



Multidisciplinary Approaches to Cancer Symposium

Smoldering Myeloma – When and How to Treat?

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Disclosures

- Consultant for Legend Biotechnology

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Socioeconomic barriers to clinical trial enrollment*
- *Higher prevalence of precursor plasma cell conditions in Blacks*
- *Disparities in care due to race/language barriers*



Definition of Smoldering Myeloma (IMWG 2014)

≥ 3g/dL M-spike OR

BMPC ≥ 10% OR

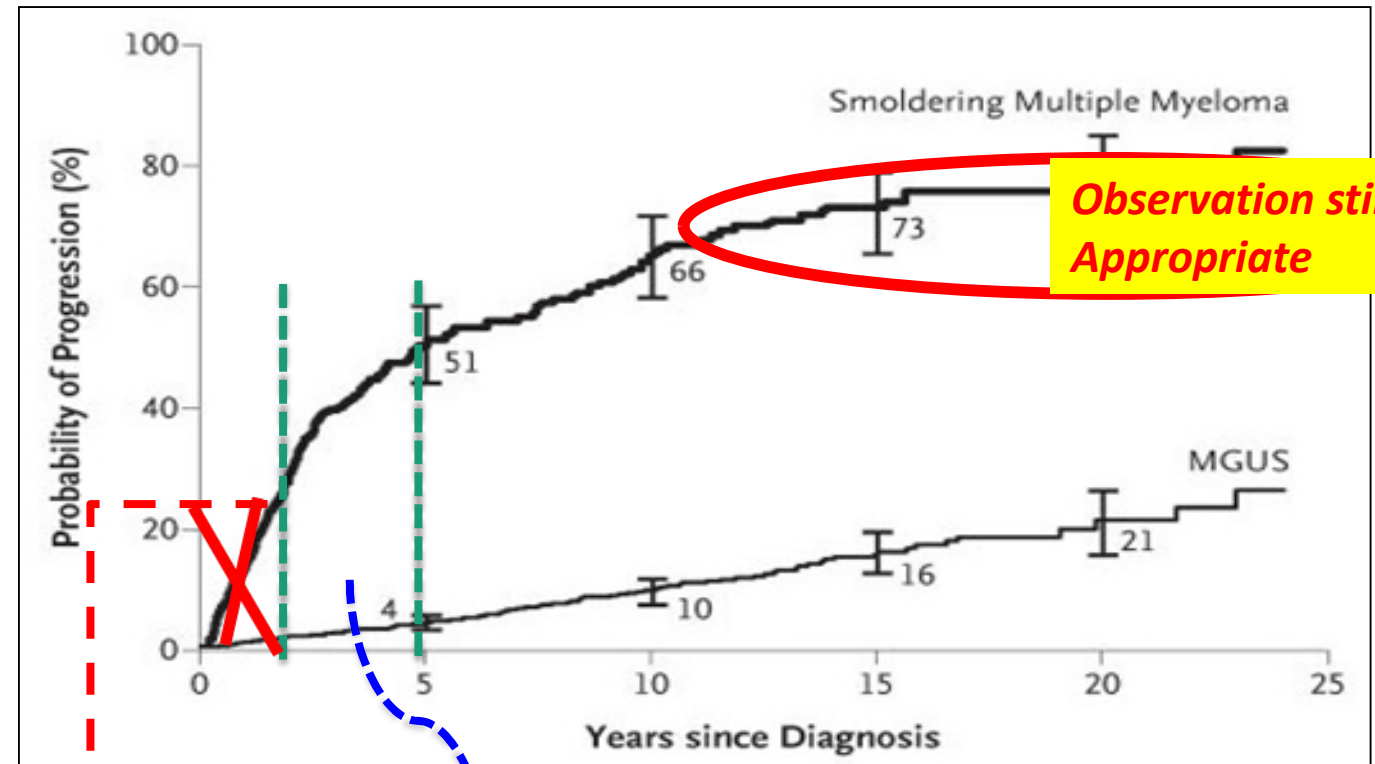
≥ 500mg/day urine monoclonal protein

AND

Absent SLiM CRAB criteria

- Clonal bone marrow plasma cell percentage ≥60%
- Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)
- >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5mm in size)

**Redefined as MM
(80% progression risk in 2 years)**



**Observation still
Appropriate**

High risk SMM (50% progression risk 2 years)

Smoldering Multiple Myeloma (SMM) Risk Models: Criteria and Progression Risk

Model	Criteria (risk factors)	Risk groups	2-year progression risk	5-year progression risk	Notes
Mayo 2008	1) Serum M-protein ≥ 3 g/dL 2) Bone marrow plasma cells $\geq 10\%$ 3) Abnormal FLC ratio (<0.125 or >8)	0 factors = Low 1 factor = Intermediate ≥ 2 factors = High	Low: 5% Intermediate: 17% High: 46%	Low: 25% Intermediate: 51% High: 76%	Natural history cohort (pre-SLiM era).
Mayo 2018 IMWG 2020 (20/2/20)	1) Bone marrow plasma cells $\geq 20\%$ 2) Serum M-protein ≥ 2 g/dL 3) FLC ratio ≥ 20	0 factors = Low 1 factor = Intermediate ≥ 2 factors = High	Low: 6 Intermediate: 18 High: 44	Low: 22.5% Intermediate: 46.7% High: 81.5%	Cohort-derived progression to MM; modern imaging/SLiM application varies by dataset.
IMWG Scoring (adds PC FISH)	Point-based score using: • FLC ratio • Serum M-protein • Bone marrow plasma cell % • High-risk FISH (t(4;14), t(14;16), del17p, +1q)	Low: ≤ 4 points Low-intermediate: 5–8 points Intermediate: 9–12 High: > 12	Low: 4% Low-intermediate: 26% Intermediate: 51% High: 73%	Low: 20% Low-intermediate: 55% Intermediate: 70% High: 85%	Refines 20/2/20 by incorporating cytogenetics. But not validated in an independent cohort.
AQUILA	Clonal BMPCs $\geq 10\%$ AND 1. Serum M-protein ≥ 3 g/dL 2. IgA SMM 3. Immunoparesis 4. Serum involved: uninvolved FLC ratio ≥ 8 and <100 5. Clonal BMPCs $>50\%$ to $<60\%$)	All HR by Definition	Progressed or Died: 36%	Progressed or Died: 59.2%	PFS includes progression to SLiM CRAB criteria or death
PANGEA https://www.pangeamodels.org/	1. SFLC ratio 2. Creatinine 3. Age 4. BMPC 5. hgb	Risk prediction PANGEA without patient history PANGEA with patient history 20/2/20 According to the PANGEA model, the patient has a Intermediate (between 10% and 40%) risk of progressing to multiple myeloma in two years. Years in Future Probability of Progression 1 9.1% 2 15.6% 5 33.7% 10 55.1%			- With/without BMPC - With/without history



DARATUMUMAB FOR SMOLDERING MYELOMA

AQUILA: Study Design (Dec 2017 – May 2019)

International, open-label, randomized phase III study

Adults with SMM for ≤ 5 yr

Clonal BMPCs $\geq 10\%$

+

1. Serum M-protein ≥ 30 g/L
2. IgA SMM
3. Immunoparesis
4. Serum involved: uninvolved FLC ratio ≥ 8 and < 100
5. Clonal BMPCs $> 50\%$ to $< 60\%$

ECOG PS 0/1

(N = 390)



Subq Daratumumab for 3 years
(n = 194)

Active Monitoring for 3 years
(n = 196)

*Efficacy follow-up
until PD by IMWG
SLiM-CRAB criteria*

*Imaging every year
Bmbx eval at least
Q2Y
Survival follow-up
Q6M*

*Or confirmed PD, whichever happens first.

†PFS defined as time from randomization to first documented PD to active MM or death from any cause (whichever happens first).

- **Primary endpoint:** PFS by IRC using IMWG SLiM-CRAB criteria
- **Key secondary endpoints:** ORR, time to first-line MM tx, PFS on first-line MM tx, OS

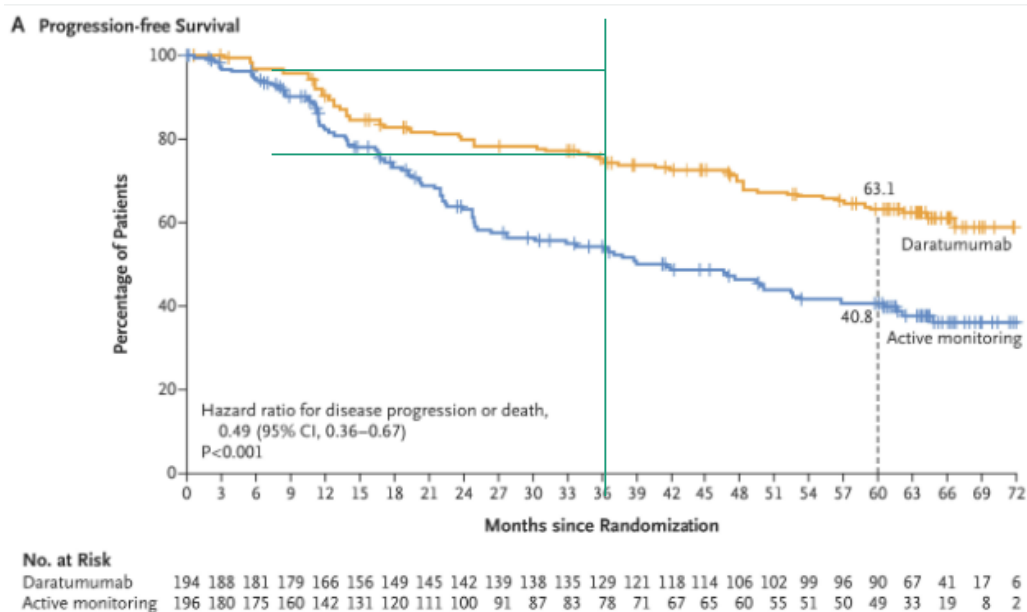


Selected Baseline Characteristics

Age		
Median (range) — yr	63.0 (31–86)	64.5 (36–83)
Distribution — no. (%)		
18 to <65 yr	106 (54.6)	98 (50.0)
65 to <75 yr	67 (34.5)	74 (37.8)
≥75 yr	21 (10.8)	24 (12.2)
Male sex — no. (%)	95 (49.0)	93 (47.4)
Race or ethnic group — no. (%)†		
White	161 (83.0)	162 (82.7)
Asian	18 (9.3)	13 (6.6)
Black	4 (2.1)	7 (3.6)
American Indian or Alaska Native	0	3 (1.5)
Native Hawaiian or other Pacific Islander	0	2 (1.0)
Multiple	1 (0.5)	0
Not reported	10 (5.2)	9 (4.6)
Risk of progression according to Mayo 2018 risk criteria‖		
Low	45 (23.2)	34 (17.3)
Intermediate	77 (39.7)	76 (38.8)
High	72 (37.1)	86 (43.9)



Primary Endpoint PFS



Progression-free survival at 5 years

63.1% vs. 40.8% (HR 0.49; 95% CI 0.36–0.67; $P < 0.001$; NNT=23)

Initiation of first-line treatment for active MM at 5 years

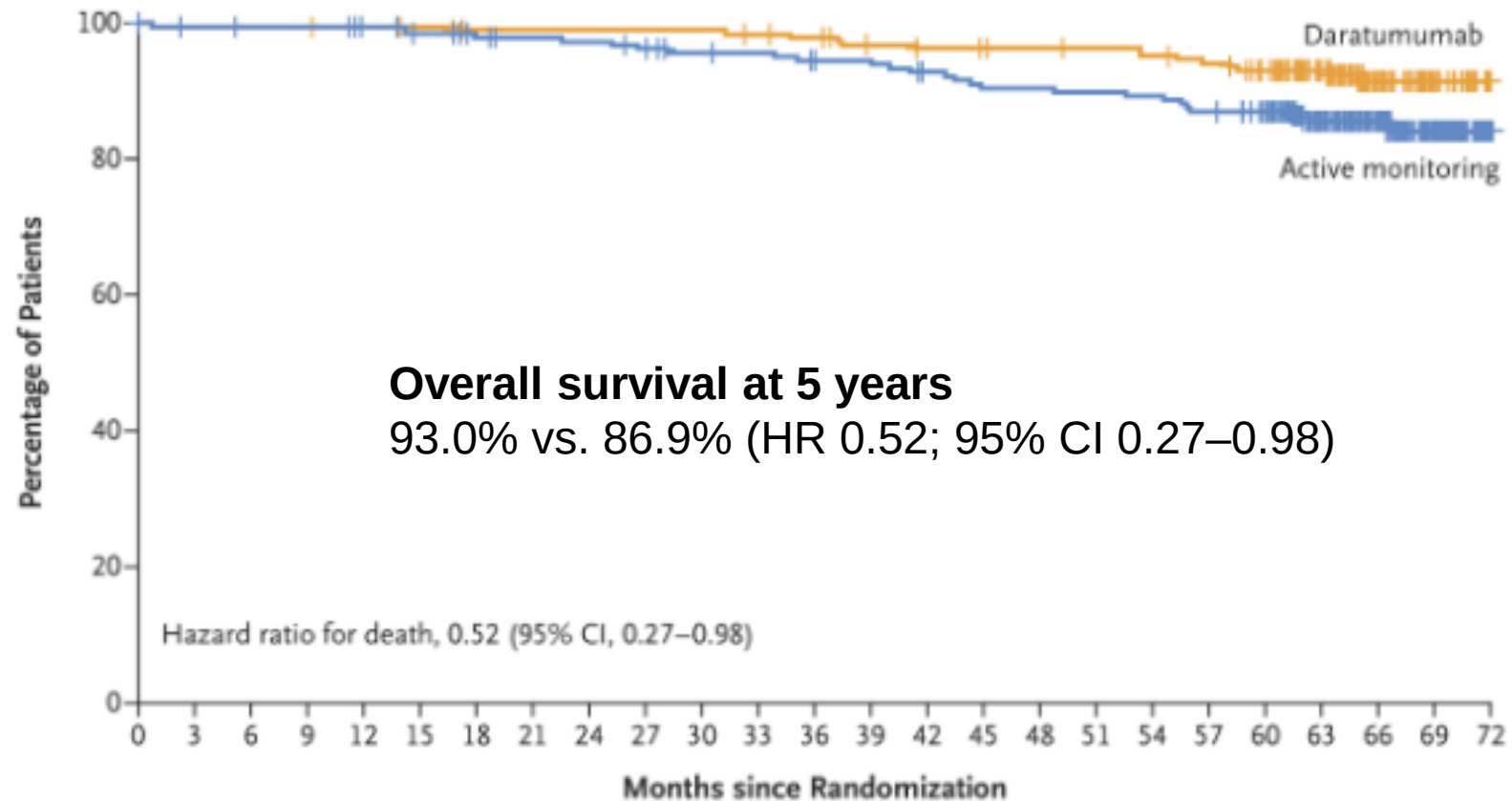
29.7% vs. 55.9% (HR 0.46; 95% CI 0.33–0.62)

Median time to disease progression (IMWG biochemical or SLiM–CRAB criteria)

44.1 months vs. 17.8 months (HR 0.51; 95% CI 0.40–0.66)

Overall Survival

B Overall Survival



No. at Risk

Daratumumab	194	194	194	193	192	191	188	188	188	188	188	186	184	179	177	176	175	174	172	169	162	128	86	38	11
Active monitoring	196	192	191	191	187	183	179	177	176	173	169	168	165	164	159	155	155	154	153	149	144	108	68	34	9

AQUILA by Mayo 2018/IMWG 2020

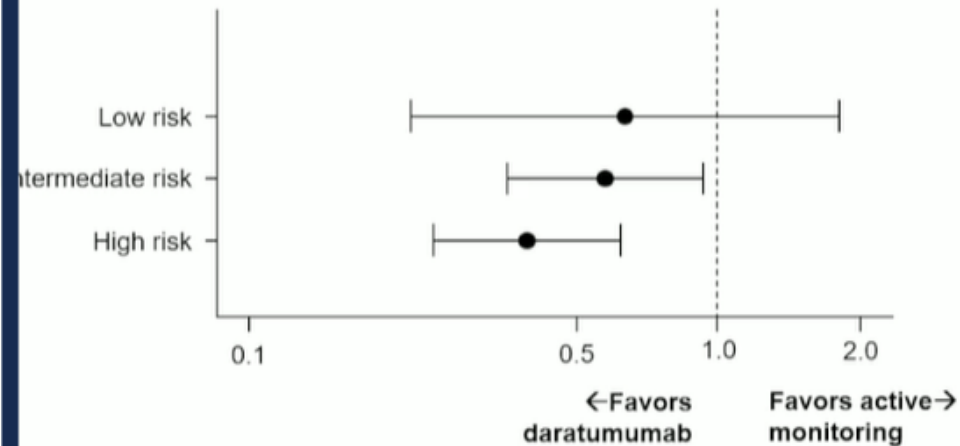
→ 60-month PFS rates, %:

IMWG 2020 Risk group	Daratumumab	Active monitoring
Low	78.2	71.6
Intermediate	56.2	42.9
High	60.4	23.6

PFS active monitoring vs daratumumab
monotherapy, high-risk group:
62.8% vs 37.5% events
HR 0.36 (95% CI: 0.23, 0.58)

PFS

Hazard ratio with 95% CI



TT TX

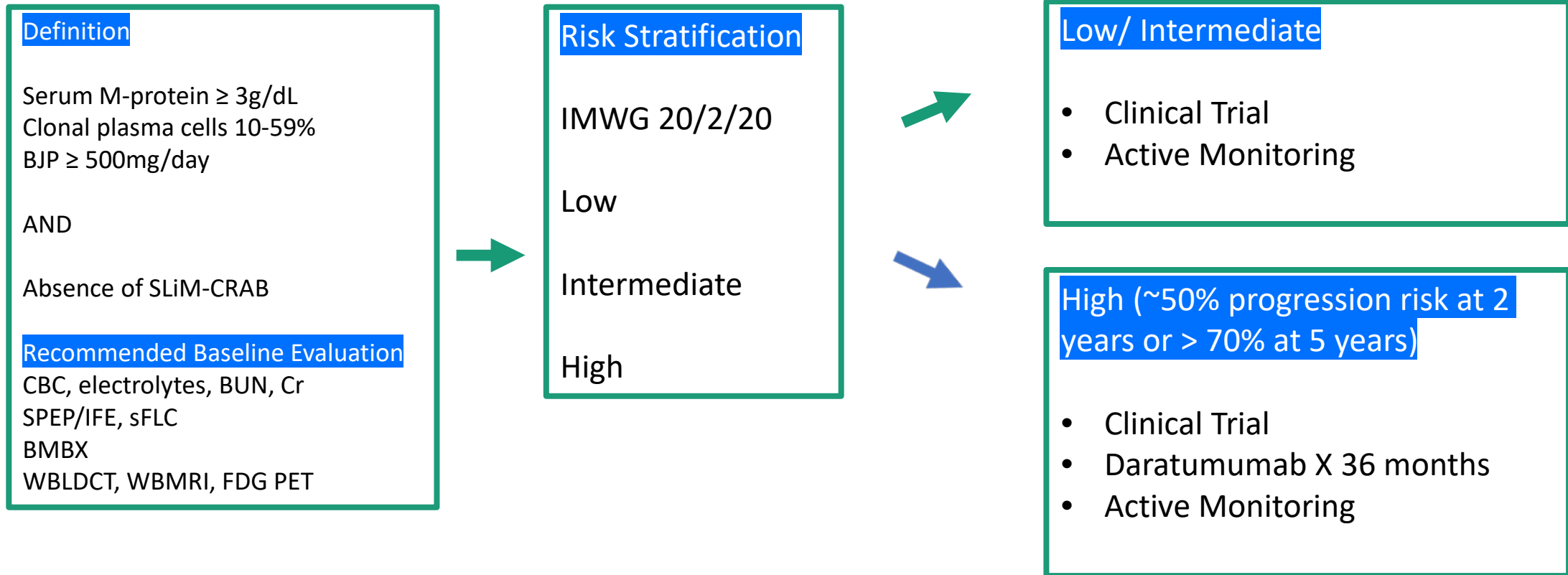
Discussion

- **Clear PFS and OS benefit**
- **Clearest trend for benefit was high and intermediate risk by 20/2/20**
- **Second primary malignancies (~9%) and overall cytopenias were similar**



- **75% of progression events was Slim CRAB**
- **Increased grade 3/4 AEs (40% vs 30%) and SAEs (29% vs 19%)**
- **What if patient do progress to MM as [29.7%](#) of patients on daratumumab did in the Aquila Trial?**
- **What if you have a patient who has rapid pace of progression but still smoldering?**

COH Smoldering MM Pathway



Consider Pangea as an alternate risk score.

Active Monitoring Guidelines

Frequency: q3 months × 2 years → q6 months

Clinical assessment and labs each visit.

Labs: CBC, CMP, SPEP, FLC, quant immunoglobulins

Imaging: Baseline; repeat if indicated

Bone marrow: Baseline; at progression



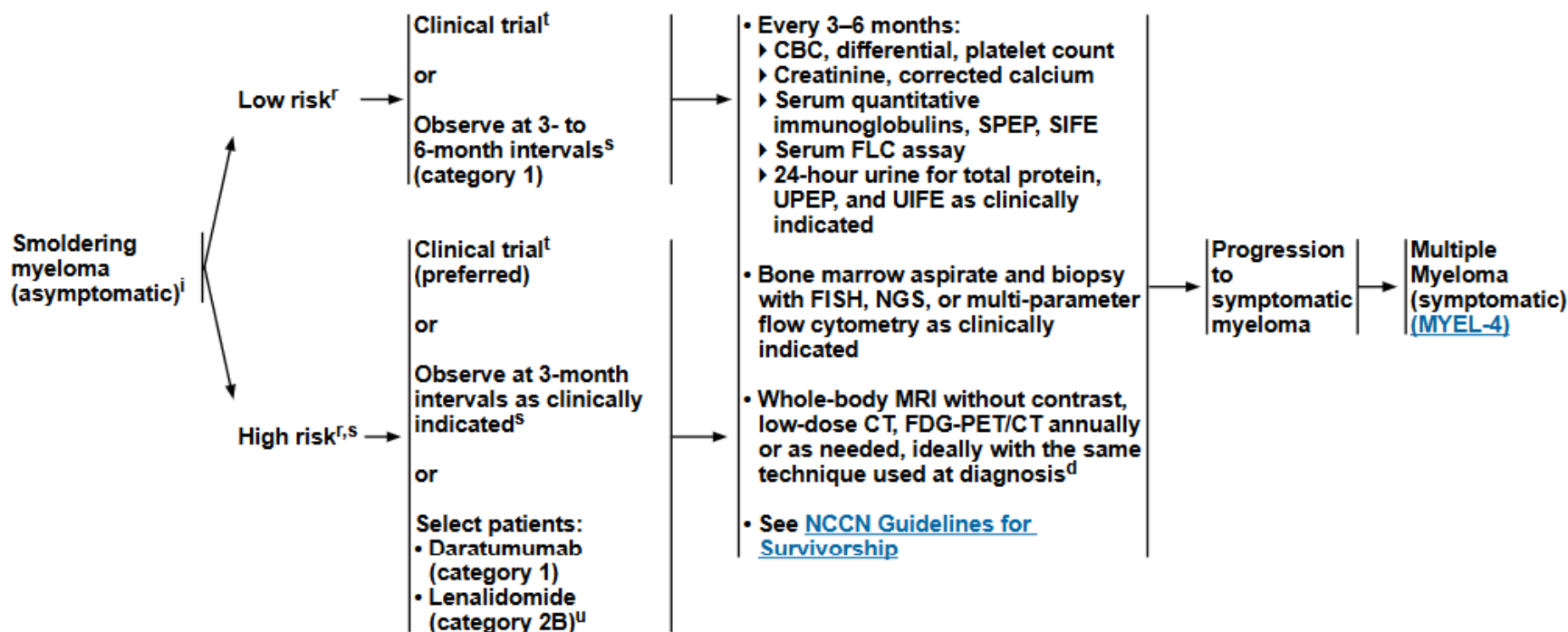
NCCN Guidelines Version 5.2026 Multiple Myeloma

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CLINICAL FINDINGS

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE



^d [Principles of Imaging \(MYEL-C\)](#).

ⁱ [Definitions of Myeloma and Related Plasma-Cell Disorders \(MYEL-A\)](#).

^r For risk criteria, refer to Lakshman A, et al. Blood Cancer J 2018;8:59 and Mateos MV, et al. Blood Cancer J 2020;10:102.

^s Patients with rising parameters are considered high risk and should be closely monitored.

^t The NCCN Panel strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.

^u Consider collection of hematopoietic stem cells for future use.

Note: All recommendations are category 2A unless otherwise indicated.



Thank You

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