Phase I Study of Bortezomib and ^{153}Sm-lexidronam Combination for Refractory and Relapsed Multiple Myeloma

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I. Abstract

Background: Multiple myeloma (MM) is a highly radiosensitive B-cell malignancy and radiation therapy has been an effective treatment for these patients. Recent preclinical studies have demonstrated that the bone-seeking radionuclide, Samarium Sm153 lexidronam (Sam) in combination with the proteasome inhibitor, bortezomib (Vel), can synergistically inhibit proliferation of myeloma cell lines *in vitro* and reduce MM growth in mice bearing human MM without significant myelotoxicity. These results provide the basis for a new therapeutic approach of combining Vel and Sam to overcome resistance and to minimize non-tumor tissue toxicity among refractory and relapsed MM patients.
Aims: The primary objective of this Phase I study is to determine the response rate, safety and tolerability of Vel + Sam combination in patients with relapsed or refractory MM.
Methods: Relapsed or refractory MM patients who had more than 2 prior treatments will be enrolled on this Phase I dose-escalation trial which involves six cohorts. Previous treatment with Vel is permissible. Dose escalations in parallel arms are as follows:

Arm 1	Sam	Vel	Arm 2	Sam	Vel
Cohort 1	0.25 mCi/kg	1.0 mg/m^2	Cohort 4	0.25 mCi/kg	1.3 mg/m^2
Cohort 2	0.5 mCi/kg	1.0 mg/m^2	Cohort 5	0.5 mCi/kg	1.3 mg/m^2
Cohort 3	1.0 mCi/kg	1.0 mg/m^2	Cohort 6	1.0 mCi/kg	1.3 mg/m^2

A complete treatment cycle is 8 weeks. Vel is given on days 1, 4, 8 and 11 followed by a 45-day rest period. Sam is administered on day 4. The cycle is repeated on Day 57 if disease is stable or improved and platelets and neutrophils recover to at least Grade 1 toxicity (delayable up to four weeks). DLT is defined as cycle 1 grade 4 hematologic or Grade ≥3 non-hematologic toxicity.
Results: Cohorts 1, 2 and 4 have been enrolled (3 patients per cohort). Two cycle has been administered thus far for two patient in cohort 4. No significant hematologic toxicities were observed. Only one patient experienced transient fever, headache and vomiting. There have been no dose limiting toxicities to date. Three patients in cohort 1 and one patient in cohort 4 showed progression of disease prior to second cycle and were taking off the study. The relapsed patient in cohort 1 had grade 3 hyperkalemia and renal failure resulted from MM renal disease.
Conclusions: The trial will continue to enroll patients in cohorts 2 and 5. Updated results from the trial will be presented at the meeting.

II. Study Objectives

Primary: To assess the safety and tolerability (MTD and DLT) of Vel and Sam for patients with relapsed or refractory MM.

Secondary: To determine response rate in this population and time to progression of disease, time to response, progression-free survival and overall survival.

III. Materials and Methods

Patient Population:
Male or female patients who are 18 years of age or older with relapsed or refractory MM and have measurable disease.

Inclusion Criteria:
•Previously diagnosed with multiple myeloma based on standard criteria (Durie, *Semin. Oncol.,* 1986; 13: 300-9)
•Currently has multiple myeloma with either:
-Measurable disease, defined as: monoclonal immunoglobulin spike on serum electrophoresis of ≥1 gm/dL and/or urine monoclonal immunoglobulin spike of ≥200 mg/24 hrs or evidence of lytic bone disease.
-Non-measurable disease (i.e. patients with nonsecretory or oligosecretory multiple myeloma).
•Relapsed following a response or stable disease to chemotherapy or high-dose chemotherapy, or refractory to their most recent chemotherapy, whether or not containing systemic corticosteroids
•Baseline platelets ≥75 x 10^9/L and ANC ≥1.5 x 10^9/L

Exclusion Criteria:
•POEMS syndrome and skin changes
•Active infection
•Serum calcium ≥ 14 mg/dL
•Major surgery within four weeks
•Chemotherapy within three weeks
•Corticosteroids (>10 mg/day prednisone or equivalent) within three weeks
•Immunotherapy, antibody or radiation therapy within 4 weeks
•Known HIV history or active hepatitis B or C viral infection
• Baseline >grade 1 neuropathy
•Extramedullary myeloma
•History of allergic reaction attributable to compounds of similar chemical or biological composition to bortezomib, boron, mannitol, EDTMP or phosphonates

IV. Results

Demographics and Treatment History

Patient #	Cohort	Age	Gender	# Prior Myeloma Tx's	Prior Bortezomib	# Study Tx Cycles*
1	1	68	M	5	Y	1
2	4	61	M	5	Y	1
3	1	48	M	3	Y	1
4	4	68	F	4	Y	2
5	1	55	F	2	N	1
6	4	66	M	1	N	2+
7	2	69	F	8	Y	1
8	5	63	M	6	Y	1+
9	2	66	F	1	N	1+
10	5	62	F	2	N	1+
11	2	51	M	2	Y	1
12	5	62	M	3	Y	1+

* + indicates patient remains on study treatment

Response to Study Treatment

Cohort 1 (0.25 – 1.0)*		Cohort 4 (0.25 – 1.3)*	
Pt. 1	PD	Pt. 2	PD
Pt. 3	PD	Pt. 4	SD
Pt. 5	PD	Pt. 6	PR
Cohort 2 (0.5 – 1.0)*		**Cohort 5 (0.5 – 1.3)***	
Pt. 7	PD	Pt. 8	SD
Pt. 9	CR	Pt. 10	SD
Pt. 11	PD	Pt. 12	SD

*(Sm-153, mCi/kg - Bortezomib, mg/m^2)

Cycle 1 Hematologic Toxicity

Nadir Value (Day of Nadir)

WBC

Cohort 1		Cohort 4	
Pt. 1	2.0 (11)	Pt. 2	2.4 (15)
Pt. 3	3.3 (43)	Pt. 4	3.6 (15)
Pt. 5	2.6 (43)	Pt. 6	3.4 (15)
Cohort 2		**Cohort 5**	
Pt. 7	3.9 (15)	Pt. 8	2.1 (29)
Pt. 9	5.0 (15)	Pt. 10	2.8 (11)
Pt. 11	1.9 (15)	Pt. 12	4.0 (15)

ANC

Cohort 1		Cohort 4	
Pt. 1	1.12 (11)	Pt. 2	0.82 (11)
Pt. 3	1.91 (15)	Pt. 4	0.85 (15)
Pt. 5	1.01 (15)	Pt. 6	0.84 (15)
Cohort 2		**Cohort 5**	
Pt. 7	1.05 (11)	Pt. 8	1.19 (36)
Pt. 9	3.45 (15)	Pt. 10	1.23 (11)
Pt. 11	0.93 (15)	Pt. 12	2.70 (15)

Platelets

Cohort 1		Cohort 4	
Pt. 1	118 (32)	Pt. 2	172 (36)
Pt. 3	162 (36)	Pt. 4	88 (15)
Pt. 5	96 (15)	Pt. 6	74 (15)
Cohort 2		**Cohort 5**	
Pt. 7	78 (15)	Pt. 8	119 (29)
Pt. 9	128 (38)	Pt. 10	210 (28)
Pt. 11	101 (15)	Pt. 12	168 (42)

Adverse Events Occurring in >1 Patient

Adverse Event	Total #
Headache	7
Neuropathy	6*
U. Respiratory Infection	4
Nausea	4
Neutropenia	4
Chills	3
Fatigue	3
Cough	3
Leg Cramps	3
Bone Pain	2
Depression	2
Joint Pain	2
Myalgia	2
Rash	2
Sciatic Pain	2
Taste Disturbance	2
Thrombocytopenia	2
Upset Stomach	2

*Neuropathy worsened over baseline in only 2 patients

Adverse Events of Severity >Grade 1

Adverse Event	Gr. 2	Gr. 3	Gr. 4	Adverse Event	Gr. 2	Gr. 3	Gr. 4
Bone Pain	1			Neuropathy	2		
Depression	1			Neutropenia		1	
Diarrhea	1			Rash	1		
Fatigue	1			Renal Dysfunction	1		
Folicolitis	1			Sacral Mass	1		
Headache	1	2		Sciatic Pain	1		
Increased creatinine	1			Shortness of Breath	1		
Increased insomnia	1			Shoulder Blade Pain	1		
Joint Pain	1			Thrombocytopenia	1		1
Leg Cellulitis	1			Thrombosis		3*	
Leg Cramps		1		U. Resp. Infection	2		
Leg Pain	1			Urinary Tract Infection	1		

*Occurred at same time in a single patient with a prior history of multiple thrombotic events

V. Conclusions

- The combination of Samarium-153 lexidronam and bortezomib appears to be well-tolerated at the doses studied to date.
- The primary toxicity observed has been a transient decrease in platelets and neutrophils.
- No instances of DLT have been observed.
- Among the 12 patients enrolled, 2 patients have responded (1 CR and 1 PR) and 4 patients have shown stable disease.
- Patients are continuing to be enrolled to the last two cohorts of this Phase I study.