# DOSE FINDING AND SAFETY STUDY OF REOVIRUS WITH IRINOTECAN/FLUOROURACIL/LEUCOVORIN/BEVACIZUMAB (FOLFIRI/B) IN PATIENTS WITH KRAS MUTANT METASTATIC COLORECTAL CANCER: FINAL RESULTS

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## ABSTRACT

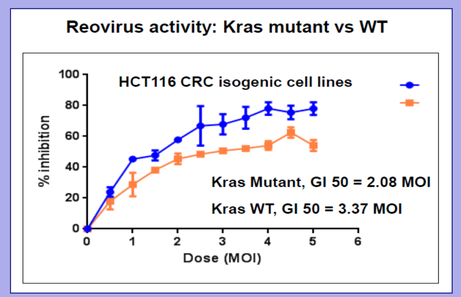
**Background:**
*KRAS* mutation is a biomarker of exclusion of anti-EGFR agents in patients with mCRC, who have limited options once they progress on oxaliplatin and irinotecan-based regimens. Reovirus is a naturally occurring, ubiquitous, non-enveloped double stranded RNA virus that selectively replicates in tumor cells harboring *KRAS* mutations. Reovirus is synergistic with irinotecan (IRI) in *in vitro* and *in vivo* models.

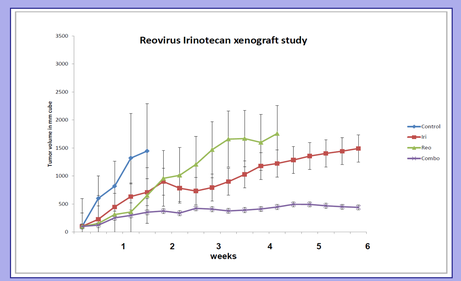
**Methods:**
This was a phase I dose escalation study of FOLFIRI/B and Reo to determine maximum tolerated dose (MTD) and recommended phase two dose (RPTD). Eligible pts were adults with oxaliplatin refractory *KRAS*-mutant mCRC. Both, IRI (150-180 mg/m$^2$) and Reovirus (1x10$^{10}$ $TCID_{50}$ to 3x10$^{10}$ $TCID_{50}$) were escalated. Reovirus was given intravenously over 1 hour on days 1-5 every 4 weeks (wk). FOLFIRI/B was delivered every 2 wk as per standard protocol. Pharmacokinetics (PK), on study tumor biopsies, and immune response was studied.

**Results:**
36 pts enrolled; 23 females (64%), median age 63 years, FOLFIRI naïve (24) and pre-treated (12). At the highest dose of 180 mg/m$^2$ of IRI, among FOLFIRI pretreated pts, 2 had dose-limiting toxicity (DLT) in cycle 1; one suffered from grade 4 thrombocytopenia, and another developed febrile neutropenia and urosepsis. However, in FOLFIRI naïve patients, none/6 had a DLT. Common (>10%) toxicities included neutropenia, anemia, thrombocytopenia, fatigue, and diarrhea. One patient died of acute renal failure. The MTD was the highest individual dose of FOLFIRI/ B (180mg/m$^2$ IRI) and reovirus (3x10$^{10}$ $TCID_{50}$), and is the RPTD. At this dose, 3 of 6 patients (50%) had a PR and the median progression free survival (PFS) and overall survival (OS) were 65.6 weeks and 107.5 weeks, respectively. There was no PK interaction noted. Immunogold staining against viral capsid protein σ demonstrated viral "homing" in the tumor cells. Flow cytometry revealed rapid dendritic cell maturation with subsequent activation of cytotoxic T cells.

**Conclusions:**
The combination of reovirus with FOLFIRI/B is safe, and well tolerated. The PFS and OS is superior to historic data and this combination deserves further exploration.

## BACKGROUND & MECHANISM OF ACTION




## METHODS

| Design | Standard phase I dose escalation |
|---|---|
| Dose | Reovirus: 1X10$^{10}$ - 3X10$^{10}$ $TCID_{50}$<br>FOLFIRI: Standard of Care |
| Administration | Reovirus: Days 1-5 every 28 days (1 Cycle)<br>FOLFIRI: Standard of Care q 2 wks |
| Infusion | Reovirus: 1 hr IV infusion<br>FOLFIRI: Standard Administration |
| Safety | Precautions for patient and family |
| CT Scan | CT Scan at 0,8,16,24,32,40,48,56,68,80… weeks |
| HbsAg/HIV | Negative |

## RESULTS

### 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%) |

### Summary of Toxicities

| | 1 | | | | 2 | | | | | 3 | | | | | 4 | | | | 5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n=3 | | | | n=12 | | | | | n=6 | | | | | n=7 | | | | n=8 | | | |
| *Grade* | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Anemia | 3 | | | | 7 | | | | | 3 | | | 1 | | 4 | | | | 7 | | 2 | |
| Hypertension | | | | | | | | | | | | | | | | | | | 3 | | 3 | |
| Neutropenia | 3 | | 1 | | 4 | 1 | 5 | 2 | | 2 | | 1 | 3 | 1 | 1 | | 4 | | | | 2 | |
| Leukocytopenia | 3 | 1 | | | 6 | 1 | | | | | | 1 | 1 | | 4 | | 1 | | 4 | | | |
| Thrombocytopenia | 1 | | | | 4 | | 1 | | | 2 | | 1 | 1 | | 4 | | | | 4 | | | |
| Fatigue | | 1 | | | 2 | | 1 | | | 2 | | | | | 1 | | | | 5 | | 1 | 1 |
| Increased INR | | | | | | | 1 | | | | | | | | | | | | | | | |
| Hyponatremia | 1 | | | | 1 | | 1 | | | 1 | | | | | 2 | | | | 5 | | 1 | |
| Hypokalemia | 3 | | | | 2 | | 2 | | | 2 | | 1 | 1 | | 2 | | | | 1 | 1 | | |
| Hyperglycemia | | | | | | 1 | 1 | | | | | | | | | | | | | | | |
| Diarrhea | | | | | 7 | 1 | | | | 2 | | | | | 3 | | | | 6 | | 2 | |
| Proteinuria | | | | | | | 1 | | | | | | | | | | | | | | 1 | |
| Acute Renal Failure | | | | | | | | | 1 | | | | | | | | | | | | | |
| Anorexia | | | | | 7 | 1 | | | | 2 | | | | | 1 | | | | 2 | | | |
| Nausea | 2 | | | | 9 | 1 | | | | | | | | | 4 | | | | 5 | | | |
| Mucositis | 1 | | | | 3 | | 1 | | | 2 | | | | | | | | | | | | |
| Anxiety | 1 | | | | | 1 | | | | | | | | | | | | | 2 | | | |
| Hypoalbuminemia | | | | | | | | | | 1 | | | 1 | | | | | | 1 | | | |
| Dyspnea | | | | | | | | | | 1 | | 1 | | | 1 | | | | 2 | | | |
| Fever | | | | | 8 | | | | | 2 | | | | | 5 | | | | 1 | | 1 | |
| Liver discomfort | | | | | | | | | | | | | | | | 1 | | | | | | |
| Increased neuropathy | | | | | | | | | | | | | | | 1 | 1 | | | 1 | | | |

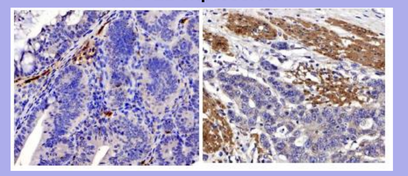
### Pharmacokinetic Analysis

| | | Without reovirus | | With reovirus | | p |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| AUC | Irinotecan | 19,196 | 12,901 | 15,989 | 8,478 | 0.48 |
| | SN-38 | 400 | 405 | 313 | 213 | 0.52 |
| | 5-FU | 130,048 | 286,864 | 155,344 | 273,560 | 0.83 |
| Clearance | Irinotecan | 23 | 13 | 25 | 13 | 0.70 |
| | SN-38 | 1,251 | 651 | 1,402 | 815 | 0.62 |
| | 5-FU | 15 | 10 | 18 | 21 | 0.67 |

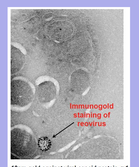
## RESULTS

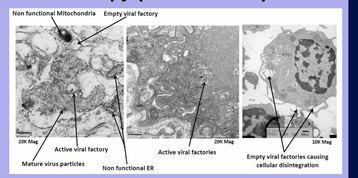
### Pharmacodynamic Analysis

Pre Reovirus Post Reovirus
PD-L1 expression

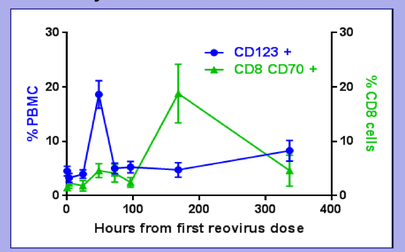


Electron Microscopy (Post reovirus)

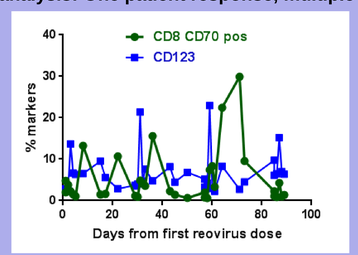



FACS analysis of immune markers from PBMC

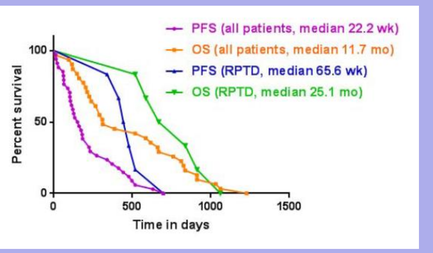



FACS analysis: One patient response, multiple cycles




## RESULTS

### PFS and OS of all patients and at RPTD




## CONCLUSIONS

Reovirus is safe and well tolerated in combination with FOLFIRI and Bevacizumab.

Reovirus administration is marked by activation of cytotoxic T cells and maturation of dendritic cells.

The combination is active and warrants further testing.

Electron microscopy reveals loss of cellular integrity, and viral factories, possibly suggesting a novel method of viral mediated cytotoxicity.

Reovirus may be considered an immunotherapeutic agent for further development

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