ORIGINAL ARTICLE

Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma

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ABSTRACT

BACKGROUND

The immunostimulatory monoclonal antibody elotuzumab plus lenalidomide and dexamethasone has been shown to be effective in patients with relapsed or refractory multiple myeloma. The immunomodulatory agent pomalidomide plus dexamethasone has been shown to be effective in patients with multiple myeloma that is refractory to lenalidomide and a proteasome inhibitor.

METHODS

Patients with multiple myeloma that was refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor were randomly assigned to receive elotuzumab plus pomalidomide and dexamethasone (elotuzumab group) or pomalidomide and dexamethasone alone (control group). The primary end point was investigator-assessed progression-free survival.

RESULTS

A total of 117 patients were randomly assigned to the elotuzumab group (60 patients) or the control group (57 patients). After a minimum follow-up period of 9.1 months, the median progression-free survival was 10.3 months in the elotuzumab group and 4.7 months in the control group. The hazard ratio for disease progression or death in the elotuzumab group as compared with the control group was 0.54 (95% confidence interval [CI], 0.34 to 0.86; P=0.008). The overall response rate was 53% in the elotuzumab group as compared with 26% in the control group (odds ratio, 3.25; 95% CI, 1.49 to 7.11). The most common grade 3 or 4 adverse events were neutropenia (13% in the elotuzumab group vs. 27% in the control group), anemia (10% vs. 20%), and hyperglycemia (8% vs. 7%). A total of 65% of the patients in each group had infections. Infusion reactions occurred in 3 patients (5%) in the elotuzumab group.

CONCLUSIONS

Among patients with multiple myeloma in whom treatment with lenalidomide and a proteasome inhibitor had failed, the risk of progression or death was significantly lower among those who received elotuzumab plus pomalidomide and dexamethasone than among those who received pomalidomide plus dexamethasone alone. (Funded by Bristol-Myers Squibb and AbbVie Biotherapeutics; ELOQUENT-3 ClinicalTrials.gov number, NCT02654132.)

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

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Despite the widespread use of immunomodulatory agents and proteasome inhibitors, relapsed or refractory multiple myeloma is common, in part because of clonal heterogeneity and genomic complexity.[1] The prognosis is poor once the disease becomes refractory to proteasome inhibitors and immunomodulatory drugs; indeed, a median overall survival of 9 months was reported after treatment failure with bortezomib and lenalidomide or thalidomide.[2]

Therapies that combine agents with different mechanisms of action have improved outcomes in patients with relapsed or refractory multiple myeloma. The triplet regimen of elotuzumab plus lenalidomide and dexamethasone is indicated for patients with multiple myeloma who have received at least one previous therapy.[3,4] Elotuzumab is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody that binds signaling lymphocytic activation molecule F7 (SLAMF7), a glycoprotein that is highly expressed on the surface of myeloma cells, natural killer cells, and some immune cells, but not on other normal tissues.[5,6] The mechanism of action of elotuzumab includes natural killer cell–mediated antibody-dependent cellular cytotoxicity on SLAMF7-expressing myeloma cells and direct activation of natural killer cells.[5-9] In addition, elotuzumab may facilitate macrophage-mediated killing of myeloma cells.[10] In the phase 3 ELOQUENT-2 trial, elotuzumab plus lenalidomide and dexamethasone was associated with a risk of progression or death that was 30% lower than that with lenalidomide and dexamethasone, without markedly increased toxic effects[11]; both efficacy and safety findings were sustained over an extended 5-year follow-up period.[12]

Pomalidomide, an immunomodulatory agent, has structural and mechanistic properties that are similar to those of lenalidomide, but it may also elicit distinct biologic effects.[13,14] Pomalidomide is approved in combination with dexamethasone for patients with multiple myeloma who have received at least two previous therapies, including lenalidomide and a proteasome inhibitor, and whose disease is refractory to their last therapy.[15,16] In pivotal phase 2 and phase 3 trials, overall response rates of 33% and 31%, respectively, and a median progression-free survival of approximately 4 months were observed in patients who had previously received lenalidomide and bortezomib.[17,18] In the United States, pomalidomide in combination with daratumumab and dexamethasone is also approved for use in patients who have received previous treatment with lenalidomide and a proteasome inhibitor[19]; a noncomparative trial involving 103 patients who received this combination regimen showed an overall response rate of 60% and median progression-free survival of 8.8 months.[20]

The combination of elotuzumab and pomalidomide may have synergistic clinical effects in patients with multiple myeloma that relapsed after treatment with lenalidomide or is refractory to lenalidomide. Because immunomodulatory drugs act through several mechanisms,[21,22] pomalidomide may enhance the immune cell–mediated killing of myeloma cells by elotuzumab. In addition to the potential for increased efficacy with elotuzumab and pomalidomide, the favorable, well-characterized safety profile of elotuzumab plus lenalidomide and dexamethasone suggests that the combination of elotuzumab and pomalidomide is unlikely to result in markedly increased toxic effects.[11,12,23] Indeed, initial safety results from a noncomparative phase 2 study of elotuzumab plus pomalidomide and dexamethasone are consistent with the predicted level of toxic effects of this regimen.[24]

Here, we report the results from ELOQUENT-3, a randomized trial in which we assessed the efficacy and safety of the monoclonal antibody elotuzumab plus pomalidomide and dexamethasone as compared with pomalidomide and dexamethasone alone in patients with refractory or relapsed and refractory multiple myeloma who had previously received treatment with lenalidomide and a proteasome inhibitor.

METHODS

STUDY DESIGN AND OVERSIGHT

This multicenter, randomized, open-label, phase 2 trial was designed by the sponsors (Bristol-Myers Squibb and AbbVie Biotherapeutics) and investigators. The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. The protocol, which was approved by the institutional review board or independent ethics committee at each participating trial center before the start of the trial, is available with the full text of this article at NEJM.org. All the patients provided written informed consent. The investigators collected the data, which were maintained by the sponsors. The manuscript was prepared with

assistance from professional medical writers who were funded by Bristol-Myers Squibb. The authors contributed to the development of the manuscript, approved the final version, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were 18 years of age or older and had measurable multiple myeloma and an Eastern Cooperative Oncology Group performance status score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability). Patients had received two or more previous lines of therapy, including at least two consecutive cycles of lenalidomide and a proteasome inhibitor alone or in combination. Eligible patients had multiple myeloma that was refractory (disease progressed while the patient was receiving treatment or within 60 days after treatment discontinuation) or relapsed and refractory (disease progressed within 6 months after treatment discontinuation after the patient had at least a partial response) to lenalidomide and a proteasome inhibitor. In addition, all patients had multiple myeloma that was refractory to their last therapy. Key exclusion criteria were previous treatment with pomalidomide, active plasma-cell leukemia, and a creatinine clearance of less than 45 ml per minute. Further details regarding the inclusion and exclusion criteria can be found in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive elotuzumab plus pomalidomide and dexamethasone (elotuzumab group) or pomalidomide and dexamethasone (control group) (Fig. S1 in the Supplementary Appendix). Randomization was stratified according to the number of previous lines of therapy (2 or 3 vs. ≥4) and the International Staging System disease stage at the time of trial enrollment (stage I or II vs. III, with higher stages indicating more severe disease). Additional details are provided in the Supplementary Appendix.

Treatment was administered in 28-day cycles until disease progression, development of unacceptable toxic effects, or withdrawal of consent (Fig. S1 in the Supplementary Appendix). Patients in the elotuzumab group received intravenous elotuzumab at a dose of 10 mg per kilogram of body weight on days 1, 8, 15, and 22 during cycles 1 and 2 and 20 mg per kilogram on day 1 of each cycle thereafter. Patients in both the elotuzumab group and the control group received oral pomalidomide at a dose of 4 mg per day on days 1 through 21 of each cycle. Patients received oral dexamethasone at a dose of 40 mg (patients ≤75 years) or 20 mg (patients >75 years) per week, except on the days of elotuzumab administration, when patients in the elotuzumab group received dexamethasone both orally (28 mg in patients ≤75 years or 8 mg in patients >75 years) and intravenously (8 mg).

Prophylaxis against thromboembolism was required for all patients according to institutional guidelines or at the discretion of the investigator. Patients in the elotuzumab group received the following medications 45 to 90 minutes before each dose of elotuzumab: diphenhydramine at a dose of 25 to 50 mg or equivalent, ranitidine at a dose of 50 mg or equivalent, and acetaminophen at a dose of 650 to 1000 mg.

END POINTS AND ASSESSMENTS

The primary end point was investigator-assessed progression-free survival, which was defined as the time from randomization to the first occurrence of disease progression (not including clinical deterioration) or death from any cause, whichever occurred first. The analysis was based on the intention-to-treat population, which included all patients who underwent randomization. Secondary end points were the overall response rate (partial response or better), as assessed by the investigators, and overall survival. Exploratory end points included the time to response, the duration of response, and safety (end points are described in detail in the Supplementary Appendix). An independent review committee whose members were unaware of the treatment assignments also assessed progression-free survival and overall response rate to confirm the results of the investigator assessment. Response assessments were based on International Myeloma Working Group consensus criteria,[25-27] except for assessment of minor (minimal) response, which was derived from European Society for Blood and Marrow Transplantation criteria (see the Supplementary Appendix).[28]

STATISTICAL ANALYSIS

For the final analysis of progression-free survival, we calculated that 114 patients would have to undergo randomization and 71 events (disease

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Elotuzumab Group (N=60)	Control Group (N=57)
Median age (range) — yr	69 (43–81)	66 (36–81)
Age category — no. (%)		
<65 yr	22 (37)	22 (39)
≥65 yr	38 (63)	35 (61)
<75 yr	47 (78)	45 (79)
≥75 yr	13 (22)	12 (21)
Male sex — no. (%)	32 (53)	35 (61)
International Staging System stage — no. (%)†		
I or II	53 (88)	50 (88)
III	7 (12)	7 (12)
Serum lactate dehydrogenase level — no. (%)		
<300 U/liter	43 (72)	41 (72)
≥300 U/ liter	14 (23)	15 (26)
Data not available	3 (5)	1 (2)
Cytogenetic abnormalities — no. (%)‡		
Del17p, t(4;14), or t(14;16)		
Yes	13 (22)	14 (25)
No	31 (52)	27 (47)
Data not available	16 (27)	16 (28)
1q21		
Yes	25 (42)	27 (47)
No	20 (33)	13 (23)
Data not available	15 (25)	17 (30)
Median no. of previous lines of therapy (range)	3 (2–8)	3 (2–8)
Number of previous lines of therapy — no. (%)		
2 or 3	36 (60)	36 (63)
≥4	24 (40)	21 (37)
Previous stem-cell transplantation — no. (%)	31 (52)	33 (58)
Previous therapies — no. (%)§		
Bortezomib	60 (100)	57 (100)
Lenalidomide	59 (98)	57 (100)
Melphalan	38 (63)	36 (63)
Thalidomide	25 (42)	19 (33)
Doxorubicin	18 (30)	15 (26)
Carfilzomib	9 (15)	16 (28)
Ixazomib	5 (8)	2 (4)
Daratumumab	1 (2)	2 (4)
Refractory status of disease to lenalidomide — no. (%)		
Refractory	54 (90)	48 (84)
Relapsed and refractory	5 (8)	7 (12)

Table 1. (Continued.)

Characteristic	Elotuzumab Group (N=60)	Control Group (N=57)
Refractory status of disease to a proteasome inhibitor — no. (%)		
Refractory	47 (78)	47 (82)
Relapsed and refractory	13 (22)	8 (14)
Refractory status of disease to lenalidomide and a proteasome inhibitor — no. (%)¶		
Refractory to both	41 (68)	41 (72)
Relapsed and refractory to both	0	3 (5)
Refractory to one, relapsed and refractory to the other	18 (30)	9 (16)
Median time since diagnosis of multiple myeloma (range) — yr	4.8 (0.5–21.9)	4.4 (0.7–17.5)

* Included are all patients who underwent randomization.
† The International Staging System consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter).
‡ Fluorescence in situ hybridization was performed at a central laboratory to detect cytogenetic mutations. Positivity for each cytogenetic mutation was based on the identification of at least 1 abnormal cell out of a minimum of 100 cells examined, with the exception of del17p, which required at least 60% abnormal cells. Positivity for 1q21 required at least three copies of 1q21 in 1 cell.
§ Only previous therapies of interest are reported. As a result of a protocol deviation, one patient in the elotuzumab group did not receive previous treatment with lenalidomide.
¶ A total of five patients (one in the elotuzumab group and four in the control group) had disease with an unknown status with respect to either lenalidomide or a proteasome inhibitor (protocol deviations).

progression or death) would have to occur to provide the trial with 85% power to detect a hazard ratio for disease progression or death of 0.57 in the elotuzumab group as compared with the control group, using a log-rank test with a two-sided experiment-wise alpha of 0.2 (additional details are provided in the Supplementary Appendix). Progression-free survival and its associated median were estimated by the Kaplan–Meier method. Progression-free survival was compared with the use of a two-sided stratified log-rank test, and the hazard ratio of the elotuzumab group to the control group was estimated with a stratified Cox proportional-hazards model, with treatment as the single covariate. Subgroup analyses of progression-free survival were also performed.

The overall response rate in the two groups (final analysis) was compared with the use of a Cochran–Mantel–Haenszel test and its corresponding estimate of treatment odds ratio. Preliminary overall survival was estimated by the Kaplan–Meier method; a preliminary hazard ratio was estimated with the use of a stratified Cox proportional-hazards model, with treatment as the single covariate.

RESULTS

PATIENTS AND TREATMENT

Patients were enrolled from March 2016 through April 2017 at 43 sites in Europe, North America, Japan, and Australia. Overall, 60 patients were randomly assigned to the elotuzumab group and 57 to the control group; all but 2 patients (both in the control group) received their assigned treatment (Fig. S2 in the Supplementary Appendix). The characteristics of the two treatment groups were generally well balanced at baseline (Table 1). The median number of previous lines of therapy was 3 (range, 2 to 8) in both groups. In all, 68% of the patients in the elotuzumab group and 72% in the control group had multiple myeloma that was refractory to both lenalidomide and a proteasome inhibitor.

At the time of the database lock (February 2018), after a minimum follow-up period of 9.1 months, 40% of treated patients in the elotuzumab group, as compared with 20% in the control group, were continuing to receive the assigned treatment (Fig. S2 in the Supplementary Appendix). The main reason for discontinuation

of the trial treatment was disease progression (43% of the treated patients in the elotuzumab group and 56% of the treated patients in the control group). The median number of treatment cycles was 9 (interquartile range, 4 to 13) in the elotuzumab group and 5 (interquartile range, 3 to 10) in the control group.

A total of 55% of the patients in the elotuzumab group and 53% in the control group received at least 90% of the planned doses of pomalidomide. Pomalidomide dose reductions occurred in 20% of the patients in each treatment group. Elotuzumab dose reductions were not permitted, but dose delays occurred in 33% of the patients in the elotuzumab group.

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

Shown are the results of the Kaplan–Meier analysis of the primary end point, progression-free survival, in all patients who underwent randomization (Panel A) and the results of an analysis of progression-free survival in subgroups defined according to baseline characteristics (Panel B). The triangles and circles in Panel A represent censored data. The International Staging System (ISS) consists of three stages, with higher stages indicating more severe disease: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter). Risk categories were based on International Myeloma Working Group (IMWG) risk stratification. High risk was defined as ISS stage II or III and t(4;14) translocation or chromosome 17p deletion (del17p) abnormality. Low risk was defined as ISS stage I or II and absence of t(4;14) translocation, del17p, and 1q21 abnormalities, and an age younger than 55 years. Standard risk was defined as not meeting the criteria for high risk or low risk. LDH denotes lactate dehydrogenase.

EFFICACY

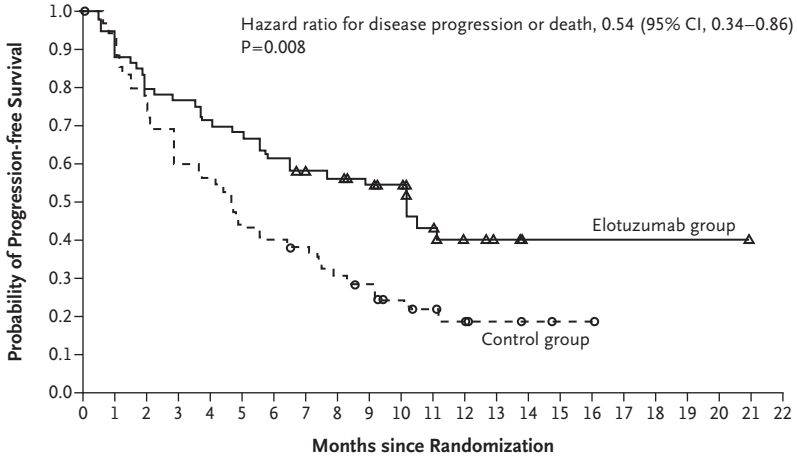
The median investigator-assessed progression-free survival was 10.3 months (95% confidence interval [CI], 5.6 to not reached) in the elotuzumab group and 4.7 months (95% CI, 2.8 to 7.2) in the control group. The hazard ratio for disease progression or death was 0.54 (95% CI, 0.34 to 0.86; P=0.008), which represents a risk of progression or death that was 46% lower in the elotuzumab group than in the control group (Fig. 1A). The corresponding Kaplan–Meier curves of progression-free survival showed early separation that was sustained over time. Thus, the progression-free survival benefit of elotuzumab plus pomalidomide and dexamethasone was significant not only at the prespecified alpha level of 0.2 that the trial was powered to detect but also at the more stringent significance level of 0.05.

The progression-free survival benefit of elotuzumab was consistently observed across key patient subgroups that were defined according to baseline characteristics, including patients whose disease was refractory to both lenalidomide and a proteasome inhibitor, patients who were assessed as having high-risk disease on the basis of International Myeloma Working Group criteria, and patients with at least one cytogenetic abnormality (chromosome 17p deletion, t[4;14] translocation, or t[14;16] translocation) or at least one of the aforementioned cytogenetic abnormalities or a high lactate dehydrogenase level (Fig. 1B, and Fig. S3 in the Supplementary Appendix). The benefit of elotuzumab was also seen in patients who had received at least four previous lines of therapy; the median progression-free survival among these patients was 10.3 months (95% CI, 3.7 to not reached) in the elotuzumab group and 4.3 months (95% CI, 1.9 to 9.3) in the control group (hazard ratio, 0.51; 95% CI, 0.24 to 1.08).

The median progression-free survival in the overall population as assessed by the independent review committee was 10.3 months (95% CI, 6.5 to not reached) in the elotuzumab group and 4.7 months (95% CI, 2.8 to 7.6) in the control group; the hazard ratio for progression-free survival was 0.51 (95% CI, 0.32 to 0.82) in favor of the elotuzumab group. Concordance between investigator assessments and independent review committee assessments of progression-free survival was 85%.

According to investigator assessments, 20% of the patients in the elotuzumab group and 9% in the control group had a very good partial response or better. The overall response rate was higher in the elotuzumab group (53%; 95% CI, 40 to 66) than in the control group (26%; 95% CI, 16 to 40), with an odds ratio of 3.25 (95% CI, 1.49 to 7.11) (Table 2). The overall response rate as assessed by the independent review committee was 58% (95% CI, 45 to 71) in the elotuzumab group as compared with 25% (95% CI, 14 to 38) in the control group, with an odds ratio of 4.62 (95% CI, 2.05 to 10.43). Concordance between investigator assessments and independent review committee assessments of overall response rate was 91%.

A Progression-free Survival



No. at Risk

Elotuzumab group	60	54	48	46	43	41	37	33	32	27	25	15	7	4	1	1	1	1	1	1	1	0
Control group	57	51	42	33	31	24	22	20	16	14	10	8	6	3	2	1	1	0	0	0	0	0

B Subgroup Analysis of Progression-free Survival

Subgroup	Elotuzumab Group *no. of events/total no. of patients*	Control Group *no. of events/total no. of patients*	Hazard Ratio (95% CI)
Age			
<65 yr	12/22	19/22	0.44 (0.21–0.91)
≥65 yr	20/38	24/35	0.61 (0.33–1.11)
<75 yr	25/47	34/45	0.52 (0.31–0.87)
≥75 yr	7/13	9/12	0.62 (0.23–1.67)
ISS stage at study entry			
I or II	27/53	36/50	0.54 (0.33–0.90)
III	5/7	7/7	0.52 (0.16–1.69)
IMWG risk category			
High	4/4	7/7	0.09 (0.01–0.78)
Low or standard	22/46	28/41	0.58 (0.33–1.02)
Serum LDH level at study entry			
<300 U/liter	21/43	31/41	0.46 (0.26–0.80)
≥300 U/liter	8/14	12/15	0.75 (0.31–1.84)
Del17p, t(4;14), t(14;16), or LDH ≥300 U/liter			
Yes	13/23	23/27	0.55 (0.28–1.10)
No	8/22	11/17	0.47 (0.19–1.16)
Del17p, t(4;14), or t(14;16)			
Yes	9/13	13/14	0.52 (0.22–1.25)
No	13/31	18/27	0.56 (0.27–1.14)
1q21			
Yes	15/25	22/27	0.56 (0.29–1.09)
No	6/20	8/13	0.43 (0.15–1.24)
No. of previous lines of therapy			
2–3	20/36	27/36	0.55 (0.31–0.98)
≥4	12/24	16/21	0.51 (0.24–1.08)
Previous stem-cell transplantation			
Yes	18/31	25/33	0.58 (0.31–1.06)
No	14/29	18/24	0.50 (0.25–1.01)
Disease refractory to lenalidomide and a proteasome inhibitor			
Yes	23/41	30/41	0.56 (0.33–0.97)
No	9/19	13/16	0.51 (0.21–1.19)

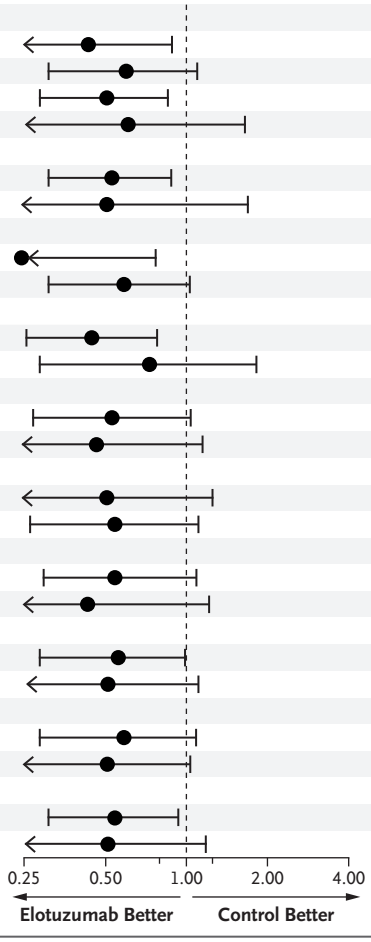


Table 2. Investigator-Assessed Treatment Response.*

Response Category	Elotuzumab Group (N=60)	Control Group (N=57)
Overall response — no. (% [95% CI])	32 (53 [40–66])	15 (26 [16–40])
Best overall response — no. (%)		
Stringent complete response	2 (3)	0
Complete response	3 (5)	1 (2)
Very good partial response	7 (12)	4 (7)
Combined response†	12 (20)	5 (9)
Partial response	20 (33)	10 (18)
Minor response	4 (7)	8 (14)
Stable disease	13 (22)	16 (28)
Progressive disease	7 (12)	9 (16)
Response could not be evaluated or was not reported	4 (7)	9 (16)

* Included are all patients who underwent randomization. Definitions of response and disease progression were modified from International Myeloma Working Group criteria,[25,26] except for the definition of minor (minimal) response, which was derived from European Society for Blood and Marrow Transplantation criteria[28] (see the Supplementary Appendix).
† Combined response was defined as very good partial response or better.

Overall survival data were immature at the time of the analysis; however, a trend favoring the elotuzumab group was observed (hazard ratio for death, 0.62; 95% CI, 0.30 to 1.28) (Fig. 2). There were 13 deaths (22%) in the elotuzumab group and 18 deaths (32%) in the control group; these 31 deaths represented 40% of the 78 deaths that would need to occur for the final analysis of overall survival. Disease progression was the main cause of death in both groups (13% of the treated patients in the elotuzumab group and 25% of the treated patients in the control group).

The median time to response was similar in the two groups: 2.0 months in the elotuzumab group and 1.9 months in the control group. The median duration of response was not reached (95% CI, 8.3 to not reached) in the elotuzumab group and was 8.3 months (95% CI, 4.6 to not reached) in the control group (Fig. S4 in the Supplementary Appendix).

SAFETY

Adverse events of any cause that were reported in at least 10% of the patients in either treatment group and adverse events of special interest are shown in Table 3. Grade 3 or 4 adverse events were reported in 57% of the patients in the elotuzumab group and in 60% in the control group; the most common events were neutropenia (13% in the elotuzumab group vs. 27% in the control group), anemia (10% vs. 20%), and hyperglycemia (8% vs. 7%). Infections of any grade were reported in 65% of the patients in each of the two groups, with grade 3 or 4 infections occurring in 13% of the patients in the elotuzumab group and in 22% in the control group. When we adjusted for exposure to the trial medication, the rate of infection was 182 events per 100 patient-years in the elotuzumab group and 230 events per 100 patient-years in the control group (Table S1 in the Supplementary Appendix).

The incidence of serious adverse events was 53% in the elotuzumab group and 55% in the control group. One patient in the control group had a second primary cancer (grade 4 invasive breast carcinoma) that resulted in discontinuation of treatment. The most common treatment-related adverse events were neutropenia (18% in the elotuzumab group vs. 20% in the control group), hyperglycemia (18% vs. 11%), and anemia (10% vs. 15%) (Table S2 in the Supplementary Appendix).

Adverse events that led to discontinuation of treatment occurred in 18% of the patients in the elotuzumab group and in 24% of the patients in the control group; infections led to discontinuation in 7% of the patients in the elotuzumab group and in 5% in the control group. No deaths in either group were considered by the investigators to be due to the trial medication.

At the time of the database lock, a total of 816 infusions of elotuzumab had been adminis-

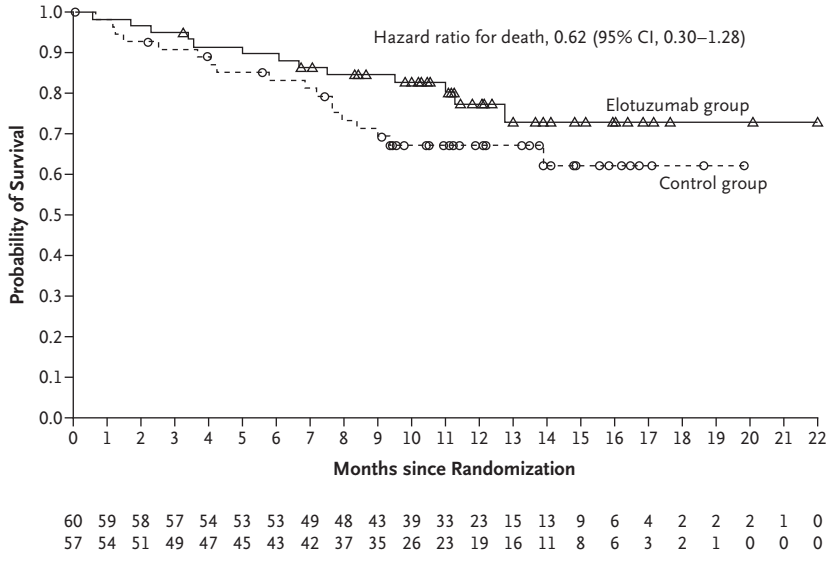


Figure 2. Preliminary Overall Survival.

Shown are the results of the Kaplan–Meier analysis of overall survival in all patients who underwent randomization. The triangles and circles represent censored data.

tered; three infusion reactions had occurred (deafness, chest discomfort, and an unspecified infusion-related reaction occurred in one patient each). All the infusion reactions were grade 1 or 2, and all resolved.

DISCUSSION

The findings from this randomized trial showed that the addition of the monoclonal antibody elotuzumab to pomalidomide and dexamethasone resulted in a significant improvement over pomalidomide and dexamethasone alone in treatment outcomes of relapsed or refractory multiple myeloma. Specifically, the Kaplan–Meier curves for progression-free survival showed early separation that was sustained over time, with a risk of progression or death that was 46% lower in the elotuzumab group than in the control group. In addition, the odds ratio for the overall response rate showed that patients in the elotuzumab group were 3.25 times as likely to have a response to treatment as patients in the control group. These clinical data confirm the findings of preclinical studies in mice, which showed that elotuzumab, pomalidomide, and dexamethasone synergize to kill myeloma cells (Fig. S5 in the Supplementary Appendix).

Therapies approved for patients with multiple myeloma that is refractory to lenalidomide and a proteasome inhibitor include pomalidomide and dexamethasone, daratumumab monotherapy, and daratumumab plus pomalidomide and dexamethasone.[16,19] In the phase 3 trial (MM-003) of pomalidomide and dexamethasone, the median progression-free survival was 4.0 months and the overall response rate was 31%,[18] findings that are consistent with those reported in the control group in our trial (4.7 months and 26%, respectively). In the current trial, the median progression-free survival with elotuzumab plus pomalidomide and dexamethasone was 10.3 months and the overall response rate was 53%, which shows the superiority of that treatment over pomalidomide and dexamethasone alone. In a noncomparative phase 1b trial that evaluated daratumumab plus pomalidomide and dexamethasone in 103 patients who had received a median of four previous lines of therapy, the median progression-free survival was 8.8 months and the overall response rate was 60%.[20] In our trial, the treatment effect of elotuzumab was observed across several subgroups, including patients who had received at least four previous lines of therapy, with a median progression-free survival of 10.3 months as compared with 4.3 months in the control group, and a hazard ratio for disease progression or death of 0.51. The benefit of combining a

Table 3. Adverse Events (All Treated Patients).*

Event	Elotuzumab Group (N=60)		Control Group (N=55)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	58 (97)	34 (57)	52 (95)	33 (60)
Nonhematologic adverse events				
Constipation	13 (22)	1 (2)	6 (11)	0
Hyperglycemia	12 (20)	5 (8)	8 (15)	4 (7)
Diarrhea	11 (18)	0	5 (9)	0
Fatigue	9 (15)	0	9 (16)	2 (4)
Bone pain	9 (15)	2 (3)	5 (9)	0
Dyspnea	9 (15)	2 (3)	4 (7)	1 (2)
Pyrexia	8 (13)	0	14 (25)	0
Insomnia	8 (13)	1 (2)	6 (11)	0
Peripheral edema	8 (13)	0	4 (7)	0
Muscle spasms	8 (13)	0	3 (5)	0
Asthenia	7 (12)	1 (2)	5 (9)	2 (4)
Rash	6 (10)	0	6 (11)	1 (2)
Hypokalemia	4 (7)	0	7 (13)	3 (5)
Increased blood creatinine	3 (5)	0	6 (11)	2 (4)
Malignant neoplasm progression	1 (2)	1 (2)	6 (11)	2 (4)
Hematologic adverse events	31 (52)	23 (38)	30 (55)	23 (42)
Anemia	15 (25)	6 (10)	20 (36)	11 (20)
Neutropenia	14 (23)	8 (13)	17 (31)	15 (27)
Thrombocytopenia	9 (15)	5 (8)	10 (18)	3 (5)
Lymphopenia	6 (10)	5 (8)	1 (2)	1 (2)
Adverse events of special interest				
Infections	39 (65)	8 (13)	36 (65)	12 (22)
Nasopharyngitis	10 (17)	0	8 (15)	0
Respiratory tract infection	10 (17)	0	5 (9)	1 (2)
Upper respiratory tract infection	7 (12)	0	8 (15)	1 (2)
Bronchitis	6 (10)	1 (2)	5 (9)	1 (2)
Pneumonia	4 (7)	3 (5)	6 (11)	5 (9)
Herpes zoster infection	3 (5)	0	1 (2)	0
Other adverse events				
Vascular disorders	8 (13)	2 (3)	5 (9)	0
Cardiac disorders	7 (12)	4 (7)	6 (11)	2 (4)
Neoplasms†	1 (2)	1 (2)	12 (22)	6 (11)

* Listed are adverse events that occurred on or after the first dose until 60 days after the last dose. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Only adverse events that were reported in at least 10% of patients in either treatment group are shown, except for adverse events of special interest, for which no cutoff in percentage was applied. Adverse events that resulted in death (grade 5 events) occurred in five patients (8%) in the elotuzumab group and in eight patients (15%) in the control group. In the elotuzumab group, three patients died from infection and one each from cardiac failure and general physical health deterioration. In the control group, one patient died from infection, one from multiorgan failure and infection, one from myocardial infarction, one from plasma-cell myeloma, and four from malignant neoplasm progression.

† This term includes malignant, benign, and unspecified neoplasms. Grade 5 neoplasms were reported in five patients (9%) in the control group and in no patients in the elotuzumab group.

third agent with pomalidomide and dexamethasone has also been shown in a randomized, phase 2 trial of pomalidomide and dexamethasone with or without cyclophosphamide, in which the overall response rate was 1.7 times as high in the cyclophosphamide group as in the control group.[29] In the current trial, the overall response rate in the elotuzumab group was twice as high as the rate in the control group. Collectively, these data suggest that elotuzumab plus pomalidomide and dexamethasone is an effective combination and represents an alternative treatment option to other pomalidomide and dexamethasone–based regimens. However, caution is warranted when comparing results across trials.

Elotuzumab plus pomalidomide and dexamethasone was associated with a rate of grade 3 or 4 adverse events (57%) that was similar to that observed with pomalidomide and dexamethasone alone (60%); no new safety signals were identified beyond the findings reported with other elotuzumab and pomalidomide regimens.[11,12,17,18,23] Despite a longer duration of exposure to the trial medication in the elotuzumab group than in the control group, the incidence of adverse events that led to discontinuation of treatment was lower in the elotuzumab group than in the control group. When we adjusted for exposure to the trial medication, infections were less common in the elotuzumab group than in the control group. The occurrence of infusion reactions was minimal, a finding that is consistent with that in other elotuzumab trials.[11,23] Treatment with pomalidomide and dexamethasone has been reported to be associated with neutropenia, a risk that may be increased with the addition of daratumumab.[20] In contrast, the addition of elotuzumab did not result in a higher rate of treatment-related neutropenia than that without elotuzumab (18% in the elotuzumab group and 20% in the control group). Neutropenia and anemia of any cause were less common in the elotuzumab group than in the control group, even though the dose intensity of pomalidomide in the two groups was balanced. In addition, the similarity of the dose intensity of pomalidomide in the two groups suggests that elotuzumab does not affect pomalidomide dosing. Overall, these results support the initial findings of an ongoing noncomparative, phase 2 trial,[24] which suggests that elotuzumab plus pomalidomide and dexamethasone has a safety profile that is similar to that of elotuzumab plus lenalidomide and dexamethasone and that elotuzumab is not associated with a higher rate of toxic effects than pomalidomide and dexamethasone alone.[17,18]

This trial, which was specifically designed to detect a large treatment effect in a relatively small sample, showed a significant benefit of elotuzumab plus pomalidomide and dexamethasone with respect to the primary end point of progression-free survival. Furthermore, the progression-free survival results, as assessed by the investigators, were confirmed by blinded, independent central review. Monthly administration of elotuzumab starting in cycle 3 was effective and provided a potentially more convenient dosing schedule for patients than the approved dosing schedule of every other week.[3,4] The results thus far are encouraging, but extended follow-up is warranted to determine long-term efficacy and safety outcomes, including the final analysis of overall survival. This trial showed the therapeutic potential of a second elotuzumab-based combination therapy for relapsed or refractory multiple myeloma. Elotuzumab plus lenalidomide and dexamethasone is approved for multiple myeloma after treatment with at least one previous therapy[3,4] on the basis of the results of the phase 3 ELOQUENT-2 trial, in which most patients had not received lenalidomide.[11] In contrast, patients in the current trial had multiple myeloma that was refractory or relapsed and refractory to lenalidomide.

In conclusion, among patients with multiple myeloma that was refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor, the combination of elotuzumab plus pomalidomide and dexamethasone resulted in significantly longer progression-free survival and a higher overall response rate than pomalidomide and dexamethasone alone. The previously reported safety profile of this regimen was confirmed and was similar to that of pomalidomide and dexamethasone alone.

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

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