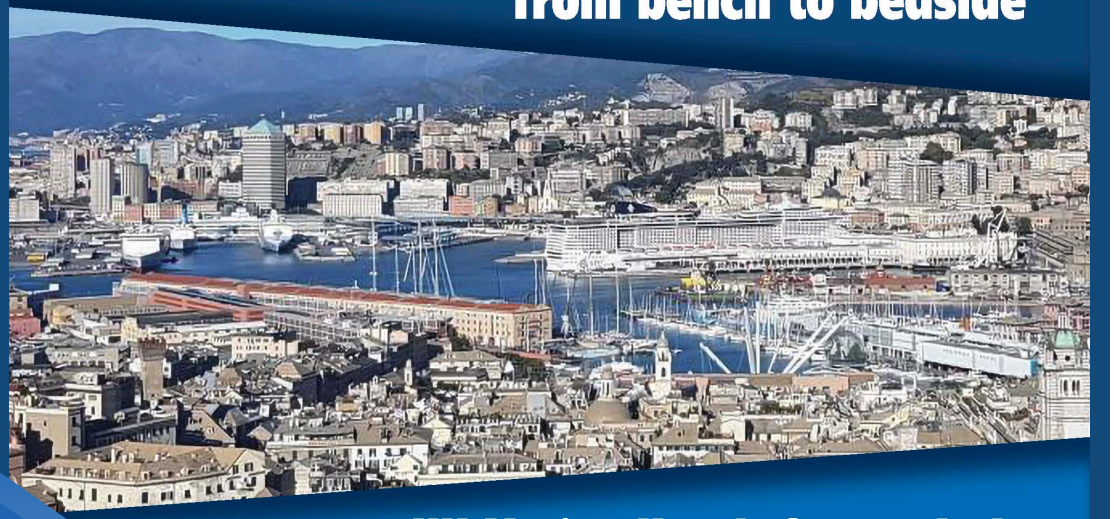
2023 Multiple Myeloma updates:
from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

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The consultant’s guide to smoldering multiple myeloma

When do I suspect a SMM?
Diagnostic criteria

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Symptomatic Multiple Myeloma
M-spike	< 3 g/dL serum AND	≥ 3 g/dL serum AND/OR	Present (*serum/urine*) AND
Plasma cell BM infiltration	< 10% AND	10-59% AND	> 10%[b] AND
Myeloma-defining event	Absent	Absent	Present

Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡

Rajkumar SV et al. The Lancet Oncology 2014

What is the definition of Myeloma-defining events?

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

- **This new definition means that patients called SMM in the past should be now considered as MM**
- The recommended work out for the suspect of SMM should include all assessments to exclude the presence of MDE

Concomitant diseases that can mimic MM:

-Cronic kidney disease due to diabetes or hypertension

-Anemia due to iron-vitamin deficiency, chronic disease,..

-Diffuse osteoporosis

-Hyperparatiroidism

-Single asymptomatic bone lesion

Rajkumar SV et al. The Lance Oncoogy 2014

How to discriminate among patients with sFLC ratio > 100 (for years)

Monoclonal proteinuria predicts progression risk in (SMM) with a sFLC ratio ≥100

Study Population

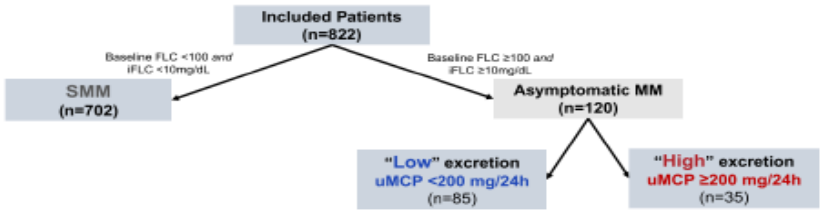


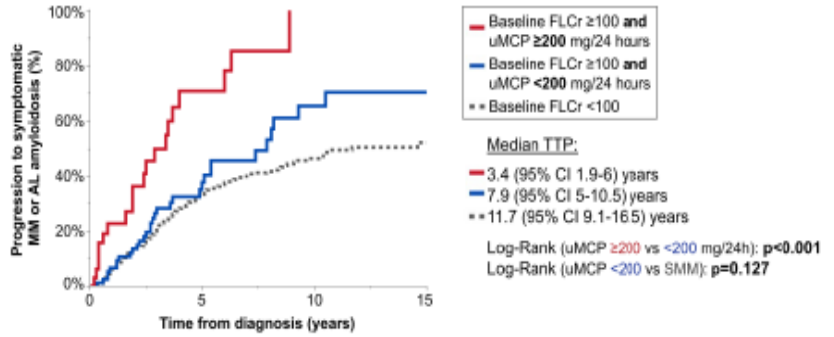
Table 1. Baseline characteristics of patients meeting the FLCr SLiM criteria for MM, and SMM patients

	Baseline FLCr <100	Baseline FLCr ≥100	
	SMM (n=702)	uMCP <200 mg/24h (n=85)	uMCP ≥200 mg/24h (n=35)
Median age at diagnosis - years(IQR)	65 (57-79)	66 (56-72)	67 (55-74)
Male - n(%)	418 (60)	37 (44)	16 (46)
Median diagnostic disease parameters (IQR)			
serum MCP - mg/dL	1.7 (1-2.5)	1.9 (1-2.9)	1.8 (0-2.6)
urine MCP - mg/24h	0 (0-24)	0 (0-83)	465 (290-879)
BMPC - %	15 (10-22)	21 (15-32)	30 (20-40)
iFLC - mg/dL	7.2 (2.8-20.6)	66.5 (33.2-116.5)	101 (44.9-169)
FLCr - n	8 (3-25)	195 (133-360)	259 (144-554)
Light chain isotype (kappa/lambda) - n(%)	456 (65) / 243 (35)	55 (65) / 30 (35)	15 (43) / 20 (57)
Creatinine - mg/dL	1 (0.7-1.2)	0.9 (0.6-1.1)	0.9 (0.7-1.3)
eGFR* - mL/min/1.73m²	68.9 (41.1-82.9)	74.6 (50.2-88)	74.4 (53.2-88.3)
Cross-sectional imaging at diagnosis or prior to progression - n(%)	489 (70)	53 (62)	14 (40)
Missing 24hUP at baseline - n(%)	332 (47)	-	-
Mayo 2018 SMM risk score at baseline (Low/ Intermediate/ High) - n(%)	217 (39) /227 (32) / 204 (29)	-	-

*-Calculated using CKD-Epi formula, assuming that all patients were Caucasian

Progression outcomes

TTP stratified by baseline FLCr and uMCP excretion

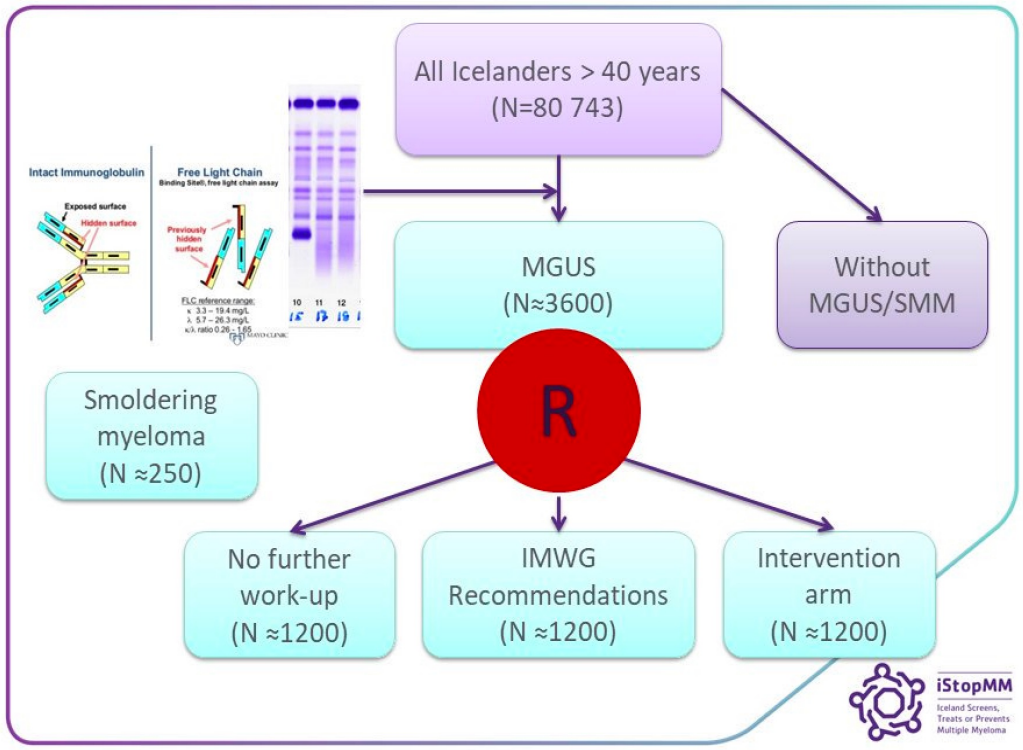


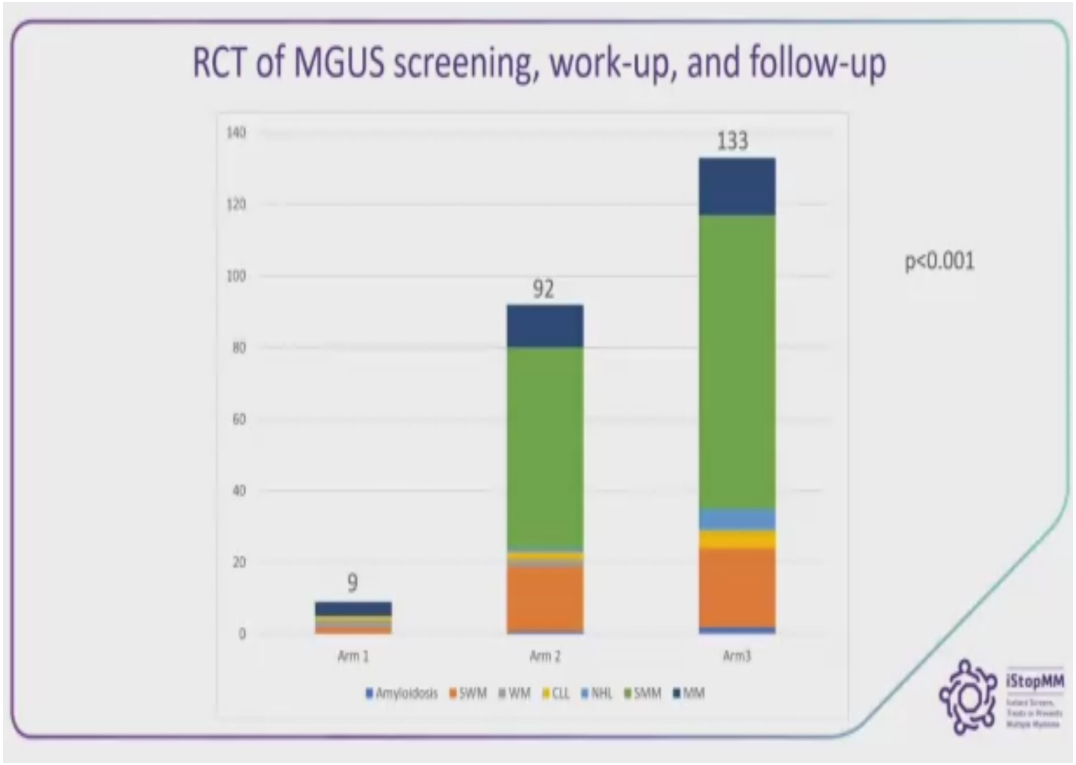
- The progression risk was 2.8 times higher in patients with high versus low uMCP excretion *(2-year progression risk 36.2% vs. 13.5%, respectively; HR 2.79, 95% CI 1.57-4.96, p<0.001)*
  - *Similar results when population was restricted to those with cross-sectional imaging to rule out lytic lesions*
- The progression risk remained 2.7 times higher in patients with high versus low uMCP excretion after adjusting for baseline eGFR, BMPC burden, and iFLC, and light chain isotype the progression risk *(HR 2.66, 95% CI 1.39-5.10, p=0.003)*.
- The TTP was similar between patients with a baseline FLCr <100 vs. **FLCr ≥100 and low uMCP excretion** *(2-year progression risk 13% versus 13.5% respectively)*

- Light chain aggregation falsely increase serum FLC estimation: due to **impaired renal clearance** and increased nephelometric quantification due to **aggregated proteins** falsely increasing the level of FLC
- Among patients wih a baseline serum FLC ratio ≥100, those with a **uMCP <200 mg/24h** have a low risk of progression to MM comparable to SMM with sFLC ratio <100
- **These findings underscore the importance of conducting a 24-hour urine assessment at diagnosis**

Visram et al. ASH 2021

What is the incidence of SMM?





- **Active screening** identifies significantly **higher number** of individuals with **full-blown malignancy and SMM**
- Early detection and early intervention is achievable

Kristinson S et al. ASH 2021: abstract 15

Unexpectedly high incidence of SMM in the arm 3 of iStopMM project

Prevalence of SMM

- 1,279 individuals were randomized to arm 3
- Bone marrow sampling performed in 970
- Of those, 105 (10.8%) were diagnosed with SMM

- **The prevalence of SMM in the total population was estimated to be 0.53% (95% CI: 0.49-0.57%) in individuals 40 years of age or older**

- Prevalence in men 0.70% (95% CI: 0.64-0.75%)
- Prevalence in women 0.37% (95% CI: 0.32-0.41%)
- Increases with age

iStopMM

➢ 0.5% in persons over age 40 years

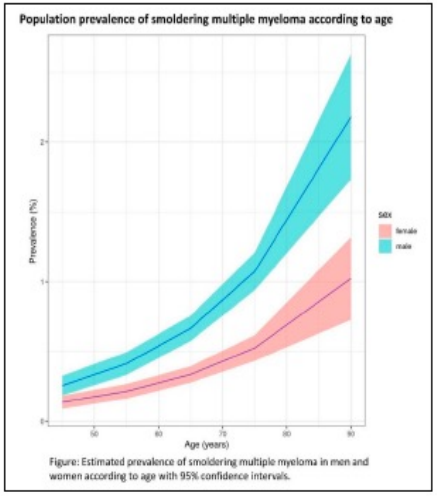


Figure: Estimated prevalence of smoldering multiple myeloma in men and women according to age with 95% confidence intervals.

- The incidence of SMM is 0.5% in persons over 40 years of age
- This **high prevalence** has implications for future treatment policies in MM like **early detection** and **early intervention** to avoid to increase the number of patients with active disease

Tthorsteinsdottirs et al. ASH 2021: abstact number 151

How do I follow a patient with SMM?

Recommended work up at 3 months after the first identification of SMM

- **Medical History and physical examination**
- **Complete blood count**
- **Creatinine and calcium values**
- **Protein studies**

  - Total serum protein and serum electrophoresis (serum M-protein)
    24-h urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
  - Serum free light chain mesurement (FLC ratio)

Only if results show stabilization of the disease, diagnosis of SMM is confirmed

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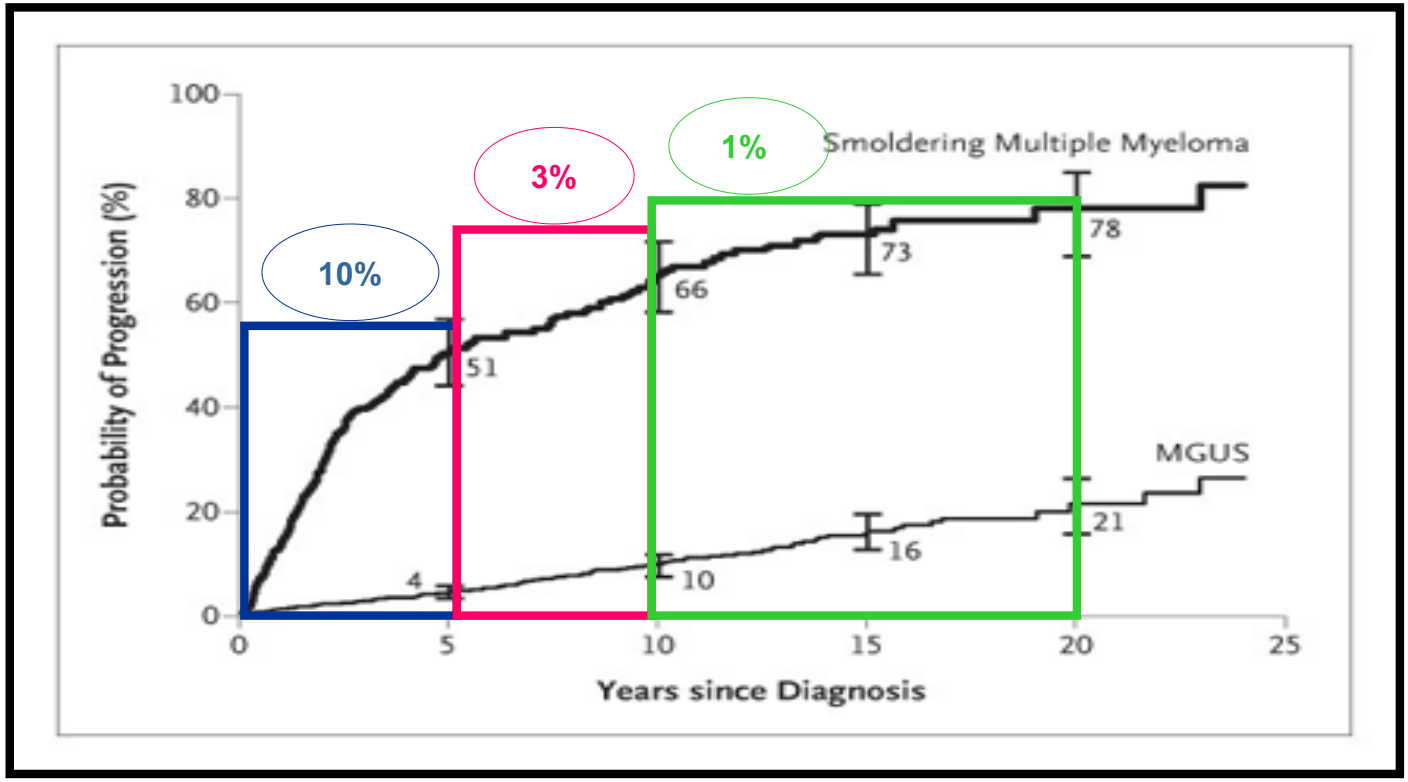
Mateos MV et al. Current hematologic malignancy reports. 2013; 8(4): 270-6

How do I risk-stratify a patient with SMM?

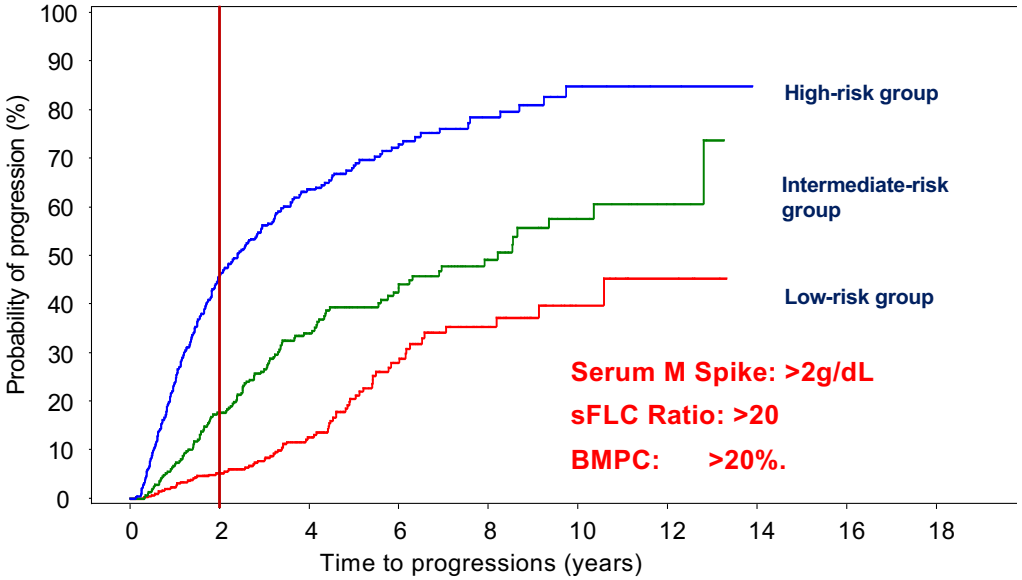
Risk of progression to active disease

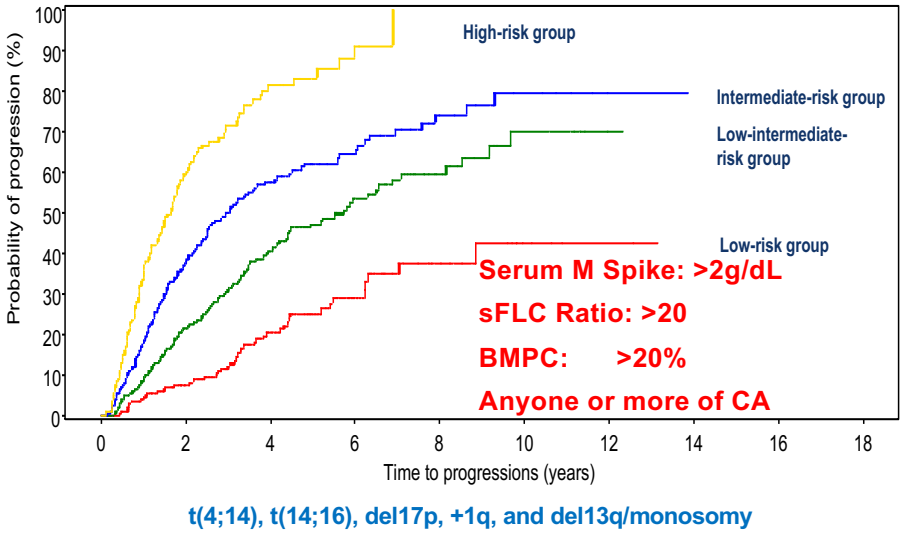


It is mandatory to identify the individual risk for each new SMM patient and to inform to the patient

Kyle R. N Engl J Med 2007; 356:2582-90 and 2018

Current risk stratification model SMM incorporating the revised IMWG diagnostic criteria (n>1000 pts): the 20-20-20 model





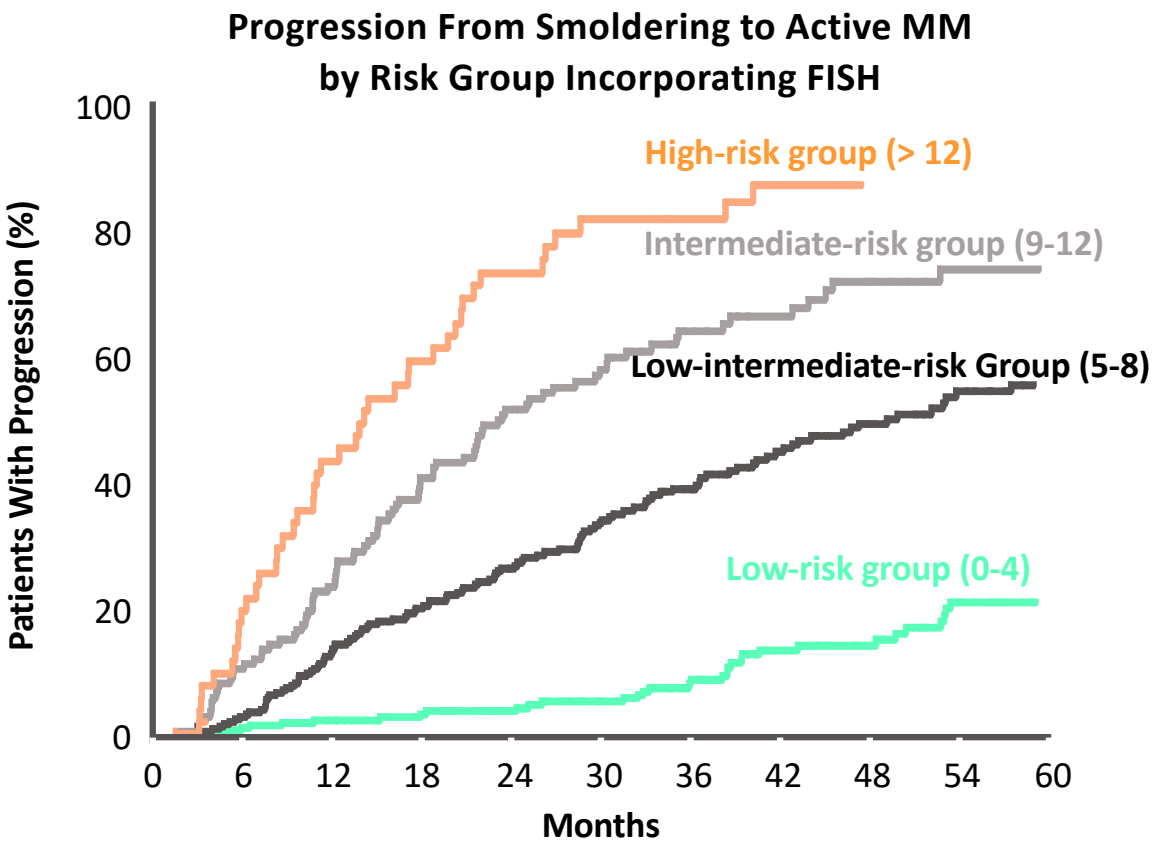
t(4;14), t(14;16), del17p, +1q, and del13q/monosomy

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%)

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

Mateos MV et a. BCJ 2020

IMWG: Risk Score to Predict Progression Risk at 2 Yrs

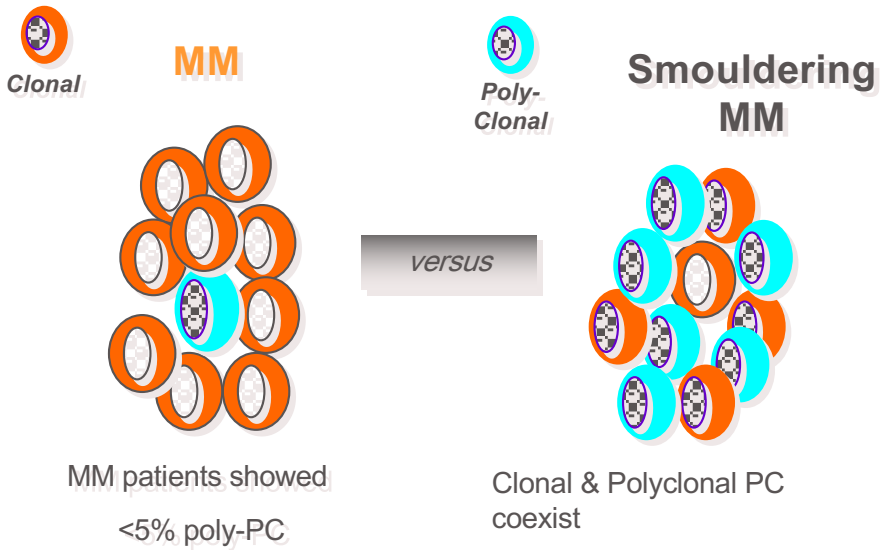


Risk Factor	Coefficient	*P* Value	Score
FLC Ratio			
0-10 (reference)	--	--	0
> 10-25	0.69	.014	2
> 25-40	0.96	.004	3
> 40	1.56	< .0001	5
M protein (g/dL)			
0-1.5 (reference)	--	--	0
> 1.5-3	0.95	.0002	3
> 3	1.30	< .0001	4
BMPC%			
0-15 (reference)	--	--	0
> 15-20	0.57	.04	2
> 20-30	1.01	.0002	3
> 30-40	1.57	< .0001	5
> 40	2.00	< .0001	6
FISH abnormality	0.83	< .0001	2

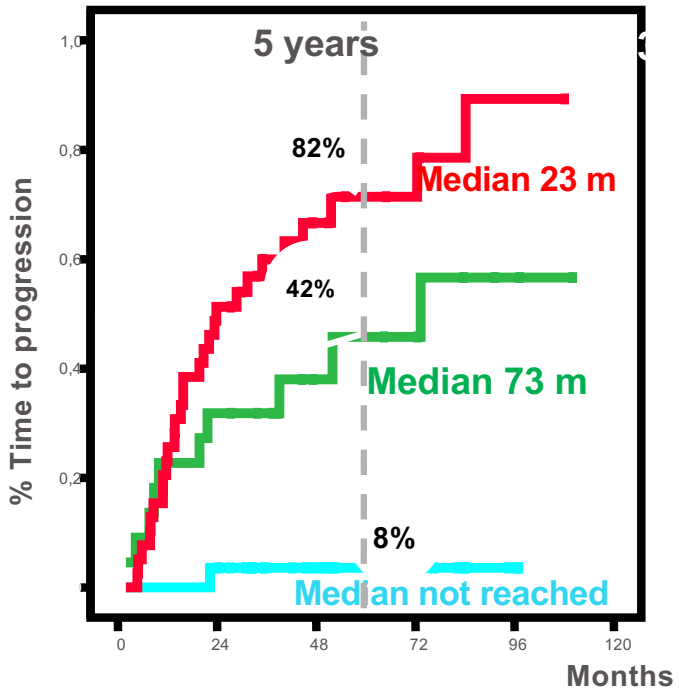
Total Risk Score	2-Yr Progression, n (%)
0-4	3.7%
5-8	25.4%
9-12	48.9%
> 12	72.6%

Mateos MV et a. BCJ 2020

Spanish Model:
Analysis of the PC compartment by flow cytometry



Immunoparesis: Low levels of uninvolved immunoglobulins: >25% of the lowest level for each immunoglobulin



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

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

No adverse factors
n= 28 (1 progr.)

1. Ocqueteau M, Am J Pathol 1998, 152: 1655
2. Pérez E. Blood 2007; 110:2586-92

Other models to evaluate the risk of progression to MM

- **Mayo clinic model** (BMPC % and M spike levels + sFLC)
- There are other models for the identification of SMM patients with a 50% progression risk at 2 years:
  - Bence Jones proteinuria in 24-hours urine: + or >500 mg/24 h urine
  - Evolving pattern of the M-spike or M-spike and hemoglobine level
  - PET-CT: positive uptake in PET with no lytic lessions in the CT

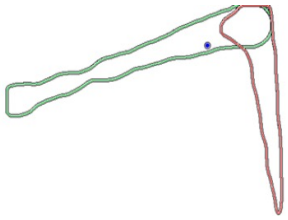
- **Whatever model can be valid**
- All these models are based on clinical markers, world wide available
- New models are emerging based on biological or molecular markers

Are we satisfied by the current risk model?

The ideal identification of the risk of progression to MM should include **dynamic clinical and biological markers**

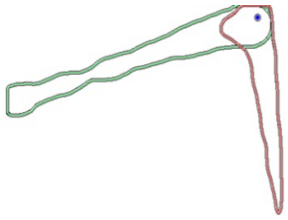
Identification of MGUS-like profile phenotype as predictor of outcome: 5,114 pts with monoclonal gammopathies

MGUS-like



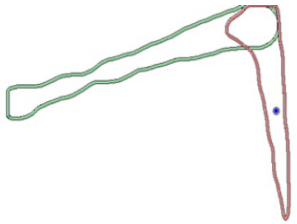
- Plasma cells: 4.2%
  - Clonal plasma cells: 78.4%
  - Normal plasma cells: 21.6%

Intermediate-like



- Plasma cells: 1.4%
  - Clonal plasma cells: 99.0%
  - Normal plasma cells: 1.0%

MM-like



- Plasma cells: 27%
  - Clonal plasma cells: 99.9%
  - Normal plasma cells: 0.1%

Development:

- 548 MGUS
- 2,011 NDMM
  - Transplant-eligible
    - GEM2000 (n = 486)
    - GEM2005MENOS65 (n = 330)
    - GEM2012MENOS65 (n = 450)
  - Transplant-ineligible
    - GEM2005MAS65 (n = 239)
    - GEM2010MAS65 (n = 230)
    - CLARIDEX (n = 276)

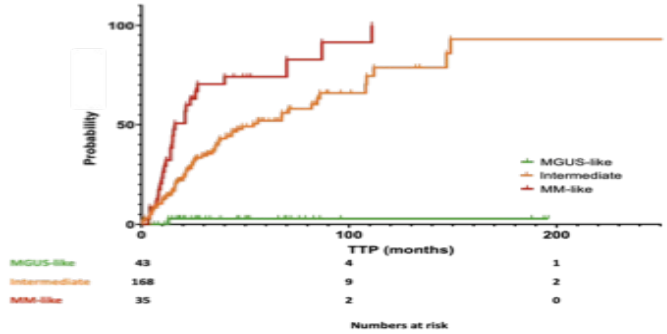
Application:

- 392 SMM
  - Untreated (n = 186)
  - GEM QUIREDEX (n = 116)
  - GEM CESAR (n = 90)
- 102 AL Amyloidosis

Validation:

- 96 SMM Arkansas
- 1,859 NDMM Czech Republic
- 105 AL Pavia

Prognostic value in SMM (spanish series validated in the Arkansas series)

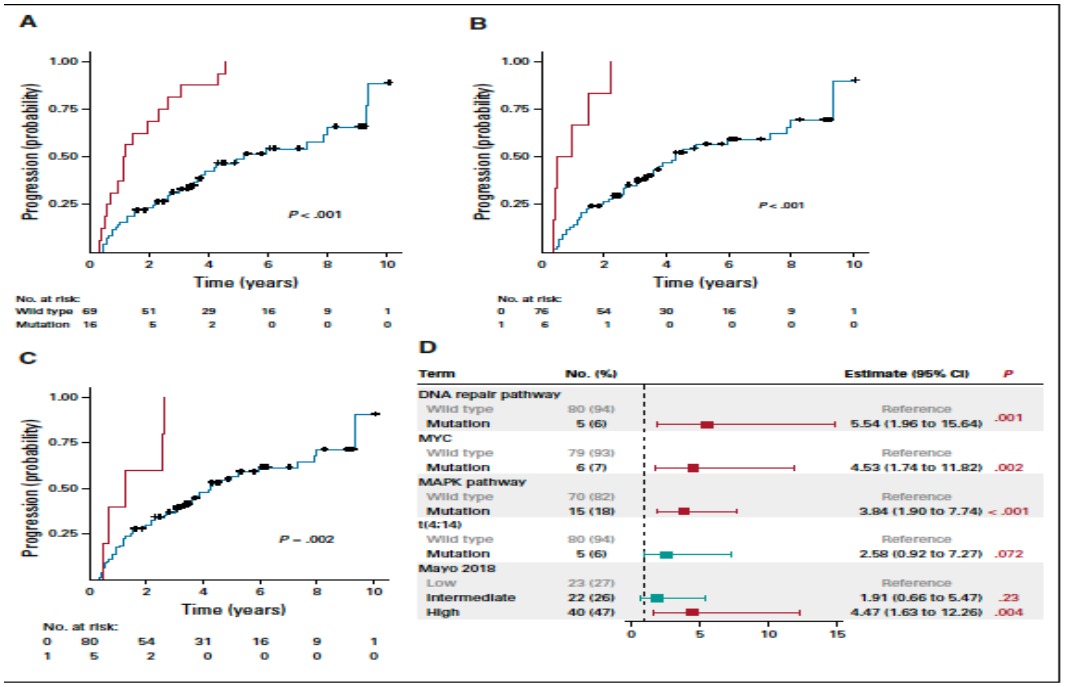


In SMM, patients with **MGUS-like phenotype** could potentially be spared from clinical trials investigating early treatment

Leire B et al. ASH 2021: oral presentation

Genomic profiling of Smoldering Myeloma identifies patients at a high-risk of disease progression

NGS to study 214 SMM pts, whole exome sequencing on 166 tumors



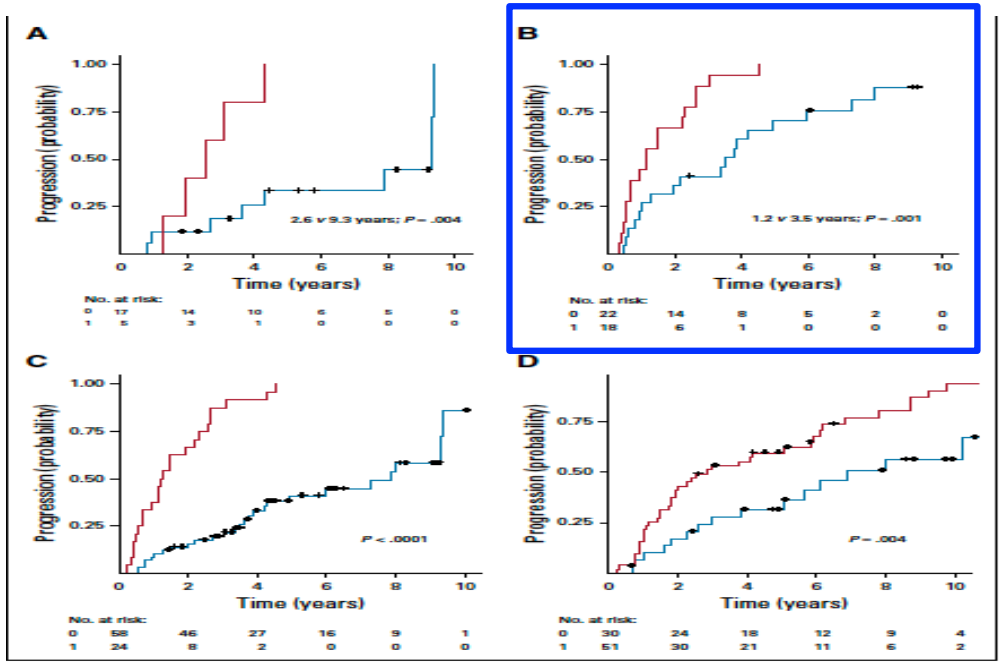


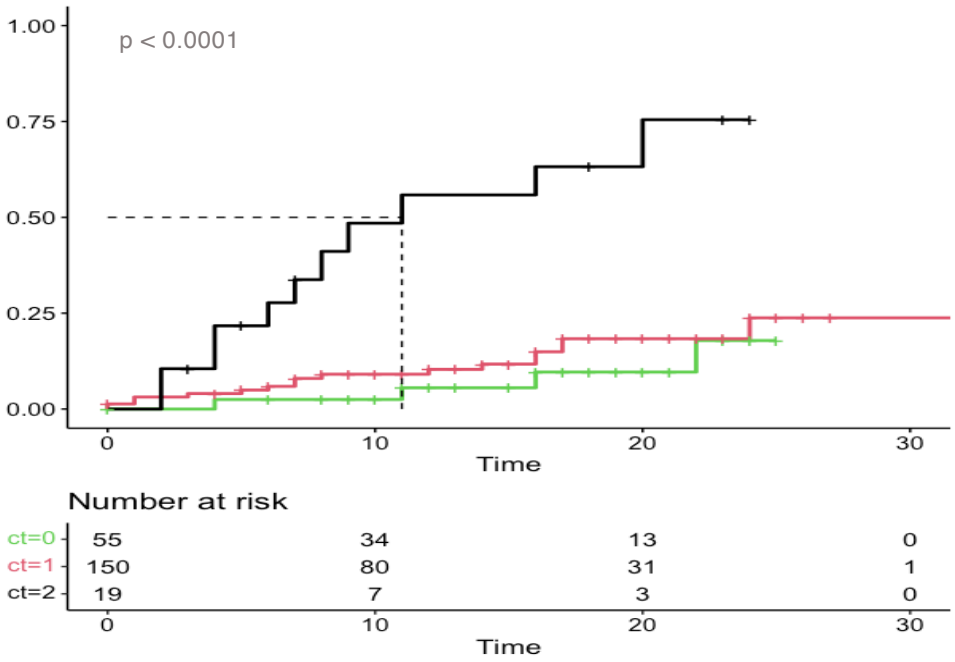
FIG 5. Kaplan-Meier curves for analysis of time to progression of (A) clinically high-risk patients with (red) or without (blue) the high-risk genomic alterations, (B) clinically intermediate-risk patients with or without the high-risk genomic alterations, (C) patients with or without the high-risk genomic alterations in the Dana-Farber multicenter cohort, and (D) patients with or without the high-risk genomic alterations in the Mayo Clinic validation cohort.

Genomic studies will contribute to optimize the risk models

Bustoros M et al. JCO 2020

Circulating Tumor Cells in Smoldering and Active Multiple Myeloma

Untreated SMM patients with ≥0.02% CTCs have ultra-high-risk of transformation



- iMMunocell (n = 230), untreated SMM patients…
  - with high CTC levels (**≥0.02%**) showed ultra-high risk of transformation (11 months) vs those with **<0.02% CTCs** and **undetectable CTCs**
- CTCs were selected as an independent prognostic factor in multivariate analysis of TTP, together with the M-protein and sFLC ratio (the % of BM tumor cells was not significant)

Garcés JJ et al. ASH 2021: oral presentation

How do I manage a patient with SMM?

- Management should be risk-adapted
  - **Low risk** should be managed like MGUS patients
  - **Intermediate risk** should be followed closely than low risk at the beggining: Every 4-6 months during the first 2 years to know the pattern of evolution and annually thereafter

    Evaluations: CBC, creat and calcium plus protein studies

    Bone evaluation: If 1 FL at MRI: alternating WBMRI with WBLDCT/6m; the rest-> yearly WBMRI or at clinical suspicion
  - **High risk** should be included in trials/treated

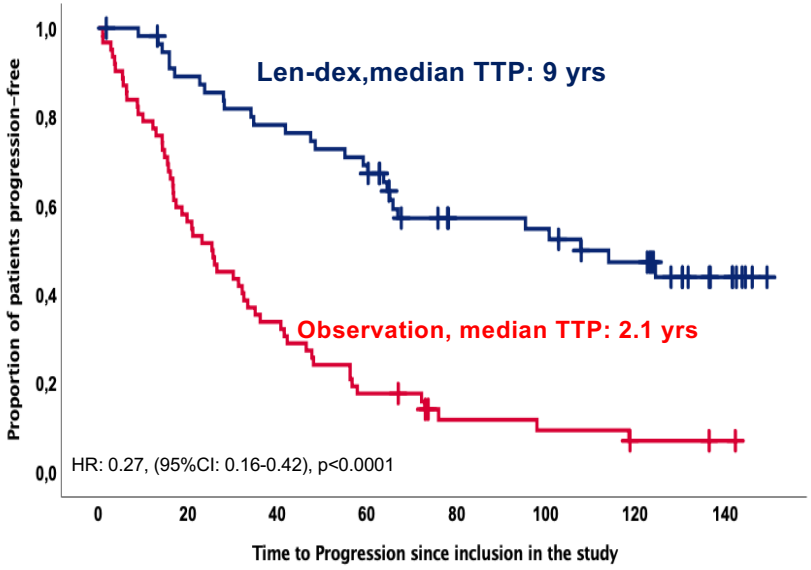
What about treatment of SMM outside clinical trials?

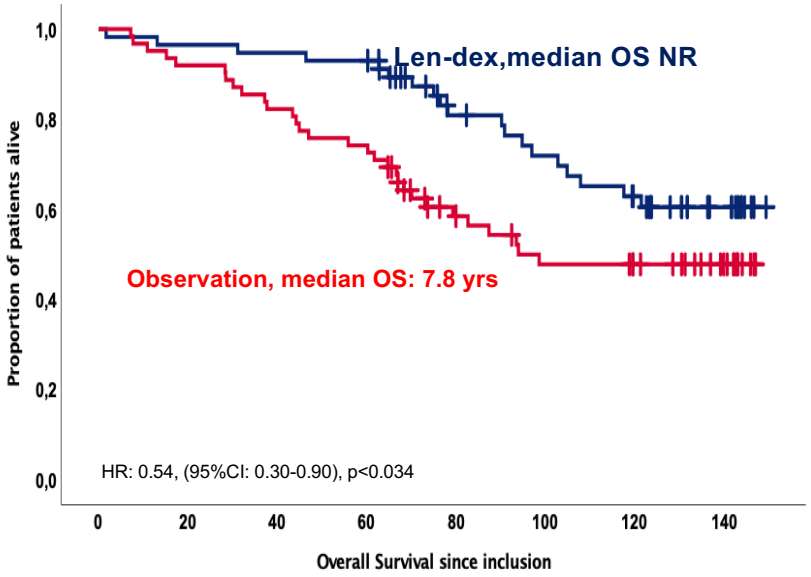
QuiRedex:

Len-dex x 9 cycles + len maintenance x 2 years vs no treatment: TTP to active disease (n = 119)

Per-protocol Patients population

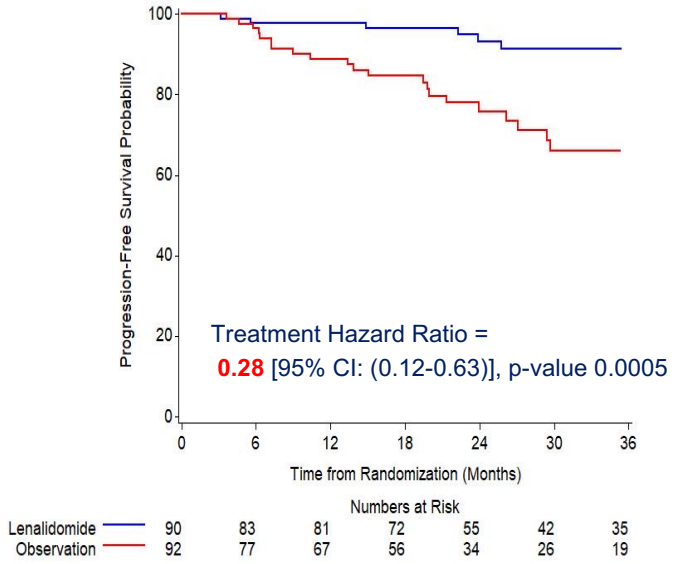
Median follow-up: 10.8 years



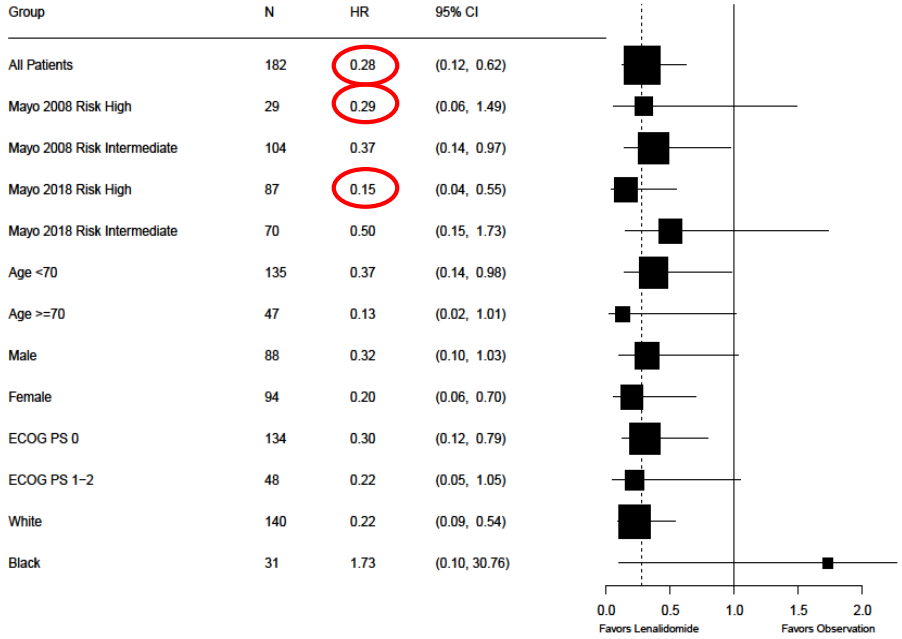


Mateos MV, et al. European Journal of Cancer 2022

E3A06: Len until PD/intolerance vs Observation in patients with SMM (n=182)



Criteria: PCBM ≥ 10% and sFLC ratio >8 or <0.125



Early treatment with R significantly prevented the progression to MM especially in the patients at high risk of progression

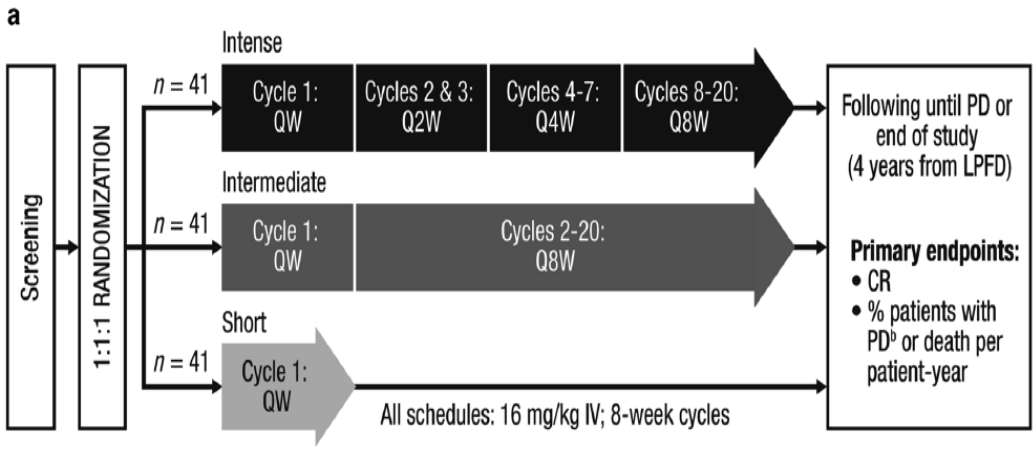
Lonial S et al. JCO 2020

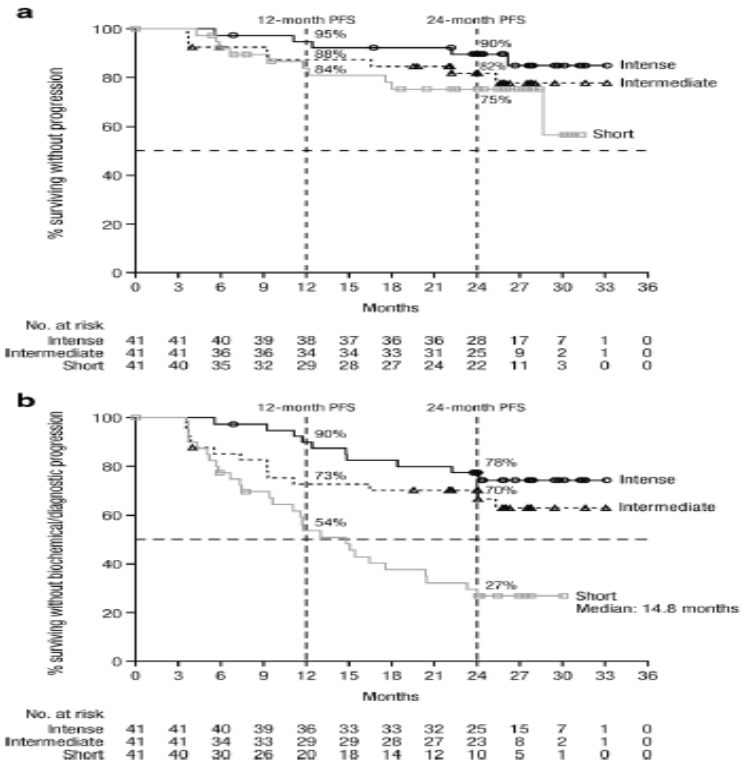
How to improve the treatment of SMM?

2 different aims:

- Delay progression
- Curative strategies

Dara monotherapy in SMM patients: phase 2 Centaurus study





- High/Intermediate -risk SMM

PCBM ≥10 and ≤ 60% plus plus:

- M-protein ≥3g/dL (IgA ≥2g/dL)
- U-protein >500 mg/24h
- Abnormal FLC ratio (<0.126 or >8), or
- Involved FLC >100 with a ratio abnormal (but not >100)

CR rate is not different

Dara monotherapy in the intense scheme delays both PD and BonePD and gave the rationale for the Aquilea phase 3 trial comparing Dara versus observation

Landgren O et al. Leukemia 2020

Lenalidomide as backbone for the treatment of intermediate-high risk SMM patients: phase 2 studies

Elo Rd/ Ixa Rd/ K Rd

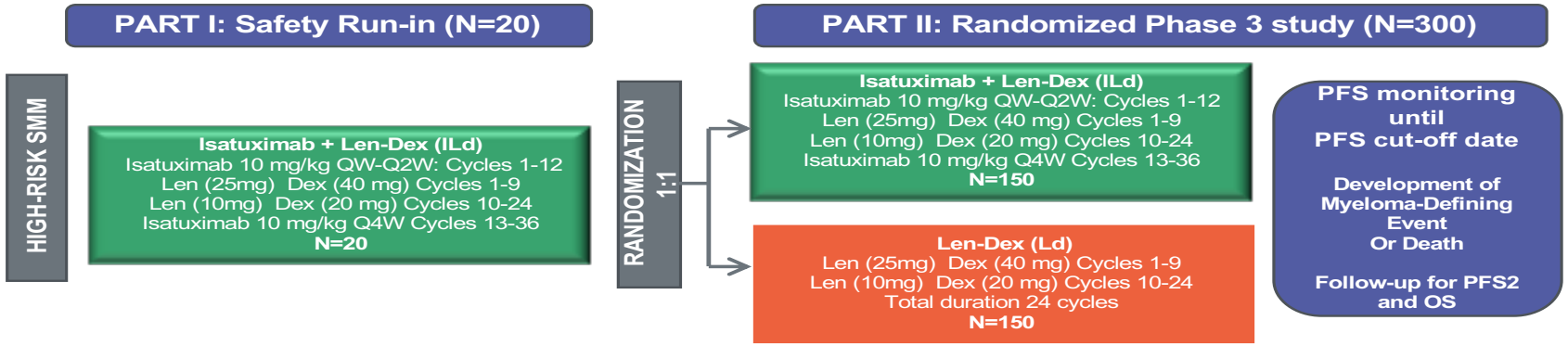
	Phase	n	ORR/CR/MRD-ve	PFS/OS
Elo-Rd	2	50	84%/6%/NE	100%/1 death
Ixa-Rd	2	26	89%/19%/12%	100%/-
KRd	2	12	100%/100%	-

"Exciting results" even better than Rd alone but....

We need to measure the efficacy of the combinations with more modern approaches beyond response rates and CR rates and to know long-term survival outcomes

Ghobrial I, et al. ASH 2018: abstract 154
Ghobrial I et al. ASH 2018: abstract 804
Landgren O et al. JAMA 2017

Rd ± anti-CD38 MoAb in HR-SMM patients: phase 3 Ithaca and ECOG studies



Stratification on:
- Age (≤ 65 vs > 65)
- BMPC (<20% vs ≥20%)
- Serum involved/uninvolved FLC ratio (≤ 20 vs >20 but ≤100)

Inclusion criteria:
- IMWG model 2/20/20
- Presence of ≥10% BMPC and at least one of the following: serum M-protein ≥3g/dL, i/uFLC ratio ≥8, ≥95% of BMPCs phenotypically aberrant plus immunoparesis, evolving pattern

Patients with high-risk smouldering MM

(N = 288)

24 x 28-day cycles

Lenalidomide 25 mg/day on Days 1-21 +

Dexamethasone 40 mg/day weekly

Daratumumab SC conventional schedule

Lenalidomide 25 mg/day on Days 1-21 +

Dexamethasone 40 mg/day weekly

Primary endpoint

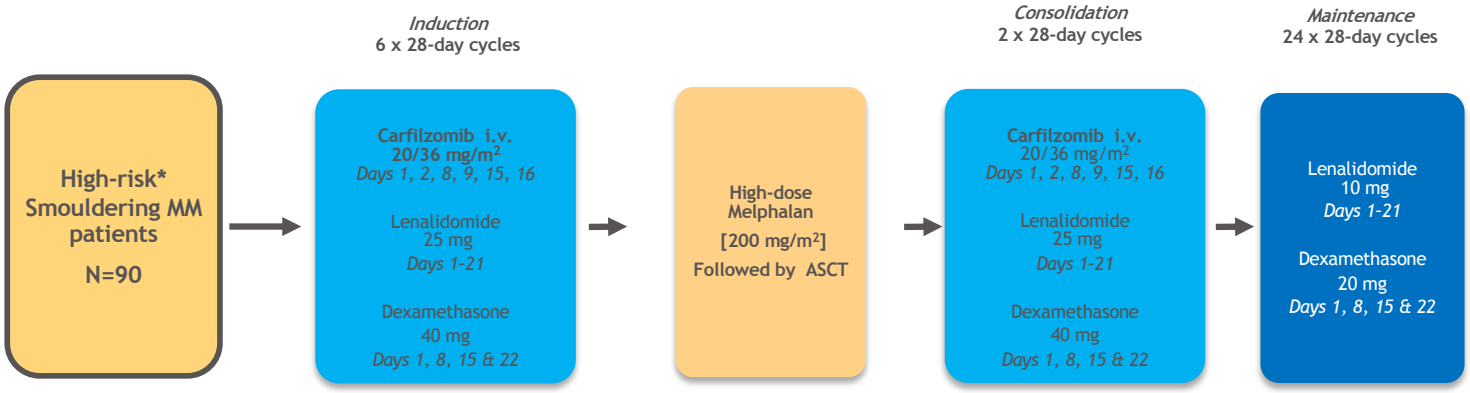
- Overall Survival
- Functional Assessment of Cancer-therapy General score

Inclusion criteria:
- Presence of ≥10% and less than 60% BMPC and at least one of the following: serum M-protein ≥3g/dL, i/uFLC ratio ≥8, or high risk CA

Curative strategies

GEM-CESAR: Study Design

- Multicenter, open-label, phase II trial



High-risk was defined according to the Mayo and/or Spanish models

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

Primary end point: MRD-ve rate after ASCT and maintained at 3 and 5 years post ASCT

Mateos MV et al. ASH 2021. poster presentation

GEM-CESAR

Primary end-point: Undetectable MRD rate after HDT-ASCT and sustained at 4/5 years post HDT-ASCT

	3 months after HDT-ASCT (n=82)	4 years post ASCT (n=58)
MRD-ve 10^{-5}	56/82→ 68.3%	28/58→ 48%
MRD-ve 10^{-6}	39/82→ 48%	25/58→ 43%

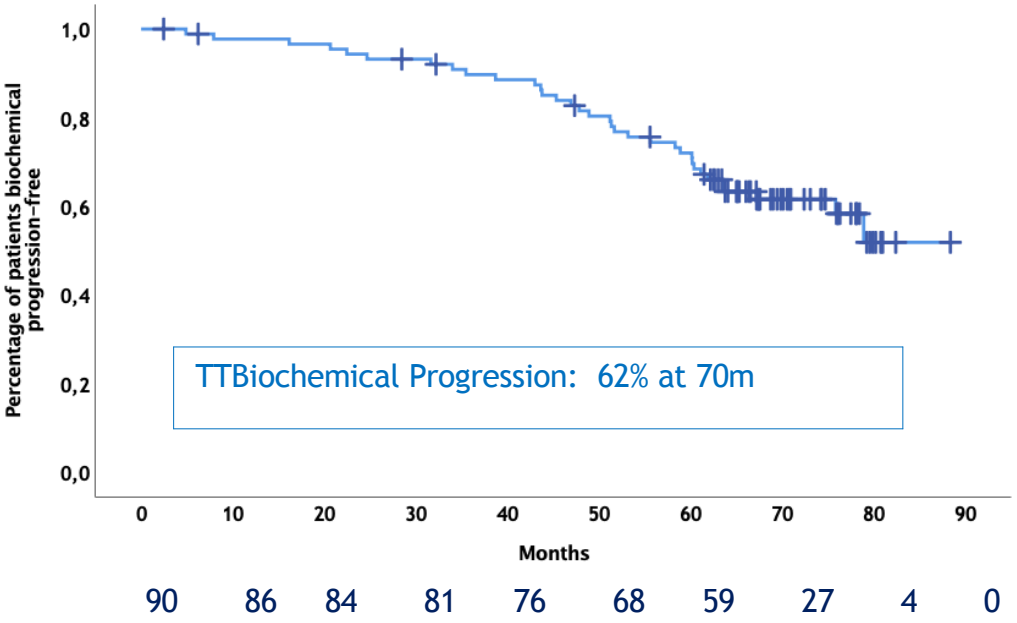
Evaluable patients include: Patients at risk with the Bone Marrow and MRD assessment performed as well as those patients who have discontinued earlier than the specific time point because of progressive or biochemical progressive disease (they qualify as MRD +ve)

GEM-CESAR :Outcomes: Time to Biochemical Progression to MM

Median follow-up: 70.1 (6.2-88.8) months

Type of biochemical progression	n (%)
- Progressive disease	8 (24%)
- Relapse from CR	19 (56%)
- Ultrasensitive MRD relapse: Conversion from MRD-ve to +ve confirmed twice with sensitivity $\geq 10^{-5}$ or increase in >1log between 1st and 2nd determination (if sensitivity 10^{-6})	7 (21%)

TTP to biochemical progression

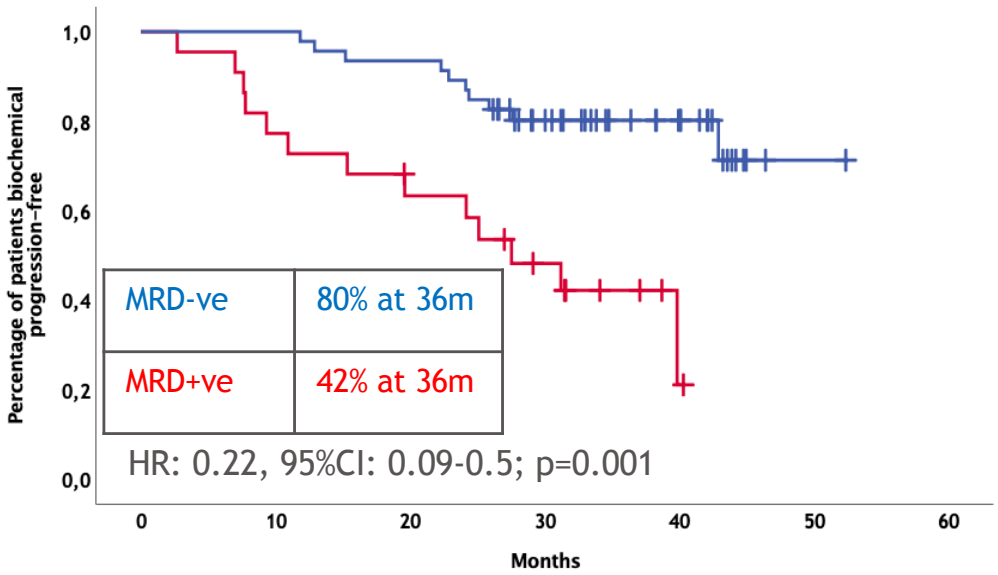


34 pts progressed biochemically: 9 pts during treatment phase and 8 during the first 4 years after trx and 17 (50%) between the 4th and 5th year post trasplant

GEM-CESAR : Factors predicting Biochemical Progression to MM

Median follow-up: 70.1 (6.2-88.8) months

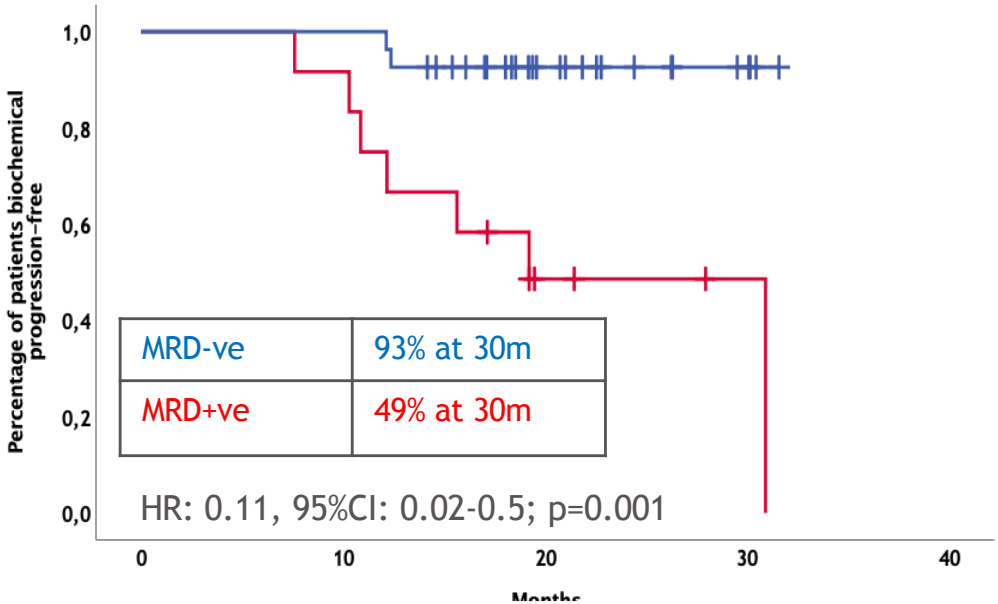
Landmark TT Biochemical Progression by MRD at the end of maintenance



Number of patients at risk

MRD-ve	46	45	42	28	14	1	0
MRD+ve	22	16	12	7	0		

Landmark TT Biochemical Progression by MRD 4 yrs after TRX



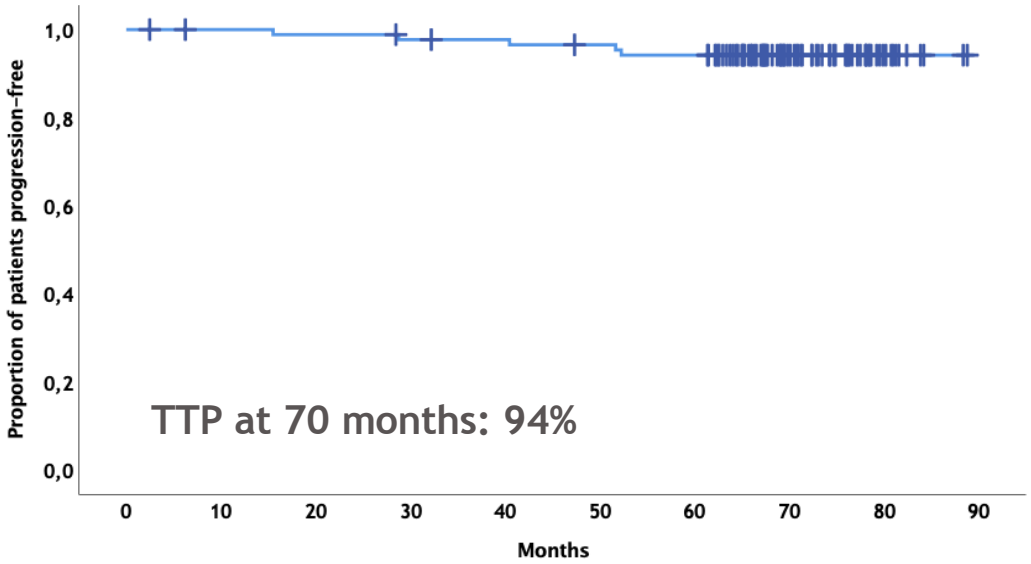
Number of patients at risk

MRD-ve	27	27	27	18	0
MRD+ve	12	12	11	6	1

GEM-CESAR :Outcomes: Time to Progression to MM and OS

Median follow-up: 70.1 (6.2-88.8) months

TTP to active MM



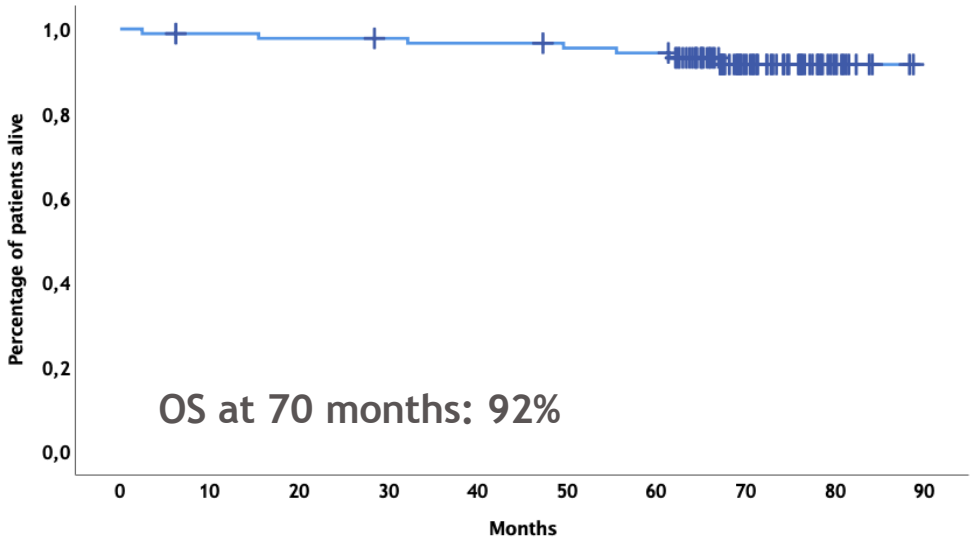
TTP at 70 months: 94%

Number of patients at risk

90	88	86	85	83	82	80	41	10	0

5 pts progressed to symptomatic disease and in 4 pts, the progression was first asymptomatic

OS



OS at 70 months: 92%

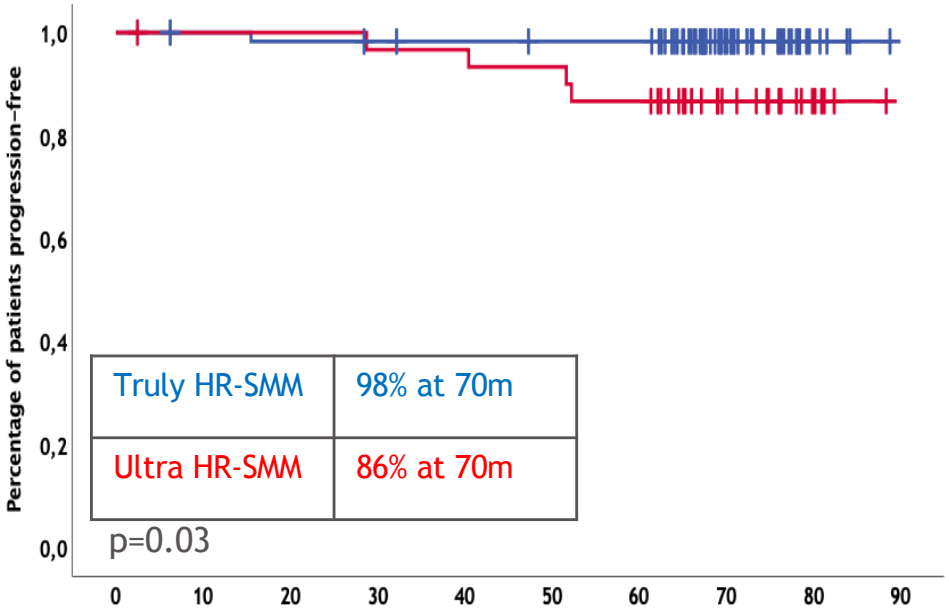
7 pts have died:

- 3 progressive disease-related (1 after rescue therapy with DaraPd);
- 1 cardiac arrest not treatment-related
- 1 massive ischemic stroke during induction
- 1 lung cancer
- 1 MDS

GEM-CESAR : Factors predicting Progression to MM

Median follow-up: 70.1 (6.2-88.8) months

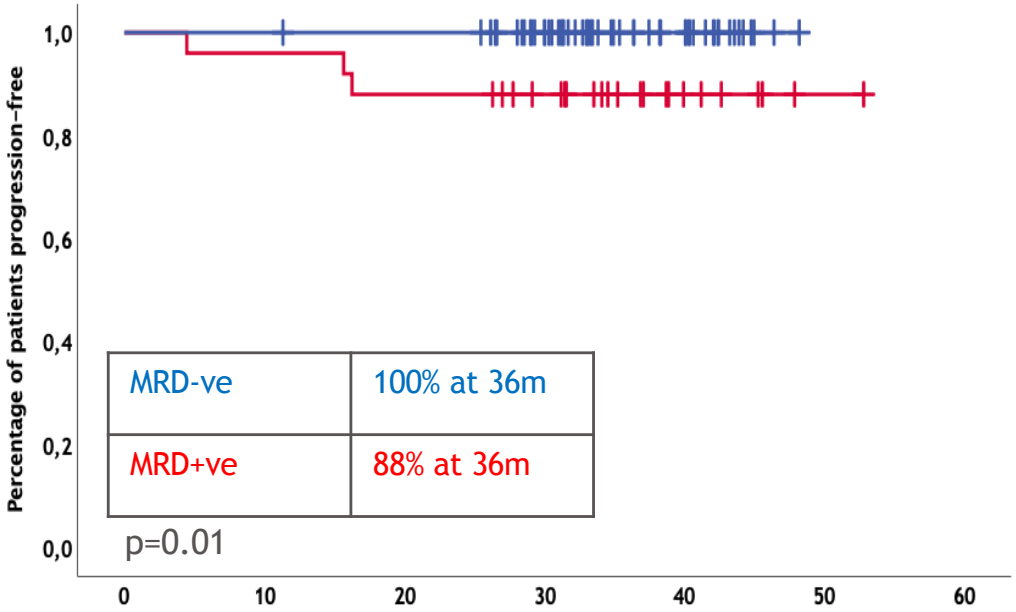
TTP to active MM by risk



Number of patients at risk

HR-SMM 59	58	57	57	55	54	53	27	4
Ultra HR 31	30	30	29	28	27	26	13	4

Landmark TTP to active MM by MRD after maintenance



Number of patients at risk

MRD-ve	46	45	42	28	14	0
MRD+ve	22	16	12	7	0	0

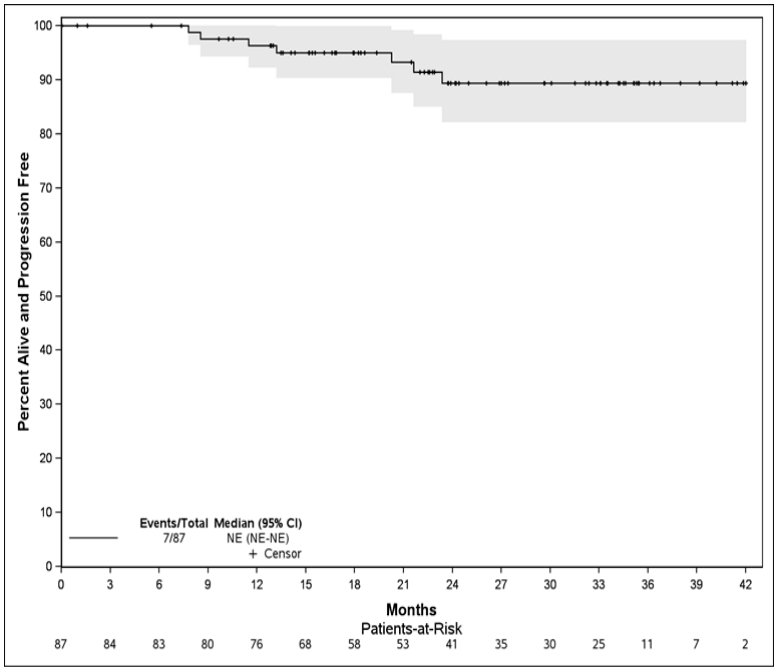
ASCENT trial: Curative approach in HR-SMM patients

INDUCTION
(***4-week cycles for 6 cycles***)
- Carfilzomib (36 mg/m² twice weekly or 56mg/m² weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (weekly for 8, every other week for 16 weeks)
- Dexamethasone 40 mg weekly

CONSOLIDATION
(***4-week cycles for 6 cycles***)
- Carfilzomib (36 mg/m² twice weekly or 56mg/m² weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (every 4 weeks)
- Dexamethasone 20 mg weekly

MAINTENANCE
(***4-week cycles for 12 cycles***)
- Lenalidomide (10 mg daily for 3 weeks)
- Daratumumab (q 8 weeks)

- 87 HRSMM patients according to the IMWG 2/20/20 model



ORR: 97% with 94% of VGPR or better

MRD-ve rate: 84%

- Three patients have progressed, median PFS for the cohort has not been reached; PFS rate (95%CI) at 3 years was 89.9% (82.3-98.3%)

Kumar S et al.. ASH 2022: oral presenttation

Summary

- **SMM** is a precursor plasma cell disorder with a **prevalence of 0.5 % in people >40 years**
- **The outcome is not uniform and the progression risk is different over time**
- **Management of SMM should be risk-adapted**
- **Spanish and ECOG trials support the treatment with Rd/R to prevent progression to MM**
- **Trials currently ongoing** will clarify about **other** potential combinations, including the **curative-ones**
- **Genomic models** can help us to identify patients that could benefit of early treatment in addition to the models based on clinical markers
- **Further studies will help us to identify who will benefit from preventive vs curative strategies although it seems HRSMM are closer and closer to MM**