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Sponsor: Sanofi **Drug substance(s):** SAR125844	**Study Identifiers:** UTN U1111-1126-7527, NCT01657214 **Study code:** TED12337
Title of the study: A Phase 1 dose escalation study of safety, pharmacokinetics, and pharmacodynamics of SAR125844 administered weekly as intravenous infusion in Asian adult patients with advanced malignant solid tumors	
Study center(s): 8 sites: 4 sites in Japan and 4 sites in the Republic of Korea	
Study period: Date first patient enrolled: 14/Sep/2012 Date last patient completed: 02/Jan/2016	
Phase of development: Phase 1	
Objectives: The primary objectives were: • To determine the maximum tolerated dose (MTD) of SAR125844 according to the dose limiting toxicity(ies) (DLTs) observed in Asian patients with advanced solid tumors. • To evaluate the preliminary anti-tumoral effect of SAR125844 in patients with measurable *MET*-gene amplified tumors (including a sub-group of gastric cancer patients) treated at the recommended dose of SAR125844. The secondary objectives were: • To characterize and confirm the global safety profile of SAR125844 including cumulative toxicities. • To assess preliminary antitumor activity of SAR125844 in patients with measurable disease, according to RECIST 1.1 criteria. • To explore the pharmacodynamic effects of SAR125844. • To evaluate the pharmacokinetic profile of SAR125844. • To explore the relationship of *MET* gene amplification status with anti-tumor effects. • To evaluate other pharmacodynamic biomarkers and help selection of patients who could benefit from SAR125844, as an exploratory objective. • To evaluate volumetric tumor response as an exploratory objective at the recommended dose.	
Methodology: Single arm, open-label, dose escalation and dose expansion study	
Number of patients**:** Planned: approximately 70 safety-evaluable patients with 25 to 45 patients in the dose escalation cohort and up to 25 patients in the expansion part including at least 15 gastric cancer patients. Treated: 38 Evaluable for DLT: 28 (15 in dose escalation and 13 in dose expansion) Efficacy: 38 Safety: 38 Pharmacokinetics: 38 Pharmacodynamic: 38	

Diagnosis and criteria for inclusion: In the dose escalation part, patients with a solid tumor for which no standard treatment is available. In the dose expansion cohort, patients with any type of measurable advanced solid tumor for which no standard therapy is available and with *MET* gene amplification (≥10% of cells with FISH >4 gene copies and ratio ≥2), including a sub group of 15 gastric cancer patients.

Study treatments

Investigational medicinal product(s): SAR125844

Formulation: 15 mg/mL

Route(s) of administration: intravenous infusion

Dose regimen: 260 mg/m² to 570 mg/m² once weekly

Duration of treatment: All patients were treated until disease progression, unacceptable toxicity, or patient withdrawal.

Duration of observation: Patients were screened within 21 days prior to the first administration of SAR125844 and followed until 30 days after the last administration. Patients with ongoing SAEs or with treatment-related AEs at the end of treatment were followed until resolution or stabilization. Patients who achieved stable disease (SD), complete response (CR), partial response (PR), or non-CR/non-progressive disease (PD) were followed until disease progression or initiation of another specific anti-tumor treatment.

Criteria for evaluation:

Safety: The safety/all treated population is defined as all registered patients exposed to the investigational drug regardless of the amount of treatment administered.

Safety assessments were conducted at regular intervals throughout the study and included vital signs, physical examinations, ECOG PS, 12-lead ECG, laboratory safety tests (including complete blood counts, serum biochemistry, and urinalysis), and adverse events reported by the patient or noted by the Investigator. Adverse events (AEs) were collected from the signing of the study main informed consent and up to 30 days after the last SAR125844 administration. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 were used in this study to grade adverse events and laboratory data.

The maximum tolerated dose is defined as the dose having the highest probability to be in the targeted interval (ie, to generate between 20% and 35% of IMP related DLT in the whole Asian population), and verifying overdosing constraints (in the global population and in reach country stratum). Dose limiting toxicities were predefined as any of the following during the first cycle of treatment: neutropenia Grade 4, febrile neutropenia, thrombocytopenia Grade 4 or Grade 3 with bleeding requiring a transfusion, any clinical adverse event Grade 3 or higher, nonhematological laboratory abnormality Grade 3 or Grade 4, and SAR125844 toxicity resulting in 2 or more missed doses. These AEs were considered as related to the study drug in absence of clear evidence to the contrary and if not related to disease progression, grading using NCI-CTC AE scale (version 4.03). In the dose escalation part and in the dose expansion part, only patients completing at least one 4-week Cycle were evaluated for DLTs.

Efficacy: Preliminary anti-tumor activity was assessed using the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 by CT scan or MRI and other exams as clinically indicated to assess target and non-target lesions. Volumetric response was assessed by CT scan for exploratory purpose. These exams were performed at baseline (screening), at end of Cycle 1, and then every 8 weeks (2 Cycles), and whenever disease progression is suspected, using the same method(s) for each assessment.

The activity/efficacy population is defined as all registered patients who have received at least one cycle of the investigational drug (at least one cycle defined as at least 2 infusions during the first cycle), and provide a baseline and at least one post-baseline assessment for the efficacy variable of interest. In addition, patients with an early progression as per RECIST 1.1 will also be included in this set.

Pharmacokinetics: SAR125844 blood concentrations were used to determine the following pharmacokinetic parameters using standard non-compartmental analysis (NCA) on Day 1 and Day 22 of Cycle 1: C_{max} (maximum blood concentration observed), t_{max} (time to reach C_{max}), AUC_{last} (area under the blood concentration versus time curve calculated using the trapezoidal method from time zero to the real time corresponding to the last concentration above the limit of quantification), AUC (area under the blood concentration versus time curve extrapolated to infinity), $AUC_{0\text{-}168}$ (area under the blood concentration versus time curve over the dosing interval), CL (total body clearance of drug from blood on Day 1), CL_{ss} (total body clearance of drug from blood at steady state, on Day 22), V_{ss} (volume of distribution at steady state) and $t_{1/2z}$ (terminal half-life associated with the terminal slope), SAR125844 blood concentrations observed before treatment administration during repeated dosing (C_{trough}), were obtained on Day 8, Day 15, Day 22 from Cycle 1 to Cycle 4.

Urinary samples were to be collected at Cycle 1 Day 1. For some patients, no urine collection was performed. For others, urine samples were not collected according to the recommended procedure (using CHAPS), described in the laboratory/investigator manual. Consequently, these samples were not assayed by the Bioanalytical unit.

In addition, PK of Captisol® (or SBE-β-CD used as excipient in the SAR125844 formulation) has been evaluated. The following PK parameters were calculated from Captisol plasma concentrations after the 1st administration of SAR125844: C_{max}, t_{max}, $AUC_{last,}$ AUC and $t_{1/2z}$.

Sampling times: Blood samples (1.2 mL each) were collected for analysis of SAR125844 (using dried blood spot [DBS] technology) in Cycle 1 at mid-infusion, 5 minutes before the end of infusion (EOI) and then 15 minutes, 30 minutes, 1, 2, 3, 5, 7, 9, 24, 48, 72, 120, 168 hours after the end of infusion for the 1st (Day 1) and the 4th (Day 22) administrations Additional samples were drawn before the start of the infusion (predose) on Day 15 (infusion 3) and Day 22 (infusion 4). For Cycle 2 to Cycle 4, blood samples were collected immediately before the start of the infusion on Days 1, 8, 15, and 22.

Blood samples for Captisol analysis in plasma were collected in all patients at Cycle 1 at before the 1st administration and 15 minutes, 30 minutes, 1, 2, 3, 5, 7, 9, 24 hours after the end of the 1st administration of SAR125844. Urine samples concentrations were collected for SAR125844 measurement at the following periods: -12 to 0 hours at Day -1 (predose), and at Day 1, 0 to 12 hours and 12 to 24 hours.

Bioanalytical methods: The concentration of SAR125844 in blood was determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) assay method with a lower limit of quantification (LLOQ) of 2.0 ng/mL. The concentration of Captisol in plasma was determined using a validated LC-MS/MS assay method with a LLOQ of 5.00 µg/mL.

Pharmacodynamics: Sampling times: Blood samples for the determination of shed MET and hepatocyte growth factor (HGF) in plasma were collected on Cycle 1 at baseline and at several time points after treatment that coincide with PK sampling time points, 5 minutes before End of Infusion (EOI), 3, 5, 24 and 168 hours after EOI on C1D1 and 5 minutes before End of Infusion (EOI), 3, 5, 48 (escalation) or 96 (expansion) and 168 hours after EOI on C1D22.

Evaluation of tumor tissue for total-MET and phospho-MET was conducted on samples collected from the dose escalation cohort at Cycle 1 before infusion 1 and at 48 hours after infusion 4, and on samples collected from the expansion cohort at Cycle 1 before infusion 1 and at 96 hours after infusion 4.

Bioanalytical methods: Pharmacodynamic biomarkers were shed MET and HGF in plasma, and total MET and phospho-MET expression in tumor tissue. Enzyme-linked immunoabsorbent assay (ELISA) was used to evaluate plasma Shed MET and HGF. IHC was used to evaluate total-MET and phospho-MET.

Pharmacogenetics/Pharmacogenomics:

Blood samples were collected on Day 1 (predose) to enable investigation of allelic variants of drug metabolism enzymes (including CYP2D6) and as a source of normal DNA for the analysis of genetic variants identified in tumor tissue by genotyping or sequencing studies in all patients.

Deoxyribonucleic acid (DNA) was extracted from whole blood and assayed using a validated Affymetrix DMET Plus Assay method for different allelic variants of drug metabolizing enzymes and transporters. Fluorescence in situ hybridization (FISH) or silver-enhanced in situ hybridization (SISH) assays were performed to evaluate *MET* gene amplification in tumor tissue in the dose expansion cohort.

Statistical methods: Descriptive statistics were used to summarize patient characteristics, exposure, safety, efficacy, and laboratory variables. The co-primary endpoints were determination of SAR125844 MTD and antitumoral response. The MTD was determined by evaluation of DLTs during the first cycle of study treatment. An adaptive Bayesian design with overdose control was used to provide dose recommendation on the dose escalation from 260 to 570 mg/m². Antitumoral response was evaluated based on the primary endpoint of overall response rate (ORR) according to RECIST 1.1 criteria and on 2 secondary endpoints, including response duration (time from initial response to first document tumor progression) and time to progression (TTP; time from informed consent to signature until objective tumor progression).

The sample size of 25 to 45 patients to establish the recommended dose was based on simulations of various scenarios.

Statistical analyses on PK parameters included:

- Dose proportionality for the AUC_{0-168} of SAR125844 at Cycle 1 Day 1 and Day 22.
- Dose effect for the half-life (at Cycle 1 Day 1 and Day 22), CL (Day 1) and CL_{ss} (Day 22) of SAR125844.
- Accumulation ratio for the AUC_{0-168}, C_{max} of SAR125844 at Cycle 1.

Summary: The current report is an abbreviated report, and as such, only the safety results are presented in full.

Study patients: Thirty-eight Asian adult patients were treated, including 19 patients in the dose escalation part and 19 patients in the dose expansion part with *MET* gene amplified tumors, which included 14 patients with gastric cancer. The median age was 64 years (range 28 to 78 years) and 23 (60.5%) were male. The median duration of treatment was 4.1 weeks (median 4 infusions), range 2 to 38 weeks. All 38 patients discontinued treatment and for 36 patients (94.7%), the reason was disease progression. Two patients discontinued due to bacteremia (considered not related to treatment) and investigator decision, respectively. Twenty-eight patients (73.3%) were evaluable for DLTs, including 15 patients in the dose escalation cohort and 13 patients in the dose expansion cohort. All 38 patients (100%) were evaluable for both safety and efficacy.

Safety results: One primary objective of the study was to determine the maximum tolerated dose of SAR125844 according to defined dose-limiting toxicities (DLTs). In the dose escalation cohort, 19 patients received one of four SAR125844 dose levels, 260, 340, 440, or 570 mg/m². Among the 15 patients evaluable for DLT, none experienced any DLTs during treatment Cycle 1 (4 weekly infusions) and no adverse event meeting DLT criteria was observed in subsequent cycles. Based on the safety profile at 570 mg/m² (and the comparable exposure to SAR125844 in TED11449, a similar study with non-Asian patients), the dose of 570 mg/m² was selected as the recommended dose to be further explored in the expansion part. In the expansion part, 1 patient among the 13 evaluable experienced an AE meeting DLT criteria at Cycle 1 (reversible transaminases and creatinine increase after dose omission and reduction). The overall safety profile of SAR125844 over the dose range 260 to 570 mg/m² was considered favorable. The PK profile for patients treated in TED12337 and TED11449 over the dose tested, and the potential risk to expose patients to severe acute liver failure and Grade 3 transaminases increase, strengthened the decision to consider the 570 mg/m² as the final RD.

Overall, SAR125844 was well tolerated in the 38 patients in the dose escalation and expansion cohorts. No deaths due to AEs were reported. There was no apparent dose response effect observed for related AEs. The side effects of SAR125844 and the intensity of side effects seemed to be not clearly related to the dose. Considering the most common all grade TEAEs (in ≥5 patients), regardless of relationship to the study drug, many were gastrointestinal, including nausea, vomiting, constipation, abdominal pain, and diarrhea; but others included decreased appetite, fever, fatigue, back pain, and injection site reaction/phlebitis.

Nine patients had at least one dose modification (omission, delay, reduction, or interruption) due to AE. Most of the dose modifications, when due to related AE, were due to lab abnormalities (proteinuria, AST, ALT, ALP, and creatinine) which were considered as related to the study drug. However, none of these lab abnormalities led to dose discontinuation.

Eight patients reported at least one treatment emergent SAE, but no SAE was assessed as related to the study drug. Seven patients died (1 patient within 30 days of last study drug in the expansion cohort and 6 patients more than 30 days after last study drug). All deaths were attributed to disease progression. No major safety concerns were reported on lab parameters, blood pressure, and electrocardiogram. Few transient transaminase and creatinine increases were noted, leading to dose modification in some cases. Anemias were observed mainly in gastric cancer patients and were due to primary cancer.

Overall, SAR125844 up to 570 mg/m² was well-tolerated without major safety issues.

Efficacy results: For the 19 patients in the dose escalation part, no partial responses were observed and conclusions about efficacy cannot be drawn since the tumors in these patients were not driven by MET and SAR125844 is anticipated to be active in a targeted MET gene amplified population. Nineteen patients in the dose expansion part with MET-gene amplified tumors were treated with SAR125844 at recommended dose of 570 mg/m² (including 14 gastric cancer patients) and evaluated for tumor response per RECIST 1.1 criteria. A partial response was reported in 2 patients (both with gastric cancer with MET-gene amplification), stable disease in 7 patients (6 with gastric cancer), and progressive disease in 10 patients (6 with gastric cancer). The median time to progression was 0.92 months (1.18 months in patients with gastric cancer).

Pharmacokinetic results: Blood PK parameters of SAR125844 following a single or repeated weekly infusions (Day 1, 1st infusion and Day 22, 4th infusion) are summarized in the table below:

SAR125844 PK parameters in blood at Cycle 1 Day 1
Mean ± SD (Geometric Mean) [CV%]

	260 mg/m^2	340 mg/m^2	440 mg/m^2	570 mg/m^2
N	6	2	3	21
C_{max} (ng/mL)	4140 ± 1070 (4040) [26]	4290 ± NC (4280) [NC]	6390 ± 1010 (6330) [16]	6570 ± 1680 (6390) [26]
AUC_{0-168} (ng•h/mL)	11800 ± 2960 (11500) [25][a]	16400 ± NC (16400) [NC]	22100 ± NC (21800) [NC][b]	36100 ± 11800 (34400) [33][c]
AUC (ng•h/mL)	11800 ± 2950 (11500) [25][a]	16400 ± NC (16400) [NC]	22000 ± NC (21800) [NC][b]	36200 ± 11800 (34400) [33][c]
CL (L/h)	36.5 ± 7.68 (35.8) [21][b]	33.9 ± NC (33.3) [NC]	31.8 ± NC (31.6) [NC][b]	27.8 ± 8.94 (26.3) [32][c]
V_{ss} (L)	232 ± 57.5 (227) [25][a]	246 ± NC (242) [NC]	202 ± NC (200) [NC][b]	241 ± 55.3 (235) [23][c]
$t_{1/2z}$ (h)	12.6 ± 6.05 (11.7) [48][a]	12.9 ± NC (12.9) [NC]	12.1 ± NC (12.1) [NC][b]	22.8 ± 9.47 (21.0) [42][c]

a n = 5, Patient not included in calculation of summary statistics – $t_{1/2}$ not calculable

b n = 2, Patient not included in calculation of summary statistics – $t_{1/2}$ not calculable

c n = 20, Patient not included in calculation of summary statistics – $t_{1/2}$ not calculable

NC = not calculated

Profiles of 6 patients were excluded

SAR125844 PK parameters in blood at Cycle 1 Day 22 (4th infusion)
Mean ± SD (Geometric Mean) [CV%]

	260 mg/m2	340 mg/m2	440 mg/m2	570 mg/m2
N	2	3	3	17
C_{max} (ng/mL)	3550 ± NC (3540) [NC]	4700 ± 976 (4640) [21]	5840 ± 1420 (5710) [24]	6330 ± 1270 (6210) [20]
AUC_{0-168} (ng•h/mL)	12700 ± NC (12700) [NC]	16500 ± 2390 (16400) [14]	25300 ± 5220 (25000) [21]	35100 ± 14900 (33000) [43]
AUC (ng•h/mL)	12600 ± NC (12600) [NC]	16500 ± 2390 (16400) [14]	25400 ± 5300 (25100) [21]	35100 ± 15000 (33100) [43]
CL_{ss} (L/h)	32.0 ± NC (32.0) [NC]	33.4 ± 8.01 (32.8) [24]	30.2 ± 7.54 (29.5) [25]	28.9 ± 8.48 (27.6) [29]
V_{ss} (L)	186 ± NC (186) [NC]	291 ± 52.6 (288) [18]	490 ± 366 (413) [75]	287 ± 105 (271) [37]
$t_{1/2z}$ (h)	12.6 ± NC (12.6) [NC]	20.6 ± 4.69 (20.2) [23]	27.5 ± 8.24 (26.8) [30]	21.2 ± 4.94 (20.6) [23]

NC = not calculated

Profiles of 5 patients were excluded

Over the dose range of 260 to 570 mg/m² of SAR125844, exposure (AUC_{0-168}) increased slightly more than expected by the dose proportionality: a 2.19-fold increase in dose resulted in a 3.00- and a 2.69-fold increase in AUC_{0-168}, on Day 1 (1st weekly infusion) and Day 22 (4th weekly infusion), respectively. The PK of SAR125844 were similar between Day 1 and Day 22. No accumulation was observed between both days. No significant dose effect on clearance (CL) (p=0.25) or on CL_{ss} (p=0.79), was observed at Cycle 1 Day 1 and Day 22. Overall, the mean clearance (CL) was medium (around 31 L/h).The volume of distribution at steady state (V_{ss}) was large, with geometric mean values of V_{ss} ranging from 200 to 242 L on Day 1 and from 186 to 413 L on Day 22. Overall, at the MTD (570 mg/m²), V_{ss} was around 253 L.A slight dose effect on $t_{1/2z}$ on Day 1 (p=0.019) and on Day 22 (p=0.027), was observed, probably due to the difference in time interval used for the calculation of the slope for $t_{1/2z}$ determination. At 570 mg/m² (MTD), the geometric mean estimate of $t_{1/2z}$ was 21.0 hours [90% CI: (18.0 to 24.5)] on Day 1 and 20.6 hours [90% CI: (18.6 to 22.8)] on Day 22.
Issue date: 01-Mar-2017