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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01392924, U1111-1118-9727
Drug substance(s): SAR245408	**Study code:** TED11883
Title of the study: An Open Label, Dose Escalation Study Evaluating the Safety and Pharmacokinetics of SAR245408 Administered Orally Daily in Patients with Solid Tumors	
Study center(s): 2 study centers in Japan	
Study period: Date first patient enrolled: 01/Aug/2011 Date last patient completed: 10/Nov/2014	
Phase of development: Phase 1	
Objectives: **Primary Objective:** To confirm safety and tolerability of global recommended phase three dose (RPTD) of SAR245408 tablets when administered on continuous once daily dosing (CDD) in patients with solid tumors. Secondary Objectives: • To evaluate the plasma pharmacokinetics (PK) of daily oral administration of SAR245408 in CDD treatment schedule in patients with solid tumors. • To gather preliminary efficacy data after repeated administration of SAR245408 in patients with solid tumors according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.	
Methodology: This was a Phase 1, open-label, non-randomized dose escalation study evaluating the safety, tolerability and PK of SAR245408 in patients with solid tumors, for which no standard treatment exists. Dose escalation followed a standard 3 + 3 design. The planned dose levels were 200 mg, 400 mg and 600 mg SAR245408 administered orally daily in 28-day cycles. The administration dose in this study was not to exceed the global RPTD in monotherapy with tablet. Cycle 1 (Day 1 through Day 28) was defined as the dose-limiting toxicity (DLT) observation period. Safety, tolerability, and development of potential toxicity were assessed on an ongoing basis. A patient could participate in this study until unacceptable toxicity, disease progression, or withdrawal of consent. Efficacy: Evidence of antitumor activity in patients with measurable disease was assessed by computed tomography, magnetic resonance imaging, or other appropriate imaging and/or clinical examination after every two cycles of treatment using RECIST Version 1.1. Enrollment was completed at the 400 mg CDD dose level and safety of global RPTD was confirmed. The supply of investigational medicinal product (IMP) was then terminated and the study was discontinued. Complete analysis of the secondary objectives, including analysis of the PK data, was not performed.	

Number of patients**:**	Planned: 12 to 24
	Treated: 10
	Safety: 10
Evaluated:	
	DLT evaluable: 9
	Efficacy: 10
	Pharmacokinetics: 10

Diagnosis and criteria for inclusion: Patients eligible for inclusion were ≥20 years of age with histologically or cytologically confirmed solid tumor that was metastatic or unresectable and refractory to standard therapies, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and adequate organ and bone marrow function. The disease was to be measurable as defined according to RECIST Version 1.1. Additionally, patients' results for anticoagulation parameters were to be below 1.3 × the laboratory upper limit of normal at screening.

Study treatments

Investigational medicinal product(s): SAR245408 (XL147)

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

Route(s) of administration: Oral

Dose regimen: SAR245408 tablets were administered at the appropriate strength level (planned doses of 200 mg, 400 mg and 600 mg; dose of 600 mg not administered) for CDD in 28-day cycles. Patients fasted for 2 hours prior to and for 1 hour after each dose of SAR245408.

Duration of treatment: At least 1 cycle (28 days), however, treatment could continue until unacceptable toxicity, disease progression, or withdrawal of consent.

Duration of observation: The duration of the study for an individual patient included a screening period up to 28 days, a treatment period of at least 1 cycle of study treatment, and a follow-up period of 28 days (±7 days) following the last administration of IMP. The end of study occurred when all patients had completed the 28-day post-treatment visit.

Criteria for evaluation:

Safety: Safety was assessed by evaluation of adverse events (AEs), DLTs, concomitant medications, changes in vital signs, 12-lead electrocardiograms (ECGs), physical examinations, ECOG PS, and clinical laboratory tests (including hematology, coagulation, clinical chemistry, urinalysis, fasting plasma glucose and glycosylated hemoglobin). Severity of AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.0.

Pharmacokinetics: Plasma samples were collected on Cycle 1 Day 1 and Day 28 at predose and 0.5, 1, 2, 4 and 8 hours postdose; as well as at predose on Cycle 1 Days 2, 15 and 22, on Cycle 2 Day 1, on Cycle 4 Day 1, and on Day 1 of every fourth cycle after Cycle 4 to assess the PK of SAR245408 in a CDD treatment schedule.

Bioanalytical method: Plasma concentrations of SAR245408 were measured using validated liquid-chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1.00 ng/mL.

Pharmacokinetic Parameters: The following SAR245408 PK parameters were to be calculated: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the concentration time curve from time 0 to 24 hours (AUC_{0-24}), trough concentration (C_{trough}) and accumulation ratios (Day 28/29 versus Day 1/2 of Cycle 1) of C_{max} and AUC_{0-24}.

Pharmacogenetics: At screening, a blood sample was to be collected to enable investigations of genetic variants that may affect drug response, tolerability, PK or metabolism of SAR245408. The samples were collected but not analyzed.

Efficacy: The overall objective response was determined at each time point (every 2 cycles) by the Investigator according to RECIST Version 1.1 guidelines. The best overall response was defined as the best response across all tumor assessments from the start of the study until the end of study.

Statistical methods:

Sample size calculation: The sample size was expected to vary depending on DLTs observed, cohort sizes and number of dose levels. The study was conducted with a conventional 3 + 3 dose escalation design. If more than one patient with DLT of 3 patients was observed on the dose level, an additional 3 patients were enrolled at the dose level.

Analysis populations:

- The all-treated/safety population included all registered patients exposed to SAR245408, regardless of the amount of treatment administered.
- The DLT-evaluable population was the subset of patients from the all treated population with a DLT assessment at Cycle 1 without an important protocol deviation.
- The PK population consisted of enrolled patients who had evaluable PK after receiving SAR245408. However, this analysis population was not applicable as statistical analyses for PK parameters were not performed.
- The Efficacy population included all registered patients who received at least 1 dose of the investigational drug, and provided a baseline and at least one post-baseline assessment for the tumor performed according to RECIST guidelines. Patients with an early progression as per RECIST 1.1 were also included in this population.

Analysis of safety: Descriptive statistics and listings were used to summarize patient characteristics, treatment administration and safety variables. The summary of safety results were presented by actual dose level on the safety population. Details for DLTs were provided in a listing by patient.

The number (%) of patients with treatment-emergent AEs (TEAEs) was summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, by all grades and Grade $\geq$3, and causality for IMP. For patients with multiple occurrences of the same preferred term, the maximum grade was used. Serious AEs (SAEs) and deaths were listed regardless of IMP relatedness. Skin AEs were also listed separately.

Separate summary tables were produced for TEAEs, SAEs, drug-related TEAEs and SAEs. The AEs related to DLTs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification (dose reduction or interruption), all TEAEs listed within standardized MedDRA query and post treatment AEs were also summarized separately. Abnormalities in laboratory tests and ECGs, and potentially clinically significant abnormalities or changes in vital signs were provided for the safety population.

Analysis of pharmacokinetics: SAR245408 PK parameters were to be summarized using descriptive statistics. Statistical analysis of PK parameters for evaluation of dose proportionality, occurrence of steady state, and accumulation was planned. However, the statistical analyses for PK parameters were cancelled for this synopsis style report.

Analysis of efficacy: Tumor assessments were presented according to the actual dose level.

Summary:

Study patients:

A total of 10 patients with diverse tumors were enrolled (4 patients at 200 mg CDD and 6 patients at 400 mg CDD). The study population consisted of 3 men and 7 women with a mean age of 51.4 years (range: 23-74 years).

Study treatment lasted for a mean of 96.8 days at the 200 mg CDD dose (median of 46.0 days; range 16-279 days) and 261.0 days at the 400 mg CDD dose (median of 57.5 days; range: 33-1088 days).

Six of 10 (60%) patients discontinued study treatment due to disease progression, 2 (20%) patients due to AEs, 1 (10%) patient due to subject request and 1 patient due to the study being terminated.

Safety results:

There was 1 DLT (non-serious drug related maculo-papular rash of Grade 3) reported in 1 of 6 patients enrolled at the highest dose level studied, 400 mg CDD. The DLT started 9 days after start of dosing and study drug was interrupted 11 after start of dosing. The maculo-papular rash was treated with prednisolone, betamethasone valerate, alclometasone diproprionate and white soft paraffin, and was resolved after 10 days. Study drug was resumed at a reduced dose (200 mg CDD) and there was no recurrence of rash. There were no DLTs at the 200 mg CDD dose level in the 3 DLT-evaluable patients. One patient was excluded from the DLT-evaluable population for insufficient IMP exposure due to disease progression during Cycle 1.

The most common TEAEs were nasopharyngitis (in 60.0% of patients), maculo-papular rash (50.0%), vomiting (40.0%), diarrhea (40.0%) and fatigue (40.0%).

All maculo-papular rash AEs were assessed as related to IMP; 1 patient (400 mg CDD) was discontinued due to an AE of maculo-papular rash. Another patient (200 mg CDD) was discontinued due to an AE of increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) which was assessed as related to IMP.

Three patients experienced SAEs (30.0%), all of whom were treated at the 400 mg CDD dose level. There were no SAEs considered to be related to IMP. No deaths were reported.

There were 2 patients (20.0%) who reported a Grade 3 ALT increase. One of the patients also experienced AEs of AST increased and gamma glutamyl transpeptidase increased at Grade 3; the patient was discontinued from treatment and the AEs were recovering at follow-up. One patient (10.0%) experienced a hematological abnormality of lymphopenia at Grade 3. With the exception of a Grade 3 creatinine increase in one patient with pneumonia, all other observed hematology and chemistry abnormalities were of Grade 1 or 2.

One patient (400 mg CDD) experienced a non-serious Grade 1 hyperglycemia that was considered related to IMP.

Two of 4 patients at the 200 mg CDD dose level experienced one potentially clinically significant abnormality for diastolic blood pressure. Both patients had decrease from baseline ≥10 mm Hg for diastolic blood pressure and diastolic blood pressure ≤45 mm Hg, which was transient and recovered without any action.

Pharmacokinetic results:

Due to discontinuation of the study, the planned PK analyses were not performed. A listing of individual plasma concentrations of SAR245408 is presented in the bioanalytical report.

Efficacy results: According to RECIST 1.1, the best overall response was progressive disease in 5 patients and stable disease in 5 patients. At the 200 mg CDD dose, 3 patients had progressive disease and 1 patient had stable disease (completed 10 cycles). At the 400 mg CDD dose, 2 patients had progressive disease and 4 patients had stable disease (1 patient completed 39 cycles).

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