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 a replication-deficient reovirus (RV) Serotype 3 – Dying Strain is a naturally occurring, ubiquitous, non-enveloped RNA virus. RV alone selectively enters 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 limping but PD-1 inhibition alone has not been effective in myeloma (Lewinski, JCO, 2019). Pelareorep upregulates PD-1 regulated gene expression, CTL infiltration, and the PD-1/PD-L1 on myeloma cell lines (Kelly RF et al, Leukemia, 2015) and in patients with brain tumors (Sammon A et al, Sci Trans Med, 2018).
• In PART ONE of our trial, Carfilzomib (Kyprolis, Kyprolis) refractory patients were accrued. Correlative studies concluded bone marrow aspirate predosement 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.

Part one

In PART ONE, there were 2 VPS32Ps, 2 PRs, 1 MR, and one patient with stable disease after cycle 4. 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.

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. Microscopic fields (200x) were initially scored looking at all cells, primarily in fields with at least 50% myeloma cells and no MM cells. PD-L1 expression was measured in the myeloma cells using the Ventana BOND Max, 20 mg/mL Formalin Fixed Paraffin Embedded, 4-μm tissue sections, and the Ventana Kit for PD-L1 (clone SP166). A minimum of 5000 cells were counted per section.

Methods

Correlative studies:

Staining for reovirus RNA and protein (biomarker of viral proliferation), and apoptosis (caspase-3) will be conducted using the Ventana BOND MM immunostaining. Quantitative analysis will be performed using Ventana Visi Vis Caliper Biosystems Neusense.

Treatment plan:

Patients were treated with RV+IVD-Dox days 1, 2, 3, 6, 7, 8, 12, and 14 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.

For questions or collaboration, please contact craig.hofmeister@emory.edu or 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 Tsafekk Owohnikoko (U01 PI, Emory University) for resources for this trial, and Oncolytics Biotech for providing drug via NCI-CTEP.