

## **Response to second line treatment following 5,10-methylenetetrahydrofolic acid (CoFactor) with 5-fluorouracil as first line treatment in metastatic colorectal cancer**

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**Background:** 5-Fluorouracil (FU) plus Leucovorin (LV) has historically been the standard first line treatment of colorectal cancer. Although LV modestly enhances FU activity, it can increase systemic toxicity and also must be intracellularly converted in multiple steps to its active metabolite, 5,10-methylenetetrahydrofolate (CoFactor®, CO). Unlike 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. We evaluated CO+FU chemotherapy in patients with previously untreated mCRC. We also evaluated the response to investigator-initiated second line treatment after progression or discontinuation.

**Methods:** Patients (pts) had performance status ECOG 0-2 and objectively measurable mCRC. Prior adjuvant therapy was allowed including FU+LV. Fifty pts were enrolled and treated with CO 60mg/m<sup>2</sup> and FU 450mg/m<sup>2</sup> (weekly IV bolus) for 6 weeks. Treatment cycles were 7 weeks in length. Response was measured at 16 wks (WHO criteria). Patients remained on treatment until progression or toxicity.

**Results:** Patient demographics: median age = 65 (range 42-86), M/F = 60%/40%. Objective response rate (CR + PR) to first line treatment with CO+FU based on independent blinded review was 35% (2 CR, 14 PR, 4 MR, 19 SD, 7 PD; 95% CI: 21.4-50.2) based on 46 pts evaluable for response. Median time to tumor progression was 162 days (95% CI: 105 -166). 28 pts are deceased and median survival was 459 days (95% CI: 335-699). Post study information was captured on all 50 patients, including responses to second line agents. Four patients underwent surgical resection for potential cure, 29 patients received chemotherapy with irinotecan or oxaliplatin, alone or in combination with 5-FU/LV, as well as other agents. Seventeen patients received no post-study intervention. Of the 29 patients who received chemotherapy, 4 patients had an objective response.

**Conclusions:** The results suggest that CO+FU is a safe, well tolerated, and active first line treatment in mCRC. Results to second line therapies following discontinuation of CO+FU are currently being evaluated. In the optimum treatment strategy afforded by the availability of numerous drugs, the high level of activity and low toxicity of CO+FU suggests that this combination may be a good initial treatment in a sequential strategy of mCRC management.