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Sponsor / Company: sanofi-aventis **Drug substance(s):** XRP9881 (larotaxel)	**Study Identifier:** NCT00387907 **Study code:** TCD10037

Title of the study: Open label, uncontrolled, study of XRP9881 (Larotaxel) in combination with weekly trastuzumab (Herceptin®) in patients with HER2 positive metastatic breast cancer (MBC)

Study center(s): 4 centers in the USA instead of 10-15 initially planned

Study period:

Date first patient enrolled: 29 September 2006

Date last patient completed: 20 March 2008

Phase of development: Phase 2

Objectives:

Primary:
To evaluate the antitumor activity of larotaxel in combination with trastuzumab as assessed by objective response rate (RR) observed during the study period (up to 6 months after the last patients enrolled).

Secondary:

- To assess the safety and tolerability of larotaxel in combination with trastuzumab
- To assess any pharmacokinetic (PK) interaction of larotaxel and trastuzumab when given in combination
- To evaluate the progression free survival (PFS) and overall survival (OS)

Methodology: Multicenter, open-label, uncontrolled study of larotaxel administered at the dose of 90 mg/m² every 3 weeks (q3w) in combination with trastuzumab administered at a loading dose of 4 mg/kg followed by 2 mg/kg weekly (qw).

The study was prematurely stopped due to poor enrolment performance, hence the current report is a synopsis style report.

Number of patients: Planned: 49 Randomized: NA Treated: 6

Evaluated: Efficacy: 6 Safety: 6 Pharmacokinetics: 6

Diagnosis and criteria for inclusion: Female patients aged at least 18 years with HER2 positive metastatic breast cancer (MBC), Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, histologically or cytologically proven diagnosis of metastatic or locally recurrent breast cancer (adenocarcinoma) and inoperable with a curative intent, having received an anthracycline and/or taxane prior to entry with a cumulative dose that did not exceed 360 mg/m² of doxorubicin or 750 mg/m² of epirubicin, evidence of measurable disease as defined by response evaluation criteria in solids tumors (RECIST), having completed all prior chemotherapy, immunotherapy, targeted non-cytotoxic therapy and radiotherapy ≥3 weeks, adequate organ function as defined by laboratory parameters, no evidence of cardiac function compromise. Patents with asymptomatic brain were eligible provided they had not received cranial irradiation.

Investigational product: XRP9881 (larotaxel) 40 mg/mL vial

Dose: 90 mg/m² as q3w

Administration: 1-hour intravenous (IV) infusion. Patients received IV premedication including dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines, dexamethasone 8 mg or equivalent steroid, at least 30 minutes prior to larotaxel administration

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity or withdrawal of consent

Duration of observation: Patients were followed for safety up to 30 days after last infusion

Combination therapy: Trastuzumab (Herceptin®)

Dose: 4 mg/kg as a loading dose, day 1 of the first cycle (D1)

2 mg/kg weekly on Cycle 1, D8, D15 and on Day 22 (C2) and subsequent cycles

Administration: 90-minute IV infusion

Criteria for evaluation:

Efficacy: Tumor assessments were done at baseline and every 2 cycles (at the end of Cycles 2, 4, 6, 8, etc.) using the same method for each assessment; by computer tomography (CT) scan, magnetic resonance imaging (MRI) (unless CT contrast is contraindicated) or clinical examination, based on RECIST criteria. The main endpoint was the objective RR defined as a confirmed complete response (CR) or a confirmed partial response (PR) during the study period (up to 6 months after last enrolled patient), as defined by the RECIST criteria.

Safety: Adverse events (AEs), vital signs, physical examinations, ECOG PS and laboratory safety tests (including complete blood counts and serum chemistry) were recorded prior to drugs administration, at designated interval throughout the study and up to 30 days after the end of study treatment. Adverse events were graded according to the NCI-CTCAE v.3.0. Left ventricular ejection fraction (LVEF) was assessed at baseline, every 3 cycles and at the end of treatment.

Pharmacokinetics: For larotaxel, PK assessments done for all patients were done at Cycle 1 and at Cycle 6 (if applicable at Cycle 6), on D1 before the start of infusion, 5 min before the end of infusion, 5 min, 20 min, 1 h, 5 h, 21 h after the end of infusion (D2) and on D5 (approximately 93 h).

For trastuzumab, PK assessments were done at Cycle 6 in all patients (if applicable) on D1 before the start of infusion, 5 min before the end of infusion, then 1.5 h, 2.5 h, 4.5 h, 6.5 h, after the end of infusion of trastuzumab and on D2 (22.5 h after the end of infusion), D5 and D8 (just before the next trastuzumab infusion); and a predose sample collected at Cycle 1 and trough (Cmin) levels of trastuzumab on D22 (before trastuzumab infusion) from Cycle 1 to the end of trastuzumab treatment. Pharmacokinetic results will be submitted in a separate document.

Statistical methods: All safety criteria were analyzed based on the review of the individual values and using descriptive statistics. All treated patients were evaluated for safety, efficacy and pharmacokinetics.

Summary:

Efficacy results: In all, 3 patients out of the 6 treated patients had a partial or complete response. The best overall responses were complete response in 1 patient, partial response for 2 patients, stable disease for 1 patient and progressive disease for 1 patient. One patient was not evaluable since no tumor assessments were performed due to patient withdrawal after the first treatment.

For one patient, progressive disease was documented by the investigator at the cycle 4 tumor assessment. However, despite this, the investigator continued to treat the patient and perform tumor assessments up until cycle 16.

Safety results: All patients withdrew from the study treatment due to the following reasons: withdrawal of consent (3 patients), disease progression (1 patient), AE (1 patient, neuropathy peripheral grade 2), and other reason (complete response, 1 patient), The 6 patients received a total of 1 to 16 cycles of treatment.

All patients experienced at least 1 treatment-emergent adverse event (TEAE). For all patients, the worst National Cancer Institute (NCI) grade reported was severe (3) or life threatening (4). Most of them were graded mild and moderate. Grade 3 events consisted of neutropenia (n = 1), thrombocytopenia (n = 1), diarrhea (n = 2), asthenia (n = 2), paronychia (n = 1), hyponatremia (n = 1), headache (n = 1), neuropathy peripheral (n = 1) and pleural effusion (n = 1). The following Grade 4 events were observed: neutropenia (n = 3) and ataxia (n = 1).

Three patients experienced serious adverse events (SAEs): ataxia, pleural effusion and diarrhea.
One patient died 133 days after last dose due to disease progression; she previously discontinued the treatment due to AE (neuropathy peripheral).

Results of laboratory tests showed that there were 3 patients with grade 3 or 4 leukocytes/white blood cells, 1 patient with grade 3 platelets; and 5 patients with grade 3/4 neutropenia. No grade 3/4 was reported for blood chemistry parameters.

Date of issue: 12 June 2012