Should Some patients with Stage I MM receive treatment: NO

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Disclosures

Consultant for: Millennium, Celgene, BMS, Novartis, Merck, Onyx

Disclosures

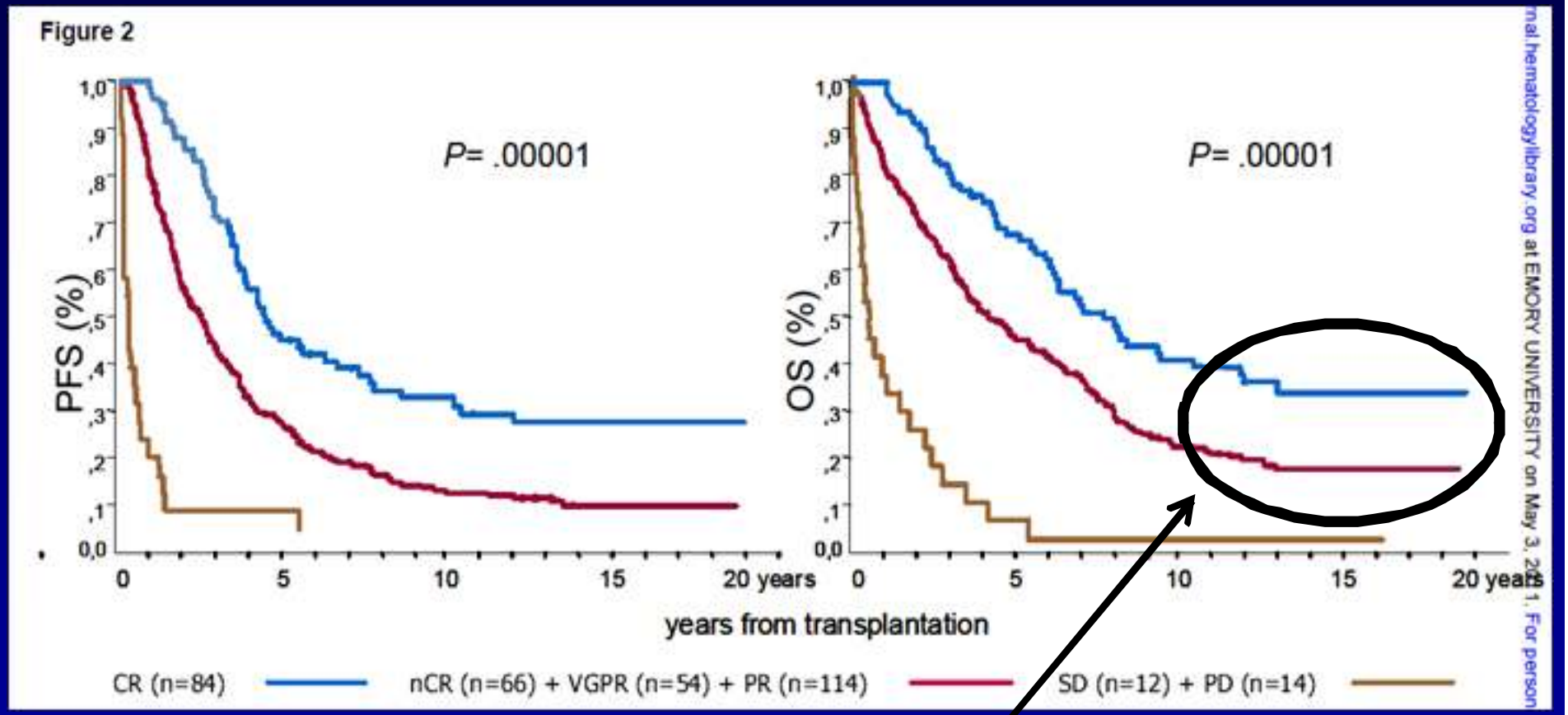
- I can’t win this Debate!!
  - You can’t beat Spain
  - You can’t beat PETHEMA
  - You can’t beat Dr Mateos

You Can’t Beat Spain

Espania

You Can’t Beat Spain…

You Can't Beat PETHEMA Investigators



Functional cure with **interferon**?????

Martinez-Lopez et al, Blood 2011

Why this debate is intrinsically unfair

VS

Dr Mateos, AKA Mrs Cruz
Internationally renown
Won awards in Many different areas
Has many different talents
Key figure in the PETHEMA Group

Dr Lonial , AKA Mr Bean
Virtually unknown
Has been to many different areas
Still trying to find a useful talent
Can't find his keys….

Will probably vote for Dr Mateos in this debate

Criteria for Diagnosis of Myeloma

MGUS

- < 3 g M spike
- < 10% plasma cells

SMM

- ≥ 3 g M spike
- ≥ 10% plasma cells

Active MM

- ≥ 10% plasma cells
- M spike +

AND

No anemia, bone lesions, normal calcium, and kidney function

AND

Anemia, bone lesions, high calcium, or abnormal kidney function

MGUS = monoclonal gammopathy of unknown significance; SMM = smoldering multiple myeloma.
Kyle et al, 2009.

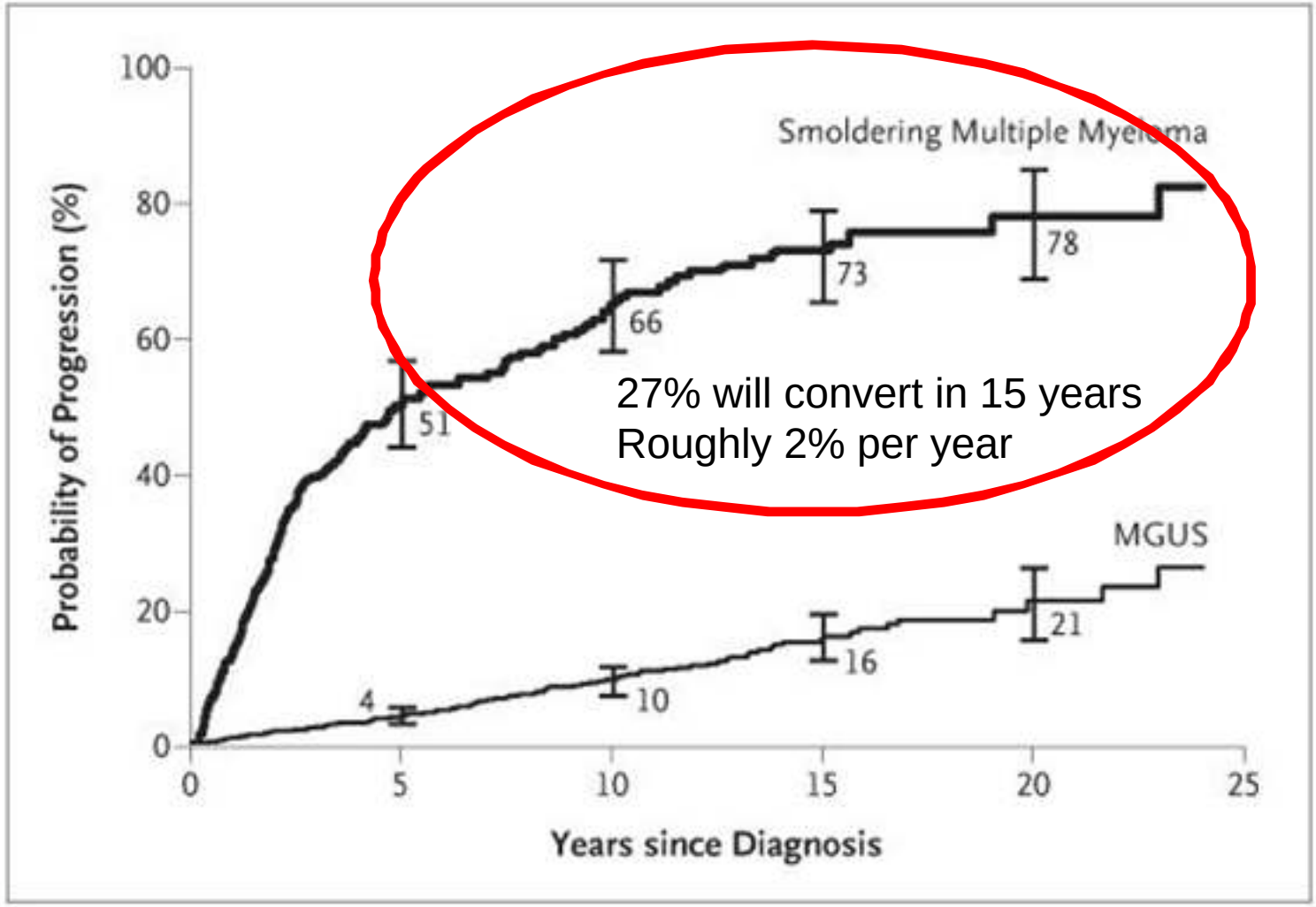
So what is the real question at hand?

Lets rephrase " Should Some patients with Stage I MM receive treatment" to say

"Should <u>all</u> patients with Asymptomatic or Smoldering MM (AMM) receive treatment."

NO….Absolutely Not

Smoldering Multiple Myeloma



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

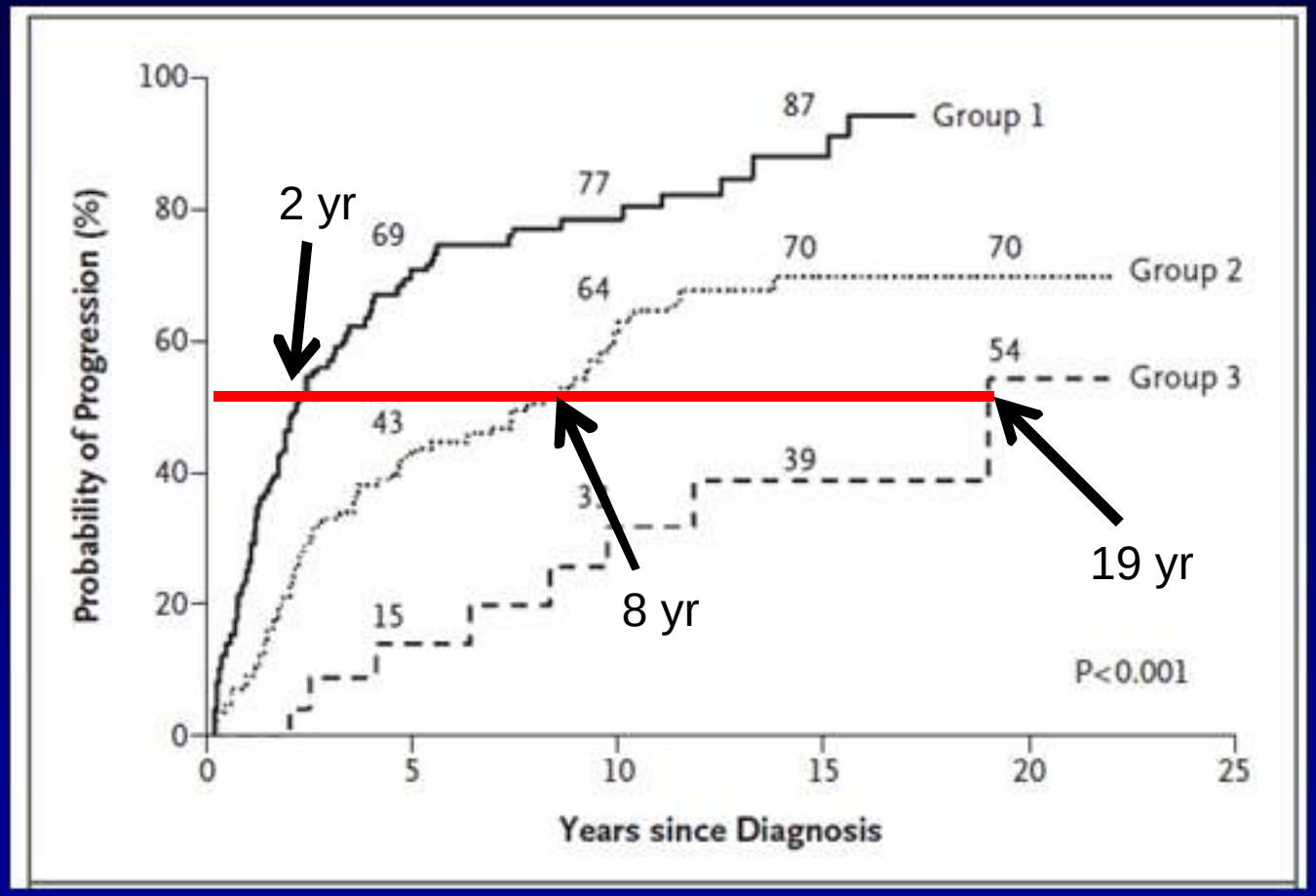
SMM "Conversion"

- Clearly not all patients are the same with SMM
- Is there a way to identify 'Some' of the patients such that…

"Should patients with high risk Asymptomatic or Smoldering MM (AMM) receive treatment as routine care?"

<u>This is the point for discussion</u>

Initial Risk Stratification



Patients with >10% plasma cells and >3gm/dl M protein are at higher risk

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

Free Light is Useful for Risk Assessment in AMM

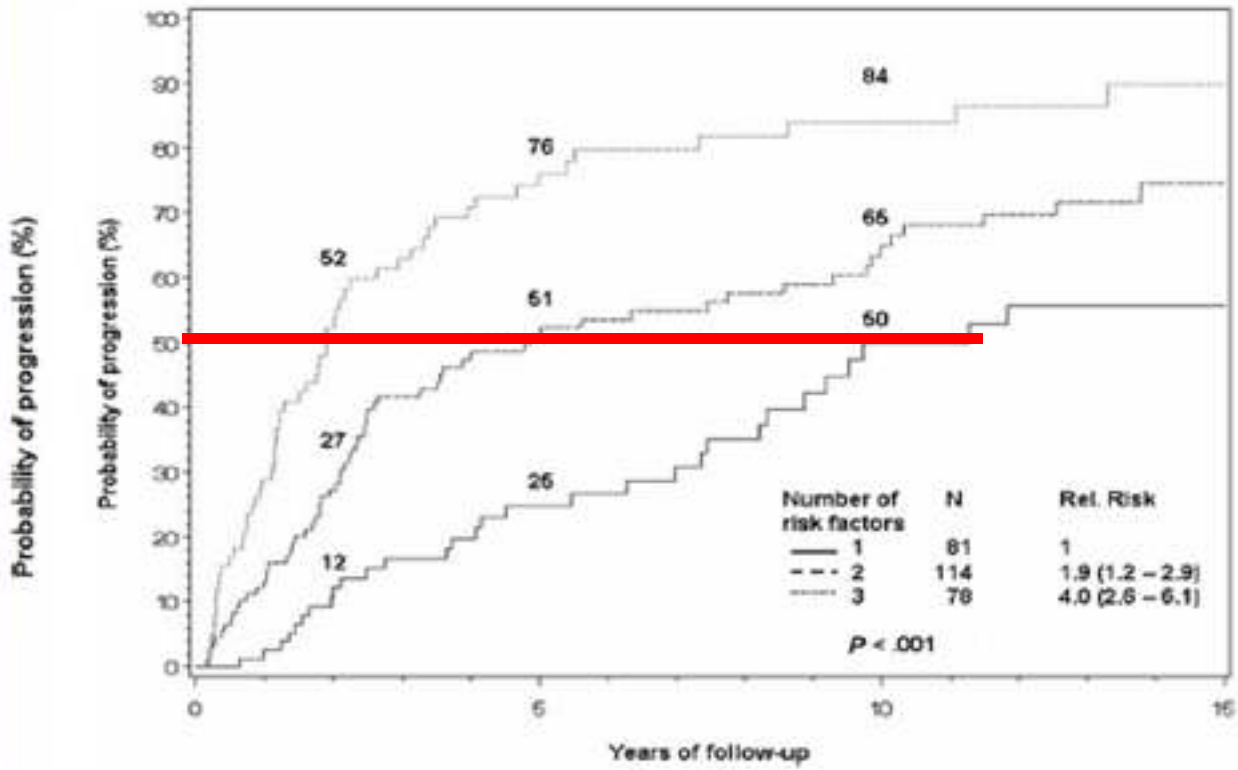


Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

Prognostic factor	Hazard ratio (95% CI)	*P*
Bone marrow plasma cells more than 10%	3.1 (1.6-6.3)	< .01
Abnormal FLC ratio less than 0.125 or more than 8	1.9 (1.3-2.7)	< .01
Serum M protein size, more than 30 g/L	1.9 (1.4-2.6)	< .01

Dispenzeri et al Blood 2008

There are patients with higher risk of progression to MM

- These patients can be defined by the use of simple testing
- There is a subset of high risk AMM patients that progress to MM on average within 2 years.

- Can we change the natural history of their disease for these patients?

What are the Elements of Effective therapy for a patient who HAS NO SYMPTOMS?

- Well tolerated treatment
- Reduces depth of disease
- Helps all biologic (genetic) subsets of disease
- Improves overall survival compared to observation

Three Themes

- Remember the lessons of the past
- First do no Harm
- Listen to our Elders

Trials with old treatments

- Use of MP was tested in 3 small trials in the past
- No improvement in outcomes was noted
- Risk of MDS among early treated patients.

The use of Thalidomide in SMM

- 3 trials have been done to date (MDACC, Mayo, UAMS)
- 2 showed longer TTP for responders to thal,
- UAMS trial showed shorter TTP for responders to thal.
- No improvement in OS

What was the Price of Early Therapy

- Toxicity of therapy was significant
- Significant PN was noted
- Median duration of thal was short in Mayo study
- "Despite our results and those reported by others, we do not recommend the use of thalidomide for SMM."
  - Detweiler-Short et al, AMJ 2010

When is PFS an acceptable endpoint

- Initial induction therapy
  - Too many subsequent therapies that impact OS
- Refractory disease
  - Limited treatment options afterwards and PFS is proven to be associated with improvement in OS

When is PFS NOT an acceptable endpoint

- Post transplant therapy
  - Induction and consolidation can impact PFS, but not always OS
- Maintenance therapy
  - PFS not always or reliably associated with OS
  - Thal story is instructive, improved PFS, mixed OS, worse QOL
- Smoldering MM
  - **PFS is meaningless among a group of patients that do not require therapy and have no symptoms**

A Multicenter, Randomised, Open-label, Phase III Study of Lenalidomide/Dexamethasone versus Therapeutic Abstention in high-risk Smoldering MM

MV Mateos, L López-Corraz, MT Hernández, J de la Rubia, JJ Lahuerta, P Giraldo, J Bargay, L Rosiñol, A Oriol, J García-Laraña, I Palomera, F de Arriba, F Prósper, ML Martino, AI Teruel, J Hernández, G Estevez, M Mariz, A Alegre, JL Guzman, N Quintana, JL García, JF San Miguel.

On behalf of **Spanish Myeloma Group (PETHEMA/GEM)**

PETHEMA

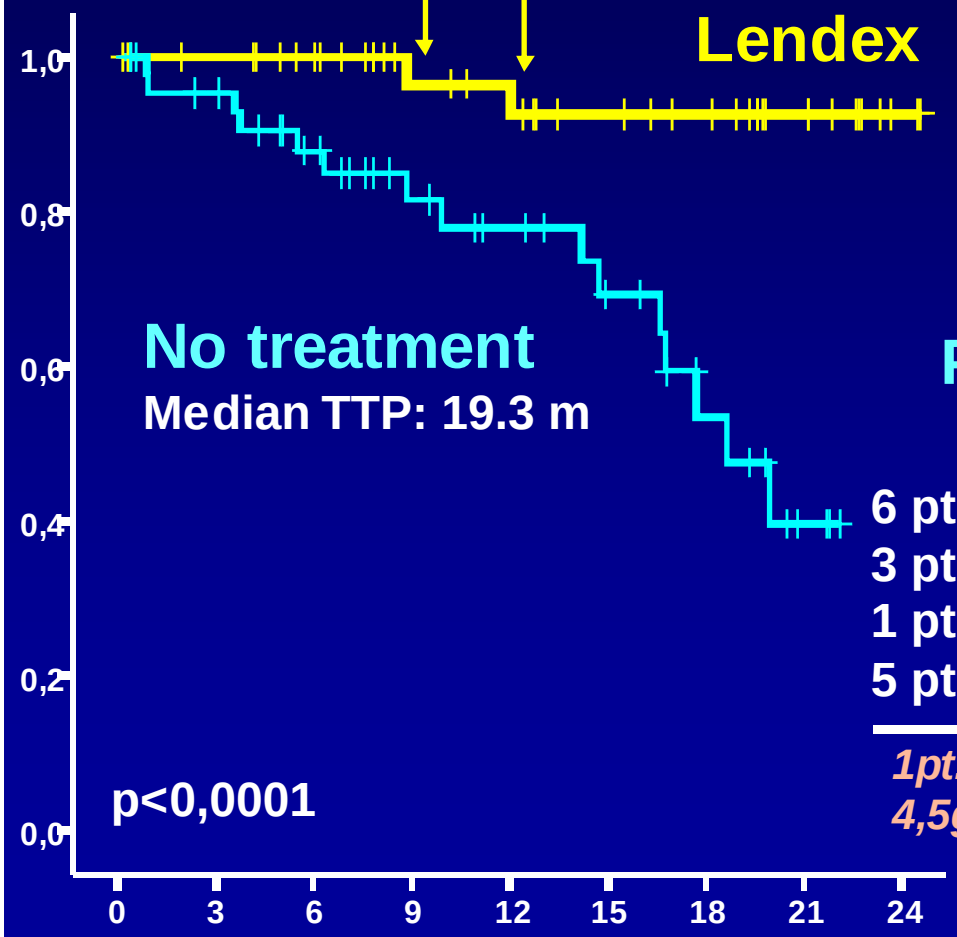
GEM

GRUPO ESPAÑOL DE MIELOMA

QuiRedex: Time to Progression (n:94)

Median follow-up: 14 m (1-24)

1 pt → IC withdrawal during the 1st cycle
1 pt → discontinuation after the 8th cycle



Progressions in abstention arm

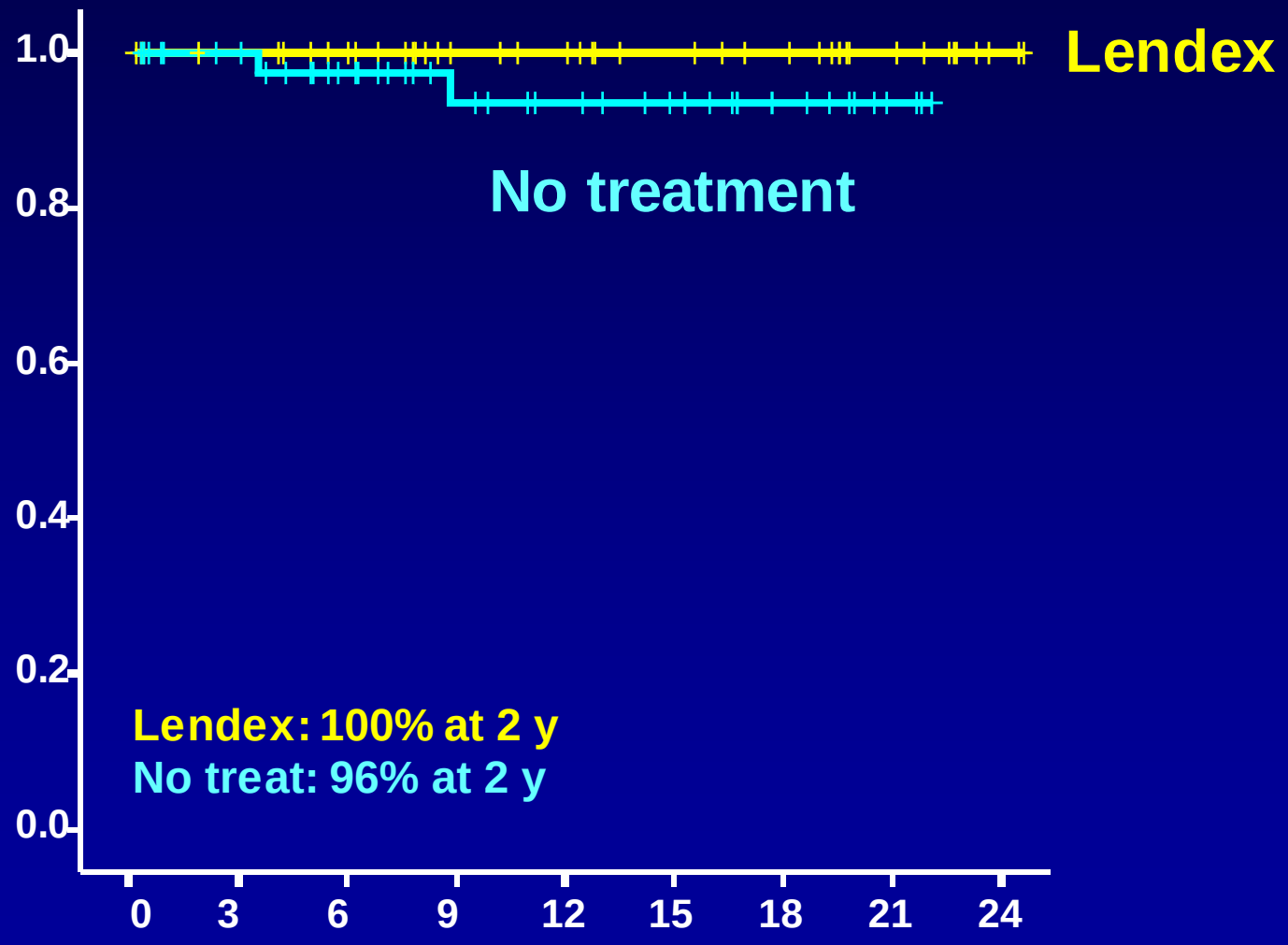
(n=16)

6 pts: lytic lesions
3 pts: lytic lesions plus anemia
1 pt: lytic lesions renal failure & hypercalcemia
5 pts: anemia

1pt: PD due to a rapid increase of BJ prot from 4,5g/24h to 9g/24h in 1 month

QuiRedex: Overall Survival (n:94)

Median follow-up: 14 m (1-24)



Lendex:Toxicity profile (n:47)

	G1-2	G3
Anemia, n (%)	8 (17%)	1 (2,6%)
Neutropenia, n (%)	10 (21%)	-
Thrombocytopenia, n (%)	5 (11%)	-
Asthenia	7 (15%)	2 (4.5%)
Anorexia	4 (9%)	
Pancreatitis	-	1 (2%)
Constipation	5 (11%)	4 (9%)
Diarrhea	3 (6%)	1 (2%)
Rash	8 (17%)	1 (2%)
Paresthesias	2 (4%)	
Infection	9 (19%)	
DVT*	3 (6%)	

Initial Review of the data

- Very impressive effect of a novel treatment approach
- Treatment not without toxicity
- Could perhaps overcome lack of OS benefit if QOL instruments showed improvement
- Dex effect?
- Preliminary encouraging data that needs further validation

Second Cancer Rates

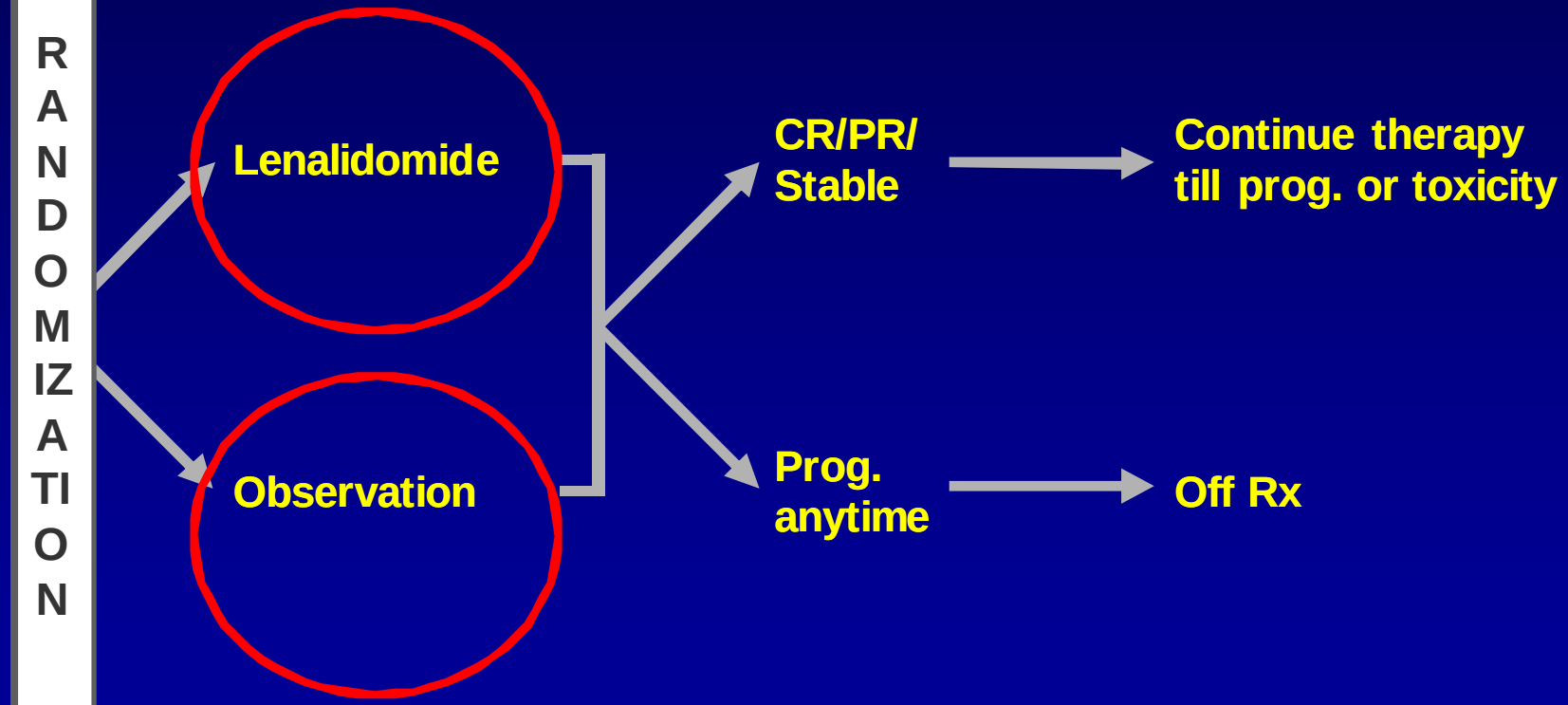
IFM			
	Len	17/299	5.5%
	Placebo	3/292	1.0%
CALGB			
	Len	15/231	6.5%
	Placebo	6/229	2.6%
MM015			
	MPR	11/355	3.1%
	Placebo	2/154	1.3%

*Numbers and % as of 2/6/11
Basal cell cancers excluded

ECOG/SWOG: Phase III – Asymptomatic Myeloma*(PI: SL)

Lenalidomide vs. observation

No Dex to isolate the effect of len



Control/standard arm

AMM Trial

- Eligible patients are high or intermediate risk AMM (Kyle et al, NEJM 2008)
- Initial Pilot study to prove safety and tolerability of the dose
- No Dexamethasone
- PBSC collection suggested for all patients
- Planned correlatives include GEP, optional MRI, Immunologic studies (SWOG)

Do No Harm

- Risk of PN, DVT, fatigue, cytopenias, and stem cell reserve cannot be underestimated.
- Need to understand what impact (if any) early intervention has on the natural history of AMM
- Showing delay in developing MM is not sufficient when treatment at progression may be compromised by initial therapy.

What do the experts say….

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management

RA Kyle[1], BGM Durie[2], SV Rajkumar[1], O Landgren[3], J Blade[4], G Merlini[5], N Kröger[6], H Einsele[7], DH Vesole[8], M Dimopoulos[9], J San Miguel[10], H Avet-Loiseau[11], R Hajek[12], WM Chen[13], KC Anderson[14], H Ludwig[15], P Sonneveld[16], S Pavlovsky[17], A Palumbo[18], PG Richardson[14], B Barlogie[19], P Greipp[1], R Vescio[2], I Turesson[20], J Westin[21] and M Boccadoro[18] on behalf of the International Myeloma Working Group[22]

Patients with smoldering myeloma with FLC ratio $\leqslant 0.125$ or $\geqslant 8$ plus $\geqslant 10\%$ plasma cells in the marrow are at high risk of progression in the first 2 years following recognition. These patients should be considered candidates for chemoprevention trials. However, off-study, observation is still the standard even in this group.

Leukemia 2010

More Experts….Our Elders..

Smoldering (Asymptomatic) Multiple Myeloma: Current Diagnostic Criteria, New Predictors of Outcome, and Follow-Up Recommendations

Joan Bladé, Meletios Dimopoulos, Laura Rosiñol, S. Vincent Rajkumar, and Robert A. Kyle

colecoxib. Until the results of additional randomized trials are available, observation remains the standard of care in SMM.

JCO 2010

You don't have to beat the Spanish if they agree with you…….

So Where does that Leave us?

- Preliminary data looks encouraging..*This I will admit..*
- Issues of toxicity of therapy and SPM need to be evaluated before this is a standard treatment for patients with AMM
- **Treatment of High risk AMM patients CANNOT be recommended for all patients at this time.**

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Golfers Against Cancer
T.J. Martell Foundation

The Leukemia & Lymphoma Society®
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And Many Others who are part of the B-cell Team