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Sponsor / Company: sanofi-aventis **Drug substance(s):** Larotaxel (XRP9881)	**Study Identifier:** NCT00417209 **Study code:** EFC6596
Title of the study: A Randomized, Open Label Multi-Center Study of Single Agent Larotaxel (XRP9881) Compared to Continuous Administration of 5-FU For The Treatment of Patients With Advanced Pancreatic Cancer Previously Treated With A Gemcitabine-Containing Regimen (EFC6596 – PAPRIKA).	
Study center(s): 105 centers worldwide (except Japan) in 21 countries.	
Study period: Date first patient enrolled: 26 December 2006 Date last patient completed: 21 November 2009	
Phase of development: Phase 3	
Objectives: Primary objective: To demonstrate a statistically significant increase in overall survival (OS) for larotaxel relative to the control group (continuous administration of 5-Fluorouracil (5-FU), either by intravenous [IV] or oral route) in patients with advanced pancreatic cancer (APC) (non operable in a curative intent, locally advanced, or metastatic) previously treated with a gemcitabine-based therapy. Secondary objectives: - To compare between the two treatment groups progression free survival (PFS), overall response rate (ORR) according to response evaluation criteria in solid tumors (RECIST), and clinical benefit, to be assessed by time to symptom worsening (TTSW) and improvement in tumor related symptoms. - To assess the overall safety of the two treatment groups. - To assess the pharmacokinetics (PK) of larotaxel in the patient population (sample size of 50 patients for sparse sampling).	
Methodology: Prospective, multicenter, multinational, open-label, randomized (1:1), parallel group study comparing larotaxel administered at the dose of 75 mg/m² every 3 weeks to a continuous administration of 5-FU every 3 weeks (either IV infusion from Day 1 to Day 4 at the dose of 1000 mg/m²/day, or oral capecitabine from Day 1 to Day 14 at the dose of 1000 mg/m² twice a day), in patients with APC (non operable in a curative intent, locally advanced, or metastatic) previously treated with gemcitabine-based therapy. The study was initiated with the starting dose of larotaxel at the recommended dose of 90 mg/m². On 06 April 2007, the recruitment in the study was paused after the occurrence of 11 serious adverse events (SAEs) in 10 patients treated in the larotaxel arm. An ad-hoc Independent Data Monitoring Committee (IDMC) meeting was held on 09 May 2007 to review the preliminary safety data of the PAPRIKA study from the 30 first patients out of 34 randomized patients. The IDMC recommended decreasing the starting dose of larotaxel to 75 mg/m², patients with pancreatic cancer being more at risk to develop severe toxicity, and recommended excluding the patients with ECOG PS 2 (leading to the deletion of this stratification factor). The trial restarted (first patient on 10 July 2007) with these recommendations that were described in an amendment (Amendment No. 2).	
Number of patients:	Planned: 400 patients (200 patients per treatment arm). Randomized: 408 patients post Amendment No. 2 and 34 patients pre-Amendment No. 2. Treated: 395 patients post Amendment No. 2 and 34 patients pre-Amendment No. 2. Efficacy: 408 patients Safety : 395 patients Pharmacokinetics: Blood samples collection was planned in 50 patients randomized in the larotaxel arm at Cycle 1, but was obtained in 38 patients.

Diagnosis and criteria for inclusion: Patients with cytologically or histologically confirmed evidence of epithelial cancer (adenocarcinoma) of the exocrine pancreas. Patient must have had advanced disease defined as non operable in a curative intent, locally advanced or metastatic disease. Patients must have been previously treated with a systemic gemcitabine-based regimen given as adjuvant chemotherapy (disease free interval must be less than 6 months) or as therapy for advanced disease.

Investigational product: Larotaxel (XRP9881) 40 mg/mL vial.

Dose: 75 mg/m² on Day 1 every 3 weeks.

Administration: 1-hour IV infusion. Patients received IV premedication including dexchlorpheniramine 5 mg or diphenhydramine 25 mg or other antihistamines; dexamethasone 8 mg or equivalent steroid, at least 30 minutes prior to larotaxel administration

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity, investigator's decision to discontinue, or withdrawal of consent.

Duration of observation: Patients were followed for safety up to 30 days after last infusion. Following treatment discontinuation, patients were followed every 6 weeks for disease status until disease progression. Then all patients were to be followed at 6 weeks intervals for survival status until death, lost-to-follow-up, withdrawal of consent, or study completion cut-off, whichever occurred first.

Reference therapy: 5-Fluorouracil (5-FU) vials.

Dose: 1000 mg/m²/day from Day 1 to Day 4 every 3 weeks

Administration: IV infusion

Reference therapy: Capecitabine tablets

Dose: 1000 mg/m² twice a day from Day 1 to Day 14 every 3 weeks.

Administration: Oral.

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was OS defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time was to be censored at the earliest of the last date the patient was known to be alive and the study cut-off date.

Secondary endpoints were PFS, overall response rate as per RECIST criteria, clinical benefit (clinical benefit responder and TTSW), and tumor marker CA 19-9.

Safety: Safety variables included treatment-emergent adverse events (TEAEs), the findings in clinical laboratory tests, including hematology and biochemistry, and the findings on physical examination, including vital signs. Adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Pharmacokinetics: Plasma concentrations of larotaxel were assessed on 38 patients randomized in the larotaxel arm at Cycle 1, using a sparse sampling strategy.

Statistical methods:

Analysis population: Four analysis populations were defined:
Pre-Amendment No. 2 population: All the patients randomized and treated prior to protocol Amendment No. 2. This population was used to describe patients' baseline characteristics, study drug exposure, best overall response, and safety data of the 34 patients randomized prior to Amendment No. 2.

Efficacy populations: Two populations were defined:
Intent-to-treat (ITT) population (primary efficacy population) included all the patients randomized after protocol Amendment No. 2. All analyses using this population were based on the treatment assigned by the interactive voice response system (IVRS).
Evaluable patient population for tumor response included all ITT and treated patients with measurable disease at study entry, without major protocol deviation, and evaluable for response. All analyses using this population were based on the treatment actually received.

Statistical methods (cont'd):

Safety population: All ITT patients who took at least one part of the study drug. All analyses using this population were based on the treatment actually received.
PK population: All treated patients in the larotaxel group with available PK samples.

Efficacy analysis: The primary efficacy analysis was to compare the OS between the two treatments by the log-rank test procedure at the 5% significant level, stratified by stratification factors as specified at the time of randomization: extent of disease (non-metastatic or metastatic) and prior adjuvant chemotherapy (Yes versus No). Overall survival was analyzed using the Kaplan-Meier method and summarized with median and 95% confidence interval (CI) of the median.

Safety analysis: TEAEs were summarized with respect to frequency, incidence, and severity. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system-organ class and preferred term. Tables were presented by grade as well as all grades/grade 3-4.
Summary tables were produced for laboratory parameters by worst NCI grade during the on-treatment period based on number of evaluable patients. The NCI grades for each laboratory variable were derived according to NCI CTCAE, version 3.0. Tables were presented by grade as well as all grades/grade 3-4.

PK analysis: Pharmacokinetic parameters for larotaxel were summarized descriptively by number of observations, mean, standard deviation (SD), coefficient of variation (CV), median, and minimum and maximum.

Summary:

Efficacy results: The OS was similar between treatment arms with a hazard ratio 1.05 (95% CI: 0.84 to 1.30) (median in months: 5.06 in the 5-FU arm and 4.80 in the larotaxel arm). The stratified p-value was 0.69. Almost all sub-group OS analyses were consistent with the primary analysis. Similar results were observed for PFS.

Safety results: The most frequent (>20%) TEAEs by preferred term in the larotaxel arm were fatigue, diarrhea including colitis and enteritis, nausea, alopecia, abdominal pain, decreased appetite, vomiting, and constipation. The most frequent (>20%) TEAEs by preferred term in the 5-FU arm were fatigue, abdominal pain, diarrhea including colitis and enteritis, nausea, stomatitis/mucositis, vomiting, decreased appetite, palmar-plantar erythrodysaesthesia syndrome.

Fatigue, diarrhea including colitis and enteritis, nausea, alopecia, constipation, neuropathy sensory and myalgia were more frequent (>10%) in the larotaxel arm than in the 5-FU arm. Palmar-plantar erythrodysaesthesia syndrome and stomatitis/mucositis were most frequent (>10%) in the 5-FU arm than in the larotaxel arm.

More patients died from adverse event during study treatment in the larotaxel arm (2.5% in 5-FU versus 9.6% in larotaxel). The most frequent fatal AEs in larotaxel arm were neutropenic complication, diarrhea/colitis/enteritis.

More patients experienced at least one SAE in the larotaxel arm (53.0%) compared to the 5-FU arm (42.6%). The most frequent SAEs were (5-FU versus larotaxel) disease progression (13.6% versus 14.2%), febrile neutropenia (6.6% versus 0%), diarrhea including colitis and enteritis (5.1% versus 2.0%), gastrointestinal haemorrhage (5.1% versus 1.5%).

More patients discontinued study treatment due to adverse event in the larotaxel arm (21.1%) versus the 5-FU arm (10.3%). The most frequent AEs leading to treatment discontinuation were: neutropenic infection, diarrhea including colitis and enteritis, fatigue, neuropathy sensory and febrile neutropenia.

More patients had grade 3-4 neutropenia in the larotaxel arm (42.1%) versus the 5-FU arm (6.3%). More patients had neutropenic complication in the larotaxel arm (15.7%) patients including 10 patients (4.9%) with fatal outcome versus the 5-FU arm (0.5% and none with fatal outcome).

Overall, more grade 3/4 TEAEs, AEs leading to treatment discontinuation, SAEs, and fatal SAEs were observed in the larotaxel arm compared to the 5-FU arm). The most critical AEs in the larotaxel arm were neutropenic complication and diarrhea.

Pharmacokinetic results: After a 1-hour IV infusion of larotaxel at 90 or 75 mg/m², mean larotaxel clearance was 31.7 ± 11.8 L/h/m² (n=37). These values were similar to the population mean of 31.4 L/h/m² (median body surface area of 1.74 m²) obtained in population analysis in Phase 1 and 2 monotherapy studies.

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