Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Luca Baldini

Fattori e modelli predittivi del rischio di progressione

Monoclonal gammohaties under «surveillance»

- MGUS is present in roughly 3-4% of the population over the age of 50 years

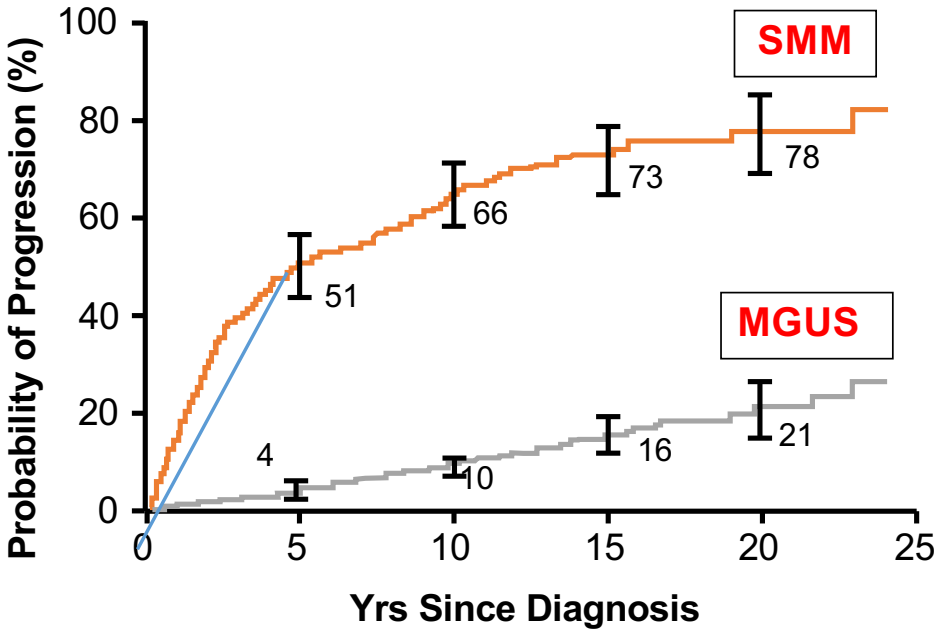
- SMM represents10-15% of all MM, with an estimated incidence of 0.5-09 cases per 100.000 persons

Rajkumar SV. Nat Rev Clin Oncol. 2011;8:479-491. Landgren O, et al. Blood. 2009;113:5412-5417. Weiss BM, et al. Blood. 2009;113:5418-5422; Kristinsson et al, N Engl J Med 2013; Ravindran et al, Blood Cancer Journal, 2016

Disease Progression in Patients with SMM and MGUS

- MGUS:
  < 1% chance per year
- SMM:

  - 10% per year during the first 5 yrs;
  - 5% per year during the following 5 years;
  - only 1% per year after 10 years



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

RISK STRATIFICATION

STRATEGY

- identify patients with high-risk of progression in symptomatic Myeloma, with the aim of preventing the organ damage

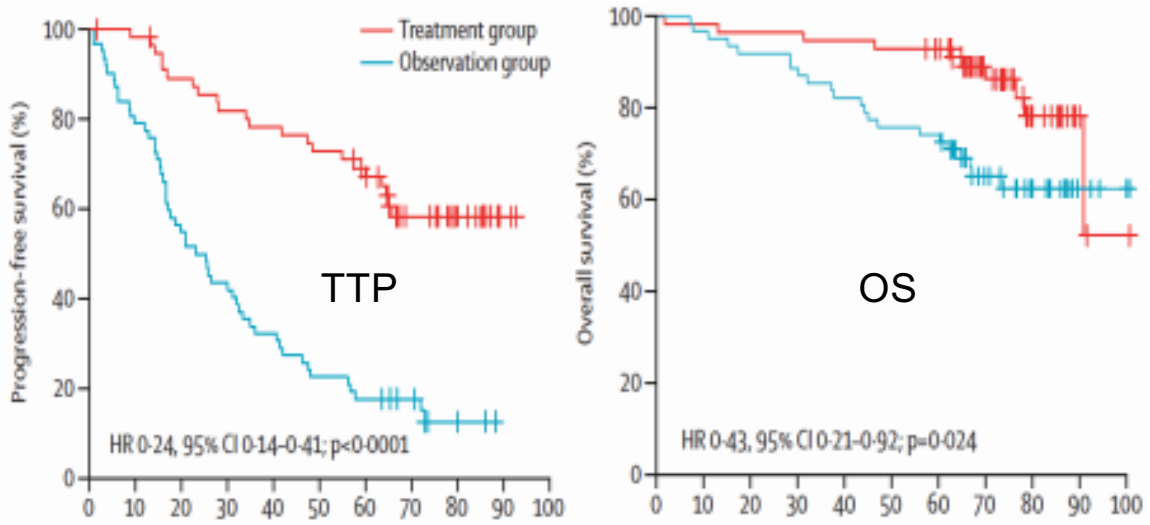
WHY?

- patient information
- increasing evidence that early treatment with new drugs for high-risk patients can lead to an improvement in TTP and, possibly, in patients' OS

Why is risk stratification important?

Len/dex (9+24 cycles)

QuiRedex phase 3 trial: Rd vs observation in high-risk SMM **(119 pts, median follow-up of 73 months)**



Spanish Model and Mayo Model identifying only high risk

Mateos et al, NEJM, 2013

Lenalidomide

E3A06 phase 3 trial: R vs observation in intermediate and high-risk SMM
(182 pts, median follow-up of 71 months)

ECOG Phase trial (E3A06)			
PFS	Len	Obs	HR
1 year	98%	89%	
2 year	93%	76%	
3 year	91%	66%	0.28 P<0.001

BMPC ≥ 10% and abnormal FLCr (< 0.26 or >1.65)

Lonial et al. J Clin Oncol 37, 2019 (suppl; abstr 8001)

GEM-CESAR trial in High-Risk SMM

90 patients: 60 high-risk SMM (according to Spanish and/or Mayo Clinic prognostic scoring) and 30 ultra-HR (according IMWG 2014 criteria)

6 cycles of induction with KRd, consolidation with ASCT followed by 2 cycles of KRd, and maintenance with Rd for 2 years

After ASCT consolidation: ORR was 100%;
CR: 78% in HR-SMM e 71% in UHR-SMM
MRD: 65% in HR-SMM e 53% in UHR-SMM

After 1 year of maintenance therapy (n=40):

- ≥CR rate: 85%
- VGPR: 10%
- PR: 5%
- MRD negativity rate: 68 %

Mateos et al, EHA, 2019

ONGOING TRIALS IN SMM

NCT number	Design	Arm(s)	N	Participants	Current status	Expected date
NCT02916771	Phase II single-arm	Ixazomib+LD	28	High-risk	Recruiting	2020-04
NCT02903381	Phase II single-arm	Nivolumab+LD	41	High-risk	Suspended	2020-06
NCT02279394	Phase II single-arm	Elotuzumab+LD	51	High-risk	Active	2020-01
NCT03301220	Phase III RCT	Daratumumab SC vs monitoring	360	High-risk	Recruiting	2021-12
NCT02415413	Phase II single-arm	Carfilzomib+LD	90	High-risk	Active	2020-05
NCT02943473	Phase II single-arm	Ibrutinib	36	High-risk	Recruiting	2023-12
NCT01484275	Phase II RCT	Siltuximab vs placebo	87	High-risk	Active	2019-08
NCT03236428	Phase II single-arm	Daratumumab	40	Low-risk	Recruiting	2020-08
NCT02697383	Phase I single-arm	Ixazomib+D	14	High-risk	Active	2019-02
NCT03289299	Phase II single-arm	Carfilzomib+Daratumumab+LD	83	High-risk	Recruiting	2022-06
NCT02886065	Phase I controlled	PVX-410+Citarinostat vs PVX-410 +Citarinostat+L	20	High-risk	Recruiting	2021-05
NCT02603887	Phase I single-arm	Pembrolizumab	13	Intermediate- and high-risk	Active	2020-07
NCT01169337	Phase II/III RCT	L vs observation	180	High-risk	Active	2020-03
NCT03631043	Phase I single-arm	Personalized vaccine	30	Intermediate- and high-risk	Not yet recruiting	2022-09
NCT02784483	Phase I single-arm	Atezolizumab	20	High-risk	Suspended	2018-12
NCT03673826	Phase II RCT	Carfilzomib+LD vs LD	120	High-risk	Not yet recruiting	2025-10
NCT02960555	Phase II single-arm	Isatuximab	61	High-risk	Recruiting	2022-02
NCT01572480	Phase II single-arm	Carfilzomib+LD	53	High-risk	Recruiting	2022-06
NCT03591614	Phase I single-arm	DKK1 vaccine	18	NA	Not yet recruiting	2019-08
NCT02492750	Phase I/II RCT	LD+anakinra vs LD+placebo	120	High-risk	Suspended	2020-07

Abbreviations: SMM, smoldering multiple myeloma; L, lenalidomide; D, dexamethasone; RCT, randomized controlled trial.

Unfortunately, no single pathological or molecular feature (biomarker) is, at the moment, available to distinguish patients with who have only clonal premalignant plasma cells (MGUS or SMM) from those with clonal malignant myeloma cells producing CRAB features

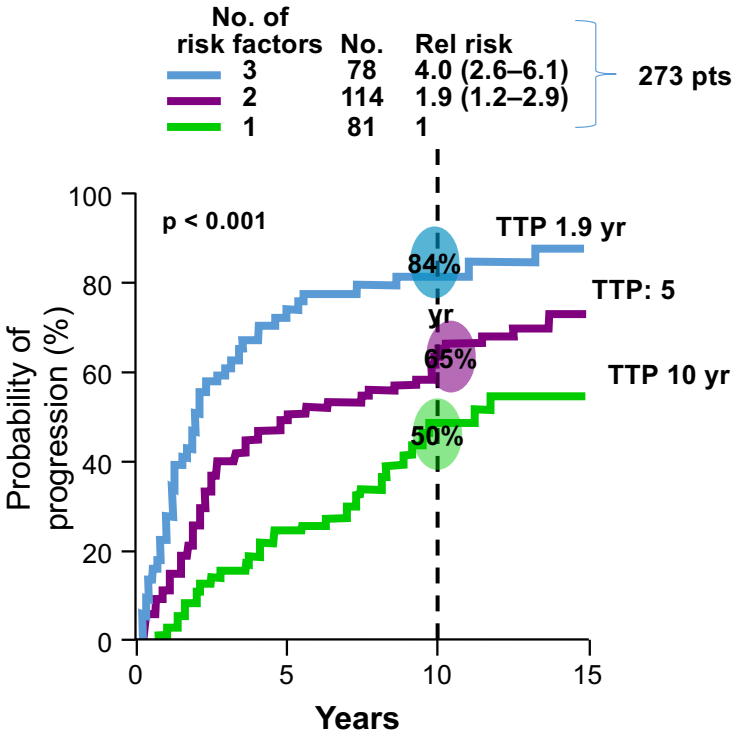
Variables identififying “high-risk”SMM (~ 50% evolution at 2 years)

- Tumor burden: serum MC > 3 g/dl + BMPC >10% and different cut-off
- Abnormal sFLC: out or between 0.125 and 8 or ratio involved/uninvolved sFLC ≥ 100 (renal involvement)
- Aberrant Bone Marrow Plasma Cells by immunophenotype (≥ 95%)
- Cytogenetic abnormalities: t(4:14), del 17p, gains of 1q24, hyperdiplody, 4 genes – RRM2 (2p25-p24), DTL (1q32),
- Plasma Cells Proliferation Index
- Pheripheral blood circulating plasma cells (> $5x10^6$/L by means CyIg CFM)
- Immunoparesis (> 25% decrease in one or both uninvolved srum Ig)
- Serum MC evolution (evolving MM): MC or FLC increase of at least 10% within first 6 mos or annual increase for 3 years
- Abnormal MR Imaging studies (MRI): newly dectected FLs or progressive FL
- Positive PET/CT whitout underlying osteolytic bone lesions

SMM: risk stratification

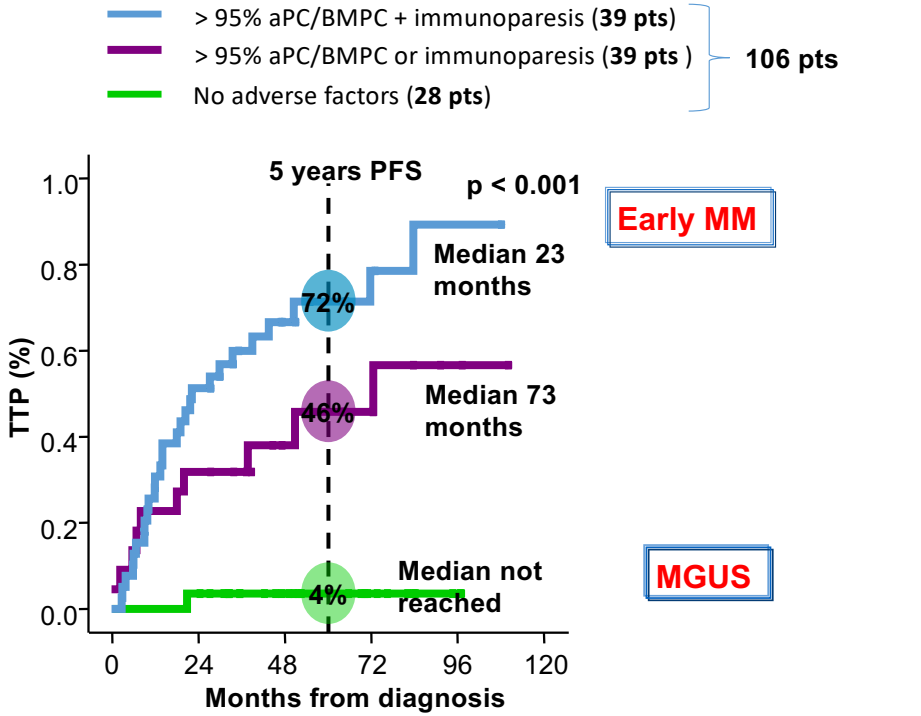
Mayo Clinic

- Serum M-protein > 3 g/dL
- BM plasma cell ≥ 10%
- Serum FLC ratio < 0.125 or > 8



Spanish PETHEMA

- Ab PC phenotype: CD19- and/or CD45-, CD56+, CD38 ↓
- Immunoparesis: serum uninvolved Ig reduction 25%



Kyle RA, et al. N Engl J Med. 2007;356:2582-90; Perez-Persona E, et al. Blood. 2007;110:2586-92.

Risk-Stratification Models: Discordance

PETHEMA risk-stratification models[1]

- 77 prospectively identified SMM pts were stratified using both models
- Significant discordance was observed between the 2 models with only 22/77 pts overlapping (28.6% concordance)
- Discordance was observed for all comparisons
  - Low vs. high: $P < 0.0001$
  - Low vs. non-low: $P = 0.0007$
  - High vs. non-high: $P < 0.0001$

SMM Risk-Stratification Model	Low Risk	Medium Risk	High Risk
Mayo Classification[1-3] (n)	38	35	4
PETHEMA Classification[1,4] (n)	17	22	38
Concordance (%)	**40**	**NR**	**19**

NR: not reported; PETHEMA: Programa para el Estudio de la Terapéutica en Hemopatía Malignas; pts: patients; SMM: smoldering multiple myeloma.

1. Cherry BM. *Leuk Lymphoma.* 2013. [Epub ahead of print]. 2. Rajkumar SV. *Blood*. 2005;106:812-817. 3. Dispenzieri A. *Blood*. 2008;111:785-789. 4. Pérez-Persona E. *Blood*

BIOMARKER OF EVOLUTION

- The IMWG recognises that biomarkers associated with a risk of progression of SMM to MM of at least 80% within 2 years can be added to the diagnostic criteria in the future.

- This biomarkers have to be substantiated by more than two independent studies

«Myeloma-Defining Events (MDE)»

Lancet Oncol 2014; 15: e538–48

«Myeloma-Defining Events (MDE)»
according to IMWG citeria 2016

- BMPc percentage ≥ 60% (2-3%)
- FLC imbalance In/Unin ≥100 (15%)
- MRI pattern (>1 focal lesion) (15%)

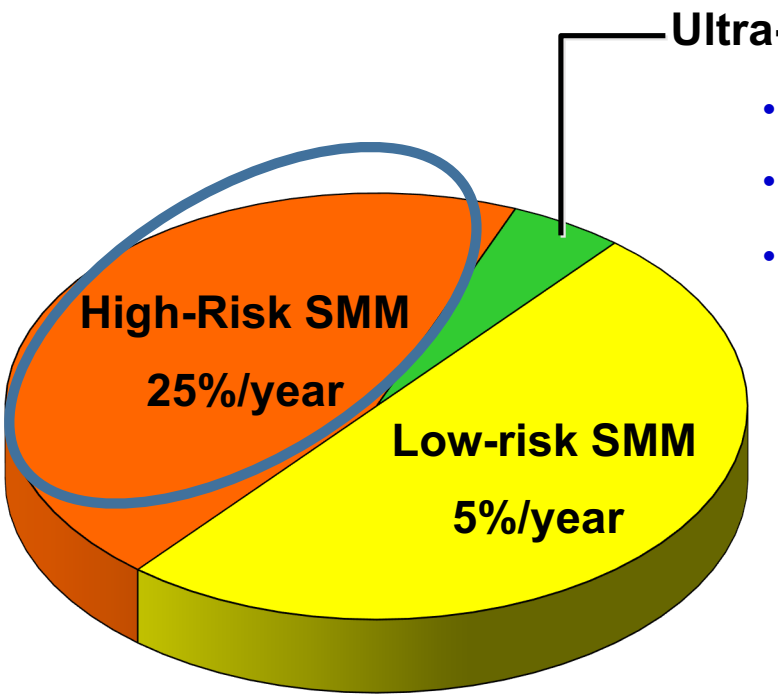
Lancet Oncol 2014; 15: e538–48

Ultra High Risk SMM = Active Myeloma

- **S (60%)**
- **Li (Light chains I/U >100)**
- **M (MRI > 1 focal lesion)**
- **C (calcium elevation)**
- **R (renal insufficiency)**
- **A (anemia)**
- **B (bone disease)**

SMOLDERING MULTIPLE MYELOMA

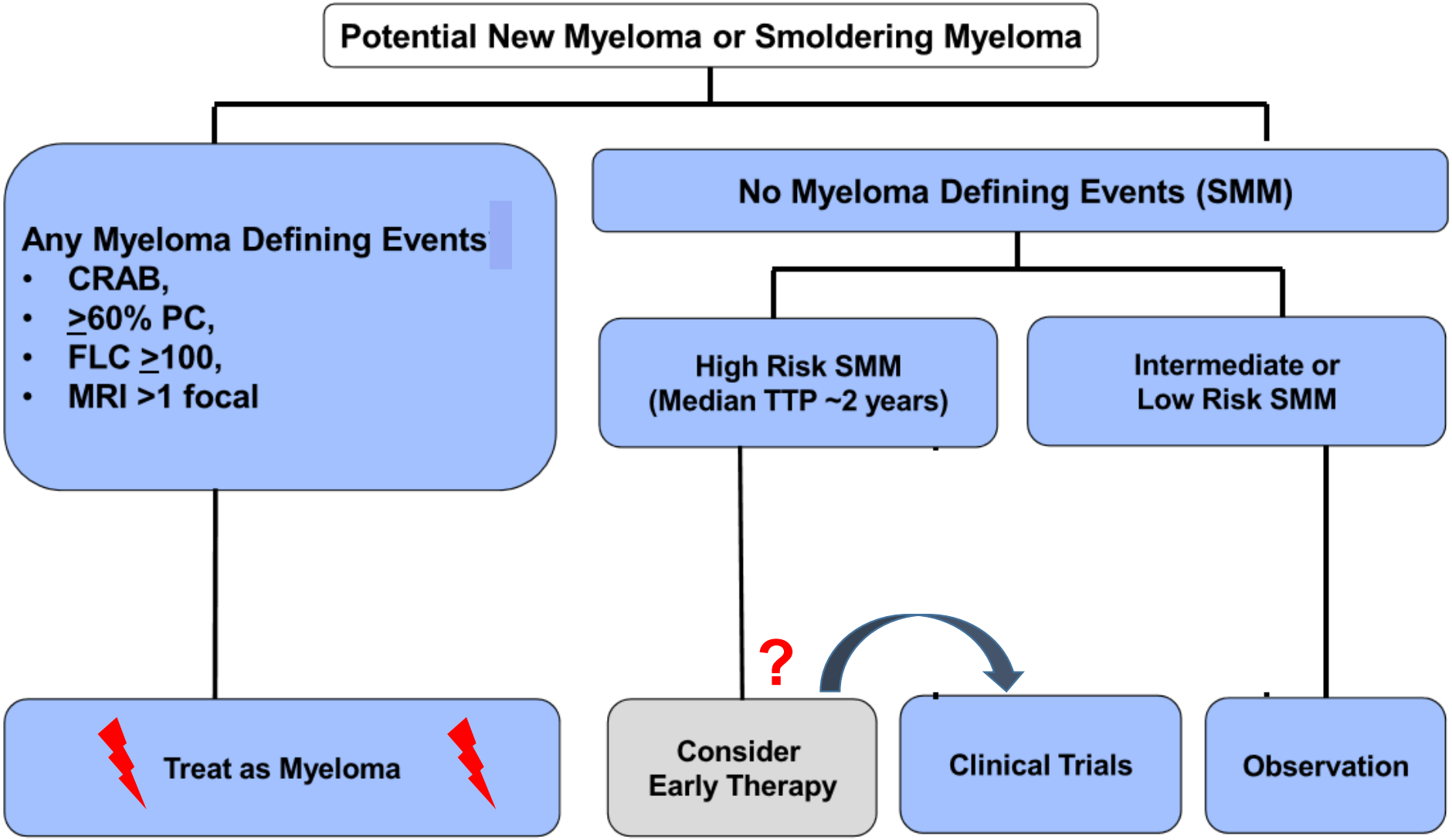
(13-15% of MM)



Ultra-High Risk (50%/year: ~15%of SMM)

- **≥60% BMPC**
- **FLCr ≥100**
- **≥1 MRI focal lesions**

Ravindran et al, Blood Cancer Journal, 2016


Potential New Myeloma or Smoldering Myeloma
Any Myeloma Defining Events
• CRAB,
• ≥60% PC,
• FLC ≥100,
• MRI >1 focal
No Myeloma Defining Events (SMM)
High Risk SMM
(Median TTP ~2 years)
Intermediate or
Low Risk SMM
?
Treat as Myeloma
Consider
Early Therapy
Clinical Trials
Observation

Modelli di stratificazione del rischio di progressione nel SMM

	Modello Mayo Clinic		Modello PETHEMA		Modello Heidelberg	Modello SWOG	Modello Danese	Modello evolutivo Mayo clinic	Modello evolutivo Spagnolo
FR	PC≥ 10% CM>3g/dL sFLCr<0,125->8 (276 pts)		PC>95% Immunop. (93 pts)		Massa tumorale (Mayo Clinic) t(4;14), del17p, or þ1q (248 pts)	CM>2 g/dl FLCc>25 mg/dL GEP risk>-0,26 (331 pts)	CM>3 g/dL Immunop. (311 pts)	eMP eHb PC>20% (190 pts)	EP (2 p) CM>3g/dL (1p) Immunop. (1p) (207 pts)
	TP5	**TP**	**TP5**	**TP**	**TP a 3 anni**	**TP a 2 anni**	**TP a 3 anni**	**m TP**	**TP a 2 anni**
0			4 %	NR		30%	5%	12,3 anni	2.4%
1	25%	10 aa	46%	6 aa	MTb+CAb 15%	29%	21%	4,2 anni	31%
2	51%	5 aa	72%	1,9 aa	MTb+CAa 42%	71%	50%	2,8 anni	52%
3	76%	1,9 aa			MTa+CAb 64%			1 an	80%
4					MTb+CAa 55%				

FR = fattori di rischio, PC = plasmacellule midollari clonali; CM = componente monoclonale; TP5 = tempo mediano alla progressione a 5 anni;GEP = *gene expression profiling*; Immunop. = immunoparesi; eMP = evolutività livelli proteina monoclonale; evolutività livelli Hb; NR = non riportato;TP = tempo mediano alla progressione; MTb = bassa massa tumorale; MTa = alta massa tumorale; CAb = citogenetica a basso rischio; CAa = citogenetica ad alto rischio; EP = pattern evolutivo.

Dispenzieri A, et al. Leukemia. 2009

Perez-Personam E, et al. Blood. 2007

Neben K, et al. J Clin Oncol. 2013

Kahn R, et al. Haematologica. 2015

Sørrig R, et al. Eur J Haematol. 2016

Ravi P, et al. Blood Cancer J. 2016

Fernández de Larrea C,et al. ASH Abs. 2014

REVISED RISK STRATIFICATION: MAYO GROUP
"20/20/20 SCORING"

VARIABLES

- 1 BMPC >20%
- sMC > 20 g/L
- FLCr > 20

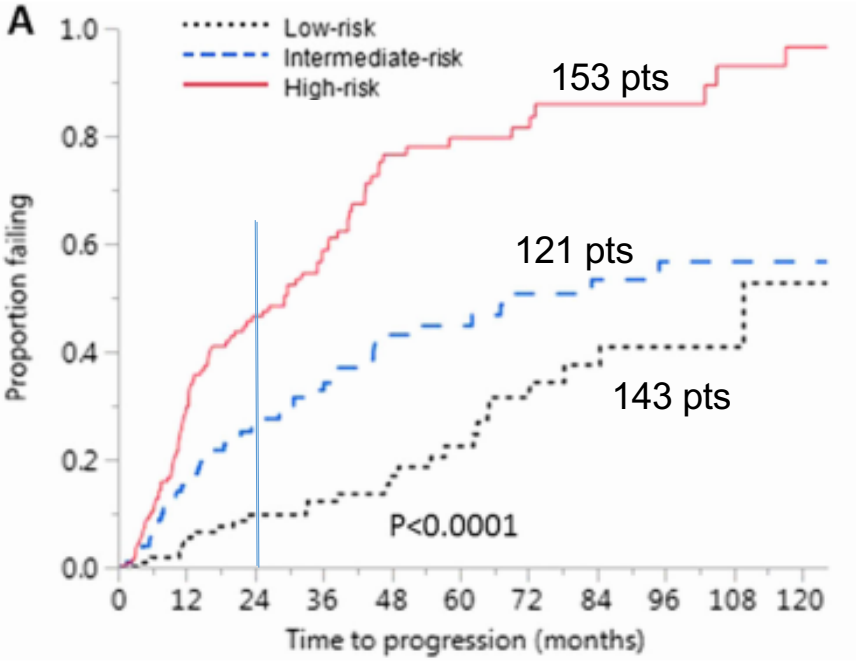
421 PTS; 2003-2015; SKELETAL X –RAY; 127 ADVANCED IMAGING

Lakshman et al. Blood Cancer J. 2018
Kumar S. 5th World Congress on Controversies in MM, 2019

TTP THE THREE RISK CATEGORIES USING THE PROPOSED AND CONVENTIONAL MAYO CLINIC MODELS

After a median follow-up period of 74.8 mos, 158 pts developed symptomatic MM; mTTP: 57 mos)

NEW SCORING

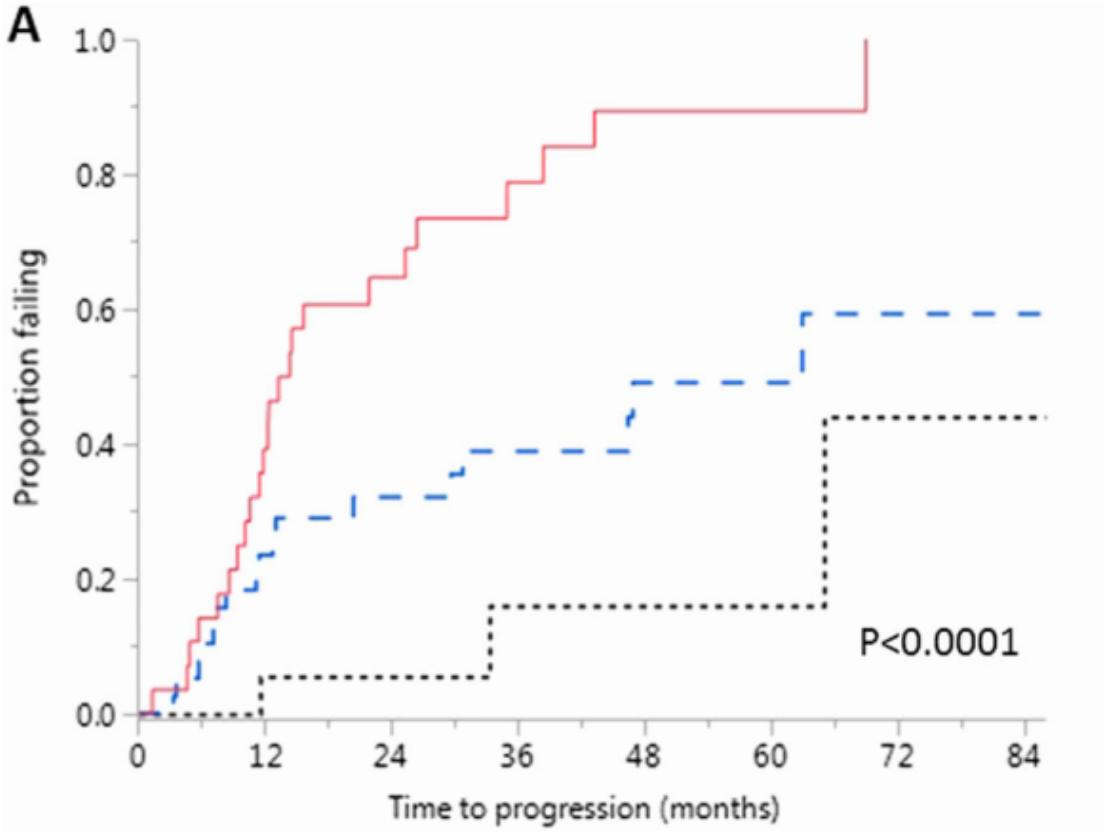


A: monoclonal protein > 20 g/L
BMPC% > 20%
FLCr > 20

Lakshman et al. Blood Cancer Journal (2018) 8:59

RISK STRATIFICATION OF SMM ACCORDING TO MAYO-CLINIC REVISED SCORING IN A SUBSET OF PTS WITH FISH TESTING

Among 297 pts, 52.5% showed t(4;14) and/or del(17p):and/or hyperdiploidy)



- BMPC >20%
- 1 FLC ratio >20
- high-risk cytogenetics

Low-risk
Intermediate-risk
High-risk

Lakshman et al. Blood Cancer Journal (2018) 8:59

Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria

Jesus San Miguel, Maria-Victoria Mateos, Veronica Gonzalez, Meletios A. Dimopoulos, Efstathios Kastritis, Roman Hajek, Carlos Fernández de Larrea Rodríguez, Gareth John Morgan, Giampaolo Merlini, Silvia Mangiacavalli, Hartmut Goldschmidt, Michele Cavo, Charalampia Kyriakou, Ming Qi, Jon Ukropec, Brendan M. Weiss, Chris Cameron, S. Vincent Rajkumar, Brian G. Durie, Shaji Kumar,

On behalf of the International Myeloma Working Group

''2-20-20 scoring''

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Study design

- **A multicenter, retrospective study of SMM patients diagnosed since January 1, 2004.**
- **Patients were included if:**
  - they had no disease progression within 6 months
  - had baseline data from diagnosis (+/- 3 months)
  - had a follow up of ≥1 year, and
  - did not participate in a therapeutic trial of SMM.

Objectives

- **To identify factors that predicted symptomatic Myeloma through the evaluation of various clinical and laboratory factor**

- **Develop a risk score to predict 2-year progression risk**

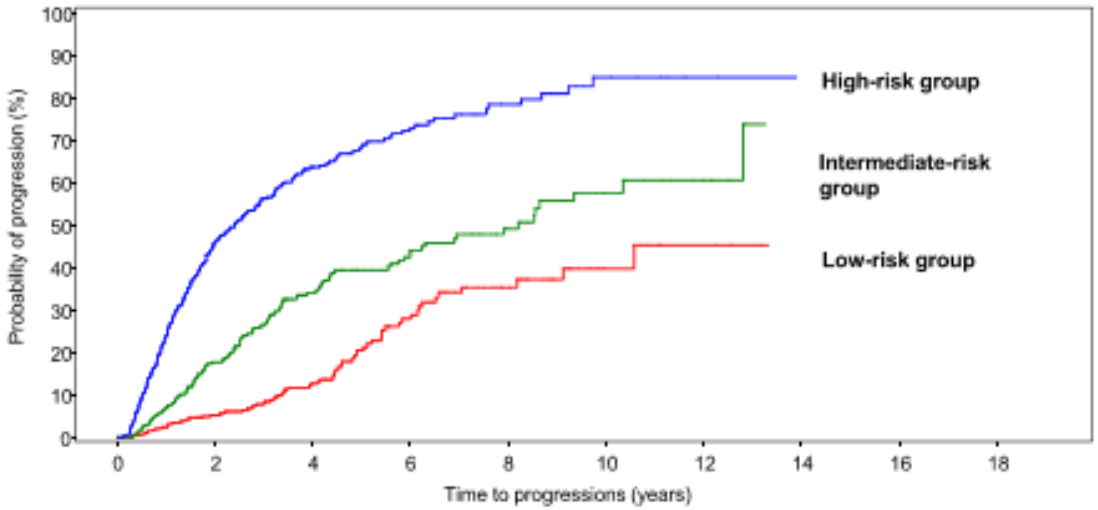
San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Patient characteristics (n=2004)

Characteristic	Number missing	n (%)	Mean (SD)	Median (IQR)	Range
Age (years)	0		63.7 (11.7)	64 (56 - 72)	(26 to 93)
Gender (Male)	0	986 (49.1%)			
Creatinine (mg/dL)	137		0.96 (0.5)	0.88 (0.71 - 1.05)	(0.12 to 9.5)
Albumin (g/dL)	180		4 (0.5)	4 (3.7 - 4.3)	(0.8 to 8.7)
Serum M protein (g/dL)	0		1.9 (1.1)	1.8 (1.1 - 2.6)	(0 to 5)
Heavy chain type					
IgA	123	454 (24.1%)			
IgD		6 (0.3%)			
IgG		1410 (74.8%)			
IgM		16 (0.9%)			
Light chain type,					
Kappa	24	1207 (60.8%)			
Lambda		778 (39.2%)			
Involved to uninvolved FLC ratio	588		34.3 (147.1)	6.4 (2.3 - 24.4)	(0.4 to 3360)
Immunoparesis	240	996 (56.3%)			
Urine M Spike (mg/24hrs)	800		118.5 (858.4)	0 (0 - 30)	(0 to 26390)
BMPC, %	0		19.9 (11.8)	15 (12 - 25)	(0 to 100)
BMPC, higher of biopsy and aspirate %	0		20.7 (11.7)	17 (12 - 25)	(0 to 100)
PET-CT Scan availability	13	374 (18.7%)			
MRI Scan availability	13	709 (35.5%)			

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Progression by risk group (n=1151 pts)



Characteristics included in the model

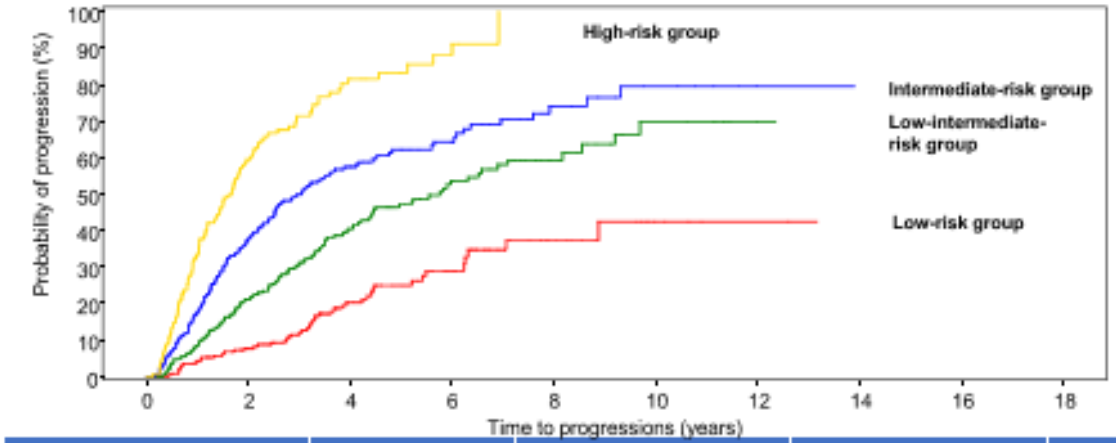
Serum M Spike: >2 g/dL
FLC Ratio: >20
BMPC: >20%

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	5%	424 (37%)
Intermediate-risk group	1	2.25 (1.68 to 3.01)	17%	312 (27%)
High-risk group	2-3	5.63 (4.34 to 7.29)	46%	415 (36%)

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Progression risk incorporating FISH (952 pts)

-The presence of any four of **t(4,14), t(14,16), 1q gain, or del13q** was defined as an additional risk factor



Characteristics included in the model

Serum M Spike: >2 g/dL
FLC Ratio: >20
BMPC: >20%

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	8%	232
Low-intermediate-risk group	1	2.25 (1.62, 3.11)	21%	322
Intermediate-risk group	2	3.69 (2.68, 5.09)	37%	253
High-risk group	>=3	7.52 (5.36, 10.54)	59%	145

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Developing a Risk Score Tool (n=689 pts)

Continuous variables were categorized as risk trend and weigh in the multivariable regression model; total risk score was calculated as the sum of all points for all risk factors

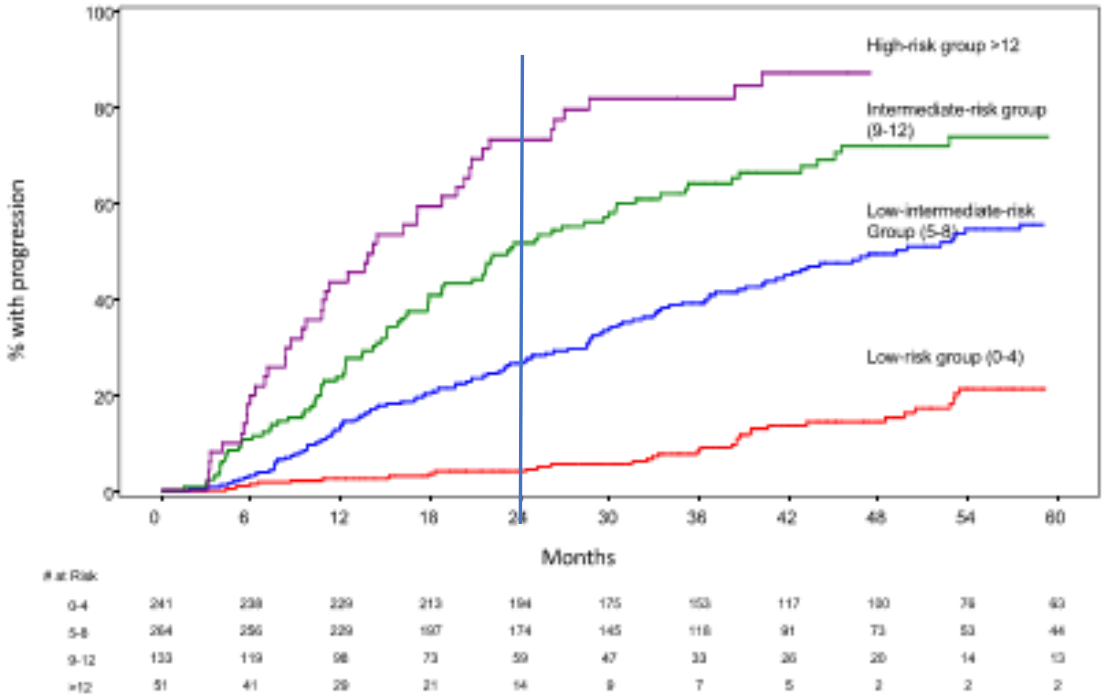
Risk Factor	Coefficient	Odds Ratio (95% CI)	P-value	Score
FLC Ratio				
0-10 (reference)	-	-	-	0
>10-25	0.69	1.99 (1.15, 3.45)	0.014	2
>25-40	0.96	2.61 (1.36, 4.99)	0.004	3
>40	1.56	4.73 (2.88, 7.77)	<0.0001	5
M protein (g/dL)				
0-1.5 (reference)	-	-	-	0
>1.5-3	0.95	2.59 (1.56, 4.31)	0.0002	3
>3	1.30	3.65 (2.02, 6.61)	<0.0001	4
BMPC%				
0-15 (reference)	-	-	-	0
>15-20	0.57	1.77 (1.03, 3.06)	0.04	2
>20-30	1.01	2.74 (1.6, 4.68)	0.0002	3
>30-40	1.57	4.82 (2.5, 9.28)	<0.0001	5
>40	2.00	7.42 (3.23, 17.02)	<0.0001	6
FiSH abnormality	0.83	2.28 (1.53, 3.42)	<0.0001	2

Total Risk score	Predicted risk at 2-years	% of sample
0	3.2	11.6
2	6.2	8.1
3	8.5	11.0
4	11.6	4.2
5	15.7	14.4
6	20.8	6.8
7	27	8.4
8	34.3	8.7
9	42.5	5.1
10	51	6.2
11	59.5	4.9
12	67.5	3.1
13	74.6	2.3
14	80.5	2.0
15	85.4	1.7
16+	89.2	1.3

*689 of the original 2286 had complete data for all risk factors

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

Progression risk



Risk Stratification Groups	Hazard Ratio (95% CI) Versus Low-risk group (censored 2 year)
0-4	Reference
5-8	7.56 (3.77 to 15.2)
9-12	17.3 (8.63 to 34.8)
>12	31.9 (15.4 to 66.3)

Total Risk score	2 year progression n (%)
0-4	9 / 241 (3.7%)
5-8	67 / 264 (25.4%)
9-12	65 / 133 (48.9%)
>12	37 / 51 (72.6%)

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

CONCLUSIONS

- The 2/20/20 model is validated in the current analysis and potentially can be usefull in circumstances where additional variables are not available
- Availability of FISH results can add to refining system (~ 10% more progressions, at 3 years)
- Ability to use the entire range of values for the single risk factors allow for maximum utilization of the variables for calculating the progression risk
- Alternative risk stratification systems may be used in individual trials, as long as they are able to identify a subset of patients with a risk of evolution at 2 years of at least of 50%

San Miguel et al. J Clin Onc. 2019 Jun 02. Abstract #8000

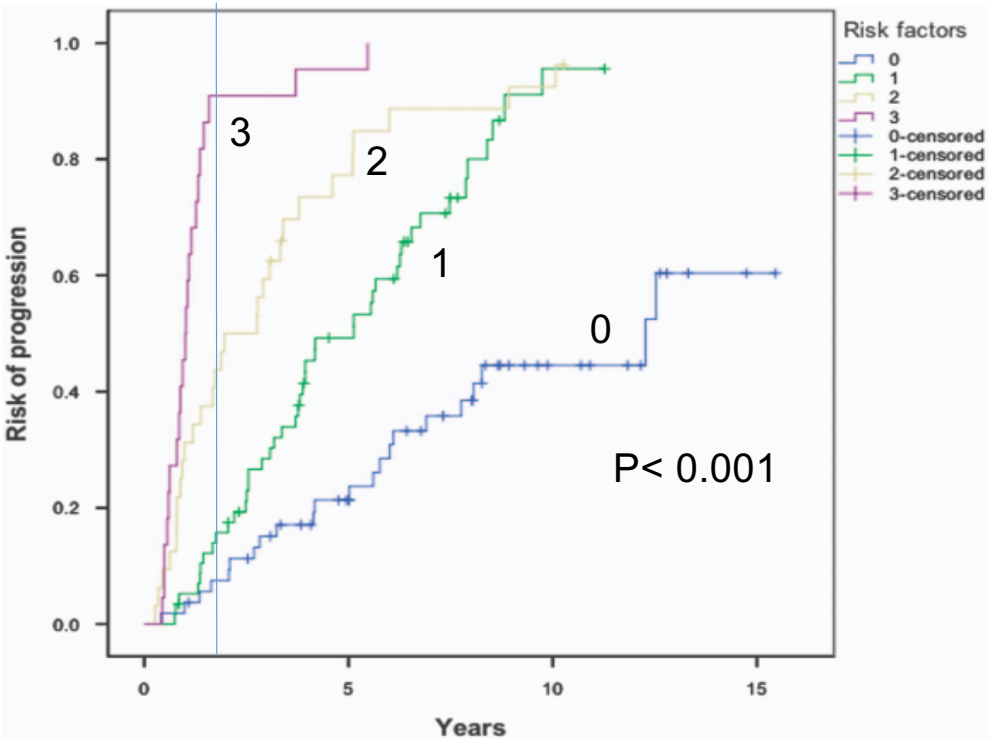
THE PREDICTIVE ROLE OF EVOLVING VARIABLES DURING AN ESTABLISHED TIME AFTER DIAGNOSIS

Evolving changes in disease biomarkers and risk of early progression in SMM

190 SMM pts, 1973-2014, after a median follow-up 10.4 years, 70.5% of pts evolved in MM, MAYO Clinic

DEFINITION OF EVOLVING TYPE:
- increase of at least of 10% in M-protein within the first 12 mos, is MC ≥ 30 g/L
- increase of 0.5 g/dl in M-protein and/or 500 mg/dl in Ig, if MC <30 g/L
- evolving Hb defined as ⩾0.5 g/dl decrease within 12 months

TTP into active MM



Risk of progression in SMM patients, stratified by the number of risk factorsat diagnosis
1 eMP
1 eHb
1 BMPC ⩾20%

Ravi et al, Blood Cancer J,, 2016

Risk stratification of smoldering multiple myeloma: predictive value of free light chains and group-based trajectory modeling

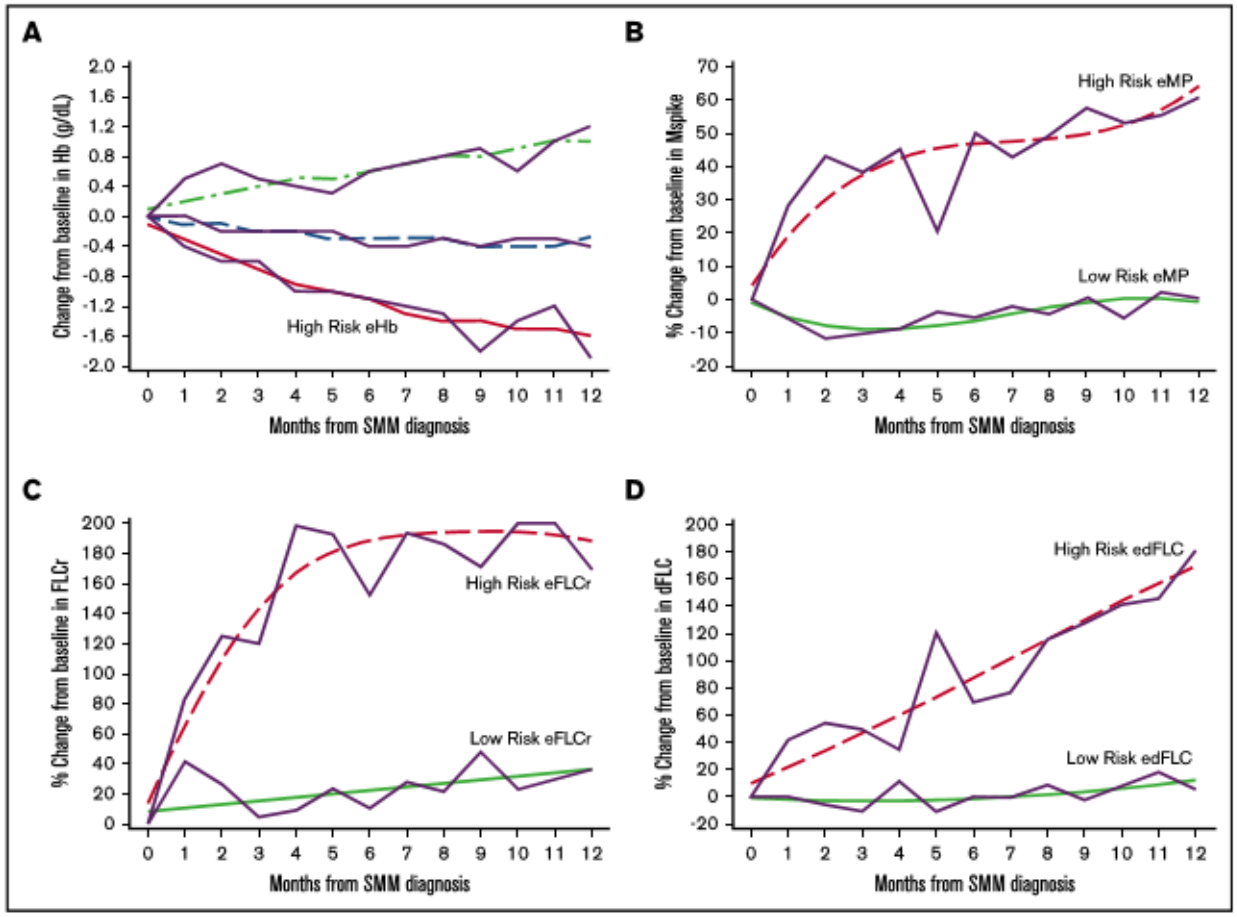
273 SMM pts at Mount Sinai Hospital/Columbia University Medical Cente (2010-2015)
Initial imaging performed to rule out MM included bone surveys (52%), PET-CT (24%), and MRI (24%) scans

With a median follow-up of 67 months, the median TTP 74 months

GBTM: Group-Based Trajectory Modeling identified high-risk groups of patients based on 1 year post-SMM diagnosis trajectories of their Hb, m-protein, FLCr and dFLC

Wu et al, Blood Advances, 2018

EVOLVING CHANGES IN HB, SERUM MC, FLC RATIO, AND DIFFERENCES IN FLC IDENTIFIED THROUGH GBTM 1 YEAR AFTER DIAGNOSIS OF SMM



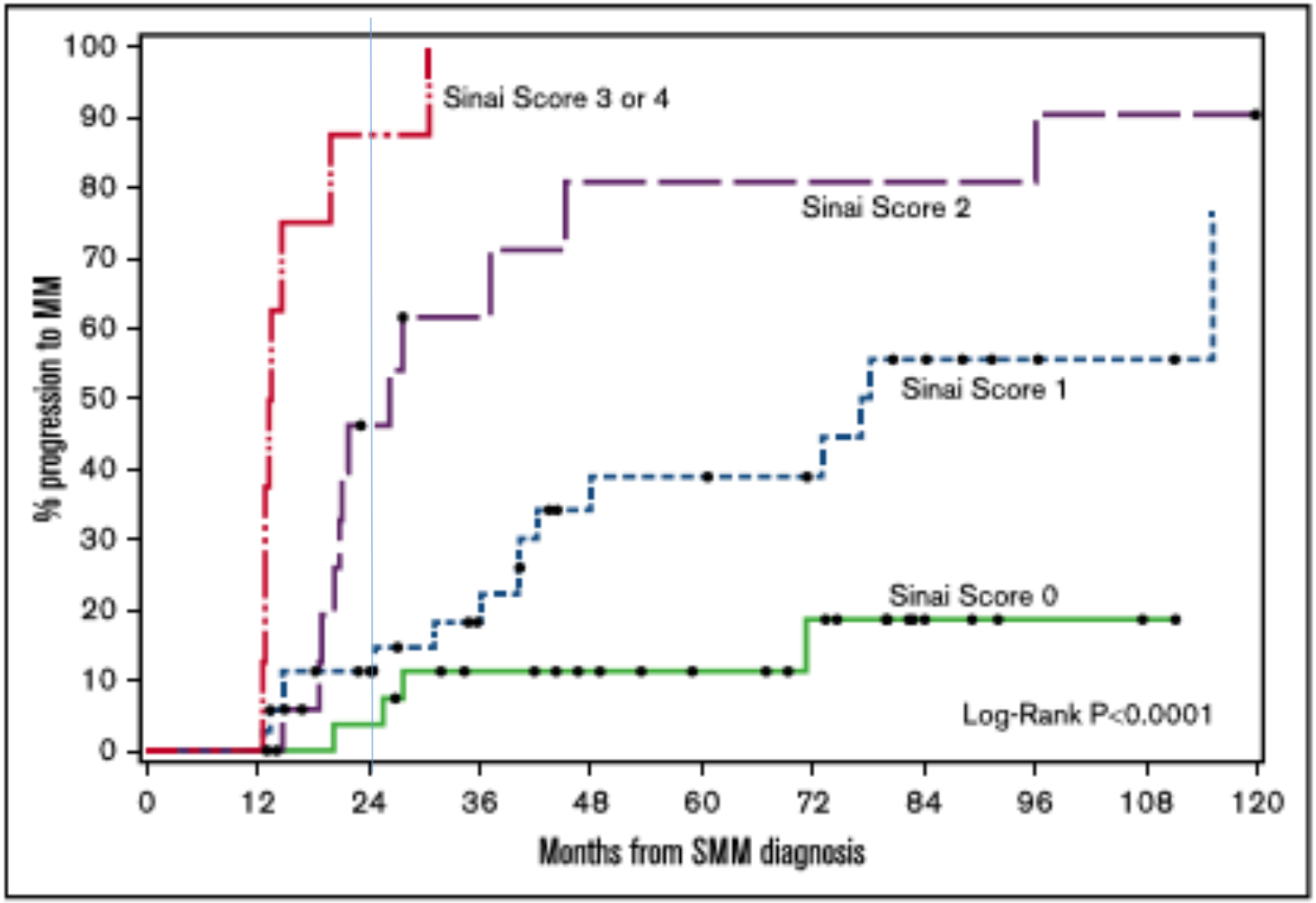
GBTM: Group-Based Trajectory Modeling identified high-risk groups of patients based **on 1 year** post-SMM diagnosis trajectories of their Hb, m-protein, FLCr and dFLC

- High-risk eHb group: decrease of 1.57 g/dL
- High-risk eMP group: increase of of 64%
- High-risk edFLC group: increase of 169%

A Changes in Hb are in g/dL. Changes in MC **(B)** FLC ratio **(C)**, and differences in FLC ratio **(D)** are % from baseline. The trajectories of high risk evolving GBTM groups are indicated.

Wu et al, Blood Advances, 2018

TTP to symptomatic myeloma stratified based on risk factors (immunoparesis, eHb GBTM, eMP GBTM, and edFLC GBTM)



SCORING SYSTEM

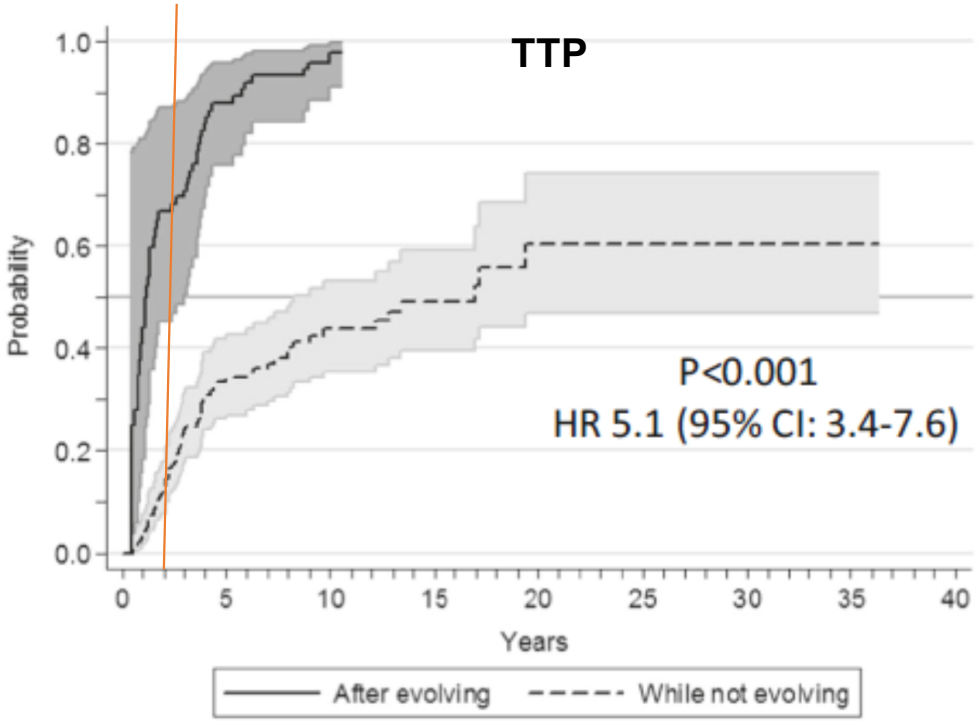
- High-risk eHb group
- High-risk eMP group
- High-risk edFLC group
- Immunoparesis

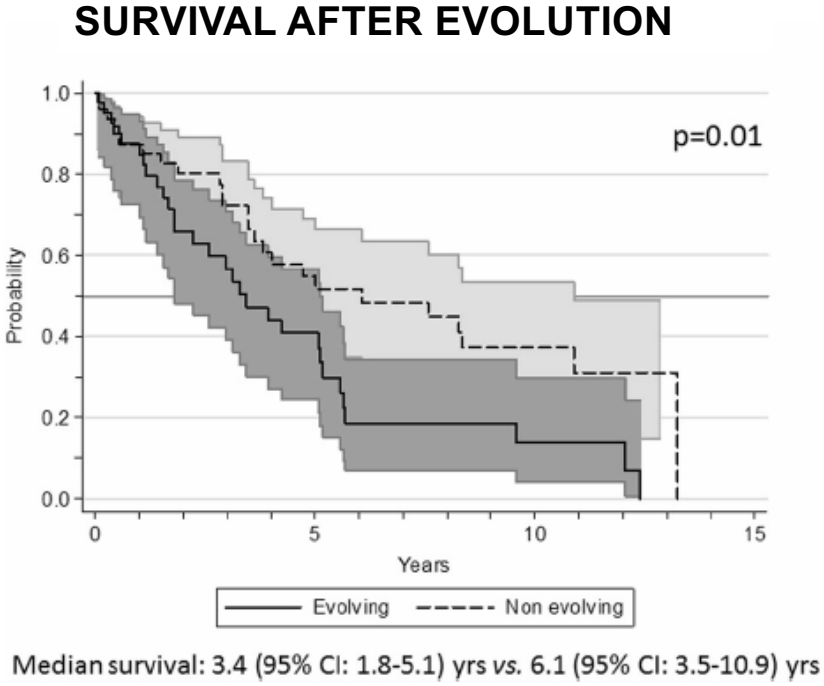
Wu et al, Blood Advances, 2018

Evolving M-protein pattern in pts with SMM: impact on early progression

206 SMM pts, 1973-2012, after a median follow-up 6.8 years, 52% of pts evolved in MM

DEFINITION OF EVOLVING TYPE:
- increase of at least of 10% in M-protein within the first 12 mos, is MC >30 g/L
- progressive annual increase over a period of 3 years, if MC <30 g/L





Median survival: 3.4 (95% CI: 1.8-5.1) yrs *vs.* 6.1 (95% CI: 3.5-10.9) yrs

Fernandez de Larrea et al, Leukemia 2018

CONCLUSIONS

- The availability of new drugs, characterized by a more specific activity on neoplastic PC, raises the problem of an earlier therapeutic intervention in SMM
- To date there is no a reliable biological marker of evolution in symptomatic MM
- The definition of Ultra-High-Risk SMM introduced the concept of *Myeloma-Defining Events (MDE)* but identifies only a small part of SMM
- New pognostic scoring sisyems seem to identify more consistent cohorts of pts with different risk of evolution but the for their retrospective nature, these studies not always are based on modern imaging techiques for evaluating bone lesions and does not evaluate the kinetics of the variables after the diagnosis
- In borderline cases, the evolution during the an establised time after the diagnosis of the variables related with tumor burden could be better considered at least in clinical practice