Phase I/II Study of Elotuzumab Plus Lenalidomide/Dexamethasone in Relapsed/ Refractory Multiple Myeloma: Updated Phase II Results and Phase I/II Long Term Safety

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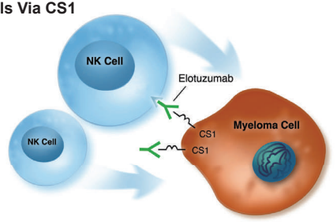
Introduction

- Elotuzumab is a humanized monoclonal antibody being investigated for the treatment of multiple myeloma (MM)
- Elotuzumab targets CS1, a protein that is highly expressed on the surface of myeloma cells and mediates the adhesion of MM cells to bone marrow stromal cells (**Figure 1**)[1]
- Elotuzumab enhances natural killer (NK) cell-mediated killing of myeloma cells primarily via antibody-dependent cell-mediated cytotoxicity (ADCC)[1–4]
- Elotuzumab in combination with lenalidomide and low-dose dexamethasone has encouraging objective response rates (ORRs) and median progression-free survival (PFS) in relapsed and relapsed/refractory MM[5,6]
- The analysis presented here expands on the previous results with the initially enrolled dose-escalation phase 1 cohort, and safety and efficacy phase 2 cohort
  - Updated phase 2 efficacy data (n=73) and long-term safety data from both cohorts (N=98) will be provided

Figure 1. Elotuzumab, a Humanized Monoclonal Antibody Binds to Myeloma Cells Via CS1

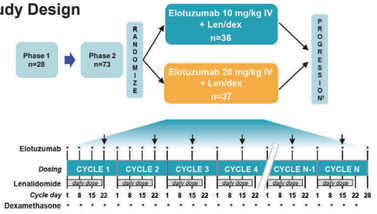


Methods

- In the phase 1 cohort, patients were treated with elotuzumab 5 mg/kg, 10 mg/kg, or 20 mg/kg intravenously (IV) using a standard 3 + 3 dose escalation design in a 28-day cycle[5]
  - Patients treated with the 5 mg/kg dose (n=3) were not included in this analysis
- In the phase 2 study, patients with relapsed/refractory MM were randomized to elotuzumab 10 or 20 mg/kg IV combined with lenalidomide 25 mg orally (PO) and low-dose dexamethasone 40 mg PO (**Figure 2**)
  - Premedication 30 to 60 minutes prior to elotuzumab doses for infusion reactions included methylprednisolone 50 mg or dexamethasone 8 mg IV, diphenhydramine 25–50 mg PO or IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650–1000 mg (PO)
- Inclusion criteria:
  - Relapsed and/or refractory MM with 1–3 prior therapies
  - Measurable disease by M protein
  - Creatinine clearance ≥50 mL/min (Cockcroft-Gault method)
- Exclusion criteria:
  - Prior lenalidomide
  - Thalidomide, bortezomib, or corticosteroids within 2 weeks of the first elotuzumab dose
- The study's primary endpoint was ORR (≥ partial response [PR] per International Myeloma Working Group [IMWG Criteria]), with key secondary endpoints assessing PFS and safety
- Treatment was continued until disease progression or unacceptable toxicity
- This report contains follow-up data up to April 24, 2013

Results

Figure 2. Study Design



Stratification in phase II: prior therapies (1 vs 2 or 3 lines), prior thalidomide or thalidomide analogs.
Len/dex: lenalidomide plus low dose dexamethasone.
↓ Assessments were performed once per cycle.
†Progression defined by IMWG Criteria.

Table 1. Baseline Demographics

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Patients, N	39	59	98
Age, median years (range)	63 (39-77)	61 (41-83)	62 (39-83)
Years since first diagnosis, median (range)	4.4 (1.2-12.6)	4.8 (0.7-13.6)	4.4 (0.7-13.6)
≥2 prior therapies, n (%)	22 (56)	37 (63)	59 (60)
Prior transplant (autologous), n (%)	35 (90)	44 (75)	79 (81)
Refractory to last therapy, n (%)	13 (33)	20 (34)	33 (34)
High-risk cytogenetics*, n (%)	9 (23)	3 (5)	12 (12)
β2 microglobulin ≥3.5 mg/L, n (%)	21 (55)	19 (33)	40 (42)
Prior bortezomib, n (%)	24 (62)	38 (64)	62 (63)
Prior thalidomide, n (%)	24 (62)	35 (59)	59 (60)

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

- Across phase 1 and 2 cohorts, 98 patients received study drug at either 10 mg or 20 mg, and were included in the safety analysis
- From the phase 2 cohort, 73 patients were included in the efficacy analysis
- Baseline characteristics for patients receiving elotuzumab 10 mg/kg or 20 mg/kg regimens were as expected for the patient population

Table 2. Patient Disposition

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Total dosed (safety population), n	39	59	98
Number of cycles*, median (range)	17 (3-41)	16 (1-54)	16.5 (1-54)
Still on study (receiving study drugs), n(%)	11 (28)	14 (24)	25 (26)
Treatment cessation, n (%)	28 (72)	45 (76)	73 (74)
Disease progression	16 (41)	20 (34)	36 (37)
Adverse event	3 (8)	12 (20)	15 (15)
Other†	9 (23)	13 (22)	22 (22)

***28 days per cycle.**
†Reasons include: investigator decision (n=10; M-protein level progression, patient eligible for transplant, clinical and radiological progression), patient decision (n=11; relocation, consent withdrawn, declined further treatment, distance/financial impact), or unknown (n=1).

Results (con't)

Table 3. Most Common Treatment Emerging Grade 3/4 AEs Before and After 18 Months of Treatment

Grade 3/4 AEs,* n (%)	Onset: Elotuzumab 10 mg/kg ≤18 months n=39	Elotuzumab 10 mg/kg + len/dex +18 months n=20	Elotuzumab 20 mg/kg ≤18 months n=59	Elotuzumab 20 mg/kg + len/dex >18 months n=31
Neutropenia	8 (21)	1 (5)	13 (22)	1 (3)
Thrombocytopenia	8 (21)	1 (5)	10 (17)	0
Lymphopenia	10 (26)	1 (5)	5 (9)	0
Anemia	5 (13)	1 (5)	7 (12)	0
Hyperglycemia	2 (5)	0	7 (12)	0
Fatigue	3 (8)	1 (5)	5 (9)	0
Diarrhea	4 (10)	2 (10)	3 (5)	0
Leukopenia	3 (8)	1 (5)	4 (7)	0
Hypokalemia	3 (8)	1 (5)	3 (5)	1 (3)
Pneumonia	3 (8)	0	3 (5)	2 (7)

***In ≥ 5% of patients across elotuzumab 10 and 20 mg/kg.**

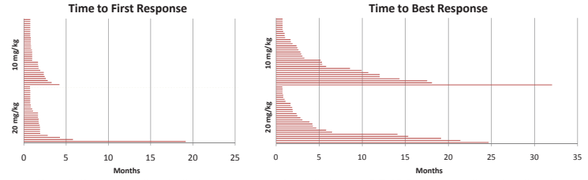
- Across dosages, 51 patients received therapy for over 18 months
- Most treatment-emergent adverse events (AEs) occurred within 18 months of therapy

Table 4. Best Response from the Phase 2 Cohort

	Phase 2 Elotuzumab 10 mg/kg	Phase 2 Elotuzumab 20 mg/kg	Total
Patients, n	36	37	73
ORR (≥PR), n (%) (95% CI)*	33 (92) (78-98)	28 (76) (59-88)	61 (84) (73-91)
CR/stringent CR, n (%)	5 (14)	4 (11)	9 (12)
VGPR, n (%)	18 (50)	14 (38)	32 (44)
PR, n (%)	10 (28)	10 (27)	20 (27)
<PR, n (%)	3 (8)	9 (24)	12 (16)

***By Clopper-Pearson method.**

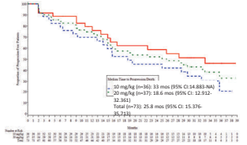
Figure 3. Time to First and Best Responses from the Phase 2 Cohort



- Overall, the median time to first response was 1 month (range, 0.7-19.2); the overall median time to best response was 2.6 months (range, 0.7-32)
- At time of data cut-off, median duration of objective response was 17.8 months (range, 1.0-37.1)

Results (con't)

Figure 4. Progression-free Survival from the Phase II Cohort



- In the 10 mg/kg cohort, median PFS was 33 months after a median follow-up of 20.8 months
- In the 20 mg/kg cohort, the median PFS was 18 months after a median follow-up of 17.1 months
- Patient follow-up is ongoing and updated results will be presented in the future

Summary and Conclusions

- Elotuzumab plus lenalidomide and low-dose dexamethasone was generally well tolerated across evaluated doses
  - Adverse events occurring after 18 months of therapy were consistent with the safety profile observed with this combination[5,6] and no new safety signal has been identified
- Elotuzumab plus lenalidomide and low-dose dexamethasone was effective in the treatment of relapsed/refractory multiple myeloma*
  - ORR was 84%, with 92% for patients receiving elotuzumab 10 mg/kg
  - 33 month median PFS for patients receiving elotuzumab 10 mg/kg

*Historically, treatment with lenalidomide plus high dose dexamethasone (no elotuzumab) resulted in an ORR of 60-61% and median TTP of 11.1-11.3 months from two randomized Phase 3 studies with similar patient populations.[7,8] Median overall survival (OS) achieved with lenalidomide was longer by 9.4 months (29.6 vs 20.2 months)[7] or more (not reached vs. 20.6 months)[8] than median OS with placebo.

Future Directions

- Two Phase III trials are currently underway evaluating elotuzumab 10 mg/kg plus lenalidomide and low-dose dexamethasone
  - ELOQUENT-1 in previously untreated MM patients (CA204-006; NCT01335399)
  - ELOQUENT-2 in relapsed/refractory MM patients (CA204-004; NCT01239797)
- Additional trials of elotuzumab with new combination partners or settings in MM are ongoing
  - Bortezomib plus dex ± elotuzumab in relapsed/refractory MM (CA204-009; NCT01478048)
  - Bortezomib plus len/dex ± elotuzumab in high-risk MM (SWOG S1211; NCT01668719)
  - Elotuzumab plus thalidomide + dex in relapsed/refractory MM (CA204-010; NCT01632150)
  - Elotuzumab in high-risk smoldering MM (CA204-011; NCT01441973)
  - Elotuzumab plus len/dex in MM patients with impaired renal function (CA204-007; NCT01393964)

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