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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00494338
Generic drug name:	Docetaxel	**Study Code:**	XRP6976J_2504
		Date:	29/June/2007

Title of the study:	A Phase II trial of docetaxel and celecoxib in patients with metastatic androgen independent prostate cancer		
Investigator(s):	Coordinating investigator: Oren Smaletz Av. Albert Einstein, 627/701 - Morumbi – CEP 05651-901 - São Paulo - SP Brazil		
Study center(s):	Multicenter study (7 BR sites)		
Publications (reference):	None		
Study period: Date first patient enrolled: 08-Nov-2004 Date last patient completed: 29-Apr-2005	**Phase of development:** Phase II		
Objectives:	- Primary: Efficacy of Docetaxel and celecoxib by PSA response rate, evaluated by PSA working Group criteria: Proportion of patients with at least 50% of reduction in PSA, confirmed by a second measure at least 4 weeks after the first one. During this period, can not be observed radiological progression disease in the patient. - Secondary: Response rate (only for measurable disease), evaluated by RECIST criteria; Time to disease progression: time between treatment start and the clinical / radiological progression or PSA progression (the first happening). The PSA progression is defined as 50% increase in the Nadir. The nadir increase, when occurred, has to be confirmed by a second measure, at least two weeks after the first one. Overall survival: time between treatment start and death. Safety: Adverse events occurrence. The adverse events would be graded by Common Terminology Criteria of Adverse Events v 2.0 of National Cancer Institute (CTC-NCI 2.0).		
Methodology:	Multi-center study, non-comparative and open label.		
Number of patients:	Planned: 39	Randomized: NA	Treated: 6
Evaluated:	Efficacy: 4	Safety: 6	
Diagnosis and criteria for inclusion:	Histologically confirmed MAIPC, previously treated with hormonal therapy; Documented progressive disease in bone, soft issue or PSA despite castrate levels of testosterone; Karnofsky Performance status =70%.		

Investigational product: Dose: Administration:	Docetaxel // celecoxib (Celebrex®) 75mg/m² // 400mg One hour Intravenous infusion // Oral BID daily
Duration of treatment: Docetaxel: over one hour on Day one, every three weeks (Q3W), for 6 cycles. Celecoxib: 2 times a day (BID), beginning 7 days before the Day 1 of first cycle until the Day 21 of the last cycle of Docetaxel. Six cycles of treatment, each one repeated every 21 days in the absence of disease progression or unacceptable toxicity.	**Duration of observation:** Until the documented progression disease (PSA or tumor) or the administration of another anti cancer therapy.
Reference therapy: Dose: Administration:	NA NA NA
Criteria for evaluation:	
Efficacy:	Proportion of patients that achieve at least 50%, post therapy confirmed, decline in PSA, maintained on two consecutive evaluations at least 4 weeks apart.
Safety:	Adverse events reported by the patient or noted by the investigator, standard hematology and blood chemistry laboratory tests. It should be performed a safety interim analyzes after completion of the first cycle by 6 patients to confirm the safety and tolerability of the dosage scheme. In case of at least two patients presented one of the toxicities described below, an alternative scheme would be proposed. - Neutropenia grade 4, lasts more than 7 days; - Febrile neutropenia (CAB<1000/mm3 and axilar temperature = 38ºC); - Thrombocytopenia grade 4; - Gastrointestinal, renal, neurological or cardiovascular toxicity grade = 3.
Statistical methods:	It was defined the Intent to treat population, compound by all patients who received any amount of either docetaxel or celecoxib. This population was used to evaluate the safety and efficacy parameters The primary efficacy analyses comprised calculation to the proportion of patients with PSA decreases of, at least, 50% and the respective 95% confidence Interval. Only descriptive methods were used to adverse events occurrence. It was performed a safety interim analyses describing the number of patients who presented the toxicity events as described in the criteria for evaluation safety above.

Summary:

Between 08/Nov and 08/Dec/2004, six patients were enrolled to the study.

The patients were predominantly from the white ethnic (5 pts; 83%), with median age of 75 years (65-80 years) and mean Karnofsky index of 88% (70 to 100%).

Two patients (33%) received previous surgical treatment for cancer. Previous radiotherapy treatment was reported for two patients and all patients enrolled received previous hormonal treatment.

The mean testosterone, at baseline, was 18.4 ng/mL, ranged from 0.15 to 27.9 ng/mL and the mean PSA level was 548.6 ng/mL, ranged from 7.4 to 1840 ng/mL.

From the total, five (83%) patients received at least one dose of study medication (celecoxib and Docetaxel) and the other one used only celecoxib, due to an adverse event (hyperglycemia) occurred before chemotherapy treatment starting, leading to your study withdrawn.

Four (67%) patients received all 6 cycles of docetaxel. One (17%) patient, due to the occurrence of a serious adverse event (pneumonia), had the third infusion delayed for four weeks, leading to his withdrawal from the study, after having received two cycles of chemotherapy.

The following flow chart describes the distribution of patients:

6 enrolled

?

6 treated

1 received celecoxib only due to adverse event (hyperglycemia) and withdrawn from the study before the start of chemotherapy with Docetaxel

?

1 withdrawn during treatment phase due to serious adverse event (pneumonia)

4 completed

A total of 26 infusions of Docetaxel were administered, being in 10 (38.5%) cycles delivered at 75mg/m² and in 16 (61.5%), delivered at 60 mg/m². The reason for the dose reduction was the adverse events: febrile neutropenia or neutropenia grade IV. From the total, 3 (11.5%) infusions were delayed, in two cases due to holiday and in the other one due to personal reason.

After inclusion of the six first patients, on 30/11/2004, the enrollment was suspended due to febrile neutropenia occurrence in two (33.3%) of them, in order to conduct an interim safety analysis.

Due to the advisory, released by the FDA, of potential Cardiovascular risk with Celecoxib, the inclusion was no more opened, although no cardiovascular events had occurred until that moment.

Efficacy results:

From the total number of patients included, two didn't have the PSA response evaluation at the end of study. One of them due to no PSA measurement at baseline and, the other one, due to an adverse event (hyperglycemia) occurred before chemotherapy treatment, leading to the patient withdrawal from the study.

Table 1 presents PSA response evaluation results.

Table 1- PSA response evaluation.

Number of patient	PSA Baseline	PSA evaluation End of Study			Comments
	ng/mL	ng/mL	Evaluation	Reduction	
101	ND	114	-	-	The first measurement was done in the 2nd cycle (220 ng/mL)
102	325	117	Response	36%	
401	510	316	Stable	62%	
501	7,4	7,1	Stable	96%	
701	1840	ND	-	-	Left the study due to AE hyperglycemia
702	60,35	70,3	Stable	116%	Left the study due to SAE (pneumonia) - The last evaluation was performed after cycle 2

Only one (17%) patient had PSA response reported by the investigator. The CI 95% associated for this rate of PSA response is [2%;32%].

Safety results:

All six patients included in the study have reported some adverse event. The most frequently adverse events were febrile neutropenia (83%) and abdominal pain (67%), followed by Aalopecia, diarrhea and peripheral edema (all of them presented in 50% of the patients).

The most frequent WHO grade 3 and 4 toxicities were febrile neutropenia (5 pts, 83%) and neutropenia with no fever (2 pts, 33%).

The table 2 shows all adverse events observed and the number of patients that presented each one, taking in account the higher degree of the events.

Table 2 - Adverse events (higher degree) – Number of patients (Intent to treat population).

Adverse Event	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	n	%	n	%	n	%	n	%	n	%
Nº of patients									*6*	*100%*
Febrile Neutropenia							5	83%	5	83%
Abdominal pain	3	50%	1	17%					4	67%
Alopecia	3	50%							3	50%
Diarrhea	3	50%							3	50%
Peripheral edema	2	33%	1	17%					3	50%
Asthenia/Fatigue	1	17%	1	17%					2	33%
Constipation	2	33%							2	33%
Edema Lower Limb	2	33%							2	33%
Epigastralgia	2	33%							2	33%
Nausea	2	33%							2	33%
Neutropenia							2	33%	2	33%
Vomiting	2	33%							2	33%
Anorexia	1	17%							1	17%
Anxiety	1	17%							1	17%
Back pain	1	17%							1	17%
Coryza	1	17%							1	17%
Cramp	1	17%							1	17%
Dermatitis	1	17%							1	17%
Dyspepsia	1	17%							1	17%
Hyperglycemia					1	17%			1	17%
Insomnia	1	17%							1	17%
Intestinal colica	1	17%							1	17%
Lacrimation	1	17%							1	17%
Leukopenia							1	17%	1	17%
Lumbago					1	17%			1	17%
Paresthesia	1	17%							1	17%
Pneumonia					1	17%			1	17%
Rectal bleeding	1	17%							1	17%
Shoulder pain	1	17%							1	17%
Sore throat	1	17%							1	17%
Syncope					1	17%			1	17%
Taste alteration	1	17%							1	17%
Taste reduced	1	17%							1	17%
Urinary dificulty	1	17%							1	17%
Visual acuity reduced	1	17%							1	17%

Safety results (continuation):	Serious adverse events were reported in 5 patients. The events are showed below, in the Table 3. Table3 – Serious adverse events (Number of patients). **Serious Adverse Event** / **Nº of patients** *Total Number of patients: 6 (100%)* Febrile Neutropenia — 5 (83%) Neutropenia — 2 (33%) Rectal bleeding — 1 (17%) Syncope — 1 (17%) Pneumonia — 1 (17%) For one patient, due to the occurrence of pneumonia, the chemotherapy was delayed for four weeks, leading to his withdrawal from the study, after having received two cycles of chemotherapy. All patients who experienced febrile neutropenia or neutropenia grade 4 with no fever had a decrease in docetaxel dosage from 75mg/m² to 60mg/m² in the next chemotherapy cycles. After inclusion of the six first patients, the enrollment was suspended due to febrile neutropenia occurrence in two (33.3%) of them, and it was conducted an interim safety analysis. As a result, it was decided to decrease the docetaxel dose to 60mg/m² in all cycles and the submission of a new protocol amendment with this new feature, but the study was definitely interrupted due to celecoxib safety issues released by the FDA.
Date of report:	06-Jun-2007