11:45 AM–12:30 PM

Smoldering Myeloma

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Smoldering Multiple Myeloma: To Treat or Not To Treat?

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Disclosures

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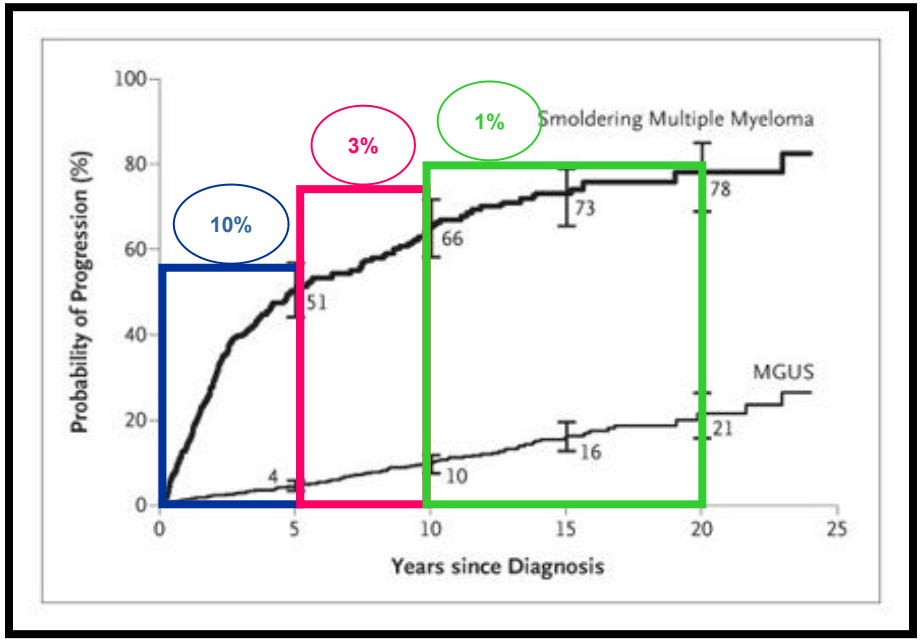
- **Honorarium**: Karyopharm, BMS, Janssen

A heterogenous entity!



Diagnosis	Disease definition
Non-IgM MGUS	Both criteria must be met
	Serum M protein (IgG or IgA) <3 g/dL and clonal BMPCs <10%, and
	Absence of **myeloma defining events (MDEs)** or amyloidosis
Smoldering Multiple Myeloma	Both criteria must be met:
	Serum M protein (IgG or IgA) ≥3 g/dL or urinary M protein ≥500 mg/24 h and/or clonal BMPCs 10%-60%, and
	Absence of MDEs or amyloidosis

Kyle R. *N Engl J Med*. 2007;356:2582-2590.

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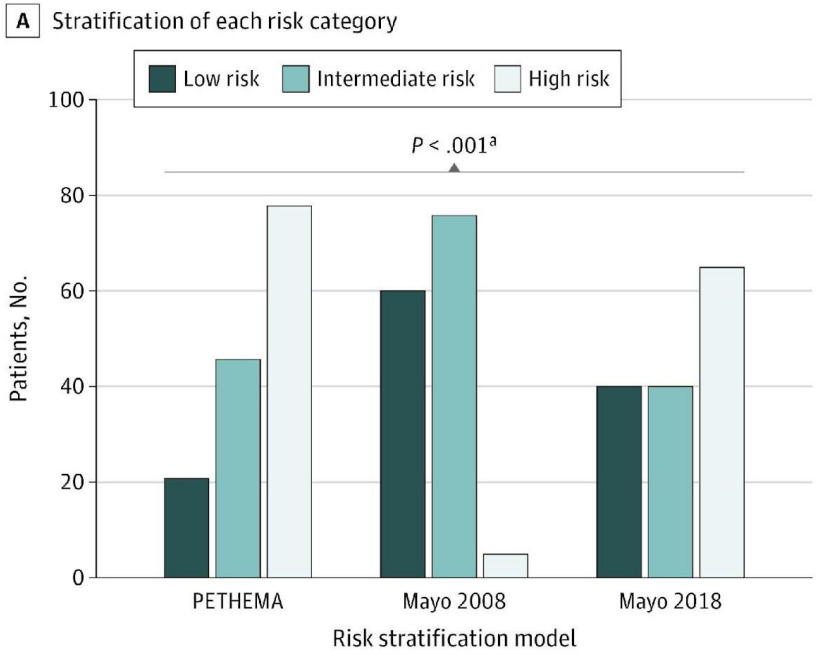
Models of progression of SMM to MM

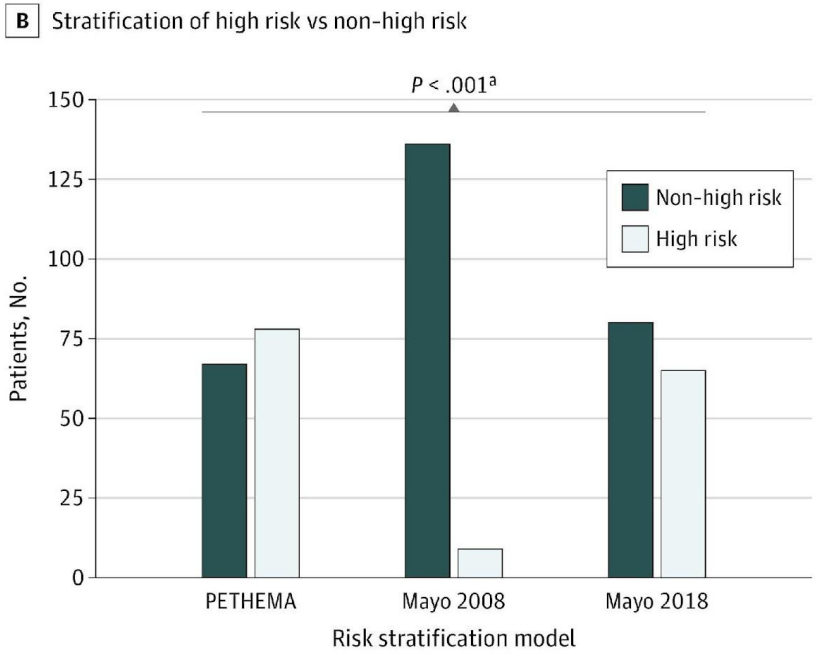
PETHEMA	≥95% aberrant PCs Immunoparesis
Mayo 2008	BPMCs ≥10% M spike ≥3 g/dL sFLC ratio ≤0.125 or ≥8
Mayo 2018	BPMC >20% M spike >2 g/dL sFLC ratio < .05 or > 20
IMWG 2020	sFLC ratio M spike BMPCs FISH abnormalities*

* t (4;14), t (14;16),1q gain, del13q/monosomy 13

Vaxman et al. *Blood*. 2022.

High rates of discordance among the models





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Hill E et al. *JAMA Oncol*. 2021.

Therapeutic approaches in SMM: Opportunities and Challenges

- Current guidelines recommend monitoring patients with SMM every 3 to 6 months for active MM before initiating treatment.[1]

- Most patients with high- or intermediate-risk SMM **do** progress to MM.[2,3]

- Intercepting high-/intermediate-risk SMM may yield clinical benefit.

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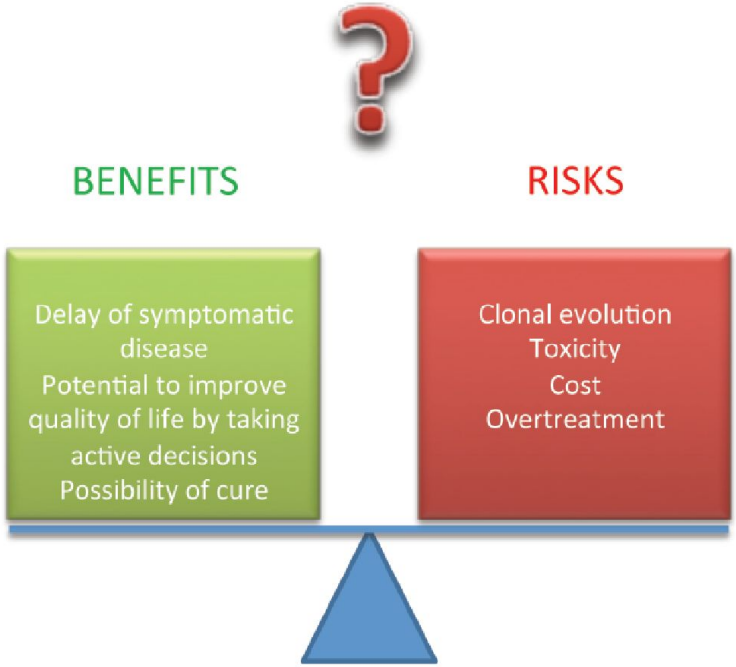
1. National Comprehensive Cancer Network. https://www.nccn.org/patients/guidelines/myeloma/files/assets/common/downloads/files/myeloma.pdf. Accessed October 20, 2017.
2. Dispenzieri A et al. *Blood*. 2008;111(2):785-789.
3. Pérez-Persona E et al. *Blood*. 2007;110(7):2586-2592.

To treat or not to treat?



Criteria to identify SMM for high risk of progression: Validation and refinement

True prevalence of SMM: 0.53%

Divergent treatment philosophies:
- CURE (intensive approach)
- CONTROL (less intensive approach)

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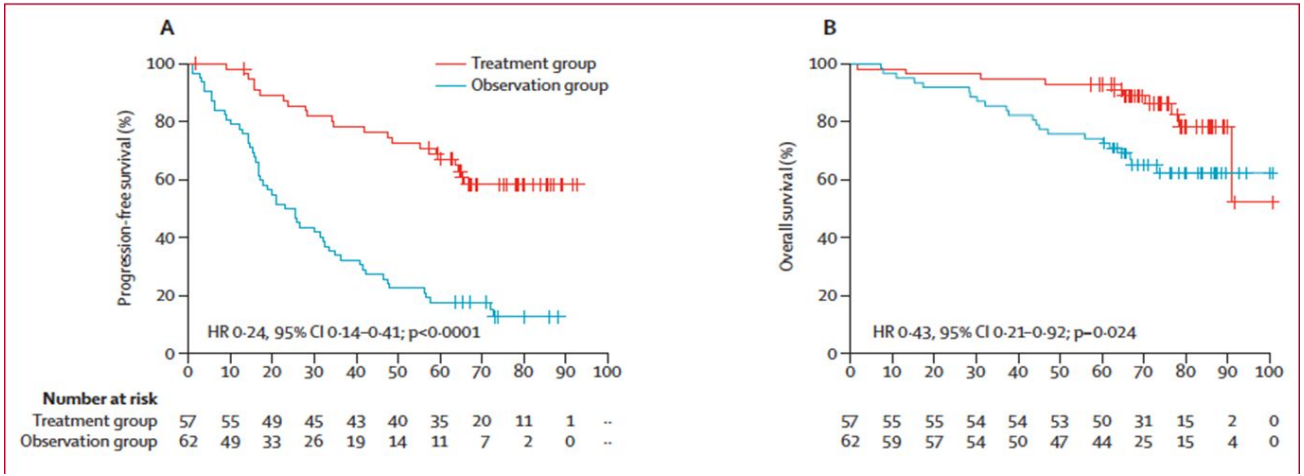
Manasanch et al. *Hematologica*. 2014; Thorsteindottir S et al. *Nat Med*. 2023; Vaxman et al. Blood. 2022.

QuiRedex Phase 3 trial: First Randomized Trial Showing Benefit in SMM



119 patients with high-risk SMM (by PETHEMA) randomized to:

- Lenalidomide plus dexamethasone for nine cycles followed by Len maintenance for 2 years
- Observation only

Mateos MV et al. *N Engl J Med*. 2013
Mateos MV et al. *Lancet Oncol*. 2016.

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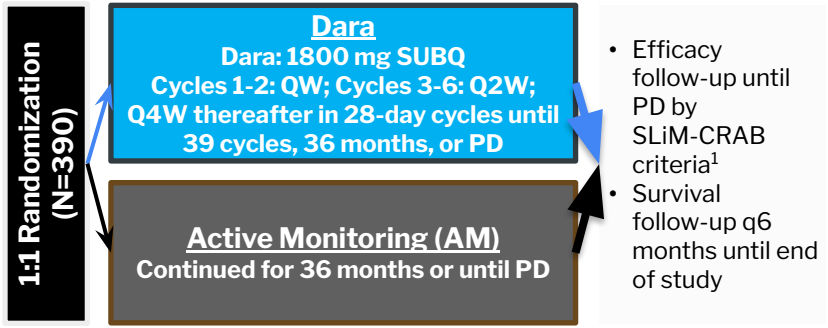
Phase 3 AQUILA Study of Dara vs Active Monitoring in High-Risk Smoldering MM: Study Design and Patients

Key Eligibility Criteria

- Confirmed SMM diagnosis (per IMWG) for ≤5 years
- ECOG PS 0-1
- Clonal BMPCs ≥10% and ≥1 of the following risk factors:
  Serum M-protein ≥30 g/dL; IgA SMM; Immunoparesis with ↓ of 2 uninvolved Ig isotypes; Serum involved:uninvolved FLC ratio ≥8 and <100; Clonal BPMCs >50% to <60%



Primary end point: PFS (by IRC per IMWG SLiM-CRAB criteria)
Key secondary end points: ORR, time to 1L treatment for MM, PFS on 1L treatment for MM, OS

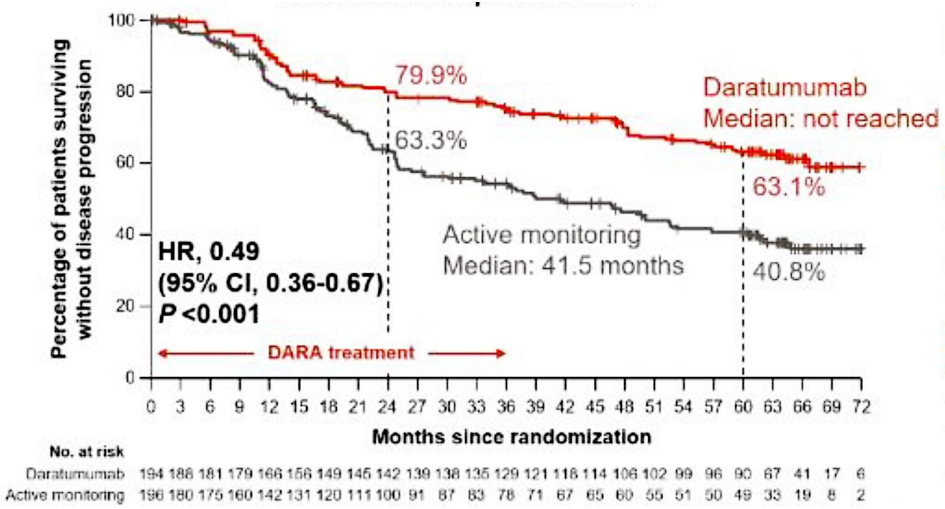
Median age (range), years		63.0 (31-86)	64.5 (36-83)
18 to <65 years, n (%)		106 (54.6)	98 (50.0)
65 to <75 years, n (%)		67 (34.5)	74 (37.8)
≥75 years, n (%)		21 (10.8)	24 (12.2)
ECG PS, n (%)	0	165 (85.1)	160 (81.6)
	1	29 (14.9)	36 (18.4)
Median years from diagnosis of SMM to randomization (range)		0.80 (0-4.7)	0.67 (0-5.0)
Median BPMCs (range), %		20.0 (8.0-59.5)	20.0 (10.0-55.0)
Type of SMM, n (%)	IgG	127 (65.5)	138 (70.4)
	IgA	55 (28.4)	42 (21.4)
	Other	12 (6.2)	16 (8.2)
AQUILA risk factors, n (%)	<3	154 (79.4)	156 (79.6)
	≥3	40 (20.6)	40 (20.4)
Cytogenetic risk profile[a], n/N (%)		29/167 (17.4)	22/170 (12.9)
Mayo 2018 risk criteria, n (%)	Low	45 (23.2)	34 (17.3)
	Intermediate	77 (39.7)	76 (38.8)
	High	72 (37.1)	86 (43.9)

[a] ≥1 of del(17p), t(4;14), and/or t(14;16).

1. Rajkumar SV et al. *Lancet Oncol.* 2014;15(12):e538-e548.
Dimopoulos MA et al. ASH 2024. Abstract 773. Dimopoulos MA et al. *N Engl J Med.* 2024. Epub ahead of print (12-9-24).

Phase 3 AQUILA Study of Dara vs Active Monitoring in High-Risk Smoldering MM: PFS and ORR

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



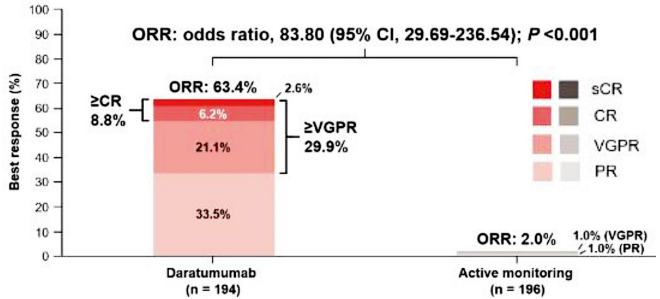
Retrospective Review of PFS in Patients With High-Risk by Mayo 2018 Criteria

- Median PFS: NR with Dara vs 22.1 months with AM (HR 0.36 [95% CI, 0.23-0.58])

PFS event	67 (34.5)	99 (50.5)
Death without PD	5 (2.6)	5 (2.6)
PD	62 (32.0)	94 (48.0)
CRAB criteria	12 (6.2)	34 (17.3)
Calcium Elevation	0	2 (1.0)
Renal insufficiency	0	0
Anemia	2 (1.0)	14 (7.1)
Bone disease	10 (5.2)	18 (9.2)
SLiM criteria	50 (25.8)	65 (33.2)
Clonal BPMCs	5 (2.6)	16 (8.2)
Serum FLC	33 (17.0)	33 (16.8)

Best Response

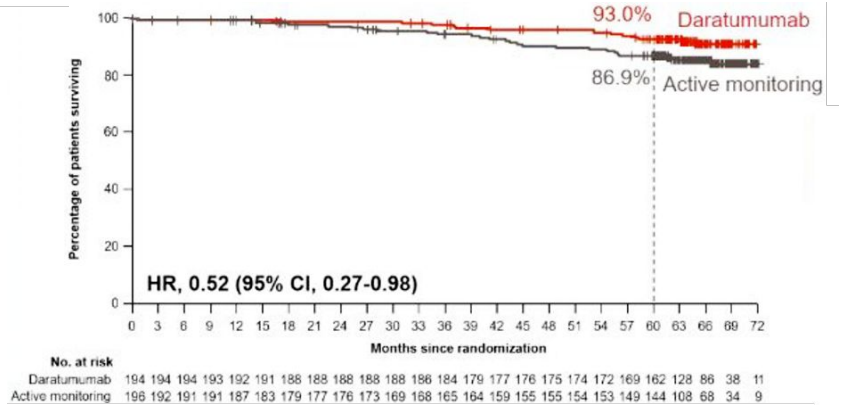
MRI



Dimopoulos MA et al. ASH 2024. Abstract 773. Dimopoulos MA et al. *N Engl J Med. 2024*. Epub ahead of print (12-9-24).

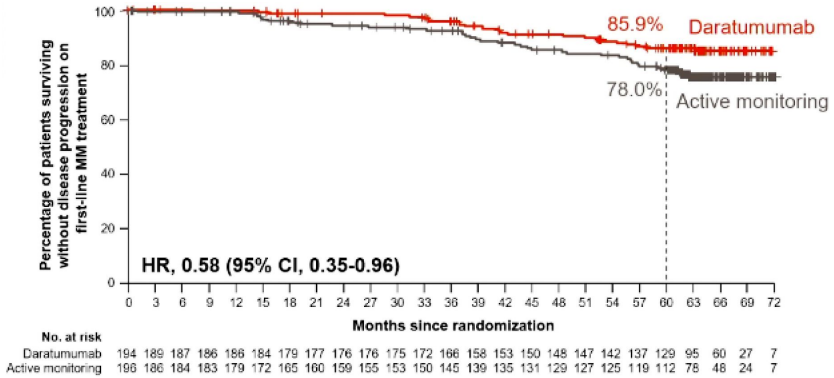
Phase 3 AQUILA Study of Dara vs Active Monitoring in High-Risk Smoldering MM: OS and PFS2

OS



OS		Dara (n=194)	AM (n=196)
Deaths, n (%)		15 (7.7)	26 (13.3)
Primary cause, n	PD	3	9
	AE	2	4
	Other[a]	10	13

PFS on 1L Treatment for MM (PFS2)



- VRd was the most common 1L therapy
  - 29.7% (19/64) in the Dara arm
  - 27.6% (29/105) in the AM arm
- Received anti-CD38 mAb-based therapy
  - 25.0% (16/64) in the Dara arm
  - 33.3% (33/105) in the AM arm

Dimopoulos MA et al. ASH 2024. Abstract 773. Dimopoulos MA et al. *N Engl J Med. 2024.* Epub ahead of print (12-9-24).

Summary of Phase 2 and 3 Studies in SMM

	Patient population	ORR	Additional Notes
Phase 3 Studies			
Len/dex (Mateos)	Int/high-risk SMM	79%	TTP Rd 9.5 vs Observations 2.1 years
Lenalidomide (Lonial)	Low/int/high-risk SMM	48.9%	3-year PFS of 91% for the lenalidomide arm vs 66% for the observation arm
Daratumumab vs observation (Dimopoulos)	High-risk SMM	63.4%	60-month PFS: 63.1% vs 40.8% 60-month OS: 93% vs 86.9% CR rate 8.8%
Phase 2 Studies (Curative Intent)			
KRD + ASCT (GEM-CESAR)	High-risk SMM	94%	MRD-ve (10^{-5}): 62% after consolidation, 31% after 4 years TTBP: 70 months
Dara-RVD (B-PRISM)	High-risk SMM	98%	MRD-ve (10^{-5}): 65% after 24 months
KRd-D (ASCENT)	High-risk SMM	97%	MRD-ve (10^{-5}): 84%; median time to MRD: 6.6 mo

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Mateos et al. *N Engl J Med*; Lonial et al. *J Clin Oncol*; Dimopolous et al. *N Engl J Med*; Mateos et al. *J Clin Oncol*; Nadeem e

Immunotherapy in SMM: Rationale

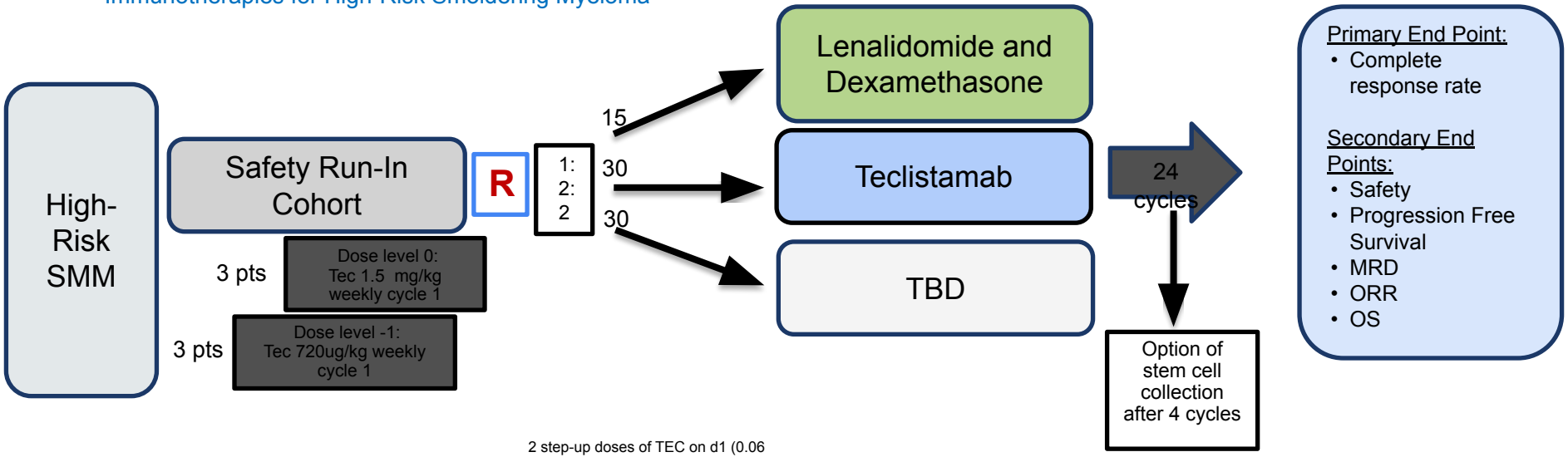
- The immune system is less dysfunctional in SMM and therefore a great opportunity to study **benefit** compared to patients with RRMM
- The tumor burden is lower; therefore, potential for **less CRS and toxicities**
- Avoid **combination therapy** and SCT and reserve for use at the time of progression
- Avoid **resistance by short, fixed duration** of therapy and modify schedule to limit further toxicity
- Compare to previous standard of care such as lenalidomide and dexamethasone to prove superiority

Immunotherapy Trials in HR-SMM

ImmunoPRISM: Teclistamab vs lenalidomide/dex in HR-SMM (NCT05469893)
Elrantamab in HR-SMM (NCT06183489)
Linvoseltamab in HR-SMM (NCT05955508)
Linvoseltamab in HR-MGUS and LR-SMM (NCT06140524)
Teclistamab and talquetamab with daratumumab in HR-SMM (NCT06100237)
CAR-PRISM: Ciltacabtagene autoleucel in HR-SMM (NCT05767359)

TCE in Smoldering Myeloma

Immuno-PRISM: A Randomized Phase II Platform Study of Select Immunotherapies for High-Risk Smoldering Myeloma



Teclistamab Dosing Schedule

2 step-up doses of TEC on d1 (0.06 mg/kg) and d3 (0.3mg/kg) for cycle 1

Screening	C1	C2	C3	C4	C5	C6	C7 +

C1-2:* ***TEC 1.5 mg/kg QW***

C3-6: ***TEC 3 mg/kg Q2W***

C7-24: ***3 mg/kg Q4W***

Nadeem/Ghobrial et al ASH 2023

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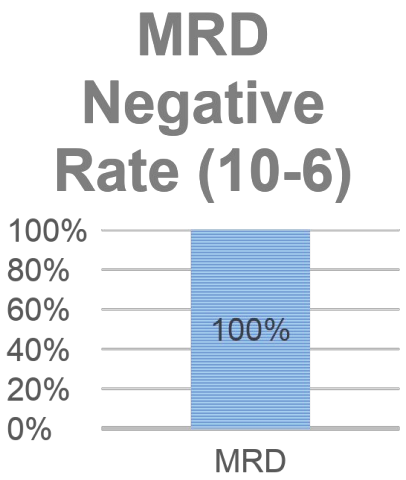
TCE in Smoldering Myeloma

TEC-Treated Cohort (12 patients)

Best response	n	%
CR	**10**	**83**
VGPR	**2**	**17**
Overall response rate	**12**	**100**

- No patients have progressed on treatment.



**1 patient with 0-1 cells/mL (detected below LOD)*

Infections (Grade 2 or Greater)	N=12	
	Grade 2	**Grade 3**
Salmonella	0	1
Sinusitis	2	1
Upper respiratory infections		0
COVID-19	1	0
Adenovirus	1	0
Nonspecific	1	0

- CRS occurred in 7 of 12 (58%) patients treated with teclistamab.
- Two patients developed grade 2 CRS requiring tocilizumab.
- No patients with grade 3 or greater CRS.

Nadeem/Ghobrial et al. ASH 2023.

CAR-T in Smoldering Myeloma

CAR-PRISM: Cilta-cel in High-Risk Smoldering Myeloma

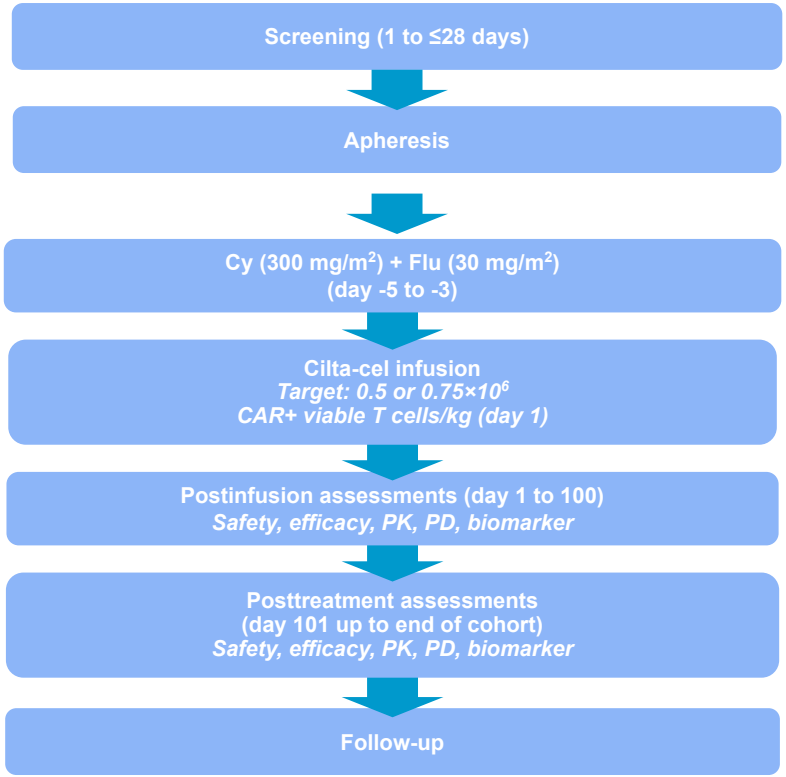
- The first 3 patients treated at **a lower target dose** of **0.5 x 10^6 CAR + viable T cells/kg** with FDA review of safety prior to dose escalation
- The next 3 patients treated at target dose of **0.75 x 10^6 CAR + viable T cells/kg**
- **Staggered enrollment** with one patient dosed every 60 days

Primary end point

- Safety

Secondary end points

- Efficacy: ORR, CR, MRD negativity, PFS
- Incidence and severity of AEs



Nadeem O et al. ASH 2024

CAR-T in Smoldering Myeloma

CAR-PRISM: Cilta-cel in High-Risk Smoldering Myeloma

Safety: No DLTs were observed in the safety run-in cohort

Cytokine Release Syndrome	N=6
Grade 1	4
Grade 2	2

- **No grade 3 or greater CRS**
- 4 patients received tocilizumab and 2 patients received dexamethasone

DLT Definition:
- Grade 4 nonhematologic toxicity
- Grade 3 CRS that does not improve to grade 3 within 72 hours
- Grade 3 neurologic toxicity
- Grade 3 toxicity of any vital organs or any grade 3 toxicity lasting > 72 hours
- Grade 4 neutropenia or thrombocytopenia lasting more than 28 days

- One patient experienced grade 1 Bell's palsy that was self-limiting and resolved within 2 weeks.
- One patient experienced grade 4 immune-related thrombocytopenia, which resolved within 2 weeks.

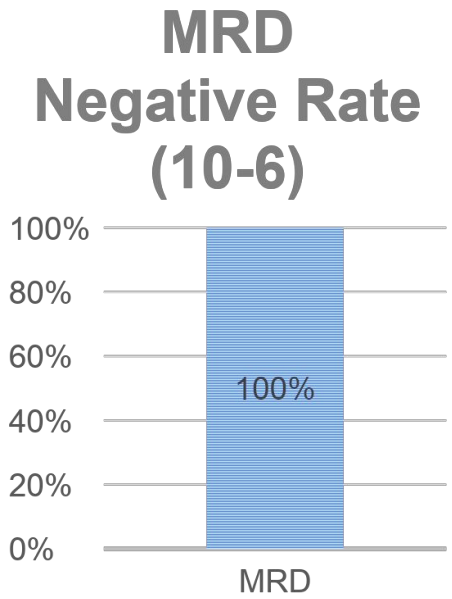
- Hematologic toxicities including grade 3 neutropenia that was transient without any febrile neutropenia
- Transient grade 3 AST/ALT elevation in one patient, which resolved
- No grade 3 infections
- No secondary malignancies to date

Nadeem O et al. ASH 2024

CAR-PRISM: Cilta-cel in High-Risk Smoldering Myeloma

Median follow-up: 10.5 months for safety run-in cohort

Best response	n	%
Complete Response	6	100
Overall response rate	6	100



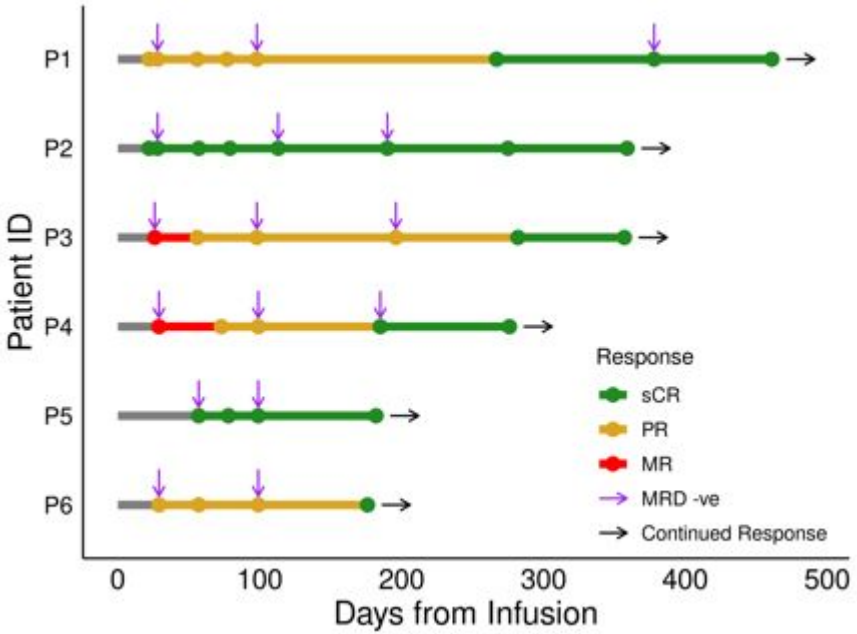
Stem cell collection was successful in all eligible patients with an average stem cell yield of 8.94 x 10^6 CD34+ cells/kg.

Nadeem O et al. ASH 2024

CAR-T in Smoldering Myeloma

CAR-PRISM: Cilta-cel in High-Risk Smoldering Myeloma

Swimmer's plot and response to therapy

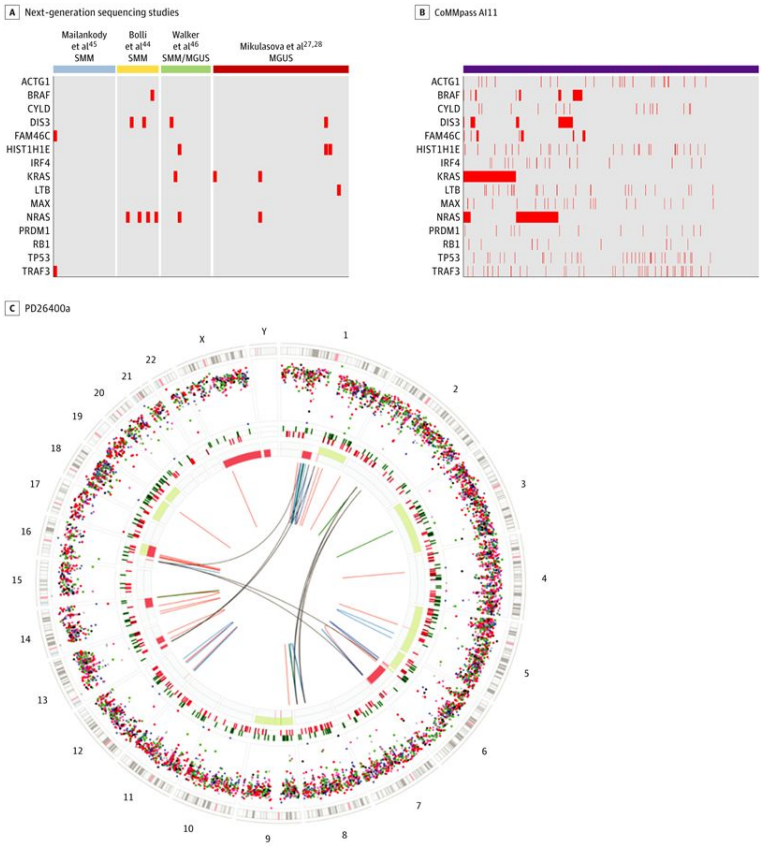


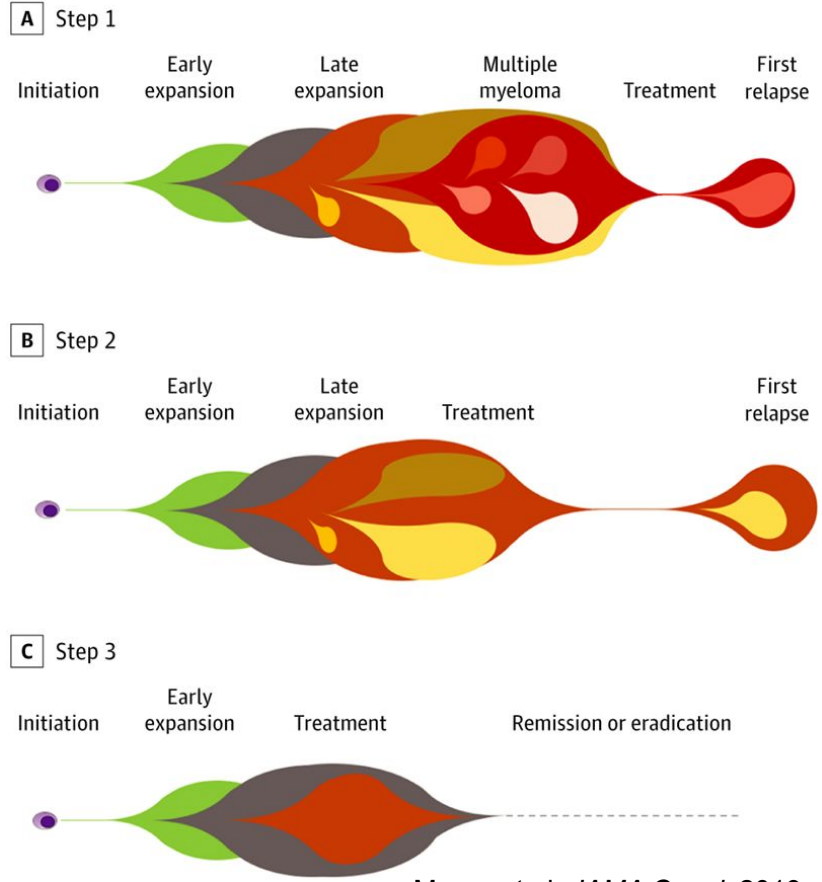
- Responses continue to deepen over time.
- MRD negativity occurs early prior to achieving best serologic response.
- The first 3 patients have **sustained MRD** negativity after 1 year of follow-up.
- The remainder of patients remain MRD negative at the time of their last follow-up.

No patients have developed biochemical or SLIM-CRAB progression to date.

Nadeem O et al. ASH 2024

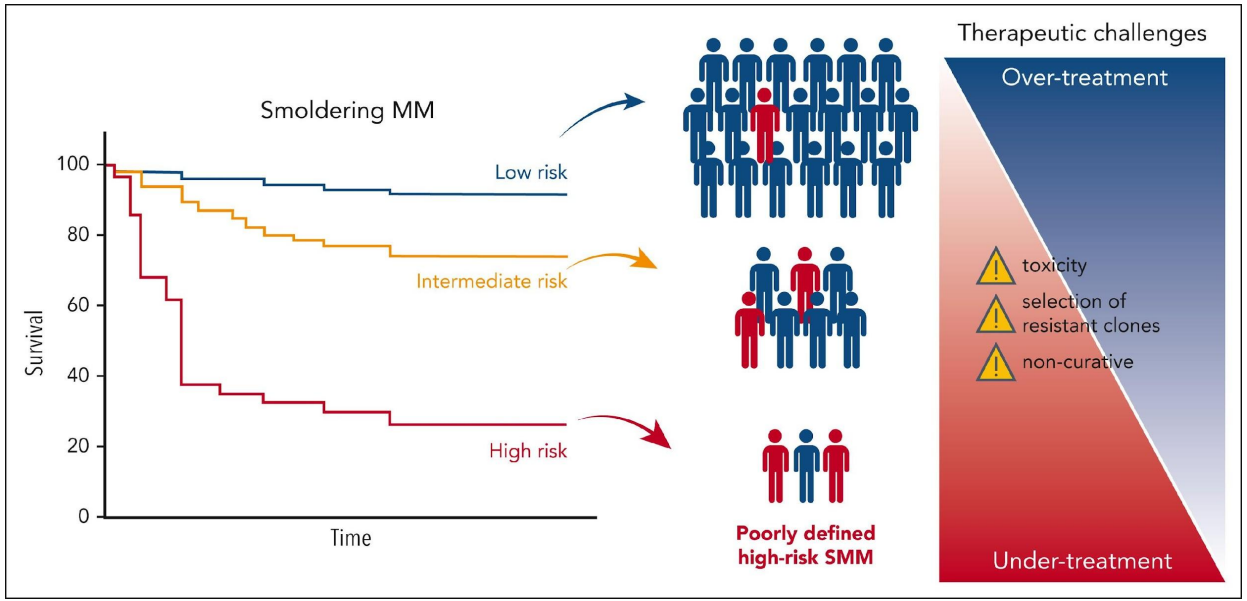
Genomics: Better Stratification?





Maura et al. *JAMA Oncol*. 2019.

Unresolved Questions



Is it a true precancerous condition?

Does early treatment eradicate the clone?

Treated as MM?

Are the current/ongoing trials adequate to answer the question?

Avet- Loiseau et al. *Blood*. 2024.

Conclusions

- Not a single disease
- Risk stratification evolving and will be refined with time
- Treatment results are encouraging; fundamental questions remain
- Close “watch and see” vs clinical trials in patients with high-risk SMM
- Risk-benefit ratio and personalized treatment approaches
- Early immunotherapy vs combination?

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THANK YOU

PANEL DISCUSSION

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