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Phase I Trial of Anti-CS1 Monoclonal Antibody Elotuzumab in Combination With Bortezomib in the Treatment of Relapsed/Refractory Multiple Myeloma

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See accompanying editorial on page 1904 and articles on pages 1949, 1953, and 2013

A B S T R A C T

Purpose
To evaluate the maximum-tolerated dose (MTD), safety, and efficacy of elotuzumab in combination with bortezomib in patients with relapsed or relapsed and refractory multiple myeloma (MM).

Patients and Methods
Elotuzumab (2.5, 5.0, 10, or 20 mg/kg intravenously [IV]) and bortezomib (1.3 mg/m² IV) were administered on days 1 and 11 and days 1, 4, 8, and 11, respectively, in 21-day cycles by using a 3 + 3 dose-escalation design. Patients with stable disease or better after four cycles could continue treatment until disease progression or unexpected toxicity. Responses were assessed during each cycle by using European Group for Blood and Marrow Transplantation (EBMT) criteria.

Results
Twenty-eight patients with a median of two prior therapies were enrolled; three patients each received 2.5, 5.0, and 10 mg/kg of elotuzumab and 19 received 20 mg/kg (six during dose escalation and 13 during an expansion phase). No dose-limiting toxicities were observed during cycle 1 of the dose-escalation phase, and the MTD was not reached up to the maximum planned dose of 20 mg/kg. The most frequent grade 3 to 4 adverse events (AEs) were lymphopenia (25%) and fatigue (14%). Two elotuzumab-related serious AEs of chest pain and gastroenteritis occurred in one patient. An objective response (a partial response or better) was observed in 13 (48%) of 27 evaluable patients and in two (67%) of three patients refractory to bortezomib. Median time to progression was 9.46 months.

Conclusion
The combination of elotuzumab and bortezomib was generally well-tolerated and showed encouraging activity in patients with relapsed/refractory MM.

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INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy characterized clinically by increased levels of monoclonal immunoglobulin in serum or urine and evidence of end-organ damage, including bone lesions, renal failure, hypercalcemia, or anemia.[1] In 2008, median survival was about 4 years from initial diagnosis for patients with MM first diagnosed in the prior decade.[2] In the United States, MM accounts for 1.3% of new cancer cases and 1.9% of cancer deaths annually.[3]

Since the mid-1990s, the introduction of new therapies, notably bortezomib, thalidomide, and lenalidomide, and the widespread adoption of autologous stem-cell transplantation have led to clinically meaningful increases in overall survival and progression-free survival in patients with MM.[2,4,5] However, none of these therapies are curative and, regardless of their response to initial therapy, nearly all patients relapse.

Over the past decade, therapy based on monoclonal antibodies (mAbs) has demonstrated efficacy against several B-cell malignancies. For example, the anti-CD20 mAb rituximab is indicated for the treatment of non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia.[6] The success of mAb-based therapy in these and other cancers has led to the investigation of mAbs in the treatment of MM.

To date, the development of mAbs as therapeutic agents in MM has been hampered by the lack of unique targets that are highly expressed in MM but not on normal cells.[7] Elotuzumab (HuLuc63) is a

humanized immunoglobulin G1 mAb directed against the cell surface glycoprotein CS1 (CD2 subset 1).[7,8] CS1 is highly and uniformly expressed on normal plasma cells and MM cells, with lower expression on natural-killer (NK) cells and little to no expression on normal tissues.[7,8]

Elotuzumab binds with high affinity to MM cells and blocks their adhesion to bone marrow stromal cells, which potentially overcomes the stimulatory effects of bone marrow stromal cells on MM growth and survival.[7] The primary mechanism of action of elotuzumab is NK cell–mediated antibody-dependent cellular cytotoxicity (ADCC),[8] which has been demonstrated in MM cell lines resistant to conventional chemotherapeutic agents and in MM cells from patients resistant to conventional and novel therapeutics.[7] In vivo xenograft studies have shown that elotuzumab induces inhibition of MM tumor growth in mouse models.[7,8] In phase I/II studies in relapsed/refractory MM, elotuzumab monotherapy demonstrated 32% stable disease[9] and encouraging clinical activity (81% to 82% objective response [OR]) in combination with lenalidomide and dexamethasone, suggesting synergy.[10,11]

Preclinical studies suggested that combining elotuzumab and bortezomib may have synergistic effects in MM. In cell lines, bortezomib enhanced ADCC-mediated MM cell death induced by elotuzumab via downregulation of major histocompatibility complex type 1, a negative regulator of NK-cell activity.[12] In a mouse model, elotuzumab plus bortezomib reduced mean tumor volumes by 89% ($P < .001$) and 87% ($P < .001$) compared with elotuzumab and bortezomib monotherapy, respectively.[12] Importantly, bortezomib did not alter the cell surface expression of CS1, preserving pretreatment expression levels of this target of elotuzumab-induced ADCC.[12]

On the basis of these results, a phase I clinical study (ClinicalTrials.gov identifier: NCT00726869) was conducted of elotuzumab plus bortezomib in patients with previously treated relapsed/refractory MM.

PATIENTS AND METHODS

Study Objectives

This was a phase I, multicenter, open-label, dose-escalation study of elotuzumab in combination with bortezomib in patients with MM and one to three previous therapies. The study protocol was approved by the ethics committee at every institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

The primary objective was to identify the maximum-tolerated dose (MTD) of elotuzumab in combination with a fixed dose of bortezomib, with MTD defined as the highest dose level at which dose-limiting toxicities (DLTs) occur in one or fewer of six patients. Secondary objectives were to evaluate the

efficacy, safety/tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of elotuzumab in combination with bortezomib.

Study Population

Men and women age ≥ 18 years with confirmed MM and one to three prior MM therapies were eligible. Other inclusion criteria were measurable serum and/or urine M-protein, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate liver function (ALT/AST $\leq 3 \times$ upper limit of normal), adequate bone marrow (BM) function (absolute neutrophil count $> 1.0 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, and hemoglobin ≥ 8 g/dL), and serum calcium less than or equal to the upper limit of normal. Exclusion criteria were life expectancy less than 3 months; prior malignancy (except for adequately treated basal cell carcinoma/squamous cell carcinoma, cervical cancer in situ, or other malignancies from which the patient had been disease-free for > 2 years); uncontrolled medical problem(s); stem-cell or BM transplantation less than 12 weeks before the first dose; neuropathy grade ≥ 2 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v3.0); and thalidomide, lenalidomide, or corticosteroid therapy or radiotherapy less than 2 weeks before screening. On January 27, 2009, the protocol was amended to enroll only those patients with no prior bortezomib treatment and those who were responsive (those with a partial response [PR]) or better to prior bortezomib treatment for a minimum of 3 months, or who were responsive to prior bortezomib treatment at the time of switching to another treatment or ceasing treatment) and to exclude patients who had been treated with bortezomib less than 3 months before the initial dose.

Study Design

Bortezomib was administered at 1.3 mg/m² intravenously (IV) on days 1, 4, 8, and 11 of a 21-day cycle (Fig 1). Elotuzumab was administered at one of four escalating doses (2.5, 5.0, 10, or 20 mg/kg) IV within 30 minutes of bortezomib infusion on days 1 and 11 of each cycle. Treatment continued for at least four cycles; if progressive disease (PD) occurred at the end of cycle 4, study medication was discontinued. To mitigate infusion-related adverse events (AEs), the protocol was amended to require a premedication regimen of methylprednisone 50 mg IV (or equivalent), diphenhydramine 25 to 50 mg orally (PO) or IV (or equivalent), and acetaminophen 650 to 1,000 mg PO, 30 to 60 minutes before each elotuzumab infusion.

DLTs were assessed at the end of cycle 1. DLTs were defined as any of the following: grade ≥ 3 nonhematologic toxicity, except fatigue, diarrhea, and grade 3 peripheral neuropathy; thrombocytopenia (platelet counts $\leq 10 \times 10^9$/L during one or more assessments, and/or requiring more than one platelet transfusion, and/or failure of platelet recovery to $> 25 \times 10^9$/L despite withholding bortezomib for up to 7 days); grade 4 neutropenia persisting for more than 7 days; and grade ≥ 3 febrile neutropenia (temperature $\geq 101°F$).
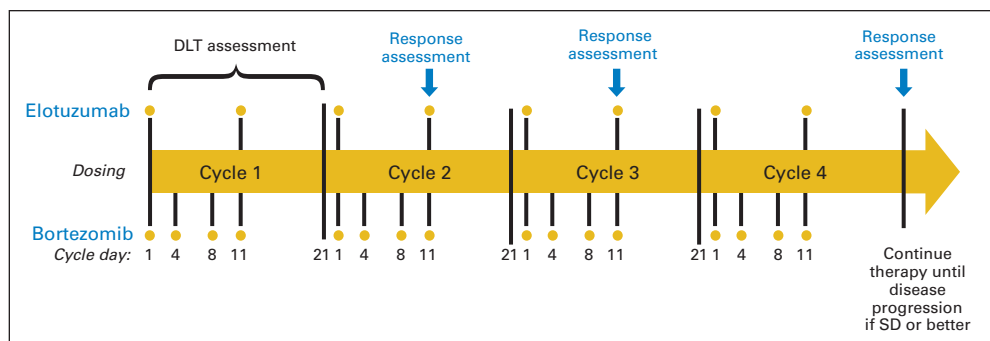
A 3 + 3 dose design was used, with dosing cohorts (three to six patients per cohort) added sequentially on the basis of one DLT or fewer in each cohort. If one DLT or fewer was observed in the first three patients in the 20-mg/kg cohort, then an additional three patients were to be enrolled to further evaluate this dose. Once an MTD was reached (or one DLT or fewer was observed at the

Fig 1. Study design schematic. DLT, dose-limiting toxicity; SD, stable disease.

maximum planned dose [MPD] of elotuzumab of 20 mg/kg), 12 to 18 additional patients could be enrolled at the MTD (or the MPD) during an expansion phase.

Response Assessment

Per protocol design, responses were assessed by using European Group for Blood and Marrow Transplantation (EBMT) criteria.[13] Responses were assessed at day 11 of cycles 2 and 3 and at the end of cycle 4. If PD occurred during cycles 2 or 3, dexamethasone 20 mg PO could be administered on days 1, 2, 4, 5, 8, 9, 11, and 12 of subsequent cycles. If a complete response (CR), PR, or stable disease was reached at the end of cycle 4, treatment with elotuzumab + bortezomib (+ dexamethasone if added during cycles 2 or 3) could be continued for an additional six or more cycles or until PD or unacceptable toxicity. If PD occurred at the end of cycle 4, study medication was discontinued.

Patients who completed two or fewer cycles of therapy or progressed earlier were evaluable for response. Time to progression (TTP) was also assessed. Safety was assessed by using the NCI CTCAE (v3.0). The following additional assessments were performed: vital signs, laboratory tests (including hematology, serum chemistries, and serum cytokine assessment), chest x-ray, physical examinations/ECOG assessment, and urinalysis.

A list of potential infusion reaction AEs was predefined by the study sponsor. Any of these that occurred on the day of or the day following elotuzumab infusion were considered to be possible infusion reactions, regardless of causality, and were defined as peri-infusion AEs.

Pharmacokinetics/Pharmacodynamics

Serum concentrations of elotuzumab were assessed by using an enzyme-linked immunosorbent assay. Bone marrow $CD38^+$ MM cells and lymphocyte subsets were stained for CS1 expression level by flow cytometry at screening, after dosing during treatment, and at 30-day follow-up. Elotuzumab serum levels were correlated with elotuzumab saturation of CS1 binding sites on BM MM cells.

Statistical Considerations

Continuous data were summarized by using descriptive statistics (mean, median, standard deviation, and range). Categorical data were summarized by number and percentage of patients. TTP was plotted on Kaplan-Meier graphs with median TTP reported.

RESULTS

Patient Characteristics and Disposition

This study enrolled participants between May 2008 and November 2009. Patient demographics, selected baseline disease and treatment characteristics, and disposition are summarized in Table 1. Twenty-eight patients were enrolled, 28 received at least one dose of elotuzumab, and 27 (93%) were evaluable for response. Eleven patients (39%) had been treated previously with bortezomib, three (not four, as previously reported) were refractory to prior bortezomib (ie, they had progressed during or within 60 days of receiving a bortezomib-containing therapy), and 12 (43%) were refractory to their most recent treatment. Fifteen patients were enrolled during the dose-escalation phase (three each at 2.5, 5.0, and 10 mg/kg, and six at 20 mg/kg). The MTD was not reached at 20 mg/kg, and an additional 13 patients were enrolled at the MPD of 20 mg/kg of elotuzumab during an expansion phase. Patients were treated for a median of six cycles (range, one to 32 cycles). Twenty-six patients discontinued treatment because of disease progression (n = 9), AEs (n = 7), investigator decision (n = 3), or patient decision (n = 7). As of August 20, 2010, two patients remain on therapy.

Table 1. Patient Demographics, Baseline Characteristics, and Disposition

Characteristic	No.	%
Patients	28	
Age, years		
Median	63	
Range	41-77	
Male	18	64
Years since first MM diagnosis		
Median	3.5	
Range	1.1-11.4	
No. of prior MM therapies		
Median	2	
Range	1-3	
≥ 2	18	64
Prior bortezomib	11	39
Prior lenalidomide	13	46
Prior autologous stem-cell transplantation	19	68
Refractory to last therapy	12	43
ECOG PS		
Median	1	
Range	0-2	
High-risk cytogenetics*	10	36
Patient disposition		
Cycles of therapy		
Median	6	
Range	1-32	
Remaining on therapy	2	
Completed/discontinued therapy	26	
Disease progression	9	
Adverse event	7†	
Investigator decision	3‡	
Patient decision	7§	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MM, multiple myeloma; PS, performance status.
*Defined as del13 by metaphase or t(4;14), t(14;16), or del17p by fluorescent in situ hybridization.
†Adverse events: one each of peripheral neuropathy, sepsis, acute myocardial infarction, hypercalcemia, gastroenteritis, pain in extremity, peripheral sensory neuropathy.
‡Investigator decision: two with weight loss, one with painful neuropathy.
§Patient decision: two moved, one desired natural remedy, four withdrew consent.

Safety

No DLTs were observed during the first treatment cycle in patients who received 2.5 to 20 mg/kg elotuzumab. Treatment-emergent AEs are listed in Table 2. The most frequent AEs (any grade) were fatigue, anemia, diarrhea, and thrombocytopenia (68% to 82%). The most frequent grade 3 to 4 AEs were lymphopenia (25%), fatigue (14%), thrombocytopenia, neutropenia, hyperglycemia, pneumonia, and peripheral neuropathy (11% each). There were two serious AEs assessed as possibly or probably related to elotuzumab, both in the same patient in the 20-mg/kg expansion group: one episode of grade 3 chest pain that developed during cycle 3 on day 11 (following completion of elotuzumab infusion) and resolved within 24 hours while at home (assessed as a medically significant event and therefore a serious AE); and a subsequent episode of grade 3 gastroenteritis during cycle 4 on day 3 (2 days after elotuzumab infusion), leading to hospitalization (this event resolved with supportive care including hydration and antinausea medications).

Twenty (71%) of 28 patients experienced at least one predefined peri-infusion AE; all except one were grade 1 or 2. The most common

Table 2. Treatment-Emergent Adverse Events Reported by Patients (N = 28)		
Adverse Event	% of Patients (≥ 25%) Reporting Any Grade	% of Patients (≥ 4%) Reporting Grade 3 to 4*
Any adverse event	100	79
Fatigue	82	14
Anemia	71	7
Diarrhea	71	0
Thrombocytopenia	68	11
Hyperglycemia	61	11
Nausea	61	0
Lymphopenia	54	25
Neutropenia	50	11
Leukopenia	50	7
Peripheral neuropathy	46	11
Constipation	46	0
Chills	36	0
Vomiting	36	4
Peripheral edema*	32	0
Headache	32	0
Pyrexia	32	0
Upper respiratory tract infection	32	4
Cough	29	0
Dyspnea	29	0
Hypocalcemia	29	0
Hyponatremia	25	0
Insomnia	25	0
Peripheral sensory neuropathy	25	0
Pneumonia	21	11
Acute myocardial infarction	4	4
Chest pain	11	4
Noncardiac chest pain	4	4
Hypersensitivity	7	4
Gastroenteritis	7	4
Sepsis	4	4
Blood bilirubin increased	4	4
Blood creatinine increased	18	4
Lymphocyte count decreased	7	7
Weight decreased	11	4
Hypercalcemia	4	4
Hypokalemia	21	7
Bone pain	14	4
Pain in extremity	21	4
Metabolic encephalopathy	4	4
Neuralgia	11	4
Agitation	4	4
Suicidal ideation	4	4
Exertional dyspnea	14	4

*Excludes one patient with missing grade; 4% = one patient.

were nausea (36%; n = 10), chills (21%; n = 6), dyspnea (21%; n = 6), headache (14%; n = 4), dizziness (14%; n = 4), vomiting (11%; n = 3), and rash (11%; n = 3). One patient experienced a grade 3 hypersensitivity reaction.

Efficacy

Best confirmed responses to elotuzumab plus bortezomib are summarized in Table 3. The objective response rate (ORR; less than or equal to a PR) was 48% by the EBMT criteria, and 63% of patients achieved a minor response (MR) or better. Responses observed among patients with prior bortezomib treatment, those with bortezomib-refractory disease, those with prior lenalidomide, those with lenalidomide-refractory disease, and those refractory to their most recent treatment were consistent with those observed in the overall study population. Notably, two of three patients refractory to bortezomib responded to this regimen. Patients with high-risk cytogenetics exhibited an ORR of 70% (seven of 10) including one patient with CR.

In general, response rates were higher among patients with one prior MM therapy than those with two or three prior therapies. Among 10 patients with one prior therapy, six (60%) achieved an OR and seven (70%) achieved an MR or better; among 17 patients with two or three prior therapies, seven (41%) achieved an OR and 10 (59%) achieved an MR or better.

Dexamethasone 20 mg was added to the treatment regimen in cycle 3 for two patients. One of these patients subsequently achieved an MR and the other experienced continued PD.

Kaplan-Meier analyses of TTP for all evaluable patients are presented in Figure 2. Median TTP was 9.46 months for evaluable patients. Of the patients who achieved an OR, four progressed while on therapy, and no additional patients progressed within 60 days of follow-up.

Pharmacokinetics/Pharmacodynamics

Figure 3 illustrates the relationship between administered elotuzumab dose, elotuzumab serum levels, and saturation of CS1 binding sites. At doses of 10 mg/kg and 20 mg/kg, CS1 targets were saturated to a median of 80% and 95%, respectively; peak elotuzumab serum levels were 100 μg/mL or greater at each dose, which was shown to be optimal with respect to generating responses in preclinical studies in murine tumor explant models.[7] Elotuzumab serum trough levels and CS1 saturation were unaffected by the addition of bortezomib (data not shown).

DISCUSSION

This study showed that the anti-CS1 human monoclonal antibody elotuzumab, when added to bortezomib, was generally well-tolerated, with evidence of activity among patients with previously treated relapsed or relapsed and refractory MM. There were no DLTs observed at doses up to 20 mg/kg, and the MTD was not reached at this dose. The most common grade 3 to 4 AEs that emerged during treatment were lymphopenia (25%), fatigue (14%), neutropenia, thrombocytopenia, peripheral neuropathy, and hyperglycemia (11% each). Previous phase II and phase III studies of single-agent bortezomib in relapsed/refractory MM have reported treatment-emergent grade 3 to 4 thrombocytopenia (31% and 30%), fatigue (12% and 5%), peripheral neuropathy (12% and 8%), and neutropenia (14% and 14%), respectively.[14,15]

AEs attributable to elotuzumab in this study were primarily peri-infusional, which are not unexpected with infused mAbs, and they typically resolved the same day either spontaneously or with treatment as indicated. Before implementation of a steroid-based premedication regimen that also included antihistamines and analgesics, one patient (4%) experienced elotuzumab-related grade 3 infusion reaction of hypersensitivity. Following regimen implementation, no further grade ≥ 3 or serious infusion reactions were reported.

Table 3. Best Confirmed Responses to Elotuzumab + Bortezomib, According to EBMT

Response	All Patients		Prior Bortezomib		Refractory to Bortezomib*		Prior Lenalidomide		Refractory to Lenalidomide		Refractory to Most Recent Therapy*		High Risk Cytogenetics	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Evaluable patients†	27		11		3		12		7		11		10	
CR	2	7	0		0		1	8	1	14	1	9	1	10
PR	11	41	5	45	2	67	4	33	2	29	4	36	6	60
MR	4	15	0		0		1	8	1	14	2	18	0	
SD	8	30	5	45	0		4	33	2	29	3	27	3	30
≥ PR	13	48	5	45	2	67	5	42	3	43	5	45	7	70
≥ MR	17	63	5	45	2	67	6	50	4	57	7	64	7	70
PD	2	7	1	9	1	33	2	17	1	14	1	9	0	

Abbreviations: CR, complete response; EBMT, European Group for Blood and Marrow Transplantation; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease.
*A March 2011 data analysis confirmed that three patients were refractory to bortezomib, not four as previously reported.
†Patients completed two cycles of therapy or progressed earlier.

Analysis of elotuzumab serum levels indicate that elotuzumab at 10 to 20 mg/kg reaches concentrations of 100 μg/mL or greater, which were shown to be optimal with respect to generating responses in preclinical studies in murine tumor explant models.[7] Pharmacodynamic studies of MM cells isolated from patient bone marrow biopsies demonstrated that these threshold concentrations were associated with high saturation (80% and 95%, respectively) of available CS1 binding sites at doses of 10 mg/kg and 20 mg/kg, similar to that seen in murine models and in a clinical study of elotuzumab monotherapy.[9] Binding of elotuzumab to CS1 is believed to be a necessary and critical step in the induction of ADCC, which is thought to be the primary cell-killing mechanism of elotuzumab.[7,8] Neither elotuzumab serum trough levels nor CS1 saturation was affected by the addition of bortezomib.

An OR (a PR or better) was observed in 48% and an MR or better was observed in 63% of 27 evaluable patients; observed responses were generally durable, with a median TTP of more than 9 months. Responses were observed at similar rates in both bortezomib-pretreated and bortezomib-refractory patients; notably, two of three patients refractory to bortezomib achieved PRs. In previous phase II and III bortezomib monotherapy studies in the setting of either relapsed/refractory or mostly relapsed MM, 27% and 38% of patients achieved a PR or better and 35% and 46% achieved an MR or better, respectively; the median TTPs in these studies were 7 months and 6.22

months, respectively.[14,15] Bortezomib-treated patients in the phase III bortezomib study (Assessment of Proteasome Inhibition for Extending Remissions [APEX trial]) had received numbers of prior therapies similar to the numbers in this study; 60% received two or more lines of treatment compared with 61% in this study.[15] Unlike this study, none of the prior therapies in the phase II or phase III study included bortezomib. In addition, we presume that more patients in this study were refractory to their last therapy (43%) compared with those in the APEX study, which excluded patients refractory to dexamethasone. Similarly, this study had more refractory patients compared with a randomized phase III study of bortezomib with or without pegylated liposomal doxorubicin for the treatment of relapsed or refractory MM, in which less than 10% of patients were refractory to their last therapy. In this study, a PR or better was seen in 41% of patients in the bortezomib arm and in 44% in the bortezomib + pegylated liposomal doxorubicin arm.[16] Although it is not possible to directly compare results across studies, the current ORR of 48% and clinical response rate of 63%, the durability of the observed responses, and the evidence of activity in patients with prior bortezomib, including several patients refractory to bortezomib, suggest that the combination of elotuzumab and bortezomib is active in this setting. In addition, patients with high-risk cytogenetics exhibited high ORR (70%) with this combination.

Elotuzumab is also being evaluated in a phase I/II study in combination with lenalidomide and low-dose dexamethasone; the ORR
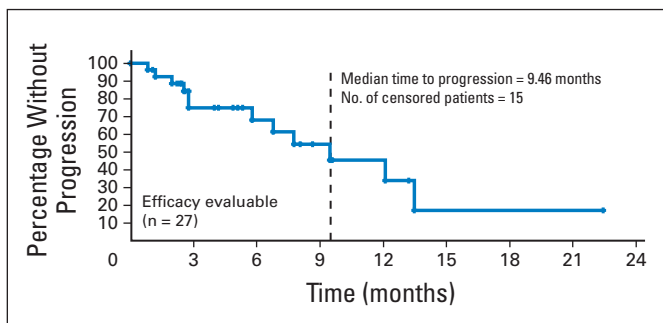
Fig 2. Kaplan-Meier analysis of time to disease progression.
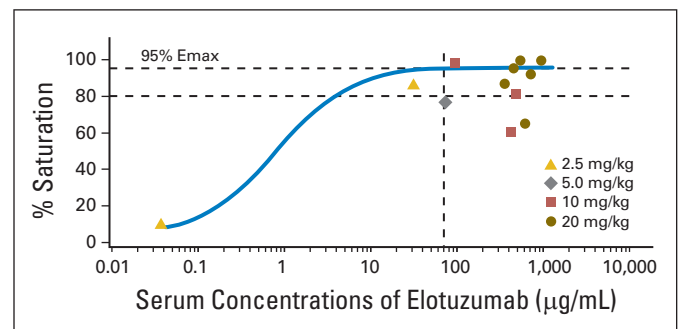
Fig 3. Elotuzumab saturation of CD38+ bone marrow multiple myeloma cells. Emax, maximum effect.

during phase I was 82% for all patients (N = 28).[10] Preliminary phase II results include an ORR of 81% for all patients; 37% of all patients achieved CR or a very good PR.[11] Although the ORR was lower in combination with bortezomib, no dexamethasone was used in this study. Translational studies are ongoing to determine possible mechanisms of synergy between elotuzumab and lenalidomide or bortezomib.

In conclusion, in this study, elotuzumab was generally well tolerated and demonstrated potential utility in combination with bortezomib for the treatment of relapsed/refractory MM, suggesting that CS1 may be a clinically valuable target of anti-MM therapy. The primary elotuzumab-related AEs were mild to moderate peri-infusion AEs, which typically resolved the same day either spontaneously or with treatment as indicated. These results also suggest a potential of higher activity of the combination versus bortezomib alone, which warrants further assessment. A controlled, randomized, phase II study of bortezomib and dexamethasone with or without elotuzumab is planned to further determine the contribution of elotuzumab in this combination. A phase III study of elotuzumab in combination with lenalidomide and dexamethasone in relapsed MM is ongoing (ELOQUENT - 2; CA204-004; NCT01239797).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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