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Sponsor / Company: Sanofi **Drug substance:** XRP6258 (Cabazitaxel)	**Study Identifiers:** NCT01497964, UTN U1111-1121-6247 **Study code:** ARD12417
Title of the study: A Phase 2, Multicenter Study of Cabazitaxel Single Agent Administered as a 1-Hour Intravenous Infusion Every 3 Weeks to Evaluate the Safety, Tolerability and Anti-tumor Activity in Patients with Advanced Gastric Adenocarcinoma Who Have Failed Prior Chemotherapy Regimens	
Study center: 1 active center in Korea	
Study period: Date first patient enrolled: 28/Dec/2011 Date last patient completed: 23/May/2013	
Phase of development: Phase 2	

Objectives:

Primary Objective

- To evaluate the anti-tumor activity of cabazitaxel by assessing objective tumor response rate (ORR) at the recommended dose (RD) when administered as a single agent every 3 weeks in patients with advanced gastric adenocarcinoma who have failed prior chemotherapy regimens.

Secondary Objectives

- To determine the RD of cabazitaxel when administered as a single agent every 3 weeks.
- To evaluate safety of cabazitaxel when administered as a single agent every 3 weeks.
- To estimate the overall survival (OS) and progression free survival (PFS).
- To assess the pharmacokinetics (PK) profile of cabazitaxel.

Methodology: This was a Phase 2, multinational, multi-center, open-label, non-randomized, dose escalation study to evaluate the safety, tolerability and anti-tumor activity in patients with advanced gastric adenocarcinoma who had failed 2 prior chemotherapy regimens. Patients meeting the eligibility criteria were enrolled and received single agent treatment of cabazitaxel once every 3 weeks.

The study consisted of 2 parts. In Part 1 (Phase 1), 9-18 Asian patients received cabazitaxel in a standard 3 + 3 dose escalation design. Dose levels included 20 mg/m^2 (level 1), 25 mg/m^2 (level 2) and 15 mg/m^2 (level -1). Treatment was to continue until disease progression or unacceptable toxicity. Prophylactic granulocyte-colony stimulating factor (G-CSF) was not permitted at cycle 1. Part 1 aimed to determine the maximum tolerated dose (MTD) of cabazitaxel based on dose-limiting toxicity in cycle 1 and to determine the RD for Part 2 (Phase 2).

In Part 2, approximately 33 patients were planned to be treated at the RD, including at most 6 patients treated at the RD in Part 1, provided that these patients had a measurable lesion. Granulocyte-colony stimulating factor could be administered prophylactically or therapeutically at any time during Part 2 of the study. The primary endpoint was overall response rate (ORR), defined as the proportion of patients in Part 2 with the best tumor response of confirmed complete response (CR) or partial response (PR) according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, relative to the total number of patients in the analysis population. Secondary efficacy endpoints include Overall Survival (OS) and Progressive-Free Survival (PFS). The planned efficacy population included modified intention-to-treat (mITT) population and ORR evaluable population. In addition, PK sampling was planned for 12 Chinese patients enrolled in Part 2.

Due to a decision by the Sponsor, Part 2 was canceled and no patients were recruited after Part 1 completion. The planned efficacy endpoints including ORR, OS, and PFS were not analyzed. Tumor assessment results of patients in Part 1 were presented as efficacy results. PK samples were collected in Part 1 patients only.

Number of patients:	Planned: 45 (9 to 18 patients for Part 1)
	Randomized: 16
	Treated: 16
Evaluated:	
	Efficacy: 16 patients in Part 1
	Safety: 16
	DLT evaluable: 15
	Pharmacokinetics: 16

Diagnosis and criteria for inclusion:

Inclusion Criteria:

- Histologically or cytologically confirmed unresectable or metastatic gastric adenocarcinoma including adenocarcinoma of gastroesophageal junction, which have failed 2 prior chemotherapy regimens. (For countries where a standard of care had not been established for the 2nd line treatment for advanced gastric cancer, those who failed 1 or 2 prior chemotherapy regimens could be included)
  - Prior chemotherapy should have included at least one of the following: 5-FU or derivatives, taxanes, platinum, or irinotecan.
  - Prior (neo) adjuvant chemotherapy with relapse within 6 months after the end of treatment was to be considered retrospectively as the 1st prior palliative chemotherapy.
- Signed informed consent
  - Patients needed to sign a separate consent form for Part 1 and Part 2, respectively.

Exclusion Criteria:

Related to methodology:

- Patients who had received >2 prior systemic chemotherapy regimens for advanced gastric cancer.
- For patients entering Part 2, those without at least one measurable lesion at baseline according to RECIST 1.1 criteria.
- Eastern Cooperative Oncology Group (ECOG) performance status >1.
- Age <18 years or >85 years.
- Life expectancy <2 months.

- Inadequate organ and bone marrow function as evidenced by:
  - Hemoglobin <9.0 g/dL
  - Absolute neutrophil count (ANC) <1500/mm^3
  - Platelet count <100 000/mm^3
  - Total bilirubin ≥1.5 x Upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥2.5 x ULN if no evidence of liver metastases or AST and/or ALT ≥5.0 x ULN with liver metastases
  - Serum creatinine >1.5 x ULN. If creatinine 1.0 to1.5 x ULN, estimated glomerular filtration rate (eGFR) was to be calculated according to CKD-EPI formula. Patients with eGFR <60 mL/min/1.73 m^2 were to be excluded
- Prior surgery, chemotherapy, targeted agents, investigational agents, or other anti-cancer therapy within 4 weeks prior to enrollment in the study (6 weeks for mitomycin-containing regimens).
- Prior radiation therapy within 6 weeks prior to enrollment (except palliative radiation for a local pain control).
- Previous treatment with cabazitaxel.
- Hematopoietic growth factors including G-CSF or blood transfusion administered within 2 weeks prior to enrollment in the study.
- Known brain or leptomeningeal involvement of cancer.
- Patients with known acquired immunodeficiency syndrome (AIDS) related illness or known human immunodeficiency virus (HIV) infection requiring antiretroviral treatment.
- Patients with active varicella zoster infection, or known hepatitis B or C infection.
- Active secondary cancer including prior malignancy from which the patient had been disease-free for ≤5 years. However, adequately treated superficial skin cancer other than melanoma or in situ cervix cancer more than 4 weeks prior to enrollment was not to be considered cause for exclusion.
- Other concurrent serious illness or medical condition, including active infection requiring systemic antibiotic/anti-fungal medication.
- Failure to recover to National Cancer Institute Common Terminology Criteria for Adverse Events Version, 4.03 (NCI CTCAE v.4.03) ≤grade 1 from all clinically significant toxic effects of previous anti-cancer therapy except alopecia and grade 2 peripheral neuropathy.
- Concurrent treatment in another clinical trial or with any other anti-cancer therapy including chemotherapy, targeted therapy, radiation therapy, or plans to receive these treatments during the study.
- Unwillingness or inability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
- Any severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the patient's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.
- For women of childbearing potential: pregnancy, breast feeding, lack of a negative pregnancy test within 7 days prior to registration, or lack of agreement on protection by a highly effective contraceptive method of birth control during period from the time the patient gives informed consent until 3 months after last study drug administration.
- Patient status as investigator, sub-investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the protocol.

Related to the current knowledge of Cabazitaxel:

- History of severe hypersensitivity reaction ≥ grade 3 to drugs formulated with polysorbate 80 such as docetaxel.
- Concurrent or planned treatment with strong inhibitors or inducers of CYP3A. A one-week washout period was required prior to the first dose of study treatment for patients already on these drugs.

Study treatments

Investigational medicinal product: Cabazitaxel

Formulation: Cabazitaxel was supplied as a sterile, non-pyrogenic, non-aqueous, and yellow to brownish yellow concentrate for solution for infusion at 60 mg/1.5 mL and packaged in a 15 mL clear type I glass vial stoppered with a rubber closure. The closure is crimped to the vial with an aluminum cap covered with a light green plastic flip-off cap. The solution contains polysorbate 80 as the excipient.

The cabazitaxel concentrate for solution for infusion was diluted before use as described in the clinical study protocol.

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. The rubber closure was crimped to the vial with a gold-color aluminum cap covered with a clear plastic flip-off 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 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 of administration: Intravenous (IV) infusion over 1 hour

Dose regimen:

Part 1:

In Part 1, a "3 + 3" dose escalation design was employed to determine the maximum tolerated dose (MTD) of cabazitaxel by assessing the dose-limiting toxicity (DLT) of cabazitaxel when administered as a single agent every 3 weeks. Sequential cohorts of 3 to 6 patients were treated. Patients were administered cabazitaxel on Day 1 of every 3 weeks at the dose specified for each dose level. The dose levels evaluated in Part 1 included 20 mg/m^2 (Level 1), 25 mg/m^2 (Level 2), and 15 mg/m^2 (Level 1).

Required IV premedication included: antihistamine (dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent antihistamines); corticosteroids (dexamethasone 8 mg or equivalent steroids); H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist). These premedications were administered by IV infusion at least 30 minutes before each dose of cabazitaxel. Anti-emetic prophylaxis (oral or intravenous) could be administered whenever necessary. For safety reasons, the maximum body surface area (BSA) to be used for the actual dose calculation of cabazitaxel was 2.1 m^2. However, BSA cut-off was not used in this study given that the maximum BSA in the safety population was 1.8 m^2.

The dose escalation decision rules are defined in the following table. Dose escalation was based on DLT observed during Cycle 1, with decisions made by the Steering Committee (SC). No intra-patient dose escalation was permitted.

Cabazitaxel Dose Escalation Decision Rules

Number of patients with DLT at Level 1 during Cycle 1	Decision
0 of first 3 patients	Open Level 2 and enter 3 patients.
1 of first 3 patients	Enter 3 additional patients at the same dose level.
	If 0 of the 3 additional patients experienced DLT in Cycle 1, then open Level 2 and enter 3 patients.
	If ≥1 of the 3 additional patients experienced DLT, open Level -1*.
≥2 of first 3 patients	Open Level -1*.

*: if there were ≥2 of 6 patients experience DLT during Cycle 1 at Level -1, decision for next steps was to be made by the Study Committee.

For those patients who had a DLT, further treatment could be continued at the same or lower dose according to the guideline for dose modifications.

Enrollment to the next dose level were not to proceed before at least 3 patients treated at the current dose level had received at least 1 cycle of study treatment (3 weeks) and safety had been evaluated for the criteria defining a DLT.

Patients not evaluable for DLT during Cycle 1 and/or withdrawn during Cycle 1 for any reason other than a DLT were to be replaced.

Definition of Dose-limiting toxicity (DLT):

To qualify for DLT, the adverse event (AE) or laboratory abnormality had to be study drug-related as assessed by the investigator.

The DLT was defined according to the NCI CTCAE v.4.03 as any of the following events during Cycle 1:

- Hematological toxicities defined as:
  - Grade 4 neutropenia >7 days duration
  - Grade 3 or 4 neutropenia complicated by documented infection
  - Grade 3 or 4 neutropenia with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than an hour with life threatening consequences (grade 4 febrile neutropenia)
  - Grade 3 or 4 neutropenia with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than an hour without life threatening consequences (grade 3 febrile neutropenia) could be considered DLT if neutropenia does not improve to <grade 3 within 7 days and results in treatment delay or dose reduction despite adequate treatment including the appropriate use of G-CSF
  - Grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by serious bleeding

- Non-hematological toxicities defined as:
  - Grade 4 non-hematological toxicities
  - Grade 3 non-hematological toxicities **EXCEPT** the followings that were manageable with appropriate treatment, unless the investigator and sponsor agreed that such inclusion is necessary (eg, if these events were excessive in frequency or duration, or required excessive use of supportive therapy):
    a) Grade 3 fever without documented infection and without concomitant grade 3 or 4 neutropenia
    b) Grade 3 anorexia, nausea, or vomiting
    c) Grade 3 diarrhea in the absence of maximal effective therapy
    d) Grade 3 fatigue
    e) Grade 3 peripheral neuropathy that recovers to grade 1 or baseline prior to next treatment cycle
    f) Delay of Cycle 2 by more than 2 weeks due to delayed recovery of toxicities

In Part 1, G-CSF could be administered prophylactically after Cycle 1 or therapeutically at any time during the study if the patient demonstrates evidence of neutropenia and/or its clinical consequence. The use of G-CSF was at the investigator discretion, and needed to be recorded in the electronic case report form (e-CRF).

Study treatment had to be delayed for any patient who experienced a DLT, but could resume after the toxicity had resolved to ≤grade 1 or baseline at the same or lower dose according to the guideline for dose modification specified in Section 8.3.3.2.2. Study treatment could be delayed by a maximum of 2 weeks to permit resolution of toxicity.

New cycles were not to begin until ANC ≥1500/mm^3, platelet count ≥75 000/mm^3, serum creatinine ≤1.5 x ULN, liver function tests were within the range indicated in exclusion criteria, and non-hematological toxicities (except alopecia, local reactions, and other toxicities that were uncomfortable but did not cause serious morbidity to patients) had recovered to grade ≤1 or baseline. Dose modification was to be done for any significant toxicity (see Table 3: cabazitaxel dose reduction schedule). A maximum of 2 weeks treatment delay was allowed between treatment cycles. Patients were to discontinue study treatment if treatment delay was more than 2 weeks.

Cabazitaxel Dose Reduction Schedule

	Projected Initial Dose (mg/m^2)	Does Reduction 1	Dose Reduction 2
Cabazitaxel	20	15	come off study
	25	20	15

Duration of treatment: All patients were to receive 1 infusion of cabazitaxel every 3 weeks, with maximum delay of 2 weeks in case of unresolved toxicity, until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

Duration of observation: From informed consent to Post-treatment follow-up period (from 31 days after the last dose of study medication to the end of the follow-up).

Criteria for evaluation:

Efficacy:

Anti-tumor activity was assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and any other areas if clinically indicated. These exams were performed at baseline (screening), every 6 weeks, whenever disease progression was suspected, or until disease progression. Patients who discontinued study treatment prior to disease progression continued to have tumor assessments every 6 weeks until disease progression or the start of new anti-cancer therapy.

Safety:

The safety assessments were evaluated by summarizing AEs graded according to NCI-CTCAE version 4.03 and coded with Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1, vital signs (blood pressure and temperature); physical examinations, electrocardiogram (ECG) parameters (only baseline and end of treatment), ECOG performance status, and laboratory data.

Maximum tolerated dose (MTD) and recommended dose (RD):

Maximum tolerated dose and RD were determined in Part 1 by assessing DLT of cabazitaxel when administered as a single agent during Cycle 1.

The MTD was defined as the highest dose level up to 25 mg/m^2 at which less than 33% of all evaluable patients experience DLT during Cycle 1. That was the highest dose level at which at most one out of 6 patients experience DLT.

The RD of cabazitaxel for Part 2 was to be the dose level as the same as or below the MTD but not above 25 mg/m^2. It was to be decided by the SC considering MTD, overall safety (during and after Cycle 1) and PK profiles. It was to be defined based on at least 6 patients.

Pharmacokinetics:

Pharmacokinetic profile of cabazitaxel and parameters of maximal plasma concentration (C_{max}), first time to reach C_{max} (t_{max}), area under the concentration-time curve (AUC), AUC from time 0 to the last measurable concentration (AUC_{last}), terminal half-life ($t_{1/2z}$), plasma clearance (CL) and the volume of distribution at steady state (V_{ss}) were determined using Standard non-compartmental analysis (NCA) CL and V_{ss} normalized by BSA were also calculated.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

For every patient in Part 1, 16 blood pharmacokinetic samples were taken at the following time points:

Cycle 1: 30 minutes prior to infusion, within 2 minutes before end of infusion, 5 minutes, 15 minutes, 30 minutes after the end of infusion, then 2, 4, 6, 9 , 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), 120 hours (Day 6), 168 hours (Day 8), and 216 hours (Day 10) after start of infusion.

Cycle 2: 30 minutes prior to infusion (C2D1 ie, 504 hours).

Cabazitaxel was assayed in plasma using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with a Lower Limit of Quantification (LLOQ) of 1 ng/mL (study report DOH0958).

In the original protocol, PK sampling and analysis were also planned for 12 Chinese patients enrolled in Part 2. However, the planned analysis was no longer applicable following cancellation of Part 2.

Statistical methods:

Sample size determination:

The Part 1 of the study was to determine the MTD of cabazitaxel by assessing the DLT observed during Cycle 1, and to determine the RD for Part 2. The number of evaluable patients in the Part 1 ranged from 9 to 18.

Analysis Population:

- **DLT evaluable population:** This population included all registered patients in Part 1 who received a full dose of study drug and completed evaluation for DLT in Cycle 1 or received a partial dose of study drug and developed DLT during Cycle 1. Analyses related to DLT evaluation were conducted based on the DLT evaluable population.
- **Safety population:** This population was to include all patients who received at least one dose (including a partial dose) of study drug. Safety analysis was to be performed in Part 1 and 2, respectively. Due to cancellation of Part 2, safety population included all patients in Part 1 who received at least one dose (including a partial dose) of study drug. This population was used in all safety summaries.
- **PK population:** All subjects without any major deviations related to study drug administration (ie, non adherence to cabazitaxel dosing, administration of prohibited concomitant treatments) and for whom any PK parameters was available, were included in the pharmacokinetic population.
- **Efficacy population:** Due to cancellation of Part 2, the planned efficacy population including mITT population and ORR evaluable population in Part 2 not performed. Tumor response data were collected for patients in Part 1.

Statistical Analyses

Efficacy: The planned efficacy endpoints included ORR (primary endpoint), OS, and PFS (secondary endpoints). Due to cancellation of Part 2, no efficacy endpoints were analyzed. Tumor assessment results of patients in Part 1 were presented as efficacy results.

Safety: The safety profile of cabazitaxel including AEs/serious adverse reactions (SAEs) and laboratory parameters were summarized by frequency in patients and by worst grade. Worst grade per patient and per cycle were tabulated for selected AEs and laboratory measurements using NCI CTCAE v.4.03.

Pharmacokinetics: Cabazitaxel concentrations and PK parameters were summarized by descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum, geometric means, and coefficient of variation [CV]) for each dose level. For $t_{1/2z}$ and CL (and CL normalized with BSA), dose effect was assessed using a linear fixed effect model. Point estimates and 90% confidence interval (CI) for the geometric mean were provided across dose levels, and separately for each dose group. For C_{max}, $AUC_{last,}$ and AUC, dose proportionality was assessed using an empirical power model along with an "estimation" interpretation, fit on a log-transformed scale.

Summary:

Population characteristics: A total of 16 patients, including 8 males and 8 females, were enrolled in Part 1 of the study. All patients were Asian/Oriental. Median age of the patients was 50.0 years (range 28 to 67 years); and, 14 (87.5%) out of 16 patients were <65 years of age. All patients had ECOG performance status 1 at baseline.

Primary tumor site was the stomach and disease status was metastatic (stage IV) for all 16 patients. Common tumor histopathology was poorly differentiated (9/16 patients, 56.3%) and moderately differentiated (5/16 patients, 31.3%). Seven (43.8%) patients had 2 organs involved at baseline, 4 (25%) patients had 1 organ involved at baseline, and other patients had 3 or >3 organs involved at baseline. The most frequently involved organs included peritoneum (9 patients, 56.3%), lymph nodes (8 patients, 50%), liver (5 patients, 31.3%), stomach (3 patients, 18.8%), and ovaries (3 patients, 18.8%). Median time from initial diagnosis to first cabazitaxel infusion was 32.3 months (range 6.7 to 68.9 month).

Thirteen (81.3%) patients underwent curative or palliative gastrectomy. One (6.3%) patient received radiotherapy. All patients received prior chemotherapy and 11 (68.8%) patients had prior taxane exposure. Median number of regimens was 2 (range 2 to 3). Median time from last administration of chemotherapy to first infusion of cabazitaxel was 1.1 months (range 1.0 to 24.3 months).

Efficacy results: Of the 16 patients treated with cabazitaxel in Part 1, 1 (6.25%) patient treated at 15 mg/m^2 had PR as the best overall response. Eight (50%) patients (5 patients treated at 20 mg/m^2, 1 patients treated at 25 mg/m^2, and 2 patients treated at 15 mg/m^2) had SD as the best overall response, including 1 patient treated at 20 mg/m^2 with an unconfirmed PR. Six (37.5%) patients had PD as the best overall response. One (6.25%) patient discontinued study treatment due to AE and had no post-baseline tumor assessment.

Safety results:

A total of 16 patients were treated with cabazitaxel in Part 1 of the study. Median numbers of cycles per patient were 3.0 (range 2 to 6 cycles) for dose level-1 (15 mg/m^2), 5.0 (range 1 to 6 cycles) for dose level 1 (20 mg/m^2), and 1.5 (range 1 to 6 cycles) for dose level 2 (25 mg/m^2). Relative dose intensity (RDI) was close to 1.00 for all patients. Overall, 5 patients (31.2%) had at least one cycle delayed, 6 patients (37.5%) had at least one dose reduction, and 2 patients (12.5%) had at least one dose interrupted. Fifteen patients discontinued the study due to PD and one patient discontinued due to AE.

The DLT evaluable population included 15 patients. In the first cohort of 3 patients treated at dose level 1 (20 mg/m^2), no DLT was observed. Level 2 (25 mg/m^2) was opened, in which 4 patients were enrolled as 1 patient discontinued prematurely. One DLT of grade 4 febrile neutropenia was observed in 1 out of 3 DLT evaluable patients. As all 4 patients treated at dose level 2 experienced febrile neutropenia, level 1 was expanded to 6 DLT-evaluable patients and 2 DLTs of grade 4 neutropenia >7 days duration were observed in 2 patients. Level -1 (15 mg/m^2) was opened and no DLT was observed in 6 DLT-evaluable patients. Therefore, the MTD of cabazitaxel was established as 15 mg/m^2. The Steering Committee that was supposed to determine RD was not convened.

All 16 patients experienced at least 1 treatment-emergent adverse event (TEAE) (any grade). Thirteen patients (81.2%) experienced at least 1 grade 3 or 4 TEAE, regardless of relationship to study treatment. Ten patients (62.5%) experienced at least 1 serious TEAE. One patient (6.25%) had a TEAE that led to permanent treatment discontinuation. There was no TEAE leading to death.

The most frequently reported TEAEs was neutropenia (11 patients, 68.8%). The most frequently reported non-hematological TEAE was decreased appetite (8 patients, 50.0%). Common grade 3 or 4 TEAEs included neutropenia (10 patients, 62.5%) and febrile neutropenia (6 patients, 37.5%).

Ten patients (62.5%) experienced at least 1 serious TEAE. The most frequently reported serious TEAE was febrile neutropenia (6 patients, 37.5%). The only serious TEAE that was related to investigational product (IP) as judged by the Investigator was febrile neutropenia.

One patient treated at dose level 2 experienced an unrelated TEAE (cholangitis) that led to permanent treatment discontinuation. Six patients (37.5%) each experienced a TEAE that led to dose reduction. Treatment-emergent AEs that led to dose reduction included grade 3 febrile neutropenia (2 patients) and grade 4 neutropenia (2 patients) at dose level 1, and grade 3 or 4 febrile neutropenia (2 patients) at dose level 2.

In hematological laboratory evaluations, both grade 3 or 4 leukopenia and grade 3 or 4 neutropenia were found in 1/6 patient (16.7%) for dose level -1, 6/6 patients (100%) for dose level 1, and 3/4 patients (75.0%) for dose level 2. No grade 3 or 4 anemia or thrombocytopenia was reported.

In biochemical laboratory evaluations, the only grade 3 or 4 liver abnormality detected was alkaline phosphatase increased, which occurred in 1/6 (16.7%) patient treated at dose level 1 and 1/4 (25.0%) patient treated at dose level 2. The only grade 3 or 4 electrolytes abnormalities detected was hypokalemia, which occurred in 1/4 (25.0%) patient treated at dose level 2. No renal or metabolism abnormalities were reported.

Of all 16 patients treated with cabazitaxel, 9 patients died by the end of the study. All deaths occurred more than 30 days after last dose of study treatment and all deaths were due to disease progression.

Pharmacokinetic results:

Cabazitaxel concentrations and pharmacokinetics parameters are summarized in the table below:

Mean ± SD (Geometric Mean) [CV%]	Plasma Cabazitaxel		
	15 mg/m^2	20 mg/m^2	25 mg/m^2
N	6	6	4
C_{max}	210 ± 165	315 ± 127	318 ± 100
(ng/ml)	(156) [78]c	(293) [40]	(306) [32]
t_{max}[a]	0.98	0.98	0.98
(hr)	(0.98 - 0.98)[c]	(0.98 - 1.15)	(0.97 - 1.08)
t_{last}[a]	60.00	143.96	191.99
(hr)	(24.00 - 216.17)	(72.00 - 216.17)	(120.00 - 216.28)
AUC_{last}	387 ± 316	502 ± 106	621 ± 106
(ng•hr/ml)	(301) [82]	(493) [21]	(614) [17]
AUC	488 ± 362	673 ± 156	780 ± 137
(ng•hr/ml)	(392) [74]	(658) [23]b	(771) [18]
$t_{1/2z}$	55.8 ± 34.9	105 ± 54.4	94.9 ± 30.9
(hr)	(45.4) [63]	(94.7) [52]	(90.7) [33]
CL	77.9 ± 57.0	48.4 ± 11.8	50.4 ± 14.0
(L/hr)	(63.0) [73]	(47.3) [24]b	(48.9) [28]
V_{ss}	3070 ± 1770	3940 ± 1370	4930 ± 2740
(L)	(2650) [58]	(3790) [35][b]	(4480) [56]
CL/BSA	48.3 ± 38.1	31.4 ± 7.76	32.9 ± 6.06
(L/hr/(m^2))	(37.9) [79]	(30.7) [25][b]	(32.5) [18]
V_{ss}/BSA	1840 ± 1020	2520 ± 676	3180 ± 1360
(L/(m^2))	(1600) [56]	(2460) [27][b]	(2980) [43]

[a] Median
(Min - Max)

[b] n=5, Subject 410001003 not included in calculation of summary statistics (AUCext>30%)

[c] n=5 Subject 410001019 not included in calculation of summary statistics (2-hour infusion duration instead of 1h)

A large variability was observed at 15 mg/m^2 on almost all PK parameters.

No deviation from dose proportionality in C_{max}, AUC_{last} and AUC was observed.

No dose effect on terminal half-life or clearance was observed over the 15 to 25 mg/m^2 cabazitaxel dose range (respective p-values were 0.0983 and 0.6057). Considering the high variability of parameters obtained at 15 mg/m^2, the overall estimate of CL and $t_{1/2z}$ was calculated on the 20 to 25 mg/m² dose range: mean clearance was high 48.1 L/h (31.6 L/h/m^2 with normalization to BSA) and mean $t_{1/2z}$ was long (92.7 hours). Volume of distribution at steady state (V_{ss}) normalized with BSA was large (2810 L/m^2).

Plasma clearance (CL) normalized with BSA data in this Asian population was within the range of values observed in Western patients in previous studies (TED6190, TED6188, and EFC6193), where the majority of patients were Caucasians (100% in TED6190, 72.0% in TED6190 [dose escalation part], and 80.6% in EFC6193 [population PK part]).

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