SESSIONE III: Quesiti sul Mieloma Multiplo

La semplice osservazione è ancora lo standard of care del mieloma smouldering?

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Disclosures of Francesca Patriarca

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene-BMS					x		
Janssen-Cilag						x	
Roche						x	
Clinigen						x	
Amgen						x	

Outline

- Current definition of SMM and risk stratification
- Recent and ongoing studies of active treatment
- Recommendations according 2021 EMN consensus statement

Criteri per la diagnosi di mieloma

	MGUS	Mieloma asintomatico	Mieloma sintomatico°
Componente monoclonale	< 30 g/L	> 30 g/L	qualsiasi
Plasmacellule midollari clonali	< 10%	> 10%	> 10%
Sintomi o danno d' organo	assente	assente	presenti

° **Danno d'organo correlato al mieloma**

(C) **ipercalcemia (calcio sierico >11.5 mg/dL o limite superiore della norma)**

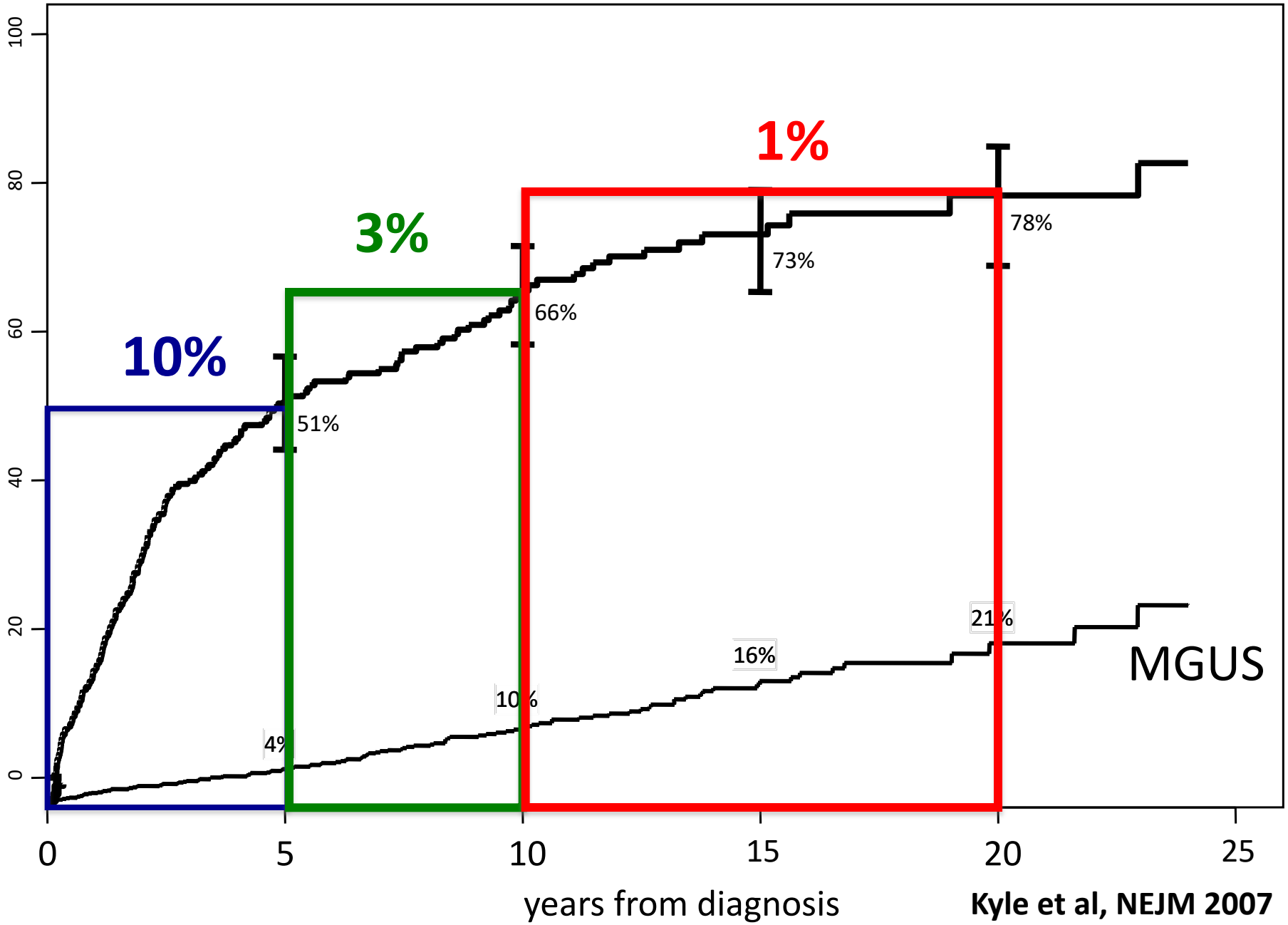
(R) **Insufficienza renale (creatinina sierica >2 mg/dL)**

(A) **Anemia (emoglobina <10 g/dL o 2g <normale)**

(B) **Lesioni litiche ossee o osteoporosi severa o fratture patologiche**

Kyle RA *et al*., IMWG guidelines on MGUS and SMM, Leukemia 2010, 24: 1121-1127

Progression to Multiple Myeloma

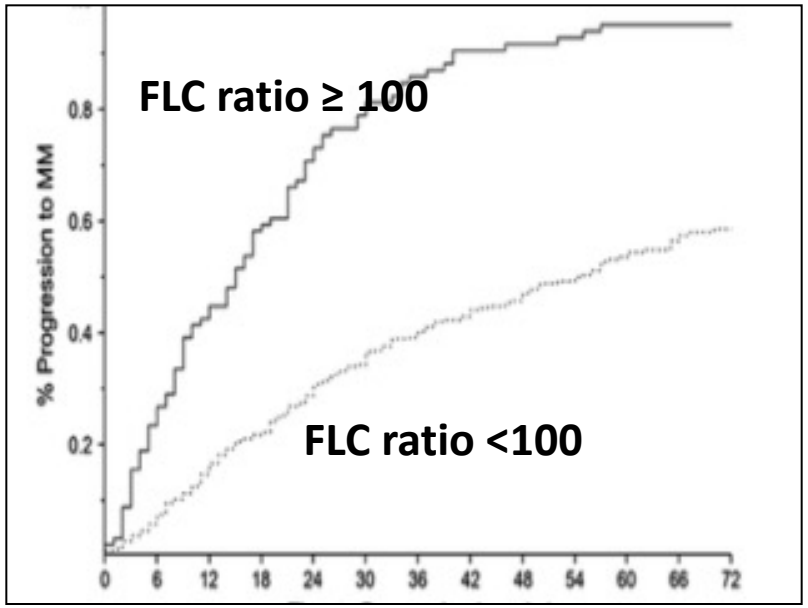


Kyle et al, NEJM 2007

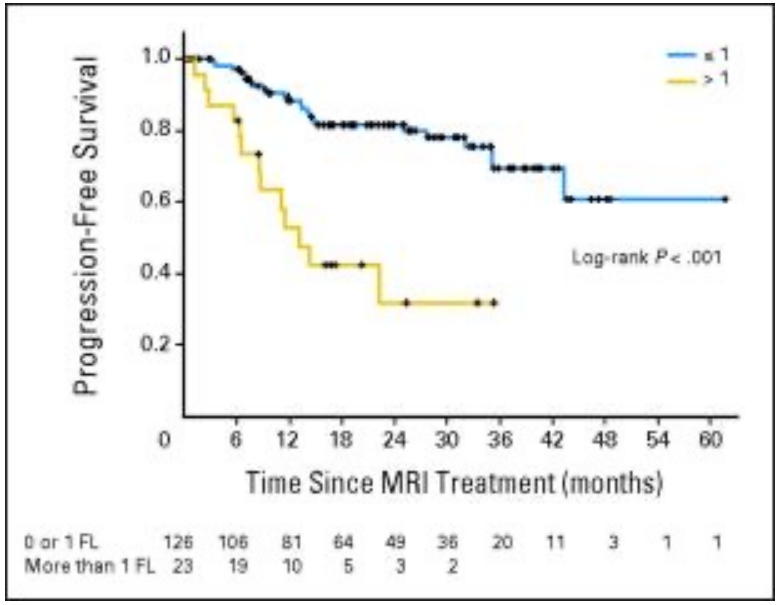
RISK STRATIFICATION OF ASYMPTOMATIC MM

	Mayo Clinic model	Spanish group model
Risk factors:	> 10 % marrow PC > 30 g/L Ig abnormal FLC (<0.125 or>8)	> 95% aPC/BMPC immunoparesis
Groups:	% to symptomatic MM progression (months)	
0	8 % at 10 y	4% at 5 y
1	50% at 10 y	46% at 5 y
2	65% at 10 y	72% at 5 y
3	84% at 10 y	

NEW BIOMARKERS OF MALIGNANCY DEFINING SYMPTOMATIC MM



Larsen JT Leukemia 2013



Jens Hillengass et al. JCO 2010

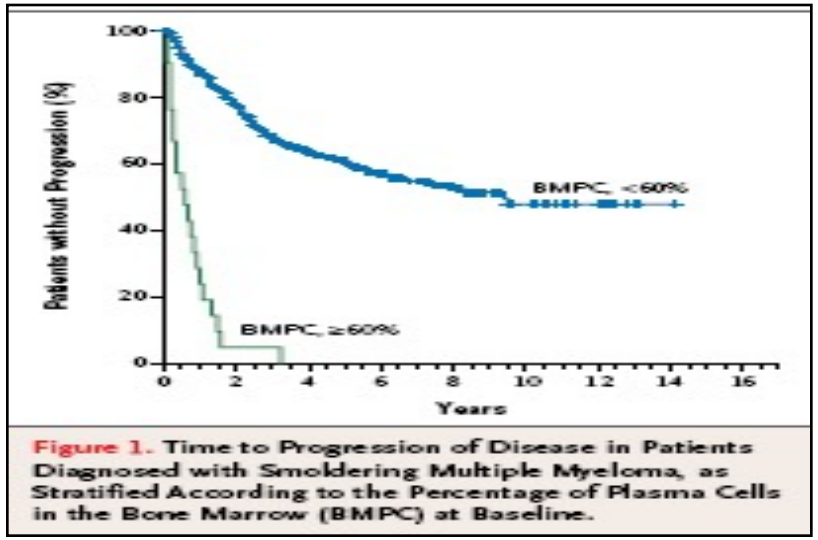


Figure 1. Time to Progression of Disease in Patients Diagnosed with Smoldering Multiple Myeloma, as Stratified According to the Percentage of Plasma Cells in the Bone Marrow (BMPC) at Baseline.

Kyle & Rajkumar NEJM 2011

Revised IMWG diagnostic criteria 2014

***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¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

S Vincent Rajkumar et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15(12):e538-e548

HIGH-RISK SMOLDERING MULTIPLE MYELOMA:
IMWG CURRENT DEFINITION

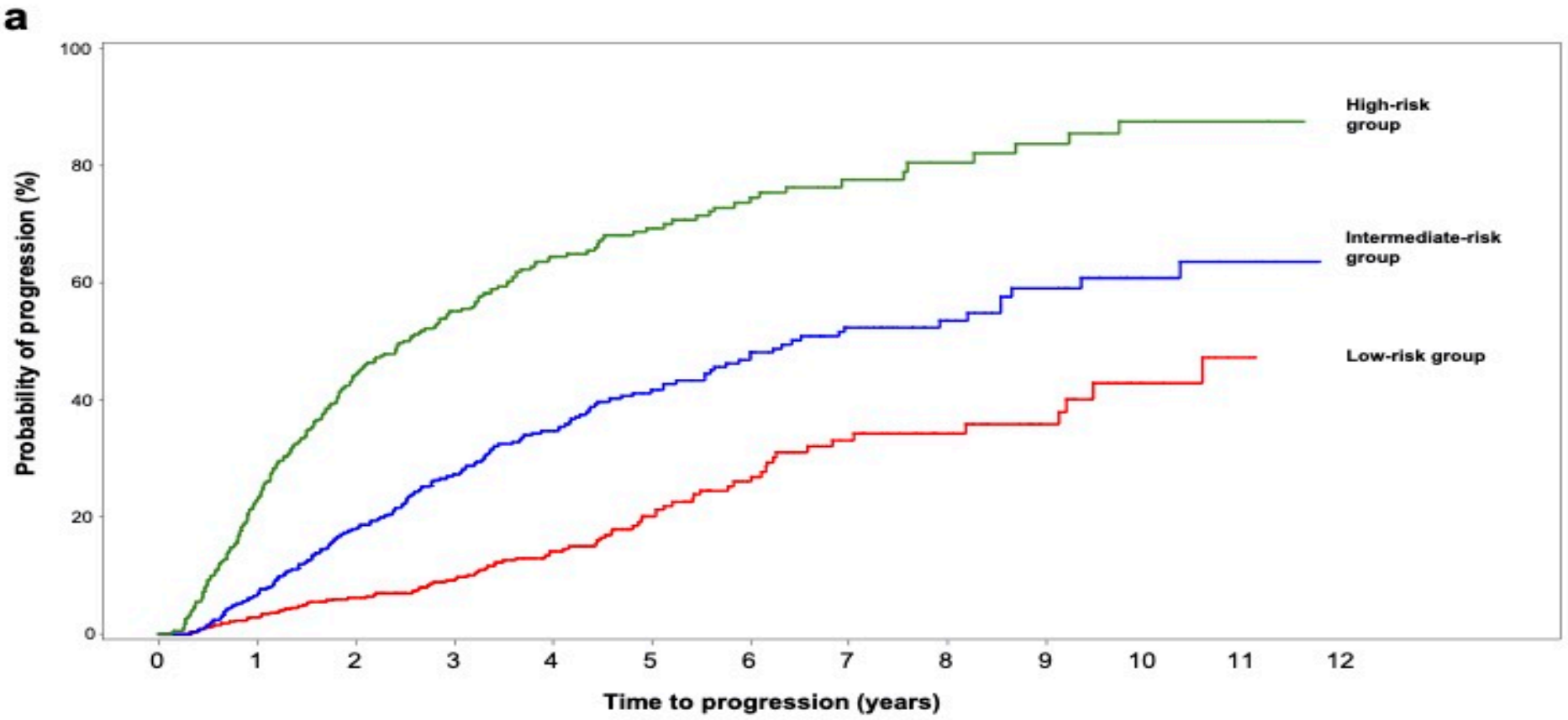
- Serum M-Protein >2 g/dL
- FLC ratio >20
- Bone marrow PC >20%
- t(4;14) or t(14;16) or +1q or del13q/monosomy 13

2/20/20 model

2/20/20 model
plus karyo abnormalities

Mateos MV et al, Blood Cancer Journal 2020

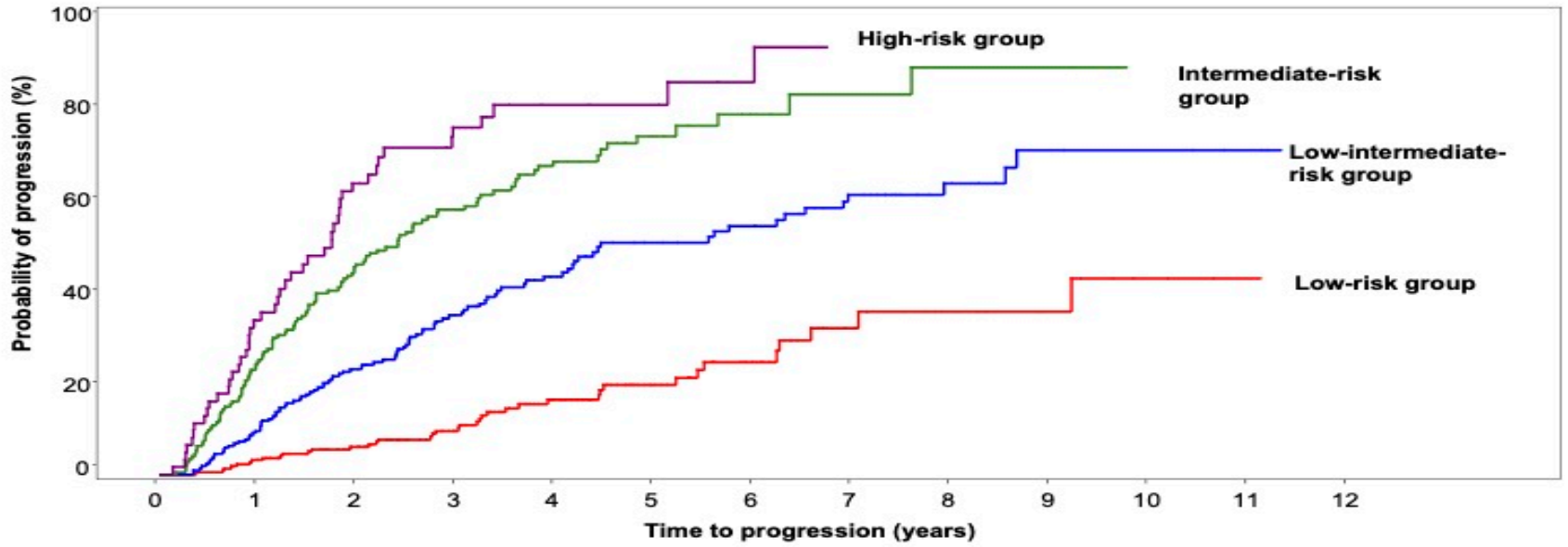
The 2/20/20 model



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)

Mateos MV et al, Blood Cancer Journal 2020

The 2/20/20 model plus cytogenetics

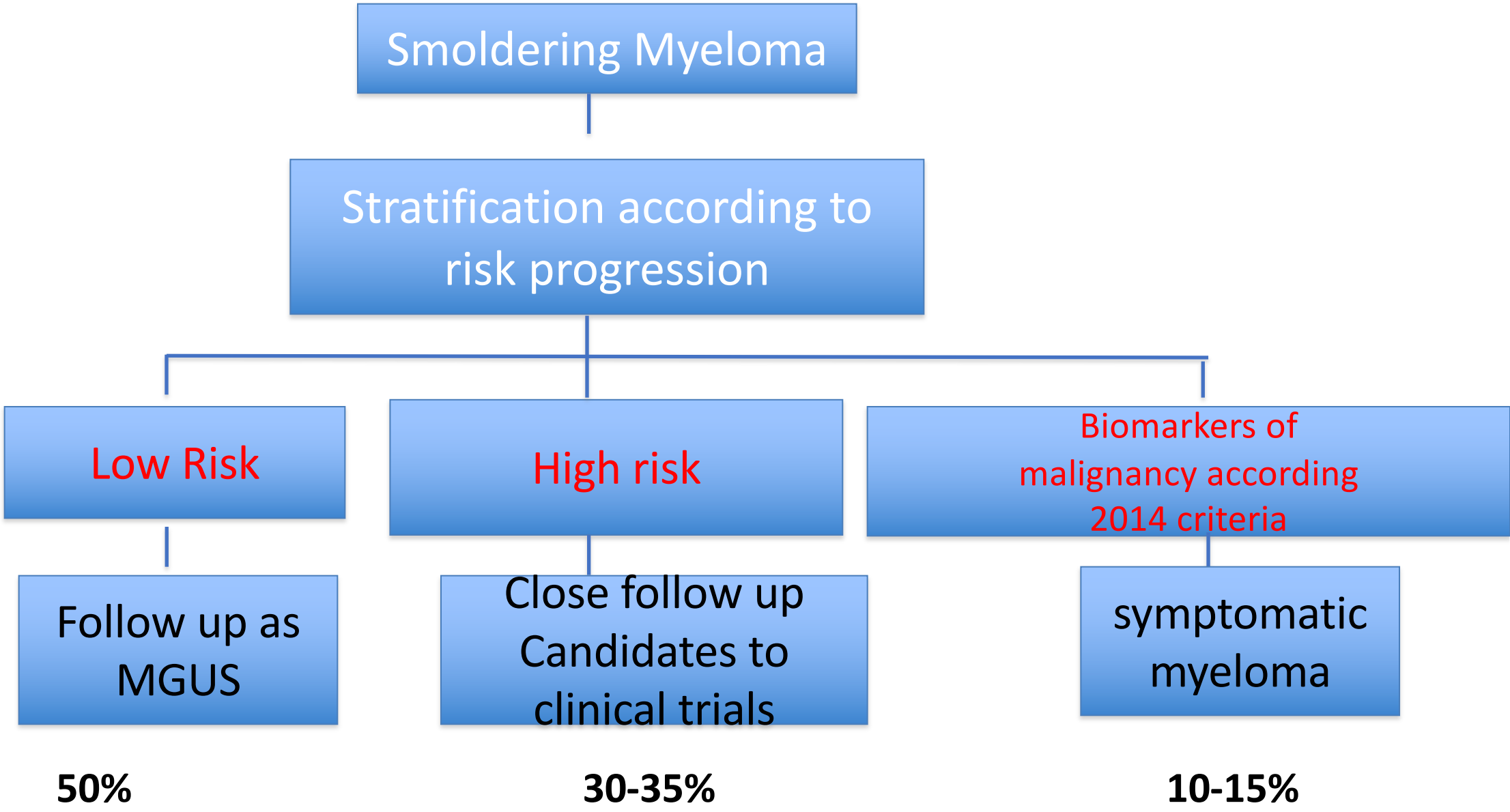


Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0	Reference	6.0%	225 (32.7%)
Low-intermediate	1	4.16 (2.26 – 7.67)	22.8%	224 (32.5%)
Intermediate	2	9.82 (5.46 – 17.7)	45.5%	177 (25.7%)
High	3-4	15.5 (8.23 – 29.0)	63.1%	63 (9.1%)

Fig. 3 Probability of progression at 2 years in the four different subgroups of patients according to the model 2/20/20 plus cytogenetic abnormalities (t(4;14), t(14;16), +1q, and/or del13q/monosomy 13). This model defined four groups of SMM patients: low risk with none of the factors had a progression risk at 2 years of 6%, low–intermediate with one factor present had a progression risk at 2 years of 23%, intermediate risk with the presence of 2 factors had a risk of progression at 2 years of 37%, and the high risk with ≥3 of the factors had a progression risk at 2 years of 63%.

Mateos MV et al, Blood Cancer Journal 2020

New Paradigm for Smoldering Myeloma



Goals of the SMM treatment

low-intense treatments → to delay progression

intense treatments → to reach MRD negativity and potentially cure the patients

LOW-INTENSE TREATMENTS

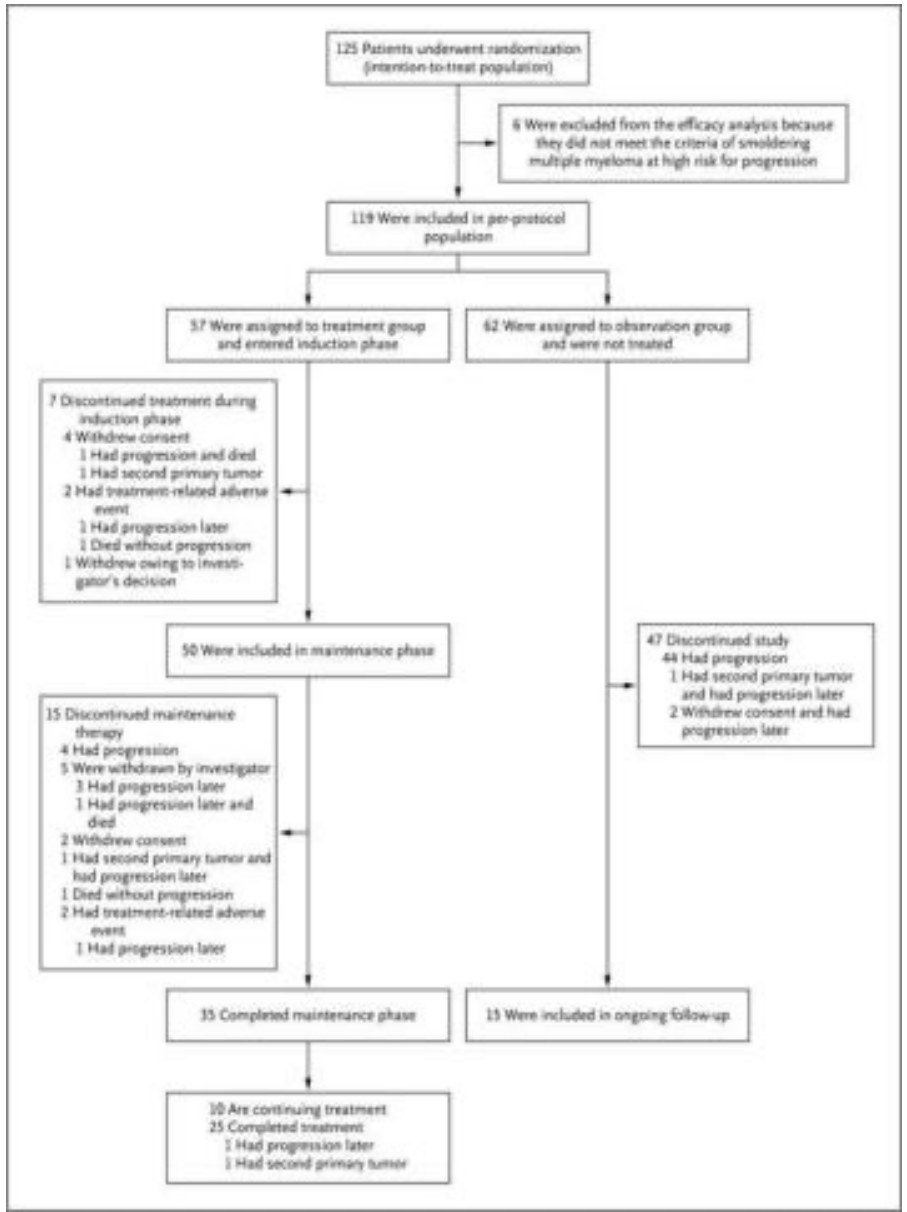
Drug/drug combination	Reference	Phase	Design	N pts
Len±dexa	Mateos et al, Lancet Oncol 2016 and Hemasphere 2020 Lonial et al, J Clin Oncol 2019	III III	C1-9: Len 25mg d1-21 +dexa 20 d1-4 e d12-15; C1-24:len 10mg 1-21 vs obs Len 25 mg d1-21 until progr vs obs	119 182
Daratumumab	Landgren et al, Leukemia 2020	II	Dara 16mg/Kg x 8-wk Extendend intense: C1 every 1 w; C2-3 every other w;C4-7every 4 w;C8-20 every 8w Interm intense :C1 every1w;C2-20 every 8 w Short dosing: C1 every 1 w	123
Elotuzumab	Jagannath et al, Br J Haematol 2018	II	Elo 20 mg/Kg d1,8, then every 4 w Elo 10 mg/Kg d1,8,15,22, then every 2 w	31
Isatuximab	Manasanch et al, Blood 2019	II	Isa 20 mg/kg i.v. in 4 w cycle [C1] every w; [C2-6] every other w; [C7-30] every 4 w	24 (planned 61)

The Spanish trial

Experimental Arm

C1-9: Len 25mg d1-21
plus dexa 20 d1-4 e d12-15;

C10-24:len 10mg 1-21



Control arm:

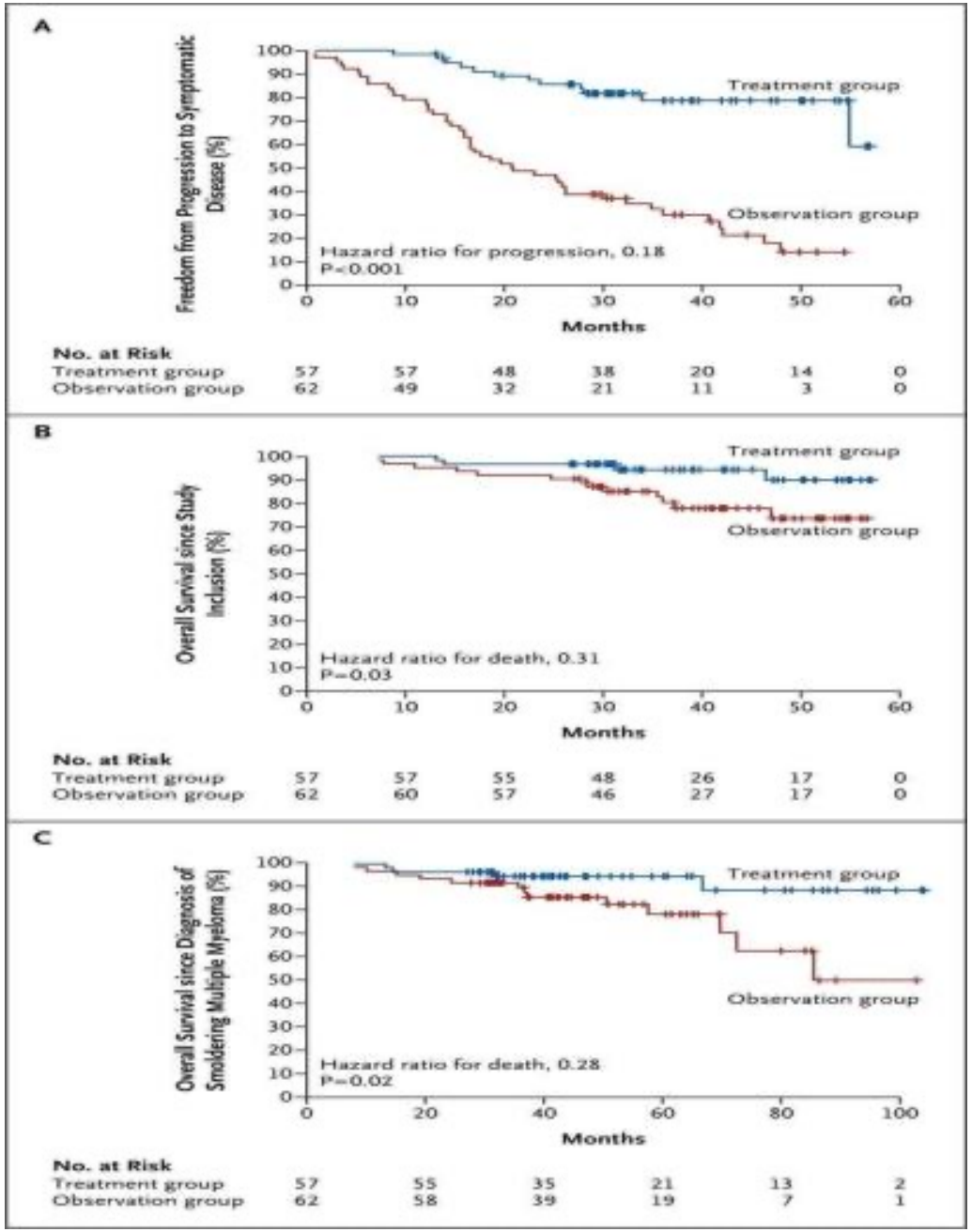
observation

Mateos MV et al, NEJM 2013

Table 1. Baseline Demographic and Clinical Characteristics of the Per-Protocol Population.*

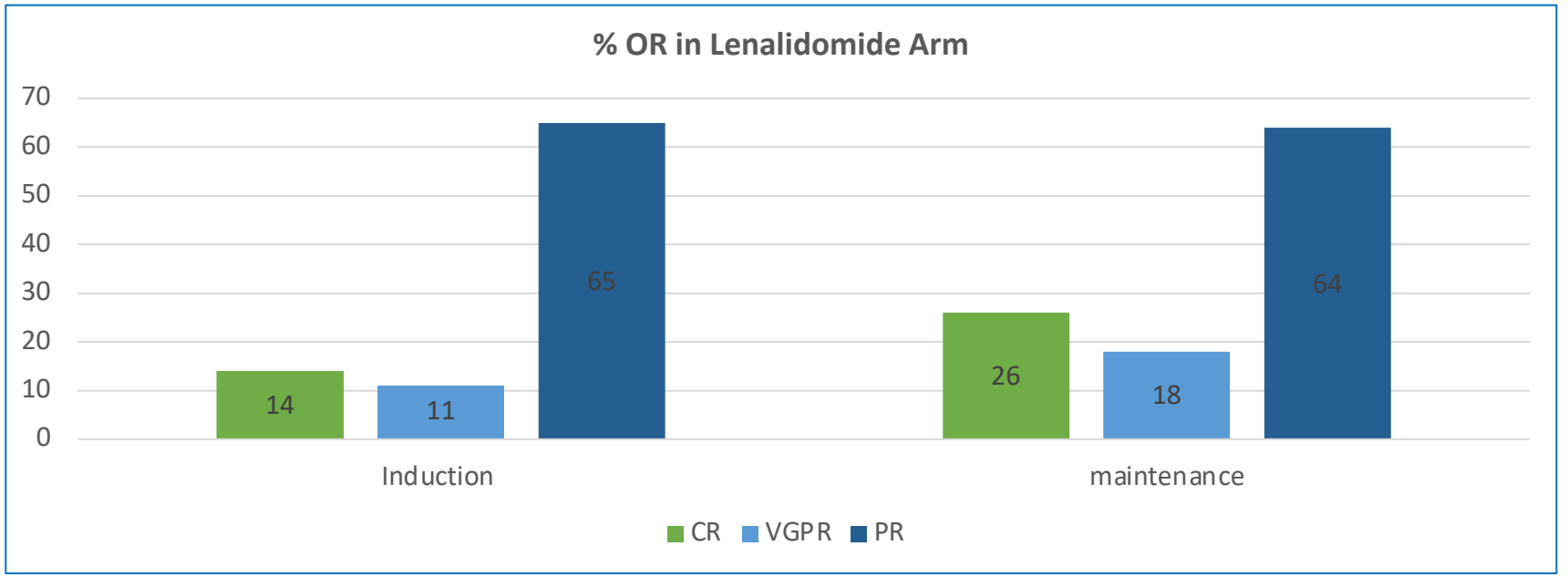
Characteristic	Treatment (N = 57)	Observation (N = 62)
Age — yr		
Median	63	69
Range	42–91	38–83
Sex — no. (%)		
Male	25 (44)	28 (45)
Female	32 (56)	34 (55)
Time since diagnosis — no. (%)		
≤6 mo	25 (44)	26 (42)
>6 mo	32 (56)	36 (58)
Criteria for high-risk smoldering myeloma — no. (%)		
Monoclonal component and plasma-cell bone marrow infiltration†	10 (18)	8 (13)
≥95% aberrant plasma cells plus immunoparesis‡	23 (40)	24 (39)
Both criteria	24 (42)	30 (48)
Monoclonal component		
In serum — g/dl		
Median	27.0	27.4
Range	0–56.6	0–64.5
In urine — g/24 hr		
Median	0	0.002
Range	0–16.2	0–18.2
Level of plasma-cell bone marrow infiltration — %		
Median	18	16
Range	2–48	4–64

* No significant differences were observed between the two study groups.
† The monoclonal-component level indicating high-risk disease was defined as an IgG level of at least 3 g per deciliter, an IgA level of at least 2 g per deciliter, or Bence Jones proteinuria of more than 1 g per 24 hours. A level of plasma-cell infiltration into bone marrow of at least 10% also indicated high-risk disease.
‡ Aberrant plasma cells were detected by means of flow cytometry. Immunoparesis was defined as reductions in one or two uninvolved immunoglobulins of more than 25%, as compared with normal values.



Median survival 40 months

Mateos MV et al, NEJM 2014



In the treatment group, 11/57 (19%) went off treatment (1 fatal infection, 4 severe AE, 6 consent withdrawal).

In the observation group, 2/62 (3%) patients withdrew informed consent.

at median follow-up of 75 months

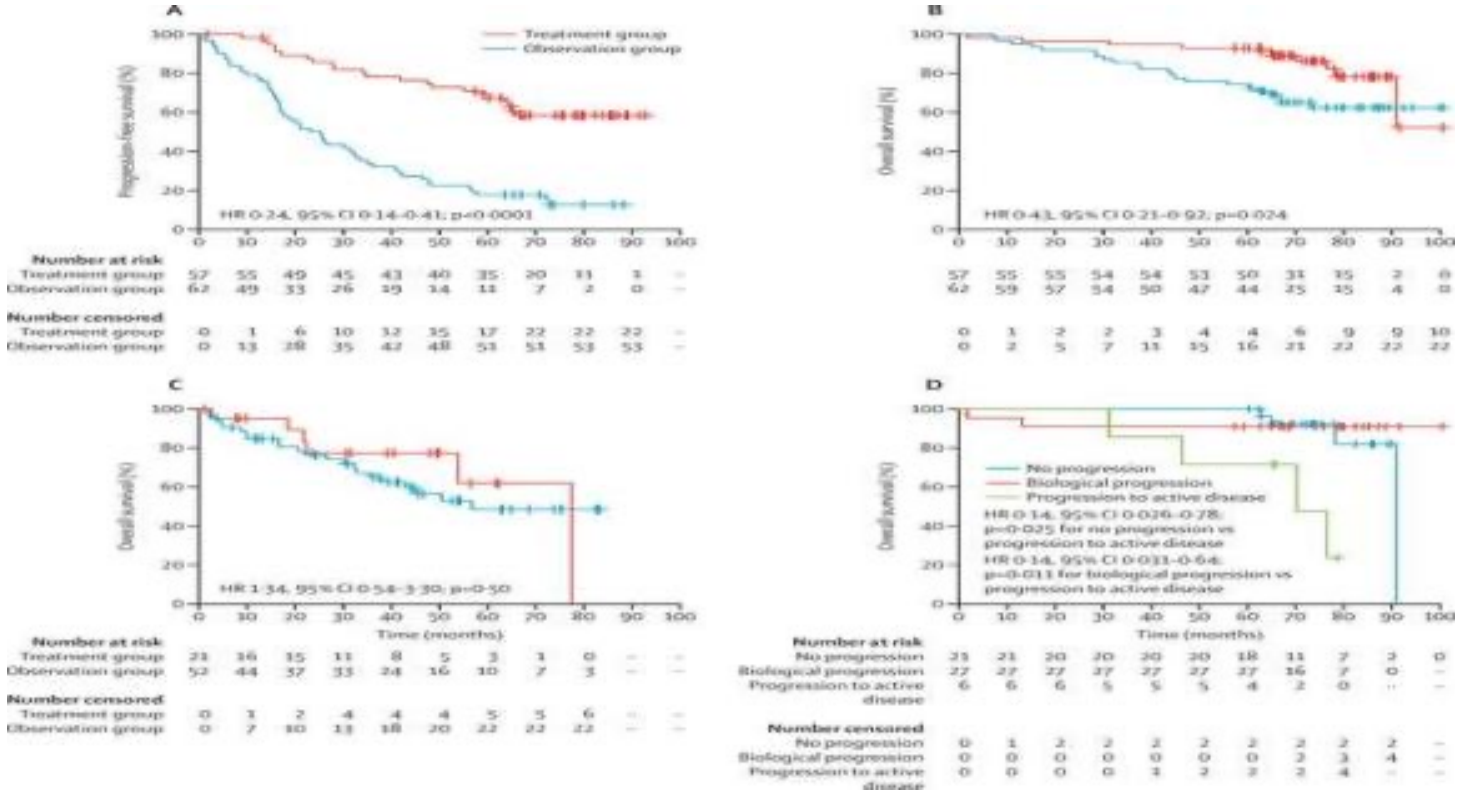


***Figure 2*: Progression-free and overall survival**
(A) Time to progression to myeloma. (B) Overall survival from the point of enrolment into the trial. (C) Overall survival from the point of progression to myeloma. (D) Overall survival from the point of inclusion in the trial according to type of progression versus no progression. Vertical lines indicate censored patients. HR=hazard ratio.

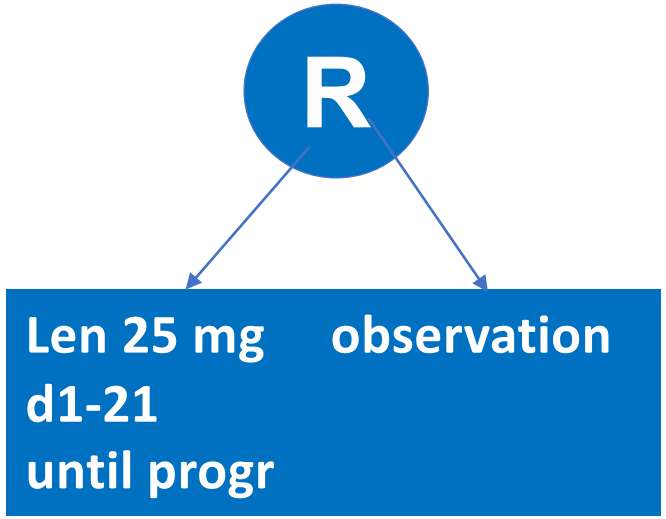
At median follow-up of 10.8 years (range: 5-12.5):
The median TTP in the treatment arm was 9.0 years and in the control arm 2.1 years (HR: 0.27 (95% confidence interval, 0.16 to 0.42; P < 0·0001).
Median OS has not been reached in the treatment arm while it was 7.8 years in the control arm (HR, 0.54; 95% confidence interval, 0.3 to 0.9; P = 0·034).

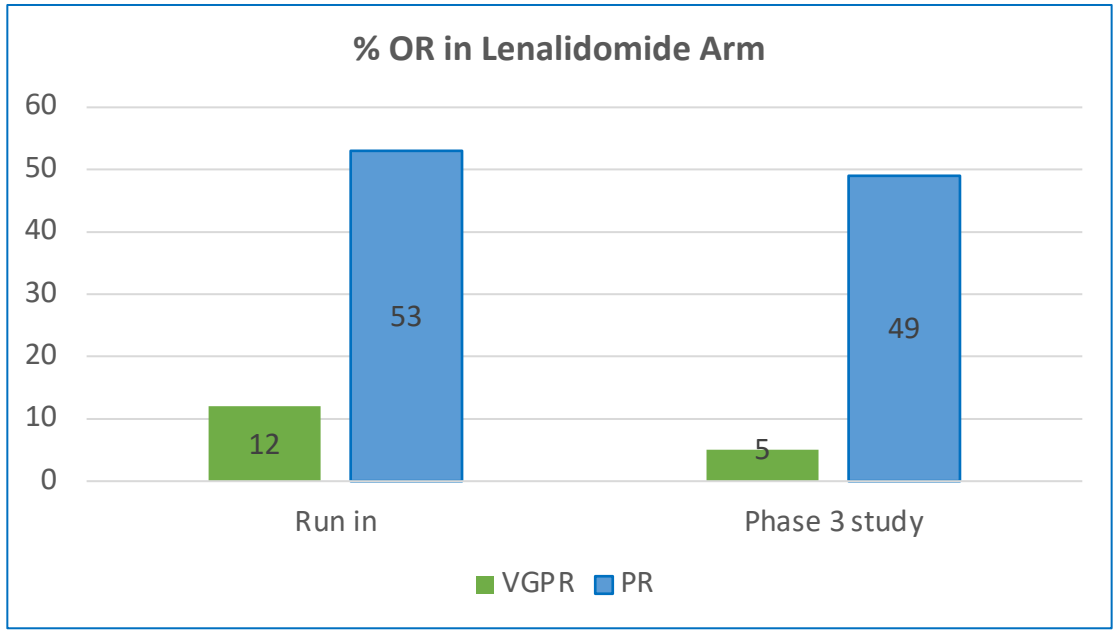
Mateos et al, Lancet Oncology 2016; Hemasphere 2020 p950

The American study

TABLE 1. Baseline Patient Characteristics

Characteristic	Phase II Run In	Phase III Randomized Trial		
	Lenalidomide (n = 44)	Lenalidomide (n = 90)	Observation (n = 92)	Total (N = 182)
Median age, years (range)	62 (36-83)	63 (31-82)	64 (33-96)	64 (31-86)
Mayo 2018 risk stratification, No. (%)‡				
Low (zero risk factors)	7 (15.9)	31 (34.4)	27 (29.4)	58 (31.9)
Intermediate (one risk factor)	12 (27.3)	34 (37.8)	34 (37.0)	68 (37.4)
High (two to three risk factors)	25 (56.8)	25 (27.8)	31 (33.7)	56 (30.8)





Lonial S et al, J Clin Onc 2019

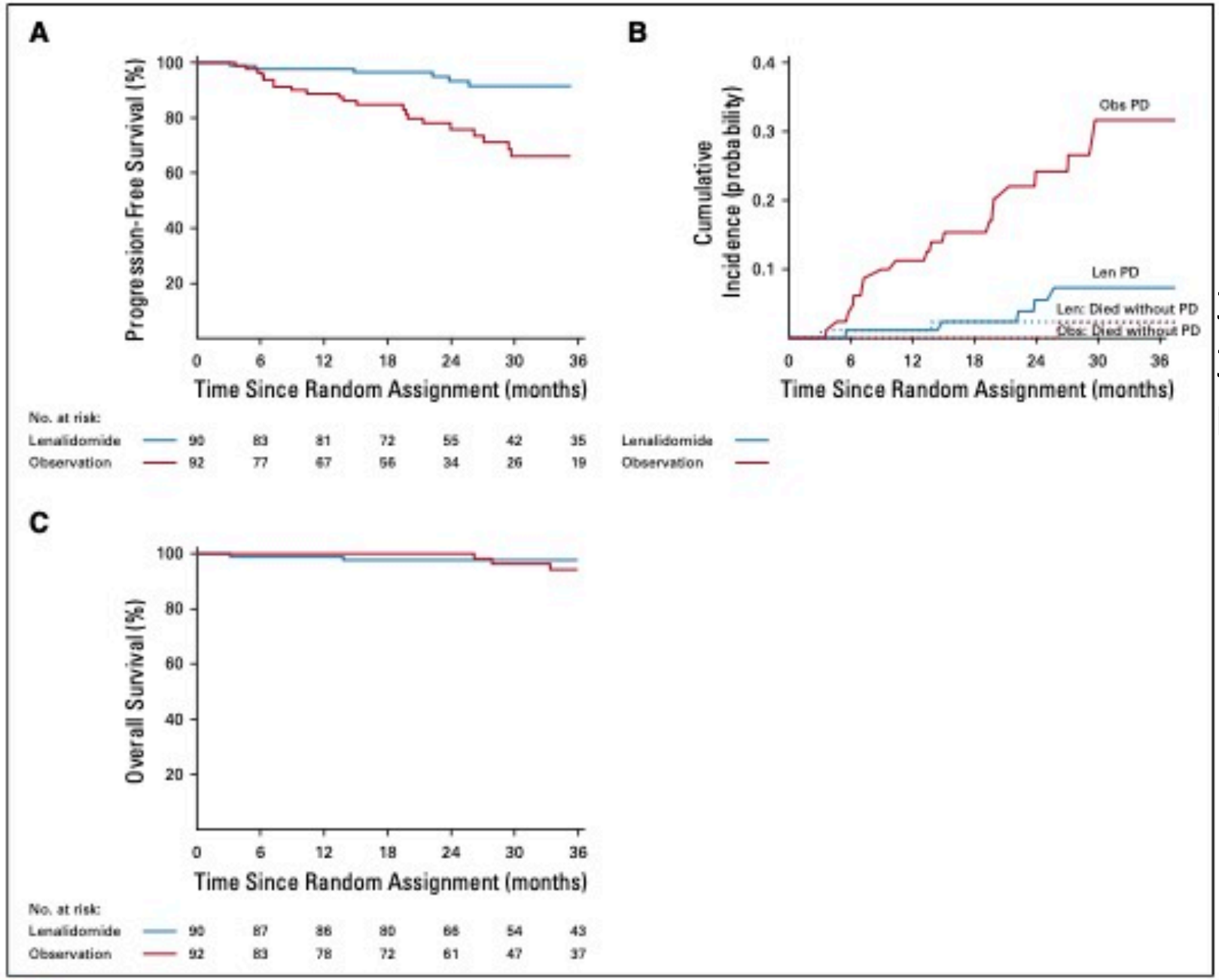


FIG 2. Time to event estimates by treatment arm in phase III: (A) progression-free survival, (B) cumulative incidence of progression, and (C) overall survival in patients with smoldering multiple myeloma. Len, lenalidomide; Obs, observation.

36/90 (40%) experienced grade 3-4 AE, 18/90 (20%) went off Lena treatment for AE

Median follow-up 35 months

Lonial S et al, J Clin Onc 2019

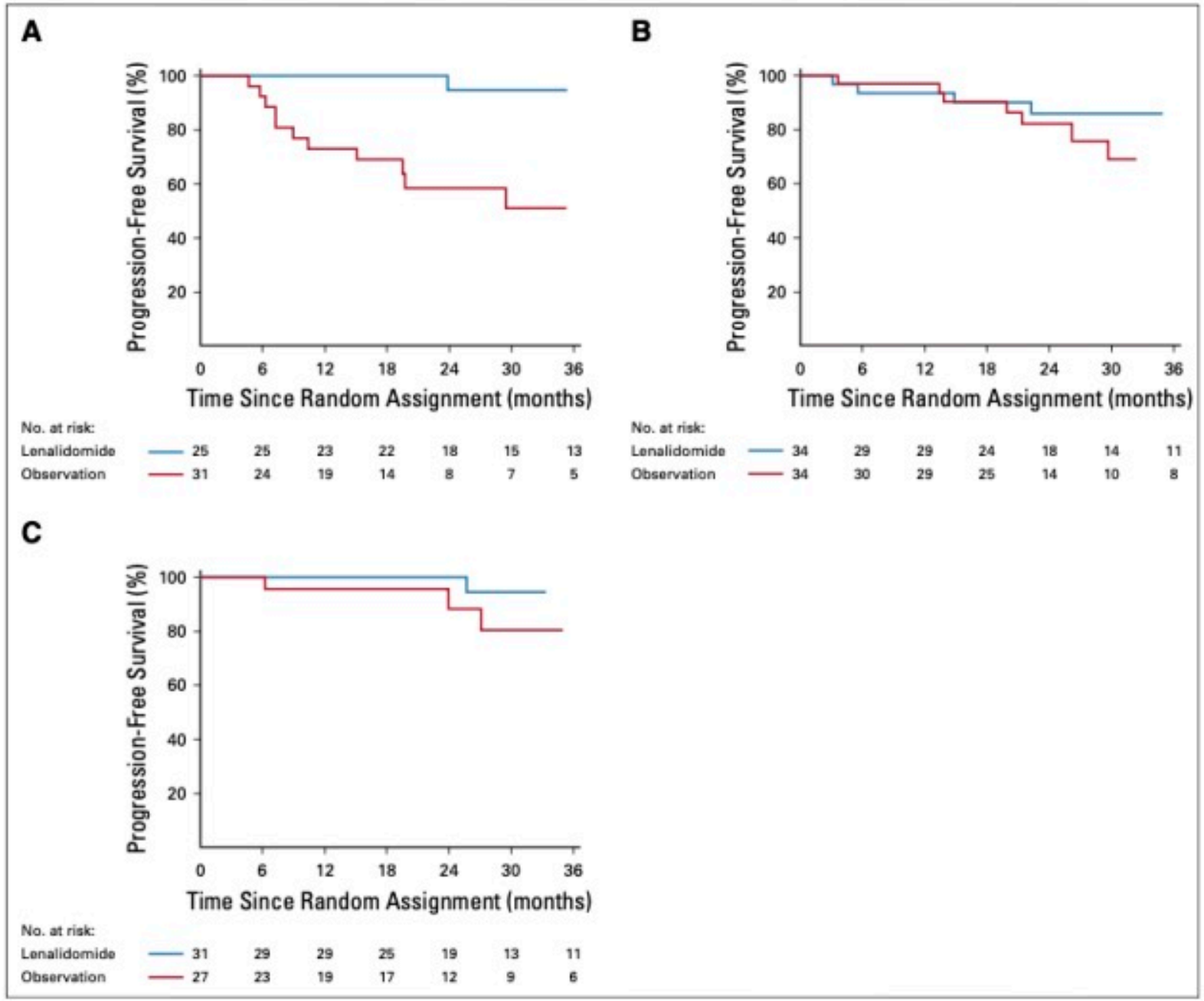


FIG 5. Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2018 risk subgroup: (A) high risk, (B) intermediate risk, and (C) low risk.

PFS benefit of Len more pronounced in Mayo 2018 high-risk SMM (HR 0.09) and Intermediate risk SMM HR 0.52).

Median follow-up 35 months

Lonial S et al, J Clin Onc 2019

These studies, however, have not changed the current “no treatment” paradigm, due to several limitations:

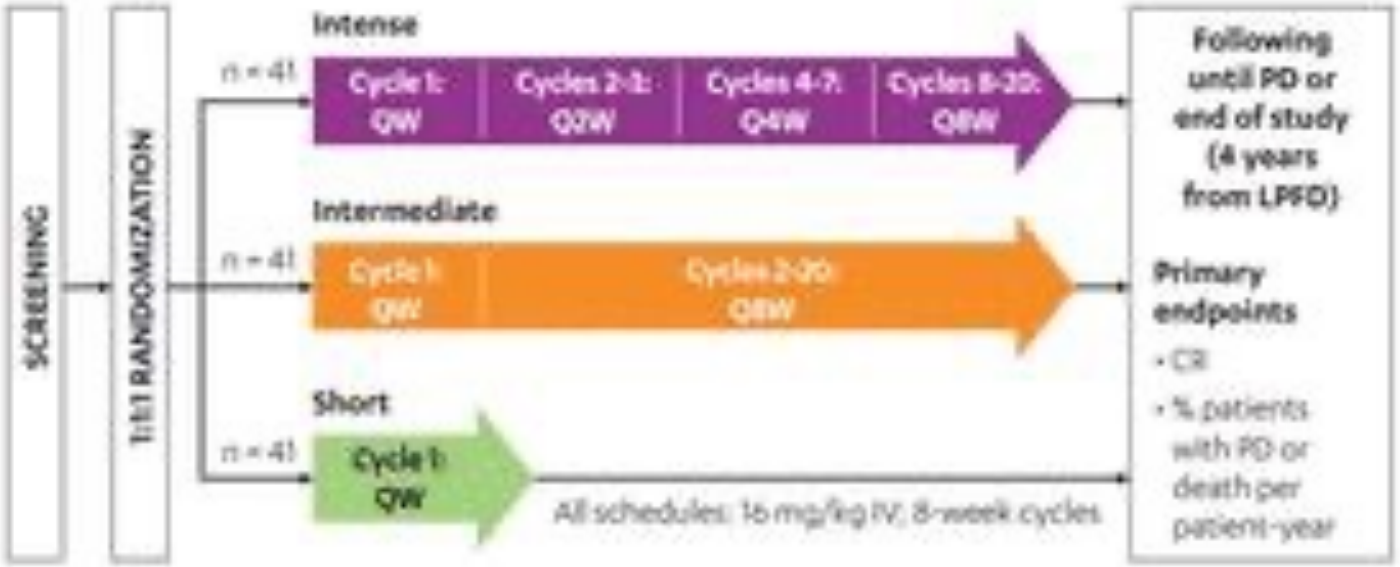
1) both trials had a limited number of patients and started before the 2014 update criteria had been settled, therefore, a proportion of the patients enrolled were likely to be reclassified as having active disease;

2) a relevant number of patients discontinued the experimental treatment voluntarily or because of adverse effects;

3) clinical results of the studies were not presented to the regulatory agencies for the drug authorization in the market.

CENTAURUS TRIAL:
Study Design and Treatment

- **This was a randomized, open-label, multicenter, phase 2 study with daratumumab monotherapy in patients with high-risk or intermediate-risk SMM**



Key inclusion criteria:

- Diagnosis of SMM for <5 years
- Bone marrow plasma cells ≥10% to <60% and ≥1 of the following:
  - Serum M-protein ≥3 g/dL (immunoglobulin A ≥2 g/dL)
  - Urine M-protein >500 mg/24 hours
  - Abnormal free light chain (FLC) ratio (<0.126 or >8) and serum M-protein <3 g/dL but ≥1 g/dL
  - Absolute involved serum FLC ≥100 mg/L with an abnormal FLC ratio (<0.126 or >8, but not ≤0.01 or ≥100; added following a protocol amendment)

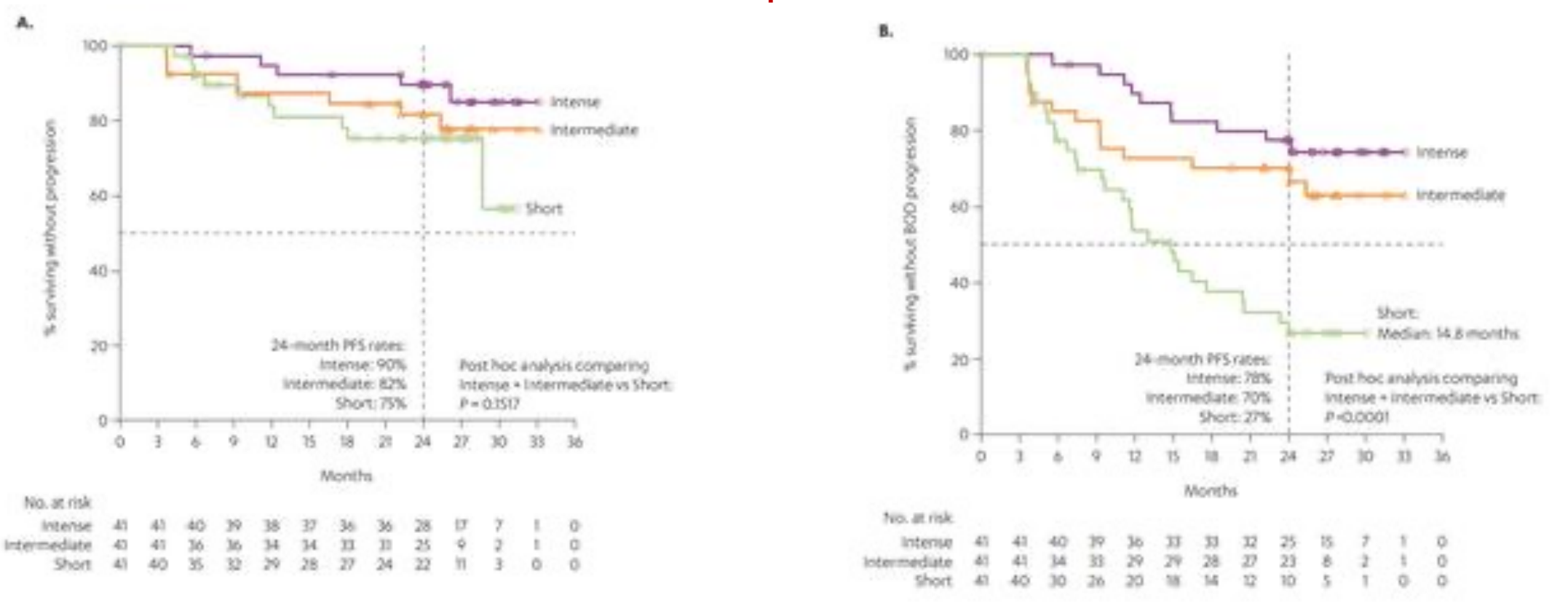
Key exclusion criteria:

- Presence of ≥1 SLiM-CRAB myeloma-defining event

Landgren, C.O., et al. Leukemia. 2020

CENTAURUS STUDY: PFS

median follow-up of 25.9 months

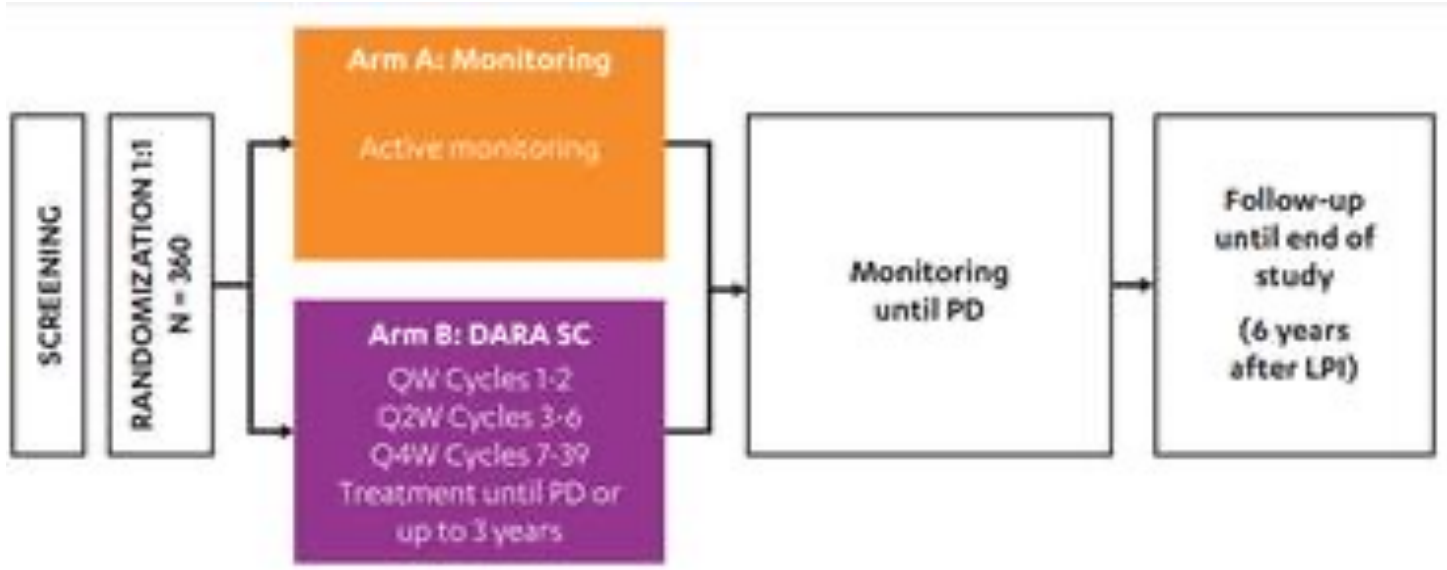


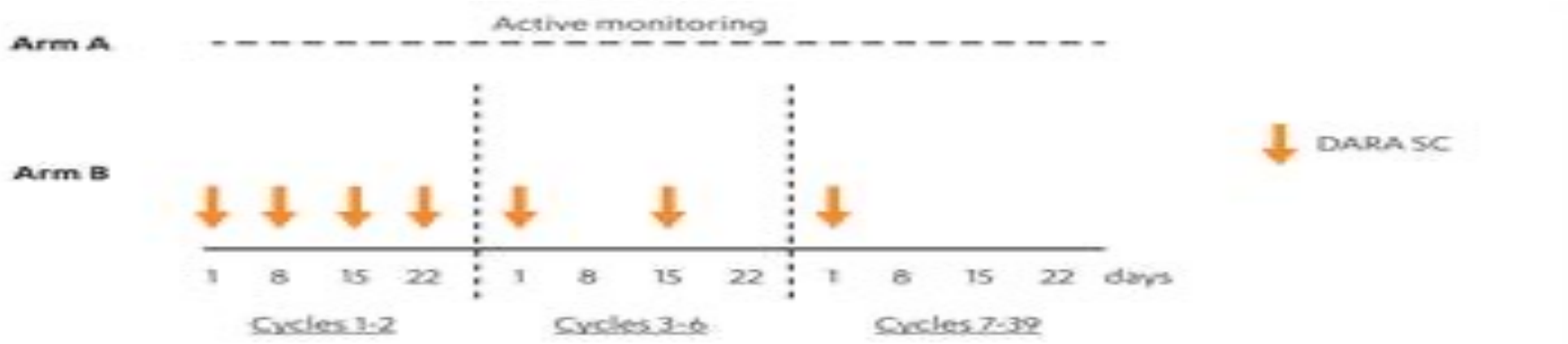
- Using SLiM-CRAB criteria, median PFS was not reached in any arm with 24-month PFS rates of 90%, 82% and 75% in the intense, intermediate and short treatment arms, respectively. o No statistical difference was noted in the combined intense and intermediate treatment arms versus the short treatment arm (P=0.1517).
- Using BOD, median PFS was reached only in the short treatment arm (14.8 months) with 24-month PFS rates of 78%, 70%, and 27% in the intense, intermediate and short treatment arms, respectively.
- A significantly longer median BOD PFS was noted in the combined intense and intermediate treatment arms than in the short treatment arm (P<0.0001).

Landgren, C.O., et al. Leukemia. 2020

AQUILA trial:Study Design

- AQUILA is an ongoing, phase 3, randomized, open-label, multicenter study in patients with high-risk SMM. The study will include approximately 170 sites that span 25 countries
- **Primary End-point: PFS**





S. Vincent Rajkumar, ASCO 2018 poster TPS8062

Intense treatments

Drug/drug combination	Reference	Phase	Design	N pts
KRd	Kazandjian et al, JAMA Oncology 2021	II	C1-8: K20/36 mg d1,2,8,9,15,16+len 25 d mg1-21 + 20 mg (C1-4) or 20 mg (d 1,2,8,9,15,16 C1-24: len 25 mg d1-21	18
KRd plus ASCT	Mateos et al, Blood 2019; Puig et al, Blood 2020	II	C1-6: K20/36 mg d1,2,8,9,15,16+len 25 d mg1-21 + 20 mg (C1-4) or 20 mg (C5-8) d 1,2,8,9,15,16 ASCT melphalan 200 mg/mq C7-8 = C1 C1-24: len 25 mg d1-21 + dexa 20 d1,8,15,2	90
Dara-KRd	Kumar et al, Blood 2020a	II	C1-6: K20/36 mg d1,2,8,9,15,16+len 25 d mg1-21 + 40 mg d 1,8,15,22+ darat16 mg/kg for 8 w, every other w for 16 w C7-12: K36 mg d1,2,8,9,15,16+len 25 d mg1-21 + 20 mg d 1,8,15,22+ dara 16 mg/kg every 4 w C8-20:len 10 mg 1-21+ dara every 4 w	46 (83 planned)
Ixa-Rd	[14]Mailankody et al, J Clin Oncol 2019	II	C1-94 mg: Ixa 4 mg d 1,8,15+len 25 d mg1-21 + Dexa 40 mg d 1,8,15 C10-24: Ixa 4 mg d 1,8,15+len 15 d mg1-21	26 (56 planned)
Elo-Rd	[15]Liu et al, Blood 2018a	II	C1-2: Elo10 mg/Kg d1,8,15,22 +len 25 mg 1-21+dexa 40 mg1,8,15,22 C2-8: PBSC collection and Elo10 mg/Kg d1,15+len 25 mg d1-21+dexa 40 mg d1,8,15 C9-C24: Elo10 mg/Kg d1+len 25 mg d1-21	50

KRd trial: study design

- Single-arm, single-center ,phase II trial

Patients newly diagnosed with high-risk* smoldering MM (N = 54)

Induction
8 x 28-day cycles

Carfilzomib IV 20/36 mg/m^2 D1, 2, 8, 9, 15, 16

Lenalidomide 25 mg D1-21

Dexamethasone 40 mg D1, 8, 15, 22

Maintenance
24 x 28-day cycles

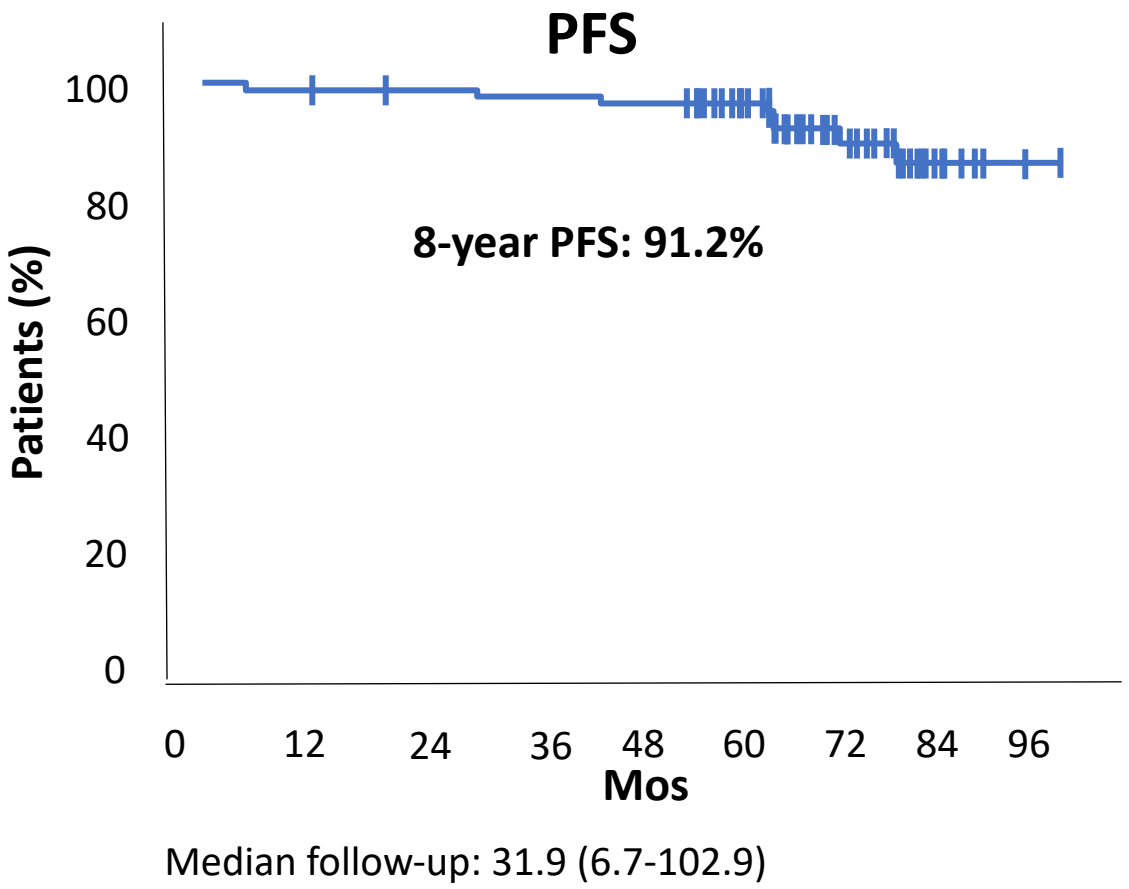
Lenalidomide 10 mg D1-21

*Using Mayo and/or Spanish models (pre-2014 diagnostic criteria): ≥ 3 g/dL serum M-protein and ≥ 10% PCs in BM or either ≥ 3 g/dL serum M-protein or ≥ 10% PCs in BM and > 95% of aberrant PCs within PCs BM by immunophenotyping and immunoparesis.

- Primary endpoint: MRD negativity CR rate
- Secondary endpoints: response, TTP, PFS, OS, safety

Kazandjian et al, JAMA Oncology 2021

CLINICAL RESULTS



Median follow-up: 31.9 (6.7-102.9)

MRD neg CR rate 70.4%

No grade 5 adverse effects
No grade 4 adverse effects
38% grade 3 non hematological adverse effects

- No deaths occurred

Kazandjian D et al, JAMA Oncology 2021

GEM-CESAR Trial: study design

- Multicenter, open-label phase II trial

Patients newly diagnosed with high-risk* smoldering MM (N = 90)

Induction
6 x 28-day cycles

Carfilzomib IV 20/36 mg/m^2 D1, 2, 8, 9, 15, 16

Lenalidomide 25 mg D1-21

Dexamethasone 40 mg D1, 8, 15, 22

High-dose melphalan 200 mg/m^2 followed by ASCT

Consolidation
2 x 28-day cycles

Carfilzomib IV 20/36 mg/m^2 D1, 2, 8, 9, 15, 16

Lenalidomide 25 mg D1-21

Dexamethasone 40 mg D1, 8, 15, 22

Maintenance
24 x 28-day cycles

Lenalidomide 10 mg D1-21

Dexamethasone 20 mg D1, 8, 15, 22

*Using Mayo and/or Spanish models (pre-2014 diagnostic criteria): ≥ 3 g/dL serum M-protein and ≥ 10% PCs in BM or either ≥ 3 g/dL serum M-protein or ≥ 10% PCs in BM and > 95% of aberrant PCs within PCs BM by immunophenotyping and immunoparesis.

- Patients with ≥ 1 biomarkers predictive for imminent risk of progression were included
- Patients with bone disease on CT or PET/CT at screening excluded

- Primary endpoint: sustained MRD negativity (by flow cytometry) after HDT-ASCT and at 3 and 5 yrs after HDT-ASCT
- Secondary endpoints: response, TTP, PFS, OS, safety

Mateos. ASH 2019. Puig. ASH 2020

GEM-CESAR: Outcomes

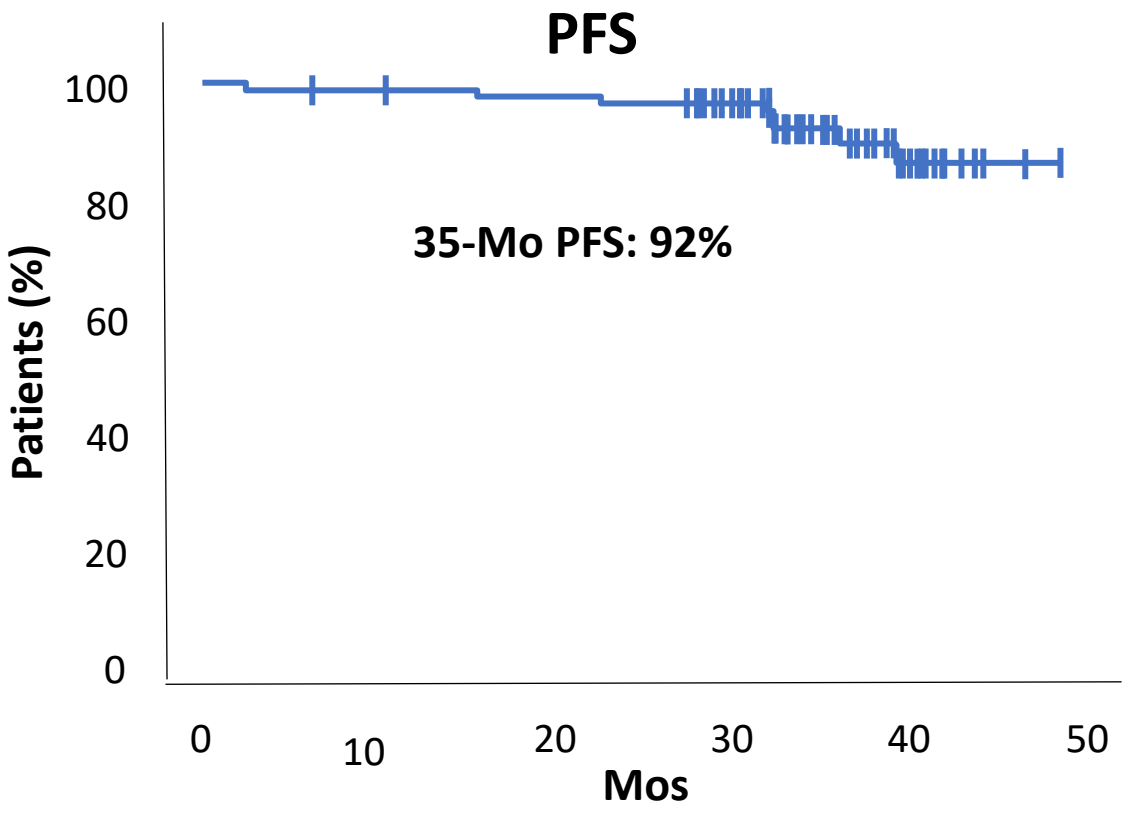
77 patients completed induction, HDT-ASCT, consolidation, and 1 yr of maintenance

Response, %	Induction (KRd x 6) (n = 77)	HDT-ASCT (n = 77)	Consolidation (KRd x 2) (n = 77)	Maintenance (Rd x 1 Yr) (n = 77)
≥ CR	43	63	75	81
VGPR	43	24	18	13
PR	13	13	7	5
Progressive disease	--	--	--	1*
MRD negative	33	49	65	62

*Biological progressive disease at end of maintenance, MRD positive.

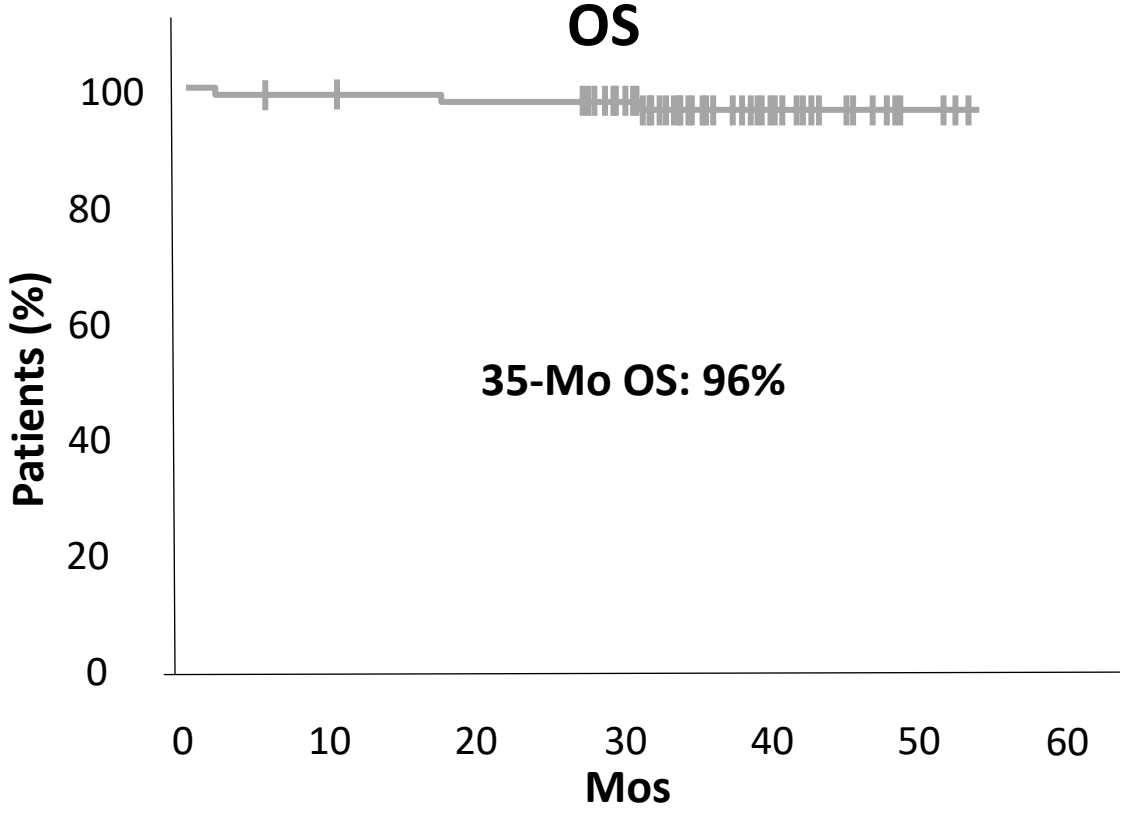
Mateos. ASH 2019. Puig .ASH 2020.

GEM-CESAR: PFS and OS



Median follow-up: 35.2 (5.4-53.2)

- 6 patients progressed (biological PD, n = 5)
- 4 patients with PD were at ultrahigh risk



Median follow-up: 35.2 (5.4-53.2)

- 3 patients died; only 1 was considered a treatment-related death

Mateos. ASH 2019. Abstr 781.

ASCENT Trial : Study Design

- The ASCENT trial was designed to examine if an intense but limited duration therapy can provide significant elimination of tumor burden and potentially lead to long term responses in SMM[1,2]

N = ~ 83

Key inclusion criteria:

- High-risk SMM
- Age 18–80 years

Induction 6 x 28-day cycles	Consolidation 6 x 28-day cycles	Maintenance 12 x 28-day cycles
KRdD Carfilzomib 56 mg/m^2 IV: days 1, 8, 15 Lenalidomide 25 mg PO: days 1–21 Daratumumab 16 mg/kg IV: days 1, 8, 15, 22 of cycles 1–2; days 1, 15 of cycles 3–6 Dexamethasone 40 mg PO: days 1, 8, 15, 22 of cycles 1–6	**KRdD** Carfilzomib 56 mg/m^2 IV: days 1, 8, 15 Lenalidomide 25 mg PO: days 1–21 Daratumumab 16 mg/kg IV: day 1 of cycles 7–12 Dexamethasone 20 mg PO: days 1, 8, 15, 22 of cycles 7–12	**RD** Lenalidomide 10 mg PO: days 1–21 Daratumumab 16 mg/kg IV: day 1 of odd cycles for cycles 13–24

Primary endpoint: sCR rate*

Secondary endpoints: MRD negativity,† OS, PFS, adverse events

*A confirmed sCR on 2 consecutive evaluations at any time during the course of treatment. †MRD negativity after induction, consolidation, and maintenance; persistent MRD negativity rate will be evaluated at 1 year after completion of induction, consolidation, and maintenance.

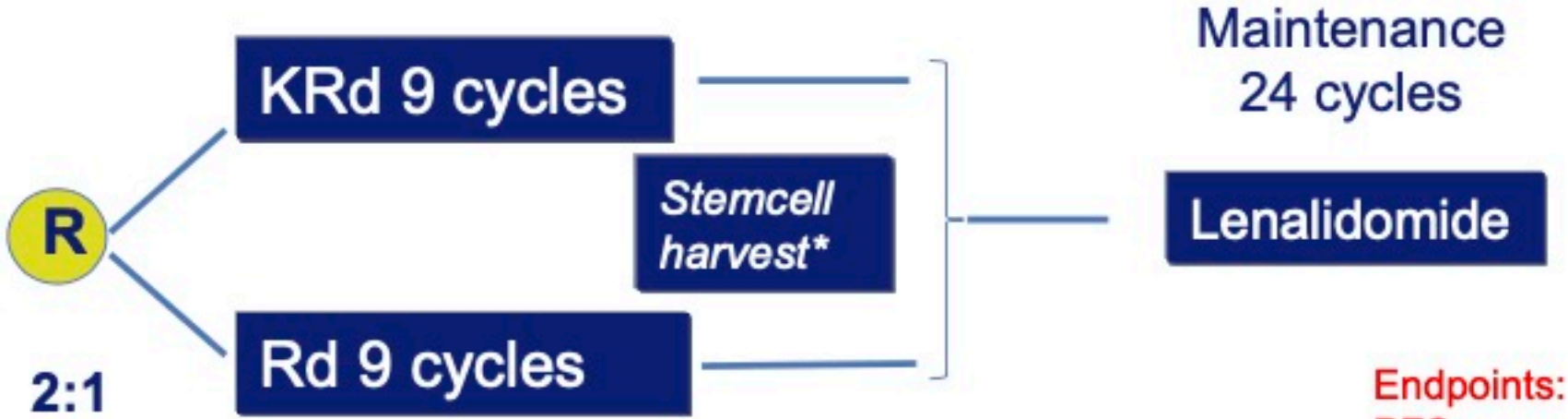
IV, intravenous; KRdD, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PO, oral administration; RD, lenalidomide, daratumumab; sCR, stringent complete response; SMM, smoldering multiple myeloma.

1. Kumar S, et al.ASH, 2020; Abstract 2285..

EMN015/ HOVON147

Collaboration with MSKCC, O. Landgren

Erasmus MC Kanker Instituut



Carfilzomib 36 mg/m2

* If eligible for subsequent HDM/ASCT in the future, stemcell harvest after 4th cycle

Target number of patients: 120

Expected accrual period: 2 years

Follow-up every 3 months until 5 years after randomization or death, whatever comes first

2021 European Myeloma Network review and consensus statement on smoldering multiple myeloma: how to distinguish (and manage) Dr. Jekyll and Mr. Hyde

Pellegrino Musto,[1] Monika Engelhardt,[2] Jo Caers,[3,4] Niccolo' Bolli,[5,6] Martin Kaiser,[7,8] Niels van de Donk,[9] Evangelos Terpos,[10] Annemiek Broijl,[11] Carlos Fernández de Larrea,[12] Francesca Gay,[13] Hartmut Goldschmidt,[14] Roman Hajek,[15] Annette Juul Vangsted,[16] Elena Zamagni,[17] Sonja Zweegman,[9] Michele Cavo,[17] Meletios Dimopoulos,[18] Hermann Einsele,[19] Heinz Ludwig,[20] Giovanni Barosi,[21] Mario Boccadoro,[13] Maria-Victoria Mateos,[22] Pieter Sonneveld[11] and Jesus San Miguel[23]

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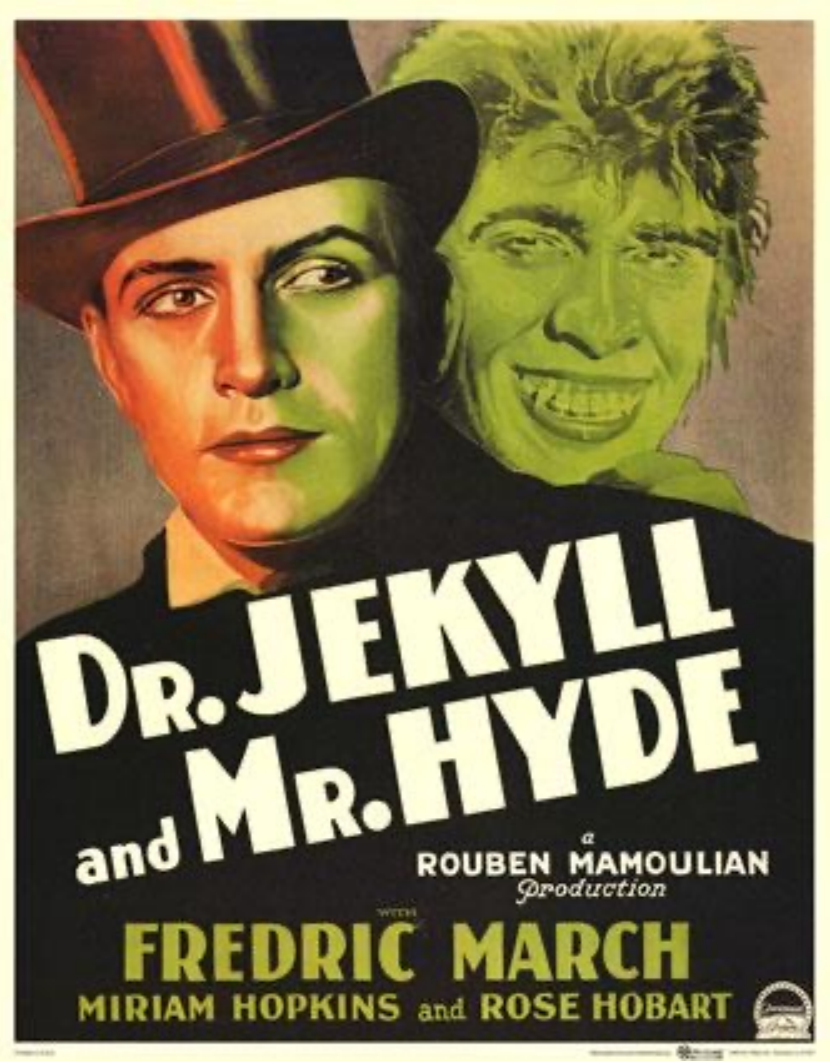
Ferrata Storti Foundation



Which are the diagnostic procedures that are necessary for diagnosing SMM?

- An adequate diagnostic work-up for SMM should include hemogram and biochemistry, morphological and phenotypic quantification of clonal PCs in bone marrow smears and bone trephine biopsy, with cytogenetics by FISH or validated equivalent molecular method on purified PCs, evaluation serum involved/uninvolved FLC ratio and their absolute values.
- Diagnostic imaging should comprise LDWBCT and whole-body MRI, if LDWBCT is negative. Axial MRI or PET-CT are reasonable alternatives, according to availability and specific diagnostic needs.

Musto et al, Haematologica 2021

How should SMM be monitored?

- Clinical and laboratory monitoring of SMM should be initially performed every 2-3 months after diagnosis for 6-12 months . If test results are stable, patients may be followed every 4-6 months for another year and every 6-12 months thereafter.
- However, follow-up should be individualized based on risk of progression.
- Imaging evaluation might be preferably repeated annually with MRI (because of the higher sensitivity for early damage) for the first 5 years, then at clinical suspicion/pain.
- Appropriate information about their possible future clinical outcome should be given to lower and higher risk SMM patients, according to current risk models.

Musto et al, Haematologica 2021

Who are the patients with SMM that might benefit by an early treatment?

- Regarding patients with lower risk SMM, diagnosed according to current criteria,

only active observation is recommended.

- About high-risk SMM early treatment, there is no consensus yet.

The Panel agreed that therapy in selected, very high-risk SMM patients,
should be similar to that offered to patients with active myeloma, and that treatment
should be performed in a controlled setting, such as clinical trial.

Musto et al, Haematologica 2021

What should be done in the close future to further improve the management of SMM?

Before definitively changing the current paradigms for the management of SMM, comparable future trials will have to be performed, aiming to define the following, relevant primary objectives:

1) new predictive biomarkers (clinical, molecular/genomics, immunological, microenvironment, imaging) for further refining risk prediction
2) balance between reduced risk of progression with early treatment vs short- and long-term possible adverse effects, specifically deteriorating HRQoL, SPM and induction of refractory disease,
3) To determine which intensity and type of treatment is preferable in selected high-risk SMM, i.e. short term, intensive approaches with “curative” intent vs prolonged immunological control of the disease.

Musto et al, Haematologica 2021