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

Sponsor/company:	Sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00399750
		Study Code:	L_8851
Generic drug name:	oxaliplatin	**Date:**	7 March 2007

Title of the study:	A Randomized, Prospective Study Comparing Three Regimens of Eloxatin™ Plus Fluoropyrimidine (Tree1 Study) with the Addition of Avastin™ (Tree2 Study) for Evaluation of Safety and Tolerability in First Line Treatment of Patients with Advanced Colorectal Cancer (ARD-5099)
Investigator(s):	Howard Hochster, MD (Principal Investigator) – NYU School of Medicine
Study center(s):	33 active centers (TREE1), 57 active centers (TREE2) in the United States
Publications (reference):	Hochster, H., Hart, L., Ramanathan, RK., Hainsworth, J., Griffing, S., Mass, R., Nagarwala, Y., Jirau-Lucca, G., Shpilsky, A., Childs, BH.: Safety, tolerability and efficacy of the addition of bevacizumab to oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer (mCRC): Results of TREE2 cohort of the TREE study. (abstract) ECCO 13, October 30-November 3, 2005, Paris. Published in EJC. Vol 3 (2), Poster 615, page 173, October 2005. Welles, L., Hochster, H., Ramanathan, R., Wong, L., Hart, L., Shpilsky, A., Jirau-Lucca, G., Emanuel, D.: Preliminary results of a randomized study of the safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer (CRC) ("Tree" study). ASCO 2004, abstract #3537. Hochster, H., Welles, L., Hart, L., Ramanathan, RK., Hainsworth, J., Jirau- Lucca, G., Shpilsky, A., Griffing, J., Mass, R., Emanuel, D.: Safety and efficacy of bevacizumab (bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE1 & 2 studies. ASCO 2005, abstract #3515. Hochster, H., Welles, L., Hart, L., Ramanathan, RK., Hainsworth, J., Jirau- Lucca, G., Shpilsky, A., Griffing, J., Mass, R., Emanuel, D.: Bevacizumab (B) with oxaliplatin (O)-based chemotherapy in the first-line therapy of metastatic colorectal cancer (mCRC): Preliminary results of the TREE2 trial. GI ASCO 2005, abstract #10148. Hochster, HS, Hart, LL, Ramanathan, RK, Hainsworth, JD, Griffing, S, Mass, RD, Nagarwala, Y., Jirau-Lucca, G., Shpilsky, A., Childs, BH.: Results of the TREE-2 cohort: Safety, tolerability and efficacy of bevacizumab added to three oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer. GI ASCO 2006.

Study period: Date first patient enrolled: TREE 1: 12/3/2002 TREE 2: 11/14/2003 Date last patient completed: TREE 1: 6/13/2005 TREE 2: 10/25/2005 Cutoff date for analysis: 12/5/2005		**Phase of development:** II
Objectives:	The primary objective was to evaluate the safety and efficacy of three oxaliplatin -fluoropyrimidine regimens combined with bevacizumab as therapy for previously untreated metastatic colorectal cancer. The secondary objectives were to assess the efficacy of three oxaliplatinfluoropyrimidine regimens alone or in combination with bevacizumab as therapy for previously untreated metastatic colorectal cancer (TREE1 and TREE2) and to evaluate the safety and tolerability of three oxaliplatinfluoropyrimidine regimens alone or in combination with bevacizumab as therapy for previously untreated metastatic colorectal cancer (TREE1 and TREE2).	
Methodology:	A randomized, controlled, open-label, 3-arm, multicenter trial to assess the safety and efficacy of 3 oxaliplatin-fluoropyrimidine containing regimens: FOLFOX, bFOL, CapeOx ± bevacizumab as first line therapy for advanced metastatic colorectal cancer	
Number of patients: **Evaluated:**	Planned: 370; TREE1: 160 TREE2: 210 Efficacy : 330 TREE1: 128 TREE2: 202	Randomized: 373; TREE1: 150 TREE2: 223 Safety: 360 TREE1: 147 TREE2: 213

Diagnosis and criteria for inclusion:	**TREE 1** Inclusion Criteria a) Histologically documented adenocarcinoma of the colon or rectum. b) Metastatic/recurrent disease not amenable to potentially curative treatment (e.g., inoperable metastatic disease). c) No prior chemotherapy for metastatic/recurrent disease. Prior adjuvant treatment with 5-FU/LV is allowed if it is completed at least 6 months before study registration. d) Age ≥ 18 years. e) ECOG Performance Status (PS) 0- 1 . f) At least one unidimensionally measurable lesion with a diameter ≥ 20 mm using conventional computed tomography (CT) or magnetic resonance imaging (MRI) scans or ≥10 mm using spiral CT scans. If a single lesion is identified as the target lesion, a histological or cytological confirmation of adenocarcinoma is required. g) Recovery in full from any previous surgical procedure. h) No other serious concomitant disease. i) Serum creatinine ≤ 1.5 x upper limit of normal (ULN). j) Bilirubin ≤ 2 x ULN. k) SGPT (ALT) and SGOT (AST) ≤ 3 x ULN. l) Absolute Neutrophil Count ≥1500/mm3 and platelets ≥ 100,000/mm3. m) Men and women of reproductive potential must agree to use an effective contraceptive method. n) Signed informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice. o) Able to take oral medication (absence of malabsorption syndrome, swallowing difficulties). Exclusion Criteria a) Any uncontrolled infection. b) History of myocardial infarction within the previous six months or current clinical evidence of congestive heart failure, or non-stable coronary artery disease. c) History of any other cancer (except non melanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission and off all therapy for that cancer for at least 5 years. d) Central nervous system metastases. e) Peripheral neuropathy of any cause. f) Pregnant or lactating women. Documentation of a negative serum HCG pregnancy test is required prior to enrollment in women with childbearing potential. g) Hypersensitivity to one of the study drugs or ingredients. h) Participation in any investigational drug study within 4 weeks preceding enrollment. i) Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome. j) Medical or psychiatric disorders that would interfere with informed consent, compliance or make them a poor risk for participation in this trial. k) Patients with known dihydropyrimidine dehyrogenase (DPD) deficiency. l) Patients with interstitial pneumonia or extensive symptomatic fibrosis of the lungs. m) Patients with calculated creatinine clearance of <30 ml/min using Cockroft and Gault formula. n) Organ allografts.

Diagnosis and criteria for inclusion (continued):	**TREE 2** Inclusion Criteria 1. Histologically documented adenocarcinoma of the colon, rectum or appendix. 2. Metastatic/recurrent disease not amenable to potentially curative treatment (e.g., inoperable metastatic disease). 3. No prior chemotherapy for metastatic/recurrent disease. Prior adjuvant treatment with 5-FU/LV and/or IFL is allowed if it is completed at least 6 months before study registration. 4. Age = 18 years. 5. ECOG Performance Status 0- 1. 6. At least one unidimensionally measurable lesion with a diameter = 20 mm using conventional CT or MRI scans or = 10 mm using spiral CT scans. If a single lesion is identified as the target lesion, a histological or cytological confirmation of adenocarcinoma is required. 7. Recovery in full from any previous surgical procedure. 8. No other serious concomitant disease. 9. Required baseline laboratory parameters: · Absolute neutrophil count (ANC) = 1,500/mm^3 · Platelets = 100,000/mm^3 · Hemoglobin = 8.0 g/dL · Creatinine = 1.5 x ULN · Total bilirubin = 2.0 x ULN · Serum glutamate-oxalate transferase (SGOT, AST) Serum glutamic pyruvic transaminase (SGPT, ALT) = 3 x ULN · Urinalysis – dipstick Protein < +1 · Coagulation PT/PTT (INR) within normal limits (WNL) for the institution · Serum pregnancy test for females of childbearing potential. Negative within 7 calendar days of randomization to study 10. Men and women of reproductive potential must agree to use an effective contraceptive method. 11. Signed informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice. 12. Able to take oral medication (absence of malabsorption syndrome, swallowing difficulties).

Diagnosis and criteria for inclusion (continued):	**TREE 2** Exclusion criteria 1. Prior treatment with oxaliplatin or bevacizumab. 2. Any uncontrolled infection. 3. History of myocardial infarction within the previous six months or current clinical evidence of congestive heart failure, non-stable coronary artery disease, clinically significant hypertension (blood pressure of >160/110 mmHg on medication), or symptomatic peripheral vascular disease. 4. History of any other cancer (except non melanoma skin cancer or carcinoma *in situ* of the cervix) unless in complete remission and off all therapy for that cancer for at least 5 years. 5. Central nervous system metastases. 6. Peripheral neuropathy of any cause. 7. Pregnant or lactating women. Documentation of a negative serum HCG pregnancy test is required prior to enrollment in women with childbearing potential. 8. Hypersensitivity to one of the study drugs or ingredients. 9. Participatio n in any investigational drug study within 4 weeks preceding enrollment. 10. Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome. 11. Medical or psychiatric disorders that would interfere with informed consent, compliance or make them a poor risk for participation in this trial. 12. Patients with known DPD deficiency. 13. Patients with interstitial pneumonia or extensive symptomatic fibrosis of the lungs. 14. Patients with calculated creatinine clearance of <30 ml/min using Cockroft and Gault formula. 15. Patients who have received an organ allograft. 16. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study entry. 17. Chronic, daily treatment with aspirin (>325 mg/day) or nonsteroidal anti-inflammatory medications (intermittent or "p.r.n." use for pain is permitted). 18. Evidence of a bleeding diathesis or coagulopathy. 19. Subjects found to have proteinuria at baseline – If patients are found to have =1+ proteinuria at baseline screening they should undergo a 24-hour urine collection, which must have been an adequate collection and must have demonstrated < 2 g of protein/24 hr to allow participation in the study. 20. Chronic therapeutic warfarin therapy.

Investigational product:	
Dose:	ARM 1—Oxaliplatin plus infusional 5-FU/LV (FOLFOX) – TREE1 Oxaliplatin at 85 mg/m² intravenously (IV) over 2 hours - Day 1 of each cycle Leucovorin at 350 mg IV over 2 hours - Day 1 of each cycle 5-Fluorouracil at 400 mg/m² bolus followed by 2400 mg/m² IV infusion over 46 hours – Day 1 of each cycle Treatment was to be repeated every 14 days. ARM A (TREE2): same treatment regimen with the addition of bevacizumab at 5 mg/kg over 30-90 minutes – day 1 of each cycle. ARM 2—Oxaliplatin plus weekly bolus 5-FU/LV (bFOL) – TREE1 Oxaliplatin at 85 mg/m² IV over 2 hours - Day 1 and Day 15 of each cycle Leucovorin at 20 mg/m² IV bolus over 10-20 minutes - Days 1, 8, and 15 of each cycle 5-Fluorouracil at 500 mg/m² bolus – Days 1, 8, and 15 of each cycle Treatment was to be repeated every 28 days. ARM B (TREE2): same treatment regimen with the addition of bevacizumab 5 mg/kg infused over 30-90 minutes added on days 1 and 15 of each cycle. ARM 3—Oxaliplatin plus Capecitabine (CapeOx) – TREE1 Oxaliplatin at 130 mg/m² IV over 2 hours - Day 1 of each cycle Capecitabine at 1000 mg/m² twice daily - Days 1 –15 (Day 1 PM dose only, Day 15 AM dose only) of each cycle. The protocol was subsequently amended (Amendment 4) to reduce the starting dose of capecitabine to 850 mg/m² twice daily. From 750 mg/m² to 650 mg/m² for patients with moderate renal impairment, defined as creatinine clearance between 30 and 50 ml/min. Treatment was to be repeated every 21 days. ARM C (TREE2): same treatment regimen with the addition of bevacizumab 7.5 mg/kg infused over 30-90 minutes added on day 1 of each cycle.
Administration:	IV and oral (capecitabine)
Duration of treatment: For both TREE1 and TREE2, therapy consisted of 2 week (FOLFOX), 3 week (CapeOx), or 4 week (bFOL) cycles. Cycles were to be repeated until progression or unacceptable toxicity.	**Duration of observation:** TREE1: observation through 12 months after study discontinuation TREE2: observation until death.

Reference therapy:	None
Criteria for evaluation:	
Efficacy:	Time to tumor progression (TTP), time to treatment failure (TTF), overall survival (OS), and objective response rate (ORR). Tumor assessments were obtained every 12 weeks (TREE1) and every 6 weeks (TREE2). Response was based on RECIST criteria.
Safety: Tolerability:	National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0 for adverse events and Neurotoxicity Scale for oxaliplatin dose adjustments. Actual doses given, dose reductions, omissions, and de lays; actual andrelative dose intensity.
Statistical methods:	Data were summarized separately for each of the treatment arms within both the TREE1 and the TREE2 studies. Continuous data was summarized using means, medians, standard deviation, and ranges. Categorical data were summarized using counts and percents. Time to the occurrence of an event was summarized using the Kaplan-Meier method. Although no formal statistical comparisons were made among arms or between studies, observed differences will be noted in this report. Since the various cohorts were based on similar populations and treated at the same investigational sites, such informal comparisons are a legitimate exercise.

Summary:	
Efficacy results:	These studies measured the TTP, TTF, ORR and survival of patients treated with FOLFOX, bFOL or CapeOx with or without bevacizumab. The highest confirmed response rates were seen on the FOLFOX arm of TREE1 and on FOLFOX + bevacizumab on TREE2. In both studies, the lowest response rates occurred on bFOL (± bevacizumab). The addition of bevacizumab (TREE2) increased the response rates for each regimen, going from 44% to 53% for FOLFOX, 22% to 41% for bFOL and 35% to 48% for CapeOx. TTP on TREE1 for the FOLFOX arm was 8.7 months, 6.9 months for bFOL, and 5.9 months for CapeOx. The addition of bevacizumab on TREE2 increased the median TTP for FOLFOX to 9.9 months, to 8.3 months for bFOL and to 10.3 months for CapeOx. These data were censored for second line therapy. When the results were calculated without censoring for second line treatment, the results were virtually unchanged. There is insufficient follow-up to comment on the effect of these regimens on overall survival.
Safety results:	The results of these studies show that oxaliplatin may be combined safely with a variety of fluoropyrimidine regimens including infusional 5-FU (FOLFOX), bolus 5-FU (bFOL) and capecitabine (CapeOx). In addition, bevacizumab may be safely added to any of these regimens. As expected, the major side effects observed included gastrointestinal symptoms of nausea, vomiting and diarrhea, neurotoxicity (especially paresthesias), neutropenia, thrombocytopenia, palmar-plantar dysesthesia, and a variety of other expected side effects. The high incidence of diarrhea and dehydration on the CapeOx arm of TREE1 was lowered considerably by adjusting the capecitabine dose downward in TREE2. The addition of bevacuzimab did not compromise the ability to deliver any of the regimens, with a relative dose intensity of approximately 85% on all arms. Depending on the arm, from 6- 20% of patients treated with bevacuzimab experienced non-arterial thromboembolic events. In no more than 10% of patients on all three arms were these events considered severe (Grade 3 or 4). No patient treated with FOLFOX on either TREE1 or TREE2 died as a result of an AE. In TREE1, there was one death on bFOL and three deaths on CapeOx and in TREE2, there were 3 deaths on each of these two arms. The deaths in both studies were due to a varie ty of causes including disease progression, myocardial infarction, arrhythmia, diarrhea, bowel obstruction, bowel perforation, CVA and sepsis.
Date of report:	21MAR2006