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Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma

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ABSTRACT

BACKGROUND

Daratumumab, an anti-CD38 monoclonal antibody, has been approved for the treatment of multiple myeloma. Data are needed regarding the use of daratumumab for high-risk smoldering multiple myeloma, a precursor disease of active multiple myeloma for which no treatments have been approved.

METHODS

In this phase 3 trial, we randomly assigned patients with high-risk smoldering multiple myeloma to receive either subcutaneous daratumumab monotherapy or active monitoring. Treatment was continued for 39 cycles, for 36 months, or until confirmation of disease progression, whichever occurred first. The primary end point was progression-free survival; progression to active multiple myeloma was assessed by an independent review committee in accordance with International Myeloma Working Group diagnostic criteria.

RESULTS

Among the 390 enrolled patients, 194 were assigned to the daratumumab group and 196 to the active-monitoring group. With a median follow-up of 65.2 months, the risk of disease progression or death was 51% lower with daratumumab than with active monitoring (hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.67; P<0.001). Progression-free survival at 5 years was 63.1% with daratumumab and 40.8% with active monitoring. A total of 15 patients (7.7%) in the daratumumab group and 26 patients (13.3%) in the active-monitoring group died (hazard ratio, 0.52; 95% CI, 0.27 to 0.98). Overall survival at 5 years was 93.0% with daratumumab and 86.9% with active monitoring. The most common grade 3 or 4 adverse event was hypertension, which occurred in 5.7% and 4.6% of the patients in the daratumumab group and the active-monitoring group, respectively. Adverse events led to treatment discontinuation in 5.7% of the patients in the daratumumab group, and no new safety concerns were identified.

CONCLUSIONS

Among patients with high-risk smoldering multiple myeloma, subcutaneous daratumumab monotherapy was associated with a significantly lower risk of progression to active multiple myeloma or death and with higher overall survival than active monitoring. No unexpected safety concerns were identified. (Funded by Janssen Research and Development; AQUILA ClinicalTrials.gov number, NCT03301220.)

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*A complete list of AQUILA Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Smoldering multiple myeloma is an asymptomatic precursor disease of active multiple myeloma,[1] and the current standard care is observation. However, patients with smoldering multiple myeloma who are at high risk for progression to active multiple myeloma may benefit from early treatment, although no treatments have been approved for this indication.[1,2]

Daratumumab, a human IgGκ monoclonal antibody targeting CD38, has been approved for use as monotherapy or in combination with standard regimens for multiple myeloma.[3,4] The phase 2 CENTAURUS study showed that daratumumab had single-agent activity in patients with intermediate-risk or high-risk smoldering multiple myeloma.[5] Results from this study supported the daratumumab dosing strategy chosen for the phase 3 AQUILA trial and confirmed the side-effect profile of daratumumab in patients with smoldering multiple myeloma. We conducted AQUILA to determine whether subcutaneous daratumumab monotherapy, as compared with active monitoring, would delay progression to active multiple myeloma among patients with high-risk smoldering multiple myeloma. We report the results from the primary analysis.

METHODS

TRIAL DESIGN AND OVERSIGHT

AQUILA was a phase 3, open-label, multicenter, randomized trial. Patients were enrolled at 124 sites in 23 countries; details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. An independent ethics committee or institutional review board at each site approved the trial protocol, available at NEJM.org. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation, principles originating from the Declaration of Helsinki, and regulations specific to each site. All the patients provided written informed consent.

The trial sponsor (Janssen Research and Development) and investigators designed the trial and compiled, maintained, and analyzed data that were collected by the investigators. All the authors had access to the data and were not restricted by confidentiality agreements. Professional medical writers (funded by Janssen Global Services) prepared the manuscript, and all the authors reviewed and revised it. The sponsor and authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Patients who were 18 years of age or older were eligible for inclusion in the trial if they had received a confirmed diagnosis of smoldering multiple myeloma, in accordance with International Myeloma Working Group (IMWG) criteria,[6] within the past 5 years; had measurable disease; and had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale ranging from 0 to 5, with a score of 0 indicating no symptoms and higher scores indicating greater disability). Patients were required to be at high risk for progression to active multiple myeloma, with a percentage of clonal plasma cells in bone marrow of at least 10% and the presence of at least one of the following risk factors (which were based on data available at the time of trial development[7-10]): a serum M-protein level of at least 30 g per liter, IgA smoldering multiple myeloma, immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes, a ratio of involved free light chains to uninvolved free light chains (FLC ratio) in serum of 8 to less than 100, or a percentage of clonal plasma cells in bone marrow of more than 50% to less than 60%. Additional eligibility criteria are described in the Supplementary Appendix.

TRIAL TREATMENTS

Patients were randomly assigned in a 1:1 ratio to receive either subcutaneous daratumumab monotherapy or active monitoring. Randomization was performed with the use of an interactive Web-based response system and was stratified according to the number of risk factors associated with progression to multiple myeloma (<3 vs. ≥3), as well as the presence of a serum M-protein level of at least 30 g per liter (yes vs. no), the presence of IgA smoldering multiple myeloma (yes vs. no), the degree of immunoparesis (reduced levels of two uninvolved immunoglobulins vs. reduced levels of less than two uninvolved immunoglobulins), the presence of a serum FLC ratio of at least 8 (yes vs. no), and the percentage of clonal plasma cells in bone marrow (>50% to <60% vs. ≤50%).

Patients in the daratumumab group received subcutaneous daratumumab (1800 mg) coformulated with recombinant human hyaluronidase PH20 (2000 U per milliliter of solution; Halozyme)

on a weekly basis in cycles 1 and 2, every 2 weeks in cycles 3 through 6, and every 4 weeks thereafter in 28-day cycles. Treatment was continued for 39 cycles, for 36 months, or until confirmation of disease progression, whichever occurred first. Patients in the active-monitoring group did not receive disease-specific treatment. Active monitoring was continued for 36 months or until confirmation of disease progression, whichever occurred first. Medications administered before and after daratumumab or active monitoring are described in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was evaluated in an analysis of the time from randomization to the initial documentation of progression to active multiple myeloma or death from any cause, whichever occurred first. Disease progression was assessed by an independent review committee in accordance with IMWG SLiM–CRAB diagnostic criteria for multiple myeloma,[6] which are provided in the Supplementary Appendix. Secondary efficacy end points reported here are overall response (partial response or better) and complete response as assessed with the use of a validated computer algorithm in accordance with IMWG response criteria,[11-13] as well as the following time-to-event end points: disease progression as assessed with IMWG biochemical or SLiM–CRAB criteria, the initiation of first-line treatment for active multiple myeloma, and death from any cause. Disease evaluations were performed in both groups by a central laboratory every 12 weeks until confirmation of disease progression. Definitions of the secondary end points and details regarding imaging and safety assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 360 patients (180 per group) and 165 events would provide the trial with 85% power to show a 37.5% lower risk of disease progression or death in the daratumumab group than in the active-monitoring group, as assessed with a log-rank test at a two-sided alpha level of 0.05. The primary analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization. The safety population included all the patients who had undergone randomization (in both groups) and had received at least one dose of the assigned treatment (in the daratumumab group).

If the primary analysis showed a significant difference between the two groups, the following secondary end points were to be tested sequentially: overall response, progression-free survival after the initiation of first-line treatment for active multiple myeloma (not reported), and overall survival. In the hierarchical testing approach, each test was performed at an overall two-sided alpha level of 0.05 to control the type I error rate.[14] For other secondary end points, the widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Data for time-to-event end points, including the primary end point, were compared between groups with the use of a stratified log-rank test. Hazard ratios and 95% confidence intervals were estimated with the use of a Cox proportional-hazards regression model with treatment as the sole explanatory variable and with stratification according to the number of risk factors associated with progression to multiple myeloma (<3 vs. ≥3). Landmark estimates and 95% confidence intervals were derived with the use of the Kaplan–Meier method. Data for response end points were compared between groups with the use of a stratified Cochran–Mantel–Haenszel test. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

From December 10, 2017, through May 27, 2019, a total of 390 patients were enrolled in the trial. Of these patients, 194 were randomly assigned to receive subcutaneous daratumumab monotherapy and 196 to receive active monitoring (Fig. 1). One patient in the daratumumab group did not receive the assigned treatment. By the clinical cutoff (May 1, 2024), 127 patients (65.5%) in the daratumumab group had completed 39 cycles or 36 months of treatment, and 80 patients (40.8%) in the active-monitoring group had completed 36 months of active monitoring. The most common reason for discontinuation of treatment or active monitoring was progressive disease (in 21.8% and 41.8% of the patients in the daratumumab group and the active-monitoring

group, respectively). A total of 30 patients (15.5%) in the daratumumab group and 51 patients (26.0%) in the active-monitoring group discontinued the trial; the most common reasons for trial discontinuation were death (in 7.7% and 13.3%, respectively) and patient withdrawal (in 6.2% and 11.7%).

Characteristics of the patients at baseline were balanced between the two groups (Table 1). The median age of the patients was 64 years (range, 31 to 86), and the median time from the initial diagnosis of smoldering multiple myeloma to randomization was 0.72 years (range, 0 to 5.0). Black patients were underrepresented in the trial population, accounting for 2.8% of the population; Asian patients made up 7.9% of the population (Table S1 in the Supplementary Appendix). The median percentage of clonal plasma cells in bone marrow was 20%. At least one high-risk cytogenetic abnormality (del[17p], t[4;14], or t[14;16]) was present in 15.1% of the patients, and at least three risk factors associated with progression to multiple myeloma were present in 79.5%. In accordance with the Mayo 2018 risk criteria[15] (published after the trial was initiated), 40.5% of the patients were retrospectively classified as having high-risk disease.

The median duration of treatment or active monitoring was 35.0 months (range, 0 to 36.1) in the daratumumab group and 25.9 months (range, 0.1 to 36.0) in the active-monitoring group. The median number of daratumumab cycles was 38 (range, 1 to 39).

EFFICACY

With a median follow-up of 65.2 months (range, 0 to 76.6), progression to active multiple myeloma (IMWG SLiM–CRAB criteria) or death had occurred in 67 patients (34.5%) in the daratumumab group and in 99 patients (50.5%) in the active-

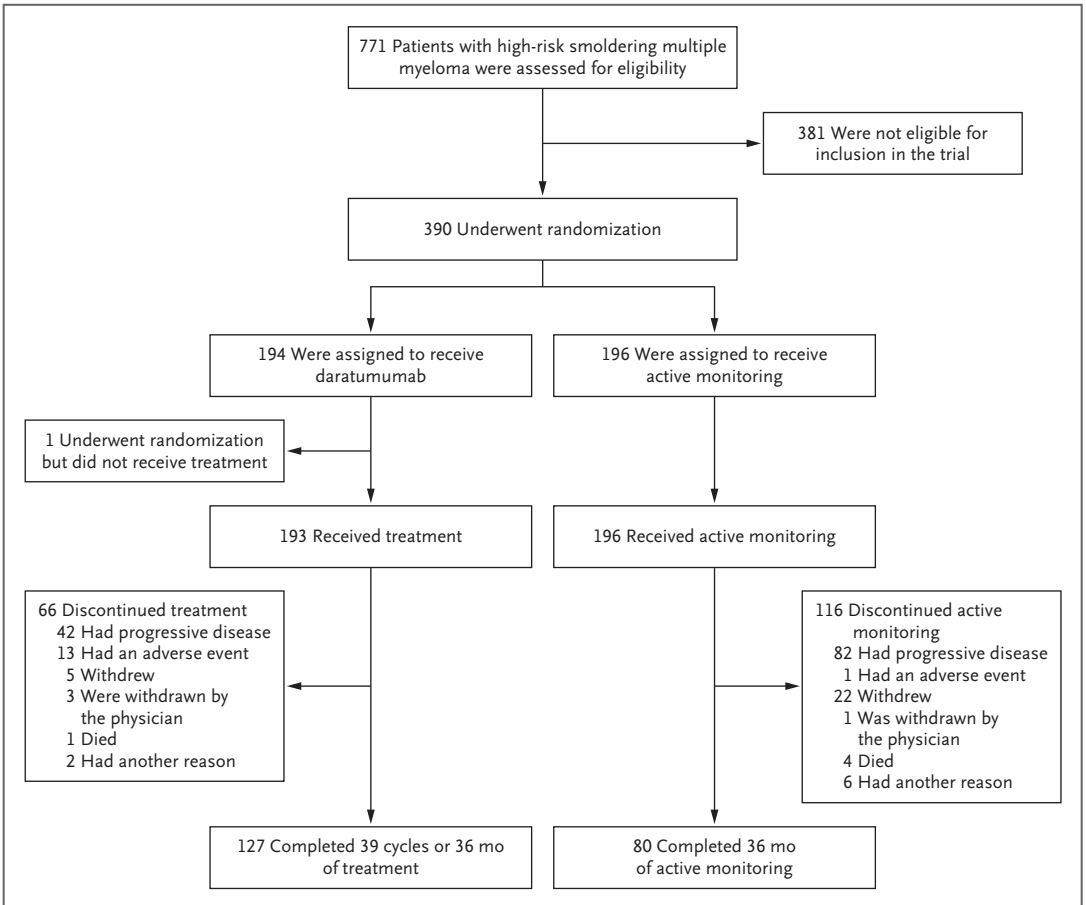

Figure 1. Screening, Randomization, and Treatment.

monitoring group (hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.67; P<0.001) (Fig. 2A). Progression-free survival at 5 years was 63.1% in the daratumumab group, as compared with 40.8% in the active-monitoring group. A summary of progression events is provided in Table 2. Progression-free survival in prespecified subgroups is shown in Fig. S1. The results from prespecified sensitivity analyses of progression-free survival supported the results from the primary analysis, showing high concordance in the determination of disease progression across assessments by the independent committee, the investigator, and a computer algorithm (Fig. S2). The median time to the occurrence of disease progression (IMWG biochemical or SLiM–CRAB criteria) was 44.1 months in the daratumumab group and 17.8 months in the active-monitoring group (hazard ratio, 0.51; 95% CI, 0.40 to 0.66) (Fig. S3).

A complete response or better was observed in 17 patients (8.8%) in the daratumumab group and in no patients in the active-monitoring group. A very good partial response or better was observed in 58 patients (29.9%) and in 2 patients (1.0%), respectively (Fig. S4).

By the clinical cutoff, first-line treatment for active multiple myeloma had been initiated in 64 patients (33.2%) in the daratumumab group and in 105 patients (53.6%) in the active-monitoring group (hazard ratio, 0.46; 95% CI, 0.33 to 0.62) (Table S2). The 5-year estimate for the initiation of first-line treatment for active multiple myeloma was 29.7% in the daratumumab group and 55.9% in the active-monitoring group (Fig. S5).

By the clinical cutoff, 41 patients had died: 15 (7.7%) in the daratumumab group and 26 (13.3%) in the active-monitoring group (hazard ratio, 0.52; 95% CI, 0.27 to 0.98) (Table S3). Overall survival at 5 years was 93.0% in the daratumumab group, as compared with 86.9% in the active-monitoring group (Fig. 2B). Trial follow-up is ongoing.

PATIENT-REPORTED OUTCOMES

The baseline scores on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30, the EORTC Quality of Life Questionnaire–Multiple Myeloma Module, and the EuroQol 5-Dimension 5-Level questionnaire (Table S4) were maintained over the trial duration in both groups. The scores obtained during treatment or active monitoring did not differ substantially between the daratumumab group and the active-monitoring group (Table S5).

SAFETY

A summary of adverse events is shown in Table 3. Grade 3 or 4 adverse events occurred in 40.4% and 30.1% of the patients in the daratumumab group and the active-monitoring group, respectively; the most common grade 3 or 4 adverse event was hypertension (5.7% vs. 4.6%). Serious adverse events occurred in 29.0% and 19.4% of the patients in the daratumumab group and the active-monitoring group, respectively; the most common serious adverse event was pneumonia (3.6% vs. 0.5%). Adverse events that led to treatment discontinuation occurred in 11 patients (5.7%) in the daratumumab group. Adverse events that led to death occurred in 2 patients (1.0%) in the daratumumab group (coronavirus disease 2019 [Covid-19] and Covid-19 pneumonia) and in 4 patients (2.0%) in the active-monitoring group (pulmonary edema, cardiac arrest, pulmonary embolism, and cardiac failure).

The incidence of grade 3 or 4 infections was 16.1% in the daratumumab group and 4.6% in the active-monitoring group (Table S6). The incidence of Covid-19 adverse events (either Covid-19 or Covid-19 pneumonia that occurred during the reporting period) was 8.8% and 5.1%, respectively. In the daratumumab group, 32 patients (16.6%) reported systemic reactions related to treatment administration (with 2 patients [1.0%] reporting grade 3 or 4 reactions), and 53 patients (27.5%) reported local reactions at the injection site (with none reporting grade 3 or 4 reactions). Second primary cancers were observed in 18 patients (9.3%) in the daratumumab group and in 20 patients (10.2%) in the active-monitoring group (Table S7).

DISCUSSION

Results from the primary analysis of AQUILA, with a median follow-up of 65.2 months, showed that subcutaneous daratumumab monotherapy was associated with a 51% lower risk of progression to active multiple myeloma or death among patients with high-risk smoldering multiple myeloma than active monitoring, the current standard care for this patient population. These find-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Daratumumab (N=194)	Active Monitoring (N=196)
Age		
Median (range) — yr	63.0 (31–86)	64.5 (36–83)
Distribution — no. (%)		
18 to <65 yr	106 (54.6)	98 (50.0)
65 to <75 yr	67 (34.5)	74 (37.8)
≥75 yr	21 (10.8)	24 (12.2)
Male sex — no. (%)	95 (49.0)	93 (47.4)
Race or ethnic group — no. (%)†		
White	161 (83.0)	162 (82.7)
Asian	18 (9.3)	13 (6.6)
Black	4 (2.1)	7 (3.6)
American Indian or Alaska Native	0	3 (1.5)
Native Hawaiian or other Pacific Islander	0	2 (1.0)
Multiple	1 (0.5)	0
Not reported	10 (5.2)	9 (4.6)
ECOG performance-status score — no. (%)‡		
0	165 (85.1)	160 (81.6)
1	29 (14.9)	36 (18.4)
Type of myeloma — no. (%)		
IgG	127 (65.5)	138 (70.4)
IgA	55 (28.4)	42 (21.4)
Other	12 (6.2)	16 (8.2)
Clonal plasma cells in bone marrow — no. (%)		
<10%	1 (0.5)	0
10% to ≤20%	124 (63.9)	102 (52.0)
>20% to <40%	50 (25.8)	66 (33.7)
≥40%	19 (9.8)	28 (14.3)
Risk factors for progression to multiple myeloma — no. (%)§		
<3	154 (79.4)	156 (79.6)
≥3	40 (20.6)	40 (20.4)
Cytogenetic risk profile — no./total no. (%)¶		
≥1 High-risk cytogenetic abnormality	29/167 (17.4)	22/170 (12.9)
del(17p)	3/166 (1.8)	8/166 (4.8)
t(4;14)	19/151 (12.6)	11/157 (7.0)
t(14;16)	7/146 (4.8)	3/145 (2.1)
Risk of progression according to Mayo 2018 risk criteria‖		
Low	45 (23.2)	34 (17.3)
Intermediate	77 (39.7)	76 (38.8)
High	72 (37.1)	86 (43.9)

Table 1. (Continued.)

Characteristic	Daratumumab (N=194)	Active Monitoring (N=196)
Median time from diagnosis of smoldering multiple myeloma to randomization (range) — yr	0.80 (0–4.7)	0.67 (0–5.0)

* Percentages may not total 100 because of rounding.
† Race was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with a score of 0 indicating no symptoms and higher scores indicating greater disability.
§ Risk factors are a serum M-protein level of ≥30 g per liter, IgA smoldering multiple myeloma, immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes, a ratio of involved free light chains to uninvolved free light chains (FLC ratio) in serum of 8 to <100, or a percentage of clonal plasma cells in bone marrow of >50% to <60% with measurable disease.
¶ Cytogenetic risk was assessed by means of fluorescence in situ hybridization. The denominators indicate the number of patients with an evaluable cytogenetic result for the specific probe.
‖ The Mayo 2018 risk criteria are a serum M-protein level of >20 g per liter, a serum FLC ratio of >20, and a percentage of clonal plasma cells in bone marrow of >20%.[15] The presence of no factors indicates low risk, the presence of one factor indicates intermediate risk, and the presence of two or three factors indicates high risk.

ings suggest that the use of daratumumab may delay or even prevent end-organ damage and progression to active multiple myeloma, providing clinical benefit independent of effecting a deep response. The findings are notable given that results of a recent real-world longitudinal study suggested that close monitoring alone may not prevent the occurrence of clinically significant end-organ damage in patients with high-risk smoldering multiple myeloma.[16] In our trial, baseline values for patient-reported outcomes were similar to or slightly better than general population norms[17] and were maintained over the trial duration in both groups; values with daratumumab were similar to those with active monitoring, which suggests that the use of daratumumab does not negatively affect patients' quality of life.

Daratumumab had a predominantly low-grade safety profile in patients with smoldering multiple myeloma, which is consistent with the known profile of daratumumab monotherapy in patients with relapsed or refractory multiple myeloma.[18,19] Grade 3 or 4 adverse events, grade 3 or 4 infections, and serious adverse events generally occurred less frequently than in previous studies of treatments for multiple myeloma, whereas reactions related to the administration of daratumumab occurred more frequently.[20-23] The occurrence of second primary cancers was similar in the two groups. The decrease in adverse events and the increase in survival with daratumumab highlight the favorable benefit–risk ratio for early disease intervention in this healthier population.

Standard care for smoldering multiple myeloma has been active monitoring for progression to symptomatic multiple myeloma.[1,2,24] Approximately one third of patients with smoldering multiple myeloma have adverse prognostic factors and are considered to have high-risk disease, with a 50% risk of progression to active myeloma within 2 years.[2] Yet, clinicians typically wait until serious organ damage occurs before initiating treatment. Over the past 50 years, numerous treatments have been evaluated in patients with high-risk smoldering multiple myeloma to determine whether early intervention can prevent organ damage and delay or prevent progression to active multiple myeloma.[1]

Most earlier studies did not show significant clinical benefits. More recently, the phase 3 QuiRedex trial evaluated early treatment with lenalidomide plus dexamethasone (Rd) as compared with active monitoring in patients with high-risk smoldering multiple myeloma (defined by ≥10% clonal plasma cells in bone marrow and the presence of a monoclonal component, or one of these criteria plus ≥95% phenotypically aberrant plasma cells in the clonal bone marrow plasma cells with immunoparesis), and there was evidence of benefit.[25] With a median follow-up of 12.5 years, the median time to progression to multiple myeloma was 9.5 years with Rd, as compared with 2.1 years with active monitoring (hazard ratio, 0.28; 95% CI, 0.18 to 0.44; P<0.001); 33 of 57 patients (58%) in the Rd group were alive as of the data cutoff, as compared with 25 of 62

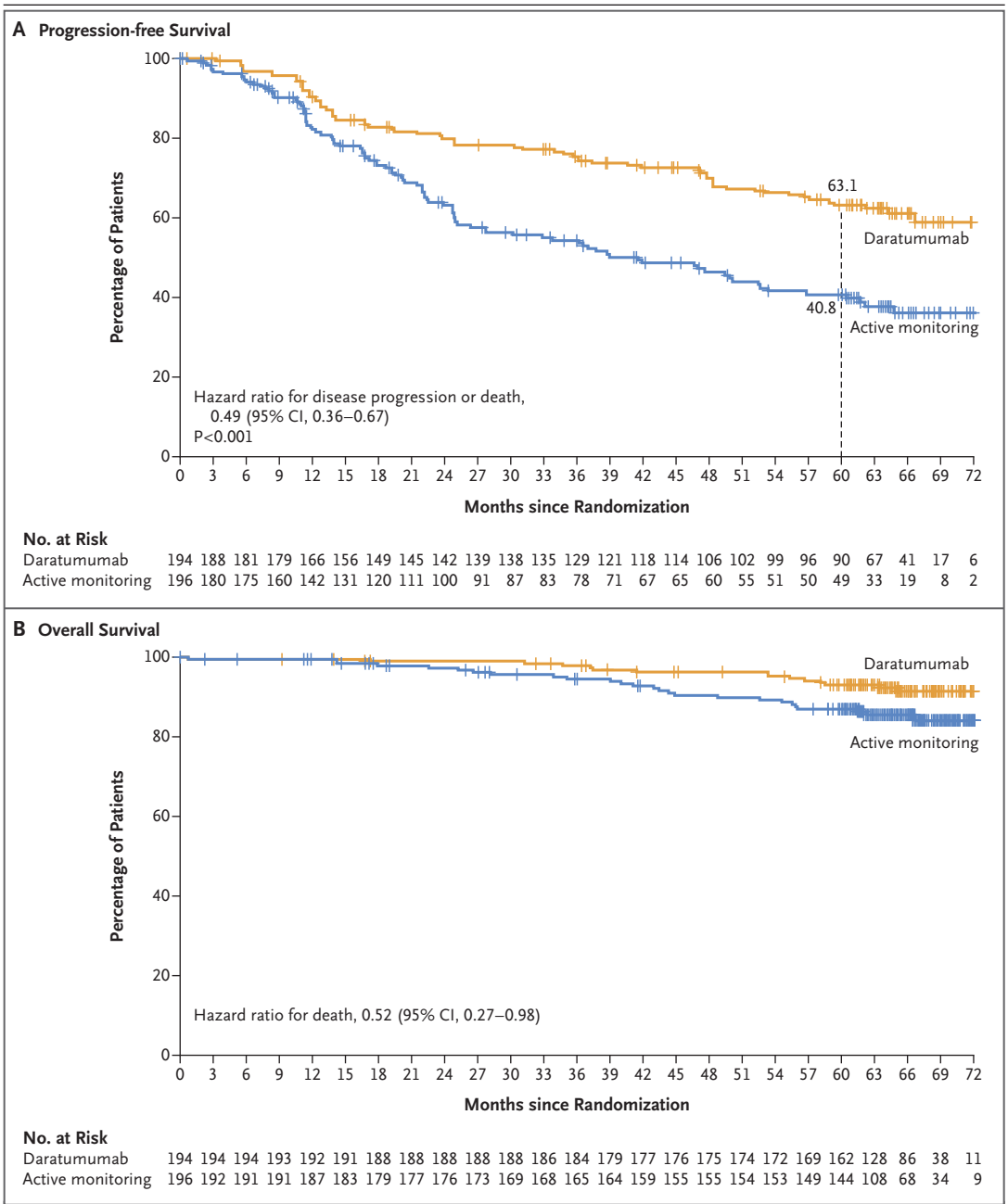

Figure 2. Progression-free Survival and Overall Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival in the intention-to-treat population. Progression-free survival was evaluated in an analysis of the time from randomization to the initial documentation of progression to active multiple myeloma or death from any cause, whichever occurred first. Disease progression was assessed by an independent review committee in accordance with the International Myeloma Working Group SLiM–CRAB diagnostic criteria for multiple myeloma.[6] The primary analysis of progression-free survival was performed after 166 events had occurred. Tick marks indicate censored data. The dashed line indicates the 5-year estimate. Panel B shows Kaplan–Meier estimates of overall survival in the intention-to-treat population.

Table 2. Summary of Progression Events (Intention-to-Treat Population).

Event	Daratumumab (N=194)	Active Monitoring (N=196)
Disease progression or death — no. (%)	67 (34.5)	99 (50.5)
Disease progression — no./total no. (%)*	62/67 (92.5)	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)
Death without disease progression — no./total no. (%)	5/67 (7.5)	5/99 (5.1)

* Disease progression was assessed by an independent review committee in accordance with the International Myeloma Working Group SLiM–CRAB diagnostic criteria for multiple myeloma.[6] A patient could meet more than one criterion for disease progression.

patients (40%) in the active-monitoring group (hazard ratio for death, 0.57; 95% CI, 0.34 to 0.95; P=0.03). The phase 3 ECOG E3A06 trial evaluated lenalidomide as compared with active monitoring in patients with intermediate-risk or high-risk smoldering multiple myeloma (defined by ≥10% clonal plasma cells in bone marrow and an abnormal serum FLC ratio [<0.26 or >1.65]). With a median follow-up of 35 months, progression-free survival was significantly longer with lenalidomide (hazard ratio for disease progression or death, 0.28; 95% CI, 0.12 to 0.62; P=0.002), but no difference in overall survival was apparent.[26] Despite some evidence of benefit, these trials did not result in approved treatments for high-risk smoldering multiple myeloma. In AQUILA, we found a significant clinical benefit of early intervention in patients with high-risk smoldering multiple myeloma.

The clinical benefit observed with daratumumab strengthens results from the phase 2 CENTAURUS study, which evaluated treatment for patients with intermediate-risk or high-risk smoldering multiple myeloma. In the final analysis of CENTAURUS (with a median follow-up of approximately 7 years), daratumumab monotherapy (administered once weekly in cycle 1, every 2 weeks in cycles 2 and 3, every 4 weeks in cycles 4 through 7, and every 8 weeks thereafter) was associated with an overall response of 58.5% in the group assigned to the daratumumab dosing strategy most similar to that used in AQUILA; overall survival at 7 years was 81.3%.[5] With extended follow-up, no new safety concerns were noted with daratumumab in this patient population. Whether alternative daratumumab dosing strategies or regimens (e.g., daratumumab-based combination therapy) may be more appropriate is currently unknown, but collective results from CENTAURUS and AQUILA support the use of daratumumab monotherapy for a finite duration for the treatment of high-risk smoldering multiple myeloma. A fixed treatment duration allows patients time without daratumumab exposure, which may prevent or delay the development of anti-CD38–refractory disease and may allow for subsequent use of daratumumab-based and other anti-CD38–based quadruplet therapies after the evolution of high-risk smoldering multiple myeloma to active multiple myeloma, given the proven efficacy and safety of such quadruplet therapies for this disease in the PERSEUS, CEPHEUS, and IMROZ studies.[20,27,28]

Ongoing trials are exploring more intensive combination approaches. For example, in a phase

Table 3. Summary of Adverse Events (Safety Population).

Event	Daratumumab (N=193)	Active Monitoring (N=196)
	number of patients (percent)	
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)
Arthralgia	52 (26.9)	35 (17.9)
Nasopharyngitis	49 (25.4)	23 (11.7)
Back pain	46 (23.8)	38 (19.4)
Insomnia	43 (22.3)	5 (2.6)
Grade 3 or 4 adverse event	78 (40.4)	59 (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)

* Adverse events of any grade that were reported in ≥20% of the patients in either group are listed.
† Adverse events that led to death were coronavirus disease 2019 (Covid-19) and Covid-19 pneumonia in the daratumumab group and pulmonary edema, cardiac arrest, pulmonary embolism, and cardiac failure in the active-monitoring group.

2 study of carfilzomib plus Rd (KRd) induction therapy followed by lenalidomide maintenance therapy (with a median follow-up of 60.2 months), 70.4% of the patients had minimal residual disease (MRD)–negative status and a complete response by the end of induction therapy and 39% maintained durable MRD-negative status and a complete response for at least 2 years.[29] In the phase 2 GEM-CESAR study, which is evaluating pretransplantation KRd induction therapy and post-transplantation KRd consolidation therapy followed by Rd maintenance therapy for up to 2 years in patients with high-risk smoldering multiple myeloma (with a median follow-up of 70.1 months), 94% of the patients were alive and progression-free and 31% had sustained MRD-negative status for 2 years after stopping maintenance therapy.[30] The phase 2 ASCENT study is evaluating quadruplet induction and consolidation therapy with daratumumab plus KRd followed by maintenance therapy with daratumumab plus lenalidomide as a potentially curative strategy for high-risk smoldering multiple myeloma.[31] With a median follow-up of 25.8 months, disease progression had occurred in 3 patients, and the estimated 3-year progression-free survival was 89.9%; MRD-negative status was observed in 84% of patients. Although these more aggressive combination approaches are promising, longer follow-up is needed to determine whether a significant effect with respect to overall survival among patients with smoldering multiple myeloma can be achieved while balancing toxic effects. Ongoing randomized trials of interest for the treatment of high-risk smoldering multiple myeloma include DETER-SMM (evaluating daratumumab plus Rd vs. Rd; ClinicalTrials.gov number, NCT03937635), ITHACA (evaluating isatuximab plus Rd vs. Rd; NCT04270409), and HOVON147 (evaluating KRd vs. Rd).

One important limitation across studies is that the criteria defining high-risk smoldering multiple myeloma have evolved over the years and differ among the studies, highlighting a need for more uniform criteria. In AQUILA, the criteria for high-risk smoldering multiple myeloma were based on data available at the time of trial development, before the establishment of the Mayo 2018 risk criteria.[15] In addition, although recent evidence suggests that longitudinal assessments may more accurately predict the risk of disease progression,

these assessments were not included in our trial because these insights were not available at the time of trial design. As the treatment of patients with high-risk smoldering multiple myeloma continues to evolve, so will the selection of subsequent frontline treatment for multiple myeloma. Recent data from the PERSEUS, CEPHEUS, and IMROZ studies[20,27,28] confirm the efficacy of daratumumab-based and other anti-CD38–based quadruplet therapies, which was initially identified in the GRIFFIN study.[32] However, in our trial, various subsequent therapies were initiated at the time of disease progression on the basis of IMWG SLiM–CRAB criteria, which may complicate the evaluation of long-term outcomes such as overall survival. Finally, although our trial may have implications regarding screening for monoclonal gammopathy of unknown significance, particularly in high-risk populations, screening recommendations require international consensus, and we await results of the population-based screening trial iStopMM (NCT03327597).[33]

With a median follow-up of more than 5 years, subcutaneous daratumumab monotherapy was associated with a significantly lower risk of progression to active multiple myeloma or death than active monitoring among patients with high-risk smoldering multiple myeloma. Daratumumab had an acceptable safety profile in patients with smoldering multiple myeloma.

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