MECHANISM OF PELAREOREP (REOLYSIN®)-MEDIATED CELL DEATH IN A PHASE I STUDY IN COMBINATION WITH IRINOTECAN/ FLUOROURACIL/ LEUCOVORIN/ BEVACIZUMAB (FOLFIRI/B) IN PATIENTS WITH KRAS MUTANT METASTATIC COLORECTAL CANCER

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ABSTRACT

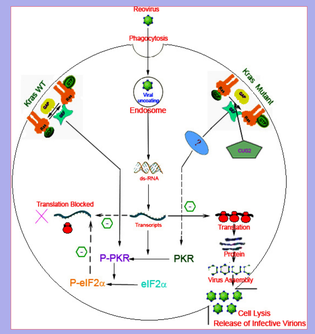
Background: Pelareorep (REOLYSIN®, R) an unmodified reovirus Type 3 Dearing (T3D) strain, is a systemically delivered immuno-oncolytic virus (IOV) being investigated in solid tumors and hematological malignancies. R selectively replicates in tumor cells harboring gene mutations that downregulate the IFN-induced antiviral response (e.g., KRAS-mutations) which results in their lysis. R is synergistic with irinotecan (IRI) in *in vitro* and *in vivo* models.

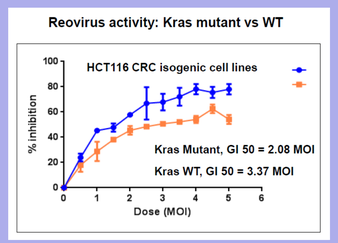
Methods: This is a phase I dose escalation study of FOLFIRI/B+R. Eligible pts are adults with oxaliplatin refractory KRAS-mutant mCRC. Both, IRI (150-180 mg/m^2) and R (1x10^{10} $TCID_{50}$ to 3x10^{10} $TCID_{50}$) were escalated. R was given IV over 1 hr days 1-5 every 4 weeks (wk). Primary objectives were to determine toxicity, recommended phase two dose (RPTD), and pharmacokinetics. Secondary objectives were response rate, progression-free and overall survival (PFS and OS). Tumor biopsies post R were optional and subject to electron microscopy (EM).

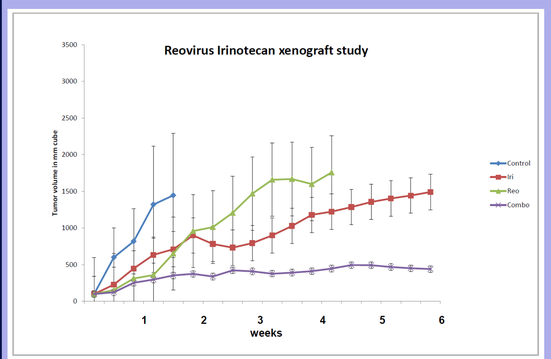
Results: 36 pts enrolled; FOLFIRI naïve (23) and pre-treated (11). Common (>10%) grade 3-4 toxicity include: neutropenia, anemia, and thrombocytopenia. At 180 mg/m^2 of IRI, among FOLFIRI pretreated pts, 2 had dose-limiting toxicity (DLT) in cycle 1; in FOLFIRI naïve patients, none/6 had a DLT, with a median PFS of 63 wk (range: 27-101 wk). 3 patients are currently on therapy. The RPTD is IRI 180 mg/m^2 and R 3x10^{10} $TCID_{50}$. Of 32 evaluable pts, 3 had a partial response. EM of tumor biopsies showed dying cells with degenerating endoplasmic reticulum, large nonfunctional mitochondria, heterochromatin, condensed DNA, and viral factories, both empty and active. There were discrete holes in the cytoplasm leading to dampening of cellular proliferation. Immunogold staining against viral capsid protein σ demonstrated viral "homing" in the tumor cells. Flow cytometry reveals expansion of dendritic cells with consequent activation of cytotoxic T cells (the data presented is preliminary based on investigator assessment).

Conclusions: At the highest dose, the combination was safe, well tolerated, with a PFS of 63 (range 27-101) wk, superior to historic data (18-27 wk). Electron Microscopic and immune changes seen consistently among patients.

BACKGROUND & MECHANISM OF ACTION







METHODS

Design	Standard phase I dose escalation
Dose	Pelareorep: 1X10^{10} - 3X10^{10} $TCID_{50}$ FOLFIRI: Standard of Care
Administration	Pelareorep: Days 1-5 every 28 days (1 Cycle) FOLFIRI: Standard of Care q 2 wks
Infusion	Pelareorep: 1 hr IV infusion FOLFIRI: Standard Administration
Safety	Precautions for patient and family
CT Scan	CT Scan at 0,2,4,6,8 months
HbsAg/HIV	Negative

RESULTS

Dose Cohorts

Dose Level	Reovirus	Irinotecan	# patients	Prior FOLFIRI	Bevacizumab	DLT
1	1 X 10^{10} $TCID_{50}$	150 mg/m2	3	Yes	No	0
2	3 X 10^{10} $TCID_{50}$	150 mg/m2	12	Yes	No	0
3	3 X 10^{10} $TCID_{50}$	180 mg/m2	6	Yes	No	2**
2 (new)	3 X 10^{10} $TCID_{50}$	150 mg/m2	7	No	Yes	0
3 (new)	3 X 10^{10} $TCID_{50}$	180 mg/m2	8	No	Yes	0

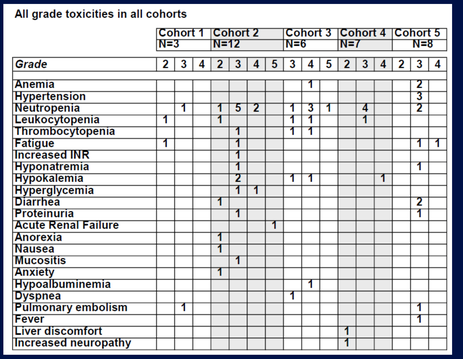
DLT=dose limited toxicity
** = DLT was grade 4 thrombocytopenia in a heavily pretreated patient (incl FOLFIRI)
**= DLT was urosepsis in a patient with prior FOLFIRI treatment

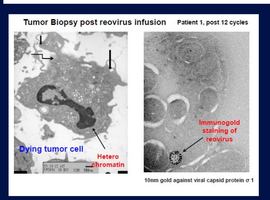
Baseline Characteristics

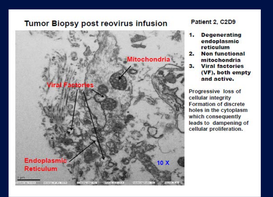
	Total = 36
Sex	
Male	13 (36%)
Female	23 (64%)
Age (years: mean, range)	57 (31-77)
Ethnicity	
Black	12 (33%)
White	19 (53%)
Hispanic	4 (11%)
Asian	1 (3%)
ECOG Performance Status	
0	3 (8%)
1	32 (89%)
2	1 (3%)
Prior treatment	
Surgery	32 (89%)
Radiotherapy	13 (37%)
Bevacizumab	9 (25%)
Chemotherapy	36 (100%)
FOLFIRI	13 (37%)

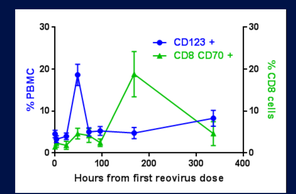
All grade toxicities in all cohorts

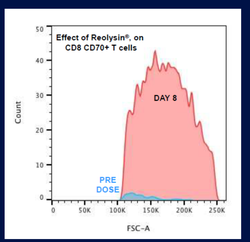
	Cohort 1 N=3			Cohort 2 N=12			Cohort 3 N=6			Cohort 4 N=7			Cohort 5 N=8		
Grade	2	3	4	2	3	4	5	3	4	5	2	3	4	2	3	4
Anemia								1							2	
Hypertension															3	
Neutropenia		1		1	5	2		1	3	1		4			2	
Leukocytopenia	1			1				1	1			1				
Thrombocytopenia					1			1	1							
Fatigue	1				1										1	1
Increased INR					1											
Hyponatremia					1										1	
Hypokalemia					2			1	1			1				
Hyperglycemia					1	1										
Diarrhea				1											2	
Proteinuria					1										1	
Acute Renal Failure							1									
Anorexia				1												
Nausea				1												
Mucositis					1											
Anxiety				1												
Hypoalbuminemia								1								
Dyspnea								1								
Pulmonary embolism		1													1	
Fever															1	
Liver discomfort											1					
Increased neuropathy											1					

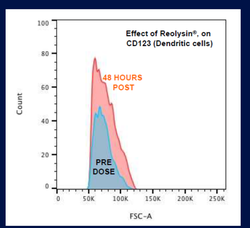












CONCLUSIONS

Pelareorep is safe and well tolerated in combination with FOLFIRI/Bevacizumab.

The combination is active and warrants further testing.

Electron microscopy reveals loss of cellular integrity, holes in cytoplasm, degenerating ER, nonfunctional mitochondria and viral factories, possibly suggesting a novel method of viral mediated cytotoxicity.

Patients mount a robust immune response with early dendritic cell maturation followed by activation of cytotoxic T (CD8+) cells

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