

Phase I Trial of Bortezomib (Vel) and Samarium (Sam) in Multiple Myeloma

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I. Abstract

Background: 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 growth of multiple myeloma (MM) both *in vitro* and *in vivo*. These results provide the basis for a new therapeutic approach combining Vel and Sam to overcome resistance and to minimize non-tumor tissue toxicity among refractory and relapsed MM patients.

Materials and Methods: Relapsed or refractory MM patients who failed prior treatments were enrolled on this phase I dose-escalation trial. Previous treatment with bortezomib was permissible. Enrollment in six cohorts occurred in two parallel arms (Vel 1.0 or 1.3 mg/m²) with escalating Sam (0.25, 0.50 or 1.0 mCi/kg). Each cycle was 8 weeks with a maximum of 4 cycles. Vel was given on days 1, 4, 8, and 11 followed by a 45 day rest period. Sam was administered on day 3. The cycle was repeated on Day 57 if disease was stable or improved and platelets and neutrophils recovered to at least Grade 1 toxicity (delayable up to four weeks). Dose-limiting toxicity (DLT) was defined as cycle 1 grade 4 hematologic or Grade ≥3 non-hematologic toxicity.

Results: Thirty-three patients have been enrolled in cohorts 1-6 and 32 are currently evaluable. Responses (minimal [MR], partial [PR], or complete [CR]) occurred in 6 of 32 patients (19%), including three immunofixation-negative CRs (9%) and three MRs (9%). Two of the six patients who were progressing on bortezomib therapy at the time of enrollment responded to this therapy. Nine patients (28%) have stable disease. Six patients developed transient Grade 4 thrombocytopenia. Two of these episodes occurred during Cycle 1 in patients in cohort 6; and, as a result, this was a dose-limiting toxicity. Thus, cohort 3 has been expanded to a total of 15 patients. Eight patients showed transient Grade 3 neutropenia. Only three patients (9%) showed treatment emergent neuropathy one of which resolved while on study. To date, eight patients remain on study and four patients have completed four cycles of therapy.

Conclusion: In this phase I trial evaluating the novel combination of Vel and Sam, we have determined the maximum tolerated dose to be Vel 1.0 mg/m² and Sam 1.0 mCi/kg. This regimen appears to be a promising and safe new treatment option that deserves further evaluation for MM patients. A large multicenter Phase II study using this combination (1.0mg/m² Vel/1.0 mCi/kg Sam) for patients refractory or recently relapsed from bortezomib-containing regimens will begin enrolling next month.

II. 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 MM based on standard criteria (Durie, *Semin. Oncol.*, 1986; 13: 300-9)
- Currently has MM 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 MM).

- 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

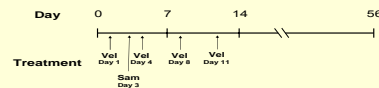
- Baseline platelets ≥75 x 10⁹/L and ANC ≥1.5 x 10⁹/L

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

Study Treatment Schedule

- Each treatment cycle is 8 weeks
- Maximum of 4 cycles permitted



III. Results

Demographics and Treatment History

Patient #	Cohort	Age	Gender	# Prior Myeloma Tx's	Prior Bortezo mib	Patient #	Cohort	Age	Gender	# Prior Myeloma Tx's	Prior Bortezo mib
1	1	68	M	5	Y	18	3	66	M	2	N
2	4	61	M	5	Y	19	6	68	M	4	N
3	1	48	M	3	Y	20	6	63	M	1	Y
4	4	68	F	4	Y	21	6	60	M	4	Y
5	1	55	F	2	N	22	3	66	M	3	Y
6	4	66	M	1	N	23	3	66	M	4	Y
7	2	69	F	8	Y	24	3	52	F	1	N
8	5	63	M	6	Y	25	6	74	M	2	N
9	2	66	F	1	N	26	6	44	F	7	Y
10	5	62	F	2	N	27	6	74	M	1	N
11	2	51	M	2	Y	28	3	68	M	8	Y
12	5	62	M	3	Y	29	3	71	F	1	Y
13	3	73	M	3	Y	30	3	70	F	1	Y
14	3	69	M	7	Y	31	3	52	F	3	Y
15	3	78	F	7	Y	32	3	65	M	1	N
16	3	71	M	2	N	33	3	66	F	6	Y
17	3	46	M	2	N						

Demographics Summary

Age (yr): 63.7±8.5 (44-78) Median: 66
 Gender: 21M/12F
 # Prior Tx's: 3.4±2.2 (1-8) Median: 3
 Prior Vel: 21Y/12N

Response to Study Treatment

Cohort 1 (0.25 - 1.0) ¹	# Tx Cycles	Cohort 4 (0.25 - 1.3) ¹	# Tx Cycles
Pl. 1	PD 1	Pl. 2	PD 1
Pl. 3	PD 1	Pl. 4	SD 2
Pl. 5	PD 1	Pl. 6	CR ² 4
Cohort 2 (0.5 - 1.0)¹			
Pl. 7	PD 1	Pl. 8	SD 4
Pl. 9	CR ² 2	Pl. 10	SD 3
Pl. 11	PD 1	Pl. 12	MR 4
Cohort 3 (1.0 - 1.0)¹			
Pl. 13	PD 1	Pl. 19	PD 1
Pl. 14	PD 1	Pl. 20	MR 3+
Pl. 15	PD 1	Pl. 21	SD 2
Pl. 16	PD 1	Pl. 25	PD 1
Pl. 17	PD 1	Pl. 26	PD 1
Pl. 18	CR 4	Pl. 27	SD 3+
Phase I/Extension			
Pl. 22	PD 1		
Pl. 23	SD 3+		
Pl. 24	PD 1		
Pl. 28	PD 1		
Pl. 29	SD 2+		
Pl. 30	SD 2+		
Pl. 31	MR 2+		
Pl. 32	SD 1+		
Pl. 33	NYE 1+		

¹(Sm-153, mCi/kg - Bortezomib, mg/m²) + indicates patient still on study
 NYE - Patient currently on study not yet evaluable for response
 * Not confirmed by bone marrow exam per patient choice

Grade 3 and 4 Adverse Events (33 patients, 60 treatment cycles)

Adverse Event	Grade 3	Grade 4
Altered Mental Status	1*	0
Anemia	2	0
Bone Pain	1	0
Dyspnea	1*	0
Elevated Creatinine	1*	0
Headache	2*	0
Hyperbilirubinemia	1*	0
Elevated General Weakness	1*	0
Lass/ Cramps	1*	0
Muscle Weakness	1*	0
Neuropathy*	1	0
Neutropenia	8	3
Pneumonia	1	0
Renal Failure	1*	0
Syncope	1	0
Thrombocytopenia	2	6
Thrombosis	1*	0

*Two patients with Cr: 1 neuropathy at baseline progressed to Cr: 2. One case resolved while on Tx. †Judged to be not related to study medications

Cycle 1 Hematologic Toxicity

ANC		PLT	
Cohort 1 (n=3)	Cohort 4 (n=3)	Cohort 1 (n=3)	Cohort 4 (n=3)
1.35 (1.01 - 1.91)	0.84 (0.62 - 0.85)	125 (98 - 152)	111 (74 - 172)
Cohort 2 (n=3)	Cohort 5 (n=3)	Cohort 2 (n=3)	Cohort 5 (n=3)
1.81 (0.93 - 3.45)	1.71 (1.19 - 2.70)	102 (78 - 128)	166 (119 - 210)
Cohort 3 (n=15)	Cohort 6 (n=6)	Cohort 3 (n=15)	Cohort 6 (n=6)
1.41 (0.3 - 2.62)	0.83 (0.4 - 1.32)	108 (84 - 135)	89 (51 - 133)

IV. Conclusions

- This Phase I study evaluating the combination of Samarium-153 lexidronam and bortezomib establishes the safety and shows efficacy of this combination in patients with relapsed or refractory multiple myeloma.
- The primary treatment-related toxicity has been a transient decrease in platelets and neutrophil counts.
- Dose-limiting toxicity was observed in cohort 6 (1.3 mg/m² Vel/1.0 mCi/kg Sam) in which 2 patients developed Grade 4 hematologic toxicity during cycle 1.
- Thus, additional patients have been enrolled in an extension of cohort 3 (1.0mg/m² Vel/1.0 mCi/kg Sam) of this study and continue to be evaluated.
- The incidence of treatment emergent neuropathy has been low (9%) with one case of Grade 3 and two cases of Grade 2 toxicity.
- Among the 32 patients evaluable for response: 6 have responded (3 CR and 3 MR) 9 have shown stable disease
- A multicenter Phase II study using 1.0mg/m² Vel/1.0 mCi/kg Sam for patients refractory or recently relapsed from bortezomib-containing regimens will begin enrolling next month.