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Sponsor / Company: sanofi-aventis **Drug substance(s):** XRP9881 (Larotaxel)	**Study Identifier:** NCT00485979 **Study code:** EFC10073
Title of the study: A randomized, open-label, multi-center study of larotaxel at 90mg/m² or docetaxel every 3 weeks, alone or in combination with trastuzumab according to Her2neu status, administered after a combination regimen of anthracycline and cyclophosphamide as pre-operative therapy in patients with high risk localized breast cancer	
Study center(s): 35 sites in 8 countries	
Study period: Date first patient enrolled: 11 June 2007 Date last patient last surgery: 03 July 2009	
Phase of development: Phase 2	

Objectives:

Primary objective:

To assess the pathological complete response (pCR) rate by treatment arm (according to Chevallier criteria)

Secondary objectives:

To assess in each treatment arm:

- The clinical response rate (RR)
- The breast conservation rate (BCR)
- The progression-free survival (PFS)
- The overall survival (OS)
- The safety and tolerability profile
- The pCR according to National Surgical Adjuvant Breast and Bowel Project (NSABP) and Sataloff criteria (added by amendment No. 3)

To rank docetaxel and larotaxel alone in Her2 -ve patients, or combined with trastuzumab in Her2 +ve patients, according to the pCR rate

Methodology:

Randomized, multi-center, open-label study, evaluating the treatment of larotaxel or docetaxel every 3 weeks, alone or in combination with trastuzumab according to Her2neu status, administered after a combination regimen of anthracycline and cyclophosphamide as pre-operative therapy in patients with high risk localized breast cancer.

Patients received a 4 run-in treatment cycles of anthracycline and cyclophosphamide. Within each cohort of either Her2 -ve or Her2 +ve and after the run-in treatment, patients were randomized to receive docetaxel or larotaxel, alone or in combination with trastuzumab according to Her2neu status (combination only in Her2 +ve cohort).

Her 2-ve cohort:			
Number of patients:	Planned: 220	Randomized: 237	Treated: 237
Evaluated:	Efficacy: 237	Safety : 238	Pharmacokinetics : Not applicable
Her 2+ve cohort:			
Number of patients:	Planned: 90	Randomized: 93	Treated: 92
Evaluated:	Efficacy: 92	Safety :91	Pharmacokinetics : Not applicable

Diagnosis and criteria for inclusion: Patients with newly diagnosed localized invasive breast cancer who were not candidate for conservative surgery or whose characteristics make pre-operative chemotherapy highly recommended.

Investigational product:

All patients received:

Cycle 1 to 4:

Epirubicin 90 mg/m² intravenous (IV) or doxorubicin 60 mg/m² IV + cyclophosphamide 600 mg/m² IV (Day 1) every 3 weeks, repeated for 4 cycles.

Patients with Her2 -ve breast cancer

Docetaxel –containing regimen

Docetaxel premedication: Oral corticosteroid

Docetaxel 100 mg/m² IV (Day 1) every 3 weeks, repeated for 4 cycles (cycle 5 to 8).

Larotaxel –containing regimen

Larotaxel premedication: Histamine H1 antagonist and steroid administered by IV route

Larotaxel 90 mg/m² 1-hour IV infusion (Day 1) every 3 weeks, repeated for 4 cycles (cycle 5 to 8).

Patients with Her2 +ve breast cancer

Docetaxel –containing regimen

Docetaxel 100 mg/m² IV (Day 1) repeated for 4 cycles (cycle 5 to 8) + trastuzumab 8 mg/kg IV (Day -1, cycle 5) and 6 mg/kg IV (Day 1, cycles 6, 7 and 8) every 3 weeks.

Larotaxel –containing regimen

Larotaxel 90 mg/m² IV (Day 1) repeated for 4 cycles (cycle 5 to 8) + trastuzumab 8 mg/kg IV (Day -1, cycle 5) and 6mg/kg IV (Day 1, cycles 6, 7 and 8) every 3 weeks.

Duration of treatment: According to the primary endpoint of pCR, the study duration was expected to be 7 months for each patient.

Duration of observation: Follow-up period on study for progression/survival up to 2 years after the last patient randomized.

Criteria for evaluation:

Efficacy:

The pathologist performed macroscopic and microscopic examination of oriented tumorectomy/mastectomy, and of the whole axillary specimen. Pathological assessment was done using pathological response according to Chevallier, NSABP and Sataloff criteria assessed by the Investigators and the pathological response committee.

Safety:

Vital signs, physical examinations, Eastern Cooperative Oncology Group Performance Status (ECOG PS) laboratory safety tests (including complete blood counts and serum chemistry), electrocardiogram (ECG) and left ventricular ejection fraction (LVEF) were recorded prior to the run-in treatment administration and at designated interval throughout the study. Adverse events (AEs) were collected from the first dose of anthracycline-containing regimen up to 30 days after the end of study treatment; they were graded according to the National Cancer Institute classification (NCI-CTCAE v.3.0).

Statistical methods: The primary efficacy endpoint was the pCR according to the Chevallier criteria. The primary analysis showed pCR rate with two-sided 95% confidence interval (CI). The secondary analysis showed pCR rate, according to NSABP and Sataloff criteria, with two-sided 95% CI. Clinical RR, BCR were analyzed descriptively. Progression-free survival and OS were analyzed using Kaplan-Meier method.

Summary: This report presents the final results of the primary efficacy endpoint (ie, pathological response) and safety data.

A total of 330 female patients with newly diagnosed localized invasive breast cancer were enrolled and randomized: 237 patients in the Her2 -ve cohort (docetaxel arm: 117 patients; larotaxel arm: 120 patients), and 93 patients in the Her2 +ve cohort (docetaxel + trastuzumab arm: 48 patients; larotaxel + trastuzumab arm: 45 patients).

Efficacy results: The primary endpoint, pCR rate, according to Chevallier was assessed in the evaluable for pathological response population.

In the Her2 -ve cohort, the pCR rate was 15.9% [9.72: 24.00] in docetaxel and 8.6% [4.21: 15.28] in larotaxel.

In the Her2 +ve cohort, the pCR rate was 41.3% [27.00: 56.77] in docetaxel + trastuzumab and 24.4% [12.36: 40.30] in larotaxel + trastuzumab.

Safety results: Patients with Her2 –ve breast cancer

A majority of treated patients experienced treatment emergent adverse events (TEAEs) (docetaxel arm: 98.3%, 28.2% with Grade 3-4; and larotaxel: 97.5%, 27.3% with Grade 3-4).

Fatigue (51.3%), neuropathy sensory (48.7%), stomatitis (48.7%), myalgia (44.4%), nails disorders (35.9%), diarrhea including colitis and enteritis (33.3%) (colitis reported by 1 patient), edema peripheral (24.8%), arthralgia and nausea (20.5% each) were the most frequent AEs reported in the docetaxel arm. Fatigue (52.1%), neuropathy sensory (49.6%), diarrhea (47.9%), myalgia (41.3%), nausea (36.4%), abdominal pain (24.8%), and vomiting and arthralgia (24.0% each) were the most frequent AEs reported in the larotaxel arm. No colitis and enteritis were reported in larotaxel arm.

Twelve patients (10.3%) in the docetaxel arm and 8 patients (6.6%) in the larotaxel arm had at least 1 treatment emergent serious adverse event (SAE) in the Her2 -ve cohort. No deaths occurred in the Her2 -ve cohort.

Patients with Her2 +ve breast cancer

A majority of treated patients experienced TEAEs (docetaxel + trastuzumab arm: 95.8%, 33.3% with Grade 3-4; and larotaxel + trastuzumab arm: 97.7%, 25.6% with Grade 3-4).

Fatigue (35.4%), stomatitis (33.3%), neuropathy sensory (29.2%), diarrhea (29.2%), myalgia (27.1%), nausea and oedema peripheral (20.8% each) were the most frequent TEAEs reported in the docetaxel + trastuzumab arm. Diarrhea (53.5%), fatigue (41.9%), neuropathy sensory (41.9%), nausea (34.9%), stomatitis (32.6%), myalgia (30.2%), arthralgia (25.6%) and vomiting (20.9%) were the most frequent TEAEs reported in the larotaxel + trastuzumab arm. No colitis and enteritis were reported in both arms.

Six patients (12.5%) in the docetaxel + trastuzumab arm and 6 patients (14%) in the larotaxel + trastuzumab arm had at least 1 treatment emergent SAE in the Her2 +ve cohort. One death occurred within the 30 days following the dose of study treatment (related multi-organ failure after Cycle 5).

Date of issue: 06-Jun-2012