Elotuzumab In Combination with Lenalidomide and Dexamethasone In Patients with Relapsed Multiple Myeloma: Interim Results of a Phase 2 Study

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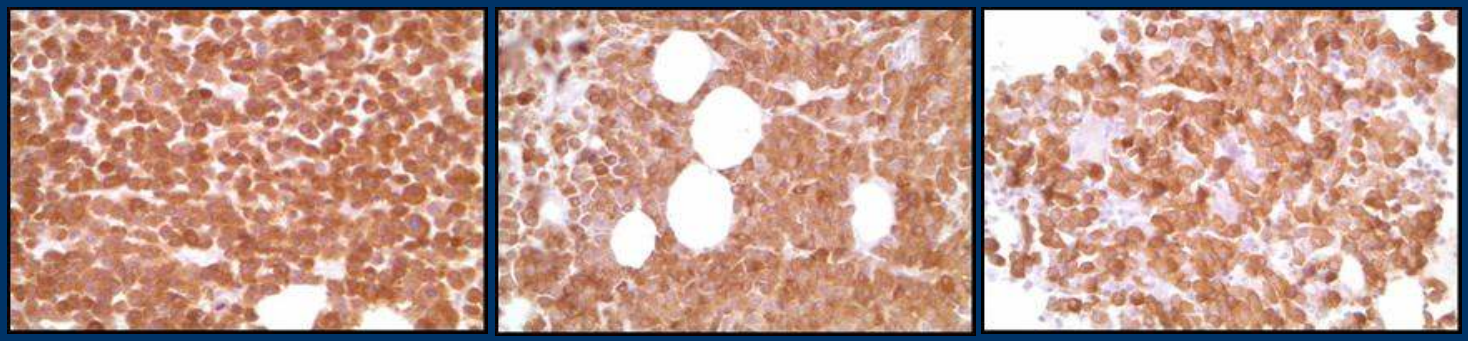
*Facet Biotech is now Abbott Biotherapeutics Corp.

Elotuzumab: Background

- Elotuzumab (HuLuc63) is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly and uniformly expressed on MM cells[1–3]
  - Restricted expression on NK cells
  - Little to no expression on normal tissues



- In a MM xenograft mouse model, the antitumor activity of elotuzumab was enhanced by the addition of lenalidomide[4]

MM, multiple myeloma; NK, natural killer.

1. Hsi ED et al. *Clin Cancer Res*. 2008;14:2775-2784. 2. Tai YT et al. *Blood*. 2008;112:1329-1337.
3. van Rhee F et al. *Mol Cancer Ther*. 2009;8:2616-2624. 4. Lonial S et al. *Blood*. 2009;114:432.

Elotuzumab + Lenalidomide + Low-dose Dexamethasone Phase 1 Results[1,2]

- Elotuzumab tested at 5, 10, and 20 mg/kg
  - Elotuzumab-related AEs were primarily infusion-related
  - 89% experienced at least 1 infusion reaction AE, no DLTs observed and MTD not reached

	Total	Lenalidomide-naïve	Prior Thalidomide	Refractory to Most Recent Therapy
Total Pts, n	28	22	16	12
≥ PR, n (%)	23 (82)	21 (95)	15 (94)	10 (83)
CR/VGPR, n (%)	11 (39)	10 (45)	7 (44)	5 (42)
PR, n (%)	12 (43)	11 (50)	8 (50)	5 (42)

- Median TTP not reached at a median 12.7 mos follow-up
- Elotuzumab saturation of CS1 binding sites in BM MM cells >80% at both 10 (n=1) and 20 mg/kg (n=4)

AEs, adverse events; CR, complete response; PR, partial response; VGPR, very good partial response.

1. Lonial S et al. ASCO 2010; Abstract 8020 (Oral); 2. Lonial S et al. ASH 2010; Abstract 1936.

Randomized Phase 2 Study Objectives

- **Primary objective**

  Evaluate efficacy [ORR (≥ PR)] of the combination in relapsed and relapsed and refractory MM pts with 1–3 prior therapies

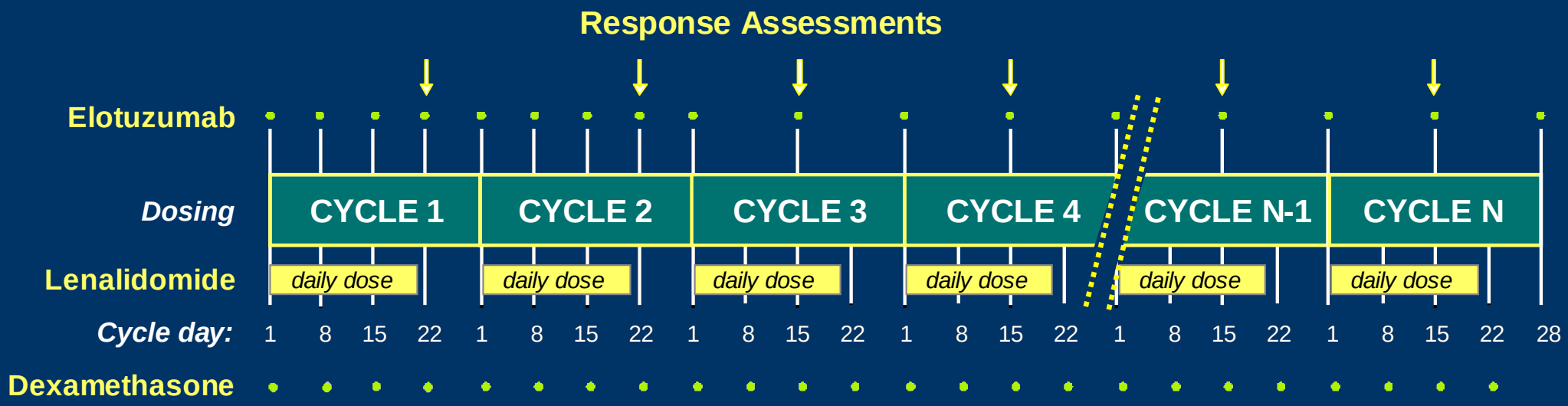
- **Secondary objectives**

  Evaluate safety, progression-free survival, pharmacokinetics, immunogenicity, and pharmacodynamics of the combination

  - **Evaluate effectiveness of the premedication regimen for minimizing infusion-related reactions**

- **Determine optimum dose of elotuzumab (10 mg/kg or 20 mg/kg) for subsequent testing**

Randomized Phase 2 Study Schema



- Pts randomized to receive elotuzumab 10 or 20 mg/kg IV, in combination with lenalidomide 25 mg PO and low-dose dexamethasone 40 mg PO wkly (28-day cycles)
- Treatment continued until PD or unacceptable toxicity
- Premedication regimen (30–60 mins prior to elotuzumab infusion)
  - Methylprednisone 50 mg IV
  - Diphenhydramine 25–50 mg PO or IV (or equivalent)
  - Ranitidine 50 mg IV (or equivalent)
  - Acetaminophen 650–1000 mg PO

Randomized Phase 2 Key Eligibility Criteria

- **Inclusion**
  - Relapsed and Relapsed and Refractory MM with 1-3 prior therapies
  - Measurable disease by M protein
  - Creatinine clearance ≥50 mL/min
- **Exclusion**
  - Thalidomide, bortezomib, or corticosteroids within 2 wks of the first dose
  - Prior lenalidomide

Baseline Characteristics
Safety Population (N=63)

Attribute	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Pts, n	31	32	63
Age, median yrs (range)	63 (39–77)	63 (41–82)	63 (39–82)
Yrs since first diagnosis, median (range)	4.8 (1.2–12.6)	3.7 (1.1–13.6)	4.3 (1.1–13.6)
≥2 prior therapies, n (%)	19 (61)	17 (53)	36 (57)
Prior transplant (autologous), n (%)	27 (87)	25 (78)	52 (83)
Refractory to last therapy, n (%)	10 (32)	9 (28)	19 (30)
High-risk cytogenetics,* n (%)	5 (16)	1 (3)	6 (10)
β2 microglobulin ≥3.5 mg/L, n (%)	18 (58)	14 (45)	32 (52)
Prior bortezomib, n (%)	18 (58)	16 (50)	34 (54)
Prior thalidomide, n (%)	19 (61)	18 (56)	37 (59)

*Defined as del13 by metaphase or t(4;14), t(14;16) or del17p by fluorescence in situ hybridization (FISH).

Efficacy
Best Confirmed Response (IMWG Criteria) [N=63]

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Pts, n	31	32	63
≥ PR, n (%)	28 (90)	23 (72)	51 (81)
Stringent CR, n (%)	1 (3)	1 (3)	2 (3)
CR, n (%)	2 (7)	1 (3)	3 (5)
VGPR, n (%)	10 (32)	8 (25)	18 (29)
PR, n (%)	15 (48)	13 (41)	28 (44)
SD, n (%)	3 (10)	7 (22)	10 (16)
PD, n (%)	0 (0)	0 (0)	0 (0)
Not evaluable, n (%)	0 (0)	2 (6)	2 (3)

CR, complete response; IMWG, International Myeloma Working Group; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Efficacy: Prior Thalidomide or Bortezomib Patients
Best Confirmed Response (IMWG Criteria)

Parameter	Prior Thalidomide		Prior Bortezomib	
	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg
Pts, n	19	18	18	16
≥ PR, n (%)	17 (90)	12 (67)	15 (83)	10 (63)
sCR/CR, n (%)	1(5)	1 (5)	2 (11)	1 (6)
VGPR, n (%)	5 (26)	4 (22)	7 (39)	3 (19)

CR, complete response; IMWG, International Myeloma Working Group; PR, partial response; sCR, stringent CR; VGPR, very good partial response.

Efficacy: Prior Therapies and β2M ≥3.5mg/L at Screening
Best Confirmed Response (IMWG Criteria)

No. of Prior Therapies	Parameter	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
1	≥ PR, n (%)	12/12 (100)	13/15 (87)	25/27 (93)
	≥ VGPR, n (%)	6/12 (50)	6/15 (40)	12/27 (44)
≥2	≥ PR, n (%)	16/19 (84)	10/17 (59)	26/36 (72)
	≥ VGPR, n (%)	7/19 (37)	4/17 (24)	11/36 (31)

β2M ≥3.5mg/L, Parameter	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
≥ PR, n (%)	17/18 (94)	9/14 (64)	26/32 (81)
≥ VGPR, n (%)	8/18 (44)	4/14 (29)	12/32 (38)

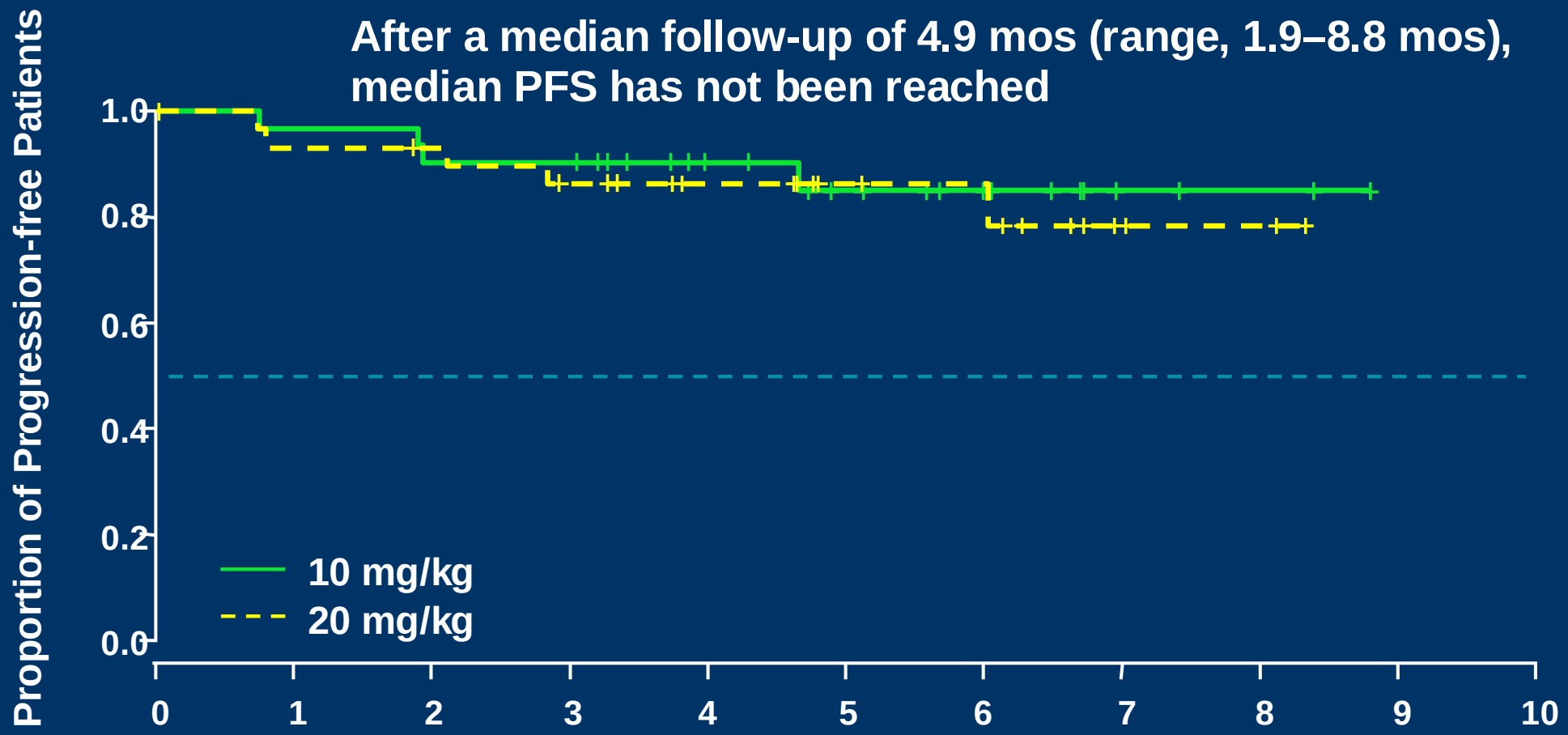
β2M, beta-2 microglobulin; IMWG, International Myeloma Working Group; PR, partial response; VGPR, very good partial response.

Time to Objective Response (≥ PR)
(IMWG Criteria)

Time to Parameter	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Pts, n*	28	23	51
Median time to response, mos (range)	0.9 (0.8–3.3)	1.7 (0.7–3.1)	1.0 (0.7–3.3)
Median time to best response, mos (range)	2.1 (0.8–5.8)	1.9 (0.7–4.3)	1.9 (0.7–5.8)

*Pts with an objective response.

Progression-free Survival



Number of Pts at Risk:											
10 mg/kg	31	30	28	28	18	13	10	3	2	0	0
20 mg/kg	32	28	27	22	17	12	11	3	2	0	0

Adverse Events: Elo+Len+Dex
(All Gr ≥20% or Gr 3/4 ≥5%)*

Preferred Term, n (%)	Elotuzumab 10 mg/kg, N=31	Elotuzumab 20 mg/kg, N=32	Total	
			Any Grade	Grades 3/4
Muscle Spasms	16 (52)	16 (50)	32 (51)	1 (2)
Constipation	12 (39)	14 (44)	26 (41)	0
Fatigue	16 (52)	10 (31)	26 (41)	2 (3)
Pyrexia	10 (32)	11 (34)	21 (33)	2 (3)
Diarrhea	7 (23)	13 (41)	20 (32)	2 (3)
Nausea	12 (39)	8 (25)	20 (32)	1 (2)
Anemia	9 (29)	7 (22)	16 (25)	5 (8)
Asthenia	5 (16)	10 (31)	15 (24)	1 (2)
Neutropenia	9 (29)	5 (16)	14 (22)	9 (14)
URI	5 (16)	9 (28)	14 (22)	2 (3)
Hyperglycemia	6 (19)	7 (22)	13 (21)	4 (6)
Lymphopenia	7 (23)	6 (19)	13 (21)	9 (14)
Thrombocytopenia	6 (19)	6 (19)	12 (19)	8 (13)
Leukopenia	5 (16)	4 (13)	9 (14)	3 (5)

*Additional Gr 3/4 AEs seen in 2 (3%) pts are hypokalemia, rash, blood bicarbonate decreased, ALT increased, febrile neutropenia, syncope, activated PTT prolonged, dehydration, TIA.

- Pts with one or more Gr 3/4 AEs: 56%
- No treatment-related mortality

Elotuzumab-Related Adverse Events*
(All Gr ≥10% or Gr 3/4 ≥5%†)

Preferred Term, n (%)	Elotuzumab 10 mg/kg N=31	Elotuzumab 20 mg/kg N=32	Total	
			Any Grade	Grade 3/4
Fatigue	8 (26)	5 (16)	13 (21)	0
Pyrexia	6 (19)	3 (9)	9 (14)	2 (3)
Lymphopenia	2 (7)	5 (16)	7 (11)	4 (6)
Diarrhea	3 (10)	4 (13)	7 (11)	0
Nausea	4 (13)	3 (9)	7 (11)	1 (2)
Constipation	5 (16)	1 (3)	6 (10)	0
Neutropenia	2 (7)	4 (13)	6 (10)	5 (8)

*Events attributed to elotuzumab by investigators.
† Additional elotuzumab-related Gr 3/4 AEs are 2 (3%) leukopenia; and 1 (2%) each of: febrile neutropenia, thrombocytopenia, gastrointestinal disorders, nausea, edema peripheral, decreased appetite, dehydration, hyperuricemia, tumor lysis syndrome, muscle spasms, glomerulonephritis, rash, rise of C-reactive protein.

- Pts with one or more Gr 3/4 elotuzumab-related AEs: 24%
- No elotuzumab-related mortality

Infusion Reactions*

Infusion Reaction Designation		Elotuzumab 10 mg/kg N=31 n (%)	Elotuzumab 20 mg/kg N=32 n (%)	Total N=63 n (%)
Predefined by sponsor	Any AE	16 (52)	15 (47)	31 (49)
	Grade 3 AEs†	1, Rash‡	0	1(2)
Investigator designated	Any AE	5 (16)	3 (9)	8 (13)
	Grade 3 AEs†	1, Rash‡	0	1 (2)

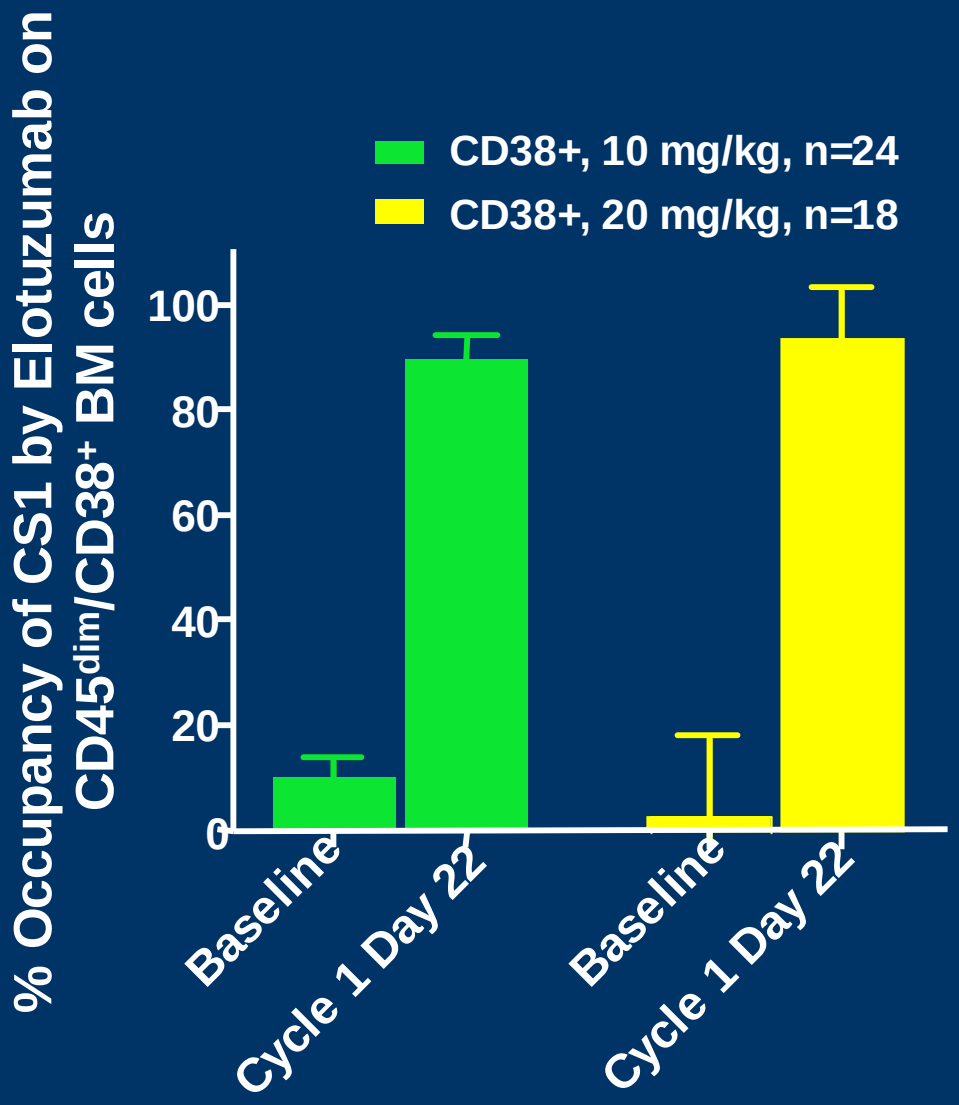
Infusion Reactions (Infusion reaction AEs ≥3% pts)*

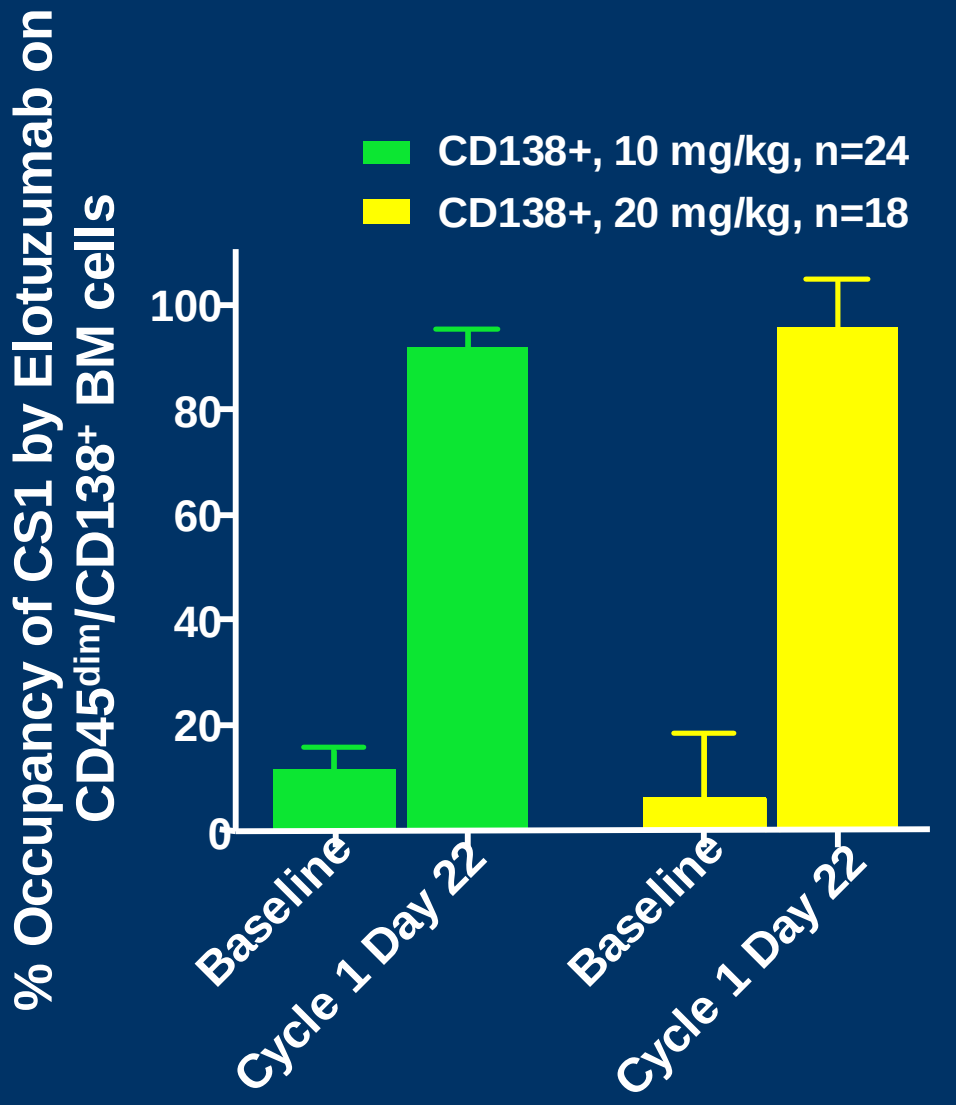
Nausea, dizziness, headache, pyrexia ≥10%
Cough, vomiting, dyspnea, chills, rash ≥5%
Flushing, hypotension, edema, erythema 3%

******Infusion reaction*** was predefined by the sponsor as the occurrence, regardless of causality, of one or more of approximately 110 adverse events deemed potential manifestations, that occurred on the day of or the day after elotuzumab infusion.**
†There were no Gr 4 infusion reaction AEs.
‡1 pt experienced 1 infusion reaction (rash), which was both predefined by sponsor and investigator designated.

AE, adverse events.

CS1 Saturation on CD38+ and CD138+ in Patient BM MM Cells





Conclusions

- **Elotuzumab + len/dex was generally well tolerated**
  - Gr 3/4 AEs >10%: neutropenia (14%), lymphopenia (14%), thrombocytopenia (13%)
  - Premedication regimen appears to mitigate the incidence and severity of infusion reactions
- **High ORR in previously-treated MM pts**
  - Phase 1: 82%[1,2]
  - Phase 2: 81% ORR, 37% VGPR/CR
- **10 mg/kg elotuzumab is recommended Phase 3 dose**
  - High activity (90% ORR, 42% VGPR/CR), similar safety and CS1 saturation to 20 mg/kg
  - High ORR in β2M ≥3.5 mg/L, prior thalidomide and median ≥2 prior therapies
- **Phase 3: Randomized, Open Label Trial of Lenalidomide/Dexamethasone With or Without Elotuzumab in Relapsed or Refractory MM anticipated to start early 2011 (NCT 01239797)**

1. Lonial S et al. ASCO 2010; Abstract 8020 (Oral). 2. Lonial S et al. ASH 2010; Abstract 1936.

Acknowledgments

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- Multiple Myeloma Research Consortium
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*Facet Biotech is now Abbott Biotherapeutics.

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