# Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

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# AQUILA: Study Design

**AQUILA enrollment period: December 2017 to May 2019 at 124 sites in 23 countries**

## Screening

**Key eligibility criteria:**

- ≥18 years of age
- Confirmed SMM diagnosis (per IMWG criteria) for ≤5 years
- ECOG PS score of 0 or 1
- Clonal BMPCs ≥10% and ≥1 of the following risk factors:
  - Serum M-protein ≥30 g/L
  - IgA SMM
  - Immunoparesis with reduction of 2 uninvolved Ig isotypes
  - Serum involved:uninvolved FLC ratio ≥8 and <100
  - Clonal BMPCs >50% to <60%

All patients were required to have CT/PET-CT and MRI imaging during screening

1:1 randomization (N = 390)

Stratified by number of risk factors[a] for progression to MM (<3 vs ≥3)

## Treatment/active monitoring phase

**DARA monotherapy**

**1800 mg SC[b] QW Cycles 1-2, Q2W Cycles 3-6, Q4W thereafter in 28-day cycles until 39 cycles/36 months***

**Active monitoring**

**No disease-specific treatment, with AE monitoring up to 36 months***

*Or confirmed disease progression (whichever occurred first).

**Disease evaluation schedule**

- Laboratory efficacy – Every 12 weeks by central lab until disease progression
- Imaging (CT/PET-CT, MRI) – Yearly (central review)
- Bone marrow – At least every 2 years

## Follow-up phase

- Efficacy follow-up until progression by SLiM-CRAB
- Survival follow-up every 6 months until end of study

**Primary endpoint:**

- PFS by IRC per IMWG SLiM-CRAB criteria[c]

**Key secondary endpoints:**

- ORR
- Time to first-line treatment for MM
- PFS on first-line treatment for MM
- Overall survival

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.



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# AQUILA: Baseline Demographics and Disease Characteristics

| Characteristic | DARA (n = 194) | Active monitoring (n = 196) |
|---|---|---|
| Age | | |
| Median (range), years | 63.0 (31-86) | 64.5 (36-83) |
| 18 to <65 years, n (%) | 106 (54.6) | 98 (50.0) |
| 65 to <75 years, n (%) | 67 (34.5) | 74 (37.8) |
| ≥75 years, n (%) | 21 (10.8) | 24 (12.2) |
| Sex, n (%) | | |
| Female | 99 (51.0) | 103 (52.6) |
| Male | 95 (49.0) | 93 (47.4) |
| ECOG PS score, n (%) | | |
| 0 | 165 (85.1) | 160 (81.6) |
| 1 | 29 (14.9) | 36 (18.4) |
| Median time from diagnosis of SMM to randomization (range), years | 0.80 (0-4.7) | 0.67 (0-5.0) |
| Median BMPCs (range), % | 20.0 (8.0-59.5) | 20.0 (10.0-55.0) |

| Characteristic | DARA (n = 194) | Active monitoring (n = 196) |
|---|---|---|
| Type of SMM, n (%) | | |
| IgG | 127 (65.5) | 138 (70.4) |
| IgA | 55 (28.4) | 42 (21.4) |
| Other | 12 (6.2) | 16 (8.2) |
| AQUILA risk factors for progression to MM, n (%)[a] | | |
| <3 | 154 (79.4) | 156 (79.6) |
| ≥3 | 40 (20.6) | 40 (20.4) |
| Cytogenetic risk profile[b] | n = 167 | n = 170 |
| ≥1 of del(17p), t(4;14), and/or t(14;16), n (%) | 29 (17.4) | 22 (12.9) |
| Mayo 2018 risk criteria, n (%)[c] | | |
| Low | 45 (23.2) | 34 (17.3) |
| Intermediate | 77 (39.7) | 76 (38.8) |
| High | 72 (37.1) | 86 (43.9) |

**Baseline characteristics were generally balanced between groups**

[a]Risk factors: serum M-protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved:uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease. [b]Cytogenetic risk was assessed by fluorescence in situ hybridization. [c]Mayo 2018 risk criteria: serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%. Patients with 0 factors = low risk, 1 factor = intermediate risk, ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J*. 2018;8(6):59).



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# AQUILA: Treatment or Active Monitoring Disposition

| | DARA | Active monitoring |
|---|---|---|
| Randomized patients (ITT population), n | 194 | 196 |
| Median (range) duration of DARA or monitoring, months | 35.0 (0-36.1) | 25.9 (0.1-36.0) |
| Median (range) number of DARA cycles | 38 (1-39) | – |
| Patients who discontinued treatment/monitoring, n (%)[a] | 66 (34.2) | 116 (59.2) |
| Reason for treatment/monitoring discontinuation, n (%)[a] | | |
| Progressive disease | 42 (21.8) | 82 (41.8) |
| AE[b] | 13 (6.7) | 1 (0.5) |
| Patient refused further treatment/monitoring | 5 (2.6) | 22 (11.2) |
| Physician decision | 3 (1.6) | 1 (0.5) |
| Death | 1 (0.5) | 4 (2.0) |
| Other | 2 (1.0) | 6 (3.1) |

**The low rate of DARA discontinuation due to AEs suggests DARA was well tolerated**

ITT, intent-to-treat. [a]Percentages based on the number of patients treated or monitored. [b]Includes 2 patients who discontinued DARA due to AEs that occurred >30 days after the last dose of DARA and therefore were not considered "treatment-emergent." AEs leading to discontinuation were not necessarily considered related to DARA or active monitoring.



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# AQUILA: Study Disposition

| | DARA | Active monitoring |
|---|---|---|
| Randomized patients (ITT population), n | 194 | 196 |
| Median (range) follow-up, months | 65.2 (0-76.6) | |
| Patients ongoing in follow-up, n (%) | 163 (84.0) | 145 (74.0) |
| Patients who discontinued the study, n (%) | 30 (15.5) | 51 (26.0) |
| Reason for study discontinuation, n (%) | | |
| Death | 15 (7.7) | 26 (13.3) |
| Withdrawal by patient | 12 (6.2) | 23 (11.7) |
| Lost to follow-up | 1 (0.5) | 1 (0.5) |
| Other | 2 (1.0) | 1 (0.5) |

- **Patient retention on the study was excellent with most patients in ongoing follow-up**
- **Deaths leading to study discontinuation were nearly double with active monitoring**

Percentages are based on the number of patients in the ITT population.



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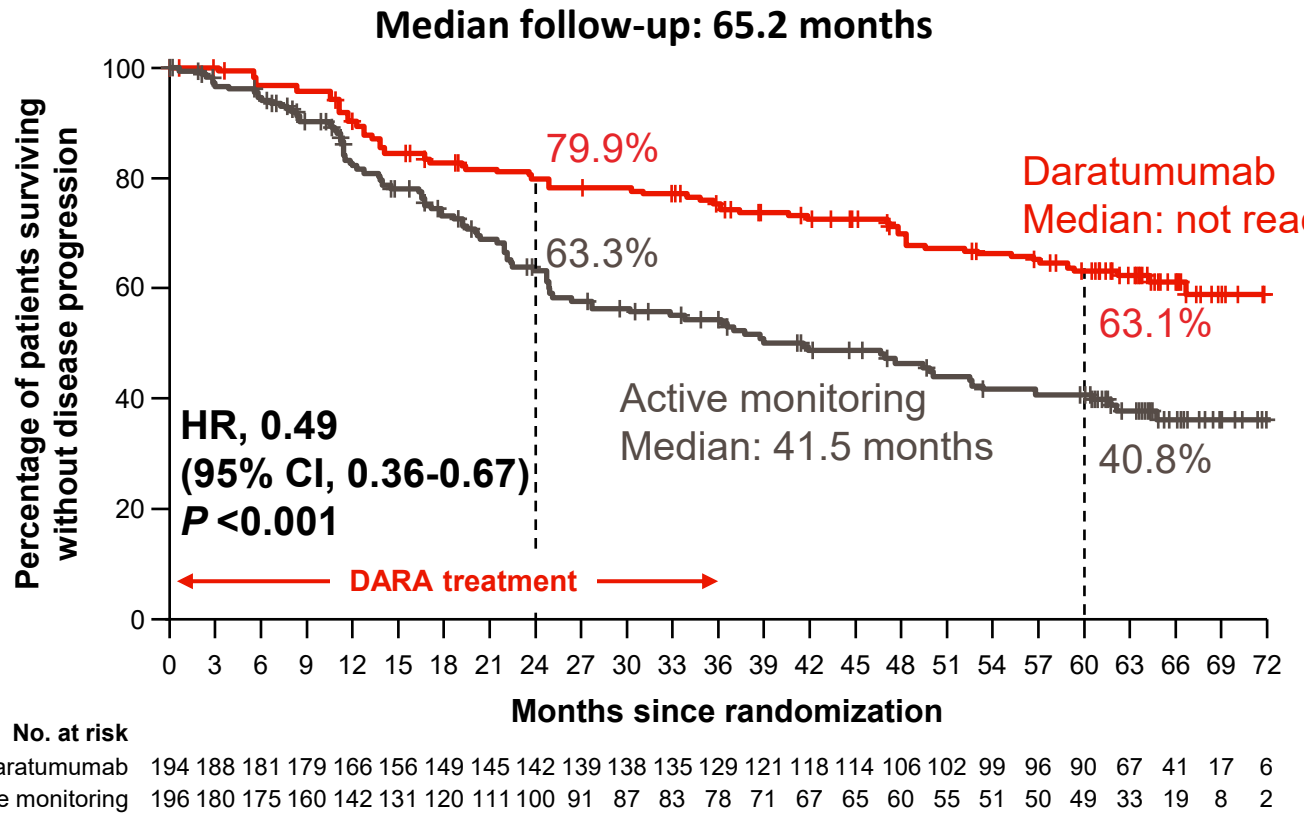
# AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria (IRC Assessment)




| | 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[a] | 62 (32.0) | 94 (48.0) |
| CRAB criteria | 12 (6.2) | 34 (17.3) |
| Calcium elevation | 0 | 2 (1.0) |
| Renal insufficiency[b] | 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) |

**DARA significantly reduced the risk of progression to MM or death by 51% versus active monitoring; the benefit continued beyond 36 months**

HR, hazard ratio; CI, confidence interval. [a]A patient may show disease progression based on ≥1 criterion. [b]Some patients met the CRAB criteria for renal insufficiency, but the investigator attributed this to a cause other than disease progression to MM. Adapted with permission © The *New England Journal of Medicine* (2024).



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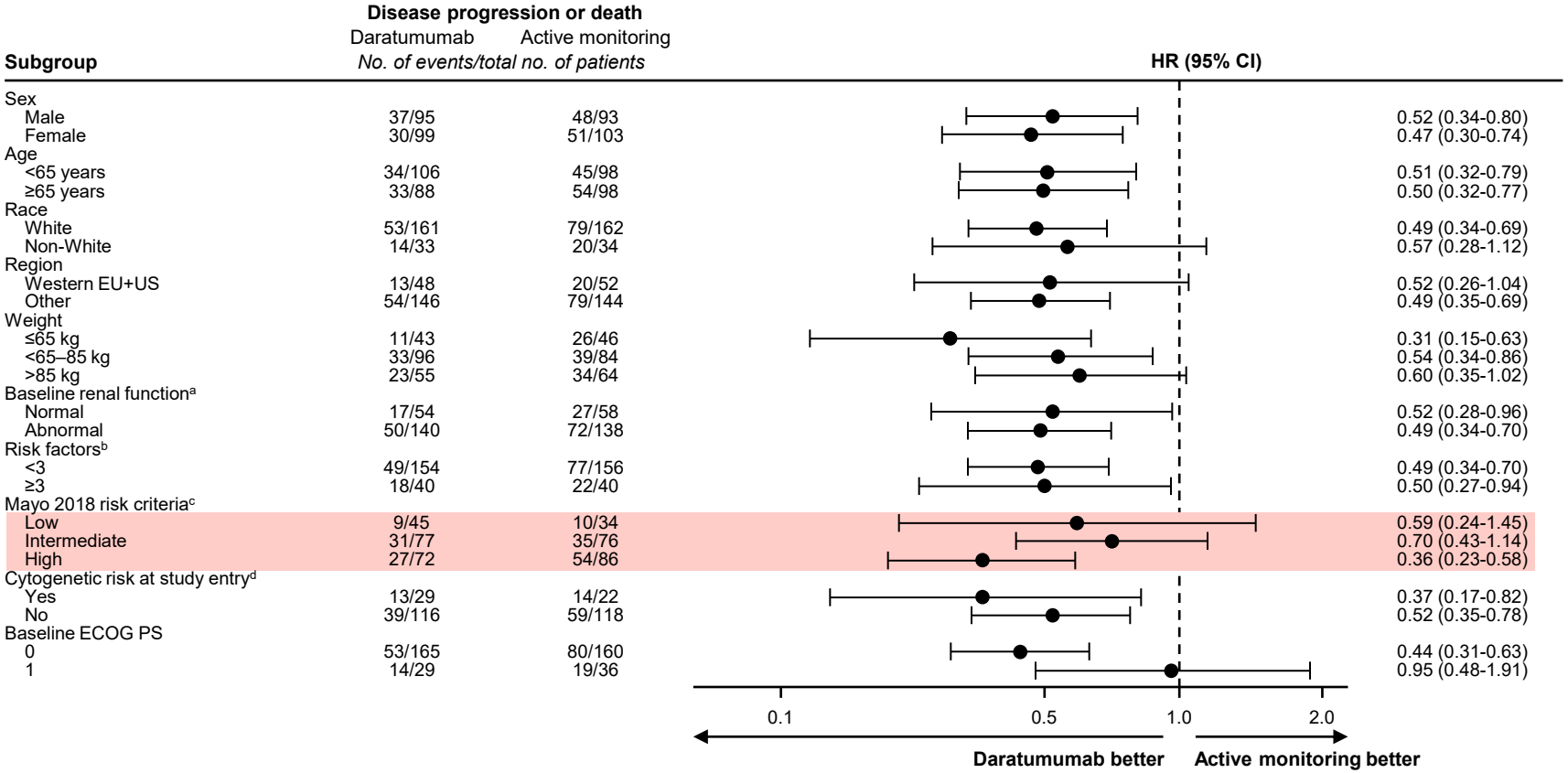
# AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria in Prespecified Subgroups




**PFS benefit with DARA was seen across all prespecified subgroups, including all Mayo 2018 risk criteria groups**

[a]Normal renal function is a glomerular filtration rate ≥90 mL/min/1.73 $m^2$. [b]Risk factors were serum M-protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, serum involved:uninvolved FLC ratio ≥8 and <100, or clonal BMPCs >50% to <60% with measurable disease. [c]Mayo 2018 risk was retrospectively assessed; criteria included serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%. Patients with 0 factors = low risk, 1 factor = intermediate risk, ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J*. 2018;8(6):59). [d]Cytogenetic risk was assessed by fluorescence in situ hybridization; "yes" = presence of del(17p), t(4;14), or t(14;16) and "no" = testing for these probes but no abnormality. Reproduced with permission © The *New England Journal of Medicine* (2024).



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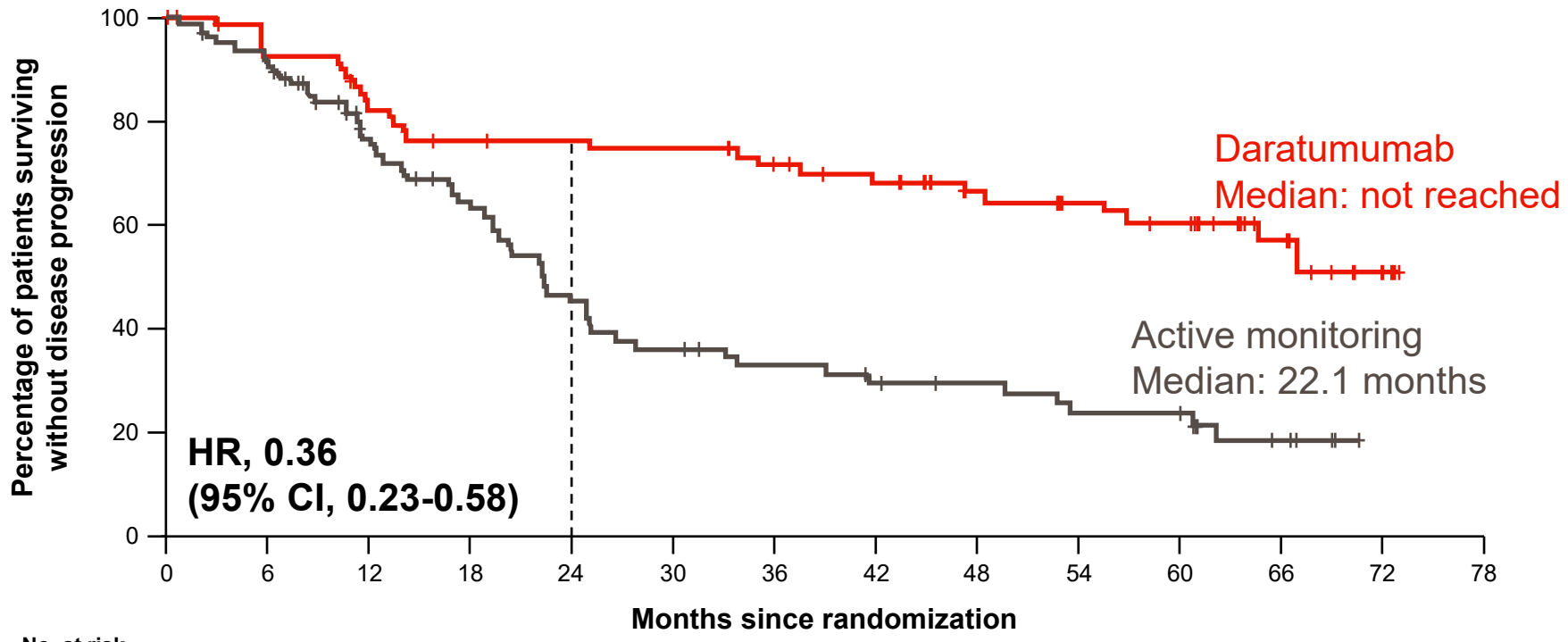
# AQUILA: Progression to MM by IMWG SLiM-CRAB Criteria in Patients With High Risk per Mayo 2018 Criteria




| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Daratumumab | 72 | 63 | 55 | 50 | 49 | 48 | 44 | 40 | 35 | 32 | 29 | 16 | 3 | 0 |
| Active monitoring | 86 | 73 | 53 | 42 | 30 | 24 | 20 | 17 | 15 | 12 | 11 | 5 | 0 | 0 |

- Retrospective review of high risk per Mayo 2018 criteria showed median PFS was not reached for DARA vs 22.1 months for active monitoring
- The benefit of DARA was sustained after completing treatment
- The majority of patients remained DARA sensitive

**PFS benefit with DARA was most pronounced using the current Mayo 2018 (20/2/20) criteria for high-risk SMM**

Mayo 2018 risk was retrospectively assessed; criteria included serum M-protein >2 g/L, involved:uninvolved FLC ratio >20, and clonal BMPCs >20%.
Patients with ≥2 factors = high risk (Lakshman A, et al. *Blood Cancer J*. 2018;8(6):59).



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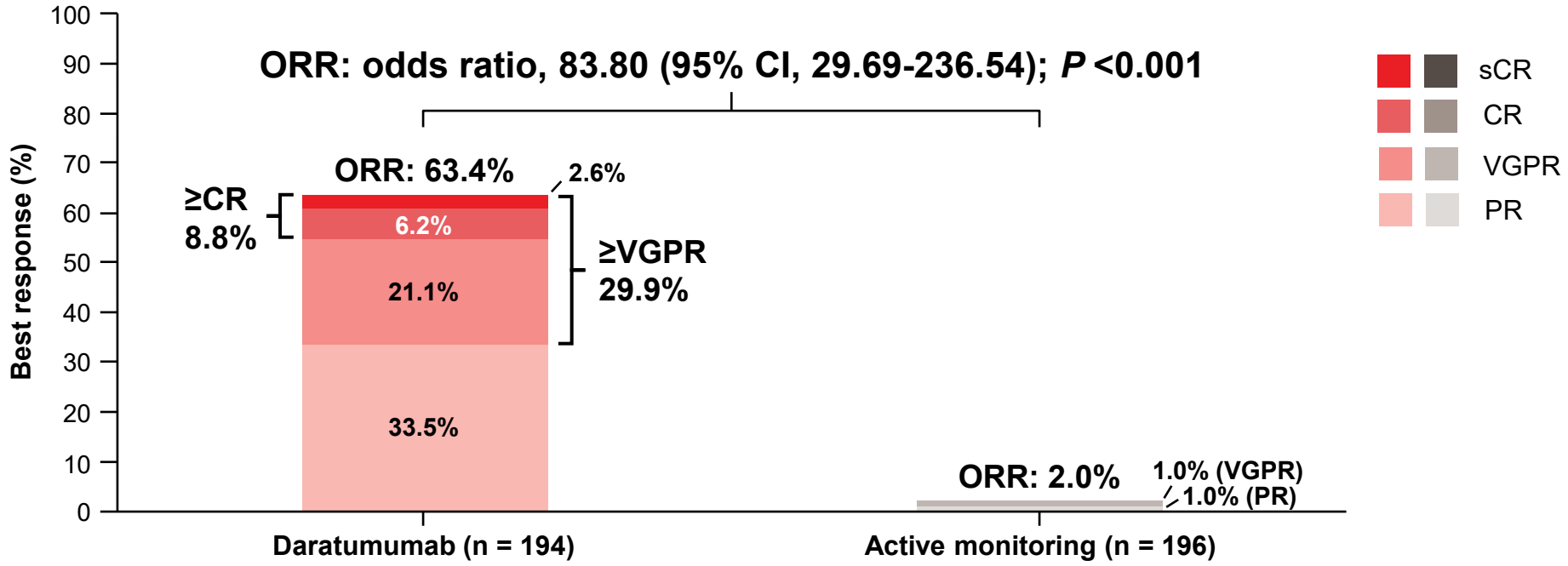
# AQUILA: Response Rates




**Overall response rate was 63.4% with DARA**

ORR, overall response rate; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response. ORR was defined as the proportion of patients with sCR, CR, VGPR, or PR based on computerized algorithm per the IMWG response criteria before the start of subsequent antimyeloma treatment. In the active monitoring group, 2 VGPRs and 1 PR were due to isolated spike in urine M-protein detection and 1 PR was due to serum M-protein detection. Adapted with permission © The *New England Journal of Medicine* (2024).



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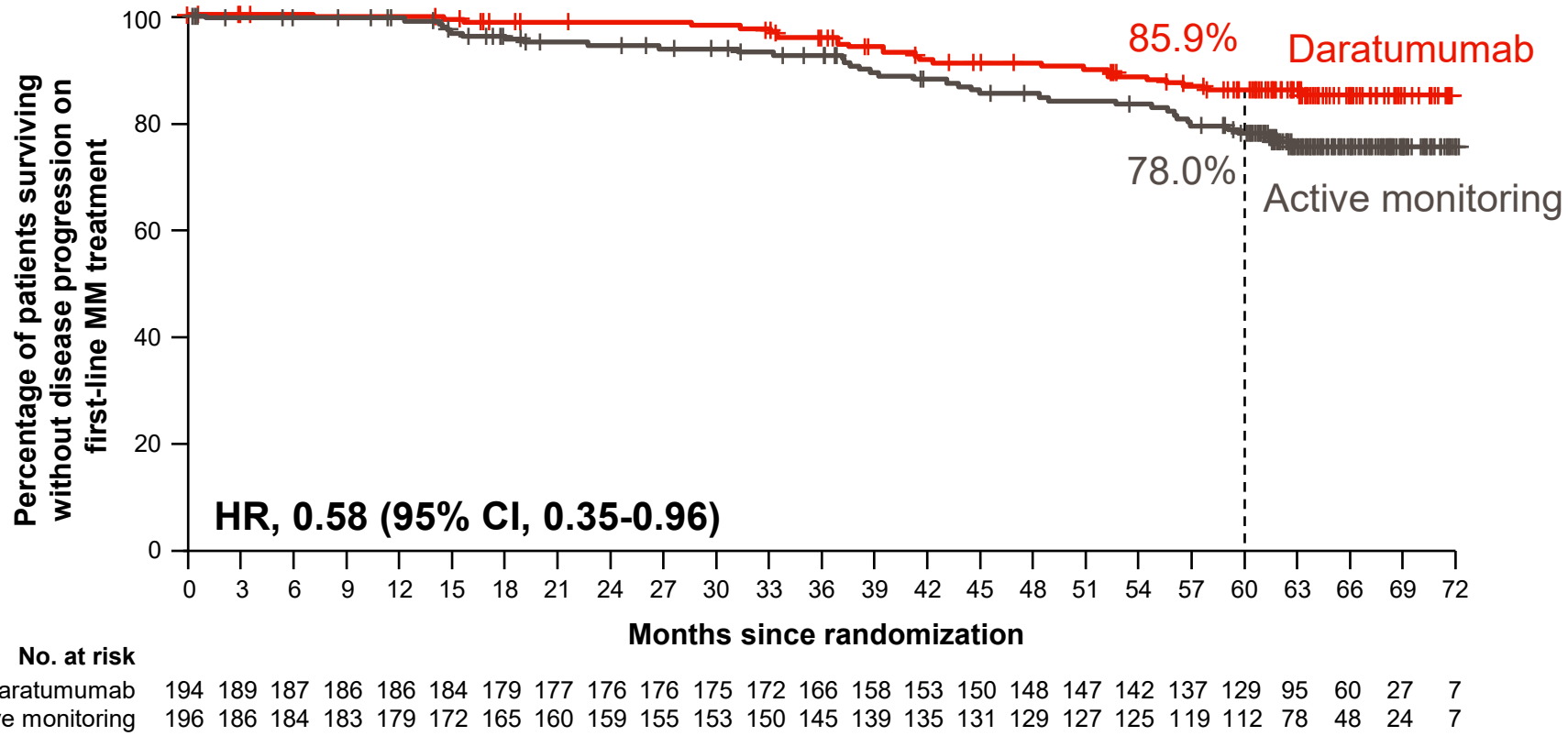
# AQUILA: PFS on First-line Treatment for MM (PFS2)[a]




- 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

**DARA improved PFS on first-line treatment for MM versus active monitoring and does not appear to impair later treatment for MM**

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.





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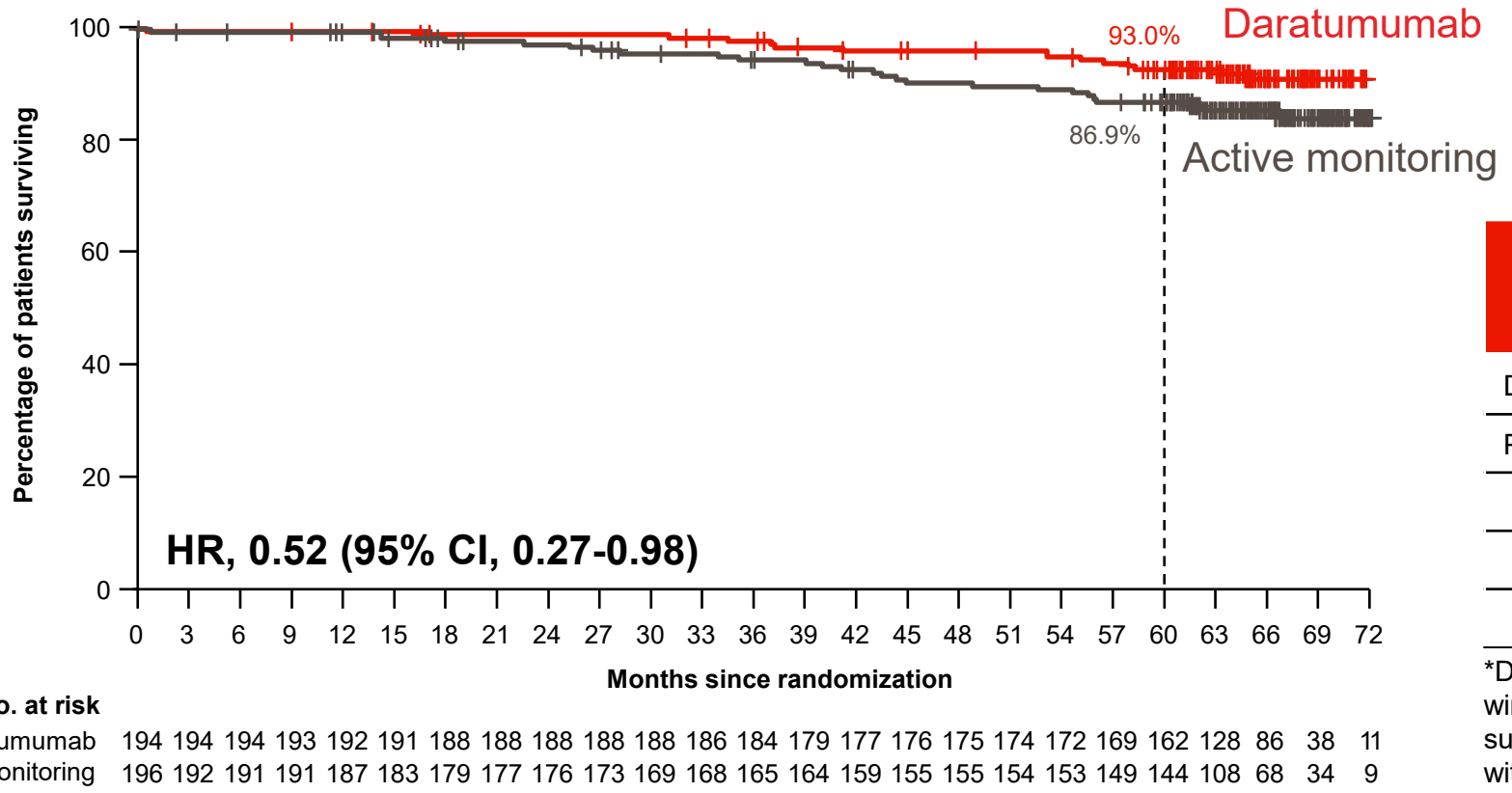
# AQUILA: Overall Survival




| | 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.

**Early intervention with fixed duration DARA extended overall survival versus active monitoring**





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# AQUILA: Safety Overview

| Event, n (%) | DARA (n = 193) | Active monitoring (n = 196) |
|---|---|---|
| Median duration of AE reporting | 35 months | 26 months |
| Any grade TEAEs | 187 (96.9) | 162 (82.7) |
| Grade 3 or 4 TEAEs | 78 (40.4) | 59 (30.1) |
| Most common grade 3 or 4 TEAEs (≥5% in either group) | | |
| Hypertension | 11 (5.7) | 9 (4.6) |
| Serious TEAEs | 56 (29.0) | 38 (19.4) |
| Most common serious TEAEs (≥2% in either group) | | |
| Pneumonia | 7 (3.6) | 1 (0.5) |
| Grade 5 TEAEs[a] | 2 (1.0) | 4 (2.0) |

| Event, n (%) | DARA (n = 193) | Active monitoring (n = 196) |
|---|---|---|
| Treatment discontinuations due to a TEAE[b] | 11 (5.7) | – |
| Dose modifications due to a TEAE[c] | 90 (46.6) | – |
| COVID-19 TEAEs | 17 (8.8) | 10 (5.1) |
| Serious COVID-19 TEAEs | 5 (2.6) | 1 (0.5) |
| Deaths due to COVID-19 | 2 (1.0) | 0 |

**Low rate of DARA discontinuation due to TEAEs, and no new safety concerns were identified**

TEAE, treatment-emergent adverse event. TEAEs include all AEs occurring during the 36-month treatment/monitoring phase or for 30 days after discontinuation of DARA or active monitoring, or until the start of subsequent treatment for MM. [a]Grade 5 TEAEs included COVID-19 infection and COVID-19 pneumonia in the DARA group and pulmonary edema, cardiac arrest, pulmonary embolism, and cardiac failure in the active monitoring group. [b]The most frequently reported TEAEs leading to DARA discontinuation were fatigue, dyspnea, and anxiety (n = 2 each). [c]Dose modifications include dose delays within a cycle, cycle delays, and skipped doses.



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# AQUILA: AEs of Special Interest

| 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 |

- **Grade 3 or 4 infections were of short duration, and the majority recovered or resolved**
- **Comparable frequency of second primary malignancies**



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# AQUILA: Conclusions

- In this large phase 3 study in a well-defined population with high-risk SMM, DARA SC monotherapy for 36 months demonstrated a statistically significant PFS benefit versus active monitoring (HR, 0.49 [95% CI, 0.36-0.67])
  - The greatest PFS benefit with DARA was observed among patients with high-risk SMM retrospectively identified by Mayo 2018 criteria (HR, 0.36 [95% CI, 0.23-0.58])
- DARA prolonged PFS on first-line treatment for MM (HR, 0.58 [95% CI, 0.35-0.96])
- DARA demonstrated a favorable safety profile, with a low rate of treatment discontinuation due to TEAEs
- Patients' health-related quality of life with DARA was maintained compared with active monitoring
- DARA extended overall survival (HR, 0.52 [95% CI, 0.27-0.98])

**AQUILA strongly favored early intervention with DARA monotherapy in patients with high-risk SMM, representing an opportunity to delay or avoid end-organ damage and progression to MM and to extend overall survival**



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ORIGINAL ARTICLE

# Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma

M.A. Dimopoulos, P.M. Voorhees, F. Schjesvold, Y.C. Cohen, V. Hungria, I. Sandhu, J. Lindsay, R.I. Baker, K. Suzuki, H. Kosugi, M.-D. Levin, M. Beksac, K. Stockerl-Goldstein, A. Oriol, G. Mikala, G. Garate, K. Theunissen, I. Spicka, A.K. Mylin, S. Bringhen, K. Uttervall, B. Pula, E. Medvedova, A.J. Cowan, P. Moreau, M.-V. Mateos, H. Goldschmidt, T. Ahmadi, L. Sha, A. Cortoos, E.G. Katz, E. Rousseau, L. Li, R.M. Dennis, R. Carson, and S.V. Rajkumar, for the AQUILA Investigators*

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