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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NCT00174564**
		Study Code:	**C_8552**
Generic drug name:	**Oxaliplatin**	**Date:**	**10 December 07**

Title of the study:	A multicentre phase II trial of gemcitabine and oxaliplatin (GEMOX) in patients with biliary tract cancer N°C-8552		
Investigator(s):	Coordinating investigator: Thierry André, Hopital Tenon, Paris, FRANCE		
Study center(s):	7 active sites in 5 countries: France (2), Germany (2), Austria (1), Chile (1), United Kingdom (1).		
Publications (reference):	ASCO 2006, Poster 4135		
Study period: Date first subject/patient enrolled: 14/04/2003 Date last subject/patient completed: 30/09/2006		**Phase of development:** II Exploratory	
Objectives:	Primary objective: to evaluate the efficacy of the GEMOX treatment as 1rst line therapy in patients with advanced biliary tract cancer based on response rate measured by the RECIST unidimentional criteria. Secondary objectives: progression-free survival, overall survival and safety.		
Methodology:	This was a multicentre phase II , one armed study of gemcitabine and oxaliplatin (GEMOX) in the treatment of biliary tract cancer		
Number of patients:	Planned: 70	Treated: 67	
Evaluated:	ITT: 70	Safety:67	

Diagnosis and eligibility criteria :	- Informed consent - Histologically proven, locally advanced or metastatic carcinoma of the biliary tract (gallbladder, intrahepatic bile ducts, extrahepatic bile ducts, ampula of Vater) In case of intrahepatic bile duct carcinoma, if biliary tract origin was not evident by imaging or surgical exploration, and so equivalent to liver metastasis with unknown primary site, inclusion was possible if: ➢ Unknown primary site after exhaustive search ➢ Hystological examination compatible with adenocarcinoma of bile ducts with the immunostaining expression of cytokeratin: 7+, 20- and 19+ - No prior chemotherapy for advanced disease (first line) - Unidimensionally measurable disease - Age> 18 years - For female patients of child bearing potential, neither pregnant nor breast feeding, and under active contraception - ECOG PS<=2 - ANC >1.5 x 10^9/l, platelets >100 x 10^9/l, creatinine < 1.5 x ULN, SGPT (ALT) < 5x ULN - Bilirubin < 2.5 x ULN; patients with jaundice or evidence of bile duct obstruction and in whom the biliary tree could be decompressed by endoscopic percutaneous endoprothesis, with subsequent reduction in bilirubin < 2.5 x ULN were eligible for the study. - No CNS metastases - No prior malignancy - No peripheral neuropathy grade ≥2 - No known allergy to one of the study treatments - No radiation therapy within 4 weeks prior to first Gemcitabine administration (Amendment 1)
Investigational product:	GEMOX
Dose/Administration:	Gemcitabine 1000 mg/m² on Day 1 and Oxaliplatin 100 mg/m² on Day 2 of each 14-day cycle
Duration of treatment: until death, progression or unacceptable toxicity, patient refusal.	**Duration of observation:** from date of informed consent to study completion
Reference therapy:	No reference therapy
Criteria for evaluation:	
Efficacy:	Primary efficacy endpoint: response rate as assessed by RECIST criteria (one dimension) Secondary efficacy endpoints: progression free survival, overall survival
Safety:	Hematological toxicity, non—hematological toxicity
Statistical methods:	Efficacy analysis: Intention-to-treat analysis using descriptive statistics. Efficacy data were also analyzed on the exposed population. Kaplan Meier curves were computed for survival analyses. Patients with missing data were viewed as non-responders. Safety analysis: descriptive statistics based on the exposed population

Summary:	This was a phase II one-armed, open label study designed to evaluate the efficacy and safety of a combination of oxaliplatin and gemcitabine (GEMOX) as first-line treatment of locally advanced or metastatic biliary tract carcinoma. Seventy patients were enrolled into the study (ITT population) and 67 patients received at least one treatment administration (EXP population). Patients were evaluated for efficacy after completion of cycle 4 and then every 4 cycles on therapy and every 3 months during follow-up for patients going off treatment due to any reason but progressive disease. Exposed population: median age was 62 years (30-83). Sex ratio (male: female) was 27:40. The site of primary tumour was intrahepatic bile ducts in 29 (43.3%) patients, gallbladder in 23 (34.3%) patients, extrahepatic bile ducts in 13 (19.4%) patients, Ampula of Vater in 1 (1.5%) patient and both intra and extra-hepatic bile ducts in 1 (1.5%) patient. Of the 67 exposed patients, 73.1% had metastatic disease and 26.9% had locally advanced BTC. Thirty seven patients (37/67) had undergone abdominal surgery prior to study initiation. All patients were chemo-naïve. Most patients (85.1%) had started GEMOX within 6 months of first diagnosis.
Efficacy results on the EXP Population:	RECIST-1: Of the 67 exposed patients, 10 patients (14.9%) achieved a confirmed partial response (95% [CI] 7.4-25.7). Stable disease was observed in 24 patients (35.8%) and progressive disease in 27 patients (40.3%). Progressive disease was inferred for 6 additional patients (9.0%) who were not assessable due to early study withdrawal as a result of S(AEs). There were no complete responses. The partial and stable disease response rates were notably higher in patients with non-gallbladder carcinoma: the RR in the subgroup populations of gallbladder and non-gallbladder carcinoma was 4.3 % and 20.5 %, respectively. Median time to disease progression was 3.4 months, (95% [CI] 2.5-4.6) and median time to death was 9.3 months (95% [CI]: 6.9-11.4). Exploratory subgroup time to event analyses revealed that gallbladder carcinoma seemed to be associated with a much shorter time to recurrence (median PFS: 2.5 vs 3.8 months) and a shorter survival period (median OS: 6.1 vs 11.0 months).
Safety results:	Gastrointestinal disorders affected 86.6% of patients. Hematological toxicity was frequently reported but generally moderate; anemia and thrombocytopenia occurred in 77.6% and 68.7% of patients, respectively. Neutropenia was observed in 38.8% of patients. Other common adverse events included fatigue (73.1%), peripheral sensory neuropathy (67.2%), liver enzyme increase (59.7%) and weight loss (59.7%). Infection was observed in 14 cases and neutropenic infection in 2 cases. Febrile neutropenia occurred in one patient. Overall, (CTC) Grade 3-4 toxicities occurred in 47 patients (70.1%); Most common Grade 3 toxicities were (% of pts) thrombocytopenia (13.4%), liver enzyme increase (11.9%), pain (11.9%) and vomiting (10.4%). Most common grade 4 toxicities were neutropenia (4.5%) and anemia (3.0%). Grade 3 neuropathy was seen in 6.0% of patients. There were no grade 4 neuropathies. According to the sponsor, 3 death cases may have possibly resulted from treatment toxicity.
Date of report:	July 11, 2007