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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:**	**NCT00617968**
		Study Code:	**XRP6976D_2502**
Generic drug name:	**Docetaxel**	**Date:**	**18 February 2008**

Study title	A multicenter, randomized, open-label, phase II study to evaluate the efficacy and safety of neoadjuvant treatment consisting of either a docetaxel (Taxotere®) – letrozole (Femara®) combination or letrozole (Femara®) alone in women over 60 years of age suffering from grade I or II operable hormone receptor-positive breast tumor. GETNA 2	
Protocol no.	XRP6976D/2502	
Research Coordinator/Country	Prof. Philippe CHOLLET, Centre Jean Perrin, Clermont-Ferrand, France.	
Active centers	o Centre Jean Perrin, Clermont-Ferrand – Professor Chollet o Besancon Teaching Hospital – Professor Pivot o Hôpital Tenon, Paris – Professor Lotz	
Duration of the study	First enrollment: 10/10/2003 Last enrollment: 21/10/2004	Phase II randomized With direct individual benefit
Study objectives	<u>Primary:</u> To evaluate the rates of clinical and radiological response in the 2 groups <u>Secondary:</u> – To evaluate, in both groups: Rate of histological response Rate of conservative surgery Rate of local and metastatic relapse Survival without relapse 5-year survival Time until relapse The frequency and severity of intercurrent events according to the NCI-CTC scale.	

Methodology	Multicenter, randomized study, stratified by age (= 70 years or > 70 years), open-label, phase II with direct individual benefit.

<table>
<tr><td rowspan="10">Number of patients</td><td colspan="4">Number of patients (%)</td></tr>
<tr><td></td><td>Arm A
(D100 mg/m²+l 2.5 mg/d)</td><td>Arm A
(D75 mg/m²+l 2.5 mg/d)</td><td>Arm B
(letrozole 2.5 mg/j)</td></tr>
<tr><td>Randomized</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Treated (ITT)</td><td>1*</td><td>1</td><td>3</td></tr>
<tr><td>Evaluable for clinical response</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Evaluable for radiological* response (mammography)</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Evaluable for radiological** response (ultrasound)</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Evaluable for histological response (Chevallier)</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td>Evaluable for histological response (Sataloff)</td><td>1</td><td>1</td><td>3</td></tr>
<tr><td colspan="4">* Did not receive docetaxel</td></tr>
<tr><td>Inclusion criteria</td><td colspan="4">

Female patients with breast cancer histologically proven by microbiopsy (14G or 16G) enabling confirmation of the diagnosis, and evaluation of the histological prognostic grade, hormonal receptors and HER2 status.
Tumor T2 or T3, non-metastasized, non-inflammatory, unilateral
Clinically or radiologically measurable lesion >2 cm (ultrasound and/or mammogram)
Receptors RE+ and/or RP+ (positive status determined according to the criteria of the investigating centers)
HER 2 / neu status of 0, 1+ or 2+ in immunohistochemistry
Histological grade I or II
Menopausal patients aged = 60 years
Patients with ECOG PS = 2
Satisfactory hematological, hepatic and renal functions:

</td></tr>
</table>

	✚ Hemoglobin =10 g/dL ✚ Platelet count =100x109/L ✚ Polynuclear neutrophil count > 1.5x109/L ✚ Creatinine = 1.5 ULN ✚ AST/ALT = 1.5 ULN ✚ Alkaline phosphatases = 2.5 ULN ✚ Patients able to be followed throughout the study ✚ Patient's consent obtained.
Non-inclusion criteria	✚ Inflammatory or T4 breast cancer ✚ T1 tumor ✚ Patients whose tumor is deemed by the doctor to be difficult to evaluate ✚ Tumor that is metastatic from the outset (M1) or locally advanced and inoperable from the outset ✚ RE and RP receptors negative or unknown ✚ HER 2/neu positive at 3 + ✚ Non-menopausal patients ✚ Surgical biopsy and/or ganglion dissection before neoadjuvant treatment ✚ Significant poorly controlled cardiac disorders, such as unstable angina pectoris, poorly controlled heart failure, arrhythmia requiring treatment, or myocardial infarction within the last 3 months ✚ Cardiovascular, hepatic, neurological or endocrine disease, or other major systemic disease that makes it difficult to conduct the protocol or to interpret the results ✚ Previous history of cancer that occurred within the last 10 years, with the exception of cervical cancers and basocellular skin cancers that were

	properly treated - Allergy to polysorbate 80 - Hypersensitivity to docetaxel - Participation in another clinical trial with one of the study medicinal products during the 30 days prior to entry in the study - Patients who are unable to undergo medical monitoring for geographical, social or psychological reasons
Study treatment, route of administration, posology	Patients are randomized receive, depending on their treatment arm: **Arm A:** docetaxel: 60 to 70 years of age: 100 mg/m², and 71 years of age and up: 75 mg/m² by intravenous route every 21 days, 6 cycles, i.e. 15 weeks, combined with letrozole per os 2.5 mg / day, i.e. 1 tablet / day for 18 ± 1 weeks. Docetaxel will be administered with the following premedication (mandatory): - Methylprednisolone (Medrol®): 48 mg per dose at H–12, H–3 and H–1 (the night before, the morning of, and 1 hour before the docetaxel infusion), then 48 mg every 12 hours for the next 2 days, i.e. a total of 6 doses. - Or Prednisolone (Solupred®): 60 mg per dose according to the same regimen. - The dose of docetaxel will be adjusted in case of toxicity. **Arm B:** Letrozole per os: 2.5 mg / day, i.e. 1 tablet per day for 18 ± 1 weeks
Evaluation endpoints	**Primary:** - Rate of clinical and radiological response evaluated according to RECIST criteria. **Response** was determined by the trial monitoring committee after reviewing the clinical and radiological documents. To be eligible for response, the patients had to have received at least 2 treatment cycles (arm A) or 8 weeks of treatment (arm B) with at least one tumor evaluation. If early progression occurred (before administration of the 2nd cycle or before the 8th week of treatment with letrozole (Femara®)), the patient was considered not to be evaluable and was declared to be in early progression.

	Clinical evaluation of the tumor (palpation and measurement of the clinical size of the tumor) was to be performed on D64 and at the end of treatment (D127). Radiological evaluation of the tumor (mammography and ultrasound) was to be performed before the start of the 4th cycle (D64) and at the end of treatment (D127). In cases of multicentric or multifocal tumors, evaluation was performed by taking the total of all lesions. **Secondary:** - Rate of histological response, - Rate of conservative excision, - Rate of local and metastatic relapse, - Survival without relapse, - Overall 5-year survival. **Safety** was to be evaluated in each patient who received the study products, according to the following criteria: - Vital signs (temperature, blood pressure, heart rate), previous medical history, complete physical examination prior to the start of treatment in both arms, before each cycle in arm A, at D64 and D127 in both arms. - ECOG performance status, weight prior to the start of treatment in both arms, before each cycle in arm A, on D64 and D127 in both arms. - Front/profile lung x-ray during the four weeks prior to randomization and at the end of treatment (D127). - Laboratory tests: *Hematology:* Blood assay: hemoglobin, platelets, white cells and leukocyte formula during the 7 days prior to the start of treatment, before each cycle in arm A, on D64 and D127 in both arms. *Biochemistry:* Serum creatinine, transaminases, alkaline phosphatases, bilirubin, GGT during the 7 days prior to the start of treatment, before each cycle in arm A, on D64 and D127 in both arms.

Statistical methods	A multi-step plan inspired by Flemming's designs was used. It was necessary to enroll a maximum of 140 evaluable patients (70 per arm), with intermediate evaluation of the first 70 patients enrolled (35 per arm). If one of the 2 arms (or both) showed insufficient efficacy (i.e. <30%), enrollment in this arm (or possibly in both arms) was to be stopped. The stop rule was as follows, identical for both arms: • if, of the first 35 patients enrolled who were evaluable from a clinical and/or radiological standpoint, 10 or fewer than 10 responses were observed, the treatment was deemed to have insufficient efficacy, and enrollment in this arm was stopped. • if 11 or more than 11 responses were observed, the second step was implemented, in which 35 additional patients were enrolled (for a total of 70). At the end of this step: • if 28 or more responses were observed among these 70 patients, the treatment could be proposed in phase III. • if 27 or fewer than 27 responses were observed, the efficacy of the corresponding arm was considered to be insufficient, with efficacy less than or equal to 30%. At the end of this evaluation, one and/or the other of the therapeutic arms would be proposed for a phase III trial, except in the event that neither of the treatments demonstrated sufficient efficacy.
Number of patients	With these hypotheses, it was necessary to enroll a total of 70, 105 or 140 evaluable patients, depending on the results of the intermediate statistical analysis.
Exposure to treatment	**Arm A: docetaxel and letrozole:** One patient randomized to this treatment arm received only letrozole (dispensed in 2 blocks, i.e. 180 tablets without docetaxel) (reason not indicated). A second patient randomized in this treatment arm received 6 cycles at the dose of 75 mg/m^2 and letrozole at the dose of 2.5 mg, i.e. one (1) tablet per day throughout chemotherapy with docetaxel (i.e. 16 weeks after the start of treatment). **Arm B: Letrozole (Femara®):** Letrozole was administered at the dose of 2.5 mg, i.e. one (1) tablet per day for 19 weeks in one patient and for at least 17 weeks in a second patient and for 19 weeks in a third patient.

		Number of patients (%)		
		Arm A N= 2	Arm B N= 3	Total N= 5
	Age: Years (min.–max.)	[64–79]	[68–79]	[64–79]
	Performance index (WHO) (%) 0	2 (100)	3 (100)	5 (100)
	Initial stage at diagnosis (%) IIA IIB IIIA	2 (100) 0 (0) 0 (0)	0 (0) 3 (100) 0 (0)	2 (100) 3 (100) 0 (0)
	Histological characteristics – Invasive duct carcinoma – Invasive lobular carcinoma – Mucinous carcinoma	 1(50) 1(50) 0(0)	 1(33.3) 1(33.3) 1(33.3)	 2 (40) 2 (40) 1 (20)
	Scarff-Bloom-Richardson Grade I II III	0 (0) 1 (50) 0 (0)	0 (0) 3 (100) 0 (0)	0 (0) 4 (80) 0 (0)
	Elston Ellis Grade I II III	 0 (0) 1 (50) 0 (0)	 0 (0) 0 (0) 0 (0)	 0 (0) 1 (20) 0 (0)
	Hormone receptors $RE^+ + RP^+$ $RE^+ + RP^-$ $RE^- + RP^+$ $RE^- + PR^-$	 2 (100) 0 (0) 0 (0) 0 (0)	 1 (33.3) 2 (66.7) 0 (0) 0 (0)	 3 (60) 2 (40) 0 (0) 0 (0)

	HER 2 Neu Immunohistochemistry Status (ICH): **0** **1 +** **2++** **3+++**	 2 (100) 0 (0) 0 (0) 0 (0)	 3 (100) 0 (0) 0 (0) 0 (0)	 5 (100) 0 (0) 0 (0) 0 (0)
Results of Efficacy	Only one complete histological response was observed in a patient randomized to Arm A **(docetaxel and letrozole)** according to Chevallier and Sataloff classifications. It should be noted that this patient never received docetaxel. All patients were evaluable for clinical response. One patient presented a Complete response and one patient a partial response in arm A and in arm B two patients presented a partial response. The five patients were evaluable for mammographic response, and only four patients were evaluable for ultrasound response. Two patients in Arm A and two patients in Arm B presented a partial Radiological (mammography) response No complete ultrasound responses were observed in randomized patients. Only one patient presented with a partial response, 33.3% in Arm B versus 0% in Arm A. Only one patient received conservative surgery, in Arm A.			
Safety	No grade 3–4 hematological and/or non-hematological toxicity was observed. Only grade 1 non hematological toxicities were observed in this study and three patients were concerned. The non hematological toxicities were asthenia, nausea, anemia….			
Date of the report	28 June 2005			