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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**Not Applicable**
		Study Code:	**EFC_7276**
Generic drug name:	**Oxaliplatin**	**Date:**	**10 April 2007**

Title of Study: Phase II Study of Oxaliplatin in Combination with 5-Fluorouracil (5-FU) in 1st Line Treatment of Locally Advanced or Metastatic Squamous Cell Carcinoma of the Head and Neck

Protocol Number: EFC 7276

Study Period: **Phase of Development:** II
Date of first enrollment: 03 May 2000
Date of last completed: 06 February 2003

Principal Investigator: Dr D. De Raucourt
Investigator(s): Dr. B Laguerre; Dr. F Husseini; Dr. L Martin; Dr. C Borel; Dr. M Debled

Study Center(s): Six (6) centers located in France were involved in this study.

Publication(s): Debled M, Gervais R, Laguerre B, Borel C, Husseini C, Martin L, et al. Phase II study of oxaliplatin (OXA) in combination with 5-fluorouracil (5-FU) in first line treatment of locally advanced (LA) or metastatic squamous cell carcinoma (SCC) of the head and neck. Proc Am Soc Clin Oncol 22: 2003 (abstr 2049). The abstract contains preliminary data.

Objectives:
Primary:
To evaluate the efficacy of first line oxaliplatin in combination with 5-fluorouracil (5-FU) in patients with advanced inoperable or metastatic head and neck cancer.
Secondary:
To investigate the safety profile of this regimen in the above indication and consider other criteria of efficacy (clinical benefit, survival).

Study Design: Open-label, non-randomized, multi-center, phase II, modified 2-step (Simon) study. Patients received a treatment cycle every 3 weeks. Treatment continued until the intervention of disease progression, unacceptable toxicity, absence of clinical benefit, patient refusal, or treatment delay > 2 weeks. Patients were considered to be on-study for the duration of their treatment and in the 30 days following treatment discontinuation (day of last oxaliplatin or 5-FU administration). All included patients were followed up until recovery from residual toxicities/adverse events (AEs), progressive disease (PD), or death. After the end of study treatment (whatever the reason for discontinuation), all included patients were followed for the last cycle.

Number of Patients (planned and analyzed):
Planned: Fifteen patients in the first step and increased to 43 patients.
Analyzed: Seventeen patients were registered and evaluable for safety (intent-to-treat [ITT] population); 15 patients were evaluable for efficacy (per protocol [PP] population). Overall response rate < 9, therefore the cohort was not increased to 43 patients and the study was terminated.

Diagnosis and Main Criteria for Inclusion: Patients aged 18-70 years, with inoperable locally advanced or metastatic squamous cell carcinoma of the head and neck (stage III-IV) histologically proven, no prior chemo and/or hormone therapy for metastatic disease or local recurrence (adjuvant or neo-adjuvant chemotherapy or radio-chemotherapy was allowed if finished since more than 6 months before inclusion and cisplatinum total dose used ≤ 300 mg/m² or carboplatinum total dose used ≤ 1200 mg/m²), at least 1 target lesion (measurable in 2 dimensions ≥ 20 mm on computed tomography (CT) or magnetic resonance imaging (MRI) evaluated < 15 days before start of study treatment, outside of irradiated fields), performance status (PS) ≤ 2 World Health Organization (WHO), weight loss < 5% normal weight, hemoglobin ≥ 10 g/dL, neutrophils ≥ 2000/mm^3, platelets ≥ 100,000/mm^3, creatinine ≤ 1.5 x upper limit of normal (ULN), bilirubin ≤ 1.5 x ULN, alanine amino-transferase (ALT)/aspartate amino-transferase (AST) ≤ 2.5 x ULN (5 x ULN if liver metastases), clotting: prothrombin time (PT) ≥ 60%. Written informed consent signed by patient and doctor prior to all study procedures.

Test Products, Dose and Mode of Administration, and Lot Number(s):
Oxaliplatin: 130 mg/m² in 500 mL of 5% glucose solution as a 2-hour intravenous (IV) infusion on Day 1 and repeated every 3 weeks;
5-FU: following oxaliplatin administration, 1000 mg/m²/day as a continuous IV infusion from Day 1 to Day 4, every 3 weeks.
Dose adjustments were made if the patient experienced AEs.

Duration of Treatment: Until disease progression, unacceptable toxicity, absence of clinical benefit, patient refusal to continue treatment, or treatment delay > 2 weeks. All included patients were followed up until recovery from residual toxicities/AEs, until progressive disease was observed, or until death occurred.

Criteria for Evaluation:
Efficacy: Patients must have received at least 2 cycles of treatment (6 weeks on study) to be evaluable for response, unless disease progression occurred.
Primary endpoint:
Tumor response rate (WHO/Union Internationale Contre le Cancer [International Union Against Cancer] [UICC] criteria).
Secondary endpoints:
Progression free survival and overall survival in the ITT population, clinical benefit by follow-up of pain, analgesic consumption, PS and weight.

Safety: Characterization of toxicity using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and the Oxaliplatin Specific Neurological Toxicity Scale, serious adverse events (SAEs) and treatment withdrawals.

Statistical Methods:
Efficacy:
Primary efficacy endpoint:
The best overall response was analyzed in the PP and ITT populations. Response rate was characterized using descriptive statistics (value and 95% confidence interval [CI]).
Secondary efficacy endpoints:
Time-related parameters (progression free survival and overall survival) were analyzed in the ITT population using the Kaplan-Meier method. Duration of response was analyzed in the PP and ITT populations using the Kaplan-Meier method. In the absence of the pain scales on the case report form (CRF), clinical benefit assessment was invalid as set out in the Protocol. Analgesic consumption, weight and PS were presented in a listing by patient and visit.
Safety:
The extent of exposure to the treatments was characterized for oxaliplatin and for 5-FU. Study treatment delays were summarized. Dose reductions were tabulated. Descriptive statistics were employed to characterize the toxicity, toxic deaths, SAE and toxicity-related treatment discontinuation profiles. AEs were presented per patient and per cycle. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 5.0.
Blood chemistry laboratory abnormalities were summarized. Hematological and biochemical parameters were described at each time point over the course of the study. Concomitant treatments were tabulated by preferred term.

Efficacy Results: Overall response rate was 5 (31.3%) and 4 (26.7%) for the ITT and PP populations, respectively. No complete responses (CRs) were observed in this study. The overall response was observed in < 9/15 evaluable patients. Therefore, the cohort was not increased and the study was terminated.
Median [95% CI] progression-free survival for the ITT population was 2.8 [2.0;4.5] months. Median [95% CI] overall survival for the ITT population was 7.2 [4.6;8.8] months. In both the ITT and the PP populations, 2 patients had progression events and the median [95%CI] duration of response was 8.1 [3.0;.] months. Univariate analyses of the response rate using Fisher's exact test showed that PS at entry, stage of disease, tumor localization and stage were not prognostic factors for response rate.
In the absence of the pain scales in the CRF, clinical benefit could not be determined as initially planned in the protocol. Eleven patients did not consume analgesics and 1 patient did not increase their baseline analgesic consumption during the study. One patient decreased and 2 patients increased their baseline analgesic consumption during the study. Analgesic consumption was only reported during 1 cycle for 2 patients. Four patients had their PS unchanged during the study. At end of treatment, 1 patient had decreased PS compared to baseline, 5 patients had PS increased 1 level, 4 patients had PS increased 2 levels and 2 patients had returned to baseline PS after an increase of 1 level during the study. The majority of patients (14/17) had lost weight at end of treatment. During the study, 5 patients experienced weight gains, but none were > 7%.

Safety Results: A total of 81 cycles were administered. The median duration of oxaliplatin dosing duration was 120.0 minutes for cycles 1, 3, 5 and 6, 160.0 minutes for cycle 2 and 180.0 minutes for cycle 4. The median 5-FU dosing duration was 4.0 days for all cycles 1 to 12. Three (17.6%) patients had a cycle delay: 2 (11.8%) had 1 cycle and 1 (5.9%) had 3 cycles delayed. Five cycles were delayed: 3 (60.0%) were delayed for 3-6 days and 2 (40.0%) for 7-13 days. The main reasons for delays were AEs of hematological and non-hematological toxicity (4 [80.0%] cycle delays each). One (5.9%) patient had a dose reduction in oxaliplatin, due to a grade 1 hematological toxicity and due to a neurotoxicity.
The majority of AEs reported during the study were grade 1 or 2 AEs. The most frequently reported hematological AEs were anemia (88.2% patients) and thrombocytopenia (41.2% patients). The majority of hematological AEs were of grade 1 or grade 2. Two patients reported grade 4 hematological AEs of neutropenia and leukopenia (1 patient each). The proportion of patients with hematological AEs tended to increase from cycle 1 to cycle 3. At end of treatment, the proportion of patients was similar to baseline. The most frequently reported non-hematological AEs considered to be related to study treatment were paraesthesia (11 [64.7%] patients), vomiting not otherwise specified (NOS) (6 [35.3%] patients), weight decreased and nausea (4 [23.5%] patients each).
No grade 3 or grade 4 neurotoxicities were reported during the study. Eleven (64.7%) patients experienced paraesthesia; 3 (17.6%) patients experienced dysaesthesia. All neurotoxicities reported during the study were considered likely related to study treatment.
Three patients died during the study; 2 deaths were considered not related and 1 death had an unknown relationship to study treatment (no autopsy performed). Five patients reported 12 non-fatal SAEs: 1 patient experienced 1 SAE, 1 patient experienced 2 SAEs and 3 patients experienced 3 SAEs. Of the non-fatal SAEs reported, 1 event (febrile neutropenia) was considered to be likely related to study treatment. One patient experienced a non-serious AE (paraesthesia) that led to study treatment being permanently discontinued:

Date of Report: 18 January 2007