Controversies in Cancer Care: Evidence, Interpretation, & Clinical Decision Making

Should High-Risk Smoldering Myeloma be Routinely Treated?

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Disclosures

- Grant/Research Support –Gilead Sciences, GSK, Kite, and Poseida Therapeutics.
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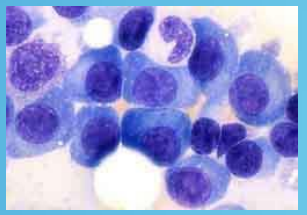
This presentation has been peer-reviewed and no conflicts were noted.

Learning Objectives

- ✓ **Define HR-SMM and confirm exclusion of active MM (SLiM-CRAB)**
- ✓ **Summarize randomized controlled trials and meta-analysis evidence for early treatment vs observation**
- ✓ **Apply 2026 guideline direction to real-world decision-making (who to treat, with what, and when)**

Clonal plasma cells ≥10%



The evolution of multiple myeloma diagnostic criteria represents a major shift from a **reactive** approach to a **proactive** approach in oncology

Diagnostic Era	Key Framework	Medical Philosophy	Treatment Strategy
2003 – 2014	**Calcium Criteria** **Renal** **Anemia** **Bone**	**Wait for organ damage** to occur.	Treatment started *only* after physical damage appeared.

Evolution of the SMM definition and risk

Era / model	Who was considered SMM?	Approx. 2-year progression risk
Pre-2014 SMM	≥10% BM plasma cells and/or M-protein ≥3 g/dL, no CRAB	~20–25% overall
2014 SLiM-CRAB	Removed patients with BMPC ≥60%, FLC ratio ≥100, or >1 MRI focal lesion	Lower overall risk
2018 Mayo 20/2/20	Modern SMM + stratification by BMPC >20%, M-protein >2 g/dL, FLC ratio >20	6–46%, depending on risk group
2020 IMWG 2/20/20 + FISH	Adds t(4;14), t(14;16), +1q, del13q	6–63%, depending on number of factors
Contemporary, imaging-intensive cohorts	**Modern SLiM-defined SMM with better imaging and diagnostic workup**	**~8% overall in one contemporary cohort**

Mayo 2018 — 20/2/20 risk stratification for SMM

Number of Risk Factors	BM Plasma Cells	M-protein	FLC ratio	Risk Category	Approx. 2 y risk of progression	Median Time to Progression
0	≤20%	≤2 g/dL	≤20	**Low risk**	9.7%	~110 months
1	>20% OR >2 g/dL OR >20	One criterion present	One criterion present	**Intermediate risk**	26.3%	~68 months
2	Any 2 of the 3 criteria			**High risk**	47.4%	~29 months
3	All 3 criteria			**High risk**	47.4%	~29 months

20/2/20 is a risk model—not a diagnostic definition.

Why treating SMM is controversial?

- **SMM is asymptomatic: higher bar for treating (toxicity, cost, overtreatment)**
- **But HR-SMM has substantial near-term progression risk (goal: prevent/delay active MM and potential organ damage)**
- **Historically: “observe until progression”**

First principle: "*primum non nocere*" *
don't undertreat active MM

- **Before labeling "SMM", ensure no myeloma-defining events (SLiM-CRAB)**
  - **Don't treat active MM as "smoldering"**

- **Misclassification inflates apparent benefit of early therapy in older trials (pre-2014 era)**
  - **Apply modern IMWG diagnostic assessment; exclude myeloma-defining events**
  - **Older SMM trials predate IMWG 2014 revisions → possible inclusion of patients who would now be "active MM"**

* *Of The Epidemics* (Book1); Hippocrates of Kos, 400 BCD

What is “High-Risk” SMM? (models vary; impacts routine treatment)

- **Multiple HR definitions exist → non-concordant patient selection drives controversy**
- **EHA–EMN highlights “20-2-20” and cytogenetic augmentation; reported 2-yr progression ~44% (3-factor) and ~63% (4-factor) in a retrospective dataset**
- **AQUILA used a specific High-risk definition (not identical to 20-2-20)**
- **Problem: “High-risk” varies across systems → overtreatment risk if definition is broad**

QuiRedex- 1st RCT showing that treating selected HR SMM could delay PFS and improve OS

Study type	Phase III, randomized, open-label, multicenter
Sites	19 centers in Spain + 3 in Portugal
Enrollment	Nov 2007–Jun 2010
Patients randomized	**125**
Treatment	**Lenalidomide + dexamethasone (Rd) vs observation**
Randomization	1:1
Population	High-risk SMM by older criteria
Primary endpoint	TTP to symptomatic MM
Secondary endpoints	**Response, OS, safety**
Treatment duration	**9 cycles induction → lenalidomide maintenance, total treatment limited to 2 years**

QuiRedex – 1st RCT showing that treating selected HR SMM could **delay PFS and improve OS**

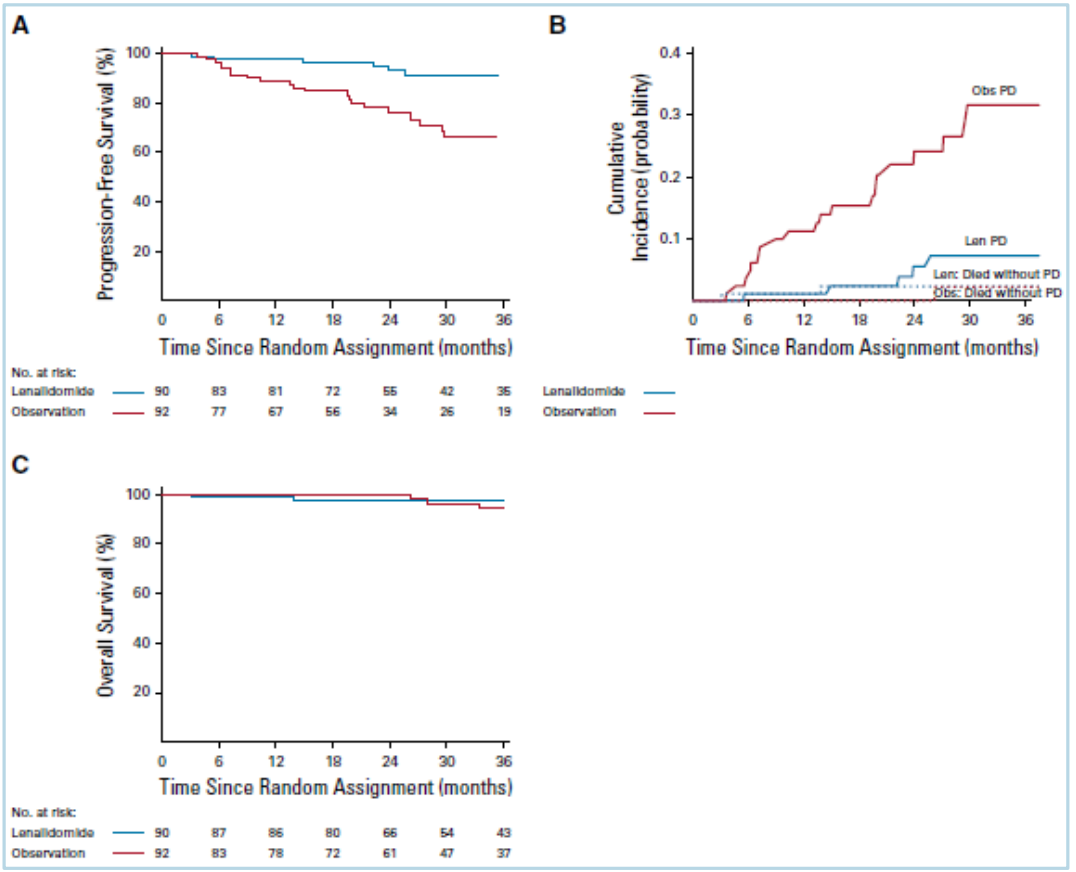
Endpoint	2013 NEJM*	2016 follow-up	2022 follow-up
Median follow-up	~40 mo	~75 mo	**12.5 yr**
TTP	NR vs 21 mo	NR vs 23 mo	**9.5 vs 2.1 yr**
HR for progression	**0.18**	**0.24**	**0.28**
OS	3-yr: **94% vs 80%**	HR **0.43**	HR **0.57**
Median OS	NR	NR	**NR vs 8.5 yr**
Response	~79% ≥PR after induction	~90% overall	—
Conclusion	Delays progression and OS signal	Benefit persists	**Sustained TTP and OS benefit**

*Important Limitation: Study was conceived before the modern **SLiM-CRAB** criteria and before the **20/2/20** model.

NEJM 2013
1st long-term analysis Lancet Oncology 2016
European Journal of Cancer 2022; 12.5-year follow-up in

ECOG-E3A06

Population	Intermediate or high-risk SMM
Design	Randomized phase II/III, open-label
Phase III patients	182
Intervention	**Lenalidomide 25 mg PO days 1–21 every 28 days**
Control	Observation
Dexamethasone	None
Treatment duration	Until progression, toxicity, or withdrawal
Primary endpoint	PFS
Median follow-up in primary publication	**35 mo**
Key result	**PFS HR 0.28**
3-year PFS	**91% vs 66%**
OS	Not significantly different at that follow-up



The Price of Delaying Progression

Among patients receiving lenalidomide:

- **28% experienced grade 3–4 nonhematologic adverse events**
- **Grade 3/4 neutropenia** occurred in approximately **14%** in the full publication.
- **Grade 3 infections** occurred in approximately **20.5%.**
- About **20% discontinued lenalidomide because of adverse events**.
- **Dose reductions were extremely common; approximately 80% of treated patients ultimately required dose reduction.**

80%

required dose reduction

28%

grade 3–4 nonhematologic AEs

Lenalidomide-based RCTs: benefit + limitations for “routine” use (What did we learn?)

ECOG-E3A06 (JCO 2019); n=182

- **PFS HR 0.28 (95% CI 0.12–0.62; P=0.002)**
- **Grade 3–4 nonhematologic AEs 28% on lenalidomide**

QuiRedex (NEJM 2013 / long follow-up 2022); n=119 randomized

- **Long follow-up (median 12.5 years) confirms TTP and OS signal; TTP HR 0.28 and OS HR 0.57**

Key limitation for “routine” adoption: older criteria likely included patients who would now meet active MM definitions; guideline panels flag this explicitly

ASCO 2026: lenalidomide not routinely recommended in HR-SMM

AQUILA (NEJM 2025): daratumumab vs active monitoring (practice-changing)

Design: Phase 3, Multicenter, Open-Label, Randomized in High Risk Smoldering Multiple Myeloma

- **Sites: 124 sites in 23 countries**
- **n = 390 (194 dara vs 196 active surveillance); median follow-up 65.2 months**
- **Experimental arm: Subcutaneous daratumumab monotherapy**
- **Treatment duration: up to 39 cycles/36 months, or until progression**
  - **Weeks 1–8: weekly**
  - **Weeks 9–24: every 2 weeks**
  - **Week 25 onward: every 4 weeks**
- **Primary endpoint: PFS**
- **Progression assessment: Independent review committee using IMWG criteria.**
- **Key secondary endpoints: Time to first-line MM therapy and Overall Survival**

Who qualified as “high-risk SMM”* in AQUILA?

Patients had clonal bone-marrow plasma cells ≥10% and at least one of the following:

- **Serum M-protein ≥3 g/dL (30 g/L)**
- **IgA SMM**
- **Immunoparesis involving two uninvolved immunoglobulin isotypes**
- **Involved/uninvolved serum FLC ratio ≥8 but <100**
- **Clonal bone-marrow plasma cells >50% but <60%**

*** These criteria reflected the risk models available when the study was designed (rather than “20-2-20” definition)**

This distinction is very important when applying AQUILA today.

What constituted progression?

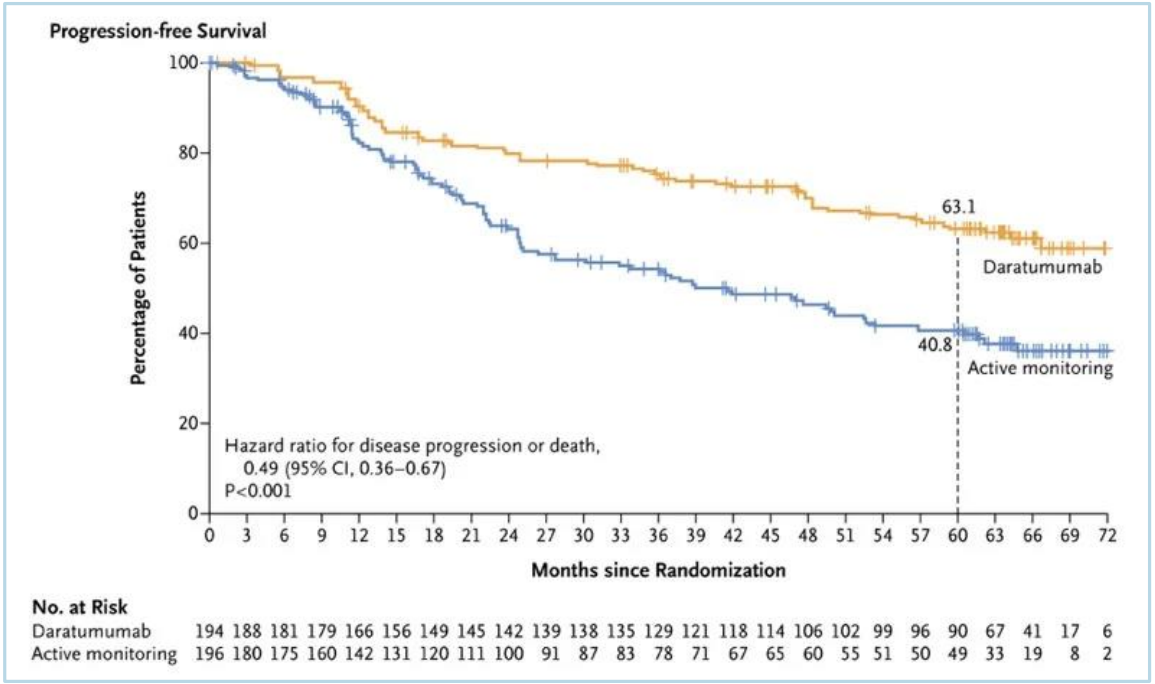
Progression was based on the IMWG SLiM-CRAB criteria, meaning that patients could progress because of either traditional myeloma-defining events or certain biomarkers/imaging findings, including:

- **≥60% clonal plasma cells in marrow**
- **FLC ratio ≥100 with involved FLC ≥100 mg/L**
- **1 focal lesion on MRI**
- **Hypercalcemia**
- **Renal dysfunction**
- **Anemia**
- **Bone lesions**

Thus, AQUILA did not require development of symptomatic CRAB myeloma before declaring progression.

AQUILA (NEJM 2025): daratumumab vs active monitoring (practice-changing)

- **PFS HR 0.49 (95% CI 0.36–0.67; P<0.001)**
- **5-yr PFS 63.1% vs 40.8%**
- **OS HR 0.52 (95% CI 0.27–0.98); deaths 7.7% vs 13.3%; 5-yr OS 93.0% vs 86.9%**
- **Discontinuation due to AEs 5.7% (dara arm)**



Relevance: modern progression criteria + structured surveillance; strongest contemporary RCT for a targeted, fixed-duration approach.

Caveats

High-risk definition was an older definition, not exactly today's 20-2-20.

Open-label trial.

PFS, could be triggered by biomarker/imaging criteria before symptomatic disease.

The OS result was secondary. Trial not powered for OS.

Subsequent therapy after progression was not necessarily identical between arms.

Study provides very strong evidence for delaying progression, but early treatment improving survival is less clear.

Meta-analysis summary: magnitude of benefit and harms

5 studies; 844 patients

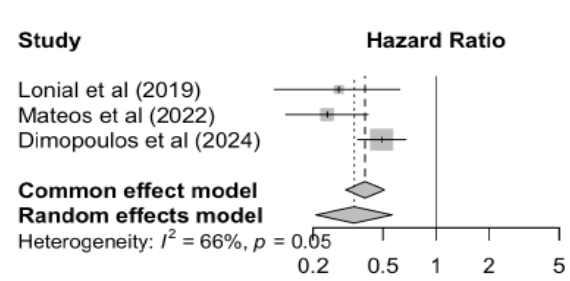
Intermediate or High risk sMM

Treatment vs observation or placebo

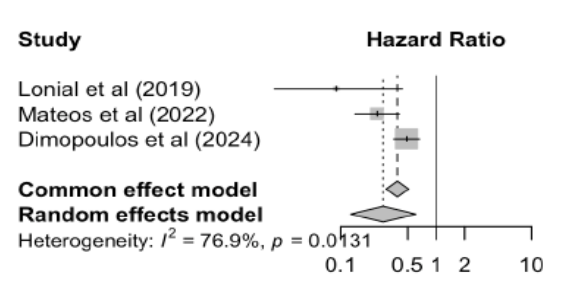
3 trials with only observation in the control group

- **66% lower risk for disease progression or death (HR = 0.34, 95%CI: 0.21-0.56) in the treatment group vs control group.**
- **58% reduced risk for progression to active MM (HR = 0.42, 95%CI: 0.29-0.61) for the treatment vs those who didn't.**

Supplementary Figure 2. Pooled PFS (HR) for trials with observation controls



Supplementary Figure 3. Pooled PFS (HR) for trials with observation controls only on high-risk patients



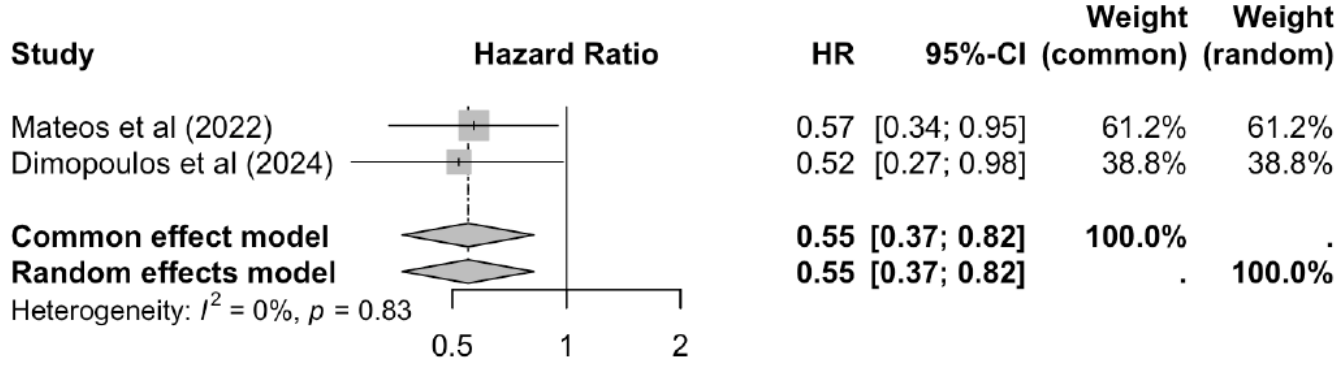
Ntanasis-Stathopoulos, et al., *Blood Cancer J*. 2025 May 26;15(1):104

Meta-analysis summary: magnitude of benefit and harms

Only 2 trials mature OS outcomes

Pooled effect estimate - 45% lower risk for death (HR = 0.55, 95% CI: 0.37–0.82) in HR on treatment vs observation

Supplementary Figure 4. Pooled OS (HR) between trial arms



Adverse events

3.5×

higher odds of a grade 3–4 event

Odds for a grade 3–4 adverse event on any anti-myeloma treatment was as 3.5 times as high (OR = 3.53, 95% CI: 1.14, 10.91) vs the control group.

Pooled proportion of grade 3–4 adverse events in the treatment arms was 40% (95% CI: 35%–45%).

No statistically significant differences observed in second primary malignancies (SPMs) between treatment and control groups (OR = 1.54, 95% CI: 0.57–4.17) in three studies with pertinent available data.

Meta-analysis summary: magnitude of benefit and harms

Interpretation for “routine” treatment:

- Consistent delay in progression
- Toxicity burden is real
- OS evidence limited/heterogeneous

- The evidence is much stronger for delaying progression than for proving that every HR-SMM patient should be treated.

Guideline positions (what you can say in 2026)

- **ASCO–Ontario Health 2026 living guideline: HR-SMM → active monitoring OR daratumumab (≤36 months); lenalidomide not routinely recommended (conditional; moderate evidence)**

- **EHA-ESMO 2021: "watch-and-wait" remains recommended; HR-SMM encouraged for RCTs (noting lenalidomide PFS benefit but approval gaps/uncertainty)**

Takeaway:

2026 guidance supports selective early therapy, not automatic treatment for every HR-SMM patient.

The “routine treatment” argument (PRO)

- **RCTs show substantial reduction in progression risk (e.g., AQUILA PFS HR 0.49)**
- **Meta-analysis supports a consistent PFS signal across regimens**
- **Potential OS signal exists (AQUILA; QuiRedex) but not uniformly established**

PRO

The “routine treatment” counterargument (CON)

Why observation remains valid

- **HR definitions vary → risk of overtreating patients who might remain stable for years**
- **Many endpoints reflect progression (often lab/imaging-defined) rather than unequivocal prevention of irreversible morbidity (depends on surveillance quality)**
- **Treatment increases grade 3–4/serious AEs in pooled RCT evidence**

CON

To Treat or Not To Treat: that is the question.

Treatment is reasonable (discuss strongly) when:

- There is confirmed HR-SMM by a contemporary model (20/2/20) + clinical judgment, and patient prioritizes delaying progression
- Patient can commit to therapy and monitoring; accepts immunotherapy risks/visits

Observe is reasonable when:

- HR label is borderline/discordant across models, or patient is risk-averse to toxicity
- Significant comorbidity, frailty, infection risk, or adherence concerns

Bottom line

In 2026, active monitoring and fixed-duration daratumumab are both reasonable options for appropriately selected patients

A practical risk-adapted SMM algorithm

1 CONFIRM — **No SLiM–CRAB myeloma-defining event** — If present → manage as active multiple myeloma

2 STRATIFY — **20/2/20 + high-risk FISH + biomarker trajectory**

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

Assign the branch that best reflects current risk

HIGHER RISK

≥2 20/2/20 factors

and/or high-risk FISH

Evolving M-protein or FLC strengthens concern

ACTION

High risk + evolving → discuss starting treatment

Not clearly evolving → clinical trial or very close monitoring

INTERMEDIATE RISK

1 risk factor

or discordant risk signals

Trajectory may clarify direction over time

ACTION

Clinical trial or very close monitoring

Reclassify if biomarkers evolve

LOWER RISK

0 risk factors

No high-risk FISH

Non-evolving biomarkers

ACTION

Close monitoring

Escalate the branch if risk markers evolve

At every branch: shared decision-making + serial reassessment; risk category can change over time.

Dr. Robert A. Kyle
The Father of Multiple Myeloma
2028 - 2026

"*Ten percent of patients with smoldering multiple myeloma progress during the first year and then they decrease after that and ultimately after 10–15 years, progress at a rate of 1–2% per year. It all fits so beautifully, I think.*"
- Robert A. Kyle, MD; 2022

Thank you