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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NA
		Study Code:	EFC_7496
Generic drug name:	oxaliplatin	**Date:**	09 January 2008

Title of Study: Parallel Randomized Open Phase II Study of Oxaliplatin (L-OHP) alone and in Combination with 5-Fluorouracil (5-FU) in Patients with Locally Advanced or Metastatic Endometrial Cancer Previously Treated with One Line of Chemotherapy Containing Cisplatin or Carboplatin

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

Date of first enrollment: 16 January 2001

Date of last completed: 08 March 2005

Principal Investigator: Dr. C. Lhomme

Investigator(s): Prof. P. Fumoleau/Dr. D. Berton-Rigaud, Dr. O. Rixe, Dr. B. Weber, Dr. T. Petit, Prof. Bougnoux, Dr. A. Floquet, Dr. F. Mayer, Dr. F. Joly

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

Publication(s): None

Objectives:

Primary: To determine the efficacy (response rate [RR], time to progression and survival) of oxaliplatin as a single agent and oxaliplatin in combination with 5-FU in patients with advanced/metastatic endometrial cancer pretreated with one prior chemotherapy regimen containing cisplatin (CDDP) or carboplatin. Secondary: To define the safety profile of each arm of the above-mentioned regimens in these patients.

Study Design: Phase II, multi-center, 2-arm, open-label, randomized, modified 2-step (Gehan) study. Patients received a treatment cycle every 3 weeks. Treatment continued until the intervention of disease progression, unacceptable toxicity, 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 oxaliplatin /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: 28 patients (14 per arm) in first step and increased to 50 patients (25 per arm).

Analyzed: 31 patients were included in the intent-to-treat (ITT) and safety populations, and 29 patients were included in the per protocol (PP) population.

Diagnosis and Main Criteria for Inclusion: Patients aged at least 18 years, with locally advanced, recurrent or metastatic endometrial adenocarcinoma, histologically diagnosed; at least 1 bidimensionally measurable lesion (≥ 2 cm on computed tomography [CT]/magnetic resonance imaging [MRI] or ≥ 1 cm clinical lymph node confirmed by ultrasound or ≥ 1 cm skin lesion confirmed by photograph with ruler) located in a non-irradiated area measured less than 2 weeks before inclusion, according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Patients previously treated for locally advanced/metastatic disease with chemo-radiotherapy (total CDDP dose ≥ 100 mg/m^2) or chemotherapy containing CDDP or carboplatin with at least 4 weeks' washout period from discontinuation of prior chemotherapy and fully recovered from toxic effects of prior chemotherapy (except for symptomatic peripheral neuropathy ≤ NCI-CTC grade 1 or alopecia). Patients with clinically or radiologically documented PD or recurrence during or after last chemotherapy and hormone therapy (hormone therapy stopped before study entry), Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2, life expectancy ≥ 3 months, adequate bone marrow reserve, normal renal and liver function (neutrophil count ≥ 2000/mm³; platelet count ≥ 100 000/mm³; creatinine levels ≤ 1.5 x the upper limit of normal [ULN] of institutional values or creatinine clearance > 60 mL/min; total bilirubin level < 1.5 x ULN; [alanine amino-transferase/aspartate amino-transferase < 2.5 x ULN without liver metastases, < 5 x ULN with liver metastases]). Laboratory values obtained in the week preceding study entry. Signed informed consent (prior to all study procedures).

Test Product, Dose and Mode of Administration:
Oxaliplatin (Arms A and B): 130 mg/m² as a 2-hour intravenous (IV) infusion in 500 mL of 5% glucose solution on Day 1 and repeated every 3 weeks.
5-FU (Arm B only): following oxaliplatin administration, 1000 mg/m²/day as a continuous IV infusion from Day 1 to Day 4, repeated every 3 weeks.

Reference Therapy, Dose and Mode of Administration: Not applicable.

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

Criteria for Evaluation:

Efficacy: Patients must have received a minimum of 2 cycles of treatment (6 weeks on study) to be evaluable for response, unless early disease progression occurred.

Primary endpoint:
Overall RR (World Health Organization [WHO]/Union Internationale Contre le Cancer [International Union Against Cancer] [UICC] criteria).

Secondary endpoint:
Progression free-survival, duration of response and overall survival.

Characterization of toxicity using NCI-CTC version 2.0 and specific neurotoxicity scales, AEs, serious AEs (SAEs) and treatment withdrawals.

Statistical Methods:

Efficacy:

Primary Efficacy Endpoint:

Overall response was analyzed for the ITT and PP populations. The RR was calculated as the proportion of patients who had either a partial response (PR) or a complete response (CR) recorded at the end of the study in best overall response. RR was presented using descriptive statistics (percentage value and 95% confidence interval [CI]). The 95% CI was calculated with the binomial distribution.

Secondary Efficacy Endpoints:

The time-related parameters were duration of response, progression-free survival and overall survival. Duration of response was presented for the ITT and PP populations. Progression-free survival and overall survival were only evaluated for the ITT population. Duration of response, progression-free survival and overall survival were analyzed using the Kaplan-Meier method.

Safety:

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

AEs were summarized using frequency counts and percentages. 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:

Arm A received oxaliplatin alone and Arm B received oxaliplatin in combination with 5-FU. Overall response was observed in 3 (9.7%) patients in the ITT population, all in Arm B. Median duration of response was 8.5 months (95% CI: [8.2; 21.5]), median time to progression was 2.2 months (95% CI: [2.1; 3.0]) and median overall survival was 6.4 months (95% CI: [3.4; 8.3]) in the total population. Patients in Arm B had the longest overall survival: median 8.0 months (95% CI: [4.7; 9.3]) while patients in Arm A had a median overall survival of 4.1 months (95% CI: [2.7; 8.2]).

Safety Results:

Overall median number of cycles received in the total population was 3 (range: 1 to 10 cycles), with a larger proportion of patients having received 3 cycles than any other number of cycles. The number of cycles received was similar between the 2 treatment arms. One cycle was delayed for 3 to 6 days in Arm A and 3 cycles were delayed for 3 to 6 days in Arm B. Two cycles in each treatment arm were delayed for 7 to 13 days. Of the 15 patients in Arm A who received = 2 cycles, none of them had 1 dose reduction in oxaliplatin. Of the 14 patients in Arm B who received = 2 cycles, 2 patients had 1 dose reduction in oxaliplatin, and 1 patient had 1 dose reduction in 5-FU.

Anaemia was the most common hematological AE experienced in both treatment arms (14, 87.5% patients in Arm A and 13, 86.7% patients in Arm B experienced *anaemia* (all grades). Of these, 4 (25.0%) patients in Arm A and 6 (40.0%) patients in Arm B experienced grade 3-4 *anaemia*.

The occurrence of non-hematological AEs was similar in both treatment arms.

The most commonly experienced neurotoxicities (all grades) were *paraesthesia*, in both treatment arms (7, 43.8% patients in Arm A and 6, 40.0% patients in Arm B) and *dysaesthesia* (6, 40.0% patients in Arm B). More than double the proportion of patients in Arm B (6/15, 40.0% patients) experienced *dysaesthesia* (all grades) than in Arm A (3/16, 18.8% patients). When using the Oxaliplatin Specific Neurological Toxicity scale, no patients presented with grade 3-4 neurotoxicity. However, when using the NCI grading, 1 (6.3%) patient in Arm A and 2 (13.3%) patients in Arm B experienced grade 3 *paraesthesia*.

Nine patients died during the study, 6 patients due to the underlying disease (*malignant neoplasm progression*). One patient's death was due to toxicity caused by *thrombocytopenia* and *vasculitis NOS*. One patient in Arm A experienced a non-fatal SAE, while 3 patients in Arm B experienced at least 1 non-fatal SAE, all with relationship to study treatment of likely, unknown or missing. Eleven patients experienced at least 1 non-fatal SAE. Nine patients experienced SAEs/AEs that led to study treatment being permanently discontinued.

Date of Report: 22 October 2007