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Sponsor / Company: sanofi-aventis **Drug substance(s):** Larotaxel (RPR109881, XRP9881)	**Study Identifier:** NCT00087958 **Study code:** EFC6088

Title of the study: Phase 2 multicenter, open label, non-randomized study of intravenous RPR109881 q 3 weeks in patients with metastatic breast cancer progressing after therapy with anthracyclines, taxanes, and capecitabine.

Study center(s): 63 sites worldwide enrolled at least 1 patient: 20 in North America, 8 in Latin America, 26 in Europe, 6 in Asia and 3 in others countries (Turkey/South Africa).

35 sites did not enroll any patients.

Study period:

Date first patient enrolled: 20-Aug-2004

Study cut-off date: 20-Feb-2007

Phase of development: Phase 2

Objectives:

Primary objective:

To determine the objective response rate (RR) of larotaxel administered as a 1 hour intravenous (IV) infusion every 3 weeks in patients with metastatic breast cancer (MBC) relapsing or progressing after therapy with anthracyclines, taxanes, and capecitabine

Secondary objective:

- To assess the safety and tolerability of larotaxel in this patient population;
- To assess the impact of larotaxel on pain control and analgesic use;
- To assess the impact of larotaxel on the maintenance of performance status and body weight;
- To determine the effect of larotaxel on clinical benefit as assessed by progression free survival (PFS), overall survival(OS), and the composite clinical event of complete response (CR), partial response (PR), and stable disease (SD) ≥12 weeks [per Amendment 2]. Other efficacy variables were time to tumor response (TTR) and duration of response (DR).

Methodology:

Multicenter, open label single arm, non-randomized Phase II clinical trial

Number of patients: Planned: 162 Randomized: N/A Treated: 168

Evaluated: Efficacy: 168 Safety: 168 Pharmacokinetics: 0

Diagnosis and criteria for inclusion:

Histologically or cytologically proven diagnosis of breast adenocarcinoma that was metastatic or locally recurrent and inoperable. Patients must have had measurable disease as defined by RECIST at study entry. Patients must have received prior treatment for the breast cancer including antracyclines, taxanes, and capecitabine.

Investigational product: Larotaxel

Dose: For patients with ECOG performance status (PS) 0 or 1, no prior history of febrile neutropenia, and no suspected bone marrow involvement, starting dose was 90 mg/m^2 IV infused over 1 hour.

For patients with ECOG PS 2, history of febrile neutropenia (as defined using the NCI CTCAE v.3.0 or bone marrow involvement, the starting dose was 75 mg/m2 IV infused over 1 hour. If bone marrow involvement was suspected, further bone marrow assessment was recommended. Patients were treated for 2 cycles and assessed for safety and activity of larotaxel. If there had been no progression, and in the absence of dose-limiting toxicity (DLT), the dose for subsequent cycles was 90 mg/m2 IV infused over 1 hour.

Administration: Intravenous (IV)

Duration of observation:

Patients continued to receive treatment until documented disease progression, treatment intolerance, wish to stop, withdrawal of consent, or Investigator decision. Following treatment discontinuation, patients were followed to document subsequent anticancer therapies and survival status until death, lost-to-follow-up, withdrawal of consent, or study completion cut-off, whichever occurred first.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the objective response rate (RR = CR+PR) as assessed by RECIST, reviewed by an independent review committee (IRC). Secondary efficacy variables were PFS, OS, and the composite clinical event of CR, PR, and SD ≥12 weeks. Other efficacy variables were time to tumor response (TTR) and duration of response (DR).

Safety: Safety analyses were based on incidence, severity (as graded by the NCI CTCAE v.3.0), chronicity, and cumulative nature of treatment emergent adverse events (TEAEs).

Pharmacokinetics: A PK substudy was added during the main study period to investigate the potential inhibitory effect of larotaxel on CYP3A4 activities in vivo, by assessing the effect of larotaxel on oral simvastatin PK (per Amendment 3). No patients were enrolled in the PK substudy during the main study. The PK substudy will be continued under Amendment 4 until the required numbers of patients for PK analyses are acquired; data from patients enrolled on the PK substudy will be analyzed and reported separately.

Pharmacokinetic sampling times and bioanalytical methods: Will be reported in the PK substudy report.

Statistical methods:

The analysis for the primary efficacy variable was the estimate of the objective response rate (number of CR + PR determined by the IRC divided by the number of treated patients and the corresponding 95% confidence interval, using the normal approximation method. A p-value based on the two-sided Chi-square test will be provided to test the null hypothesis: RR = 0.05, at the 5% significance level.

The Kaplan-Meier method was used for the evaluation of the time to event for the secondary variables OS and PFS. The event rates and corresponding 95% confidence intervals were provided for the composite clinical event of CR, PR, and SD ≥12 weeks. The other efficacy variables were summarized using descriptive methods.

A futility analysis was conducted, and a sanofi-aventis Study Conduct Review Committee (SCRC) reviewed the safety and the responses determined by the IRC on the first 45 patients treated with at least 2 post baseline tumor assessments or evidence of progressive disease or death.

Summary:

Efficacy results:

Based on the IRC evaluation, RR was 7.7% (13 PRs) (P=0.10, 95% CI: 4.2-12.9). Median PFS was 13.0 weeks (95% CI: 11.1-16.1). Median OS was 43.3 weeks (95% CI: 36.3-53.1).

Summary of RR and PFS - as Treated population (IRC evaluation)

	IRC LAROTAXEL (N=168)
RR (CR + PR), n(%)	13 (7.7)
95% Exact CI	(4.2,12.9)
P-value	0.1034
Median PFS (weeks)	13.0
95% C.I.	(11.1,16.1)

Note 1: % = n/N where N is the total number of patients in the treatment group
Note 2: RR=response rate, CR=complete response, PR=partial response, PFS=progression free survival
Note 3: P-value based on two-sided Chi square test of null hypothesis RR<=0.05

Safety Results:

Nearly all patients (166, or 98.8%) experienced TEAEs; 61% of patients had reported Grade 3 or 4 events. Neutropenia and its complications were the main hematological toxicities and diarrhea and fatigue/asthenia were the main non hematological toxicities. Grade 3 to 4 febrile neutropenia, Grade 3 to 4 neutropenia infection, and Grade 3 to 4 infection were observed, respectively, in 6.5%, 1.8%, and 1.2% of the total patients. Seventy patients (41.7%) experienced serious adverse events (SAEs). Fourteen (8.3%) patients were withdrawn from study treatment due to AEs. Of these 14 patients, 11 withdrew due to drug related AEs. There were 98 deaths as of the study cutoff date (58.3%); the majority (51.8%) were due to disease progression. Seven deaths (4.2%) on study-treatment (ie, within 30 days of last dose) related to study drug were reported: septic toxicity from study drug (6 patients) and 1 sudden death.

Summary of treatment emergent adverse events by grouping at worst NCI grade, all grades and Grade 3 to 4, based on number of patients - as treated population

	Number (%) of patients	
	LAROTAXEL (N=168) Worst grade	
Derived: AE Category Main Event	**All**	**3/4**
Total number of patients with grouping-related TEAEs	**166(98.8)**	**98(58.3)**
Gastrointestinal	**134(79.8)**	**36(21.4)**
Diarrhea	96(57.1)	16(9.5)
Nausea	75(44.6)	5(3.0)
Vomiting	58(34.5)	5(3.0)
Anorexia	53(31.5)	4(2.4)
Constipation	35(20.8)	1(0.6)
Stomatitis	33(19.6)	1(0.6)
Dysgeusia	21(12.5)	0(0.0)
Dyspepsia	13(7.7)	1(0.6)
Dry mouth	13(7.7)	0(0.0)
Gastrointestinal inflammation	12(7.1)	2(1.2)
Dehydration	6(3.6)	4(2.4)
Bile duct obstruction	2(1.2)	2(1.2)
Intestinal obstruction	1(0.6)	1(0.6)
General body systems	**134(79.8)**	**24(14.3)**
Fatigue	119(70.8)	25(14.9)
Fever	26(15.5)	0(0.0)
General physical health deterioration	11(6.5)	3(1.8)
Insomnia	11(6.5)	0(0.0)
Weight Loss	10(6.0)	0(0.0)
Pain	**128(76.2)**	**29(17.3)**
Musculoskeletal pain	112(66.7)	19(11.3)
Gastrointestinal pain	45(26.8)	4(2.4)
General pain	30(17.9)	6(3.6)
Neurological pain	30(17.9)	4(2.4)
Pulmonary/upper respiratory pain	19(11.3)	1(0.6)

Summary (continued):

Dermatology/Skin	**98(58.3)**	**2(1.2)**
Alopecia [a]	82(48.8)	1(0.6)
Rash	11(6.5)	0(0.0)
Nail disorders	10(6.0)	0(0.0)
Hot flush	9(5.4)	1(0.6)
Peripheral oedema	8(4.8)	0(0.0)
Pruritus	8(4.8)	0(0.0)
Palmar-plantar erythrodysaesthesia	5(3.0)	0(0.0)
Flushing	4(2.4)	0(0.0)
Urticaria	3(1.8)	0(0.0)
Neurotoxicity	91(54.2)	19(11.3)
Peripheral Sensory Neuropathy	73(43.5)	7(4.2)
Neuropathy[b]	55(32.7)	6(3.6)
Dizziness	20(11.9)	3(1.8)
Peripheral Motor Neuropathy	11(6.5)	1(0.6)
Mood alteration	8(4.8)	1(0.6)
Syncope	2(1.2)	2(1.2)
Confusion	2(1.2)	1(0.6)
Brain Edema	1(0.6)	1(0.6)
Cognitive disturbance	1(0.6)	1(0.6)
Cranial Neuropathy	1(0.6)	1(0.6)
Hemiplegia	1(0.6)	1(0.6)
Metastases to central nervous system	1(0.6)	1(0.6)
Ataxia	1(0.6)	0(0.0)
Encephalopathy	1(0.6)	0(0.0)
Hematology-clinical	71(42.3)	57(33.9)
Leucopenia	59(35.1)	53(31.5)
Neutropenia	56(33.3)	50(29.8)
Anemia	28(16.7)	2(1.2)
Thrombocytopenia	8(4.8)	5(3.0)
Pulmonary/upper respiratory	53(31.5)	7(4.2)
Dyspnea	35(20.8)	8(4.8)
Cough	22(13.1)	0(0.0)
Pleural effusion	2(1.2)	0(0.0)
Pneumothorax	2(1.2)	0(0.0)
Infection	**27(16.1)**	**5(3.0)**
Infection	18(10.7)	2(1.2)
Neutropenic sepsis	10(6.0)	3(1.8)
Cardiovascular	**14(8.3)**	**0(0.0)**
Hypotension	8(4.8)	0(0.0)
Arrhythmia	4(2.4)	0(0.0)
Cardiac ischemia	1(0.6)	0(0.0)
Thromboembolism	1(0.6)	0(0.0)

Summary (continued):

Allergic Reaction	**11(6.5)**	**0(0.0)**
Febrile neutropenia	**11(6.5)**	**11(6.5)**
Hemorrhage/bleeding	**5(3.0)**	**2(1.2)**
Gastrointestinal hemorrhage	5(3.0)	2(1.2)
Hepatobiliary/pancreas	**1(0.6)**	**0(0.0)**
Liver Dysfunction	1(0.6)	0(0.0)
Renal and urinary disorders	**1(0.6)**	**1(0.6)**
Renal failure	1(0.6)	1(0.6)

Note 1: All: Grade = 1, 2, 3, 4, or 5. Grade 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life Threatening, 5 = Death

Note 2: % = n/N where N is the total number of patients in the treatment group

Note 3: The numbers within a column may not add to the total number of patients with TEAEs or in a MedDRA category, since a patient may have had more than one TEAE.

Note 4: All the hematological values reported in this table were reported in the AE CRF pages (Leucopenia, neutropenia, anemia, thrombocytopenia)

[a] Alopecia was reported grade 3 in one patient but the grade was aberrant

[b] Neuropathy includes the preferred terms peripheral sensory neuropathy, cranial neuropathy, neuropathy, peripheral neuropathy, and peripheral motor neuropathy.

Summary of hematological laboratory tests at worst NCI grade, Grade 0, all grades, and Grade 3 to 4, under treatment based on number of patients - as treated population

	Number (%) of patients LAROTAXEL (N=168)			
Laboratory parameters	**Grade 0**	**All grades**	**Grade 3-4**	**Missing**
WBC / Leukocytes	7 (4.2)	157 (93.5)	**106 (63.1)**	4 (2.4)
Neutrophils (ANC)	15 (8.9)	149 (88.7)	**131 (78.0)**	4 (2.4)
Platelets	109 (64.9)	55 (32.7)	**12 (7.1)**	4 (2.4)
Hemoglobin	19 (11.3)	145 (86.3)	**8 (4.8)**	4 (2.4)

Note 1: Grade 0 = All values within the normal range; All grades: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life Threatening
Note 2: % = n/N where N is the total number of patients in the treatment group
Note 3: Missing refers to patients with laboratory unit or normal range missing or no post-baseline laboratory data

Summary of biochemical laboratory tests at worst NCI grade, Grade 0, all grades, and Grade 3 to 4, under treatment based on number of patients - as treated population

		Number (%) of patients LAROTAXEL (N=168)		
Laboratory parameters	**Grade 0**	**All grades**	**Grade 3-4**	**Missing**
Total bilirubin	139 (82.7)	24 (14.3)	**3 (1.8)**	5 (3.0)
Alkaline phosphatase	68 (40.5)	95 (56.5)	**3 (1.8)**	5 (3.0)
SGOT (AST)	58 (34.5)	104 (61.9)	**7 (4.2)**	6 (3.6)
SGPT (ALT)	66 (39.3)	97 (57.7)	**11 (6.5)**	5 (3.0)

Note 1: Grade 0 = All values within the normal range; All grades: 1 = Mild, 2 = Moderate, 3= Severe, 4 = Life Threatening
Note 2: % = n/N where N is the total number of patients in the treatment group
Note 3: Missing refers to patients with laboratory unit or normal range missing or no post-baseline laboratory data

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