SYNOPSIS

Title of the study:	A Phase 1/2 Study of XL147 (SAR245408) Administered in Combination with Trastuzumab or Paclitaxel and Trastuzumab in Subjects with Metastatic Breast Cancer Who Have Progressed on a Previous Trastuzumab-Based Regimen (ARD11439)
Investigator:	[redacted]
Study centers:	Eight centers in Spain and the United States.
Publications (reference):	Tolaney S, Burris H, Gartner E, Mayer I, Saura C, Maurer M, et al. A Phase 1/2 Study of SAR245408 (S08) in Combination with Trastuzumab (T) or Paclitaxel (P) and T in Patients with HER2+ Metastatic Breast Cancer (MBC) Who Progressed on a Previous T-Based Regimen. Cancer Res. 2011;71(24 Supplement):P1-17-02.
Study period:	
Date first patient enrolled:	22 Feb 2010
Date last patient completed:	03 Dec 2012
Phase of development:	Phase 1/2

Objectives: The primary and secondary objectives listed below were evaluated in patients with trastuzumab-refractory human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) (Arm 1), and in patients with taxane- and trastuzumab-refractory HER2-positive MBC (Arm 2).

The primary objectives were:

- To evaluate the safety and tolerability of SAR245408 in combination with trastuzumab and in combination with trastuzumab and paclitaxel.
- To determine the maximum tolerated dose (MTD) of SAR245408 when administered in combination with trastuzumab and in combination with trastuzumab and paclitaxel (Phase 1).
- To estimate the efficacy endpoint of objective tumor response rate (ORR) in the study population (Phase 2).

The secondary objectives were:

- To estimate duration of response and progression-free survival (PFS), including landmarks such as PFS at 6 months (Phase 2).
- To assess the pharmacokinetics and pharmacodynamics of SAR245408 and trastuzumab when given in combination, and of SAR245408, trastuzumab, and paclitaxel when given in combination.

The exploratory objectives were:

- To evaluate the correlation of the pre-existing PIK3CA mutations and other alterations of the phosphoinositide 3-kinase (PI3K)/PTEN pathway components/modulators with clinical outcome in subjects treated with SAR245408 and trastuzumab, or with SAR245408, trastuzumab, and paclitaxel.
- To describe the functional activation state of the PI3K pathway in tumors using a Reverse Phase Protein Lysate Microarray or similar technologies, and to explore whether this activation state is associated with response to study drug treatment.
- To profile tumors for previously identified molecular alterations (eg, mutations, gene silencing) in known oncogenes/tumor suppressor genes that directly and/or indirectly are involved in HER2 and PI3K signaling and/or resistance to paclitaxel.

Methodology: This was a multicenter Phase 1/2, non-randomized and open-label study to establish the MTD, to evaluate safety, and to estimate the efficacy endpoint ORR of SAR245408 in combination with selected systemic anticancer therapies. The study had 2 treatment arms: Arm 1 evaluated SAR245408 in combination with trastuzumab and Arm 2 evaluated SAR245408 in combination with trastuzumab and paclitaxel.

The study was not completed due to limited drug supply, and the study was terminated in February 2012 following the completion of Phase 1.

Number of patients:

Planned: approximately 100 patients. Approximately 40 patients (12 patients each for Arms 1 and 2) were planned to be enrolled in Phase 1. Approximately 25 evaluable patients were to be enrolled in each arm (50 total evaluable) in Phase 2. Up to 10 additional patients whose tumors had PIK3CA mutations could also have been enrolled (Arm 1 only).

Randomized: Not applicable

Treated: 42 (21 patients each in Arm 1, Phase 1 and Arm 2, Phase 1)

Evaluated: 42

Efficacy: 39

Safety: 42

Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Patients must have been female and had pathologically and radiologically confirmed metastatic HER2-positive breast cancer (Stage IV disease). Patients must have received and progressed on at least one prior trastuzumab-containing regimen for metastatic disease (Arm 1 and Arm 2) and must have received at least one prior taxane-containing regimen as adjuvant treatment or for metastatic disease (Arm 2, Phase 1) or must have been taxane-refractory, defined as tumor progression within 6 months of the last taxane dose in the metastatic setting (Arm 2, Phase 2). Patients must have had at least one lesion that was not within a previously radiated field and was measurable on computerized tomography or magnetic resonance imaging scan per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Study treatments

Investigational medicinal product: SAR245408

Formulation: 100-, 150-, and 200-mg tablets

Route of administration: Oral

Dose regimen: 200, 300, or 400 mg administered once daily

Batch numbers: [redacted]

Noninvestigational medicinal product: Trastuzumab

Formulation: Trastuzumab is commercially available (Herceptin®) and was provided as a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration.

Route of administration: IV infusion

Dose regimen: Trastuzumab was administered as an 8-mg/kg loading dose for the first IV infusion (administered over 90 minutes), followed by a 6-mg/kg dose (administered over 30 minutes) every 21-day cycle thereafter. Patients who were receiving trastuzumab on either a 21-day cycle or weekly schedule received treatment on the 21-day cycle without a loading dose if they received the last trastuzumab dose ≤28 days prior to initiating protocol therapy. For these patients, there must have been at least a 3-week or 7-day interval, respectively, since their last dose of trastuzumab.

Batch numbers: [redacted]

Noninvestigational medicinal product: Paclitaxel

Formulation: Paclitaxel (TAXOL®) Injection is commercially available and was provided as a clear, colorless to slightly yellow viscous solution. It was supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to IV infusion.

Route of administration: IV infusion

Dose regimen: Paclitaxel was administered as an 80-mg/m^2 dose (administered over 1 hour) weekly. On Day 1 of every 21-day cycle, paclitaxel was administered after the trastuzumab infusion. On Days 8 and 15 of every 21-day cycle, paclitaxel was administered 30 minutes after SAR245408 administration.

Batch numbers: [redacted]

Duration of treatment: Patients could have received treatment with study drug until progressive disease or unacceptable treatment-related adverse events (AEs) for up to 1 year, and beyond 1 year with the agreement of the sponsor and the investigator.

Duration of observation: Patients were screened within 28 days prior to the first administration of study drug and were followed until 30 to 37 days after the last dose of SAR245408.

Criteria for evaluation: The current report is an abbreviated report because sanofi does not intend or anticipate that the data resulting from this uncontrolled study of SAR245408 in combination with trastuzumab or with trastuzumab and paclitaxel will directly contribute to the evaluation of product effectiveness in the future. As such, only the safety results are being presented in full.

Safety: The following safety criteria were evaluated, and analyzed using descriptive statistics: AEs, vital signs, electrocardiograms, multiple-gated acquisitions or echocardiograms, laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment were assessed by the investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.

Efficacy: Tumor response was assessed using RECIST Version 1.1. Patients were assessed using magnetic resonance imaging or computerized tomography scan within 28 days before the first dose of study treatment, and every 6 weeks (-5/+ 4 days) from the date of first dose of study treatment until the earliest of radiographic disease progression (per RECIST Version 1.1), initiation of subsequent anticancer therapy, or death. Responses were confirmed by repeat assessments that were performed at least 4 weeks after the response criteria were first met. Evaluation of tumor markers was not required in this study.

Pharmacodynamics: Blood and tumor tissue samples (and nontumor tissue obtained at the same time as a prior tumor biopsy if available) were obtained from consented patients for analysis of a variety of established and exploratory pharmacodynamic markers on a defined schedule throughout the study.

Pharmacokinetics: SAR245408 (plasma), paclitaxel (plasma), and trastuzumab (serum) concentrations.

Sampling: During Phase 1, plasma samples for the analysis of SAR245408 and paclitaxel concentrations were collected; pre-SAR245408 dosing and at 0.5, 2, 3, 6, and 8 hours postdosing on Cycle 1 Day 1; pre-SAR245408 dosing and at 0.5, 1, 2, 6, and 8 hours postdosing on Cycle 2 Day 2; pre-SAR245408 dose and 4 hours postdosing on Cycle 1 Day 2, Cycle 1 Day 15, Cycle 2 Day 2, and Cycle 2 Day 15; and pre-SAR245408 dose on Cycle 1 Day 8, Cycle 2 Day 8, and every Day 1 of every fourth cycle after Cycle 4. During Phase 2, plasma samples for the analysis of SAR245408 and paclitaxel were to be collected pre-SAR245408 dose and at 1 and 2 hours postdosing on the first day of Cycles 1, 2, 3, 4, and then every fourth cycle. Serum samples were collected for the analysis of trastuzumab concentrations at the same times as described for the plasma samples.

Bioanalytical methods: Plasma concentrations of SAR245408 were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Plasma concentrations of paclitaxel were determined using validated LC-MS/MS methods from 2 different laboratories with an LLOQ of 1 and 5.0 ng/mL, respectively. Serum concentrations of trastuzumab were determined using a validated LC-MS/MS method with an LLOQ of 7.0 ng/mL.

Pharmacogenomics: Blood samples were collected and genotyped. The analyses of pharmacogenomic testing along with the pharmacogenomic data used to explore the association between the main enzyme systems for SAR245408 metabolism and safety and other potential associations between genes variations and clinical outcomes will be presented in a separate report.

Statistical methods: Phase 1 employed a 3 + 3 design. Formal statistical tests were not planned or performed for the safety analysis. Safety was assessed by summarizing AEs and laboratory results.

The primary efficacy endpoint was ORR, defined as the proportion of subjects for whom the best response was a confirmed complete response or confirmed partial response. Determination of response and progression was based on evaluation per RECIST (Version 1.1).

The study was designed to estimate the efficacy endpoint and planned to enroll 25 evaluable subjects in Phase 2 in each arm (50 total evaluable). Since Phase 2 was stopped, the efficacy analysis was conducted on all patients with an evaluable post-baseline tumor assessment. Two-sided 90% confidence intervals (CIs) were computed.

The secondary efficacy endpoint, PFS, was estimated for each arm. Confidence intervals for proportions were constructed using exact methods.

Although multiple CIs were constructed at the 90% level, no adjustment was made for multiplicity.

Summary:

Efficacy results: Overall, out of 39 patients with an evaluable post-baseline tumor assessment, 4 patients (10.3%) achieved ORR (90% CI 3.6%, 22.0%). In Arm 1, 0 patients achieved ORR; while in Arm 2, out of 20 patients with an evaluable post-baseline tumor assessment, 4 patients (20.0%) achieved ORR (90% CI 7.1%, 40.1%). All 4 patients had confirmed partial response in Arm 2 after treatment with SAR245408, trastuzumab, and paclitaxel. Three patients received a 200-mg dose and 1 patient was dosed with 400 mg SAR245408.

The majority of patients experienced stable disease as their best overall response by RECIST (23 of 39 patients [59.0%] total) and at a similar frequency in both treatment arms (63.2% and 55.0% in Arms 1 and 2, respectively).

Overall, PFS for ≥24 weeks was reported for 9 of 39 patients (23.1%). The proportion of patients with PFS was higher in Arm 2 (8 of 20 patients [40.0%]) than in Arm 1 (1 of 19 patients [5.3%]).

Safety results: Overall, 42 patients with advanced, refractory HER2-positive breast cancer received either the combination of SAR245408 and trastuzumab or SAR245408, trastuzumab, and paclitaxel; 21 patients in each arm. No unexpected toxicities were observed, and toxicities were similar in both arms. The most common drug-related treatment-emergent AEs (TEAEs) occurring in >15% of the safety population were consistent with the known safety profiles of trastuzumab, paclitaxel, and SAR245408 and included: diarrhea, rash, fatigue, nausea, anemia, neutropenia, and peripheral neuropathy.

Five of 42 patients (11.9%) experienced treatment-emergent drug-related serious AEs (SAEs) and one patient experienced a drug-related SAE that was not treatment-emergent. None of the drug-related SAEs were fatal. Five of 42 patients (11.9%) discontinued treatment due to AEs. The most common reason for discontinuation (ie, the only reason reported for more than 1 patient) was rash. SAR245408 administered in combination with trastuzumab or with trastuzumab and paclitaxel in patients with advanced, refractory HER2-positive MBC was safe and well tolerated.

The MTD was tested in both arms at once daily doses of SAR245408 of 200, 300, and 400 mg. The MTD of SAR245408 in combination with trastuzumab or in combination with trastuzumab and paclitaxel was determined by the Cohort Review Committee to be 400 mg, which is the MTD of SAR245408 monotherapy.

Conclusions: [redacted]

Date of report: 08-Oct-2013