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## Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma.

**Published in:**

New England Journal of Medicine

**Publication status and date:**

Published: 25/01/2024

**DOI (link to publisher):**

[10.1056/NEJMoa2312054](https://doi.org/10.1056/NEJMoa2312054)

**Document Version**

Publisher's PDF, also known as Version of record

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**Citation for the published version (APA):**

Sonneveld, P., Dimopoulos, M. A., Boccadoro, M., the PERSEUS Trial Investigators, Quach, H., Ho, P. J., Beksac, M., Hulin, C., Antonioli, E., Leleu, X., Mangiacavalli, S., Perrot, A., Cavo, M., Belotti, A., Broijl, A., Gay, F., Mina, R., Nijhof, I. S., Van De Donk, N. W. C. J., ... Moreau, P. (2024). Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *New England Journal of Medicine*, 390(4), 301-313. <https://doi.org/10.1056/NEJMoa2312054>

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# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 25, 2024

VOL. 390 NO. 4

## Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Sonneveld, M.A. Dimopoulos, M. Boccadoro, H. Quach, P.J. Ho, M. Beksac, C. Hulin, E. Antonioli, X. Leleu, S. Mangiacavalli, A. Perrot, M. Cavo, A. Belotti, A. Broijl, F. Gay, R. Mina, I.S. Nijhof, N.W.C.J. van de Donk, E. Katodritou, F. Schjesevold, A. Sureda Balari, L. Rosiñol, M. Delforge, W. Roeloffzen, T. Silzle, A. Vangsted, H. Einsele, A. Spencer, R. Hajek, A. Jurczynszyn, S. Lonergan, T. Ahmadi, Y. Liu, J. Wang, D. Vieyra, E.M.J. van Brummelen, V. Vanquichelberghe, A. Sitthi-Amorn, C.J. de Boer, R. Carson, P. Rodriguez-Otero, J. Bladé, and P. Moreau, for the PERSEUS Trial Investigators\*

### ABSTRACT

#### BACKGROUND

Daratumumab, a monoclonal antibody targeting CD38, has been approved for use with standard myeloma regimens. An evaluation of subcutaneous daratumumab combined with bortezomib, lenalidomide, and dexamethasone (VRd) for the treatment of transplantation-eligible patients with newly diagnosed multiple myeloma is needed.

#### METHODS

In this phase 3 trial, we randomly assigned 709 transplantation-eligible patients with newly diagnosed multiple myeloma to receive either subcutaneous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy (D-VRd group) or VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group). The primary end point was progression-free survival. Key secondary end points were a complete response or better and minimal residual disease (MRD)–negative status.

#### RESULTS

At a median follow-up of 47.5 months, the risk of disease progression or death in the D-VRd group was lower than the risk in the VRd group. The estimated percentage of patients with progression-free survival at 48 months was 84.3% in the D-VRd group and 67.7% in the VRd group (hazard ratio for disease progression or death, 0.42; 95% confidence interval, 0.30 to 0.59;  $P < 0.001$ ); the  $P$  value crossed the prespecified stopping boundary ( $P = 0.0126$ ). The percentage of patients with a complete response or better was higher in the D-VRd group than in the VRd group (87.9% vs. 70.1%,  $P < 0.001$ ), as was the percentage of patients with MRD-negative status (75.2% vs. 47.5%,  $P < 0.001$ ). Death occurred in 34 patients in the D-VRd group and 44 patients in the VRd group. Grade 3 or 4 adverse events occurred in most patients in both groups; the most common were neutropenia (62.1% with D-VRd and 51.0% with VRd) and thrombocytopenia (29.1% and 17.3%, respectively). Serious adverse events occurred in 57.0% of the patients in the D-VRd group and 49.3% of those in the VRd group.

#### CONCLUSIONS

The addition of subcutaneous daratumumab to VRd induction and consolidation therapy and to lenalidomide maintenance therapy conferred a significant benefit with respect to progression-free survival among transplantation-eligible patients with newly diagnosed multiple myeloma. (Funded by the European Myeloma Network in collaboration with Janssen Research and Development; PERSEUS ClinicalTrials.gov number, NCT03710603; EudraCT number, 2018-002992-16.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Sonneveld can be contacted at [p.sonneveld@erasmusmc.nl](mailto:p.sonneveld@erasmusmc.nl) or at Erasmus MC Cancer Institute, Rm. 822, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.

\*A complete list of PERSEUS Trial Investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on December 12, 2023, at [NEJM.org](http://NEJM.org).

*N Engl J Med* 2024;390:301-13.

DOI: 10.1056/NEJMoa2312054

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**I**NDUCTION THERAPY WITH BORTEZOMIB, lenalidomide, and dexamethasone (VRd) followed by autologous stem-cell transplantation, consolidation therapy with VRd, and maintenance therapy with lenalidomide is considered to be standard care for transplantation-eligible patients with newly diagnosed multiple myeloma.<sup>1-4</sup> However, new strategies are needed to increase the depth of response and prevent relapse in order to attain long-term disease control.

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with direct on-tumor<sup>5-8</sup> and immunomodulatory<sup>9-11</sup> mechanisms of action. Daratumumab has been approved for use in combination with various regimens for the treatment of patients with newly diagnosed multiple myeloma, including a regimen for those who are eligible for transplantation (bortezomib–thalidomide–dexamethasone) and regimens for those who are ineligible for transplantation (lenalidomide–dexamethasone and bortezomib–melphalan–prednisone).<sup>12-14</sup>

The randomized, phase 2 GRIFFIN study evaluated the efficacy and safety of intravenous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy for the treatment of transplantation-eligible patients with newly diagnosed multiple myeloma. At the time of the prespecified final analysis (median follow-up, 49.6 months), the use of the daratumumab-based therapy had led to a greater depth of response and longer progression-free survival than the use of VRd induction and consolidation therapy and lenalidomide maintenance therapy alone. Moreover, no new safety concerns were observed with extended follow-up.<sup>15</sup>

The subcutaneous formulation of daratumumab has been found to be noninferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and has a similar safety profile, but it is associated with a significant reduction in infusion-related reactions, can be administered in a single dose for all patients, and has a shorter duration of administration (3 to 5 minutes).<sup>12-14,16</sup> We conducted the phase 3 PERSEUS trial to evaluate the efficacy and safety of subcutaneous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy (D-VRd group), as compared with VRd induction and consolidation therapy and lenalidomide maintenance therapy

alone (VRd group), for the treatment of transplantation-eligible patients with newly diagnosed multiple myeloma.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

In this open-label, multicenter, phase 3 trial, we randomly assigned patients to one of the two treatment groups between January 19, 2019, and January 3, 2020, at 115 sites in 14 countries in Europe and Australia (see 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 International Council for Harmonisation Good Clinical Practice guidelines, the principles originating from the Declaration of Helsinki, and site-specific regulations. All the patients provided written informed consent.

The trial was sponsored by the European Myeloma Network in collaboration with Janssen Research and Development. The sponsors and investigators designed the trial and compiled, maintained, and analyzed the data collected by the investigators. The authors had access to the data and were not restricted by confidentiality agreements. The manuscript was prepared by professional medical writers, who were funded by Janssen Global Services. The authors reviewed, revised, and approved the manuscript before it was submitted for publication. The sponsors and the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### PATIENTS

Patients were eligible for inclusion in the trial if they were 18 to 70 years of age, had newly diagnosed multiple myeloma,<sup>17</sup> were eligible for high-dose therapy and autologous stem-cell transplantation, and had an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a scale from 0 to 5, with higher scores indicating greater disability). Additional eligibility criteria are listed in the Supplementary Appendix.

### TRIAL TREATMENTS

Patients were randomly assigned in a 1:1 ratio to receive either subcutaneous daratumumab

combined with VRd induction therapy before transplantation, with VRd consolidation therapy after transplantation, and with lenalidomide maintenance therapy (D-VRd group) or VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group) (Fig. S1 in the Supplementary Appendix). Randomization was stratified according to the International Staging System (ISS) disease stage (I, II, or III) and cytogenetic risk (standard risk or high risk, defined as the absence or presence, respectively, of a del[17p], t[4;14], or t[14;16] cytogenetic abnormality).

All the patients were to receive VRd in six 28-day cycles (four induction cycles and two consolidation cycles). VRd consisted of subcutaneous bortezomib (1.3 mg per square meter of body-surface area on days 1, 4, 8, and 11 of each cycle), oral lenalidomide (25 mg on days 1 through 21 of each cycle), and oral or intravenous dexamethasone (40 mg on days 1 through 4 and days 9 through 12 of each cycle). Patients in the D-VRd group also received subcutaneous daratumumab (1800 mg per week during cycles 1 and 2; 1800 mg every 2 weeks during cycles 3 through 6), which was coformulated with recombinant human hyaluronidase PH20 (2000 U per milliliter of solution) (ENHANZE drug delivery technology, Halozyme).

Within 6 weeks after the completion of induction therapy (cycle 4), stem-cell mobilization was performed with the use of the local standard regimen, such as cyclophosphamide, granulocyte colony-stimulating factor, and plerixafor. A second round of stem-cell mobilization or bone marrow harvest was permitted if the stem-cell yield was considered by the investigator to be inadequate. Patients underwent conditioning with melphalan (200 mg per square meter of body-surface area) over a period of 24 to 48 hours, followed by autologous stem-cell transplantation. Consolidation therapy began 30 to 60 days after transplantation.

After the completion of consolidation therapy (cycle 6), all the patients received lenalidomide in 28-day maintenance cycles. Oral lenalidomide (10 mg per day, with the dose increased to 15 mg per day after three cycles at the investigator's discretion) was administered until disease progression or toxic effects resulted in discontinuation. Patients in the D-VRd group also received subcutaneous daratumumab (1800 mg every 4 weeks) until disease progression or toxic effects resulted in discontinuation.

After at least 24 months of maintenance therapy, daratumumab therapy was discontinued in patients who had a complete response or better and had sustained minimal residual disease (MRD)-negative status (the absence of malignant cells at a sensitivity threshold of  $10^{-5}$  or lower) for at least 12 months; these patients continued to receive lenalidomide until disease progression or toxic effects resulted in discontinuation. Patients resumed daratumumab therapy if they had a confirmed loss of complete response without disease progression (the reappearance of serum or urine M protein on immunofixation or electrophoresis or the presence of  $\geq 5\%$  plasma cells in bone marrow) or a recurrence of MRD (the presence of malignant cells at a sensitivity threshold of  $10^{-4}$  or higher). Details regarding all medications administered before and after the infusions are provided in the Supplementary Appendix.

#### COVID-19 PANDEMIC ADJUSTMENT

Most patients were receiving active therapy during the coronavirus disease 2019 (Covid-19) pandemic. In patients who were affected by local closures of autologous stem-cell transplantation units due to the pandemic, stem cells were collected after the completion of cycle 4 in accordance with the protocol, but transplantation was performed immediately after the completion of cycle 6. After recovery from transplantation, these patients proceeded directly to maintenance therapy.

#### END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was evaluated in an analysis of the time from randomization to disease progression or death (whichever occurred first). Key secondary end points included a complete response or better, MRD-negative status with a complete response or better (hereafter referred to as MRD-negative status), and overall survival. A complete response or better was defined as a complete response or a stringent complete response occurring at any time during the trial after randomization. MRD-negative status was defined as both the absence of malignant cells at a sensitivity threshold of  $10^{-5}$  (with the capacity to detect 1 tumor cell per  $10^5$  white cells) and a complete response or better occurring at any time during the trial after randomization. In an exploratory analysis, MRD-negative status was assessed at a sensitivity threshold of  $10^{-6}$  (with the capacity to

detect 1 tumor cell per  $10^6$  white cells). Additional efficacy end points are listed in the Supplementary Appendix.

Tumor response and disease progression were assessed with the use of a validated computerized algorithm in accordance with International Myeloma Working Group response criteria.<sup>18</sup> Disease assessments were performed at a central laboratory. MRD was assessed by means of next-generation sequencing of bone marrow aspirate (clonoSEQ assay, version 2.0; Adaptive Biotechnologies) in accordance with International Myeloma Working Group guidelines.<sup>19</sup> MRD assessments were performed in patients who had a very good partial response or better after consolidation therapy and when a complete response or better was suspected at any time during the trial. Assessment schedules are provided in the Supplementary Appendix. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events were reported until 30 days after the last dose of any component of the treatment regimen.

#### STATISTICAL ANALYSIS

We estimated that a sample of approximately 690 patients would provide the trial with 85% power to detect a risk of disease progression or death in the D-VRd group that was 31% lower than the risk in the VRd group, at a two-sided alpha level of 0.05. The primary analysis described in this article (i.e., the prespecified first interim analysis) was performed in the intention-to-treat population, which included all patients who had undergone randomization. The safety population included all patients who had received at least one dose of the assigned treatment.

Data for time-to-event end points, including the primary end point (progression-free survival), were compared between treatment groups with the use of a stratified log-rank test. The assumption of proportionality was examined, and it was concluded that the proportional-hazards assumption held. Hazard ratios and 95% confidence intervals were estimated with the use of a stratified Cox proportional-hazards regression model with treatment as the sole explanatory variable and with stratification according to ISS disease stage (I vs. III and II vs. III) and cytogenetic risk (standard vs. high and indeterminate

vs. high). The Kaplan–Meier method was used to estimate the distributions. For the primary end point, data for patients who had an event immediately after two or more consecutive missing disease assessments were censored at the date of the last disease assessment.

The overall occurrence of a complete response or better and the overall occurrence of MRD-negative status were compared between treatment groups with the use of a stratified Cochran–Mantel–Haenszel chi-square test. For the key secondary end point of MRD-negative status, patients who had MRD-positive or ambiguous results and those who were not tested were considered to not have MRD-negative status and were included in the denominator.

A hierarchical testing procedure proposed by Tang and Geller<sup>20</sup> was used to control the overall familywise type I error for the primary end point and key secondary end points. Two interim analyses and one final analysis of progression-free survival were planned; the interim analyses were to be performed after approximately 143 events (50% information fraction) and 185 events (65% information fraction) had occurred, and the final analysis was to be performed after 285 events had occurred. The significance level at each analysis of progression-free survival was to be determined on the basis of the observed number of events at each analysis with the use of the Hwang–Shih–De Cani alpha spending function.<sup>21</sup> A total of 153 algorithm-based events had been observed at the time of the current analysis (i.e., the first interim analysis), representing approximately 54% of the events planned for the final analysis, with a stopping boundary of a two-sided P value of 0.0126.

The statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for additional secondary or other outcomes. The results for these outcomes are reported as point estimates and 95% confidence intervals; the widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

## RESULTS

### PATIENTS AND TREATMENT

A total of 709 patients were enrolled in the trial, of whom 355 were randomly assigned to the D-VRd

<b>Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*</b>		
<b>Characteristic</b>	<b>D-VRd (N=355)</b>	<b>VRd (N=354)</b>
Median age (range) — yr	61.0 (32–70)	59.0 (31–70)
Male sex — no. (%)	211 (59.4)	205 (57.9)
Race — no. (%)†		
Asian	4 (1.1)	6 (1.7)
Black	5 (1.4)	4 (1.1)
White	330 (93.0)	323 (91.2)
Other	4 (1.1)	3 (0.8)
Missing data	12 (3.4)	18 (5.1)
ECOG performance-status score — no. (%)‡		
0	221 (62.3)	230 (65.0)
1	114 (32.1)	108 (30.5)
2	19 (5.4)	16 (4.5)
3	1 (0.3)	0
Type of measurable disease — no. (%)		
IgG	204 (57.5)	185 (52.3)
IgA	65 (18.3)	85 (24.0)
Other§	13 (3.7)	11 (3.1)
Detected in urine only	43 (12.1)	46 (13.0)
Detected in serum free light chains only	29 (8.2)	27 (7.6)
Type could not be evaluated	1 (0.3)	0
ISS disease stage — no./total no. (%)¶		
I	186/355 (52.4)	178/353 (50.4)
II	114/355 (32.1)	125/353 (35.4)
III	55/355 (15.5)	50/353 (14.2)
Cytogenetic risk — no. (%)		
Standard	264 (74.4)	266 (75.1)
High	76 (21.4)	78 (22.0)
Indeterminate	15 (4.2)	10 (2.8)
Median time since diagnosis of multiple myeloma (range) — mo	1.2 (0.0–46.5)	1.1 (0.1–184.6)

\* Patients in the D-VRd group were randomly assigned to receive subcutaneous daratumumab combined with bortezomib, lenalidomide, and dexamethasone (VRd) induction and consolidation therapy and with lenalidomide maintenance therapy. Patients in the VRd group were randomly assigned to receive VRd induction and consolidation therapy and lenalidomide maintenance therapy alone. The intention-to-treat population included all patients who had undergone randomization.

† Race was reported by the patient.

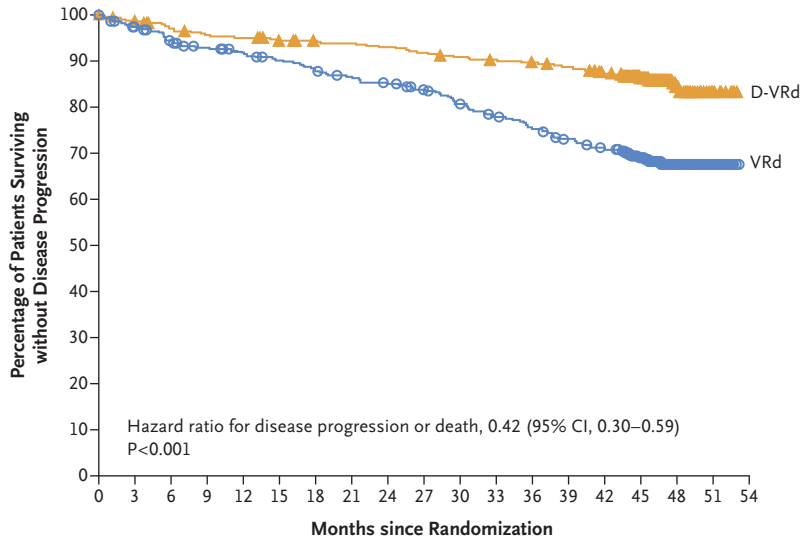
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. In one patient, the ECOG performance-status score was 0 at randomization but had increased to 3 at baseline.

§ Other types of measurable disease include IgD, IgM, IgE, and biclonal.

¶ The International Staging System (ISS) consists of three disease stages, with higher stages indicating more severe disease: stage I, defined by a serum  $\beta_2$ -microglobulin level of less than 3.5 mg per liter (300 nmol per liter) and an albumin level of 3.5 g per deciliter or more; stage II, defined as neither stage I nor stage III; and stage III, defined by a serum  $\beta_2$ -microglobulin level of 5.5 mg per liter (470 nmol per liter) or more.

|| Cytogenetic risk was assessed by means of fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), or t(14;16).

**A Kaplan–Meier Estimates**

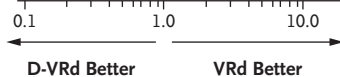


**No. at Risk**

D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0
VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0

**B Subgroup Analyses**

Subgroup	Disease Progression or Death		Median Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
	D-VRd	VRd	D-VRd	VRd	
	no. of events/total no. of patients		mo		
<b>Sex</b>					
Male	36/211	61/205	NE	NE	0.51 (0.34–0.77)
Female	14/144	42/149	NE	NE	0.29 (0.16–0.53)
<b>Age</b>					
<65 yr	30/261	84/267	NE	NE	0.30 (0.20–0.46)
≥65 yr	20/94	19/87	NE	NE	0.97 (0.52–1.81)
<b>Race</b>					
White	47/330	95/323	NE	NE	0.42 (0.30–0.60)
Other	3/25	8/31	NE	NE	0.40 (0.11–1.50)
<b>ISS disease stage</b>					
I	18/186	35/178	NE	NE	0.46 (0.26–0.81)
II	19/114	43/125	NE	NE	0.37 (0.22–0.64)
III	13/55	25/50	NE	41.9	0.42 (0.22–0.83)
<b>Type of multiple myeloma</b>					
IgG	28/204	58/185	NE	NE	0.36 (0.23–0.57)
Non-IgG	13/78	31/96	NE	NE	0.46 (0.24–0.88)
<b>Cytogenetic risk</b>					
Standard	25/264	62/266	NE	NE	0.35 (0.22–0.56)
High	24/76	38/78	NE	44.1	0.59 (0.36–0.99)
Indeterminate	1/15	3/10	NE	NE	0.16 (0.02–1.56)
<b>ECOG performance-status score</b>					
0	28/221	60/230	NE	NE	0.42 (0.27–0.66)
≥1	22/134	43/124	NE	NE	0.41 (0.25–0.69)



**Figure 1 (facing page). Progression-free Survival.**

Panel A shows Kaplan–Meier estimates of progression-free survival among patients who were randomly assigned to receive either subcutaneous daratumumab combined with bortezomib, lenalidomide, and dexamethasone (VRd) induction and consolidation therapy and with lenalidomide maintenance therapy (D-VRd group) or VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group) in the intention-to-treat population. The first interim analysis of progression-free survival was performed after 153 events of disease progression or death had occurred (53.7% of the 285 events planned for the final analysis). Panel B shows the results of prespecified subgroup analyses of progression-free survival in the intention-to-treat population. The International Staging System (ISS) consists of three disease stages, with higher stages indicating more severe disease: stage I, defined by a serum  $\beta_2$ -microglobulin level of less than 3.5 mg per liter (300 nmol per liter) and an albumin level of 3.5 g per deciliter or more; stage II, defined as neither stage I nor stage III; and stage III, defined by a serum  $\beta_2$ -microglobulin level of 5.5 mg per liter (470 nmol per liter) or more. The subgroup analysis for type of multiple myeloma was performed with data from patients who had measurable disease in serum. Cytogenetic risk was assessed by means of fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), or t(14;16). Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NE denotes could not be estimated.

group and 354 to the VRd group (Fig. S2). A total of 698 patients (351 in the D-VRd group and 347 in the VRd group) received at least one dose of the assigned treatment. The demographic and clinical characteristics of the patients were well balanced between the treatment groups; however, Black patients were underrepresented in the trial population (Table 1). The demographic characteristics of the patients in the trial were generally consistent with those of real-world patients with multiple myeloma (Table S1). The median age of the patients was 60.0 years (range, 31 to 70); 14.8% had ISS stage III disease, and 21.7% had high cytogenetic risk (del[17p], t[4;14], or t[14;16]).

As of the clinical cutoff date (August 1, 2023),

322 (91.7%) of the patients who had started the induction phase in the D-VRd group and 300 (86.5%) of those in the VRd group had continued into the maintenance phase. A total of 315 patients (89.7%) in the D-VRd group and 302 patients (87.0%) in the VRd group had undergone autologous stem-cell transplantation; 58 patients had undergone transplantation out of sequence (after cycle 6) because of the Covid-19 pandemic. A total of 25.9% of the patients in the D-VRd group and 54.2% of those in the VRd group had discontinued treatment; the number of patients who discontinued treatment during each trial phase is reported in Figure S2. Across all phases of the trial, the most common reasons for treatment discontinuation were an adverse event (9.1% in the D-VRd group and 22.5% in the VRd group) and progressive disease (8.3% and 20.7%, respectively). The median duration of treatment and median relative dose intensity are shown in Table S2.

**EFFICACY**

At a median follow-up of 47.5 months (range, 0 to 54.4), disease progression or death had occurred in 50 of 355 patients (14.1%) in the D-VRd group and 103 of 354 patients (29.1%) in the VRd group. The estimated percentage of patients with progression-free survival at 48 months was 84.3% (95% confidence interval [CI], 79.5 to 88.1) in the D-VRd group and 67.7% (95% CI, 62.2 to 72.6) in the VRd group. The hazard ratio for disease progression or death in the D-VRd group as compared with the VRd group was 0.42 (95% CI, 0.30 to 0.59;  $P < 0.001$ ); the  $P$  value crossed the prespecified stopping boundary for superiority for the first interim analysis ( $P = 0.0126$ ) (Fig. 1A). Prespecified subgroup analyses suggested a consistent benefit with respect to progression-free survival in the D-VRd group as compared with the VRd group across clinically relevant subgroups, including patients with ISS stage III disease and those with high cytogenetic risk (Fig. 1B).

The percentage of patients with a complete response or better was higher in the D-VRd group than in the VRd group (87.9% vs. 70.1%,  $P < 0.001$ ), as was the percentage of patients with MRD-



Variable	D-VRd (N = 355)	VRd (N = 354)	P Value*
<b>Tumor response†</b>			
Overall response — no. (% [95% CI])	343 (96.6 [94.2–98.2])	332 (93.8 [90.7–96.1])	—
Response — no. (%)			
Stringent complete response	246 (69.3)	158 (44.6)	—
Complete response	66 (18.6)	90 (25.4)	—
Very good partial response	26 (7.3)	68 (19.2)	—
Partial response	5 (1.4)	16 (4.5)	—
Complete response or better — no. (%)	312 (87.9)	248 (70.1)	<0.001
Very good partial response or better — no. (%)	338 (95.2)	316 (89.3)	—
Stable disease — no. (%)	4 (1.1)	9 (2.5)	—
Progressive disease — no. (%)	2 (0.6)	1 (0.3)	—
Response could not be evaluated — no. (%)	6 (1.7)	12 (3.4)	—
<b>MRD status‡</b>			
MRD-negative status — no. (%)			
10 <sup>-5</sup> sensitivity threshold	267 (75.2)	168 (47.5)	<0.001
10 <sup>-6</sup> sensitivity threshold	231 (65.1)	114 (32.2)	—
Sustained MRD-negative status, assessed at 10 <sup>-5</sup> sensitivity threshold, for ≥12 mo — no. (%)	230 (64.8)	105 (29.7)	—

\* P values were calculated with the use of a stratified Cochran–Mantel–Haenszel chi-square test.

† Tumor response was assessed with the use of a validated computerized algorithm in accordance with International Myeloma Working Group response criteria.<sup>18</sup> The tumor response was obtained at any time during the trial.

‡ Minimal residual disease (MRD) was assessed by means of next-generation sequencing of bone marrow aspirate (clonoSEQ assay, version 2.0; Adaptive Biotechnologies) in accordance with International Myeloma Working Group guidelines.<sup>19</sup> MRD-negative status was defined as both the absence of malignant cells at a sensitivity threshold of 10<sup>-5</sup> and a complete response or better occurring at any time during the trial. In an exploratory analysis, MRD-negative status was assessed at a sensitivity threshold of 10<sup>-6</sup>. Sustained MRD-negative status for at least 12 months was defined as two consecutive MRD-negative results at least 12 months apart, without any MRD-positive results in between.

negative status assessed at a sensitivity threshold of 10<sup>-5</sup> (75.2% vs. 47.5%,  $P < 0.001$ ) (Table 2). The percentage of patients who had sustained MRD-negative status for at least 12 months was 64.8% in the D-VRd group and 29.7% in the VRd group. The percentage of patients with MRD-negative status assessed at a sensitivity threshold of 10<sup>-6</sup> was 65.1% in the D-VRd group and 32.2% in the VRd group. Subgroup analyses of the overall occurrence of a complete response or better (Fig. S3) and the overall occurrence of MRD-negative status assessed at a sensitivity threshold of 10<sup>-5</sup> (Fig. S4) appeared to favor D-VRd over VRd across clinically relevant subgroups. At the time of clinical cutoff, 207 of the 322 patients who had entered the maintenance phase in the

D-VRd group had discontinued daratumumab therapy in accordance with the protocol (i.e., after they had received ≥24 months of maintenance therapy and attained a complete response or better and sustained MRD-negative status for ≥12 months).

Death occurred in 34 patients in the D-VRd group and 44 patients in the VRd group (Table S3). Data regarding overall survival are immature; longer-term follow-up is ongoing (Fig. S5). Death from Covid-19 occurred in 7 patients (4 in the D-VRd group and 3 in the VRd group).

#### SAFETY

Table 3 shows the most common adverse events of any grade (occurring in ≥20% of patients in

**Table 3. Most Common Adverse Events (Safety Population).\***

Event	D-VRd (N=351)		VRd (N=347)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Any adverse event	349 (99.4)	321 (91.5)	344 (99.1)	297 (85.6)
Hematologic adverse event				
Neutropenia	243 (69.2)	218 (62.1)	204 (58.8)	177 (51.0)
Thrombocytopenia	170 (48.4)	102 (29.1)	119 (34.3)	60 (17.3)
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
Nonhematologic adverse event				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	188 (53.6)	15 (4.3)	179 (51.6)	14 (4.0)
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infection	305 (86.9)	124 (35.3)	266 (76.7)	95 (27.4)
Coronavirus disease 2019	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)
Second primary cancer	37 (10.5)	NA	25 (7.2)	NA
Any infusion-related reaction	21 (6.0)	3 (0.9)	NA	NA

\* The safety population included patients who had received at least one dose of the assigned treatment. Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group are listed. NA denotes not applicable.

either group) and grade 3 or 4 adverse events (occurring in  $\geq 10\%$  of patients in either group). The most common grade 3 or 4 adverse events were neutropenia (62.1% in the D-VRd group and 51.0% in the VRd group), thrombocytopenia (29.1% and 17.3%, respectively), diarrhea (10.5% and 7.8%), pneumonia (10.5% and 6.1%), and febrile neutropenia (9.4% and 10.1%). Grade 3 or 4 peripheral neuropathies occurred in 6.0% of the

patients in the D-VRd group and 4.9% of those in the VRd group.

Serious adverse events occurred in 57.0% of the patients in the D-VRd group and 49.3% of those in the VRd group (Table S4). The most common serious adverse event was pneumonia (11.4% in the D-VRd group and 6.1% in the VRd group). Adverse events that led to treatment discontinuation were reported in 8.8% of the pa-

tients in the D-VRd group and 21.3% of those in the VRd group. Adverse events that occurred after the start of treatment and led to death were reported in 13 patients (3.7%) in the D-VRd group and 16 patients (4.6%) in the VRd group. Covid-19 as an adverse event that occurred after the start of treatment and led to death was reported in 4 patients (1.1%) in the D-VRd group and 1 patient (0.3%) in the VRd group. A second primary cancer was observed in 37 patients (10.5%) in the D-VRd group and 25 patients (7.2%) in the VRd group (Table S5).

The median CD34+ cell yield was  $5.5 \times 10^6$  per kilogram of body weight in the D-VRd group and  $7.4 \times 10^6$  per kilogram in the VRd group. The percentage of patients who proceeded to transplantation was similar in the two groups (89.7% and 87.0% in the D-VRd and VRd groups, respectively), as was the median time to complete hematopoietic reconstitution (14 days in both groups).

## DISCUSSION

The results of the first interim analysis of the PERSEUS trial, with a median follow-up of 47.5 months, showed that the addition of subcutaneous daratumumab to VRd induction and consolidation therapy and to lenalidomide maintenance therapy conferred a significant benefit with respect to progression-free survival among transplantation-eligible patients with newly diagnosed multiple myeloma. The risk of disease progression or death in the D-VRd group was significantly lower than the risk in the VRd group. The daratumumab-based therapy also conferred a significant benefit with respect to the depth of response, with a higher overall occurrence of a complete response or better and a higher overall occurrence of MRD-negative status in the D-VRd group than in the VRd group. It is notable that the percentage of patients who had sustained MRD-negative status for at least 12 months in the D-VRd group was more than twice that in the VRd group (64.8% vs. 29.7%). These results further strengthen the existing evidence supporting the use of daratumumab in combination regimens for patients with newly diagnosed multiple myeloma.<sup>15,22-24</sup>

Prespecified subgroup analyses suggested a consistent benefit with respect to progression-free survival in the D-VRd group as compared

with the VRd group across clinically relevant subgroups, including patients with ISS stage III disease and those with high cytogenetic risk. Interpretation of the results for progression-free survival among patients 65 years of age or older is limited by the small number of events observed in this subgroup, as well as the imbalance of patients with high cytogenetic risk between treatment groups (25.5% in the D-VRd group vs. 19.5% in the VRd group) in this subgroup. The overall occurrence of a complete response or better and the overall occurrence of MRD-negative status within the D-VRd group among patients 65 years of age or older were consistent with those in the intention-to-treat population. In addition, the risk of adverse events that led to treatment discontinuation and the risk of adverse events that led to death within the D-VRd group among patients 65 years of age or older were consistent with those in the population of patients who had received at least one dose of the assigned treatment (Table S6). Further maturation of data for this subgroup is needed.

The safety profile of daratumumab combined with VRd in the trial was consistent with the known safety profiles for daratumumab<sup>15,24,25</sup> and VRd<sup>2-4</sup> in this patient population. The percentage of patients with serious adverse events in the D-VRd group was higher than that in the VRd group. However, the percentage of patients with adverse events that led to treatment discontinuation in the D-VRd group was lower than that in the VRd group. Although the median stem-cell yield was lower in the D-VRd group than in the VRd group, the time to complete hematopoietic reconstitution after transplantation was similar in the two groups.

The clinical benefits of daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy that were seen in the PERSEUS trial reinforce those observed in the phase 2 GRIFFIN study.<sup>15</sup> The depth of response associated with this treatment increased throughout the GRIFFIN study. At the time of the prespecified final analysis (median follow-up, 49.6 months), the percentage of patients with a stringent complete response and the percentage of patients with sustained MRD-negative status for at least 12 months were significantly higher, and progression-free survival was significantly longer, among those receiving the

daratumumab-based therapy than among those receiving VRd induction and consolidation therapy and lenalidomide maintenance therapy alone.

The benefits seen in the PERSEUS trial are also consistent with those observed in the phase 3 CASSIOPEIA trial, which evaluated daratumumab combined with bortezomib, thalidomide, and dexamethasone (VTd) induction and consolidation therapy as compared with VTd induction and consolidation therapy alone (first randomization), followed by daratumumab maintenance therapy as compared with observation alone (second randomization), for the treatment of transplantation-eligible patients with newly diagnosed multiple myeloma.<sup>24,26</sup> Progression-free survival was longer and the percentages of patients who had a complete response or better and had MRD-negative status with a complete response or better were higher among those receiving the daratumumab-based therapy. Although differences in study design preclude direct comparisons of these studies, the results of the GRIFFIN study, the CASSIOPEIA trial, and now the PERSEUS trial show a benefit with respect to the depth of response and progression-free survival after the use of daratumumab-based quadruplet therapy followed by daratumumab-containing maintenance therapy in transplantation-eligible patients with newly diagnosed multiple myeloma.

Unlike previous studies of treatments for transplantation-eligible patients with newly diagnosed multiple myeloma, the PERSEUS trial did not have a second randomization to main-

nance therapy. This aspect of the PERSEUS trial design allows for clearer interpretation of the benefit of adding daratumumab across the entire treatment regimen, from VRd induction therapy through lenalidomide maintenance therapy, which is standard care for this patient population. However, this aspect of the trial design may confound the ability to determine the contribution of each treatment component to the efficacy of each phase of treatment independently.

With almost 4 years of follow-up, the results from the PERSEUS trial of subcutaneous daratumumab combined with VRd induction and consolidation therapy and with lenalidomide maintenance therapy showed a significant and clinically meaningful benefit with respect to progression-free survival, the occurrence of a complete response or better, and the occurrence of MRD-negative status, with a favorable benefit-risk profile.

Supported by the European Myeloma Network in collaboration with Janssen Research and Development.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in this trial, their families, and the staff members at the trial sites who cared for them; the members of the independent data and safety monitoring committee (Martin Kaiser, M.D., Alessandro Gozzetti, M.D., and Jerome Lambert, Ph.D.); representatives of the sponsor who were involved in data collection and analyses; and Lisa Shannon, Pharm.D., and Kimberly Carmony, Ph.D., of Lumanity Communications, for medical writing support with an earlier version of the manuscript.

#### APPENDIX

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## REFERENCES

- Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Hemasphere* 2021; 5(2):e528.
- Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med* 2017;376:1311-20.
- Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med* 2022;387:132-47.
- Rosiñol L, Oriol A, Rios R, et al. Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplant in multiple myeloma. *Blood* 2019;134:1337-45.
- de Weers M, Tai Y-T, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol* 2011;186:1840-8.
- Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood* 2014;124:3474. abstract.
- Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs* 2015;7:311-21.
- Overdijk MB, Jansen JHM, Nederend M, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcγ receptor-mediated cross-linking. *J Immunol* 2016; 197:807-13.
- Krejci J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38<sup>+</sup> immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood* 2016;128:384-94.
- Adams HC III, Stevenaert F, Krejci J, et al. High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry A* 2019;95:279-89.
- Casneuf T, Adams HC III, van de Donk NWCJ, et al. Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. *Leukemia* 2021;35:573-84.
- Darzalex (daratumumab) injection. Horsham, PA: Janssen Biotech, 2023 (package insert) (<https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX-pi.pdf>).
- Darzalex faspro (daratumumab and hyaluronidase-fihj) injection. Horsham, PA: Janssen Biotech, 2022 (package insert) (<https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf>).
- European Medicines Agency. Darzalex 20 mg/ml concentrate for solution for infusion ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/004077/WC500207296.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf)).
- Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol* 2023;10(10):e825-e837.
- Mateos M-V, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 2020;7(5):e370-e380.
- Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15(12):e538-e548.
- Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011;117:4691-5.
- Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016;17(8):e328-e346.
- Tang DI, Geller NL. Closed testing procedures for group sequential clinical trials with multiple endpoints. *Biometrics* 1999;55:1188-92.
- Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med* 1990;9:1439-45.
- Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAiA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:1582-96.
- Mateos M-V, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet* 2020;395:132-41.
- Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and au-

tologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021;22:1378-90.

25. Chari A, Rodriguez-Otero P, McCarthy H, et al. Subcutaneous daratumumab

plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): an open-label phase II study. *Br J Haematol* 2021;192:869-78.

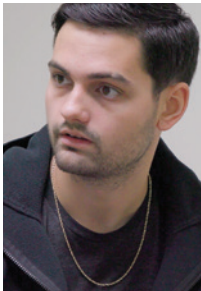
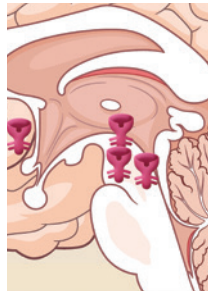
26. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexameth-

asone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019;394:29-38.

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## Double Take Video: Effective Treatments for Opioid Use Disorder — Finding Recovery and Staying Safe



This Double Take video focuses on a health care provider and her son through his opioid addiction and recovery, providing an overview of medications, harm-reduction techniques, and overdose response.

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