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Sponsor / Company: sanofi-aventis **Drug substance(s):** XRP9881 (larotaxel)	**Study Identifier:** NCT00327743 **Study code:** TCD6511

Title of the study: A dose-escalating, multicenter, single arm, open-label study of XRP9881 in combination with capecitabine (Xeloda®), in metastatic breast cancer patients with disease progressing after anthracycline and taxane therapy

Study center(s): 8 sites in 2 countries (2 in France and 6 in the United States)

Study period:

Date first patient enrolled: 1 August 2006

Date last patient completed: 16 March 2009

Phase of development: Tolerance study in combination escalating dose (Phase I / II)

Objectives:

Primary Objective:

Part 1:

- To determine the Maximum Administered Dose (MAD) and the Dose Limiting Toxicities (DLTs) of XRP9881 administered as a 1-hour infusion every 3 weeks in combination with capecitabine (Xeloda®) tablets twice daily for 2 weeks in 3-week cycles;
- To determine the Maximum Tolerated Dose (MTD) of XRP9881 in combination with capecitabine. The MTD (determined once the MAD was reached in the Part 1), was used in the Part 2 of the study to assess the antitumor response.

Part 2:

- To determine the antitumor activity, in an additional cohort of patients with metastatic breast cancer (MBC) progressing after anthracycline and taxane, of XRP9881 in combination with Xeloda® as assessed by objective response according to Response Evaluation Criteria in Solid Tumors (RECIST).

Secondary Objectives:

- To assess the safety profile of the combination regimen of XRP9881 with capecitabine;
- To assess the pharmacokinetic (PK) profile of XRP9881 in combination with capecitabine and to evaluate any PK interaction between capecitabine, its metabolite and XRP9881;

To determine the Progression Free Survival (PFS), duration of response, composite of clinical event of complete response (CR), partial response (PR), and stable disease (SD) ≥ 12 weeks of the extended cohort of patients treated in the Part 2 of the study.

Methodology: This study was open-label, single arm, multicenter, dose-escalation of XRP9881 in combination with capecitabine and organized in 2 parts.

Number of patients:

Planned: 30 (Parts 1 and 2 of the study)	Randomized: Not applicable	Treated: 34 (Parts 1 and 2)
Efficacy: 16 (Part 2)	Safety: 34 (Parts 1 and 2)	Pharmacokinetics: 34 (Parts 1 and 2)

Diagnosis and criteria for inclusion: Female patients aged at least 18 years old with MBC progressing after anthracycline and taxane therapy, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and with a measurable disease as defined by RECIST criteria.

Investigational product: XRP9881 (larotaxel)

Dose:

Part 1: 60 and 75 mg/m² (starting dose) (1-hour infusion on Day 1 each cycle of 3 weeks)

Part 2: 60 mg/m² (1-hour infusion on Day 1 each cycle of 3 weeks). The dose could be reduced in case of severe toxicity.

Administration: Intravenous (IV) route

Duration of treatment: All patients were treated until disease progression, unacceptable toxicities, withdrawal of consent, or Investigator's decision, whichever came first.

Duration of observation: Patients were followed up for safety 30 days post treatment, last infusion.

Combination product: Capecitabine (Xeloda®)

Dose:

Part 1: 750, 825 (starting dose) and 1000 mg/m² (twice daily from Day 1 to Day 14 each cycle of 3 weeks)

Part 2: 825 mg/m² (twice daily from Day 1 to Day 14 each cycle of 3 weeks). The dose could be reduced in case of severe toxicity.

Administration: Oral route.

Criteria for evaluation:

Efficacy: Tumor assessments were done by using computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. These exams were performed by the investigator based on RECIST criteria at baseline (screening), at the end of each even-numbered treatment cycle, whenever disease progression was suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment.

Safety: Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) PS (performance status), and laboratory safety tests (including hematology and biochemistry) were obtained prior to drugs administration and at designated intervals throughout the study. Treatment-emergent adverse events (TEAEs) were collected during the study and up to 30 days after the end of study treatment. Adverse events were graded according to the National Cancer Institute-Common Terminology Criteria version 3.0

Pharmacokinetics: For XRP9881, individual PK parameters were to be determined by Bayesian estimation using nonlinear mixed effect modeling (NONMEM software version V or more recent, Globomax TM Ellicot city, MD). Pharmacokinetic analyses of the plasma concentrations obtained for capecitabine and its metabolite 5-FU were to be performed by a non-compartmental analysis using WinNonlin® software.

Pharmacokinetic sampling times and bioanalytical methods:

For Parts 1 and 2, venous blood samples were collected for XRP9881 and capecitabine PK evaluation at designated time-points before and after concomitant administration of these products, on Day 1 and Day 8 of Cycle 1. For Part 2 only, venous blood samples were collected for capecitabine PK evaluation at specified time-points on Day 14 of Cycle 1.

The plasma concentrations of XRP9881 were determined by a liquid chromatography mass spectrometry technique (LC/MS/MS). The plasma concentrations of capecitabine and its active metabolite 5-FU were also measured by a validated LC/MS/MS assay.

Statistical methods:

Efficacy: The analyses of the efficacy variables applied only to Part 2 of the study.

Primary efficacy variable:

The primary efficacy endpoint was the best overall response (BOR) in the "As Treated (AT)" population during the study period. The response rate (RR) was defined by the proportion of patients with confirmed complete response (CR) or partial response (PR) according to RECIST criteria. The primary analysis showed RR, including its estimate and its corresponding 95% confidence interval (CI) using the Clopper-Pearson exact method.

Secondary efficacy variables:

Progression Free Survival event curve was estimated using the Kaplan-Meier method performed on the AT population.

Safety: The analyses of the safety variables applied to Part 1 and Part 2 of the study and were descriptively analyzed.

Summary:

A total of 34 female Caucasian patients with HER2 positive metastatic breast cancer were included and received at least 1 cycle of XRP9881 and capecitabine: 19 patients were treated in the Part 1 (8, 4 and 7 patients in the 75/1650, 60/1500 and 60/1650 dose level groups, respectively) and 16 in the Part 2, including 1 patient who received the MTD in Part 1 and who fulfilled eligibility criteria for Part 2 and was therefore also qualified for Part 2.

Safety results:

Part 1

Three patients out of 19 experienced DLTs at Cycle 1 (1 febrile neutropenia, 1 Grade 4 neutropenia > 7 days and 1 septic shock associated with Grade 4 neutropenia). All these DLTs occurred in the first dose level (XRP9881 75 mg/m2 + capecitabine 1650 mg/m2). The MTD was reached at the XRP9881 60 mg/m² + capecitabine1650 mg/m² dose level.

All 19 treated patients experienced at least one TEAE.

In the 75/1650 dose level group, the most frequent non laboratory TEAEs any grade were vomiting (7/8 patients), nausea (6/8 patients), diarrhea including colitis and enteritis (6/8 patients, enterocolitis reported by 1 patient), anorexia (5/8 patients), fatigue (5/8 patients), neuropathy sensory (4/8 patients), and dehydration (4/8 patients). Seven patients out of 8 experienced at least one treatment emergent SAE. Two patients died within the 30 days following the last dose of study treatment (pneumonia and septic shock). Four patients out of 8 experienced an AE leading to discontinue the treatment. All AEs (cystitis, diverticulitis, septic shock, diarrhea and pulmonary edema) were of Grade 3-4.

In the 60/1500 dose level group, the most frequent non laboratory TEAEs any grade were diarrhea (4/4 patients), fatigue (4/4 patients), nausea (3/4 patients), alopecia (3/4 patients), vomiting (2/4 patients), constipation (2/4 patients), pulmonary embolism (2/4 patients) and fever (2/4 patients). Three patients out of 4 experienced at least one treatment emergent SAE. One patient died within the 30 days following the last dose of study treatment (pulmonary embolism). Two patients out of 4 experienced an AE leading to discontinue the treatment. One patient experienced a Grade 3-4 AE (death/pulmonary embolism).

In the 60/1650 dose level group, the most frequent non laboratory TEAEs any grade were fatigue (6/7 patients), diarrhea (5/7 patients), abdominal pain (5/7 patients), arthralgia (5/7 patients), pain in extremity (5/7 patients), palmar-plantar erythrodysaesthesia syndrome (5/7 patients), and neuropathy sensory (5/7 patients). No colitis and enteritis were reported. Two patients out of 7 experienced at least one treatment emergent SAE. No death occurred within the 30 days following the last dose of study treatment. One patient out of 7 experienced an AE leading to discontinue the treatment (Grade 2 asthenia).

Part 2

All 16 treated patients experienced at least one TEAE.

Fatigue (81.3%), nausea (68.8%), diarrhea (68.8%), abdominal pain (56.3%), vomiting (43.8%), alopecia (50.0%), palmar-plantar erythrodysaesthesia syndrome (43.8%), anorexia (43.8%), constipation (31.3%), dysgeusia (31.3%), headache (25.0%), arthralgia (25.0%), neuropathy sensory (25.0%), and stomatitis (25.0%) were the most frequent non laboratory TEAEs any grade reported in the study Part 2. No colitis and enteritis were reported.

Six patients out of 16 (37.5%) experienced at least one treatment emergent SAE. One patient died within the 30 days following the last dose of study treatment due to disease progression.

Six patients out of 16 (37.5%) experienced an AE leading to discontinue the treatment. For 2 patients (12.5%), the grade of AEs (stomatitis, abdominal pain and tumor pain) was 3-4.

Efficacy results (Part 2):

The objective response rate (RR) was 43.8% (95% CI: [19.8%: 70.1%]). Partial response and stable disease were the best overall responses obtained for 14 patients (87.5%). The median PFS was 13.8 months (95% CI, [4.37:13.83]).

Pharmacokinetic results:

The PK analysis was not performed following XRP9881 development discontinuation.

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