Evaluation of the Safety and the Tolerability of Durvalumab Plus Tremelimumab Combined With FOLFOX in mCRC (MEDITREME)

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Purpose: 5-Fluorouracil plus irinotecan or oxaliplatin alone or in association with target therapy are standard 1st line therapy for metastatic colorectal cancer (mCRC). Checkpoint inhibitors targeting PD1/PD-L1 demonstrated efficacy mCRC with microsatellite instability but remain ineffective alone in microsatellite stable tumor which represent 95% of mCRC. 5-Fluorouracil plus oxaliplatin were known to present immunogenic properties. 5-Fluorouracil could eliminate Myeloid derived suppressor cells and oxaliplatin could induce immunogenic cell death and increase the immunogenicity of microsatellite stable tumors. Durvalumab (D) is a human monoclonal antibody (mAb) that inhibits binding of programmed cell death ligand 1 (PD-L1) to its receptor (PD-1). Tremelimumab (T) is a mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). This study is designed to evaluate whether the addition of PD-L1 and CTLA-4 inhibition to FOLFOX increases treatment efficacy.

Experimental Design: This phase II study (ClinicalTrials.gov NCT03202758) will assess the efficacy and safety of FOLFOX/D/T association in patients (pts) with mCRC (n = 48). Good performance status pts (ECOG < 2) with untreated, RAS mutational status mCRC will be eligible. Prior adjuvant therapy is allowed provided recurrence is > 6 months post-completion. There is a safety lead in of 9 pts receiving FOLFOX/D/T. Assuming no safety concerns the study will go on to include 39 additional pts. Pts will receive folinic acid (400mg/m²)/5-fluorouracil (400mg/m² as bolus followed by 2400mg/m² as a 46h infusion)/ Oxaliplatin (85mg/m²) q14 days with D (750 mg) D1 q 14 days and T (75 mg) D1q 28 days. After 6 cycle of FOLFOX only D/T will continue disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Primary endpoint is safety and efficacy according to progression free survival; secondary endpoints include overall response rate and quality of life. For statistical plan 6 months PFS will be analyzed. Hypothesis is that
a PFS of 50% at 6 months is insufficient and a PFS of 70.7% is expected (With $\alpha=10\%$, $\beta=10\%$). Blood, plasma, and tumor tissue will be collected and assessed for potential prognostic and predictive biomarkers.

**Conclusion:** As of November 21, 2017, 4 pts have been enrolled. Safety analysis and first biological and clinical data will be presented. [Clinical trial information: NCT03202758](https://clinicaltrials.gov/ct2/show/NCT03202758).

**References**:

