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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00620100
		Study Code:	XRP6976A_2504
Generic drug name:	Taxotere	**Date:**	18/Feb/2008

Title

A Multicenter, open label, phase II trial evaluating docetaxel (Taxotere®) + anthracycline (epirubicin or doxorubicin) x 4 cycles followed by docetaxel (T) single agent x 4 cycles as first-line therapy in patients with Her2 negative locally advanced or metastatic breast cancer who have relapsed ≥12 months from completion of neoadjuvant/adjuvant Taxotere®-based chemotherapy.

Investigator(s), study site(s)

29 centers opened in 9 countries (Austria, Canada, France, Germany, Hungary, Lebanon, Poland, Romania, South Africa)

Two sites recruited patients (Center 101-Austria; Center 601-Poland)

Study duration and dates	**January 2004 to March 2005**	**Phase**	**II**

Objectives

Original objectives:

Primary:

To determine the Objective Response Rate of 4 cycles of docetaxel + anthracycline (epirubicin or doxorubicine) followed by 4 cycles of docetaxel single agent.

Secondary:

To determine the Time to Tumor Progression (TTP), the Response Duration, the Overall Survival.

To confirm the safety profile

New objectives:

The study was terminated early due to a lack of recruitment. As a result, this abbreviated clinical study report only describes the patients' characteristics and the reported adverse events.

Study design

Multicenter, multinational, open label, phase II study

Number of subjects planned

Approximately 100 subjects planned; two patients were actually recruited.

Inclusion criteria

1. Female patient with histologically or cytologically documented breast adenocarcinoma
2. First local or metastatic relapse
3. Patients who had received a prior neoadjuvant or adjuvant Taxotere®-based chemotherapy regimen, provided this chemotherapy was completed ≥12 months prior to enrollment date
4. Prior hormone or immune therapy was allowed. Antitumoral adjuvant hormone therapy might have been continued during the study period, provided it was started >12 months prior to study enrollment
5. Her2/neu negative tumor demonstrated by immunohistochemistry (IHC 0 or 1+) or by fluorescence *in situ* hybridation (FISH -). A patient with tumor assessed as 2+ by IHC could be enrolled if the tumor was negative by FISH.
6. Age ≥ 18 years
7. ECOG performance status of 0 to 2
8. Normal cardiac function confirmed by LVEF or shortening fraction (MUGA scan or echocardiography, respectively, within normal limits for the institution) assessed within 3 months prior to study entry. An ECG had to be obtained within 4 weeks prior to study entry and had to demonstrate no clinically significant abnormality.
9. Patients were required to have at least one measurable lesion according to RECIST guidelines
10. Adequate organ function defined by :
    - Hematology: Neutrophils = 2.0 10^9/L, Platelets = 100 10^9/L, Hemoglobin = 10 g/dL
    - Hepatic function: Total bilirubin within normal limits, AST (SGOT) and ALT (SGPT) = 1.5 UNL, alkaline phosphatase = 2.5 UNL (unless accompanied by extensive bone metastases)
11. Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential
12. Written informed consent prior to beginning specific protocol procedures had to be obtained and documented according to the local regulatory requirements

Treatments

Cycles 1 to 4: doxorubicin 50 mg/m2 or epirubicin 75 mg/m² IV route over 5-10 minutes, immediately followed by docetaxel 75 mg/m² 1-hour IV infusion administered on day 1 every 3 weeks (one Cycle)
Cycles 5 to 8: docetaxel 100 mg/m² IV every three weeks
Primary prophylaxis with G-CSF might be used at the discretion of the investigator. Antiemetic therapy with 5HT3 receptor antagonist was required during the first 4 cycles and was optional for the last 4 cycles. Corticosteroids premedication was required with each administration of docetaxel.
Study treatment had to be discontinued in case of progressive disease, unacceptable toxicity or patient's decision. Treatment was to be continued beyond 8 cycles if the patient continued to derive from clinical benefit.
Guidelines for dose and schedule adjustment were provided in the protocol.

Safety data

Safety was assessed on every patient who received the study drug. It was evaluated on:

- Physical examination at each cycle
- Left Ventricular Ejection Fraction (LVEF) after cycle 4 and after cycle 8 if abnormality was detected at cycle 4.
- Laboratory tests: hemoglobin, platelets, WBC and differential, ALT, AST, alkaline phosphatases, and total bilirubin before each cycle

Toxicities were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC AE) version 3.0

Statistical procedures

Initial procedure: described in the protocol

The primary efficacy analysis was to be defined as overall clinical response, as described in the protocol. A 95% confidence interval for the observed response rate was to be determined based on binomial distribution.

Secondary efficacy analyses were to be performed as follows: TTP, response duration, and OS were to be estimated using the Kaplan-Meier method. Medians based on the Kaplan-Meier method and their 95% confidence intervals based on the Greenwood method were to be calculated. Potential prognostic factors were to be assessed by the Cox proportional hazard model for time to event data (TTP, response duration and OS) and logistic regression for the response rate.

Descriptive analyses were to be performed with regard to patients' demographic and tumor characteristics, study drug exposure, adverse events, and laboratory findings. No systematic comparison was planned.

This study assumed a null hypothesis of a 30% overall clinical response rate (i.e, a treatment effect that was considered clinically uninteresting for combination chemotherapy in MBC) and an alternative hypothesis of a 45% response rate (i.e., a response that was deemed clinically relevant in the management of MBC). With type I error no more than 0.025 and power of at least 80%, the study required 83 patients. But discreteness of binomial distribution used in performing test and confidence interval caused the undesirable property that one patient more would have decreased the power. In order to keep at least 80% of power even if there were 3 patients more or less than planned (due to uncertainty about the exact inegibility rate), 91 patients were estimated to be required in the study. If at least 37 of 91 patients were deemed to have a clinical response, the null hypothesis was rejected. This gave the study an actual type I error of 0.02 and power of 82.5%. Assuming a 10% ineligibility rate, a total of 100 patients should have been enrolled in this study.

Revised procedure:

Due to early study termination and since only 2 patients were recruited, no statistical analysis could be made. This report consists only in the description of the patients.

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

Two patients were included in the study.

The first patient received one cycle of study drugs and discontinued the study due to a serious grade 3 febrile leucopenia. No response evaluation was performed. The patient was lost to follow-up after cycle 1.

The second patient received 6 cycles of full dose study drugs without any delay and died during cycle 6, due to pulmonary embolism. Stable disease was recorded at the end of cycle 3 but no other tumor assessment was done.

Results - Pharmacokinetics and pharmacodynamics

Not Applicable

Results – Efficacy

No conclusion can be drawn on the efficacy parameters with the data of the two included patients.

Results – Safety

No sign of unexpected toxicities were reported during the study.

Date of Report

13 October 2006