These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert

For product information, please log-on to the web site www.eloxatin.com or contact one of our Medical Information Specialists at (800) 633-1610.

Proprietary Drug Name: ELOXATIN®	**INN:** Oxaliplatin injection	**Therapeutic area and FDA approved indications:** Used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum
Name of Sponsor/Company:	Sanofi-Synthelabo, Inc., a member of the sanofi-aventis group.	

Title of Study: (EFC 7154) Phase I/II Trial of Oxaliplatin and Irinotecan Administered Once Every Three Weeks to Patients with Metastatic Colorectal Cancer

Principal Study Investigator: Paulo M. Hoff, M.D.

Department of Gastrointestinal Medical Oncology, Unit 426

The University of Texas M. D. Anderson Cancer Center

1515 Holcombe Boulevard. Houston, TX 77030

Study center(s): one center, Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center Houston, TX

Publication(s): This is the reference for the phase I: Hoff PM, Saad ED, Pazdur R, Wolff R, Lassere Y, Bogaard KR, Abbruzzese JL. Phase I trial of combined irinotecan and oxaliplatin given every three weeks to patients with metastatic colorectal cancer. *Invest New Drugs.* 2004 Aug;22(3):307-13. PMID: 15122078 [PubMed - indexed for MEDLINE]

The publication of phase II subsequent study is pending.

Studied period (years): (date of first enrolment) (date of last completed): June 1999-June 2000	**Phase of development:** Phase I / II

Objectives: To determine the dose-limiting toxicity and the maximum tolerated dose of combined irinotecan and oxaliplatin given every three weeks for patients with metastatic

colorectal cancer.

Methodology: Cohorts of patients with MCC previously treated with 5-Fluorouracil received escalating doses of irinotecan (150, 175, and 200 mg/m2) and a fixed dose of oxaliplatin (130/mg/m2), both given intravenously every 3 weeks. DLT was evaluated within the first week of treatment. Objective responses were evaluated every two courses and were confirmed at least four weeks later.

Number of patients (planned and analyzed): At least three patients were enrolled in each dose level. If dose –limiting toxicity was recorded in only one of the three patients in a given level, another three patients were enrolled in that level. Fourteen patients were treated and evaluated.

Diagnosis and main criteria for inclusion: Eligible patients were at least 18 years old, had pathologically confirmed metastatic adenocarcinoma of the colon or rectum with at least one lesion, and an ECOG performance status score of 0 or 1. In addition, they had adequate organ function, as indicated by absolute neutrophil count (ANC) ³ 1,500/mL, platelet count ³ 100,000/mL, serum creatinine £ 2.0 mg/dL, serum bilirubin £ 1.5 mg/dL, and serum alanine aminotransferase £ 2.5 times higher than the upper limit of normal (except in cases with liver involvement when a value £ 5 times the upper limit of normal was accepted). Other eligibility criteria required full recovery from previous surgery (at least 2 weeks) or radiation therapy (at least 4 weeks).

No previous chemotherapy treatment for metastatic disease was allowed, but patients who had received adjuvant chemotherapy with fluoropyrimidines were eligible if the interval since the end of adjuvant therapy was greater than 6 months. If the disease had progressed while the patient was still undergoing adjuvant chemotherapy or within 6 months of its completion, it was considered a failure to prior chemotherapy for metastatic disease, and the patient was ineligible for this study. Patients who had previously been treated with irinotecan or oxaliplatin or radiation therapy to the pelvis were excluded from the study, as were pregnant and breast-feeding women. Other exclusion criteria included clinically apparent central nervous system metastases, prior malignancies (other than non-melanoma skin cancer or in situ cervical cancer) within the previous 5 years, uncontrolled infection or diabetes mellitus, serious psychiatric disorders, myocardial infarction within the previous 6 months, heart failure, and history of epilepsy or use of anticonvulsant medications. Patients with known Gilbert syndrome were also excluded from participation because of reports of excessive irinotecan toxicity in such patients.

Test product, dose and mode of administration, batch number: Oxaliplatin was diluted in 250 or 500 mL of 5% dextrose solution and infused intravenously over 120 minutes. After the Oxaliplatin infusion was complete, irinotecan was diluted in 250 mL of 5% dextrose solution and infused intravenously over 30 minutes. Antiemetic premedication consisted of 10 mg dexamethasone and a 5-hydroxytryptamine-3 antagonist. No prophylactic atropine, loperamide, or granulocyte colony-stimulating factor (G-CSF) was used, but their therapeutic use was allowed. Patients were instructed to take loperamide for diarrhea occurring more than 8 hours after treatment. Early cholinergic symptoms were treated with intravenous atropine (0.25 to 1.0 mg), which could also be used as secondary prophylaxis for patients who had experienced these symptoms in prior courses of therapy. Batch Number unknown.

Duration of treatment: Single intravenous injection every three weeks for a maximum of eight courses.

Reference therapy, dose and mode of administration, batch number: combination of oxaliplatin at 130 mg/m2 followed by irinotecan at 175 mg/m2 administered intravenously in the outpatient setting, batch number unknown.

Criteria for evaluation:

Efficacy: Objective responses were evaluated every two courses and were confirmed at least four weeks after the initial determination. After every two courses, response to treatment was evaluated using the World Health Organization (WHO) criteria, and each patient's best response was recorded. "Complete response" was defined as the complete disappearance of all measurable and evaluable disease for at least 4 weeks with no evidence of new lesions. "Partial response" was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks with no evidence of new lesions or worsening of evaluable disease. "Progressive disease" was defined as an increase of at least 25% in the sum of the products of the largest perpendicular diameters of all measurable lesions, the reappearance of any lesion that had disappeared, or the appearance of new lesions. "Stable disease" was defined as a response that did not fit into any of the other categories.

Safety: The use of oxaliplatin is associated with peripheral neurotoxicity, which may include paresthesias and dysesthesias of the hands, feet, and perioral region, and with a distinctive laryngopharyngeal dysesthesia that is characterized by an acute sensation of respiratory discomfort without any objective evidence of such distress. Neurologic toxicity (ie, peripheral neuropathy) was graded according to the scale shown in Table 1 (below). Other toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria.

The dose-limited toxicity (DLT) was defined as any of the following, occurring within the first course of treatment: grade ³ 3 nausea, vomiting, or diarrhea, uncontrolled by aggressive support; grade 4 neutropenia or leukopenia lasting longer than 3 days or febrile neutropenia, defined as a body temperature ³ 38.5°C and an absolute neutrophils count (ANC) < 1,000/mL; grade ³ 3 hematologic toxicity other than neutropenia or leukopenia; or grade ³ 3 nonhematologic toxicity. The maximum tolerated dose (MTD) for the irinotecan/oxaliplatin combination was defined as

the dose that caused DLT in one third or fewer of the patients treated at a given dose level.

Table 1. Toxicity Scale for Peripheral Neuropathy

Grade	Symptoms
0	None
1	Paresthesias or dysesthesias of short duration with complete resolution prior to next treatment
2	Paresthesias or dysesthesias, without functional impairment, that persisted at the time of next treatment
3	Functional impairment

Statistical methods: The primary endpoint of the trial was the response rate, and a 40% response rate was considered to be of interest. Any response rate of less than 20% was unacceptable. Therefore, the trial was conducted using a two-stage design, with 90% power to detect a response rate of 40% and <5% chance of continuing the trial if the response was less than 20%. The trial was designed to treat an initial cohort of 19 patients, with termination of the trial if there were 4 or less responses. If there were more than 4 responses, the trial would proceed to the second stage, with the enrollment of 35 additional patients. Secondary endpoints included median time to progression and overall survival.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: A total of 55 patients were enrolled and treated in this trial. A total of 53 patients were evaluable for response; 18 had a partial response (34%), 27 had stable disease (51%), and 8 had progression of disease (15%) as their best response to the treatment. The intent-to-treat median survival for all patients was 16.4 months, and time to progression was 4.8 months. Of note, a total of 19 (34.5%) patients had median survivals greater than 20 months.

SAFETY RESULTS: Toxicity could be evaluated in all 55 enrolled patients; the most significant finding was neutropenia, which tended to be more protracted as the treatment continued, consistent with a pattern of cumulative toxicity. A total of 40% of the patients developed grade 3 or 4 neutropenia as the treatment continued. Other significant grade 3 and 4 toxicities included diarrhea in 25% and vomiting in 24% of the patients. Severe neuropathy was seen in 11% of the patients, a percentage consistent with that reported in studies of other oxaliplatin-based regimens.

Date of the report: 13 September, 2004