My Evolving Management of Patients with Smoldering Multiple Myeloma

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Atrium Health Wake Forest Baptist | Comprehensive Cancer Center

NCI Comprehensive Cancer Center
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48-year-old woman screened for myeloma as part of a work-up for an elevated serum total protein. She is asymptomatic. She has no relevant past medical history. She is a physician practicing at a University Health Center. She is pursuing a Masters Degree in Public Health and has 2 children in Middle School.

Scenario #1

- CBC, Cr, Ca normal
- IgA kappa M spike 1.2 g/dL
- Serum free kappa light chains 22.5 mg/L, FLC ratio 2.3
- BMBx: 30% PCs by CD138 IHC
- FISH: +t(11;14)
- Whole body MRI: No focal bone lesions

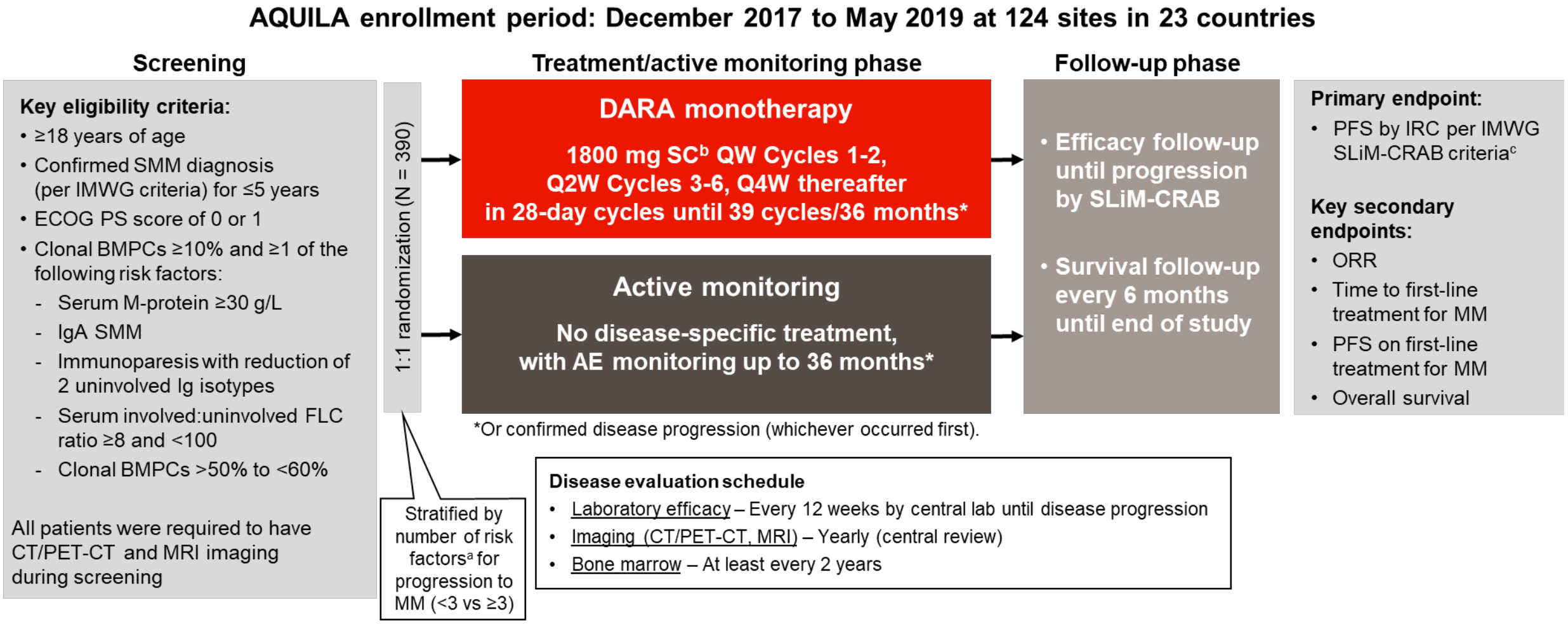
Scenario #2

- CBC, Cr, Ca normal
- IgG kappa M spike 2.6 g/dL
- Serum free kappa light chains 360 mg/L, FLC ratio 28
- BMBx: 20% PCs by CD138 IHC
- FISH: +del(13q)
- Whole body MRI: No focal bone lesions

Scenario #3

- CBC, Cr, Ca normal
- IgG kappa M spike 3.2 g/dL
- Serum free kappa light chains 420 mg/L, FLC ratio 54
- BMBx: 50% PCs by CD138 IHC
- FISH: +gain 1q21, t(4;14)
- Whole body MRI: No focal bone lesions

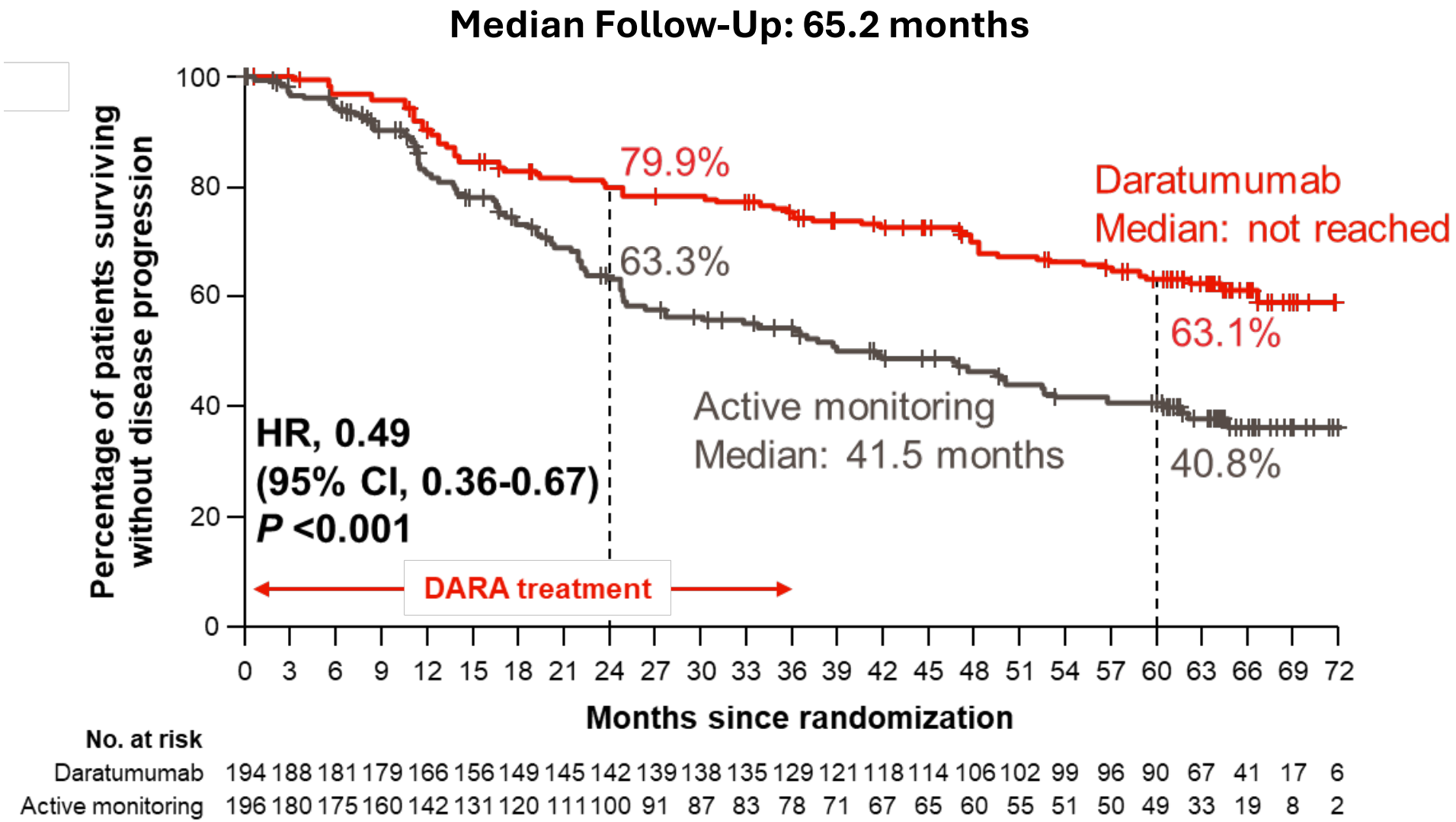
The Phase III AQUILA Trial



IMWG, International Myeloma Working Group; ECOG PS, Eastern Cooperative Oncology Group performance status; BMPC, bone marrow plasma cell; FLC, free light chain; CT, computed tomography; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; AE, adverse event; IRC, independent review committee; ORR, overall response rate. [a]Risk factors included involved:uninvolved FLC ratio ≥8 (yes vs no), serum M-protein ≥30 g/L (yes vs no), IgA SMM (yes vs no), immunoparesis (reduction of 2 uninvolved immunoglobulins vs other), or clonal BMPCs (>50% to <60% vs ≤50%). [b]DARA SC (1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc.]). [c]PFS was defined as duration from randomization to initial documented progression to active MM or death due to any cause, whichever occurred first.

Dimopoulos MA et al. ASH 2024.

Daratumumab vs Observation for High-Risk Smoldering Myeloma: The Phase III AQUILA Trial



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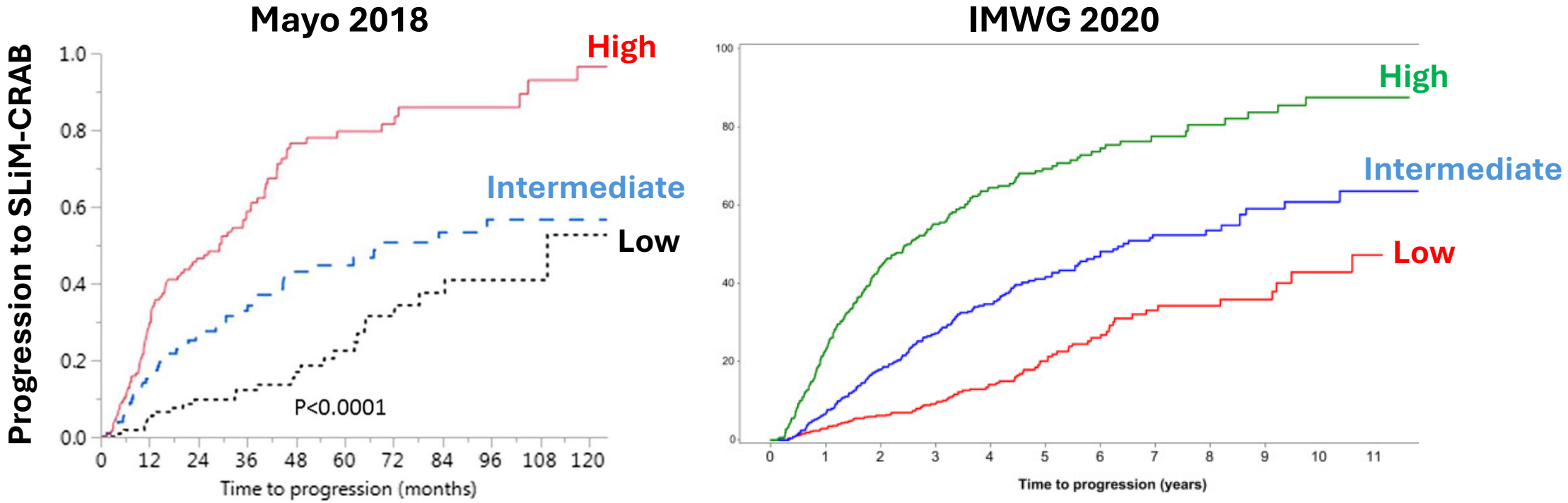
The patient population is too heterogeneous

IMWG 2020 (20/2/20)



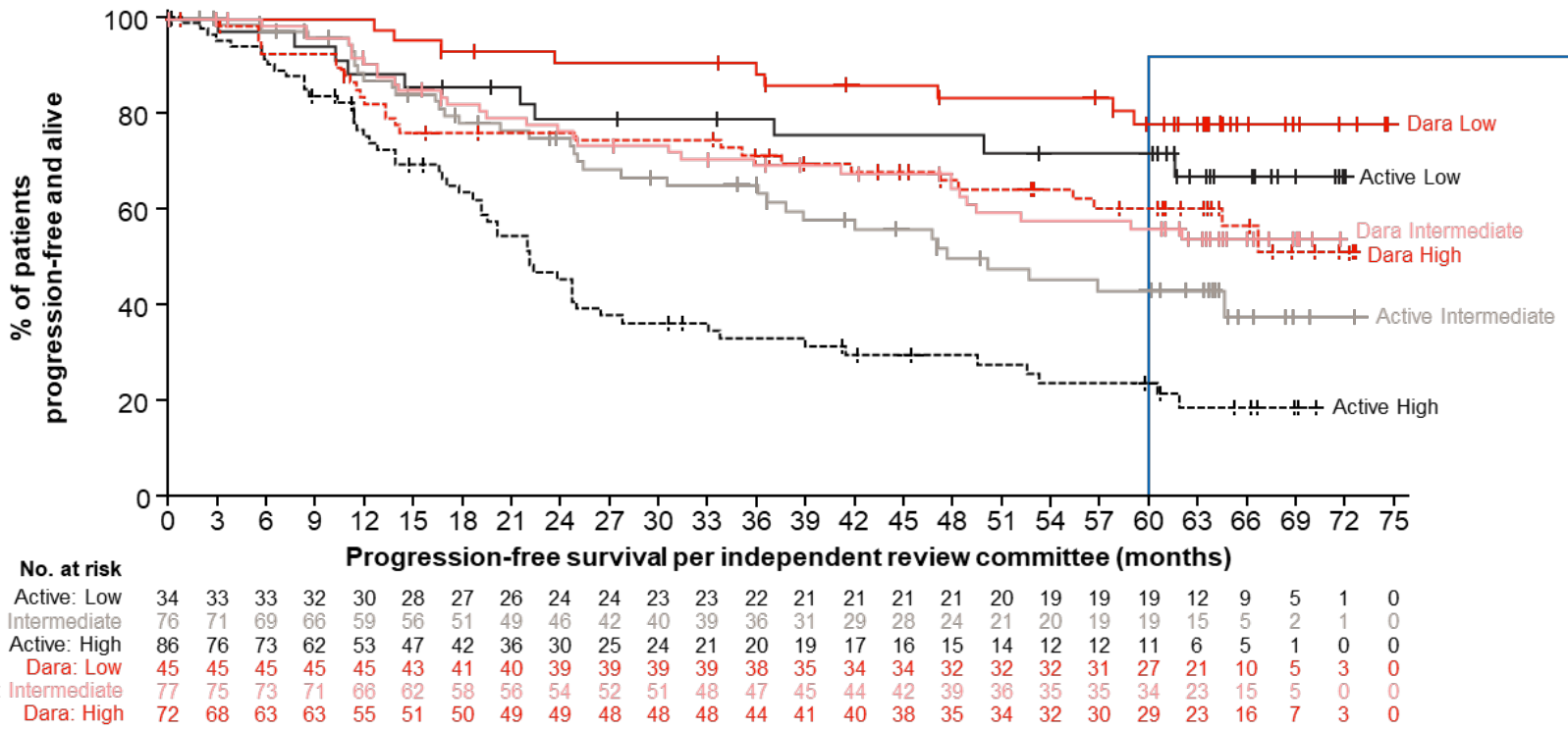
Progression to SLiM-CRAB	Mayo 2018			IMWG 2020
	2-Year	5-Year	10-Year	2 Year
High (≥2 risk factors)	47.4%	81.5%	96.5%	44.2%
Intermediate (1 risk factor)	26.3%	46.7%	65.3%	17.9%
Low (0 risk factors)	9.7%	22.5%	52.7%	6.2%

Risk factors: M protein >2 g/dL, affected to unaffected FLC ratio >20, BMPCs >20%

Lakshman A, et al. Blood Cancer J 2018;8:59.
Mateos M-V, et al. Blood Cancer J 2020;10:102.

AQUILA by IMWG 2020

72 of 194 patients in the daratumumab arm (37.1%) and 86 of 196 patients in the active monitoring arm (43.9%) met criteria for high-risk smoldering myeloma by IMWG 2020 criteria



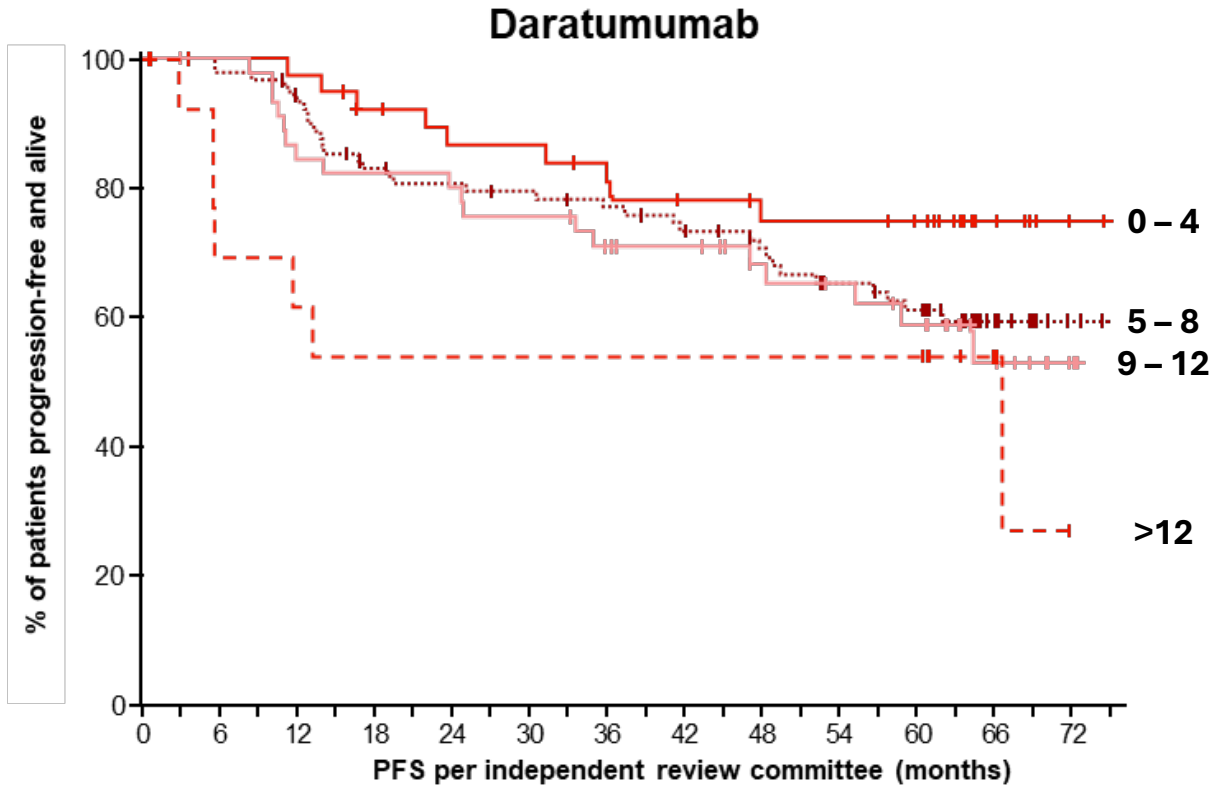
60-month PFS rates, %:

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)

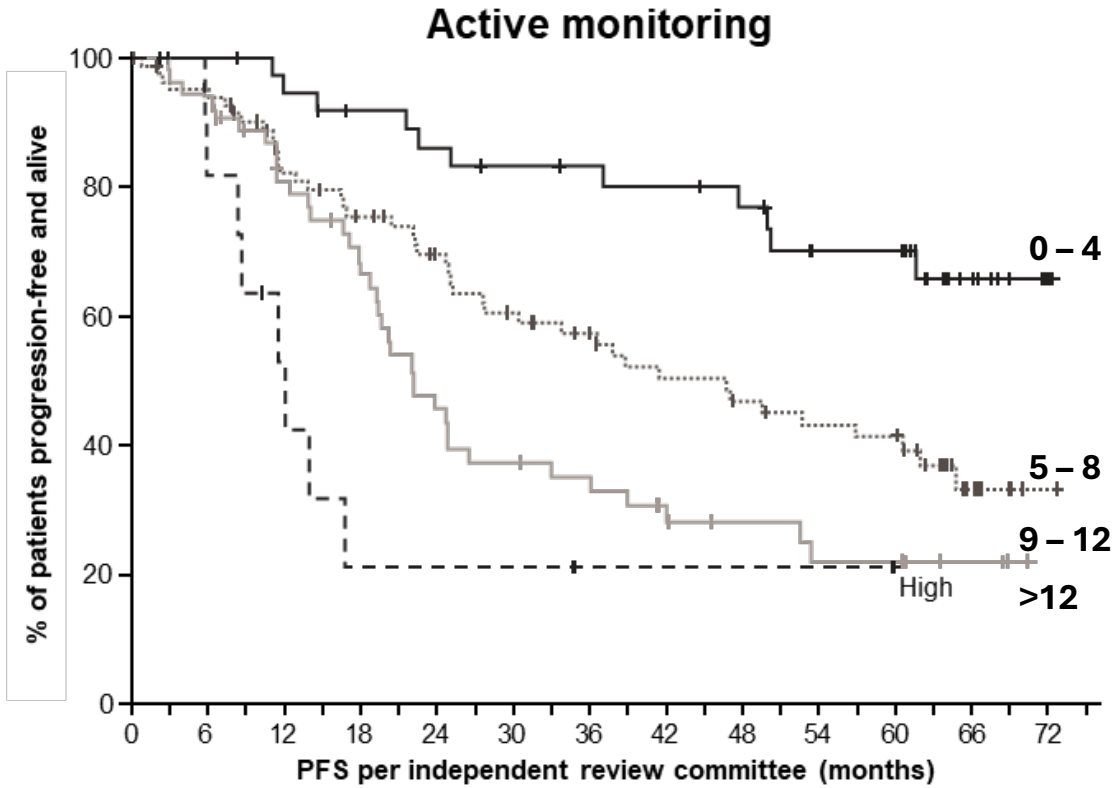
Voorhees P et al. ASH 2025.

AQUILA by IMWG Scoring System



No. at risk

Dara: Low	41	40	39	39	38	37	34	33	31	31	31	30	29	26	25	25	23	23	23	23	21	15	6	3	1	0
Dara: Low/intermediate	91	90	88	87	82	75	71	68	68	67	66	64	63	60	58	56	53	50	48	46	44	33	22	9	3	0
Dara: Intermediate	48	46	45	44	38	37	37	37	36	34	34	34	30	28	28	26	23	22	21	20	18	14	9	4	2	0
Dara: High	14	12	9	9	8	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	5	4	1	0	0



No. at risk

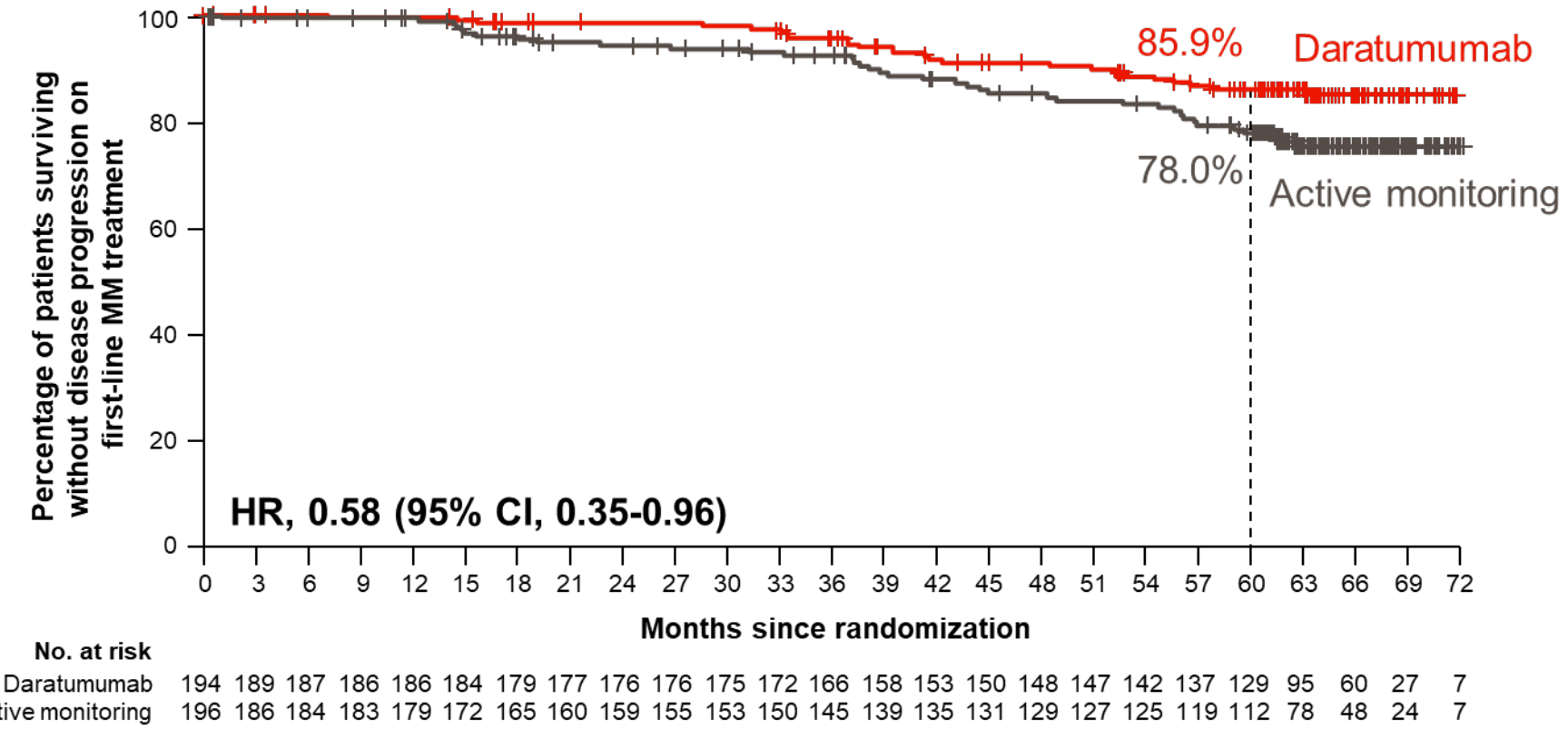
Active: Low	39	38	38	37	35	33	32	32	30	29	28	28	27	26	26	25	24	21	20	20	20	14	9	4	1	0
Active: Low/intermediate	87	78	77	71	62	58	54	51	46	42	39	37	34	30	29	29	26	24	23	22	22	15	7	3	1	0
Active: Intermediate	57	53	51	45	40	37	32	26	22	18	18	16	16	14	11	10	9	9	7	7	7	4	3	1	0	0
Active: High	13	11	9	7	5	3	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0

- **M protein (g/dL):** 0 – 1.5 g/dL: 0 points; >1.5 – 3: 3 points; >3: 4 points
- **Affected to unaffected FLC ratio:** 0 – 10: 0 points; >10 – 25: 2 points; >25 – 40: 3 points; >40: 5 points
- **BMPCs (%): 0 – 15: 0 points;** >15 – 20: 2 points; >20 – 30: 3 points; >30 – 40: 5 points; >40: 6 points
- **Cytogenetics [t(4;14), t(14;16), del(13q) or monosomy 13, gain(1q21)]:** No: 0 points; Yes: 2 points

Voorhees P et al. ASH 2025.

Early intervention could negatively impact treatment for active myeloma

AQUILA: PFS2



- VRd most common first-line regimen:
  - 29.7% (19/64) in DARA arm
  - 27.6% (29/105) in active monitoring arm
- Received anti-CD38 mAb-based therapy (varied):
  - 25.0% (16/64) in DARA arm
  - 33.3% (35/105) in active monitoring arm

VRd, bortezomib/lenalidomide/dexamethasone; mAb, monoclonal antibody. [a]PFS2 was defined as the time from randomization to progression on first-line treatment for MM or death, whichever occurred first.
Adapted with permission © The *New England Journal of Medicine* (2024).

Most patients on this study with access to CD38 mAb-based therapy as part of 2nd line therapy for active myeloma

Dimopoulos MA et al. ASH 2024.

Progression-free survival is not clinically meaningful

SLiM-CRAB Disease Progression Events in AQUILA

	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (2.6)	5 (2.6)
Disease progression	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 BMPCs	5 (2.6)	16 (8.2)
Serum FLC	33 (17.0)	33 (16.8)
Focal lesion by MRI	12 (6.2)	16 (8.2)

- More CRAB events in the active monitoring arm
  - Most were anemia or new lytic bone lesions
  - Symptoms related to anemia and bone-related events not captured
- More SLiM events in the active monitoring arm
- SLiM events were more common than CRAB events in both arms

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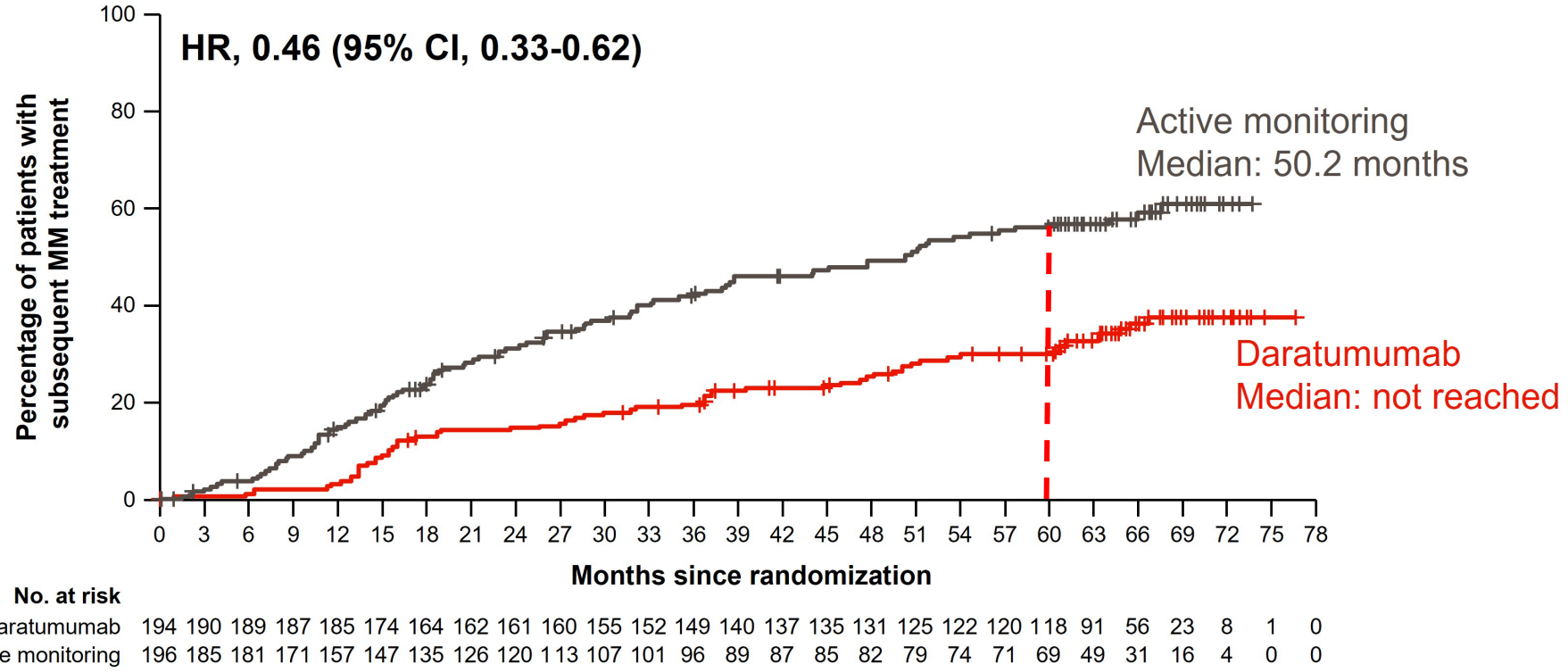
Time to Next Treatment in AQUILA



- The likelihood of requiring active myeloma treatment in 5 years:
  - 29.7% in the DARA group
  - 55.9% in the active monitoring group
- First-line treatment for MM was initiated by:
  - 33.2% (64/193) in the DARA group
  - 53.6% (105/196) in the active monitoring group

Is a delay in the need for multiagent myeloma therapy valuable?

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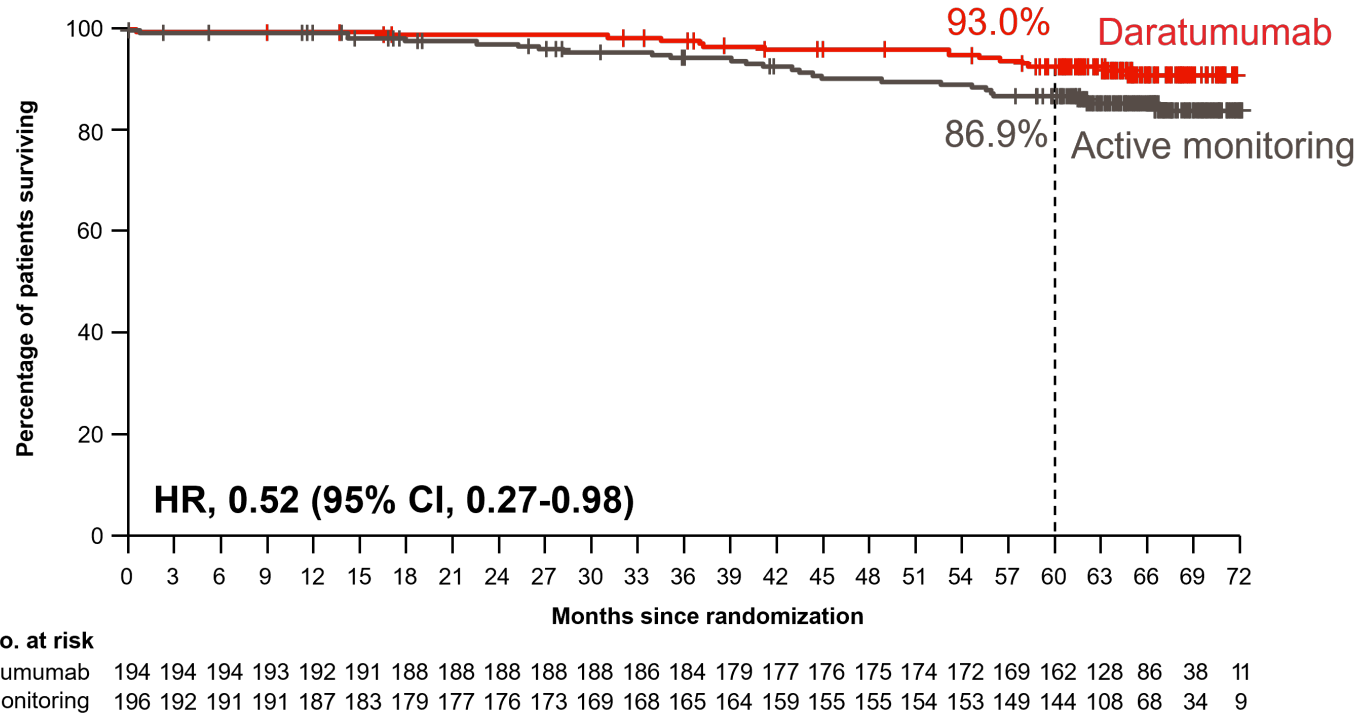
Overall Survival in AQUILA



	DARA (n = 194)	Active monitoring (n = 196)
Deaths, n (%)	15 (7.7)	26 (13.3)
Primary cause, n		
Disease progression	3	9
AE	2	4
Other*	10	13

*Deaths due to an event occurring after the AE reporting window (ie, events that happened after patient started subsequent therapy or >30 days after last dose) or deaths with unknown reason.

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Why subject patients to side effects of treatment for an asymptomatic condition?

Adverse Events of Special Interest in AQUILA

Event, n (%)	DARA (n = 193)	Active monitoring (n = 196)
Systemic infusion-related reactions	32 (16.6)	–
Grade 3 or 4	2 (1.0)	–
Local injection-site reactions	53 (27.5)	–
Grade 3 or 4	0	–
Second primary malignancies	18 (9.3)	20 (10.2)
Noncutaneous	9 (4.7)	11 (5.6)
Cutaneous	7 (3.6)	3 (1.5)
Hematologic	3 (1.6)	6 (3.1)

Event, n (%)	DARA (n = 193)	Active monitoring (n = 196)
Cytopenias (all grades)	23 (11.9)	24 (12.2)
Neutropenia	13 (6.7)	5 (2.6)
Anemia	9 (4.7)	19 (9.7)
Thrombocytopenia	4 (2.1)	3 (1.5)
Lymphopenia	3 (1.6)	1 (0.5)
Grade 3 or 4 infections	31 (16.1)	9 (4.6)
Number of grade 3 or 4 infections	37	11
Recovered or resolved	35 (94.6)	8 (72.7)
Median duration of infection	9 days	5 days

6.7% vs 0.5% of patients discontinued therapy due to AEs

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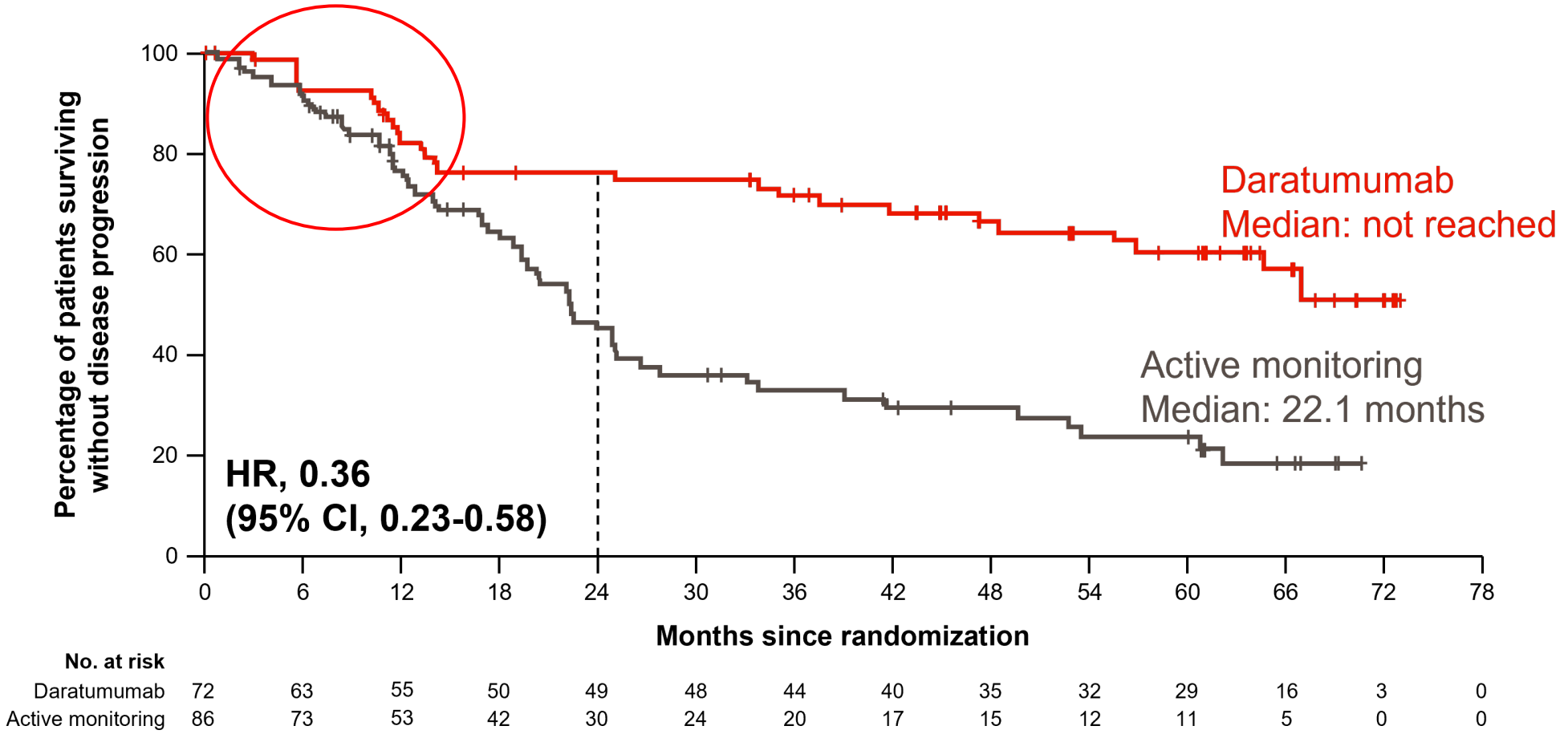
You are undertreating patients

AQUILA by IMWG 2020



How do we better identify the highest risk patients in need of more aggressive therapy?

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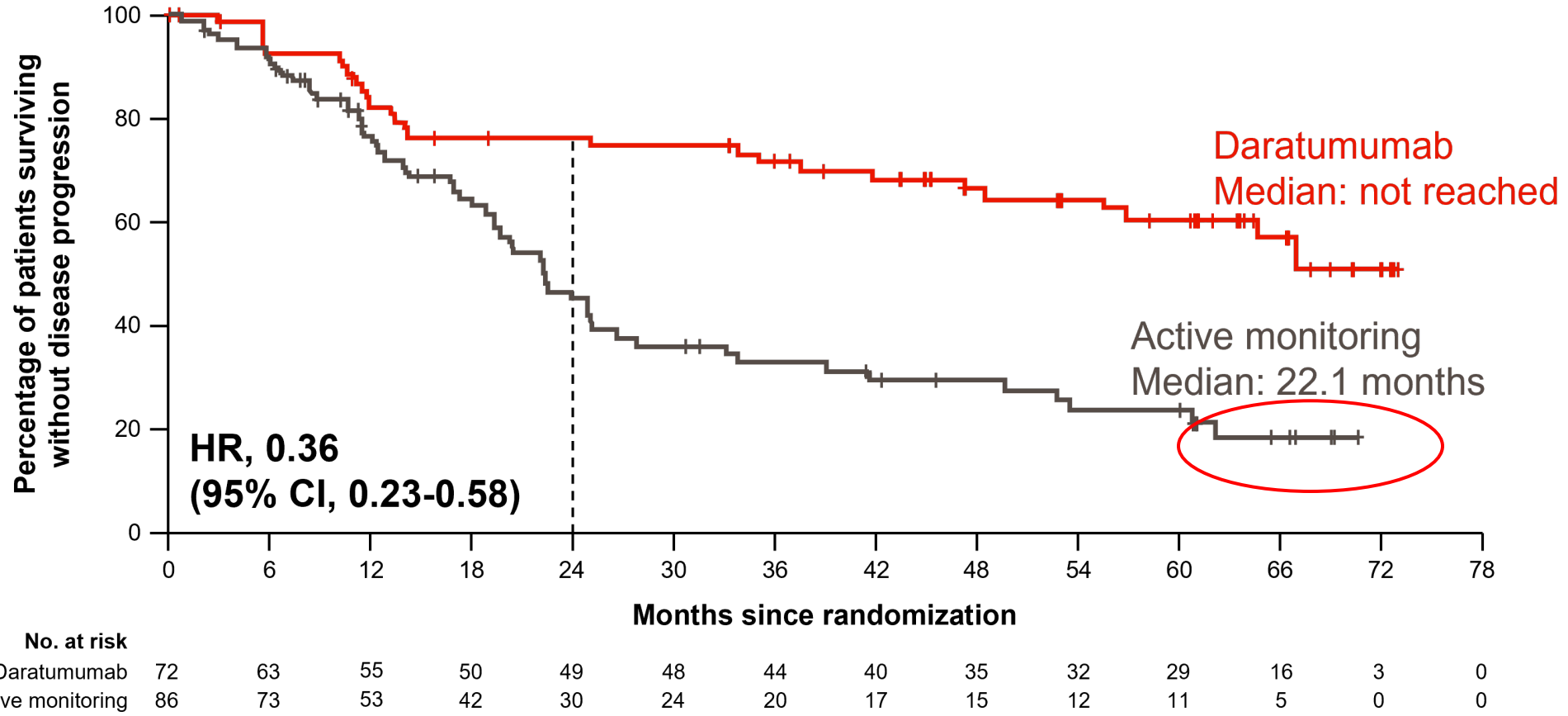
You are overtreating patients

AQUILA by IMWG 2020



- **23.6% of patients in the active monitoring arm did not progress to active myeloma over 5 years**
  - **How do we better identify the patients who do not need any therapy?**

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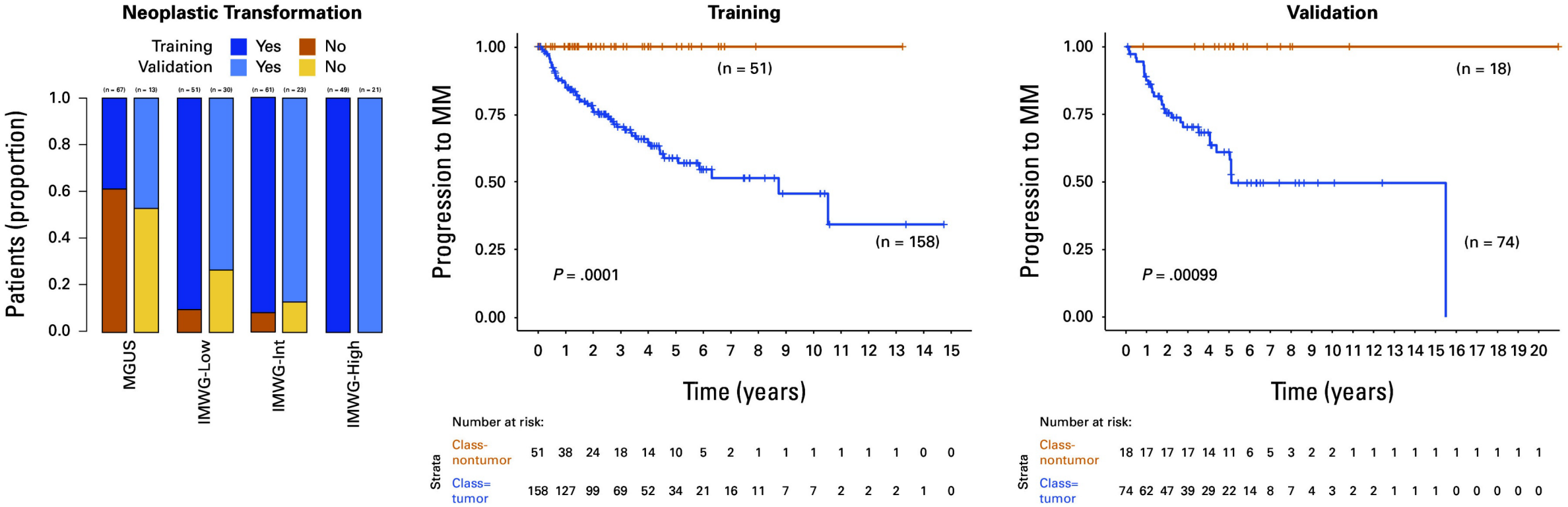
Genomically-Defined MGUS vs Myeloma

MGUS vs Myeloma determination based on 28 Myeloma Genomic Defining Events associated with progression to active myeloma



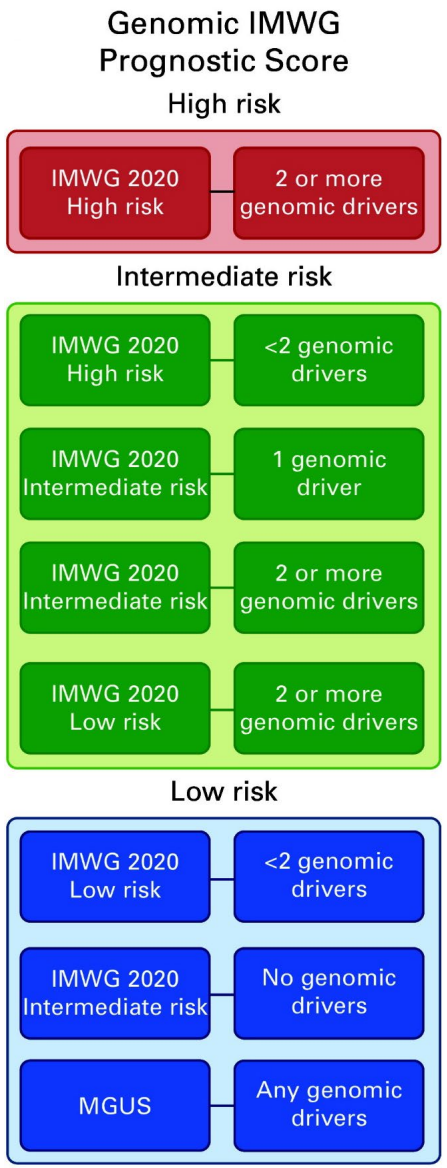
Genomic MGUS does not progress to active myeloma

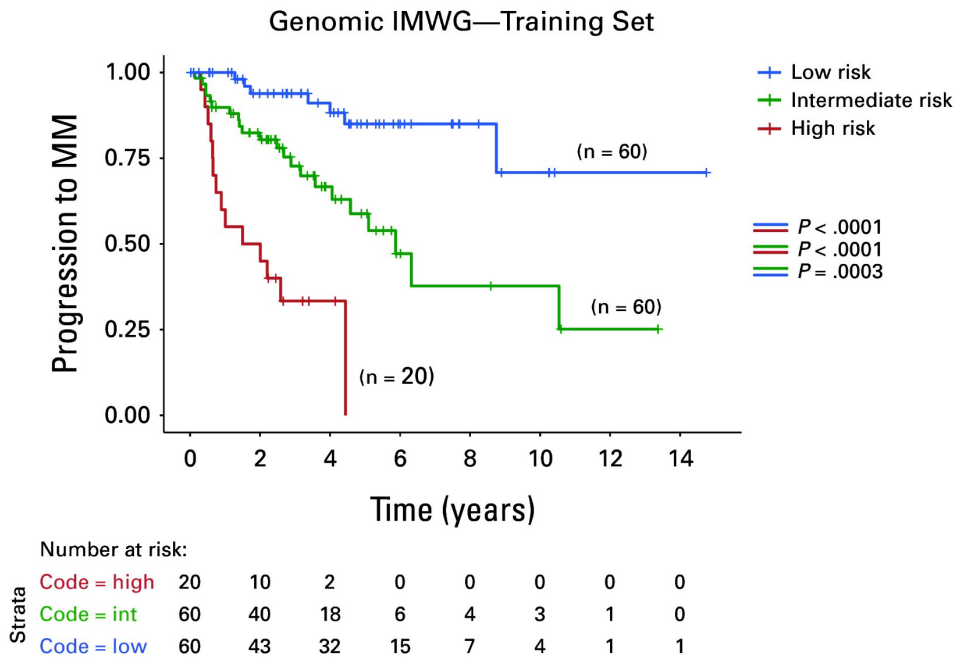
- 5 of 62 patients (8%) enrolled onto interventional trials for high-risk smoldering myeloma were classified as genomic MGUS

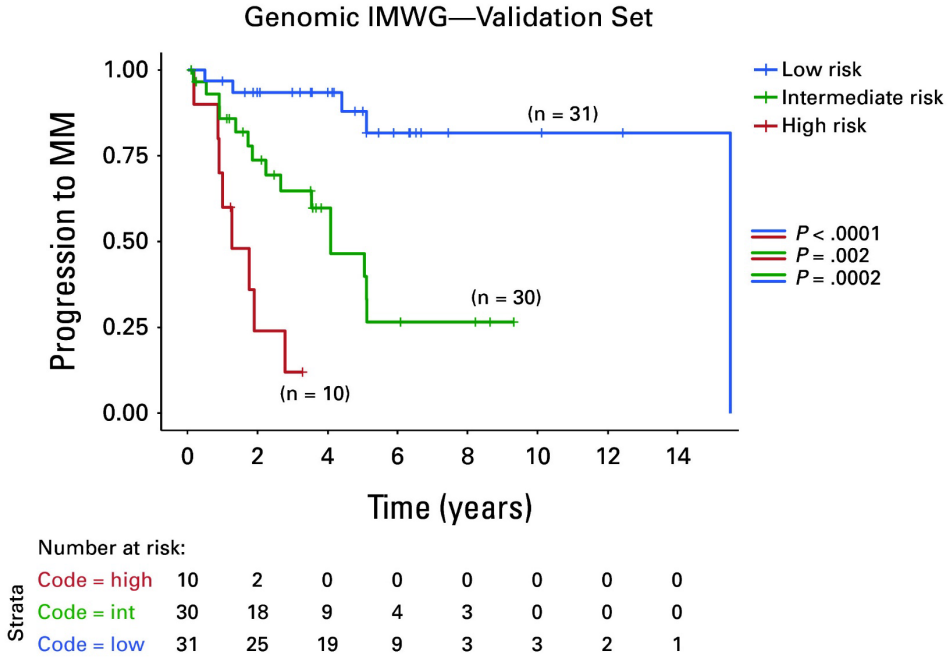
Genomic active myeloma is clinically heterogeneous

Maura F, et al. J Clin Oncol 2026;44:188-99.

Genomic and Clinical Risk Stratification of Smoldering Myeloma



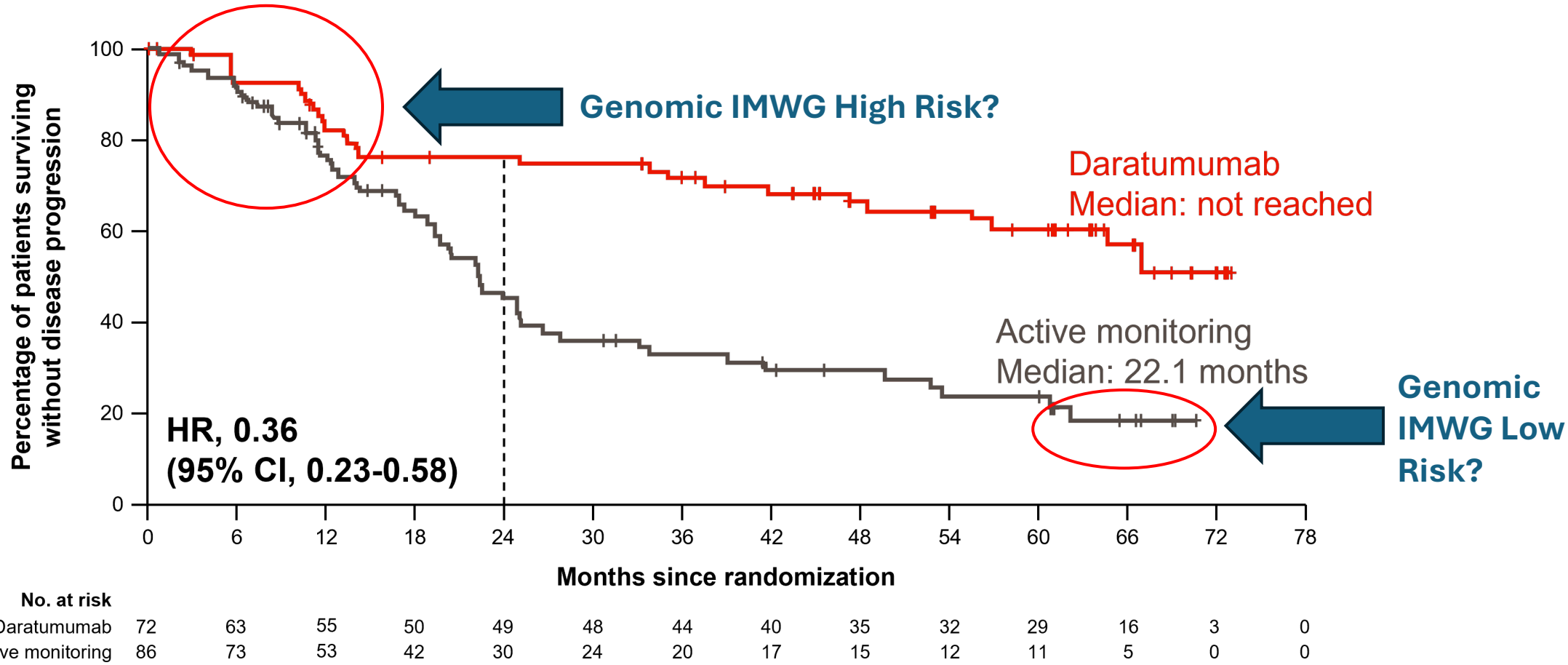




Genomic Drivers of SMM Progression: RAS mutations, genomic events involving MYC, neoplastic CNV signatures, APOBEC mutagenesis

Maura F, et al. J Clin Oncol 2026;44:188-99.

AQUILA: Outcomes by IMWG 2020



Dimopoulos MA et al. ASH 2024.

48-year-old woman screened for myeloma as part of a work-up for an elevated serum total protein.

Is daratumumab monotherapy appropriate?

Scenario #1

- CBC, Cr, Ca normal
- IgA kappa M spike 1.2 g/dL
- Serum free kappa light chains 22.5 mg/L, FLC ratio 2.3
- BMBx: 30% PCs by CD138 IHC
- FISH: +t(11;14)
- Whole body MRI: No focal bone lesions

IMWG 2020: Intermediate risk
IMWG Score: 3
Treatment appropriate? NO

Scenario #2

- CBC, Cr, Ca normal
- IgG kappa M spike 2.6 g/dL
- Serum free kappa light chains 360 mg/L, FLC ratio 28
- BMBx: 20% PCs by CD138 IHC
- FISH: +del(13q)
- Whole body MRI: No focal bone lesions

IMWG 2020: High risk
IMWG Score: 10
Treatment appropriate? YES

Scenario #3

- CBC, Cr, Ca normal
- IgG kappa M spike 3.2 g/dL
- Serum free kappa light chains 420 mg/L, FLC ratio 54
- BMBx: 50% PCs by CD138 IHC
- FISH: +gain 1q21, t(4;14)
- Whole body MRI: No focal bone lesions

IMWG 2020: High risk
IMWG Score: 17
Treatment appropriate? NO

Conclusions

- **Daratumumab monotherapy is an appropriate standard of care for smoldering myeloma patients**
  - **Restrict treatment to IMWG 2020 high risk patients!!!**
  - The IMWG score and PANGEA 2.0 can further inform decision making
  - Patients need to understand the risks: Not curative, could close doors on future clinical trial opportunities in current state, impact on subsequent CD38 mAb-based therapy not well defined.
- **Progression to SLiM-CRAB is an appropriate primary endpoint for SMM trials**
  - OS not feasible as a primary endpoint but a key secondary endpoint to establish safety and risk-benefit of new therapies
  - Capture of time to therapy for active myeloma and performance of subsequent therapy key
  - QoL and PROs are critical
    - What level of toxicity are we willing to accept for a disease control vs curative strategy?
    - Rigorous capture of symptoms related to myeloma progression is key
- **Define your patient population well**
  - IMWG 2020 works
  - Genomic MGUS should not be allowed on smoldering myeloma studies
- **Daratumumab represents a new benchmark against which new therapies should be measured**

Needs Going Forward

- **Clarify role of MRD as an endpoint in SMM trials**
  - What is the magnitude of MRD- benefit needed to see an improvement in SLiM-CRAB PFS? OS?
- **Improve the definition of high-risk smoldering myeloma**
  - Genetic markers, immune markers, micro-biome
  - Incorporation of evolving disease markers (e.g. PANGEA 2.0)
- **Allowance of prior therapy in clinical trials for newly diagnosed active myeloma**
- **Randomized studies of other treatment paradigms for intervention in smoldering myeloma**
  - Proactive (e.g. AQUILA) vs reactive (at biochemical progression or evolution of smoldering myeloma).
  - Control vs eradication (LINKER-SMM2: Linvo vs Dara)
  - When to treat previously treated smoldering myeloma: Biochemical PD vs SLiM-CRAB PD?