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 Generic drug name: Oxaliplatin	ClinicalTrials.gov Identifier: NCT00174616 Study Code: C_8601 Date: 30 September 2009

Title of the study:	Phase 2 study of weekly oxaliplatin and capecitabine (XELOX) in combination with preoperative radiotherapy in patients with MRI defined locally advanced rectal cancer; CORE : Capecitabine, Oxaliplatin, Radiotherapy and Excision		
Investigator(s):	Principal Investigator: Dr David Sebag-Montefiore, Cookbridge Hospital - Leeds, UK		
Study center(s):	France (4 centers), Italy (3 centers), Belgium (2 centers), England (2 centers), Germany (1 center), Netherlands (1 center) and Spain (1 center)		
Publications (reference):	Rutten H et al. Capecitabine, Oxaliplatin, Radiotherapy, and Excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: results of an international multi-center phase II study. ASCO 2006 - poster #3528; ASCO 2009 - poster #10264		
Study period: Date first patient enrolled: 15 July 2003 Cut-off date: 10 November 2007		Phase of development: 2	
Objectives:	Primary: Pathological complete response (ypTON0) rate Secondary: Histopathological R0 resection rate (CRM-negative) Pathological down-staging (ypT0-T2N0) One month surgical complication rate Predictive value of pre-operative MRI for surgical, pathological and clinical outcomes Safety Local and distant recurrence rates Progression free survival Overall survival		
Methodology:	Open-label phase 2 multi-center non comparative study		
Number of patients:	Planned: 87	Randomized: NA	Treated: 85
Evaluated:	Included/ITT: 87	Safety: 85	

Diagnosis and criteria for inclusion:	• Informed consent signed
	• Patient ≥ 18 years
	• Histopathological proven adenocarcinoma of the rectum (tumor ≤ 12 cm from the anal verge)
	• No evidence of distant spread
	• No prior chemotherapy or radiation therapy for rectal cancer
	• Patient considered locally advanced by MRI
	  o Tumor beyond mesorectal fascia, or
	  o Tumor ≤2 mm from mesorectal fascia, or
	  o T3 tumor < 5 cm from the anal verge
	• ECOG PS ≤ 2
	• No peripheral neuropathy > grade 1
	• No uncontrolled diarrhea or fecal incontinence
	• No significant small bowel (> 200c or 6x6x6 cm) delineated with the radiation field
	• ANC > 1500 x 10^9/L, platelets > 100 x 10^9/L, creatinine < 1.5xIULN, bilirubin < 1.25 IULN, SGPT (ALT) < 2.5 IULN
	• No other serious uncontrolled illness
	• Female patient of childbearing potential, neither pregnant nor breastfeeding and under active contraception

Investigational product: Oxaliplatin Dose/Administration	Treatment plan: 1. Pre-operative chemoradiation therapy (XELOX-RT) Oxaliplatin 50 mg/m^2 administered weekly, for 5 weeks, as a 2-hour IV infusion combined with capecitabine 825 mg/ m^2 PO administered twice daily x 5 days x 5 weeks and Radiotherapy 1.8 Gy/fraction x 5 days (total radiation dose 45 Gy) x 5 weeks, then 2. Total Mesorectal Excision (TME) in resectable patients followed by 3. Post-operative XELOX chemotherapy for patients achieving histopathological R0/R1 resection; one cycle consisting of oxaliplatin 130 mg/ m^2 given as a 2-hour IV infusion on Day 1; capecitabine 825 mg/ m^2 administered PO twice daily from Day to Day 14 of each 21-day cycle of therapy; 6 cycles
Reference therapy:	No reference therapy
Criteria for evaluation: Efficacy:	Primary endpoint: Pathological complete response (ypT0N0) rate *(Investigator and central review data)* Secondary endpoints: • Histopathological R0 rate = rate of patients having a minimum distance of tumor of CRM of > 1 mm (Investigator's data) • Down-staging rate *(Investigator and central review data)* • Surgical complications • Local recurrence/distant recurrence date • Survival (progression-free and overall)
Safety:	NCI-CTC version 2 for adverse events/Standard hematology and blood chemistry

Duration of treatment: • Preoperative XELOX-RT: Oxaliplatin 50 mg/m^2: weekly x 5 doses Capecitabine 825 mg/ m^2: 5 days/week x 5 weeks Radiotherapy: daily dose fraction 1.8 Gy x 5 days x 5 weeks • Postoperative XELOX adjuvant chemotherapy: Cycle length: 21 days, 6 cycles planned Oxaliplatin: 130 mg/ m^2 on Day 1 Capecitabine: 825 mg/ m^2 bid day x 2 weeks	Duration of observation: Follow-up observation continued until death or until 24 months after the last patient completed study.
Statistical methods:	Study treatment was to be accepted or rejected for further study based on the results showing the treatment to be active or insufficiently active. The inactivity cut-off equal to 25%; hence the hypotheses of interest H0: r ≤ 10 % against HA: r ≥ 25 % where r is the pathological complete response rate (yp T0N0). Primary efficacy analysis was performed on the ITT population using descriptive statistics. Patients not undergoing TME surgery or without an evaluable pathological specimen are considered as non-responders in the calculation of pathological complete response and pathological down-staging. Supportive analysis for the primary endpoint was repeated on the Per Protocol (PP) population. Investigator and central review data were analyzed separately for both ITT/PP populations. The 2 PP populations were: The Expert PP population - all subjects who fulfill all inclusion and exclusion criteria according to the expert radiologist and who receive within 80 % of the recommended dose of XELOX-RT, who undergo TME as protocol defined, and have a pathology assessment available for the central review. The Investigator PP population - all subjects who fulfill all inclusion and exclusion criteria according to the site radiologist and who receive within 80 % of the recommended dose of XELOX-RT, who undergo TME as protocol defined, and have a pathology assessment available for the investigator site review. Treat 70 evaluable patients: • Declare XELOX-RT insufficiently active if 11 pathological complete responses or less are observed. • Declare XELOX-RT active if 12 or more are observed (observed response rate of 17 %). The error rate of the first type (α probability of accepting and insufficiently active treatment, a false positive outcome) was set to 0.05 (i.e. a 5 % or less chance of accepting as interesting for further research a regimen with a true underlying pathological complete response rate of no more than 10 %). The error rate of the second type (β probability of rejecting an active treatment, a false negative outcome) was set to 5 % (i.e. a power of 95 % not to reject a regimen with a true underlying pathological complete response rate of at least 25 %). Secondary efficacy analyses were carried out on the ITT population. Survival curves at 1 year, 2 years and 3 years were estimated according the Kaplan-Meier method. Correlation of outcome with clinical and pathological variables was not evaluated using the Cox proportional hazard model as planned due to the relatively limited sample size.

Summary:	A total of 87 patients were enrolled. Of these, 2 were not exposed to treatment and 6 were withdrawn during the preoperative XELOX-RT phase including one patient who died during surgery. Hence, surgery was completed for 79 patients including 77 TME. 30 patients were withdrawn after surgery (14 for general deterioration, 4 for rectal abcess, 3 for toxicity, 3 for disease progression, 2 for refusal, 2 for misclassified R2, 1 for complete remission and 1 for death). In addition to preoperative chemoradiation, 49 patients received postoperative chemotherapy and 36 patients completed the full treatment. ITT population: mean age was 61.2 years (35-82). Sex ratio (male:female) was 61:26. Fifty-six patients (64.4 %) had low rectal cancer, 25 (28.7 %) had medium and 6 (6.9 %) had upper rectal cancer. MRI staging at baseline (Central Review): 11 patients were assessed as being T2 at baseline; 62 patients were T3 and 8 patients were T4; data was missing or uninformative in 6 patients.
Efficacy results:	Primary endpoint was analyzed on ITT population. 10.3 % (9 patients, 0.95 % CI, 3.94-16.74 %) as per Expert review and 11.5. % (10 patients, 95% CI, 5.48-20.5 %) as per investigator assessment showed a pathological complete response (ypT0N0). Secondary endpoints: • The histopathological R0 rate (CRM negative) was 74.7% (Investigator's data). • Down-staging rate was 46.0 % according to investigator data (TNM) and 22.7% according to central review data (T value only). • Twenty-two patients (27.8 %) were reported to have one-month surgical complications. The most common postoperative complications were diarrhea, intestinal obstruction, peritonitis and small intestinal obstruction. • The MRI accuracy in depicting T staging compared to histopathological results was 57.6% and 58.7% according to investigator's data and central review, respectively. MRI accuracy of predicting the likelihood of an R0 resection was 65.8 % for investigator population and 61.7 % for expert population, respectively. • The incidence of local recurrence was 5.7 % and the incidence of distant recurrence 27.5 % (ITT population). • With a median follow-up of 34.6 months, Progression Free Survival rate at 1 year was 74.4%, 2 years 62.8% and 3 years 55.3% (the median PFS was not reached). Overall survival rates for 1, 2 and 3 years were 86%, 81.4%, 75.3% respectively (the median OS was not reached).

Safety results:	For preoperative treatment, the median relative dose intensity of oxaliplatin and capecitabine were 100.0% and 97.1% respectively. The median cumulative dose of radiotherapy of 45.0 Gy (min. 36, max 49). Forty-nine patients received postoperative adjuvant chemotherapy with a median relative dose intensity of 97.0% and 94.7% for oxaliplatin and capecitabine respectively. The most frequent side effects (all grades) during the preoperative phase (XELOX-RT) were diarrhea (58.8%), peripheral sensory neuropathies (35.3%) with dysgeusia (1.2%) and paresthesia (1.2%), pain (35.3%) and fatigue (31.8%). Decreased hemoglobin occurred in 25.9% of patients, thrombocytopenia in 24.7% and neutropenia in 11.8%. Hypersensitivity reactions were reported in 8 patients (9.4%) and were generally reversible. The most common acute grade 3 toxicity was diarrhea (15.3%). In the postoperative phase, anemia occurred in 44.9% and neutropenia was observed in 51.0% of patients (all grades). Thrombocytopenia occurred in 38.8% of patients. Mild to moderate elevation of transaminases (ALAT) was reported in 18.4% of patients. The most frequent grade 3 toxicities were sensory neuropathy (8.2%), diarrhea (6.1%), fatigue (6.1%) and neutropenia (6.1%). Overall, treatment related serious adverse events occurred in 32 patients (37.6%), leading to treatment withdrawal in 12 patients (14.1%). Twenty-one deaths were reported during the study: 1 prior to treatment exposure, 5 during the treatment period (3 during preoperative phase and 2 during postoperative treatment) and 15 during follow-up more than 30 days after last study treatment. Two death cases were considered as possibly related to study treatment by the Sponsor although the investigator had ruled out a causal relationship: one patient died while playing squash during cycle 4 of adjuvant therapy. This patient had a history of cerebral bleeding. Another patient died at home for an unknown etiology during cycle 1 of adjuvant therapy. This patient had a history of coronary artery disease.
Date of report:	15 June 2009