

# Oncolytic Virus Replication Using Pelareorep and Carfilzomib in Relapsed Myeloma Patients Increases PD-L1 Expression with Clinical Responses



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## Introduction

- Pelareorep is fusible Reovirus (RV) Serotype 3 – Dearing Strain is a naturally occurring, ubiquitous, non-enveloped RNA virus. RV alone selectively entered MM cells but did not actively proliferate, with no objective responses
- Immune checkpoint inhibitors, including those targeting programmed cell death protein 1 (PD-1), are tempting but PD-1 inhibition alone has not been effective in myeloma (Lesokhin, JCO, 2016). Pelareorep upregulates IFN-regulated gene expression, CTL infiltration, and the PD1/PD-L1 axis in myeloma cell lines (Kelly KR et al, Leukemia, 2018) and in patients with brain tumors (Samson A et al, Sci Trans Med, 2018).
- In PART ONE of our trial, Carfilzomib (Kyprolis)-sensitive patients were accrued. In PART TWO, Carfilzomib-refractory patients were accrued. Correlative studies included bone marrow aspirate pretreatment on cycle 1 day 1 and cycle 1 day 9 to assess RV infection of myeloma cells, replication within myeloma cells, and PD-L1 expression on myeloma cell surface.

## Methods

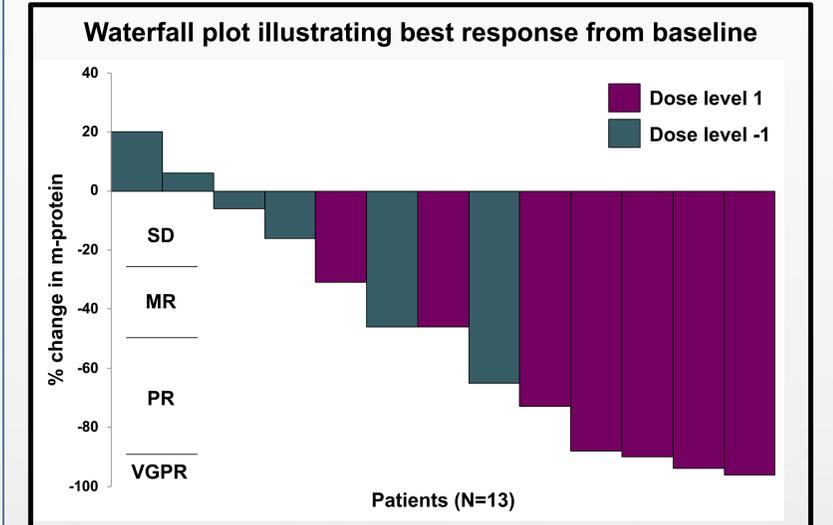
**Correlative studies:** Staining for reovirus RNA and protein (biomarker of viral proliferation), and apoptosis (caspase-3) will be conducted using the Leica BOND MAX immunostainer. Quantitative analysis will be performed using Ventana Vias and Caliper Biosystems Nuance.

**Treatment plan:** Patients are treated with RV+CFZ+Dex days 1, 2, 8, 9, 15 and 16 of a 28-day cycle, unless MR or better is evident after cycles 4 and 11, then weekly or biweekly dosing, respectively, can be considered to increase tolerability

Dose level	N	Decadron (IVP)	Carfilzomib (IVPB)	Reolysin (IVPB)
Part two (starting)	3		C1 D1 & 2 – 20 mg/m <sup>2</sup> /d C1 D8 & onward – 56 mg/m <sup>2</sup> /d	3 x 10 <sup>10</sup> TCID <sub>50</sub> /d
Part one (dose level 1)	7	20 mg before each dose of Carfilzomib	C1 D1 & 2 – 20 mg/m <sup>2</sup> /d C1 D8 & onward – 27 mg/m <sup>2</sup> /d	3 x 10 <sup>10</sup> TCID <sub>50</sub> /d
Part one (dose level -1)	5		20 mg/m <sup>2</sup> /d	3 x 10 <sup>9</sup> TCID <sub>50</sub> /d

## Part one

In **PART ONE**, there were 2 VGPRs, 2 PRs, 1 MR, and one patient with stable disease after cycle 1. All evaluable patients showed RV infection and replication in the post-treatment BM aspirates. In the 4 bortezomib-refractory patients in the first cohort, all have shown viral replication, and this correlated directly with activated caspase-3 in the MM cells and clinical response.



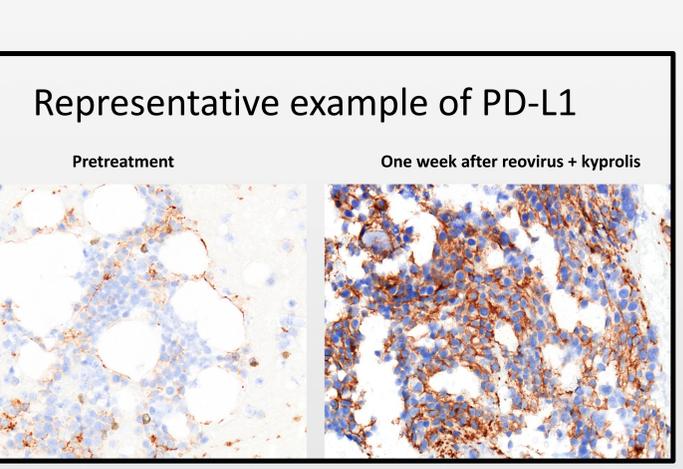
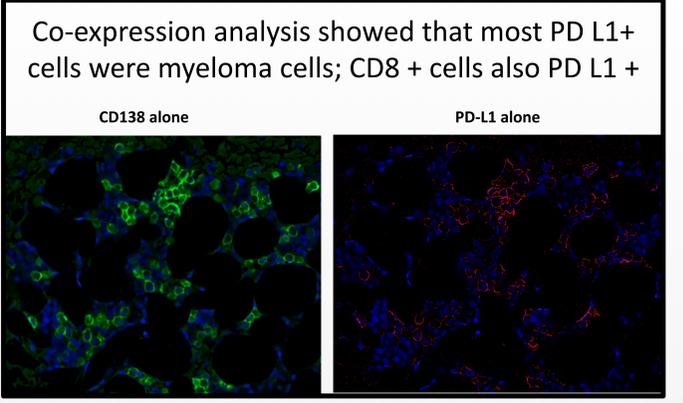
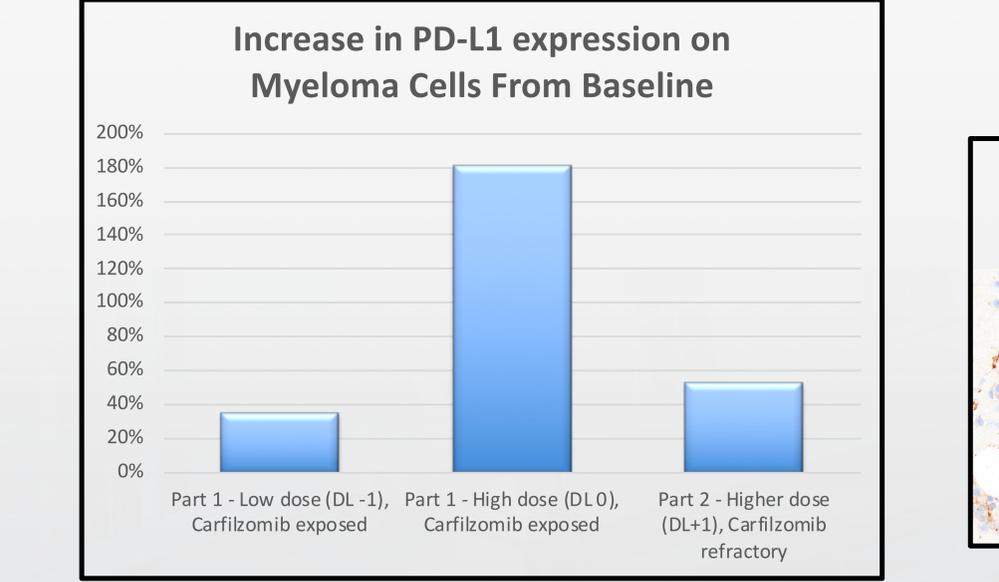
- Median duration of follow-up is 77 days
- Best responses include VGPR (3), PR (3), MR (3), and SD (3)
- One patient has been treated for 16 cycles and remains on treatment
- One patient (CFZ-sensitive) progressed during cycle 1
- All CFZ-refractory patients were treated at DL-1, the best response was MR (46% decrease in m-protein), 3 other patients had SD
- Patients treated at DL 1 have evidence of deeper and more prolonged response

Oncolytic virus outcome measure	Reovirus alone (Previous trial)	Low-dose Reovirus plus Carfilzomib (Part one)	High-dose Reovirus plus Carfilzomib (Part one)
Reovirus genome as % of total CD138+ve cells (Infection)	73.4%	69%	66%
Reoviral capsid protein as % of total infected MM cells (Transcription)	0.7%	2.4%	7.6%

## Part two

In **PART TWO**, seven patients have been enrolled to date with no documented PRs in the 2 evaluable patients to date. In 3 patients processed to date with both pre- and posttreatment biopsies available, RV infection was detected in myeloma cells (2 patients) and endothelial cells (one patient). Replication was not seen. In these patients there was no strong evidence of increased activated caspase-3 expression in myeloma cells, nor was there a statistically significant increased CD8 cell infiltration or checkpoint protein expression after treatment.

Microscope fields (200x) were initially scored looking at all cells, primarily in fields with at least 50% myeloma cells based on CD138 expression in serial sections. The staining had to be clearly cytoplasmic otherwise it was considered background. Staining controlled for myeloma cell content was required in cases where 50% myeloma cells per field was not present.



- There are situations where there is a lot of viral DNA or RNA and little host response (eg, early HIV-1 infection) with few clinical signs of infection.
- While infection remains consistent in any reovirus containing regimen, in patients with a clinical response there was concomitant CD8, PD L1, NK cell response, and activated caspase-3 expression.
- In patients treated with Reovirus, there appears to be some PD-L1 upregulation independent of clinical response, but PD-L1 expression increased significantly more in patients with clinical response.

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For questions or collaboration, please contact [craig.hofmeister@emory.edu](mailto:craig.hofmeister@emory.edu) or [douglas.sborov@hsc.utah.edu](mailto:douglas.sborov@hsc.utah.edu) regarding clinical development and Flavia Pichiorri for correlative science. We thank the clinical research coordinators, regulatory agents, and of course the patients that allowed this trial to accrue. We also would like to thank Michael Grever (U01 PI, Ohio State) and Taofeek Owonikoko (U01 PI, Emory University) for resources for this trial, and Oncolytics Biotech for providing drug via NCI-CTEP