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Sponsor / Company: Sanofi Drug substance(s): XRP6258 (Cabazitaxel)	Study Identifiers: NCT01576029, UTN U1111-1119-8381 Study code: CABAZ_L_05933
Title of the study: Phase II randomized study of continuing treatment with DOCETAXEL versus switching to CABAZITAXEL after minor prostate antigen specific response to DOCETAXEL in the first line treatment of patients with castration-resistant metastatic prostate cancer (CABAZ_L_05933)	
Study center(s): 08 sites opened in Brazil with 04 active sites (screened patients)	
Study period: Date first patient enrolled: 29/Aug/2012 Date last patient completed: 06/Dec/2013	
Phase of development: Phase 2	
Objectives: The primary objective of the study was to compare the continuation of treatment with docetaxel versus switching to cabazitaxel regarding the time to prostate-specific antigen (PSA) progression (Time to Progression [TTP]-PSA) in patients with castration-resistant metastatic prostate cancer (CRPC) who, after 4 cycles of docetaxel, had minor PSA response (defined as reduction between 1% and 49%) or increase of up to 24% in PSA levels, and TTP-PSA as the primary endpoint of the study. In this study, PSA progression was defined as an increase of at least 25% in the serum marker PSA compared to the nadir value. Nadir value is defined as the minimum PSA level when compared to all PSA values obtained for the patient from Screening visit (inclusive). The secondary objectives were to compare continuation of treatment with docetaxel versus switching to cabazitaxel in patients with CRPC that, after 4 cycles of docetaxel, had minor PSA response (defined as reduction between 1% and 49%) or increase of up to 24% in the PSA levels; and PSA response rate (decrease of at least 50%), as well as overall survival (OS) and incidence of adverse events (AEs).	
Methodology: Phase 2, national, multicenter, randomized, open-label, parallel - comparative study with active comparator (docetaxel). Randomization was to follow a 1:1 ratio, and stratification was to be done according to PSA response after 4 cycles of docetaxel (reduction of 1% to 24%, 25% to 49%, or increase of up to 24%). It was planned to randomize 78 patients (39 per treatment arm): - Control group: docetaxel at conventional dose (75 mg/m^2 on Day 1 every 21 days) + prednisone (or prednisolone) 5 mg orally twice daily. - Experimental group: cabazitaxel (dose of 25 mg/m^2 on Day 1 every 21 days) + prednisone (or prednisolone) 5 mg orally twice daily. The study comprised the visits described below: Screening and Randomization: - V1 and V0: Enrollment visits, maximum of 7 days after administration of the last dose of docetaxel (4th cycle of the pre-study period). - RV: Randomization visit, within a maximum period of 21 days after administration of the last dose of docetaxel (4th cycle of the pre-study period). Treatment Period: - V1, V2, V3, V4, and VF: Treatment visits, every 21 days until the VF - End of Treatment Visit (30 to 98 days or until PSA progression or occurrence of unacceptable toxicity). Follow-up Period: - OS analysis every 12 weeks, planned for 2 years after End of Treatment Visit.	

Number of patients:	Planned: 78
	Randomized: 2
	Treated: 2
Evaluated:	
	Safety: 2

Diagnosis and criteria for inclusion:

Men ≥18 years old with histological documented prostate cancer, stage 4 or metastatic CRPC who progressed with hormone deprivation, including the withdrawal of antiandrogen-class drugs for at least 4 weeks, and 6 weeks for bicalutamide or if documented that PSA did not decrease during 3 months of this therapy; documentation of metastasis by imaging (computerized tomography [CT], magnetic resonance imaging, or bone scan), in patients with PSA <20 ng/mL at the time of inclusion; provide minor PSA response (characterized by a reduction between 1% and 49%) or increase up to 24% in PSA levels, in relation to the value measured before starting docetaxel therapy, measured at least 7 days after the fourth cycle of docetaxel (only rounded values to natural numbers should be considered); patient has received 4 cycles of docetaxel at a dose of 75 mg/m^2; performance status of 0 or 1, according to the Eastern Cooperative Oncology Group scale; marrow, liver, and renal function within acceptable values (serum creatinine <1.5 × upper limit of normal [ULN], total bilirubin <1 × ULN, aspartate transaminase [AST]/serum glutamic oxaloacetic transaminase [SGOT] <1.5 × ULN, alanine transaminase [ALT]/serum glutamic pyruvic transaminase [SGPT] <1.5 × ULN, white blood cells ≥3000/mm^3, granulocytes ≥1500/mm^3, hemoglobin ≥10 g/dL, neutrophils ≥1500/mm^3, platelets ≥100 000/mm^3); life expectancy exceeding 12 weeks; PSA ≥2 ng/mL; and testosterone level ≤50 ng/dL (for patients with no history of orchiectomy).

Main exclusion criteria: Prior use of chemotherapy, except for docetaxel for 4 cycles; documented disease progression during treatment with docetaxel (first 4 cycles) characterized by the appearance of new lesions on CT scan, bone scan, or clinical examination; patients with metastases resulting in neurological damage; inability to continue receiving gonadotropin-releasing hormone agonists in patients with no history of orchiectomy; use of recombinant methionyl human granulocyte-colony stimulating factor non-glycosylated (G-CSF) in the 24 hours preceding V0; any other current neoplasia or over the past 5 years, except for basal cell skin carcinoma or squamous skin cell carcinoma; known seropositivity for human immunodeficiency virus; concomitant diseases, such as significant neurological or psychiatric disease; and uncontrolled hyperkalemia or any other serious comorbidity.

Study treatments

Investigational medicinal product(s): Cabazitaxel - Jevtana® - test drug

Formulation: Infusion concentration of 60 mg/1.5 mL in a package with one 15 mL vial containing 1.5 mL and one 15 mL vial containing 4.5 mL of diluent.

Route of administration: Intravenous (IV)

Dose regimen: 25 mg/m^2 - administered as a 1-hour IV infusion every 3 weeks

Investigational medicinal product(s): Docetaxel - TAXOTERE® - reference drug (active control)

Formulation:

- Taxotere 20 mg: Each vial contains 21.35 mg of docetaxel trihydrate, equivalent to 20 mg of anhydrous docetaxel in 0.5 mL of polysorbate 80 (volume: 24.4 mg/0.61 mL).

- Taxotere 80 mg: Each vial contains 85.4 mg of docetaxel trihydrate, equivalent to 80 mg of anhydrous docetaxel in 2.0 mL of polysorbate 80 (volume: 94.4 mg/2.36 mL).

Each mL of product contains no infusion concentrate of 40 mg of anhydrous docetaxel.

Route of administration: IV

Dose regimen: 75 mg/m^2 every 3 weeks

Duration of treatment: Treatment duration was until disease progression by PSA levels or progression for measurable or non-measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST), or appearance of unacceptable toxicity, whichever came first. These factors were to be assessed periodically during the study.

Duration of observation: Screening occurred within a maximum period of 21 days after administration of the last dose of docetaxel (4th cycle of the pre-study period). After randomization, study visits were conducted every 21 days until the end of treatment (30 to 98 days or until PSA progression or occurrence of unacceptable toxicity). The number of visits performed by the patients depended on the duration of their treatment. Post-treatment follow-up for OS analysis planned for 2 years after End of Treatment Visit or until the occurrence of death, whichever came first. Visits would take place every 12 weeks.

The first patient was included in August 2012 and the second in December 2012. The study was kept open until December 2013, but no more patients could be enrolled with a minor PSA response (defined as reduction between 1% and 49%) or increased up to 24% in PSA levels after administration of four cycles of docetaxel.

Criteria for evaluation:

Efficacy:

Primary Criteria: The primary efficacy endpoint was TTP-PSA, considering the time elapsed between the start of treatment until disease progression by PSA. In this study, progression was defined as an elevation of at least 25% in serum PSA levels compared to nadir value together with an absolute increase of more than 2 ng/ml, and requiring two consecutive increases in PSA (considering only values rounded to integers), obtained at least 3 weeks apart. The evaluation of disease progression was performed every 21-day treatment cycle, in both groups, using PSA. PSA progression was to be recorded at the time of the first increase ≥25% compared to nadir.

Secondary Criteria: PSA response rate (≥50% reduction) and OS will be considered secondary efficacy endpoints.

1) PSA response rate was defined by reduction of at least 50% of PSA values (≥50% reduction) compared to nadir. For such, it was to be required at least two PSA measurements, with at least 3 weeks apart.
2) Overall survival was defined as the time elapsed between the date of starting treatment until death by any cause, censoring patients for whom there was no death and those who were lost to follow-up or if the final analysis date has been reached, whichever came first. The evaluation of OS was to continue for another two years after patient completed treatment, and it was anticipated that this assessment could be compromised if a large number of patients in the control group received cabazitaxel after progression.

Safety: Regardless of relationship and possibly related. Patients were evaluated throughout the study regarding the occurrence of AEs and serious adverse events (SAEs). These were listed along with the degree of severity (all grades and grades ≥3) for both groups. There was also a comparative analysis of AEs of interest (AEI) between groups and, for this study, the following are selected as AEI: neutropenia, febrile neutropenia, anemia, leucopenia, and diarrhea. Data were collected from the electronic case report form, through the section Adverse Event, in order to compare the occurrence of AEs in the cabazitaxel group with the docetaxel group.

Efficacy was not evaluated once the study was prematurely terminated due to low recruitment, so only descriptive analysis was performed.

Summary:

Patient Selection

Between 29/Aug/2012 and 23/May/2013, 4 patients were screened for the study in four different sites. Of these patients, 3 met all inclusion criteria and none of the exclusion criteria, being then randomized, both to the docetaxel arm.

The patients were randomized to Sites 007 and 006.

First randomized patient –Patient 001
The dates of visits on Site 007 are presented in the following table. Note that the last follow-up visit (VPT3) occurred on 14/Nov/2013.

Table 1. Date of visits on Site 007

Visit (*)	Date
V-1	19/Oct/2012
V0	26/Oct/2012
VR	30/Oct/2012
V1	22/Nov/2012
V2	13/Dec/2012
V3	03/Jan/2013
V4	24/Jan/2013
V5	14/Feb/2013
VPT1	14/May/2013
VPT2	13/Aug/2013
VPT3	14/Nov/2013

(*) VX: Visit X; VPTX: Follow-up Visit X

Prostatic cancer history: The histologic diagnosis of prostatic cancer occurred on 15/Jul/2010, with stage TNM TX, NX, M1, Gleason grade 4, and the patient had metastasis on the cervical column.

Previous docetaxel for prostate cancer: The patient received 4 docetaxel 75 mg/m² doses.

Previous hormonal therapies for prostate cancer: The patient received hormonal therapy with bicalutamide.

Prior surgery for androgen ablation: On 30/Sep/2010, bilateral orchiectomy surgery was performed.

Concomitant medication: During the treatment, the following concomitant medications were used by the patient: simvastatin, metoclopramide, amitriptyline, methadone, cyclobenzaprine, dipyrone, omeprazole, calcium carbonate, cholecalciferol, magnesium hydroxide, nystatin, zoledronic acid, prednisone, and Duasorb.

PSA evaluation during treatment: The PSA was measured in all patient visits. They decreased along the visits.

Premedication: Dexamethasone was administered to the patient prior to docetaxel at all visits. Antihistamine and H2 antagonist were not administered at any of the visits.

Prednisolone or prednisone: It was administered as planned during all treatments (5 mg twice a day).

Administration of docetaxel: The administration of docetaxel (75 mg/m²) occurred as planned. The dose was neither reduced nor interrupted. There were no problems during the administration of this drug.

End of treatment: The date of early discontinuation and of last contact was 14/Feb/2013, and the date of last administration of the study treatment was 24/Jan/2013. The reason to discontinue or end of the study treatment was “Intolerable adverse event related to the administration of study treatment”. The duration of treatment was 87 days (Date of last administration - Date of first administration + 1).

Death: Occurred on 04/Dec/2013 and the primary cause of death was an unrelated bacterial intestinal infection. No autopsy was performed. The death occurred during the follow-up period, 314 days after study treatment. This information was reported in the "Death Form", and not as an SAE, according to the protocol: During the follow-up period, only AEs/SAEs related to the study medication per investigator's judgment should be reported.

Second randomized patient – Patient 002

The dates of visits at Site 006 are presented in the following table. Note that the last follow-up visit (VPT1) occurred on 06/Dec/2013.

Table 2. Date of visits on Site 006

Visit (*)	Date
V-1	05/Dec/2012
V0	10/Dec/2012
VR	17/Dec/2012
V1	08/Jan/2013
V2	29/Jan/2013
V3	19/Feb/2013
V4	12/Mar/2013
V5	09/Apr/2013
V6	30/Apr/2013
V7	21/May/2013
V8	18/Jun/2013
V9	09/Jul/2013
V10	30/Jul/2013
V11	20/Aug/2013
V12	10/Sep/2013
V13	15/Oct/2013
VPT1	06/Dec/2013

(*) VX: Visit X; VPTX: Follow-up Visit X

Prostatic cancer history: The histologic diagnosis of prostatic cancer occurred on 23/Jun/2000, with stage TNM T2, N0, M0 and Gleason unknown grade. The patient later presented with bone metastasis in 2012 (bone scan 13/Dec/2012).

Previous docetaxel for prostate cancer: The patient received 4 docetaxel 75 mg/m² doses.

Previous hormonal therapies for prostate cancer: The patient received the following hormonal therapy for prostatic cancer:

1) Zoladex 10.8 mg every three months, since 06/Sep/2010;
2) Casodex 50 mg every day, between 27/Apr/2011 and 21/Dec/2011;
3) Ketoconazole 200 mg three times a day, between 07/Mar/2012 and 19/Sep/2012.

.*Prior surgery for androgen ablation:* Not performed.

Concomitant medications: During the treatment, the following concomitant medications were used by the patient: tramadol, tramadol hydrochloride, morphine, thiamine, benfotiamine, gabapentin, glibenclamide, losartan, bromopride, loperamide, ondansetron, diosmin+hesperidin, saline solution 0.9%, norfloxacin, pregabalin, thioctacid, amitriptyline, ciprofloxacin, prednisone, zoledronic acid, goserelin, and Imosec.

PSA evaluation during treatment: The PSA was measured in all visits with decreasing values up to the last visit (V13), when an increase in relation to nadir was noticed.

Premedication: Dexamethasone was administered to the patient prior to docetaxel at all visits. Antihistamine and H2 antagonist were not administered at any of the visits.

Prednisolone or prednisone: It was administered as planned during all the treatment (5 mg twice a day).

Administration of docetaxel: The administration of docetaxel (75 mg/m²) occurred at visits VR, V1 to V12. At Visit 5 the administration was delayed by an AE (diarrhea grade 2 and vomiting grade 2). In neither of them was the dose reduced or the treatment interrupted.

End of treatment: The date of early discontinuation and of last contact was 15/Oct/2013, and the date of last administration of the study treatment was 10/Sep/2013. The reason to discontinue or end of the study treatment was "Intolerable adverse event related to the administration of study treatment". The duration of treatment was 267 days (Date of last administration - Date of first administration + 1).

Adverse Events

During the study, no SAE or overdose was reported.

A total of 31 AEs were reported for both randomized patients from docetaxel group, and 19 of them were considered related to the study treatment. Specific AEs caused the withdrawal of both patients from the study. The summary result is presented on Table 3.

Table 4 presents a list of AEs by patient, according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The 2 patients presented with 11 and 20 AEs, respectively. Only one AE, Gastrointestinal Disorders (SOC) - Diarrhea (PT), reported by the second patient had a start date more than 30 days after the last dose (last dose administration: 10/Sep/2013; AE: 13/Oct/2013).

Table 5 presents a list of all AEs related to the study treatment, according to MedDRA SOC and PT. The most frequently reported events were related to SOC "Gastrointestinal Disorders", with 4 episodes of diarrhea and 4 of vomiting, all reported by the second patient. The PT "Oedema Peripheral" was the only AE reported for both patients.

Adverse events that caused the withdrawal from the study are described below:

The first patient presented with General Disorders and Administration site conditions (SOC) - Oedema Peripheral (PT), grade 3, and corrective treatment was performed (outcome: recovered - 14/May/2013). The patient also presented with a grade 3 Nervous System Disorders (SOC) - Paresthesia (PT) AE for which no corrective treatment was taken (outcome: not recovered).

The second patient presented with Nervous System Disorders (SOC) - Polyneuropathy (PT), grade 2, which started on 25/Jun/2013, possibly related to the study treatment. No corrective treatment was taken (outcome: recovering). On 03/Oct/2013, the AE increased to grade 3. The patient received corrective treatment and was permanently discontinued from the study (outcome: not recovered).

Table 4. Adverse Events Summary

Adverse Events	Test Group (Cabazitaxel Group) Nb. Patients (N=0)	Nb. Events	Control Group (Docetaxel Group) Nb. Patients (N=2)	Nb. Events
Any	-	-	2 (100%)	31
Related to, according to the investigator to study treatment	-	-	2 (100%)	19
Serious	-	-	-	-
Serious and related to study treatment	-	-	-	-
Causing death	-	-	-	-
Related and causing death	-	-	-	-
Leading to study withdrawal	-	-	2 (100%)	3
Related and leading to study withdrawal	-	-	2 (100%)	3

Table 5. List of Adverse Events by patient, according to MedDRA System Organ Class (SOC) and Preferred Term (PT)

SOC	PT	Patient 001	Patient 002	Total
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	-	1	1
EYE DISORDERS	LACRIMATION INCREASED	1	1	2
GASTROINTESTINAL DISORDERS	DIARRHEA	-	8	8
	VOMITING	-	4	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	1	-	1
	MUCOSAL INFLAMMATION	-	1	1
	OEDEMA PERIPHERAL	2	2	4
	SWELLING	1	-	1
INFECTIONS AND INFESTATIONS	PARONYCHIA	1	-	1
	URINARY TRACT INFECTION	-	2	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	LIMB INJURY	1	-	1
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	1	-	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	1	-	1
NERVOUS SYSTEM DISORDERS	DIZZINESS	1	-	1
	PARAESTHESIA	1	-	1
	POLYNEUROPATHY	-	1	1
Total		11	20	31

Table 6. List of Adverse Events related to the study treatment, according to MedDRA System Organ Class (SOC) and Preferred Term (PT)

Adverse Events related to study treatment		Test Group (Cabazitaxel Group)		Control Group (Docetaxel Group)	
SOC	PT	Nb. Patients (N=0)	Nb. Events	Nb. Patients (N=2)	Nb. Events
EYE DISORDERS	LACRIMATION INCREASED	-	-	1 (001)	1
GASTROINTESTINAL DISORDERS	DIARRHEA	-	-	1 (002)	4
	VOMITING	-	-	1 (002)	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	-	-	1 (001)	1
	MUCOSAL INFLAMMATION	-	-	1 (002)	1
	OEDEMA PERIPHERAL	-	-	2	3
	SWELLING	-	-	1 (001)	1
INFECTIONS AND INFESTATIONS	PARONYCHIA	-	-	1 (001)	1
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	-	-	1 (001)	1
NERVOUS SYSTEM DISORDERS	PARAESTHESIA	-	-	1 (001)	1
NERVOUS SYSTEM DISORDERS	POLYNEUROPATHY	-	-	1 (002)	1

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