Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015;373:621-31. DOI: 10.1056/NEJMoa1505654

Supplementary Appendix

Supplement to: Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma.

Contents

Additional Methods

Eligibility criteria

A maximum of 10% of patients with prior lenalidomide could enroll in the study. This limit was imposed for ethical reasons to limit the number of patients in the control group receiving a regimen from which they may not derive significant benefit. Prior lenalidomide exposure was permitted if patients achieved a best response of a partial response or better, did not have disease progression during lenalidomide therapy or within 9 months of the last dose, did not discontinue lenalidomide due to a grade 3 or higher related adverse event, did not receive more than nine cycles of lenalidomide, and had at least 9 months between the last dose and progression.

Patients with non-secretory, oligosecretory, or serum-free light chain–only myeloma, active plasma cell leukemia, and/or clinically significant cardiac disease were excluded from the study.

Patients with an absolute neutrophil count of <1000 cells per mm^3, platelet count of <75,000 cells per mm^3, and/or hemoglobin value of <8 g per deciliter were excluded. Patients with creatinine clearance of <30 mL per minute measured by 24-hour urine collection or estimated by the Cockcroft-Gault formula were also excluded.

Randomization

The randomization sequence was generated using an interactive voice response system and stratified by selected baseline characteristics (β_2-microglobulin [<3.5 mg per liter vs. ≥3.5 mg per liter], number of prior lines of therapy [one vs. two or three], prior immunomodulatory drug therapy [none vs. prior thalidomide only or other]) via permuted blocks within each stratum. No more than 10% of patients with prior lenalidomide therapy were enrolled; this restriction was implemented using the interactive voice response system.

Assessments

Efficacy end points were centrally assessed using European Group for Blood and Bone Marrow Transplantation (EMBT) criteria, and based on a blinded review of tumor assessments by an Independent Review Committee (IRC). International Myeloma Working Group (IMWG) Uniform Response Criteria were incorporated into the independent review committee assessment for stringent complete response and very good partial response.

Complete Response /stringent complete response

A complete response requires that all of the following criteria be achieved:

1. Negative immunofixation on both serum and urine, maintained for a minimum of 6 weeks and
2. A bone marrow aspirate or biopsy containing < 5% plasma cells. It is not essential to perform a trephine biopsy, but if a biopsy is performed this must also contain < 5% plasma cells (although not required for documentation of complete response using the EBMT criteria, light chain restriction (flow or immunohistochemistry for kappa and lambda light chain in the bone marrow should also be assessed to assist in classification of stringent complete response using the IMWG criteria) and
3. If skeletal survey showed osteolytic bone lesions, there should be no increase in the size or number (development of a compression fracture does not exclude response) and
4. If screening scans showed extramedullary plasmacytomas, complete disappearance of any must be noted.

For assessment of stringent complete response, per IMWG criteria, all criteria for complete response must be upheld. In addition, bone marrow sample must be assessed for light chain restriction (as mentioned in bullet 2 above) and serum free light chains must be normalized at two time points at least 6 weeks apart, at the time of complete response assessment.

Partial Response

Patients in whom some, but not all, the criteria for complete response are fulfilled are classified as having a partial response, providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

1. Greater than or equal to 50% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Reduction of ≥ 90% in urinary light chain excretion or a decrease to < 200 mg/ 24 hours, maintained for a minimum of 6 weeks.
3. Greater than or equal to 50% reduction in the size of extramedullary plasmacytomas present at baseline (by radiography or clinical examination using bidimensional measurements).
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Very Good Partial Response

Very good partial response, a subset of partial response, is not formally included in the EBMT criteria but is derived from the IMWG criteria. Because very good partial response is commonly used to measure depth of response in multiple myeloma, this response must be reported by investigator and IRC and is defined by:

1. Serum and Urine M-protein detectable by immunofixation but not on electrophoresis and that is confirmed in a subsequent assessment OR
2. 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h and that is confirmed in a subsequent assessment.

Minor (Minimal) Response

Patients who have reduction in M-protein or plasmacytoma but do not meet the criteria for partial response are classified as having a minor response if they meet all of the following definitions:

1. Between 25% and 49% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Between 50% and 89% reduction in urinary light chain excretion which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks.
3. Between 25% and 49% reduction in the size of extramedullary plasmacytomas.
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

Progression of disease

Progression describes a definite increase in disease activity relative to the nadir in 2 consecutive assessments in patients not in complete response, whereas the term ‘relapse from complete response’ applies to a recurrence of evident disease in subjects previously in complete response. The date of EBMT-based disease progression is the first date of two consecutive values fulfilling the criteria for disease progression. Any of the following list is sufficient for progression of disease:

1. Increase of > 25% in serum M-protein (also an absolute increase of at least 5 g/L) and confirmed by at least 1 investigation.
2. Increase of > 25% urinary light chain excretion (which must also be an absolute increase of at least 200 mg/24-hours and confirmed by at least 1 investigation.
3. Increase of > 25% plasma cell percentage in the marrow (which must also be an absolute increase of at least 10%).
4. Definite increase in the size or number of lytic bone lesions or extramedullary plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).

5. Development of hypercalcemia (corrected serum calcium greater than 11.5 mg/dL; 2.8 mmol/L) not attributable to any other cause.

Relapse from complete response (for patients in complete response)

Patients who have documented complete response and then achieve at least one of the following criteria are classified as relapse from complete response. According to the EBMT criteria, relapse from complete response is considered to be progression of disease. The date of EBMT based relapse from complete resposne is the first date of two consecutive values fulfilling the criteria for relapse.

1. Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal reconstitution.
2. Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Any of the definitions met for progression of disease

Stable Disease/No Change

Patient does not meet the criteria for any of the categories above.

Tumor assessments were performed every 4 weeks following the first dose of study medication until disease progression, death, or withdrawal of consent. Confirmation of a tumor response was required after at least 6 weeks. Patients who discontinued study medication for reasons other than disease progression continued tumor assessments until disease progression for the intent-to-treat analyses. Patients were followed every 12 weeks after disease progression for survival and subsequent myeloma treatment. Follow-up for survival was continued every 12 weeks until study end, the patient died, or withdrawal of consent. Patients who were lost to follow-up had shorter follow-up for this reason. All laboratory assessments were performed at a central laboratory (ICON Central laboratories,

Dublin, Ireland), except corrected calcium and bone marrow assessments for plasma cell percentage and light chain restriction, which were assessed locally. Pain severity and pain interference was assessed at baseline, on day 1 of each cycle, and at the end of treatment or withdrawal from the study using the Brief Pain Inventory–Short Form (BPI-SF). The BPI-SF is a 15-item instrument that measures pain (five-item sensory dimension) and the impact of pain on daily life, including general activity, mood, ability to walk, normal work both outside the home and housework, relationships, sleep, and enjoyment of life (seven-item reactive dimension). Health-related quality of life was assessed at baseline, on day 1 of each cycle, and at the end of treatment or withdrawal from the study using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30) and myeloma-specific module (EORTC QLQ-MY20). The EORTC QLQ-C30 questionnaire comprises five functional scales, three symptom scales, and a global health/quality-of-life scale. Scale scores range from 0 to 100, with higher scores representing a better health state for the functional scores and lower scores representing a better health state for the symptom scores. The EORTC QLQ-MY20 consists of a 20-item questionnaire grouped into four scales: disease symptoms, treatment adverse effects, social support, and future perspective. Scale scores range from 0 to 100, with higher scores representing poorer health.

Statistical analysis

Baseline characteristics and efficacy were analyzed for all randomized patients. Exposure and safety were analyzed for all randomized patients who had received at least one dose of any study medication (all treated patients).

Primary analysis of progression-free survival

Progression-free survival was analyzed using the IRC assessment of tumor response and the primary definition of progression-free survival. Median follow-up is reported for patients

with no events. The primary definition of progression-free survival was the time from randomization to the first documented tumor progression or death due to any cause, and included patients for whom death or progression did not occur more than 10 weeks (two or more assessment visits) after the last adequate tumor assessment. Clinical deterioration was not considered progression. Censoring rules for the primary progression-free survival definition were applied to patients with subsequent anti-myeloma therapy, and those with an event more than 10 weeks after the last adequate tumor assessment. Patients who neither received subsequent therapy prior to progression nor had a progression event were censored at their last tumor assessment.

Supportive analyses of progression-free survival

Supportive analyses of progression-free survival used the IRC assessment of tumor response and intent-to-treat definition of progression-free survival, as well as investigator assessment of tumor response with both the primary and intent-to-treat definitions of progression-free survival. The intent-to-treat definition of progression-free survival was the time from randomization to the first documented tumor progression (as determined by the IRC) or death due to any cause. Clinical deterioration was not considered progression. Patients who neither progressed nor died were censored on the date of their last tumor assessment. There was no censoring for subsequent therapy prior to progression or for progression events following missing assessments.

A multivariate Cox regression model was used to adjust progression-free survival for baseline characteristics: age (<75 vs. ≥75 years), sex (male vs. female), Eastern Cooperative Oncology Group Performance status (0 to 1 vs. 2), prior stem cell transplantation (yes vs. no), high myeloma risk (yes vs. no), time from initial diagnosis, creatinine clearance (<60 mL/min vs. ≥60 mL/min), and lactate dehydrogenase (<300 IU/L vs. ≥300 IU/L).

Analysis of progression-free survival

The number of events and power for progression-free survival were calculated assuming an exponential distribution for each arm. The alpha level for progression-free survival (alpha = 0.0239%) was adjusted for the planned interim analysis using Lan-DeMets α-spending function with the O'Brien-Fleming type of boundary, and was calculated based on the actual number of events observed at the time of analysis (384 [82%] of the 466 required events). Progression-free survival distribution and median were summarized using the Kaplan-Meier method. Hazard ratios were calculated using a stratified Cox proportional hazards model. The Brookmeyer-Crowley method was used to calculate the 95% confidence interval for the median progression-free survival. Progression-free survival was compared between groups using a stratified log-rank test according to the factors used for randomization.

Analysis of overall response rate

Overall response rate was compared between groups using a two-sided 0.5% level Cochran-Mantel-Haenszel test stratified by β_2-microglobulin (<3.5 mg/L vs. ≥3.5 mg/L), prior lines of therapy (one vs. two or three), prior immunomodulatory drug therapy (no vs. prior thalidomide only or other). The associated odds ratio and 99.5% confidence interval were calculated. The response rate and corresponding 95% confidence interval were calculated for each group.

Analysis of pain severity/interference and health-related quality of life

Mean change from baseline was compared between groups using a longitudinal model, with fixed effects for treatment arm, time point (categorical), and baseline score, and a banded longitudinal covariance matrix.

Exposure-adjusted adverse events

To control for duration of treatment, exposure-adjusted adverse events were calculated as the incidence rate per 100 patient-years of exposure.

Figure S1. Study Design.

Patients received mandatory premedication prior to elotuzumab infusion* and thromboembolic prophylaxis†. *A premedication regimen consisting of diphenhydramine (25–50 mg) or equivalent, ranitidine (50 mg) or equivalent, and acetaminophen (650–1000 mg) or equivalent was administered 30 to 90 minutes prior to elotuzumab. †Mandatory thromboembolic prophylaxis (e.g., aspirin, low molecular weight heparin, or vitamin K antagonists) was administered per institutional guidelines or at the discretion of the investigator.

Elo denotes elotuzumab, IV intravenously, PD progressive disease, PO by mouth.

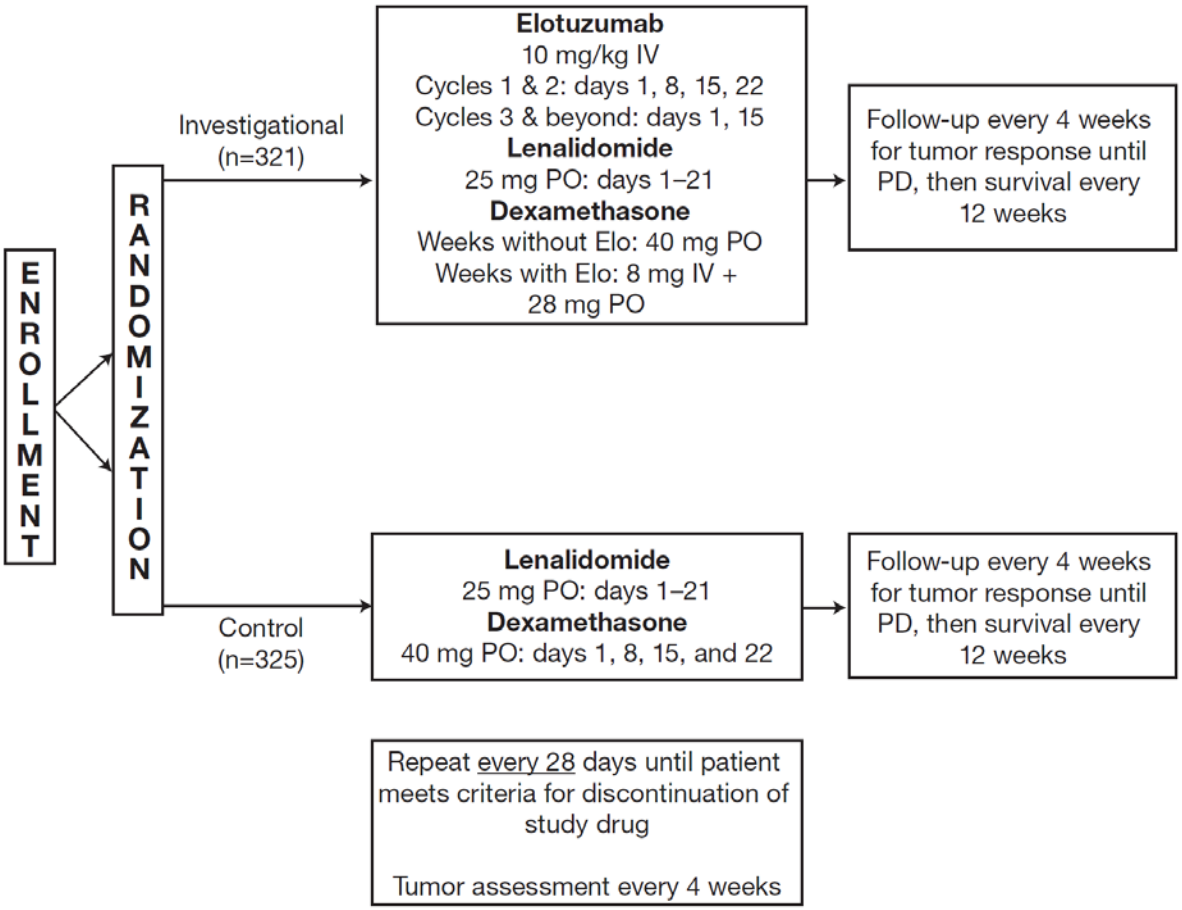


Figure S2. CONSORT Patient Disposition Flow Diagram.

Patients in the elotuzumab group received elotuzumab plus lenalidomide and dexamethasone. Patients in the control group received lenalidomide plus dexamethasone. *Patients with disease progression as primary reason for discontinuing treatment. For progression-free survival, all documented progressions/deaths at treatment discontinuation or after are included.

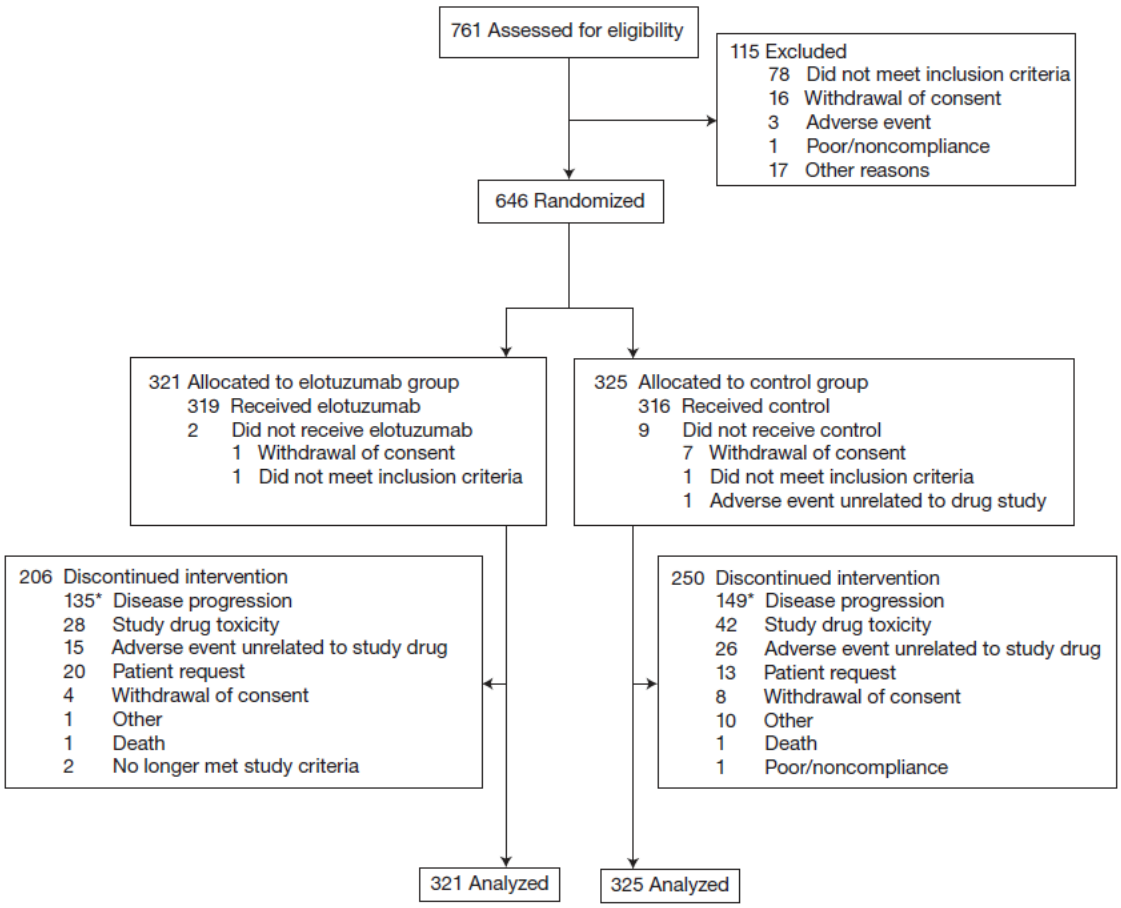
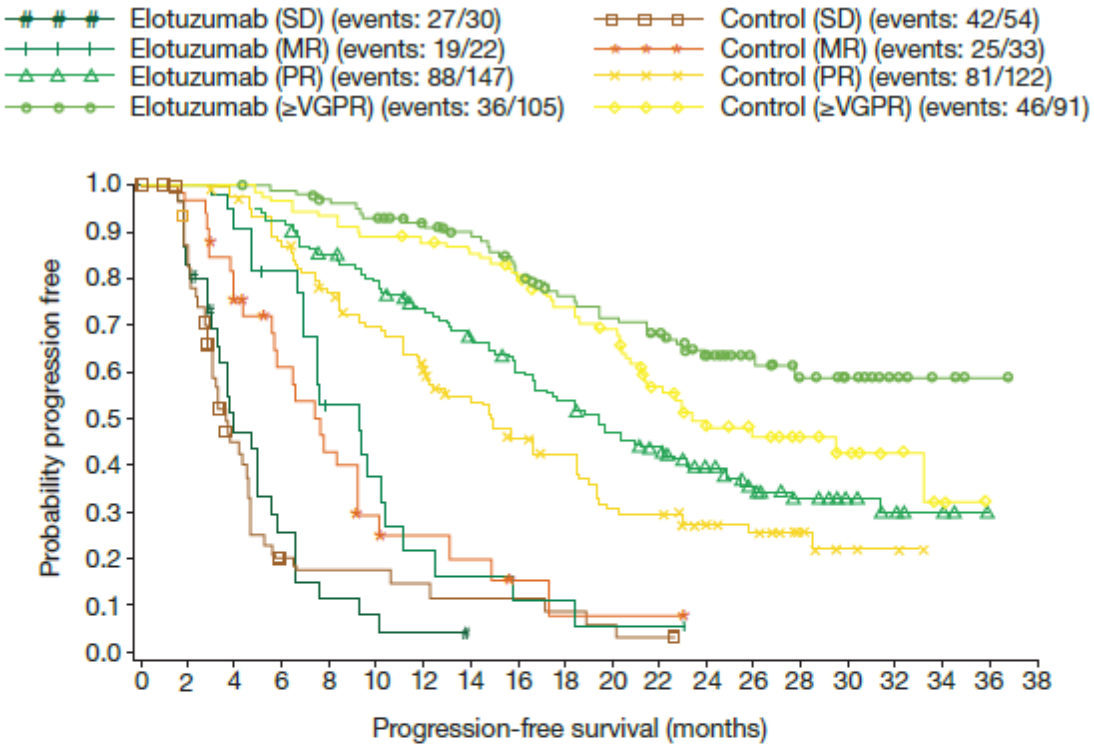


Figure S3. Progression-Free Survival by Tumor Response (Primary Analysis; All Randomized Patients).

≥VGPR denotes stringent complete response plus complete response plus very good partial response, PR partial response, MR minimal response, SD stable disease.



No. of patients at risk

SD																		
Elotuzumab	30	26	13	7	3	2	1											
Control	54	44	18	7	6	6	5	4	4	3	2	1						
MR																		
Elotuzumab	22	22	20	17	10	7	4	3	2	2	1	1						
Control	33	32	24	17	12	7	5	4	2	1	1	1						
PR																		
Elotuzumab	147	147	140	131	119	110	99	89	79	71	61	55	40	28	20	14	6	4
Control	122	122	116	104	89	79	69	57	47	40	29	28	18	15	8	4	2	
≥VGPR																		
Elotuzumab	105	105	105	103	99	95	90	85	75	69	65	60	44	31	22	18	6	3	1
Control	91	91	91	88	85	81	79	76	70	62	57	42	30	21	13	9	5	2	

Figure S4. Duration of Response for Patients with a Partial Response or Better (All Randomized Patients).

CI denotes confidence interval.

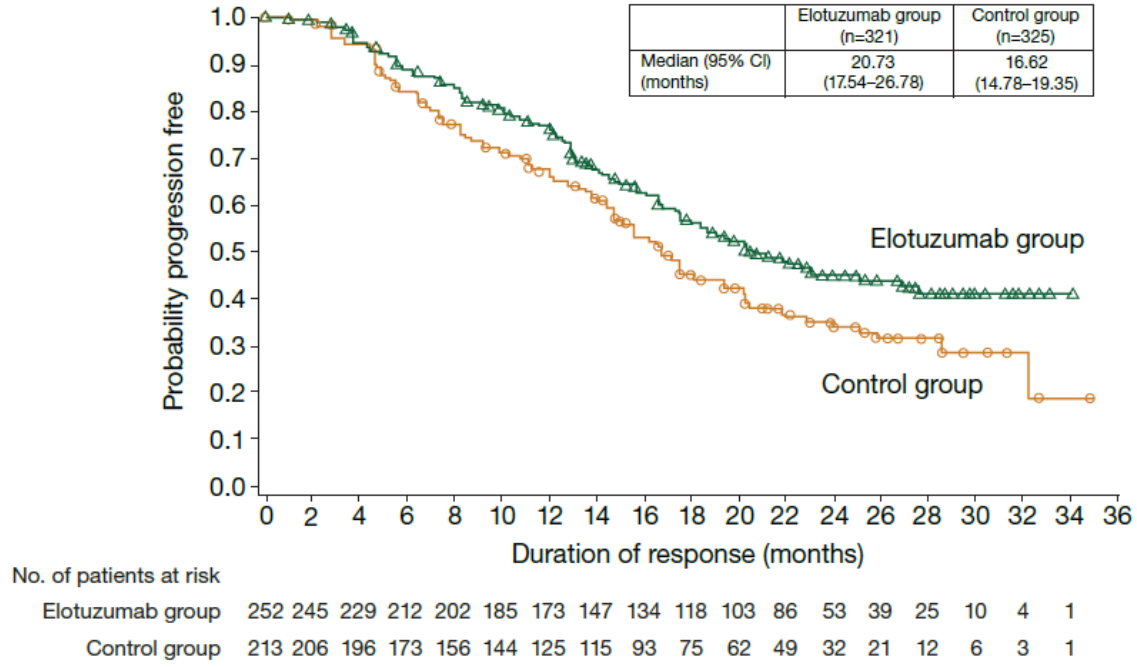


Figure S5. Mean Percentage Change from Baseline to Cycle 26 in Lymphocytes (All Treated Patients).

BL denotes baseline, C cycle number, D day.

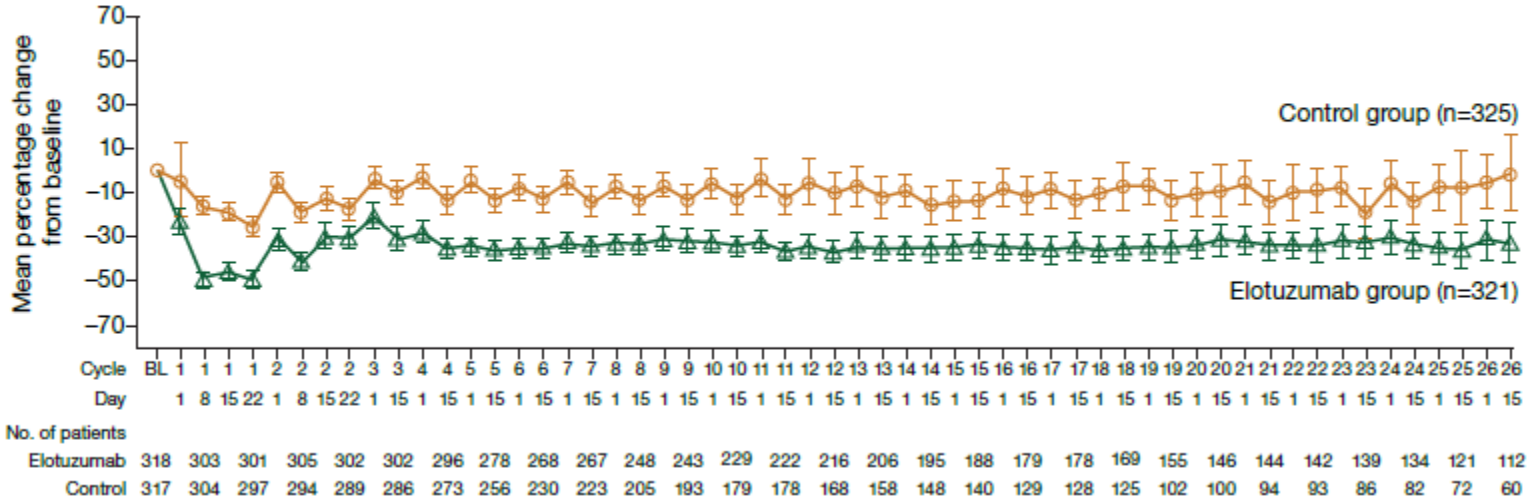


Table S1. Additional Baseline Characteristics (All Randomized Patients).

Characteristic	Elotuzumab Group (N = 321)	Control Group (N = 325)	Total (N = 646)
Female sex – no. (%)	129 (40)	132 (41)	261 (40)
ECOG performance status – no. (%)			
0	159 (50)	145 (45)	304 (47)
1	138 (43)	146 (45)	284 (44)
2	24 (8)	34 (11)	58 (9)
Race – no. (%)*			
White	264 (82)	280 (86)	544 (84)
Black or African American	13 (4)	10 (3)	23 (4)
Asian	33 (10)	31 (10)	64 (10)
Native Hawaiian, other Pacific Islander, or Other	10 (3)	4 (1)	14 (2)
Time since diagnosis – mo			
Median	41.6	41.9	41.6
Range	3.6–208.1	0.9–194.3	0.9–208.1
Myeloma type – no. (%)			
IgG	218 (68)	234 (72)	452 (70)
IgA	69 (22)	62 (19)	131 (20)
IgM	1 (0.3)	1 (0.3)	2 (0.3)
IgD	3 (1)	5 (2)	8 (1)
Light chain disease	27 (8)	20 (6)	47 (7)
Biclonal	2 (1)	3 (1)	5 (1)
Not classified	1 (0.3)	0	1 (0.2)
Cytogenetics†			
t(14;16)			

Characteristic	Elotuzumab Group (N = 321)	Control Group (N = 325)	Total (N = 646)
Yes	11 (3)	5 (2)	16 (3)
No	302 (94)	317 (98)	619 (96)
Not reported	8 (3)	3 (1)	11 (2)
Creatinine clearance – no. (%)			
<30 mL/min	6 (2)	3 (1)	9 (1)
30 to <60 mL/min	90 (28)	72 (22)	162 (25)
60 to <90 mL/min	122 (38)	129 (40)	251 (39)
≥90 mL/min	103 (32)	121 (37)	224 (35)
Response to most recent line of therapy – no. (%)‡			
Refractory	113 (35)	114 (35)	227 (35)
Bortezomib refractory	72 (22)	69 (21)	141 (22)
Thalidomide refractory	30 (9)	34 (11)	64 (10)
Relapsed	207 (65)	211 (65)	418 (65)

*For one patient in the elotuzumab group (0.3%), race was not reported.†Cytogenetic analysis was performed at the screening visit at a central laboratory using karyotype and fluorescence in situ hybridization.

‡One patient in the elotuzumab group (0.3%) had an unknown response to the most recent line of therapy.

ECOG denotes Eastern Cooperative Oncology Group, Ig immunoglobulin, mo month.

Table S2. Supportive Analyses for Progression-Free Survival (All Randomized Patients).

Parameter	PFS (Primary Definition)				PFS (Intent-to-Treat Definition)			
	IRC*		Investigator		IRC		Investigator	
	Elotuzumab group†	Control group‡	Elotuzumab group†	Control group‡	Elotuzumab group†	Control group‡	Elotuzumab group†	Control group‡
Events – no. (%)	179 (56)	205 (63)	167 (52)	201 (62)	192 (60)	231 (71)	181 (56)	226 (70)
Median PFS – mo	19.4	14.9	22.7	16.7	18.5	14.3	21.4	16.5
1-year PFS rate – %	68	57	72	61	68	56	71	59
2-year PFS rate – %	41	27	47	31	39	26	45	29
Hazard ratio	0.70		0.65		0.68		0.64	
95% CI	0.57–0.85		0.53–0.80		0.56–0.83		0.53–0.79	
P-value	0.0004		<0.0001		0.0001		<0.0001	

*Primary analysis (primary definition of PFS and IRC-assessed tumor response) provided for comparison.

†N=321.

‡N=325.

CI denotes confidence interval, IRC Independent Review Committee, PFS progression-free survival.

Table S3. Treatment Responses According to Investigator Assessment of Tumor Response (All Randomized Patients).

	Elotuzumab Group (N = 321)	Control Group (N = 325)
Best overall response – no. (%)		
Complete response (sCR + CR)	34 (11)	37 (11)
Very good partial response	96 (30)	66 (20)
Partial response	142 (44)	136 (42)
Minimal response	19 (6)	24 (7)
Stable disease	17 (5)	35 (11)
Progressive disease	6 (2)	8 (3)
Not evaluable	7 (2)	19 (6)
Overall response rate* – no. (%)	272 (85)	239 (74)
95% CI	80.3–88.5	68.4–78.3
P-value†	0.0004	

*Defined as partial response or better, using European Group for Blood and Marrow Transplantation criteria.

†P-value based on the Cochran-Mantel-Haenszel chi-square test stratified by randomization factors.

CI denotes confidence interval, CR complete response, sCR stringent complete response.