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	ClinialTrials.gov Identifier: NCT00160030 Study Code: L_9326 Date: 24-Oct-2008

Title of the study:	Phase II-III Study Comparing Radiochemotherapy with the FOLFOX-4 Regimen versus Radiochemotherapy with 5-FU-cisplatin (Herskovic Regimen) in First Line Treatment of Patients with Inoperable Oesophageal Cancer.
Investigator:	Coordinating investigator: Professor Thierry Conroy, Centre Alexis Vautrin, 6 Avenue de Bourgogne, 54511 Vandoevere Les Nancy
Study centres:	21 active centres, France
Publications (reference):	Conroy et al (2007)
Study period: Date first patient enrolled: 15-Oct-2004 Date last patient completed: 25-Oct-2007	Phase of development: Phase II
Objectives:	Primary: • To assess the feasibility (completion of full treatment) of combination chemotherapy containing oxaliplatin, 5-fluorouracil (5-FU) and folinic acid (FOLFOX-4 regimen) or 5-FU/cisplatin (Herskovic regimen) with concomitant radiotherapy in first line treatment of inoperable advanced oesophageal cancer. • To assess endoscopic complete response (CR) rate in both arms. Secondary: • To assess the toxicity profile of each arm using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. • To evaluate the quality of life using EORTC (European Organisation for Research and Treatment of Cancer) quality of life questionnaire (QLQ) -C30 (version 3) and a validated disease- specific module EORTC QLQ-OES 18 (results were to be analysed during phase III part of the study only, so the results are not reported here).
Methodology:	Multicentre, randomised, open-label, parallel group design phase II study. The phase III study is sponsored by «la Fédération Nationale des Centres de Lutte Contre le Cancer.»

Number of patients:	Planned: 88 patients to be enrolled to provide 80 evaluable patients 40 in each arm)	Randomised: 97 patients (53 in Treatment Arm A [Folfox-4], 44 in Treatment Arm B [Herskovic])	Treated: 95 patients (52 in Treatment Arm A, 43 in Treatment Arm B)
Evaluated:	ITT population N = 53 Eligible population N = 51 Tumour response evaluable population N = 47 PP population N = 46	Safety: N = 52	
Diagnosis and Main criteria for inclusion:	Patients aged ≥ 18 years with histologically proven adenocarcinoma, squamous cell or adenosquamous carcinoma of the oesophagus; inoperable and locally advanced (any tumour stage, N0 or N1, M0 or M1a); no prior treatment (surgery, chemo- or radiotherapy) received for oesophageal cancer.		
Investigational product: Dose: Administration:	FOLFOX-4 regimen (oxaliplatin, folinic acid, 5-FU), concomitant with 5 weeks' radiotherapy (Treatment Arm A) 85 mg/m^2 oxaliplatin, 200 mg folinic acid, 400 mg and 600 mg 5-FU Six 2-weekly cycles of FOLFOX-4; oxaliplatin administered as 2-hour infusion on Day 1 of each cycle, folinic acid administered as separate 2-hour infusion on Days 1 and 2 of each cycle, followed by 400 mg intravenous (IV) bolus 5-FU on Days 1 and 2 of each cycle then 600 mg 5-FU continuous IV infusion on Days 1 and 2 of each cycle.		
Duration of treatment: Arm A: 12 weeks per patient Arm B: 11 weeks per patient	Duration of observation: If feasible, post-treatment follow-up was pursued until patient's death.		
Reference therapy: Dose: Administration: Radiotherapy:	Herskovic regimen (cisplatin and 5-FU) concomitant with 5-weeks' radiotherapy (Treatment Arm B): 2 cycles of 5-FU/Cisplatin on Weeks 1 and 5 of radiotherapy, and 2 cycles on Weeks 8 and 11. 75 mg/m^2 cisplatin and 1000 mg/m^2 5-FU/day Continuous cisplatin infusion (1 mg/minute) on Day 1 of each cycle followed by continuous 5-FU infusion 1000 mg/m^2/ day from Days 1 to 4 of each cycle. 2 Gray (Gy) per fraction, 5 fractions per week, during 5 weeks to achieve a total dose of 50 Gy during the study (maximum dose to the spinal cord of 40 Gy).		
Criteria for evaluation: Efficacy:	Percentage of endoscopic CR in the 2 treatment arms.		
Safety:	Primary endpoint: the percentage of patients who completed full treatment in the 2 arms. Secondary endpoints: description of the safety profile of each arm using the NCI-CTC scale. Target variables: • Laboratory and adverse event (AE) toxicities • Serious adverse events (SAEs) • Treatment withdrawals		
Statistical methods:	Continuous data were described using the number of observations (N), mean (mean), standard deviation (std), minimum (min), median (median), and maximum (max). Categorical data were described using the N and frequencies (%) with percentages based on the total population. Descriptive analyses were summarised by treatment arm and overall only for the presentation of baseline characteristics. The Chi-square test was used to compare proportions (replaced by Fisher's exact test if the expected frequency in any one of the cells of the contingency table was <5). The 95% confidence interval (CI) for proportions was calculated using the exact Clopper-Pearson method. Exploratory Analysis: The Kaplan-Meier method was used to analyze survival data and estimate the median survival time. The 95% CI for the median survival time was calculated using the Brookmeyer and Crowley method. Hazard ratios and their 95% CIs were estimated from Cox proportional hazards models adjusted for the		

	stratification factor used in the randomisation (investigator centre and histology type).
Summary:	The median age was 59 years in Treatment Arm A and 58 years in Treatment Arm B. Approximately 85% of patients were male in both treatment arms. The 2 treatment arms were generally similar with respect to demographic and baseline characteristics, although slightly more patients in Treatment Arm A had an ECOG PS of 0 at baseline than in Treatment Arm B. Most patients (approximately 80% in both treatment arms) had oesophageal squamous cell carcinoma. The most frequently reported TNM classifications at baseline were Stage III T3/N1/M0 and Stage IIA T3/N0/M0. The most frequently reported location of the primary tumour was the middle thoracic. The majority of patients had not had cancer previously. The majority of patients in both treatment arms had 1 or 2 index lesions. All patients reported the oesophagus as the location of known deposits. Almost half of all patients also reported lymph nodes as the location of known deposits. The most frequently reported procedures for the evaluation of target lesions were CT scans and endoscopy.
Efficacy results:	Analysis of the primary endpoint, complete endoscopic response between the 2 treatment arms assessed by the IDMC, showed that more patients who received the FOLFOX-4 regimen reported a CR than patients who received the Herskovic regimen (44.7% versus 29.3%) but the difference was not statistically significant (p = 0.136). There were no notable differences between the 2 treatment regimens with respect to the number of patients who had an overall response of CR; however, more patients who received FOLFOX-4 reported an overall response of PR than patients who received the Herskovic regimen (36.2% versus 24.4%). There were no secondary efficacy variables but exploratory analyses were performed, the results of which showed a non-statistically significant treatment advantage for patients who received FOLFOX-4 compared with those who received the Herskovic regimen. There was no notable difference in the number of observed events for event free survival between the 2 treatment regimens but event free survival rates were slightly higher for patients who received FOLFOX-4 than those who received the Herskovic regimen at up to 3, 6 and 9 months. There were fewer deaths in patients who received FOLFOX-4 than those who received the Herskovic regimen (23 patients [43.4%] versus 27 patients [61.4%]) and median survival time was greater for patients who received FOLFOX-4 (22.7 months and 15.1 months, respectively, hazard ratio: 1.76), although the difference was not statistically significant. Survival rates appeared greater in patients who received FOLFOX-4 than those who received the Herskovic regimen at each time point measured. The time to treatment failure was slightly greater for patients who received FOLFOX-4 than for those who received the Herskovic regimen (8.1 months versus 7.2 months; hazard ratio: 1.18). There were no notable differences in treatment failure-free rates between the 2 treatment arms at any of the time points measured. The median time to progression was greater for patients who received FOLFOX-4 than those who received the Herskovic regimen (15.2 months versus 9.2 months) and progression free rates also appeared greater for patients who received FOLFOX-4 at all time points measured. Secondary analyses performed using the ITT and PP populations were supportive of the results obtained for the primary analyses.

Safety results:	The safety findings in this study were consistent with the known safety profiles of the components of the FOLFOX-4 and Herskovic regimens. The primary safety endpoint was the percentage of patients who completed the full treatment in the 2 arms. Almost all patients (>95%) in both treatment arms in the ITT population completed radiotherapy and approximately 90% of patients completed the first sequence of chemotherapy with concomitant chemoradiotherapy (88.7% of patients who received FOLFOX 4 and 93.2% of those who received the Herskovic regimen). Slightly more patients of patients who received FOLFOX 4 than those who received the Herskovic regimen completed treatment (73.6% and 65.9%, respectively). Approximately 75% of patients in Treatment Arm A and 70% of patients in Treatment Arm B completed the required number of chemotherapy cycles (6 cycles for patients who received FOLFOX 4 and 4 cycles for those who received the Herskovic regimen). Almost all patients (> 97%) in both treatment arms completed at least 5 weeks of radiotherapy. There was no notable difference between the treatment arms with respect to the mean radiotherapy dose received (49.585 Gy for patients who received the FOLFOX-4 regimen and 49.163 Gy for the Herskovic regimen). There were no notable differences between the treatment arms with respect to reductions in chemotherapy dose. All patients in both treatment arms reported at least 1 TEAE and almost all reported a treatment related TEAE (98.1% of patients who received FOLFOX-4 and 95.3% who received the Herskovic regimen). The most frequently reported TEAEs by body system were gastrointestinal disorders (92.3% of patients who received FOLFOX-4 and 93.0% who received the Herskovic regimen) and general disorders and administration site conditions (78.8% and 72.1%, respectively). The 2 treatment arms were generally similar with respect to the incidence of TEAEs, except for nervous system disorders and vascular disorders, which were reported by twice as many patients who received FOLFOX-4 than the Herskovic regimen (65.4% versus 30.2% for nervous system disorders and 21.2% versus 9.3% for vascular disorders, respectively). The most frequently reported TEAEs by preferred term were nausea (57.7% of patients who received FOLFOX-4 and 58.1% who received the Herskovic regimen), decreased weight (50.0% and 39.5%, respectively) and dysphagia (50.0% and 26.5%, respectively). Although the 2 treatment arms were similar with respect to the incidence of many TEAEs, more patients who received FOLFOX-4 reported paraesthesia, dysphagia, decreased weight, odynophagia and abdominal pain upper than those who received the Herskovic regimen and anaemia, vomiting, alopecia, epistaxis and insomnia were reported by more patients who received the Herskovic regimen. The most frequently reported treatment related AEs were nausea (51.9% of patients who received FOLFOX-4 and 58.1% who received the Herskovic regimen), and neutropenia (32.7% and 25.6%, respectively). The incidence of treatment-related AEs was generally similar, although treatment-related paraesthesia occurred in more patients who received FOLFOX-4 than the Herskovic regimen (46.2% versus 4.7%). A total of 39 patients (75.0%) who received FOLFOX-4 and 31 patients (72.1%) ho received the Herskovic regimen reported TEAEs that were toxicity grade 3 or 4. The most frequently reported grade 3 or 4 TEAEs were neutropenia (23.1% and 20.9%, respectively) and dysphagia (32.7% and 23.3%, respectively). The incidence of grade 3 and 4 TEAEs was generally similar between the 2 treatment arms.

	A total of 5 patients (9.6%) who received FOLFOX-4 and 4 patients (9.3%) who received the Herskovic regimen died during the study. In patients who received FOLFOX-4, Patient 5 died due to both PD and an AE of arterial haemorrhage, Patient 44 died of AEs of denutrition and right pneumopathy (lung disorder), Patient 74 committed suicide, Patient 83 died of AEs of abdominal pain and dyspnoea and Patient 88 experienced sudden death. For patients who received the Herskovic regimen, Patient 15 died of AEs of pulmonary infection with grade 4 neutropenia, dehydration and stroke, Patient 47 died of AEs of anaemia, pantocytopenia and thrombocytopenia, Patient 81 died of cardiac ischaemia and Patient 87 died of an AE of infection with neutropenia. Four deaths were considered to be related to treatment with study medication, of which just one death occurred in patients who received FOLFOX-4 (Patient 5 who received FOLFOX-4 and Patients 15, 47 and 87 who received the Herskovic regimen). A further 18 patients (34.6%) who received FOLFOX-4 and 22 patients (51.2%) who received the Herskovic regimen died during follow-up. SAEs were reported by 61.5% of patients who received FOLFOX-4 and 55.8% of patients who received the Herskovic regimen. The most frequently reported SAEs were dysphagia (23.1% and 11.6%, respectively) and febrile neutropenia (7.7% and 7.0%, respectively). There were no notable differences between the treatment arms with respect to the incidence of SAEs, except that dysphagia occurred in more patients who received FOLFOX-4. A total of 34.6% of patients who received FOLFOX-4 and 44.2% of those who received the Herskovic regimen reported SAEs that were considered to be related to treatment with study medication. The most frequently reported treatment-related SAEs were again dysphagia and febrile neutropenia. Most other treatment-related SAEs were reported by no more than 1 patient per treatment arm. The 2 treatment groups were generally similar with respect to the incidence of treatment-related SAEs, except for dysphagia, which was reported by more patients who received FOLFOX-4. A total of 13 patients (25.0%) who received FOLFOX-4 and 13 patients (30.2%) who received the Herskovic regimen permanently discontinued study medication because of an AE. Ten patients in Treatment Arm A and 8 patients in Treatment Arm B had TEAEs leading to permanent discontinuation of study medication that were considered to be related to treatment with study medication. The AEs that most frequently caused permanent discontinuation were thrombocytopenia (5.8% and 7.0%, respectively) and dysphagia (7.7% of patients who received FOLFOX-4 only). Almost all (> 97%) patients in both treatment arms reported haematology toxicities; however, the majority of toxicities were grades 0, 1 or 2. The most frequently reported grade 3 or 4 haematology toxicities were for leucocytes (40.4% of patients who received FOLFOX-4 and 30.2% who received the Herskovic regimen) and neutrophils (40.4% and 39.5%, respectively). The incidence of grade 3 and 4 toxicities was similar between the 2 treatment arms. Almost all patients (> 97%) reported blood chemistry toxicities but no grade 3 or 4 toxicities were reported in either treatment arm. Almost all patients (≥ 93%) in both treatment arms reported NCI CTC blood ionogram toxicities. The most frequently reported grade 3 or 4 toxicities were low sodium (19.2% of patients who received FOLFOX-4 and 9.3% who received the Herskovic regimen) and low potassium (9.6% and 11.6%, respectively). Almost all patients' PS remained ≤ 2 throughout the study. Changes in weight during the study were generally small (<5%) and there were no notable differences between the treatment arms with respect to changes in weight (either loss or gain) during the study.
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