A Phase 2 Study of Elotuzumab in Combination With Lenalidomide and Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

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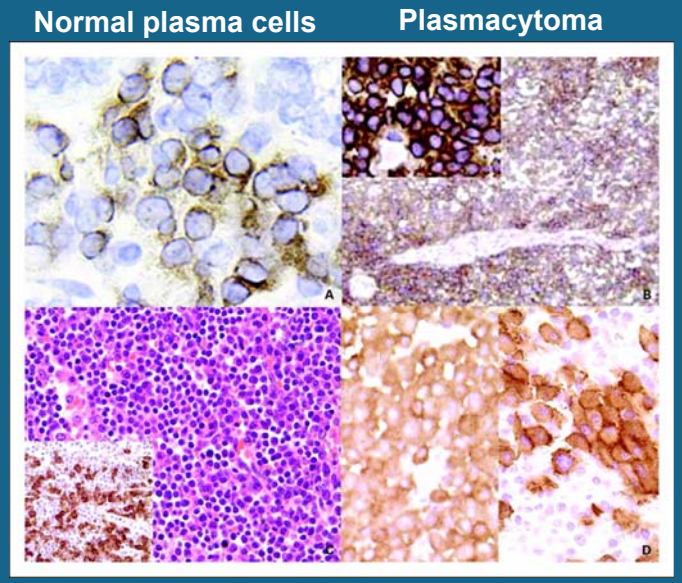
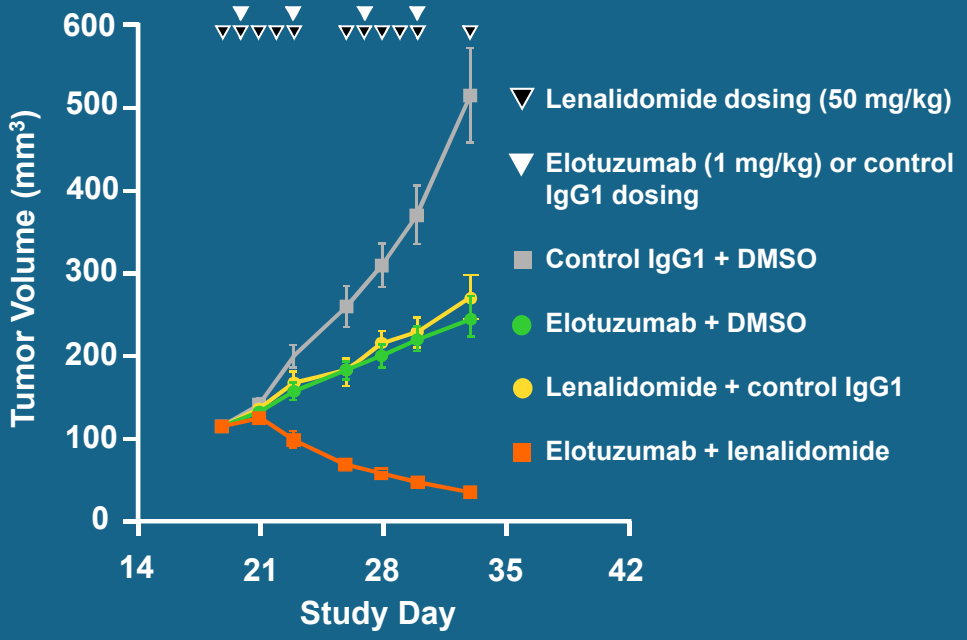
Elotuzumab Background

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly expressed on >95% of MM cells[1-3]
  - Lower expression on NK cells
  - Little to no expression on normal tissues
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells[1,2]
- In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone[4]



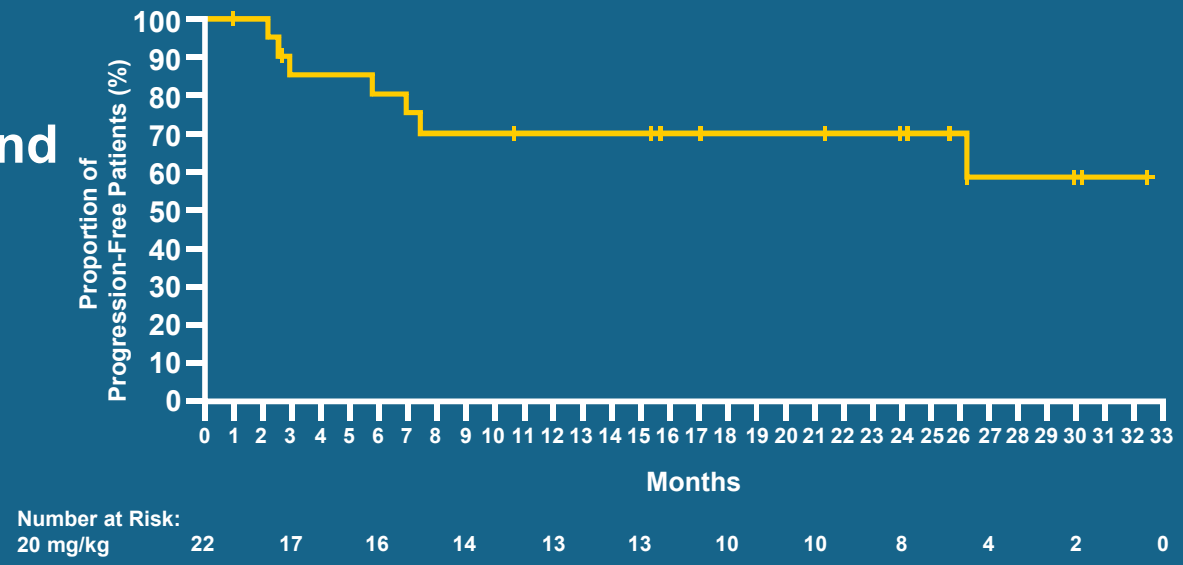


ADCC = antibody-dependent cellular cytotoxicity; DMSO = dimethyl sulfoxide;
mAb = monoclonal antibody; MED = maximum efficacious dose; MM = multiple myeloma; MoA = mechanism of action; NK = natural killer

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:Abstract 432

Summary of 1703 Phase 1 Data*

- 28 patients received elotuzumab 5, 10, or 20 mg/kg in combination with lenalidomide and low-dose dexamethasone
- The ORR was 82% with 43% ≥VGPR
- At median follow-up of 16.4 mos (2.2–32.5 mos), median PFS had not been reached
  - PFS rate was ~70%
- No DLT was observed and MTD was not reached
- The combination was generally well tolerated in heavily pretreated patients with MM



*Data as of October 26, 2011

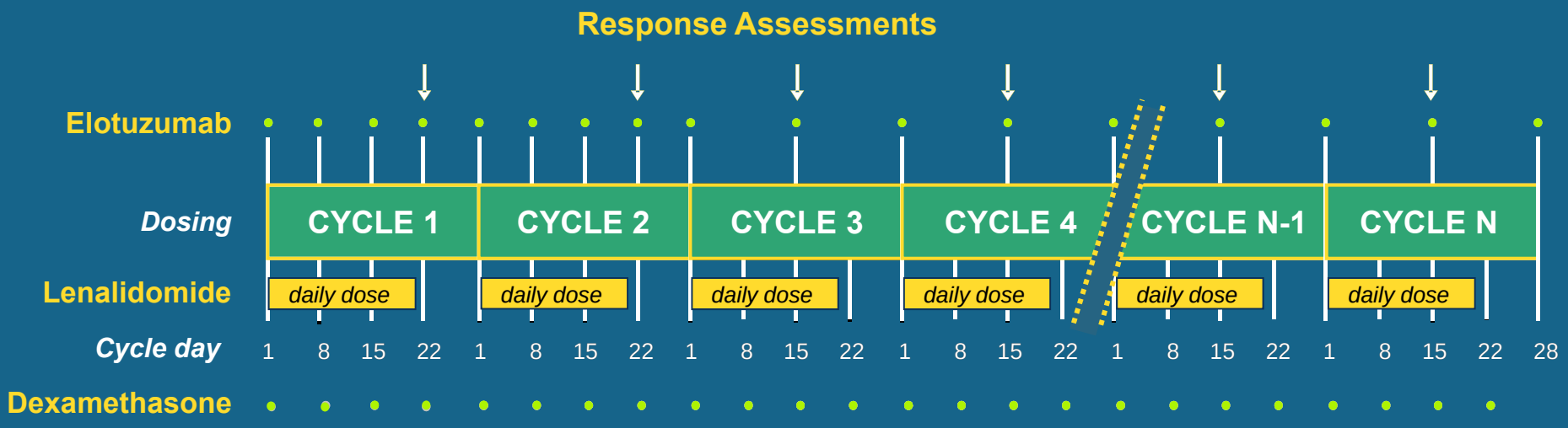
DLT = dose-limiting toxicity; ORR = objective response rate; MM = multiple myeloma; MTD = maximum tolerated dose
PFS = progression-free survival; VGPR = very good partial response

Study Objectives

- Primary objective
  - Efficacy (ORR: ≥PR) of the combination in relapsed and/or refractory MM pts with 1-3 prior therapies
- Secondary objectives
  - Safety, immunogenicity, and PK/PD of the combination
    - Effectiveness of premedication regimen for minimizing infusion reactions
  - PFS
  - Determine optimum dose of elotuzumab (10 mg/kg or 20 mg/kg) for Phase 3 studies

MM = multiple myeloma; MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; PR = partial response; PK/PD = pharmacokinetics/pharmacodynamics

Study Design



- Patients randomized to elotuzumab 10 or 20 mg/kg IV in combination with
  - Lenalidomide 25 mg PO
  - Low-dose dexamethasone 40 mg PO
- Treatment continued until disease progression or unacceptable toxicity

Premedication Regimen

- Administered 30-60 minutes prior to each elotuzumab infusion
  - Methylprednisolone 50 mg IV or dexamethasone 8 mg IV
  - Diphenhydramine 25-50 mg PO or IV (or equivalent)
  - Ranitidine 50 mg IV (or equivalent)
  - Acetaminophen 650-1000 mg PO

Key Eligibility Criteria

- **Inclusion**
  - Relapsed and/or refractory MM with 1-3 prior therapies
  - Measurable disease by M protein
  - Creatinine clearance ≥50 mL/min (Cockcroft-Gault method)
- **Exclusion**
  - Prior lenalidomide
  - Thalidomide, bortezomib, or corticosteroids within 2 weeks of the first elotuzumab dose

Baseline Characteristics *(N=73)*

Attribute	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Patients, n	36	37	73
Age, median years (range)	63 (39-77)	63 (41-82)	63 (39-82)
Years since first diagnosis, median (range)	4.7 (1.2-12.6)	4.4 (0.7-13.6)	4.5 (0.7-13.6)
≥2 prior therapies, n (%)	20 (56)	20 (54)	40 (55)
Prior transplant (autologous), n (%)	32 (89)	28 (76)	60 (82)
Refractory to last therapy, n (%)	12 (33)	12 (32)	24 (33)
High-risk cytogenetics*, n (%)	8 (22)	2 (5)	10 (14)
β2 microglobulin ≥3.5 mg/L, n (%)	18 (50)	15 (41)	33 (45)
Prior bortezomib, n (%)	22 (61)	22 (60)	44 (60)
Prior thalidomide, n (%)	21 (58)	24 (65)	45 (62)

Data as of October 26, 2011

*Defined as del13q by metaphase or t(4;14), t(14;16) or del17p by fluorescence in situ hybridization

Patient Disposition

Attribute	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Total enrolled (ITT population), n	36	37	73
Number of cycles*, median (range)	16 (3-23)	12 (1-23)	15 (1-23)
Still on study (receiving study drugs), n (%)	20 (56)	18 (49)	38 (52)
Treatment cessation, n (%)	16 (44)	19 (51)	35 (48)
Disease progression	10	8	18
Adverse event	2	8	10
Other	4	3	7

*28 days per cycle

ITT = intent-to-treat; MM = multiple myeloma

Efficacy
Best Response *(IMWG Criteria)*

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Patients, n	36	37	73
ORR (≥PR), n (%)	33 (92)	27 (73)	60 (82)
CR/stringent CR, n (%)	5 (14)	4 (11)	9 (12)
VGPR, n (%)	14 (39)	12 (32)	26 (36)
PR, n (%)	14 (39)	11 (30)	25 (34)
<PR, n (%)	3 (8)	10 (27)	13 (18)

- Median time to response: 1 month (range, 0.7-5.8)
- Median time to best response: 2.2 months (range, 0.7-17.5)

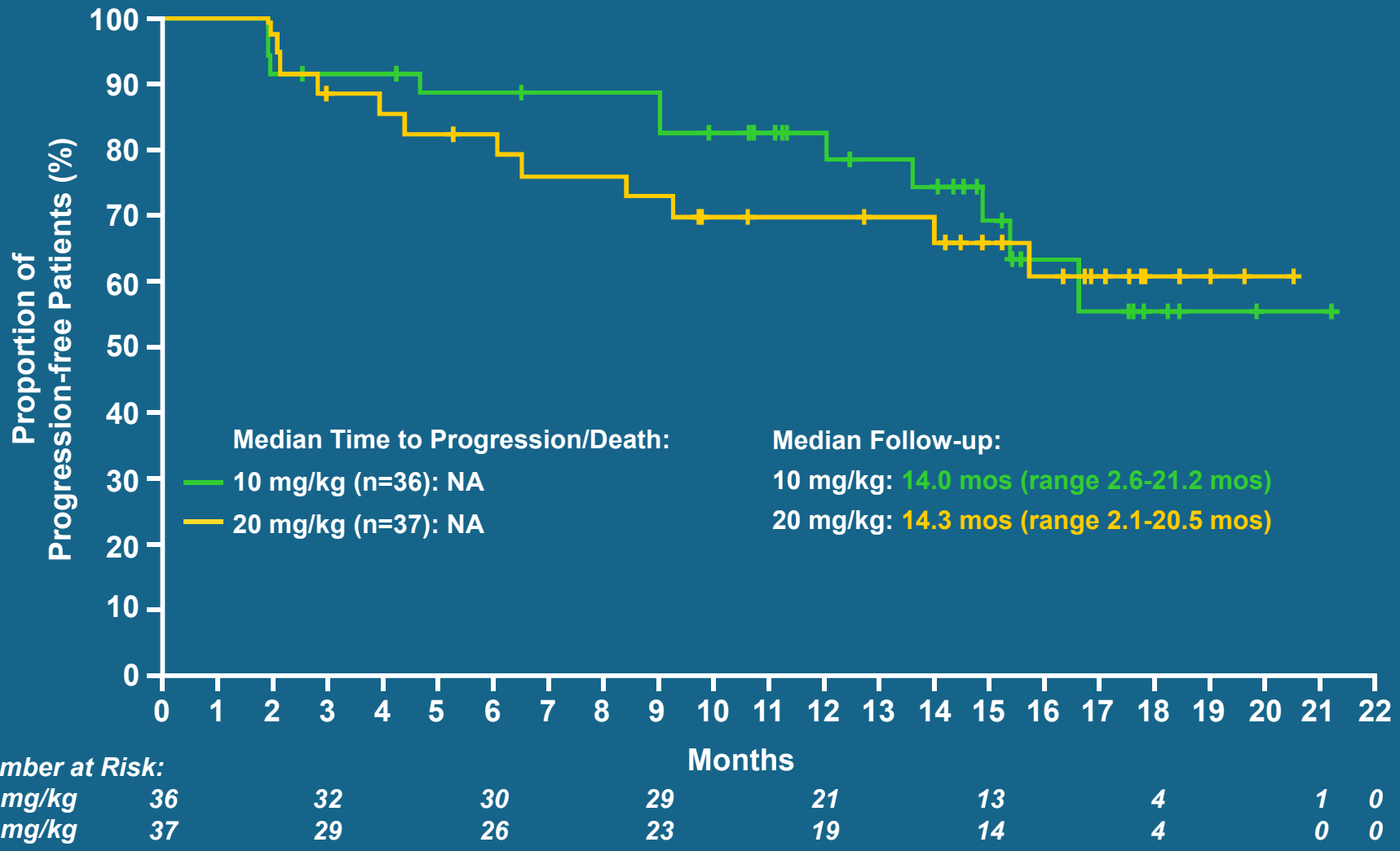
CR = complete response; IMWG = International Myeloma Working Group; PR = partial response; VGPR = very good partial response

Best Response by Number of Prior Therapies at Screening *(IMWG Criteria)*

No. of Prior Therapies	Parameter	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
1	Patients, n	16	17	33
	ORR (≥PR), n (%)	16 (100)	14 (82)	30 (91)
	≥VGPR, n (%)	9 (56)	6 (35)	15 (45)
≥2	Patients, n	20	20	40
	ORR (≥PR), n (%)	17 (85)	13 (65)	30 (75)
	≥VGPR, n (%)	10 (50)	10 (50)	20 (50)

IMWG = International Myeloma Working Group; ORR = objective response rate; PR = partial response; VGPR = very good partial response

Progression-free Survival



Number at Risk:

10 mg/kg	*36*	*32*	*30*	*29*	*21*	*13*	*4*	*1*	*0*
20 mg/kg	*37*	*29*	*26*	*23*	*19*	*14*	*4*	*0*	*0*

At a median follow-up of 14.1 months, the median PFS was not reached

- **PFS rate was 75% (10 mg/kg) and 65% (20 mg/kg)**

Treatment-emergent AEs*
(All Grade ≥25% or Grade 3/4 ≥5%)

Preferred Term, n (%)	Elotuzumab 10 mg/kg, n=36	Elotuzumab 20 mg/kg, n=37	Total, N=73	
			Any Grade	Grade 3/4[†]
Muscle spasms	19 (53)	21 (57)	40 (55)	2 (3)
Diarrhea	20 (56)	19 (51)	39 (53)	4 (5)
Fatigue	19 (53)	16 (43)	35 (48)	5 (7)
Constipation	14 (39)	19 (51)	33 (45)	0
Nausea	16 (44)	15 (41)	31 (42)	1 (1)
Upper respiratory tract infection	17 (47)	13 (35)	30 (41)	2 (3)
Pyrexia	14 (39)	14 (38)	28 (38)	1 (1)
Anemia	13 (36)	10 (27)	23 (32)	8 (11)
Insomnia	9 (25)	13 (35)	22 (30)	1 (1)
Peripheral edema	12 (33)	9 (24)	21 (29)	1 (1)
Back pain	11 (31)	8 (22)	19 (26)	2 (3)
Hyperglycemia	7 (19)	12 (32)	19 (26)	7 (10)
Neutropenia	11 (31)	8 (22)	19 (26)	12 (16)
Thrombocytopenia	11 (31)	7 (19)	18 (25)	12 (16)
Lymphopenia	10 (28)	7 (19)	17 (23)	12 (16)
Leukopenia	7 (19)	5 (14)	12 (16)	6 (8)
Hypokalemia	5 (14)	6 (16)	11 (15)	4 (5)

AE = adverse event

*Events emerging from treatment with elotuzumab plus lenalidomide/low-dose dexamethasone (not present at baseline)

[†]Grade 5: 1 patient, pneumonia complicated by cellulitis and sepsis leading to multi-organ failure

The 4 most common AEs of any Grade and Grade 3/4 are highlighted

Peri-infusion AEs*

- **Peri-infusion AEs (all Grades) reported in 49 of 73 (67%) patients**
  - **Nausea, headache, pyrexia, cough, dizziness (≥10%)**
  - **Dyspnea, erythema, rash, vomiting, chills, flushing, hyperhidrosis, edema, palpitations (5.0%-9.9%)**
  - **Grade 3 peri-infusion AEs reported in 2 of 73 (3%) patients**
    - **1 rash and 1 nausea**
  - **There were no Grade 4 peri-infusion AEs**

*Peri-infusion AEs predefined as: 110 AE terms of potential signs/symptoms of infusion reaction occurring the day of / day after elotuzumab infusion regardless of investigator assessed causality

Investigator-designated Infusion Reactions

- Investigator-designated infusion reactions are AEs identified by the investigator as a sign or symptom of an elotuzumab-related infusion reaction
- AEs that occurred in ≥ 2 subjects included nausea, pyrexia and rash

	Elotuzumab		
Parameter, n (%)	10 mg/kg n=36	20 mg/kg n=37	Total N=73
Any AE	5 (14)	4 (11)	9 (12)
Grade 1	3 (8)	2 (5)	5 (7)
Grade 2	1 (3)	2 (5)	3 (4)
Grade 3*	1 (3) Rash	0	1(1)

AE = adverse event
*There were no Grade 4 infusion reaction AEs

Conclusions

- **Elotuzumab plus lenalidomide and low-dose dexamethasone has a high ORR in relapsed and relapsed/refractory MM**
  - **82% for all patients (91% in patients who had received only 1 prior therapy)**
  - **92% for patients treated with elotuzumab 10 mg/kg**
- **At a median follow-up of 14.1 months, the median PFS was not reached**
  - **PFS rate was 65% to 75%**
- **The combination was generally well tolerated**
  - **Most common Grade 3/4 treatment-emergent AEs were neutropenia (16%), thrombocytopenia (16%), and lymphopenia (16%)**
  - **Premedication regimen decreased incidence and mitigated severity of infusion reactions***

*Richardson PG et al. J Clin Oncol 29: 2011 (suppl; abstr 8014)

Future Directions

- **10 mg/kg elotuzumab is the recommended Phase 3 dose**
  - **High ORR and similar safety profile for 10 and 20 mg/kg dose**
- **Two Phase 3 trials of 10 mg/kg elotuzumab plus lenalidomide and low-dose dexamethasone are ongoing**
  - **ELOQUENT1 in previously untreated MM patients (CA204-006; NCT01335399)**
  - **ELOQUENT2 in relapsed/refractory MM patients (CA204-004; NCT01239797)**

Poster Presentation Monday December 12

Poster 3968

Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in High-Risk and/or Stage 2-3 Relapsed and/or Refractory Multiple Myeloma: A Retrospective Subset Analysis of the Phase 2 Study

Presenter: Sundar Jagannath

Hall GH, 6:00 – 8:00 PM

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