

A Simon two stage study of CoFactor (CO) with 5-fluorouracil (FU) as first line treatment in metastatic colorectal cancer (mCRC).

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Background: We are conducting an open label, Simon 2 stage study to assess the safety and efficacy of CO, 5,10 methylenetetrahydrofolic acid, with FU for first line treatment in mCRC. Unlike leucovorin (LV), CO directly modulates FU inhibition of thymidylate synthase without the need for metabolic conversion. Preclinical models show reduced hematologic toxicity of CO+FU with enhanced efficacy compared to FU+LV. **Methods:** Eligible patients (pts), age ≥ 18 with ECOG 0-2 and measurable mCRC, with or without adjuvant FU+LV, irinotecan, or oxaliplatin, but no prior chemotherapy for mCRC. Patients received ≥ 2 cycles each consisting of CO (60 mg/m^2) and FU (450 mg/m^2) weekly IV bolus for 6 weeks, followed by 14 day rest. Pre-established response criteria are ≥ 4 of 23 for stage 1, ≥ 12 of 48 for stage 2. Response is defined as complete response (CR, complete disappearance), partial response (PR, $\geq 50\%$ reduction in total tumor size), stable disease (SD, $\leq 50\%$ reduction), progressive disease (PD, $\geq 25\%$ increase) at week 16. **Results:** Response data are available for 48 patients. Safety data are available for all patients. No grade 3/4 blood toxicity was observed and overall incidence of grade 3/4 non-hematological toxicity was 2 (bowel obstruction and malignant pleural effusion). **Conclusions:** We have met the response criteria defined for the study. CO+FU has been well tolerated. The overall rate of clinical benefit for this regimen is 64.5% with an objective response rate of 37.5% suggesting that the direct availability of CoFactor increases the potentiation of 5-FU and seems associated with a lower toxicity when compared to the historical data available for LV+5-FU.