ABSTRACT

Reovirus is a 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.

METHODS

Design

Dose: Reservoir: 1X10^7 - 2X10^9 TCID_50 FOLFIRI: Standard dose escalating

Administration: Days 1-5 every 28 days (1 Cycle) FOLFIRI: Standard of Care 2 wks

Infusion: Reovirus: 1X by IV infusion FOLFIRI: Standard Administration

Safety

Precautions for patient and family

CT Scan: CT Scan at 0, 1, 4, 12, 24, 32, 48, 64, 88... weeks

Hb, Ag/HIV: Negative

Pharmacodynamic Analysis

Pre Reovirus

Post Reovirus

PD-L1 expression

Pharmacokinetic Analysis

Summary of Toxicities

FACS analysis of immune markers from PBMC

Electron Microscopy (Post reovirus)

FACS analysis: One patient response, multiple cycles

RESULTS

ABC

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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Patients with cCR or those who had prior treatment with FOLFIRI and Fluorouracil/Leucovorin/Bevacizumab (FOLFIRI/B) were enrolled in this phase 1, dose finding study. FOLFIRI/B was given standard of care every 2 weeks (1 cycle). FOLFIRI was as follows: 1 hr IV infusion on days 1, 8, 15, and 22. FOLFIRI/B was escalated in 21-Day cycles from 100 to 180 mg/m^2 to find the maximum tolerated dose. Eligible patients were to have KRAS selected tumors and had histologic confirmation of the KRAS gene with an activating mutation and were refractory to at least one previous treatment regimen. The study MTD was defined as the dose at which less than 2 of 12 patients achieved DLT. The study included a total of 65 patients with a median age of 63.6 years. Grade 1-2 toxicities included neutropenia, anemia, thrombocytopenia, hypertension, fatigue, and diarrhea. Two patients died of acute renal failure. The study concluded that reovirus was safe and well tolerated in combination with FOLFIRI/B. This study offers promise for a potential novel method of treatment for patients with advanced KRAS selected tumors.