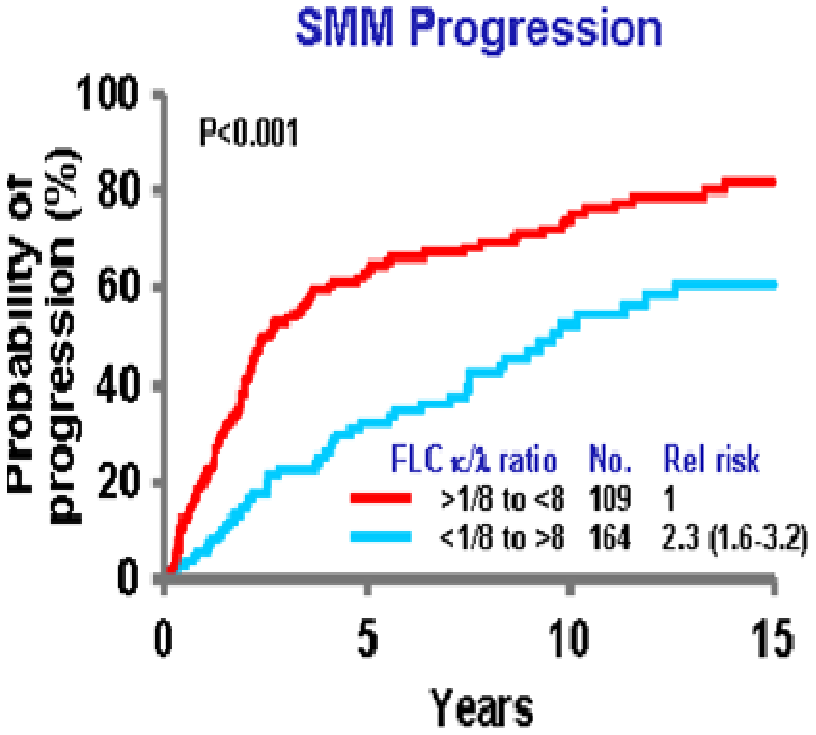
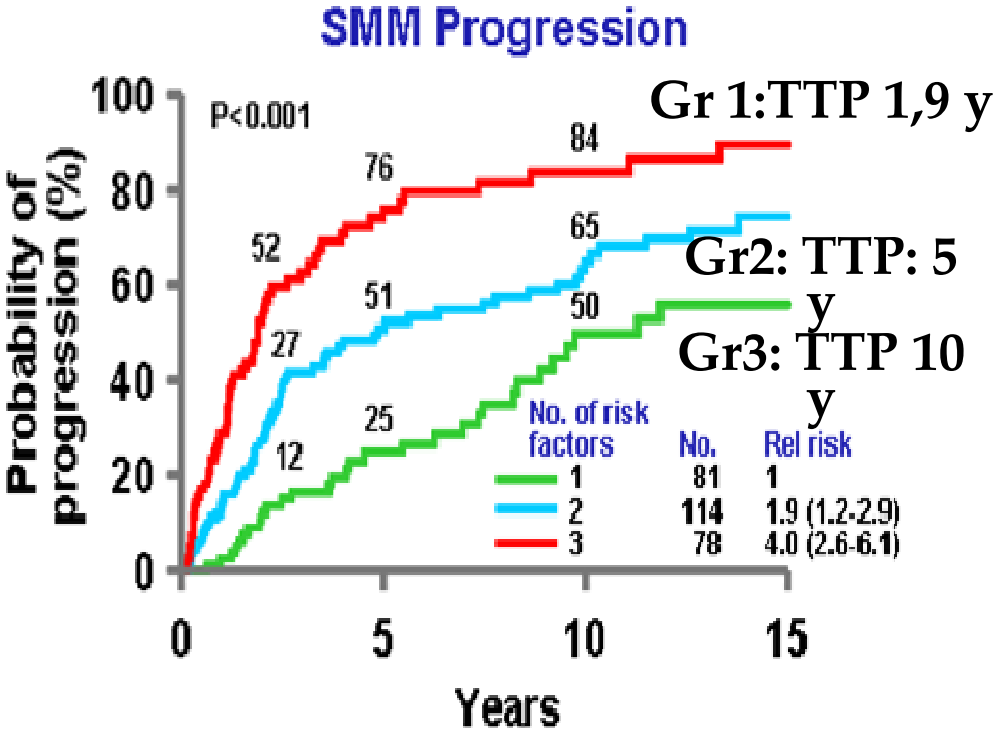
SMOLDERING MULTIPLE MYELOMA: SERUM IMMUNOGLOBULIN FREE-LIGHT CHAIN (FLC) RATIO (n:273)

Serum FLC ratio >0.125 or < 8

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





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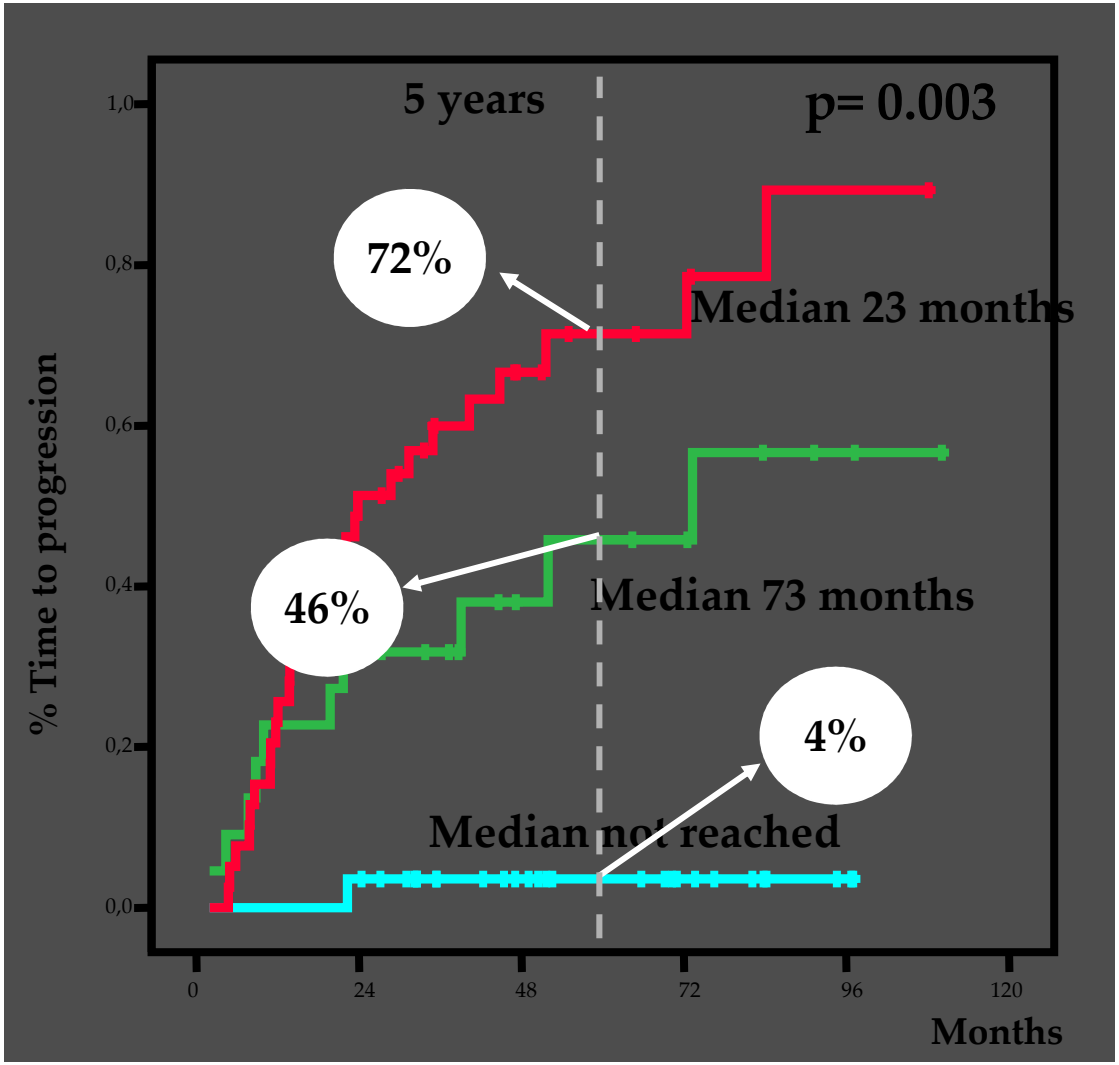
SMOLDERING MULTIPLE MYELOMA: ABERRANT PCs BY IMMUNOPHENOTYPE PLUS IMMUNOPARESIS



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

>95% aPC/BMPC or paresis
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No adverse factors
n= 28 (1 progr.)

Pérez E. Blood 2007; 110:25

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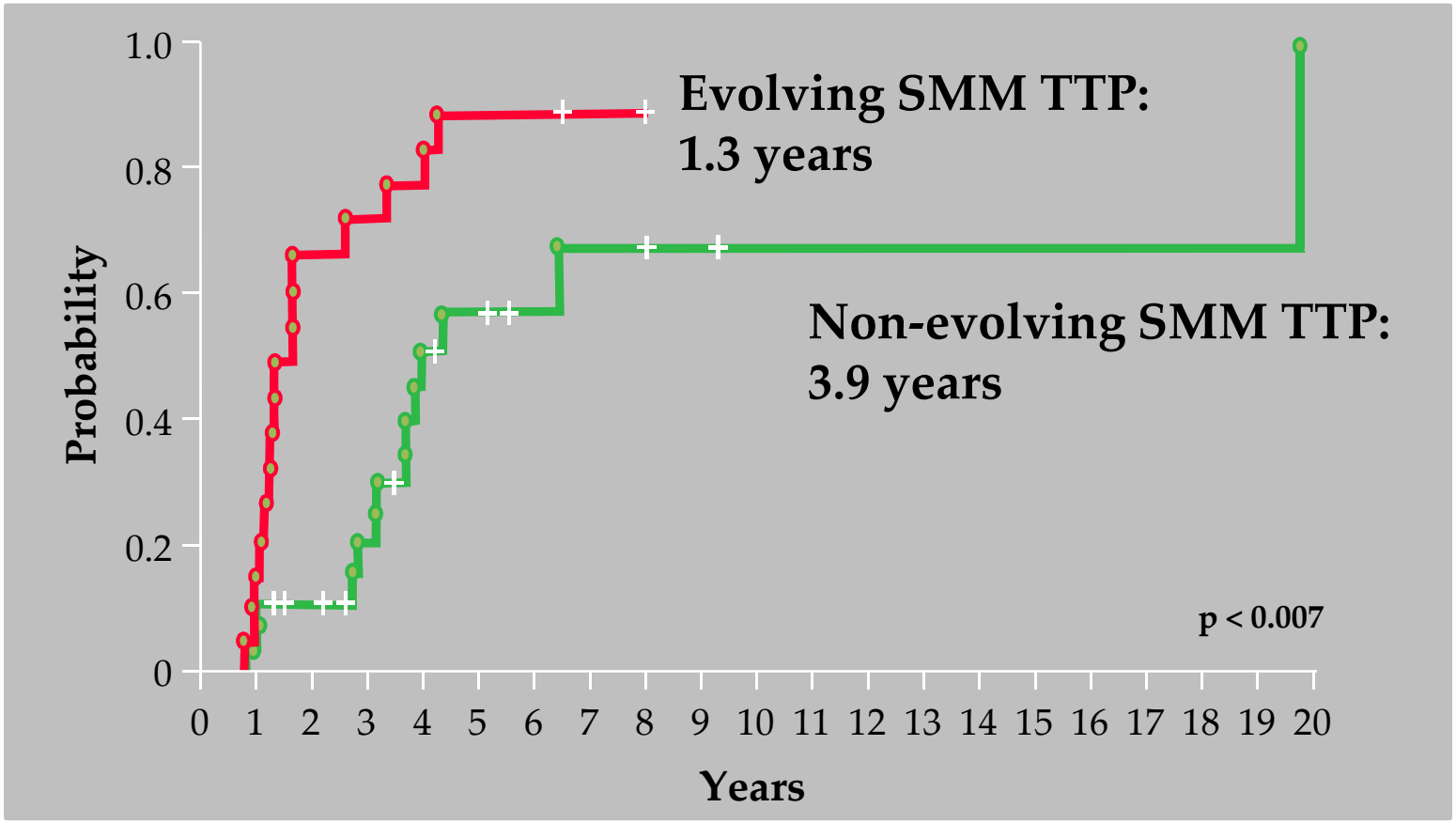
SMOLDERING MULTIPLE MYELOMA: EVOLUTION PATTERN: EVOLVING VS NONEVOLVING (n:48)

Evolving SMM (22): **Previous history of MGUS; progressive increase of M-protein**

Non-evolving (26): **Stable serum M-protein until progression occurs**



Rosiñol et al. Br J Haematol 2003; 123(4):631-6

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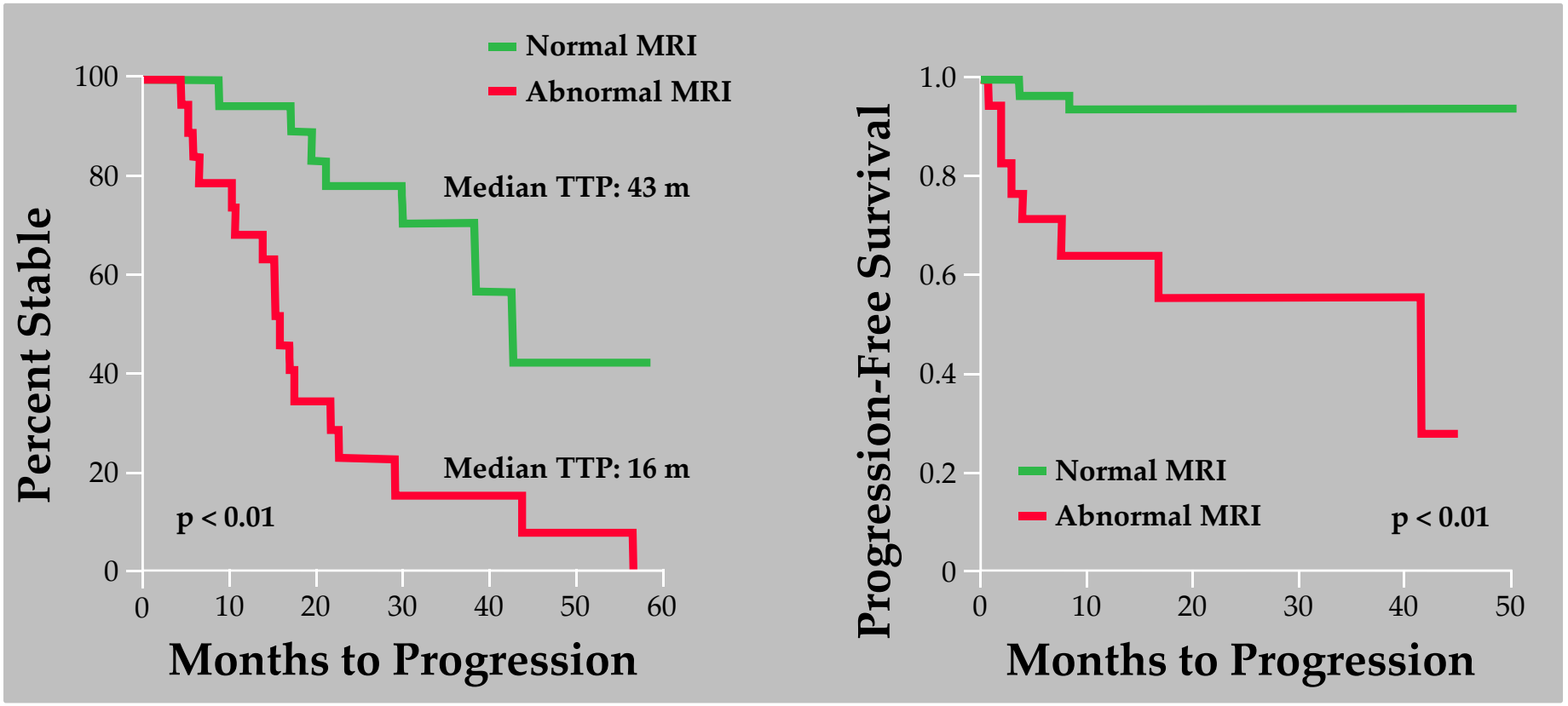
SMOLDERING MULTIPLE MYELOMA: MRI

43 pts with asymptomatic MM
Spinal MRI: 50% of pts: marrow involv
Patterns: Diffuse, variegated and focal

55 pts with stage I MM
Spinal MRI: 31%% of pts: marrow inv
Patterns: Diffuse, variegated and focal



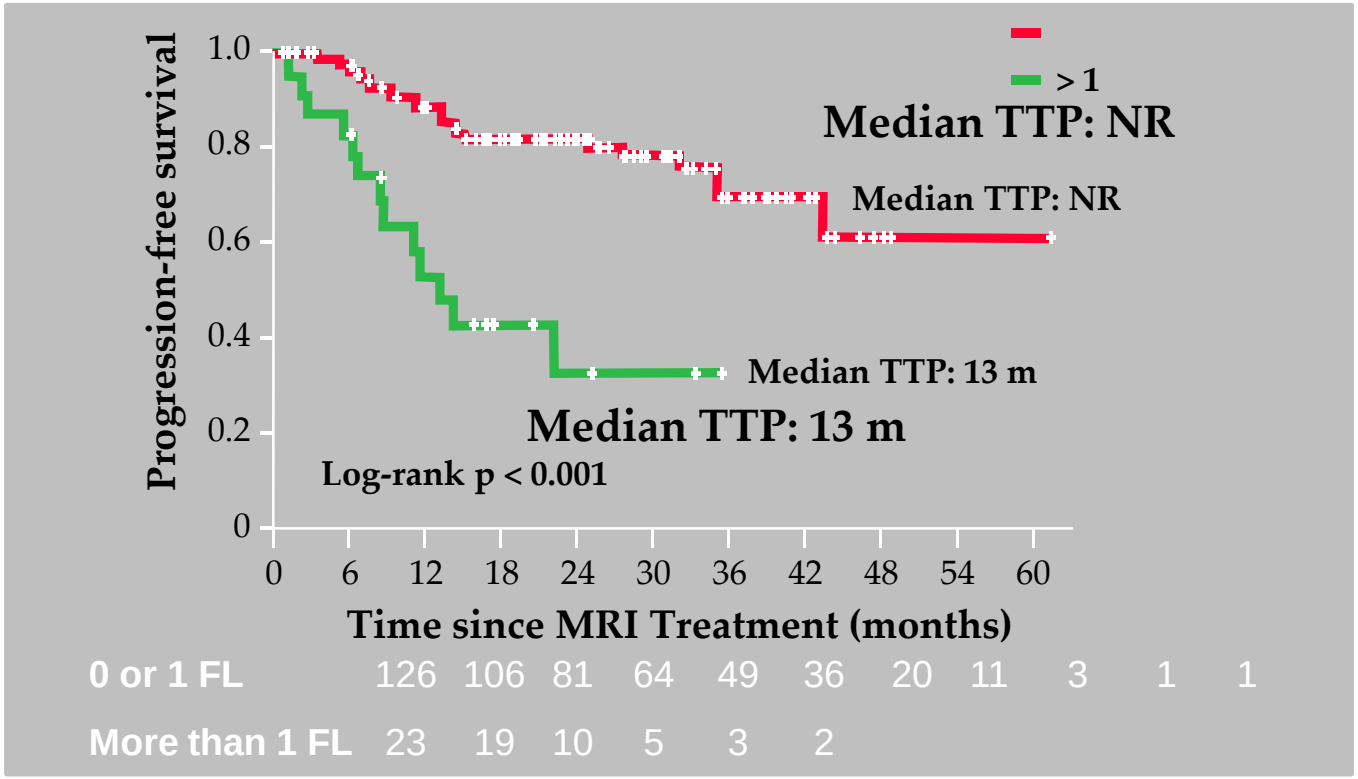
Moulopoulos et al. J Clin Oncol 2005; 13:251-6

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

SMOLDERING MULTIPLE MYELOMA: WHOLE MRI

149 patients with asymptomatic MM

Whole MRI: 28% of pts: Focal lessions



> 1 Focal lession plus diffuse pattern → adverse prognosis

Hillengass J et al. J Clin Oncol 2010; 28: 1606-10

PROGNOSTIC SIGNIFICANCE OF WHOLE MRI FOR PATIENTS WITH SMM

- **Retrospective study: whole body MRI**
  - **157 pts with SMM**
- **Results**

	SMM patients
Focal lesions	**34.4%**
Diffuse infiltration	**45.9%**
Adverse prognostic factors for PFS	**Plasma cell percentage, moderate diffuse infiltration (but not focal lesions), beta2-microglobulin**

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

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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
- Presence of t(11;14) and del(13q14) of no statistical significance

	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. ASH 2012 (Abstract 1806), poster presentation

FISH TESTING & OUTCOMES

Leukemia. 2013 Mar 21. doi: 10.1038/leu.2013.86. [Epub ahead of print]

Impact of Primary Molecular Cytogenetic Abnormalities and Risk of Progression in Smoldering Multiple Myeloma.

Rajkumar SV, Gupta V, Fonseca R, Dispenzieri A, Gonsalves WI, Larson D, Ketterling RP, Lust JA, Kyle RA, Kumar SK.

Source

Abstract

We studied 351 patients with SMM in whom the underlying primary molecular cytogenetic subtype could be determined based on cytoplasmic immunoglobulin (cIg) fluorescent in situ hybridization (FISH) studies. 154 patients (43.9%) had

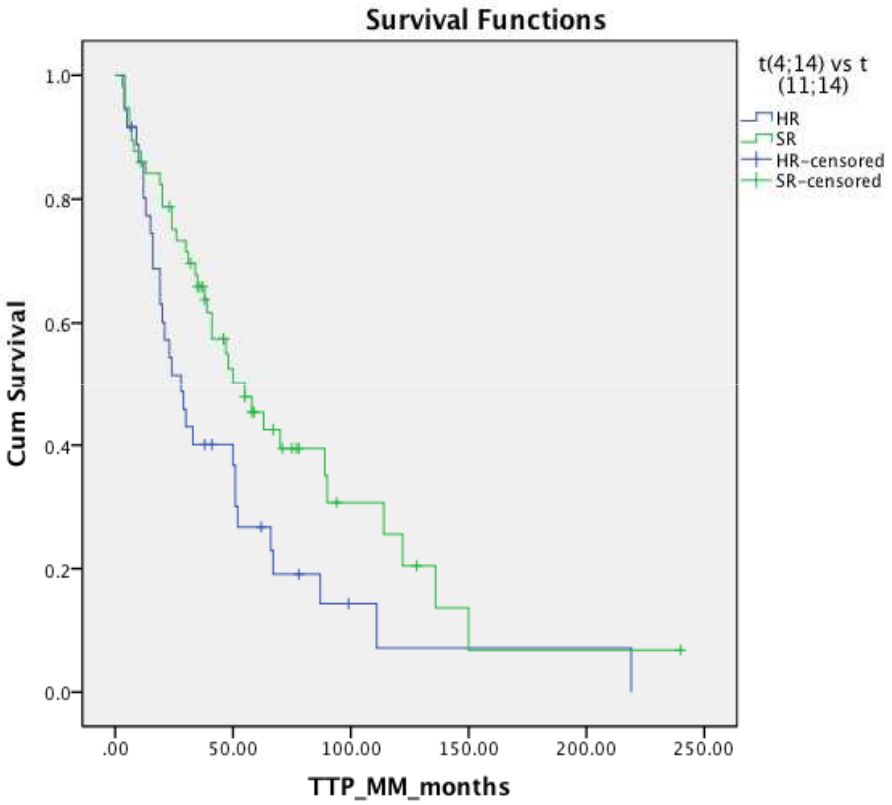
DISTRIBUTION of PRIMARY CYTOGENETIC CATEGORIES of SMOLDERING MULTIPLE MYELOMA

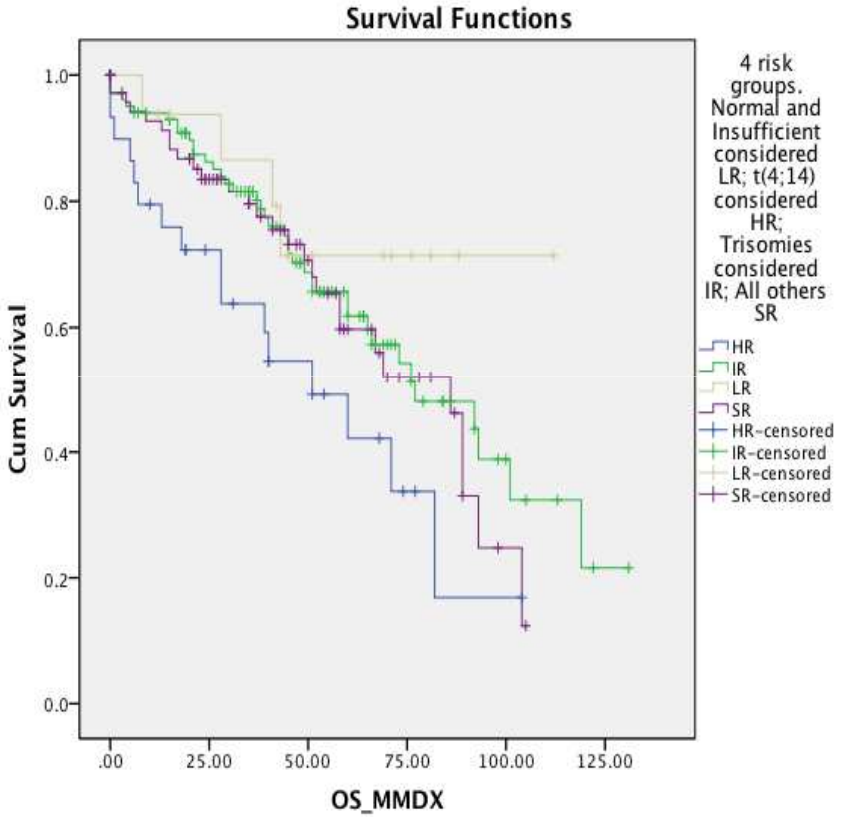
Cytogenetic Classification by fluorescent in situ hybridization	Overall (n=351) No. of patients (%)*
Trisomy(ies) without IgH translocation	154 (43.9%)
t(11;14)(q13;q32)	57 (16.2%)
t(4;14)(p16;q32)	36 (10.3%)
MAF translocations [t(14;16)(q32;q23) and t(14;20)(q32;q11)]	11 (3.1%)
Other/ unknown IgH translocation partner	23 (6.6%)
Both IgH translocation and trisomy (ies)	14 (4%)
Monosomy13/del(13q) in absence of IgH translocation or trisomies	3 (0.9%)
Normal or Insufficient	53 (15.1%)

CYTOGENETICALLY DEFINED RISK BASED CLASSIFICATION

Risk	Cytogenetic Class	No. of patients (%)*	Median TTP to Myeloma (months)[a]	Median TTP to Myeloma or related disorder (months)[b]	Median OS from SMM diagnosis (months)[c]	Median OS from MM diagnosis (months)[d,e]
High-Risk*	t(4;14) del(17p)	44 (12.5%)	24	24	105	60
Intermediate-Risk	Trisomy (ies) without IgH translocation	148 (42.2%)	34	34	135	77
Standard-Risk	t(11;14) *MAF* translocations, t14;16 or t(14;20) Other/ unknown IgH translocation partner Both trisomies and IgH translocation except t(4;14) Monosomy13/del(13q) in absence of IgH translocation or trisomies	106 (30.2%)	55	54	147	86
Low-Risk	No abnormalities (normal or insufficient)	53 (15.1%)	Not reached	101	135	112

TTP and OS Relative to Risk





TTP: t[4;14]vs. t[11;14]

OS: 4 risk groups

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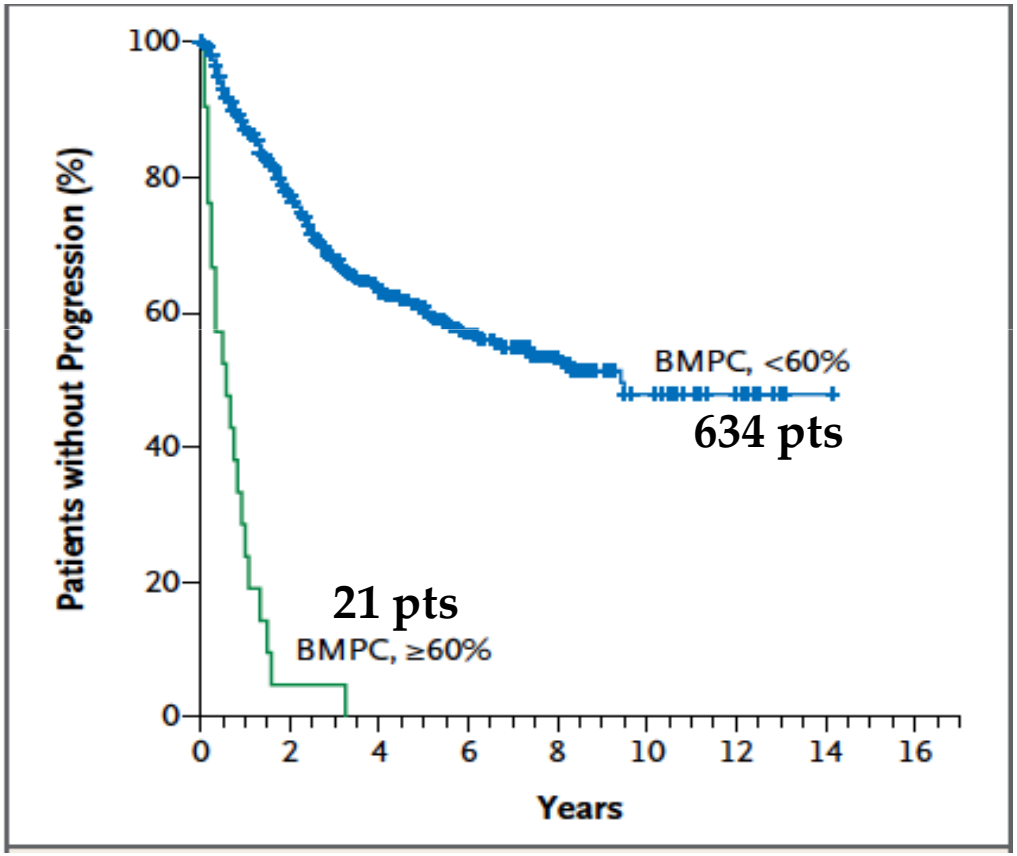
ULTRA HIGH-RISK SMOLDERING MULTIPLE MYELOMA: ≥ 60% PLASMA CELLS IN THE BONE MARROW AT BASELINE

N= 655 patients

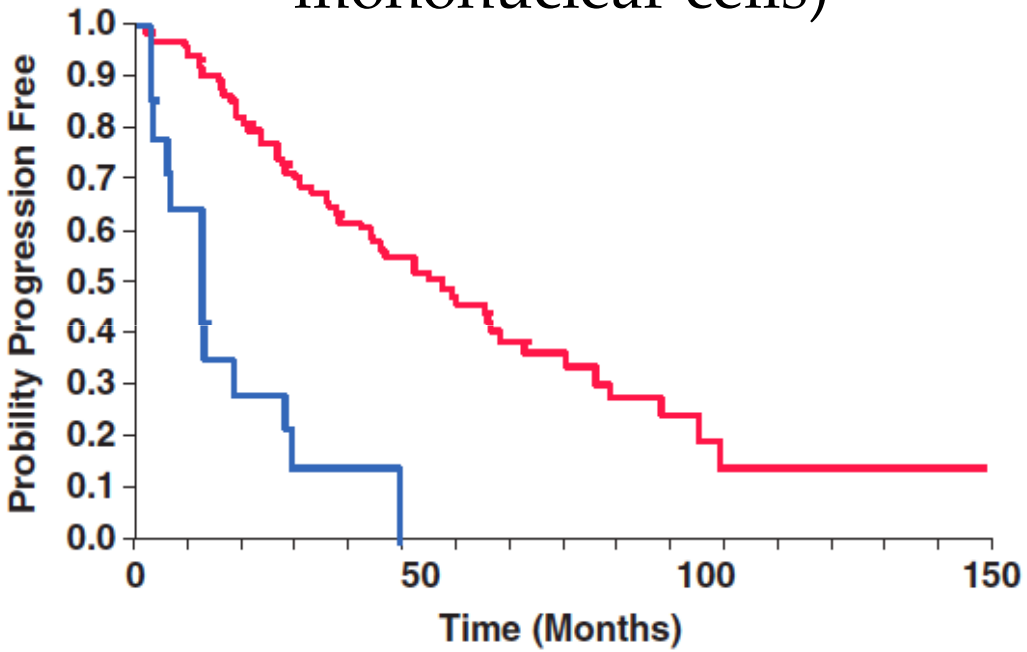


95% of patients with ≥60% of PCs in BM will progress within 2 years

Rajkumar SV et al. N Engl J Med 2011; 365:474-475

ULTRA HIGH-RISK SMM: PERIPHERAL BLOOD PLASMA CELL CIRCULATING

(>5x10^6/L and/or 5% per 100 cytoplasmic Ig-positive PB mononuclear cells)



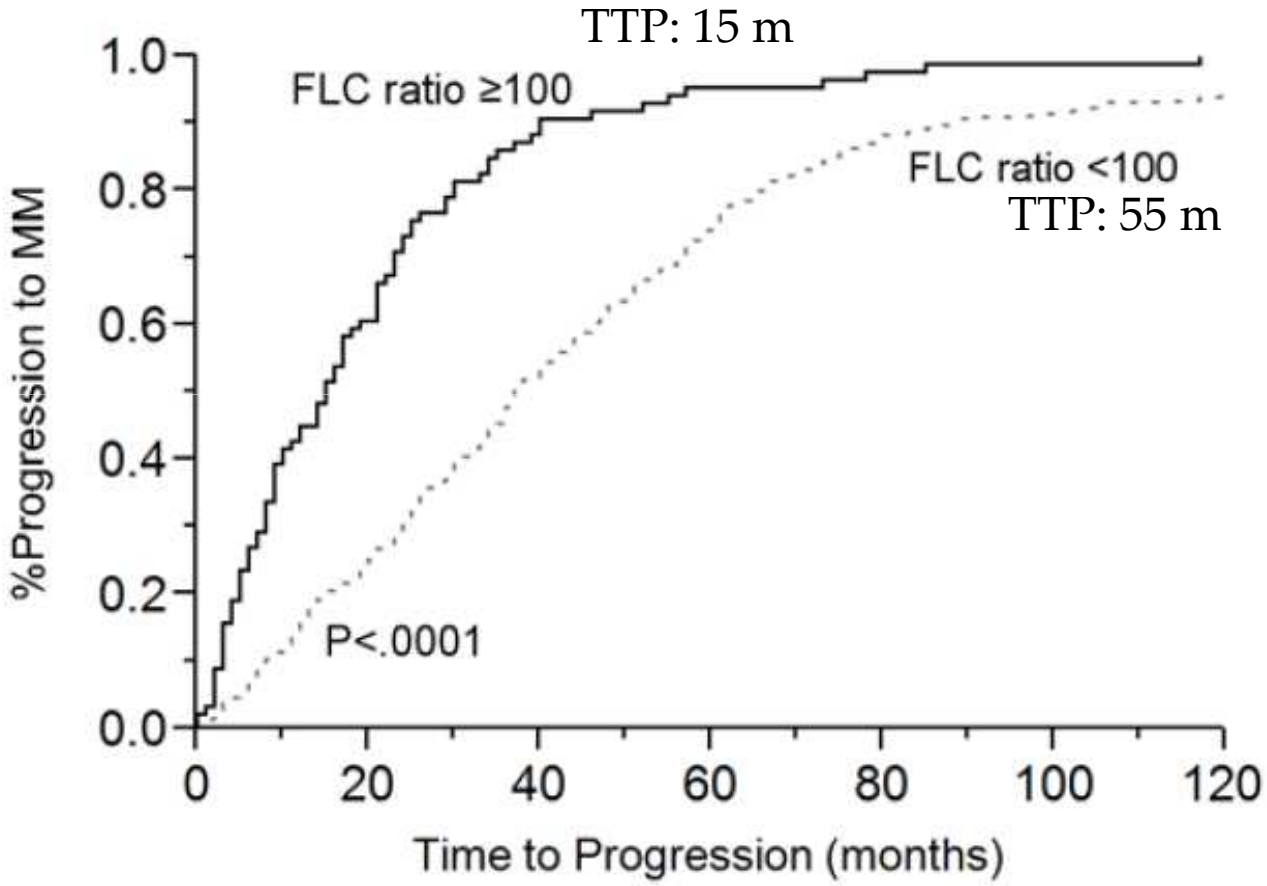
		Median TTP (months)
High circ PC	14 pts (15%)	12
Low circ PC	77 pts (85%)	57

P value: <0.001

71% of patients with high circulating PC in PB will progress in 2 years

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

SMOLDERING MULTIPLE MYELOMA: SERUM IMMUNOGLOBULIN FREE-LIGHT CHAIN (FLC) RATIO

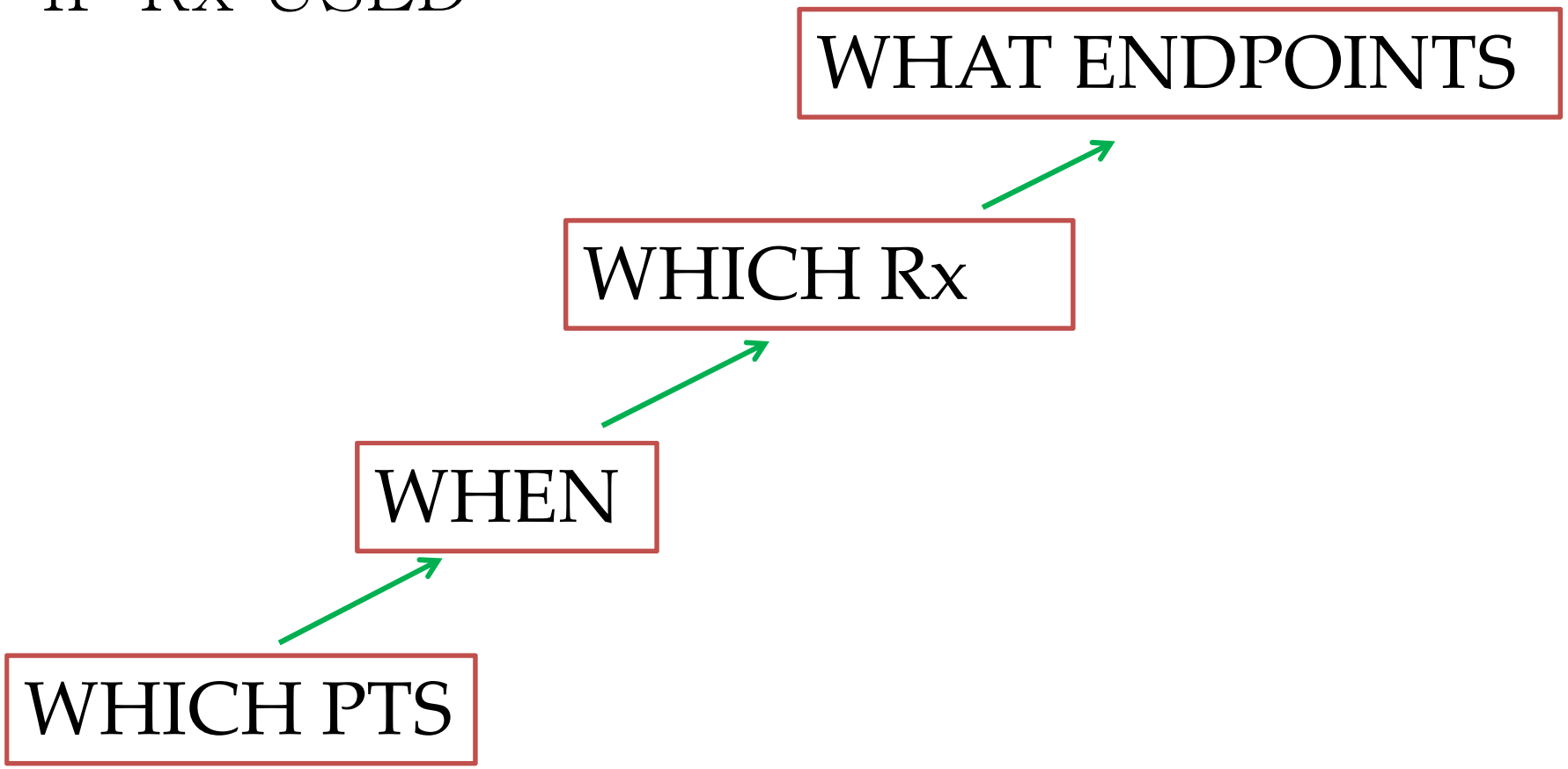


70% of patients with FLC ratio >100 will progress in 15 months

Larsen JT et al. Leukemia 2012; online Oct. 1

KEY QUESTIONS MOVING FORWARD

IF Rx USED



CLINICAL CASE

- Mrs Lopez is an asymptomatic, active 53-year-old lawyer
- In a routine exam, an elevated ESR was detected with elevated serum proteins (90 g/L)
- Complementary studies revealed: Hb 11.7 g/dL; creatinine 1.2 mg/dL, B_2M 2.6 mg/dL
- M component: 35 g/L; PCs BM: 33%
- FISH analysis: Rb deletion and t(4;14)
- No lytic lesions were detected; MRI showed osteoporosis with 1-2 focal lesions

SMOLDERING MM: OBJECTIVES

1. Diagnosis
2. Prognostic factors
3. Therapeutic approaches

SMOLDERING MM: DIAGNOSTIC CRITERIA

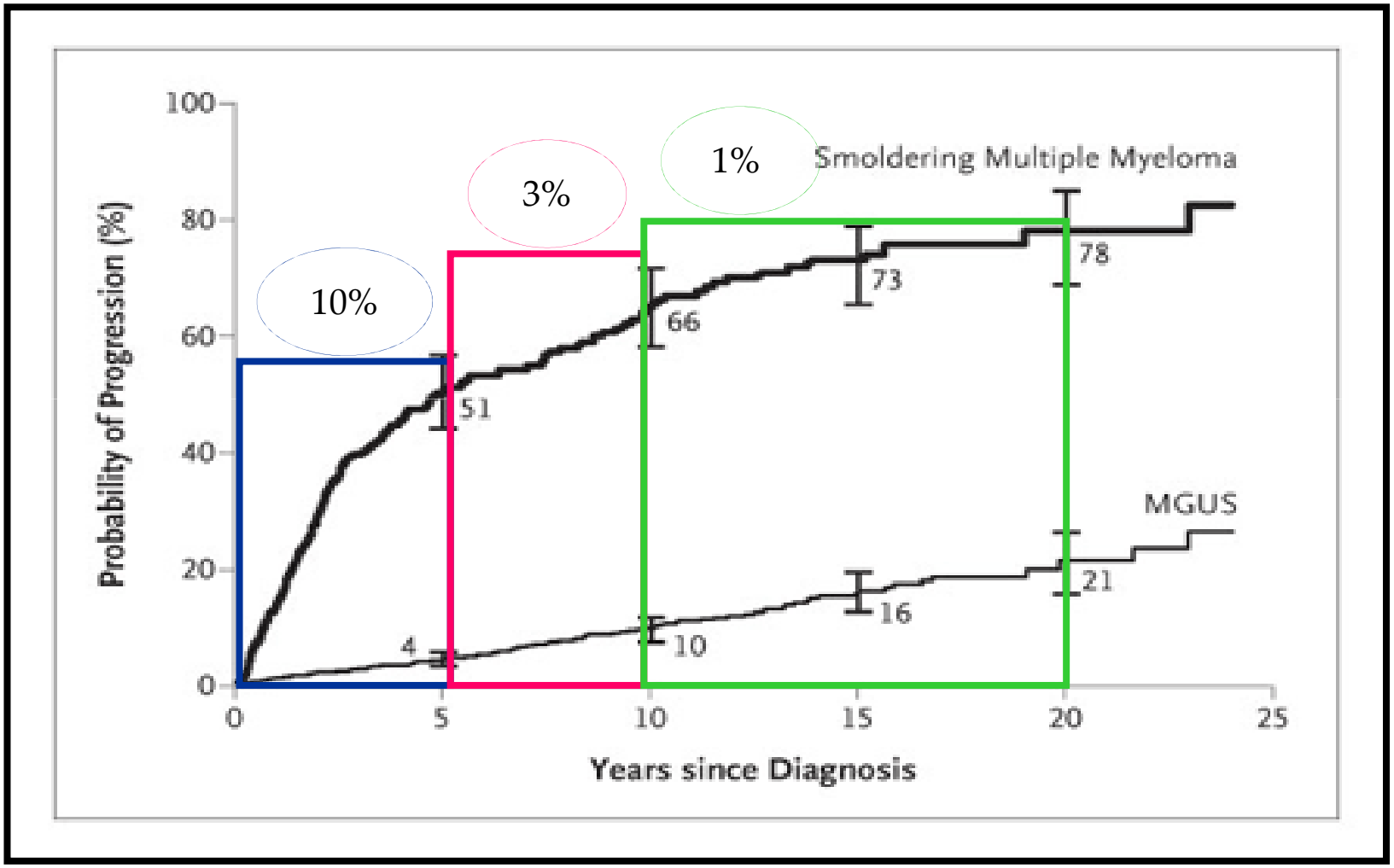
	Monoclonal Gammopathy of Uncertain Significance (MGUS)	Smoldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥ 3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10	≥ 10	> 10[b]
	AND	AND	AND
End-Organ Damage[a]	Absent	Absent	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.

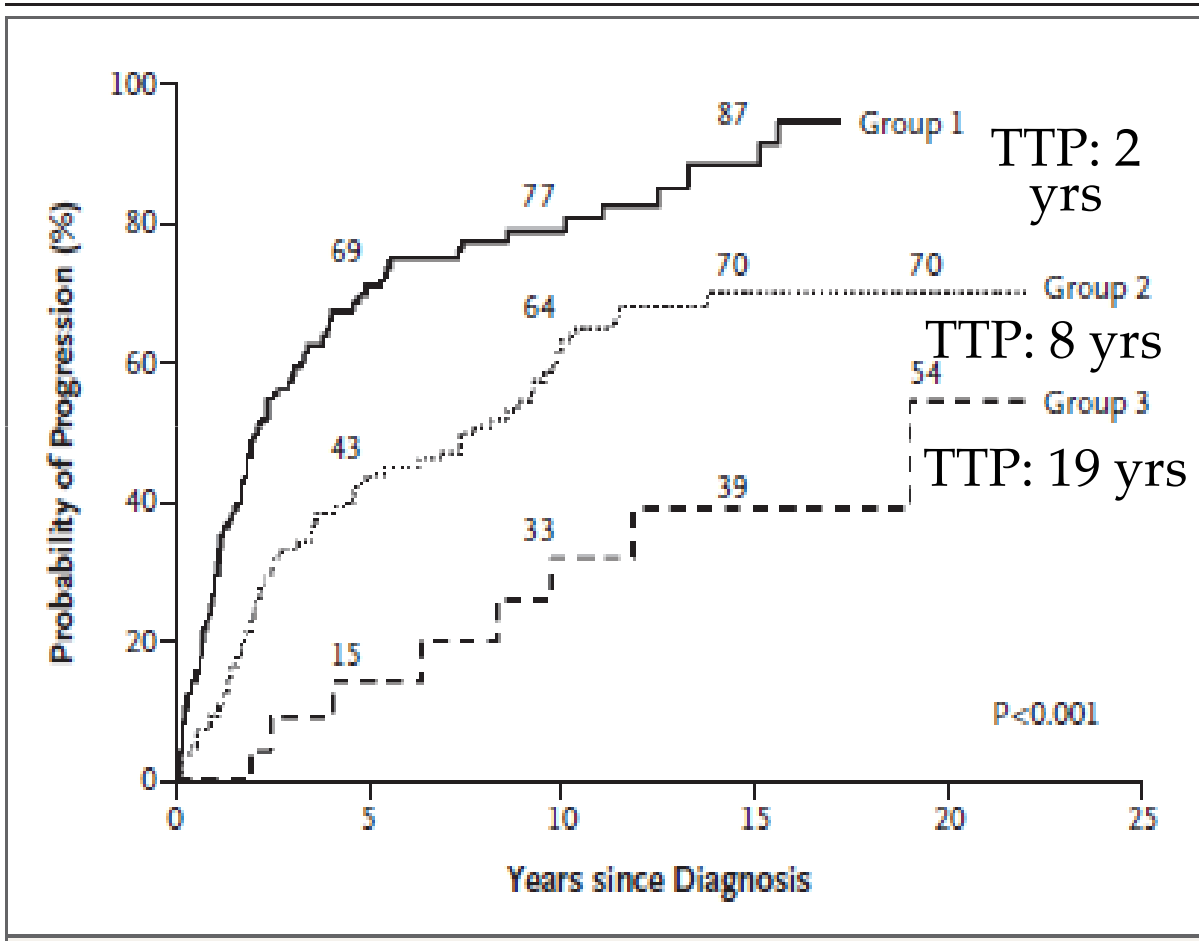
SMOLDERING MULTIPLE MYELOMA: RISK OF PROGRESSION TO ACTIVE DISEASE



Can we predict the risk of progression to active disease?

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

SMOLDERING MM: PCs BM INFILTRATION AND SERUM M-COMPONENT LEVEL



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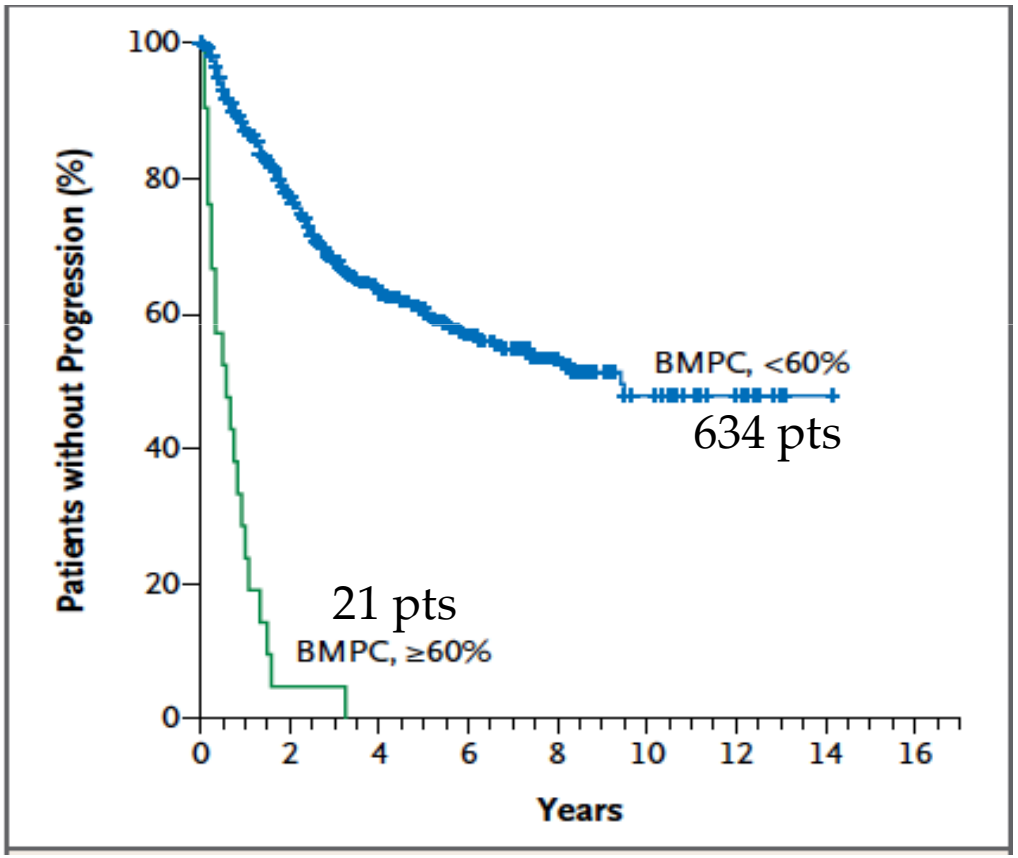

In these patients (3,2%) the median TTP was 7m and 95% of them progressed to symptomatic MM within 2 y

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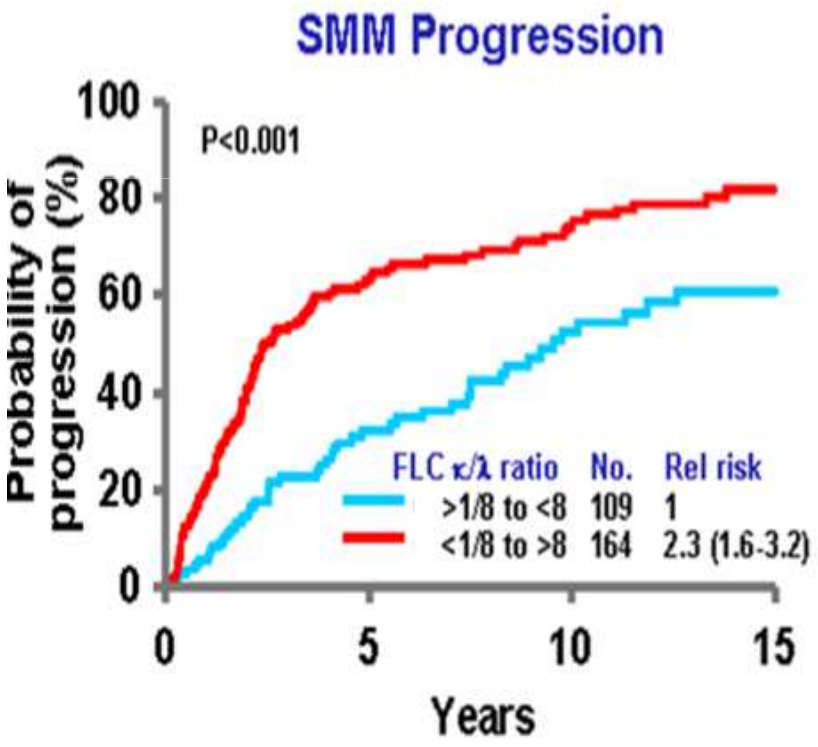
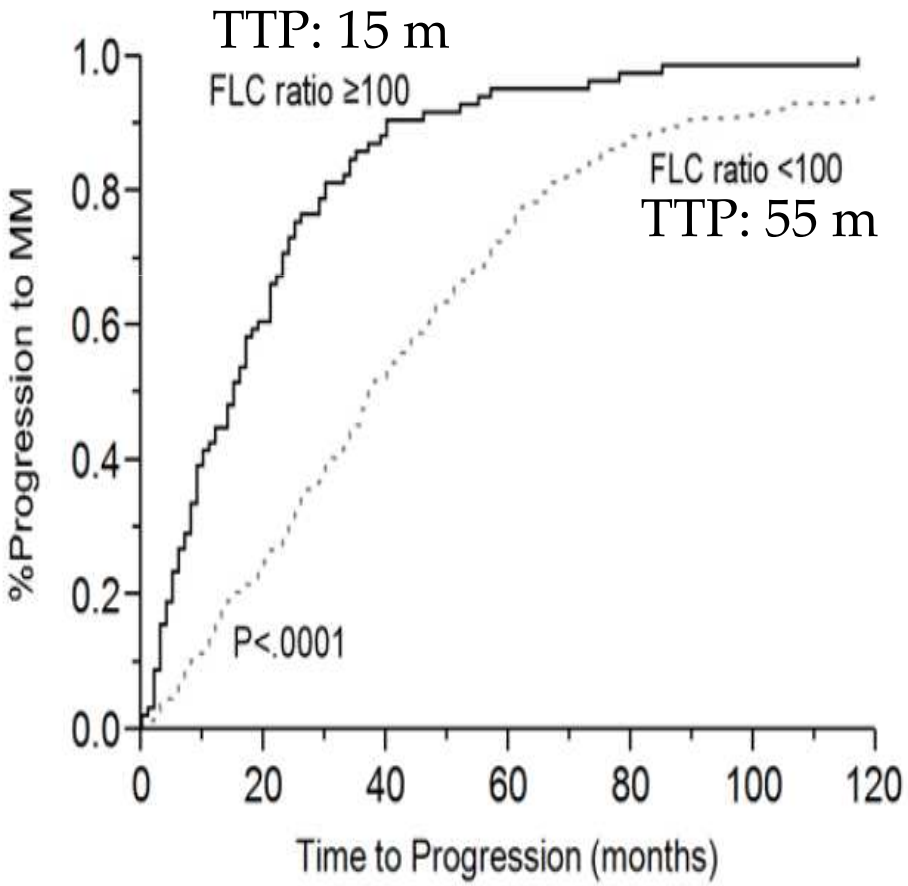
SMOLDERING MM: SERUM IMMUNOGLOBULIN FREE-LIGHT CHAIN (FLC) RATIO

Higher risk of progression with serum FLC ratio > 0.125 or < 8 (N = 273)



Dispenzieri A, et al. Blood. 2008;111:785-789.

Higher risk of progression: FLC ratio > 100



Larsen JT et al. Leukemia 2012; online Oct. 16

DIFFERENTIAL DIAGNOSIS BETWEEN MM AND MGUS

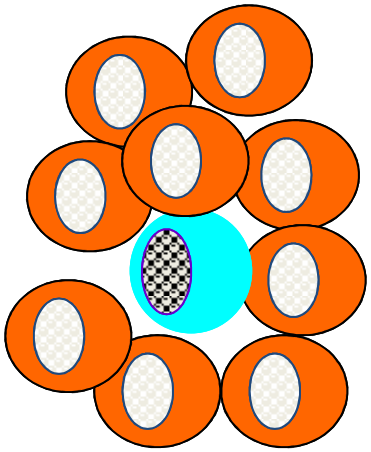
Based on the distribution of clonal and Polyclonal PC: Analysis of the PC compartment

Clonal

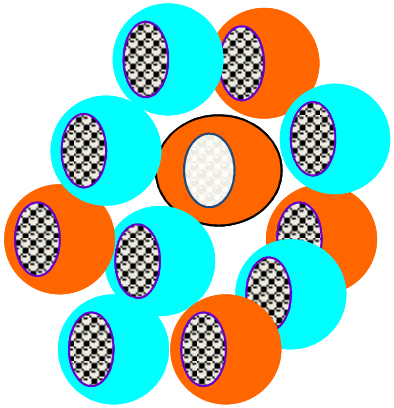
MM

Poly-Clonal

MGUS



versus



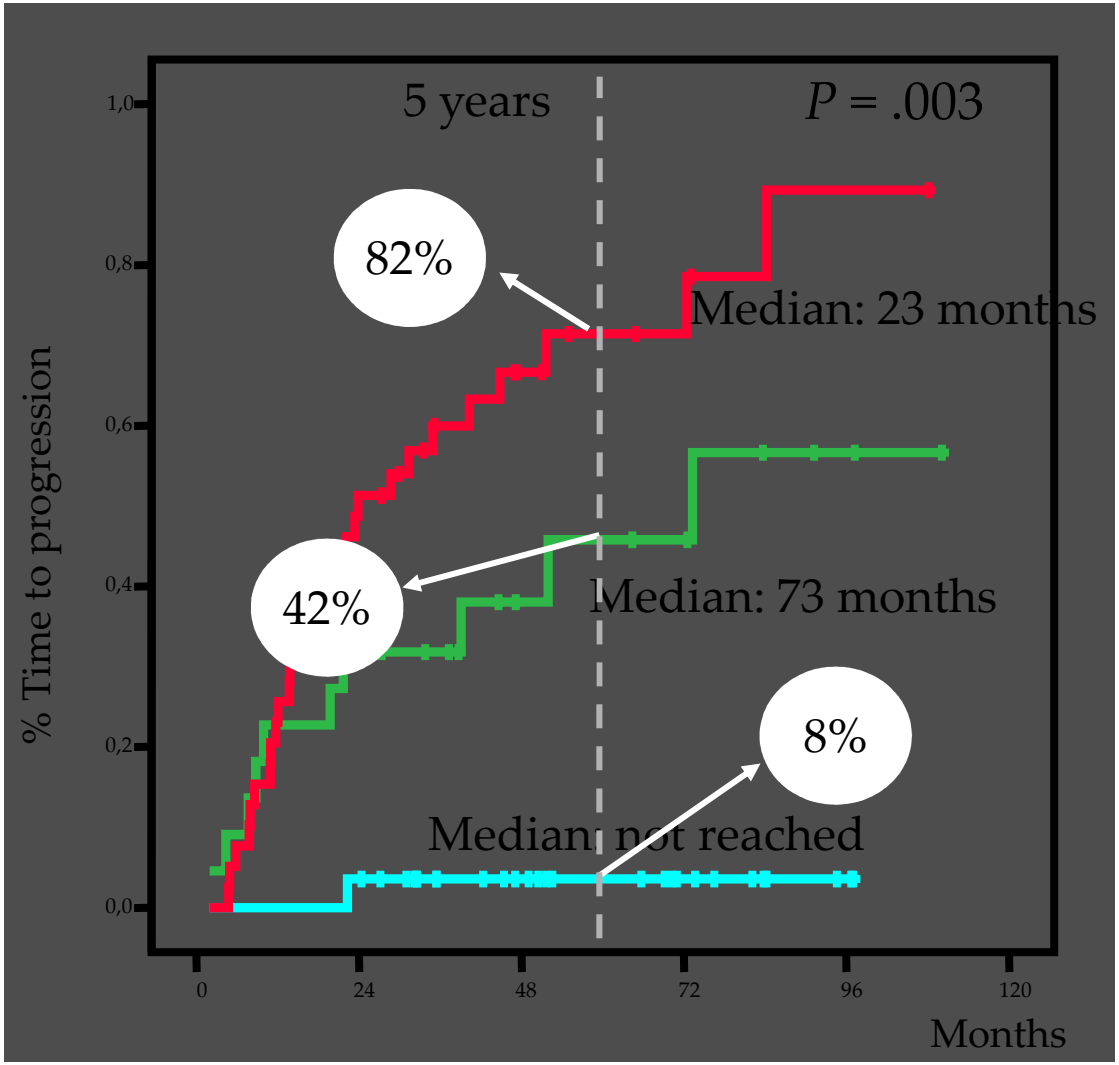
MM patients showed <5% poly-PC

Clonal & Polyclonal PC coexist

The most powerful single criteria for differential diagnosis (even in stage I MM)

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

EFFECT OF PROGNOSTIC INDEX ON TTP IN SMOLDERING MM: BY IMMUNOPHENOTYPE PLUS IMMUNOPARESIS



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> 95% aPC/BMPC or paresis
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No adverse factors
n = 28 (1 progr.)

Pérez-Persona E, et al. Blood. 2007;110:2586-2592.

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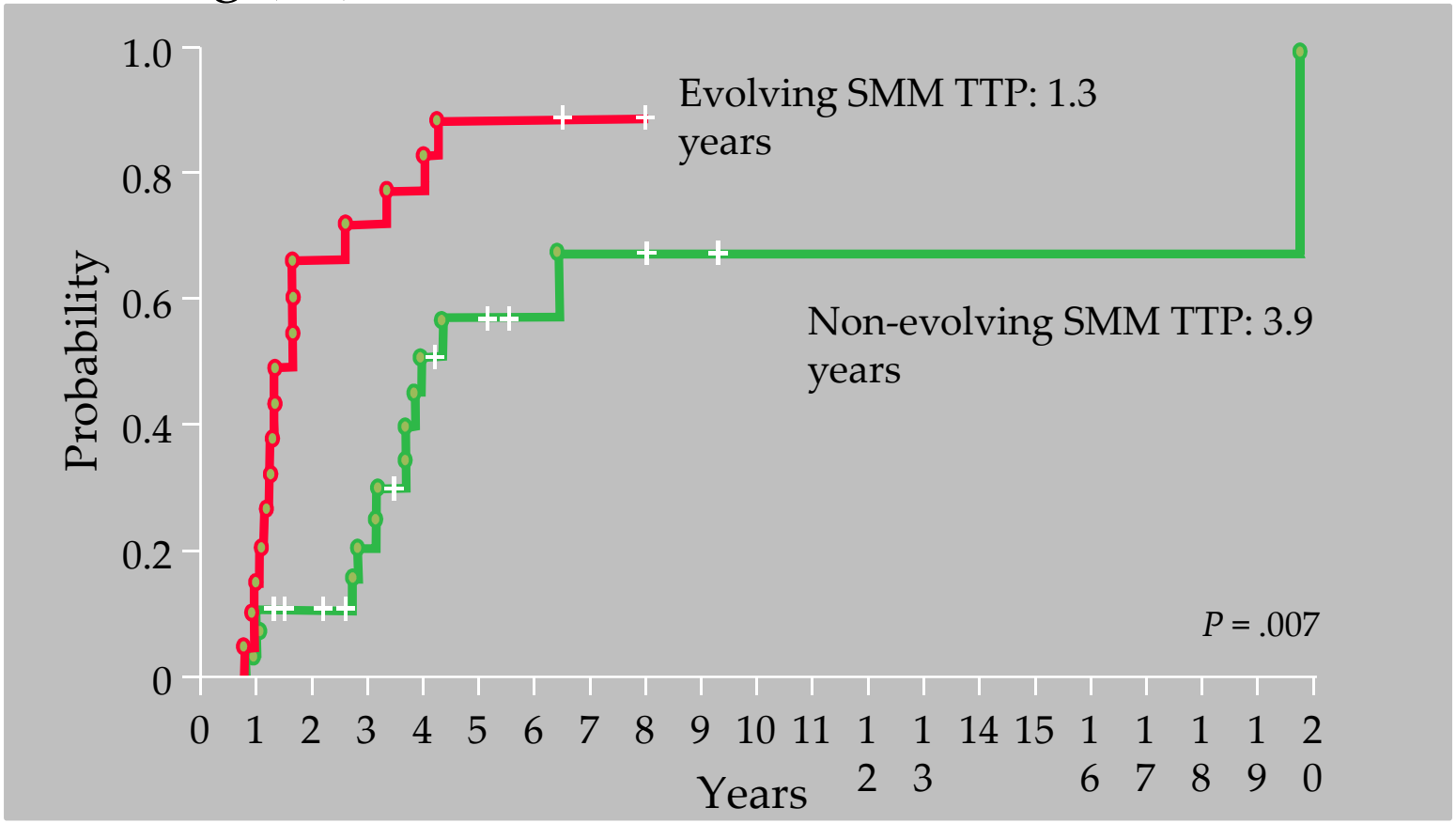
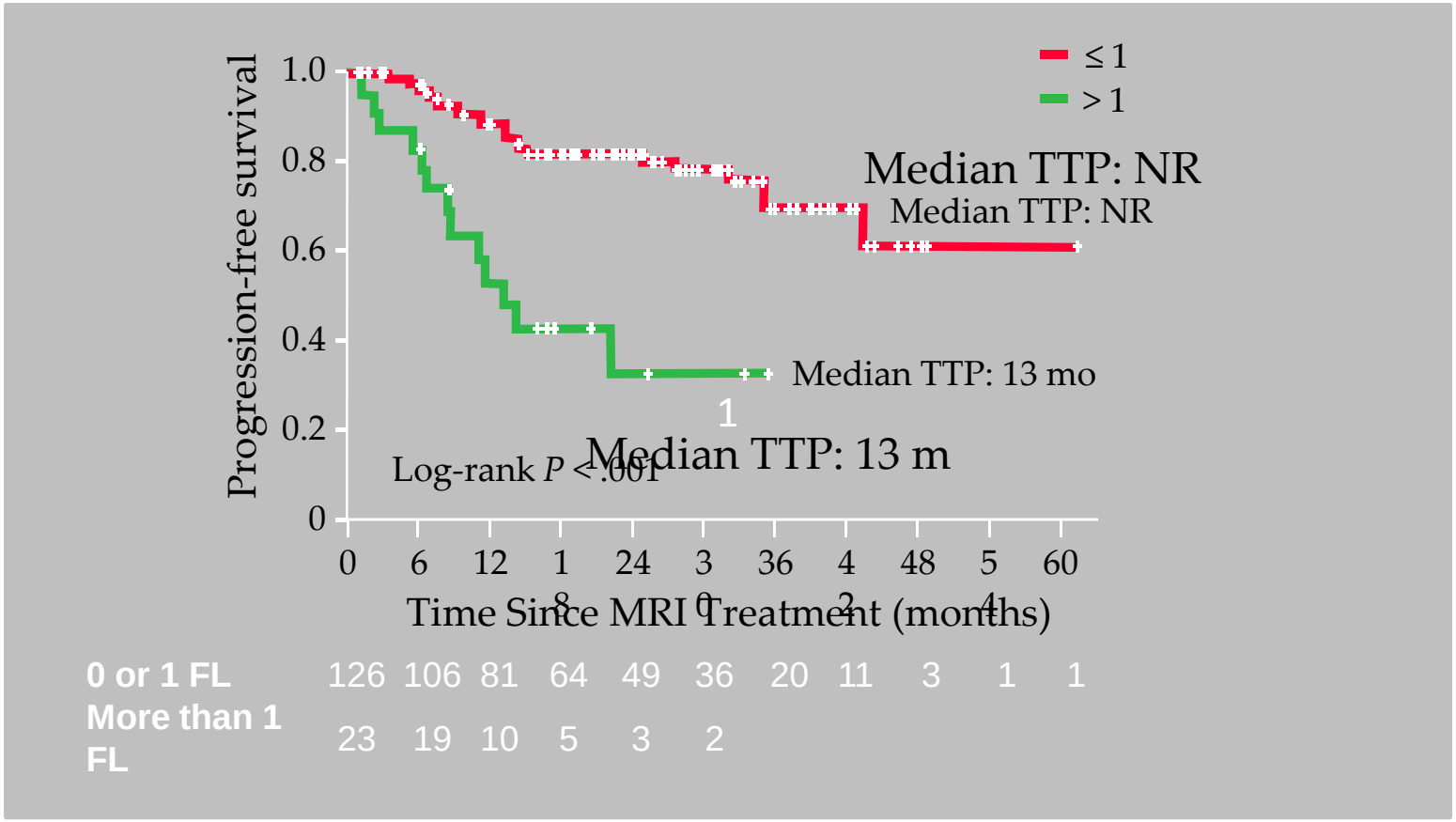


Rosiñol L, et al. Br J Haematol. 2003;123:631-636.

SMOLDERING MM: WHOLE-BODY MRI

149 patients with asymptomatic MM

Whole-body MRI: focal lesions in 28% of pts (1-20 FL/pt)

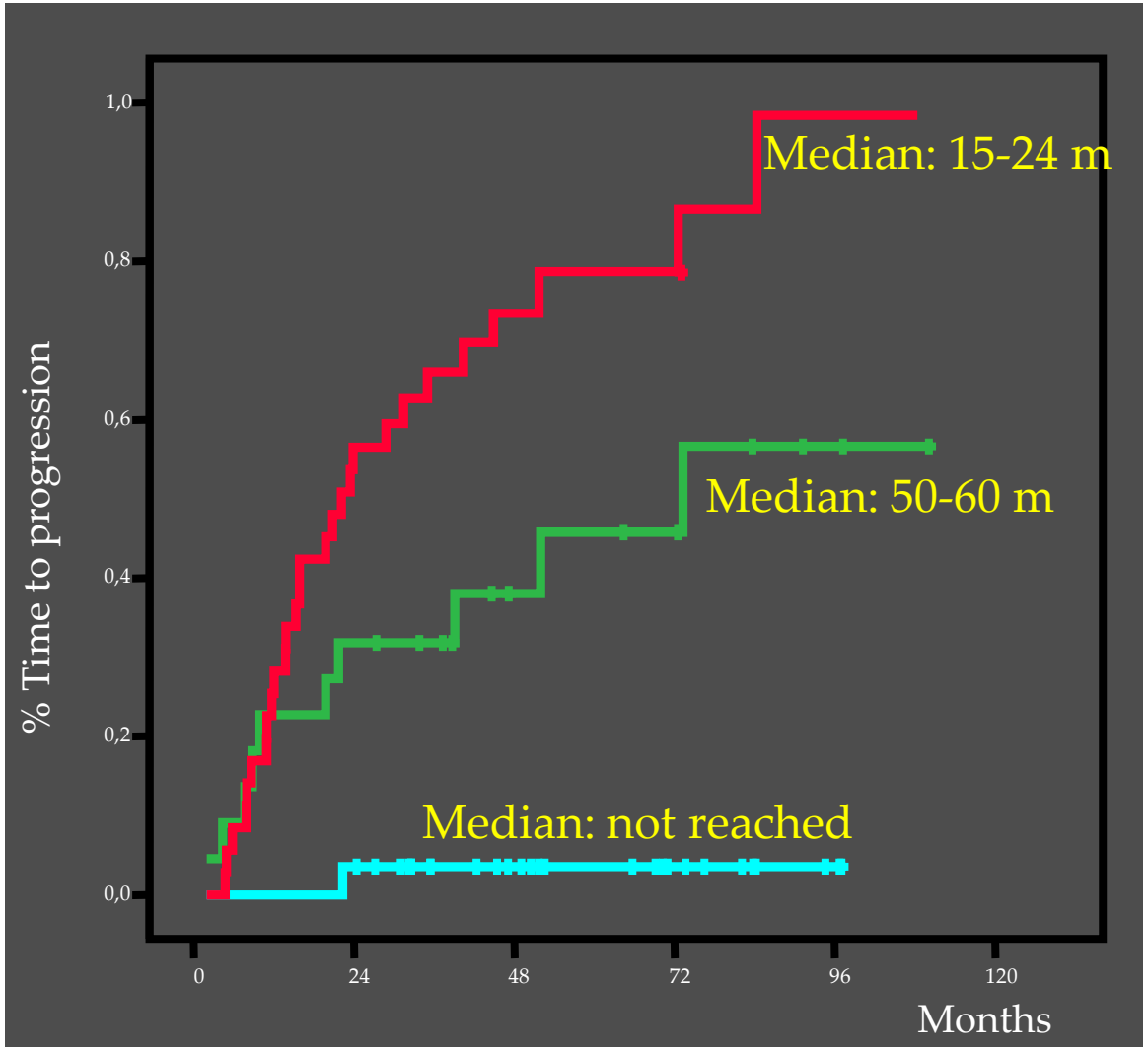


> 1 focal lesion plus diffuse pattern → adverse prognosis

Moulopoulos LA, et al. J Clin Oncol. 1995;13:251-256
Mariette X, et al. Br J Hematol. 1998;104:723-729

Hillengass J, et al. J Clin Oncol 2010;28:1606-1610.

SMOLDERING MM: RISK CATEGORIES



High Risk SMM (Early MM)

Standard Risk SMM

Low Risk SMM (MGUS)

Pérez-Persona E, et al. Blood. 2007;110:2586-2592.

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2. Prognostic factors
3. Therapeutic approaches

SMOLDERING MULTIPLE MYELOMA: MANAGEMENT

*The standard of care is **no treatment** until disease progression occurs*

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: 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: THALIDOMIDE

Regimen	n	ORR (%)	TTP	OS	Reference
Thalidomide* GK10	29	34	63% at 2 yrs	96% at 2 yrs GK11	Rajkumar SV, et al. Leukemia 2003; 17: 775-779.
Thalidomide plus Pamidronate** GK14	76	25	60% at 4 yrs	91% at 4 yrs	Barlogie B, et al. Blood. 2008;112:3122-125.
Thal+Zol vs Zol *** GK12	68	37-0%	4,3 -3,3y	74-[illegible] GK13 at 5y	Witzig TE, et al. Leukemia 2012; Epub ahead of print 20 August 2012

* 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).

***30% discontinued due to AE; 30% refused to further treatment.

Slajd 44

GK10 Thalidomide is a "novel agent"? With a nearly 10-year-old ref for this setting and use going back decades?
gkelley; 10.09.2012

GK11 The original data in these two boxes not in ref, edited to match ref.
gkelley; 10.09.2012

GK12 Changed from 55% per Table 5 in ref.
gkelley; 10.09.2012

GK13 Median PFS is listed as 45 mo in the abstract. No access to presented data, so I did not change this.
gkelley; 10.09.2012

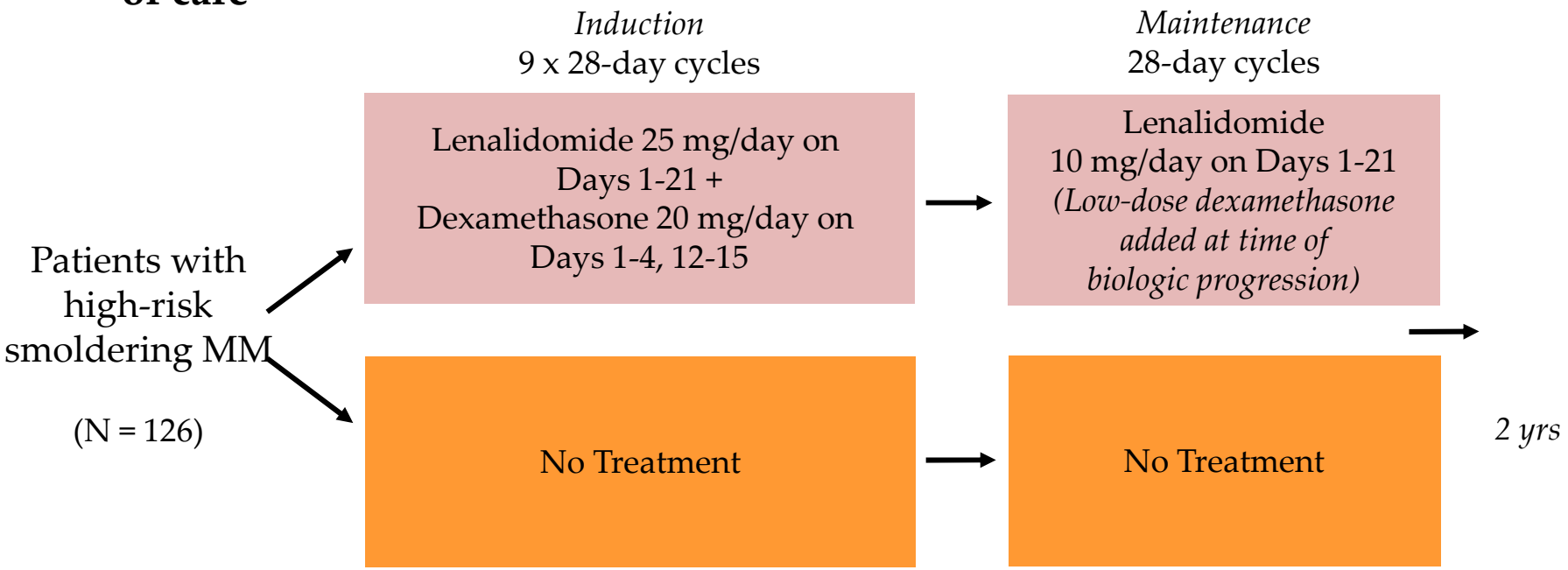
GK14 Fact-checked this row.
gkelley; 10.09.2012

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: STUDY DESIGN

- **Multicenter, open-label, randomized phase III trial**
  - **Evaluated new treatment regimen for smoldering MM vs current standard of care**



Amendment in August 2011: Stop treatment after 2 years

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

HIGH-RISK SMM (QuiRedex): LEN/DEX VS NO TREATMENT

Inclusion Criteria

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: no more than 5 years

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

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

QuiRedex: OBJECTIVES

Primary objective

- Time to progression to symptomatic MM

Secondary objectives

- Response rates
- Duration of response
- Safety and tolerability
- Progression-free survival, overall survival

External CRO: monitoring data

Independent Data Monitoring Committee: Inclusion criteria and primary endpoint

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

QuiRedex: BASELINE CHARACTERISTICS (N = 119)

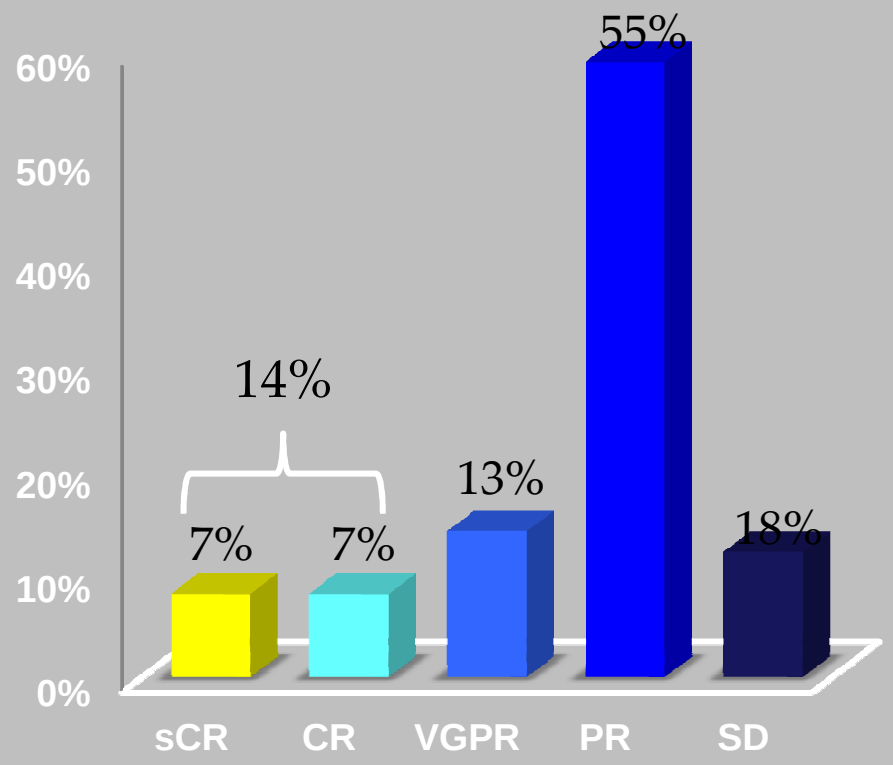
	Len/Dex (n = 57)	No Treatment (n = 62)
Mean age, yrs	61 (39-89)	65 (42-80)
IgG / IgA / light chain, %	66/32/2	66/29/5
Mean PCsBM infiltration, %	20	21
Mean serum MC, g/L	32	30
Mean urine MC, mg/dL	0.65	0.31
High PCBM+ High MC, %	47	53
aPC ≥ 95% plus immunoparesis, %	41	46
High-risk CA, % t(4;14) ± t(14;16) ± del(17p)	23.5	23.3

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

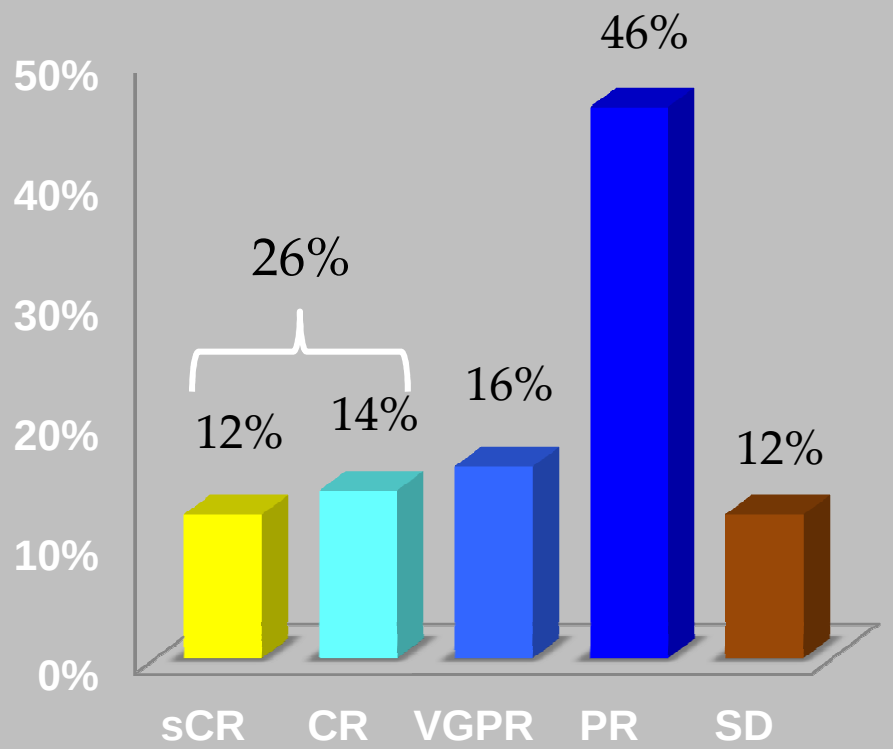
No significant differences

LENALIDOMIDE + DEX: RESPONSE RATE

On ITT(n = 57)……ORR: 82%

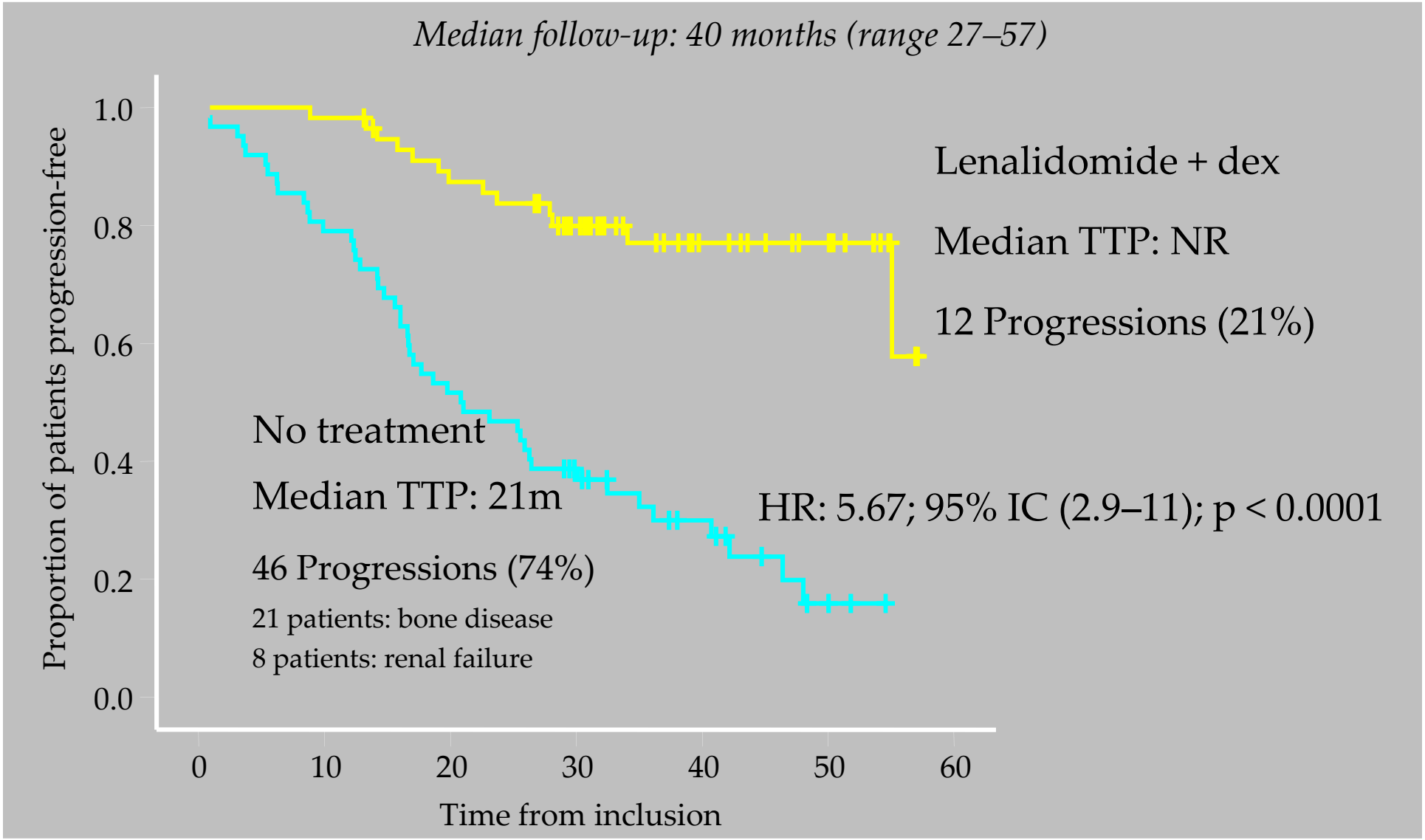


After a median of 15 maintenance cycles (2-41) (n=50)



*IMWG criteria.

LEN-DEX VS NO TREATMENT: TTP TO ACTIVE DISEASE (n = 119) ITT ANALYSIS



Mateos MV. Updated data not communicated

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

QuiRedex: TOXICITY PROFILE DURING INDUCTION

Adverse Event	Len/Dex (n = 57)		No Treatment (n = 62)
	G1-2	G3	G1-2
Anemia	28%	2%	
Neutropenia	20%	5%	
Thrombocytopenia	13%	2%	
Asthenia	20%	7%	11%
Constipation	18%	-	2%
Diarrhea	24%	2%	4%
Rash	33%	4%	
Paresthesias	5%	-	
Tremor	13%	-	2%
Infection*	46%	6%	26%
DVT**	5%		

**One infection was Grade 4*

***DVT prophylaxis with aspirin (100 mg) in 1 pt, oral anticoagulation in 1 pt with low INR levels, and none in 1 pt*

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

QuiRedex: TOXICITY PROFILE DURING INDUCTION (n:119)

Adverse Event	Len-dex (n:57)		No Treatment (n = 62)
	G1	G2	G1-2
Anemia	11 (20%)	4 (7%)	
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 (PV) 3(Ca Prost x2 & breast x1)		1 pt (MDS)

QuiRedex: TOXICITY PROFILE DURING MAINTENANCE

Adverse Event	Len/Dex (n = 50)		No Treatment (n = 62)
	G1	G2	G1-2
Anemia	11%	3%	
Neutropenia	3%	9%	
Thrombocytopenia	-	9%	
Asthenia		2%	
Paresthesias		2%	
Tremor	2%		
Infection	21%	11%	19%

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

LEN/DEX: SECOND PRIMARY MALIGNANCIES (n: 70)

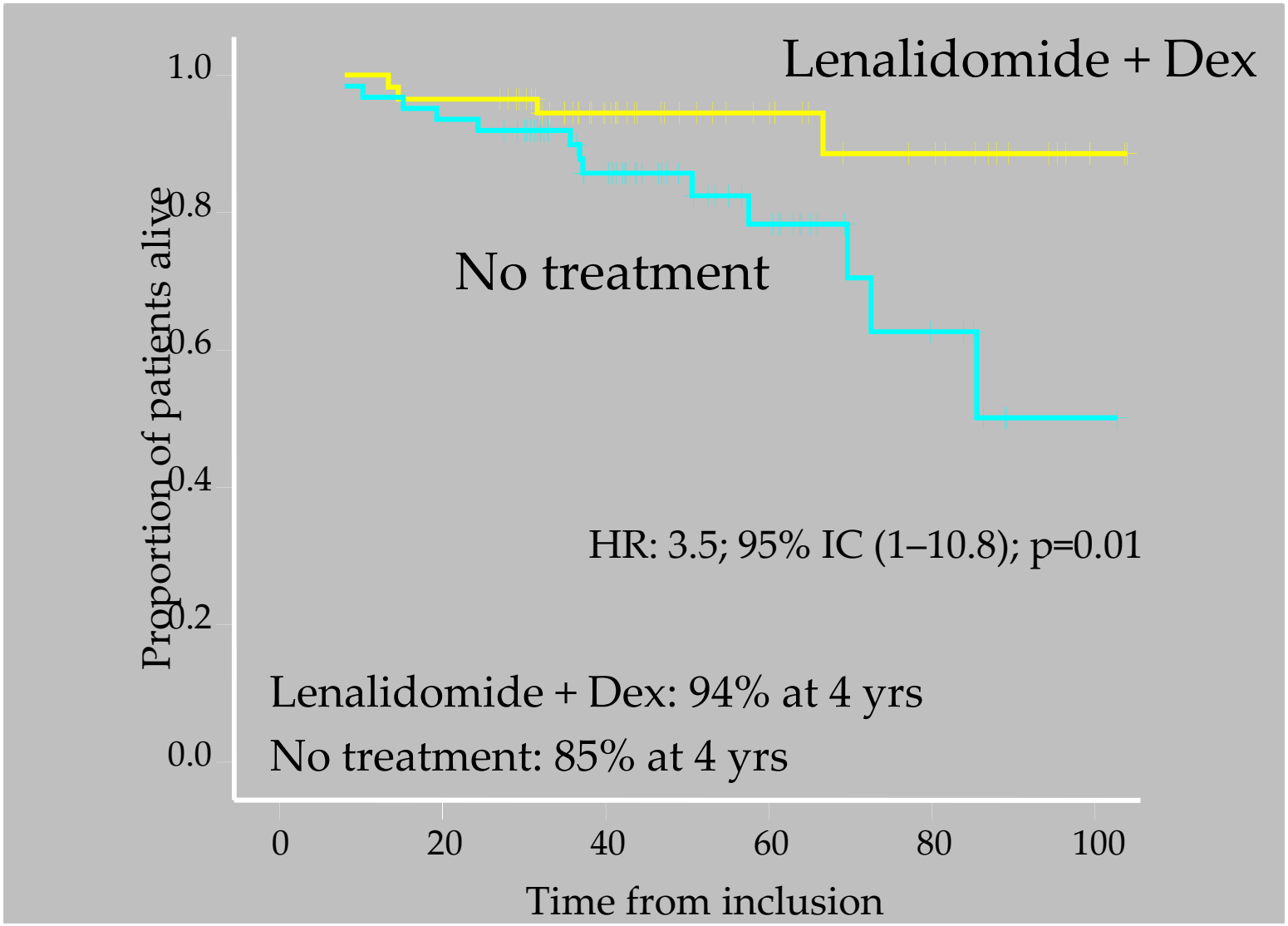
4 patients → Polycythemia vera (1); prostate cancer (2); breast (1)
1 MDS in the abstention arm

54 yrs. After induction and 10 maint. Cycles Hb: 15g/dL→JAK2+ Polycythemia Vera	We went back to the sample obtained at the moment of inclusion in the study (frozen DNA)→ JAK2+
68 yrs. 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
61 yrs. After induction and 16 maint cycles PSA x3→Prostate enlargement with compression symptoms Bx: Prostate Cancer	We went back to the medical records. Prostate hyperplasia since 2003 Follow-up by urologist

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

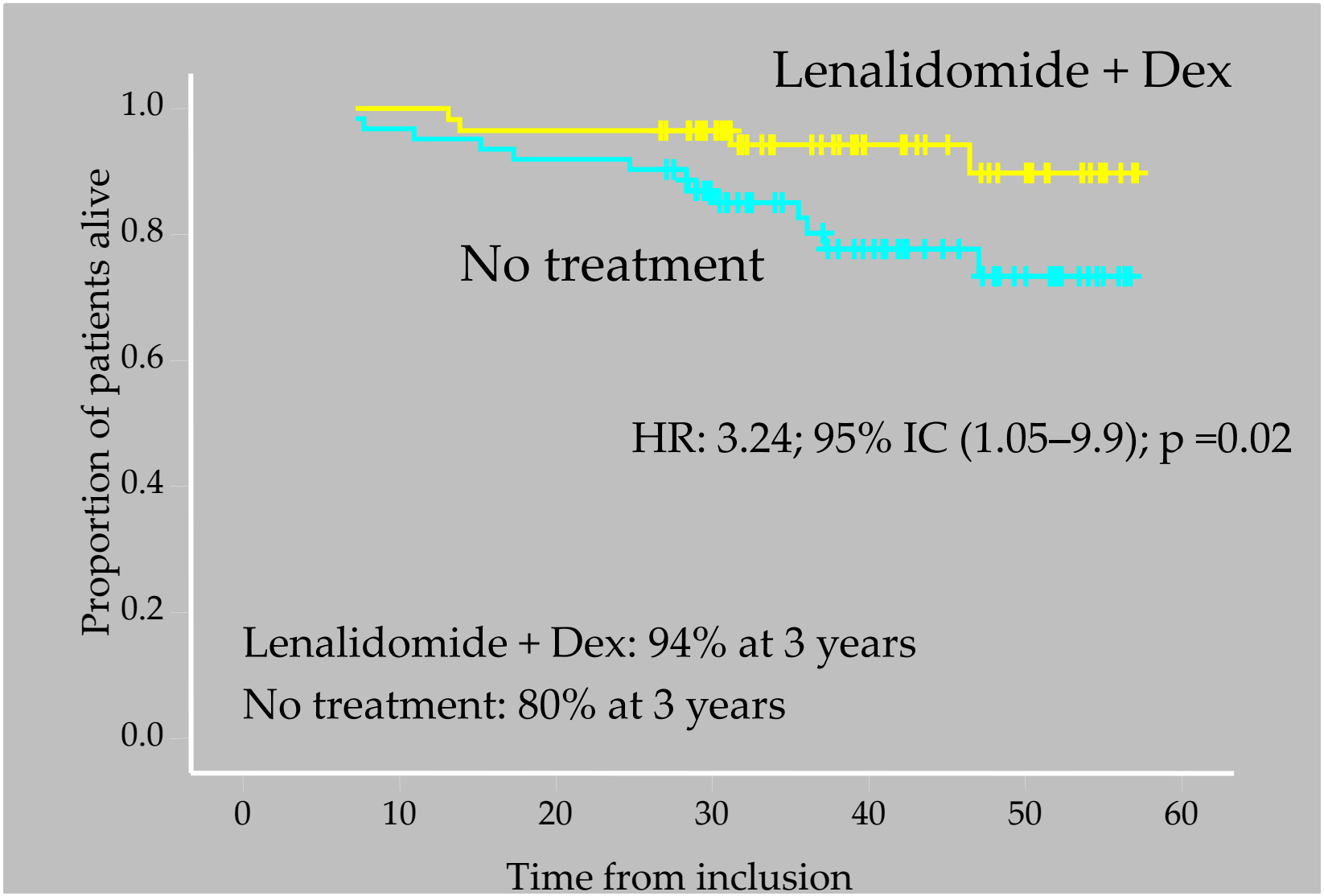
LEN-DEX VS NO TREATMENT: OS FROM DIAGNOSIS (n:119)

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



LEN-DEX VS NO TREATMENT: OS FROM INCLUSION (n:119)

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



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]**
- **Carfilzomib, lenalidomide, and dexamethasone (phase II)[5]**
- **MLN9708 and dexamethasone (phase II)[6]**

1. ClinicalTrials.gov. NCT01169337.
2. ClinicalTrials.gov. NCT01441973.
3. ClinicalTrials.gov. NCT01484275.
4. ClinicalTrials.gov. NCT01302886.
5. ClinicalTrials.gov. NCT01572480.
3. ClinicalTrials.gov. NCT01660997.