ADVOCATE HEALTH

From Monoclonal Gammopathy to Myeloma: Decoding the Smoldering Phase

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Disclosures

The following faculty speakers and/or planning committee members have disclosed the following:

Faculty Name	Name of Ineligible Companies	Nature of Relationship
Grace Elsey, PharmD, BCOP	Jazz Pharmaceuticals	Consultant, Pegasparaginase in ALL

The other planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose. All of the relevant financial relationships listed for [this individual/these individuals] have been mitigated.

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Abbreviation Key

AL: Amyloid Light Chain Amyloidosis
BMPCs: Bone Marrow Plasma Cells
CBC: Complete Blood Count
CrcI: Creatinine Clearance
CT: Computed Tomography
ECOG: Eastern Cooperative Oncology Group
FDG: Fludeoxyglucose-18
FISH: Fluorescence in Situ Hybridization
IHC: Immunohistochemistry
IMWG: International Myeloma Working Group
LLN: Lower Limit of Normal
MGUS: Monoclonal Gammopathy of Undetermined Significance
MM: Multiple Myeloma
MRI: Magnetic Resonance Imaging
NCCN: National Comprehensive Cancer Network
PET-CT: Positron Emission Computed Tomography
PFS: Progression Free Survival
Q2W: Every 2 Weeks
Q4W: Every 4 Weeks
Q8W: Every 8 Weeks
QW: Every Week
SMM: Smoldering Multiple Myeloma
TEAE: Treatment Emergent Adverse Event
TTP: Time to Progression
Tx: Treatment
ULN: Upper Limit of Normal
VTE: Venous and Arterial Thromboembolism

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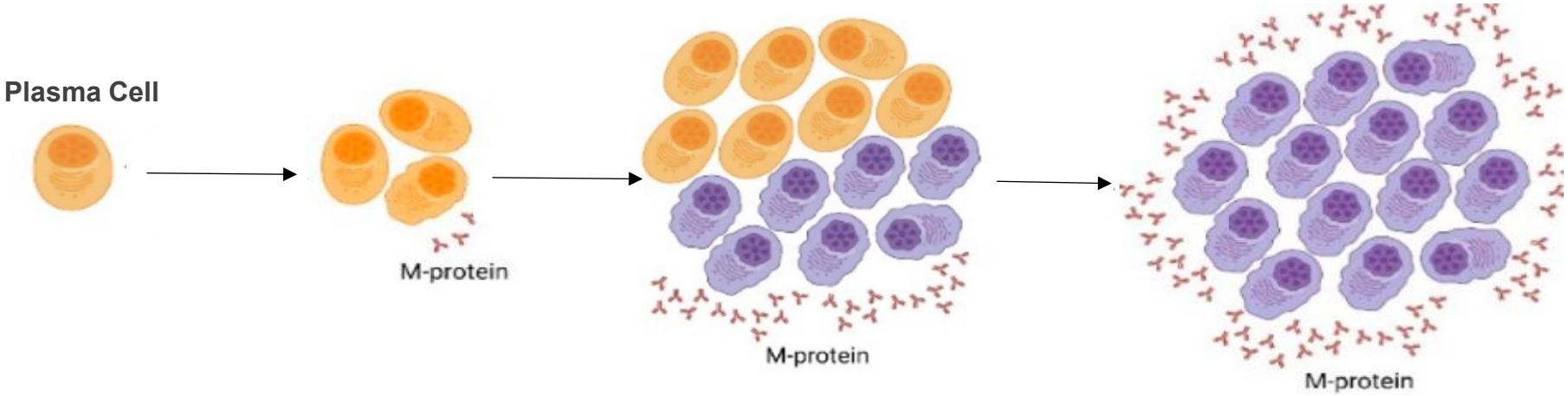
Learning Objectives

At the end of this session, learners should be able to:

- Differentiate between MGUS, SMM, and MM based on current diagnostic criteria
- Describe NCCN guidelines and IMWG guidelines for the risk of stratification, monitoring and management of patients with SMM
- Clinically assess the benefits and drawbacks of early therapeutic intervention in SMM
- Review recent clinical trial data to support evidence-based decision making in the management of SMM

Background

Plasma Cell Disorders



Monoclonal Gammopathy of Undermined Significance (MGUS) → **Smoldering Multiple Myeloma (SMM)** → **Multiple Myeloma (MM)**

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Risk of Progression

Plasma Cell Disorder	Risk of Progression to Multiple Myeloma
Monoclonal Gammopathy of Undermined Significance	1% per year
Smoldering Multiple Myeloma	First 5 years: 10% per year Next 5 years: 3% per year Next 10 years: 1-2% per year

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Hematology American Society Hematologic Education Program, 2022. (1): 551-559.

Diagnostic Workup

History and physical exam

Laboratory markers

- CBC w/ differential, serum creatine, Crcl, electrolytes, liver function tests, albumin, calcium, serum uric acid, lactate dehydrogenase, beta-2 microglobulin

Protein analysis

- Serum and urine protein electrophoresis (SPEP), (UPEP)
- Serum and urine immunofixation electrophoresis (SIFE), (UIFE)
- Serum free light chain (FLC) assay

Imaging

- Whole body FDG-PET/CT

Bone marrow biopsy

- IHC
- FISH

Diagnostic Criteria: International Myeloma Working Group Diagnostic Criteria (IMWG)

Diagnostic Criteria

MGUS	SMM	MM
Serum monoclonal protein < 3 gm/dL	Serum monoclonal protein ≥ 3 gm/dL **or** urinary monoclonal protein ≥ 500 mg/24 hr	Any level of M protein
Clonal BMPCs < 10%	Clonal BMPCs 10% to 59%	Clonal BMPCs ≥ 10%
Absence of myeloma defining events	**Absence** of myeloma defining events	**Presence** of ≥ 1 myeloma defining event (CRAB or SLiM)

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Rajkumar. Blood Cancer Journal. 2022;12(129).

Myeloma Defining Events

CRAB and SLiM-CRAB

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Myeloma Defining Events: CRAB Criteria

C
- **Hypercalcemia**: serum calcium >1 mg/dL higher ULN or > 11 mg/dL

R
- **Renal insufficiency**: Crcl < 40 mL/min or scr > 2 mg/dL

A
- **Anemia**: Hemoglobin > 2 g/dL below the LLN or hemoglobin < 10 g/dL

B
- **Bone lesions**: one or more osteolytic lesions on skeletal radiography, CT or PET-CT

***Criteria met if ≥ 1 component present**

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IMWG. Br J Haematol. 2003.

Myeloma Defining Events: SLiM-CRAB Criteria

S
- ≥ 60% clonal Bone Marrow Plasma Cells

Li
- Involved Free Light Chains (FLC) ≥ 100 mg/L

M
- > 1 focal lesion by MRI

***Criteria met if ≥ 1 component present**

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Rajkumar. Br J Haematology, 2024. 205 (4): 1337-1345.

Assessment Question #1

Which of the following is required for the diagnosis of Smoldering Multiple Myeloma (SMM) according to the IMWG criteria?

A. Serum monoclonal protein < 3 gm/dL with clonal BMPCs < 10%
B. Presence of CRAB features
C. Clonal BMPCs of 10% to 59% with the absence of myeloma defining events
D. Presence of myeloma defining biomarker

Smoldering Multiple Myeloma (SMM) Risk Stratification

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Evolution of Risk Stratification

2008

Mayo Criteria

(Older Model)

2020

IMWG Criteria

(Current Model)

In Progress

IMWG Model

(Developing Model)

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Risk Stratification Comparison

Risk Factors	Older Model (2008)	Current Model (2020)
Bone Marrow Plasma Cells (%)	≥ 10%	> 20
Serum M-protein (g/dL)	≥ 3	> 2
Serum Free Light Chain Ratio	≤ 0.125 or ≥ 8	> 20

Number of Risk Factors	Risk Category
0	Low Risk
1	Intermediate Risk
2-3	High Risk

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Wang. Blood Cancer J, 2022.140 (8): 828-838.

IMWG Model (Developing)

IMWG Model	
Risk Factor	**Score**
Free Light Chain (FLC) ratio	
> 10-25	2
> 25-40	3
> 40	5
M protein (g/dL)	
> 1.5-3	3
> 3	4
BMPC (%)	
> 15-20	2
> 20-30	3
> 30-40	5
> 40	6
FISH abnormality	**2**

**del(17p), t(4;14), t(14;16)

International Myeloma Working Group	
Total Risk Score	**Corresponding Current Risk Category**
High risk SMM >12	**High risk**
Intermediate 9-12	**High risk**
Low-intermediate 5-8	**Intermediate risk**
Low 0-4	**Low risk**

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Rajkumar. Blood Cancer Journal. 2022;12(129).

Management: Smoldering Multiple Myeloma Guidelines

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International Guidelines: 2010 IMWG

Management of Smoldering Multiple Myeloma

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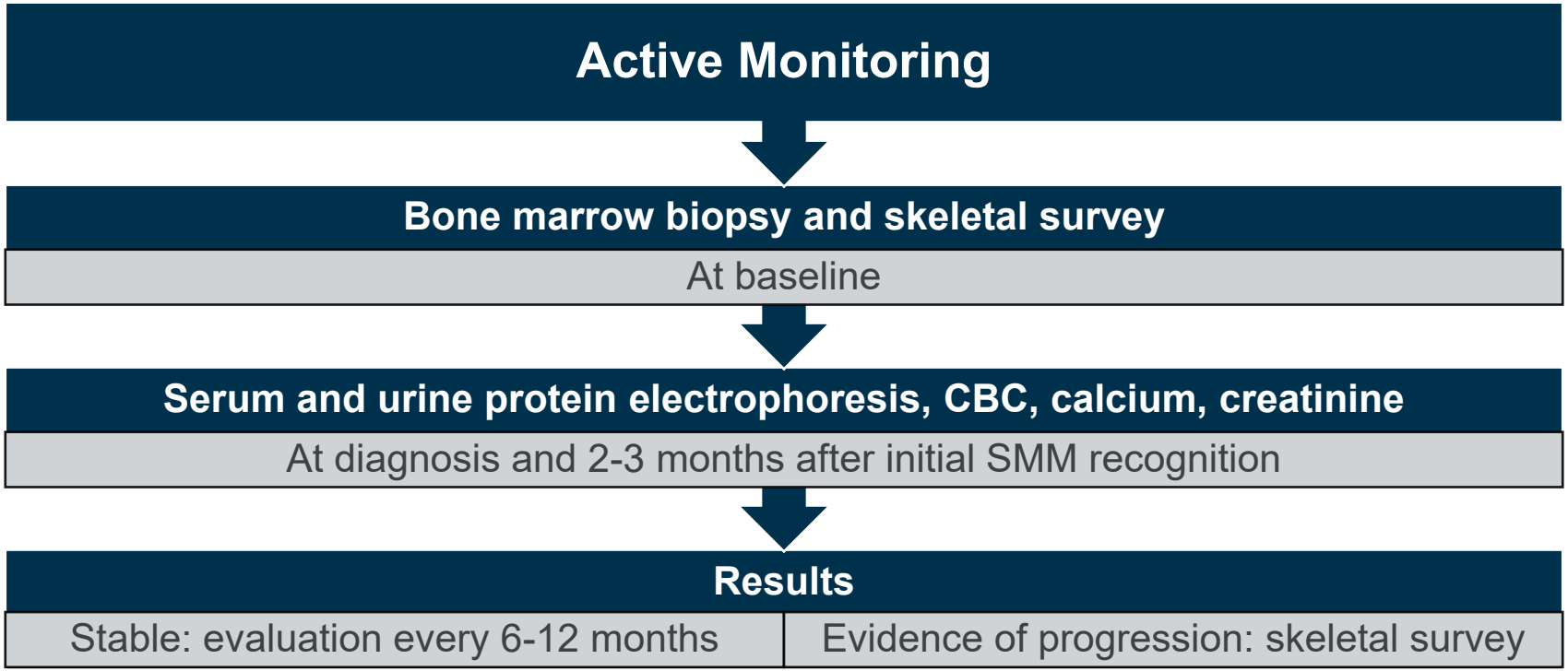
IMWG Smoldering Guidelines



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Kyle. Leukemia, 2010. 24 (6); 1121-1127.

NCCN Guidelines: MM

Primary Therapy For HCT Candidates (Multiple Myeloma)
Preferred • **Daratumumab**/Lenalidomide/Bortezomib/Dexamethasone (category 1) • Isatuximab-irfc/Bortezomib/Lenalidomide/Dexamethasone (category 1)
Other Recommended • Bortezomib/Lenalidomide/Dexamethasone (category 1) • Carfilzomib/Lenalidomide/Dexamethasone • **Daratumumab**/Carfilzomib/Lenalidomide/Dexamethasone • Isatuximab-irfc/Carfilzomib/Lenalidomide/Dexamethasone

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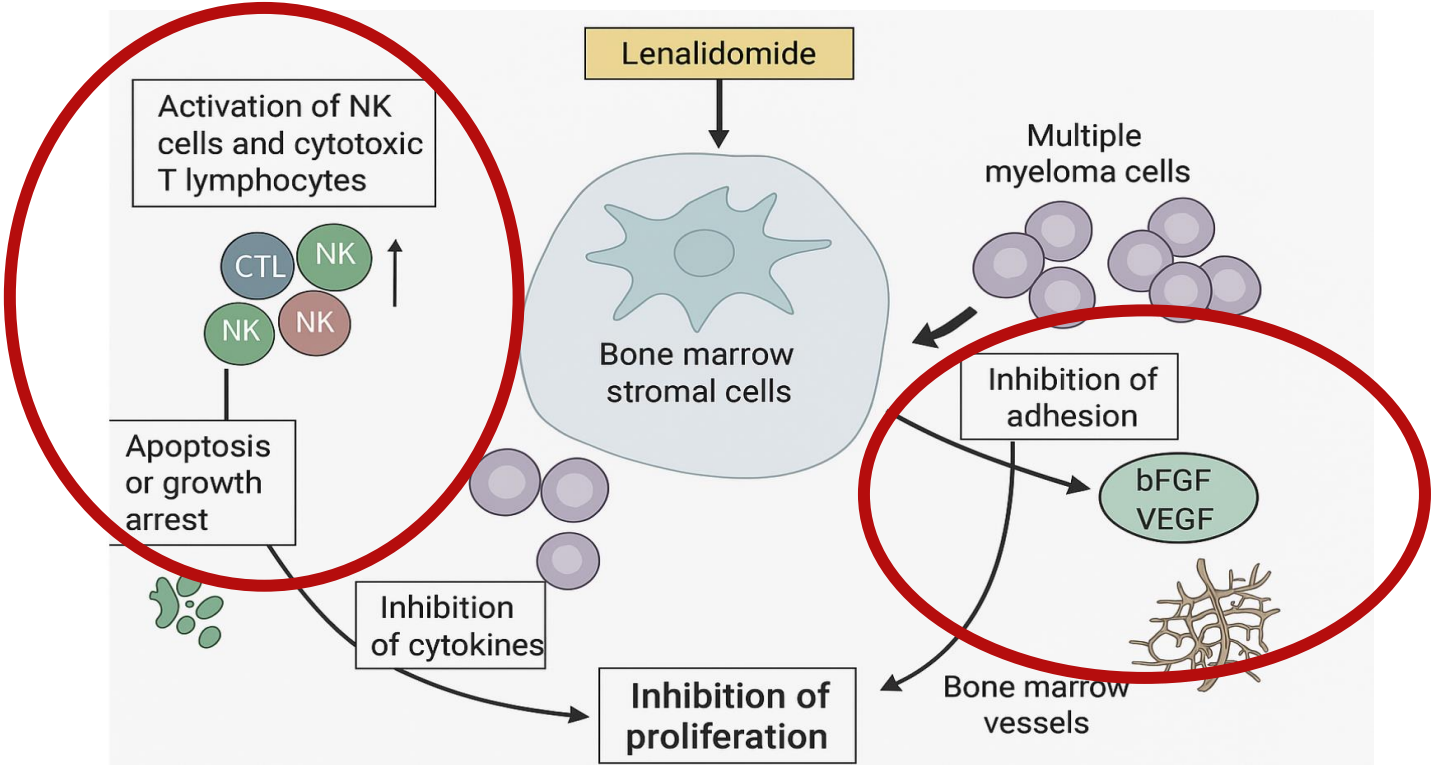
Lenalidomide



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Lenalidomide

Indications	Administration	Side Effects	Pearls
• Multiple myeloma • Select lymphomas • **Off label use: SMM**	• Orally • SMM dosing: • 25 mg days 1 to 21; 28 day cycle	• Myelosuppression • Thromboembolic events • Secondary primary malignancies • Hepatotoxicity • Diarrhea • Increased mortality • Rash	• Boxed warning: Embryo-fetal toxicity, significant hematologic toxicities, VTE • REMS program • Anti-thrombotic prophylaxis recommended • Dose adjustments for hematologic toxicities, renal impairment

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Revlimid [Lenalidomide] Package Insert. Princetown, NJ. Bristol-Myers Squibb. 2025.

Active Surveillance

Trial	Study Design	Intervention	Results
Mateos et al, (2013) QuiReDex	Randomized phase 3 control trial Patients: 119 high risk SMM (according to older model)	Lenalidomide + Dexamethasone v observation	• TTP: not reached vs. 21 months (HR 0.18; P < 0.001) • 3 year survival rate: 94% vs. 80% (HR 0.31; P=0.03) • Limitations: outdated risk criteria, ended early, imaging, adverse effects/toxicity
Lonial, et al, (2019) ECOG- ACRIN E3A06	Randomized phase 3 control trial Patients: 188 high risk SMM (according to current model)	Lenalidomide v observation	• PFS (3 years): 91% vs. 66% (HR 0.28; P=0.002) • Overall survival; 2 vs. 4 (HR 0.46; CI 0.08 - 2.53) • Limitations: ended early, adverse effects/toxicity

Mateos. N. England Journal Medicine, 2013. 369, 438-447.
Lonial. J Clin Oncol. 2020 Apr 10;38(11):1126-1137

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Active Surveillance Summary

- Standard of care
- Limited high quality evidence for early intervention
- Delayed progression without consistent overall survival benefit
- Toxicity and long term safety concerns → avoid lenalidomide
- Evolving definition of high risk SMM
- Uncertain benefit risk balance supported continued surveillance

National Guidelines: 2025 NCCN

Management of Smoldering Multiple Myeloma

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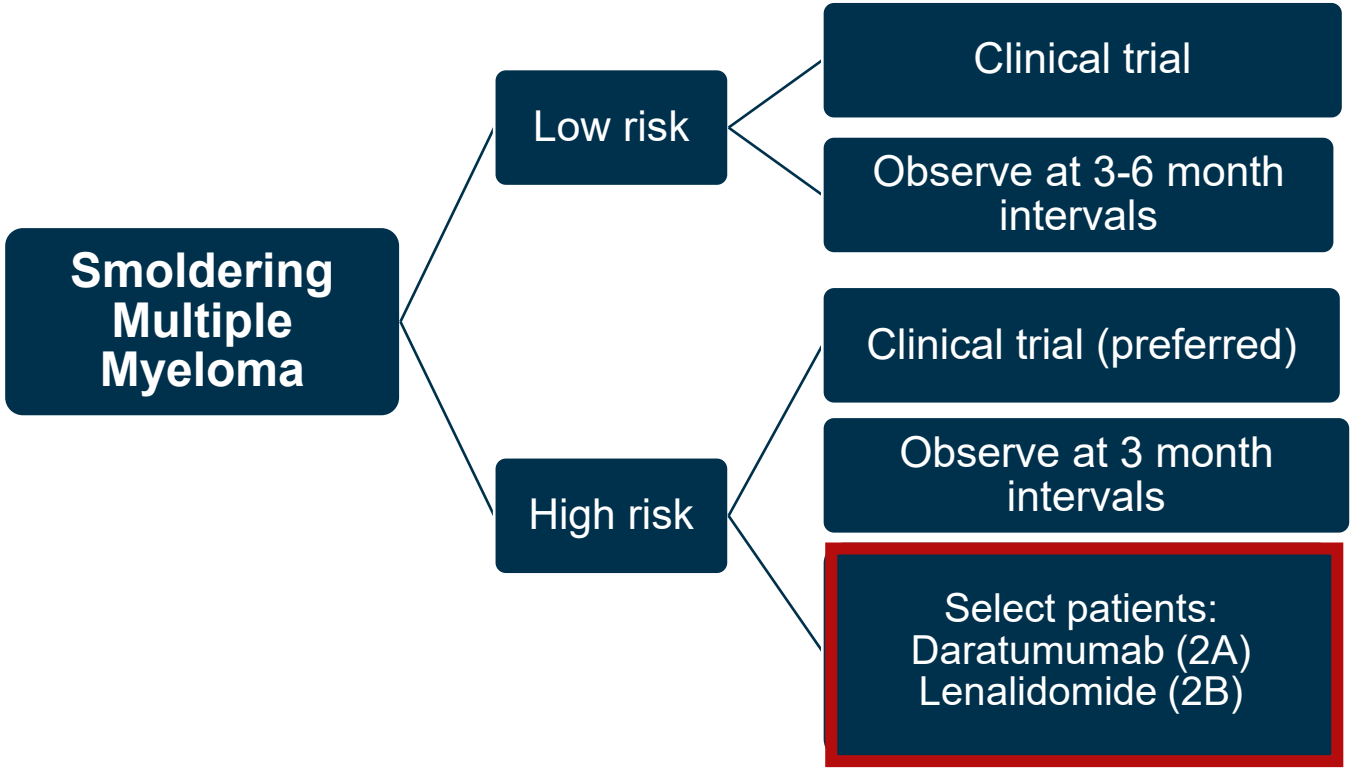
NCCN Guidelines: SMM



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NCCN Guidelines: MM

Primary Therapy For HCT Candidates (Multiple Myeloma)
Preferred
• **Daratumumab**/Lenalidomide/Bortezomib/Dexamethasone (category 1)
• Isatuximab-irfc/Bortezomib/Lenalidomide/Dexamethasone (category 1)
Other Recommended
• Bortezomib/Lenalidomide/Dexamethasone (category 1)
• Carfilzomib/Lenalidomide/Dexamethasone
• **Daratumumab**/Carfilzomib/Lenalidomide/Dexamethasone
• Isatuximab-irfc/Carfilzomib/Lenalidomide/Dexamethasone

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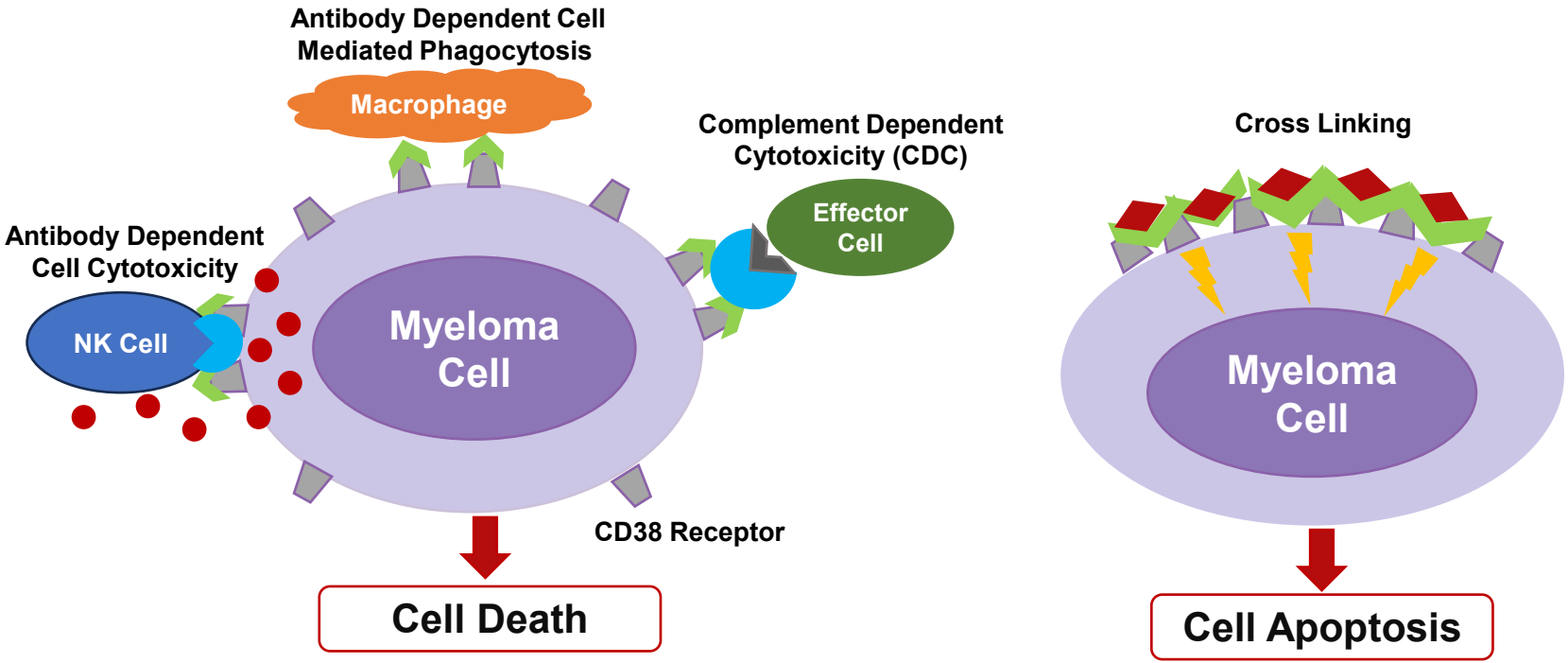
Daratumumab Hyaluronidase



Varga. Br J Haematol, 2018.181 (4) 447-459.

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Daratumumab Hyaluronidase

<table>
<tr><th>Indications</th><th>Administration</th><th>Side Effects</th><th>Pearls</th></tr>
<tr>
<td>• Select indications</td>
<td>• 1,800 mg daratumumab and 30,000 units hyaluronidase (15 mL) over 3-5 minutes
• Subcutaneous injection

SMM dosing
<table>
<tr><th>Cycles</th><th>Schedule</th></tr>
<tr><td>1-2</td><td>Weekly (8 doses)</td></tr>
<tr><td>3-6</td><td>Biweekly (8 doses)</td></tr>
<tr><td>7-39 (until MM diagnosis or maximum 3 years)</td><td>Every 4 weeks</td></tr>
</table>
</td>
<td>• Infections
• Neutropenia
• Thrombocytopenia
• Embryo-fetal toxicity</td>
<td>• Pre-medication: corticosteroid, acetaminophen and histamine-1 receptor antagonist
• Antiviral HSV reactivation prophylaxis
• Interference with serological testing and determination of complete response</td>
</tr>
</table>

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Darzalex Faspro [daratumumab] Package Insert. Hosham, PA. Janssen Biotech, Inc. 2025.

Assessment Question #2

Lenalidomide is generally well tolerated and demonstrates a more favorable safety profile compared to daratumumab.

A. True
B. False

CENTAURUS Trial

- **Randomized, open label, multicenter, phase 2 study**
- **Purpose:** Identify a less toxic SMM intervention
- **Study Design:** 1:1:1 ratio, three daratumumab dosing schedules

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Landgren. Leukemia, 2020. 34 (7):1840-1852.

Patient Population

Inclusion Criteria	Exclusion Criteria
• Adult patients (≥ 18) diagnosed high risk or intermediate risk SMM for < 5 years (according to older model) • ECOG performance score 0 or 1	• Presence of at least one SLiM-CRAB myeloma defining event • Pretreatment clinical laboratory values indicating clinically relevant organ damage • Concurrent bisphosphonate treatment for SMM or MM

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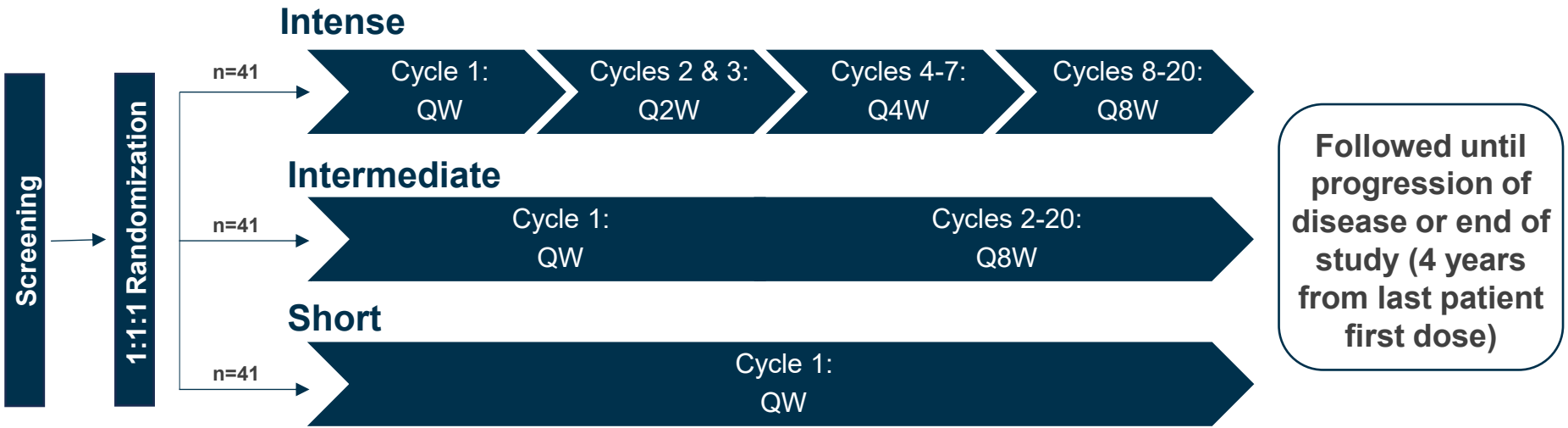
Leukemia, 2020. 34 (7):1840-1852.

Interventions



Dosing: Daratumumab 16 mg/kg IV; 8 week cycles

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Leukemia, 2020. 34 (7):1840-1852.

Results

Outcome	Intense (n=41)	Intermediate (n=41)	Short (n=41)
Primary Outcome(s)			
Complete response rate **P value**	2 (4.9) 0.9569	4 (9.8) 0.7567	0 -
Progressed or died, n(%) **24 month PFS rates (%)**	5 (12.2) 89.9	8 (19.5) 82	10 (24.4) 75.3
PD/death rate **P value**	0.059 < 0.0001	0.107 < 0.0001	0.150 < 0.0001
Secondary Outcome(s) **ORR, n (%)** **90% CI**	 23 (56.1) 42.1-69.4	 22 (53.7) 39.8-67.1	 15 (37.5) 24.7-51.7
Safety Summary **Fatigue**	 **17 (41.5)**	 **25 (61.0)**	 **9 (22.5)**
Upper Respiratory Tract Infection	**15 (36.6)**	**14 (34.1)**	**4 (10.0)**
Cough	**15 (36.6)**	**13 (31.7)**	**11 (27.5)**
Grade 3 or 4 TEAEs, n (%)	18 (43.9)	11 (26.8)	5 (15.0)

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Leukemia, 2020. 34 (7):1840-1852.

Conclusions

- Daratumumab demonstrates acceptable efficacy and tolerability in intermediate risk and high risk SMM (older criteria)
- Standard daratumumab dosing offers promising disease control and may delay progression of SMM, however it lacked an active comparator
- Standard dosing schedule for phase III study justified

Leukemia, 2020. 34 (7):1840-1852.

Assessment Question #3

According to available guidelines, which of the following best reflects the **current** standard of care for smoldering multiple myeloma?

A. Daratumumab in all patients
B. Active surveillance until multiple myeloma diagnosis in most patients
C. Lenalidomide in all patients
D. Treat as multiple myeloma

AQUILA Trial

Randomized, open label, multicenter, phase 3 study

Purpose: Determine if daratumumab would delay progression to active MM among high risk SMM patients

Study Design: 1:1; daratumumab v active monitoring

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Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Patient Population

Inclusion Criteria	Exclusion Criteria
• Adult patients with confirmed diagnosed SMM within past 5 years • High risk SMM (according to older model) • ECOG performance score 0 or 1 • ANC ≥ 1.0 x 10^9/L • Platelet count ≥ 50 x 10^9/L • ALT and AST ≤ 2.5 times ULN • Total bilirubin level ≤ 2.0 times ULN	• Presence of SLiM-CRAB • Prior exposure to daratumumab or other anti-CD38 treatments • Prior exposure to approved or investigational treatments for SMM or MM

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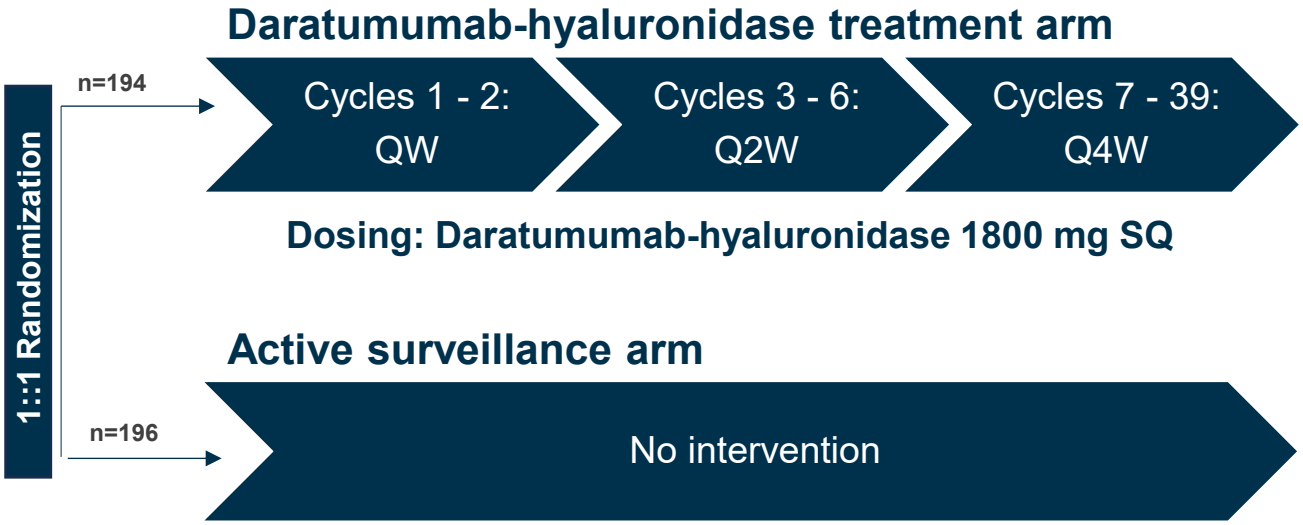
Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Intervention



Follow-up Phase

Efficacy follow up until progression by SLiM-CRAB

- Primary endpoint: PFS

Survival follow up every 6 months until end of study

- Key secondary endpoints: Time to first line treatment for MM, OS

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Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Baseline Characteristics

	Daratumumab (n=194)	Active Monitoring (n=196)
Median age, years (range)	63 (31-86)	64.5 (36-83)
Male sex, n (%)	95 (49.0)	93 (47.4)
White, n (%)	161 (83.0)	162 (82.7)
Risk factors < 3, n (%)	159 (79.4)	156 (79.6)
% BMPCs, n (%) **10% to ≤ 20%**	124 (63.9)	102 (52.0)
≥ 1 High risk cytogenic abnormalities, n/total n (%)**	29/167 (17.4)	22/170 (12.9)
Median (range) time from SMM diagnosis to randomization, yrs	0.8 (0-4.7)	0.67 (0-5.0)
ECOG performance score 0, n (%)	165 (85.1)	160 (81.6)

**del(17p), t(4;14), t(14;16)

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Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Study Outcomes

Primary Outcome

- Progression free survival (PFS)
  - Disease progression

Secondary Outcomes

- Overall survival (OS)
- Time to event endpoints
  - Disease progression
  - Initiation of first line treatment for active MM

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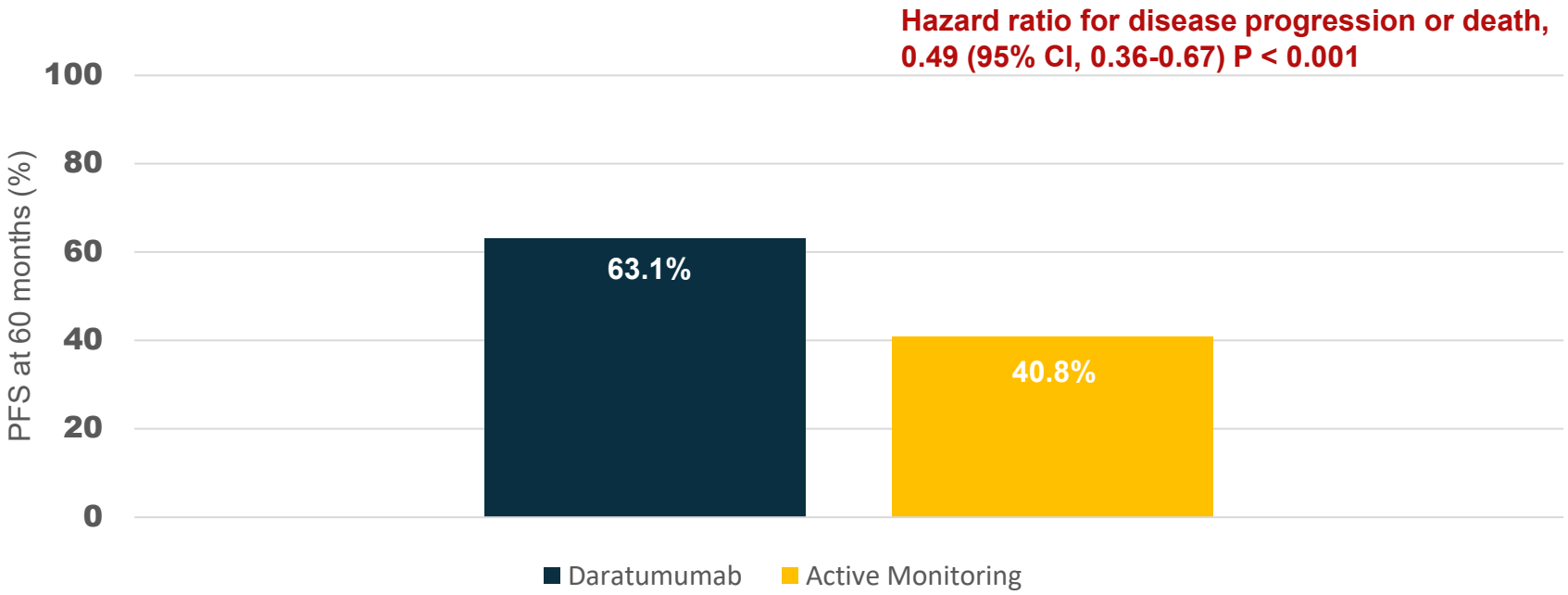
Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Primary Outcome: PFS



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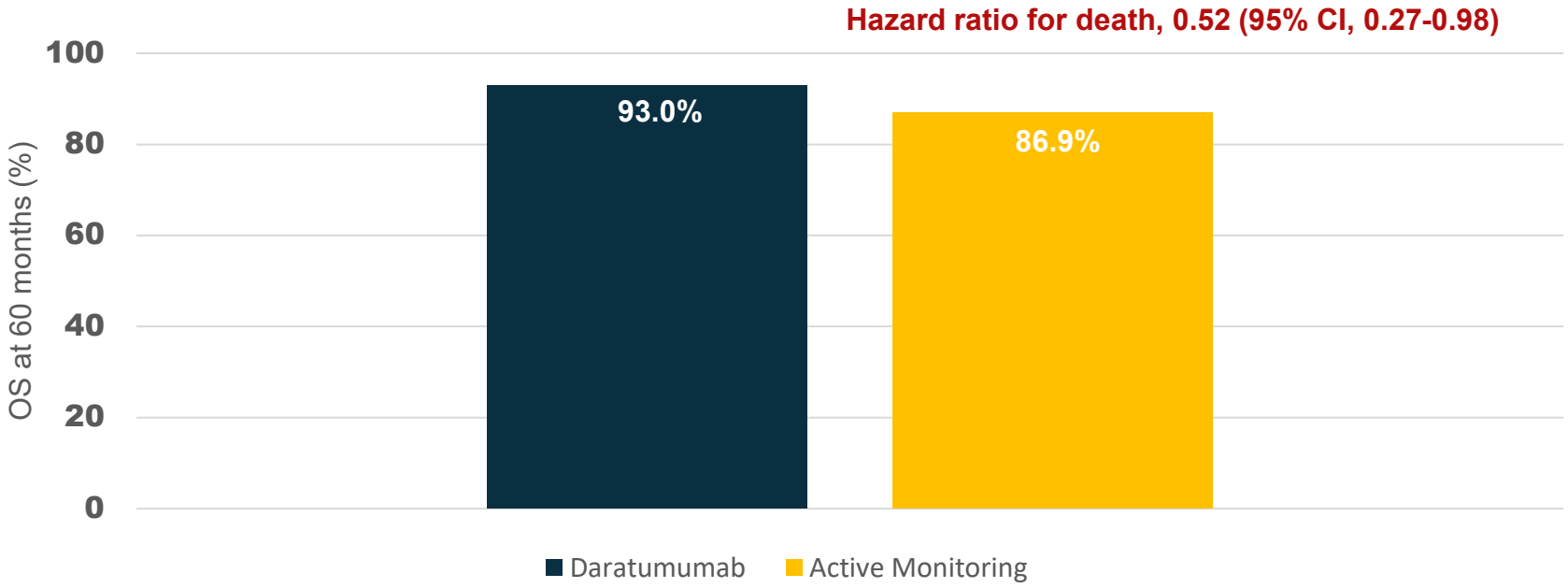
Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Secondary Outcome: OS



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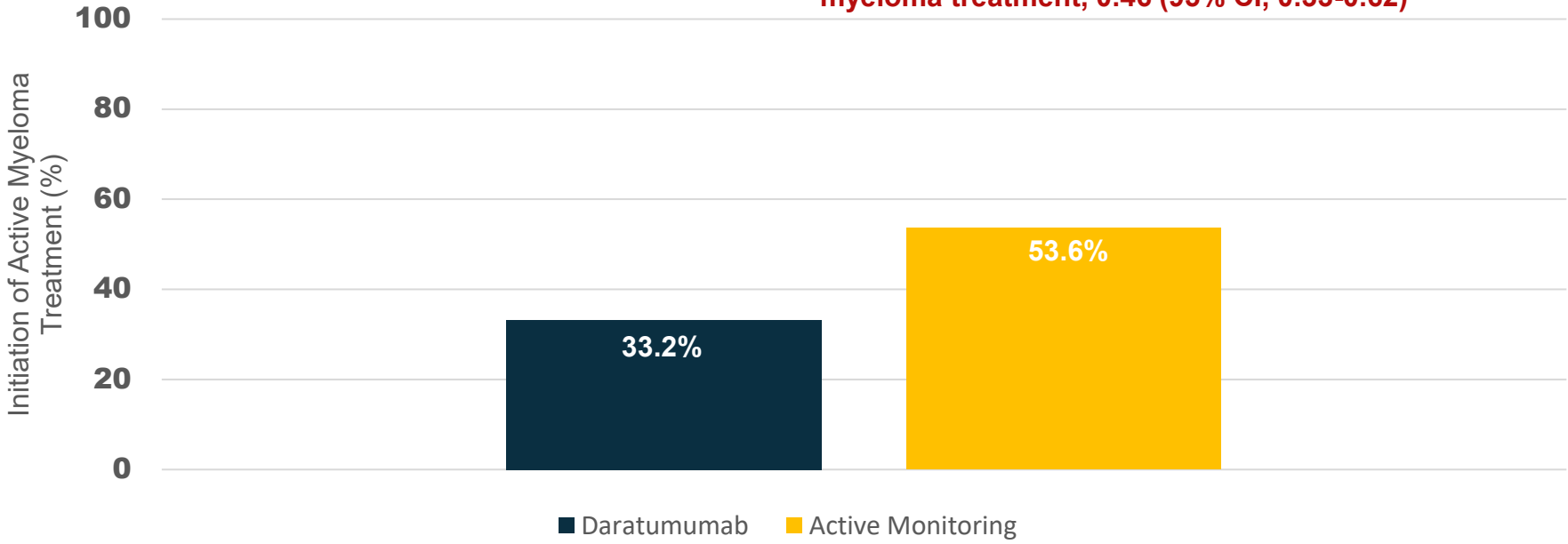
Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Secondary Outcome: Treatment

Hazard ratio for time to first line multiple myeloma treatment, 0.46 (95% CI, 0.33-0.62)



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Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Safety Outcomes

Outcome, n (%)	Daratumumab (n=194)	Active Monitoring (n=196)
Any adverse event	187 (96.9)	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)
Grade 3 or 4 adverse event	78 (40.4)	59 (30.1)
Serious adverse event	56 (29.0)	38 (19.4)
Adverse event that led to death	2 (1.0)	4 (2.0)
Second primary cancer	18 (9.3)	20 (10.2)

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Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Conclusions

- Daratumumab was associated with a significantly lower risk of progression to active MM or death and is associated with higher OS than active monitoring
- Overall survival, power analysis
- Findings difficult to extrapolate given utilization of older risk stratification model

Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

Strengths and Limitations

Strengths

- Large, international, randomized trial
- First trial evaluating subcutaneous daratumumab-hyaluronidase for SMM
- Active comparator arm

Limitations

- Disease progression defined using SLiM-CRAB criteria
- Trial not powered for OS, benefit remains unproven
- High risk SMM misclassification, absence of current risk stratification model during time of study

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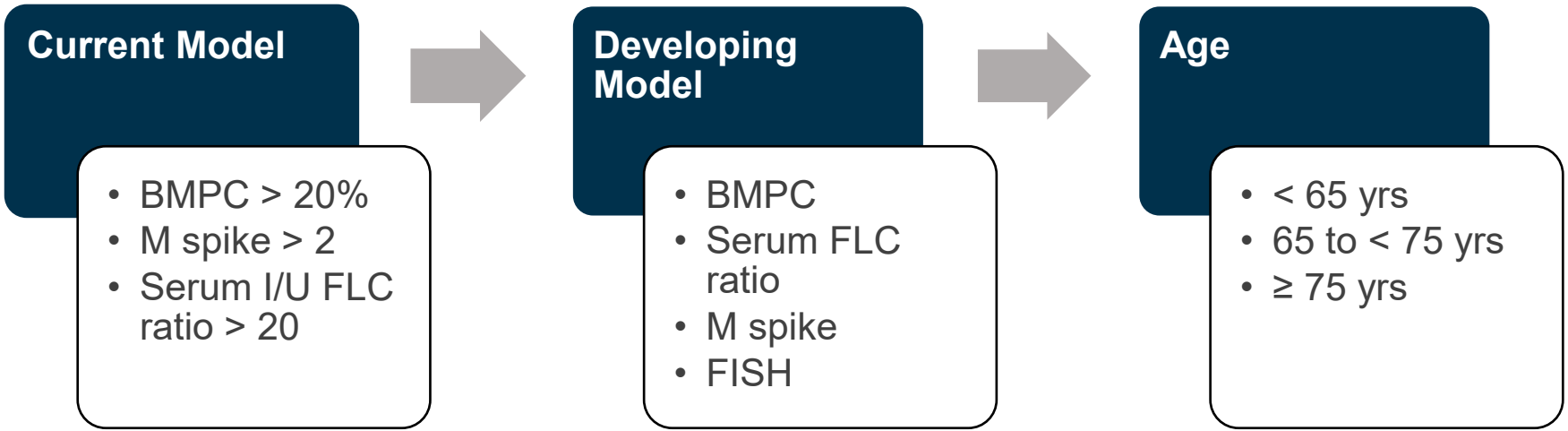
Dimopoulos. N Engl J Med. 2025. 392 (18) : 1777-1788.

AQUILA: Future Direction

- Progression free survival and safety is clear, though which risk categories based on our current stratification model benefit most?

AQUILA Post-Hoc Analysis

- Purpose: To assess outcomes utilizing the current and developing risk models to assess which patients benefited most from daratumumab



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IMWG 2020 (Current Model)

	Daratumumab Monotherapy			Active Monitoring		
***Older* model risk stratification**	High n=194			High n=196		
***Current* model risk stratification**	Low n=45	Intermediate n=77	High n=72	Low n=34	Intermediate n=76	High n=86
Median age, years	61.0	64.0	64.0	65.0	63.0	65.0
Female sex, n (%)	20 (44.4)	43 (55.8)	36 (50.0)	19 (55.9)	39 (51.3)	45 (52.3)
White, n (%)	37 (82.2)	64 (83.1)	60 (83.3)	30 (88.2)	65 (85.5)	67 (77.9)
Baseline ECOG score, n (%) **0**	39 (86.7)	65 (84.4)	61 (84.7)	28 (82.4)	66 (86.8)	66 (76.7)

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J&J Medical Connect. American Society of Hematology (ASH) Annual Meeting; Dec 6-9, 2025.

IMWG 2020 (Current Model): PFS

60 month (5 year) PFS rates, %		
Current Model Risk Stratification	**Daratumumab**	**Active Monitoring**
Low	78.2	71.6
Intermediate	56.2	42.9
High	60.4	23.6

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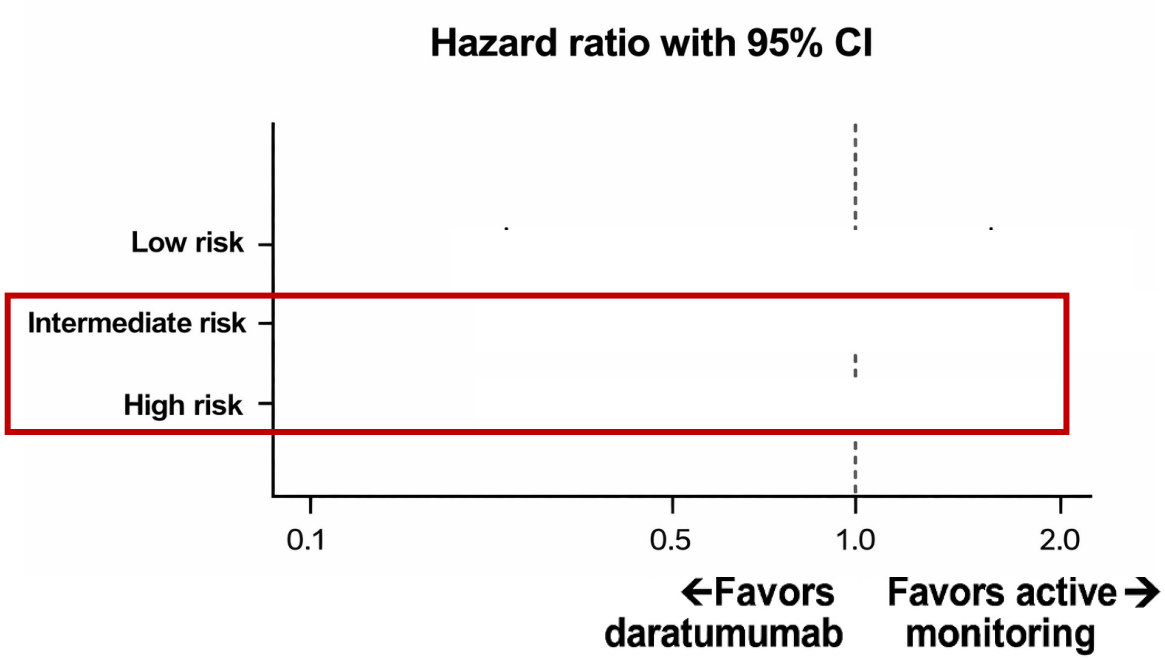
J&J Medical Connect. American Society of Hematology (ASH) Annual Meeting; Dec 6-9, 2025.

IMWG 2020 (Current Model): Time to MM treatment



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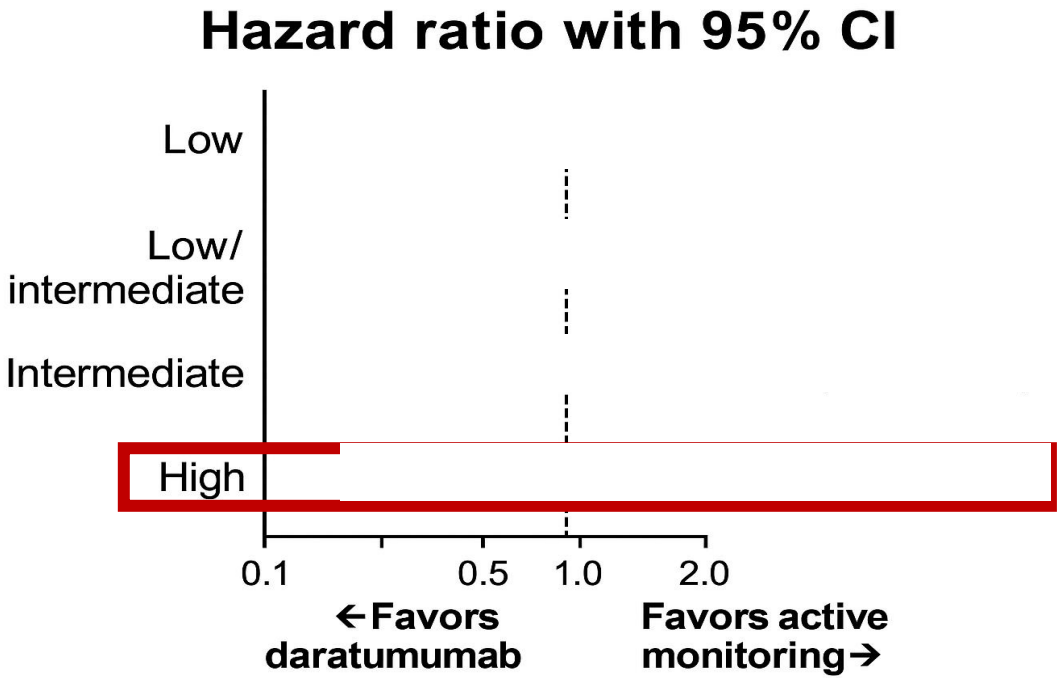
J&J Medical Connect. American Society of Hematology (ASH) Annual Meeting; Dec 6-9, 2025.

IMWG (Developing Model): PFS



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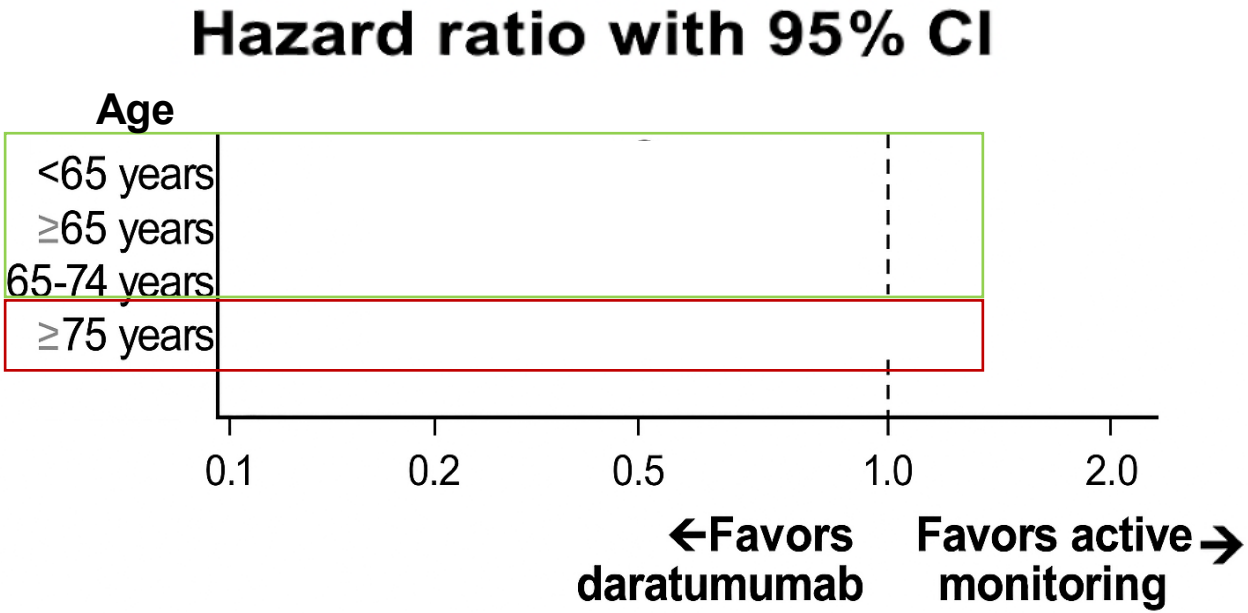
J&J Medical Connect. American Society of Hematology (ASH) Annual Meeting; Dec 6-9, 2025.

Age Subgroup, PFS



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J&J Medical Connect. American Society of Hematology (ASH) Annual Meeting; Dec 6-9, 2025.

AQUILA Trial: Impact on Clinical Practice

- Active monitoring was the standard in all patients regardless of risk classification prior to AQUILA
- AQUILA provided rationale for early intervention in high-risk SMM patients
- **Led to FDA approval for daratumumab in SMM on November 2025**
- Post-hoc analysis shows promising benefit in high risk patients (current model) aged less than 74

Assessment Question #4

Which of the following statements best reflects the current understanding of smoldering multiple myeloma prognosis and progression?

A. All patients with SMM will progress to MM within 2 years
B. Risk stratification and age impact the decision on who would benefit from earlier intervention vs active surveillance
C. The risk of progression is the same regardless of biomarkers
D. Early intervention should be recommended for all SMM patients to improve overall survival

Considerations of Early Pharmacologic Intervention

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Benefits and Drawbacks: Early Intervention

Advantages	Disadvantages
Delayed progression to active myeloma	Risk of overtreatment and unnecessary exposure to toxicities
Improved progression free survival	Potential development of CD38 resistance and/or limiting future trial enrollment
Prevents irreversible organ damage	Financial burden, frequent monitoring, impact on QOL despite asymptomatic

Key Takeaways

High risk patients (according to current criteria) benefit from early intervention with daratumumab

In patients aged 75 or older, active monitoring should be considered over early intervention

Patient specific considerations including QOL, financial burden, and comorbidities emphasize need for shared decision making

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Questions?

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From Monoclonal Gammopathy to Myeloma: Decoding the Smoldering Phase

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