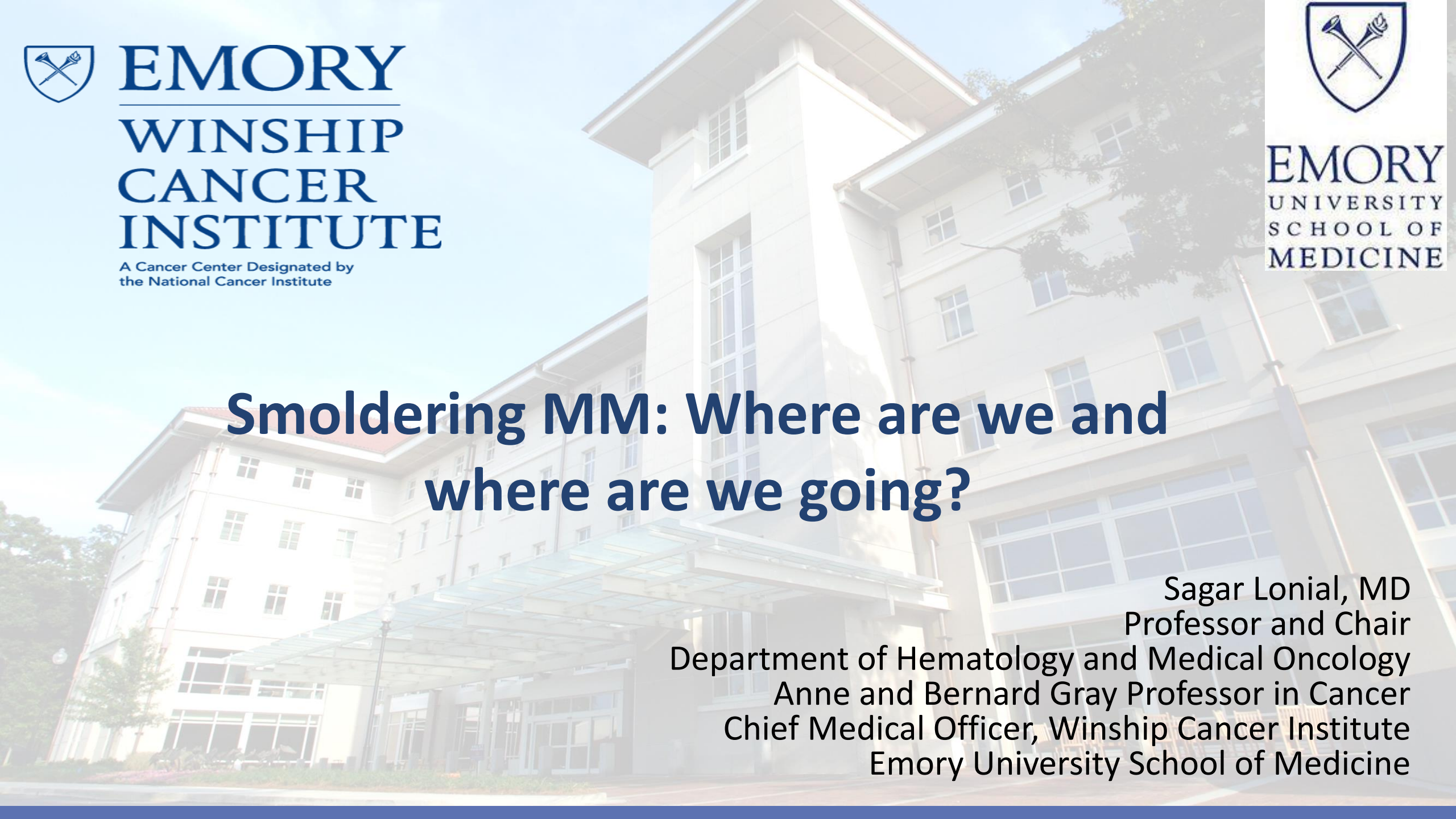

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Smoldering MM: Where are we and where are we going?

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

Conflict of Interest Disclosure

- **Sagar Lonial MD**

- I disclose the following financial relationships over the past 24 months with any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

- Scientific Advisory Board: Takeda, Amgen, Novartis, BMS, GSK, ABBVIE, Genentech, Pfizer, Regeneron, Janssen, BMS (all<10k per year)
- Research support for Clinical Trials: Novartis, BMS, Janssen, Takeda
- Board of Directors with Stock : TG Therapeutics (Neurology and autoimmune indications)

Diagnostic criteria for SMM

	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

Monoclonal proteinuria predicts progression risk in ...ith a

Study Population

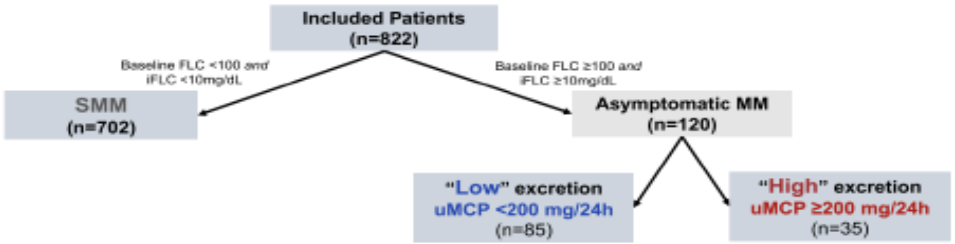


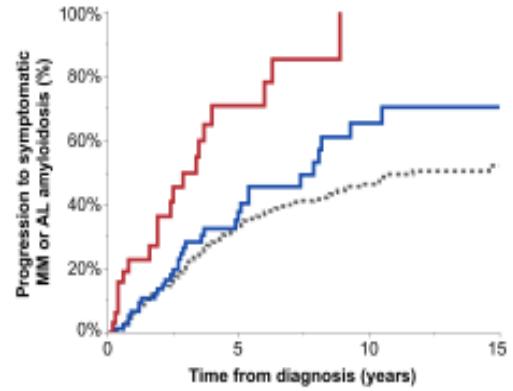
Table 1. Baseline characteristics of patients meeting the FLCr SLiM criteria for MM, and SMM patients

	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[a] - 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)	-	-

[a]-Calculated using CKD-Epi formula, assuming that all patients were Caucasian

Progression outcomes

TTP stratified by baseline FLCr and uMCP excretion



Median TTP:
- 3.4 (95% CI 1.9-6) years
- 7.9 (95% CI 5-10.5) years
- 11.7 (95% CI 9.1-16.5) years

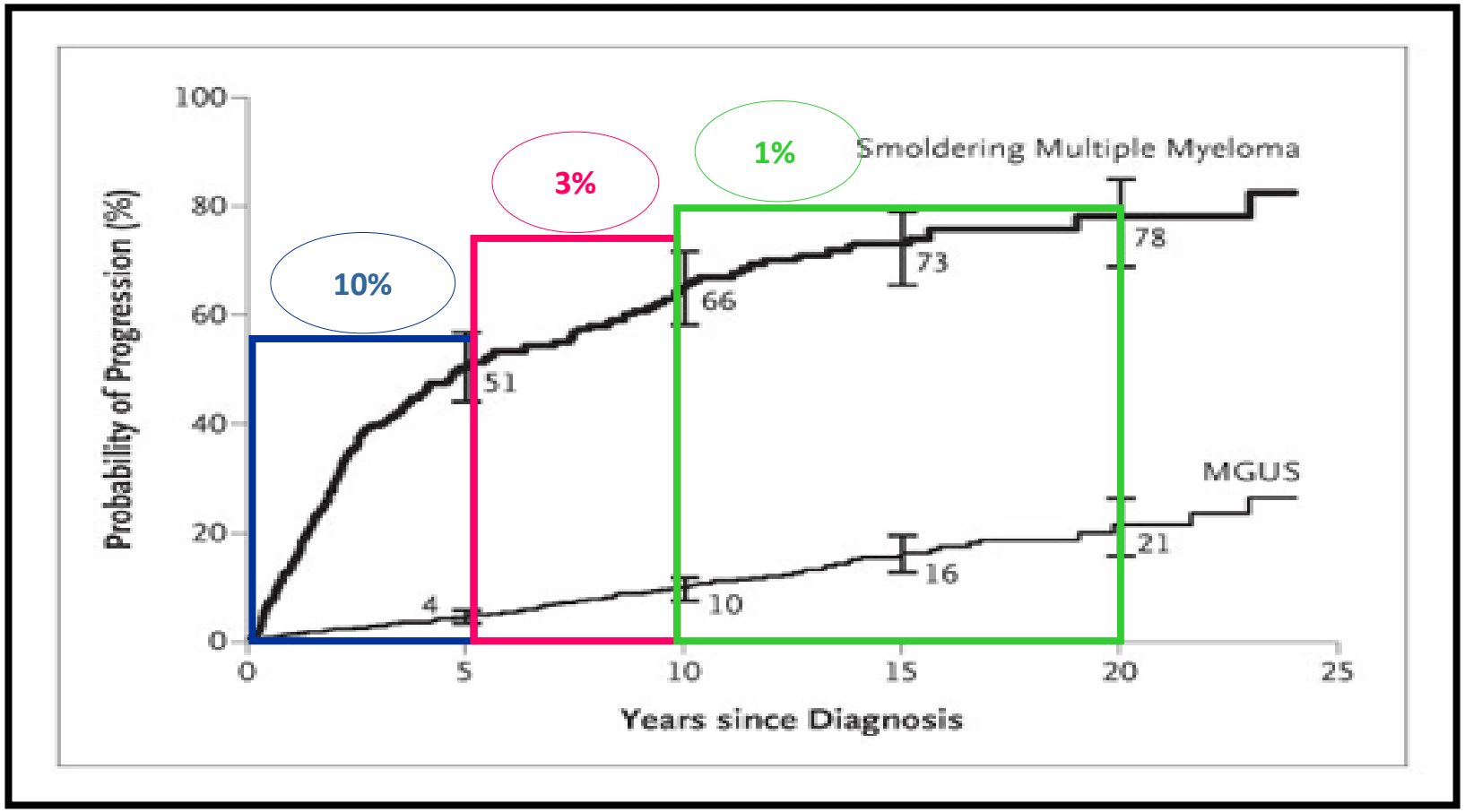
Log-Rank (uMCP ≥200 vs <200 mg/24h): **p<0.001**
Log-Rank (uMCP <200 vs SMM): **p=0.127**

- 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 aggregatted 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

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

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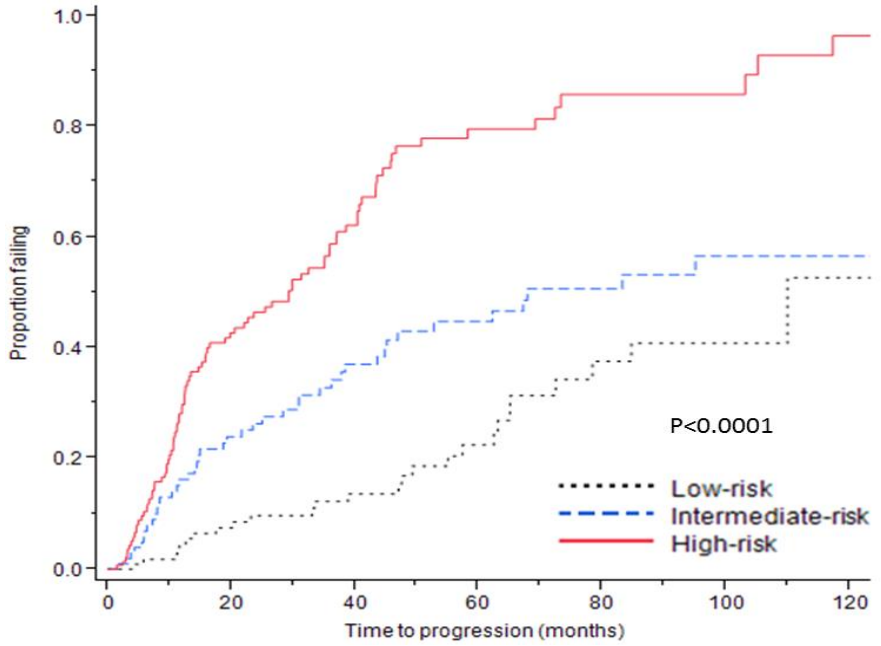
Kyle R. N Engl J Med 2007; 356:2582-90

Revised risk stratification (20/2/20)



Factors

- BMPC >20%
- M Spike >2g/dL
- FLC ratio >20

Stratification

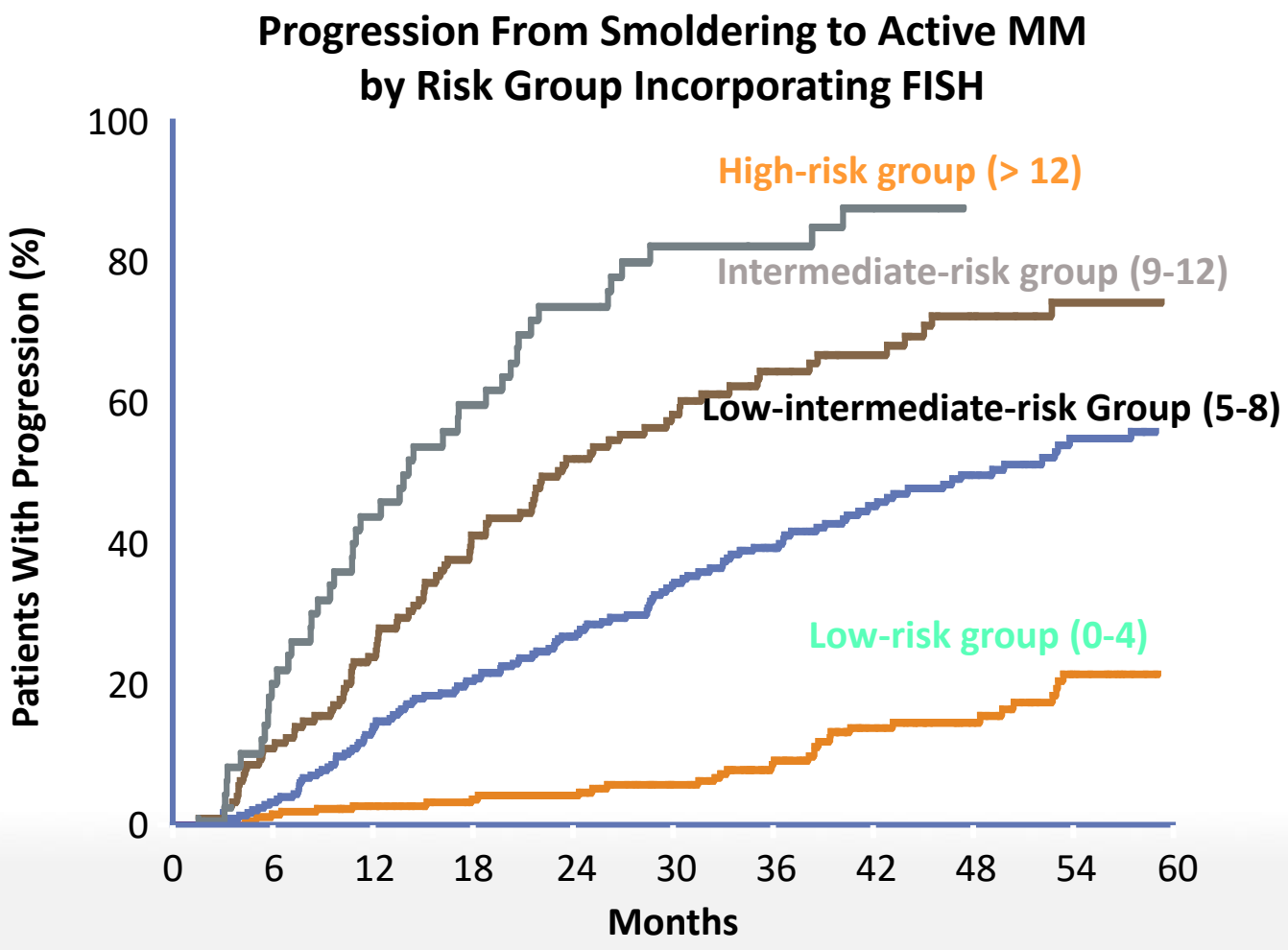
Low-risk: 0 Intermediate-risk: 1
high-risk: >=2

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

Lakshman A, et al. *Blood Cancer J*. 2018;8:59.

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%

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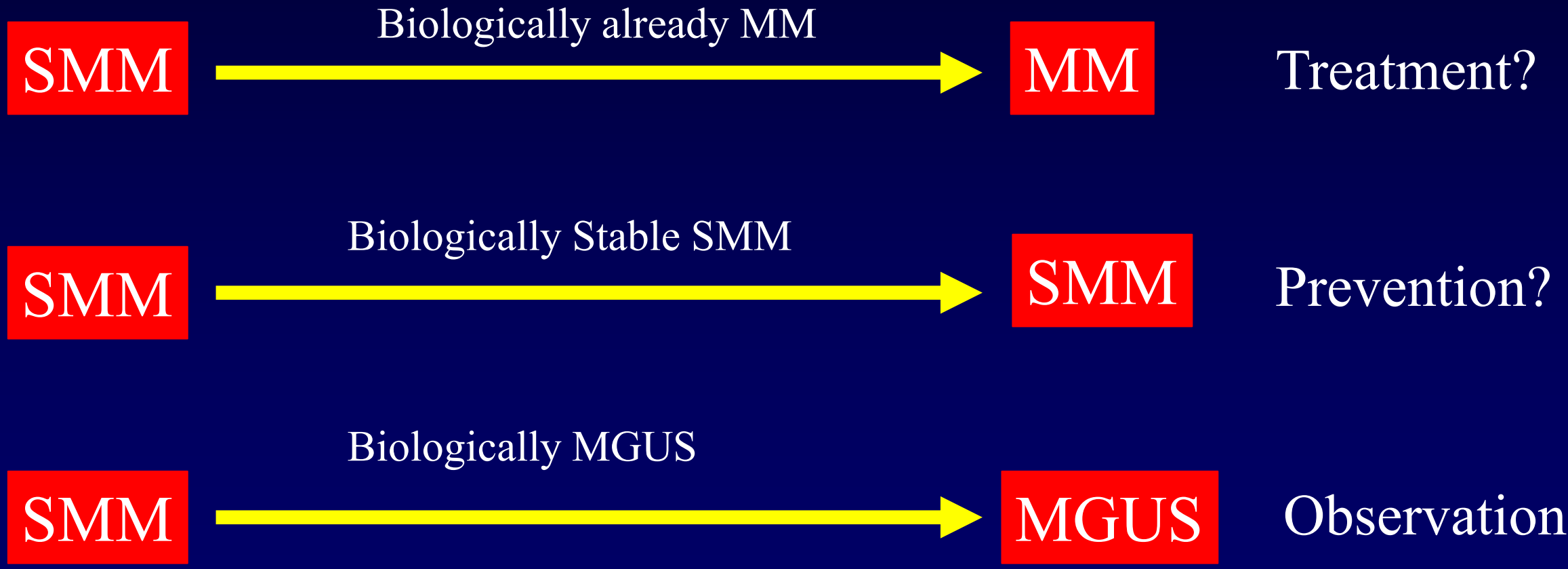
Mateos MV et a. BCJ 2020

Points to Consider

- Genetically SMM looks identical to MM
  - The concept of ‘curative treatment’ earlier is interesting, but not currently supported by data
- What differentiates SMM from MM is immune control
  - Aggressive Tx that suppresses immunity may make things worse.
- We as a community have made the leap to say that prevention of organ damage is an important goal
  - Biomarker driven criteria for definition of MM

Types of SMM


SMM
Biologically already MM
MM
Treatment?
SMM
Biologically Stable SMM
SMM
Prevention?
SMM
Biologically MGUS
MGUS
Observation

Approaches to Smoldering

Immunologic Therapy
Prevention Approach

Intensive therapy
Curative Intent

Len, Len/Dex, Dara

IRD, KRD, ERD

Cesar, Ascent

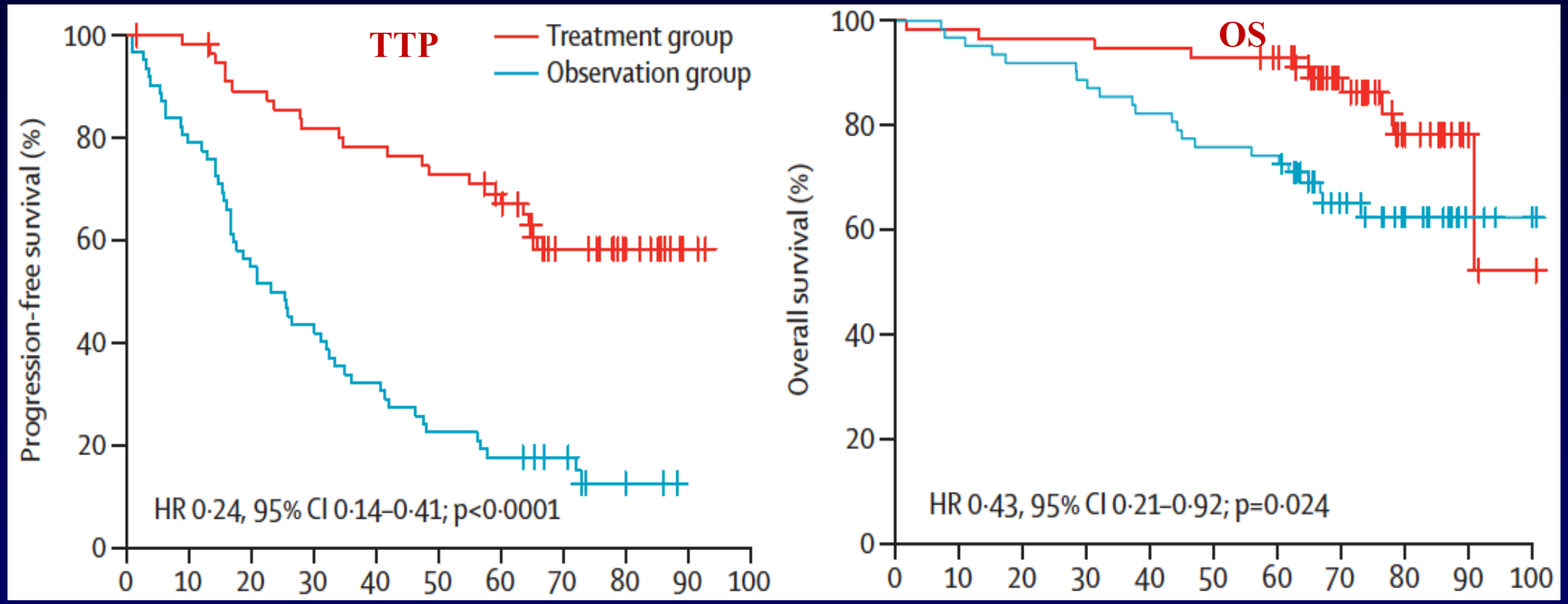
Pros
-Fewer side effects
-More likely to induce long term effects

Cons
-low ORR
-does not eliminate the clone

Pros
-High ORR
-Deep responses

Cons
-Toxicity similar to MM Tx
-May result in resistant clones

First Demonstration of Benefit for Early Therapy



QuiRedex phase 3 trial: Rd vs observation in **high-risk** SMM

Mateos MV, et al, *N Engl J Med*, 2013;369:438-447.

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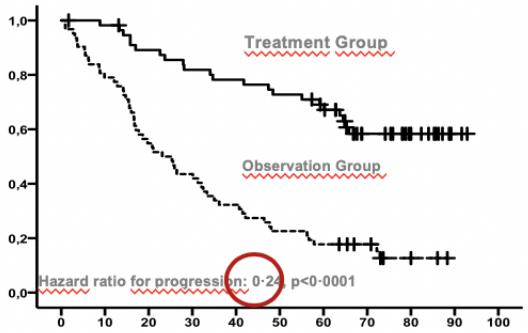
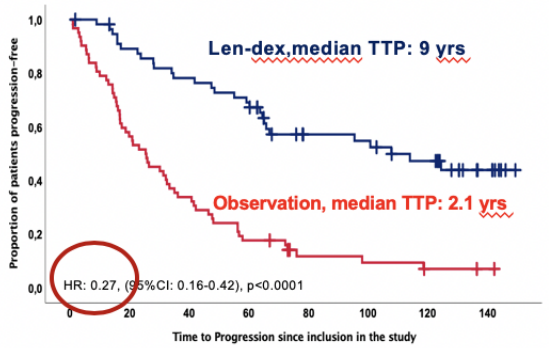
Update for Original SMM trial from Spanish Group

Median f/u: 6.2 year



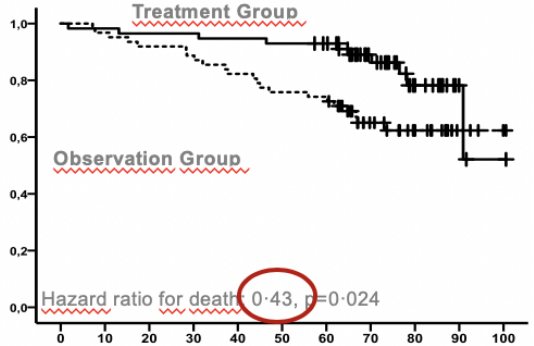
Median f/u: 10.8 years



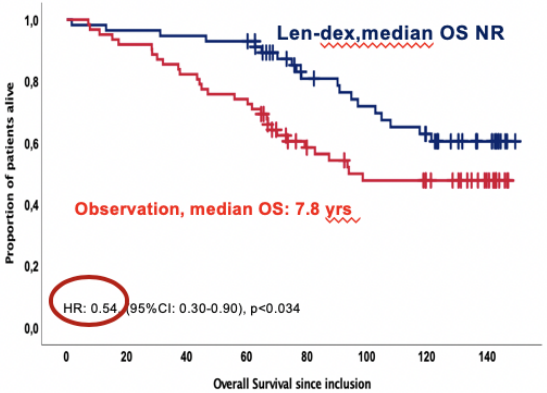
Mateos MV, et al. Lancet Oncology 2016

TTP

Median f/u: 6.2 year



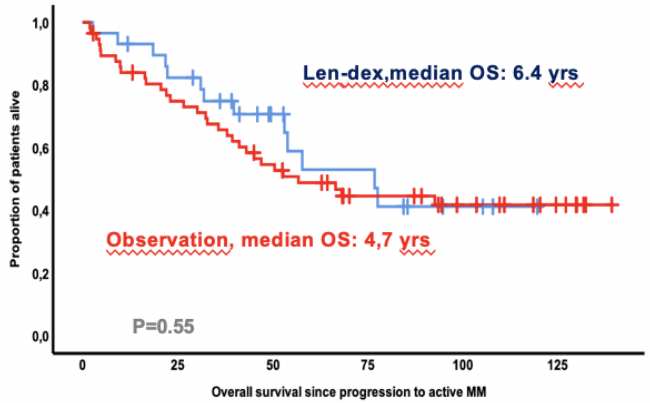
Median f/u: 10.8 years



Mateos MV, et al. Lancet Oncology 2016

OS

Median f/u: 10.8years

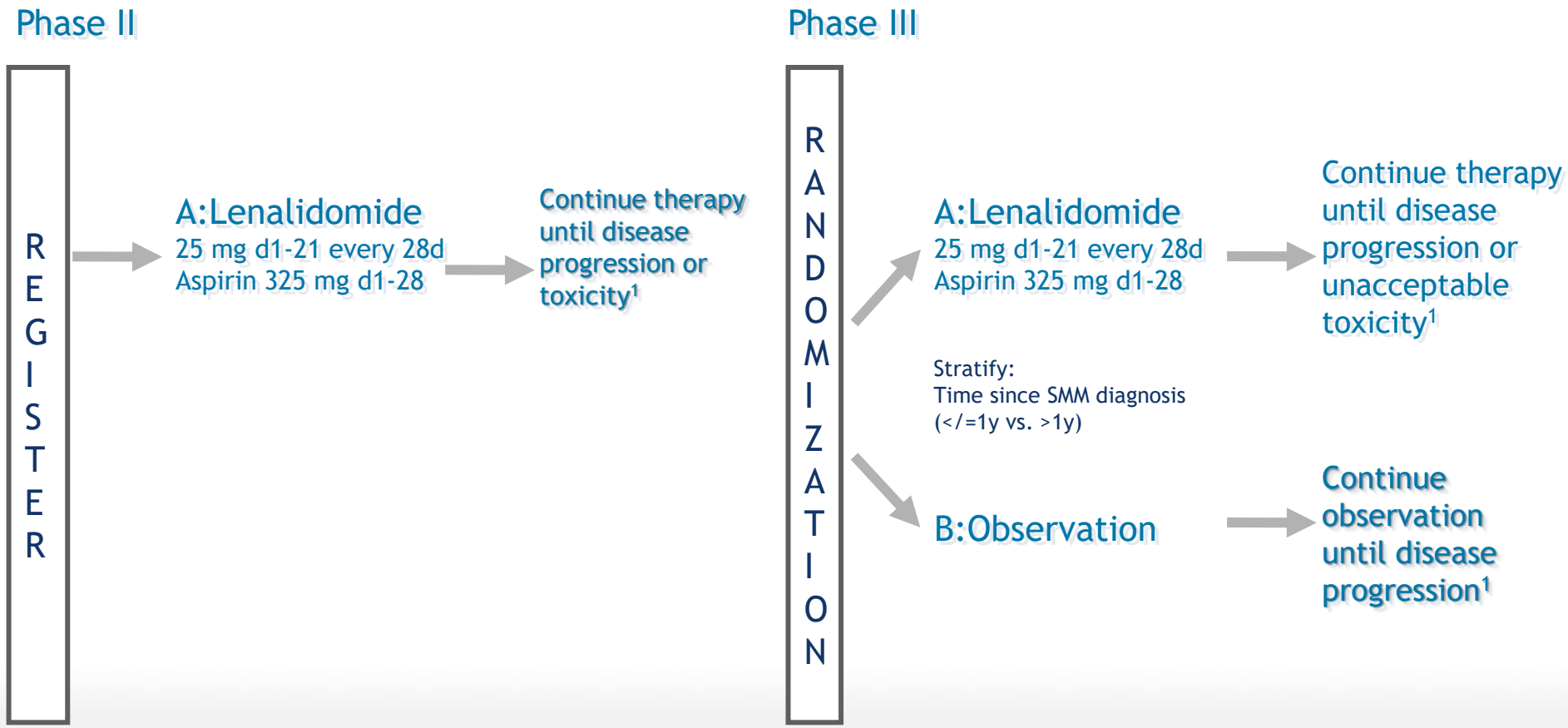


OS post progression shows no induced resistance

Mateos et al, EHA 2020

Schema

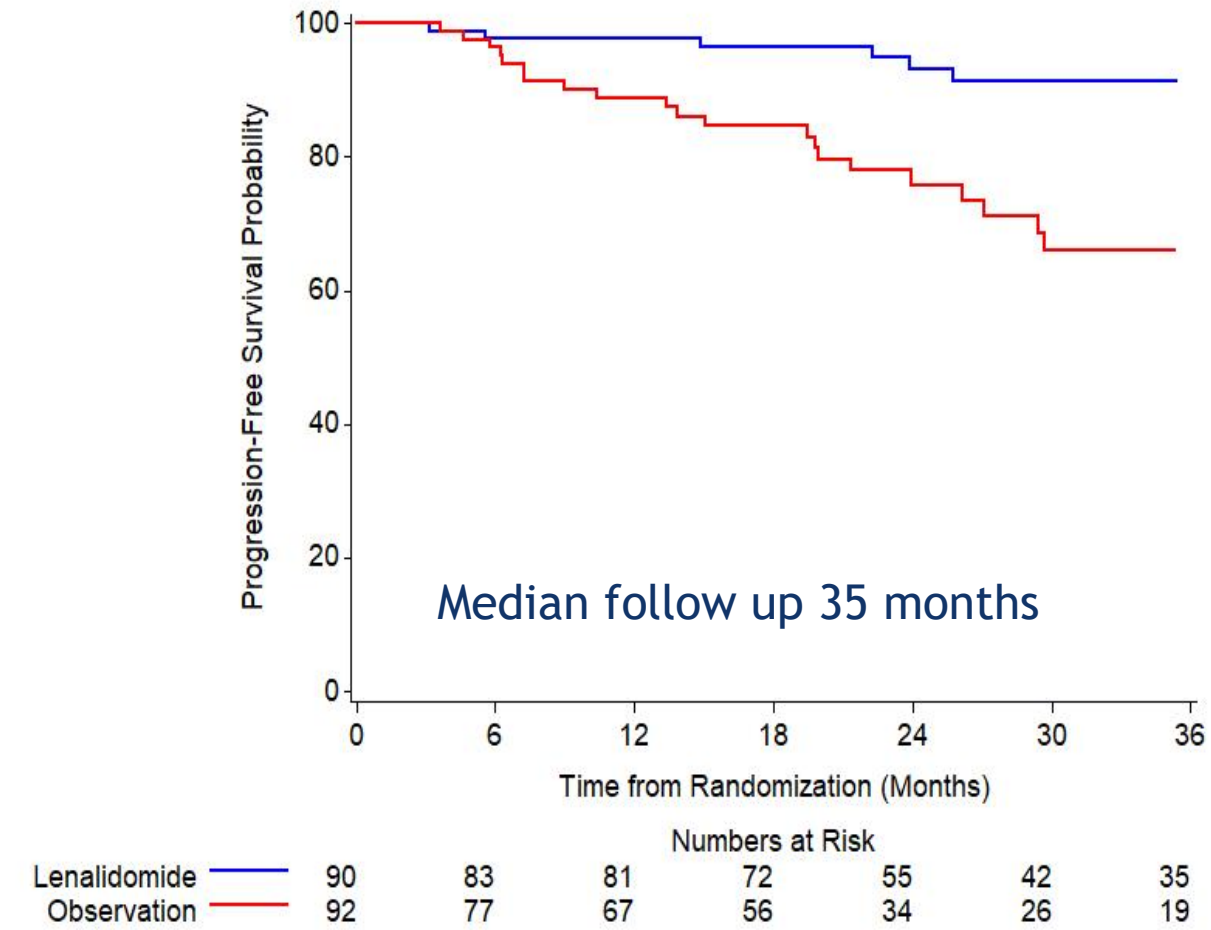
E3A06: Phase II/III Study
A: Lenalidomide vs B: Observation



[1]Mobilize stem cells following 4-6 cycles of therapy. While stem cell collection is suggested strongly, it is not required

Lonial S, et al. ASCO 2019. Abstract 8001.

Phase III PFS ITT^



Treatment Hazard Ratio = 0.28 [95% CI: (0.12-0.63)]

one-sided stratified log-rank test p-value = 0.0005

Phase 3 PFS	Len	Obs
1 yr	0.98	0.89
2 yr	0.93	0.76
3 yr	0.91	0.66

^The DSMC advised release of data in fall 2018 when at the 2nd planned interim analysis (39% full information), the observed p-value from the one-sided stratified log-rank test crossed the related boundary of nominal significance

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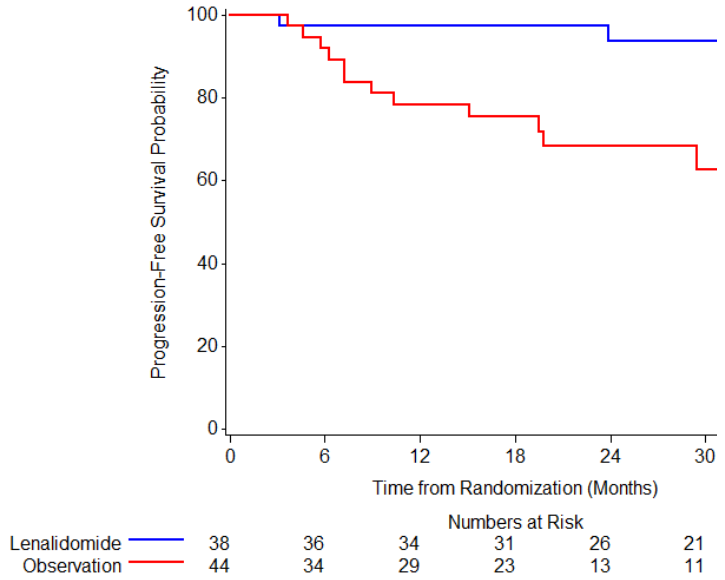
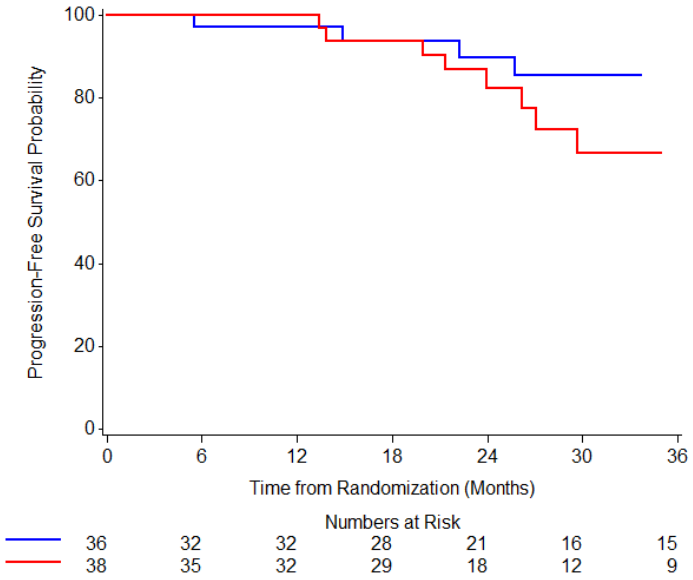
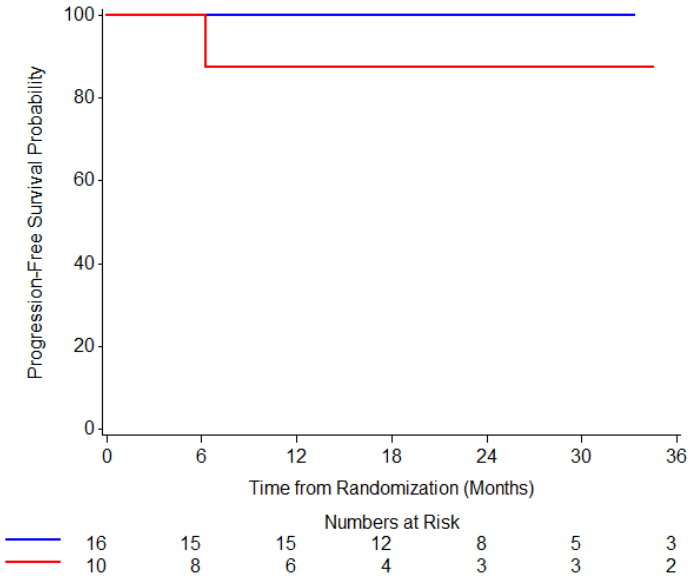
ECOG-ACRIN cancer research group
Reshaping the future of patient care

Lonial S, et al. JCO 2019.

Phase III PFS by Mayo 2018 Risk Criteria







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High Risk

Intermediate Risk

Low Risk

Lonial S, et al. JCO 2019.

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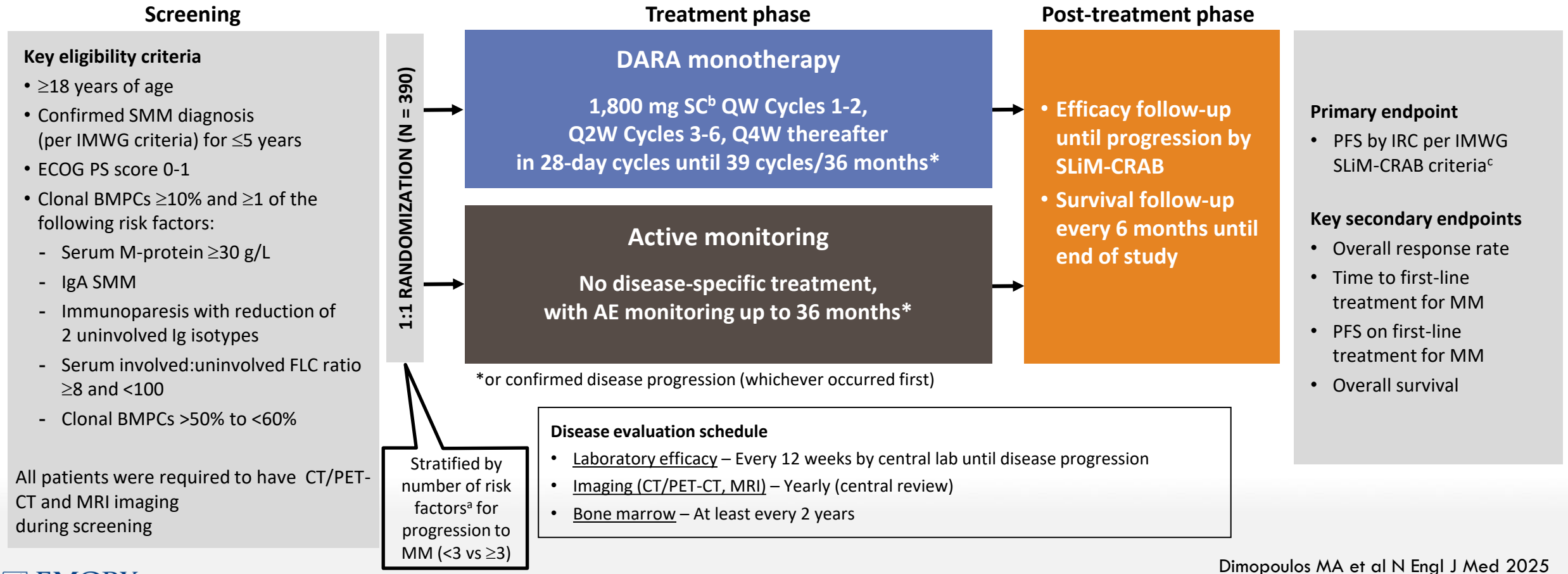
AQUILA: Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With Smoldering Multiple Myeloma

AQUILA enrolled patients between December 10, 2017, and May 27, 2019 at 124 sites in 23 countries



Dimopoulos MA et al N Engl J Med 2025

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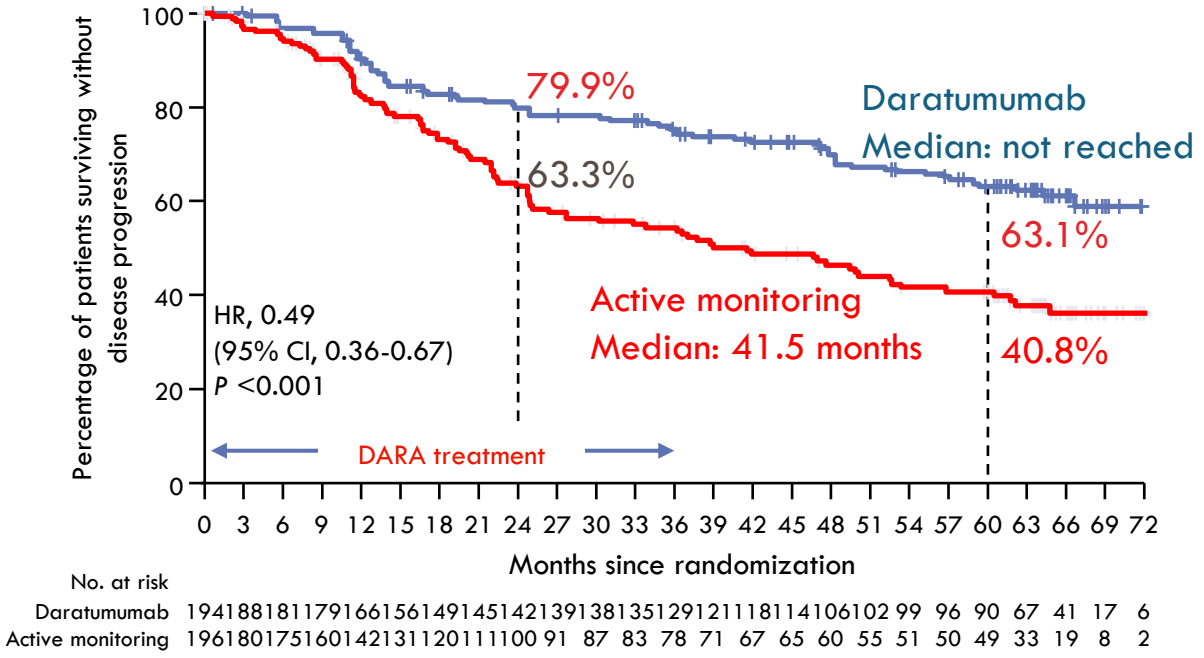
Flobies

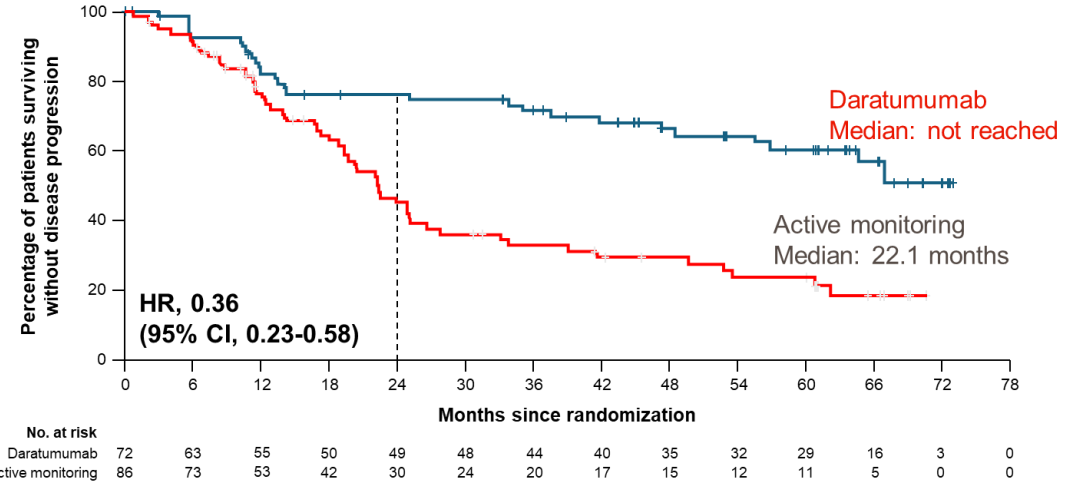
AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria (IRC Assessment)

Median follow-up: 65.2 months

PFS at 5 years was 63.1% with dara and 40.8% with active monitoring



AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria in Patients With High Risk per Mayo 2018 Criteria



- Retrospective review of high risk per Mayo 2018 criteria showed median PFS was not reached for DARA vs 22.1 months for active monitoring

- DARA significantly reduced the risk of progression to MM or death by 51% versus active monitoring for all subsets and risk categories, more pronounced in high risk SMM
- The benefit continued beyond 36 months
- May 20, 2025: FDA ODAC positive vote

- Data from large study
- SMM populations per current definitions (IMWG 2014)
- Advanced imaging used at baseline and every year

Dimopoulos MA et al N Engl J Med 2025

AQUILA: Daratumumab for High-Risk SMM

	AQUILLA	
Treatment	Daratumumab SC 36 months n = 194	Observation n =196
Inclusion criteria for HR SMM	One factor: M-protein ≥ 30 g/l, IgA SMM, immunoparesis, sFLC > 8 < 100, BMPC > 50 < 60%	
Mayo 20/2/20 (%) Low Intermediate High	 45 (23.2) 77 (39.7) 72 (37.1)	 34 (17.3) 76 (38.8) 86 (43.9)
≥ CR / ≥ VGPR (%)	8.8 / 29.9	0 / 1
5 years PFS	63.1%	40.8%
	HR 0.49; [95% CI, 0.36 to 0.67]; P<0.001	
5-years OS	93%	86.9%
	HR 0.52; [95% CI, 0.27 to 0.98	
Safety G3-4 infections	 16.1%	 4.6%

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Dimopoulos et al N Engl J Med 2024

Hot off the Press

just 10 years earlier

THE LANCET

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

Studies ongoing for SMM

Regimen	N of pts	IMWG diagnostic criteria	Risk stratification	primary end point	Median PFS	Reference
GEM-CESAR KRd-ASCT-KRd-Rd (~3 years)	90	No	Mayo 2008 or GEM-Pethema	uMRD rate 3 months after ASCT	85% at 70 months (with SLiM)	Mateos MV et al J Clin Oncol 2024
KRd-R (~2.5 years)	54	Amended	Mayo 2008 or GEM-Pethema and revised 2015*	MRD-negative CR	91.2% at 60 months (IMWG 2014)	Kazandjian D et al JAMA 2021
Elotuzumab-Rd (2 years)	50	Yes	revised 2015*	PFS	?	Ghobrial I et al EHA 2022
IRd-IR (2 years)	55	Yes	revised 2015*	PFS at 2 years	48,6 months	Nadeem O et al BioRx 2024
ASCENT D-KRd- 2 years	87	Yes	20/2/20 or IMWG scoring system	sCR at end of maintenance	PFS rate at 3 years 89.9%	Kumar S et al ASH 2022
B-PRISM D-VRd – 2 years	20	Yes	20-2-20 and other*	sustained MRDneg at 2 years	?	Nadeem O et al ASCO 2022

*BMPCs ≥10% and any one or more of the following: Serum M protein ≥30g/L, IgA SMM, Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, Serum involved/uninvolved FLC ratio ≥8 (but <100), Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period), Clonal BMPCs 50%-60%, Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes, t(4;14) or del(17p) or 1q gain, Increased circulating PCs, MRI with diffuse abnormalities or 1 focal lesion, PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

DETER-SMM: Daratumumab addition to Revlimid in SM

PI: Dr. Natalie Callander

Site(s): 707 locations across the US

Design (Size): Phase 3 Trial (288 participants)

Intervention: Daratumumab + Len/Dex vs Len/Dex (2 year, Dex is 1 year)

Inclusion Criteria for SMM: High-risk is defined by the presence of 2 or more:

1. Abnormal serum free light chain ratio of involved to uninvolved >20,
2. Serum M-protein level >= 2 gm/dL
3. >20% plasma cells on biopsy or aspirate
4. Presence of t(4;14) or del 17p, del 13q or 1q gain

Primary Outcomes: Overall Survival (up to 15 years) and FACT-G score from Baseline to 24 cycles of treatment

(ITHACA IsaRd vs Rd, n=337 finished enrolling, High risk 20/2/20 and/or updated PETHEMA, no results presented yet)

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Study Link

Iberdomide +/- Dex: Intermediate or High-Risk SMM

PI: Dr. Nisha Joseph

Site(s): 1 location at Emory University Hospital/Winship Cancer Institute

Design (Size): Phase 2 Trial (68 participants)

Intervention: Iberdomide +/- Dex for 2 years

Inclusion Criteria: Intermediate or high risk SMM in Mayo 20/2/20

Primary Outcomes: Overall Response Rate assessed by IMWG response criteria (3-year timeframe)

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Study Link

Conclusions

- A goal is to evaluate who can be moved to MM vs remain SMM
- New definition for high risk SMM should be used across all studies
- For patients meeting the 20/2/20 high risk criteria, early therapy with Dara, len or len/dex should be considered **IF** a trial is not an option
- The question of prevention vs cure should be addressed in clinical trials, but absent an answer to that question, we should not continue to just *'Wait for more data'*
- **It is time to move towards early intervention for some patients**

Patients and Families

Thanks to:

Jonathan Kaufman
Ajay Nooka
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Richa Parikh
Nishi Shah
Craig Hofmeister
Vikas Gupta
Charise Gleason
Danielle Roberts
Sara Scott
Donald Harvey
Amelia Langston
Y. Gu
S-Y Sun
Ben Barwick
Mala Shanmugan
Larry Boise
Bryan Burton

sloni01@emory.edu

Golfers Against Cancer
T.J. Martell Foundation

And Many Others who
are part of the Myeloma clinical and
research team