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Sponsor: Sanofi **Drug substance(s):** SAR405838, pimasertib	**Study Identifiers:** U1111-1144-8349, NCT01985191 & 2013-002325-33 **Study code:** TCD13388
Title of the study: A Phase 1 Study of Combination Therapy with SAR405838 and Pimasertib in Patients with Advanced Cancer	
Study center(s): 4 study centers in France and in the Netherlands	
Study period: Date first patient enrolled: 03/Dec/2013 Date last patient completed: 15/Feb/2016	
Phase of development: Phase 1	

Objectives:

Primary Objectives:

- To determine safety and the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of SAR405838 and pimasertib combination therapy in adult patients with locally advanced or metastatic solid tumors during dose escalation.
- To assess the anti-tumor activities of SAR405838/pimasertib in patients with advanced/metastatic melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) based on TP53 and Ras data in tumor tissue during cohort expansion.

Secondary Objectives:

- To characterize the pharmacokinetic (PK) profile of SAR405838 and pimasertib when used in combination.
- To evaluate the pharmacodynamic (PD) effect of the SAR405838/pimasertib combination.
- To document anti-tumor activity in response to SAR405838/pimasertib in dose escalation as assessed by anatomic imaging studies.
- To characterize TP53/Ras genetic status in tumor tissue at baseline and circulating tumor DNA (ctDNA) derived from plasma both at baseline and in response to SAR405838/pimasertib treatment.

Exploratory Objectives:

- To characterize genetic variation involved in the absorption, disposition, metabolism, and elimination of SAR405838/pimasertib.

Methodology:

This was a Phase 1, open-label, dose-escalation, safety, PK, and PD study of combination therapy with SAR405838 and pimasertib administered orally once daily (QD) or twice daily (BID) in 21-day cycles in adult patients with advanced solid tumors. A 3+3 design was used.

The starting dose was SAR405838 200 mg QD/pimasertib 45 mg BID. Cohorts of 3 to 6 patients were enrolled sequentially in ascending dose levels (DLs) per the protocol and decisions of the Study Committee (Investigators and Sponsor). DL2a and DL2b were evaluated concurrently with escalation to DL3a and DL3b, respectively, determined independently and also evaluated concurrently. If 1 of 3 patients experienced a dose-limiting toxicity (DLT) in the first 2 cycles, the cohort was expanded to 6 patients for confirmation. If a DLT was observed in at least 2 out of a maximum of 6 patients at a DL, this was considered the maximum administered dose. The MTD was generally the highest DL where at most 1 patient of the cohort experienced a DLT. The RP2D was determined at the conclusion of the dose-escalation phase.

Cohort Expansion at RP2D: Once RP2D was established, 3 strata of 24, 20, and 26 efficacy-evaluable patients with advanced/metastatic melanoma, NSCLC, and CRC, respectively, were to be enrolled in the cohort expansion to further assess safety, PK, and pharmacological activities. The SAR405838 clinical development program was stopped, but not due to any safety issues. Enrollment was completed in the dose escalation phase of this study; however, the RP2D cohort expansion was not enrolled. The objectives and methods as outlined in the protocol are presented; however, the complete analysis of the objectives, including efficacy, biomarker analysis, and PD, is not presented in the results for this synoptic report.
Number of patients**:** Planned: Approximately 100 Treated: 26 **Evaluated:** Safety: 26 DLT evaluable: 20 PK: 26 Efficacy: 24
Diagnosis and criteria for inclusion: Patients eligible for inclusion were ≥18 years of age with a histologically or cytologically- confirmed solid tumor that was locally advanced or metastatic with at least 1 measurable lesion with documented wild type TP53 and Ras/Raf mutations for which no further effective standard treatment was available, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, life expectancy ≥12 weeks, and sufficient bone marrow function. For the RP2D cohort expansion, only patients with N-Ras mutated, TP53 wild type melanoma (up to 1 line of prior chemotherapy or targeted therapy for advanced disease), K-RAS mutated, TP53 wild type NSCLC (up to 2 lines of prior therapy for advanced disease), K RAS mutated, TP53 wild type CRC (up to 2 lines of prior therapy for advanced disease) were to be included. The disease was to have been measurable as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Additionally, patients with unstable central nervous system metastases, with relevant ophthalmologic disease or abnormalities, or with prior Grade 4 event associated with mitogen-activated protein/extracellular signal-regulated kinase (MEK) or human mouse double minute 2 (HDM2) inhibition (prior therapy with any MEK or HDM2 inhibitors not allowed for RP2D cohort expansion patients) were not eligible.

Study treatments

Investigational medicinal products: SAR405838 and pimasertib

Formulation: SAR405838 100-mg or 200-mg capsules; pimasertib 15-mg or 30-mg capsules

Route of administration: Oral

Dose regimen: SAR405838 and pimasertib capsules were administered at the appropriate dose QD or BID in 21-day cycles. Patients fasted for 2 hours prior to and 1 hour after each dose. Each dose of SAR405838, except Cycle 1 Day 1, was to be taken immediately after pimasertib administration, preferably in the morning of each day. An alternative dosing schedule could have been implemented if DLs were not tolerated, as decided by the Study Committee.

Duration of treatment: At least 2 cycles (6 weeks); however, treatment could have continued until precluded by toxicity, incompliance, progression, or death.

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 2 cycles of study treatment, and an end-of-study visit at least 30 days (or until the patient received another anticancer therapy, whichever was shorter) following the last administration of study treatment.

Criteria for evaluation:

Safety: Safety was assessed by the evaluation of adverse events (AEs), DLTs, changes in vital signs, 12-lead electrocardiograms (ECGs), physical examinations, ophthalmologic examinations, ECOG PS, and clinical laboratory tests (including hematology, coagulation, blood chemistry, and urinalysis). Adverse events, including DLTs, were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

A DLT was defined as any of the following drug related AEs occurred during the first 2 cycles of treatment (Days 1 to 42):

- A treatment-emergent adverse event (TEAE) that in the opinion of the safety committee was of potential clinical significance such that further dose escalation would expose patients to unacceptable risk
- Any Grade ≥3 non-hematologic toxicity **excluding**
  - Grade 3 fatigue, persistent for less than 7 days
  - Grade 3 vomiting, if controlled within 2 days by adequate therapy (eg, 5HT3 antagonists and corticosteroids)
  - Grade 3 diarrhea, if controlled within 2 days with adequate anti-diarrhea therapy
  - Asymptomatic Grade 3 creatinine phosphokinase (CPK) elevation
  - Grade 3 aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevations <7 days in duration
  - Grade 3/4 alkaline phosphatase (ALP) elevations in the context of bone metastasis
  - Grade 3 hypertension that can be controlled within a week with oral antihypertensives
- Any Grade ≥3 thrombocytopenia
- Any Grade 4 neutropenia or febrile neutropenia
- Any Grade 4 anemia
- Retinal vein occlusion
- Left-ventricular ejection fraction (EF) decrease >20% from baseline or a decrease >10% if baseline EF is 50%
- Hy's law, ie, an elevated total serum bilirubin >2 x upper limit of normal (ULN) in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic (treatment with atazanavir or other drugs), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased incidence of AST/ALT >3 x ULN
- Any treatment delay >2 weeks due to drug-related adverse effects
- Any severe or life-threatening complication or abnormality not defined in NCI-CTCAE that is attributable to the therapy
- Any toxicities resulting in an inability to complete at least 80% of planned trial medication doses during the first 2 cycles.

All DLTs were considered as AEs of special interest (AESIs), and in addition the following AEs were considered AESIs:

- Retinal vein occlusion (any grade)
- Serous retinal detachment, serous macular detachment, or similar retinal abnormality characterized by accumulation of serous fluid in the retina (any grade)
- Thrombocytopenia or anemia (≥ Grade 3), neutropenia (any Grade 4)
- Serious skin rashes (any grade)
- CPK elevation (any grade)
- Cardiac toxicities at ≥ Grade 2 (any grade of troponin elevation).

Pharmacokinetics: Blood samples were collected on Days 1 (for pimasertib only), 2, 3, 8, and 15 of Cycle 1, on Days 1 and 2 of Cycle 2, and on Day 1 of Cycles 3 and 4, as applicable to the dosing schedule and according to the protocol, to determine the whole blood and plasma concentrations of SAR405838 and pimasertib, respectively. The PK parameters that were to have been calculated included maximum concentration (C_{max}), first time to reach maximum concentration (t_{max}), time corresponding to the last concentration above the lowest limit of quantification (t_{last}), area under the concentration versus time curve (AUC) from time 0 to time t (AUC_{0-t}; 12 hours for BID or 24 hours for QD), AUC from time 0 to t_{last} (AUC_{last}), AUC extrapolated to infinity, AUC over the dosing interval (AUC_{tau}), and terminal half-life ($t_{1/2z}$).

Pharmacodynamics: Blood samples for peripheral PD biomarkers analyses for both SAR405838 and pimasertib, including macrophage inhibitory cytokine-1 (MIC-1) levels in plasma, interleukine-8 (IL-8) levels in plasma, and phosphorylated extracellular signal-regulated kinases (pERK) levels in peripheral blood mononuclear cell (PBMC), were collected on Days 1, 2, 3, 8, and 15 of Cycle 1, on Days 1 and 2 of Cycle 2, and Day 1 of Cycles 3 and 4, as applicable to the dosing schedule and according to the protocol.

Efficacy and mutation status: Objective tumor response information was obtained if patients had disease which could have been readily measured and re-assessed using RECIST 1.1. Assessments were made at least every 2 cycles or less frequently, if indicated; the Investigator performed a disease status assessment. Furthermore, a partial or complete response must have been confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy. Tumor response (complete or partial response, or stable or progressive disease, per RECIST 1.1) and duration were determined in the RP2D cohort expansion (primary endpoint) and in the dose-escalation phase (secondary endpoint).

The mutation status of *TP53*, *Ras*, and *B-Raf* in ctDNA derived from plasma was used to correlate with that from tumor tissue at screening.

Pharmacogenetics: For those patients who signed the optional specific pharmacogenetic analysis informed consent form, 2 blood samples were collected at screening for genetic profiling on drug metabolism.

Statistical methods:

Sample size calculation: It was anticipated that about 30 DLT-evaluable patients would be enrolled in the dose escalation phase with expected assessment of about 5 DLs; the actual total number of patients required depended on the incidence and timing of observed DLTs. A total of 24, 20, and 26 efficacy evaluable patients were to be enrolled in the melanoma, NSCLC, and CRC cohorts, respectively, for the RP2D cohort expansion; this sample size was enough to discern meaningful objective response rate (ORR).

Analysis populations:

- The all-treated population included all registered patients exposed to the study treatment, regardless of the amount of treatment administered.
- A patient was DLT evaluable if he or she received at least 80% of their cohort planned dose in the first 2 cycles and was evaluated for at least 6 weeks, or an earlier DLT occurrence.
- The PK population included all treated patients with available PK parameters

- The activity/efficacy evaluable population included all treated patients with baseline measurable disease, at least one post-baseline tumor assessment, and tumor cells with *Ras* mutation (or *Raf* mutation in dose escalation) and *TP53* wild type in archival/fresh tumor tissue for patients enrolled during dose escalation or in fresh tumor tissue for patients enrolled during the expansion phase. Patients with clinical progression or who died due to disease progression prior to their first scheduled response assessment were also included.
- Patients evaluable for predictive tumor biomarkers included all treated patients with at least one biomarker assessed from a pre-treatment archival or fresh tumor biopsy.
- Patients evaluable for predictive peripheral tissue biomarkers included all treated patients with at least one biomarker assessed from a pre-treatment peripheral tissue sample.
- Patients evaluable for peripheral tissue PD biomarkers included all treated patients with at least one peripheral tissue PD biomarker assessed from paired pre- and post-treatment tissue.

Safety, efficacy, PK, and PD evaluations were assessed in the all treated population. These data were descriptively summarized by each DL and overall as appropriate.

Analysis of safety: Type, frequency, severity, seriousness, and relatedness to study therapy of TEAEs, abnormalities during clinical examinations or laboratory tests, and the occurrence of any DLTs, AESIs, drug discontinuations due to AEs, serious adverse events (SAEs), and deaths were analyzed. TEAEs, including DLTs and AESIs, were analyzed by DL for all treated patients and all cycles.

Analysis of pharmacokinetics: PK variables were calculated from the blood and plasma concentration data using standard noncompartmental methods. The dose proportionality of PK parameters and potential gender effects were to be assessed.

Analysis of pharmacodynamics: PK/PD relationships were to have been descriptively analyzed within each DL from paired PK/PD sample results for peripheral PD markers. Descriptive analyses were used to contrast PD effects between DLs.

Analysis of efficacy: Efficacy was to be assessed by DL and for the RP2D expansion cohort by strata in the efficacy evaluable population. The proportion and exact 70% 2-sided confidence interval (CI) of patients with a confirmed objective tumor response (complete response/partial response per RECIST 1.1) was to be computed, as well as P-values for exact tests for an ORR ≤20% (melanoma), 25% (NSCLC), and 10% (CRC) in the RP2D expansion strata among patients with tumor *TP53* wild-type and *K-* or *N-Ras* mutation. The best on-study tumor response was to be described by patient. If feasible, Kaplan-Meier estimates and 70% CIs were to be computed for progression-free survival quartiles. The progression free rate at 3 months and 6 months and corresponding 70% CIs were also to be computed.

Summary:

Population characteristics: Twenty-six patients with advanced cancer were treated in DL1 at SAR405838 200 mg QD/pimasertib 45 mg BID (7 patients), DL2a at SAR405838 200 mg QD/pimasertib 60 mg QD (4 patients), DL2b at SAR405838 300 mg QD/ pimasertib 45 mg BID (7 patients), and DL3a at SAR405838 300 mg QD/pimasertib 60 mg QD (8 patients). The dose escalation population consisted of 16 males and 10 females with a median age of 61.7 years (range: 45-79 years) with advanced cancer diagnoses of colon (n=11, 42.3%), lung (n=8, 30.8%), and other cancers (n=6, 23.1%; including pancreatic, endometrial, intrahepatic bile duct, and right orbita), and skin melanoma (n=1, 3.8%).

No subjects were enrolled for the RP2D expansion cohort.

Twenty-one of the 26 (80.8%) patients discontinued the study due to disease progression and 5 (19.2%) due to AEs.

Safety results: At DL1, 1 patient experienced 2 DLTs. An additional 6 patients were enrolled at DL1 and did not experience a DLT; therefore, dose escalation continued to DL2a and DL2b. No DLTs occurred at DL2a. At DL2b, 2 patients experienced DLTs, thus no patients were treated at DL3b. At DL3a, 1 patient (of 4) experienced a DLT and an additional 4 patients were enrolled at DL3a and did not experience a DLT. Based on the occurrence of DLTs, DL1 was the MTD for the SAR405838 QD/pimasertib BID dosing regimen and DL3a was the MTD for the SAR405838 QD/pimasertib QD dosing regimen; however, the clinical development program was stopped and the RP2D expansion cohort was not enrolled.

Study treatment lasted for a mean of 20.54 weeks (7.0 cycles per patient) for SAR405838 and for a mean of 20.55 weeks (6.9 cycles per patient) for pimasertib.

One patient dosed at DL1 had an AE of grade 1 rash pustular (worsened to grade 2 in Cycle 1 and grade 1 in Cycle 2) which led to study treatment being withheld and then resumed in Cycle 2. This subject also had grade 1 thrombocytopenia which led to the SAR405838/pimasertib dose again being withheld in Cycle 2 (worsened to grade 2 and resolved at grade 1 all in Cycle 2). Therefore, a DLT was declared because of the incompletion of 80% of the dose. Two patients dosed at DL2b had DLTs: one patient had prolonged grade 2 thrombocytopenia in Cycle 2 (grade 1 in Cycle 4) for which the SAR405838 dose was interrupted and not resumed, leading to a DLT; one patient had non-serious grade 4 increased lipase in Cycle 1 for which the SAR405838/pimasertib dose was reduced. One patient dosed at DL3a had a DLT of thrombocytopenia (worsened from grade 1 in Cycle 1 to grade 3 in Cycle 2) which led to SAR405838 dose reduced.

A total of 22 (84.6%) patients experienced treatment-emergent AESIs with the most common AESIs (occurring in >10% of patients) including increased blood CPK (n=20, 76.9%; Grades ≥3 for n=3, 11.5%), decreased EF (n=10, 38.5%; Grades ≥3 for n=1, 3.8%), retinal detachment (n=8, 30.8%; no Grades ≥3), macular detachment (n=7, 26.9%; no Grades ≥3), thrombocytopenia (n=5, 19.2%; Grades ≥3 for n=4, 15.4%), and increased troponin T (n=5, 19.2%; no Grades ≥3). Ten (38.5%) patients out of the 22 experiencing treatment-emergent AESIs had grade 3-4 AESIs; however, a majority of all AESIs were non-serious.

All 26 patients had a TEAE, all of which had at least one TEAE considered by the Investigator to be related to study treatment. The most common TEAEs reported in all patients were diarrhea (n=21, 80.8%), increased blood CPK (n=20, 76.9%), nausea and vomiting (n=18, 69.2% and n=19, 73.1%, respectively), fatigue (n=15, 57.7%), decreased appetite (n=13, 50.0%), peripheral edema (n=12, 46.2%), and decreased EF(n=10, 38.5%), a majority of which were grade 1-2.

Fourteen (53.8%) patients had a treatment-emergent SAE, including SAEs of disease progression (n=3, 11.5%), constipation and accidental overdose (n=2, 7.7% for each) abdominal pain lower, diarrhea, nausea, vomiting, duodenal ulcer, bile duct obstruction, macular detachment, pulmonary embolism, pneumonitis, bacteremia, bronchitis, pneumonia, metastatic pain, dyspnea, and anxiety (n=1, 3.8% for each). Four (15.4%) patients had an SAE considered by the Investigator to be related to study treatment, including related SAEs of macular detachment, pneumonitis, diarrhea, nausea, vomiting and accidental overdose (n=1, 3.8% for each).

A total of 5 (19.2%) patients had a TEAE leading to permanent treatment discontinuation, including TEAEs of rash pustular, dyspnea, nausea, vomiting, increased blood CPK, and ECG T wave inversion (n=1, 3.8% for each) and fatigue (n=2, 7.7%). Additionally, 17 patients had SAR405838 dose modification, reduction, or omission and 18 patients had pimasertib dose modification, reduction, or omission.

Four patients died during the study, with 3 deaths occurring in the post-treatment period. All deaths were due to disease progression with no treatment-related deaths reported.

As described for AESIs, a total of 5 (19.2%) patients experienced TEAEs of thrombocytopenia (1 patient at DL1 [grade 1] and 2 patients at both DL2b and DL3a [grades 3-4]) of which all were non-serious and 4 were considered related to study treatment and led to dose reduction. As described for DLTs, 3 of the 5 patients with thrombocytopenia were considered to have DLTs. A total of 4 patients experienced a TEAE of anemia, including 1 AESI (DL3a), all of which were considered non-serious, not related to study treatment, and all were grade 1-2 with the exception of 1 patient at DL2a with grade 3 anemia. There were no grade 4 hematological laboratory abnormalities and no other hematological abnormalities considered as TEAEs, with the exception of 1 patient at DL1 that had a non-serious TEAE of neutrophil count decreased which led to dose reduction. As described for the DLTs, 1 patient at DL2b experienced a DLT of non-serious grade 4 increased lipase which was considered related to study treatment and led to dose reduction; an additional 2 patients experienced non-serious TEAEs of grade 4 increased lipase, one considered related to study treatment (in DL1) and one not related (in DL2a). As described for AESIs, 20 (76.9%) patients had increased CPK all of which were non-serious and considered related to pimasertib and a majority (17 of 20 events) considered as grade 1-2. Additional AESIs related to cardiac events included 10 (38.5%) patients with decreased EF, 5 (19.2%) with increased troponin T, and 1 (3.8%) with increased troponin I. Events of decreased EF were non-serious and asymptomatic, and were reversible with the exception of 1 patient (DL2b) with an outcome of not recovered. Other significant non-hematological laboratory abnormalities included 3 (11.5%) patients with non-serious TEAEs of grade 3-4 increased amylase of which 2 were considered related to study treatment. Thirteen (50.0%) patients had AESIs in the system organ class of Eye Disorders, including 8 (30.8%) patients with retinal detachment, 7 (26.9%) with macular detachment, and 1 (3.8%) each with detachment of retinal pigment epithelium, retinal exudates, and subretinal fluid. All eye disorder AESIs were considered to be related to pimasertib and all were non-serious with the exception of 1 patient (at DL3a) with an SAE of grade 2 macular detachment. No significant abnormalities in vital signs were reported. One patient experienced 2 non-serious TEAEs of grade 1 ECG T wave inversion which led to dose reduction and treatment discontinuation.

Pharmacokinetic results: Considering known variability for SAR405838, its exposure in combination with pimasertib was comparable to historical data for SAR405838 alone. The dose increase (50%) between dose levels DL1/DL2a (SAR405838 200 mg) and dose levels DL2b/DL3a (SAR405838 300 mg) did not result in SAR405838 exposure increase.

Considering known variability for pimasertib, its exposure in combination with SAR405838 was comparable to historical data for pimasertib alone. The dose increase (33%) between dose levels DL1/DL2b (pimasertib 45 mg BID) and dose levels DL2a/DL3a (pimasertib 60 mg BID) resulted in pimasertib exposure increase.

Regarding respective drug variability, only a substantial drug-drug interaction may have been evidenced.

Pharmacodynamic results: This is an abbreviated report and full PD results in blood samples will be presented in a future translational medicine report; however, PD results are noted in the Conclusions of this report.

Efficacy results: The best overall response was partial response for 1 (4.2%) patient with endometrial adenocarcinoma (stage III) at SAR405838 200 mg QD/pimasertib 45 mg BID. Stable disease was the best overall response observed for 15 (62.5%) patients, including patients with colon (7 patients, 4 at stage IV and 1 each at stages I, II, and III), lung (5 patients, all stage IV), pancreatic (1 patient, stage IV), and intrahepatic bile duct (1 patient, stage IV) cancer, and skin melanoma (1 patient, stage I). Changes in target lesion diameters were variable and were generally not dose-dependent. No inferential efficacy analysis was performed as the study ended prior to enrolling subjects for the RP2D expansion cohort.

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