

Phase 1/2 Study of Elotuzumab in Combination with Bortezomib in Patients with Multiple Myeloma Following 1 to 3 Prior Therapies: Interim Results

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Abstract

Background: Elotuzumab is a humanized monoclonal IgG1 antibody directed against CS1, a cell surface glycoprotein, which is highly and uniformly expressed in multiple myeloma (MM). In mouse xenograft models of MM, elotuzumab demonstrated significantly enhanced anti-tumor activity when combined with bortezomib compared to bortezomib alone (van Rhee et al., Mol Cancer Ther (2009) 8:2616-2624). This phase 1/2 trial will determine the maximum tolerated dose (MTD), overall safety, pharmacokinetics (PK) and clinical response of elotuzumab in combination with bortezomib in patients with relapsed and/or refractory MM following 1-3 prior therapies.

Methods: The study consists of 4 escalating dose cohorts of elotuzumab (2.5 mg/kg to 20 mg/kg) administered on Days 1 and 11 and bortezomib (1.3 mg/m²) administered on Days 1, 4, 8 and 11 of a 21-day cycle. Patients with progressive disease at the end of Cycle 2 or 3 also receive oral dexamethasone (20 mg) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each subsequent cycle. Patients with stable disease or better at the end of 4 cycles will continue treatment for 6 or more cycles unless withdrawn earlier due to unacceptable toxicity or disease progression. Key entry criteria: age ≥ 18 years; confirmed diagnosis of MM and documentation of 1 to 3 prior therapies; measurable disease M-protein component in serum and/or in urine; and no prior bortezomib treatment within 2 weeks of first dose.

Results: To date, a total of 26 MM patients with a median age of 64 years have been enrolled and dosed in the study. The median time from initial diagnosis of MM was 3.4 years and patients had received a median of 1.5 prior MM treatments. Patients have been treated in four cohorts; 3 each in 2.5, 5 and 10 mg/kg elotuzumab cohorts, and 17 in the 20 mg/kg elotuzumab cohort. No dose limiting toxicity (DLT) was observed during the first cycle of the study and the MTD was not established. Eight SAEs have been reported in six patients; two Grade 3 events, chest pain and gastroenteritis, were considered elotuzumab-related. Other SAEs include myocardial infarction, Grade 3 sepsis, vomiting, pneumonia, Grade 2 dehydration, and Grade 1 ileus. The most common AEs reported include Grade 1-3 fatigue, diarrhea, nausea, thrombocytopenia, constipation, anemia, peripheral neuropathy, lymphopenia, neutropenia, and leukopenia. The confirmed clinical response (MR or better) by combined EBMT and/or uniform criteria in 20 patients who received at least two cycles of treatment is 60% including 40% with PR or better. Median time to progression (TTP) in the study is 9.6 months.

Preliminary analysis of peripheral blood mononuclear cells and bone marrow of patients with objective responses in the study correlate well with complete or near-complete saturation of CS1 sites by elotuzumab on bone marrow plasma and NK cells.

Conclusions: The combination of elotuzumab with bortezomib has a manageable adverse event profile and shows preliminary efficacy with ≥MR in 60% of all evaluable patients and median TTP is 9.6 months. Accrual is ongoing in the expanded 20 mg/kg cohort.

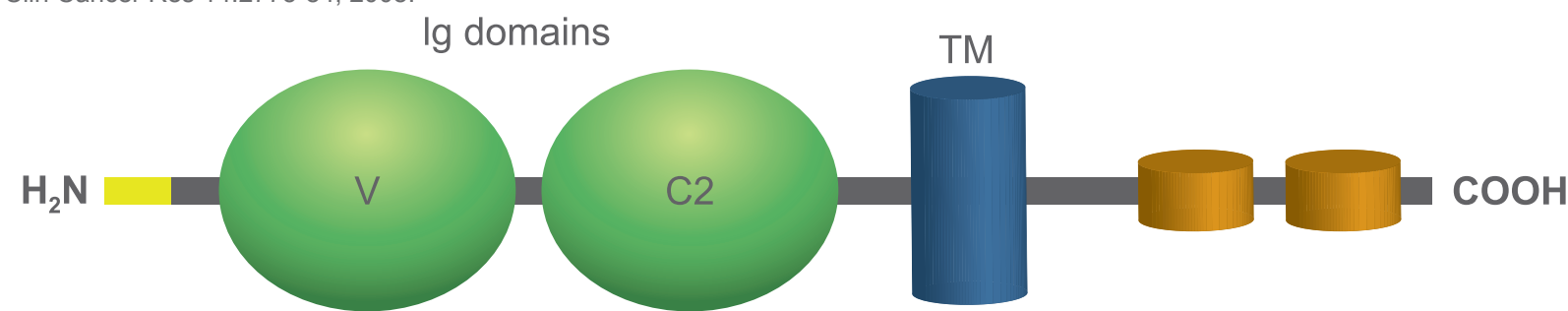
Safety/Lab Data Cutoff Oct 23 2009; Demographics/Efficacy Data Cutoff Nov 05 2009

Background

Elotuzumab

- A humanized monoclonal IgG1 targeting human CS1, a cell surface glycoprotein
- CS1 exhibits a very restricted expression profile¹
 - Multiple myeloma and normal plasma cells
 - NK, NKT, subset of CD8 T cells
 - Not expressed on normal stem cells or other normal tissues
- Pre-clinical data indicate MOA is mainly through NK-mediated antibody-dependent cellular cytotoxicity (ADCC)²

¹Hsi, et al., Clin Cancer Res 14:2775-84, 2008.



Objectives

Primary Objective

- Establish the MTD of elotuzumab in combination with bortezomib: The MTD is defined as the highest dose level of elotuzumab at which ≤ 1 of 6 subjects experienced a DLT.

Secondary Objectives

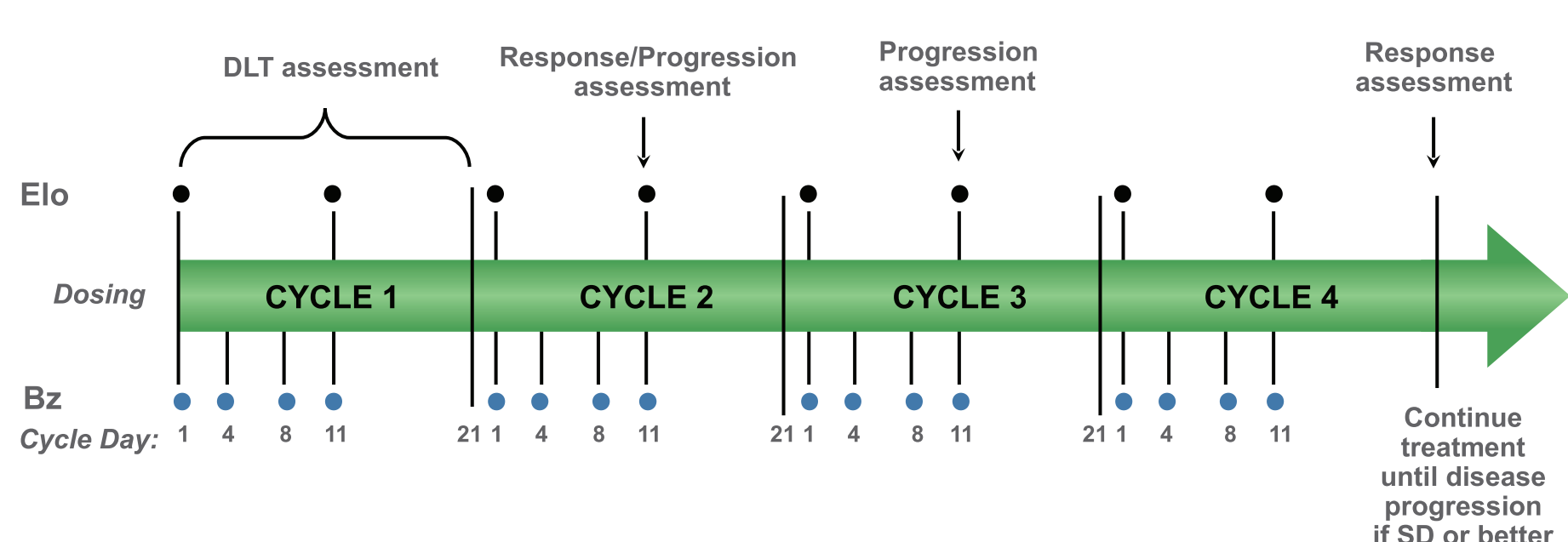
- Determine the overall safety and tolerability of the combination
- Determine pharmacokinetics, pharmacodynamics and immunogenicity of elotuzumab
- Evaluate the clinical efficacy of the combination

Dose Limiting Toxicity

A dose-limiting toxicity (DLT) will be defined as one or more of the following toxicities related to one of the study drugs during Cycle 1:

- Grade 3 or greater non-hematologic toxicity, except fatigue, diarrhea, and Grade 3 peripheral neuropathy
- Thrombocytopenia with ≤ 10,000 platelets/mm³ on more than one occasion and/or requiring more than one platelet transfusion and/or platelets not recovering to >25,000/mm³ despite withholding bortezomib for up to 7 days. Subjects' platelet counts of <10,000/mm³ should be monitored every 48 to 72 hours or more frequently at investigator's decision until the counts recover to >25,000/mm³.
- Grade 4 neutropenia persisting for more than 7 days
- Grade 3 or greater febrile neutropenia (temperature ≥ 101°F)
- Discontinuation of treatment due to disease progression will not constitute a DLT

Study Schema



- Dose escalation with 2.5, 5, 10, and 20 mg/kg elotuzumab in combination with 1.3 mg/m² bortezomib (Bz) in 3+3 design
- Expansion phase with 12 additional patients at 20 mg/kg elotuzumab
- Dexamethasone 20 mg po added at Cycle 2 or 3 on Days 1, 2, 4, 5, 8, 9, 11, 12 if disease progression noted

Key Eligibility Criteria

INCLUSION

- Multiple myeloma with documented 1-3 prior therapies
- Measurable disease M-protein of ≥ 0.5 g/dL in serum and/or ≥ 0.2 g in a 24 hr urine collection sample (n=15), subsequently amended to M-protein of ≥ 1 g/dL in serum and/or ≥ 0.5 g in a 24 hr urine (n=5)
- ECOG performance status = 0-2
- ALT or AST ≤ 3x ULN; total bilirubin ≤ 2x ULN; creatinine ≤ 3 mg/dL if related to MM, otherwise ≤ 2 mg/dL
- ANC > 1,000 cells/mm³; Platelets ≥ 75,000 cells/mm³; Hgb ≥ 8 g/dL

EXCLUSION

- Chemotherapy < 2 weeks prior to first dose
- Bortezomib < 2 weeks prior to first dose (n=15), subsequently amended to bortezomib < 3 months prior to first dose (n=5)
- Stem cell or bone marrow transplant < 12 weeks prior to first dose
- Nitrogen mustard agents, melphalan, or antibodies < 6 weeks prior to first dose
- Prior therapy with anti-CD56
- Grade ≥ 2 neuropathy

Results

Patient Disposition

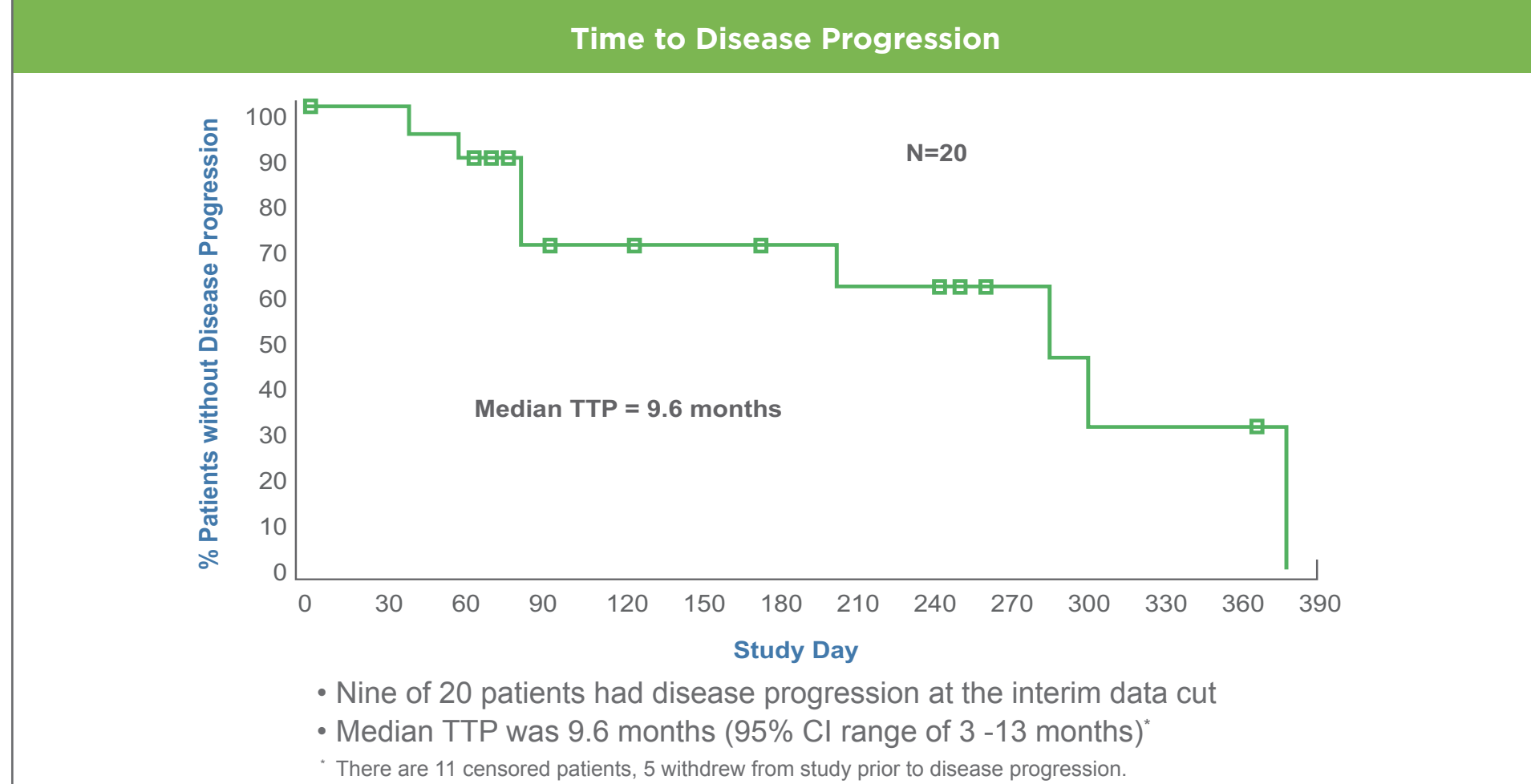
Parameter	Value	Reasons for withdrawal:	Value
Total Enrolled and Dosed	26 ¹	Disease Progression	5
Total Efficacy Evaluable (completed 2 cycles or progressed earlier)	20	Adverse Event	1
Total DLTs in dose escalation phase	0	Investigator Decision	2
Still on study (receiving study drug)	10	Patient Decision	1
Median number of cycles (range)	4.5 (1-15)	Other	1
		Missing from database	6

¹Four out of 26 patients are known to have received study drug, but do not have dosing or AE data in the database as of Oct 23 2009.

Baseline Characteristics	N=26
Median Age (range)	64 years (41-78 yrs)
Gender	17 Male, 9 Female
Race	22 White, 4 Black of African Heritage
Median time since first diagnosis (range)	3.4 (1.1-11.4) years
Median no. of prior therapies	1.5 (1-3)
Median no. of relapses since diagnosis	1 (0-3)
Median ECOG performance status	1 (0-2)
Prior transplant- Autologous	16 (62%)
Refractory to the last treatment ¹	9 (35%)
High risk based on cytogenetics [-13, -17, or t(4;14)]	5 (19%)
Prior bortezomib	8 (31%) / 4 patients are refractory to bortezomib ¹

¹Refractory population is defined as lack of complete response or partial response, or progressive disease within 6 months after initial dose

Efficacy



- Nine of 20 patients had disease progression at the interim data cut
- Median TTP was 9.6 months (95% CI range of 3 -13 months)^{*}
- ^{*} There are 11 censored patients, 5 withdrew from study prior to disease progression.

Best Confirmed Response by Combined EBMT/Uniform Criteria

Parameter	Total Patients (%)	Prior bortezomib (%)
Total evaluable patients ¹	20	6 (30%)
Objective Response Rate (≥ PR)	8 (40%)	2 (33%)
Clinical Response Rate (≥ MR)	12 (60%)	2 (33%)
CR	1 (5%)	0 (0%)
PR ²	7 (35%)	2 (33%)
MR	4 (20%)	0 (0%)
SD	6 (30%)	3 (50%) / 1 refractory to prior bz
PD	1 (5%)	1 (17%) / 1 refractory to prior bz
Missing Data	1 (5%)	0 (0%)

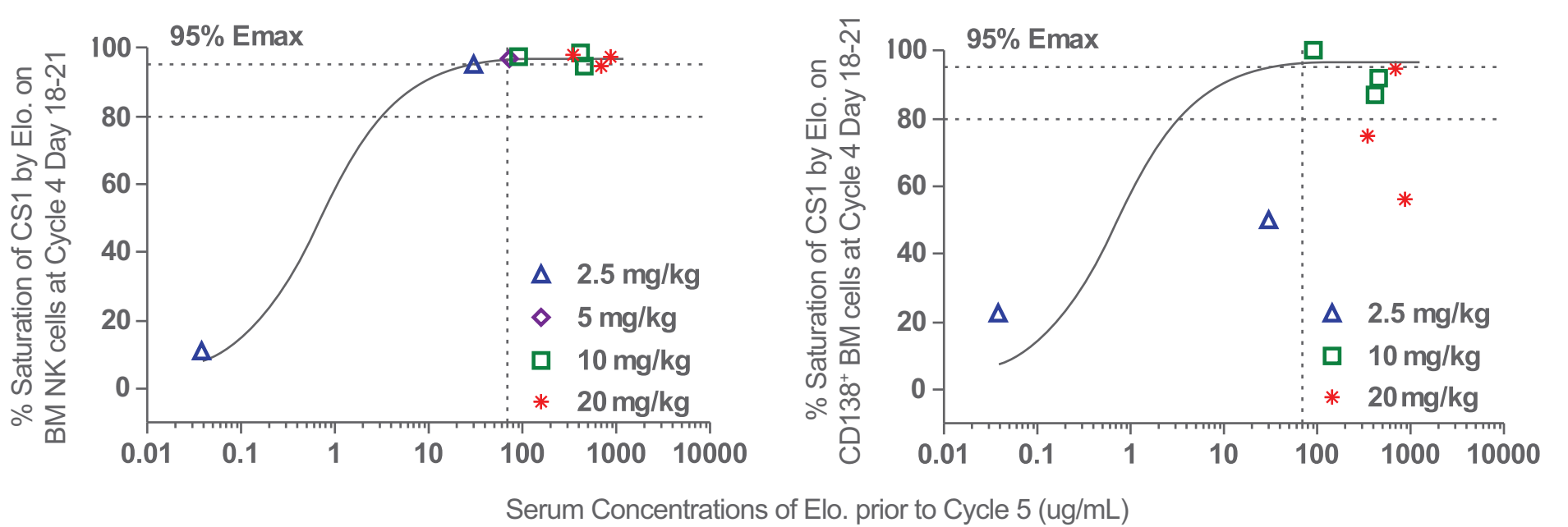
Elotuzumab Dose Level	Total Evaluable	ORR (%)	MR (%)	Clinical Response Rate (≥MR)
2.5 mg/kg	3	2 (67%)	1 (33%)	3 (100%)
5 mg/kg	3	1 (33%)	0 (0%)	1 (33%)
10 mg/kg	3	3 (100%)	0 (0%)	3 (100%)
20 mg/kg	11	2 (18%)	3 (27%)	5 (45%)
TOTAL	20	8 (40%)	4 (20%)	12 (60%)

No. of Prior Lines of Therapy	Total Evaluable	ORR (%)	MR (%)	Clinical Response Rate (≥MR)
1	8	5 (63%)	0 (0%)	5 (63%)
2	9	3 (33%)	3 (33%)	6 (67%)
3	3	0 (0%)	1 (33%)	1 (33%)
TOTAL	20	8 (40%)	4 (20%)	12 (60%)

¹Patients with ≥ 2 cycles of treatment or earlier progression. ² 5 PRs by EBMT; 7 PRs by IMWG

Pharmacokinetics and Pharmacodynamics

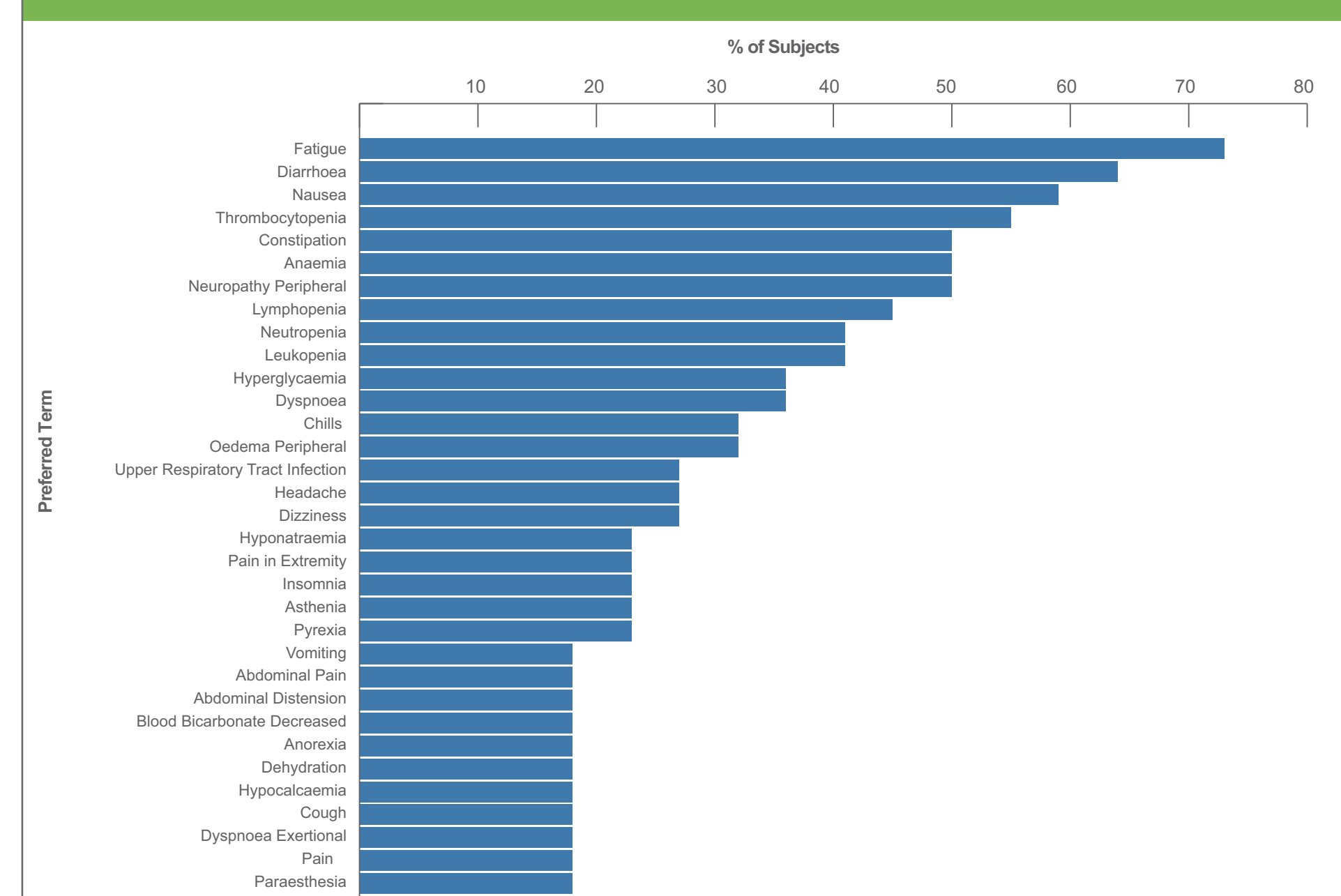
Saturation of CS1 Binding Sites in Bone Marrow NK and CD138+ Cells



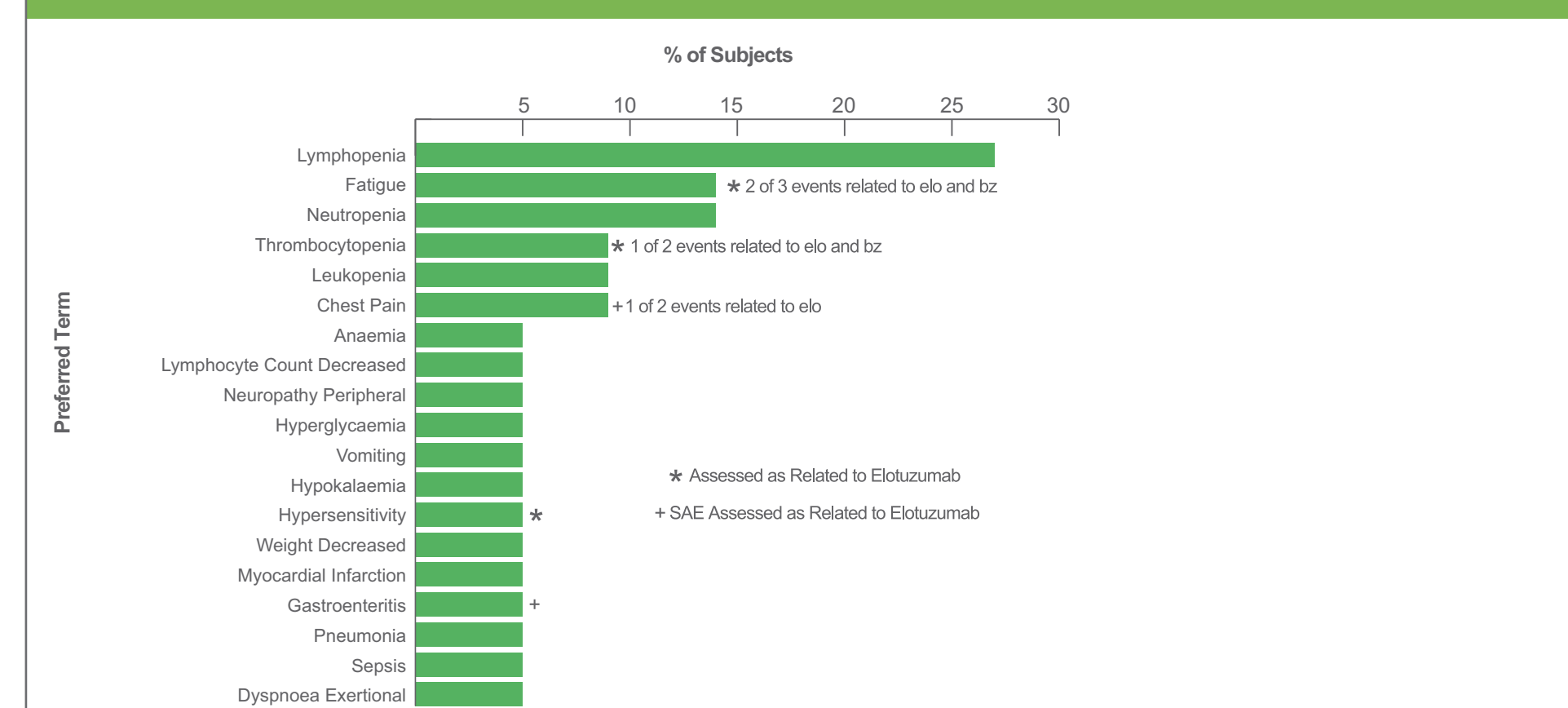
- Seven out of 12 responding subjects had bone marrow samples collected at Cycle 4 Day 18-21 or early termination.
- Elotuzumab saturated over 90% of the CS1-expressing target cells in bone marrow of all seven responding subjects who had samples available.

Safety

All Adverse Events Occurring in ≥ 15% of Patients (N=22)



Grade 3/4 Adverse Events (N=22)



Summary

Interim data from 26 patients with multiple myeloma treated with bortezomib and elotuzumab demonstrated a manageable safety profile:

- No DLTs were observed in the dose-escalation phase and the MTD was not established
- Two elotuzumab associated SAEs of chest pain and gastroenteritis reported in one patient

Preliminary efficacy data in 20 evaluable patients indicated:

- Clinical response rate (MR or better) of 60%
- Objective response rate (PR or better) of 40% by EMBT/uniform response criteria
- Median TTP is 9.6 months
- Preliminary analysis of elotuzumab saturation of CS1 sites on bone marrow plasma and NK cells suggests a correlation with objective response

Enrollment in the 20 mg/kg cohort expansion phase is ongoing

Acknowledgement

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- The patients and their families
- All study staff at each of the investigational sites
- Daniel Afar, Richard Brotherton, John Fry, Christopher Westland, Abbie Oey and Han Ding from Facet Biotech

CONFLICT OF INTEREST DISCLOSURES

Relevant Financial Relationships
 Andrzej J. Jakubowiak: Consultancy, Honoraria and Membership on an entity's Board of Directors or advisory committees for Millennium, Celgene, Centocor Ortho Biotech, Exelixis and BMS
 William Bensinger: Consultancy, Honoraria and Membership on an entity's Board of Directors or advisory committees for Millennium
 David Siegel: Speakers Bureau for Millennium and Celgene
 Todd M. Zimmerman: Speakers Bureau for Millennium and Centocor
 Don M. Benson, Jr.: There are no relevant conflicts of interest to disclose.
 Ann Mohrbacher: Honoraria and Speakers Bureau for Celgene
 Paul Richardson: Membership on an entity's advisory committees, Research Funding for Millennium; Membership on an entity's advisory committees for Celgene, Keryx, BMS, Merck
 Jan M. Van Tornout: Employment by BMS
 Carol Zhao: Employment by Facet Biotech
 Anil Singhal: Employment by Facet Biotech
 Kenneth Anderson: Consultancy, Honoraria and Membership on an entity's Board of Directors or advisory committees for Celgene, Novartis and Millennium