SYNOPSIS

Title of the study: A Dose-escalating, Multicenter, Single arm, Open-label Study of XRP6258 in combination with capecitabine (Xeloda®), in patients with metastatic breast cancer with disease progressing after anthracycline and taxane therapy (TCD6945)

Coordinating Investigator(s): [redacted]

Study center(s): 4 study centers (2 centers each in France and Belgium)

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 05 December 2006

Date last patient completed: 31 March 2009

Phase of development: Dose escalation study

Objectives:

Primary Objectives:

- Part 1:
  - To determine the Maximum Administered Dose (MAD) and the Dose Limiting Toxicities (DLTs) of XRP6258 administered as a 1-hour infusion every 3 weeks in combination with capecitabine (Xeloda®) tablets twice daily for 2 weeks in 3-week cycles, in patients (pts) with metastatic breast cancer (MBC) progressing after anthracycline and taxane.
  - To determine the Maximum Tolerated Dose (MTD) of XRP6258 in combination with capecitabine, in pts with MBC, progressing after anthracycline and taxane. The MTD, (determined once the MAD has been reached in the part 1), will be used in the part 2 of the study to assess the antitumor response.
- Part 2:
  - To determine the antitumor activity of XRP6258 in combination with Xeloda®, in an additional cohort of pts with MBC progressing after anthracycline and taxane, as assessed by objective response rate (ORR) according to RECIST.

Secondary Objectives:

- To assess the safety profile of the combination regimen of XRP6258 with capecitabine.
- To assess the pharmacokinetics (PK) of XRP6258 and its metabolite RPR123142, and of capecitabine and its metabolite 5-fluorouracil (FU) and to evaluate any PK drug-drug interaction between the compounds following this schedule of administration.
- To determine the Time To Progression (TTP) and duration of response (DR), of the extended cohort of pts treated at the MTD in the part 2 of the study.

Methodology:

An open-label, single arm, multicenter, dose-escalation of cabazitaxel in combination with capecitabine, to determine:

1. Part 1 (dose escalation part): the MAD based on safety,
2. Part 2: the activity of the combination regimen at the MTD in an extended cohort of patients.

The pharmacokinetic evaluation was performed at Cycle 1 for all the patients (Parts 1 and 2).

In the Part 1, sequential cohorts of 3 patients were treated with successively higher doses of cabazitaxel and capecitabine every 3 weeks (see investigational product dose escalation schedules and rules below).

Maximum Tolerated Dose (MTD): The MTD was defined as the highest dose at which 0 or 1 of 3 or 6 patients, respectively,

experience dose-limiting toxicity (DLT) during the first 3 weeks of combination of cabazitaxel and capecitabine.

Once the MTD of cabazitaxel in combination with capecitabine had been established, the safety, pharmacokinetics, and preliminary efficacy of this regimen were evaluated in an additional 15 patients in the Part 2 component of the study.

Part 1 and 2:

Treatment-emergent adverse events (TEAEs) and labs, by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0 Grades.

Summary statistics are provided for continuous and categorical data, following the general rules:

- For continuous variables: n, mean, standard deviation, median, minimum, and maximum values
- For categorical variables: count and percentage

Number of patients:

Planned: 50 (Part 1: 35 patients; Part 2: 15 patients)

Enrolled: 34

Treated: 33 (Part 1: 15 patients; Part 2: 18 patients). One patient was enrolled and was not treated due to occurrence of a fatal pulmonary embolism prior to receiving her first treatment.

Evaluable patients for DLT assessment: 15

Evaluable patients for pharmacokinetics: 32

Diagnosis and criteria for inclusion:

- Histologically or cytologically proven diagnosis of breast adenocarcinoma that was metastatic or locally recurrent and inoperable with curative intent.
- Prior treatment with an anthracycline and a taxane, given in the neoadjuvant/adjuvant or in the metastatic setting, could have been given concurrently or sequentially, and in combination with other drugs. Patients had received a standard dose of anthracycline and of taxane expected to have potentially resulted in a response.
- Women >18 year-old
- Adequate organ function defined as laboratory parameters within the normal ranges.

Investigational product: Cabazitaxel (XRP6258)

Cabazitaxel: Concentrated solution for infusion, at a concentration of 80 mg/2ml.
Solvent for cabazitaxel: 13% m/m ethanol solution in a 15ml vial.

Capecitabine (Xeloda®): Tablets of 150 mg and 500 mg strengths (commercial packs).

- **Dose escalation schedule:**

  Starting dose: Dose level I

Dose levels	XRP6258, mg/m² (anticipated number of pts)	Capecitabine mg/m² twice daily
- I°	*15*	*825*
I	**20 (3 pts)**	**825**
II	20 (6 pts)	1000
-III°	*25 (6 pts)*	*825*
III	25 (6 pts)	1000
IV	25 (6 pts)	1250

At Step III, if DLTs observed were mainly cabazitaxel-based toxicities, ie, hematological toxicities and/or hypersensitivity reaction and/or fluid retention and/or neurological toxicities, then up to 6 patients were included in Step II again. For any other DLTs, the patients were included in Step -III° to complete the Step with up to 6 patients, if needed.

The dose escalation criteria (described in the table below) were met at each dose level in order to enroll and treat patients at the next dose level.

Number of patients with Cycle 1 DLT at a given dose level	Dose escalation decision rule
0 of first 3	Enter at least 3 pts at the next dose level.
1 out of 3	Enter up to 3 additional pts at this dose level.
	If 0 of the 3 additional pts experience DLT, then proceed to the next dose level.
	If 1 or more of 3 additional pts experience DLT, then dose escalation will be stopped. Three (3) additional pts will be entered at the previous dose level if 3 pts were treated at that dose.
≥ 2	Dose escalation will be stopped. Three (3) additional pts will be entered at the previous dose level if 3 pts were treated at that dose.

DLT = dose-limiting toxicity; pts = patients

At each given dose level, a 1-week gap was planned to evaluate toxicity, between the inclusion of the first patient and the next 2 patients. Before escalating to the next dose level, 3 patients were evaluated for the criteria defining a DLT. Use of hematopoietic growth factors was not permitted during the first 3 weeks of study treatment unless hematological DLT was encountered.

Administration:

- Cabazitaxel: 1 hour intravenous infusion on Day 1. The actual dose of XRP6258 was adjusted to a maximum body surface area (BSA) of 2.1m^2
- Capecitabine: Oral route, twice daily from Day 1 to Day 14;
  (In a 3 weeks-cycle, Day 22 is equivalent to Day 1)

Batch number(s):

- Cabazitaxel: [redacted]
- Capecitabine: [redacted]

Duration of treatment:

Treated patients continued to receive the study treatment until disease progression or unacceptable toxicities or withdrawal of consent/Investigator's decision, whichever came first.

Duration of observation:

For Part 1: Period of observation for DLTs = Cycle 1.

For Part 2: All patients were followed up to either disease progression or consent withdrawal/Investigator's decision, or until they received at least 6 cycles of treatment, whichever came first.

Reference therapy: Not applicable

Criteria for evaluation:

Safety:

Primary endpoint in Part 1: DLTs in Cycle 1.

Main secondary endpoints in Part 2: Safety profile in terms of TEAEs/serious adverse events (SAEs) and laboratory parameters.

Efficacy:

The primary endpoint in Part 2: Objective responses (complete response [CR] and partial response [PR]) as assessed by Investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Main secondary endpoints: Time to progression (TTP), DR

Pharmacokinetics:

The plasma pharmacokinetics parameters of cabazitaxel and its metabolite RPR123142 and of capecitabine and its metabolite 5-FU were determined.

Pharmacokinetic sampling times and bioanalytical methods:

Cabazitaxel and its metabolite RPR123142:

Blood samples (3 mL each) for pharmacokinetic analysis were collected from all patients in Cycle 1, Day 1, immediately before the infusion, 5 minutes before the end of infusion and then at 5, 15, and 30 minutes, 1, 2, 3, 5, 7, and 10 hours, and on Day 2 (20-24 hours), Day 3 (approximately 48 hours), Day 4 (approximately 72 hours), Day 6 (approximately 120 hours), Day 8 (approximately 168 hours) after the end of infusion.

The plasma concentrations of cabazitaxel and its metabolite RPR123142 were determined by a validated liquid chromatography mass spectrometry technique. The limits of quantitation were 1.00 ng/mL for cabazitaxel and 0.50 ng/mL for RPR123142.

Capecitabine and its metabolite 5-FU:

Blood samples (5 mL each) for pharmacokinetic analysis were collected from all patients in Cycle 1, on Day 1, immediately before the first oral administration, and at 15 minutes, 30 minutes, and 1, 2, 3, 4, 5, 6, 8, and 10 hours after the morning dose (before the evening dose).

The plasma concentrations of capecitabine and its active metabolite 5-FU were determined by a validated liquid chromatography mass spectrometry technique. The limits of quantitation were 10.0 ng/mL for capecitabine and 2.00 ng/mL for 5-FU.

Statistical methods:

DLTs and MAD in Part 1:

To qualify for DLT, the clinical adverse event or laboratory abnormality had to be drug-related as assessed by the Investigator.

The DLTs in the first treatment cycle were defined (according to the NCI-CTCAE version 3 grading scale) as follows:

- Nonhematological toxicity Grade 3 or 4 except:
  - Grade 3 fever without documented infection
  - Grade 3 nausea and vomiting in the absence of effective maximal anti-emetic therapy
  - Grade 3 mucositis/stomatitis in the absence of effective symptomatic treatment
  - Grade 3 fatigue
  - Grade 3 anorexia
  - Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation that returned to baseline prior to next treatment cycle
  - Grade 3 hypersensitivity reaction in the absence of required medication
  - Peripheral neuropathy Grade 3 that returns to Grade 2 or less at the initiation of next treatment cycle

- Hematological toxicity defined as:
  - Febrile neutropenia: fever (of unknown origin without clinically or microbiologically documented infection) >38.5°C with neutropenia Grade 3 or 4
  - Neutropenia Grade 4 >7 days
  - Platelets/Thrombocytopenia Grade 4
- Any other life-threatening clinical drug related-toxicity

The MAD was reached at a given dose level when at least 2 patients developed DLTs at the first cycle. The MTD was defined as the highest dose at which 0 or 1 of 3 to 6 patients experienced DLT during the first 3 weeks of combination of cabazitaxel and capecitabine.

Safety

The 3 + 3 dose escalation procedure was carried out to determine the MAD and to select the MTD. The frequency distribution of the number of patients experiencing DLTs was summarized by dose level for Cycle 1 in Part I. Patient listings with dose level, actual dose received, DLTs, and NCI grade for Cycle 1 are also provided.

Patients in Part I and Part II were evaluable for safety (safety population) if they started at least 1 infusion of cabazitaxel or 1 dose of capecitabine. All adverse events (graded by the NCI-CTCAE, version 3.0) were coded using Medical Dictionary for Regulatory Activities (MedDRA) 12.0. For AEs and the main laboratory parameters, the frequency summary tables are provided by patient (worst NCI grade under treatment) and by patient-cycle (worst NCI grade in a cycle) for each dose level.

Efficacy

Descriptive statistics are provided for efficacy analyses in all patients treated at the MTD of cabazitaxel in combination with capecitabine (per-protocol [PP] population) and in all treated patients (all-treated population [AT]). The estimate of the ORR and its corresponding 95% confidence interval (CI) by using the exact method are provided. The TTP and event curve were estimated using the Kaplan-Meier method. Summary statistics were performed for the DR as a continuous variable.

Statistical analyses were carried out on UNIX® with SAS® software, Version 8.2.

In general, descriptive statistics are provided for continuous and categorical data. For continuous variables, total number, mean, standard deviation, median, minimum, and maximum values are displayed. For categorical variables, count and percentage are displayed.

Summary:

Patient disposition:

- Thirty three patients with **metastatic breast infiltrating carcinoma** were included in the study, 15 in the dose escalation phase (Part 1) (6 patients at Dose level I, 3 patients at Dose level II and 6 patients at Dose level III) and 18 patients in Part 2. **Median age was 55 years** (34 to 74 years) and 100% of patients were PS 0-1. All patients had previously received chemotherapy containing **anthracyclines** (median cumulative dose for doxorubicin 300 mg/m² [220 to 600 mg/m²]; for epirubicin 525 mg/m² [100 to 900 mg/m²]) and **taxane** therapy (best overall responses under prior taxanes were PR for 11 patients, stable disease (StD) for 14 patients, and disease progression [PD] for 4 patients). For 5 patients those drugs were given as adjuvant and/or neoadjuvant intent and for 28 patients as first-line for advanced/metastatic disease. They entered the study after **a median time from last therapy to first infusion of study treatment of 0.99 months** [0.0 to 23.7 months], after **a median time interval between the last infusion of prior taxane therapy and first infusion of study treatment of 10.94 months** [0.9 to 93.9 months]. All patients were **metastatic** at study entry with **multiple organ involvement** (median number of 3 [1-6] organs involved, mainly: bone, liver, lymph nodes). Hormonal receptor status was positive in 87.9% of tumors and **HER2-Neu status was negative** for 100% of patients,

- At the time of study cut off (31 March 2009), all patients had completed the study. Four patients had died and 27 patients completed the follow-up period in this study. Two patients discontinued the study due to other reasons (date of study cut off). All patients had discontinued the study treatment: 14 patients for PD, 9 patients for AEs, and 10 patients for other reasons (9 patients for Investigator's decision due to no further benefit and 1 patient due to her own decision).

Safety results:

The dose-limiting toxicities reported at Cycle 1 were all hematological events of the same type: neutropenia Grade 4 lasting more than 7 days.

The MAD was defined as 25 mg/m^2 cabazitaxel (Day 1) and 1000 mg/m^2 capecitabine twice daily (Day 1 to Day 14), every 3 weeks, based on the number of protocol-defined dose-limiting toxicities occurring at Cycle 1. It was confirmed by the poor feasibility of this dose level after cumulative exposure. The main toxicity leading to frequent dose/schedule adjustment and a low relative dose intensity was hand-foot syndrome.

The MTD was defined as 20 mg/m^2 cabazitaxel (Day 1) and 1000 mg/m^2 capecitabine twice daily (Day 1 to Day 14) every 3 weeks.

At the maximum tolerated dose:

One hundred and twelve cycles were administered in 21 patients with a median of 5 cycles (range: 2 to 13 cycles). The median relative dose intensity was 0.97 (range: 0.69 to 1.00) for cabazitaxel and 0.89 (range: 0.55 to 1.02) for capecitabine. The main toxicities leading to dose/schedule adjustment were neutropenia and hand-foot syndrome.

Within the safety population, 71.4% of the patients experienced Grade 3-4 TEAEs. The most frequent Grade 3 -4 nonhematological AEs were asthenia/fatigue, hand-foot syndrome, and dyspnea (9.5% each). Grade 3-4 Infection and infestations (system organ class [SOC]) occurred in 14.3% of patients. Other Grade 3-4 nonhematological TEAEs occurred only in 1 patient each. The most frequent all-grades nonhematological TEAEs were in the gastrointestinal disorders SOC (95.2%), mainly nausea (61.9%), diarrhea (57.1%), abdominal pain and vomiting (33.3% each), constipation (28.6%), and stomatitis (19%); the general disorders SOC (76.2%), mainly asthenia/fatigue (52.4%) and pyrexia (23.8%); the skin and subcutaneous disorders SOC (76.2%), mainly hand-foot syndrome (57.1%); the metabolism disorders SOC (61.9%), mainly anorexia (52.4%); and the musculoskeletal disorders SOC (52.4%), mainly arthralgia (19%), and myalgia and back pain (14.3% each). The summary of all grade and Grade 3 -4 TEAEs are presented by SOC and PT terms.

For hematological toxicities, Grade 3-4 neutropenia occurred in 57.1% of patient, including the patient who experienced a febrile neutropenia. Grade 3-4 anemia occurred in 4.8% of patients and no Grade 3-4 thrombocytopenia was reported.

The dose/schedule adjustments during the study treatment were mainly due to neutropenia and hand foot syndrome.

Overall

A total of 178 cycles were administered in 33 patients with a median of 5 cycles (range: 2 to 13 cycles). The median relative dose intensity was 0.96 (range: 0.69 to 1.01) for cabazitaxel and 0.87 (range: 0.55 to 1.03) for capecitabine.

Nine patients discontinued the study treatment due to AEs. It is to be noted that the occurrence of renal and urinary disorders such as cystitic hemorrhagic, noninfective cystitis, dysuria, hematuria, renal colic, renal failure, and urinary tract inflammation, occurring in 10 of the 33 treated patients, led to treatment discontinuation in 6 patients. No clear mechanism has been found so far.

Efficacy results:

At the MTD (21 patients), the Investigator-determined ORR was 23.8% (95% CI: 8.2% to 47.2%) with 1 CR and 4 PRs. In addition, 11 patients had a stabilization, including 2 unconfirmed PRs. The median duration of response was 3.06 months (95% CI: 2.1 to 8.4 months) with 4 of 5 responses lasting more than 3 months. The median TTP was 4.9 months (95% CI: 2.7 months to NA).

In the overall population previously treated with both taxane and anthracyclines, efficacy was observed across all dose levels with a total of 2 CRs, 5 PRs, and 20 stabilizations (including 7 unconfirmed PRs), in the 33 treated patients. Only 6 patients experienced a PD as best overall response. The median duration of response was 3.06 months (95% CI: 2.1 to 8.4 months) with 6 of 7 responses lasting more than 3 months. The median TTP was 4.9 months (95% CI: 3.4 months to NA). Interestingly, 2 of 4 patients who had a PD as best response under prior taxane therapy experienced a stabilization under the combination while 4 patients who had a stabilization as best response to prior taxane therapy experienced a response (2 CRs and 2 PRs).

Pharmacokinetic results:

Cabazitaxel exhibited a long terminal half-life (79 hours), a high total plasma CL (57.5 L/hr to 33.6 L/hr/m²), which represents almost three-fourths of the hepatic blood flow, and a large volume of distribution (3927 L to 2335 L/m²). The metabolic ratio ($AUC_{0\text{-}t}$ RPR123142/$AUC_{0\text{-}t}$ cabazitaxel) had a mean value of 2.15% and was less than 4% for all patients except 1 (15%).

Pharmacokinetic results: pharmacokinetic parameters (CL, AUC, $AUC_{0\text{-}t}$, $T_{1/2z}$, Vss) for cabazitaxel and its metabolite estimated in patients are in the range of those estimated in previous Phase I studies, but total variability of exposure parameters was moderate to very high (CV: 37% to 161%).

Capecitabine was rapidly absorbed and metabolized into 5-FU (t_{max} 0.50 to 1 hour for both compounds). Capecitabine and 5-FU were rapidly eliminated from the plasma with terminal half-lives being short (0.71 hours and 0.80 hours respectively). The metabolic ratio ($AUC_{0\text{-}t}$ 5-FU/$AUC_{0\text{-}t}$ capecitabine) had a mean value of 6.25%.

Pharmacokinetic parameters for capecitabine and 5-FU were generally comparable with those previously reported in the literature at the same dose (AUC range: 5580 to 7915 ng.h/mL and 422 to 610 ng.h/mL, respectively).

Conclusions: [redacted]

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