**Clinical Trial Note**

# Phase II Study of Oxaliplatin, Capecitabine and Endostar as First Line Treatment for Patients with Advanced Colorectal Cancer

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**ABSTRACT** Colorectal carcinomas (CRC) are characterised by enhanced VEGF expression and the corresponding high microvascular densities, indicating increased angiogenic activity and leading to worse patient survival. The bevacizumab data provide a treatment option for patients with metastatic CRC based on VEGF inhibition. It is hypothesized that other anti-angiogenic agents such as endostar, may augment the effect of chemotherapy regimens in CRC. Endostar, a recombinant human endostatin which expressed and purified in E. coli, was approved by the SFDA for the treatment of non-small-cell lung cancer in 2005. Ling et al. found that endostar suppressed the VEGF-stimulated proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs) in vitro, and the antiangiogenic effects of endostar were correlated with the VEGF-triggered signaling. A Chinese phase III clinical trial in advanced non-small-cell lung cancer, endostar--a new angiogenesis inhibitor prolonged the overall survival, time to progression and improved response rate. Based on these results, we design this phase II clinical trial of oxaliplatin, capecitabine and endostar as first line treatment, to evaluate whether endostar can bring survival benefits to patients with advanced colorectal cancer.

**KeyWords:** Advanced Colorectal Cancer; Oxaliplatin; Capecitabine; Endostar

## Introduction

In spite of increased screening and improved awareness of the disease, colorectal cancer (CRC) remains one of the leading causes of cancer-related deaths. Several randomized trials in advanced CRC have demonstrated the benefit of intravenous bolus 5-fluorouracil (5-FU)-based treatment over best supportive care in terms of overall survival (OS) and quality of life (1, 2). Capecitabine (N4-pentoxycarbonyl-50-deoxy-5-fluorocytidine; Xeloda; Hoffmann-La Roche Ltd, Basel, Switzerland) is a 5-FU prodrug developed to reduce the toxicity and enhance the intratumor concentrations of 5-FU. Capecitabine is absorbed as an intact molecule from the small bowel mucosa and converted sequentially to 5-FU in a multistep enzymatic process (3, 4). Twice-daily oral administration of capecitabine effectively mimics infusional delivery of 5-FU without the inconvenience and morbidity associated with long-term central venous access needed for prolonged 5-FU infusion (5).

Among the different combination regimens of new drugs in CRC treatment, the combination of capecitabine and oxaliplatin seems especially attractive. Both drugs have a different and relatively mild toxicity profile. In preclinical models of a human tumor xenograft, the combination of capecitabine and oxaliplatin inhibited the in vivo growth of CXF820 human colon cancer more effectively than either agent alone, administered at its maximum tolerated dose (6). Furthermore, oxaliplatin upregulated TP expression in CXF820 tumor tissue, which may have contributed to the increased activity observed with the capecitabine and oxaliplatin combination. The fact that toxicity was not enhanced with the combination may support the hypothesis that TP upregulation is a tumor-specific phenomenon (6). In phase II studies that used the recommended dose of XELOX (capecitabine 1000 mg/m2 twice daily on days 1-14 with intravenous oxaliplatin 130 mg/m2 on day 1 every 3 weeks), RRs were between 42% and 55%, with PFS times of 6.0 to 7.7 months, which showed that the XELOX combination was effective in the first-line treatment of patients with metastatic CRC (6, 7).

Colorectal carcinomas (CRC) are characterised by enhanced VEGF expression and the corresponding high microvascular densities, indicating increased angiogenic activity and leading to worse patient survival (8, 9). Recently, the final results of XELOX-1/NO16966, a study of first line therapy, confirmed that

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bevacizumab+chemotherapy (XELOX or FOLFOX) was superior to chemotherapy alone in terms of PFS (HR 0.83; p=0.0023) although the OS data did not reach statistical significance (HR 0.89; p=0.0769) (10). The bevacizumab data provide a treatment option for patients with metastatic CRC based on VEGF inhibition. It is hypothesized that other anti-angiogenic agents such as endostar, may augment the effect of chemotherapy regimens in CRC. Endostar, a recombinant human endostatin which expressed and purified in E. coli, was approved by the SFDA for the treatment of non-small-cell lung cancer in 2005. Ling et al. found that endostar suppressed the VEGF-stimulated proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs) in vitro, and the antiangiogenic effects of endostar were correlated with the VEGF-triggered signaling (11). A Chinese phase III clinical trial in advanced non-small-cell lung cancer, endostar--a new angiogenesis inhibitor prolonged the overall survival, time to progression and improved response rate (12). Based on these results, we design this phase II clinical trial of oxaliplatin, capecitabine and endostar as first line treatment, to evaluate whether endostar can bring survival benefits to patients with advanced colorectal cancer.

**Purpose**

The purpose of this study is to assess the efficacy and safety of oxaliplatin, capecitabine and endostar as first line treatment for patients with advanced colorectal cancer.

**End–points**

*Primary end–point*

The tumor response will be assessed objectively after each two courses according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the maximum response rate will be taken as the antitumor effect for that subject.

*Secondary end–point*

Response duration, time to progression, overall survival and safety will also be assessed.

**Eligibility Criteria**

(ⅰ) Histologically or cytologically confirmed metastatic or recurrent colorectal tumors with no previous treatment for advanced disease; (ⅱ) Age greater than or equal to 18 years; (ⅲ) SWOG performance status 0-1; (ⅳ) At least one measurable lesion according to the RECIST criteria which has not been irradiated (i.e. newly arising lesions in previously irradiated areas are accepted). Minimum indicator lesion size: > 10 mm measured by spiral CT or >20mm measured by conventional techniques; (ⅴ) Have a negative serum pregnancy test within 7 days prior to initiation of chemotherapy (female patients of childbearing potential); (ⅵ) Availability of tumor biopsy (paraffin embedded or fresh frozen) at the time of diagnosis and/or prior to study entry is required; (ⅶ) Patients must agree to have a 20 cc blood sample drawn in addition to routine labs with each cycle of chemotherapy.

**Exclusion criteria**

(ⅰ) Pregnant or lactating woman; (ⅱ) Life expectancy < 3 months; (ⅲ) Serious, uncontrolled, concurrent infection (s) or illness (es); (ⅳ) Any prior oxaliplatin treatment, with the exception of adjuvant therapy given > 12 months prior to the beginning of study therapy; (ⅴ) Prior unanticipated severe reaction to fluoropyrimidine therapy, known hypersensitivity to 5-fluorouracil, or known DPD deficiency; (ⅵ) Prior unanticipated severe reaction or hypersensitivity to platinum based compounds; (ⅶ) Treatment for other carcinomas within the last five years, except cured non-melanoma skin and treated in-situ cervical cancer; (ⅷ) Current, recent (within 4 weeks of first infusion on this study) or planned participation in an investigational drug study; (ⅸ) Clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) within the last 6 months; (ⅹ) History of clinically significant interstitial lung disease and/or pulmonary fibrosis; (Ⅺ) History of persistent neurosensory disorder including but not limited to peripheral neuropathy; (Ⅻ) Any of the following laboratory values: (a) Abnormal hematologic values (neutrophils < 1.5× 109/L, platelet count < 100× 109/L); (b) Urine protein: creatinine ratio >/= 1.0 Impaired renal function with estimated creatinine clearance < 30 ml/min as calculated with Cockroft et Gault equation; (c) Serum bilirubin > 1.5× upper normal limit. ALT, AST > 2.5× upper normal limit (or > 5× upper normal limit in the case of liver metastases); (d) Alkaline phosphatase > 2.5× upper normal limit (or > 5× upper normal limit in the case of liver metastases or > 10× upper normal limit in the case of bone disease).

**Treatment methods**

Oxaliplatin 130 mg/m2 iv drip D1, Capecitabine 1000 mg/m2 bid d1-14, Endostar 7.5 mg/m2 iv drip D1-14. Every 3 weeks.

**Sample size**

This study was designed to allow assessment of the treatment in 44 patients with advanced colorectral cancer. Threshold value, 40%; expected efficacy rate, 60%; $\alpha$ =0.05; and $\beta$ =0.2. (13) The duration of the registration period will be 2 years, starting in February 2009 and ending in March 2011. Subjects will be followed-up for 1 year.

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