Updates in Management of Smoldering Multiple Myeloma

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Agenda

- Definition of Smoldering Multiple Myeloma
- Risk Stratification of Smoldering Multiple Myeloma
- Treatment approaches: Preventative versus curative
- Review of clinical trials treating high-risk Smoldering multiple myeloma

Defining And Redefining Smoldering Myeloma

Rheingold et al. describe smoldering acute leukemia

"Indolent myeloma" used by Alexanian to describe asymptomatic myeloma

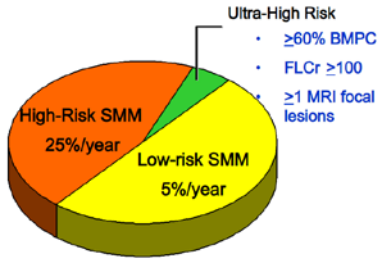
"SMM" introduced by by Kyle and Greipp

First IMWG definition of SMM

PETHEMA risk stratification model

Kyle et al. describe SMM course

Mayo 2008 risk stratification model



QuiRedex shows PFS benefit with Rd

IMWG reclassification of ultra-high risk SMM as MM

Not CRAB but now SLiM CRAB

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

Updated QuiRedex shows PFS and OS benefit

Revised Mayo "20/2/20" criteria

"20/2/20" risk stratification criteria validated by IMWG

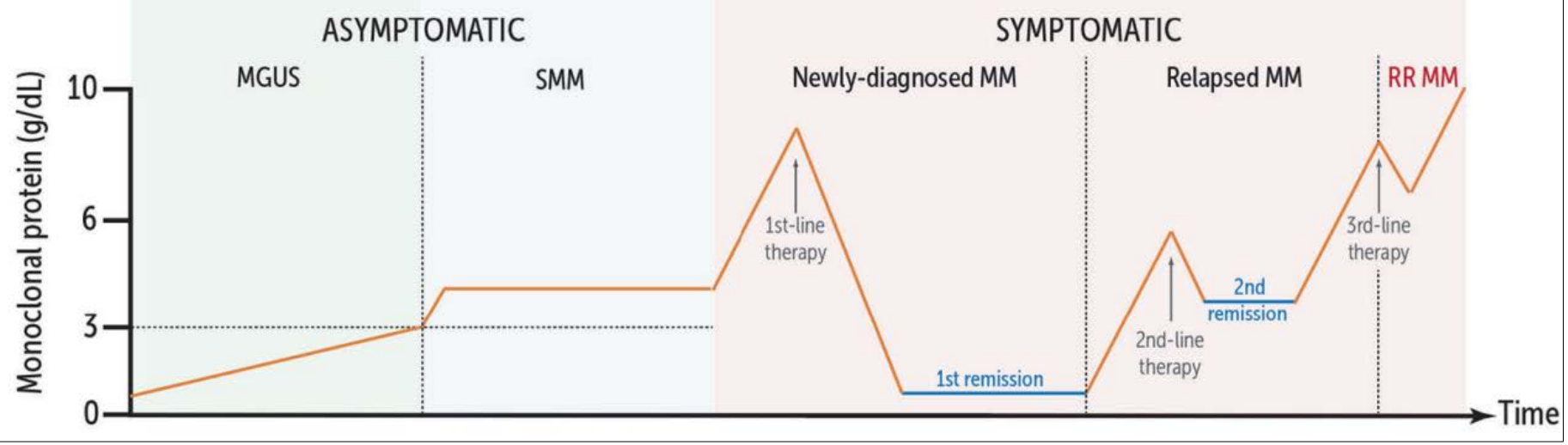
ECOG-ACRIN E3A06 trial shows PFS benefit with lenalidomide

1963 1980 2003 2007 2008 2013 2014 2016 2018

1960 2000 2010 2020

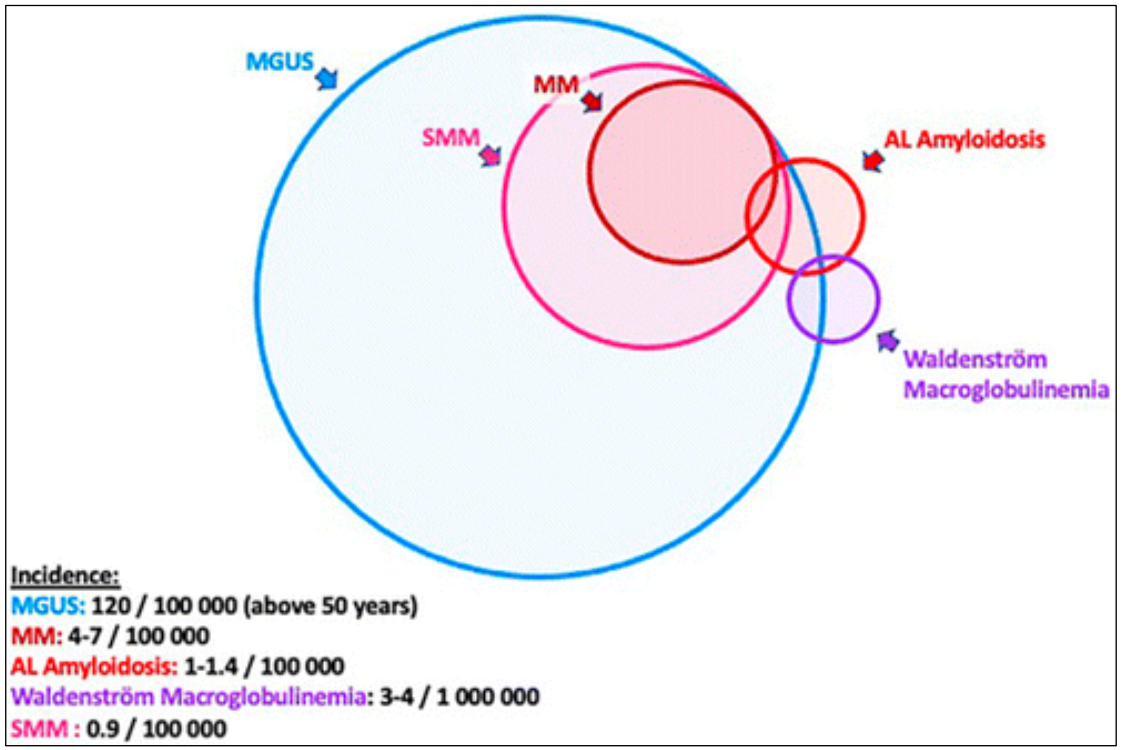
Clinical Model of Disease Progression in Multiple Myeloma

Disease stage	MGUS	SMM	Active MM
Serum M-protein	<3 g/dL	≥3 g/dL	≥1 **myeloma defining events** + (1) or (2): End-organ damage (CRAB): any one of • Hypercalcemia, renal insufficiency, anemia, bone lesions Biomarkers of malignancy: • ≥60% clonal BM plasma cells, • Serum involved/uninvolved free light chain ratio ≥100 • >1 focal lesion on MRI ≥5mm in size (1) Clonal bone marrow plasma cells ≥10% or (2) Biopsy proven plasmacytoma
Urine M-protein	N/A	≥500 mg/day	
% BM plasma cells	<10%	10-60%	
Myeloma defining events	Absence of myeloma defining events or amyloidosis		
Progression risk	1% per year	10% per year (1st 5y) 3% per year (next 5y)	

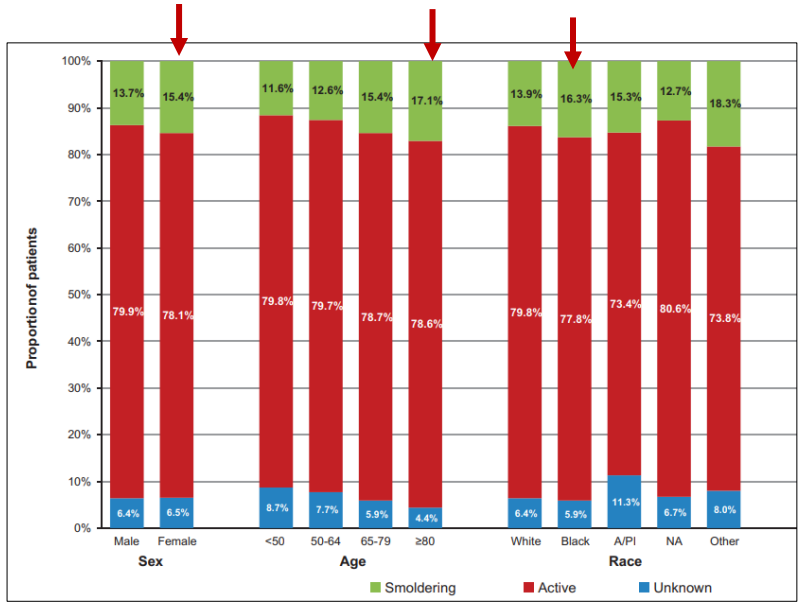


Ho et al Leukemia 2020

Epidemiology of Smoldering Multiple Myeloma



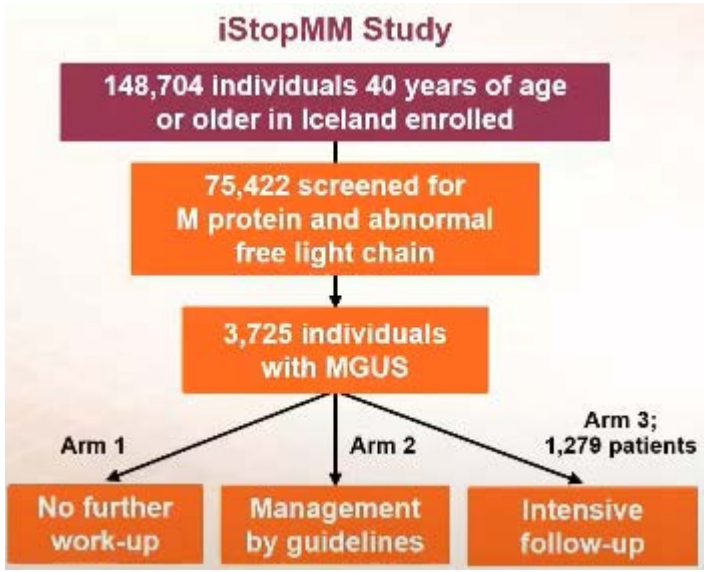
SMM is an **uncommon** entity, with an estimated standardized incidence between 0.4 and 0.9 cases per 100 000 people



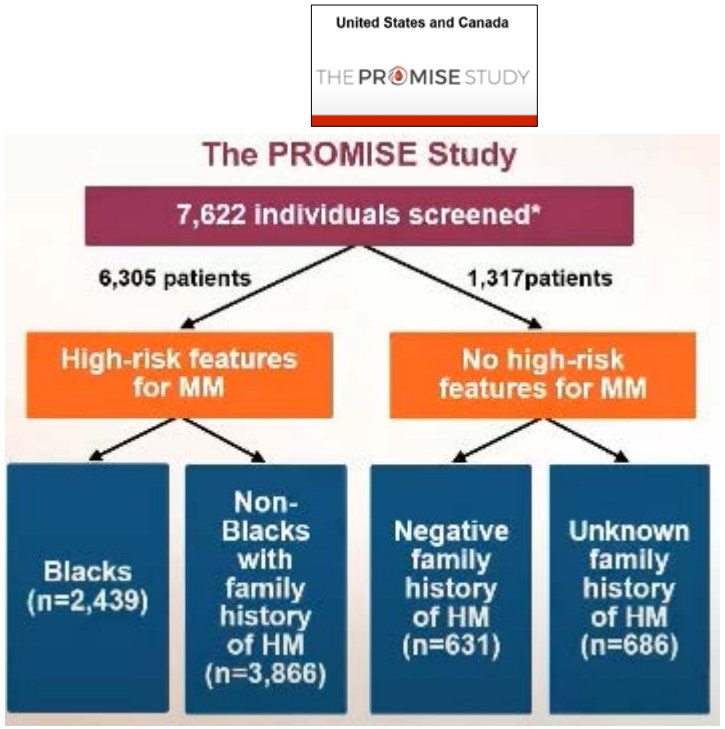
17% of patients with MM had a diagnosis of SMM (National Cancer Database)

Derman et al, ASCO, 2022
Ravindran et al Blood cancer journal 2016

Identifying Patients With Myeloma Precursor Conditions
Results of Screening Studies



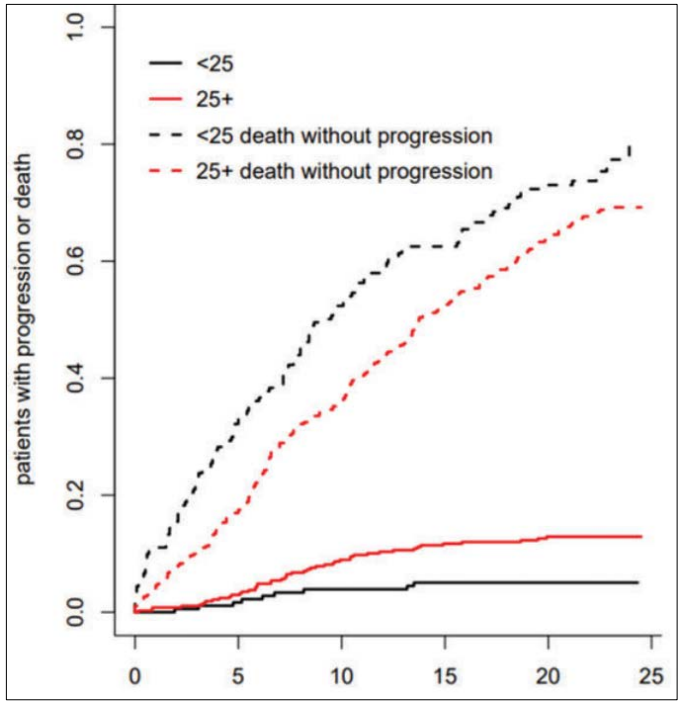
- 4.9% individuals screeded have MGUS
- 10.8% individual screened have SMM; prevalence of 0.5% in subjects >the age of 40
- One third of SMM have intermediate or high risk SMM



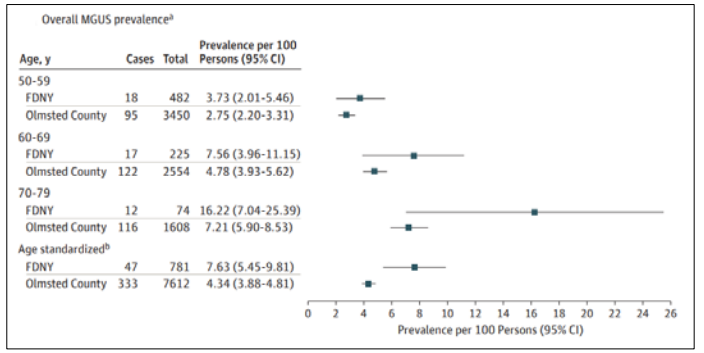
- MGUS estimated in 6% (using conventional test) of high risk screened population
- Older patients who are African American or have first degree relative with hematological malignancies have an increased prevalence of MGUS

Kristinsson et al ASH 2021
Habib El-Khoury et al ASH 2021

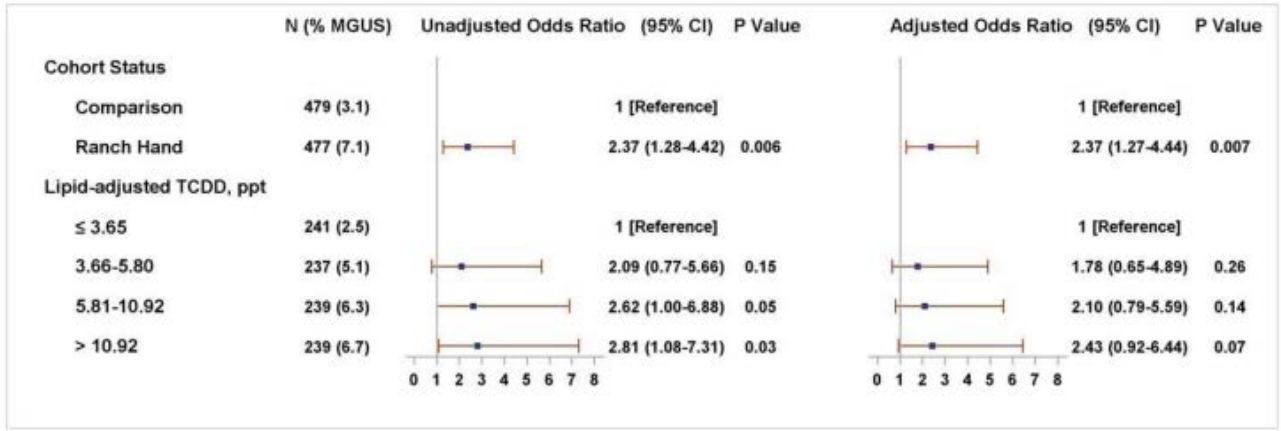
Factors Predicting Risk Of Progression In Precursor States Of Myeloma



High BMI is a prognostic factor for MGUS progression, independent of isotype, M protein, and FLC



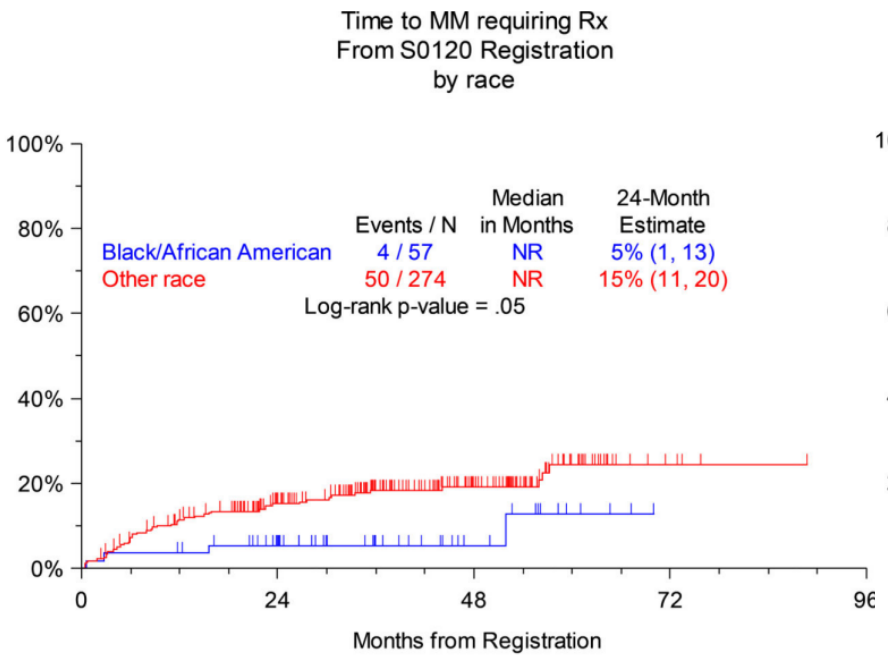
Environmental exposure to the World Trade center disaster site is associated with myeloma precursor disease

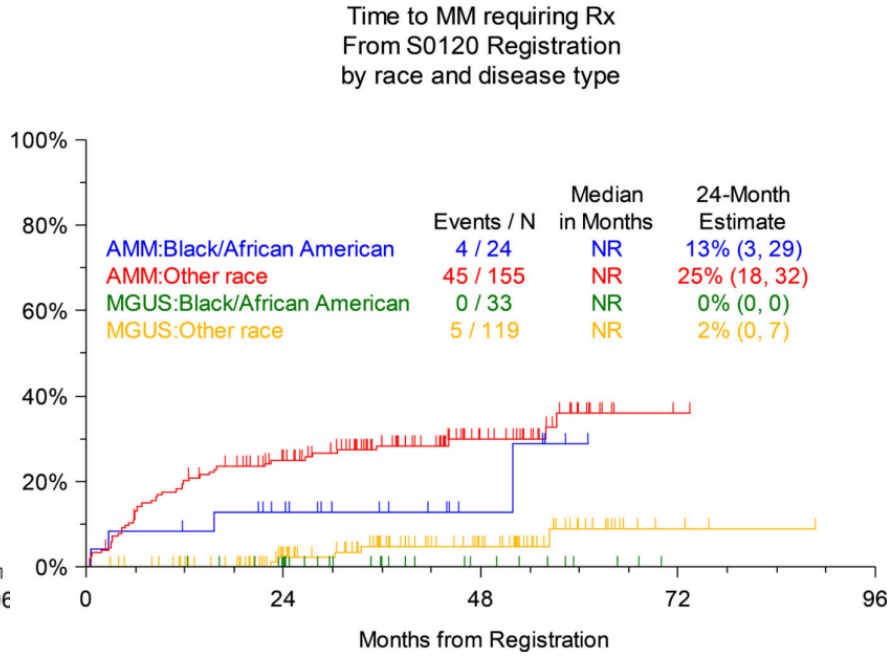


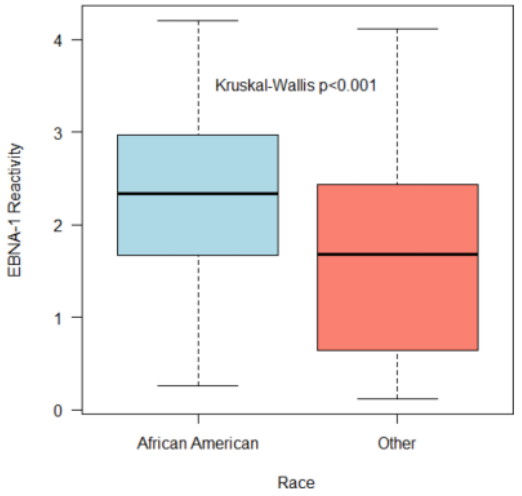
Exposure to Agent Orange is associated with an increased risk of MGUS

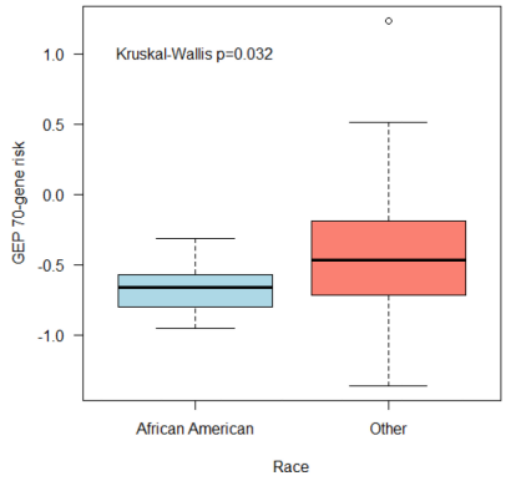
Ola Langren et al JAMA 2015 and 2020

Smoldering Myeloma In African Americans



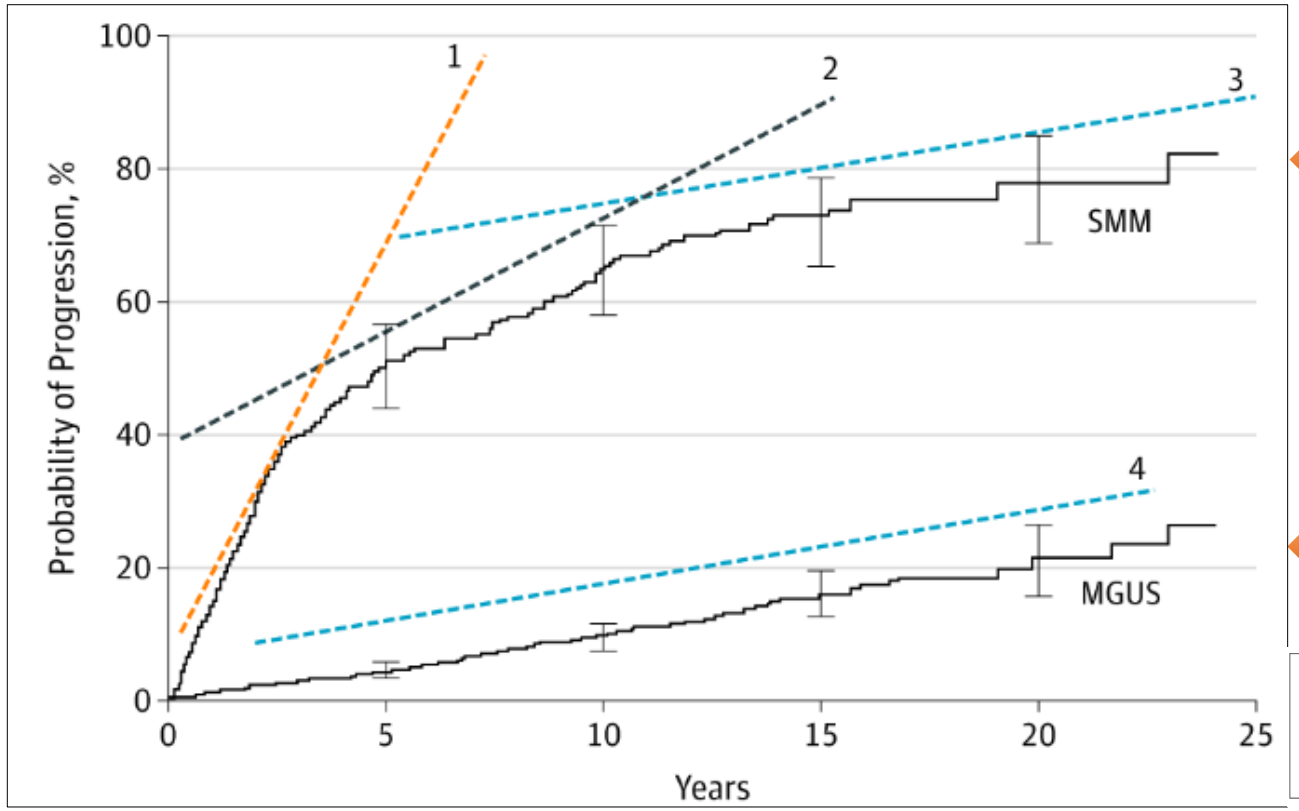






Risk of Progression is lower in African American Cohort
Lower proportion of high-risk genomic signatures in African Americans
Higher EBV exposure in African Americans ? Contribute to earlier onset of gammopathy

Smoldering Multiple Myeloma Is A Heterogenous Disease



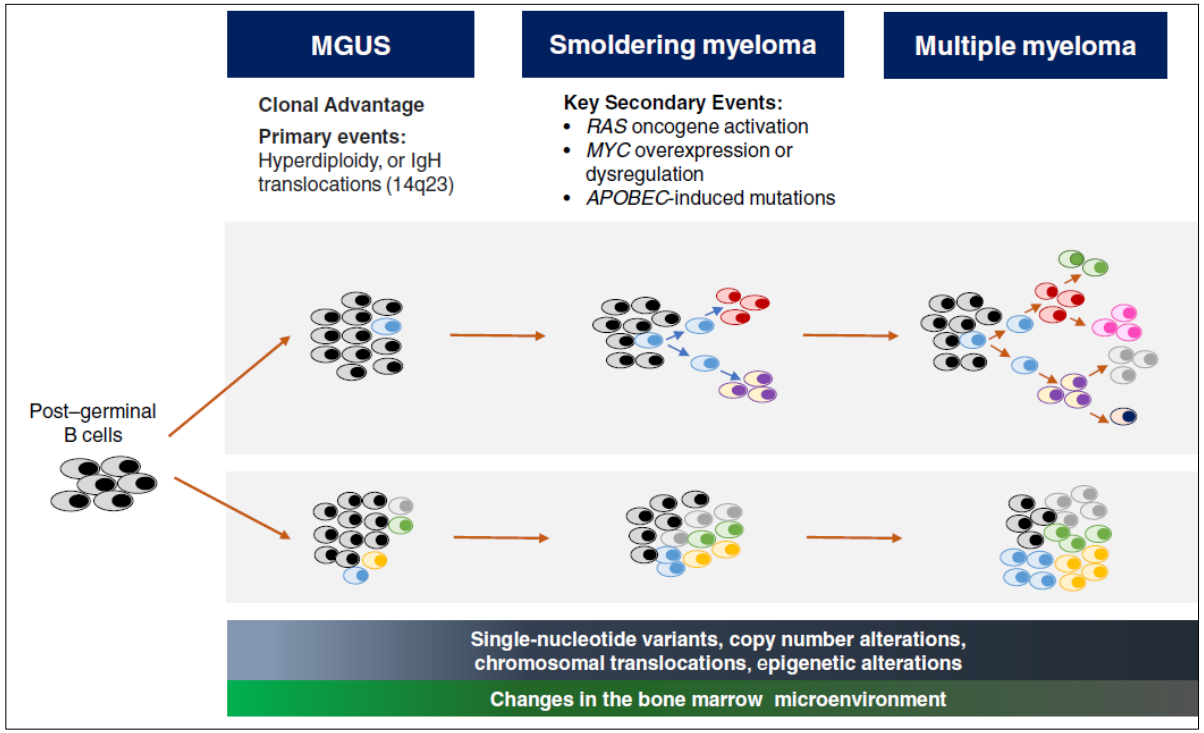
10% risk of progression per year for the first 5 year

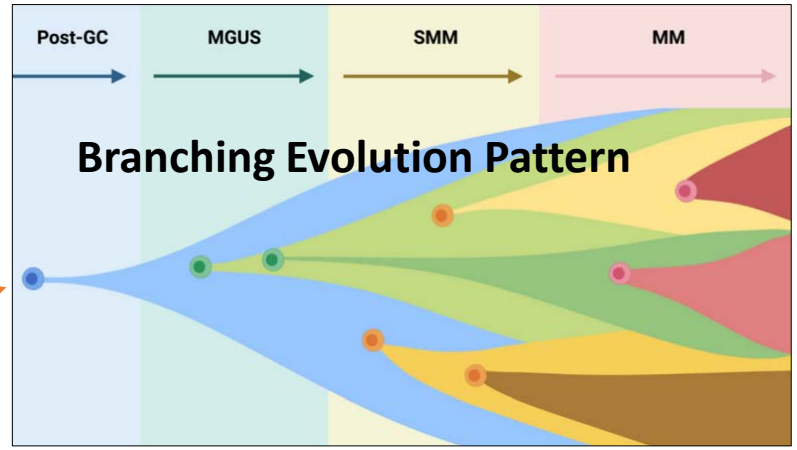
- Risk of progression ~ **3%** per year for next 5 years and **~ 1%** per year thereafter
- **30%** of patients that fulfill the criteria for SMM based on clonal burden have the same risk of progression as MGUS

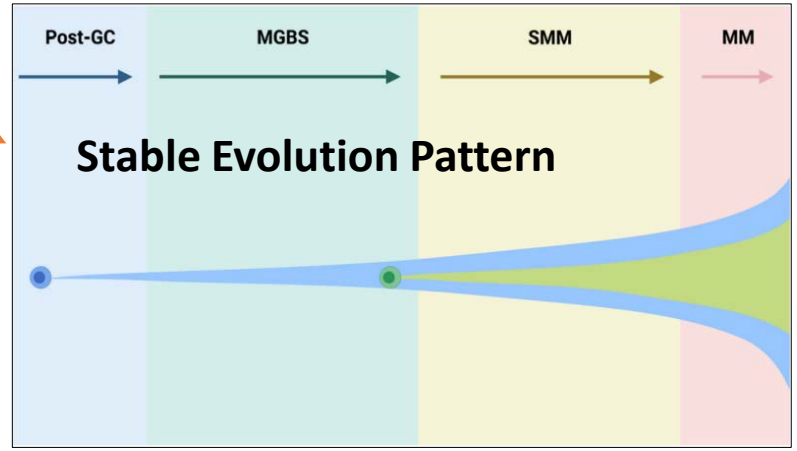
1% risk of progression per year

Clinical Model of Progression from Smoldering Multiple Myeloma to Multiple Myeloma

Genomic Underpinnings Of Smoldering Multiple Myeloma





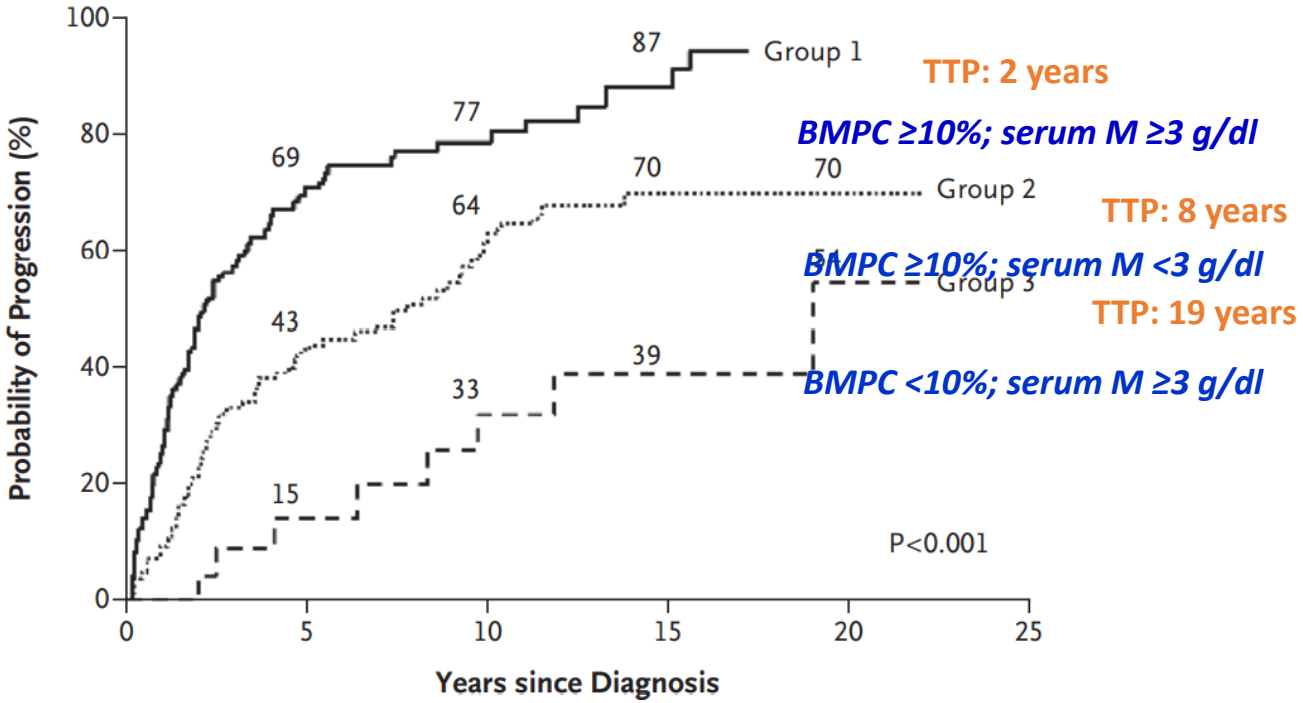


Genomic landscape of stable and progressive myeloma precursor conditions

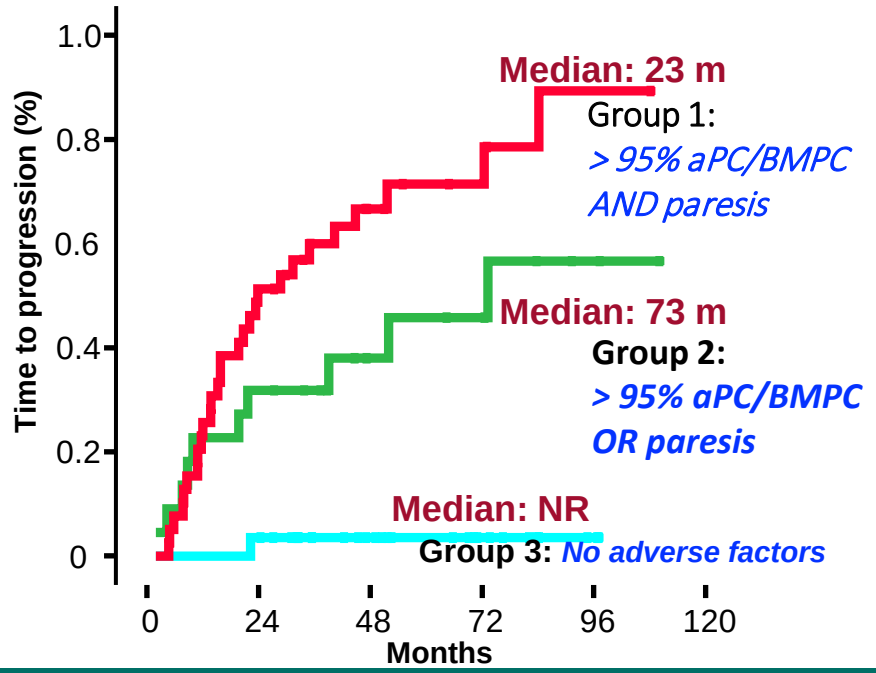
Bolli N et al. Nature Comm 2018. 9:3363

Determining the risk of progression in Smoldering Multiple Myeloma

Mayo 2008 risk stratification
BMPC ≥10% and Serum M ≥3 g/dL



PETHEMA risk stratification
BMPC ≥10% or Serum M ≥3 g/dL and 95% aPC /BMPC + paresis



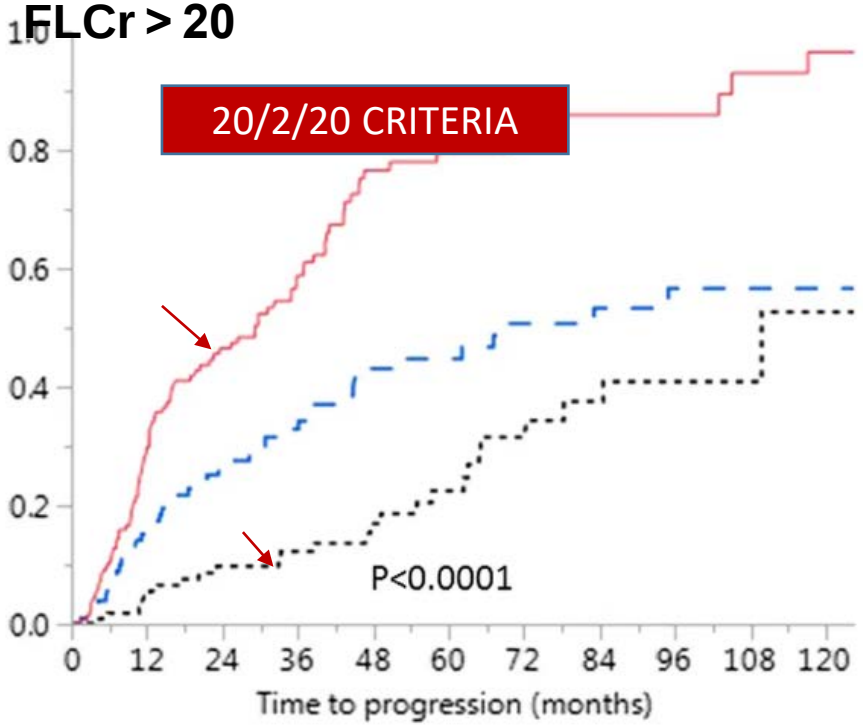
Kyle. N Engl J Med. 2007
Pérez-Persona. Blood. 2007

High-risk Smoldering Multiple Myeloma- Revised Mayo 2018 Criteria

Time from diagnosis (years)	Low risk (*n* = 143)	Intermediate risk (*n* = 121)		High risk (*n* = 153)	
	Estimated rate of progression (%)	Rate of progression, % (CI)	OR for progression relative to low-risk group (CI)	Rate of progression, % (CI)	OR for progression relative to low-risk group (CI)
2	9.7 (5.3–17.1)	26.3 (18.4–36.2)	2.71 (1.08–6.83)	47.4 (38.6–56.4)	4.89 (2.25–10.69)
5	22.5 (14.2–33.6)	46.7 (35.8–57.9)	2.08 (1.07–4.08)	81.5 (71.3–88.6)	3.63 (2.12–6.22)
10	52.7 (30.1–74.2)	65.3 (45.5–80.9)	1.24 (0.61–2.69)	96.5 (80.9–99.4)	1.83 (1.09–3.30)

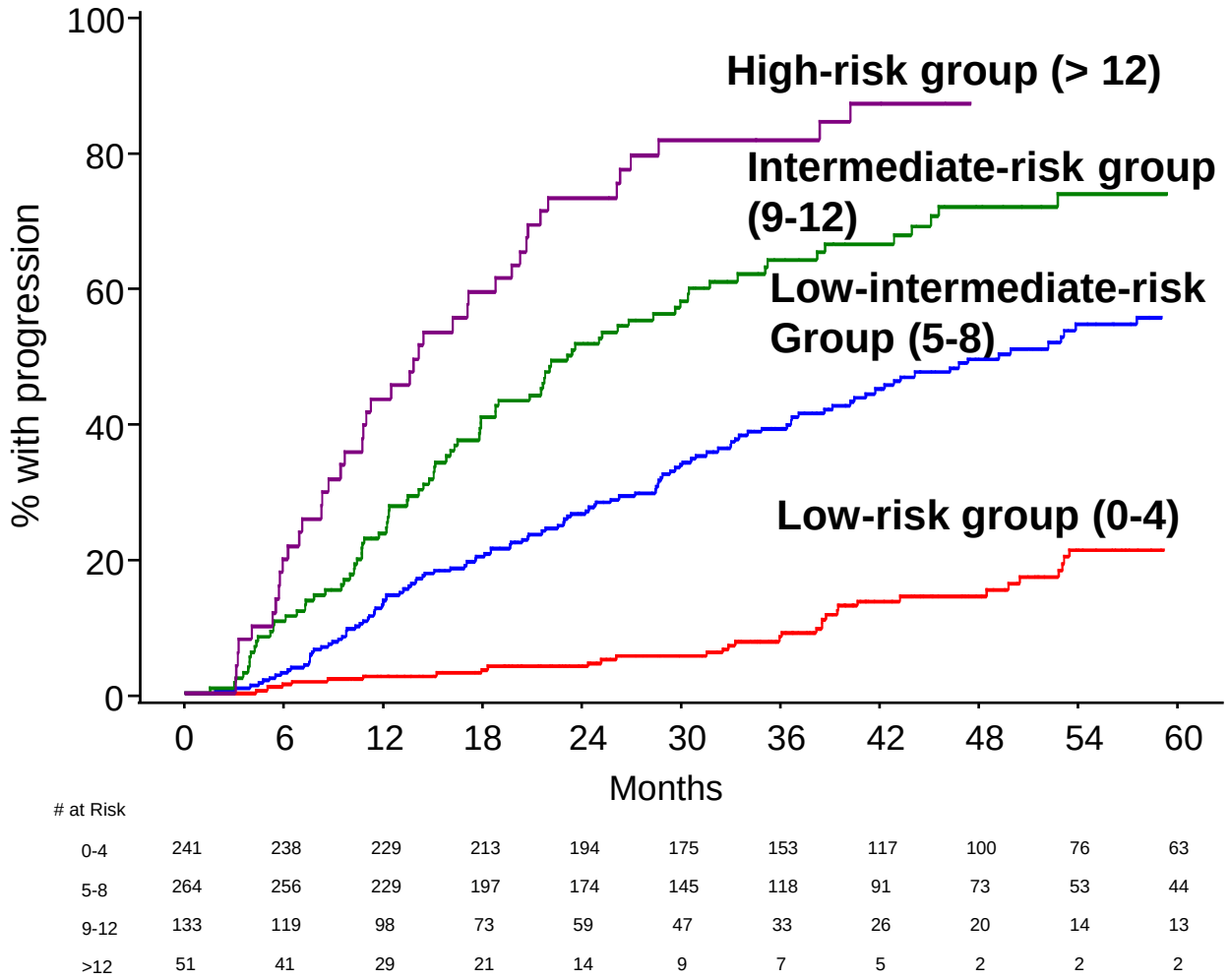
BMPC% bone marrow-plasma cell percentage, CI 95% confidence intervals, *FLCr* involved to uninvolved free light chain ratio, OR odds ratio

BMPC > 20%; M-protein > 2 g/dL; FLCr > 20



Lakshman et al Blood Cancer Journal 2018

IMWG: Risk Score To Predict Progression Risk At 2 Years



Risk Factor	Coefficient	P-value	Score
FLC Ratio			
0-10 (reference)	-	-	0
> 10-25	0.69	0.014	2
> 25-40	0.96	0.004	3
> 40	1.56	<0.0001	5
M protein (g/dL)			
0-1.5 (reference)	-	-	0
> 1.5-3	0.95	0.0002	3
> 3	1.30	<0.0001	4
BMPC%			
0-15 (reference)	-	-	0
> 15-20	0.57	0.04	2
> 20-30	1.01	0.0002	3
> 30-40	1.57	<0.0001	5
> 40	2.00	<0.0001	6
FiSH abnormality	0.83	<0.0001	2

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

San Miguel. ASCO 2019. Abstr 8000.
Mateos. Blood Cancer J. 2020;10:102.

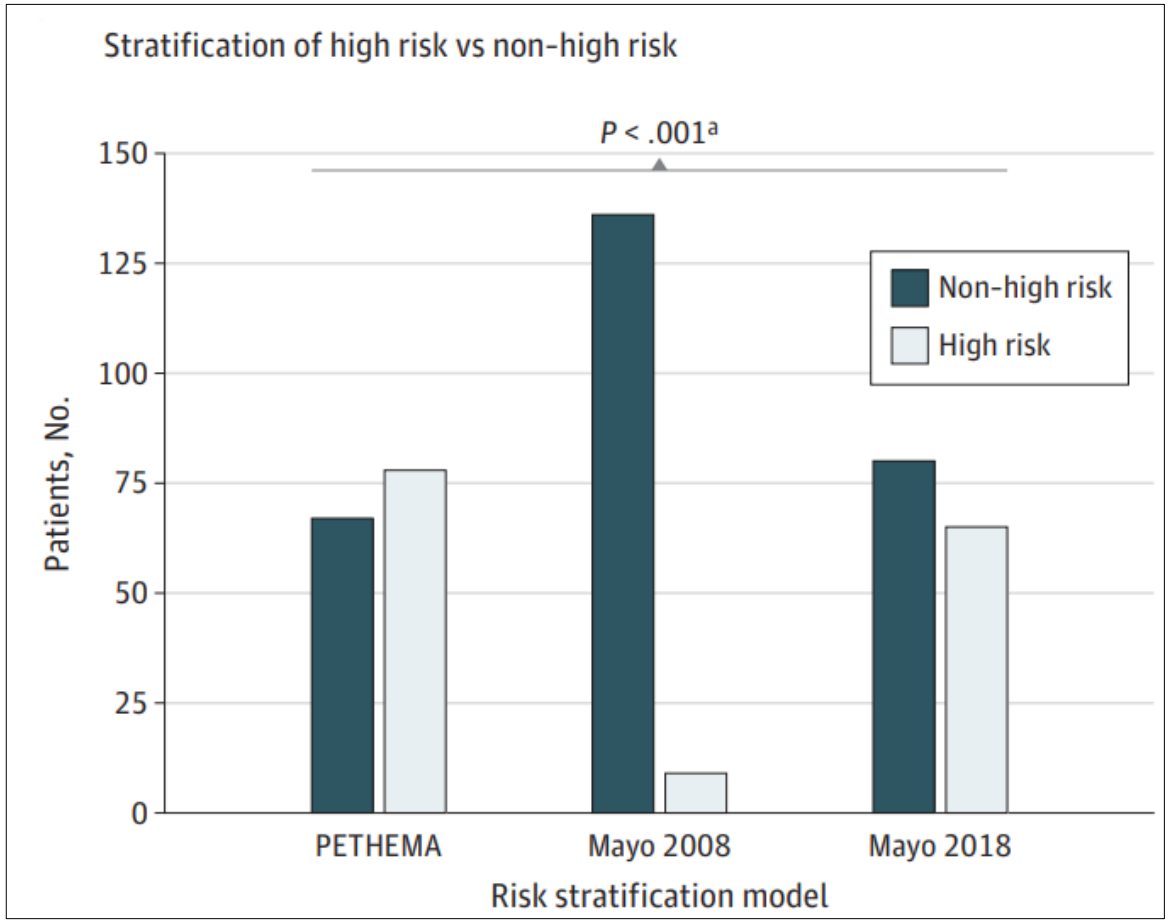
Assessment of Discordance Among Smoldering Multiple Myeloma Risk Models

Model/stratification	PETHEMA[2] No. (%) (n = 145) LR	IR	HR	Overall agreement, No./No. (%) [95% CI]
Mayo 2008				
LR	13 (9.0)	24 (16.6)	23 (15.9)	
IR	8 (5.5)	21 (14.5)	47 (32.4)	42/145 (29.0) [22.2-36.8]
HR	0	1 (0.7)	8 (5.5)	
Mayo 2018[3]				
LR	13 (9.0)	17 (11.7)	10 (6.9)	
IR	5 (3.4)	13 (9.0)	22 (15.2)	72/145 (49.7) [41.6-57.7]
HR	3 (2.1)	16 (11.0)	46 (31.7)	
Risk agreement among PETHEMA, Mayo 2008, and Mayo 2018	11 (7.6)	5 (3.5)	8 (5.5)	24/145 (16.6) [11.3-23.5]

145 patient enrolled in 2 clinical trials (NCT01572480,NCT01109407) were included in this analysis

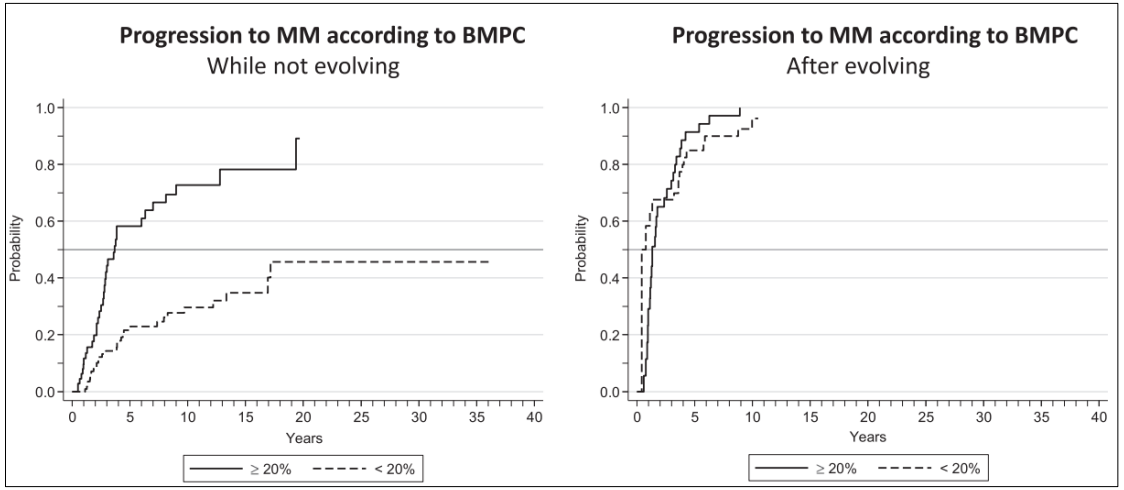
Overall global rate of agreement across the three models -16%

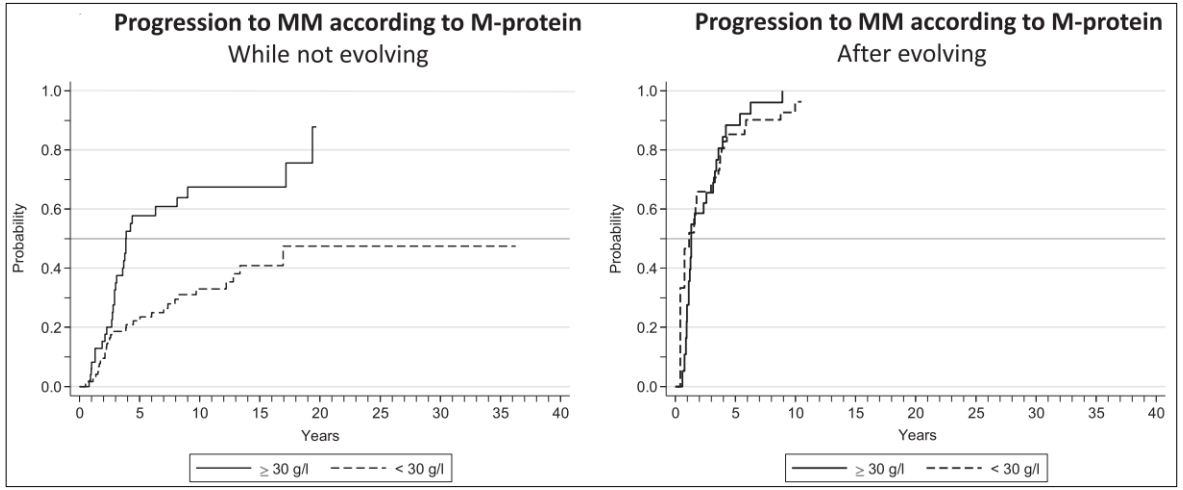
The ability of models to classify patients as HR vs non-HR was significantly different



Hill et al JAMA 2020

Evolving Pattern In Patients With Smoldering Multiple Myeloma: Impact On Early Progression





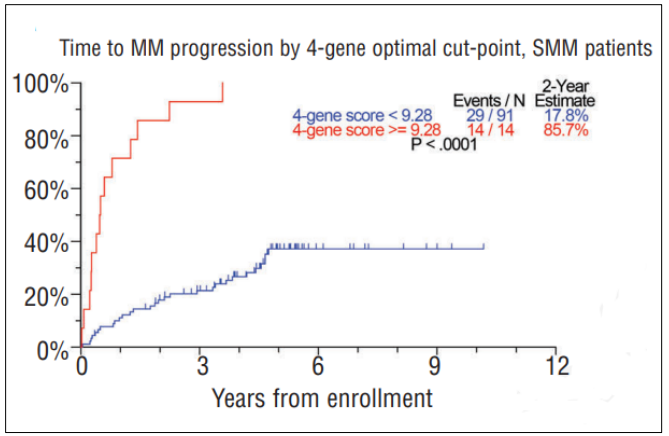
Evolving pattern accurately predicts the risk of early progression to symptomatic disease in Smoldering Myeloma

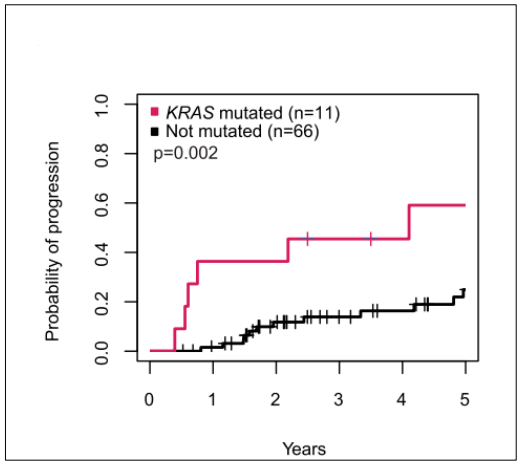
Fernández de Larrea , Leukemia 2018

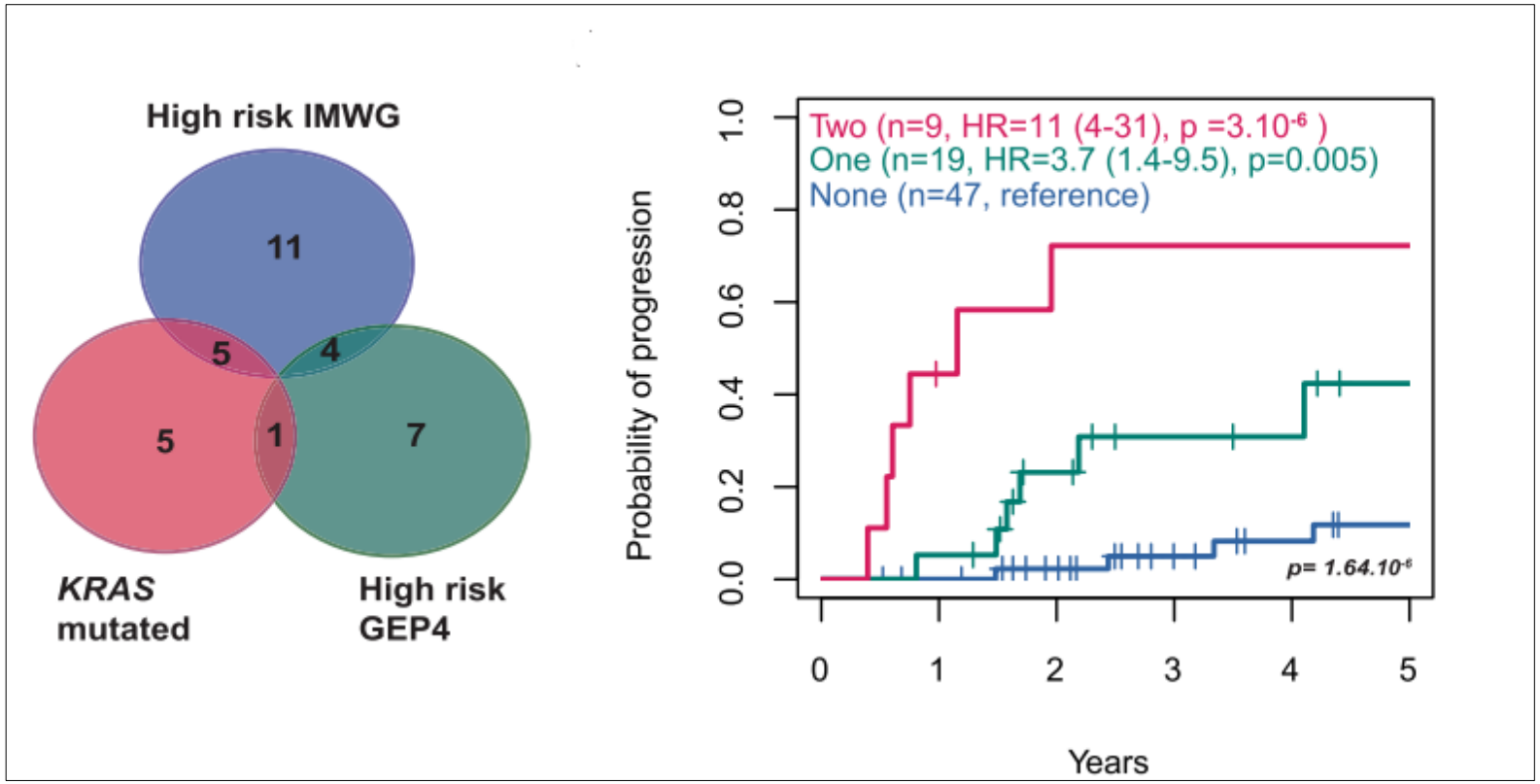
High Risk Smoldering Myeloma: More Scoring Models ?

- BJ proteinuria (>500 mg/24 hours –TTP is 13 months)
- MRI: new focal lesion or increase of an existing FL or progressive diffuse infiltration
- PET: positive PET with out lysis
- Circulating plasma cells: SMM with high levels of CTC ≥ 0.02% showed high risk of progression to MM (Time to MM -11 months)

KRAS mutation status, high-risk GEP4 and high-risk IMWG status independently associated with risk of disease progression







Khan et al Hematologica 2017
Boyle et al Nature communication 2021

Challenges in Defining High Risk Smoldering Multiple Myeloma

- Current clinical models

<u>Advantages:</u>

Builds on readily available clinical variable

<u>Disadvantages:</u>

Mainly based on tumor burden and does not reflect on tumor biology

Modest degree of concordance between the models

- Genomic models

<u>Advantages:</u>

Reflect the true biologic nature of disease

<u>Disadvantages:</u>

Does not account for the complicity of the BM microenvironment

Limited availability, uncertain validation, and cost outside of a clinical trial setting

Current approaches to treatment of high-risk smoldering multiple myeloma

Early detection and intervention is a pre-requisite for cure in most malignancies

Lenalidomide
Lenalidomide/Dexamethasone
Daratumumab

- ✓ Fewer side effect
- ✓ Low ORR
- ✓ Does not eliminate the clone

GEM-CESAR
ASCENT

- ✓ Increased toxicity
- ✓ Higher ORR
- ✓ May result in resistant clones

No Data On Overall Survival

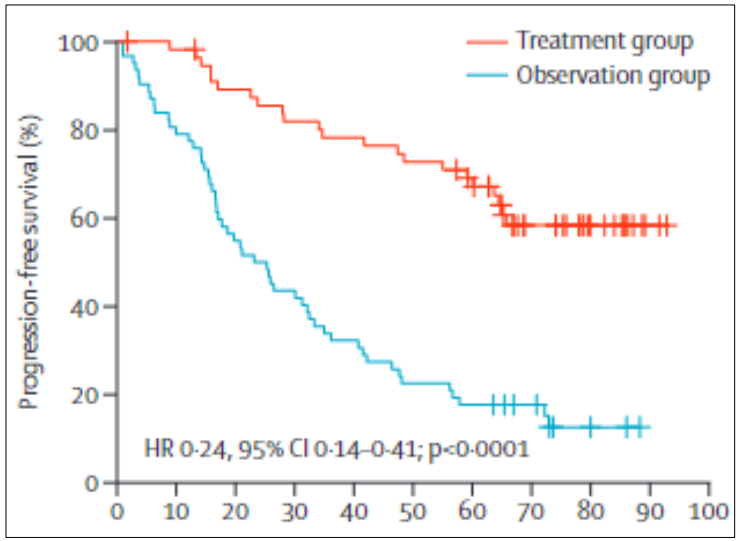
Initial Studies on Early Treatment of Smoldering Multiple Myeloma

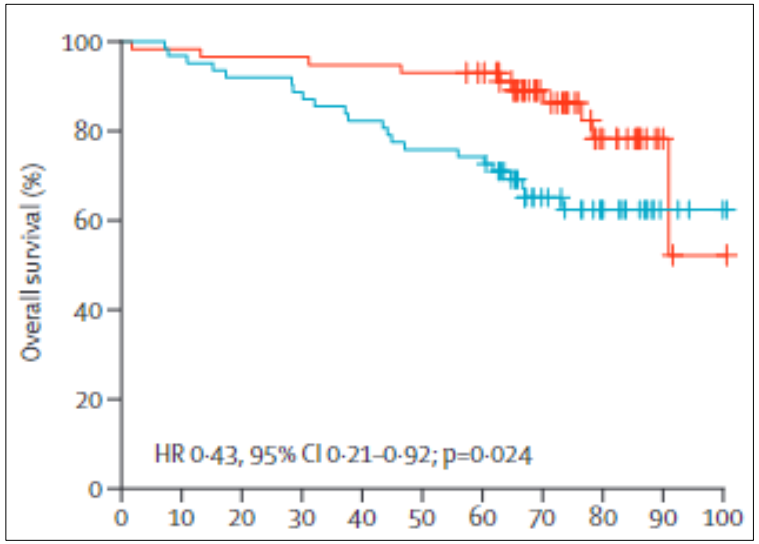
Agents	ORR (%)	TTP	OS
Early Melphalan Prednisone vs deferred Melphalan Prednisone	52 vs 55	No benefit	No benefit
Thalidomide plus Zolendronic acid vs zolendronic acid	37 vs 0	No benefit	No benefit
Bisphosphonates vs observation	0	No benefit	No benefit

Hjorth M 1993, Grignani G etl al 1996, Roccardi A et al Br J cancer 2000, Witzug TE et al Leukemia 2013, Martin et al Br J Hematology 2002, D'arena et al Leu Lymphoma 2011, Musto P et al Cancer 2008

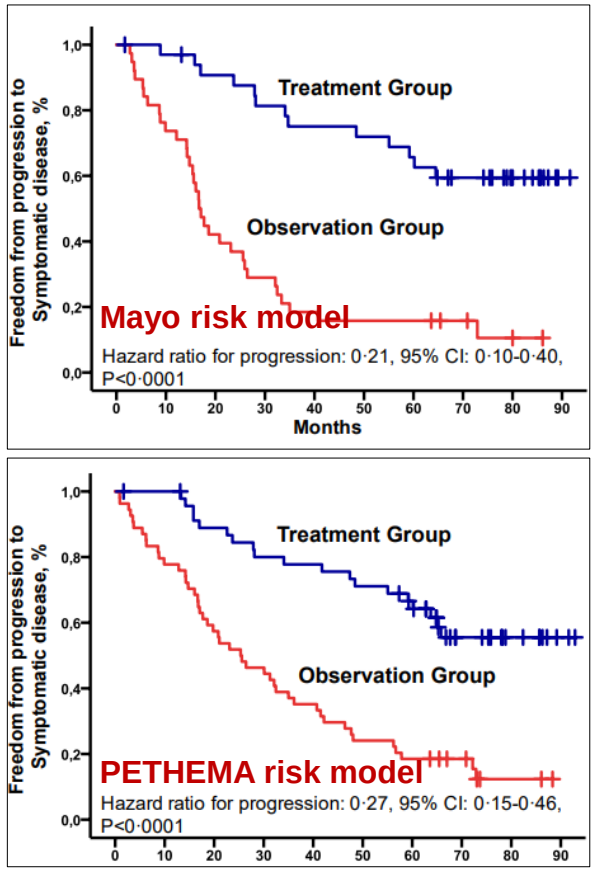
Lenalidomide plus dexamethasone versus observation in patients with high-risk Smoldering multiple myeloma

Inclusion criteria: High-risk SMM (by PETHEMA criteria) made within the past 60 months
Intervention : 9 cycles of Rd induction followed by lenalidomide maintenance for total of 2 years or observation





At a median follow-up of 75 months, there was a significant improvement in PFS and OS

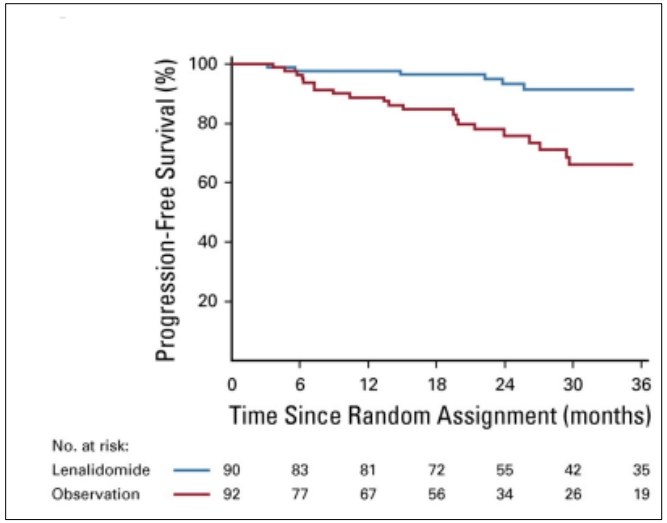


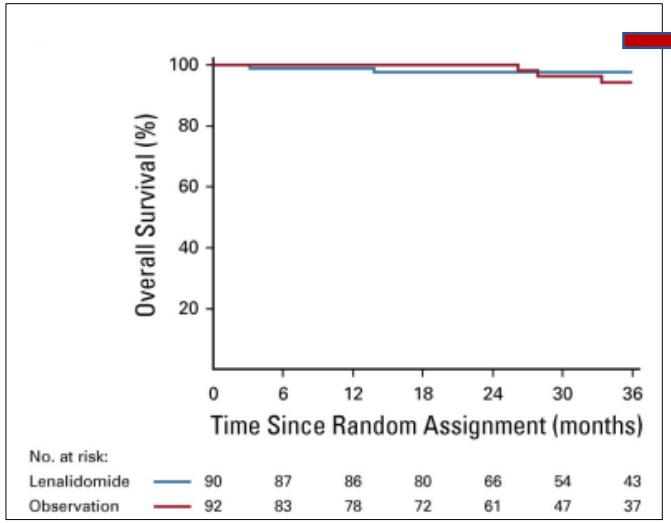
Time to Progression to Myeloma according to the risk model

Mateos. NEJM. 2013;369:438.
Mateos. Lancet Oncology 2016;17:1127
Mateos. EHA2020 Abstr EP950.

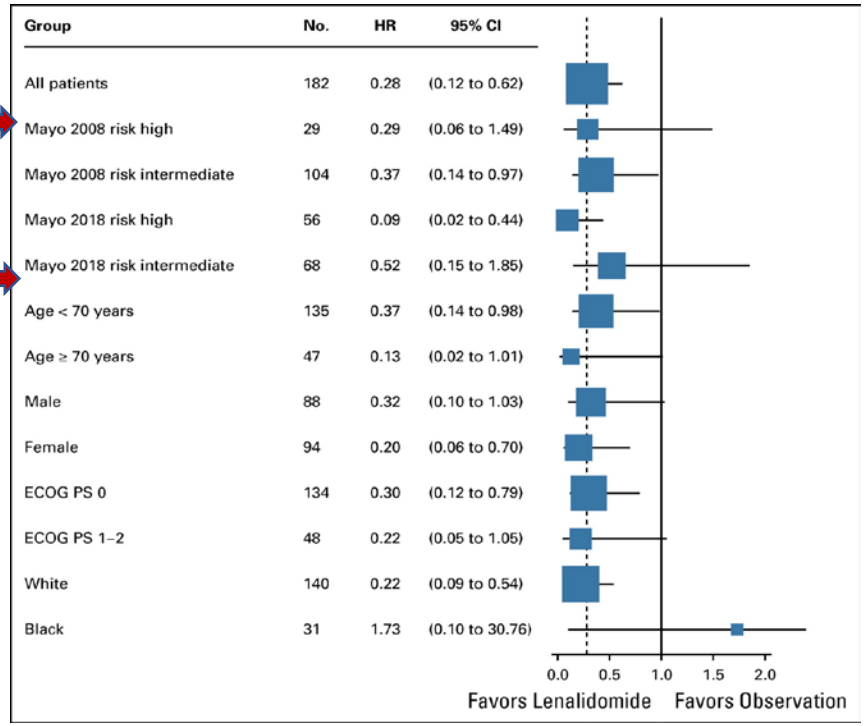
Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma: ECOG E3A06

Inclusion criteria: Intermediate or high-risk SMM (by Mayo 2008 and 2018 criteria) made within the past 60 months
Intervention : Lenalidomide monotherapy (given until disease progression) or observation





Progression-free survival was significantly longer with lenalidomide compared with observation (HR, 0.28; 95% CI, 0.12 to 0.62; P = .002)

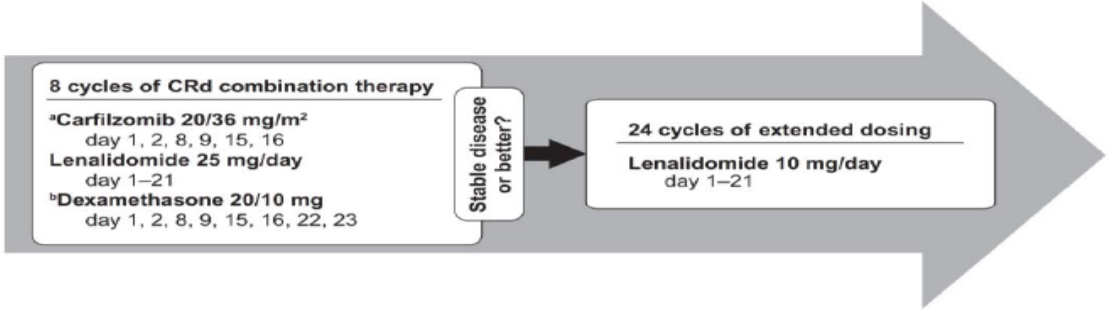


In the randomized trial, the 3-year CI of invasive second primary cancers was 5.2% in the lenalidomide arm and 3.5% in the observation arm

Caveats of the Randomized Trials of Lenalidomide in Smoldering Myeloma

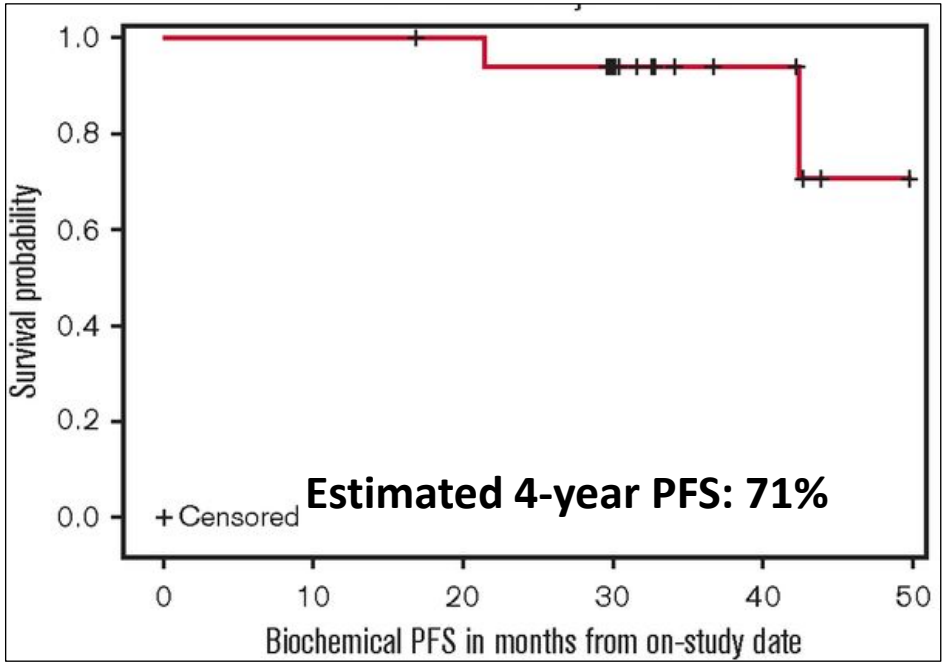
- Inconsistent Inclusion criteria : inclusion of non-high smoldering myeloma
- Intervention : Preventative approach with lenalidomide with and without dexamethasone
- Adverse effects including risk of secondary cancer
- Poor tolerance with close to 50% of patient discontinuing treatment
- Studies were powered to progression free survival and not overall survival

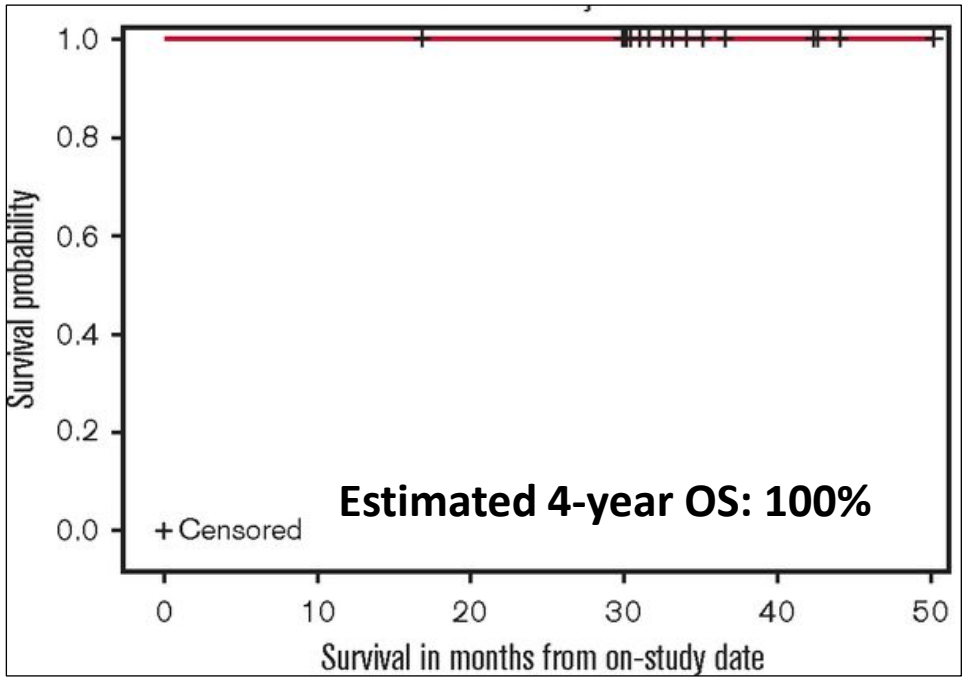
KRD/R Maintenance for Intermediate High-risk Smoldering Myeloma



ORR =100 % @ 2 years of maintenance

≥ VGPR =100% @ 2 years of maintenance (**primary end point**)



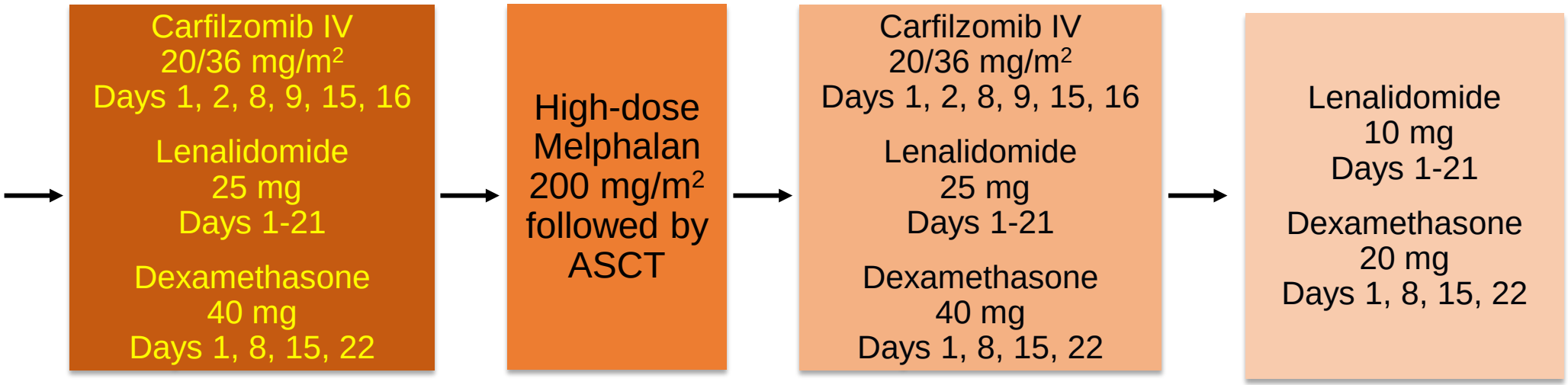


Mailankody S, Blood Adv 2017 1:1911
Korde N JAMA Onc 2015 1: 746

Curative Strategy for High-Risk Smoldering GEM-CESAR : Phase II Study Design

- Multicenter, open-label trial

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



- Primary endpoint: MRD negative rate (by flow cytometry) after induction, ASCT, consolidation/maintenance, and 3 and 5 yrs after maintenance
- Secondary endpoints: response, TTP, PFS, OS, safety

*High risk defined per Mayo and/or Spanish models (pre-2014 diagnostic criteria)

- Pts with both BM PCs ≥ 10% and serum M-protein ≥ 3g/dL, or 1 plus > 95% aberrant BM PCs by immunophenotyping plus immunoparesis
- Pts w/ bone disease on CT or PET/CT at screening excluded

Mateos MV, et al. ASH 2017. Abstract 402.

Curative Strategy for High-Risk Smoldering: Results

Response category (n=90)	Induction (n=90)	HDT-ASCT (n=90)	Consolidation (n=90)	Maintenance (n=90)
≥CR	**41%**	**65%**	**72%**	**63%**
Progressive disease	1 (1.5%)*	-	-	7 (7%)**
MRD –ve, 10^{-5}	40%	63%	68%	52%

After median follow-up of 55 months (range: 6.2-71), 3 patients progressed to symptomatic disease (all 3 had at baseline ≥1 of the biomarkers defining myeloma-defining events)

At 5 years, 94% of patients remain alive and progression-free and 95% of patients remain alive

*Progressions were biochemical
**Progressions were biochemical progressions in the 6 patients and symptomatic in 1 pt during maintenance

Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant (ASCENT)

Study design

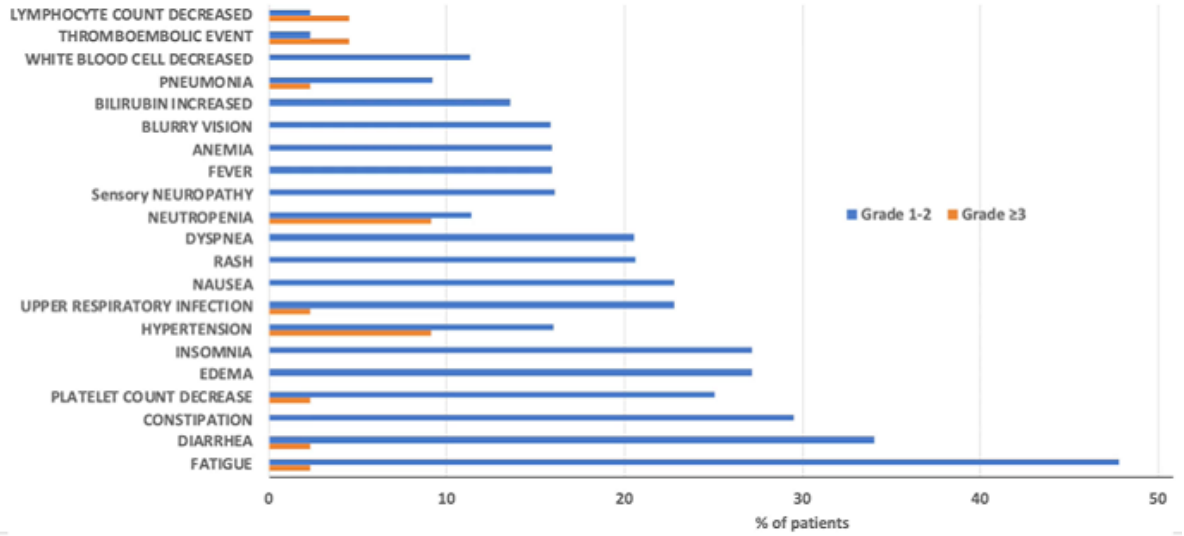
- Primary endpoint: Rate of confirmed sCR
- Secondary objectives: Safety, PFS, OS, MRD negativity

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 wee
- Daratumumab (q 8 weeks)

Toxicity profile



Results to date:

- 54 patients accrued
- Median patient age 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction and 17% in induction phase

- ≥1 patient needed a dose modification
- ≥ grade 3 AE seen in 43% of patients

Kumar et al ASH 2020

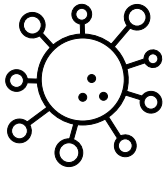
Phase II Clinical Trials of Intermediate to High-Risk Smoldering Myeloma

Studies	Phase	n	ORR/CR/MRD-ve	PFS/OS
Elo-Rd induction with Elo-R maintenance (E-PRISM)	II	50	84%/6%/NE	95%/1 death
Ixa-Rd induction with Ixa-R maintenance	II	48	94%/31%/69%	100%/-
KRd x 8 induction with R maintenance	II	54	100%/70%/53% sustain 5y	91.2% @8y
Isatuximab monotherapy	II	24	63%/-/5% (CR pts)	At 14m: 90%
Dara monotherapy intense/interm/short	II	41/41/41	ORR: 56%/54%/38% CR: 4.9%/9.8%/0%	At 24m: 90%/82%/75%

Active or planned trials for intermediate and high-risk smoldering myeloma

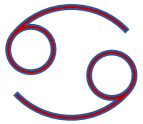
Study	Recruitment status	Interventions	Primary end-point
NCT04270409 (Phase 3 RCT)	Recruiting	Isatuximab+Rd vs Rd	PFS
DETER-SMM (Phase 3 RCT)	Recruiting	DRD vs RD upto 24 cycles	OS
AQUILA (Phase 3 RCT)	Recruiting	Daratumumab vs observation	PFS
HO147SMM (Phase 2 RCT)	Recruiting	KRD with R maintenance vs Rd with R maintenance	PFS
NCT04775550 (phase 2)	Recruiting	DVRD x 24 cycles	2-year MRD negativity rates
NCT04776395 (phase 2)	Recruiting	Iberdomide Dex induction with iberdomide maintenance vs Iberdomide	ORR

Monitoring complications of Smoldering Multiple Myeloma



Patients with SMM are at an increased risk for infectious complications due to immunosuppression including impaired response to COVID19 vaccines

Patients with myeloma precursor diseases such as MGUS and SMM are at increased risk of developing osteoporosis and bone fractures



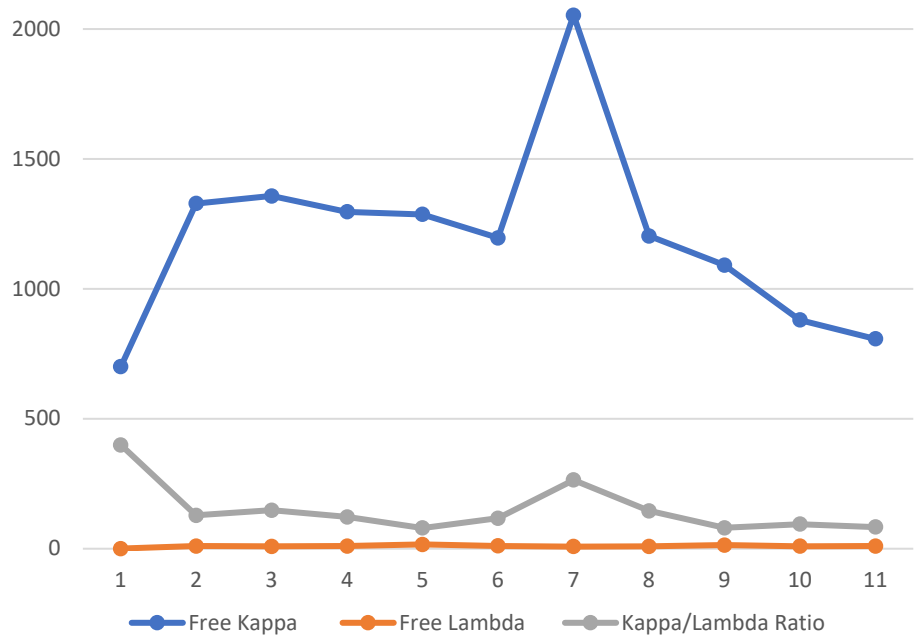
SMM are at a heightened risk for development of second malignancies

Patients with plasma cell disorders, including SMM, are at a higher risk for venous thromboembolism

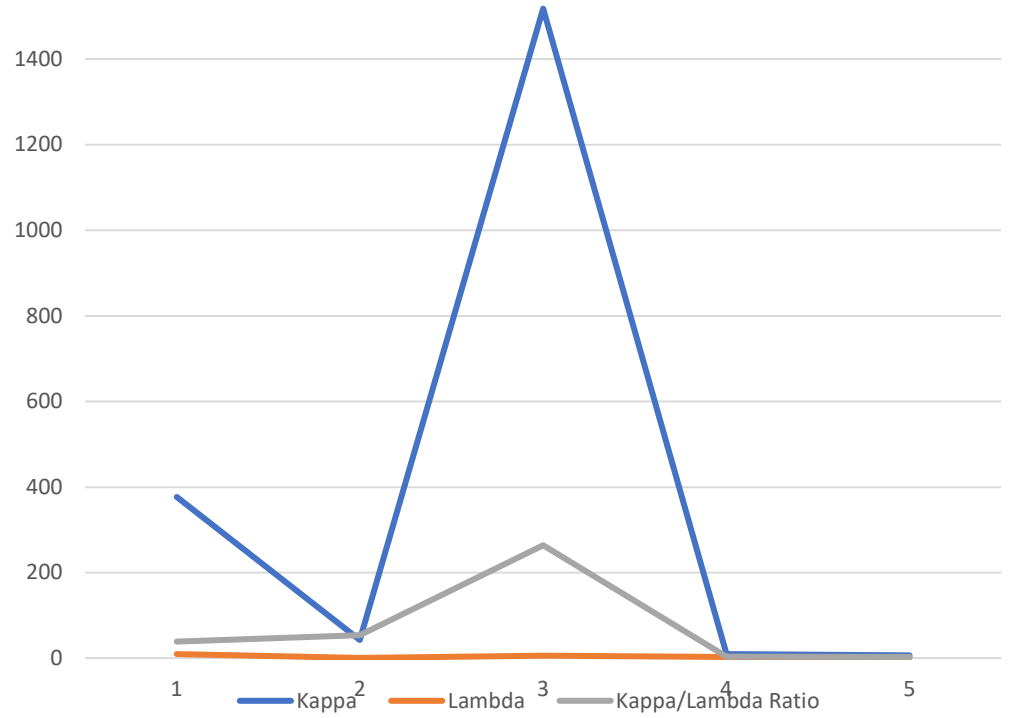
Stampfer et al, Leukemia 2021

Tale of Two Smoldering Myeloma patients

First Diagnosed with SMM in 2012
Qualified as MM by SLiM CRAB criteria
No end organ damage as of 2021
Continues to remains under observation



Diagnosed with high risk SMM in 2015
Enrolled on the ECOG E3A06 study and received Lenalidomide
Progression to MM in 2021
VGPR post Mel 200 ASCT in 2022



Clinical Case

- 55-year-old male with Smoldering Multiple Myeloma incidentally diagnosed in January of 2022.
- A serum protein electrophoresis and immunofixation show an IgG κ monoclonal protein measuring 2.8 g/dL, with a κ free light chain (FLC) of 40 mg / dL (FLC ratio 17).
- CT skeletal sur vey shows no lytic lesions, and no osseous lesions are found on whole body MRI.
- Bone marrow is normocellular, with 25 % plasma cell (PC) involvement.

“High risk” according to the Mayo Clinic 2018 model,
2 risk factors (M-protein >2 g/dL and BM PC >20%)

How do we proceed ?

Discussed the risks and benefits of beginning treatment, preventative vs curative treatment approaches

Strongly consider enrollment in a clinical trial

If lenalidomide with or with out steroids is the chosen regimen, strongly consider upfront stem cell collection

If observation is chosen follow-up should be done 2-3 months after the initial recognition of SMM. If the results are stable, the patient should be followed every 4-6 months for one year and, if stable, every 6-12 months (Kyle et al , Leukemia 2010)

Conclusion

- SMM is a complex disease entity with the presence of remarkable heterogeneity among different patient subsets.
- Formulation of new predictive biomarkers (clinical, molecular/genomics, immunological, microenvironmental, imaging) for further refining risk prediction
- There is less clarity on subset of patients who will benefit from less intense versus intense therapy for Smoldering myeloma
- Lack of data if early intervention results in improved overall survival with out negatively affecting the quality of life
- Clinical trial enrollment should be strongly considered for all SMM patients.