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Sponsor / Company: sanofi-aventis **Drug substance(s):** Larotaxel (XRP9881; RPR109881)	**Study Identifier:** NCT00081796 **Study code:** EFC6089 [XRP9881B-3001]
Title of the study: A randomized, open-label, Phase 3 study of larotaxel IV every 3 weeks versus capecitabine (Xeloda®) tablets twice daily for 2 weeks in 3-week cycles in patients with metastatic breast cancer (MBC) progressing after taxanes and anthracycline therapy (EFC6089)	
Study center(s): 240 centers activated worldwide; patients were enrolled at 142 centers	
Study period: Date first patient enrolled: 01 April 2004 Date last patient completed: 30 September 2006 (data cut-off date)	
Phase of development: 3	
Objectives: ***Primary***: The primary objective of this study was to compare progression free survival (PFS) in patients with MBC, progressing after taxanes and anthracycline therapy, when treated with larotaxel versus capecitabine. ***Secondary***: The secondary objectives were to compare survival and other measures of anti-tumor efficacy (response rate [RR], time to tumor response [TTR], duration of response [DR], single time progression rate [STPR], and time to treatment failure [TTF]) in patients treated with larotaxel versus capecitabine; to compare the safety and tolerability of larotaxel versus capecitabine; and to compare the quality of life and other clinical benefit measures in patients treated with larotaxel versus capecitabine	
Methodology: Global multi-center, open-label, two-arm randomized, Phase 3 clinical trial	
Number of patients: Planned: 800; Randomized: 438; Treated: 433 Evaluated: Efficacy: 438; Safety: 433	
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 anthracyclines, and taxanes.	
Investigational product: Larotaxel (XRP9881; RPR109881) Dose: 90 mg/m² IV larotaxel on Day 1 over 1 hour (75 mg/m² IV in patients with known bone marrow involvement). Treatment was repeated every 3 weeks Administration: Intravenous (IV)	
Duration of treatment: Patients continued to receive treatment until disease progression, patient intolerance, withdrawal of consent, or Investigator decision. **Duration of observation:** Patients were followed every 3 months to document subsequent anticancer therapy and survival status.	
Reference therapy: Capecitabine Dose: 1250 mg/m² (2500 mg/m²/day) capecitabine tablets administered orally twice daily (morning and evening) for 2 weeks followed by a 1-week rest period, to form a 3-week cycle. Administration: Oral	

Criteria for evaluation:

Efficacy: The primary efficacy variable was progression free survival (PFS), based on Independent Review Committee (IRC) analysis, which was defined as the time from randomization to first documentation of RECIST-defined objective tumor progression or death due to any cause.

The secondary efficacy variables included overall survival (OS), single time progression rate (STPR), and response rate (RR).

Other efficacy variables were time to tumor response (TTR), time to treatment failure (TTF), and duration of response (DR).

Safety: Safety parameters were adverse events, hematology, blood chemistry, vital signs, physical examinations, and ECOG performance status.

Special safety parameters included febrile neutropenia, infection with neutropenia, septic death, sensory neuropathy, diarrhea, hand-foot syndrome, and fluid retention.

Pharmacokinetics:

Statistical methods:

The primary efficacy variable was median PFS, based on IRC evaluation. The PFS was compared between the two treatment groups using a 2-sided log rank test stratified by the randomization factors "treatment setting of prior taxanes administration" and "prior taxane responsiveness" as specified at the time of randomization. The rate of PFS events was also estimated using the Kaplan-Meier method. The analyses were performed on the ITT population.

As secondary efficacy variables, OS and TTF were compared between the two treatments by the 2-sided log-rank test stratified by the stratification factors at randomization. The survival curves were estimated using Kaplan-Meier estimates. Response Rate was compared between the two treatment groups using 2-sided CMH test stratified by the same stratification factors. The other secondary efficacy variables STPR, TTR, and DR were summarized by treatment using mean, standard error, and range. The analyses were performed on the ITT population.

The study was terminated based on the recommendation of the IDMC. All safety analyses followed the sanofi-aventis safety analysis Guideline. The comprehensive analysis of safety was based on "treatment-emergent" principle. Descriptive statistics were provided for TEAE, SAE, major labs, and death.

The changes in the statistical analyses compared to the original SAP are documented in the main body of this report.

Summary: In general, patient characteristics were well balanced between arms; however, there were a higher proportion of black patients and younger patients (<50 years old) in the larotaxel arm. A slightly higher proportion of patients in the larotaxel group had liver metastases.

A pre-specified futility analysis that was performed after the first 200 patients was reviewed by the IRC and resulted in the early termination of the study since the study did not reach its primary endpoint of superiority of larotaxel over capecitabine.

Efficacy results: The primary efficacy variable, median PFS, was longer in the capecitabine group (18.4 weeks) than in the larotaxel group (14.1 weeks) according to IRC analyses; patients in the larotaxel arm responded later (median TTR: 11.1 weeks vs. 7.0 weeks) in the course of treatment but had a similar duration of response (DR) as compared with capecitabine. Median OS was 65.4 weeks in each arm.

Progression free survival – ITT population – number (%) of patients

	Investigator		IRC [a]	
	LAROTAXEL (N=219)	Capecitabine (N=219)	LAROTAXEL (N=164)	Capecitabine (N=168)
Median PFS (weeks)	12.57	15.43	14.14	18.43
95% CI	(11.00,16.86)	(13.14,18.14)	(11.86,17.86)	(17.43,24.14)
Log-rank test (p-value)[b]	0.1710		0.0482	
Hazard Ratio	1.1603		1.3306	
95% CI	(0.9394,1.4330)		(1.0032,1.7647)	

Note: [a] ITT for IRC is defined as randomized patients who had tumor assessment data reviewed.
Note: [b] P-value was based on 2-sided log-rank test after adjusting for prior taxane setting and prior taxane responsiveness

Overall survival – ITT population – number (%) of patients

	LAROTAXEL (N=219)	Capecitabine (N=219)
Number of Deaths, n(%)[a]	111 (50.7%)	108 (49.3%)
Median OS (weeks)	65.43	65.43
95% Confidence Interval	(60.571,75.286)	(54.429,78.429)
Log-rank test (p-value)	0.7740	
Hazard Ratio	1.0400	
95% Confidence Interval	(0.7960,1.3587)	

Note: [a] 2 LAROTAXEL patients censored due to partial death dates

Best overall response rates – ITT population – number (%) of patients

	Investigator		IRC[b]	
	LAROTAXEL (N=219)	Capecitabine (N=219)	LAROTAXEL (N=164)	Capecitabine (N=168)
RR (CR + PR)	38 (17.4)	54 (24.7)	15 (9.1)	28 (16.7)
95% Exact CI	(12.6,23.0)	(19.1,30.9)	(5.2,14.6)	(11.4, 23.2)
P-value[a]	0.0560		0.0408	

Note: [a] P-value was based on 2-sided CMH test stratified by prior taxane setting and prior taxane responsiveness. P-value was analyzed at an overall two-sided alpha level of 0.05.
Note: [b] ITT for IRC is defined as randomized patients and had tumor assessment data reviewed.

Safety results: Over 95% of patients in each treatment group experienced a TEAE. The percentage of patients with SAEs or who died during the study was similar in each group. The proportion of patients withdrawing from study treatment was slightly higher for larotaxel patients.

	LAROTAXEL (N=218)	Capecitabine (N=215)
Any treatment emergent AE	214 (98.2)	206 (95.8)
Any treatment emergent SAE	75(34.4)	69(32.1)
Permanent withdrawals from treatment due to AE[a]	34 (15.6)	23 (10.7)
Total number of patients who died (all causes)	113 (51.8)	108 (50.2)
Deaths within 30 days of last dose	9 (4.1)	13 (6.0)
Deaths within 60 days of first dose	8 (3.7)	9 (4.2)
[a] data derived from CRF "AE" page		

The main nonhematologic and hematologic toxicities for larotaxel and capecitabine are summarized in the following tables. Safety results were as expected with gastrointestinal events and neutropenia/febrile neutropenia predominating in the larotaxel group and gastrointestinal events and palmar-plantar erythrodysesthesia syndrome predominating in the capecitabine group.

	LAROTAXEL (N=218) n(%)	
	All	Grade 3/4
Main Nonhematologic AEs		
Diarrhoea	137(62.8)	18(8.3)
Nausea	122(56.0)	9(4.1)
Alopecia	105(48.2)	7(3.2)
Fatigue	88(40.4)	14(6.4)
Vomiting	78(35.8)	7(3.2)
Febrile neutropenia	24(11.0)	24(11.0)
Hematology laboratory results		
Leukocytes	202 (92.7)	122 (56.0)
Neutrophils	195 (89.4)	155 (71.1)
Hemoglobin	180 (82.6)	15 (6.9)
Platelets	75 (34.4)	23 (10.6)

	Capecitabine (N=215) n(%)	
	All	**Grade 3/4**
Main Nonhematologic AEs		
Palmar-plantar erythrodysaesthesia syndrome	138(64.2)	36(16.7)
Diarrhoea	118(54.9)	27(12.6)
Nausea	111(51.6)	8(3.7)
Fatigue	77(35.8)	8(3.7)
Vomiting	69(32.1)	10(4.7)
Febrile neutropenia	1(0.5)	1(0.5)
Hematology laboratory results		
Leukocytes	126 (58.6)	16 (7.4)
Neutrophils	97 (45.1)	34 (15.8)
Hemoglobin	161 (74.9)	8 (3.7)
Platelets	78 (36.3)	16 (7.4)

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