ORIGINAL ARTICLE

Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis

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ABSTRACT

BACKGROUND

Systemic immunoglobulin light-chain (AL) amyloidosis is characterized by deposition of amyloid fibrils of light chains produced by clonal CD38+ plasma cells. Daratumumab, a human CD38-targeting antibody, may improve outcomes for this disease.

METHODS

We randomly assigned patients with newly diagnosed AL amyloidosis to receive six cycles of bortezomib, cyclophosphamide, and dexamethasone either alone (control group) or with subcutaneous daratumumab followed by single-agent daratumumab every 4 weeks for up to 24 cycles (daratumumab group). The primary end point was a hematologic complete response.

RESULTS

A total of 388 patients underwent randomization. The median follow-up was 11.4 months. The percentage of patients who had a hematologic complete response was significantly higher in the daratumumab group than in the control group (53.3% vs. 18.1%) (relative risk ratio, 2.9; 95% confidence interval [CI], 2.1 to 4.1; P<0.001). Survival free from major organ deterioration or hematologic progression favored the daratumumab group (hazard ratio for major organ deterioration, hematologic progression, or death, 0.58; 95% CI, 0.36 to 0.93; P=0.02). At 6 months, more cardiac and renal responses occurred in the daratumumab group than in the control group (41.5% vs. 22.2% and 53.0% vs. 23.9%, respectively). The four most common grade 3 or 4 adverse events were lymphopenia (13.0% in the daratumumab group and 10.1% in the control group), pneumonia (7.8% and 4.3%, respectively), cardiac failure (6.2% and 4.8%), and diarrhea (5.7% and 3.7%). Systemic administration-related reactions to daratumumab occurred in 7.3% of the patients. A total of 56 patients died (27 in the daratumumab group and 29 in the control group), most due to amyloidosis-related cardiomyopathy.

CONCLUSIONS

Among patients with newly diagnosed AL amyloidosis, the addition of daratumumab to bortezomib, cyclophosphamide, and dexamethasone was associated with higher frequencies of hematologic complete response and survival free from major organ deterioration or hematologic progression. (Funded by Janssen Research and Development; ANDROMEDA ClinicalTrials.gov number, NCT03201965.)

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*A complete list of investigators in the ANDROMEDA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Immunoglobulin light-chain (AL) amyloidosis is a lethal form of systemic amyloidosis arising from clonal expansion of CD38+ plasma cells that produce misfolded immunoglobulin light chains, which form amyloid fibrils that are deposited in tissues. This process results in organ damage, most frequently to the heart and kidneys.[1] Diagnosis is often delayed, and the prognosis is poor, owing to advanced multiorgan involvement that leads to progressive disability and death.[1-3] Standard treatment involves the use of multiple myeloma–derived therapies that target plasma cells; a combination of bortezomib, cyclophosphamide, and dexamethasone is the most commonly used regimen.[3-5] Rapid and deep hematologic responses are critical; however, despite improvements with bortezomib-containing therapy, rates of hematologic complete response remain suboptimal, early mortality is high, outcomes vary depending on the extent and severity of organ involvement, and treatment-related toxic effects are frequently observed.[6] Until recently, no approved treatment options were available.

Daratumumab is a human IgG-κ monoclonal antibody that targets CD38, a glycoprotein uniformly expressed on human plasma cells. Daratumumab has a direct antitumor[7-10] and immunomodulatory mechanism,[11-13] with demonstrated efficacy as monotherapy or in combination with standard-of-care regimens for multiple myeloma.[14] In patients with relapsed or refractory AL amyloidosis, daratumumab has shown promising efficacy in terms of hematologic responses and improvement in organ function.[15-21] In the phase 3 ANDROMEDA trial, we evaluated the safety and efficacy of subcutaneous daratumumab plus bortezomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed AL amyloidosis. A safety run-in phase showed that the combination had an acceptable side-effect profile.[22] Here we report the primary results from the randomized portion of the trial.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, open-label, randomized, active-controlled trial enrolled patients between May 3, 2018, and August 15, 2019, at 109 sites in 22 countries across North and South America, Europe, the Middle East, and the Asia–Pacific region. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The trial protocol (available with the full text of this article at NEJM.org) was approved by an institutional review board or independent ethics committee at each trial site, and all the patients provided written informed consent. Efficacy data were adjudicated by an independent review committee whose members were unaware of the trial-group assignments, and an independent data monitoring committee assessed the results of the interim analysis.

A Quick Take is available at NEJM.org

The trial sponsor (Janssen Research and Development) designed the trial and compiled and maintained the data. Authors were given access to the data and were not restricted by confidentiality agreements. Professional medical writers that were funded by the sponsor prepared the manuscript. All the authors reviewed, revised, and approved the manuscript for submission. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were at least 18 years of age with a histopathologic diagnosis of systemic AL amyloidosis (affecting one or more organs) and measurable hematologic disease. Patients were excluded if they had received previous therapy for AL amyloidosis, had symptomatic multiple myeloma according to International Myeloma Working Group criteria,[23] had an Eastern Cooperative Oncology Group performance-status score of more than 2 (on a 5-point scale in which higher numbers indicate greater disability), had an estimated glomerular filtration rate of less than 20 ml per minute per 1.73 m^2 of body-surface area, or had evidence of a severe cardiovascular condition including an N-terminal pro–B-type natriuretic peptide level of more than 8500 ng per liter, a systolic blood pressure of less than 90 mm Hg, or a New York Heart Association classification of stage IIIB or IV at screening. Full eligibility criteria are provided in the trial protocol.

RANDOMIZATION AND TRIAL TREATMENTS

With the use of an interactive Web-response system, patients were randomly assigned in a 1:1 ratio to receive bortezomib, cyclophosphamide, and dexamethasone alone (control group) or the

same therapy with subcutaneous daratumumab (daratumumab group) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to cardiac stage (I, II, or IIIA on the basis of the European modification of the Mayo Clinic Cardiac Staging System),[3] availability of transplantation in the local country (countries that do or do not typically offer transplantation for patients with AL amyloidosis), and renal function (creatinine clearance, ≥60 ml per minute or <60 ml per minute). Treatment assignments were not blinded.

All the patients received subcutaneous bortezomib at a dose of 1.3 mg per square meter of body-surface area, cyclophosphamide at a dose of 300 mg per square meter orally or intravenously (500 mg maximum weekly dose), and dexamethasone at a dose of 40 mg orally or intravenously once weekly for six cycles of 28 days each. For patients who were older than 70 years of age, were underweight (body-mass index [the weight in kilograms divided by the square of the height in meters], <18.5), or had hypervolemia, poorly controlled diabetes mellitus, or previous unacceptable side effects associated with glucocorticoid therapy, dexamethasone could be administered at a dose of 20 mg weekly at the discretion of their physician. Patients who were assigned to the daratumumab group received 1800 mg of daratumumab per 15 ml administered subcutaneously, coformulated with recombinant human hyaluronidase PH20, weekly in cycles 1 and 2, every 2 weeks in cycles 3 through 6, and every 4 weeks thereafter until disease progression, the start of subsequent therapy, or for a maximum of 24 cycles from the start of the trial, whichever occurred first. Details of pre- and postadministration medications that were given with daratumumab are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was a hematologic complete response at the time of clinical cutoff in patients in the intention-to-treat population. The response had to be confirmed by a subsequent assessment during or after the trial treatment, as assessed by the independent review committee, whose members were unaware of the trial-group assignments. A hematologic complete response was defined as an involved free light-chain level less than the upper limit of the normal range with negative serum and urine immunofixation; normalization of the uninvolved free light-chain level or free light-chain ratio was not required to determine a complete response.[5,24,25] Patients who underwent randomization but were not treated, withdrew consent to participate, were lost to follow-up, or died before response assessment were considered to have not had a response. Secondary end points included survival free from major organ deterioration or hematologic progression (a composite end point including end-stage cardiac or renal failure, hematologic progression [assessed by the independent review committee], or death and analyzed with the use of an inverse-probability-of-censoring weighting method), organ response,[26,27] overall survival, hematologic complete response at 6 months, hematologic very good partial response or better, time to and duration of hematologic complete response, time to next treatment, and reduction in fatigue. Complete definitions of end points, disease evaluation timing, and definitions of hematologic and organ response are provided in the Supplementary Appendix (Additional Methods section and Tables S1 and S2).

STATISTICAL ANALYSIS

The sample size for this trial was based on the assumption that the percentage of patients with a hematologic complete response would be 15 percentage points higher in the daratumumab group than in the control group; approximately 360 patients were required to provide 85% power to detect this difference (two-sided alpha level of 0.05). If the between-group difference for the primary end point was significant, the major secondary end points of survival free from major organ deterioration or hematologic progression and overall survival, as ordered here, were tested with the use of a hierarchical testing approach that controls the type I error.[28]

Efficacy analyses were performed in the intention-to-treat population, which included all the patients who underwent randomization. The safety population comprised patients who received at least one dose of trial treatment. Between-group differences with respect to hematologic complete response were tested with the use of a stratified Cochran–Mantel–Haenszel test, and corresponding relative risk and odds ratios, 95% confidence intervals, and P values were reported. Time-to-event variables were evaluated with the

Kaplan–Meier method. The primary analysis, reported here, occurred after all enrolled patients had been in the trial for at least 6 months. Full statistical methods are described in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

A total of 388 patients (195 in the daratumumab group and 193 in the control group) underwent randomization. The demographic and clinical characteristics of the patients at baseline were balanced between the groups (Table 1). The median age was 64 years (range, 34 to 87), and the median time since diagnosis was 43 days (range, 5 to 1611). The median baseline difference between the involved and uninvolved free light-chain levels was 187 mg per liter (range, 1 to 9983). A total of 254 patients (65.5%) had two or more organs involved; 71.4% of the patients had heart involvement, and 59.0% had kidney involvement. The majority of patients (76.8%) were classified as having a cardiac stage of II or higher.

Among the 388 patients who underwent randomization, 381 (193 in the daratumumab group and 188 in the control group) received at least one dose of trial treatment (Fig. S2). At the time of clinical data cutoff for the primary analysis (February 14, 2020), a total of 52 patients (26.9%) in the daratumumab group and 68 patients (36.2%) in the control group had discontinued the intervention before the protocol-defined completion of treatment. In the control group, 121 patients (64.4%) received six cycles of treatment as specified by the protocol. In the daratumumab group, 159 patients (82.4%) completed six cycles of trial treatment, and 149 (77.2%) continued single-agent subcutaneous daratumumab after completing the first six treatment cycles; at the time of analysis, 141 of 195 patients (72.3%) were continuing to receive daratumumab. Dose reductions were similar in the daratumumab group and the control group (cyclophosphamide, 17.6% and 13.8%, respectively; bortezomib, 25.9% and 19.7%; dexamethasone, 27.5% and 27.7%; daratumumab dose reductions were not permitted). The median duration of therapy was 9.6 months in the daratumumab group and 5.3 months in the control group.

EFFICACY

With a median follow-up of 11.4 months (range, 0.03 to 21.3), 104 patients (53.3%) in the daratumumab group and 35 patients (18.1%) in the control group had a hematologic complete response (Table 2). This difference was significant (relative risk ratio, 2.9; 95% confidence interval [CI], 2.1 to 4.1; odds ratio, 5.1; 95% CI, 3.2 to 8.2; P<0.001 for both comparisons). The percentages of patients with a hematologic complete response in prespecified subgroups showed consistent benefit in the daratumumab group (Fig. 1). Landmark analysis of hematologic complete response at 6 months showed percentages consistent with overall hematologic complete response (49.7% in the daratumumab group vs. 14.0% in the control group; relative risk ratio, 3.5; 95% CI, 2.4 to 5.2; odds ratio, 6.1; 95% CI, 3.7 to 10.0; P<0.001 for both comparisons). The median time to hematologic complete response was 60 days in the daratumumab group and 85 days in the control group. The percentage of patients who had a hematologic very good partial response or better was 78.5% in the daratumumab group and 49.2% in the control group (relative risk ratio, 1.6; 95% CI, 1.4 to 1.9; odds ratio, 3.8; 95% CI, 2.4 to 5.9). An involved free light-chain level of 20 mg or less per liter was observed more frequently among patients in the daratumumab group than among those in the control group (70.5% vs. 20.2%); similar outcomes were observed for a difference between the involved and uninvolved free light-chain levels of less than 10 mg per liter (63.3% vs. 29.5%) (Table 2 and Fig. S3).

Among patients who could be evaluated for cardiac response (118 in the daratumumab group and 117 in the control group), the percentage who had a cardiac response at 6 months was 41.5% in the daratumumab group and 22.2% in the control group (Table 2); cardiac progression at 6 months was observed in 2.5% and 7.7% of the patients, respectively. Among patients who could be evaluated for renal response (117 in the daratumumab group and 113 in the control group), the percentage who had a renal response at 6 months was 53.0% in the daratumumab group and 23.9% in the control group (Table 2); renal progression at 6 months was observed in 4.3% and 11.5% of the patients, respectively.

Survival free from major organ deterioration or hematologic progression was longer in the

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

Characteristic	Daratumumab Group (N=195)	Control Group (N=193)
Age		
Median (range) — yr	62 (34–87)	64 (35–86)
Distribution — no. (%)		
<65 yr	108 (55.4)	97 (50.3)
≥65 yr	87 (44.6)	96 (49.7)
Sex — no. (%)		
Male	108 (55.4)	117 (60.6)
Female	87 (44.6)	76 (39.4)
ECOG performance-status score — no. (%)†		
0	90 (46.2)	71 (36.8)
1	86 (44.1)	106 (54.9)
2	19 (9.7)	16 (8.3)
AL isotype — no. (%)‡		
Lambda	158 (81.0)	149 (77.2)
Kappa	37 (19.0)	44 (22.8)
dFLC		
Median (range) — mg/liter	200 (2–4749)	186 (1–9983)
<50 mg/liter — no. (%)	23 (11.8)	13 (6.7)
<20 mg/liter — no. (%)	10 (5.1)	5 (2.6)
Median time since amyloidosis diagnosis (range) — days	48 (8–1611)	43 (5–1102)
Involved organs		
Median (range)	2 (1–5)	2 (1–6)
Distribution — no. (%)		
Heart	140 (71.8)	137 (71.0)
Kidney	115 (59.0)	114 (59.1)
Liver	15 (7.7)	16 (8.3)
Other§	127 (65.1)	124 (64.2)
Cardiac stage — no. (%)¶		
I	47 (24.1)	43 (22.3)
II	76 (39.0)	80 (41.5)
IIIA	70 (35.9)	64 (33.2)
IIIB‖	2 (1.0)	6 (3.1)
Renal stage — no./total no. (%)**		
I	107/193 (55.4)	101/193 (52.3)
II	67/193 (34.7)	74/193 (38.3)
III	19/193 (9.8)	18/193 (9.3)
Creatinine clearance — no. (%)		
<60 ml/min	69 (35.4)	62 (32.1)
≥60 ml/min	126 (64.6)	131 (67.9)
Residence in a country that typically offers transplantation for patients with AL amyloidosis — no. (%)		

Table 1. (Continued.)

Characteristic	Daratumumab Group (N=195)	Control Group (N=193)
Yes	147 (75.4)	146 (75.6)
No	48 (24.6)	47 (24.4)
Median NT-proBNP level (range) — ng/liter	1388.6 (51–10,182)	1746.0 (51–12,950)
Median estimated GFR (range) — ml/min/1.73 m^2	77.8 (21–126)	76.2 (20–121)

* The intention-to-treat population included all the patients who underwent randomization. AL denotes immunoglobulin light chain, dFLC the difference between involved and uninvolved free light-chain levels, GFR glomerular filtration rate, and NT-proBNP N-terminal pro–B-type natriuretic peptide.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
‡ Data are based on immunofixation or light-chain measurement.
§ Other includes gastrointestinal tract, lung, peripheral nervous system, autonomic nervous system, and soft tissue.
¶ Cardiac stage was classified in accordance with the European modification of the staging system of the Mayo Clinic.[29] Cardiac stage was based on two biomarker risk factors — NT-proBNP and high-sensitivity cardiac troponin T — that were assessed at a central laboratory.
‖ All the patients had a cardiac stage of I, II, or IIIA at screening; however, some converted to stage IIIB at cycle 1, day 1 (results determined by the central laboratory were made available only after cycle 1, day 1).
** Renal stage is based on the combination of estimated GFR and urinary protein excretion.[27]

daratumumab group than in the control group (hazard ratio for major organ deterioration, hematologic progression, or death, 0.58; 95% CI, 0.36 to 0.93; P=0.02) (Fig. 2). Hematologic progression occurred in 8 patients (4.1%) in the daratumumab group and in 25 patients (13.0%) in the control group. Survival free from major organ deterioration, hematologic progression, or subsequent treatment was also longer in the daratumumab group than in the control group (hazard ratio for major organ deterioration, hematologic progression, subsequent treatment, or death, 0.39; 95% CI, 0.27 to 0.56). A detailed listing of all observed events of major organ deterioration, hematologic progression, subsequent treatment, or death according to treatment group is provided in Table S3, and results of supportive analyses (including without censoring for subsequent treatment) are provided in Table S4.

A total of 19 of 193 patients (9.8%) in the daratumumab group and 79 of 188 patients (42.0%) in the control group received non–cross-resistant subsequent therapy. Of the 79 patients in the control group who received non–cross-resistant subsequent therapy, 48 (61%) received intravenous daratumumab as monotherapy or in combination with other therapies. A total of 13 of 193 patients (6.7%) in the daratumumab group and 20 of 188 patients (10.6%) in the control group received subsequent autologous stem-cell transplantation. Overall survival did not differ substantially between the two groups at the time of this analysis (Fig. S4).

SAFETY

The most common adverse events of any grade (occurring in >25% of the patients in either group) and of grade 3 or 4 (occurring in ≥5% of the patients in either group) are summarized in Table 3. The most common adverse events of grade 3 or 4 were lymphopenia (13.0% in the daratumumab group and 10.1% in the control group), pneumonia (7.8% and 4.3%, respectively), cardiac failure (6.2% and 4.8%), diarrhea (5.7% and 3.7%), syncope (5.2% and 6.4%), neutropenia (5.2% and 2.7%), peripheral edema (3.1% and 5.9%), and hypokalemia (1.6% and 5.3%). The incidence of grade 3 or 4 infections was 16.6% in the daratumumab group and 10.1% in the control group.

Serious adverse events occurred in 43.0% of the patients in the daratumumab group and in 36.2% of those in the control group; the most common serious adverse event was pneumonia, which occurred in 7.3% and 4.8% of the patients in the respective groups. The percentage of patients who had adverse events that led to discontinuation of trial treatment was 4.1% in the daratumumab group and 4.3% in the control group.

A total of 56 deaths occurred during the trial: 27 in the daratumumab group and 29 in the

Table 2. Summary of Overall Confirmed Hematologic Responses and Cardiac and Renal Responses at 6 Months.*

Response	Daratumumab Group (N=195)	Control Group (N=193)	P Value†
Hematologic response			
Any response — no. of patients	179	148	
Percent of patients (95% CI)	91.8 (87.0–95.2)	76.7 (70.1–82.5)	
Complete response — no. of patients‡	104§	35§	<0.001
Percent of patients (95% CI)	53.3 (46.1–60.5)	18.1 (13.0–24.3)	
Very good partial response or better — no. (%)	153 (78.5)	95 (49.2)	
Very good partial response — no. (%)	49 (25.1)	60 (31.1)	
Partial response — no. (%)	26 (13.3)	53 (27.5)	
No response — no. (%)	8 (4.1)	38 (19.7)	
Progressive disease — no. (%)	0	0	
Response could not be evaluated — no. (%)	8 (4.1)	7 (3.6)	
Involved free light-chain level ≤20 mg/liter — no./total no. (%)¶	136/193 (70.5)	39/193 (20.2)	
dFLC <10 mg/liter — no./total no. (%)‖	119/188 (63.3)	56/190 (29.5)	
Cardiac response at 6 mo			
No. of patients who could be evaluated**	118	117	
Percent with a response (95% CI)	41.5 (32.5–51.0)	22.2 (15.1–30.8)	
Renal response at 6 mo			
No. of patients who could be evaluated††	117	113	
Percent with a response (95% CI)	53.0 (43.5–62.3)	23.9 (16.4–32.8)	

* Hematologic response was assessed centrally in the intention-to-treat population. Organ response in patients with measurable organ involvement was assessed by an independent review committee whose members were unaware of the trial-group assignments, according to previously validated criteria that are outlined in the protocol.[26,27] CI denotes confidence interval.

† The P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test.

‡ Complete response was based on consensus criteria with clarifications as specified in the trial protocol that required confirmation by the independent review committee. Complete response was defined as negative immunofixation and normalization of the free light-chain ratio without confirmation,[26] a reduction in the absolute involved free light-chain level to 20 mg or less per liter,[25] and a reduction in the dFLC to less than 10 mg per liter.[5]

§ Of the 104 patients who had a hematologic complete response in the daratumumab group, 4 patients died while in complete response and no patients with a complete response had a relapse. Of the 35 patients who had a hematologic complete response in the control group, 2 patients died while in complete response and 2 patients had a relapse after a complete response.

¶ Excluded are 2 patients with an involved free light-chain level of 20 mg or less per liter at baseline (both in the daratumumab group).

‖ Excluded are 10 patients with a dFLC of less than 10 mg per liter at baseline (7 in the daratumumab group and 3 in the control group).

** Patients who could be evaluated for cardiac response were defined as those with a baseline NT-proBNP value of 650 ng or more per liter or a baseline New York Heart Association (NYHA) class of III or IV. In addition, patients must have received at least one administration of trial treatment and have had at least one postbaseline NT-proBNP measurement (if the baseline NT-proBNP was ≥650 ng per liter) or NYHA function evaluation (if the baseline NYHA class was III or IV).

†† Patients who could be evaluated for renal response were defined as those with a baseline urinary protein excretion of more than 0.5 g per day. In addition, patients must have received at least one administration of trial treatment and had at least one postbaseline measurement of urinary protein excretion.

control group (1 patient in the control group died before receiving trial treatment). Deaths during the first 60 days of treatment occurred in 13 patients in each group. Death was attributed to adverse events in 23 patients (11.9%) in the daratumumab group and in 14 patients (7.4%) in the control group. Deaths that were attributed to disease progression were less frequent in the

daratumumab group than in the control group (1.0% vs. 4.8%), as were deaths for other reasons (1.0% vs. 2.7%). The majority of adverse events leading to death and of deaths overall occurred in patients with cardiac involvement at baseline. All the patients who died owing to cardiac disorders had cardiac involvement at baseline.

Systemic administration-related reactions to daratumumab occurred in 14 patients (7.3%); all such reactions were of grade 1 or 2. The majority of these patients (86%) had a reaction at the first daratumumab administration. The median time to onset was 1.3 hours (range, 0.2 to 7.3). Local injection-site reactions to any agent occurred in 54 patients (28.0%) in the daratumumab group and in 45 patients (23.9%) in the control group. A total of 21 patients (10.9%) in the daratumumab group had local injection-site reactions related to daratumumab, all of which were of grade 1 or 2. Details of administration- and injection-related reactions are provided in Table S5.

DISCUSSION

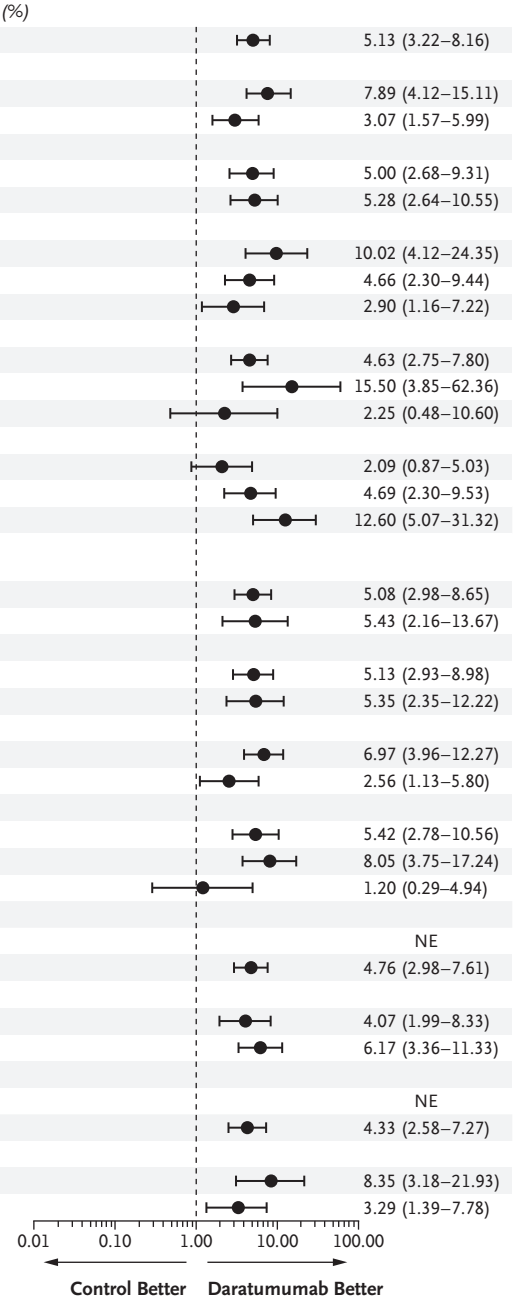
In this phase 3 trial involving patients with newly diagnosed AL amyloidosis, subcutaneous daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone resulted in a significantly higher frequency of a hematologic complete response than bortezomib, cyclophosphamide, and dexamethasone alone. Hematologic responses were deeper and occurred more rapidly in the daratumumab group. Results were consistent for patients with a cardiac stage of III and those with t(11;14) translocation (Fig. 1).

Definitions of hematologic response in patients with AL amyloidosis are evolving. All definitions of complete response that are associated with improved overall survival showed the superiority of daratumumab when analyzed, including complete response defined as negative immunofixation and normalization of the free light-chain ratio without confirmation (International Society of Amyloidosis) (Table S6),[26] a reduction in the absolute involved free light-chain level to 20 mg or less per liter,[25,30,31] and a reduction in the difference between the involved and uninvolved free light-chain levels to less than 10 mg per liter.[5,32] Reductions in the absolute involved free light-chain level to 20 mg or less per liter and in the difference between the involved and uninvolved free light-chain levels to less than 10 mg per liter occurred more rapidly among patients in the daratumumab group (Fig. S3).

A recent clarification to International Society of Amyloidosis criteria[33] defines complete response as negative immunofixation and a free light-chain ratio within the reference range or abnormal free light-chain ratio if the uninvolved free light-chain level is higher than the involved free light-chain level; when these criteria are used, results of the ANDROMEDA trial are consistent with those of the primary analysis that used the definition of complete response specified in our trial (54.4% in the daratumumab group vs. 26.9% in the control group; relative risk ratio, 2.0; 95% CI, 1.5 to 2.6; odds ratio, 3.1; 95% CI, 2.1 to 4.8; P<0.001 for both comparisons) (Table S6). Given the importance of rapid and deep hematologic response to improve the outcomes of patients with AL amyloidosis, these results are promising; outcomes with first-line bortezomib-based regimens have consistently resulted in frequencies of hematologic complete response of approximately 24%.[3-5,26] In addition, 48 patients in the control group went on to receive daratumumab-based therapy in the next line of treatment. Longer follow-up is needed to determine whether the addition of daratumumab to standard therapy improves overall survival.

The percentages of patients who had a cardiac or renal response were substantially higher in the daratumumab group than in the control group, an important finding given that organ responses are also a predictor of improved survival.[34,35] Patients in the daratumumab group were more likely than those in the control group to have survival free from major organ deterioration or hematologic progression, an objective measure of clinically relevant and observable end points for patients with AL amyloidosis. We acknowledge that the maintenance therapy received by patients in the daratumumab group may affect outcomes such as survival free from major organ deterioration or hematologic progression and survival free from major organ deterioration, hematologic progression, or subsequent therapy. Despite this longer duration of therapy, analysis without censoring for subsequent therapy still showed significantly longer survival free from major organ deterioration or hematologic progression in the daratumumab group than in the control group (Table S4).

Subgroup	Control	Daratumumab	Odds Ratio (95% CI)
	no. of patients with a response/total no. (%)		
Overall	35/193 (18)	104/195 (53)	5.13 (3.22–8.16)
Sex			
Male	16/117 (14)	60/108 (56)	7.89 (4.12–15.11)
Female	19/76 (25)	44/87 (51)	3.07 (1.57–5.99)
Age			
<65 yr	20/97 (21)	61/108 (56)	5.00 (2.68–9.31)
≥65 yr	15/96 (16)	43/87 (49)	5.28 (2.64–10.55)
Weight at baseline			
≤65 kg	8/74 (11)	34/62 (55)	10.02 (4.12–24.35)
>65 to 85 kg	14/74 (19)	50/96 (52)	4.66 (2.30–9.44)
>85 kg	13/45 (29)	20/37 (54)	2.90 (1.16–7.22)
Race			
White	28/143 (20)	80/151 (53)	4.63 (2.75–7.80)
Asian	3/34 (9)	18/30 (60)	15.50 (3.85–62.36)
Other	4/16 (25)	6/14 (43)	2.25 (0.48–10.60)
Cardiac stage at baseline			
I	12/43 (28)	21/47 (45)	2.09 (0.87–5.03)
II	16/80 (20)	41/76 (54)	4.69 (2.30–9.53)
IIIA or IIIB	7/70 (10)	42/72 (58)	12.60 (5.07–31.32)
Residence in a country that typically offers transplantation for patients with AL amyloidosis			
Yes	26/146 (18)	77/147 (52)	5.08 (2.98–8.65)
No	9/47 (19)	27/48 (56)	5.43 (2.16–13.67)
Creatinine clearance at baseline			
≥60 ml/min	25/131 (19)	69/126 (55)	5.13 (2.93–8.98)
<60 ml/min	10/62 (16)	35/69 (51)	5.35 (2.35–12.22)
Cardiac involvement at baseline			
Yes	22/137 (16)	80/140 (57)	6.97 (3.96–12.27)
No	13/56 (23)	24/55 (44)	2.56 (1.13–5.80)
Renal stage at baseline			
I	15/101 (15)	52/107 (49)	5.42 (2.78–10.56)
II	15/74 (20)	45/67 (67)	8.05 (3.75–17.24)
III	5/18 (28)	6/19 (32)	1.20 (0.29–4.94)
Alkaline phosphatase at baseline			
Abnormal	0/15	5/11 (45)	NE
Normal	35/178 (20)	99/184 (54)	4.76 (2.98–7.61)
ECOG performance-status score at baseline			
0	14/71 (20)	45/90 (50)	4.07 (1.99–8.33)
1 or 2	21/122 (17)	59/105 (56)	6.17 (3.36–11.33)
Cytogenetic risk at baseline			
High risk	0/19	8/17 (47)	NE
Standard risk	31/147 (21)	74/138 (54)	4.33 (2.58–7.27)
Presence of t(11;14) mutation on FISH			
Yes	7/55 (13)	28/51 (55)	8.35 (3.18–21.93)
No	13/52 (25)	23/44 (52)	3.29 (1.39–7.78)



The safety profiles of daratumumab and bortezomib, cyclophosphamide, and dexamethasone in this trial were consistent with their known profiles and the underlying disease. As in previous trials of daratumumab involving patients with multiple myeloma, an increase in hematologic adverse events and infections was observed.[14] Peripheral neuropathy was more frequent in the daratumumab group than in the control group, but the incidence of grade 3 or 4 peripheral sensory neuropathy was low and similar in the two groups. In a multisystem disease such as AL amyloidosis, it may be difficult to differentiate between disease manifestations and treatment-related complications, and adverse events from multidrug regimens represent a

Figure 1 (facing page). Prespecified Subgroup Analysis of Hematologic Complete Response.

Shown are the results of an analysis of hematologic complete response in prespecified subgroups in the intention-to-treat population, which included all the patients who underwent randomization. Patients in the daratumumab group were assigned to receive treatment with daratumumab, bortezomib, cyclophosphamide, and dexamethasone; patients in the control group were assigned to receive treatment with bortezomib, cyclophosphamide, and dexamethasone. Race was reported by the patient. Cardiac stage is based on the combination of N-terminal pro–B-type natriuretic peptide and high-sensitivity cardiac troponin T. Patients who had a cardiac stage of IIIB at screening were excluded from the trial according to the protocol. The category of cardiac stage IIIA or IIIB includes patients who had a cardiac stage of IIIA at screening but progressed to stage IIIB at cycle 1, day 1. Renal stage is based on the combination of estimated glomerular filtration rate and urinary protein excretion. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. High cytogenetic risk was defined by fluorescence in situ hybridization (FISH) testing as a t(4;14) mutation, t(14;16) mutation, or 17p deletion or by karyotype testing as a t(4;14) mutation or 17p deletion. AL denotes immunoglobulin light chain, and NE could not be estimated.

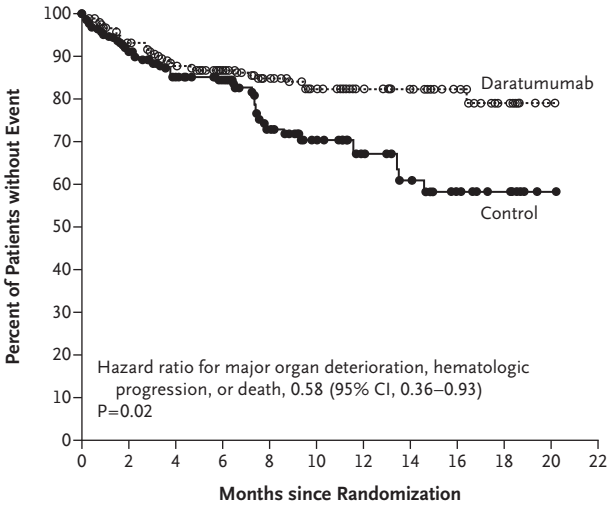


Figure 2. Kaplan–Meier Estimates of Survival Free from Major Organ Deterioration or Hematologic Progression.

Shown are the results of the Kaplan–Meier estimates of survival from major organ deterioration or hematologic progression among patients in the intention-to-treat population. Major organ deterioration was defined as end-stage cardiac or renal failure.

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

Event	Daratumumab Group (N=193)		Control Group (N=188)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Diarrhea	69 (35.8)	11 (5.7)	57 (30.3)	7 (3.7)
Peripheral edema	69 (35.8)	6 (3.1)	68 (36.2)	11 (5.9)
Constipation	66 (34.2)	3 (1.6)	54 (28.7)	0
Peripheral sensory neuropathy	60 (31.1)	5 (2.6)	37 (19.7)	4 (2.1)
Fatigue	52 (26.9)	8 (4.1)	53 (28.2)	6 (3.2)
Nausea	52 (26.9)	3 (1.6)	52 (27.7)	0
Upper respiratory tract infection	50 (25.9)	1 (0.5)	21 (11.2)	1 (0.5)
Lymphopenia	36 (18.7)	25 (13.0)	28 (14.9)	19 (10.1)
Hypokalemia	24 (12.4)	3 (1.6)	28 (14.9)	10 (5.3)
Neutropenia	21 (10.9)	10 (5.2)	12 (6.4)	5 (2.7)
Pneumonia	21 (10.9)	15 (7.8)	12 (6.4)	8 (4.3)
Syncope	14 (7.3)	10 (5.2)	12 (6.4)	12 (6.4)
Cardiac failure†	18 (9.3)	12 (6.2)	14 (7.4)	9 (4.8)

* The safety population included patients who received at least one administration of trial treatment. Shown are adverse events of any grade that occurred in more than 25% of the patients in either group and grade 3 or 4 events that occurred in at least 5% of the patients in either group.

† This category includes overall and congestive cardiac failure.

challenge for these patients, who are often frail and have multiorgan involvement. When adjusted for exposure to trial treatment, the incidence of overall and grade 3 or 4 adverse events was lower in the daratumumab group than in the control group (Table S7). The incidences of all deaths and deaths due to adverse events within 60 days after the first dose of trial treatment were balanced between the treatment groups. Overall, deaths in both groups were primarily due to AL amyloidosis–related cardiomyopathy, reported either as an adverse event or as progression of organ disease.

From a clinical standpoint, subcutaneous daratumumab provides important advantages for the population of patients with AL amyloidosis. These include reduced systemic administration-related reactions and negligible volume of administration.[36]

In this prospective, randomized trial involving patients with newly diagnosed AL amyloidosis, the addition of subcutaneous daratumumab to bortezomib, cyclophosphamide, and dexamethasone resulted in significantly better outcomes.

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