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

Sponsor / Company: Sanofi **Drug substance(s):** XRP6258 (cabazitaxel)	**Study Identifiers:** NCT01324583, UTN U1111-1115-4154 **Study code:** TED11576
Title of the study: An open label, dose escalation, safety and pharmacokinetics Phase I study with cabazitaxel administered as a 1-hour intravenous infusion every 3 weeks in combination with daily prednisolone in patients with Hormone Refractory Prostate Cancer	
Study center(s): 21 sites in Japan	
Study period: Date first patient enrolled: 24/Jan/2011 Study Cut-off Date for statistical analyses: 07/May/2013 Safety data update: 13/Mar/2015 Date last patient completed: 20/Nov/2014 (last patient last vist)	
Phase of development: Phase 1	
Objectives: **Primary:** • To assess the tolerability of cabazitaxel at 2 to 3 dose levels including global dose in Japanese patients when given as a short (1 hour) intravenous (IV) infusion. **Secondary:** • To define the safety profile of the drug. • To evaluate pharmacokinetic (PK) profile. • To evaluate preliminary antitumor activity.	
Methodology: Multicentre, open-label dose-escalation study, nonrandomized.	
Number of patients: Planned: Approximately 3 to 6 patients for each dose levels (20 and 25 mg/m^2) in the dose-escalation cohort of the study, and 40 patients in the expansion cohort of the study at maximum tolerated dose (MTD) Enrolled-treated: 7 (dose escalation cohort); 41 (expansion cohort) **Evaluated:** Safety: 7 (dose escalation cohort); 41 (expansion cohort) Efficacy: 41 (expansion cohort) DLT: 6 (dose escalation cohort); 41 (expansion cohort) Pharmacokinetics: 7 (dose escalation cohort); 10 (expansion cohort)	

Diagnosis and criteria for inclusion:

Main Inclusion criteria:

I 01. Diagnosis of histologically or cytologically proven prostate adenocarcinoma, that is refractory to hormone therapy (received prior castration by orchiectomy and/or internal medicine, and documented progression of disease or relapse) who has previously been treated with docetaxel.

I 02. Signed informed consent prior to beginning protocol specific procedures.

I 03. Patients with prostate specific antigen (PSA) >20 ng/mL at screening (expansion cohort).

Main Exclusion criteria:

E 01. Age <20 and >74.

E 02. Life expectancy <12 weeks.

E 03. Eastern Cooperative Oncology Group (ECOG) performance status ≥2.

E 04. Prior surgery ≤4 weeks of registration in the study.

E 05. Active secondary cancer including prior malignancy from which the patient has been disease-free for ≤5 years (however, adequately treated superficial basal cell skin cancer before 4 weeks prior to registration can be eligible to the study).

E 06. Inadequate organ function including:

- Neutrophils <2.0 x 10^9/L
- Platelets <100 x 10^9/L
- Hemoglobin <9.0 g/dL (transfusion prohibition within 14 days before registration)
- Creatinine >1.5 mg/dL
- Total bilirubin >1.5 times the upper normal limits of the institutional norms
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >1.5 times the upper normal limits of the institutional norms

E 07. Patients who have received previous treatment with chemotherapy including taxane provided that they have any residual signs of its toxicity (except alopecia any grade and peripheral neuropathy Grade 1).

E 08. Known brain or leptomeningeal involvement.

E 09. Previous extensive radiotherapy (>25% of bone marrow area).

E 10. Current peripheral neuropathy of Grade ≥2 according to the National Cancer Institute (NCI) common toxicity criteria (ver 4.0).

E 11. Other serious illness or medical conditions:

a) Congestive heart failure or angina pectoris even if medically controlled. Previous history of myocardial infarction within 1 year from study registration, uncontrolled hypertension or arrhythmias.
b) Existence of significant neurologic or psychiatric disorders including dementia or seizures.
c) Active infection.
d) Uncontrolled peptic ulcer, unstable diabetes mellitus or other contra-indications (eg, posterior subcapsular cataract) for the use of corticosteroids.
e) Active uncontrolled Gastroesophageal Reflux Disease (GERD).

E 12. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational drug within 28 days prior to patient registration.

E 13. Concurrent treatment with any other anticancer therapy or radiotherapy within 28 days prior to patient registration.

E 14. Known acquired immunodeficiency syndrome (AIDS-related illnesses) or known HIV disease requiring antiretroviral treatment.

E 15. Active varicella zoster infection, anti-hepatitis virus (HCV) antibody-positive (excluding patients negative for HCV virus in blood test or nonactive seropositive patients with no hepatic abnormalities[AST, ALT, etc]), or hepatitis B surface (HBs) antigen-positive.

E 16. Patients who cannot adhere to the effective contraception during period from the time the patient gives informed consent until 3 months after last study drug administration.

E 17. Prior history of severe hypersensitivity reaction (Grade ≥3) or intolerance to prednisolone.

E 18. Prior history of severe allergic reaction to taxane.

E 19. Prior history of severe hypersensitivity reaction (Grade ≥3) to polysorbate 80 containing drugs.

E 20. Concurrent or planned treatment with strong inhibitors of CYP3A4. A 1 week washout period is necessary for patients who are already on these treatments.

E 21. Patients with alcoholic hypersensitivity.

E 22. Previous treatment with <225 mg/m^2 cumulative dose of Taxotere® (or docetaxel) (expansion cohort).

Study treatments

Investigational medicinal product(s): Cabazitaxel

Formulation:

Cabazitaxel:

Cabazitaxel was supplied as a sterile, non-pyrogenic, non-aqueous yellowish to brownish yellow, 60 mg/1.5 mL concentrate for solution for infusion. It was packaged in 15 mL single dose clear type I glass vial stoppered with a rubber closure. The stopper was crimped to the vial with a light green flip-off aluminum cap. The solution contained the following excipient: Polysorbate 80.

Solvent:

The solvent for cabazitaxel was supplied as a 13% w/w ethanol solution in water for injection. This solvent was supplied in a 15 mL single dose clear type I glass vial stoppered with a rubber closure and capped with a light gray flip-off aluminum cap.

The preparation of the cabazitaxel infusion solution for administration required preparation of a premix solution at 60 mg/6 mL (nominal concentration). This had to be done with a 13% w/w ethanol solution in water for injection supplied with the cabazitaxel concentrate for solution for infusion.

Each cabazitaxel vial and each solvent vial were overfilled to ensure that 60 mg dose could be extracted after the preparation of the premix. Each vial of cabazitaxel had to be diluted with the ENTIRE content of the solvent vial.

Route(s) of administration: IV infusion

Dose regimen:

Patients were to receive cabazitaxel as the dose of corresponded level 1-hour intravenous infusion every 3 weeks plus prednisolone 10 mg orally given daily:

Dose Level	Cabazitaxel Dose
Level -1	15 mg/m²
Level 1	20 mg/m²
Level 2	25 mg/m²

These premedications were to be administered by IV infusion, at least 30 minutes prior to each dose of cabazitaxel.

- Antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or other antihistamine)
- Steroid (dexamethasone 8 mg or equivalent steroid)
- H2 antagonist (Ranitidine or other H2 antagonist with the exception of cimetidine)

Dose escalation:

1. At first, 3 patients were to be treated with cabazitaxel at the initial dose level 1 of 20 mg/m² and were to be assessed for dose limiting toxicities (DLTs) in Cycle 1. If none of the 3 patients experience any DLTs in Cycle 1, the dose were to be escalated to the next level 2 (25 mg/m²). If 1 of the 3 patients experiences DLT(s), 3 patients were to be additionally enrolled to this dose level 1, and the safety profiles were to be evaluated for all of the 6 patients. If no more than 1 of the 6 patients experiences DLT(s), the dose were to be escalated to the next level 2.
2. At dose level 2 of 25 mg/m², if none of the 3 patients experience any DLTs in Cycle 1, this dose is to be the MTD, and no further dose escalations were to be conducted in this study. If 1 of the 3 patients experiences DLT(s), 3 patients were to be additionally enrolled to this dose level 2. If no more than 1 of the 6 patients experiences DLT(s), the dose was to be the MTD.
3. If 2 or more of the 6 patients experience any DLTs at dose level 2 of 25 mg/m² in Cycle 1, the dose level1 of 20 mg/m² was to be the MTD and the dose level 2 of 25 mg/m² was to be the maximum administered dose (MAD).

4. The safety profiles of cabazitaxel was to be evaluated in more detail at the MTD in 40 patients. When approximately 10 additional patients had completed cycle 1, the Efficacy and Safety Evaluation Committee were to evaluate safety in these patients and were discuss with the Sponsor whether any safety issue is detected; and, were to provide any recommendation (including continuation of this study) as required. The Sponsor was to decide whether or not to continue this study based on discussion with the Efficacy and Safety Evaluation Committee and the Investigators. In addition, conditional probability distribution for the number of DLT occurrences (at the end of the study) were to be estimated and reported to the members of Efficacy and Safety Evaluation Committee (a meeting was to be held if needed), each time when 10 new patients in the expansion cohort have completed cycle 1 (ie, when 10, 20, 30, and 40 patients had completed cycle 1). Assuming non-informative prior which was a beta distribution Be(1,1), updated posterior was to also be estimated and reported at the same timing.

In general, the safety profiles in Cycle 1 periods were used to decide the dose escalations. All of the dose escalations were to be conducted after coming to an agreement between the Investigators and the Sponsor.

Duration of treatment: The duration of screening within 28 days, treatment 3 weeks/cycle.

Duration of observation: The duration of follow-up 30 days after the last cabazitaxel administration.

The patients who continue to receive the investigational product (IP) after the study cut-off date were to be followed until disease progression, unacceptable toxicity or willingness to stop, with a minimum of 30-day follow-up after the last IP administration.

Criteria for evaluation:

Efficacy:

Prostate specific antigen response (in patients with PSA >20 ng/mL at screening): Response requires a PSA decline of ≥50% confirmed by a second PSA value at least 3 weeks later.

Time to PSA progression (all patients): Evaluate time to PSA progression in PSA responders and non-responders.

Overall Response Rate (in patients with measurable disease): Objective responses (complete response [CR] and partial response [PR]) for measurable disease as assessed by Investigators according to Response Evaluation Criteria in Solid Tumors (RECIST ver 1.1).

Safety:

Dose limiting toxicity during the first cycle of IV cabazitaxel.

Physical examination, laboratory safety tests, adverse events (AEs).

Pharmacokinetics:

Maximum plasma concentration (C_{max}), Area under concentration time curve (AUC), clearance (CL), Distribution Volume at steady state (V_{ss}), Terminal half-life ($t_{1/2\gamma}$), Concentration at trough (C_{trough}).

Statistical methods:

Determination of the sample size:

At each dose level, 3 or 6 patients were to be registered and treated (as the dose escalation cohort). After completion of the dose escalation cohort, 40 patients were to be registered and treated at the MTD. The actual sample size may vary depending on the incidence of DLT during Cycle 1. Approximately, 46 patients were to be registered and treated in the trial.

Assuming a true incidence of DLT to be 20%, with a sample size of 43 patients in the 25 mg/m^2 group, there was a greater than 90% probability that the 90% CI half-width of estimated DLT rate were to be no more than 0.13. This sample size also provided an expected 90% CI from 10.9% to 32.5% which does not exceed the targeted 33% DLT rate.

Analysis Population:

The safety population was to be the all treated patients defined as enrolled patients who received at least 1 (even if incomplete) infusion of cabazitaxel. The efficacy population was to include all patients enrolled as the expansion cohort. Pharmacokinetic analysis was to be performed in patients who receive the treatment and have at least 1 post dose sample.

Patients evaluable for DLT assessment (DLT population) was the subset of patients from the all treated population with dose limiting toxicity form completed during Cycle1. In practice, a "Dose Limiting toxicities" form should have been filled in at the end of the cycle1. Patients with important protocol deviations during Cycle 1 were not to be included in the evaluable for DLT population. However patients experience a DLT during Cycle1 were to be considered as evaluable for DLT. Patients excluded from this population were to be replaced. Investigators and the sponsor discussed and confirmed them, if necessary.

Safety and efficacy Analysis:

For safety analysis, dose limiting toxicities were to be summarized by dose level. Treatment emergent adverse events (TEAEs) were to be summarized with respect to frequency, incidence, intensity/severity (as graded by the NCI Common Terminology Criteria for Adverse Events [CTCAE], ver. 4.0) by dose level. All AEs were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system. Serious adverse event (SAE) and deaths were to be listed regardless of study drug relatedness.

Anti-tumor activity as assessed by the best overall response using RECIST version 1.1, time to PSA progression, and PSA response were to be listed by dose level.

Overall response rate (ORR), PSA response, and time to PSA progression were to be summarized for the expansion cohort.

Pharmacokinetic analysis:

Pharmacokinetics parameters were to be summarized with descriptive statistics.

Planned Databases lock date:

Data base lock was planned 4 weeks after from last patient last visit.

Summary:

Population characteristics:

This report was prepared based on data for cycles that have been completed by 07 March 2013. A total of 48 patients were administered with cabazitaxel in this study. In the dose escalation cohort, 4 patients were treated in the 20 mg/m^2 and 3 patients in the 25 mg/m^2 dose. In the expansion cohort, 41 patients were treated at the 25 mg/m^2 dose. All 48 patients (4 patients in the 20 mg/m^2 and 44 patients in the 25 mg/m^2) were included in the safety population. Of these, 46 patients (3 patients in the 20 mg/m^2 and 43 patients in the 25 mg/m^2) were evaluable for DLT.

Safety results:

Total of 57 and 338 cycles were administered at 20 and 25 mg/m^2 dose levels, respectively. In the 20 mg/m^2 dose level, the median number of cycles was 8.0 (range: 5 - 36), and the median relative dose intensity was 0.839. In the 25 mg/m^2 dose level, the median number of cycles was 7.5 (range: 1 - 29), and the median relative dose intensity was 0.817.

None of the evaluable patients in the dose escalation cohort expressed a DLT, and 25 mg/m^2 was selected as the MTD. In the dose expansion cohort (25 mg/m^2), 2 patients expressed DLTs. Observed DLTs were necrotizing fasciitis (Grade 4) and septic shock (Grade 4) in 1 patient, and otitis media chronic (Grade 3) and bronchopneumonia (Grade 3) in another patient. At the MTD (25 mg/m^2), the occurrence rate of DLT was 4.7% (90% CI: 0.8% - 13.9%).

All patients had at least 1 any grade and Grades 3, 4 TEAEs. At the MTD (25 mg/m^2), common all grade TEAEs were neutropenia in 44 patients (100%), febrile neutropenia and fatigue in 25 patients (56.8%) each, nausea in 23 patients (52.3%), diarrhoea in 23 patients (52.3%), and decreased appetite in 21 patients (47.7%). Common Grade 3, 4 TEAEs were neutropenia in 44 patients (100%), febrile neutropenia in 25 patients (56.8%), and anaemia in 14 patients (31.8%).

There was no TEAE with an outcome of death within 30 days of the last dose of study drug. One patient in the expansion cohort (25 mg/m^2) died 34 days after the last cabazitaxel administration due to disease progression. Another patient in the expansion cohort (25 mg/m^2) died 61 days after the last cabazitaxel administration due to AE (preferred term [PT]; disease progression). The Investigator judged these events as unrelated to study treatment.

Serious TEAEs were observed in 2 out of 4 patients (50.0%) in 20 mg/m^2 cohort, and 28 out of 44 patients (63.6%) in the 25 mg/m^2 cohort. Common serious TEAEs at MTD (25 mg/m^2) were neutropenia in 10 patients (22.7%), febrile neutropenia in 8 patients (18.2%), and disease progression in 3 patients (6.8%).

Treatment emergent adverse events leading to dose modification (dose reduction, dose interruption, or dose delay) were observed in 3 patients (75.0%) and 28 patients (63.6%) in 20 and 25 mg/m^2 cohorts, respectively. Common TEAEs leading to dose modification at MTD (25 mg/m^2) were neutropenia in 7 patients (15.9%), febrile neutropenia in 6 patients (13.6%), anaemia and AST increased in 5 patients (11.4%) each, and ALT in 4 patients (9.1%).

Treatment emergent adverse events leading to permanent treatment discontinuation were observed in 14 patients (31.8%) in the 25 mg/m^2 cohort. Fatigue and disease progression were reported as TEAE leading to discontinuation in 3 and 2 patients respectively. All other TEAEs were reported in 1 patient each.

In hematological laboratory evaluations at MTD (25 mg/m^2), common Grades 3, 4 abnormalities were neutrophil count decreased in all 44 patients (100%), white blood cell decreased in 42 patients (95.5%), lymphocyte count decreased in 23 patients (52.3%), and anaemia in 21 patients (47.7%).

In biochemical laboratory evaluations majority of the abnormalities were of Grade 1 or 2. Most frequent Grades 3, 4 abnormalities at MTD were alkaline phosphatase increased in 6 patients (13.6%), hypokalemia in 4 patients (9.1%), creatinine increased, hyponatremia and hypocalcemia in 2 patients each (4.5%).

Pharmacokinetic results:

The elimination profile was triphasic and characterized by rapid initial and intermediate phases with mean $t_{1/2\alpha}$ of 0.0548 hours (3.29 minutes) and $t_{1/2\beta}$ of 1.65 hours respectively and by a long terminal phase with $t_{1/2\gamma}$ of 114 hours.

Cabazitaxel exhibited a rather high CL (overall mean CL value of 47.4 L/hr or 26.8 L/hr/m²) representing approximately 54% of the hepatic blood flow (87 L/hr), a large V_{ss} (overall mean V_{ss} value of 5610 L or 3170 L/m²).

A low inter-patient variability of the pharmacokinetic parameters was observed overall treatment levels for CL and $t_{1/2\gamma}$ (coefficient of variation [CV] of 28.2% and 23.9%, respectively) while it was higher for V_{ss}/body surface area (BSA) (CV: 44.5%).

Efficacy results:

Efficacy was evaluated with overall response rate, time to PSA progression and PSA response. In the expansion cohort in the MTD (25 mg/ m^2 dose level), the overall response rate was 16.7% (95% CI: 2.1 to 48.4) with 2 PR out of 12 evaluable patients. All the remaining 10 patients had SD, and none had PD as best overall response. Median time to PSA progression in the expansion cohort was 3.680 months (95%CI 1.3470 to 4.6324). PSA response rate in the expansion cohort was 29.3% (95% CI: 16.1% to 45.5%) with 12 PSA responders out of 41 evaluable patients.

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