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Sponsor / Company: Sanofi **Drug substance(s):** SAR245408	**Study Identifiers:** NCT01357330, UTN U1111-1117-9893 **Study code:** TCD11742
Title of the study: A Phase 1 dose escalation study of combination therapy with oral SAR245408 (XL147) and oral MSC1936369B in patients with locally advanced or metastatic solid tumors	
Study center(s): 3 study centers	
Study period: Date first patient enrolled: 02/May/2011 Date last patient completed: 18/Jun/2012	
Phase of development: Phase 1	
Objectives: Primary • To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of SAR245408 and MSC1936369B when combined in adult patients with locally advanced or metastatic solid tumors. Secondary • To characterize the safety and tolerability of SAR245408 and MSC1936369B combination therapy administered orally to adult patients with locally advanced or metastatic solid tumors. • To evaluate the pharmacokinetic (PK) profile of SAR245408 and MSC1936369B used in combination. • To evaluate the pharmacodynamic (PD) effect of the SAR245408/MSC1936369B combination by assessing target and pathway inhibition. Exploratory • To describe preliminary antitumor activity, based on response rate (RR), in patients with evaluable disease. • Explore potential correlations between alterations of phosphoinositide 3-kinase/phosphatase with tensin homology (PI3K/PTEN) pathway and mitogen-activated protein kinase (MAPK) pathway components/modulators, oncogenes/tumor suppressor genes that are directly and/or indirectly involved in these pathways and the response following SAR245408/MSC1936369B combination therapy.	
Methodology: This was a multicenter, open-label, nonrandomized Phase 1 dose escalation study of combination therapy with SAR245408, hereafter referred to as "SAR", and MSC1936369B, hereafter referred to as "MSC", in patients with locally advanced or metastatic solid tumors with either a prevalence of PI3K and MAPK pathway alterations (such as alterations of phosphatase and tensin homolog, v-raf murine sarcoma viral oncogene homolog B1, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, neuroblastoma RAS viral oncogene homolog, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, erythroblastic leukemia viral (v-erbB) oncogene homolog, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2) or where a rationale existed for the use of the combination. These tumors included pancreatic, thyroid, colorectal, non-small cell lung, endometrial, renal, breast, ovarian carcinoma, or melanoma that was unresponsive to standard therapies or for which there was no approved or curative therapy. The study was terminated early due to the deprioritization of the program.	

MSC1936369B monotherapy cohort: It was planned to evaluate the safety of the continuous administration regimen at 1 level above the starting dose, ie, 30 mg of MSC continuous daily dosing (CDD), prior to enrollment of the SAR/MSC combination cohorts. However, this initial MSC monotherapy cohort was omitted as data were already available prior to the start of the study.

Dose escalation phase: Cohorts of 3 to 6 patients were enrolled sequentially in ascending dose levels of combination therapy with SAR and MSC. The SAR or MSC doses were alternately increased until a MTD was identified at a specified combination. During the dose escalation process, in order to allow subjects with tumor types with frequent alteration in the MAPK and PI3K signaling pathways to have greater access to this combination therapy, in addition to the patients treated per dose level, up to 3 additional patients (total of 6 for each cohort) could have been enrolled in some lower dose level cohorts for additional PK and safety data, as well as the assessment of pharmacodynamic activity to test dose dependency of the pharmacodynamic effects. Enrollment into a lower dose level was based upon the decision of the Safety Monitoring Committee (SMC) and depended on observed signals of safety and pharmacodynamic or clinical activity. Enrollment of patients into lower dose level cohorts was possible only after the ongoing dose escalation cohort was completed for dose-limiting toxicity (DLT) evaluation.

Patients enrolling in lower dose level cohorts had to have a tumor accessible for biopsies and agree to pretreatment and on-treatment tumor biopsies and sampling of normal tissue (peripheral blood mononuclear cells and hair follicles). Sampling of a malignant effusion, confirmed as malignant by cytopathologist, could have fulfilled the tumor biopsy requirement. Data from patients enrolling in the lower dose level cohorts were not to have contributed to the primary DLT determination and dose escalation decision at that dose level. However, safety data from the lower dose level cohorts was reviewed by the SMC on an ongoing basis.

Dose-limiting toxicities were monitored centrally and the decision to dose escalate (or de-escalate) to the next dose level was made by the SMC. If a DLT occurred in a previous dosing cohort, dose escalation of MSC and SAR for subsequent cohorts was not to have exceeded a dose that was expected to yield an exposure 50% higher than the exposure seen at the previous dose levels (eg, instead of escalating from a 100-mg capsule of SAR to a 100-mg tablet of SAR, escalation was to a 50-mg tablet of SAR as the exposure of capsules was approximately one-half the exposure of the same mg dose of the tablet). If an MTD was not reached for any combination, dose escalation was to have been stopped at the previously determined single agent MTD of SAR and MSC. Dose escalation could have also been stopped prior to reaching the MTD if the SMC felt that reaching an MTD was not necessary or possible.

Maximum tolerated dose expansion cohorts: It was planned to enroll patients at the defined MTD(s) to collect safety, PK, and pharmacodynamic data from up to a total of 12 patients and to determine the RP2D; however, no patients were enrolled in these cohorts as the study was terminated early.

Number of patients**:**	Dose escalation: Approximately 6 to 72 patients
	Maximum tolerated dose expansion cohort: Approximately 12 patients
	Treated: 18
	Evaluated: 18
	Efficacy evaluable: 16
	Safety/DLT evaluable: 16

Diagnosis and criteria for inclusion: Patients with advanced solid tumors for which there was no approved or curative therapy and who had any advanced solid tumor with diagnosed alteration in 1 or more genes of the PI3K, and MAPK pathways and/or had a histologically or cytologically confirmed diagnosis of 1 of the following solid tumors: pancreatic, thyroid, colorectal, non-small cell lung, endometrial, renal, breast, ovarian carcinoma and melanoma, were enrolled in this study.

Study treatments

Investigational medicinal product(s): SAR245408, MSC1936369B

Formulation: SAR245408: 25- and 100-mg hard gelatin capsules as well as 50-mg and 100-mg tablets

MSC1936369B: 4-, 15- and 30-mg hard gelatin capsules

Route(s) of administration: Oral

Dose regimen: Combination therapy with SAR and MSC were administered in repeating 21-day cycles. Both SAR and MSC were given orally, in a fasting state, once daily. The starting dose of SAR was a 25-mg capsule once daily. The starting dose of MSC in combination was 15 mg once daily. The dose of MSC in monotherapy was 30 mg once daily.

At Dose Level 1 and Dose Level 2, MSC was initially given once within 2 to 5 days prior to the start of combination therapy, for comparison of drug exposure (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve over the dosing interval [AUC_T]) of MSC when administered alone versus as combination treatment.

This protocol allowed for some alteration from the planned dosing scheme. Decisions for alteration from the current protocol were made jointly by the SMC based upon data from ongoing preclinical and/or clinical studies. Dose levels included the following:

- Dose Level 1: SAR 25 mg capsule/MSC 15 mg capsule;
- Dose Level 2: SAR 50 mg capsule/MSC 15 mg capsule;
- Dose Level 3: SAR 75 mg capsule/MSC 15 mg capsule;
- Dose Level 4a: SAR 100 mg capsule/MSC 15 mg capsule;
- Dose Level 4b: SAR 75 mg capsule/MSC 23 mg capsule (15mg + two 4 mg capsules).

Enrollment of levels with 'a' and 'b' portions had to occur simultaneously.

Duration of treatment: The patient could have continued study treatment until disease progression, unacceptable toxicity, or consent withdrawal.

Duration of observation: The duration of the study for 1 patient included a period for screening of up to a maximum of 28 days, a pretreatment evaluation period of up to 5 days (only for Dose Level 1 and Dose Level 2), the on-treatment period, followed by a minimum of 30-day follow-up after the last study treatment administration.

The expected overall duration of the study was 28 months. The cutoff date was after all patients included in the expansion cohort discontinued from treatment or completed 4 cycles of 21-days therapy, whichever was first.

Patients who continued to receive the study treatment after the study cutoff date were to have been followed as per institution standard practice, until disease progression, unacceptable toxicity, or willingness to stop, with a minimum of 30-day follow-up after the last study treatment administration. For those patients, limited data collection was proposed as defined by the SMC.

Criteria for evaluation:

Safety:

Primary variables

The primary safety variables were the identification of DLTs and the MTD. A DLT was defined as any of the following toxicities at any dose level that were judged as possibly or probably related to the study treatment by the Investigator and/or Sponsor during the first cycle of treatment (Days 1 to 21):

- A treatment-emergent adverse event (TEAE) that in the opinion of the SMC was of potential clinical significance such that further dose escalation would have exposed patients to unacceptable risk
- Any ≥Grade 3 nonhematological toxicity excluding
  - Grade 3 nausea and vomiting, unless lasting longer than 48 hours despite supportive care,
  - Grade 3 diarrhea, unless lasting longer than 48 hours despite supportive care,
  - Grade 3/4 alkaline phosphatase (ALP) elevations in the context of bone metastasis, and
  - Alopecia.

- Any Grade 4 neutropenia or febrile neutropenia,
- Grade 4 thrombocytopenia or ≥Grade 3 with bleeding,
- Any treatment delay >2 weeks due to treatment-related adverse effects,
- Any severe or life-threatening complication or abnormality not defined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) that was attributable to the therapy.

The dose level below the maximum administered dose (MAD) was to have been considered the preliminary MTD, provided study treatment-related DLTs were observed in less than 2 of the 6 treated patients (or fewer than one-third if more than 6 patients enrolled) at that dose level. The MTD was generally the highest dose level where at most 1 patient of the cohort experienced a study treatment-related DLT. It was possible that more than 1 MTD could have been obtained with the combination of the 2 treatments, thus each of them was to have been evaluated at increasing dose levels.

Secondary variables

Safety parameters included collection of TEAEs; serious TEAEs; vital signs; electrocardiogram (ECG), whenever applicable; laboratory tests (including complete blood count including HbA1C, and differential and platelet counts; serum chemistry including fasting glucose, ALT/AST, total bilirubin, coagulation, brain natriuretic peptide, serum calcium, Vitamin D, and phosphate), echocardiogram or multigated acquisition (MUGA) scan, ophthalmologic exam (including slit lamp exam of the anterior segment, intraocular pressure, visual acuity, visual field, color vision, fundoscopy, and optical coherence tomography), and concomitant medications. The seriousness, severity grade, and relationship of TEAEs to study treatment were assessed by the Investigator. Severity grade was defined by the NCI CTCAE Version 4.0.

Adverse Events of Special Interest (AESI) included and were limited to the following:

- Retinal vein occlusion;
- Serous macular detachment or serous retinal detachment or similar retinal abnormality characterized by accumulation of serous fluid in the retina; and
- Potential and treatment-related DLTs.

Pharmacokinetics:

Blood samples for PK analysis were collected from all patients at determined time points listed in the study protocol. For combination cohorts Dose Level 1 and Dose Level 2, MSC was initially given once at least 2 days prior to the start of combination therapy with PK sampling collected at specified times from predose to 24 hours postdose for combination cohorts. After a 48-hour washout from the time of MSC single dose, the combination therapy began.

Pharmacodynamics:

Peripheral Blood and hair follicles: Samples were obtained from consented patients for analysis of a variety of established and exploratory pharmacodynamic markers on a schedule defined in the protocol throughout the study. Matched sampling of hair and peripheral blood mononuclear cell was required at the same visits where tumor samples were collected.

Tumor biopsy samples for pharmacodynamic and/or pharmacogenomic analysis: An optional tumor biopsy was planned for patients participating in the escalation phase of the study. A mandatory tumor biopsy at baseline and at Week 3 (Cycle 1 Day 21, 4-8 hours post dose) was planned for patients enrolled in the lower dose level and the MTD expansion cohorts. There was also an optional tumor biopsy performed in patients at the time of disease progression (restricted to patients with objective response or stable disease for longer than 4 months). A patient who had a research biopsy procedure for the purpose of this protocol, and in whom inadequate tissue was obtained, was not obligated to have a repeat biopsy. For patients who had effusions containing malignant cells as verified by a cytopathologist and were willing to have the optional invasive tumor biopsies, samples from the effusions could have substituted for a tumor biopsy.

When possible, pharmacodynamic sample collection was to have coincided with scheduled PK time points.

Efficacy: Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Patients had to be assessed using magnetic resonance imaging (MRI) or computerized tomography (CT) scan within 28 days before the first dose of study treatment, and every 6 weeks thereafter until the earliest of radiographic disease progression (per RECIST Version 1.1), or study treatment withdrawal. Responses could have been confirmed by repeat assessments performed at least 4 weeks after the response criteria were first met.

Statistical methods:

Unless otherwise specified in the statistical analysis plan, analyses were descriptive and separated by initial dosing group (cohorts with same dose levels were combined). Since there was no control group involved and all patients were treated with the same study drugs, a combined summary of all treated patients were provided in most cases, unless otherwise specified.

Continuous data were summarized using number of available data, mean, standard deviation, median, minimum, and maximum for each dose level. Categorical and ordinal data were summarized using number and percentage of patients in each respective group.

All efficacy variables were analyzed in the efficacy evaluable population using all data prior to any use of additional non-study anticancer therapy. The overall tumor response (ie, complete response [CR], partial response [PR], stable disease, and progressive disease) at each visit based on RECIST was presented and best overall response was summarized. The overall clinical benefit rate (CBR) was calculated by the proportion of patients experiencing a best overall response of confirmed CR, confirmed PR, or stable disease ≥12 weeks. Summary data were provided for all patients combined. Confidence interval (90%) for the CBR was calculated based on Clopper Pearson exact method for reference purpose only.

Determination of sample size

The study employed a traditional "3 + 3" design and dose expansion. Formal statistical tests were not planned. The total number of patients enrolled depended on the number of dosing cohorts required to identify the selected doses for the combination. Assuming a maximum of 12 dose levels were tested, the maximum number of patients needed in the dose escalation part of the protocol was 72.

A total of up to 84 patients could have been enrolled into the study. The final sample size, however, could have been higher if more dose levels were tested or expanded and if there was a need to replace patients who were not evaluable for a DLT.

Analysis Populations

Safety population (all treated population): All enrolled patients who took at least 1 dose of any study medication (SAR or MSC). Unless otherwise specified, all safety related analyses were summarized in the safety population. Patients were summarized based on their initial dose level received.

DLT evaluable population: All enrolled patients who completed assessments for DLT evaluation and received at least 80% of the doses of SAR and MSC during the first cycle of combination therapy, or received an incomplete study treatment and developed DLT during the first cycle. Patients not evaluable for DLT were typically replaced. This was a subset of the safety population.

Efficacy evaluable population: All enrolled patients who took at least 1 dose of any study medication and had valid baseline and at least 1 postbaseline tumor assessment.

Pharmacokinetic analysis population: PK analysis was not conducted due to early study termination.

Summary:

Population characteristics: Eighteen patients were enrolled and treated as follows: 3 in the SAR 25 mg capsule (cap) + MSC 15 mg cap; 6 in the SAR 50 mg cap + MSC 15 mg cap; 3 in the SAR 75 mg cap + MSC 15 mg cap; 2 in the SAR 75 mg cap + MSC 23 mg cap; and 4 in the SAR 100 mg cap + MSC 15 mg cap cohort, respectively. Of those patients, 17 completed the Cycle 1 treatment (1 in the SAR 50 mg cap + MSC 15 mg cap cohort did not).

All 18 patients were included in the safety population and evaluable for DLTs. Sixteen patients were included in the efficacy evaluable population as follows: 3 in the SAR 25 mg cap + MSC 15 mg cap; 5 in the SAR 50 mg cap + MSC 15 mg cap; 3 in the SAR 75 mg cap + MSC 15 mg cap; 2 in the SAR 75 mg cap + MSC 23 mg cap; and 3 in the SAR 100 mg cap + MSC 15 mg cap cohort, respectively. Two patients (1 in the SAR 50 mg cap + MSC 15 mg cap and 1 in the SAR 100 mg cap + MSC 15 mg cap cohort) were not evaluable for efficacy since they did not have a valid post-baseline assessment.

All 18 patients discontinued study treatment. The primary reasons for discontinuation included disease progression (16 patients) and AEs (2 patients). At last study contact, 14 patients were alive and 4 had died.

Overall, there were 7 males and 11 females enrolled in the study. Most patients were white (17) and 1 was of other ethnicity. Median age for all patients was 62.0 years (range: 49 to 74 years) and all had ECOG PS of 0 or 1. The primary tumor sites at initial diagnosis were in the colon/rectum, pancreas, breast, endometrium, and other site. Median time from initial diagnosis for all patients was 3.48 years (range: 0.1 to 11.9 years). Most patients had Stage II (5 patients) or Stage IV cancer (8 patients) at initial diagnosis. Nine patients had abnormal KRAS pathway, 1 patient had abnormal PI3KCA pathway, and 1 patient had another abnormal pathway at baseline.

Safety results:

Exposure

The median number of weeks on SAR treatment was 6.14 for the SAR 25 mg cap + MSC 15 mg cap; 6.00 for the SAR 50 mg cap + MSC 15 mg cap; 12.00 for the SAR 75 mg cap + MSC 15 mg cap; 8.86 for the SAR 75 mg cap + MSC 23 mg cap; and 8.57 for the SAR 100 mg cap + MSC 15 mg cap cohort, respectively. The median number of weeks on MSC treatment was similar to SAR for all treatment cohorts. Most patients received between 1 and 2 cycles (11 patients) and 3 and 4 cycles (4 patients) of SAR and MSC treatment; only 3 had received more than 4 cycles.

Patients on study treatment for >10 weeks included those with sites in the colon/rectum (4 patients), and endometrium, pancreas, and other (1 patient each).

Median relative dose intensity (RDI) of SAR was 1.000 for the SAR 25 mg cap + MSC 15 mg cap; SAR 50 mg cap + MSC 15 mg cap; and SAR 75 mg cap + MSC 15 mg cap cohort, respectively. Median RDI of SAR was 0.988 for the SAR 75 mg cap + MSC 23 mg cap and 0.877 for the SAR 100 mg cap + MSC 15 mg cap cohort, respectively. Median RDI for MSC treatment was similar for all treatment cohorts. In Cycle 1, median RDI of SAR and MSC was 1.000 for all treatment cohorts.

Based on the exposure dataset, 1 patient in the SAR 75 mg cap + MSC 15 mg cap cohort had at least 1 dose reduction of SAR during the study. Three patients in the SAR 50 mg cap + MSC 15 mg cap, 2 patients in the SAR 75 mg cap + MSC 15 mg cap, 1 patient in the SAR 75 mg cap + MSC 23 mg cap, and 4 patients in the SAR 100 mg cap + MSC 15 mg cap cohort, respectively, had at least 1 dose interruption of SAR during the study. Of those patients, 2 in the SAR 50 mg cap + MSC 15 mg cap and 4 in the SAR 100 mg cap + MSC 15 mg cap cohort had a dose delay/interruption for ≥5 days; 1of the patients in the SAR 100 mg cap + MSC 15 mg cap cohort had a dose delay/interruption for >2 weeks.

Dose reductions of MSC did not occur during the study. Two patients in the SAR 50 mg cap + MSC 15 mg cap, 2 in the SAR 75 mg cap + MSC 15 mg cap, 1 in the SAR 75 mg cap + MSC 23 mg cap, and 4 in the SAR 100 mg cap + MSC 15 mg cap cohort, respectively, had at least 1 dose interruption of MSC during the study. Of those patients, 1 in the SAR 50 mg cap + MSC 15 mg cap and 4 in the SAR 100 mg cap + MSC 15 mg cap cohort had a dose delay/interruption for ≥5 days; 1 of the patients in the SAR 100 mg cap + MSC 15 mg cap cohort had a dose delay/interruption for >2 weeks.

Dose-Limiting Toxicities

One patient in the SAR 50 mg cap + MSC 15 mg cap cohort experienced a DLT of Grade 3 enteritis that was considered to be an SAE related to both SAR and MSC; study treatment was interrupted, and the SAE resolved. The patient had a recurrence of symptoms on rechallenge, and was discontinued from the study due to fatigue and facial edema.

Treatment-Emergent Adverse Events

All 18 patients had at least 1 TEAE (all grades), of which 17 had treatment-related TEAEs. Six patients had at least 1 Grade 3-4 TEAE, of which 3 had treatment-related Grade 3-4 TEAEs.

The most common TEAEs (reported by >5 patients) in all cohorts (all grades) were diarrhea (9 patients); decreased appetite and nausea (8 patients each); fatigue (7 patients); and constipation, dermatitis acneiform, and peripheral edema (6 patients each). The only Grade 3-4 TEAE reported by more than 1 patient was hyperglycemia (2 patients in the SAR 50 mg cap + MSC 15 mg cap cohort).

There were no cases of retinal vein occlusion, serous macular detachment, serous retinal detachment, similar retinal abnormality characterized by accumulation of serous fluid in the retina.

Three patients had at least 1 serious TEAE. One patient in the SAR 50 mg cap + MSC 15 mg cap cohort had Grade 3 treatment-related enteritis (the DLT) and myositis that resolved; 1 patient in the SAR 75 mg cap + MSC 15 mg cap cohort had Grade 3 unrelated acute renal failure and syncope that resolved; and 1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort had fatal disease progression that was unrelated to study treatment.

Four patients died during the study, of which 1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort died on-study (within 30 days of the last dose of study treatment) and as the result of a serious TEAE (disease progression) that was unrelated to study treatment. The remaining 3 deaths were due to disease progression.

Based on the AE dataset, 4 patients had at least 1 TEAE leading to dose delay/interruption. One patient in the SAR 50 mg cap + MSC 15 mg cap cohort had TEAEs of enteritis and nausea; 1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort had a TEAE of dysarthria; 1 patient in the SAR 100 mg cap + MSC 15 mg cap had a TEAE of blood creatinine increased; and 1 patient in the SAR 50 mg cap + MSC 15 mg cap cohort had a TEAE of ejection fraction increased. One patient in the SAR 100 mg cap + MSC 15 mg cap cohort had a TEAE of palmar-plantar erythrodysesthesia syndrome that led to dose reduction.

Two patients had at least 1 TEAE that led to permanent discontinuation of study treatment; 1 patient in the SAR 50 mg cap + MSC 15 mg cap cohort had Grade 2 nonserious treatment-related TEAEs of face edema and fatigue, and 1 patient in the SAR 75 mg cap + MSC 15 mg cap cohort had a Grade 3 serious unrelated TEAE of acute renal failure.

Laboratory Results - During the study, Grade 3 hematological abnormalities included anemia (1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort) and decrease in lymphocytes (1 patient in the SAR 50 mg cap + MSC 15 mg cap cohort). No patient had a Grade 4 hematological abnormality.

Grade 3 chemistry abnormalities during the study included elevated ALP (2 patients; 1 in the SAR 50 mg cap + MSC 15 mg cap and 1 in the SAR 75 mg cap + MSC 23 mg cap cohort), elevated AST (1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort), elevated ALT (1 patient in the SAR 100 mg cap + MSC 15 mg cap cohort), elevated creatinine (1 patient in the SAR 75 mg cap + MSC 15 mg cap cohort), hyponatremia (1 patient in the SAR 75 mg cap + MSC 15 mg cap cohort), and hyperglycemia (2 patients; 1 in the SAR 50 mg cap + MSC 15 mg cap and 1 in the SAR 100 mg cap + MSC 15 mg cap cohort). No patient had a Grade 4 chemistry abnormality.

One patient in the SAR 100 mg cap + MSC 15 mg cap cohort had a clinically significant change in laboratory results that was reported as a nonserious Grade 3 TEAE of blood creatinine increased, which led to a 1-day interruption in study drug administration. The Investigator considered the TEAE to be unrelated to SAR and MSC, and the TEAE resolved.

Vital Signs

Two patients, both in the SAR 75 mg cap + MSC 15 mg cap cohort, had systolic blood pressure (SBP) of ≤95 mmHg and a decrease from baseline of ≥20 mmHg. Five patients (1 in the SAR 25 mg cap + MSC 15 mg cap, 3 in the SAR 50 mg cap + MSC 15 mg cap, and 1 in the SAR 75 mg cap + MSC 23 mg cap cohort) had SBP of ≥160 mmHg and an increase from baseline of ≥20 mmHg.

One patient, in the SAR 75 mg cap + MSC 15 mg cap cohort, had diastolic blood pressure (DBP) of ≤45 mmHg and a decrease from baseline of ≥10 mmHg; no patient had DBP of ≥110 mmHg and an increase from baseline of ≥10 mmHg.

Two patients (1 in the SAR 50 mg cap + MSC 15 mg cap and 1 in the SAR 100 mg cap + MSC 15 mg cap cohort), had a ≥5% decrease in weight from baseline, and 1 patient in the SAR 50 mg cap + MSC 15 mg cap cohort had an ≥5% increase in weight from baseline.

Electrocardiograms

No patient had an abnormal increase or decrease in heart rate from baseline. Two patients (1 in the SAR 25 mg cap + MSC 15 mg cap and 1 in the SAR 50 mg cap + MSC 15 mg cap cohort) had PR of ≥220 msec and an increase from baseline of ≥20 msec. QRS was ≥120 msec for 1 patient in the SAR 50 mg cap + MSC 15 mg cap cohort. One patient in the SAR 50 mg cap + MSC 15 mg cap cohort had prolonged QTc (defined as >450 msec [Male]; >470 msec [Female]; <500 msec), and no patients had prolonged QTcF or QTcB.

One patient in the SAR 50 mg cap + MSC 15 mg cap cohort had a clinically significant change in ECG result that was reported as a nonserious Grade 3 TEAE of ejection fraction decreased; the TEAE led to a dose modification in study drug administration. The Investigator considered the TEAE to be related to both SAR and MSC, and the event had not resolved by the end of the study.

Pharmacokinetic results: Pharmacokinetic analysis was not conducted due to early study termination; PK results will not be available. Pharmacodynamic results: Biomarker data will be provided in a separate translational medicine report. Efficacy results: Sixteen patients were evaluable for tumor response. No patient had confirmed CR or PR. Seven patients had stable disease (3 of which had stable disease ≥12 weeks) and 9 patients had progressive disease. The CBR was 18.75% (90% CI: 0.0531 to 0.4166).
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