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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**Not applicable**
		Study Code:	**EFC_7407**
Generic drug name:	**Oxaliplatin**	**Date:**	21 May 2007

Title of Study: Phase II Study of Combined Oxaliplatin and Paclitaxel for Metastatic Germ Cell Tumors

Protocol Number: EFC 7407

Study Period: **Phase of Development:** II

Date of first enrolled patient: 19 December 2000

Date of last completed patient: 25 March 2004

Principal Investigator: Pr. J.P. Droz

Investigator(s): Seven investigators in France participated in this study: Jean-Pierre Droz, Pr., Christine Chevreau, MD, Lionel Geoffrois, MD, Pierre Kerbrat, MD, Jean-Pierre Lotz, Pr., Christine Théodore, MD, Binh Bui, MD.

Study Center(s): Seven centers located in France were involved in the study.

Publication(s):

Theodore C, Flechon A, Fizazi K, Chevreau C, Delord JP, Lotz JP, et al. A phase II multicenter study of oxaliplatin (Ox) in combination with paclitaxel (Px) in patients (Pts) who failed cisplatin (CDDP)-based chemotherapy (CT) for germ cell tumors (GCT) (poster). 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), New Orleans, Louisiana, United States of America (USA), 5-8June 2004.

Theodore C, Flechon A, Fizazi K, Chevreau C, Delord JP, Lotz JP, et al. A phase II multicenter study of oxaliplatin (Ox) in combination with paclitaxel (Px) in patients (Pts) who failed CDDP based chemotherapy (CT) for germ cell tumors (GCT) (abstract 4524). Abstracts of the 40th Annual Meeting of the American Society of Clinical Oncology (ASCO), New Orleans, Louisiana, USA, 5-8June 2004. Ann. Meet. Proc. Am. Soc. Clin. Oncol., 2004, 23, p.389.

Note: the data used in the poster were preliminary data.

Objectives:

Primary:

To evaluate the efficacy of the oxaliplatin-paclitaxel combination i.e. evaluation of tumor response rate using World Health Organization/Union Internationale Contre le Cancer (WHO/UICC) and Indianapolis tumor marker (human chorionic gonadotropin [hCG], alpha fetoprotein [AFP]) criteria in metastatic germ cell cancer patients.

Secondary:

- To evaluate safety, i.e., evaluation of toxicity using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and specific neurotoxicity scales, serious adverse events (SAEs) and treatment withdrawals
- To evaluate response duration, time to progression (TTP) and overall survival
- To document further treatment options (curative surgery, high-dose chemotherapy).

Study Design: Open-label, non-randomized, multi-center, phase II, 2-step (Gehan) study. Patients received a treatment cycle every 3 weeks. A clinical and biological evaluation of the disease was performed after each treatment cycle, and a radiological evaluation every 2 cycles. Patients continued on treatment until the intervention of disease progression, unacceptable toxicity, interruption to attempt cure, 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-paclitaxel administration). All included patients were followed up until 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: Fourteen (14) patients in the first step. If = 1 response was observed in the first 14 patients, 11 further evaluable patients were to be recruited, in order to evaluate the response rate more precisely.
Analyzed: 27 patients were included in the intent-to-treat (ITT) population, 24 patients were included in the per protocol (PP) population, and 26 patients were included in the safety population.

Diagnosis and Main Criteria for Inclusion: Patients aged at least 18 years, with histologically proven germ cell cancer (gonadal [including ovarian] or extragonadal, seminomatous or non-seminomatous, or clinical presentation of a germ cell tumor [GCT] with elevated AFP level and/or hCG level [≥ 100 x upper limit of normal {ULN}] when a biopsy was not available). Metastatic GCT patients, with progression disease defined as > 10% increase in hCG and/or AFP markers (and/or documented progressive disease [PD]) during a platinum-based chemotherapy or less than 6 months after the last cycle (in the case of growing non-seminomatous tumor, without increased markers, a histological documentation of malignant tumor was required, to exclude growing mature teratoma), and at least 1 prior line of chemotherapy containing cisplatin (CDDP) + etoposide (prior regimen with high-dose chemotherapy and hematopoietic stem cell support was permitted). Patients with a performance status (PS) (Eastern Cooperative Oncology Group [ECOG] grade) ≤ 2, at least 1 bidimensionally measurable lesion by imaging (computed tomography [CT] scan) of ≥ 20 mm outside an irradiated area OR significantly increased tumor markers > 2 x ULN (on ≥ 2 consecutive tests, even in the absence of measurable lesions), adequate bone marrow reserve (neutrophil count ≥ 1500/mm^3; platelets ≥ 100,000/mm^3); creatinine < 3 x ULN; transaminases ≤ 2.5 x ULN, total bilirubin < 1.5 x ULN (if liver metastases, transaminases ≤ 5 x ULN); neurosensory ≤ grade 1 NCI-CTC. Laboratory values obtained in the week preceding study entry. Signed informed consent obtained prior to all study procedures.

Test Product, Dose and Mode of Administration:
Paclitaxel: 175 mg/m² in 500 mL of 5% glucose solution as a 3-hour intravenous (IV) infusion on Day 1, and repeated every 3 weeks.
Oxaliplatin: following paclitaxel administration, 130 mg/m² in 250-500 mL of 5% glucose solution as a 2-hour IV infusion on Day 1, and repeated every 3 weeks.
Dose adjustments were made if the patient experienced adverse events (AEs).

Duration of Treatment: Patients continued on treatment until the intervention of disease progression, unacceptable toxicity, interruption to attempt cure, 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-paclitaxel administration). All included patients were followed up until death.

Criteria for Evaluation:
Efficacy: Patients must have received a minimum of 1 cycle of treatment (3 weeks on study) with at least 1 follow-up tumor assessment to be considered evaluable for response, unless disease progression occurred.
Primary endpoint:
Objective response rate (tumoral and/or biological), using WHO/UICC and Indianapolis tumor marker (hCG, AFP) criteria.
Secondary endpoints: Response duration; TTP; overall survival; further treatment options used (curative surgery, high-dose chemotherapy).
Safety:
Characterization of toxicity using the NCI-CTC version 2.0 and specific neurotoxicity scales, SAEs and treatment withdrawals.

Statistical Methods:

Efficacy:

Response was analyzed in PP and ITT populations. The analysis of the Independent Expert Panel (IEP) evaluation was carried out on the PP population. The analysis of the investigator evaluation was carried out on the ITT population.

Primary Efficacy Endpoint:

The overall response rate was calculated as the proportion of patients who had a complete response (CR) or a partial response (PR) with marker negative. Response rate was presented using descriptive statistics (value and 95% confidence interval [CI]). The 95% CI was calculated with the binomial distribution. The mean, median, standard deviation and range of the value were not presented, as the value was a percentage.

Secondary Efficacy Endpoints:

The time-related parameters were progression-free survival and overall survival. The analysis was performed on the ITT population, using the investigator evaluation. Time to progression and overall survival were analyzed using the Kaplan-Meier method.

The duration of response was summarized in the PP population and ITT population. The duration of response was the duration of CR or the duration of PR according to the best response. Duration of progression was analyzed using the Kaplan-Meier method.

Efficacy parameters were also further subjected to appropriate analysis, considering correlation with factors of probable prognostic value such as patient PS at entry, tumor marker at initial diagnosis, and tumor localization. Response parameters underwent a univariate analysis using the Pearson $?^2$ test. Univariate analyses of time parameters were carried out using the log-rank test.

Safety:

All patients who received at least 1 dose of study treatment were considered evaluable for safety.

The AEs and SAEs that occurred during treatment or within 30 days after the last study treatment administration, laboratory abnormalities measured under treatment or within 30 days after the last study treatment administration were summarized separately from those that occurred or were measured more than 30 days after last study treatment administration.

Descriptive statistics were used to characterize and analyze the toxicity, toxic deaths, SAEs and toxicity-related treatment discontinuation profile.

AEs were summarized using frequency counts. On-study deaths (in particular the toxic ones) were listed. Non-fatal SAEs were summarized using frequency counts by relationship to study treatment.

Efficacy Results: No patients had CR or a marker negative partial response. Disease progression occurred in the majority of the patients in both the PP and ITT populations (66.7% and 61.5%, respectively). One patient had marker positive partial response. A tumor marker decrease =50% was observed in 10 (37.0%) patients; of these, 6 had a tumor marker decrease = 90%.

Median overall duration of response for the PP population was 4.0 months (95% CI: [1.6%; 6.2%]) and for the ITT population 4.2 months (95% CI: [2.5%; 5.7%]). Median overall time to progression for the ITT population was 1.4 months (95% CI: [1.3%; 2.0%]). Median overall survival for the ITT population was 8.8 months (95% CI: [5.0%; 11.6%]). Baseline characteristics such as ECOG PS, primary site at entry and tumor marker at initial diagnosis had no statistically significant effect on progression-free survival, or overall survival.

Safety Results: Median number of cycles received was 3.5 (range: 1 to 7 cycles), with the majority of patients having received either 2 or 4 cycles (34.6% for each). Seven (58.3%) cycles were delayed for 3 to 6 days, and 5 (41.7%) cycles were delayed for 7 to 13 days. All but 1 patient experienced *anemia* (96.2%); 65.4% of patients experienced *thrombocytopenia*. No patients experienced a neurotoxic event and no toxic deaths occurred during the study. Six patients experienced AEs or SAEs that led to study treatment being permanently or temporarily discontinued. The most common AE that led to discontinuation was *malignant neoplasm progression* (3 patients). Eight patients experienced at least 1 non-fatal SAE. Four patients died during the study, all due to disease progression. One of these patients died before receiving study treatment.

Date of Report: 07 February 2007