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Sponsor: Sanofi **Drug substance(s):** SAR428926	**Study Identifiers:** U1111-1168-4706, NCT02575781, 2015-001441-92 **Study code:** TED14147
Title of the study: A first-in-human Phase 1 dose escalation study of SAR428926 in patients with advanced solid tumors.	
Study center(s): 3 Active study centers located in France, Denmark, and Spain for dose escalation (DE) phase	
Study period: Date first participant enrolled: 05/Oct/2015 Date last participant completed: 15/Jun/2018 Study Status: Completed	
Phase of development: Phase 1	
Objectives: **Primary Objectives:** ***Dose Escalation Phase (Part 1)*** • To determine the maximum tolerated dose (MTD) of SAR428926 when administered as a single agent in patients with advanced solid tumors. ***Expansion Phase (Part 2)*** (Not conducted)	
Methodology: This study is a first in human (FIH), open-label, non-randomized, dose escalation (DE) study for the evaluation of safety, pharmacokinetic and anti-tumor activity of SAR428926 administered as a single agent via intravenous (IV) infusion every 2 weeks (q2w) in a 14-day cycle in patients with advanced solid tumors with no standard alternative therapeutic options and expressing (or likely expressing) LAMP1 on their plasma membrane. Two parts were planned for the study: Part 1, Dose escalation (DE) phase and Part 2, Expansion Phase. The DE Phase enrolled patients with advanced solid tumors expressing or likely to be expressing LAMP1: any molecular sub-type of HER2-negative breast cancer (BC), gastric adenocarcinoma (including esophagogastric junction adenocarcinoma [EGJ] (Siewert type II and III), CRC, ovarian adenocarcinoma, prostate adenocarcinoma and NSCLC with no standard alternative treatment options, and regardless of LAMP1 expression status. An accelerated DE was used for the first 3 dose levels (DL); assessment of safety was based on the occurrence of toxicities observed during the first two cycles of treatment in 1 patient. Dose escalations of 100% increments were to be done until the report of any investigational medicinal product (IMP) related adverse event (AE) Grade ≥2. If an IMP-related AE Grade ≥2 was observed at any of the first 3 DLs, 2 additional patients would be treated at the same DL and the DE would proceed using adaptive Bayesian design with DE with overdose control (EWOC) starting at DL4 (40 mg/m^2).	

Number of participants:

Planned: 110 (54 in DE, 56 in two expansion cohorts)

Enrolled: 34

Evaluated:.

Dose limiting toxicity (DLT) evaluable population: 31

Safety: 34

Pharmacokinetics: 34

Diagnosis and criteria for inclusion:

Patients eligible for this study have been diagnosed with advanced, unresectable or metastatic solid malignant disease without available standard therapy, and meet the following inclusion criteria:

Inclusion Criteria:

- For DE Phase, main cohort: Inclusion was restricted to patients with tumor types likely to be expressing LAMP1: HER2 negative BC (any molecular sub-type), gastric cancer (including [EGJ]) adenocarcinoma (Siewert type II and III), CRC, ovarian adenocarcinoma, prostate adenocarcinoma, and NSCLC, regardless of LAMP1 expression status.
- For dose escalation phase, Lamp-1 positive tumor cohort (LPT) during DE Phase: Inclusion was restricted to patients with the same tumor types listed above for DE Phase cohorts, who gave consent to prospective evaluation of LAMP1 expression in most recent FFPE archival tumor tissue sample (optional) in which a LAMP1 expression at the plasma membrane in ≥25% of tumor cells is demonstrated. Note: There were no LPT patients screened in the study, thus an LPT cohort was not open.

Study products:

Investigational medicinal product(s): SAR428926

Formulation: Supplied as a 20 mL extractable volume of concentrate for solution for infusion of 100 mg (5mg/mL) contained in a 25 mL glass vial.

Route of administration: IV

Dose regimen: Accelerated Escalation: 5, 10, 20 mg/m^2

Escalation phase with overdose control 40, 80, 100, 120, 150, 180, 210 mg/m^2 (30 and 60 mg/m^2 optional dose levels)

Duration of treatment: 2 weeks/cycle until unacceptable toxicity, disease progression, or patient's decision to stop treatment occur.

Duration of observation:

A period for inclusion of up to 4 weeks (base line period), an end-of treatment (EOT) visit around 30 days following the last dose of therapy, and at least one follow-up visit 30 days after EOT visit for immunogenicity and AE evaluation. Additional follow-up visits may be required if the patient discontinued the treatment for reasons other than progressive disease, or until SAEs or related AEs have been resolved or stabilized.

Criteria for evaluation:

The following safety criteria were evaluated, and analyzed using descriptive statistics; treatment exposure, laboratory tests, and treatment-emergent adverse events.

Statistical methods: Statistical analyses will be descriptive and performed based on the all-treated population.

Summary Results:

Population characteristics

Of the 34 patients in the study, 21 (61.8%) were female and 13 (38.2%) were male. The median age of all patients was 58.5 years (range: 29 to 77 years), and the majority of patients were white (25 patients, 73.5%)

The most frequent primary tumor site locations among these patients were the colon (12 patients, cecum, colon, colon-sigmoid), ovaries (5 patients, 14.7%), rectum (4 patients, 11.8%), breast (6 patients, breast, breast-left, breast-right), and gastric: (4 patients, gastroesophageal junction, stomach), gastroesophageal junction (1 patient).Half of the patients had stage IV cancer, and 9 patients (26.5%) had stage III cancer at diagnosis. The main histology was adenocarcinoma (24 patients, 70.6%). Most patients had three (6 patients or 17.6%), four (7 patients or 20.6%), five (4 patients or 11.8%), or six (7 patients or 20.6%) prior anti-cancer therapies. The median time elapsed between initial diagnosis and first treatment infusion was 3.8 years (range: 1 to13 years).

At study entry, all patients had metastatic disease. The median number of organ involvement was 3, and the most frequent metastatic sites were the liver (25 patients, 73.5%), lymph node (22 patients, 64.7%), lung (18 patients, 52.9%), and peritoneum (12 patients, 35.3%). Lamp 1 expression was available for 20 patients, and was positive in 18.

All patients discontinued study treatment, 31 (91.2%) of patients discontinued due to progressive disease, 2 (5.9%) patients discontinued due to an AE (keratopathy and stress cardiomyopathy), and 1 patient decided to stop (reason other).

Safety

Exposure

The median duration of treatment for the 34 patients was 8 weeks (range: 2 to 42.7 weeks). Overall, the median cumulative dose was 340.42 mg/m^2 with an actual median dose intensity of 50 mg/m^2/week. Ten patients (29.4%) were exposed to 4 treatment cycles (range: 1 to 20 cycles). Thirty-one patients (91.2%), were exposed to at least 2 cycles of treatment. A total of 9 patients (26.5%) had at least one dose modification, including 9 patients (26.5%) with at least one cycle delayed, and 4 patients (11.8%), with in addition at least 1 dose reduction. Of note, among these 4 patients with a dose reduction, 3 were treated at DL of 180. In addition, 7 patients (20.6%) had at least 1 dose interruption. Of these 7 patients, 2 had a dose interruption due to an AE. One patient presented with an infusion related reaction leading to dose interruption at 150 mg/m^2. The 2nd patient experienced vomiting leading to a dose interruption at 180 mg/m^2. The 5 remaining patients experienced dose interruption due to pump dysfunction.

Description of dose escalation and DLT

Thirty-one patients were evaluable for DLT out of 34 treated (1 pt at each DL 40, 80, and 180 mg/m^2 was not evaluable). There were no IMP related Grade 2 AEs reported during the accelerated DE phase. As a consequence, 1 patient per DL was treated for the 1st 3 DLs. Then 1 patient experienced a DLT at each DL of 80 mg/m^2 and 100 mg/m^2 resulting in expansion of 6 treated patients in each DL (keratopathy at cycle 2 and cycle 2 delay more than 2 weeks due to related thrombocytopenia respectively). At 180 mg/m^2, 2 patients developed a DLT among the 1st 3 evaluable patients (Cohort 1): Grade 3 vomiting at Cycle 2, and Grade 3 stress cardiomyopathy at Cycle 1. Because the 2 DLTs in the 1st cohort were debatable, the decision was made to expand the DL, and recruit 3 additional patients (Cohort 2). Of the 3 additional patients, 1 developed a DLT of bilateral keratitis (Cycle 2, Grade 2). Finally, 1 patient had TNBC, and experienced a DLT of palmar plantar erythrodysaesthesia syndrome (Cycle 2, Grade 3). The DL of 180 mg/m^2 was considered to be the MAD.

Treatment-emergent adverse events

All 34 patients (100%) experienced a TEAE, and 20 patients (58.8%) experienced a TEAE of Grade ≥3. The most frequent TEAEs (≥5% of patients) regardless of relationship to study treatment of any grade were nausea, decreased appetite, vomiting, diarrhea, fatigue, abdominal pain, constipation, dyspnea, stomatitis, cough, pyrexia, weight decrease, and tumor pain. The most frequent TEAEs (≥5% of patients) of Grade ≥3 were spinal cord compression, vomiting, constipation, ascites, disease progression, and asthenic conditions. Twenty-five patients (73.5%) experienced a TEAE of any grade related to study drug, and 4 patients (11.8%) experienced a Grade ≥3 TEAE related to study drug. The most frequent related TEAEs (≥5%) by decreasing frequency were nausea, decreased appetite, vomiting, diarrhea, and asthenic conditions (either asthenia or fatigue). Related TEAEs of Grade ≥3 included: stress cardiomyopathy, vomiting, palmar-plantar erythrodysaesthesia, abdominal pain, and asthenia (1 patient each, 2.9%). Of note, only 2 patients experienced a keratitis (or punctated keratitis), at 80 mg/m^2 and 180 mg/m^2. Both occurred at Cycle 2, and recovered with corrective treatment. All patients were compliant with prophylactic measures. In general, the highest dose of study drug (180 mg/m^2) was associated with a greater frequency of TEAEs. However, at lower doses (120 mg/m^2, 100 mg/m^2, 80 mg/m^2, and ≤40 mg/m^2) there was no apparent relationship between TEAE frequency and dose.

Deaths

There were a total of 16 deaths (47%), all attributed to disease progression. One patient (2.9%) died within 30 days of the last administration of study drug, and 15 patients (44.1%) died more than 30 days after last administration of the study drug.

Serious Adverse Events

SAEs occurred in 15 patients (44.1%), and SAEs of Grade ≥3 occurred in12 patients (35.3%). The most frequent SAE of both any grade and Grade ≥3 observed in 2 patients were spinal cord compression and disease progression.

SAEs related to study drug of any grade were stress cardiomyopathy (1 patient, 2.9%) and infusion related reactions (1 patient, 2.9%). SAEs related to study drug of Grade ≥3 was stress cardiomyopathy reported in 1 patient (2.9%).

TEAEs leading to treatment discontinuation

Two patients (5.9%) discontinued SAR428926 due to a TEAE. These TEAEs included (1 patient each) punctated keratitis, Grade 2, and stress cardiomyopathy, Grade 3.

TEAEs leading to dose modification

Seven patients (20.6%) experienced a TEAE of any grade leading to dose modification. These included thrombocytopenia, neuralgia, keratitis, upper gastrointestinal hemorrhage, vomiting, palmar plantar erythrodysaethesia syndrome, asthenia, increased alanine aminotransferase, decreased platelet count, and a road traffic accident (1 patient each, 2.9%). Three patients (8.8%) experienced a TEAE of Grade ≥3 resulting in dose modification. These included upper gastrointestinal hemorrhage, vomiting, and palmar plantar erythrodyasethesia syndrome.

Adverse events of special interest (Dose limiting toxicities)

See details above relating to DLTs.

Efficacy

Best overall tumor response was partial response (1 patient, 2.9%), stable disease (8 patients, 23.5%), progressive disease (20 patients, 58.8%). Three patients were not evaluable for tumor response (8.8%) due to non-measurable disease at study entry, or no evaluable tumor assessment in the protocol defined timeframe. In addition the overall response was missing for 2 patients, (5.9%) due to lack of post-baseline tumor assessment.

Laboratory Results

Hematology: During the treatment period, anemia was reported in 26 patients (76.5%). Fifteen patients (44.1%), experienced a decreased lymphocyte count, and 12 patients (35.3%), experienced a reduction in their platelet count. The neutrophil count was decreased in 3 patients (8.8%). Four patients (11.8%) were reported to have hematological toxicity of Grade 3/4. Two patients (5.9%) reported the first occurrence of this toxicity in cycle 1 of treatment.

Biochemistry: During the treatment period, the most common (≥40% of patients) abnormal biochemical parameters of all grades were alkaline phosphatase (26 patients, 76.5%), aspartate aminotransferase, hypoalbuminemia (both effects seen in 23 patients, 67.6%), hyperglycemia (21 patients, 61.8%), and alanine aminotransferase, hyponatremia (both effects seen in 14 patients, 41.2%).

Pharmacokinetic

PK of SAR428926 in patients was characterized by a mean plasma clearance of 5.57 L/day, a volume of distribution of 3 L, and a terminal half- life of approximately 9.5 hours. No dose effect was observed on clearance. Exposure to SAR428926 (C_{max} and AUC) increased in a dose proportional manner. Both maytansinoid derivative 4 (DM4) and methylated maytansinoid derivative 4 (Me-DM4) were observed as circulating entities, while concentrations of the naked antibody were below the limit of quantitation in almost all samples. DM4 and Me-DM4 accounted for approximately 2% and 20-40% of SAR428926 exposure, respectively on a molar basis.

Immunogenicity

All patients treated were evaluable for immunogenicity: 11 out of 34 patients showed a treatment induced immunogenicity leading to an incidence of 32.3%. Positive anti-treatment antibodies (ATA) patients were treated in the dose range of 40 to 180 mg/m^2.

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