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Sponsor / Company: Sanofi **Drug substance:** Oxaliplatin	**Study Identifiers:** NCT01121848, UTN U1111-1116-9746 **Study code:** OXALI_L_04918
Title of the study: A randomized Phase III study of 5-fluorouracil-based regimen with or without oxaliplatin as second-line treatment of advanced or metastatic pancreatic cancer in patients who have previously received gemcitabine-based chemotherapy	
Study centers: 15 Canadian centers	
Study period: Date first patient enrolled: 06/Jul/2010 Date last patient completed: 15/Oct/2013	
Phase of development: Phase 3	
Objectives: Primary: To demonstrate that the addition of oxaliplatin to 5-fluorouracil (5-FU) and leucovorin (LV) improves the progression-free survival. Progression was based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria or death. Secondary: To evaluate other measures of tumor responses, safety, quality of life (QOL), and health utility assessment.	
Methodology: This was a Canadian, multi-center, open-label, randomized (1:1), Phase 3 study with two treatment arms (modified FOLFOX-6 versus 5-FU/LV).	
Number of patients: Planned: 128 patients Randomized: 108 (mFOLFOX-6: N=54, 5-FU/LV: N=54) Treated: 102 (mFOLFOX-6: N=49, 5-FU/LV: N=53) **Evaluated:** Efficacy: 108 (mFOLFOX-6: N=54, 5-FU/LV: N=54) Safety: 102 (mFOLFOX-6: N=49, 5-FU/LV: N=53) QOL/health utility: 83 (mFOLFOX-6: N=39, 5-FU/LV: N=44)	
Diagnosis and criteria for inclusion: Patients with locally advanced or metastatic pancreatic carcinoma >18 years of age, previously (at least 2 weeks prior to randomization) given gemcitabine-based chemotherapy (single agent or combination) as first-line therapy, confirmed radiographic disease progression within 4 weeks prior to randomization, adequate liver, kidney and hematological function, and a life expectancy of >3 months.	
Study treatments Investigational medicinal product: Oxaliplatin Formulation: Solution Route of administration: Intravenous (IV) Dose regimen: Day 1: oxaliplatin (85 mg/m^2) with LV (400 mg/m^2) given as 2-hour infusion followed by 5-FU bolus (400 mg/m^2) followed by continuous infusion for 46 hours (2400 mg/m^2). This chemotherapy regimen was administered every 2 weeks.	

Noninvestigational medicinal product: 5-FU, LV

Formulation: Solution

Route of administration: IV

Dose regimen: Day 1: LV 400 mg/m^2 given as a 2-hour infusion, Day 1 and 2: 5-FU given as a bolus IV 400 mg/m^2 dose on Day 1 followed by 2400 mg/m^2 continuous infusion over 46 hours. This chemotherapy regimen was administered every 2 weeks.

Duration of treatment: 3 months (average)

Duration of observation: 7 months (average)

Criteria for evaluation:

Efficacy: The primary outcome variable was progression based on RECIST criteria or death taking into account when the progression took place. Secondary endpoints were overall response rate (ORR), duration of response, disease controlled rate (DCR), median overall survival (OS), dose reduction, dose delays, dose discontinuation, and relative dose intensity.

Safety: Adverse events (AEs) reported by the patients or noted by the Investigator, standard hematology and blood chemistry, Grade 3 or 4 toxicities according to National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE), vital signs.

QOL and health utility assessed via patient-completed questionnaires.

Statistical methods:

The primary efficacy endpoint was analyzed in the intent-to-treat (ITT) population defined as all randomized patients. The primary analysis was based on the comparison of the Kaplan-Meier curves for progression-free survival (PFS) using the log-rank statistic. With 64 patients in each arm there was an 80% chance of detecting a 25% absolute improvement at approximately 12 weeks in the percentage of patients with progression when the percentage of patients with progression in the comparator arm was approximately 72.5% based on a log-rank statistic and a two-sided type 1 error rate of 0.05. If superiority of the experimental arm was proven then this supported an improvement in the time of median PFS observed in this study. Percentages of patients with ORR and DCR were compared using a Cochran-Mantel-Haenszel procedure controlling for pooled site. The analysis for OS was similar to that for the primary efficacy variable.

Summary:

Population characteristics: The planned enrollment was 128 patients. However, due to slow accrual, the study was terminated prematurely. As a consequence, 119 patients were screened, 108 were randomized, and 102 received at least one dose of study medication (mFOLFOX-6: N=49, 5-FU/LV: N=53). Patients' median age was 65 years (range 38 to 82 years), most of them (56.5%) were male, and the vast majority of patients (94 out of 108 patients) were white. Patients were well balanced between treatment groups with regard to previous chemotherapy. The most common reason for study termination in the total population was disease progression (62.0%, 67 out of 108 patients, ITT).

Efficacy results: No difference was found between the two treatment groups for PFS (p=0.8283). The median time to disease progression was 3.0 months in the mFOLFOX-6 group and 2.8 months in the 5-FU/LV group. By the end of treatment, 87.0% and 90.7% of the patients treated with mFOLFOX-6 and 5-FU/LV, respectively, had progressed (hazard ratio 0.96, 95%CI 0.64 to 1.44, p=0.8387).

Similar ORRs were found in the two treatment groups with 5 patients (13.2%) in the mFOLFOX-6 group and 4 patients (8.5%) in the 5-FU/LV group (p=0.5378). The median duration of response was 8.7 months in the mFOLFOX-6 group and 8.1 months in the 5-FU/LV group. DCR at the end of treatment was 22 patients (57.9%) in the mFOLFOX-6 group and 30 patients (63.8%) in the 5 FU/LV group (p=0.5240). OS was statistically significantly inferior (p=0.0355) in patients receiving mFOLFOX-6 (median 6.0 months) compared to patients receiving 5-FU/LV (9.8 months). A statistically significant treatment-by-subgroup interaction for median PFS and median OS was seen in the age pre-specified subgroups.

The time to first occurrence of dose reduction and dose delay was statistically significantly shorter in patients receiving mFOLFOX-6 compared to patients receiving 5-FU/LV. Dose reductions and delays were reported for more patients in the mFOLFOX-6 group than in the 5-FU/LV group. There were no statistically significant differences between treatments with regard to the number of patients who permanently discontinued chemotherapy as well as for the time to dose discontinuation. More patients on 5-FU/LV than on mFOLFOX 6 received subsequent therapy (p=0.0238).

Patients' QOL-measured using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep), EuroQol_Five dimension (EQ-5D), and European Organization for Research and Treatment of Cancer (EORTC) questionnaires-deteriorated over the course of the study, with patients in the mFOLFOX-6 group deteriorating more than patients in the 5-FU/LV group. At the end of treatment, the differences between groups were statistically significant for the change from baseline in the FACT-Hep total score (p=0.0127), the FACT-G total score (p=0.0120), the HepCS score (p=0.0361), the EQ-5D VAS (p=0.0061), and the EORTC physical functioning score (p=0.0107). Patients in the mFOLFOX-6 group reported higher levels of neurotoxicity (measured using the FACT/GOG NTX-12 questionnaire) compared to patients in the 5-FU/LV group. The differences between groups for the change from baseline were statistically significant at Cycle 12 (p=0.0034), Cycle 18 (p=0.0189), and at the end of treatment (p=0.0001).

Safety results: Forty-eight (48) of 49 patients (98.0%) receiving mFOLFOX-6 experienced treatment-emergent adverse events (TEAEs) and 52 of 53 patients (98.1%) receiving 5-FU/LV experienced TEAEs. More patients in the mFOLFOX-6 group (27 patients; 55.1%) than in the 5 FU/LV group (10 patients; 18.9%) reported treatment-emergent serious adverse events (SAEs). The percentage of patients who discontinued the study due to TEAEs was higher in the mFOLFOX-6 group (16 of 49 patients; 32.7%) than in the 5-FU/LV group (3 of 53 patients; 5.7%). TEAEs leading to death occurred in 11 patients (22.4%) in the mFOLFOX-6 group and 1 patient (1.9%) in the 5-FU/LV group. TEAEs of Grade 3, 4 or 5 were reported in more patients treated with mFOLFOX-6 (43 of 49 patients; 87.8%) than in patients treated with 5-FU/LV (23 of 53 patients; 43.4%).

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