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/m²) and R (1x10¹⁰ TCID₅₀ to 3x10¹⁰ TCID₅₀) 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/m² 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/m² and R 3x10¹⁰ TCID₅₀. 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). EM and immune changes seen consistently among patients.