

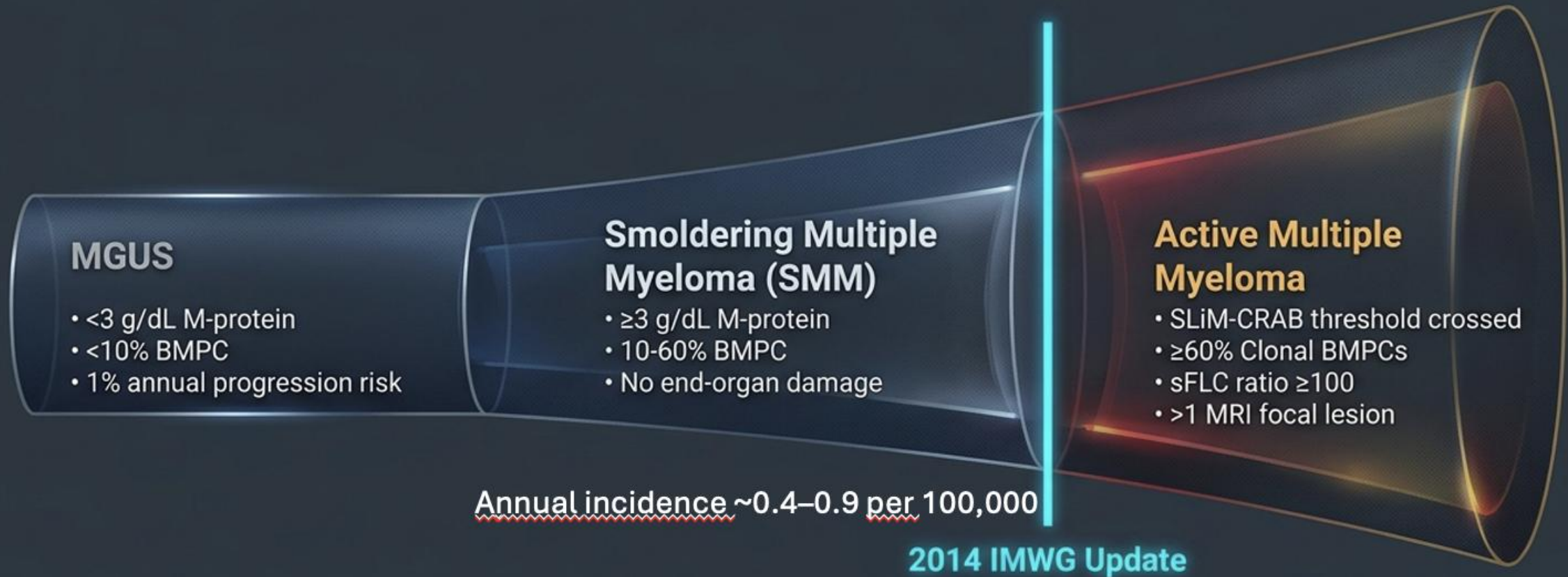
# Smoldering Myeloma in 2026: Who Should We Treat and How Early?

A Paradigm Shift in the Management of  
High-Risk Smoldering Multiple Myeloma

Yıldız Yiğit, MD

SBU Hamidiye International Faculty of Medicine &  
Kartal Dr. Lütfi Kırdar City Hospital

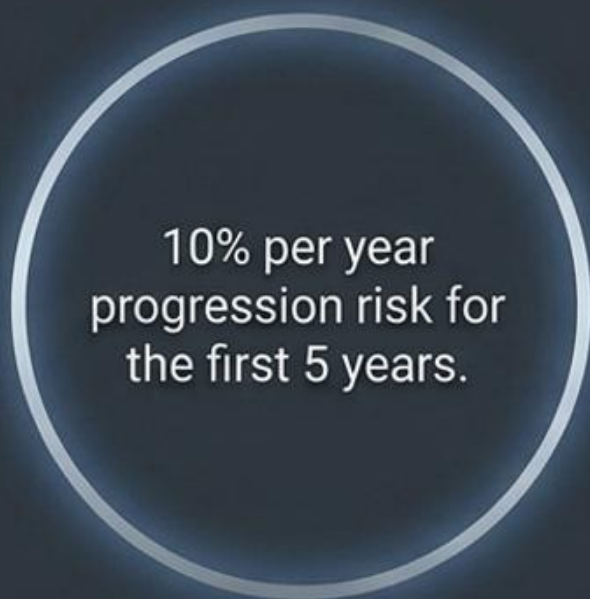
# From MGUS to Active Myeloma: Defining the Disease Spectrum



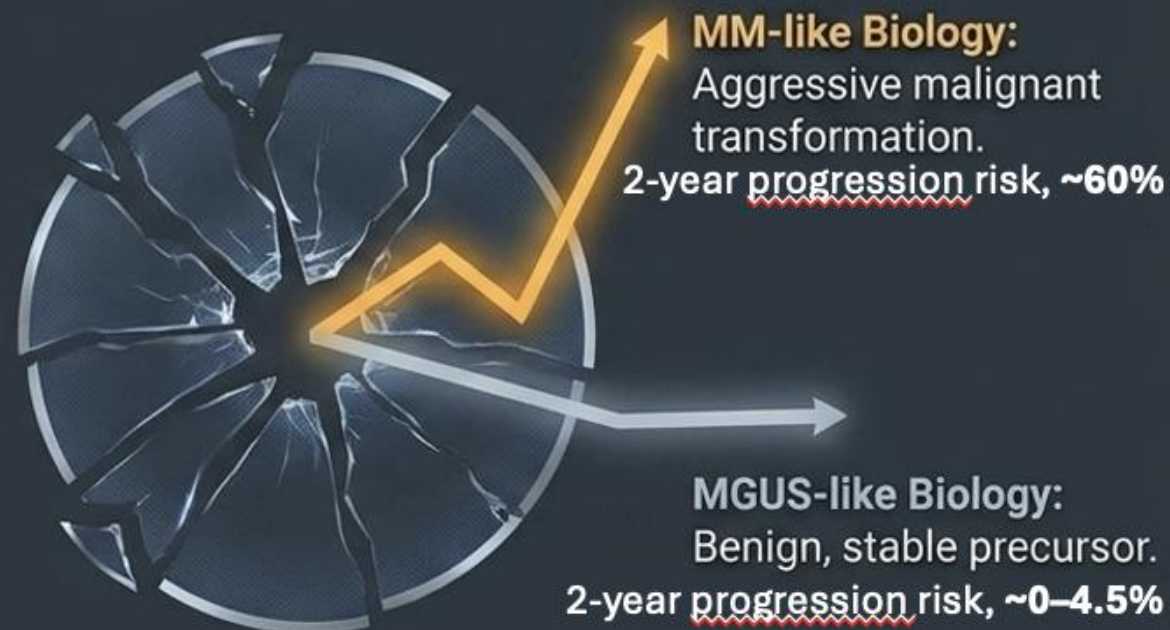
The 2014 update acknowledged that 'ultra-high-risk' SMM (80% progression risk at 2 years) was actually active myeloma. The remaining SMM population is what we must now risk-stratify.

# The illusion of the 'average' progression risk

## The Illusion



## The Reality

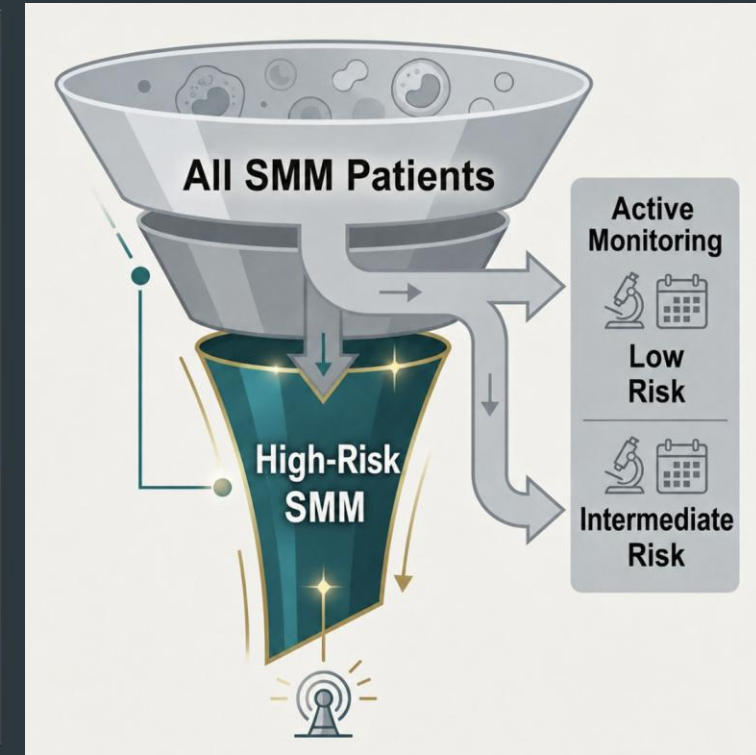
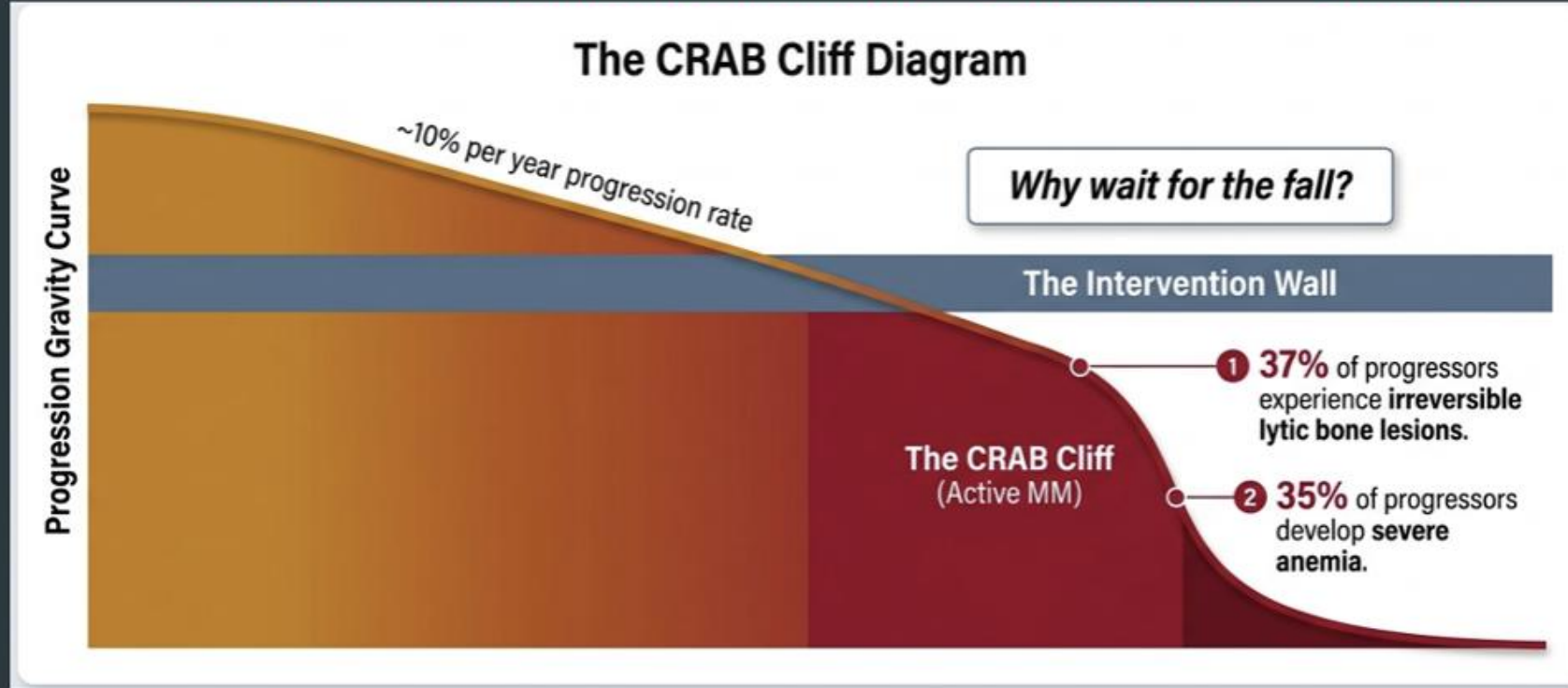


If SMM is not a single entity, but a mix of benign precursors and occult malignancies, is therapeutic abstention ("watch and wait") still justifiable for the aggressive cohort?



# Why Consider Treatment in an Asymptomatic Disease?

**Goal:** prevent progression-related harm in selected high-risk patients



Mayo Clinic series: **observed high-risk SMM patients 71 patients (51/71 progressed)**  
**Median follow-up: 3.9 years , Median TTP 2.2 years**  
**45% had clinically significant MDEs / end-organ damage**

# Risk Stratification: Who Is Truly High Risk?

- **Mayo 2018 / IMWG 20/2/20 model**

- BM plasma cells >20%, M-protein >2 g/dL, FLC ratio >20  
≥2 factors = high risk, 2-year progression risk: ~44–50%

- **IMWG 2020 model**

- Adds high-risk cytogenetics to 20/2/20  
t(4;14), t(14;16), +1q, del13q / monosomy 13  
≥3 factors = high risk, 2-year progression risk: ~63%

- **PANGEA-SMM**

- Dynamic risk monitoring using evolving biomarkers:  
M-protein, FLC ratio, creatinine, and hemoglobin

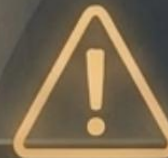
- **Genomic profiling**

- Emerging molecular layer: FISH in routine practice; NGS-based mutation profiling is evolving  
May help distinguish MGUS-like from MM-like biology

# The Clinical Standard: IMWG 20/2/20 Risk Stratification

Identifying the high-risk cohort with a  $\geq 50\%$  progression probability at two years.

The 3 Pillars	Risk Tiers	2-Year Progression Risk
<ul style="list-style-type: none"><li>Bone Marrow Plasma Cells <math>&gt;20\%</math></li><li>Serum M-protein <math>&gt;2</math> g/dL</li><li>FLC ratio <math>&gt;20</math></li></ul>	<ul style="list-style-type: none"><li>Low (0 factors)</li><li>Intermediate (1 factor)</li><li>High (2-3 factors)</li></ul>	<ul style="list-style-type: none"><li>6%</li><li><math>\sim 18\%</math></li><li><math>\sim 45-50\%</math></li></ul>



## The IMWG Cytogenetic Overlay

Adding high-risk cytogenetics (t(4;14), t(14;16), +1q, del13q) pushes the 2-year progression risk beyond 60%.



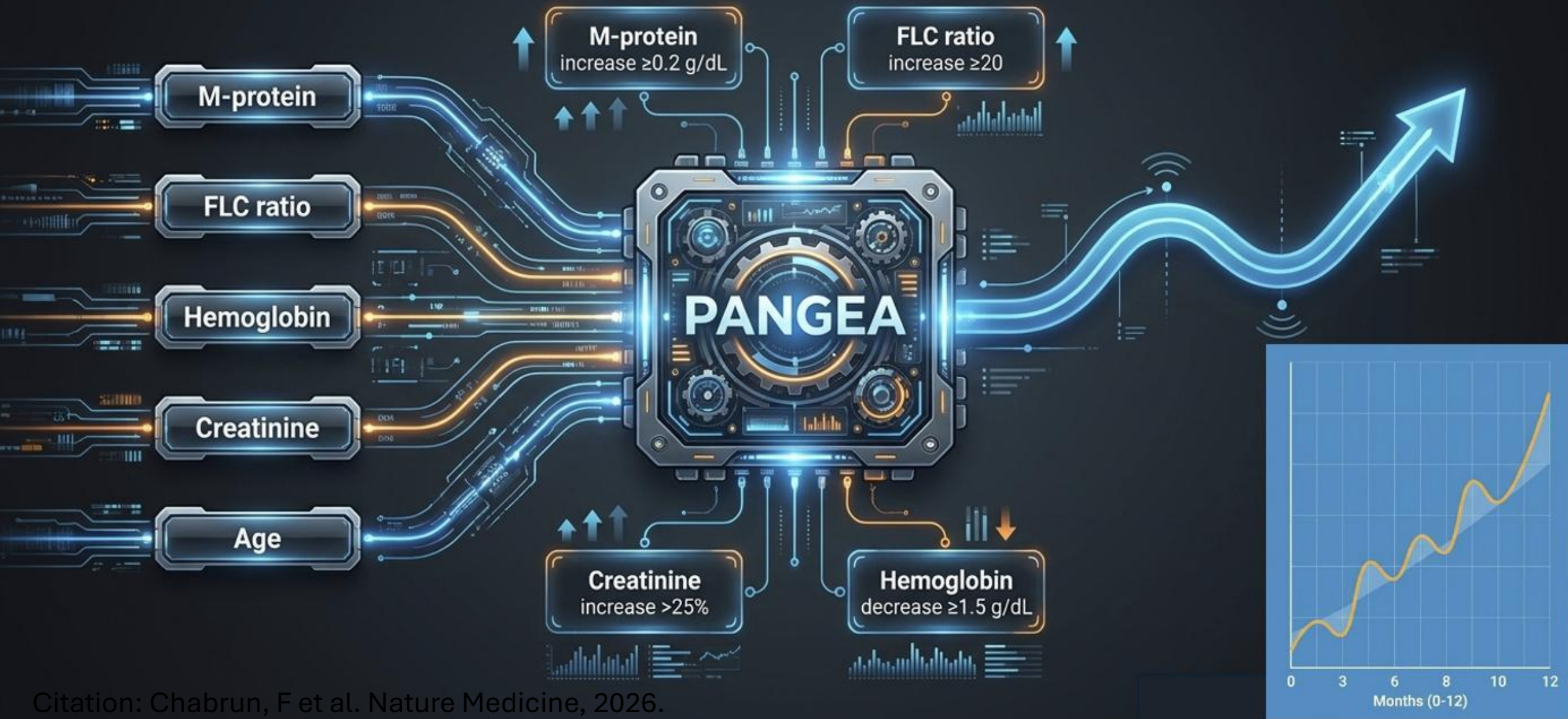
# IMWG Risk Stratification: From 3-Factor to 4-Factor Model

	IMWG 3-Factor Model (2018)	IMWG 4-Factor Model (2020)
<b>Core concept</b>	Clinical risk based mainly on tumor burden	Clinical risk refined by clonal biology
<b>Variables</b>	Bone marrow plasma cells >20% Serum M-protein >2 g/dL Involved/uninvolved FLC ratio >20	Bone marrow plasma cells >20% Serum M-protein >2 g/dL Involved/uninvolved FLC ratio >20 High-risk cytogenetics
<b>High-risk cytogenetics</b>	Not included	t(4;14), t(14;16), +1q, del13q / monosomy 13
<b>Risk groups</b>	0 factors: Low risk 1 factor: Intermediate risk 2–3 factors: High risk	0 factors: Low risk 1 factor: Low-intermediate risk 2 factors: Intermediate risk ≥ <b>3 factors: High risk</b>
<b>2-year progression risk</b>	0 factors: ~6% 1 factor: ~18% 2–3 factors: ~44%	0 factors: ~6% 1 factor: ~23% 2 factors: ~46% <b>≥3 factors: ~63%</b>

**20/2/20 tells us tumor burden; cytogenetics tells us biological acceleration**

# THE PANGEA ALGORITHMIC ENGINE

PANGEA-SMM (PANGEA 2.0)



Citation: Chabrun, F et al. Nature Medicine, 2026.



# The Genomic Divide: Rethinking the SMM Label

Next-generation sequencing reveals that SMM is not a single premalignant state, but a mix of truly indolent biology and fully transformed malignancy.

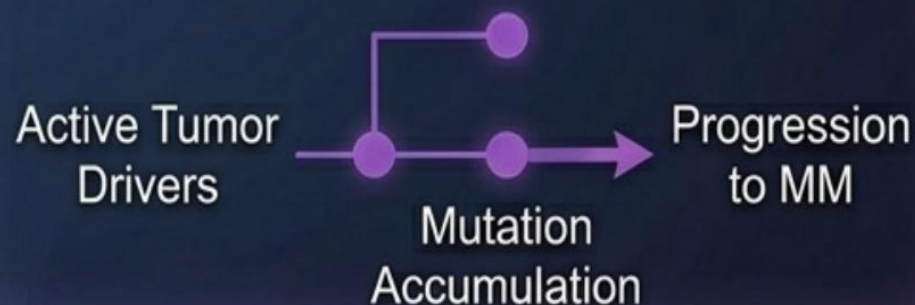
## Genomic MGUS

- Represents ~10% of SMM
- Low mutational load
- Absence of chromosome 8 CNAs
- Immune microenvironment containment
- Virtually 0% progression to active MM



## Genomic MM

- Represents the vast majority of SMM
- Established tumor drivers (KRAS/NRAS, MYC translocations)
- APOBEC mutagenesis signatures
- Dynamic, inevitable progression



The benefit–risk balance may favor intervention in carefully selected high-risk patients

### **Risk of Observation**

- Progression to active myeloma
- Potential CRAB-related organ damage
  - Renal impairment
  - Lytic bone disease / fractures
  - Anemia
  - Hypercalcemia
- Risk is highest in biologically high-risk / evolving disease

### **Risk of Early Treatment**

- Infections and immune suppression
- Treatment burden in an asymptomatic patient
- Cost and access issues
- Overtreatment of patients who may not progress
- Future sequencing after early anti-CD38 exposure

Early intervention may be reasonable when the risk of near-term progression and organ damage outweighs treatment toxicity and overtreatment risk.

**The goal is not to treat risk; the goal is to prevent harm.**



# Which endpoint should drive early intervention?

In SMM, the bar is higher because the patient is asymptomatic.

## Useful but indirect

- Response rate / depth of response
- MRD negativity
- Biochemical progression delay
- M-protein or FLC kinetics

Surrogate signals



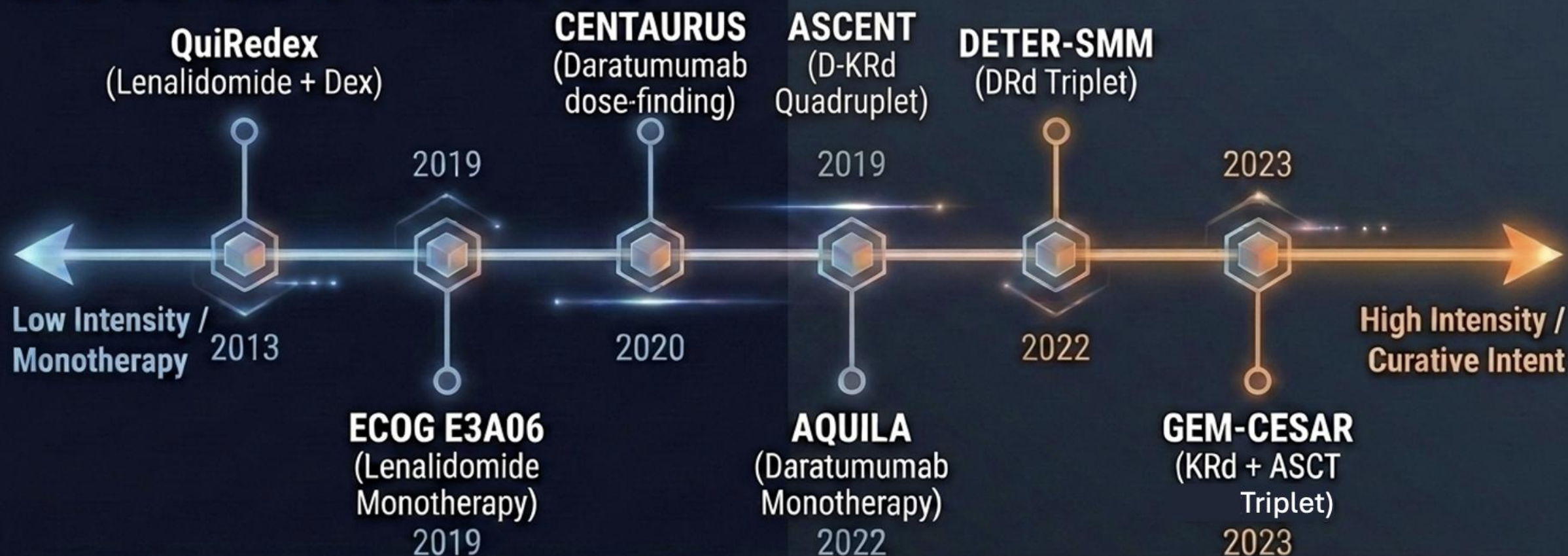
## Patient-relevant

- SLiM-CRAB-free survival
- Prevention of bone disease, anemia, renal injury
- Time to first-line myeloma therapy
- Overall survival and quality of life

Clinical benefit

**The right question is not “Can we make the clone smaller?”  
It is “Can we prevent irreversible harm without creating new harm?”**

# The Intervention Landscape: 2013 to Present



**Strategic Evolution:** The paradigm represents a shift in strategy—from clumsily delaying progression, to safely managing the disease state, to attempting deep, MRD-negative eradication.



# Historical Validation of the Early Intervention Paradigm

2013, QuiRedex (Phase III)

**Intervention:** Lenalidomide + Dexamethasone (Rd) induction → R maintenance.

**Outcome:** Demonstrated a clear Overall Survival (OS) benefit.

Hazard Ratio (HR): 0.57

Median Time to Progression (TTP): 9.5 vs 2.1 years.

2020, ECOG E3A06 (Phase III)

**Intervention:** Lenalidomide monotherapy until progression.

**Outcome:** 3-year Progression-Free Survival (PFS) of 91% vs 66%.

~40% treatment discontinuation rate due to toxicity (GR3-4 Aes)

**The Shift:** These trials provided the first definitive proof that early intervention alters the natural history of the disease, effectively ending the era of mandatory "watch and wait" for high-risk patients.



# AQUILA delivers a paradigm shift, proving survival and PFS benefits with a highly tolerable subcutaneous agent.

## Protocol

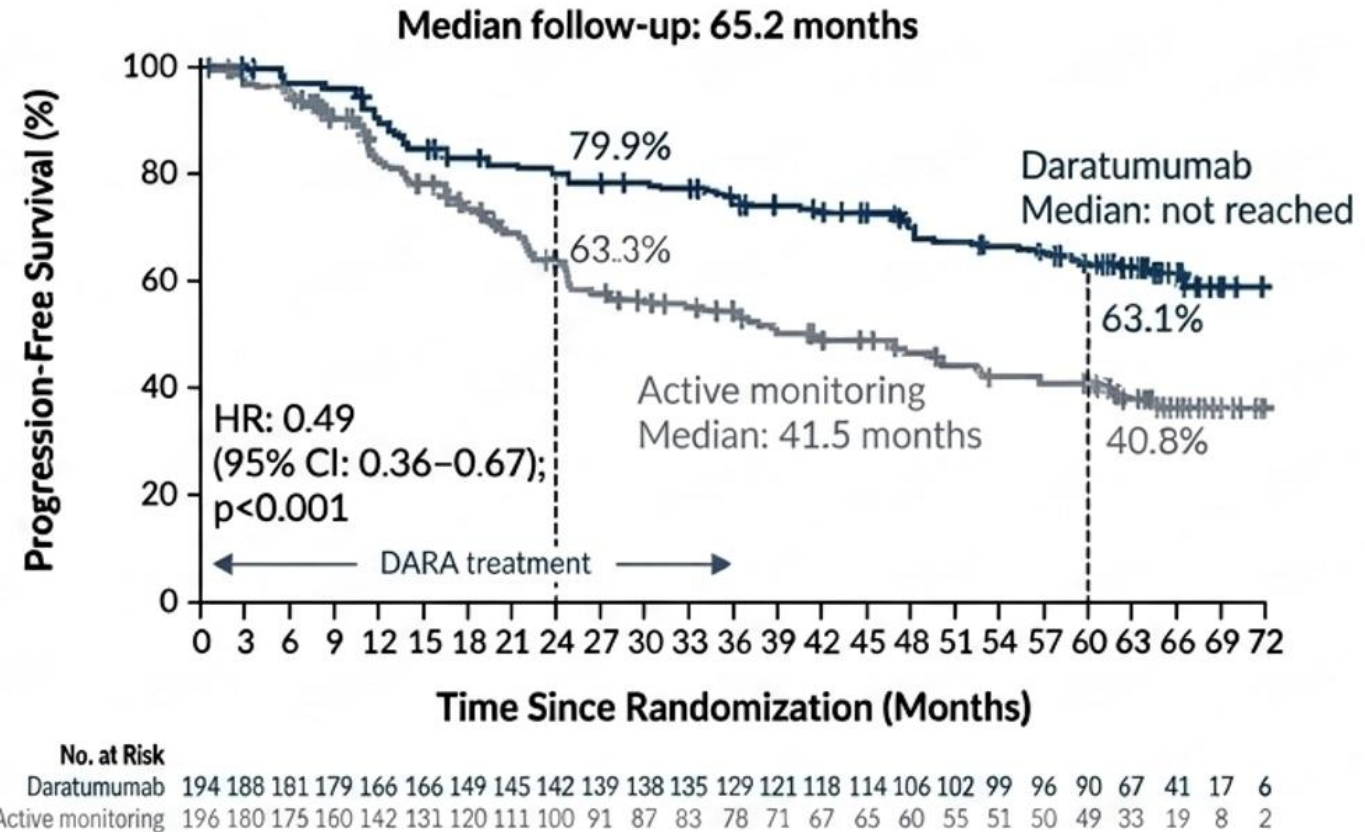
**Study Phase:** Phase III

**Regimen:** Subcutaneous Daratumumab monotherapy (up to 39 cycles / 36 months) vs. Active Monitoring.

n=390, 1:1 randomized

## Key Efficacy Results:

- **5-Year PFS:** 63.1% (Dara) vs 40.8% (Observation). Median PFS not reached.
- **5-Year OS:** 93.0% vs 86.9% (HR 0.52).
- **Risk Reduction:** 51% reduction in progression to MM or death (HR 0.49) (Risk of progression or death, based on PFS HR 0.49).



**Study Limitations:** Criteria predated the Mayo 2018 guidelines; retrospectively, only 40.5% of the cohort met the modern Mayo 2018 high-risk classification.



# AQUILA effectively delayed SLiM-CRAB progression without introducing prohibitive long-term toxicities.

## Efficacy Breakdown

- Fewer patients transitioned to first-line MM treatment (33.2% vs 53.6%).
- Time to first MM therapy was significantly prolonged (HR 0.46).

## Disease Progression Breakdown (CRAB vs SLiM Criteria)

Disease progression or death — no. (%)	67 (34.5)	vs	99 (50.5)
Disease progression — no./total no. (%)*	62/67 (92.5)	vs	94/99 (94.9)
CRAB criteria			
Calcium level elevation	0/62		2/94 (2.1)
Renal insufficiency	0/62		0/94
Anemia	2/62 (3.2)		14/94 (14.9)
Bone disease	10/62 (16.1)		18/94 (19.1)
SLiM criteria			
≥60% Clonal plasma cells in bone marrow	5/62 (8.1)		16/94 (17.0)
Serum FLC ratio ≥100	33/62 (53.2)		33/94 (35.1)
>1 Focal lesion on magnetic resonance imaging	12/62 (19.4)		16/94 (17.0)

## Safety Profile

- **Discontinuation:** Only 5.7% of patients discontinued Daratumumab due to adverse events.
- **Severe Tox:** Grade 3-4 AEs were 40.4% (Dara) vs 30.1% (Control).
- **Specifics:** Hypertension was the most frequent Grade 3-4 AE (5.7%). Pneumonia was the most common serious AE (3.6%).

## Most Common Adverse Events Percentage Breakdown

Any adverse event	187 (96.9)	vs	162 (82.7)
Most common adverse events†			
Fatigue	66 (34.2)		26 (13.3)
Upper respiratory tract infection	58 (30.1)		15 (7.7)
Diarrhea	53 (27.5)		10 (5.1)
Arthralgia	52 (25.9)		35 (17.9)
Nasopharyngitis	49 (25.4)		23 (11.7)
Back pain	46 (23.3)		38 (19.4)
Insomnia	43 (22.3)		5 (2.6)
Grade 3 or 4 adverse event	75 (40.4)		95 (30.1)
Most common grade 3 or 4 adverse event: hypertension	11 (5.7)		9 (4.6)
Serious adverse event	56 (29.0)		38 (19.4)
Most common serious adverse event: pneumonia	7 (3.6)		1 (0.5)
Adverse event that led to death†	2 (1.0)		4 (2.0)
Second primary cancer	18 (9.3)		20 (10.2)

**Takeaway: Subcutaneous administration optimized convenience while maintaining safety margins acceptable for asymptomatic patients.**

# 2026 guidance: a conditional shift, not blanket treatment

## ASCO–Ontario Health Living Guideline

### High-risk SMM

Daratumumab may be offered as an alternative to active monitoring for up to 36 months.

Conditional recommendation; moderate-quality evidence.

**Not a mandate to treat every asymptomatic patient.**

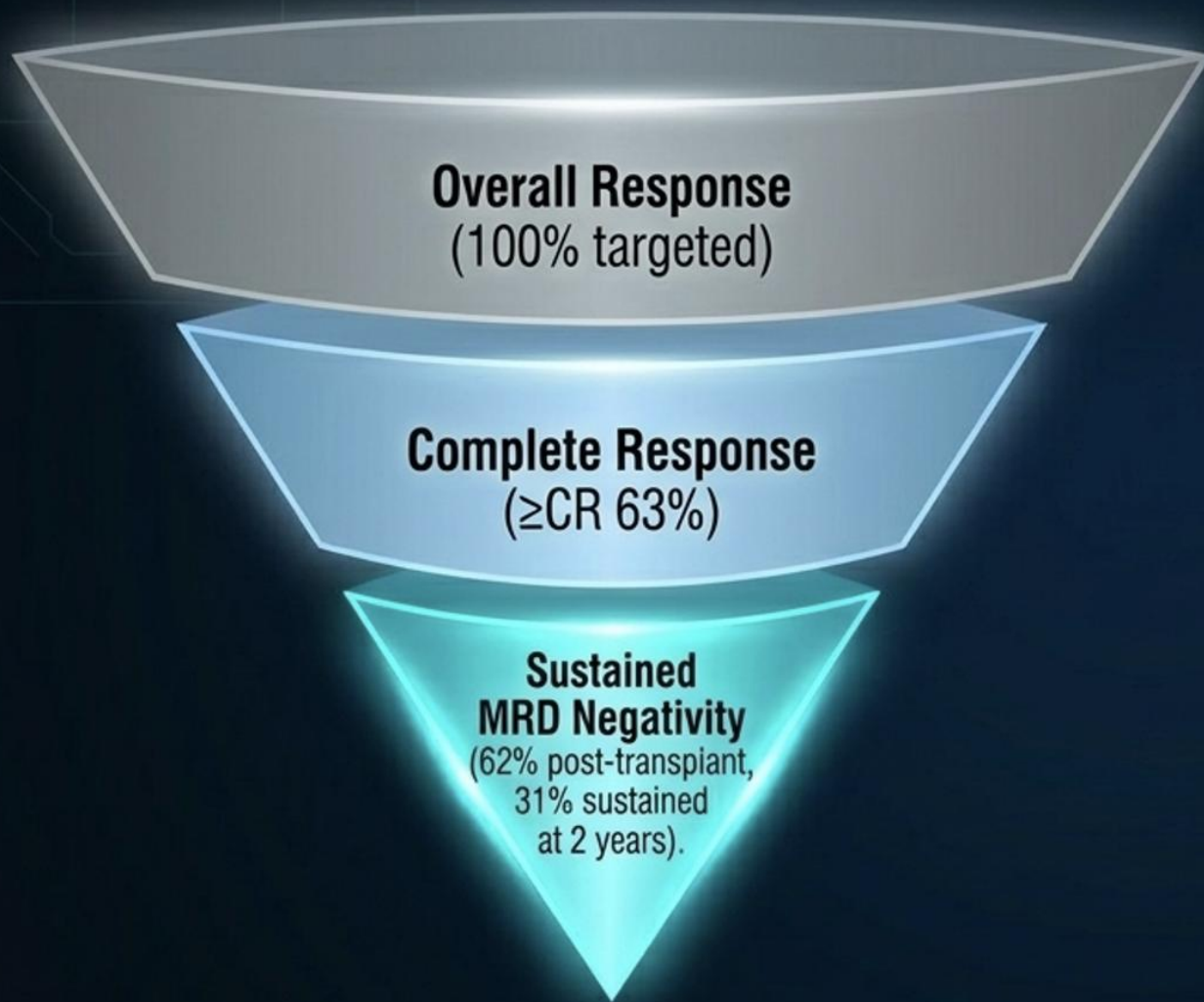
## Clinical translation

- Confirm true SMM: no SLiM-CRAB, modern imaging negative
- Use contemporary high-risk definition, not older labels alone
- Look for evolving phenotype and near-term progression risk
- Discuss infection risk, burden, cost, and patient preference

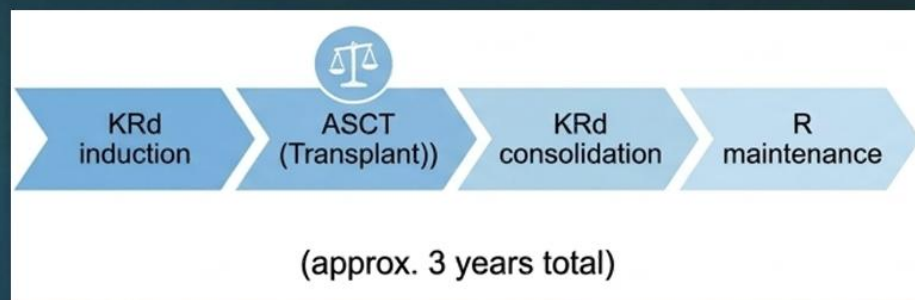
**Take-home: treat biology + trajectory, not the diagnosis code.**



# GEM-CESAR asks a new question: Can early intervention eradicate the clone?



## Phase 2 Trial Specifications n=90



- **Efficacy:** 5-year PFS 94%, 5-year OS 95%.

## Limitations

High treatment intensity  
Grade  $\geq 3$  infections ~18%  
Treatment-related mortality concerns  
Limited to fit, transplant-eligible patients

# ASCENT utilizes quadruplet combinations to achieve deep remissions

## Trial Specifications

- **Phase:** Phase 2 , n=87
- **Regimen:** Dara-KRd induction → DR maintenance (24 months). Fixed duration.

**High-risk : IMWG 20/2/20 criteria**

**ORR**  
97%

**3-year PFS**  
89.9%

**MRD-negativity**  
achieved in 84%  
of patients.

## Limitations:

Phase II, small cohort;  
high non-hematologic toxicity;  
longer follow-up needed to validate survival benefit.



# DETER-SMM: Chasing Overall Survival

**The Trial:** Ongoing Phase III ECOG trial (EAA173).

**The Ultimate Endpoint:** Unlike previous trials focused on PFS or CRAB endpoints, DETER-SMM is boldly powered for Overall Survival (OS).

## Triplet (DRd)

Daratumumab +  
Lenalidomide + Dex

VS

## Doublet (Rd)

Lenalidomide + Dex

### Specific Limitations / Risks:

- **The Timing Paradox:** Because OS takes so long to read out in precursor diseases, the interventional approach (DRd) may be obsolete by the time the data matures (est. 2029).
- **Comparative Ambiguity:** Will quantify triplet vs doublet benefit, but will not answer if Dara monotherapy (AQUILA) is superior to Lenalidomide monotherapy (ECOG).



# Expanding the CD38 Arsenal: Isatuximab

## ISAMAR (Phase II)

- **Design:** Isatuximab +/- lenalidomide in HR-SMM.
- **Result:** ORR of 89% in the combination arm.
- **Patient Experience:** Notable for improved patient-reported anxiety, though myalgia was reported.

## ITHACA (Phase III - Ongoing)

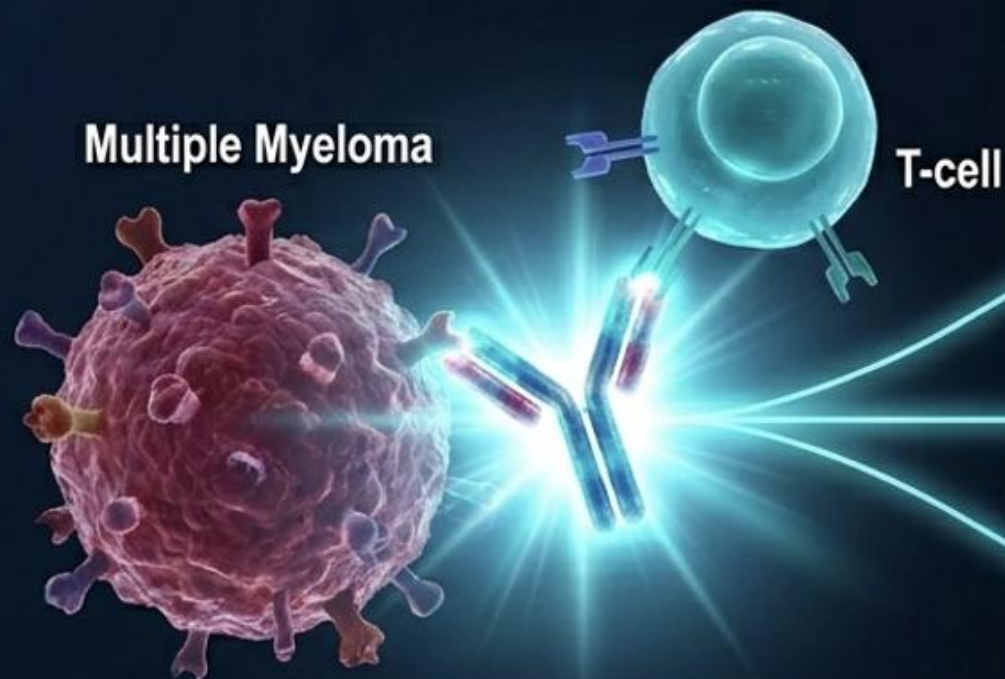
- **Design:** Isatuximab + Rd vs. Rd (approx. 36 months).
- **Status:** Recruitment finalized.
- **Early Data:** Interim data indicates manageable toxicity and  $\geq$  VGPR in 73.9% of participants.



# Bispecific antibodies: Exploiting lower tumor burden and preserved immunity in high-risk SMM

## The Biological Advantage in SMM:

- Unlike relapsed/refractory MM, SMM patients have lower tumor burdens and highly functional, less exhausted T-cell repertoires.
- Continuous T-cell engagement via BsAbs capitalizes on this healthier immune state.



## The Vanguard of BCMA/CD3 Bispecifics in HR-SMM:

**Teclistamab**  
(Immuno-PRISM Trial)

**Linvoseltamab**  
(LINKER-SMM1 Trial)

**Elranatamab**  
(ERASMM / EMN34 Trial)

Can we achieve deep MRD-negative responses with acceptable safety in asymptomatic patients?



# The Bispecific Efficacy Showdown

Metric	Teclistamab (Immuno-PRISM)	Elranatamab (ERASMM)	Linvoseltamab (LINKER-SMM1)
Phase	II n=12	II n=50	II n=19
Target	BCMAxCD3	BCMAxCD3	BCMAxCD3
ORR	100%	92%	100%
CR Rate	Pending	72%	>86%
MRD Negativity ( $10^{-6}$ )	100%	90%	100%

**Takeaway:** Across three distinct molecules, BCMA-targeted bispecifics consistently achieve near-perfect response rates and profound MRD negativity in HR-SMM.

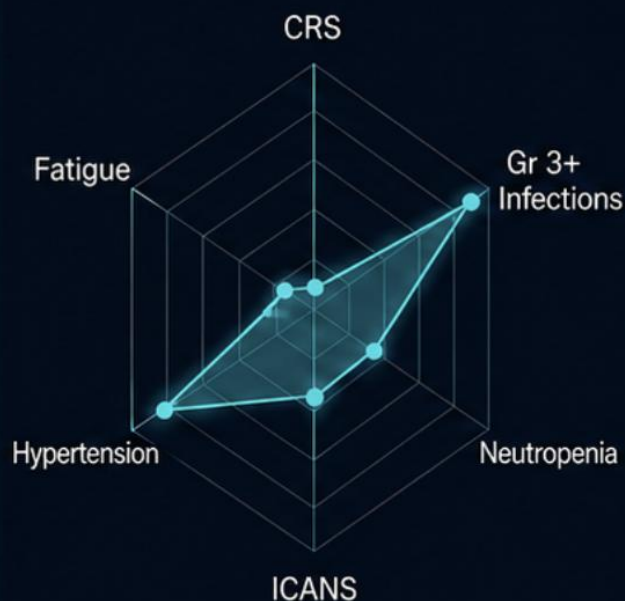


# Safety Defines How Far Early Intervention Can Go

*Efficacy is essential, but the safety threshold is even higher in asymptomatic SMM.*

## Daratumumab (AQUILA): Monoclonal Safety Footprint

### The Safety Radar: mAbs



### Data Highlights for AQUILA Daratumumab



#### Low Systemic Toxicity

Treatment discontinuation due to AEs was remarkably low at just 5.7%.



#### Infectious Risk

Grade 3/4 infections: 16.1% (compared to 4.6% in active monitoring).



#### Hypertension

5.7% Grade 3/4.

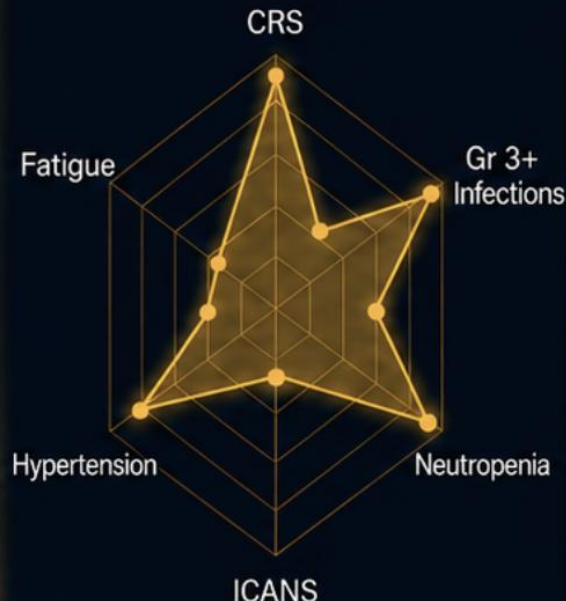


#### Administration

Subcutaneous formulation drastically reduces infusion-related reactions (systemic reactions in 16.6%, mostly Grade 1/2).

## Bispecific Antibodies: Safety Footprint

### The Safety Radar: BsAbs



### Data Highlights for Class Effects in SMM (Early Phase 2 Trials)



#### Cytokine Release Syndrome (CRS)

High incidence (e.g., 70% in ERASMM, 42% in LINKER-SMM1), but predominantly Grade 1/2. Managed with prophylactic tocilizumab.



#### Neurotoxicity (ICANS)

0%. Notably absent across SMM trials to date.



#### Neutropenia

Significant hematologic toxicity (e.g., ERASMM Grade 3/4 neutropenia at 40%).



#### Infections

Manageable, but requires rigorous prophylactic Ig replacement (86% of patients in ERASMM).



**Key Takeaway:** Both mAbs and BsAbs offer encouraging safety profiles, but meaningful risks remain.  
**In asymptomatic patients, the safety threshold must be extremely high.**

# CAR-PRISM: Phase II Study of Ciltacabtagene Autoleucel (Cilta-Cel) in SMM

## Safety Summary

### Study DLT Definitions

Grade 4 nonhematologic toxicity  
Grade 3 CRS that does not improve to grade 1 within 72 hr  
Grade 3 neurological toxicity  
Grade 3 toxicity of any vital organ(s) or any grade 3 toxicity lasting >72 hr  
Grade 4 neutropenia or thrombocytopenia lasting >28 days

**Median FU in safety run-in cohort:** 15.3 mo

- At median follow-up: no DLTs observed

## Efficacy Summary

Response	n = 20
ORR, n (%)	20 (100)
CR/sCR, n (%)	18 (90)
MRD negative $10^{-6}$ by NGS, n (%)	20 (100)
Time to MRD negativity ( $10^{-6}$ ), mo	2

- No PD or death observed
- Median PFS and median OS: not reached

AEs of Interest,* n (%)	n = 20	
	All Grade	Grade 3/4
CRS <sup>†</sup>	20 (100)	0
Non-ICANS neurotoxicity	7 (35)	0

\*No ICANS or fatal neurotoxic events reported. <sup>†</sup>17 patients received tocilizumab and 13 received dexamethasone for CRS.

- No difference in response or durability of response in high-risk vs standard-risk cytogenetics
- 5/7 patients with NINTs received  $0.5\text{--}0.8 \times 10^6$  CAR+ T-cells per kg dose
- 4/7 NINTs included cranial nerve palsies (3 grade 1; 1 grade 2)
  - Median time to onset: 21 days (range: 10–52)
  - All 4 improved after 2 wk with full resolution in 4–8 wk
  - The grade 2 event included bilateral cranial nerve VII palsies with mononeuritis multiplex in a patient with possible predisposing risk factor of DM; received dexamethasone and IVIG → full resolution

# Who should we not treat?

Early therapy is justified only when near-term progression risk clearly outweighs treatment burden.

Low-risk SMM

Observation remains the default; avoid turning surveillance into therapy.

Stable intermediate-risk SMM

Monitor dynamic biomarkers; do not treat a static risk score alone.

“High-risk” by older criteria only

Re-stage with 20/2/20, cytogenetics, and modern imaging before deciding.

Frail / infection-prone / high competing risk

Toxicity may exceed the benefit of delayed progression.

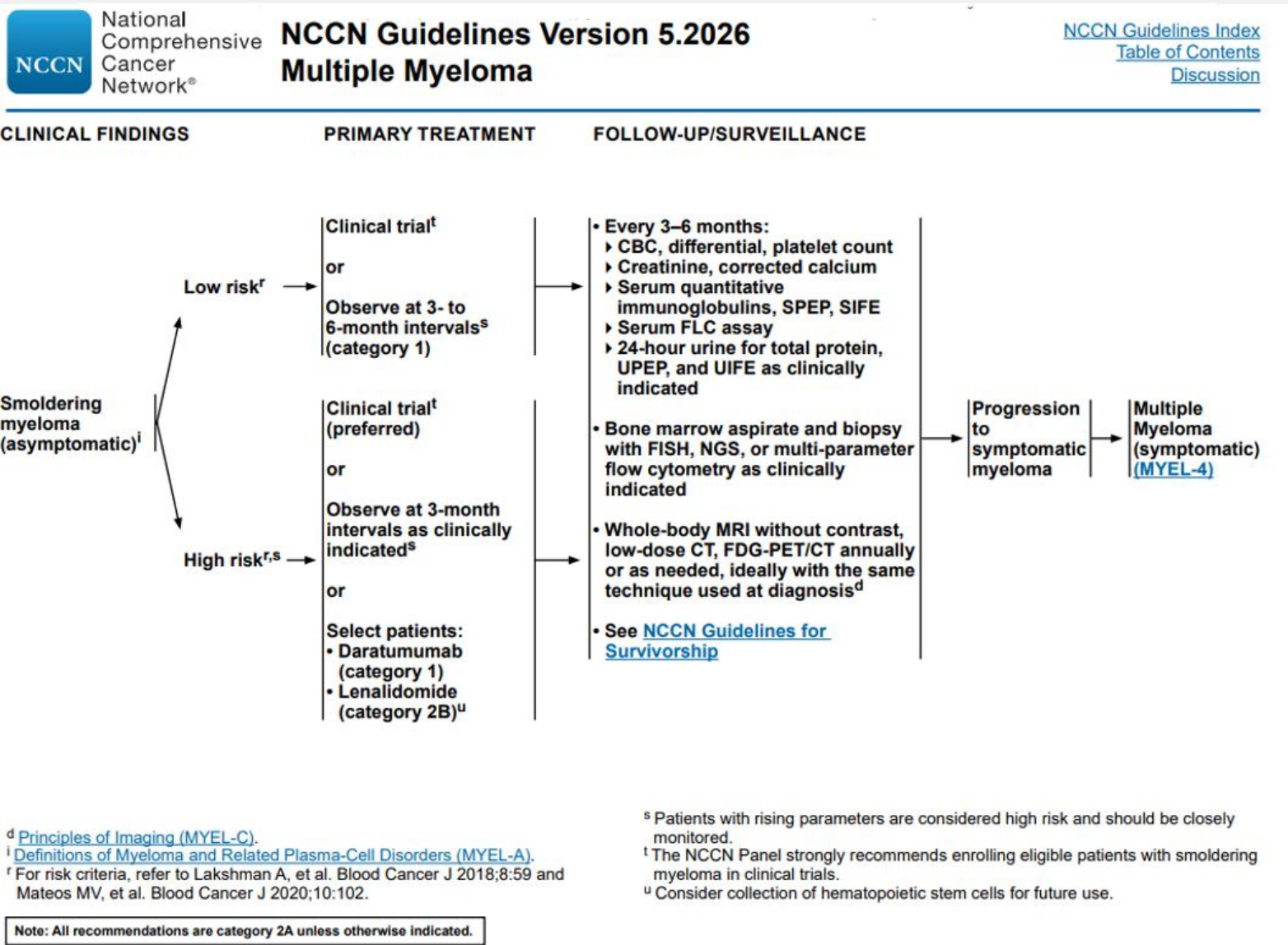
Uncertain patient preference

Shared decision-making is mandatory in an asymptomatic precursor state.

**Practical rule: if you cannot explain why this patient is likely to be harmed soon by observation, do not start therapy.**

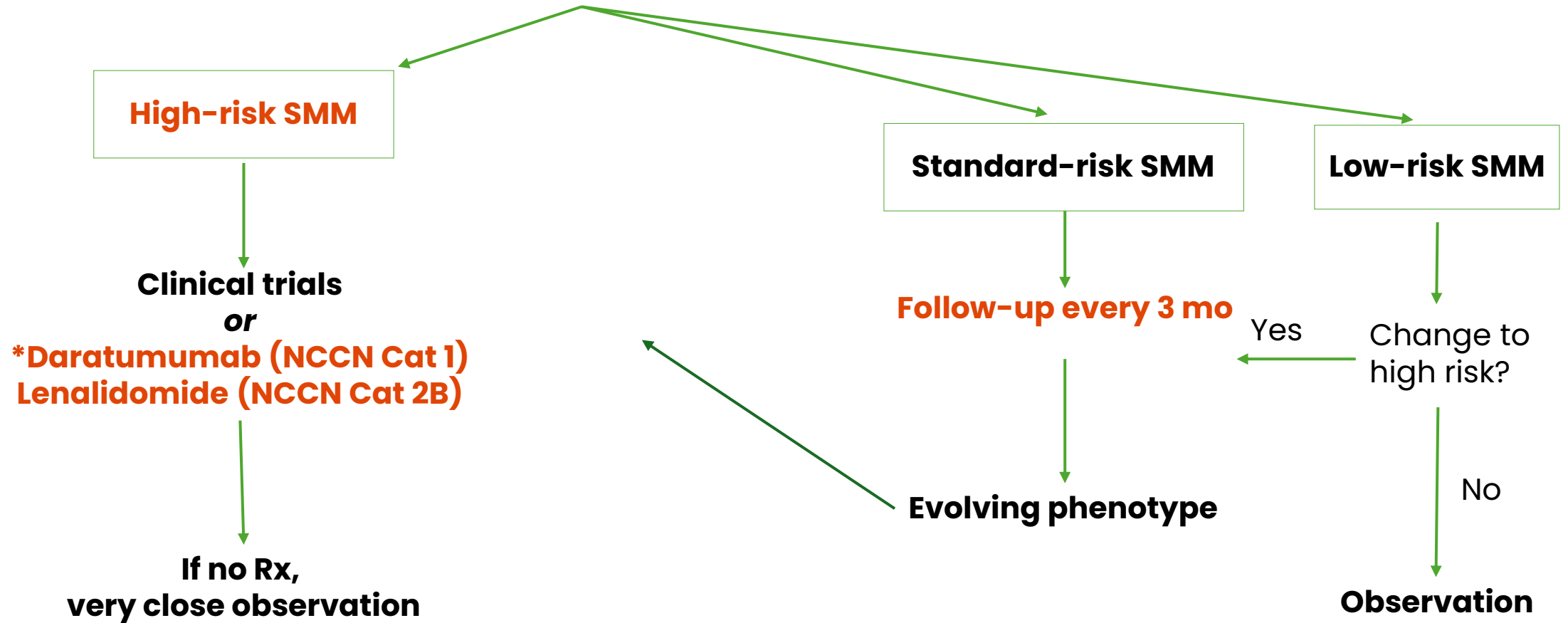


# NCCN: Recommendations for Patients With Smoldering Myeloma



# Expert's Algorithm for Managing Smoldering Myeloma

**Confirm SMM Diagnosis, Advanced Imaging Required**



\*FDA approval granted in 2025; use in selected high-risk SMM.



Thank you