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Sponsor: Sanofi **Drug substance(s):** SAR125844	**Study Identifiers:** UTN U1111-1117-9878, NCT01391533, EudraCT 2010-021398-36 **Study code:** TED11449
Title of the study: Dose escalation, safety, pharmacokinetic and pharmacodynamic, first in man study of SAR125844 single agent administered as slow intravenous infusion in adult patients with advanced malignant solid tumors	
Study center(s): 10 sites in France, Italy, Spain, and the United States	
Study period: Date first patient enrolled: 29/Jul/2011 Date last patient completed: 9/Apr/2016	
Phase of development: Phase 1	

Objectives:

Primary Objectives

- Dose escalation part (Part 1)
  - To determine the maximum tolerated dose (MTD) of SAR125844 according to the Dose Limiting Toxicity(ies) (DLTs) observed in patients with advanced solid tumors.
- Expansion part (Part 2)
  - To confirm safety profile of SAR125844 when administered as single agent at the MTD.
  - To evaluate the preliminary anti-tumoral effect of SAR125844 in patients with *MET*-gene amplified solid tumors (including sub-group of *MET*-amplified Non-small Cell Lung Cancer [NSCLC] patients) and in patients with Phospho-MET positive tumors without *MET*-gene amplification.

Secondary Objectives

- To characterize the global safety profile including cumulative toxicities.
- To evaluate the pharmacokinetic profile of SAR125844 in the proposed dosing schedule(s).
- To assess preliminary antitumor activity in patients with measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and on volumetric response evaluation.
- To explore the pharmacodynamic (PD) effects of SAR125844.
- To explore *MET*-gene amplification status in Circulating Tumoral Cells (CTCs) and on tumor biopsies collected during the study, in the escalation part only.
- To evaluate other PD biomarkers and help selection of patients who could benefit from SAR125844.
- To explore *MET*-gene amplification status in circulating DNA (only for patients in the expansion part).

Methodology: Single arm, open-label, dose escalation (classic 3+3 scheme) and dose expansion study.

Number of patients:

Planned: maximum approximately 60 patients in dose escalation part and approximately 60 patients in the dose expansion part, including 35 in the *MET*-gene amplified cohort and 25 in the Phospho-MET (P-MET) positive cohort.

Treated: 72

Efficacy: 68

Safety: 72

Pharmacokinetics: 72

Diagnosis and criteria for inclusion:

In the dose escalation part:

- Adult patients with a solid tumor for which no standard therapy is available.
- Patients with high total MET protein expression (≥50% of tumor cells with 2+ or 3+ positive membrane stain on immunohistochemistry [IHC]) or with *MET*- gene amplification (≥10% of cells with MET fluorescence in situ hybridization [FISH] >4 gene copies and ratio ≥2).

In the expansion part:

- Adult patients with any type of measurable advanced solid tumor for which no standard therapy is available.
- In the *MET*-gene amplified cohort, patients with diagnosed *MET*- gene amplified tumors (≥10% of cells with FISH >4 gene copies and ratio ≥2), including patients with non-small cell lung cancer (NSCLC).
- In the P-MET positive tumor cohort, P-MET positive solid tumor (H-score ≥15) without *MET*-gene amplification.

Study treatments

Investigational medicinal product(s): SAR125844

Formulation: 10 mg/mL solution for SAR125844 doses up to 200 mg/m^2; 15 mg/mL solution for SAR125844 doses ≥260 mg/m^2. Planned dose levels were 50, 100, 200, 260, 340, 440, 570, 740 and 960 mg/m^2.

Route(s) of administration: intravenous infusion (1.5 hours for 50 to 340 mg/m^2; 3 hours for 440 to 740 mg/m^2).

Dose regimen: 50 mg/m^2 to 960 mg/m^2 once weekly, 1 cycle corresponds 4 once-weekly infusions.

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 serious adverse events (SAEs) or with treatment-related adverse events (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 were followed until disease progression (PD) or initiation of another specific anti-tumor treatment.

Criteria for evaluation:

Safety:

Safety was assessed by evaluation of vital signs, physical examinations, Eastern Cooperative Oncology Group Performance Status (ECOG PS), chest X-ray, laboratory safety tests (including complete blood counts, serum biochemistry and urinalysis) and ophthalmology tests obtained prior to study drug administration and at designated intervals throughout the study. Adverse events were collected from the signing of the informed consent up to 30 days after the last study drug administration. During the follow-up period, SAEs and ongoing or new study treatment-related AEs were followed until resolution or stabilization. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v.4.03) and coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 16.

The MTD was based on the assessment of DLTs. The MTD was defined as the highest level at which no more than 1 patient of a maximum of 6 patients experienced a DLT. Dose limiting toxicities were predefined as any of the following during the first cycle of treatment: neutropenia Grade 4 for 7 or more consecutive days, febrile neutropenia, neutropenic infection, thrombocytopenia Grade 4 or Grade 3 with bleeding requiring a transfusion, any clinical adverse event Grade 3 or higher, asymptomatic Grade 4 nonhematological laboratory abnormality, and SAR125844 toxicity resulting in 2 or more missed doses. These AEs were considered related to the study drug in the absence of clear evidence to the contrary and if not related to disease progression, and were graded using NCI CTCAE (version 4.03). In the dose escalation part and in the dose expansion part, patients were evaluated for DLT if they completed one 4-week cycle, or if they discontinued the study drug before Cycle 1 completion due to DLT.

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

Efficacy:

Antitumor activity was assessed according to RECIST 1.1 by computerized tomography (CT) scan or other exams as clinically indicated to assess target and non-target lesions. Volumetric response was assessed by CT or magnetic resonance imaging (MRI) scan as an exploratory investigation. These exams were performed at baseline (screening), at end of Cycle 1, and then every 8 weeks (2 cycles), and whenever disease progression was suspected, using the same method(s) for each assessment.

The activity/efficacy population was 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 were included in this set.

Pharmacokinetics:

Blood samples (1.2 mL each) were collected, using dried blood spot technology, for analysis of SAR125844 in Cycle 1 at mid-infusion, 5 min before the end of infusion (EOI) and then 15 min, 30 min, 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 and 22 during Cycle 1 and on Day 1, 8, 15, and 22 from Cycle 2 to Cycle 4. 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. SAR125844 blood concentrations were used to determine the following pharmacokinetic parameters using standard non-compartmental analysis on Day 1 and Day 22 of Cycle 1: C_{max} (maximum blood concentration observed), t_{max} (time to reach C_{max}), AUC_{0-168} (area under the blood concentration versus time curve using the trapezoidal method from time zero to the end of the dosing interval ie, 168h), AUC (area under the blood concentration versus time curve extrapolated to infinity), CL or CL_{ss} (total body clearance of drug from blood on Day 1 or Day 22, assuming steady state), V_{ss} (volume of distribution at steady state) and $t_{1/2z}$ (terminal half-life associated with the terminal slope), C_{trough} (blood concentrations observed before treatment administration during repeated dosing) obtained on Day 8, Day 15, Day 22 from Cycle 1 to Cycle 4.

In addition, in dose escalation part and in the two expansion cohorts, dried blood spot samples were to be collected from peripheral blood (at finger) at specific time points and on a subset of subjects considered sufficient to compare concentrations with results obtained from venous sampling.

In the dose escalation part, blood samples for the analysis of Captisol® (or SBE-β-CD used as excipient in the SAR125844 formulation) in plasma were collected in all patients at Cycle 1 before the 1st administration and 15 min, 30 min, 1, 2, 3, 5, 7, 9, 24 hours after the end of the 1st administration of SAR125844. Concentrations of Captisol® in plasma were determined using a validated LC-MS/MS assay method with a LLOQ of 5.00 µg/mL. Captisol® plasma concentrations were used to determine following PK parameters on Day 1 of Cycle 1 when more than 32 g/administration was intravenously injected (ie, up to 740 mg/m² DL): C_{max}, t_{max}, AUC_{last} (area under the 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 and $t_{1/2z}$.

Pharmacogenetics/Pharmacogenomics:

Blood samples were collected on Day1 (predose) to enable investigation of allelic variants of drug metabolism enzymes and transporters. 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.

Pharmacodynamics:

Pharmacodynamic biomarkers were shed MET and hepatocyte growth factor (HGF) in plasma, and total MET and P-MET expression in tumor tissue.

Blood samples for the determination of shed MET and 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 Cycle 1 Day 1, and 5 minutes before EOI, 3, 5, 24, and 168 hours after EOI on Cycle 1 Day 22. An ELISA was used to evaluate plasma Shed MET and HGF.

Evaluation of tumor tissue for total-MET (t-MET) and P-MET was conducted by IHC on samples collected from the dose escalation part at Cycle 1 before infusion 1 and at 48 hours (optional) after infusion 4, and on samples collected from the expansion part at Cycle 1 before infusion 1 and at 96 hours (optional) after infusion 4.

Baseline biomarkers:

The correlation between *MET* amplification level measured by FISH and drug response was assessed. Moreover, level of MET expression before treatment was compared with the drug responses.

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. 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 first infusion to objective tumor progression).

Statistical analyses on PK parameters included:

- Dose proportionality for the $AUC_{0\text{-}168}$ 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 $AUC_{0\text{-}168}$, C_{max} of SAR125844 at Cycle 1.

Summary:

Study patients:

Seventy-two adult patients were treated in study TED11449, including 33 patients in the dose escalation part and 39 patients in the dose expansion part.

In the dose escalation part, 9 dose levels were tested: 50 mg/m² and then 100, 200, 260, 340 440, 570, 650 (intermediate DL, not initially planned in the protocol), and 740 mg/m².

Among the 39 patients in the expansion part treated at 570 mg/m², 10 patients had a P-MET positive tumor without *MET*-gene amplification and 29 patients had a *MET*-gene amplified tumor, including a subcohort of 21 NSCLC patients. Of note, 2 patients treated in the dose escalation part had a tumor with *MET*-gene amplification (NSCLC at 570 mg/m² and triple-negative breast cancer at 740 mg/m²). At the recommended dose of 570 mg/m², 47 patients were treated including 8 patients from escalation part and 39 patients in the dose expansion part.

In addition to the safety population (N=72), dose escalation part (N=33), dose expansion part (N=39), *MET*-amplified expansion cohort (N=29), and P-MET expansion cohort (N=10), results are presented on the following subgroups: *MET*-amplified NSCLC patients (N=22 including 1 patient treated at 570 mg/m² from the dose escalation and 21 from dose expansion), NSCLC population at the recommended dose (N=29 including 22 with *MET* amplification and 7 without *MET* amplification), and the patients treated at 570 mg/m² whatever their *MET* amplification status (N=47).

All 72 patients (100%) were evaluable for safety, 59 (81.9%) were evaluable for DLTs, including 28 patients in the dose escalation part and 31 patients in the dose expansion part, and 68 (94.4%) were evaluable for efficacy. Overall, the median age was 59 years (range 27 to 79 years) and 55.6% of patients were male with an ECOG performance status at study entry of 0, 1 or 2 (20, 51, and 1 patients, respectively).

Overall, the most frequent sites of the primary cancer at study entry were lungs (47.2%, 34 of patients), colon/rectum (16.7%, 12 patients), and head/neck (8.3%, 6 patients). Adenocarcinoma was the most frequent histological type (75%). The median time from initial diagnosis to the first study treatment was 2.27 years, range 0.5 to 24.4 years. The median number of prior advanced anti-cancer therapies was 3 with a range of 1 to 8. A total of 21 patients were previously exposed to 1 to 3 EGFR inhibitors (cetuximab, gefitinib, or erlotinib) given either as single agent or in combination with chemotherapy (including 12 NSCLC adenocarcinoma and 5 colorectal cancer). The median number of organs involved at study entry was 3. The organs most frequently involved (including the primary tumor when still present) at baseline was lungs in 81.9% of patients, lymph nodes in 62.5%, liver in 38.9%, bone in 23.6%, adrenal in 22.2%, and pleura in 22.2%.

In the dose escalation, all patients were evaluable for t-MET expression (IHC) and were t-MET positive at study entry according to the protocol criteria but one. Diagnosis of *MET* amplification on archival tissue was done on 27 patients out 33 treated. Two of them were enrolled based on the *MET*-gene amplification from local MET FISH or CGH testing. The results for *MET* amplification were confirmed centrally and t-MET expression was assessed centrally, once patients were enrolled. One (1) patient (breast cancer) was enrolled based on local gene amplification CGH positive with 83% MET (data not included in database) and confirmed centrally with a MET FISH positivity of 26%. T-MET expression for this patient was assessed centrally but didn't fulfill entry criterion of membrane staining of IHC ≥50% of tumor cells with 2+ or 3+.

Among the 29 patients in the dose expansion part with centrally confirmed *MET*-gene amplification treated at 570 mg/mm^2, the primary cancer at study entry was lungs (72.4% of patients), head/neck (10.3%), colon/rectum (6.9%), choroid melanoma (3.4%), gastrointestinal tract (3.4%), and intrahepatic biliary tract (3.4%). The main histological tumor type was adenocarcinoma (25 patients). All patients were evaluable for t-MET expression (IHC) and 19 (76%) were t-MET positive at study entry according to the protocol criteria. *MET* amplification (FISH) were confirmed centrally for all patients.

For the subset of 22 patients with *MET*-gene amplified NSCLC (1 patient from dose the escalation part and 21 from the dose expansion part), all patients had adenocarcinoma and were metastatic at study entry. The median time from initial diagnosis to the first study treatment was 1.15 years, range 0.5 to 24.4 years. The median number of organs involved was 3.5 at study entry and the organs most frequently involved (including the primary tumor when still present) at baseline was lungs in 95.5% of patients, lymph nodes in 86.4%, adrenal in 40.9%, pleura in 36.4%, and bone in 18.2%. These patients had a median of 2 prior advanced anticancer therapies (range 1 to 6). Four patients (18.2%) with known epidermal growth factor receptor (EGFR) mutation were previously treated by EGFR inhibitors. Among the 18 other patients with EGFR wild type tumor, 3 patients were previously exposed to 1 or 2 EGFR inhibitors given either as a single agent or in combination with chemotherapy.

Among the 10 patients in the dose expansion part with P-MET tumors treated at 570 mg/mm^2, the primary cancers at study entry were lung (40%), head/neck (20%), colon/rectum (10%), glioblastoma (10%), kidney (10%), and sertoli and leydig cell tumor of the testis (10%). Among the 10 patients, 1 patient had the EGFR mutation and was previously treated with EGFR inhibitors. The median number of prior advanced anticancer therapies was 2 (range 1 to 6). All patients were evaluable for t-MET expression (IHC) and 7 (77.8%) were t-MET positive at study entry according to the protocol criteria. MET FISH on archival tissue was done and confirmed the absence of *MET* amplification. Eight patients were evaluable for P-MET expression (IHC) and 7 were P-MET positive at study entry according to the protocol criteria with a median P-MET H-Score of 65 (15 to 299).

All 72 patients discontinued treatment and for 67 patients (93.1%), the reason was disease progression. Two patients discontinued due to adverse events, both at 570 mg/m², one patient for alanine aminotransferase (ALT) increased (considered related to treatment) and one patient (in the dose expansion part) for impaired renal function (acute kidney injury considered related to treatment). Three patients discontinued treatment for other reasons, two patients for personal reasons and one patient for investigator decision.

Safety results:

The current report is a synopsis style report, and as such, only the safety results are presented in full.

Treatment exposure: For all 72 patients, the median duration of treatment was 8.1 weeks (median 7.5 infusions), range 1 to 60 weeks. A total of 933 infusions were administered; 29 patients had at least one infusion omitted, 7 patients had at least one infusion dose reduced, 5 patients had at least one infusion delayed, and 9 patients had at least one infusion interrupted.

For the 47 patients treated at the MTD (570 mg/mm^2), the median duration of study treatment was 8 weeks (median 7 infusions), range 1 to 51 weeks. A total of 617 infusions were administered; 23 patients had at least one infusion omitted, 5 patients had at least one infusion dose reduced, 5 patients had at least one infusion delayed, and 7 patients had at least one infusion interrupted.

For the subgroups treated at 570 mg/mm^2, including the P-MET cohort (10 patients) and *MET*-gene cohort (29 patients), and the NSCLC cohort (29 patients) respectively, the median duration of treatment (and number of infusions) was 4.5 (4.5), 8.3 (8), and 12 (11) weeks.

Dose escalation part and dose selection: One primary objective of the study was to determine the maximum tolerated dose (MTD) of SAR125844 according to defined dose-limiting toxicities (DLTs). In the dose escalation part, 28 of 33 patients were evaluable for DLT. At the highest dose level tested, 740 mg/m², 2 of 3 patients treated experienced a DLT (hepatic cytolysis [hepatocellular injury with Grade 3 ALT increased, Grade 3 AST increased, and Grade3 alkaline phosphatase increased] and Grade 2 serum creatinine level increased, respectively) at Cycle 1 which led to dose reduction in both patients. Both events recovered. The third patient treated at this DL also experienced Grade 3 transaminases elevation, but considered not related to the study drug. All 3 patients had liver involvement at baseline, however, despite dose decrease, transient elevations in liver function tests were again observed (at a lower grade) after subsequent administrations. As a consequence, the dose of 740 mg/m² was considered not feasible and was identified as the maximum administered dose (MAD).

A total of 8 patients in the dose escalation part were treated at 570 mg/m^2. Among the 7 patients evaluable for DLTs, 1 patient experienced a DLT on 2 different infusions (Grade 3 ALT increased ≥4 days and Grade 2 serum creatinine increase associated with creatinine clearance decrease). The overall safety profile at 570 mg/m^2 was considered acceptable and this dose was selected as the MTD to be further evaluated in the expansion part of the study. In addition, antitumor activity was observed in one patient (PR in a NSCLC patient with *MET*-gene amplification) treated at this dose.

A total of 4 patients in the dose expansion part experienced a DLT: 3 patients presented with an increase in either ALT or ALT and AST, and the fourth patient presented with acute renal failure (acute kidney injury).

None of the 59 patients evaluable for DLTs in the dose escalation and dose expansion parts experienced an AE meeting DLT criteria after Cycle 1.

Adverse events: Considering all 72 patients, 100% had at least 1 TEAE and 83.3% had a TEAE considered related to the study treatment; 58.3% had a TEAE ≥Grade 3, and 19.4% were considered TEAE ≥Grade 3 and related to the study treatment; 41.7% of patients had a treatment emergent SAE and 8.3% were considered a SAE and related to the study treatment. There were 5 patients who died during the treatment period due to progressive disease, and the fatal TEAEs were disease progression (3 patients), pulmonary lymphangitis (1 patient), and arterial thromboembolic event due to progressive disease (arterial embolism) in one patient with head and neck cancer. In addition, 3 patients had a fatal TEAE (progressive disease) and died in the post-treatment period.

The most common any grade TEAEs (in ≥10% of patients [≥7 patients]), regardless of relationship to the study drug, excluding lab abnormalities included (from most to least frequent): asthenic conditions (asthenia/fatigue, 58.3%), nausea (31.9%), dyspnea (27.8%), gastrointestinal and abdominal pains (abdominal pain and upper abdominal pain, 27.8%), constipation (27.8%), cough (26.4%), vomiting (26.4%), peripheral edema (23.6%), pyrexia (23.6%), musculoskeletal and connective tissue pain (back pain, flank pain, musculoskeletal pain, musculoskeletal chest pain, neck pain, pain in extremity, 23.6%), decreased appetite (19.4%), diarrhea (19.4%), headache (18.1%), noncardiac chest pain (16.7%), weight decreased (16.7%), insomnia (16.7%), administration site reaction (catheter site edema, infusion site phlebitis, 11.1%), and disease progression (11.1%). There was no apparent correlation between dose and occurrence of a TEAE. In addition, the severity of the observed TEAE seemed to be not clearly related to the dose. Main laboratory abnormalities Grade 3 or 4 included (from most to least frequent): ALT increased (18.1%), AST increased (16.7%), alkaline phosphatase increased (9.7%), blood bilirubin increased (6.9%), and creatinine increased (4.2%).

Thirty-three patients had at least one dose modification (omission, delay, or reduction) and 9 patients had a dose interruption. Most of the dose interruptions were due to gastrointestinal disorders (nausea, gastric pain, vomiting) considered related to the study drug. Twenty-four patients had dose modification due to an AE. Most of the dose modifications were due to lab abnormalities (neutropenia, AST, ALT, and creatinine) which were considered as related to the study drug. One patient in the dose escalation part at 570 mg/m² presented ALT increased (considered related to treatment) leading to dose discontinuation. Another patient in the dose expansion cohort presented with acute renal failure (acute kidney injury, considered related to treatment) leading to dose discontinuation. Twenty-four patients died (5 patients within 30 days of last study drug and 19 patients more than 30 days after last study drug). All deaths were attributed to disease progression.

A total of 47 patients were treated at the recommended dose of 570 mg/m^2. In this group, the most common any grade TEAEs (in ≥10% of patients [≥5 patients]), regardless of relationship to the study drug, excluding lab abnormalities, included (in order of most to least frequent): asthenic conditions (asthenia/fatigue, 55.3%), nausea (34%), dyspnea (31.9%), cough (31.9%), constipation (29.8%), musculoskeletal and connective tissue pain (29.8%), peripheral edema (25.5%), gastrointestinal and abdominal pains (23.4%), vomiting (23.4%), decreased appetite (19.1%), weight decreased (19.1%), noncardiac chest pain (19.1%), diarrhea (17%), insomnia (14.9%), headache (14.9%), disease progression (14.9%), arthralgia (12.8%), pyrexia (12.8%), and stomatitis (10.6%). Thirty patients (63.8%) had a TEAE Grade ≥3, 2 patients (4.3%) had a TEAE leading to treatment discontinuation (ALT increased and acute renal failure (acute kidney injury), both at 570 mg/m^2, and 22 (46.8%) had a treatment emergent SAE. Forty patients (85.1%) had at least one TEAE assessed as related to the study treatment and the most frequent of these were nausea, asthenia/fatigue, vomiting, constipation, gastrointestinal and abdominal pains, and decreased appetite. Liver and renal function test abnormalities Grade 3 were observed as follows: ALT increased in 9 patients (19.1%), AST increased in 7 patients (14.9%), alkaline phosphatase increased in 4 patients (8.5%), blood bilirubin increased in 2 patients (4.3%), creatinine increased in 2 patients (4.3%). No Grade 4 liver or renal function test abnormality was observed.

Twenty-nine of the 47 patients treated 570 mg/m^2 had NSCLC. In this subgroup, the safety profile appears comparable to the overall population treated at 570 mg/m².

Treatment-emergent adverse events and laboratory abnormalities thought to be associated with SAR125844 are infusion site phlebitis and liver and renal function test abnormalities.

- Among 23 patients with peripheral administration of SAR125844, 7 patients developed Grade 1 (6 patients) or Grade 2 (1 patient) infusion site phlebitis (5 patients at Cycle 1 and 2 patients at Cycle 3). All 7 patients recovered.

- Fourteen patients with at least one Grade 3 or 4 liver function abnormality at dose level 570 mg/m^2 included 9 patients with ALT increased, 7 patients with aspartate aminotransferase increased, 4 patients with alkaline phosphatase increased, and 2 patients with blood bilirubin increased. Among these 14 patients, 7 had liver metastasis and 2 patients had bone metastasis at study entry. In addition, 5 patients had new liver lesions and two patients had new bone lesions. When liver function abnormalities were related to the study drug, the events recovered.
- An increase in blood creatinine was observed in 7 patients (6 patients at dose level 570 mg/m^2 and 1 patient at 740 mg/m^2), all were Grade $\leq$2. In 2 patients, blood creatinine increase occurred as a DLT in the dose escalation part. At 740 mg/m², a Grade 2 creatinine increase was observed on Day 8 that led to Cycle 1 Day 8 omission. Creatinine values recovered within 8 days. At 570 mg/m², on Day 8 of Cycle 1, a Grade 2 serum creatinine increase and severe creatinine clearance decrease to 27 ml/minute (at study entry estimated clearance was about 60 ml/minute and creatinine was within normal range) were observed which lead to Cycle 1 Day 8 dose omission. Renal ultrasound ruled out a post renal origin, and no dehydration or any other event was noted in favor of pre-renal origin.

Overall, SAR125844 up to 570 mg/m² was well-tolerated without major unexpected safety issues and the safety profile in NSCLC population with *MET*-gene amplification was similar in comparison to other cancers with or without *MET*-gene amplification treated at the same dose.

Efficacy results:

Sixty-eight patients were evaluable for efficacy. Symptomatic deterioration was reported in 2 patients during Cycle 1 and 2 other patients received only one infusion during Cycle 1. No post-baseline tumor assessment was performed for these patients. Among 68 patients evaluable for tumor response (per RECIST 1.1 criteria), 5 patients had a partial response, 38 had stable disease, 23 had progressive disease, and 2 patients with non-measurable disease at study entry had nonCR/nonPD. Considering the 5 patients with a partial response, all were treated with SAR125844 570 mg/m^2 and all had *MET*-gene amplified tumors. Four of these 5 patients had NSCLC (adenocarcinoma); they received 7 to 13 cycles of treatment, TTP ranged from 4.67 to 10.05 months, and response duration ranged from 3.8 to 9.1 months. The other patient with a partial response had a biliary tract tumor (cholangiocarcinoma); TTP was 2.6 months and response duration was 1.8 months.

Among the 22 evaluable NSCLC patients harboring *MET*-gene amplification treated at 570 mg/m², 4 partial responses and 13 stable disease, including 1 minor response (no further imaging for confirmation), were observed. Overall, 59% of *MET* amplified NSCLC patients experienced a decreased in target lesions and tumor regression in NSCLC was observed only in tumors with *MET* amplification (compared to NSCLC patients without *MET* amplification).

For tumor volume response in 40 evaluable patients at the 570 mg/m^2 dose level, 15% (6 patients) had a partial volumetric response, 35% (14) had stable disease, 47.5% (19) had progressive disease, and 2.5% (1) were not assessed.

In the 22 evaluable patients with *MET*-gene amplified tumors, 5 patients experienced a partial response was observed in 22.7%, and stable disease was observed in 11 patients (50%).

Pharmacokinetic results:

Pharmacokinetic parameters of SAR125844 were determined from venous blood concentrations following a single (Day 1) or repeated (Day 22) weekly infusions over the 50 to 740 mg/m² dose range. The MTD was further confirmed in the dose expansion part. Over the 14.8-fold dose rage, SAR125844 exposure ($AUC_{0\text{-}168}$) did not deviate significantly from dose proportionality whatever the day. The PK of SAR125844 was similar between Day 1 and Day 22 with no observed accumulation. SAR125844 showed a medium clearance (CL), constant across dose range tested (34.6 L/h on Day1 and 31.0 L/h on Day 22). Terminal elimination half-life was 15 or 16 hours, on Day1 or Day 22 respectively, whatever the dose. The volume of distribution at steady state (Vss) was large, around 282 L (Day1) and 310 L (Day22). No PK analysis was performed for peripheral blood or urine concentrations of SAR125844. Maximum exposure to Captisol® in the escalation phase was observed at 650 mg/m² dose level (AUC = 3980 ± 589 µg.h/mL; N=3).

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