LB207: Continuous subcutaneous lenalidomide delivery improves the therapeutic index and avoids drug-related grade 3/4 hematologic toxicity in patients with relapsed/refractory multiple myeloma

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Abstract

Introduction: In a multiple myeloma mouse model (MM), we determined that subcutaneous (SC) continuous lenalidomide (Len) delivery demonstrated superior tolerability and efficacy to the active control Len given by daily i.p. over a 28-day cycle. Healthy volunteer studies showed that at a daily dose of 9.6 mg a day (400 mcg/h) the Len $AUC_{0\text{-}24}$ was ~60% less than that observed with an oral 25 mg Len dose. We hypothesized that this modality could improve Len's therapeutic index by lowering the hematologic toxicity while maintaining or improving the efficacy.

Methods: A phase 1b study in 2nd line or greater relapsed/refractory MM was performed to confirm the animal findings and determine if continuous Len can improve its therapeutic index with no negative impact on the cellular immune system. In brief, an RVd regimen was utilized wherein SC Len 9.6 mg/day was administered with an FDA registered ambulatory pump in a continuous fashion using a 28-day cycle. Patients were either trained to operate their pump and change the pre-filled cassettes at home or were managed in the clinic on M-W-F. All patients were seen in the clinic to receive weekly bortezomib 1.3mg/m^2 and dexamethasone dosed weekly at 40/20mg, according to age. Patients who received bortezomib in a prior cycle were required to demonstrate sensitivity defined as durability for 6 months after discontinuation of the bortezomib.

Results: Between September 2023 and November 2024, 6 relapsed/refractory MM patients were enrolled from 2 US community-based investigational sites in the phase 1b study. Median age was 73, male to female ratio 1/1, Caucasian 100%, and median lines of previous therapy were 2 (range 1-7). Two patients were refractory and 4 were relapsed to their prior treatment. Four patients were previously exposed to Len, one of which was discontinued from a prior regimen because of severe fatigue, and 6 had received prior bortezomib. Patients had received 3-12 cycles of study therapy. No drug-related grade 3/4 hematologic or non-hematologic toxicity occurred within cycle 1. No patients experienced drug-related anemia, neutropenia, leukopenia, or thrombocytopenia greater than grade 2 in up to 12 cycles of therapy. All 6 patients achieved an objective response (CR=1 / PR=5). One patient who achieved a partial response experienced grade 2 skin reaction during cycle 3 and withdrew from the study. Five patients are continuing treatment per protocol with a median PFS of > 10 mo. Len pharmacokinetics produced median steady-state blood levels (Cmax) of 39 ng/mL (range 26-94) (N=6) and were above the minimum target of 25 ng/mL. The Len regimen produced a median $AUC_{0\text{-}24}$ of 921 $^{-1h*ng/ml}$ (range 630-1503). Immune profiling did not show significant increases in immune checkpoint expression associated with T-cell exhaustion while CD19+ B cells were significantly depleted.

Conclusion: Continuous delivery of low dose Len provides meaningful efficacy and improved tolerability with no grade ≥3 drug-related hematologic toxicity. Further studies in MM and chronic lymphocytic leukemia are planned.

Introduction

- Lenalidomide is a mainstay of treatment for MM
- The half-life of lenalidomide is very short necessitating high daily doses to maintain effective concentrations leading to toxicity
- RVd is associated with Grade 3-4 hematologic toxicity over 22%[3] and can lead to dose reductions or discontinuation
- Predicted effective blood levels of Len are > 0.1 µM (25 µg/L)

Methods and Materials

- Patients were 2nd line or greater RRMM
- Regimen: Bortezomib 1.3 mg/m^2 and dexamethasone 20-40 mg weekly dosing on 28-day cycle. Lenalidomide continuous SC infusion at 400 µg/h (9.6 mg a day) with 28-day cycle
- Len delivered SC 24/7 continuously by Smith Medical Solis VIP ambulatory device
- Patient trained to administer Len infusion at home or could come to clinic 3 times a week

Results – Baseline Findings

- Median age 73 yo; 100% Caucasian; M/F ratio 1:1
- Median prior lines 2 (range 1-7 lines)
- 2 patients refractory to prior line/4 with relapsed disease
- SPEP at baseline ranged from 0.2 – 2.1 g/dL
- FLC ratio ranged from 0.01 – 387.9
- UPEP 24 hr ranged from 17-1812 mg

Results - Hematology Nadirs on Study

Table 1. Nadir of hematology parameters during the study

	Hemoglobin		White Blood Cells		Absolute Neutrophils		Platelets	
	g/dL	Grade	×10⁹/L	Grade	×10⁹/L	Grade	×10⁹/L	Grade
CTCAE Grade	*<LLN – 10.0*	*1*	*<LLN – 3.0*	*1*	*<LLN – 1.5*	*1*	*<LLN - 75*	*1*
	<10.0 -8.0	*2*	*<3.0 – 2.0*	*2*	*<1.5 – 1.0*	*2*	*<75 – 50*	*2*
	<8.0	*3*	*<2.0 – 1.0*	*3*	*<1.0 – 0.5*	*3*	*<50 - 25*	*3*
Patient number								
101-01	12.8	0	5.3	0	2.5	0	147	0
101-02	6.1[a]	3	2.4	2	1.1	2	117	1
101-03	8.5	2	3.7	1	2.1	1	151	0
101-04	12.5	0	5.3	0	3.6	0	74	2
102-01	11.4	1	4.8	0	2.4	1	108	1
102-02	9.4	2	4.9	0	2.5	0	234	0

a = Patient 101-02 experienced a GI bleed and Hgb was corrected following treatment

Results – Treatment Emergent Adverse Events

Table 2 Lists TEAE that occurred in 2 or more patients

Preferred Term	Number of Participants N=6	
	TEAE	Treatment-related TEAE[a]
Any event	6	5
Fatigue	5	2
Diarrhoea	4	3
Injection site erythema	3	2
Injection site reaction	3	1
Bone pain	2	0
Decreased appetite	2	0
Dyspnoea	2	0
Injection site rash	2	1
Muscle spasms	2	2
Myalgia	2	0
Rash[b]	2	2

All events were either grade 1 or grade 2 (except 1 episode of fatigue of grade 3.
Two nonrelated injection site events were associated with S.C. bortezomib
b = One patient discontinued with a grade 2 abdominal rash

Results – PK and Responses

Table 3: Len PK Steady State, Best Response, Prior lines, PFS

Patient	Prior # of lines	Steady State Concentration ± SD (µg/L)	Best Response On-study	PFS
101-01	3	28.0 + 3.2	PR	18*
101-02	2	62.2 + 16.3	PR	17*
101-03	1	43.3 + 2.7	PR	13*
101-04	7	36.8 + 1.3	PR	6
102-01	1	41.8 + 4.1	CR	11*
102-02	4	35.0 + 1.8	PR	9

* ongoing response

Results – Immune Biomarkers

Table 4-5 Immune biomarkers over 2 cycles of treatment

Cycle	n	Mean Percentage (%) in CD45+ Cells					
		CD19+ B cells	CD3+ T cells	CD4+	CD8+	NK cells	NKT cells
1	6	10.23	37.47	22.27	13.78	9.23	2.97
1.5	6	4.85	33.99	18.69	13.89	17.25	3.55
2	6	4.39	41.45	26.09	14.12	10.83	3.32
3	5	2.16	32.87	17.64	13.58	8.40	2.93

Cycle	n	Mean Percentage (%) in Raw Cells									
		CD4+ CD25+	CD4+ CD69+	CD4+ LAG3+	CD4+ PD1+	CD4+ TIM3+	CD8+ CD25+	CD8+ CD69+	CD8+ LAG3+	CD8+ PD1+	CD8+ TIM3+
1	6	5.74	5.58	0.64	5.60	1.80	0.63	10.25	0.93	2.21	1.27
1.5	6	8.61	9.68	1.12	7.38	3.22	0.84	11.28	1.36	2.48	2.92
2	6	8.41	8.63	0.95	6.74	2.56	1.12	10.99	1.55	2.59	3.01
3	5	6.00	13.10	1.25	7.15	2.36	1.38	14.14	1.49	2.12	2.23

Discussion

- The number of patients treated was small and caution should be used evaluating the data
- The rationale for the selection of the Len dose is based on in vitro activity of Len on IL-2 and IFN-g[1] production and Ikaros ubiquitination[2]
- The Len target blood levels of > 25 µg/L were achieved and we observed excellent ORR and tolerability with a continuous dose of 400 µg/h
- Data suggests low-dose continuous lenalidomide improves the therapeutic index vs. oral Len and avoids the hematologic toxicity of >22% observed in a literature-based report with oral Len in 2nd line RRMM using RVd[3]

Conclusions

- The PK/PD data minimized Cmax and lowered AUC while achieving biologically active doses and reducing toxicity
- Continuous Len for ≥ 6+ cycles didn't result in any drug-related Grade 3-4 hematologic toxicity
- Non-hematologic toxicities didn't exceed Grade 2
- All patients achieved an objective response (1 CR and 5 PR)
- Continuous treatment with Len does not appear to significantly increase immune checkpoints associated with T cell exhaustion
- Based on these data, new delivery formulations are under development and include an on-body injector, transdermal patches, and controlled release oral tablets
- Further study in CLL and MM are planned

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References

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