Abstract 303983: Oncolytic virus Pelareorep [P] plus Carfilzomib & Dexamethasone [Kd] phase 1 trial in Carfilzomib-refractory patients (NCI9603): responses with cytokine storm

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Introduction

- **Pelareorep** is an infusible form of human **Reovirus** (RV) Serotype 3 – Dearing Strain, a naturally occurring, ubiquitous, non-enveloped double-stranded RNA virus.
- Our single-agent phase 1 RV trial in relapsed refractory multiple myeloma (RRMM) showed RV selectively infected MM cells but not the bone marrow (BM) stroma. However, apoptosis of cancer cells or objective clinical responses were not observed (PMID: 25294913).
- Our ongoing phase 1b trial investigating carfilzomib and Pelareorep (NCT 02101944) showed that treatment of carfilzomib-sensitive patients (n=7) at the highest dose level was associated with a 100% clinical benefit rate 100% and 71% ORR. In these patients, combination treatment upregulated CD8+ T-cells (but not NK cells), PD-L1 expression, and caspase-3.
- Recently, our group showed that 1) carfilzomib inhibits the early innate pro-inflammatory immune response and via augmentation of the CD14+ monocyte fraction increases RV entry, infection, replication, and subsequent MM cell killing via augmentation of the CD14+ monocyte fraction, 2) RV increases phagocytic activity against MM cells, and 3) the carfilzomib-RV combination increases the total frequency of cytotoxic T-cells.

Methods

- The present ongoing phase 1b study investigates the combination of carfilzomib and Pelareorep in patients with carfilzomib-refractory RRMM.

Inclusion criteria

- Relapsed or refractory MM fitting or that did fit the IMWG diagnostic criteria for symptomatic disease
- Prior IMiD and PI exposure and disease progression within 60 days of the most recent therapy, carfilzomib-refractory
- Dialysis-dependent patients were eligible, but adequate marrow (ANC $\geq$ 1000/uL, plt count $\geq$ 50,000/uL) and liver function required

Treatment plan

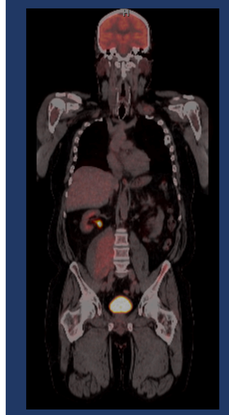
- Patients were treated days 1, 2, 8, 9, 15 and 16 of a 28-day cycle

Table 1. Dose levels 1 – 3.

Dose level	Reolysin	Carfilzomib	Dexamethasone
1	3 x 10^{10} $TCID_{50}$	20 mg/m^2 C1D1/2 56 mg/m^2 thereafter	20 mg
2	4.5 x 10^{10} $TCID_{50}$		
3	9.0 x 10^{10} $TCID_{50}$		

This trial was supported by the NCI Division of Cancer Therapy Evaluation Program (CTEP)

A cytokine storm



58-year-old gentleman with R-ISS stage 1 IgG-K multiple myeloma (MM) with 7 prior lines of therapy including two autoHSCT and IMiD, PI, Dara and Elo refractoriness. Prior to treatment he was working full time, had evidence of extensive extramedullary disease, 10% BMPCs including gain 1q21 (9.0%), m-protein of 5.2 g/dL, normal TTE, baseline CKD, and anemia.

The patient received 2 doses at dose level 2. On day 3, he was febrile, hypoxic requiring intubation, hypotensive requiring pressor support, had worsening renal and hepatic function, evidence of evolving tumor lysis syndrome, biventricular heart failure (resolved within 12 days), and evidence of a profound steroid- and tocilizumab-responsive immune-mediated response consistent with a hemophagocytic-like syndrome (Table 2).

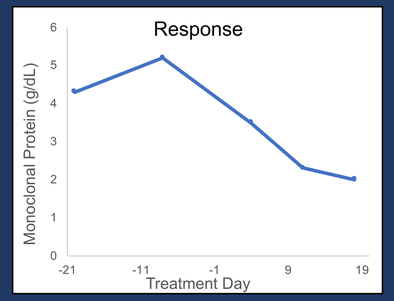
Table 2. Clinical and laboratory features

Ferritin	(peak 25,552 ng/mL)
Soluble IL-2 receptor	(1411 pg/mL)
IL-6	(31 pg/mL)
d-dimer	(peak 5.9 ug/mL)
LDH	(peak 2554 U/L)
AST/ALT	(peak 2109/1204 U/L)
Fever	
Respiratory failure requiring ventilator support	
Severe hypotension requiring pressor support	
Altered mental status	
Tumor lysis syndrome	

Table 3. Autopsy findings.

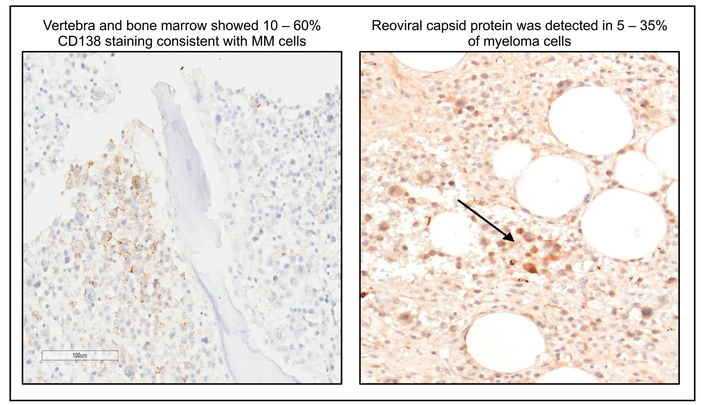
Organ	Finding
CNS	Microglial nodule encephalitis, hypoxic/ischemic damage in the cerebellum and hippocampus
Heart	Biventricular hypertrophy and dilation, focal severe atherosclerosis in LAD (up to 90%)
Lungs	Extensive neutrophilic pneumonia
4th rib	Lipoma
Bone marrow	Multiple myeloma
Pleura	Plasmacytoma
Retroperitoneum	Plasmacytoma
Other	Paraprotein deposits in lung alveolar spaces

Though the patient had a partial response within 2 weeks of starting treatment, he passed away as a result of hospital-acquired pneumonia not attributable to study drug. Autopsy findings are listed below and staining for reovirus capsid protein (marker of productive reovirus infection) was evident in post-mortem bone biopsies.



Immunohistochemistry

- Minimal MM cells were identified in the collection of autopsy biopsies. In those myeloma cells identified, reoviral capsid protein was evident, indicating that the virus was actively proliferating



Patient demographics and response

ID	Dose Level	Age	Gender	MM subtype	AEs	Cycles	Best response
25	1	70	F	LLC	Grade 1 flu-like symptoms	1 cycle	MR
26		52	M	LLC	MAS-like syndrome	< 1 cycle	PR
27		55	M	IgG-K	Grade 1 fatigue	2 cycles	SD
28	2	58	M	IgG-K	HLH-like syndrome	2 doses	PR
29		66	F	KLC	Grade 3 thrombocytopenia	1 cycle	PD
30		62	F	LLC	Grade 2 thrombocytopenia	1.5 cycles	PR

Conclusions

- Six carfilzomib-refractory patients have been treated in the present cohort with evidence of partial response (n=3), MR (n=1), SD (n=1)
- Carfilzomib combined with Pelareorep activates a profound inflammatory response that is associated with ORR 50% and CBR 83%, even in patients receiving limited doses of drug
- This is the 1st report of cytokine storm after oncolytic virus in a patient with a hematologic malignancy, a syndrome thought to be related to T-cell activation resulting from combination carfilzomib/RV treatment
- Patients treated with carfilzomib and Pelareorep should be treated with tocilizumab +/- steroids with early clinical signs of cytokine activation

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