Oncolytic Reovirus Immune Priming: A Phase 1b Study of Reolysin with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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Background

While novel agents have improved the outcome for multiple myeloma (MM), the disease remains incurable. Our preclinical work has shown that MM cells from relapsed/refractory patients are very sensitive to the combination of Reolysin (a proprietary formulation of an oncolytic reovirus) and bortezomib (BZ), resulting in synergistic levels of endoplasmic reticulum (ER) stress. A pilot phase 1 study showed that Reolysin was well tolerated in relapsed/refractory MM patients and was associated with prolonged stable disease.

Methods

Relapsed/refractory MM patients including patients refractory to BZ were included. This is a phase 1b study of 3 escalating doses of Reolysin (cohort 1; 3 x10^{10} $TCID_{50}$, cohort 2; 4.5 x10^{10} $TCID_{50}$, and cohort 3; 9 x10^{10} $TCID_{50}$). Reolysin is given on days 1, 2, 8, 9, 15, and 16. Patients receive 40 mg dexamethasone and 1.5 mg/m2 bortezomib on days 1, 8, and 15. Cycles are repeated every 28 days in the absence of disease progression or unacceptable toxicity.

Results

Nine patients have been enrolled, 8 were male and the median age was 56 (range, 33 – 66) (Table 1). The median number of prior therapies was 4 (range 1 to 6). All patients were previously exposed to BZ, and 7 patients were previously exposed to both immunomodulatory agents and carfilzomib.

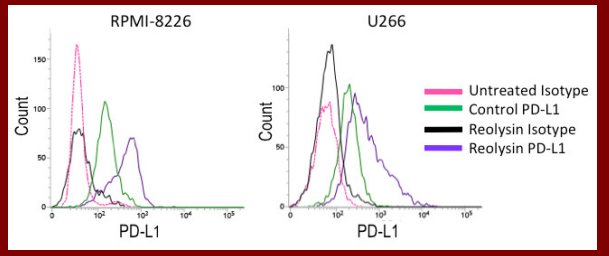
The combination was well tolerated and most treatment emergent toxicities were transient and easily managed with supportive care. The most common treatment related toxicities were grade 1 diarrhea, grade 1 fatigue, grade 1 flu-like symptoms and grade 1 headache.

Cohort 1 (3x10^{10} $TCID_{50}$)	Age	Cytogenetics	Prior Treatment	Comments
1	56	Normal	CyBorD	40% Reduction in KLC, SD for 4 cycles, PD after C4.
2	54	-13	CyBorD, Len/Dex, Carfil/Dex, BT062/Pom	Off protocol for Clinical Deterioration after C1D1.
3	48	Normal	CyBorD	Withdrew consent after C1D1.
4	33	t(4,14)	CyBorD , Carfil/Dex, Thal, Len/Dex , Pom/Dex, and PACE	PD after C2D1.
5	66	+5, +17	Len/Dex, CyBorD, Carfil/Dex	Withdrew consent after completion of C3. 36%. Reduction in KLC.
Cohort 2 (4.5x10^{10} $TCID_{50}$)				
6	61	Normal	CyBorD , Len/Dex , Pom/Dex , Carfil/Dex , Dara, Auto Tx	PD after C1.
7	54	1q+,	CyBorD, Len/Dex , Len/BT062 and Carfil/Dex	Completed 7 Cycles, 23% reduction in PP. Remains on Protocol.
8	57	-13	CyBorD, Carfil/Dex, Len/Dex, V-PACE	PD after completion of C1.
Cohort 3 (9x10^{10} $TCID_{50}$)				
9	62	1q+, t(11,14)	CyBorD, Carfil/Dex,	SD for 3 Cycles. Remains on Protocol.

Table 1. Patient Details. CyBorD, Cyclophosphamide, bortezomib and dexamethasone; Dex, Dexamethasone Carfil; Carfilzomib; Thal, Thalidomide; Len, lenalidomide; PACE, cisplatin, doxorubicin, cyclophosphamide and etoposide; Pom, pomalidomide; V, bortezomib; Auto Tx, autologous stem cell transplant, KLC, kappa light chain, PP, paraprotein. SD, stable disease; PD, progressive disease.

Results

No dose limiting toxicities occurred in cohort 1 or 2. Two patients failed to complete 1 cycle of treatment (1 withdrew consent and 1 patient had clinical deterioration due to underlying disease). Three patients completed 1 cycle of treatment only, 2 completed 3, 1 completed 4 and 1 completed 7. Two patients remain on protocol (1 completed 3 and the other 7 cycles). Reasons for treatment discontinuation included disease progression (n=4), clinical deterioration (n=1) and patient withdrawal (n=2). Six patients were evaluable for response, 4 patients had stable disease lasting at least 1 cycle whereas 3 patients had progressive disease at the end of cycle 1. Ex vivo treatment of primary MM cells and MM cell lines (U266 and RPMI-8226) with Reolysin revealed a dramatic induction of PD-L1 expression as measured by qRT-PCR and flow cytometry (Figure 1, top). Furthermore, ex vivo treatment of MM patient mononuclear cells with Reolysin resulted in NK and T cell activation (Figure 1, bottom).



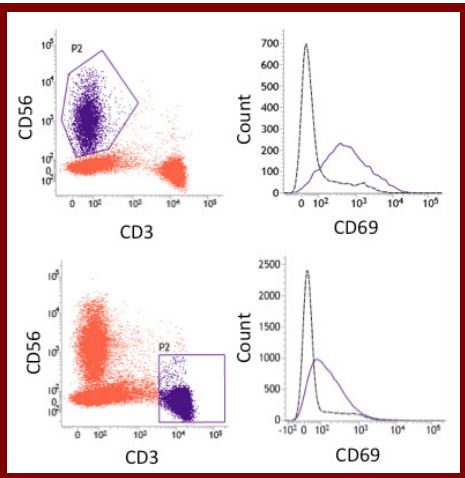


Figure 1. Top. Reovirus induces the expression of PD-L1 on MM cells. U266 and RPMI-8226 cell lines were treated with 300 PFU/cell of Reolysin and the expression of PD-L1 was determined by flow cytometry. Bottom. Reovirus activation of NK and T cells. MM patient peripheral blood mononuclear cells (PBMCs) were isolated and either left untreated, or treated with 10 PFU/cell reovirus for at least 16 h and stained with antibody for CD3, CD56 and CD69 (Affymetrix, Santa Clara, California) and subjected to flow cytometry. Expression of CD69 (an early activation marker) on CD3–/CD56+ NK cells (Top) and CD3+ T cells (bottom) was determined.

Conclusions

The combination of Reolysin, BZ and dexamethasone is well tolerated in a heavily pretreated MM patient population. Cohort 3 is currently enrolling at the 9 x10^{10} $TCID_{50}$ dose level of Reolysin. Preliminary evidence of activity of this combination is evident in a heavily pretreated patient population.